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REVIEW SERIES

Management of hypertension in women

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A gender-specific approach to cardiovascular (CV) diseases has been practiced for decades, although not always to the advantage of women. Based on population data showing that women are at lower risk for CV events than men female gender has generally been regarded as a protective factor for CV disease. Unfortunately, CV risk assessment has therefore received less attention in women. Despite the lower absolute risk of CV events in women compared with age-matched men, the majority of women die from CV diseases. In absolute numbers, since 1984, more women than men died of CV disease each year. Most CV events occur in women with known traditional CV risk factors. Improving risk factor management in women of all ages therefore yields an enormous potential to reduce CV morbidity and mortality in the population. Aside from smoking cessation, hypertension (HTN) control is the single most important intervention to reduce the risk of future CV events in women. This review highlights peculiarities of HTN as they pertain to women, and points out where diagnosis and management of HTN may require a gender-specific focus.
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HTN AS A CV RISK FACTOR

Hypertension (HTN) is a significant risk factor for cardiovascular (CV) disease in both women and men. There is a continuous association between higher levels of systolic and diastolic blood pressure (BP), and CV morbidity and mortality.[1] For every 20-mm Hg systolic or 10-mm Hg diastolic increase in BP, there is a doubling of mortality from both coronary heart disease (CHD) and stroke in people between the ages of 40 and 89 years.[2] The increase in relative risk (RR) of CV mortality for any given increase in BP is much more pronounced in younger individuals, whereas the absolute risk at any given BP is higher in the older population. Consequently, HTN is associated with shorter overall life expectancy and shorter life expectancy free of CV disease.[3] Total life expectancy is an estimated 4.9 years longer for normotensive women compared with hypertensive women at 50 years of age.[4] Even though for vascular mortality as a whole, gender is of little relevance to the age-specific hazard ratios associated with a given difference in usual BP, some trends in gender difference have been observed. While the age-specific associations of stroke mortality with BP appear to be slightly less extreme for women than for men, the age-specific associations of CHD mortality with BP are more profound in women than in men, albeit not significantly.[2]

The Chicago Heart Association study, which was conducted in the 1960s and 1970s, suggested that elevated BP has a stronger impact on CHD mortality in women than in men.[5] Additionally, long-term follow-up data from the Chicago Heart Association study indicated that a low CV risk profile was associated with lower long-term CV and all-cause mortality in young women.[6] Importantly, CV events rarely occur in women without CV risk factors. Among women with CHD, 85% have at least 1 of the 4 traditional risk factors.[7] Interestingly, in this study the prevalence for all risk factors except cigarette smoking was significantly higher in women than in men. Therefore, reduction in the prevalence of HTN has the potential to dramatically reduce the burden of CHD in women. In the Chicago Heart Association cohort, high BP was the most common major risk factor in women and independently increased the risk of CHD mortality (RR 3.17, 95% confidence interval (CI) 1.8–5.6).[8] The Reykjavik Study compared the impact of CV risk factors in 9681 women and 8888 men who underwent CV risk assessment from 1967 to 1991.[9] Compared with men, systolic BP was a stronger risk factor for women, as was left ventricular hypertrophy by ECG (women: hazard ratio 2.89, 95% CI 1.67–5.01; men: hazard ratio 1.11 (CI 0.86–1.43)).[9] Twenty-year follow-up data of the Healthy Women Study showed that premenopausal systolic BP was an independent predictor of vascular calcification 14.6 years later in the sample of 363 women.[10] Elevated systolic BP measured 5 years into menopause remained a significant predictor of aortic calcification.[10] Data from the Framingham Heart Study showed that even women and men with high-normal BP (130–139/85–89 mm Hg) at baseline had a higher incidence of CV disease at 10-year follow-up than those with optimal BP ($<$130/85 mm Hg).[11] These relationships persisted after adjustment for multiple CV risk factors. The rate of CV events was very low in women with optimal BP. As compared with optimal BP, high-normal BP was associated with a risk factor-adjusted hazard ratio for CV disease of 2.5 (95% CI 1.6–4.1) among women and 1.6 (95% CI 1.1–2.2) among men. The Women's Health Study also confirmed that women's risk of a major CV event was lower at lower BP, without evidence of a threshold level.[12]

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Based on these observations the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) has introduced the category 'pre-hypertension' for those with BPs ranging from 120 to 139 mm Hg systolic and/or 80 to 89 mm Hg diastolic.[13] This new designation was intended to identify individuals in whom early intervention by adoption of a healthy lifestyle could reduce BP, decrease the rate of progression of BP to hypertensive levels with age or prevent HTN entirely. The main goal of antihypertensive treatment is prevention of CV morbidity and mortality, including end-organ damage and microvascular complications in various organ systems. HTN in the elderly is particularly complex and affects women more than men.[13–15] Not only does it appear to be under-diagnosed in general and particularly among women, it also remains undertreated.[14] Epidemiologic population studies have suggested that lowering BP, while reducing risks of stroke and vascular complications, might increase mortality or adverse events among the elderly ($\geqslant$80 years of age).[16] These observations were particularly striking in older men.[17] After adjustment for baseline BP, a decrease in diastolic pressure of $\geqslant$5 mm Hg was associated with higher all-cause mortality.[17] In women, a decrease in either diastolic or systolic BP was not associated with poorer survival. Among women aged 65–84 years, the hazard of death significantly increased with increase in systolic BP, whereas this relationship was not seen in women aged 85 years and older.[17]

The Hypertension in the Very Elderly Trial (HYVET) evaluated 3845 patients aged 80 years or older (60% women) with sustained systolic BPs of 160 mm Hg. Compared with placebo, active treatment reduced the mean systolic and diastolic BPs by 15.0 and 6.1 mm Hg, respectively, and significantly reduced the risk of death from stroke and death from any cause.[18] The trial was stopped prematurely because of these compelling findings, and forms the basis of the ACCF/AHA 2011 Expert Consensus Document on Hypertension in the Elderly.[14] Unlike previous guidelines for all adults, there is limited evidence in the elderly to support a systolic BP value of 140 mm Hg as a diagnostic and therapeutic threshold. Among octogenarians, HYVET data suggest a systolic BP of 150 mm Hg as the diagnostic cut-off value and the treatment target.[18]

INCIDENCE AND PREVALENCE OF HTN IN WOMEN

Most of our knowledge regarding the prevalence and control of HTN in the United States during the past decades is based on data from The National Health and Nutrition Examination Survey (NHANES), which was designed to monitor the health and nutritional status of the US population.[19,20] Whereas NHANES-III reported that the prevalence of HTN had declined in the time period from 1976–1980 to 1988–1991, the NHANES survey from 1999–2000 reported an increase in HTN prevalence. In 1999–2000, 28.7% of NHANES participants had HTN, an increase of 3.7% from 1988 to 1991. HTN prevalence was highest in non-Hispanic Blacks (33.5%), increased with age (65.4% among those aged $\geqslant$60 years) and tended to be higher in women (30.1%). More recent data from NHANES 2005 to 2006 illustrate that the overall age-adjusted prevalence varied only slightly between 28 and 30% during the period 1999–2006. Analysis of NHANES data regarding US trends in prevalence, awareness, treatment and control of HTN from 1988 to 2008 was reported very recently.[21] Prevalence of HTN increased over time in men but not women and overall was not significantly different between men and women. HTN awareness increased with time in men but not women; however, it was greater in women than men. HTN treatment increased with time in both women and men, and was significantly higher in women than in men. The proportion of patients treated and whose HTN was controlled increased in men but only marginally in women (P=0.05), and was greater in men *vs.* women (P=0.02). In summary, the prevalence of HTN is nearly equal between women and men, averaging 30–40% in Blacks and 20–30% in Whites.[22] Even though BP control improved with time in women and men, overall fewer women than men had controlled BP levels despite treatment, which is particularly striking in the elderly (Figure 1a). Additionally, HTN becomes more prevalent in women among elderly individuals.[3] Approximately 80% of women over the age of 70 years have HTN.[3] During early adulthood women have lower systolic BP than men, but after the age of 60 years the opposite is the case (Figure 1b).[15] Decreased survival in older hypertensive men could explain this higher prevalence in older women. As women outnumber men in the population, there are more hypertensive women than men. Diastolic

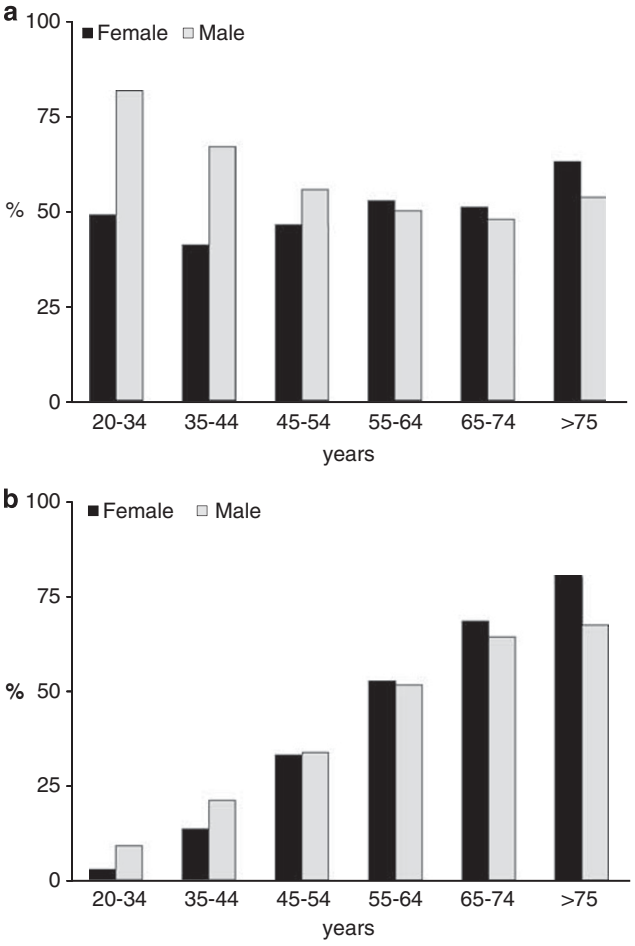

Figure 1 HTN control and prevalence among persons 20 years of age and over: United States, selected years 1988–1994 through 2005–2008. (**a**) Uncontrolled HTN among persons with diagnosed HTN. Uncontrolled HTN is defined as measured systolic BP of at least 140 mm Hg or diastolic BP of at least 90 mm Hg, among those with measured high BP or reporting taking antihypertensive medication. (**b**) Prevalence of HTN. HTN is defined as having measured high BP ($\geqslant$140/90 mm Hg) and/or taking antihypertensive medication. Those taking antihypertensive medication may not have measured high BP but are still classified as having HTN. The data are based on interviews and physical examinations of a sample of the civilian non-institutionalized population. Pregnant women excluded. Source: CDC/NCHS, National Health and Nutrition Examination Survey. Available from: http://www.cdc.gov/nchs/hus.htm (accessed 24June 2011). BP, blood pressure; HTN, hypertension.

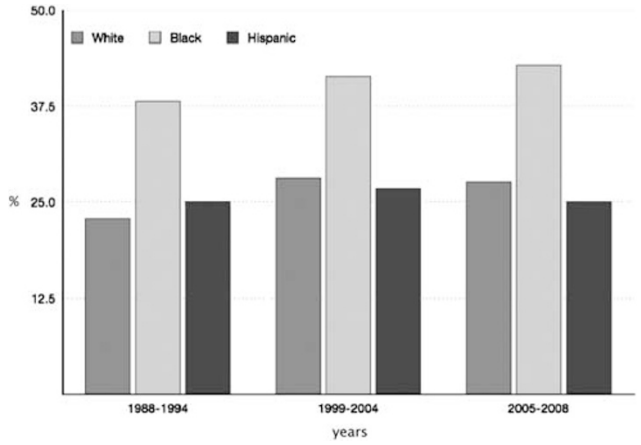

Figure 2 Age-adjusted prevalence trends for high BP in women ⩾20 years of age by race/ethnicity and survey (National Health and Nutrition Examination Survey: 1988–1994, 1999–2004 and 2005–2008). Source: National Center for Health Statistics and National Heart, Lung, and Blood Institute. Adapted from Roger *et al.* (2011). BP, blood pressure.

BP tends to be marginally lower in women than men regardless of age. Even though >70% of women with HTN are aware of their diagnosis, less than one-third achieve adequate BP control.[15] Overall, 28% of adults have pre-hypertension. The prevalence of pre-hypertension is significantly higher in men compared with women (34 and 22%, respectively).[22] Older NHANES data have previously shown that there were only minimal differences in the incidence of HTN between women and men for all age groups, but the incidence rates of HTN for Blacks were about twice the rates for Whites for almost every age–sex group.[23] Strikingly higher prevalence rates in Black women were noted overall and for each older age group; this remains present in recent data (Figure 2).[3,23]

For the subgroup of adults younger than 60 years, women (87%) are more likely than men (63%) to be aware of their HTN and seek treatment for it.[22] Whereas awareness of HTN increased with age in men, it did not change in women, so that there was no difference in awareness among hypertensive men (84%) and women (81%) aged 60 years and older. Among hypertensives aged 18–59 years, men (47%) were less likely to be treated compared with women (74%), but there was no difference in treatment between hypertensive men (78%) and women (75%) aged 60 years and older. Among treated hypertensives younger than 60 years, about 70% of patients have controlled BP and there was no significant gender difference. Success in HTN control among treated hypertensives was significantly higher in men aged 60 years and older than in women in the same age group (64% for men and 53% for women).

Pathophysiologic reasons for BP discrepancies between the sexes remain largely speculative at this time. Some data imply that menopause contributes to the development of HTN in women. Evidence from animal studies suggests a significant impact of sex hormones on renal salt handling because gonadectomy resulted in an accelerated development of salt-sensitive HTN in female animals.[24] While the BP response of premenopausal normotensive women is insensitive to dietary salt intake, BP in postmenopausal women becomes salt-sensitive.[25] This may be an explanation for the good response to dietary interventions such as sodium restriction in this patient group.[26] Menopause escalates CHD risk three-fold and thereby erodes the female protection from CV morbidity and mortality as noted in Framingham data.[27] While women and men share the same major risk factors for CHD, women experience a lower absolute risk. However, high ratios of total/high-density lipoprotein cholesterol level ratios, left ventricular hypertrophy and diabetes tend to eliminate the female advantage.[28] Despite these observations it remains controversial if hormonal factors are the causal factor for the increasing prevalence of HTN in menopausal women. Menopausal women not only seem to have higher BP values, but also a worse risk profile than premenopausal women, and some data suggest that this is due to their older age rather than altered hormonal state.[29] As well, data on female participants in the Framingham Heart Study show that a more adverse coronary risk profile before menopause is associated with an earlier age at menopause.[30] In the group of women with increasing levels of systolic BP during the premenopausal period, each 10-mm Hg increase was associated with a 3.45-year earlier menopause (95% CI −5.42 to −1.49) when adjusted for smoking. Among hypertensive women in the NHANES 1999–2004 cohort, the prevalence of uncontrolled BP, central obesity, low high-density lipoprotein and elevated $HbA1_c$ level did not differ significantly by menopause status after adjusting for age and race.[31] However, postmenopausal women had a significantly higher prevalence of elevated total cholesterol even after adjusting for age and race, but a lower proportion of current smoking. A sub-study of the Study of Women's Health Across the Nation examined the influence of aging and menopause on CV risk factors in 1054 women prospectively.[32] Only certain lipid parameters such as total cholesterol, low-density lipoprotein cholesterol, apolipoprotein-B and high-density lipoprotein demonstrated changes that appeared to be influenced by menopause, whereas other risk factors, including BP, changed in a linear pattern consistent with chronologic aging. Importantly, the investigators did not find any heterogeneity by ethnic group. Thus, CV risk factors do indeed change around the time of menopause; some related to chronologic aging and some related to the menopausal transition itself.[33] Among women with coronary risk factors undergoing coronary angiography for suspected myocardial ischemia, 20% of premenopausal women had angiographic CAD *vs.* 31% of postmenopausal women.[34] Interestingly, high systolic BP imparts a higher risk in premenopausal *vs.* postmenopausal women, suggesting that identification of HTN in premenopausal women should warrant additional risk factor evaluation and treatment. In the Royal College of General Practitioners' oral contraception study smoking (RR 4.3, CI 2.6–6.9) was the most important independent risk factor for a subsequent myocardial infarction in young and middle-aged women, followed by diabetes (RR 6.9, CI 1.1–43.8), preeclampsia (RR 2.8, CI 1.7–4.8) and HTN (RR 2.4, CI 1.4–4.1).[35]

CV RISK PROFILE AND HTN

CV risk factors

The lifetime risk of developing HTN for middle-aged and elderly women and men is 90%, indicating a vast public health burden.[36] The importance of risk factors for the development of essential HTN in women was evaluated in a prospective cohort study of 83 882 adult (age 27–44 years) women in the second Nurses' Health Study.[26] These women did not have a history of HTN, CV disease or diabetes at baseline. Six modifiable lifestyle and dietary factors were identified that reduced the risk of developing HTN. These were a body mass index of less than 25 $kg\,m^{-2}$; a daily mean of 30 min of vigorous exercise; a high score on the Dietary Approaches to Stop Hypertension (DASH) diet based on responses to a food frequency questionnaire; modest alcohol intake up to 10 $g\,day^{-1}$; use of non-narcotic analgesics less than once per week; and intake of 400 $\mu g\,day^{-1}$ or more of supplemental folic acid. All six risk factors were independently associated with lowering the risk of developing HTN during follow-up after adjusting for age, race, family history of HTN, smoking status

and use of oral contraceptives. Therefore, adopting low-risk dietary and lifestyle factors has the potential to prevent a large proportion of new-onset HTN occurring among young women. Comparing the gender-specific characteristics of people with diagnosed HTN in the NHANES 1999–2004 data, women were older, more likely to have a higher body mass index and be non-Hispanic Black, and less likely to be non-Hispanic White.[31] Furthermore, there was an increased prevalence of other CV risk factors, including central obesity, elevated total cholesterol and low high-density lipoprotein cholesterol levels, in elderly women. Although the absolute risk of CV events is lower in women than in men, the risk attributable to HTN may be greater in women than in men. The proportion of CV events preventable by BP control is 30–100% higher in women than in men.[37] Interestingly, nighttime compared with daytime BP was a stronger predictor of outcome, and RR increased more with nighttime BP elevation in women than in men. A 15-mm Hg increase in systolic BP increased the risk of CV disease by 56% in women compared with 32% in men. These data suggest that improving BP control in middle-aged women harbors enormous potential to improve CV outcomes. In a large cohort of women, cigarette smoking was modestly associated with an increased risk of developing HTN, with an effect that was strongest among women smoking at least 15 cigarettes per day.[38]

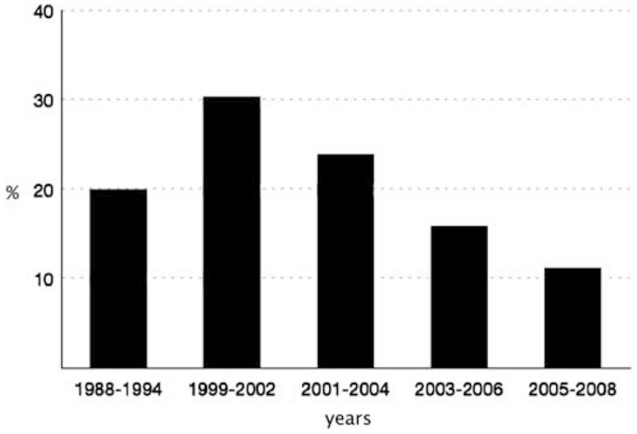

Figure 3 Sex hormone use in the past month, among women aged 45–64 years: United States, selected years 1988–1994 through 2005–2008. Primary indications for use were as contraceptives or for menopause and hot flashes. The data are based on a sample of the civilian non-institutionalized population. Source: CDC/NCHS, National Health and Nutrition Examination Survey. Available from: http://www.cdc.gov/nchs/hus.htm (accessed 24 June 2011).

Pregnancy and pregnancy complications

Pregnancy-associated HTN affects about 10% of all pregnancies and greatly increases the risks of maternal and fetal mortality. According to the American College of Obstetrics and Gynecology and the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, HTN during pregnancy can be divided into the following groups: chronic HTN, gestational HTN, preeclampsia–eclampsia and preeclampsia–eclampsia superimposed on chronic HTN. These pregnancy-associated hypertensive disorders have been extensively reviewed elsewhere.[39] It is important to remember the physiologic changes accompanying pregnancy. Significant plasma volume expansion is common and frequently associated with a decrease in systemic vascular resistance, which leads to an increased cardiac output as well as a fall in mean arterial pressure.[40] In women with mild pre-existing HTN these changes can obscure an early diagnosis of HTN. Women with pre-existing HTN are more likely to have complications during pregnancy than those with normal BP.[41] Another important aspect about preeclampsia is that it is an emerging risk factor for future CV events. Preeclampsia is defined by the development of HTN and proteinuria after 20-weeks gestation in a previously normotensive woman. Recent data from a systematic review and meta-analysis strongly support the concept that a history of preeclampsia should be considered as a risk factor when evaluating risk of CV disease in women.[42] During a 14-year follow-up period the RRs for experiencing HTN, ischemic heart disease and stroke were 3.7, 2.2 and 1.8, respectively. The relationship between hypertensive pregnancy disorders and subsequent HTN was evaluated in a registry-based cohort study in Denmark.[43] The risk of subsequent HTN was increased 5.3-fold after gestational HTN, 3.6-fold after mild preeclampsia and 6.1-fold after severe preeclampsia, confirming the strong association of hypertensive pregnancy disorders and the development of subsequent HTN. Therefore, it is important to stress the need for annual BP surveillance of these women and introduce aggressive preventive interventions regarding other CV risk factors.

Hormone replacement therapy

There are conflicting data regarding the impact of hormone replacement therapy (HRT) on the BP of menopausal women. The Postmenopausal Estrogen/Progestin Interventions Trial evaluated the effects of estrogen or estrogen/progestin regimens on CV risk factors in healthy postmenopausal women and found no detectable effect on BP.[44] A study of hypertensive women treated with HRT showed no impact on BP after 12 months of follow-up.[45] In the Women's Health Initiative (WHI) women on HRT had a higher prevalence of HTN than did women on placebo after adjustment for CV risk factors.[46] There was a slight but significant increase from baseline in systolic BP among women randomized to conjugated equine estrogen and medroxyprogesterone acetate compared with a placebo group.[47] A similar small increase in systolic BP was reported for unopposed estrogen treatment compared with placebo among women enrolled in the estrogen-only trial of WHI.[48] In 161 hypertensive menopausal women, HRT use did not have an adverse gross effect on BP, but there may have been an increased need for antihypertensive therapy during the 36-month follow-up period.[49] Overall, changes in BP owing to HRT are likely to be modest and should not preclude hormone use in normotensive or hypertensive postmenopausal women if menopausal symptoms are severe.[50] It is generally recommended that HRT should be used at the lowest effective dose for the shortest possible duration. A few women may experience a rise in BP possibly attributable to estrogen therapy.[51] Increased angiotensinogen generation has been proposed as a potential mechanism that links estrogen therapy to HTN. The use of sex hormones among women aged 45–64 years has fluctuated significantly over the past years, and recent data indicate that about 11% of these women take sex hormones (Figure 3). It is recommended that all women treated with HRT have their BP monitored regularly and it may be prudent to consider using preparations with minimal effects on hepatic production of angiotensinogen (transdermal estrogen) if BP control becomes difficult.[52]

Oral contraceptives

Oral contraceptive use can be a cause of HTN in younger women, with high BP 2–3 times more common in women taking oral contraceptives.[13] The Nurses' Health Study of more than 60 000 women showed that the adjusted RR of development of HTN was 1.8 (CI 1.5–2.3) for current users of oral contraceptives compared with women

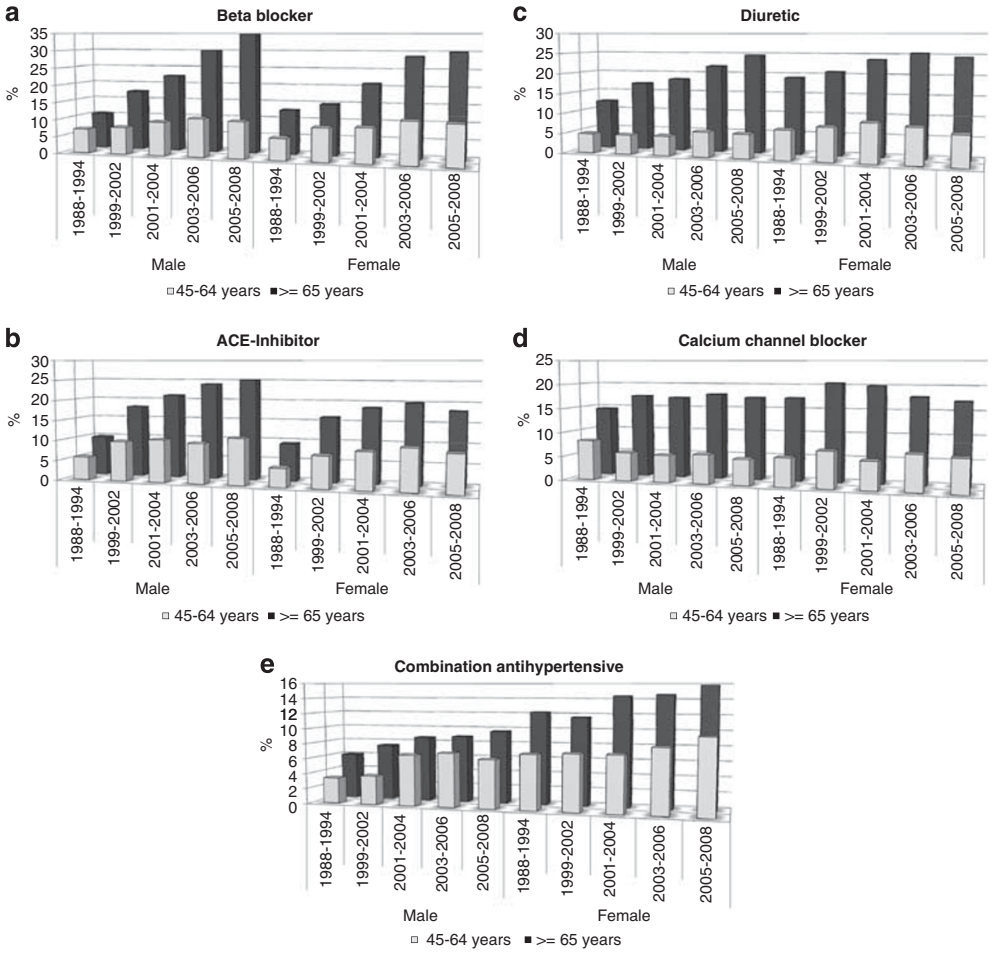

Figure 4 (**a**–**e**) Selected prescription drug classes used in the past month, by sex and age: United States, selected years 1988–1994 through 2005–2008. Primary indications for use were high BP or heart disease. The data are based on a sample of the civilian non-institutionalized population. Source: CDC/NCHS, National Health and Nutrition Examination Survey. Available from: http://www.cdc.gov/nchs/hus.htm (accessed 24 June 2011). BP, blood pressure.

who never used them. The absolute risk however is extremely low, with only 41.5 cases per 10 000 person-years attributed to oral contraceptive use.[53] BP response to combined oral contraceptives appears highly variable and only a small minority of women may experience the onset of frank HTN, which usually resolves with withdrawal of the contraceptive and changing to other forms of contraception. In the Royal College of General Practitioners' oral contraception study, current use of oral contraceptives increased the risk of a subsequent myocardial infarction only in women who also smoked.[35]

BENEFITS OF ANTIHYPERTENSIVE THERAPIES

Population research has proven that BP control effectively reduces CV morbidity and mortality. Data from the Framingham Heart Study suggest that the increasing use of antihypertensive medications in patients with HTN has lowered the incidence of left ventricular hypertrophy, a major risk factor for CV disease.[54] From 1950 to 1989, the rate of use of antihypertensive medications increased from 2.3 to 24.6% among men and from 5.7 to 27.7% among women.[54] In the same time period the age-adjusted prevalence of systolic BP of at least 160 mm Hg or diastolic BP of at least 100 mm Hg declined from 18.5 to 9.2% among men and from 28.0 to 7.7% among women.[55] NHANES data show the trends in the use of selected antihypertensives (Figures 4a–e). Control of isolated HTN in the Systolic Hypertension in the Elderly Program (SHEP) reduced CV events in both genders. In SHEP, 57% of the study cohort were women.[56] Given the limited number of women enrolled in many other antihypertensive treatment trials, there is limited information regarding gender-specific outcome, particularly whether women respond differently to specific antihypertensive therapies than do men.[57] To date the need for and the effects of BP control in women have not been studied as extensively as in men.[58] Early clinical trials of treating mild-to-moderate HTN were primarily conducted on a middle-aged male population, and most decisions regarding hypertensive treatment for women prior to the 1990s were based on data obtained from these trials.[59] Within the last two decades, women have been included in major outcome trials of antihypertensive treatment, which have generally shown comparable benefit in both women and men.[60] Therefore, treatment recommendations remain the same for women and men. The Heart Outcomes Prevention Evaluation study evaluated 9297 patients aged 55 years or older at high CV risk, of whom 27% were women.[61] Treatment with ramipril reduced the rates of death, myocardial infarction, stroke and heart failure in the total study population, and this beneficial effect on the composite outcome was also consistently observed among the women in the study. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial included 33 357 participants aged 55 years or older with HTN and at least one other CHD risk factor.[62] The study findings were consistent in the subgroup of

women, who comprised 47% of the study population, suggesting that women derive substantial CV protection from antihypertensive therapy. A meta-analysis suggested comparable treatment effects for women and men in RR reduction by antihypertensive therapy.[63] The Hypertension Optimal Treatment trial evaluated intensive BP lowering in 18 790 patients with diagnosed HTN, 47% of whom were female.[64] This study indicated that intensive BP lowering was associated with a low rate of CV events. Improved CV outcomes in patients with lower BPs and the absence of a threshold effect had led to the assumption that the lower the BP the better. However, data from the ACCORD trial with 48% of the study population being women showed that tight control of systolic BP among high-risk patients with diabetes was not associated with improved CV outcomes compared with usual BP control.[65] Observational data from 6400 diabetics (54% women) even showed a trend toward harm with aggressive BP control, suggesting a J-shaped curve for the relationship between systolic BP and mortality.[66]

It has been hypothesized that inter-individual BP variability may have a greater impact on outcome than a mean systolic BP and that treatments that reduce BP variability confer the greatest CV risk reduction.[67] While this needs to be evaluated in future research, the BP goal specified in current guidelines is effective for primary and secondary prevention of CV disease.[68] Despite the fact that this recommendation uniformly applies to women and men alike, some evidence exists for gender differences in both beneficial and adverse effects of treatment.[69] The Individual Data Analysis of Antihypertensive intervention trials group assessed the benefit of antihypertensive treatment in women by pooling data from several randomized, controlled trials.[55] HTN treatment lowered the risk of CV morbidity and mortality in women aged 55 years and older and in African-American women of all ages. Although RR reductions for CV events were similar for younger and older women, the number needed to treat for younger women is at least four times higher. The Blood Pressure Lowering Treatment Trialists' Collaboration examined if there are differences in the proportional benefits of antihypertensive treatment between women and men.[70] Thirty-one randomized trials with 103 268 men and 87 349 women were analyzed. All of the antihypertensive regimens studied provided similar protection against major CV events in women and men. For all treatment comparisons the differences in follow-up BP levels between randomized groups were highly comparable between women and men (Figure 5). The authors concluded that differences in CV risks between sexes are unlikely to reflect differences in response to BP-lowering treatments, and that other factors related to awareness, detection and management of HTN are more likely to account for these findings.[71] These results lend strong support to current BP guidelines, which make no specific recommendations for different BP targets, or for management with particular classes of drugs based on a patient's sex. In regard to pharmacotherapy, the ACCF/AHA 2011 Expert Consensus Document on Hypertension in the Elderly points out that there is no evidence that elderly women respond differently than elderly men to antihypertensive drugs.[14] However, BP control is more difficult to achieve in elderly women. Framingham data showed an age-related decrease in BP control rates that was more pronounced in women than men.[15] Gender differences in the pattern of antihypertensive medications prescribed were noted in this cohort: 38% of women but only 23% of men were taking thiazide diuretics. Whether the age-related decline in BP control among women is related to inadequate intensity of treatment, inappropriate drug choices, lack of compliance, true treatment resistance because of biological factors or to other factors is unclear.

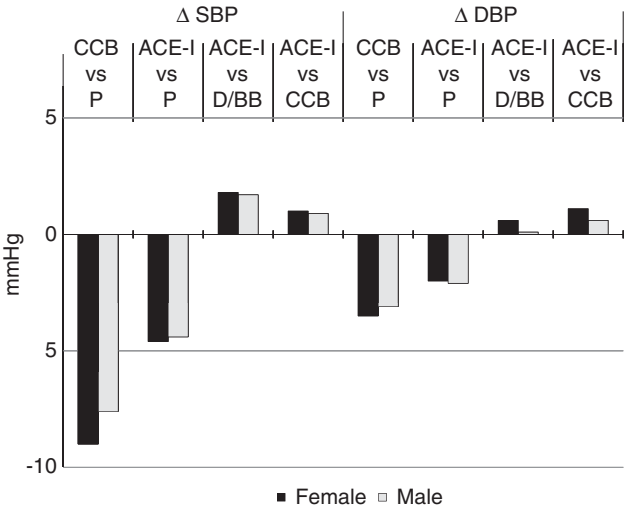

Figure 5 Follow-up BP differences between randomized groups in subgroups of women and men. The Blood Pressure Lowering Treatment Trialists' Collaboration performed a series of prospective overviews of randomized trials investigating the effects of a range of different BP-lowering regimens on CV events. Separate overviews were conducted within the broad group of trials comparing an active agent and a control, and within the broad group of trials comparing different active agents. ACE-I, ACE inhibitor; BP, blood pressure; CCB, calcium channel blocker; CV, cardiovascular; D/BB, diuretic or β-blocker; P, placebo. Adapted from Turnbull *et al.* (2008).

EFFICACY AND PRACTICE PATTERNS OF ELEVATED BP TREATMENT

Multiple factors contribute to insufficient BP control, including resistance to therapy. While NHANES-III data up to 1994 pointed out that the most commonly uncontrolled patients were elderly, male, Black and those not seen by a physician in the last year, more recent data show poorer BP control in women.[72] Between 1988–1994 and 1999–2004, HTN control increased for men from 39 to 51% but remained unchanged for women (35–37%).[73] In addition, women aged 70 and older were significantly less aware and less treated. Having BP measured within 6 months was significantly associated with greater awareness, greater treatment in men and women, and greater control in women. A history of diabetes mellitus or chronic kidney disease was significantly associated with less HTN control. In an analysis of HTN prevalence, treatment and control in NHANES (2003–2004) data, the overall prevalence of HTN was 32.2% in men and 30.5% in women.[74] Women had similar treatment rates (69.9%) as men (67.2%), but control rates tended to be lower in women (49.4%) than in men (56.5%). Data from 12 064 adult visits with primary care providers were analyzed in the publicly available 2005 National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey.[75] Women were less likely than men to have controlled HTN (54.0 *vs.* 58.7%, $P<0.02$). There was no statistically significant difference by gender in the number of medications used. Women less commonly received an angiotensin-converting enzyme inhibitor (ACE-I) (20.9 *vs.* 28.7%, $P<0.001$) and more commonly received diuretics (20.9 *vs.* 16.9%, $P=0.05$) in the treatment of HTN. These observations were made despite the fact that women in this sample had more clinician visits per year than men. No significant differences were found in the use of any BP medication or initiation of new therapy for patients with uncontrolled HTN as a function of gender. Thus, clinical inertia is a recognized barrier to effective care in both women and men.

HTN awareness and treatment are higher in women than in men, and the proportion of patients treated and controlled was higher in men than in women.[21] BP control rates in men 60, 60–79 and 80 years of age were 38%, 36% and 38%, respectively; for women in the same age groups, they were 38%, 28% and 23%, respectively.[3,15] Therefore, the most recent NHANES data suggest that raising HTN awareness and treatment is important for men, whereas controlling HTN in patients who are treated is a higher priority for women. In summary, HTN in women is not being treated aggressively enough because a large proportion, especially older women, does not have sufficient BP control. The WHI data showed that hypertensive women who had seen a healthcare provider in the past year were approximately four times more likely to be on drug treatment as those who had not seen a provider, although this was not associated with a better rate of BP control.[46] Among treated hypertensive women in the WHI, older age, non-White race and diabetes were associated with poor BP control. Surprisingly, in WHI HRT, educational level, activity level, alcohol intake, having seen a healthcare provider in the past year and the number of antihypertensive drug classes taken were not related to HTN control.[50]

ANTIHYPERTENSIVE TREATMENT FOR WOMEN

Guidelines recommend that lifestyle modification is an integral part of BP management and may even be sufficient in select mild cases. The INTERSALT Study investigated systematically the relationship between urinary sodium excretion and BP in over 10 000 people, half of whom were women.[76] The results suggested that lower average sodium intake reduces BP. More than moderate alcohol use and obesity were also identified as contributors to HTN. A re-analysis of the INTERSALT data concluded that reducing sodium intake by about 6 g day^{-1} could lower systolic BP by 3–6 mm Hg.[77] Population studies indicate that such improvements in average systolic pressure levels could substantially reduce the rates of major CV events and mortality. A Cochrane Review however could not show that simply advising patients to reduce sodium intake was associated with fewer CV events even though a beneficial effect on BP was observed.[78] In addition to weight reduction, physical activity, dietary sodium reduction and moderation of alcohol consumption, JNC-7 endorses the DASH diet for patients with elevated BP.[13] The DASH study showed that certain dietary patterns may reduce BP independent of sodium intake, alcohol intake and body weight.[79] A diet rich in fruits, vegetables and low-fat dairy products, and with reduced saturated and total fat, lowered systolic BP by 5.5 mm Hg and diastolic BP by 3.0 mm Hg more than a control diet. A diet rich in fruits and vegetables without the dairy fat restriction also reduced BP, but to a lesser extent (3.1 mm Hg for systolic BP and 2.0 mm Hg for diastolic BP). Low potassium intake may have an important role in the genesis of high BP.[80] Increased potassium intake was therefore proposed as a recommendation for prevention and treatment of HTN, especially in those who are unable to reduce their intake of sodium. A recent study, however, provided no evidence to support dietary advice to increase potassium intake above usual in women and men with early stages of HTN.[81] The ENCORE Study, which included 144 people (67% women), extended the results of the initial DASH feeding trials. It was shown that the DASH diet produced significant reductions in BP compared with a typical American diet among unmedicated, overweight or obese women and men with high BP, and that weight loss and exercise combined with the DASH diet produced additional BP lowering.[82]

Concerning pharmacotherapy, the Blood Pressure Lowering Treatment Trialists' Collaboration provides convincing evidence that women respond to antihypertensive drugs similarly to men.[70] Gender continues to have an important role in individual risk assessment, but it need not otherwise influence decisions about the need for antihypertensive therapy, the intensity of BP reduction or the choice of drug class.[71] Yet, special considerations may dictate treatment choices for women. First-line treatment for a woman who develops HTN while taking oral contraceptives is stopping the oral contraceptive and switching to a different form of birth control. Stopping birth control pills in hypertensive women can reduce systolic BP by 15 mm Hg within 6 months.[83] ACE-I and angiotensin-receptor blockers are contraindicated for women who are or plan to become pregnant because of the risk of fetal developmental abnormalities. Thresholds to initiate BP-lowering treatment during pregnancy are 160 mm Hg systolic or 110 mm Hg diastolic. Below these thresholds, treatment must be individualized because current evidence does not support more aggressive medical interventions.[84] α-Methyldopa and dihydropyridine calcium channel blockers are among the recommended antihypertensives in this situation. A study of older hypertensive women showed no difference in the rates of adverse events or deleterious effects on quality of life between atenolol, diltiazem and enalapril, whereas the effect on BP reduction was comparable between these agents.[85] Thiazide diuretics are particularly useful in elderly women, because their use was associated with decreased risk of hip fracture probably by reduction of urinary calcium loss.[86] In addition, thiazides appear effective in reducing the risk of stroke in elderly women.[56] In the Treatment Of Mild Hypertension Study, the treatment-associated differences in blood chemistry values, lipoprotein levels, side effects, incidence of ECG abnormalities and risk of clinical events did not differ between the sexes.[87] The only significant sex-by-treatment interaction for quality of life was general health; men who were assigned to treatment with active medication had a greater improvement in this measure during follow-up than men who were assigned to placebo therapy, whereas the reverse was true for women. For other quality-of-life measures, active drug treatment was associated with improved quality of life compared with that observed with placebo therapy in both sexes. Interestingly, there was a trend toward fewer side effects in women on active drug treatment compared with women on placebo. Women were less likely than men to have their BP controlled with lifestyle intervention alone, possibly owing to smaller changes in lifestyle intervention parameters; however, women were also more likely than men to be receiving no antihypertensive medication at 48 months of follow-up. Women in the Losartan Intervention for Endpoint Reduction in Hypertension Study, who represented 54% of the total study population, had more total adverse events but fewer serious drug-related adverse events than men.[88] The treatment effect of losartan was consistent in women and men for all of the end points tested, with the exception of hospitalization for angina. In 6105 patients (30% women) BP lowering with an ACE-I reduced secondary stroke risk, with large absolute benefits across groups defined by age and gender.[89] 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.[90] ACE-I-induced cough is 2–3 times as common in women as in men. Furthermore, women are more likely to suffer from calcium channel blocker-related peripheral edema and minoxidil-induced hirsutism. Centrally acting agents, β-blockers and thiazide diuretics may sometimes be associated with sexual dysfunction in women, as well as in men. Combination therapy with multiple antihypertensives at sub-maximal dose may be more effective in BP control while reducing the incidence of side effects linked to higher doses of single drugs. In the WHI, 60% of women were receiving monotherapy, 30% were receiving two drugs and $<10\%$ were

Table 1 Top 10 key points

1. Hypertension is under-diagnosed and undertreated in women—fewer women than men have controlled BP levels despite more frequent treatment—isolated systolic HTN predominates in elderly women.
2. Elevated BP has a stronger impact on CHD mortality in women than in men.
3. The rate of CV events in women is very low when BP is optimal.
4. Reduction of HTN prevalence in women has the potential to dramatically reduce CHD burden in women.
5. Although >70% of women are aware of their HTN, less than one-third achieve adequate BP control.
6. Proportion of CV events preventable by BP control is 30–100% higher in women than men.
7. Issues specific to women: hypertensive disorders of pregnancy, hormone replacement therapy, oral contraceptives.
8. Women and men have comparable benefit of HTN treatment.
9. Women respond to antihypertensive drugs similarly to men.
10. Healthcare providers have to educate their women patients about the benefits of BP control.

receiving three or more drugs.[50] Further research is needed to develop more effective strategies for controlling HTN, particularly in elderly women.

In a survey of more than 12 000 US adults, difficulties in taking antihypertensive medication were reported by 28.4% of respondents.[91] While gender did not have an impact in this study, patient–provider factors appeared more important. The authors concluded that patient education about the benefits of treatment, about side effects and discerning ways to help patients remember to take their medications needed improvement. Algorithm-driven therapy may be more effective in achieving BP goals. The VALUE Trial, which included about 42% women, showed that, with adherence to a structured treatment algorithm, including dose titration of drugs and recommendations for add-on therapy, BP targets of 140 mm Hg could be achieved in the majority of patients.[92] Team-based care involving medical doctors, pharmacists and nurses combined with extensive patient education has been shown to be associated with improved BP control and may therefore be a promising approach.[93] The ACCF/AHA/AMA-PCPI 2011 Performance Measures for Adults with Coronary Artery Disease and Hypertension was recently updated.[94,95] These new measures address not only whether HTN is treated but also whether it is controlled. Improving patient adherence and self-management of treatment regimens may require a team approach. Healthcare professionals need to be aware of certain key issues of HTN in women (Table 1), and they need to educate their patients about their BP and engage them in shared decision making in order to improve medication adherence. Achieving BP control requires both clinicians and patients to fulfill their respective roles.

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