Hypertension in women is often undiagnosed or inadequately treated, especially after menopause when cardiovascular risk increases. In premenopausal women, endogenous estrogens maintain vasodilation and thus contribute to blood pressure control. Aging and the loss of endogenous estrogen production after menopause are accompanied by increases in blood pressure, contributing to the high prevalence of hypertension in older women. Currently, ≈75% of postmenopausal women in the United States are hypertensive. The high prevalence of obesity, the lack of regular physical exercise, and dietary salt are important factors contributing to and aggravating postmenopausal hypertension. In view of the ongoing population aging throughout the world, diagnosis and treatment of hypertension in postmenopausal women are important to reduce the excess burden of associated cardiovascular disease and to improve outcomes of potentially fatal complications such as stroke and myocardial infarction. This article discusses current knowledge about the mechanisms and therapeutic issues related to postmenopausal hypertension.

Hypertension: Important Determinant of Cardiovascular Risk in Women

More than 25% of the female adult world population is hypertensive. Elevations in blood pressure in women are related to cardiovascular risk (Figure, panel A), with the prevalence of hypertension being particularly high among women aged ≥60 years. In the United States, ≈75% of postmenopausal women are hypertensive. Hypertension is often accompanied by other cardiovascular risk factors, eg, obesity, dyslipidemia, and diabetes mellitus. It is noteworthy that the prevalence of hypertension-related cardiovascular complications is greater in postmenopausal women than in age-matched men. Indeed, these complications represent the leading cause of death in women.

Clinical studies have documented beneficial effects of antihypertensive therapy on cardiovascular outcome, even in patients ≥80 years of age. Overall recognition, control, and treatment of hypertension in postmenopausal women are still poor in primary care, and hypertension is often not being treated aggressively enough. Thus, further improvements of medical and public health measures, awareness of patients and physicians, and improved information policies are needed.

Blood Pressure and Endogenous Estrogens: Role of Menopause

Prior to menopause, blood pressure is lower in women compared with age-matched men. During the menstrual cycle, blood pressure levels are inversely related to circulating estrogen concentrations and lower when 17β-estradiol levels peak, reflecting the vasodilator activity of endogenous 17β-estradiol. Similarly, increases of endogenous estrogen production during pregnancy contribute to maintenance of normotension despite marked increases in plasma volume and cardiac output. The first decade after menopause is accompanied by an increase in blood pressure (Figure, panel B). In the seventh decade of life, the prevalence of hypertension among women is even higher than in men, regardless of ethnic background. Specifically, there are pronounced increases in both systolic blood pressure and pulse pressure in postmenopausal women, whereas diastolic blood pressure remains at a similar level compared with age-matched men (Figure, panel B). Importantly, elevated systolic blood pressure is considered a more sensitive predictor of future cardiovascular events than diastolic blood pressure.

The role of endogenous estrogens in the pathogenesis of hypertension is complex. Indeed, the effects of hormonal changes after menopause are often masked by the presence of other cardiovascular risk factors, eg, vascular aging, arterial stiffening, obesity, age-dependent changes in insulin sensitivity, and dyslipidemia. Cross-sectional studies indicate that menopause increases the risk of hypertension by ≈2-fold, even after adjusting for factors such as age and body mass index. Both early onset of menopause and a long postmenopausal period are associated with higher blood pressure levels. Moreover, hypoestrogenemic premenopausal women diagnosed with the polycystic ovary syndrome and menstrual irregularities because of ovarian failure are at a higher risk of developing hypertension, coronary artery disease, and adverse cardiovascular events and experience...
menopause at an earlier age than healthy controls. Interestingly, a recent report indicates that physiological 17β-estradiol treatment in patients with premature ovarian failure results in significant reductions in blood pressure, whereas no effects on blood pressure were observed using synthetic ethinylestradiol. Consistent with the blood pressure–lowering effect of physiological estrogens in women with ovarian failure, surgically induced menopause by bilateral oophorectomy increases blood pressure within a few weeks. In conclusion, evidence strongly support the notion that endogenous estrogens contribute to a basal vasodilatory state. Therefore, the loss of endogenous estrogens facilitates the development of hypertension in postmenopausal women and increases the cardiovascular risk associated with it.

Figure. A, Cumulative incidence of cardiovascular events in women without hypertension, according to blood pressure category at the baseline examination. Vertical bars indicate 95% CIs. According to earlier classifications from the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, optimal blood pressure was defined as a systolic pressure of <120 mm Hg and a diastolic pressure of <80 mm Hg. Normal blood pressure was a systolic pressure of 120 to 129 mm Hg or a diastolic pressure of 80 to 84 mm Hg. High-normal blood pressure was a systolic pressure of 130 to 139 mm Hg or a diastolic pressure of 85 to 89 mm Hg. (reprinted, with permission, from Vasan RS, Larson MG, Leip EP, Evans JC, O’Donnell CJ, Kannel WB, Levy D. Impact of high-normal blood pressure on the risk of cardiovascular disease. N Engl J Med. 2001;345:1291–1297. Copyright © 2001, Massachusetts Medical Society. All rights reserved). B, Age-dependent changes in systolic and diastolic blood pressures in men and women and effects of ethnicity. In the first decades of life, blood pressure in women is lower than in men. However, in women, the years after menopause are associated with a continued rise in systolic blood pressure, reaching that of age-matched men (reprinted, with permission, from Burt VL, Whelton P, Roccella EJ, Brown C, Cutler JA, Higgins M, Horan MJ, Labarthe D. Prevalence of hypertension in the US adult population. Result from the Third National Health and Nutrition Examination Survey, 1988–1991. Hypertension. 1995;25:305–313). C, Projected development of the female world population over the next 4 decades. Until 2050, the proportion of individuals aged ≥50 years will continue to increase between factors 2 and 5, resulting in a pronounced shift in the overall population profile. There will also be a substantial increase in the number of postmenopausal women, who are at high risk for the development of hypertension and cardiovascular disease because of loss of endogenous estrogen production. Data are derived from current estimates provided by the US Census Bureau.
intracellular signaling cascades. ER-dependent mechanisms regulating vascular tone include endothelium-independent vasodilation, increases in NO bioavailability, inhibition of vascular smooth muscle cell (VSMC) growth and excess proliferation after balloon injury, inhibition of the vascular renin-angiotensin-aldosterone system (RAAS) and the endothelin system, and inhibition of the sympathetic nervous system.12,17,25,26

Preclinical studies have investigated the contribution of ERα and ERβ for blood pressure, and the results suggest roles for both ER subtypes, depending on the animal model studied.27 However, these data do not reflect human physiology or human ER function, nor do they take into account differences in ER function in healthy or diseased human arteries. Thus, their value for understanding human disease may be limited. Studies investigating genetic variations in the ERα and ERβ genes in women and men suggest associations of polymorphisms of both ER subtypes with hypertension.28,29 It is currently unknown whether and to what extent ER-dependent or ER-independent effects, eg, antioxidant mechanisms of estrogens or inhibitory effects on the sympathetic nervous system, are involved, and how estrogen-dependent signaling pathways controlling blood pressure are altered during different stages of human life. It is, however, likely that these pathways and mechanisms are negatively affected by the presence of cardiovascular risk factors or by overt atherosclerosis.

In addition to the classic ERs, the G protein–coupled estrogen receptor GPER (formerly known as GPR30)30 is highly expressed in human VSMCs and arteries.31 We have shown recently that selective activation of GPER causes acute vasodilation in arteries from rodents and humans, reduces blood pressure in vivo even under normotensive conditions, and inhibits human VSMC proliferation,32 similar to what has been observed with 17β-estradiol.47 Future research will help to delineate the role of individual pathways contributing to the function of each known ER and will help to assess how nuclear ERα and ERβ and GPER contribute to blood pressure control and the vasoprotective effects of estrogens.27,32,33

Estrogens and the Kidney: Salt Sensitivity and Renal Disease
Menopause increases the risk of renal disease and glomerulosclerosis in humans.34 The kidney is essential in regulating water homeostasis and, thus, controlling blood pressure, and protective effects of estrogens in renal hypertension have been suggested.34 Indeed, a slower rate of renal aging, as indicated by the decline in glomerular filtration rate, has been found in women below age 52 years compared with older women or age-matched men, again suggesting estrogen-mediated renoprotective effects.35 It is, thus, not surprising that 17β-estradiol inhibits glomerular mesangial cell proliferation.36 Furthermore, the development of glomerulosclerosis in rodents does not start until a stage in life that corresponds with the early menopausal period in humans.37 Ovariectomy aggravates renal injury and causes hypertension in laboratory animals, effects that are attenuated by sex hormone treatment.38 Moreover, estrogens may confer renal protection by inhibiting components of the RAAS, including angiotensin type 1 receptor expression, and by reducing angiotensin-converting enzyme activity.38

Hypertension evoked by increasing dietary salt intake (“salt sensitivity”) is highly prevalent in postmenopausal women.34,39,40 Salt sensitivity is associated with abnormal endothelial cell function, hyperlipidemia, microalbuminuria, and insulin resistance.41,42 In patients diagnosed with “essential hypertension,” the presence of salt sensitivity may aggravate hypertension and complicate antihypertensive therapy, and the underlying mechanisms are still known only in part.43 In the kidney, salt sensitivity is characterized by a blunted pressure-natriuresis relationship; thus, higher pressures are needed to achieve similar levels of sodium excretion, which is also regulated by the RAAS and the endothelin system.38,44 Preclinical studies suggest that the loss of endogenous estrogens reduces NO bioavailability and increases angiotensin II activity, leading to impaired renal sodium handling, oxidative stress, and hypertension.38 Salt loading in healthy premenopausal women induces marked renal vasodilation and a decrease in the filtration fraction during the luteal phase of the menstrual cycle, when estrogen levels are high.34 In contrast, normotensive, salt-sensitive postmenopausal women exposed to a high-salt diet exhibit a reduction in renal plasma flow and an increase in the filtration fraction.44 This suggests that the lack of endogenous estrogens may be one of the factors reducing the vasodilator capacity of the renal circulation in response to salt loading.38 The link between salt sensitivity and endogenous estrogens is further corroborated by the observation that after surgical menopause the loss of endogenous sex hormones is associated with the development of salt-sensitive hypertension in previously healthy salt-resistant women.45 Accordingly, transdermal administration of 17β-estradiol has been shown to effectively reduce salt sensitivity in postmenopausal women.46 These observations are further supported by preclinical work of Hinojoza-Laborde and coworkers47 using ovariectomized Dahl rats as an animal model of postmenopausal salt-sensitive hypertension. In these animals, 17β-estradiol attenuates age-related renal dysfunction. Taken together, endogenous sex hormones are important modulators of systemic and renal hemodynamics during the response to salt, and, thus, the lack of endogenous sex hormones appears to be one of the permissive factors facilitating the development of salt-sensitive postmenopausal hypertension.

Other Vasculoprotective Mechanisms of Estrogen Action
Endogenous estrogens are powerful antioxidants inhibiting the generation of reactive oxygen species and increasing NO bioavailability.13 Oxidative stress in postmenopausal women has been implicated in abnormal endothelial cell function and the development of hypertension.15 The rise in blood pressure after menopause also involves other factors, eg, obesity and aging,24 and arterial stiffness due to the presence of atherosclerosis.49

17β-Estradiol is partly metabolized to 2-hydroxyestradiol and 2-methoxyestradiol, which are converted by cytochrome P450 enzymes and catechol-O-methyltransferase and exert protective
cardiovascular and renal effects, including a reduction in blood pressure.\textsuperscript{50} 2-Hydroxyestradiol and 2-methoxyestradiol stimulate the generation of the vasodilator prostacyclin, reduce endothelin-1 synthesis, and inhibit proliferation of VSMCs and glomerular mesangial cells.\textsuperscript{50} Interestingly, increased urinary 2-hydroxyestradiol concentrations in postmenopausal women are associated with lower systolic blood pressure levels.\textsuperscript{51} Although some studies have reported ER-independent growth-inhibitory actions,\textsuperscript{36,50} others suggest that the effects of 2-methoxyestradiol are mediated through ERs.\textsuperscript{52} Thus, the molecular mechanisms whereby 2-methoxyestradiol exerts its vasculoprotective effects still remain to be clarified.

**Estrogens and Effects on Blood Pressure in Humans**

**Natural Estrogen (17β-Estradiol)**

Acute arterial vasodilation in response to 17β-estradiol has been observed in several human vascular beds,\textsuperscript{13} and 17β-estradiol treatment reduces blood pressure by improving endothelium-dependent, flow-mediated vasodilation in women early after menopause.\textsuperscript{53} These data are consistent with studies showing that variations of tonic vasodilation are highly correlated with estrogen levels during the menstrual cycle.\textsuperscript{12} Accordingly, the majority of studies investigating long-term effects of 17β-estradiol on 24-hour ambulatory blood pressure demonstrated reductions in blood pressure, especially when using transdermal application of the hormone.\textsuperscript{16} Interestingly, Fisman et al\textsuperscript{54} reported that sublingual administration of 17β-estradiol lowers blood pressure in hypertensive but not in normotensive postmenopausal women. These authors also found that hypertensive individuals showed higher peak 17β-estradiol plasma concentrations than normotensive controls after administration of the hormone,\textsuperscript{54} which suggests the possibility that hypertension might affect the bioavailability of estrogens during HT.

**Animal Hormones (“Conjugated Equine Estrogens”)**

Randomized clinical trials, including the Heart and Estrogen/progestin Replacement Study (HERS) and the Women’s Health Initiative (WHI), both using conjugated equine estrogens (CEE) obtained from the urine of pregnant horses and medroxyprogesterone acetate (MPA) for postmenopausal hormone therapy (HT), were uniformly associated with increased cardiovascular risk.\textsuperscript{55,56} However, studies have shown that, in postmenopausal women receiving HT, systolic blood pressure hardly increases over time and the nighttime fall in blood pressure (“dipping”) may be even greater than in untreated controls.\textsuperscript{16,57} In the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial, blood pressure was similar in healthy women assigned to either CEE/MPA or placebo after 3 years of follow-up.\textsuperscript{58} In both the Heart and Estrogen/Progestin Replacement Study and the Women’s Health Initiative, women assigned to HT had only minimal changes in blood pressure compared with the placebo group even after several years of follow-up, although one third of women were diagnosed as hypertensive at baseline.\textsuperscript{59,60}

Taken together, treatment with CEEs either alone or in combination with MPA appears to have negligible effects on arterial blood pressure in postmenopausal women.

Several aspects of the study design of Heart and Estrogen/Progestin Replacement Study and Women’s Health Initiative have been widely criticized, including that women receiving HT were in their mid-sixties and, thus, were many years after menopause; these patients also had several cardiovascular risk factors or even established coronary artery disease.\textsuperscript{33,61} Vascular aging in early postmenopausal women is associated with an increase in arterial stiffness, which facilitates the development of hypertension.\textsuperscript{52} Moreover, experimental and epidemiological evidence collectively suggest that any vascular effect of estrogens will depend on the stage of human life, the time since menopause, and the extent of pre-existing subclinical or clinically relevant atherosclerosis.\textsuperscript{33,60} Therefore, favorable effects on the vasculature, including blood pressure–lowering effects, may require that estrogen therapy be initiated early before the body adjusts to the withdrawal of endogenous estrogens.\textsuperscript{24,33,61} These important questions are currently being studied in the ongoing Kronos Early Estrogen Prevention Study (KEEPS) trial (http://www.clinicaltrials.gov No. NCT00114517) and the Early versus Late Intervention Trial with Estradiol (ELITE) Study (http://www.clinicaltrials.gov No. NCT00154180).

Treatment with CEEs cannot be considered as a “replacement” of natural human estrogens (Table). Indeed, CEEs are highly complex animal hormone mixtures containing a large number of equine estrogens with unknown selectivity and binding affinity for human ER subtypes, as well as other steroid hormones.\textsuperscript{24,33,61,63} Interestingly, no adverse vascular outcomes have been reported recently in the Women’s Hormone Intervention: Secondary Prevention (WHISP) Study, which was conducted in 100 women after myocardial infarction receiving either low-dose human 17β-estradiol or placebo for ≤12 months.\textsuperscript{64} Moreover, the route of administration appears to be essential in determining any detrimental effects of HT, because metabolism of orally administered estrogenic compounds via hepatic first pass attenuates the vasodilatory activity and induces the RAAS, as well as procoagulatory pathways, in the liver.\textsuperscript{61,65,66} In contrast, transdermal application of estrogens avoids hepatic first pass

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<td>HT using 17β-estradiol</td>
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<td>Cyclic administration of HT</td>
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Evidence suggests that the effects of hormone therapy (HT) on blood pressure depend on the type of estrogen and progestin used, dosage, the route of administration, the timing of treatment relative to menopause onset, and the overall age of the postmenopausal woman. Not shown are the additional worsening effects of the presence and/or inadequate treatment of other cardiovascular risk factors. CEEs are a mix of estrogens, progestins, and androgens extracted from the urine of pregnant horses.
and RAAS activation and lowers diastolic blood pressure when compared with oral CEE treatment.\(^{66–68}\) Finally, the synthetic progestin MPA not only abrogates the dilator effects of natural estrogens thereby augmenting vasoconstriction but also attenuates the estrogen-mediated inhibition of VSMC growth.\(^{69,70}\)

In the context of hypertension in women, we would like to point out that hypertension is a frequent adverse effect in premenopausal women taking oral contraceptives.\(^{26}\) In a prospective cohort study of 68,297 healthy premenopausal nurses, the relative risk of development of hypertension among users of oral contraceptives was 1.8 (95% CI: 1.5 to 2.3), even after adjustment for multiple other risk factors.\(^{71}\) This risk decreases with time since cessation of oral contraceptives but still remains increased even after \(\geq 6\) years (relative risk: 1.2; 95% CI: 1.0 to 1.4).\(^{72}\) Given that the contraceptive pill has been taken by women for the past half century,\(^{72}\) the question as to whether previous long-term contraceptive use plays a role in postmenopausal hypertension is of great importance; however, no data on this important medical question are currently available.

### Postmenopausal Hypertension: Pathophysiology and Therapeutic Considerations

Current estimates indicate that 130 million women in the Western world are inadequately treated for hypertension, a number that is expected to increase to 160 million in the next 20 years.\(^{1}\) Moreover, the world population is expected to increase by 50% from 6.6 billion today to 9.4 billion by the year 2050, which is mainly related to a substantial increase of aged individuals, \(\approx 1\) billion of which will be postmenopausal women (Figure, panel C).\(^{33}\) Aging remains one of the most important determinants for postmenopausal hypertension,\(^{3,11,73}\) and the growing prevalence of obesity, often in conjunction with a lack of physical activity, is likely to increase cardiovascular morbidity during the next decades.\(^{74}\)

Perimenopausal and postmenopausal women should be regularly assessed for cardiovascular risk factors by their primary care physician and their gynecologist.\(^{49}\) Lifestyle changes, eg, smoking cessation, establishing a low-fat diet rich in fruits and vegetables, increasing and maintaining regular physical activity, a normal body weight, and moderate alcohol consumption, are important in the prevention of high blood pressure and are required for the treatment of all patients, including those with prehypertension.\(^{5}\) If blood pressure control cannot be achieved by lifestyle changes alone, pharmacological therapy needs to be initiated, which is discussed in detail below.\(^{5}\) Although the loss of endogenous estrogen production after menopause contributes to the development of postmenopausal hypertension, postmenopausal HT is neither recommended for the treatment of postmenopausal hypertension nor for the primary prevention of cardiovascular disease.\(^{75}\) However, when treating younger, perimenopausal women for menopausal symptoms, the benefits should always be weighed against the potential risks of HT, and the type of HT should be carefully chosen (Table).\(^{75}\) Drospirenone, a novel progestin with mineralocorticoid antagonist activity, has been shown to lower blood pressure in hypertensive postmenopausal women when combined with 17\(\beta\)-estradiol.\(^{76}\) It is possible that this new therapy offers advantages for patients with postmenopausal hypertension who require progestin therapy for uterine protection during HT for menopausal symptoms.\(^{75}\) Finally, selective ER modulators, eg, raloxifene, which are agonists for the novel vasodilating estrogen receptor GPER\(^{32}\) could possibly be used in the treatment of postmenopausal hypertension.\(^{77}\)

The current US guidelines for treatment of arterial hypertension (Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) recommend the use of a thiazide-type diuretic as a first-line agent in most patients if target blood pressure cannot be achieved with lifestyle changes alone.\(^{5}\) Indeed, the high prevalence of salt-sensitive hypertension in postmenopausal women strongly supports dietary salt restriction and the use of diuretics as the preferred initial agent.\(^{5,34}\) Both reducing dietary sodium and using a thiazide-type diuretic improve blood pressure control and also reduce subsequent cardiovascular complications of hypertension.\(^{5,78}\) Interestingly, dietary salt restriction shows a more pronounced antihypertensive effect in elderly women than in men,\(^{79,80}\) again arguing in favor of a pathogenic role of cessation of endogenous estrogen production in the pathogenesis of salt sensitivity.\(^{34}\)

When target blood pressure cannot be achieved by the use of a single agent, the addition of a second drug from a different class should be initiated.\(^{5}\) This may be particularly important in postmenopausal women with the metabolic syndrome, who often present with a more severe cardiovascular risk profile and show a less favorable response to antihypertensive therapy than their lean counterparts because of resistant hypertension.\(^{81}\) The use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers has been proposed in this context.\(^{75,82}\) These drugs appear to be useful to antagonize the activation of the RAAS observed after menopause.\(^{25}\) Interestingly, a small study among 51 postmenopausal hypertensive women demonstrated recently that the blood pressure–lowering effect of the angiotensin receptor blocker irbesartan is augmented by co-administration with 17\(\beta\)-estradiol,\(^{83}\) suggesting potentiating effects of 2 different antihypertensive mechanisms and underscoring a need for further research in this area. New antihypertensive paradigms, eg, GPER agonism, which has been shown to work experimentally, could possibly evolve.\(^{32,84–86}\)

### Perspectives

The ultimate goal of primary and secondary prevention of hypertension in postmenopausal women is the reduction of morbidity and mortality of adverse clinical events, eg, stroke, myocardial infarction, and hypertensive nephropathy. Currently, control of blood pressure in postmenopausal women often remains suboptimal.\(^{4,9}\) We need to continue our efforts in screening and identifying patients, improving patient and physician awareness, and optimizing clinical care and public health measures. This includes distributing information to senior citizens and educational institutions. Finally, prevention of hypertension in women should not only be focused on adult women but must start early in life, as indicated by the
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Disclosures

None.

References


86. Lindsey SH, Cohen JA, Brosnihan KB, Gallagher PE, Chappell MC. Chronic treatment with the GPR30 agonist G-1 decreases blood pressure in ovariecotomized mREN2 Lewis rats. Endocrinology. In press.


