Review Article

Considerations in Women with Hypertension

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Abstract: Cardiovascular disease is the most common cause of death in women in the United States, and hypertension is a major contributor to cardiovascular mortality. The incidence of hypertension in women is steadily increasing, paralleling the epidemics of obesity and diabetes. Blood pressure control rates among women are suboptimal, even when secondary causes are identified and treated. There are few high-quality data describing specific hypertension-related outcomes in women. Some data comparing hypertensive women to age-matched men suggest advantages to sex-specific strategies, but further study is needed to determine optimal regimens for women throughout their lives. Pregnancy and menopause present unique, complex challenges in hypertension management.

Key Words: epidemiology, hypertension, prevention, treatment, women

Hypertension (systolic blood pressure ≥140 mm Hg and/or diastolic ≥90 mm Hg and/or receiving antihypertensive medications), an important risk factor for cardiovascular disease (CVD), affects 31% of adults 18 years and older and contributes to coronary heart and cerebrovascular disease, the leading causes of death in American women.[1] Among major cardiovascular risk factors, hypertension clusters with obesity, dyslipidemia, and glucose intolerance, which in turn associate with uncontrolled blood pressure (BP), further increasing total risk. Women often have multiple concurrent risk factors, including central obesity, elevated total cholesterol, low high-density lipoprotein, and higher systolic BP, that independently predict cardiovascular events.[2] Data are limited on specific sex-driven treatment considerations, although some information suggests regimens that may demonstrate differential benefit. Secondary hypertension and issues related to pregnancy and menopause contribute to the complexities of treating hypertensive women; therefore, it is important to understand sex-specific factors that influence risk and BP control in hypertensive women and to apply this understanding to treatment.

Sex-Specific Prevalence and Epidemiology

As presented in the National Health and Nutrition Examination Survey reports for 1988–1994 and 1999–2004, hypertension prevalence has trended upward, driven primarily by an increase in women; the proportion of women with hypertension rose two times faster than the proportion of men during this period.[3] The worldwide prevalence in women is predicted to have increased 13% between 2000 and 2025.[4] In the 1999–2004 dataset, hypertension affected 39% of non-Hispanic white and Mexican American women aged 50 to 59 years, compared with 61% of their non-Hispanic black counterparts.[3]

Hypertension is found in approximately 8% of women aged 20 to 44 years; obesity is of particular importance in this population because it affects >30% of young women in the United States. It is associated with a greater than fourfold higher risk of hypertension and is potentially modifiable.[5] Premenopausal women are at a higher risk for developing target organ damage (specifically microalbuminuria and left ventricular hypertrophy [LVH]) but are at a lower risk for clinical CVD than men of comparable age.[6]

Hypertension severity also increases with age: 48.8% of women aged 60 to 79 years and 63% of women 80 years and older have stage 2 hypertension (BP ≥160/100 mm Hg) and/or receive antihypertensive therapy. Prevalence approaches 60% in women older than 65 years, largely because of progressive arterial stiffening and abruptly falling estrogen levels, which in turn activate the renin-angiotensin-aldosterone and sympathetic nervous systems.[7] Systolic and pulse pressures are higher in women older than 45 years, whereas diastolic pressures are

Key Points

- Cardiovascular disease is the most common cause of death among women, and hypertension is a major contributor to this mortality.
- Hypertension control among women is suboptimal.
- Many sex-specific biological issues influence treatment decisions and control of blood pressure in hypertensive women; knowledge of these issues may improve outcomes.
- Pregnancy and menopause dictate additional safety and efficacy considerations during hypertension treatment.

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lower in women across all age groups, compared with age-matched men.[2,8] Higher pulse pressure (an independent predictor of cardiovascular complications) and isolated systolic hypertension (a significant risk factor for total cardiovascular mortality) also are more common among elderly women than among older men.[8] Increasing pulse pressure associated with an increase in systolic BP, independent of diastolic BP, is a powerful predictor of death from coronary heart disease, stroke, and cardiovascular and all-cause mortality in women aged 45 to 64 years.[9] A contributing factor may be greater treatment resistance among older women,[10] although this relation requires confirmation.

Secondary Hypertension

The causes of secondary hypertension in women are the same as that in men,[11] although the relative prevalences vary by age group,[12] with a gender predilection in a few select causes. Although aortic coarctation is more common in men, renal artery stenosis resulting from fibromuscular dysplasia is more common among young adult women.[12] Fibromuscular dysplasia should be considered in women who have cervical bruits or develop hypertension before age 35 and can be detected by abdominal magnetic resonance imaging or computed tomography; percutaneous catheter intervention is the preferred treatment.[4,11] Hypertension is common in women with collagen diseases (eg, lupus, systemic sclerosis), which suggests renal involvement by the diseases' autoimmune process.[11] Although the prevalence of primary aldosteronism is similar between men and women, both estrogen and progesterone can affect serum concentrations of aldosterone and renin, interfering with the diagnostic evaluation and; menstrual cycle timing and oral contraceptive use should therefore be considered when interpreting aldosterone-renin ratios calculated from direct renin concentrations.[4] Pheochromocytoma is rare but contributes to significant maternal morbidity and mortality during pregnancy and should be excluded in young hypertensive women with characteristic symptoms, including headache, palpitations, sweating, and labile BP.[11,12]

Abnormal sleep duration (<6 or >9 hours/day) is associated with a greater incidence of hypertension among women and may independently further compound their overall cardiovascular risk.[13,14] Sleep deprivation disturbs endocrine and metabolic function and augments sympathetic nervous system activity, resulting in sustained hypertension. The biological mechanisms linking excessive sleep and hypertension are less clear, but they may be related to sleep-disordered breathing, reduced physical activity, and/or poor-quality sleep.[14]

Blood Pressure Control and Treatment Considerations

Despite the long-acknowledged benefit of BP reduction on CVD and stroke risk, many hypertensive patients remain undertreated or untreated. Gender disparities exist in both BP control and treatment: Women are more likely than men to receive antihypertensive medications, but they are less likely to have achieved recommended BP targets.[15,16] Although comparison of National Health and Nutrition Examination Survey data demonstrates a significant improvement in BP control rates among men between the 1988–1994 (20.7%) and 1999–2004 (36.2%) surveys, women had only a modest, nonsignificant improvement (31.2%–34.2%) during the same period.[3] In an age-stratified analysis of control rates between men and women, a sex-by-age interaction was identified. Women in the 18- to 49- and 50- to 64-year-old age groups had better control rates, whereas those older than 65 had worse control rates than age-matched men.[15,17] Less adequate control of BP in older women may be related to the decrease in circulating estrogen concentrations, a greater increase in body mass index, and less-aggressive management by their healthcare providers.[7,8,15,17]

Nonpharmacologic and (when needed) pharmacologic treatments are recommended to lower BP in both men and women. Nonpharmacologic interventions addressing concomitant risk factors, especially those directed at reducing central obesity (eg, caloric and sodium restriction, modest alcohol consumption, regular physical activity) may be particularly important adjuncts for improving BP control and reducing vascular risk in hypertensive women.[2,7,18–20]

National guidelines emphasize the importance of a diuretic-based multidrug regimen to achieve therapeutic goals when drug therapy is necessary[21,22]; however, less than half of hypertensive patients receive more than one drug and fewer still receive a diuretic.[15] Although antihypertensive medication use is higher overall among women, they less often receive regimens containing three or more drugs compared with similar male patients.[15,16] Approximately one-third of hypertensive women (vs one-fourth of men) report using diuretics. Significantly more women with diabetes and kidney disease take diuretics; diabetic women also are more likely than diabetic men to use angiotensin receptor blockers (ARBs), whereas significantly fewer with kidney disease receive angiotensin-converting enzyme inhibitors (ACE-Is). There appears to be no sex difference in the use of beta-blockers or calcium channel blockers (CCBs).[15]

In general, men and women do not demonstrate differential responses to antihypertensive medications and both receive similar benefits in cardiovascular morbidity and mortality reduction from BP control.[4,7,16,21] Thiazide-type diuretics, the cornerstones of antihypertensive regimens in many outcome trials, reduce cardiovascular and stroke risks and therefore should be considered a first-line therapy in most women.[16] American Heart Association guidelines recommend that initial drug treatment for women at high risk with compelling indications (eg, coronary disease, chronic kidney disease, multiple cardiovascular risk factors in addition to hypertension) should include a beta-blocker and/or an ACE-I or ARB, with the addition of a diuretic as needed to achieve BP control.[22] In

postmenopausal women, thiazide-type diuretics also may reduce the risk of bone loss and hip fracture and therefore are particularly attractive choices in this population.[4,16]

In an analysis of 31 randomized trials performed by the Blood Pressure Lowering Treatment Trialists Collaboration, regimens based on CCBs conferred marginally greater protection than regimens based on ACE-Is in women, whereas beta-blockers and diuretics showed similar benefits to other drug classes in both sexes.[4] Because of potential teratogenicity, ACE-Is, ARBs, and direct renin inhibitors are contraindicated in women who are or intend to become pregnant[4,16]; however, they may be appropriate for postmenopausal women because they do not negatively affect the menopausal metabolic syndrome.[18]

There appear to be sex-specific differences in drug tolerability and adverse effect frequency. In the Treatment of Mild Hypertension Study, women reported twice as many adverse effects as did men, although the incidence of adverse effects was similar between placebo- and drug-treated cohorts.[11,21] Women were more likely than men to develop diuretic-induced hyponatremia and hypokalemia, complain of CCB-related peripheral edema, and develop an ACE-I–related cough.[4,11,16,21]

Renal denervation therapy is gaining interest as a modality in the treatment of resistant hypertension[23,24] and may be of particular benefit in controlling BP and other metabolic abnormalities associated with polycystic ovary syndrome.[25]

Hypertension in Pregnancy

Hypertension is the most common medical disorder complicating pregnancy, affecting thousands of women annually in the United States.[5,26] The four major hypertensive disorders in pregnancy—chronic hypertension, preeclampsia-eclampsia, gestational hypertension, and postpartum hypertension (reclassified as chronic hypertension if persisting >3 months after delivery[26])—may lead to maternal and perinatal complications, but preeclampsia and severe hypertension via any mechanism are related to the highest risks.[5,26] Maternal complications are placenta abruption, accelerated hypertension requiring hospitalization, and acute target organ damage, and fetal risks include growth restriction and preterm birth.[5,26]

The common pathogenic mechanism of pregnancy-induced hypertension appears to be placental ischemia, followed by placental release of vasopressor substances.[27] The increasing prevalences of obesity and chronic hypertension present additional challenges as the number of older mothers increases, and both pregnancy-specific and chronic hypertensive factors may combine to amplify BP-related adverse events.

The American Congress of Obstetricians and Gynecologists recommends that hypertensive pregnant women with a BP of 150 to 160/100 to 110 mm Hg receive antihypertensive therapy; however, in pregnant women with mild hypertension, medications may be reduced, discontinued, or withheld unless there are complicating factors (eg, cardiovascular or renal disease) or if the BP is ≥150/100 mm Hg. In the presence of chronic severe hypertension (≥160/110 mm Hg), therapy should be prescribed to reduce the risk of maternal stroke.[28]

The Food and Drug Administration classifies most antihypertensive drugs as pregnancy category C with insufficient human data and animal studies either positive for adverse fetal effects or similarly inconclusive. As such, most drugs should be prescribed only if potential benefits justify possible risks to the fetus.[5,26] Because approximately 5% of reproductive-age women take antihypertensive medications (most commonly diuretics, ACE-Is, and/or beta-blockers), it is not uncommon for antihypertensive agents to be taken during unintended or early pregnancies, an important consideration when treating women in this age group.[5]

Methyldopa, labetalol, and nifedipine in standard doses are generally considered safe for pregnant women.[26,28] Parenteral hydralazine and labetalol have been used most commonly in the setting of severely elevated BP.[28] If taken before pregnancy, thiazide diuretics may be continued during pregnancy. Conversely atenolol, a pure beta-antagonist with high lipid solubility and β_1 specificity, has been associated with fetal growth restriction and therefore is not recommended.[28] ACE-Is and ARBs are contraindicated in all trimesters,[26,29] and α-adrenergic blockers are not recommended except in the rare case of hypertension secondary to pheochromocytoma.[29]

Menopause

The onset of menopause is associated with both increased CVD risk and higher BP compared with the premenopausal period.[18,30] BP levels in the climacterium depend upon age at menopause and duration of the menopausal period, suggesting that longer estrogen deficiency may be a contributor to higher BP in elderly women.[30] Menopause promotes a derangement of the cardiocirculatory system, and the cessation of ovarian function may result not only in a marked decline in endothelium-dependent vasodilation but also in the emergence of other atherogenic factors.[18]

Menopause is linked to an increased incidence of the metabolic syndrome, the constellation of cardiovascular risk factors characterized by abdominal obesity, insulin resistance, and dyslipidemia.[31] Increasing body mass index and aberrations in glucose metabolism resulting from estrogen deficiency at menopause may contribute to the development of the metabolic syndrome in older women, conferring a higher risk of CVD and hypertension in this population.[31] The interaction of menopause, obesity, and salt sensitivity on the pathogenesis of hypertension in women has been investigated extensively[17]; therefore, an effective therapeutic approach in these patients should focus on treating comorbid conditions and risk factors to reduce total cardiovascular risk. Given the complex pathophysiology of hypertension in menopause, lifestyle modification may play a critical role in effective BP and cardiovascular risk reduction.

Hypertensive Complications

Sex-related differences have been noted in the frequency of hypertensive complications. Hypertension causes stroke more often,[32] and as a frequent cause of chronic heart failure, it produces a higher incidence of diastolic dysfunction in women than in men.[16,33] The presence of LVH is a strong risk factor for cardiovascular events and may carry a greater risk in women than in men with similar degrees of hypertrophy.[32] Women are more likely than similar men to develop LVH, but they experience less hypertrophy regression in response to antihypertensive therapy.[34] Whether a sex differential exists, the rate of chronic kidney disease development secondary to hypertension is unclear.[35]

Treatment Effects: Outcomes and Cost of Care

Although antihypertensive therapy is recommended to reduce cardiovascular risk in both sexes, benefits on clinical outcomes have not been studied in women. Data on treatment effects are limited to those available from the inclusion of women in variable proportions in large clinical trials or meta-analyses of smaller studies. The Individual Data Analysis of Antihypertensive Intervention Trials, a quantitative review assessing the benefits of hypertension treatment, found that BP-reducing therapy was associated with significant risk reductions for fatal strokes, all strokes, and CVD events in women.[36–38] A sex-specific analysis of this database revealed that treatment reduced the relative and absolute risk of cerebrovascular and cardiovascular events in women older than age 55 and in African American women of all ages, but it could not inform on the issue for younger women and women at low risk.[37,38]

Ideal treatment strategies should apply sex-specific outcome data to lower BP, promote beneficial cardiovascular and renal outcomes, and minimize unfavorable adverse effects. Present evidence-based guidelines report sex-comparable benefits of antihypertensive therapy[4,16,21] and indicate that most patients, including women, will require combination therapy with agents from different drug classes to attain BP targets. Outcome trials that compare newer drug classes (ACE-Is, ARBs, or CCBs) to older classes (diuretics and beta-blockers) in elderly, high-risk patients have shown similar benefits for both men and women.[21]

Recent data, however, suggest that sex differences in treatment-based outcomes may exist. In the Valsartan Antihypertensive Long-term Use Evaluation study, women assigned to treatment with this ARB had a greater relative risk of cardiovascular morbidity and mortality than did those assigned to the CCB amlodipine. In both the Valsartan Antihypertensive Long-term Use Evaluation and the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack trials, women had a slightly greater hypotensive response to amlodipine than to lisinopril, which was associated with a greater reduction in stroke incidence. A subgroup analysis of outcomes in women in the Losartan Intervention for Endpoint Reduction study showed greater reductions in the composite of cardiovascular death, stroke, and myocardial infarction with losartan therapy compared with atenolol treatment.[4] Although reports from the Women's Health Initiative Observational Study support current guideline recommendations for low-dose diuretic monotherapy for CVD event reduction in most hypertensive patients, their findings on dual drug combination therapy suggest that ACE-I plus diuretics or beta-blockers plus diuretics result in fewer CVD deaths in woman than do regimens combining CCBs with diuretics.[39] Prospective trials are needed to confirm these observations.

Without high-quality data directing otherwise, all drug classes should be considered appropriate for the treatment of hypertension in women. Selection of specific agents should take into account the patient's individual cardiovascular risk, specific life stage, drug tolerability, and associated diseases and compelling indications. Although intriguing, data are insufficient to suggest sex-driven deviation from present guideline recommendations at this time.[1,21]

A final yet critical consideration in management decisions is the cost of care. Recent evidence suggests that hypertension-attributable expenditures for prescription drugs, hospitalizations, and outpatient and emergency department visits are significantly higher for women than for men, a difference that diminishes and eventually reverses with advancing age.[40] These differences may reflect disparities in the treatment of hypertension and related diseases; more effective treatment in younger women aimed at reducing the observed disparities would improve quality of care while lowering the total fiscal burden of CVD to society.[40]

Conclusions

Hypertension, a major contributor to cardiovascular morbidity and mortality, continues to increase in prevalence and is inadequately controlled in most women. Clustering of hypertension with obesity, glucose intolerance, and dyslipidemia mandates a comprehensive approach to treatment. Fibromuscular dysplasia is a more common cause of secondary hypertension in women, and hormonal interactions make diagnosing primary aldosteronism more challenging in women. Although few data describe significant differences in antihypertensive drug responsiveness between men and women, age-related factors, including pregnancy and menopause, complicate therapeutic decision making. The magnitude of benefit from antihypertensive treatment is proportional to the level of CVD risk for both sexes. To optimize clinical benefits, treatment strategies should be customized to consider both the level of BP and the presence of other risk factors or additional conditions influencing morbidity and mortality in women with hypertension.

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