Hypertension in Women

Recent Advances and Lingering Questions

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Cardiovascular disease (CVD) is the leading cause of death in women in every major developed country and most emerging countries.[1,2] Hypertension, the most common modifiable risk factor for CVD, is estimated to occur in 85.7 million adults in the United States (44.9 million women and 40.8 million men).[3] Elevated blood pressure (BP) >140/90 mm Hg is associated with a shorter life expectancy overall, shorter life expectancy free of CVD, and more years lived with CVD.[3–5] Hypertension is less common in women, compared with men, in those younger than 65 years of age, but is more common in elderly (65 years and older) women than men. In the United States, between 2011 and 2014, the prevalence of hypertension in women and men by age group was 8% versus 11% (20–34 years), 23% versus 23% (35–44 years), 33% versus 36% (45–54 years), 56% versus 58% (55–64 years), 66% versus 64% (65–74 years), and 81% versus 73% (≥75 years).[3]

Awareness, Treatment, and Control

Globally, the prevalence of hypertension differs between sexes. Mills et al[6] conducted a systematic analysis of population-based studies from 90 countries with 968 419 individuals to estimate the prevalence of hypertension in various countries grouped by income. Women in middle-/low-income countries, across all age groups, had a higher prevalence of hypertension compared with high-income countries. Awareness rates were higher in women than in men in both high-income countries (72% women versus 62% men) and middle-/low-income countries (45% women versus 31% men). Furthermore, women in both high-income countries (62% women versus 49% men) and middle-/low-income countries (36% women versus 22% men) reported a higher rate of antihypertensive medication use compared with men, and hypertension control rates (BP <140/90 mm Hg) were higher in women than in men in both high-income countries (52% women versus 49% men) and middle-/low-income countries (28% women versus 23% men). Although women had better awareness, treatment, and control rates than men, there were large discrepancies between high- and middle-/low-income countries in all 3 categories, with much less favorable statistics for both sexes in middle-/low-income countries. These discrepancies are likely multifactorial, related to both poorer access to healthcare and the limited availability and high cost of antihypertensive medications in middle-/low-income countries.

In the United States, awareness, treatment, and control rates of hypertension differ between sexes. Overall, women are more likely than men to be aware of their diagnosis, to be treated with antihypertensive medication, and to have controlled hypertension.[3] Rates of awareness, treatment, and control are also higher in women compared with men in all major racial/ethnic groups (Figure S1 in the online-only Data Supplement). Non-Hispanic black women have the highest rates of awareness among women and men in all racial/ethnic groups (90%), and non-Hispanic black and white women are highly (and equally) likely to be prescribed antihypertensive medication (82%). Control rates are similar among minority women (54% non-Hispanic blacks, 55% Hispanics, and 50% Asians) and lower than in white women (59%). Among men, white men have the highest rates of controlled hypertension (74%) and Asian men have the lowest (40%). Analysis of >12 000 patient visits with primary care physicians in the United States showed no sex difference in the number of antihypertensive medications prescribed, but did reveal that women were more commonly prescribed diuretics and less frequently prescribed angiotensin-converting enzyme inhibitors (ACEIs).[7]

Women are more likely than men to be aware of their diagnosis, prescribed antihypertensives, and have controlled hypertension. However, significant disparities remain across ethnicities. Although awareness is comparable in women across ethnicities, treatment and control rates remain lower in minorities compared with white women, possibly related to access to health care and medications.

Diagnosis

Data on BP levels and hypertension prevalence have traditionally been based on manual/automated sphygmomanometer measurements in-office. However, extensive epidemiological data indicate that up to 30% of patients are incorrectly diagnosed with hypertension based on these readings.[8,9] Multiple large population-based meta-analyses have shown the superiority of ambulatory blood pressure monitoring (ABPM) and home BP monitoring (or self-monitoring) to in-office

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BP measurements in diagnosing hypertension and predicting cardiovascular outcomes (cardiovascular death, stroke, and cardiac/coronary events).[10,11] Importantly, the US Preventative Services Task Force is now recommending ABPM in all patients before the initiation of antihypertensive treatment as a Grade A recommendation.[12]

Analyses of ABPM data by sex have generally shown that women have lower day-time and night-time BPs compared with men. Kagan et al[13] investigated sex differences in ABPM and their correlation with body mass index in 989 untreated Israelis (49% women) between 2002 and 2006. Both normal weight (body mass index <25 kg/m^2) and obese (body mass index >30 kg/m^2) women were more likely than men to have normal BP (<135/85 mm Hg during the day and <120/70 mm Hg during the night). Furthermore, Spanish investigators explored sex differences in hypertension control in 29 148 treated white women and men (48% women) in the Spanish Ambulatory Blood Pressure Registry.[14] In-office BP control (BP <140/90 mm Hg) was similar in women and men (22% versus 23%), but ABPM showed significantly higher control rates in women than in men (49% versus 39%). Division-Garrote et al[15] expanded this assessment by evaluating 70 997 treated individuals (mean age, 62 years, 48% women) in the Spanish ABPM database and confirming a higher rate of BP control among women (44% versus 38%). Importantly, they also noted a significantly higher rate of hypotension (day-time ABPM <105/65 mm Hg, night-time ABPM <90/50 mm Hg, and 24-hour ABPM <100/60 mm Hg) in women compared with men (10% versus 7%). Almost half of the hypotensive individuals were on 3 or more antihypertensive medications. A possible explanation for the apparent overtreatment of BP in these women (mean age 72 years) is that treatment decisions may have been based on in-office BP readings, which are typically higher in older women compared with men.[9]

ABPM data also highlight the importance of 24-hour recordings in predicting health outcomes. IDACO (International Database of Ambulatory Blood Pressure in Relation to Cardiovascular Outcome) investigators recorded 24-hour systolic BP (SBP) and diastolic BP (DBP) measurements and health outcomes in 8341 untreated people (mean age 51 years; 47% women) from 12 countries followed for up to 17 years. They found that elevated mean 24-hour DBP predicted total and cardiovascular mortality in individuals younger than 50 years of age, whereas elevated mean 24-hour SBP predicted total and cardiovascular mortality in those over 50 years of age.[16]

Abnormal ABPM Phenotypes

Elevated Nocturnal BP/Nondippers

Night-time BP recorded by ABPM has emerged as a better predictor of total mortality, stroke, and cardiovascular death in patients with hypertension and a history of CVD than either day-time ABPM or in-office BP measurements.[10] Normally, BP varies with the circadian clock: it is higher during the day time, and decreases by 10% to 20% during sleep, a phenomenon known as dipping.[17] Patients with a diminished nocturnal BP fall or a nocturnal BP rise, termed nondippers, have a greater prevalence of coronary events, strokes, cardiovascular mortality, and total mortality.[17,18] Reverse-dippers, a specific subtype of nondippers in whom BP rises at night, are at increased risk of CVD.[19] Perez-Lloret et al[20] investigated sex differences in the prevalence of nocturnal BP elevation (night-time BP>120/70 mm Hg) in 1689 untreated individuals (51% women) from the general population of Argentina who underwent 24-hour ABPM. Women younger than 30 years of age were less likely to have nocturnal BP elevation than men (0% versus 20% men), but nocturnal BP elevation increased more rapidly in women, such that the prevalences of nocturnal BP elevation and nondipping were similar in men and women above the age of 70 years.

Overall, women are less likely to experience nondipping at younger ages, but, similar to day-time BP, night-time BP increases in women as they age. Furthermore, there may be differences in the prevalence of nondipping by ethnicity, with non-Hispanic black and Asian women having an attenuated night-time BP decrease compared with non-Hispanic white and Mexican American women.[21] The CVD outcomes related to these differences have yet to be fully assessed.

White-Coat Hypertension

White-coat hypertension is defined as elevated in-office BP (≥140/90 mm Hg) and normal ABP (awake day-time ABPM <135/85 mm Hg) in individuals not receiving antihypertensive therapy.[21] Women, particularly older or pregnant women, are at increased risk for white-coat hypertension.[9] In the United States, a higher percentage of women (43%) than men (34%) have white-coat hypertension, assessed by ABPM.[8,9] Worldwide, investigators from the international ARTEMIS project (Ambulatory Blood Pressure Registry: Telemonitoring of Hypertension and Cardiovascular Risk) diagnosed white-coat hypertension in 23% of 14 143 patients (49% women) evaluated in hypertension clinics across 5 continents with in-office BP readings and 24-hour ABPM.[22] White-coat hypertension was more common in elderly obese women and in Europe and Asia (25% versus 11% in other continents). The increased prevalence of white-coat hypertension in older women has been attributed to increased anxiety and metabolic syndrome in this population, in addition to hormonal changes.[23,24] Furthermore, pathophysiological changes with aging, including increased arterial stiffness and diminished baroreceptor sensitivity, result in larger increases of BP in response to psychological stress.[21]

White-coat hypertension is generally considered a benign hypertension phenotype because large-scale studies of different populations have shown no differences in long-term CVD morbidity/mortality in individuals with white-coat hypertension compared with normotensive individuals.[25–27] Franklin et al[21] recently challenged the concept of white-coat hypertension as a benign phenotype in an analysis of 653 untreated individuals with white-coat hypertension and 653 normotensive individuals in the IDACO database. Over a 10.6-year follow-up, individuals with white-coat hypertension and 0 to 2 additional CVD risk factors exhibited similar CVD outcomes as to normotensive individuals. In contrast, those with white-coat hypertension and >3 CVD risk factors had a 2-fold increase in CVD outcomes. Thus, low-risk individuals with white-coat hypertension had similar CVD outcomes as normotensive

individuals, whereas high-risk, older age-matched individuals with white-coat hypertension had more CVD events (70 CVD events in individuals with white-coat hypertension versus 48 in the normotensive control group). The authors postulated that the higher event rate in the high-risk group was because of underlying isolated systolic hypertension, incorrectly diagnosed as white-coat hypertension based on a single ABPM reading. This is the first study of white-coat hypertension to take CVD risk burden into consideration. It did not, however, examine CVD outcomes of individuals with white-coat hypertension by sex.

Evidence that white-coat hypertension can become sustained hypertension over the long-term further calls into question its putative benign nature.[28] Further studies are clearly needed to assess the prognostic significance of white-coat hypertension in women, particularly elderly women, at high CVD risk. In the interim, it would be reasonable for healthcare providers to evaluate these women for other CVD risk factors to determine the appropriateness of treatment.

Masked Hypertension

Masked hypertension is defined as normal in-office BP and elevated ABPM (awake day-time ABPM >140/90 mm Hg).[29] Risk factors include male sex, older age, in-office prehypertension, and diabetes mellitus. Worldwide, the prevalence of masked hypertension is 10%, with an increased prevalence in Asia.[22] Men with a history of diabetes mellitus seem particularly at risk. In the United States, the prevalence of masked hypertension diagnosed by ABPM in untreated women is half as that seen in men (7% versus 18%). The prevalence of masked hypertension in women increases with body mass index and alcohol intake, perhaps contributing to the increased rate of cardiovascular outcomes in these women.[8]

Masked hypertension is a well-known CVD risk factor, but remains a largely unrecognized clinical entity because ABPM is infrequently performed, and standards for diagnosing elevated home BPs are lacking.[30,31] As a result, there are no guidelines for evaluating or treating these patients, despite their increased CVD risk. Providers are strongly encouraged to perform ABPM and comprehensive risk factor assessment in both sexes to determine future CVD risk.

Treatment Goals

The benefit of lowering BP in reducing cardiovascular outcomes is well documented, yet optimal BP thresholds to initiate antihypertensive medications and optimal BP targets remain controversial. Most major treatment guidelines recommend a BP target of ≤140/90 mm Hg, with no differences in treatment strategy between women and men.[32–34] Recent large-scale studies have reevaluated the SBP treatment target. Ettehad et al[35] showed in a meta-analysis of 123 randomized controlled trials (RCTs) of BP-lowering treatment (613 815 patients) that an SBP target of <130 mm Hg compared with the standard target of <140 mm Hg was associated with a significantly reduced risk of major CVD events, coronary heart disease, stroke, heart failure, and all-cause mortality. The benefit of treating to a lower SBP target was further supported by Xie et al[36] in a meta-analysis of 19 RCTs (44 989 patients) that randomly assigned patients to more intensive BP-lowering treatment (achieved BP 133/76 mm Hg) versus less intensive treatment (achieved BP 140/81 mm Hg). Intensive treatment was associated with significant risk reductions in cardiovascular events, myocardial infarction, stroke, albuminuria, and retinopathy progression. Bangalore et al[37] performed a network meta-analysis of 17 RCTs (55 163 patients) to compare different BP targets (SBP <160, <150, <140, <130, and <120 mm Hg). An SBP target of <130 mm Hg was associated with an optimal balance between safety and efficacy, whereas an SBP target of <120 mm Hg was associated with similar efficacy as <130 mm Hg, but with significant increase in serious adverse effects (angioedema, hypotension, syncope, bradycardia, arrhythmia, and hypo/hyperkalemia) compared with <140 mm Hg. These studies did not analyze the outcomes of treatment by sex.

The SPRINT (Systolic Blood Pressure Intervention Trial) is the only RCT of antihypertensive therapy that compared treatment to a low SBP target (BP <120 mm Hg) versus a standard target (BP <140 mm Hg). SPRINT randomly assigned 9361 high CVD risk individuals aged 50 years or older (36% women) to intensive or standard treatment.[38] The SPRINT treatments were stopped early (3.26 years versus planned 5 years) because of a 25% reduction in the primary composite end point (first occurrence of nonfatal myocardial infarction, other acute coronary syndrome, stroke, heart failure hospitalization, or cardiovascular-related death) and 27% reduction in mortality in the intensive treatment group. The prespecified subgroup analysis of outcomes in women showed a statistically nonsignificant benefit in the intensive treatment group. The primary composite end point occurred in 77 (4.6%) women in the intensive treatment group versus 89 (5.4%) in the standard treatment group. The primary composite end point occurred in more than twice as many men as woman in both the intensive (166, 5.5%) and standard (230, 7.6%) treatment groups. The hazard ratios (intensive versus standard treatment) were 0.84 (95% confidence interval, 0.62–1.14) in women and 0.72 in men (95% confidence interval, 0.59–0.88). The lack of statistically significant benefit for women in SPRINT has been attributed to the enrollment of fewer women than expected (goal enrollment was 50%), in part, related to the small proportion of women enrolled in the Veterans Affairs Clinical Center Network of the trial. On average, hypertension trials in the last decade have included 44% women, versus 36% (n=3332) in SPRINT.[39] Early termination of the randomized treatments in SPRINT may have also contributed to the lack of statistically significant benefit in women. It has been suggested that lower event rates in women may have been, in part, because of women having an overall lower CVD risk at the onset of the trial and subsequently fewer events during the abbreviated trial period.[39]

Treatment

RCTs with CVD outcomes have provided definitive evidence that BP lowering with medications benefits both hypertensive women and men, with no consistent differences in outcomes by sex (Table S1). The INDANA intervention trials (Individual Data Analysis of Antihypertensive), a meta-analysis of 7 RCTs with 20 802 women and 19 975 men, showed no significant differences in treatment benefit between sexes.[40]

The BP-Lowering Treatment Trialists' Collaboration overview of 31 RCTs (87 349 women and 103 268 men) included comparisons of active agents with placebos, intensive versus less intensive antihypertensive medication regimens, and one active agent versus another.[41] Primary outcomes included major cardiovascular events (stroke, myocardial infarction, heart failure, and cardiovascular death). BP reductions were comparable in both sexes, and there were no significant sex-related differences in CVD outcomes. Furthermore, no differences in the effects of specific antihypertensive medications on BP or CVD outcomes by sex were identified.

Sex differences in CVD outcomes in response to some specific antihypertensive medications have been reported in individual RCTs, however. The ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), the largest RCT (15 638 women and 17 719 men) of antihypertensive treatment ever conducted, tested whether lisinopril or amlodipine was superior to chlorthalidone in reducing CVD outcomes (fatal coronary heart disease or nonfatal myocardial infarction). ALLHAT found no difference among treatment modalities in the primary outcome, but a post hoc analysis comparing lisinopril and amlodipine showed a higher stroke rate in women versus men on lisinopril during the 6-year in-trial period.[42,43] This difference was not sustained in the post-trial surveillance period. Over the total 13 years of ALLHAT, no difference in rates of the primary outcomes was seen between sexes, but women consistently had higher SBP than men.[44]

A prespecified subgroup analysis of the VALUE trial (Valsartan Antihypertensive Long-Term Use Evaluation), which compared valsartan-based to amlodipine-based treatment in 15 245 (42% women) high-risk hypertensive participants, showed higher cardiovascular morbidity/mortality with valsartan than amlodipine in women, but not in men.[45] A subgroup analysis of the LIFE study (Losartan Intervention for Endpoint Reduction in Hypertension) compared sex-specific effects of losartan versus atenolol in 9193 patients (54% women), with hypertension and left ventricular hypertrophy at baseline. Losartan-based treatment was associated with a greater reduction in the primary composite end point (cardiovascular mortality, stroke, and myocardial infarction) in women, but not in men.[46]

In contrast to the paucity of sex-based differences in the efficacy of antihypertensive treatment, clinically significant sex-based adverse effects of antihypertensive drugs have been identified. These adverse effects are more common in women.[47] ACEIs, angiotensin receptor blockers, direct renin inhibitors, and mineralocorticoid receptor antagonists are contraindicated in women of reproductive potential because of the risk of fetal abnormalities. The most common abnormalities associated with these drugs during pregnancy are oligohydramnios, anuria, and failure of the fetal kidneys to develop.[48] Mineralocorticoid antagonists are also associated with ambiguous genitalia in newborns.[49] Women are 3× more likely than men to develop an ACEI-related cough and more commonly experience calcium channel blocker–related peripheral edema and minoxidil-induced hirsutism. Women more commonly develop hyponatremia/hypokalemia from thiazide-type diuretic therapy, while men more frequently develop gout. β-blockers and thiazide-type diuretics are classically associated with sexual dysfunction in men. A subgroup analysis of SPRINT that assessed the relationship between sexual function and antihypertensive medications in women and found that ACEIs/angiotensin receptor blockers were associated with increased sexual activity in women.[50] No class of antihypertensive medication was associated with reduced sexual activity in women. Conversely, there are non-BP–related benefits of some antihypertensive drug classes. For example, thiazide-type diuretics are preferred for the use in elderly women, in part, because their use decreases risk of hip and pelvic fractures.[51]

Although the benefit of antihypertensive therapy in reducing BP and preventing CVD events is generally similar in women and men, providers should consider personalizing antihypertensive medications for women based on the adverse effect profiles and non-BP–related benefits of the different drug classes.

Special Populations

Certain forms of hypertension, including postmenopausal hypertension, oral contraceptive–induced hypertension, and pregnancy-related hypertension, occur exclusively in women.

Postmenopausal Hypertension

After menopause, there is an increase in SBP which is thought to be secondary to the withdrawal of vasodilator effects of endogenous estrogen, increased arterial stiffness and salt sensitivity, diminished endothelial nitric oxide production, and increased angiotensin II receptor expression.[52] The increase in both SBP and pulse pressure in peri- and postmenopausal women is greater than in age-matched men, whereas DBP is similar in both sexes. Importantly, isolated SBP elevation is a sensitive predictor of future CVD in both sexes.[52] Other factors predisposing to the development of hypertension that disproportionately affect postmenopausal women include obesity, which occurs in up to 40% of postmenopausal women, and higher rates of depression and anxiety.[23,24] Importantly, the effects of menopause on arterial stiffness and BP can be reversed through increased physical activity. Son et al[53] evaluated the effect of a combination of aerobic and resistance exercise in a group of hypertensive postmenopausal women (mean age 75 years, BP 152/95 mm Hg at baseline). After 12 weeks of exercise 3× a week, arterial stiffness (measured through brachial-ankle pulse wave velocity) and BP (−14/11 mm Hg) were decreased. These data illustrate the need for providers to encourage women, specifically the elderly, to maintain an active lifestyle.

Oral Contraceptive–Induced Hypertension

Oral contraceptive (OCP) use is associated with increases in BP and risk of cardiovascular events, which are generally reversible with discontinuation of the OCP. The pathogenesis is likely related to a combination of increased arterial stiffness, renin-angiotensin aldosterone activation, and salt/water retention.[48] The risk of developing OCP-induced hypertension increases with increasing age, tobacco use, duration of OCP use, and obesity. BP elevation has been associated with the concentration of ethinyl estradiol in OCP, and newer

third-generation combination OCP (estrogen/progesterone) contain less ethinyl estradiol and are associated with less marked effects on BP.[54] Drospirenone (Angeliq) is a newer progestin available in the United States and Europe with antimineralocorticoid/diuretic effects that has been shown to minimize the hypertensive effects of estrogen when used in combined OCP.[55] The American College of Obstetricians and Gynecologists recommends a trial of a low-dose combination OCP in women with well-controlled and monitored hypertension.[48] Patients with uncontrolled hypertension desiring OCP are recommended to be treated with a progestin-only OCP or the levonorgestrel-releasing intrauterine device (Mirena).

Pregnancy-Related Hypertension

The American College of Obstetricians and Gynecologists has classified hypertension during pregnancy into four categories: preeclampsia/eclampsia, chronic hypertension of any cause, chronic hypertension with superimposed preeclampsia, and gestational hypertension.[48] Preeclampsia is the syndrome of new-onset hypertension and proteinuria or, in the absence of proteinuria, hypertension associated with target organ damage, including thrombocytopenia, impaired liver function (elevated blood levels of liver transaminases to twice the normal concentration), the new-onset of renal insufficiency (elevated serum creatinine without antecedent renal disease), pulmonary edema, or new-onset cerebral or visual disturbances. The HELLP syndrome is a severe and life-threatening form of preeclampsia characterized by hemolysis, elevated liver enzymes, and low platelet count. Eclampsia is preeclampsia with seizures. Chronic hypertension in pregnancy is BP ≥140/90 mm Hg preceding the onset of pregnancy, or appearing before the 20th week of pregnancy, or lasting longer than 12 weeks postpartum. Chronic hypertension with superimposed preeclampsia is the development of preeclamptic/eclamptic symptoms in pregnant women with chronic hypertension. Gestational hypertension is elevated BP detected after the 20th week of pregnancy without features of preeclampsia.

Hypertension during pregnancy is a well-established risk factor for CVD postpartum.[48] Preeclampsia and eclampsia are the most commonly studied hypertensive disorders of pregnancy and have been associated with increased CVD morbidity and mortality postpartum.[56,57] Bokslag et al[58] investigated CVD risk in the fifth decade of life in women (n=131) who had experienced early-onset (<34 weeks of gestation) preeclampsia. At 9 to 16 years after the indexed pregnancy, a higher proportion of women with early-onset preeclampsia were diagnosed with hypertension (38%) and metabolic syndrome (18%) compared with normotensive pregnant women (14% and 2%, respectively). Behrens et al[59] further evaluated long-term risk of hypertensive disease of pregnancy by investigating the development of cardiomyopathy later in life (mean follow-up 17.9 years). A total of 76 108 women with hypertensive disease of pregnancy (preeclampsia, eclampsia, and gestational hypertension) were identified. Compared with normotensive pregnant women, pregnant women with all forms of hypertensive disease developed cardiomyopathy more frequently. Thus, increased CVD risk in women after a pregnancy complicated by hypertension is well documented. Although multiple studies have shown that the offspring of women with hypertensive disease of pregnancy will develop higher BP in adolescence, the long-term CVD risk of these children remains unclear.[60–62]

Emerging data also suggest increased morbidity/mortality from noncardiovascular causes in women who have experienced hypertensive disease of pregnancy. A retrospective cohort study of 60 580 women with a hypertensive disease of pregnancy showed significantly higher all-cause mortality compared with women with normal pregnancy, in addition to a higher mortality risk from Alzheimer disease, diabetes mellitus, ischemic heart disease, and stroke.[63] Data documenting follow-up care for women with hypertensive disease of pregnancy are sparse, but small retrospective reviews suggest deficiencies in postpartum health care and CVD screening in these women.[64,65]

For severe hypertension in pregnancy (BP >160/105 mm Hg), American College of Obstetricians and Gynecologists recommends initiation of antihypertensive therapy.[48] Below this threshold, the decision to begin therapy remains debated. A Cochrane Review meta-analysis of 49 RCTs (4723 women) evaluating the use of antihypertensives for mild-to-moderate hypertension (SBP 140–169 mm Hg and DBP 90–109 mm Hg) found that treatment was associated with a 51% reduction in the risk of developing severe hypertension but negligible reduction in the risk of preeclampsia, infant mortality, preterm birth, or small for gestational age infant.[66] The authors concluded that antihypertensive treatment may not be beneficial for these women. Furthermore, the CHIPS (Control of Hypertension in Pregnancy Study) randomly assigned pregnant women with preexisting or gestational hypertension to either less tight control of BP (target DBP ≤100 mm Hg) or tight control (target DBP ≤85 mm Hg) and found no difference in fetal loss, high-level neonatal care, or overall maternal complications. However, severe maternal hypertension was more frequent in the less-tight control.[67] The ongoing CHAP (Chronic Hypertension and Pregnancy Project; clinicaltrials.gov identifier: NCT02299414) is a multicenter RCT evaluating whether the treatment of chronic hypertension to a BP target <140/90 mm Hg during pregnancy with antihypertensive medications (labetalol or nifedipine) is associated with benefit or harm to the mother or fetus, compared with no treatment.

All antihypertensive medications cross the placenta, and no large-scale study in pregnant women has compared use of one antihypertensive drug class to another. Methyldopa has been widely used in pregnant women and its long-term safety profile is well documented.[68] Similarly, labetalol, nifedipine, and hydralazine, although less well studied than methyldopa, are considered safe in pregnancy.[69–71] Clonidine can be considered in patients in whom methyldopa or labetalol cannot be used; however, it is less preferred given the risk of rebound hypertension when abruptly stopped.[72] Drugs to avoid during pregnancy include ACEIs, angiotensin receptor blockers, direct renin inhibitors, and nitroprusside because of the risk of fetal toxicity and malformations. American College of Obstetricians and Gynecologists recommends initiation of pharmacological treatment with labetalol, nifedipine, or methyldopa as first-line agents.[48]

Conclusions

Hypertension is the most common modifiable risk factor for CVD, the leading cause of death in women worldwide. There is significant sex-related heterogeneity in the natural history of hypertension. Young women are protected from developing hypertension, in part, by endogenous estrogen. As women age, they become more likely to develop hypertension and the associated CVD outcomes. Women also have unique forms of hypertension associated with pregnancy, menopause, and the use of OCP. Current evidence supports similar BP thresholds for initiating treatment, BP targets of treatment, and choices of antihypertensive medications for women and men, with exceptions because of pregnancy and sex-specific adverse effects of some antihypertensive drug classes.

With the growing recognition of the importance of out of office BP monitoring as a predictor of CVD risk, providers are encouraged to use ABPM to aid in comprehensively stratifying CVD risk in all patients being evaluated for hypertension. White-coat hypertension occurs more commonly in women and sex-specific long-term CVD risk of individuals with white-coat hypertension has not been clearly defined. Further research is needed to understand sex-specific outcomes associated with the various hypertension phenotypes (white-coat hypertension, masked hypertension, dipping, and nondipping) defined by ABPM. Following SPRINT, there has been growing interest in identifying an appropriate BP targets for all individuals. Currently, BP treatment recommendations are similar for both sexes. Further investigation into the ideal BP target and associated clinical outcomes are needed in women. Appropriate thresholds and goals for the treatment of hypertension during and after pregnancy and the effects of BP treatment on maternal/fetal outcomes remain unclear and require further research. Hypertensive disease of pregnancy is associated with increased CVD risk postpartum, but data suggest that these women are not being consistently identified and followed. It is important for providers to obtain detailed pregnancy histories from women undergoing evaluation for hypertension, as women with a history of hypertensive disease of pregnancy have worse morbidity/mortality outcomes compared with those who had normotensive pregnancy. Finally, although the majority of guidelines recommend similar approaches in antihypertensive therapy in women and men, providers are encouraged to individualize treatment, as there are significant differences between sexes in the adverse effect profiles associated with antihypertensive medication classes. Women are more likely to experience adverse effects associated with some classes of antihypertensive medications. A personalized approach is needed to choose the ideal therapy that effectively lowers BP, prevents CVD, and minimizes adverse effects in women.

Disclosures

None.

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Hypertension in Women: Recent Advances and Lingering Questions

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HYPERTENSION IN WOMEN: RECENT ADVANCES AND LINGERING QUESTIONS

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Table S1. Summary of Relevant Included Studies

Study (Author, year)	Aim	Major Inclusion/Exclusion Criteria	Study Type	Sample Size	Sample Characteristics	Primary Outcome
Wright et al. (2015) (SPRINT)	Determine an appropriate systolic blood pressure target to reduce cardiovascular morbidity and mortality in persons without diabetes	**Inclusion**: At least 50 years of age, systolic blood pressure of 130-180 mmHg, an increased risk of cardiovascular events **Exclusion**: Diabetes mellitus, prior stroke, or heart failure	RCT	3,332 women 6,029 men	**Mean age**: 68 years (women), 68 years (men) **Baseline mean blood pressure**: 140/78 mmHg	Myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes **Conclusion**: The intervention was stopped early due to a significantly lower rate of the primary composite end point in the intensive treatment group. No significant difference was identified between genders
Gueyffier et al. (1997) (INDANA)	To quantify the average treatment effect of antihypertensives (beta blockers and thiazide diuretics) in both sexes and to determine whether available data show significant differences in treatment effect between women and men	**Inclusion**: Individual patient data from RCTs evaluating antihypertensive treatment included in the INDANA database **Exclusion**: Data from the Australian therapeutic trial in mild hypertension were not included because separate outcomes were not available without censoring bias. Data from the Veterans Administration and National Heart, Lung, and Blood Institute feasibility trial were not available in the INDANA database.	Subgroup meta-analysis (7 RCTs included)	20,802 women 19,975 men	**Age range**: 30-72 years **Baseline blood pressure range**: 159-196/77-104 mmHg	Fatal strokes, fatal and non-fatal strokes, fatal coronary events, fatal and non-fatal major coronary events, cardiovascular related mortality, major cardiovascular events **Conclusion**: Treatment benefit (relative risk reduction) did not differ between genders
Turnbull et al.	To quantify the effects	**Inclusion**: RCTs meeting	Meta-	87,349	**Mean age**: 63 years	Non-fatal stroke or death from

(2008) (BPLTTC)	of various antihypertensive regimens in each sex and determine if differences in treatment benefit exist between women and men	the following criteria: randomization of patients between a blood pressure lowering agent and control or randomization of patients between regimens based on different classes of blood pressure lowering drug and a minimum of 1000 patient-years planned follow up in the randomized group	analysis (31 RCTs included)	women 103,268 men	(women), 62 years (men) **Baseline blood pressure range**: 144-169/82-104 mmHg (women), 139-165/82-104 mmHg (men)	cerebrovascular disease, non-fatal myocardial infarction or deaths from coronary heart disease, heart failure causing death or requiring hospitalization, total major cardiovascular events, total cardiovascular deaths, total mortality **Conclusion**: All treatment regimens provided similar blood pressure reduction and similar protection against major cardiovascular disease events in both sexes
Furberg et al. (2002) (ALLHAT)	To determine whether a calcium channel blocker or angiotensin-converting enzyme inhibitor lowers the incidence of coronary heart disease or other cardiovascular disease events compared to treatment with a diuretic	**Inclusion**: At least 55 years of age, stage 1 or 2 hypertension, at least 1 additional risk factor for coronary heart disease events **Exclusion**: History of hospitalized or treated symptomatic heart failure and/or known left ventricular ejection fraction less than 35%	RCT	15,638 women 17,719 men	**Mean age**: 67 years **Baseline blood pressure range**: 145-156/84-90 mmHg	Fatal coronary heart disease or non-fatal myocardial infarction **Conclusion**: No difference in the primary outcome among treatment groups
Yamal et al. (2014) (ALLHAT)	To report stroke outcomes in ALLHAT participants	**Inclusion**: At least 55 years of age, stage 1 or 2 hypertension, at least 1 additional risk factor for coronary heart disease	RCT	15,638 women 17,719 men	**Mean age**: 67 years **Baseline blood pressure range**: 145-156/84-90	Stroke outcomes in participants in-trial and during post-trial passive surveillance period **Conclusion**: Among women,

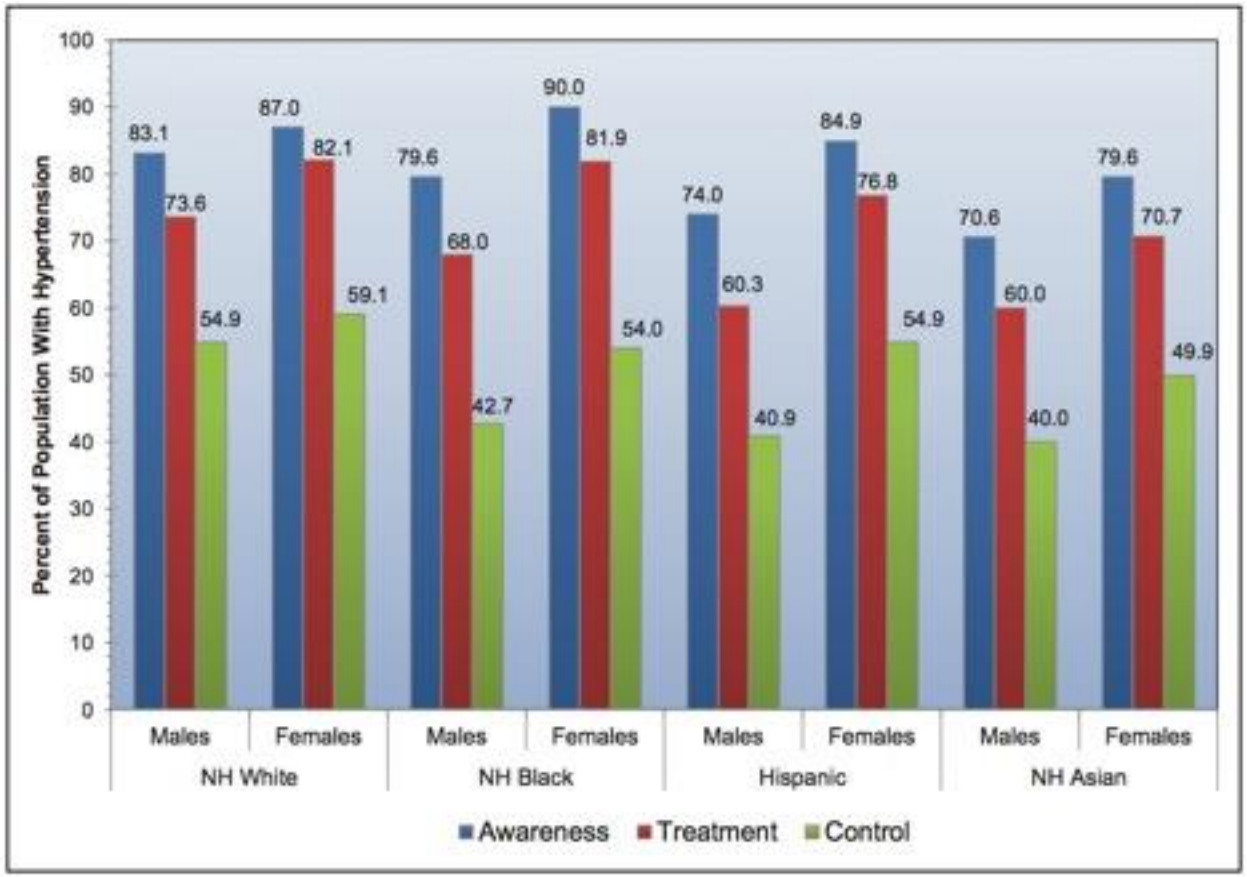
		events **Exclusion**: History of hospitalized or treated symptomatic heart failure and/or known left ventricular ejection fraction less than 35%			mmHg	but not men, lisinopril was less effective in preventing strokes than amlodipine or chlorthalidone; these differences were not seen at the end of the post-trial period
Oparil et al. (2013) (ALLHAT)	To determine whether lisinopril or amlodipine is superior to chlorthalidone in reducing cardiovascular disease incidence in sex subgroups	**Inclusion**: At least 55 years of age, stage 1 or 2 hypertension, at least 1 additional risk factor for coronary heart disease events **Exclusion**: History of hospitalized or treated symptomatic heart failure and/or known left ventricular ejection fraction less than 35%	RCT	15,638 women 17,719 men	**Mean age**: 67 years **Baseline blood pressure range**: 145-156/84-90 mmHg	Fatal coronary heart disease or non-fatal myocardial infarction. **Conclusion**: No differences in rates of the primary outcomes were seen between genders.
Zanchetti et al. (2006) (VALUE)	To perform a pre-specified subgroup analysis of the original VALUE cohort that included sex	**Inclusion**: At least 50 years of age, treated or untreated hypertension, predefined combinations of cardiovascular risk factors and cardiovascular disease **Exclusion**: Renal artery stenosis, acute myocardial infarction, congestive heart failure requiring angiotensin converting enzyme inhibitor	RCT	6,468 women 8,777 men	**Mean age**: 67 years **Baseline mean blood pressure**: 155/87 mmHg	Cardiac morbidity and mortality **Conclusion**: Higher cardiovascular morbidity/mortality with valsartan than amlodipine in women, but not in men
Os et al. (2008) (LIFE)	Post-hoc analysis from the LIFE study evaluating losartan	**Inclusion**: Aged 55-80 years with treated or untreated hypertension and left	RCT	4,963 women 4,230	**Mean age**: 68 years (women), 66 years (men)	Cardiovascular death, stroke, and myocardial infarction.

	versus atenolol therapy on the primary composite end point by sex	ventricular hypertrophy on electrocardiogram **Exclusion**: Secondary hypertension, myocardial infarction or stroke within 6 months, angina requiring beta blocker or calcium channel blocker treatment, left ventricular ejection fraction 40% or less, disorders requiring treatment with angiotensin receptor blocker, beta blocker, hydrochlorothiazide, or angiotensin converting enzyme inhibitor		men	**Baseline mean blood pressure**: 175/97 mmHg (women), 173/99 mmHg (men)	**Conclusion**: Women, but not men, in the losartan group had significant reductions in the primary end points. These treatment effects occurred in the absence of major differences in blood pressure control
Magee et al. (2015) (CHIPS)	To assess the effects of less-tight control (target diastolic blood pressure 100 mmHg) of hypertension during pregnancy compared to tight control (target diastolic blood pressure 85 mmHg)	**Inclusion**: Women with nonsevere, nonproteinuric preexisting hypertension or gestational hypertension, diastolic blood pressure of 90-105 mmHg if not on antihypertensives, diastolic blood pressure 85-105 mmHg if on antihypertensives **Exclusion**: Systolic blood pressure of 160 mmHg or higher, proteinuria	RCT	987 women	**Maternal age at expected date of delivery**: 34 years (both less and tight control groups) **Baseline mean blood pressure**: 140/92 mmHg	Pregnancy loss or high-level neonatal care for more than 48 hours during the first 28 postnatal days **Conclusion**: No significant differences were seen between the two groups with respect to the primary endpoint

CHAP (Ongoing trial)	To evaluate whether blood pressure treatment during pregnancy to a target recommended for non-pregnant reproductive age women is safe and effective.	**Inclusion**: Pregnant women with new or untreated chronic hypertension, women with known chronic hypertension on monotherapy **Exclusion**: Systolic blood pressures prior to randomization ≥160 mmHg, diastolic blood pressure prior to randomization ≥105 mmHg, receiving >1 antihypertensive	RCT	Currently in progress	Currently in progress	Fetal or neonatal death up to 2 weeks, preeclampsia with severe features, placental abruption, indicated preterm birth <35 weeks (not due to spontaneous preterm labor or membrane rupture), or small for gestational age

FIGURE S1.

Extent of Awareness, Treatment, and Control of High Blood Pressure by Race/Ethnicity and Sex (NHANES 2011-2014)



Extent of awareness, treatment, and control of high blood pressure by race/ethnicity and sex (NHANES 2011–2014). Hypertension is defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, or if the subject said "yes" to taking antihypertensive

medication. NH indicates non-Hispanic; and NHANES, National Health and Nutrition Examination Survey. Source: National Center for Health Statistics and National Heart, Lung, and Blood Institute.