

Hypertension in women

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Abstract

Hypertension is a major risk factor for coronary artery disease and stroke and contributes significantly to cardiovascular and renal morbidity and mortality in women. The effect of menopause on blood pressure (BP) is controversial, in large part because determining the role of sex hormones (or their withdrawal) on BP is complex and confounded by other effects. Studies evaluating the effects of hormone replacement therapy (HRT) on BP have reported inconsistent findings due to differences in studied patient populations, methods of measuring BP, and hormone preparations and routes of administration. Combined oral contraceptives (COCs) induce small increases in BP in the entire population of users, but a small percentage of COC users experience the onset of frank hypertension, which usually resolves with withdrawal of the COC. Major outcome trials of antihypertensive treatment have generally shown comparable benefit in both women and men. However, additional analyses and other trials have demonstrated gender differences in both benefit and adverse effects of treatment.

Key words: Hypertension; Blood pressure, Women

Introduction

Hypertension is a major risk factor for coronary artery disease and stroke and contributes significantly to cardiovascular and renal morbidity and mortality in women. Prevalence and severity of hypertension increase markedly with advancing age in women, such that after age 60 years, a majority of women have stage 2 hypertension (blood pressure [BP] $\geq 160/100$ mm Hg) or receive antihypertensive treatment¹⁻⁴.

Further, BP control is more difficult to achieve in older patients, particularly older women. Data from the Framingham Heart Study showed an age-related decrease in BP control rates that was more pronounced in women than men². Among the oldest participants with hypertension, only 23% of women (vs. 38% of men) were controlled to BP $< 140/90$ mm Hg. Gender differences in the pattern of prescribed antihypertensive medications were noted in this cohort: 38% of women but only 23% of men were taking thiazide diuretics for their BP. Whether the age-related decline in BP control among women is related to inadequate intensity of treatment or to inappropriate drug choices in

the practice setting, to true treatment resistance because of biological factors, or to other factors is unclear.

Recent data from the U.S. National Health and Nutrition Examination Survey (NHANES) 1999–2004 have highlighted a likely contributory factor to poor BP control in elderly women: an increased prevalence of concomitant cardiovascular risk factors, including central obesity, elevated total cholesterol and low high-density lipoprotein (HDL) cholesterol levels⁴. Among adults with hypertension in NHANES 1999–2004, women were at higher cardiovascular risk compared to men: 53% of women, but only 41% of men had ≥ 3 of the 6 studied risk factors ($p < 0.001$). This article will discuss clinically important issues related to hypertension in women, including menopause, menopausal hormone and oral contraceptive therapy, results of randomized controlled trials of antihypertensive treatment in women, and gender considerations in the choice of antihypertensive drugs.

Menopause and BP

The effect of menopause on BP is controversial, in

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large part because determining the role of sex hormones (or their withdrawal) on BP is complex and confounded by the effects of aging and related alterations in important cardiovascular risk factors such as body weight and lipid levels⁵⁻¹¹. As recently reviewed, conflicting results from studies of the menopause-BP relationship may result from differences among cohorts, including sample size, age ranges, length of time post menopause, use of data sets not designed to study menopause, and reliance on questionnaires⁵. While cross-sectional studies have generally found significantly higher BP in postmenopausal versus premenopausal women, prospective studies have reported variable results, including a lack of association between menopause and BP, particularly when data were controlled for age and other risk factors, such as smoking, and even a negative association between BP and years post menopause⁵. A European study that utilized 24-hour BP monitoring in follow-up found that the rate of rise in SBP tended to be steeper in postmenopausal compared to premenopausal women and that the prevalence of hypertension in postmenopausal women was more than twice that in premenopausal women, after adjustment for age and body mass index (BMI)⁷.

Recent studies have suggested that menopause-related BP elevation is dependent on BMI and age. Casiglia et al. evaluated BP, prevalence and incidence of hypertension in 9,364 men and women aged 18–70 years followed-up for 18.8 ± 7.7 years⁸. BP increases during follow-up were greater in menopausal than in fertile women, but this difference was no longer present after age-adjustment. Another study of 908 female residents of Prague, aged 45–54 years showed that the rise in BP after the menopause appeared to be due to increased BMI rather than to ovarian failure per se⁹.

The largest cross-sectional analysis available, the SIMONA epidemiological study, examined the menopause-related BP increase in more than 18,000 pre-, peri- and postmenopausal Italian women, aged 46 to 59 years, and found a small (3.4/3.1 mm Hg) but clinically significant increase in both SBP and DBP among postmenopausal women that was independent of age, BMI and, smoking¹⁰. The menopause-BP relationship was only evident in the early postmenopausal years, and was not altered by contraceptive or menopausal hormone therapy (also known as hormone replacement therapy [HRT]). The SIMONA study, though large and well conducted, suffers from the limitation of all cross-sectional studies, i.e. inability to assess temporal changes in BP. In contrast, prospective longitudinal studies are confounded by environmental changes and changes in medical management over time, a factor that would tend to minimize menopause-related BP increases

because the prevalence of treated hypertension is higher in post- than premenopausal women (35% vs. 20% in the SIMONA study)^{10,11}.

Recognizing that BP elevation presents a graded risk for cardiovascular disease, the Women's Health Initiative (WHI) determined the prevalence of prehypertension (BP 120–139/80–89 mm Hg), its association with other cardiovascular risk factors and the risk for incident cardiovascular disease events in 60,785 postmenopausal women who were followed prospectively for 7.7 years¹². Prehypertension was identified in 39% of women at baseline. Compared with normotensive women, those with prehypertension had 58% increased risk for cardiovascular death, 76% increased risk for myocardial infarction, 93% increased risk for stroke, 36% increased risk for hospitalized heart failure, and 66% increased risk for any cardiovascular event. Cardiovascular risk for women with established hypertension was even greater (nearly 3-fold increase for any cardiovascular event). Interestingly, the increased cardiovascular risk associated with prehypertension was greater than that associated with smoking (34%), reinforcing the need for treatment in the prehypertensive group. Prehypertension was associated with other modifiable risk factors, i.e. high total cholesterol and BMI, emphasizing the importance of global risk factor reduction for prevention of both hypertension and cardiovascular disease outcomes.

In general, the totality of evidence suggests that menopause is accompanied by small BP increases that may be partially accounted for by increasing age and BMI, as well as concomitant increases in other cardiovascular risk factors. Rigorous prospective studies employing state of the art techniques of BP measurement and correction for antihypertensive therapy may elucidate this relationship further. The pathophysiology of the menopause-related increase in BP has been inferred from elegant mechanistic studies in animals^{13,14} and human subjects⁵. A variety of mechanisms, including endothelial dysfunction, increased arterial stiffness, activation of the renin-angiotensin-aldosterone system (RAAS), increased salt sensitivity, oxidative stress, obesity and genetic factors have been implicated in the pathogenesis of BP increases that occur after natural menopause or ovariectomy (Figure 1)⁵.

Menopausal hormone therapy and BP

Studies evaluating the effects of HRT on BP have reported inconsistent findings due to differences in studied patient populations, methods of measuring BP, and hormone preparations and routes of administration¹⁵. Most studies have described minimal BP effects in normotensive women. The Baltimore Longitudinal Study on

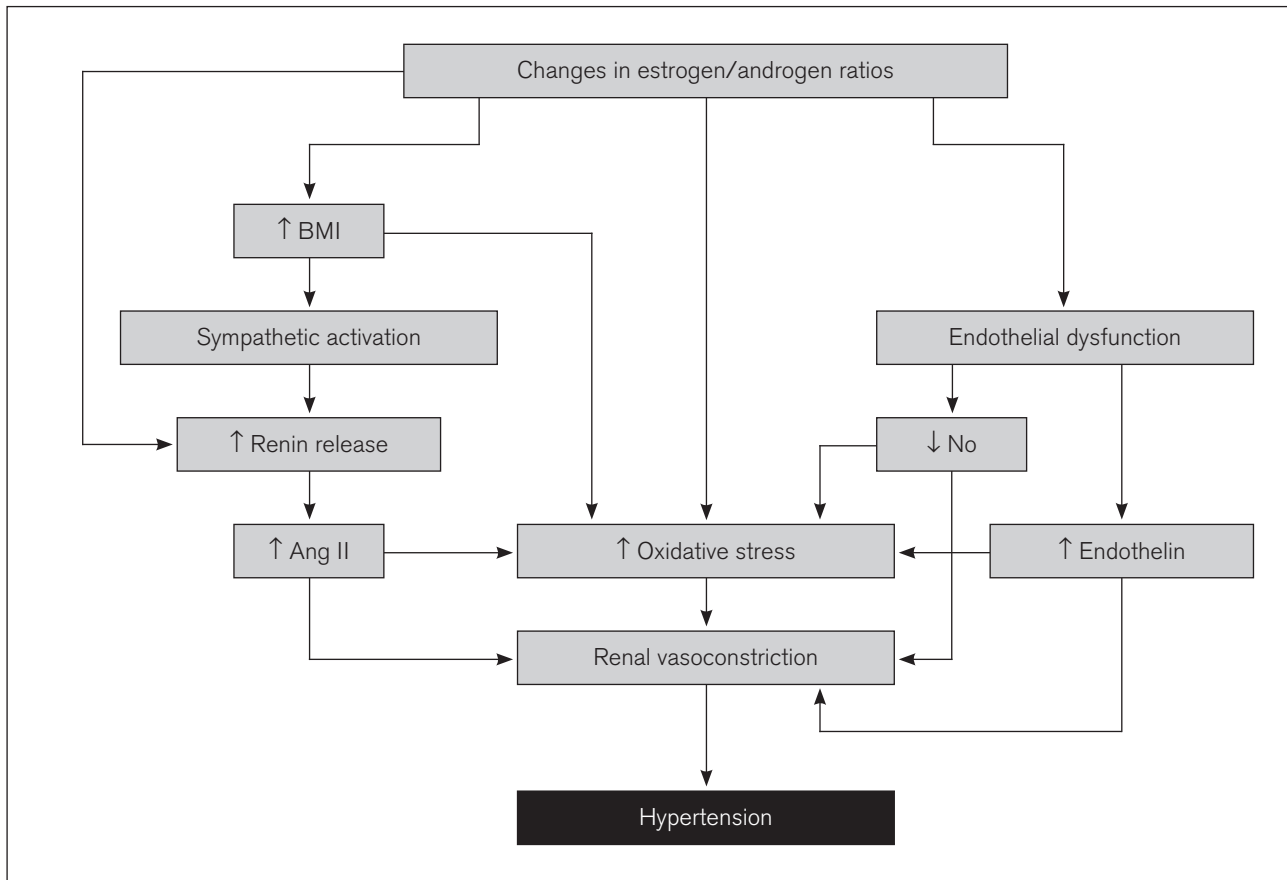


Figure 1. Mechanisms postulated to contribute to the development of hypertension after menopause. (From Coylewright M, Reckelhoff JF, Ouyang P. Menopause and hypertension: an age-old debate. *Hypertension*. 2008;51(4):952-959).

Aging (BLSA), found that women receiving HRT (oral or transdermal estrogen and progestin) had a significantly smaller (1.6 mm Hg) increase in SBP over time than non-users (8.9 mm Hg)¹⁶. DBP was not affected by HRT. The Postmenopausal Estrogen/Progestin Intervention (PEPI) trial followed 596 normotensive postmenopausal women, aged 45 to 64 years for an average of 3 years and found no significant effect on SBP or DBP¹⁷. The Women's Health Initiative (WHI)'s cross-sectional analysis of almost 100,000 women aged 50 to 79 years indicated that current HRT use was associated with a 25% greater likelihood of having hypertension compared to past use or no prior use of HRT¹. However, the estrogen+progestin arm of WHI, a placebo-controlled trial of HRT with 16,608 postmenopausal women, found a small (~1 mm Hg) increase in SBP in the HRT group compared to placebo¹⁸. A review of papers published since 1960 reported very low risk of developing hypertension during HRT. In fact, BP was often lowered with HRT in hypertensive women¹⁹. Smaller studies using 24-hour ambulatory BP monitoring have yielded inconsistent results, but overall, several of the

studies suggest that HRT improves or restores the normal nighttime reduction ("dipping") in BP that may be diminished in postmenopausal women¹⁵. Such an effect would tend to reduce total BP load and thereby reduce target organ damage.

Overall, HRT-related change in BP is likely to be minor and should not preclude HRT use in either normotensive or hypertensive women. Nevertheless, all hypertensive women treated with HRT should have their BP measured initially and then at 3–6-month intervals depending on the difficulty of control²⁰.

Oral contraceptives and BP

Combined oral contraceptives (COCs) induce small increases in BP in the entire population of users, but a small percentage of COCs users experience the onset of frank hypertension, which usually resolves with withdrawal of the COC²¹. This is true even with modern preparations that contain lower doses (< 30 µg estrogen). However, COCs occasionally precipitate accelerated, or malignant, hypertension. Genetic characteristics, such as family his-

Table 1. Contraindications for combined oral contraceptives.

Smoking in women > 35 years of age	
<15 cigarettes/day	Risk>benefit
>15 cigarettes/day	Risk unacceptable
Hypertension	
History of hypertension, current BP unknown	Risk>benefit
Adequately controlled hypertension	Risk>benefit
Elevated blood pressure levels	
Systolic 140–159 or diastolic 90–99	Risk>benefit
Systolic >160 or diastolic >100	Risk unacceptable
Vascular disease	Risk unacceptable
Multiple risk factors for cardiovascular disease	
Older age, smoking, diabetes and hypertension	Risk>benefit: may be unacceptable
Deep venous thrombosis (DVT)/pulmonary embolism (PE)	
History of or current DVT/PE	Risk unacceptable
Major surgery with prolonged immobilization	Risk unacceptable
Known thrombogenic mutations	
Factor V Leiden; Prothrombin mutation; Protein S, Protein C, and Antithrombin deficiencies)	Risk unacceptable
Ischemic heart disease	
	Risk unacceptable
Stroke	
	Risk unacceptable
Migraine	
Without aura in women > 35 years of age	Risk>benefit
With, at any age	Risk unacceptable
Diabetes	
Nephropathy/retinopathy/neuropathy	Risk>benefit/ Risk unacceptable
Other vascular disease or diabetes of >20 years' duration	Risk>benefit/ Risk unacceptable

tory of hypertension, as well as environmental characteristics, including preexisting pregnancy-induced hypertension, occult renal disease, obesity, middle age (>35 years), and duration of COC use, increase susceptibility to COC-induced hypertension.²¹ Table 1 summarizes contraindications for COCs use based on World Health Organization recommendations²².

The Nurses' Health Study found that current users of COCs had a significantly increased [relative risk (RR), 1.8; 95% confidence interval, 1.5–2.3] risk of hypertension compared with never-users²³. Absolute risk was small (41.5 cases/10,000 person-years) and risk decreased quickly with cessation of COCs. Controlled prospective studies have consistently demonstrated a return of BP to pre-treatment levels within 3 months of discontinuing COCs.

A cross-sectional survey (Health Survey for England) of 3545 premenopausal women, 892 whom were current users of oral contraceptives (815 COCs and 77 progestin-only) demonstrated significantly higher mean BP among COC users than among non-users²⁴. The BP difference tended to increase with age. In contrast, BP tended to be lower among the progestin-only users than among non-

users, suggesting that progestin-only contraceptives can be used in women with established hypertension.

Progestins have mineralocorticoid receptor antagonist effects that may account for their BP neutral or BP lowering actions. The new 4th generation progestin, drospirenone, when combined with estradiol, has been shown to reduce BP (Figure 2)²⁵. Based on these and other data, progestin-only contraceptives are recommended for women with established hypertension.

Pregnancy

Hypertensive disorders in pregnancy are a major cause of maternal, fetal, and neonatal morbidity and mortality²⁶. The diagnosis and treatment of hypertension in pregnancy can be difficult, and there is much controversy about BP management in pregnant women, particularly because evidence from randomized controlled trials is sparse²⁷. Importantly, preeclampsia, a pregnancy-specific syndrome of exaggerated vasoconstriction and reduced organ perfusion, must be differentiated from preexisting chronic hypertension because it can threaten the lives of both mother and fetus and requires specialized care²⁶. Fur-

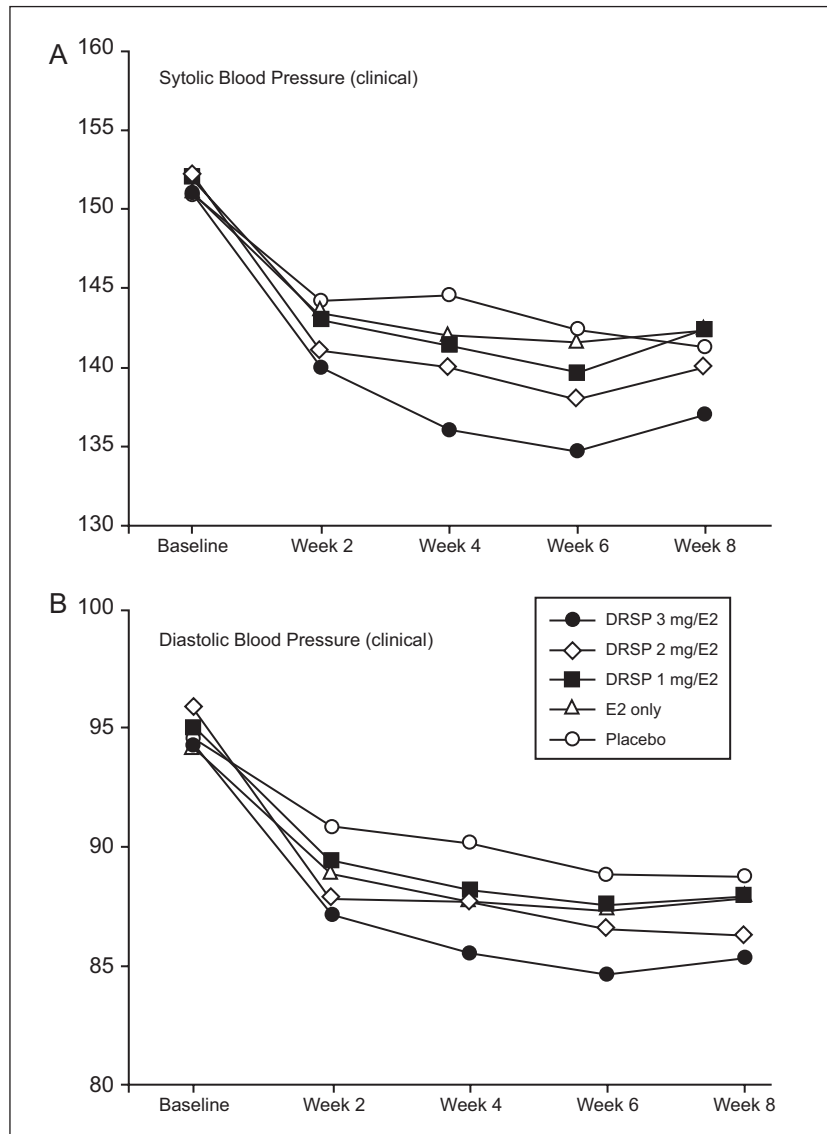


Figure 2. Blood pressure effects of drospirenone in different dosages associated with estradiol, vs estradiol only and placebo. Results of 750 postmenopausal women with stage 1 and 2 hypertension. (From White WB, Hanes V, Chauhan V, et al. Effects of a new hormone therapy, drospirenone and 17 β -estradiol, in postmenopausal women with hypertension. *Hypertension*. 2006 Aug;48(2):246-53).

ther, it has been clearly shown that preeclampsia places women at long term risk for cardiovascular disease, and careful follow-up and aggressive preventive strategies are recommended^{28,29}.

Outcomes of antihypertensive trials by gender

Major outcome trials of antihypertensive treatment, including LIFE (Losartan Intervention For Endpoint Reduction)³⁰, VALUE (Valsartan Antihypertensive Long-Term Use Evaluation Trial)³¹, ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering

Arm)³², and ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial)³³ have generally shown comparable benefit in both women and men. However, additional analyses and other trials have demonstrated gender differences in both benefit and adverse effects of treatment³⁴⁻³⁷.

A prespecified subgroup analysis of outcomes in 4963 women with hypertension and LVH enrolled in the LIFE study demonstrated significant reductions in the primary end point and most secondary end points in the losartan-based treatment group compared to the atenolol group³⁴,

The magnitude of treatment benefit was similar in women and men. Overall, as in other studies, fewer events occurred in women than in men: even after adjustment for baseline characteristics: 476 women (9.6%) and 620 men (14.7%) experienced a primary end point. Furthermore, all of the secondary end points tended to occur less frequently in women.

In contrast, the prespecified subgroup analysis of the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial showed a relative excess of the primary end point of cardiac mortality and morbidity with valsartan-based treatment compared with amlodipine-based treatment in women but not in men³⁵. Further, the trend toward less heart failure with valsartan-based treatment was not statistically significant in women. BP reduction was greater in amlodipine-treated women than in those treated with valsartan (2.8 vs 1.8 mm Hg), an effect that could partially explain the difference in outcomes. Similarly to VALUE, in ALLHAT there was a slightly greater BP response to amlodipine compared to lisinopril in women, and this finding was associated with a more pronounced reduction in stroke.

The Australian National Blood Pressure-2 Trial (ANBP2) showed that the benefit of angiotensin-converting enzyme inhibitor-based treatment compared with a diuretic-based treatment was only observed in men³⁶. The small number (524) of events in women in ANBP2 suggests that the trial was underpowered to detect a beneficial effect in hypertensive women. Similarly, the Study on Cognition and Prognosis in the Elderly (SCOPE) found no significant outcome benefit of ARB treatment compared to usual care in women and no treatment-gender interaction³⁷. Interpretation of this finding is limited by design issues and the small number of events (n=273) experienced by these women.

Gender considerations in the choice of antihypertensive drugs

Women generally respond to antihypertensive drugs similarly to men, but some special considerations may dictate treatment choices for women^{38,39}. Angiotensin-converting enzyme inhibitors and AT₁-receptor blockers are contraindicated for women who are or intend to become pregnant because of the risk of fetal developmental abnormalities. Diuretics are particularly useful in women, notably elderly women, because their use is associated with decreased risk of stroke and hip fracture. Increasing evidence suggests that antihypertensive drugs have gender-specific adverse effect profiles. In the Treatment of Mild Hypertension Study (TOMHS), in which 902 women and men received nonpharmacologic treatment plus treatment with a drug chosen at random from each class of antihy-

pertensive agent then available, women reported twice as many adverse effects as men⁴⁰. Similarly, women in the LIFE study had more total adverse events but fewer serious drug-related adverse events than men³⁴.

Biochemical responses to drugs may be gender-dependent, with women more likely to develop hyponatremia or hypokalemia and men more likely to develop gout in response to diuretic therapy^{38,39}. Angiotensin-converting enzyme inhibitor-induced cough is 2 to 3 times as common in women as in men, and women are more likely to complain of calcium channel blocker-related peripheral edema and minoxidil-induced hirsutism.

Furthermore, there is evidence that sexual dysfunction related to antihypertensive therapy may be a problem in women, as well as in men. This effect is most often associated with centrally acting agents, β -blockers, and thiazide diuretics, whereas ARB therapy may improve these symptoms^{41,42}. While in the TOMHS study women in all treatment groups reported fewer sexual problems than men⁴³, additional evaluation is needed in this area, as sexual dysfunction in women is seldom assessed in clinical trials.

Conclusion

Hypertension contributes significantly to cardiovascular and renal morbidity and mortality in women. Whether menopause or HRT contributes to high BP in women remains controversial. BP response to COCs is variable and a small minority of women may experience the onset of frank hypertension, which usually resolves with withdrawal of the COC. Major outcome trials of antihypertensive treatment have generally shown comparable benefit in both women and men but additional analyses and other trials have demonstrated gender differences in both benefit and adverse effects of treatment.

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