REVIEW SERIES

Hypertension in women

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Hypertension is an important modifiable risk factor for cardiovascular (CV) morbidity and mortality, and a highly prevalent condition in both men and women. However, the prevalence of hypertension is predicted to increase more among women than men. Combined oral contraceptives (COCs) can induce hypertension in a small group of women and, increase CV risk especially among those with hypertension. Both COC-related increased CV risk and blood pressure (BP) returns to pretreatment levels by 3 months of its discontinuation. The effects of menopause and hormone replacement therapy (HRT) on BP are controversial, and COCs and HRT containing the new generation progestin drospirenone are preferred in women with established hypertension. Despite the high incidence of cancer in women, CV disease remains the major cause of death in women and comparable benefit of antihypertensive treatment have been demonstrated in both women and men.

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INTRODUCTION

Hypertension is an important modifiable risk factor for cardiovascular (CV) morbidity and mortality, and a highly prevalent condition in both men and women. Blood pressure (BP) is generally higher in men than in women regardless of age. Mean systolic BP in the overall population increases progressively throughout adult life in both men and women. During early adulthood mean systolic BP is higher in men than women, but the subsequent rate of rise in BP is steeper for women than men. Prevalence and severity of hypertension increase markedly with advancing age in women, such that a higher percentage of women than men have high BP after 65 years.^{1–5} Furthermore, BP control is more difficult to achieve in older women. Data from the Framingham Heart Study showed gender differences in BP control rates and in the pattern of antihypertensive medications prescribed.³ An age-related decrease in BP control rates were more pronounced in women than in men. Among the oldest participants with hypertension, only 23% of women (vs. 38% of men) were controlled to BP <140/90 mm Hg. Treatment with thiazide diuretics was also more frequent among women than men (38 vs. 23%). It is unknown whether the age-related decline in BP control among women is related to true treatment resistance because of biological factors or to inappropriate drug choices in the clinical setting.

This article discusses practical aspects related to hypertension in women and some topics are discussed in detail in separate articles in this special review edition.

PREVALENCE OF HYPERTENSION AND MENOPAUSE EFFECTS ON BP

The general prevalence of hypertension is slightly higher among men than women. The National Health and Nutrition Examination Survey

(NHANES) data show that more men than women have hypertension until 45 years of age. From 45 to 64 years of age, the percentages of men and women with hypertension are similar and, after that, a higher percentage of women than men have high BP.¹ However, it has been predicted that more women than men will have hypertension in the near future.⁶ The worldwide prevalence of hypertension is predicted to increase by 9% in men and 13% in women between 2000 and 2025. In terms of absolute numbers, 483.5 million women had hypertension in 2000 and this is predicted to increase to 793.3 million in 2025 (Figure 1). Aging of world population by 2025 and longer life expectancies in women than in men are possibly related to the greater increases in the prevalence of hypertension among women.

The effect of menopause on BP is controversial and confounded by the effects of aging and clustering of other CV risk factors, such as body weight and lipid levels.^{7–13} A European study that utilized 24-h BP monitoring for diagnosis of hypertension showed that, after adjustment for age and body mass index, the prevalence of hypertension in postmenopausal women was more than twice that in premenopausal women. Furthermore, rise in systolic BP tended to be steeper in postmenopausal compared with premenopausal women.⁹ Cross-sectional studies have generally found significantly higher BP in postmenopausal vs. premenopausal women and prospective studies have reported variable results, including a lack of association between menopause and BP, and even a negative association between BP and years post menopause.⁷

Changes in BP after menopause seem to be related with alterations in estrogen and progesterone levels. Clinical and experimental studies have showed that estrogen induces vasodilatation, prevents vascular remodeling processes, inhibits vascular response to injury, provides renoprotection and decreases basal sympathetic tone. Similar to

Figure 1 Number of men and women with hypertension in 2000 and 2025. (Data from Kearney *et al.*⁶)

estrogen, progesterone induces endothelium-dependent vascular relaxation.¹⁴ However, the effects of natural estrogen and progesterone appear to be different from the synthetic preparations.

ORAL CONTRACEPTIVES AND BP

Combined oral contraceptives (COCs) induce small increases in BP in the entire population of users and has been associated with a small excess risk of CV disease among women, especially in those with hypertension.¹⁵ Hypertension is two to three times more common among women taking oral COCs, especially in those obese and at advanced age, than in those not taking these medications.^{16,17} Modern preparations that contain lower doses (<30 µg) of estrogen can also lead to development of hypertension and can precipitate accelerated or malignant hypertension. Environmental characteristics, including pre-existing pregnancy-induced hypertension, occult renal disease, obesity, middle age (>35 years) and duration of COC use, as well as genetic characteristics, such as family history of hypertension, increase susceptibility to COC-induced hypertension.^{17,18}

Controlled prospective studies have consistently demonstrated a return of BP to pretreatment levels within 3 months of discontinuing COCs.^{16,19} In the Health Survey for England, a cross-sectional survey, mean BP was significantly higher among premenopausal women who were current users of oral contraceptives (COCs and progestin-only) than among non-users.²⁰ The BP difference tended to increase with age. However, BP tended to be lower among the progestin-only users than among non-users, suggesting that progestin-only contraceptives are a better choice for women with established hypertension.

Drospirenone, which is a new fourth generation progestin with antimineralocorticoid diuretic effects, seems to reduce BP when combined to estrogen. In a randomized study, 80 women received the combination drospirenone 3 mg plus ethinylestradiol 30, 20 or 10 µg or levonorgestrel 150 µg plus ethinylestradiol 30 µg during six cycles.²¹ Systolic and diastolic BP reduced by 1–4 mm Hg with any of drospirenone combinations and increased by 1–2 mm Hg with levonorgestrel combination. Women treated with drospirenone also presented significantly weight loss from 0.8–1.7 kg. Based on these and other data, progestin-only contraceptives or COCs containing drospirenone are recommended for women with established hypertension.

The Table 1 summarizes contraindications for COCs use based on World Health Organization recommendations.²²

Table 1 Contraindications for combined oral contraceptives

<i>Smoking in women > 35 years of age</i>	
< 15 cigarettes per day	Risk > benefit
> 15 cigarettes per day	Risk unacceptable
<i>Hypertension</i>	
History of hypertension, current BP unknown	Risk > benefit
Adequately controlled hypertension	Risk > benefit
<i>Elevated BP levels (mm Hg)</i>	
Systolic 140–159 or diastolic 90–99	Risk > benefit
Systolic > 160 or diastolic > 100	Risk unacceptable
<i>Vascular disease</i>	Risk unacceptable
<i>Multiple risk factors for cardiovascular disease (older age, smoking, diabetes and hypertension)</i>	
	Risk > benefit: may be unacceptable
<i>DVT/PE</i>	
History of or current DVT/PE	Risk unacceptable
Major surgery with prolonged immobilization	Risk unacceptable
<i>Known thrombogenic mutations (for example, factor V Leiden; prothrombin mutation; protein S, protein C, and antithrombin deficiencies)</i>	
	Risk unacceptable
<i>Ischemic heart disease</i>	Risk unacceptable
<i>Stroke</i>	Risk unacceptable
<i>Migraine</i>	
Without aura in women > 35 years of age	Risk > benefit
With aura in women at any age	Risk unacceptable
<i>Diabetes</i>	
Nephropathy/retinopathy/neuropathy	Risk > benefit/risk unacceptable
Other vascular disease or diabetes of > 20 years duration	Risk > benefit/risk unacceptable

Abbreviations: BP, blood pressure; DVT, deep venous thrombosis; PE, pulmonary embolism.

HORMONE REPLACEMENT THERAPY AND BP

Conflicting results have been reported by studies that evaluated the effects of hormone replacement therapy (HRT) on BP.²³ Differences in patient populations studied, methods of measuring BP, hormone preparations and routes of administration partially explain the discrepancy between the studies.²⁴ Minimal BP effects in normotensive women have been showed in most studies. For example, in the Baltimore Longitudinal Study on Aging, women receiving HRT (oral or transdermal estrogen and progestin) had a significantly smaller (1.6 mm Hg) increase in systolic BP over time than nonusers (8.9 mm Hg) and diastolic BP was not affected by HRT.²⁵ In the Women's Health Initiative's (WHI) cross-sectional analysis, the effect of HRT on BP was evaluated on almost 100 000 women aged 50–79 years.²⁶ Current HRT use was associated with a 25% greater likelihood of having hypertension compared with past use or no prior use of HRT. However, in a placebo-controlled trial of HRT with 16 608 postmenopausal women, the estrogen plus progestin arm was related to a small (~1 mm Hg) increase in systolic BP compared with placebo.²

Similar to oral contraceptives, HRT containing drospirenone seems to reduce BP due to its antimineralocorticoid receptor effects. The combination of 17-β-estradiol and drospirenone was tested in

postmenopausal hypertensive women.^{27,28} In a randomized, double-blind, placebo-controlled study, 750 postmenopausal women with stage 1 and 2 hypertension received drospirenone 1 mg, 2 mg or 3 mg in combination with estradiol, or estradiol alone or placebo. Drospirenone 2 mg and 3 mg, but not 1 mg, in combination with estradiol significantly reduced 24 h systolic BP by 6.1 mm Hg and 4.7 mm Hg, respectively.²⁷

Overall, HRT induces, if any, small changes in BP 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 control.¹⁶

PREGNANCY

Hypertensive disorders in pregnancy are a major cause of maternal, fetal, and neonatal morbidity and mortality.²⁹ Patients with chronic hypertension, who are likely to become pregnant, need to be assessed for severity of hypertension, presence of target organ damage, adjustment of medication therapy, lifestyle changes and investigation of potentially reversible causes. The diagnosis and treatment of hypertension in pregnancy can be difficult, and BP management in pregnant women is a matter of debate.³⁰ Preeclampsia usually occurs after 20 weeks of gestation and is likely to be related to impaired placental development in early pregnancy, which causes placental oxidative stress and inflammation. Subsequent release of placental factors including soluble fms-like tyrosine kinase-1, angiotensin II type 1 receptor autoantibody and cytokines into the maternal circulation leads to widespread dysfunction of the maternal vascular endothelium.³¹ Preeclampsia, which is a pregnancy-specific syndrome of exaggerated vasoconstriction and reduced organ perfusion, must be differentiated from pre-existing chronic hypertension as the former can threaten the lives of both mother and fetus, and requires specialized care.²⁹ Treatment of hypertension during pregnancy, particularly in the second half of gestation, reduces maternal and fetus risk. Furthermore, it has been clearly shown that preeclampsia places women at long-term risk for CV diseases and that careful follow-up and aggressive preventive strategies are recommended.^{32–34} For example, a meta-analysis which includes >3 million women and almost 200 000 women with preeclampsia showed that women who had preeclampsia are 2.7 times more likely to develop hypertension, and almost twice more likely to have ischemic heart disease, stroke or venous thromboembolism.³⁴

SECONDARY HYPERTENSION IN WOMEN

Secondary hypertension is underdiagnosed and its true prevalence is unknown. Some conditions have increased prevalence in women and need to be investigated. For example, fibromuscular dysplasia, a nonatherosclerotic noninflammatory vascular disease that can affect renal arteries and cause renovascular hypertension, primarily affects women aged from age 20 to 60, but can also affects men and children.³⁵ Fibromuscular dysplasia should be investigated with non-invasive tests, such as renal artery duplex ultrasound, computed tomography angiography and magnetic resonance angiography, in young women with cervical bruits or development of hypertension <35 years. Percutaneous balloon angioplasty is the preferred treatment.

Primary aldosteronism (PA), once considered being a rare condition and not worth seeking unless hypokalemia was present, has been demonstrated to be much more prevalent than previously thought and is probably the commonest cause of secondary hypertension.³⁶ Correct diagnosis and treatment of PA can not only lead to cure of

hypertension in patients with unilateral forms of PA, but can also prevent and reverse organ deterioration independent of aldosterone effects on BP.³⁷ The prevalence of PA is similar in men and women, but estrogen and progesterone can affect aldosterone and renin levels and, consequently, can interfere with the investigation of PA. Screening with aldosterone–renin ratio can be affected by the phase of menstrual cycle and by different forms of contraception. We have demonstrated that false positive may occur during the luteal phase, especially, if direct renin concentration is used instead of plasma renin activity.³⁸ In a different study, the COCs ethinylestradiol plus drospirenone, but not subdermal etonogestrel, significantly increase the risk of false positives when direct renin concentration was used to measure renin.³⁹ These studies have shown that some oral contraceptives and menstrual phase must be taken into consideration when interpreting results of aldosterone–renin ratio determined by measuring direct renin concentration.

CV RISK IN WOMEN

Although the myth that certain types of cancer, such as breast cancer, are the main cause of death in women still prevails, CV diseases remain the main cause of death in women. In 2007, death rates for CV diseases and cancer among women were 211.6 and 151.3 per 100 000, respectively. One in 4.5 females died of cancer, whereas 1 in 2.9 died of CV diseases.¹ In the data from the NHANES 1999–2004 women were at significantly higher CV risk compared with men, with 53% of women and 41% of men with ≥ 3 of the six risk factors studied.⁵

However, hypertension control in women remains poor, especially among elderly women. The NHANES 1999–2004 showed that 50.8% of men and 55.9% of women had uncontrolled hypertension adjusted for age.⁵ Rates of uncontrolled hypertension were positively related with age with only 29% of hypertensive women aged 70–79 years having clinic BP <140/90 mm Hg compared with 41 and 37% of those 50–59 and 60–69 years of age, respectively (Figure 2).²⁶ An increased prevalence of concomitant CV factors, including central obesity, elevated total cholesterol and low high-density lipoprotein cholesterol levels are likely to contribute to poor BP control in elderly women.⁵

In the Women's Health Initiative, the prevalence of prehypertension (BP 120–139/80–89 mm Hg) and its association with other CV risk factors, and the risk for incident CV disease events were determined in 60 785 postmenopausal women who were followed for 7.7 years.⁴⁰ Prehypertension was identified in 39% of women at baseline. Compared with normotensive women, those with prehypertension had 58% increased risk for CV 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 CV event. CV risk for women with established hypertension was even greater

Figure 2 Blood pressure control rates in women according to age. (Data from Wassertheil-Smolter *et al.*²⁶)

(nearly threefold increase for any CV event). Interestingly, the increased CV 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, that is, high total cholesterol and body mass index, emphasizing the importance of global risk factor reduction for prevention of both hypertension and CV disease outcomes.

OUTCOMES OF ANTIHYPERTENSIVE TRIALS BY GENDER

Major outcome trials of antihypertensive treatment have generally shown comparable benefit in both women and men.^{41–45} However, additional analyses and other trials have demonstrated gender differences in both benefit and adverse effects of treatment.^{46–49} In the prespecified subgroup analysis of the VALUE (Valsartan Antihypertensive Long-term Use Evaluation) study, women, but not men, assigned to valsartan-based treatment presented a relative increased risk of the primary endpoint of cardiac mortality and morbidity compared with those who received amlodipine-based treatment.⁴⁷ Furthermore, the trend toward less congestive heart failure with valsartan-based treatment was not statistically significant in women. Although the difference in BP reduction between the women treated with amlodipine and valsartan (2.8 mm Hg vs. 1.8 mm Hg, respectively) was small, it could partially explain the differences in outcomes. Similarly to VALUE, the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) showed a slightly greater BP response to amlodipine compared with lisinopril in women, and this finding was associated with a more pronounced reduction in stroke.

In contrast, in the LIFE (Losartan Intervention For Endpoint Reduction) study, a prespecified subgroup analysis of outcomes in 4963 women with hypertension and left ventricular hypertrophy showed significantly greater reductions in primary end point and most secondary endpoints with losartan compared with the atenolol.⁴⁶ Despite similar BP reduction, fewer events occurred in women than in men.

GENDER CONSIDERATIONS IN THE TREATMENT OF HYPERTENSION

Non-pharmacological interventions such as weight loss, dietary salt reduction, increased physical activity, reduction of alcohol consumption and a diet rich in fruits and vegetables are recommended for both men and women.^{16,50} BP reduction achieved with antihypertensive medications is also similar in men and women. However, some special considerations may dictate treatment choices for women.^{51,52} In an overview analysis, the Blood Pressure Lowering Treatment Trialists Collaboration reviewed 31 randomized trials that included 87 349 women and 103 268 men. The main objective was to quantify the effects of BP-lowering treatment according to gender and to determine whether there are important differences in the proportional benefits of treatment between women and men.⁵³ Despite baseline BP levels were slightly higher among women than men, there was no evidence that women and men present different levels of protection from total major CV events (stroke, coronary heart disease events, heart failure and other CV death) from BP lowering. Furthermore, the data showed no evidence of an interaction of sex with BP-lowering treatment for the outcomes of coronary heart disease, heart failure, CV death or total mortality. Treatment regimens based on calcium antagonists conferred marginally ($P=0.05$) greater protection than regimens based on angiotensin-converting enzyme inhibitors in women compared with men. Treatment with beta blockers or diuretics showed similar benefit to other drug classes for either gender. Further analyses showed

no difference in treatment effects between women and men categorized by age. A limitation of this analysis was the small number of events in the young-age subgroup.

It is of importance that angiotensin-converting enzyme inhibitors and angiotensin 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, 902 women and men received nonpharmacologic treatment plus treatment with a drug chosen at random from each class of antihypertensive agent available. Women reported twice as many adverse effects as men.⁵⁴ Similarly, women in the LIFE study had more total adverse events but fewer serious drug-related adverse events than men.⁴⁶

Biochemical responses to drugs appear to be gender dependent. For example, angiotensin-converting enzyme inhibitor-induced cough is two to three times more common in women than in men, and women are more likely to complain of calcium channel blocker-related peripheral edema and minoxidil-induced hirsutism. Furthermore, women are more likely to develop hyponatremia or hypokalemia and men more likely to develop gout in response to diuretic therapy.⁵² Sexual dysfunction related to antihypertensive therapy, which is more commonly discussed with men than women, seems to 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 angiotensin receptor blocker therapy may improve these symptoms.^{55,56}

CONCLUSION

Prevalence of hypertension is expected to increase more in women than men. Although the BP effects of menopause or HRT remain controversial, hypertension importantly contributes to CV morbidity and mortality in women. Development of hypertension with COCs can occur and, usually, it resolves with withdrawal of the COC. Renal artery stenosis secondary to fibromuscular dysplasia primarily affects young women and need to be investigated. Antihypertensive treatments have comparable benefits 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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