

Management of High Blood Pressure in Blacks An Update of the International Society on Hypertension in Blacks Consensus Statement

John M. Flack, Domenic A. Sica, George Bakris, Angela L. Brown, Keith C. Ferdinand, Richard H. Grimm, Jr, W. Dallas Hall, Wendell E. Jones, David S. Kountz, Janice P. Lea, Samar Nasser, Shawna D. Nesbitt, Elijah Saunders, Margaret Scisney-Matlock, Kenneth A. Jamerson, on behalf of the International Society on Hypertension in Blacks

Abstract—Since the first International Society on Hypertension in Blacks consensus statement on the “Management of High Blood Pressure in African American” in 2003, data from additional clinical trials have become available. We reviewed hypertension and cardiovascular disease prevention and treatment guidelines, pharmacological hypertension clinical end point trials, and blood pressure-lowering trials in blacks. Selected trials without significant black representation were considered. In this update, blacks with hypertension are divided into 2 risk strata, primary prevention, where elevated blood pressure without target organ damage, preclinical cardiovascular disease, or overt cardiovascular disease for whom blood pressure consistently <135/85 mm Hg is recommended, and secondary prevention, where elevated blood pressure with target organ damage, preclinical cardiovascular disease, and/or a history of cardiovascular disease, for whom blood pressure consistently <130/80 mm Hg is recommended. If blood pressure is ≤ 10 mm Hg above target levels, monotherapy with a diuretic or calcium channel blocker is preferred. When blood pressure is >15/10 mm Hg above target, 2-drug therapy is recommended, with either a calcium channel blocker plus a renin-angiotensin system blocker or, alternatively, in edematous and/or volume-overload states, with a thiazide diuretic plus a renin-angiotensin system blocker. Effective multidrug therapeutic combinations through 4 drugs are described. Comprehensive lifestyle modifications should be initiated in blacks when blood pressure is $\geq 115/75$ mm Hg. The updated International Society on Hypertension in Blacks consensus statement on hypertension management in blacks lowers the minimum target blood pressure level for the lowest-risk blacks, emphasizes effective multidrug regimens, and de-emphasizes monotherapy. (*Hypertension*. 2010;56:780-800.)

Key Words: antihypertensive therapy ■ blood pressure ■ essential hypertension ■ ethnic groups ■ hypertension detection and control ■ obesity ■ race

The International Society on Hypertension in Blacks (ISHIB) has been at the forefront of recognizing the critical need for more effective management of hypertension (HTN) in blacks. Accordingly, in March of 2003, the ISHIB published a consensus statement on the “Management of High Blood Pressure in African American,”¹ the first such document to focus primarily on HTN in blacks or in any black population. Notable recommendations in this consensus statement were to initiate 2 antihypertensive medications when blood pressure (BP) was

>15/10 mm Hg above goal, to use renin-angiotensin system (RAS) blockers if the patient had kidney disease and/or diabetes mellitus, and to establish a BP target of <130/80 mm Hg in the presence of coexisting conditions, such as diabetes mellitus, chronic kidney disease (CKD), metabolic syndrome, known vascular disease, and/or heart disease (eg, heart failure [HF], left ventricular hypertrophy [LVH]).

Inadequate BP control remains a global problem in most hypertensive populations. The adverse consequences of HTN

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From the Department of Internal Medicine (J.M.F., S.N.), Division of Translational Research and Clinical Epidemiology, Wayne State University, Detroit, Mich; Department of Internal Medicine (D.A.S.), Division of Nephrology, Virginia Commonwealth School of Medicine, Richmond, Va; Department of Internal Medicine (G.B.), Division of Nephrology, University of Chicago-Pritzker School of Medicine, Chicago, Illinois; Department of Internal Medicine (A.L.B.), Cardiovascular Division, Washington University School of Medicine, St Louis, Mo; Association of Black Cardiologists, Department of Medicine (K.C.F.), Cardiology Division, Emory University School of Medicine, Atlanta, Ga; Department of Internal Medicine (R.H.G.), Division of Cardiology, University of Minnesota School of Medicine, Minneapolis, Minn; Department of Internal Medicine, Divisions of Hypertension (W.D.H.) and Nephrology (J.P.L.), Emory University School of Medicine, Atlanta, Ga; Department of Internal Medicine (W.E.J.), Division of General Internal Medicine, Department of Veterans Affairs Heart of Texas, Arlington, Tex; Department of Internal Medicine (D.S.K.), Section of Internal Medicine, Robert Wood Johnson Medical School, New Brunswick, NJ, and Jersey Shore University Medical Center, Neptune, NJ; Department of Internal Medicine (S.D.N.), Division of Cardiology, University of Texas Southwestern Medical Center, University of Texas Southwestern Medical Center, Dallas, Tex; Department of Internal Medicine (E.S.), Division of Hypertension, University of Maryland School of Medicine, Baltimore, Md; University of Michigan School of Nursing (M.S.-M.), Ann Arbor, Mich; Department of Internal Medicine (K.A.J.), Division of Cardiology, University of Michigan School of Medicine, Ann Arbor, Mich.

Correspondence to John M. Flack, Department of Internal Medicine, Wayne State University, University Health Center, 4201 St Antoine, 2E, Detroit, MI 48201. E-mail jflack@med.wayne.edu

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in blacks are likely attributable to a multiplicity of factors: (1) excessive prevalence of HTN; (2) disproportionate prevalence of severe HTN ($\geq 180/110$ mm Hg); (3) inadequate BP control over the long term; and (4) the high frequency of comorbid conditions (diabetes mellitus, albuminuria, CKD, and pressure-related target-organ injury), all of which substantively amplify the risk of deleterious pressure-related outcomes, in part because all confer resistance to the BP-lowering effect of antihypertensive drug therapy.

Since 2003, there has been a steep upward trajectory in obesity and diabetes mellitus among blacks, as well as in the general population^{2,3}; both conditions are closely linked to HTN, as well as to treatment resistance to several antihypertensive drug therapies.^{4,5} This updated ISHIB consensus statement addresses a range of issues that are important to the prevention, diagnosis, risk stratification, and clinical management of HTN and cardiovascular-renal risk reduction in black patients with HTN.

General Approach

Applicable HTN and cardiovascular disease (CVD) treatment and prevention guidelines were reviewed.^{1,4,6–14} HTN clinical trials reporting clinical end points were considered, including those undertaken solely in blacks¹⁵ and those with sizeable numbers of blacks^{16–28}; some of these trials reported preplanned subgroup analyses, whereas others reported post hoc subgroup analyses by racial/ethnic group. Clinical trials involving HTN treatment in individuals with important comorbidities, such as diabetes mellitus and CKD, were considered, although specific data for blacks were not reported^{29–48}; these were trials of HTN treatment in disease states that disproportionately affect blacks and magnify the risks of pressure-related complications. Also considered were the results of HTN clinical trials in blacks that focused primarily on BP lowering. However, it is not possible to formulate comprehensive HTN treatment guidelines for blacks using data solely from randomized trials focused only or predominately on this population. Thus, by necessity, we have extrapolated results from randomized trials conducted in predominately nonblack cohorts when similar data were not specifically available in blacks.

The emphasis in this updated ISHIB consensus statement is on the interpretation of the BP response and clinical end point data and how these observations mesh with the totality of the evidence available for consideration. We strongly encourage practitioners to diagnose, stratify risk, and treat blacks on an individualized basis rather than to make blanket extrapolations regarding preferred antihypertensive drugs to all blacks.

Epidemiology of HTN and BP Control in Blacks

The age-adjusted prevalence of HTN during 2006 among individuals aged ≥ 20 years in the total US population was 33.3% (73 600 000).⁴⁹ Non-Hispanic blacks had the highest age-adjusted prevalence (44.4% men and 43.9% women), non-Hispanic whites an intermediate prevalence (34.1% men and 30.3% women), and Mexican Americans the lowest prevalence (23.1% men and 30.4% women). In a different analysis among children aged 8 to 17 years in 1999–2000, systolic BP (SBP) levels were 2.9 and 1.6 mm Hg higher in non-Hispanic black

boys and girls, respectively, than in age-matched non-Hispanic whites, a finding attributable in part to an increased prevalence of overweight in black children.⁵⁰

Although blacks have widely been perceived as having the highest HTN rates in the world, they do not. Adults in Germany, Finland, and Spain all have higher age-adjusted rates of HTN (BP $\geq 140/90$ mm Hg or treatment with anti-hypertensive medication).⁵¹ Cross-continental studies show an escalating gradient of HTN prevalence in black populations, being lowest in Africa, intermediate in the Caribbean, and highest in the urban Midwestern United States.⁵² Data from within black and African populations show striking BP gradients (rural < urban) that predictably track directly with Western lifestyles.⁵³ Cooper et al⁵² studied populations in rural Cameroon, urban Cameroon, and Chicago in 1995 and showed that the HTN rates in these locations were 15%, 19%, and 33%, respectively.

Over the past 2 decades, the number of Americans aware of their HTN has increased. In an analysis of the 1999–2004 National Health and Nutrition Examination Survey, HTN awareness ranged from 81.8% in non-Hispanic black women, 73.4% in non-Hispanic white women, 67.8% in non-Hispanic black men, and 70.4% in non-Hispanic white men.⁵⁴ Treatment rates were also higher in non-Hispanic black women than in non-Hispanic white women (71.7% versus 64.0%); on the other hand, treatment rates were lower in non-Hispanic black men than non-Hispanic white men (56.4% versus 60.0%). However, BP control remains inadequate in the majority of hypertensive men and women of any racial/ethnic group, ranging from 36.0% for non-Hispanic black women, 34.5% for non-Hispanic white women, 29.9% for non-Hispanic black men, and 39.3% for non-Hispanic white men. The most dramatic improvement in HTN control occurred in non-Hispanic black men, in whom control rates rose from 16.6% to 29.9% between the time spans of 1988–1994 and 1999–2000.⁵⁴ BP control rates (< 140 mm Hg), however, remain low (45%) among drug-treated hypertensive blacks.⁵⁵

Pressure-related cardiovascular-renal complications (stroke, LVH, HF, and CKD/end-stage renal disease) occur excessively in blacks compared with whites.^{49,56,57} CKD, a relatively common finding in hypertensive blacks, appears to negatively influence population-based BP control rates.⁵⁸ Moreover, there is inadequate recognition by primary care physicians that black race/ethnicity is a risk factor for CKD.⁵⁹

HTN extracts an exceedingly high death toll from blacks. It is estimated that as many as 30% of all deaths in hypertensive black men and 20% in hypertensive black women may be because of high BP. In 2005, the death rate from HTN (per 100 000 population) was 15.1 in white men, 51.0 in black men, 15.1 in white women, and 40.9 in black women.⁶⁰

Nonphysiologic Factors Linked to Poor BP Control

Several studies have provided insight into nonphysiologic factors linked to poor BP control in hypertensive blacks.^{61–63} High levels of stress, being worried about HTN, experiencing adverse effects of antihypertensive medication, older age, self-reported medication nonadherence, and a HTN diagnosis > 5 years were linked previously to the racial/ethnic disparity

in BP control (lesser control in blacks).⁶¹ The lesser BP control in blacks, however, does not appear to be related to not taking HTN seriously. Bosworth et al⁶² reported data that blacks with HTN indeed perceived the condition as more serious than did whites. However, blacks with HTN were more likely to be nonadherent to therapeutic regimens, as well as to be unable to read and adequately follow prescription instructions.

Nonbiomedical Beliefs

Nonbiomedical beliefs appear to be relatively common among blacks with HTN. A study of 93 blacks with HTN subjected to open-ended interviews during routine ambulatory clinic visits found that 38% believed that HTN could be cured, 38% believed that taking antihypertensive medication lifelong was not necessary, and 23% thought that antihypertensive medications needed to be taken only when experiencing symptoms.⁶⁴ Clearly, these beliefs could negatively influence the likelihood that blacks with HTN will seek treatment and, once prescribed, adherence to treatment over the long term.

Patient-Provider Interactions

Blacks tend to mistrust the health system. Blacks reporting multiple episodes of discrimination delayed seeking medical care and manifested poor adherence with medical recommendations.⁶⁵ Once inside the medical system, both physician demographics and cultural competency (ie, the ability to interact effectively with individuals from different cultures) appear to affect patient satisfaction, adherence with practitioner recommendations, and patient perceptions. Black patients receiving their care from black physicians were more likely than those receiving care from nonblack physicians to rate their physicians as excellent and to report that they received all of their needed medical care during the previous year.⁶⁶ Race-concordant (patient-physician) clinic visits were longer, had higher ratings of positive patient affect, and were rated as more participatory and more satisfying to the patient.⁶⁷ A study by Paez et al⁶⁸ found significant positive correlations between physician self-reported cultural competence and patient satisfaction (black and white), as well as in patient willingness to seek and share information during the visit. Thus, health systems, clinics, and individual practitioners must be aware of, and ideally proactively minimize or eliminate, the aforementioned factors that can undermine the delivery of effective health care to black patients.

Pathophysiologic Considerations

An abundance of theories have been put forth to explain the excessive prevalence, earlier onset, and greater pressure-related target-organ injury of HTN in blacks relative to whites. Although racial/ethnic differences in metabolic, neurohumoral, hemodynamic, and pressure-related target-organ injury have been documented, these represent quantitative, not qualitative, differences.

Diet and lifestyle likely play important roles in the pathogenesis of HTN in blacks and in the excess of HTN relative to whites. Blacks, especially women, are less physically active, consume more calories, and, not surprisingly, are

more obese beginning in the preadult years than whites.^{69,70} Blacks overall consume similar amounts of sodium but less potassium than whites.⁷¹ Black hypertensive patients of higher socioeconomic status excrete significantly more urinary sodium and have higher urinary Na:K ratios than those of lower socioeconomic status.⁷² Also, blacks residing in urban areas in the South excrete less urinary potassium and have higher urinary Na:K ratios than blacks residing in the urban Midwest.⁷³

Abnormal Diurnal BP Variation

Nighttime (12:00 PM to 6:00 AM) BP levels are normally 10% to 20% lower than daytime (6:00 AM to 12:00 PM) BP levels.⁴ Individuals whose nighttime BP falls <10% from daytime levels are classified as “nondippers.”⁷⁴ Both normotensive and hypertensive blacks exhibit more nondipping during ambulatory BP monitoring than do whites.⁷⁴ A nocturnal nondipping pattern has been linked to high dietary salt intake, salt sensitivity, lower dietary intake of potassium, obesity, a higher apnea-hypopnea index, lower socioeconomic status, and CKD in blacks.⁷⁵ The lack of a nocturnal fall in BP is plausibly both a consequence and a cause of target-organ injury.

Obesity

Obesity, especially among women, is more common in blacks than in whites.² In addition, obesity is a risk factor for HTN, diabetes mellitus, and HF, all of which are more common in blacks than whites,^{4,49} and is a contributing factor to an increased apnea-hypopnea index, which, in turn, has been linked to higher BP, as well as to nondipping nocturnal BP pattern.⁷⁶ Adiposity has also been linked to resistance to antihypertensive treatment in both blacks^{5,77} and whites.⁷⁸

Obesity in humans results in oversecretion of both cortisol and aldosterone. Recent experiments with human subcutaneous adipocytes suggests that adipokines sensitize human adrenocortical cells to angiotensin II-mediated aldosterone release.⁷⁹ These observations may be of particular relevance to the excess of HTN and obesity-linked salt sensitivity, as well as to high circulating aldosterone levels that directly correlate with BP level and renal vascular resistance in hypertensive blacks.⁸⁰

Obesity may also exert an intergenerational effect on the risk for HTN and other CVD risk factors, because it is a risk factor for premature birth.^{81,82} Premature birth or low birth weight has, in turn, been linked to endothelial dysfunction, higher SBP, greater risk of diabetes, and a lower number of nephrons in blacks.^{83,84}

Renin-Angiotensin System

The RAS in blacks has typically been perceived as being less active than in whites. Several observations have contributed to this long-held and erroneous conclusion, including the tendency toward suppressed circulating renin activity^{85,86} and the lesser average BP reduction to monotherapy with angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) in blacks compared with whites.^{26,87–89} However, the majority of blacks with HTN do not have fully suppressed circulating renin levels,⁹⁰

and dietary salt-induced suppression of renin production and, thereby, circulating renin levels have been associated with higher, not lower, levels of vascular angiotensin II production.⁹¹

Several reports have highlighted the significant overlap in BP responses of blacks and whites to monotherapy with ACE inhibitors and the finding that the variation of BP response is much larger within racial/ethnic groups than between them.^{87,88} In addition, other studies of blacks and whites have suggested greater, not lesser, activation of the renal RAS in healthy blacks,⁹² as well as a blunted suppression of intrarenal RAS activity in blacks compared with whites when consuming a high-sodium diet.⁹³ This observation might also help explain why the largest racial differences in BP response during RAS blockade occur in the setting of a high dietary sodium intake; dietary sodium intake in salt-sensitive humans suppresses urinary NO metabolites^{94,95} and augments vascular angiotensin II production.⁹¹ Furthermore, the excessive rates of pressure-related target-organ injury in blacks with HTN (LVH, CKD, and proteinuria), as well as the high rates of obesity, have all been linked to RAS activation.

Functional and Anatomic Vascular Abnormalities

Blacks, even in the normotensive range of BP, have been shown to manifest more microvascular and macrovascular structural and functional abnormalities than whites.^{96,97} The abnormalities in the arterial vasculature are substantive but nonspecific and relate to both impaired endothelium-dependent and endothelium-independent vascular function.^{98–100} Similarly, greater intima-media thickening of large resistance vessels, such as the carotid artery, has also been documented.¹⁰¹ Functional vascular abnormalities occurring more often in blacks than in whites include greater stiffness of large central arteries^{97,102} and a lesser capacity of resistance vessels to dilate in response to vasodilatory stimuli.^{98,99} These abnormalities in resistance vessels have further been linked to greater pressure-related target-organ injury in blacks.¹⁰³ A recent study⁹⁶ found higher carotid and central aortic pressures, greater carotid intima-media thickness, and stiffer carotid and aortic vasculature in young normotensive ($\approx 130/75$ mm Hg) apparently healthy blacks compared with whites, although brachial BP levels were virtually identical.

Salt Sensitivity

Salt sensitivity is more common in black than white hypertensives and is also present, albeit to a lesser degree, in normotensive blacks.¹⁰⁴ Nevertheless, >50% of both blacks and whites with HTN will manifest salt sensitivity.¹⁰⁵ Salt sensitivity is a reversible intermediate BP phenotype that has been linked to obesity in both blacks and whites^{106,107} and is a likely physiological contributor to salt and water retention and plasma volume expansion that occurs during antihypertensive drug therapy. Administration of dietary sodium chloride in potassium-deficient blacks causes renal vasoconstriction that directly correlates to the rise in BP; however, both the renal vasoconstriction and the rise in BP can be abolished by high-dose (170 mmol/d) potassium bicarbonate.¹⁰⁸ Interestingly, there is a suggestion of augmented BP lowering to calcium channel blockers (CCB) in black salt-sensitive hy-

pertensives when dietary sodium intake is high.¹⁰⁹ Conversely, drugs acting primarily on the RAS produced a lesser BP response if the patient was salt sensitive and ingesting a high-salt diet.¹¹⁰

Secondary HTN

Although the overwhelming majority of black will have no identifiable cause for their HTN, secondary forms of HTN in blacks are not uncommon. Our focus will be on the 3 secondary forms of HTN most likely encountered in blacks: primary aldosteronism (PA), critical renal artery stenosis, and obstructive sleep apnea (OSA).

Primary Aldosteronism

Historically, estimates of PA prevalence among all hypertensive subjects have been in the range of $\leq 1\%$ to 2% . This percentage, however, almost assuredly underestimates the true prevalence because it was derived from hypertensive populations in which the diagnosis of PA was sought only among those with hypokalemia. The majority of hypertensive patients with PA, however, are not overtly hypokalemic.¹¹¹ In one rigorous study, the prevalence of PA was 13% in an unselected population of mostly white hypertensives.¹¹² The likelihood of PA rises with incrementally higher levels of BP. Calhoun et al¹¹³ reported a 20% prevalence of PA in 88 consecutive patients with resistant HTN referred to a university-based HTN clinic with no difference in prevalence between blacks and whites. Ambulatory BP levels in black and white hypertensives with PA tend to be higher than their cuff BP readings,¹¹⁴ a reversal of the usual relationship between cuff and ambulatory BP in unselected hypertensive subjects.

Critical Renal Artery Stenosis

Critical renal artery stenosis typically develops in persons with underlying essential HTN, although it can arise de novo in normotensive individuals. Critical obstruction of one or both renal arteries can lead to several varied clinical presentations: (1) new, worsening, and/or resistant HTN; (2) depressed kidney function (ischemic nephropathy); (3) both; or (4) neither. It has also long been thought that critical renal artery stenosis was uncommon in blacks. The prevalence of critical renal artery stenosis ($\geq 60\%$ stenosis) in a population-based sample of 834 free-living adults aged ≥ 65 years (mean age: 77 years), as estimated by renal duplex sonography, was 6.8% (6.9% in white participants versus 6.7% in blacks).¹¹⁵ Although the optimal treatment (medical management versus renal artery angioplasty and stenting) is under active investigation,¹¹⁶ it was shown previously that blacks who underwent surgical revascularization of stenosed renal arteries had similar postsurgical BP lowering and improvements in renal function as their white counterparts, despite greater preoperative heart disease and a trend toward greater renal dysfunction.¹¹⁷

Obstructive Sleep Apnea

The prevalence of OSA in hypertensive populations is estimated to range between 30% and 40% .^{76,118} OSA is more common in blacks than whites, at least at the extremes of age

(<25 years and ≥ 65 years).^{119–121} The severity of sleep apnea has been determined by the apnea (complete cessation of airflow for 10 seconds)-hypopnea (reduction in airflow followed by arousal from sleep or a drop in oxyhemoglobin saturation) index.¹²² The severity of OSA directly relates to greater body weight, a higher body mass index, and a larger neck circumference. Weight gain (10% of body weight) has been linked to significant increases in apnea-hypopnea index and an even more striking risk for developing moderate-to-severe OSA,¹²³ whereas weight loss improves the apnea-hypopnea index.¹²⁴ OSA has been recognized as a risk factor for HTN,¹²⁵ a nondipping nocturnal BP pattern, and increased BP variability.⁷⁶ Masked HTN (normal office BP but elevated ambulatory BP) was found in 30.0% of individuals with sleep apnea, a prevalence almost identical to that of sustained HTN (35.4%).¹²⁶ Although CVD risk falls with continuous positive airway pressure, few data show sustained reductions in BP after such therapy.

Risk Stratification

The concept of “high BP or HTN” is both relative and arbitrary. Over the past 50 years, the level of BP at which treatment is recommended has been lowered, because the pressure-related risks, especially those attributable to SBP, have proven to be continuous and graded across a broad range, with the escalation of risk beginning clearly within the so-called normal range. CVD risk doubles with every 20/10-mm Hg rise in BP above 115/75 mm Hg.¹²⁷ Other CVD risk factors all augment the level of absolute risk at any given BP level and do so in a continuous and absolute manner. There is no convincing evidence that significant racial/ethnic differences exist in the shape of the overall relationship across the ranges of these risk factors.

CVD in blacks or in other racial/ethnic populations will rarely be mostly genetic in origin. For most persons, CVD results from long-term chronic exposure to risk factors, such as family history and lifestyle factors, including obesity and lack of physical activity. In fact, obesity may be the most important risk factor, because it is critically linked to BP levels, lipid abnormalities, and glucose intolerance and also because it reflects the habitual (im-)balance between energy intake and energy expenditure. Absolute coronary risk should be incorporated into the decision-making process of when and how aggressively to treat. The Framingham 10-year coronary heart disease (CHD) risk score, which is widely available and relatively easy to use, accurately predicts CHD in blacks.^{128,129} We, therefore, recommend determination of the Framingham risk score for estimation of the probability of 10-year CHD risk in all patients with HTN.

Recommended actions and goal BP based on CVD risk strata are shown in Table 1. We propose 2 main risk strata: BP $\geq 135/85$ mm Hg and no evidence of end-organ damage, preclinical CVD, or CVD (primary prevention) and BP $\geq 130/80$ mm Hg and evidence of end-organ damage, preclinical CVD, or previous history of CVD event (secondary prevention). Our secondary prevention risk stratum includes all of the patients identified as high risk by the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)

Table 1. Treatment Goals According to Risk Category or Stratum

| Risk Category | Recommended Treatment | Goal BP, mm Hg |
|---|---|----------------|
| Primary prevention | Lifestyle modification* | <135/85 |
| BP $\geq 135/85$ mm Hg without target-organ damage,† preclinical CVD,‡ or CVD§ | (≤ 3 months without drugs) + Drug therapy | |
| Secondary prevention/ target-organ damage†§ | Lifestyle modification | <130/80 |
| BP $\geq 130/80$ mm Hg with target-organ damage,† preclinical CVD,‡ and/or the presence of CVD§ | + Drug therapy | |

*Data show ≤ 3 months of comprehensive lifestyle modification without drugs if BP is <145/90 mm Hg without target-organ damage or other risk-enhancing comorbidities.

†Target-organ damage is defined as albumin:creatinine ratio >200 mg/g, eGFR <60 mL/min per 1.73 m², or electrocardiographic or echocardiographic evidence of LVH.

‡Indicators of preclinical CVD include metabolic syndrome, Framingham risk score $>20\%$, prediabetes (impaired fasting glucose [100 to 125 mg/dL] and/or impaired glucose tolerance [2-hour postload glucose 140 to 199 mg/dL]) or diabetes mellitus.

§CVD includes HF (systolic or diastolic), CHD/postmyocardial infarction, peripheral arterial disease, stroke, transient ischemic attack, and/or abdominal aortic aneurysm.

plus several other patient types not included in the JNC 7 high-risk group. At present, the majority of drug-treated blacks with HTN do not attain the current slightly higher JNC 7 and ISHIB guidelines target BP levels (<140/90 mm Hg or 130/80 mm Hg for high-risk patients). An important aim of lowering the current BP targets is to increase the proportion of lower risk (primary prevention) blacks who achieve contemporary BP goals.

All of the patients should be evaluated carefully for the presence of other risk factors, including hyperlipidemia, glucose intolerance, cigarette smoking, and albuminuria (random spot urine for determination of albumin:creatinine ratio). All of the CVD risk factors should be identified and treated to target levels along with BP. Table 2 displays the recommended history, physical examination, and diagnostic testing for blacks with HTN. The practitioner should take steps to ensure accurate office BP measurement by implementing standardized BP measurement procedures.¹³⁰

Routine home BP monitoring with oscillometric devices using appropriate-sized cuffs that have proven to accurately measure BP is strongly encouraged in patients with pre-HTN, suspected HTN, and confirmed HTN¹³¹; accuracy can be easily checked by having the patient bring the home BP device to clinic to compare near simultaneous BP measurements against a mercury manometer or automated oscillometric device using appropriate-sized BP cuffs. Patients should be encouraged to measure their BP under standard conditions, to record all BP measurements in their log book, and to routinely share these BP readings with their practitioner. At least 12 morning and evening BP readings should be used for clinical decision-making.¹³¹

Table 2. Suggested Diagnostic Evaluation of Hypertensive Patients

| | |
|--|--|
| History | |
| Family history of premature-onset high BP (<40 y), early-onset stroke (especially hemorrhagic), CHD, CVD, or type 2 diabetes mellitus | |
| Previous diagnosis of high BP, known duration, typical range of BP, highest known BP, treatment history | |
| Smoking history | |
| Current alcohol consumption | |
| Leisure-time physical activity | |
| Dietary assessment | |
| Environmental assessment (neighborhood, housing, employment, and workplace) | |
| Use of street drugs (in particular, cocaine, amphetamines, and phencyclidine) | |
| Current medications (including over-the-counter medications, supplements, herbal products, and home remedies) | |
| Medical and psychiatric history (particularly those that may affect choice of antihypertensive agent, eg, COPD, erectile dysfunction, and depression) | |
| Diagnostic testing | |
| Smoking history | |
| EKG | |
| Lytes, BUN, creatinine, glucose, eGFR | |
| Fasting lipid profile | |
| Framingham 10-y CHD risk score | |
| Urinalysis and dipstick | |
| Random spot urine albumin:creatinine or protein:creatinine ratio | |
| CXR; special situations | |
| →Smoker | |
| →Specific chest-related symptomatology (eg cough) | |
| →Echocardiogram | |
| →Unexplained shortness of breath | |
| →History or exam findings suggestive of LV systolic dysfunction | |
| →May be helpful in absence of noncardiac target-organ injury or preclinical CVD when BP >130/80 mm Hg | |
| →Documentation of LVH in this situation would lead to initiation of treatment and a lower goal BP | |
| →Low threshold for ordering, especially if planning to use rate-limiting CCBs, especially in older hypertensive patients, particularly in setting of long-standing poor BP control | |
| →Home BP self-monitoring | |
| →Ambulatory BP monitoring | |
| →Selected situations when you truly need to know the BP level outside the clinic setting | |
| →Useful when symptoms suggest hypotension but cuff BP does not | |
| Physical examination | |
| →Height and weight (calculate body mass index) | |
| →Waist circumference | |
| →Cardiovascular and pulmonary examination | |
| →Measure BP using appropriate technique | |
| →Funduscopy | |
| →Assessment of peripheral pulses/bruits | |

BUN indicates blood urea nitrogen; COPD, chronic obstructive pulmonary disease; CXR, chest x-ray; EKG, electrocardiogram; LV, left ventricular.

Home BP monitoring allows for many more BP determinations than can be typically obtained in the office setting, enabling a perhaps better estimation of the true BP level, and a unique and definitive opportunity to understand BP levels in response to varied conditions (eg, postprandial, pre/postexercise, and before morning medication[s]). Home BP measurement encourages the patient to be actively involved in his or her own BP surveillance, possibly improves compliance, and is useful for monitoring therapeutic responses. Home BP determinations are also useful when considered along with office BP determinations for the detection of white coat HTN; when home BP is <125/76 mm Hg in the absence of target organ injury, the likelihood of sustained HTN is very low.¹³¹ However, when >125/76 but <135/85 mm Hg, ABPM monitoring should be pursued. When home BP is >135/85 mm Hg, then treatment is warranted.

Ambulatory monitoring will not be routinely necessary in the evaluation of hypertensive blacks. Nevertheless, 24-hour ambulatory BP monitoring can be useful in the monitoring and management of selected patients with suspected and confirmed HTN. Abnormal ambulatory BP readings are, for daytime BP, >140/90 mm Hg; for nighttime BP, >125/75 mm Hg; and for 24-hour BP, >135/85 mm Hg.¹³⁰ When home BP readings are >125/76 but <135/85 mm Hg and subsequent ABPM readings are >130/80 mm Hg, then treatment is warranted.¹³¹ When either white coat (office BP >140/90 with ambulatory or home readings <130/80 mm Hg) or masked HTN (office BP <140/90 mm Hg with ambulatory or home readings >135/85 mm Hg) is suspected, often on the basis of discordant home and office BP readings, ambulatory BP monitoring can be helpful. Masked HTN commonly occurs in persons with sleep-disordered breathing, a condition that disproportionately affects blacks.

Elevated BP Without Target Organ Damage, Preclinical CVD, or CVD (Primary Prevention)

In black patients with HTN who do not manifest target-organ injury, preclinical CVD, or a history of CVD (ie, primary prevention), we recommend modestly lowering the target BP from <140/90 to <135/85 mm Hg. Considered relevant to this recommendation are epidemiological data showing that the upward inflection point of CVD risk begins at a BP level of 115/75 mm Hg,¹²⁷ as well as recent data showing that young, normotensive black college students manifest higher central and aortic pressures and significant microvascular and macrovascular dysfunction and carotid artery thickening than do white college students, despite “normal” and virtually identical brachial BP levels.⁹⁶ There are also data from several randomized, prospective, clinical trials of antihypertensive therapy in patients without CVD that support this lower BP goal.^{132–134}

The Treatment of Mild Hypertension Study showed that treatment (with 1 of 5 different antihypertensive drug regimens) plus multifactorial lifestyle modification compared with multifactorial lifestyle modification alone in men and women aged 45 to 69 years (20% black) with diastolic BP (DBP) <100 mm Hg (baseline BP: 140/91 mm Hg) reduced the risk of the aggregate end point of pressure-related complications when SBP was lowered to ≈126 mm Hg

(lifestyle modification plus active drug) versus \approx 132 mm Hg (lifestyle modification alone).¹³² Clinical event rates were 16.2% (lifestyle modification only) versus 11.1% (active drug treatment) ($P=0.03$), and quality of life was also improved more in the active drug treatment group. The Cardio-Sis study, another prospective, randomized trial, was conducted in 1111 European nondiabetic men and women with SBP \geq 150 mm Hg plus 1 additional CVD risk factor at entry to determine whether a target SBP $<$ 130 mm Hg (tight control) was superior to SBP $<$ 140 mm Hg (usual control).¹³³ After a median 2-year follow-up, the rate of ECG-LVH (primary end point) was 37% lower ($P=0.013$) in the tight-control group compared with the usual-control group; the secondary composite CVD end point was also lower (9.4% versus 4.8%; $P=0.003$) in the tight-control group. The attained BP level at the end of 2-year follow-up was 131.9/74.0 in the tight-control group versus 135.6/78.7 mm Hg in the usual-control group (72.2% versus 27.3% achieved BP $<$ 130/80 mm Hg).¹³³ Pharmacological treatment of prehypertensive middle-aged (48.5 years) individuals in the Trial of Preventing Hypertension reduced the incidence of frank HTN by 66.3% ($P<0.001$) at 2 years and by 15.6% ($P<0.007$) at 4 years compared with placebo.¹³⁴ Finally, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the best study outcomes overall were obtained with chlorthalidone, in which group BP averaged 134/76 mm Hg at 4.9-year follow-up.¹³⁵ Collectively, these studies suggest the likely benefits of pharmacological treatment of HTN in lower risk hypertensive patients to BP levels lower than those currently recommended by JNC 7 or other organizations. Thus, our new recommendation is to maintain BP persistently $<$ 135/85 mm Hg in patients who do not have evidence of target organ damage, preclinical CVD, or overt CVD. In such patients, if BP is $<$ 145/90 mm Hg in the absence of target-organ injury or other risk-enhancing comorbidities, \leq 3 months of comprehensive lifestyle modification may be attempted without concurrent drug therapy (see Figure 1).

Evidence of Pressure-Related Target-Organ Damage, Preclinical CVD, or Previous History of CVD (Secondary Prevention)

For hypertensive patients with evidence of target-organ damage, preclinical CVD, or a history of CVD, we recommend maintaining BP levels consistently below the target level of 130/80 mm Hg (see Table 1). Patients in this category almost always have multiple risk factors and, because of their known CVD, have much higher absolute CVD risk at a given level of BP than do individuals with similar BP levels but without evidence of pressure-related target-organ injury, preclinical CVD, or overt CVD. Patients in this secondary prevention group will manifest proteinuria (albuminuria; spot urine albumin:creatinine ratio $>$ 200 mg/g), depressed renal function (estimated glomerular filtration rate [eGFR] $<$ 60 mL/min per 1.73 m²), electrocardiographic (or echocardiographic) evidence of LVH, metabolic syndrome, a Framingham risk score corresponding to $>$ 20% 10-year CHD risk, the presence of “prediabetes” (glucose intolerance [2-hour post-load glucose \geq 140 mg/dL] or impaired fasting glucose [100

to 125 mg/dL]), diabetes mellitus, and/or overt clinical CVD; this risk category includes all patients considered by JNC 7 to be high-risk hypertensives. Virtually all of the above manifestations of target-organ injury and preclinical CVD have been linked to resistance to antihypertensive treatment or to slower attainment of goal BP. The majority of patients in this risk stratum will require multiple antihypertensive drugs to consistently maintain BP levels below the target level of 130/80 mm Hg.

The complexity of the multidrug treatment regimen may undermine the likelihood of reaching this aggressive BP goal. We recommend gradual reductions of BP over several weeks (or longer) to target BP levels. Particular caution should be taken to avoid overly rapid BP lowering, which can precipitate target-organ ischemia/dysfunction, especially in patients with extensive vascular disease and/or CKD. Table 3 lists the CVD conditions and the relative preferences/avoidances for the various antihypertensive drug classes when these conditions are present.

Clinical Trial Evidence in Blacks

Lifestyle Modifications

It is important that comprehensive therapeutic lifestyle modification, as outlined in Table 4, although difficult to implement in a sustained fashion, is highly desirable in all patients with HTN. We suggest comprehensive lifestyle modification alone, without drug therapy, for \leq 3 months in our lowest risk stratum (primary prevention), in those whose BP was $<$ 145/90 mm Hg (see Table 1 and Figure 1). Comprehensive lifestyle modifications should continue even with the initiation of antihypertensive drug therapy.¹³⁶ We also endorse use of comprehensive therapeutic lifestyle modification in all blacks with BP \geq 115/75 mm Hg.

Pharmacological HTN End Point Trials

Results of clinical outcome trials in HTN, including studies with black participants, are summarized in the Appendix Table. The studies are grouped according to the control comparison group (ie, placebo or active controlled) and, within the active-comparison treatment groups, by BP goal and by drug class comparisons. The procedure for classifying by race in the studies in the Appendix Table was by participant self-identification, although few studies included sufficient numbers of blacks to report race-specific results. The trend for industry-sponsored trials to be conducted outside the United States has resulted in inadequate sample sizes in many trials to interpret outcomes by race/ethnicity, even when data suggest subgroup differences by agent (ie, inhibitors of the RAS). Thus, clinicians will continue to have significant limitations in the use of data that does not represent blacks or other minority patient populations seen in their practices and that are underrepresented in HTN clinical trials. It should be borne in mind, however, that available clinical trial data in blacks have reported significant differences in BP-lowering efficacy by race/ethnicity and that clinically significant treatment-related differences in outcomes^{23,25} may be plausibly related to the reported differences in BP lowering.²⁵

Thiazide-type diuretics and CCBs show little difference in either BP lowering or clinical outcomes by subgroups (except that thiazides are more effective in primary prevention of

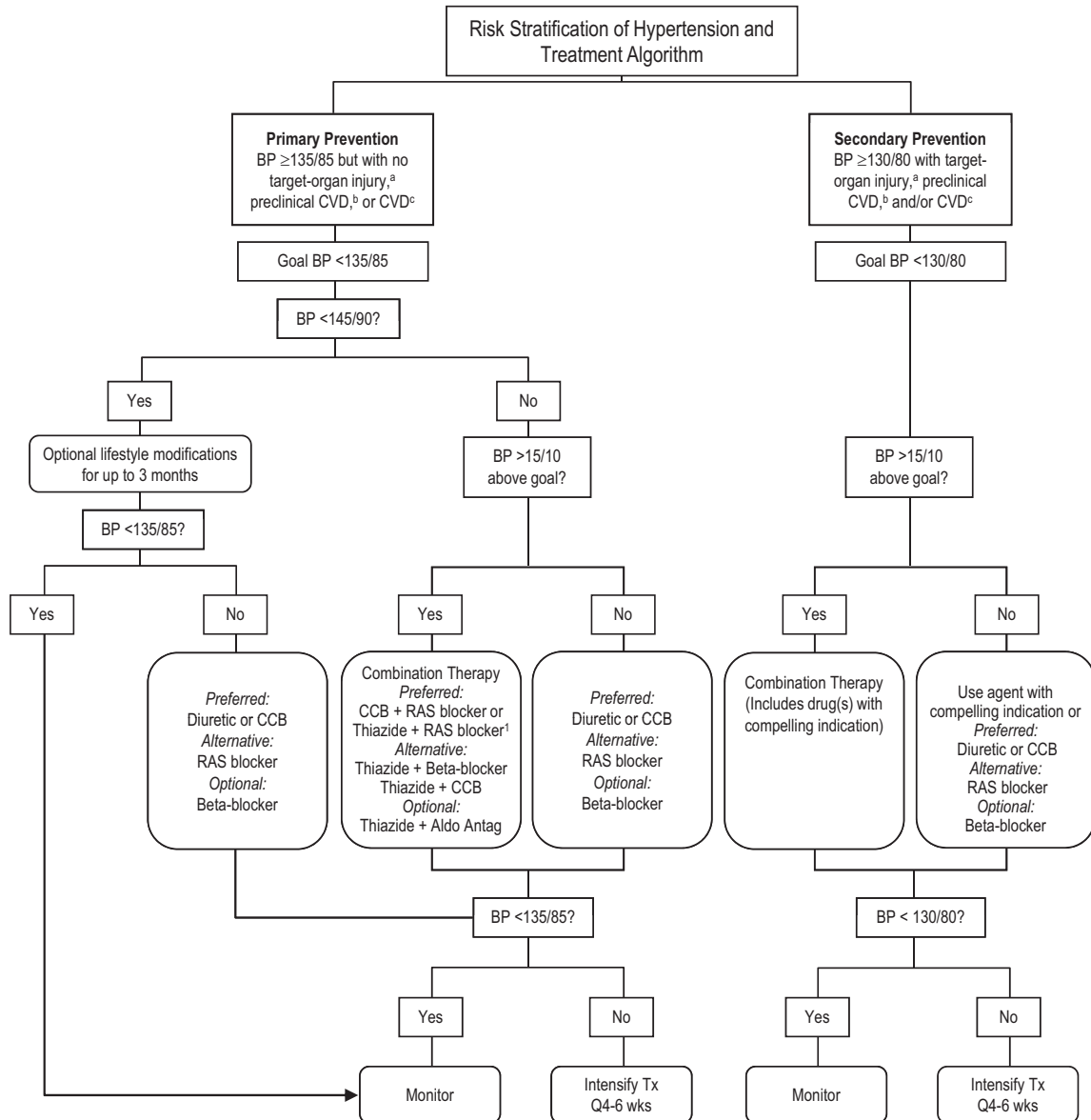


Figure 1. Risk stratification and treatment algorithm for blacks with hypertension. Aldo Antag indicates aldosterone antagonist; Tx, treatment. ^aTarget organ damage is defined as albumin:creatinine ratio >200 mg/g, eGFR <60 mL/min per 1.73 m², or electrocardiographic or echocardiographic evidence of LVH. [†]Indicators of preclinical CVD include metabolic syndrome, Framingham risk score >20%, prediabetes (impaired fasting glucose [100 to 125 mg/dL] and/or impaired glucose tolerance [2-hour postload glucose ≥140 mg/dL]) or diabetes mellitus. [‡]CVD includes HF (systolic or diastolic), CHD/postmyocardial infarction, peripheral arterial disease, stroke, transient ischemic attack, and/or abdominal aortic aneurysm. [§]Most effective 2-drug combinations: CCB+RAS blocker; thiazide diuretic+RAS blocker; thiazide diuretic+aldosterone antagonist; and thiazide diuretic+β-blocker. Recommended RAS blockers are ACE inhibitors or ARBs in ACE inhibitor-intolerant patients.¹ Preferred combination therapy in edematous and/or volume overload states.

HF), including in black populations.^{16–19,26,27,29} Excellent data are available to demonstrate that ACE inhibitors and ARBs are the most effective antihypertensive drug classes for slowing the progression of renal disease in hypertensive patients with diabetic and nondiabetic CKD, including blacks.^{15,20,21} However, in ALLHAT, the only CVD clinical outcomes trial specifically designed to compare the efficacy of different classes of antihypertensive agents, the ACE inhibitor lisinopril was less effective than the thiazide-type diuretic chlorthalidone (and a CCB) in lowering BP and in preventing many major clinical outcomes (including HF, stroke, and coronary events) in black participants.^{24–26}

Lesser reduction in CVD events was also seen in post hoc analysis of the small hypertensive black (blacks and international blacks) cohort (n=533) with electrocardiographically determined LVH with the ARB losartan compared with the β-blocker atenolol in the Losartan Intervention for End Point Reduction Trial.²³ In addition, the small black group (n=639 of 15 245 total participants) in the Valsartan Antihypertensive Long-term Use Evaluation Trial failed to show an advantage of the ARB valsartan compared with the CCB amlodipine.²⁸ Thus, the evidence does not support the use of RAS-blocking agents over thiazide diuretics (or CCBs) to lower cardiac morbidity

Table 3. Preferences for Antihypertensive Drugs by Comorbidity

| Comorbidity | ACEI | ARB | Aldo Antag | β -Blocker | CCB | Diuretic |
|-----------------------------|------|-----|------------|------------------|-----|----------|
| CHD/angina | √ | ● | | √ | √ | ● |
| CKD | √ | √ | ∅* | | ● | ● |
| Diabetes/prediabetes | √ | √ | | ● | ● | |
| HF | √ | √ | √ | √ | ∅† | ● |
| High vascular disease risk | √ | √ | | | | ● |
| Post-MI | √ | √ | √ | √ | | |
| Recurrent stroke prevention | √ | √ | | | | ● |

P indicates compelling indication (proven benefit); ●, likely benefit or safety proven; ∅, contraindication; ACEI, ACE inhibitor; Aldo-Antag, aldosterone antagonist; MI, myocardial infarction.

*If eGFR is <50 mL/min per 1.73 m², eplerenone only; use spironolactone with caution; periodically check serum potassium.

†Nondihydropyridine CCBs (diltiazem and verapamil) are contraindicated in systolic HF.

and mortality in black hypertensive patients without either a compelling indication for their use or a valid reason to avoid diuretic or CCB therapy. Where compelling indications (eg, HF or CKD) exist for prescribing RAS-blocking agents (either ACE inhibitors or ARBs) or β -blockers, these agents should be applied similarly in blacks with these comorbidities as in whites. It will usually be necessary to combine RAS blockers with diuretics and/or CCBs to achieve target BP levels.

The Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension Trial was the first study with a sizeable sample of black participants (1416 of 11 506) to compare the effect of 2 antihypertensive combinations on clinical outcomes.⁴⁸ The Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension Trial evaluated whether the combination of benazepril/amlodipine would result in lower CVD morbidity and mortality than the combination of benazepril/hydrochlorothiazide (HCTZ) in hypertensive men and women aged ≥ 55 years with SBP ≥ 160 mm Hg and evidence of CVD, renal disease, or target-organ damage; 97% of trial participants were treated hypertensives before randomization. In-office BP control was slightly better in the benazepril/amlodipine group compared with the benazepril/HCTZ group (131.6/73.3 versus 132.5/74.4 mm Hg). After a mean 30-month follow-up and with data on 979 patients with primary adjudicated end points (59.6% of the originally projected primary end points), the Data Safety and Monitoring Board recommended early stoppage of the trial in October 2007. By January 2009, when the last patients had been seen for final 3-month follow-up, data were available for 1231 patients who had reached a primary end point. There were 552 primary-outcome events in the benazepril/amlodipine group (9.6%) and 679 in the benazepril/HCTZ group (11.8%), representing an absolute risk reduction of 2.2% and a relative risk reduction of 19.6% (hazard ratio: 0.80 [95% CI: 0.72 to 0.90]; $P < 0.001$). Similar outcomes have also been observed in the black cohort

Table 4. Comprehensive Therapeutic Lifestyle Changes

| Medical Target | Realistic Personal Plan to Achieve Goal |
|--------------------------|--|
| Normal weight for height | Lose weight gradually by making permanent changes in daily diet for the entire family Set a reasonable weight loss goal (even 5 to 10 lb [2.2 to 4.5 kg] can make a difference) Eat fewer fast foods and fried foods and eat more fruits and vegetables |
| Dietary goals | Eat more grains, fresh fruits, and vegetables |
| Low fat | Eat fewer fats overall and use healthier fats such as olive oil |
| Low sodium | Eat fewer processed foods and fast foods |
| High potassium | Identify high-sodium foods (eg, potato chips, hot dogs) that can be comfortably avoided or decreased in frequency |
| Adequate calcium | Identify low-sodium, high-potassium snacks (eg, dried fruits, bananas, orange juice, raw vegetables) Do not add salt to foods when cooking; instead, taste foods first and add salt at the table if needed Use vinegar or lemon juice instead of salt for seasoning Do not season foods with smoked meats, such as bacon or ham hocks Become more aware of food sources that are rich in calcium If lactose intolerant, try lactose-free milk or yogurt, or drink calcium-fortified juices or soy milk, and consume up to 8 to 10 ounces of low-fat milk in conjunction with food/meals |
| Limit alcohol | Men: no more than 2 beers, 1 glass of wine, or 1 shot of whiskey (or hard liquor) per day Women: no more than 1 beer or 1 glass of wine per day (a shot of whiskey exceeds these recommendations) |
| Physical fitness | Increase physical activity as part of the daily routine; eg, if currently sedentary, get off the bus 6 blocks from home or walk in the evening with a spouse or friend Gradually increase time spent at an enjoyable activity to 30 to 45 minutes ≥ 5 times a week |
| No tobacco use | For nonsmokers, do not start For current smokers, attempt smoking cessation, increase tolerance for failure, and be willing to continue the effort until success is achieved Be aware that smokeless tobacco products (eg, chewing tobacco) also have associated risks |

(personal communication with Ken Jamerson). The incidence of hospitalization for HF was identical (1.7%) in the 2 treatment groups.⁴⁸ This trial provided evidence for the superiority of a CCB/ACE inhibitor combination over a diuretic combined with the same ACE inhibitor in a high-risk group of older hypertensives. However, given the lower starting dose of HCTZ used in the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension Trial (12.5 to 25.0 mg/d) than in other hard end point trials, we do not recommend HCTZ doses <25.0 mg/d in blacks.

Table 5. Undesirable Antihypertensive Drug Combinations

| Combination | Comments |
|---|---|
| ACE inhibitor+ARB | Modest incremental BP lowering when one is added to the other Heightened risk for hyperkalemia and kidney dysfunction No incremental reduction in pressure-related CVD risk Increased hypotensive symptoms |
| β -blocker+ACE Inhibitor | Minimal incremental BP lowering (in the absence of a diuretic) |
| β -blocker+nondihydropyridine CCB | Risk of both bradycardia and depressed LV systolic function, especially in older persons |
| β -blocker+central adrenergic inhibitor (eg, clonidine) | Modest incremental BP lowering Significant risk of bradycardia and orthostatic hypotension |
| α -blocker+central adrenergic inhibitor | Significant risk for orthostatic hypotension Both agents antagonize the sympathetic nervous system |

LV indicates left ventricular.

Therapeutic Approach

Basic Therapeutic Principles

The focus on BP responses to monotherapy in blacks with HTN represents misplaced emphasis, and a major advance in pharmacological antihypertensive drug therapy has been the de-emphasis on monotherapy and the simultaneous focus on the use of effective combination therapy. Despite the greater average BP-lowering response in blacks with diuretics and CCBs compared with RAS modulator drugs, BP levels typically remain above even conservative goal BP levels (<140/90 mm Hg) when diuretics or CCBs are used alone. Thus, to attain and maintain BP below target levels, multiple antihypertensive drugs will be required in most hypertensive blacks.

Target BP Levels

Target BP levels should now be considered the “ceiling” below which BP should be consistently maintained over the long term. Thus, BP levels should be lowered to levels far enough below goal to ensure that BP remains persistently below goal throughout the 24-hour dosing interval.

Combination Drug Therapy

It is logical to use 2-drug combination therapy when SBP is >15 mm Hg and/or DBP is >10 mm Hg above goal levels, because monotherapy only infrequently provides large enough placebo-adjusted BP responses to consistently control BP in this situation. This recommendation remains unchanged from our 2003 ISHIB HTN guidelines. In secondary prevention patients, the combination therapy should include a drug(s) with the appropriate compelling indications. Not all combinations are optimal; Table 5 displays antihypertensive drug combinations that should be avoided.

Speed of BP Control

More rapid attainment of goal BP was linked to greater CVD risk reduction in both the Anglo-Scandinavian Cardiac Out-

comes Trial¹³⁷ and the Valsartan Antihypertensive Long-Term Use Evaluation Trial.^{27,28} Differences in BP attainment were observed at 3 months in the Anglo-Scandinavian Cardiac Outcomes Trial and at 1 month in the Valsartan Antihypertensive Long-Term Use Evaluation. However, the greater CVD risk reduction from more rapid attainment of goal BP is almost assuredly confounded by patient characteristics (eg, the presence of albuminuria, diabetes mellitus, and obesity) that portend higher CVD risk, lesser or slower attainment of goal BP levels, and the need for more intensive antihypertensive drug therapy to reach goal BP.⁵ Accordingly, titration of antihypertensive drugs sooner than every 4 weeks seems unnecessary in most situations given that maximal BP-lowering effect may take at least this long to become fully manifest. Moreover, it has been shown previously that titration of ACE inhibitor monotherapy every 6 weeks versus every 2 weeks leads to higher BP control rates with fewer serious adverse events.¹³⁸ Thus, a prudent recommendation is to avoid therapeutic inertia by periodically up-titrating antihypertensive medication(s) when BP remains above goal levels while not titrating antihypertensive medications too frequently.

Control of Plasma Volume Expansion

Plasma volume expansion is a common and often unrecognized physiological perturbation in a high proportion of individuals with resistant HTN.^{139,140} Accordingly, patients with resistant HTN often respond with significant BP lowering when a diuretic is added or a more potent diuretic is substituted in the treatment regimen. The level of renal function is a determinant of diuretic action, and loop diuretics or long-acting thiazide diuretics, such as metolazone or chlorthalidone, are preferred therapies in patients with moderate-to-severe forms of CKD.

Role of Race/Ethnicity in Antihypertensive Drug Selection

Certain classes of antihypertensive medications, specifically diuretics and CCBs, lower BP on average more than β -blockers and RAS blockers in black patients when used as monotherapies.¹ This observation has been most consistently made in settings of ad libitum or high dietary salt intake. Nevertheless, as pointed out by Flack et al¹³⁸ and others,^{87,88} the lesser average BP response to ACE inhibitors in black compared with white hypertensives is not an accurate barometer for selection of drug therapy for individuals of either race. This is largely because the greatest source of variability in therapeutic response is within racial/ethnic groups, not between them, and also because the BP response distributions for each race/ethnicity, although shifted in relation to one another, mostly overlap. Accordingly, in clinical trials over the past 2 decades, more than two thirds of hypertensive patients, regardless of race/ethnicity, required ≥ 2 agents to achieve BP control⁴; as such, the issue of a best first therapy has been overemphasized previously. With regard to multi-drug therapy, there is no racial/ethnic difference in BP-lowering efficacy of RAS blockers or β -blockers when combined with either a diuretic or CCB.

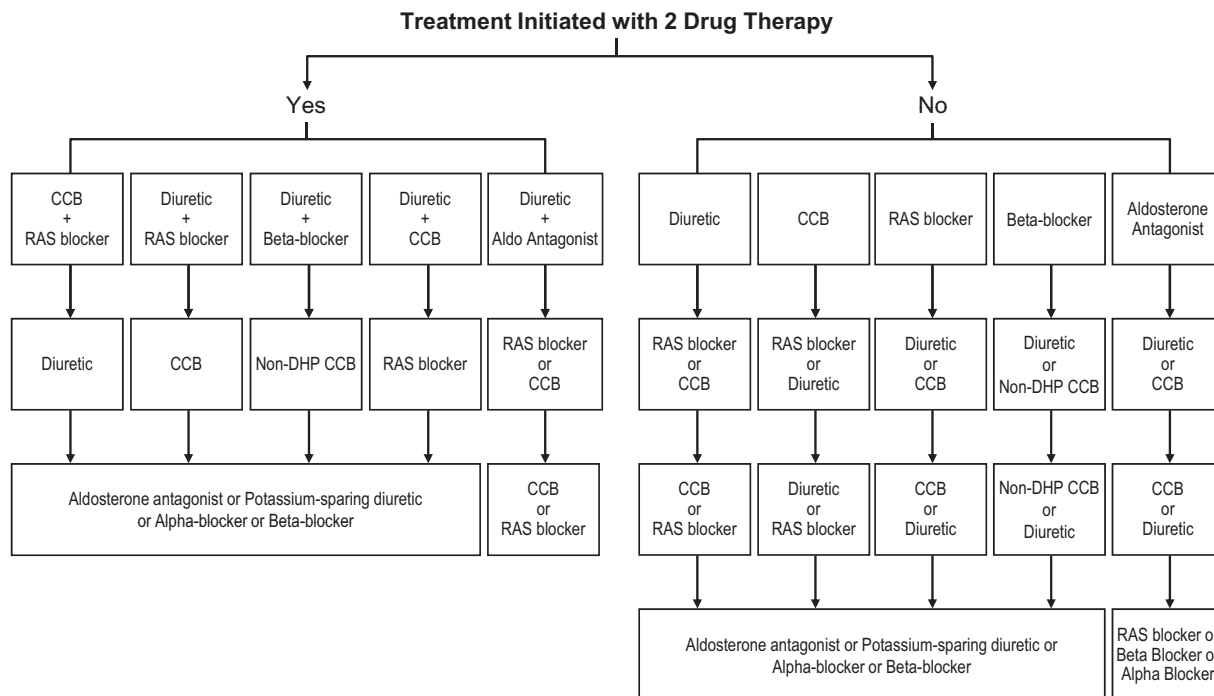


Figure 2. Guide to multidrug antihypertensive therapy in blacks with hypertension. Aldo indicates aldosterone; non-DHP, nondihydropyridine.

Only a few adequately powered CVD or renal outcome trials have examined the effects of BP lowering with specific drug classes in specific racial/ethnic groups; 2 such trials are the African American Study of Kidney Disease and ALLHAT.^{15,26} The African American Study of Kidney Disease Trial examined the effects of both different levels of mean arterial pressure (<92 versus 102 to 107 mm Hg) and initial therapy with a CCB (amlodipine), an ACE inhibitor (ramipril), or a β -blocker (metoprolol) on the rate of progression of nondiabetic CKD.¹⁵ After randomization, mean BP levels were 128/78 mm Hg in the lower BP group and 141/85 mm Hg in the higher BP group. Randomization to the lower BP goal had no significant impact on progression of kidney disease, at least over the relatively short (\approx 3-year) follow-up in this CKD cohort with minimal proteinuria. However, only a minority of patients in the low BP goal group actually attained BP <125/75 mm Hg (24.7% versus 6.2%). In contrast to previous BP-lowering monotherapy studies, use of an ACE inhibitor together with agents other than a CCB or β -blocker in blacks slowed progression of kidney disease more than CCB- or β -blocker-based regimens that did not include an ACE inhibitor.¹⁵ These data, although at odds with widely held perceptions on the efficacy of ACE inhibitors in blacks, are consistent with findings observed in other racial/ethnic groups,¹⁴¹ as well as with animal models of kidney disease.¹⁴²

Thus, at the group level, race/ethnicity crudely predicts BP response to monotherapy with RAS blockers, although not with a high degree of precision for individuals. A meta-analysis of monotherapy trials of antihypertensive drugs found the expected group differences in average BP response but found no evidence that the drugs reduced morbidity and mortality differentially in blacks once goal BP was

achieved.¹⁴³ Our interpretation is that drug selection is important in determining BP response, and different drug classes lower BP differentially both within as well as between racial/ethnic groups. Nevertheless, trends in average group BP responses do not substitute for practitioner judgment but may be used cautiously in combination with other information (see Figure 1) to determine the optimal drug choice(s) for an individual patient.

Antihypertensive Therapeutic Algorithm

Figure 1 displays our suggested approach, after appropriate risk stratification, for patients in the primary and secondary prevention risk strata. Of note, in the primary prevention, or lowest risk, stratum, goal BP has been lowered from <140/90 to <135/85 mm Hg. In this same risk stratum we include optional comprehensive lifestyle modifications (weight loss, salt and alcohol restriction, and increased physical activity) for \leq 3 months if BP is \leq 10/5 mm Hg above goal. In the absence of compelling indications, when BP is near goal levels, monotherapy with a diuretic or a CCB is preferred because of a greater likelihood of attaining goal BP with either of these agents as monotherapy in blacks. Figure 2 shows the suggested add-on therapies of \leq 4 antihypertensive agents for the most commonly used combination and single-drug therapies. When BP remains uncontrolled after prescription of 4 adequately dosed antihypertensive drugs, we recommend referral to an HTN specialist. When indicated, antihypertensive drugs with compelling indications should be selected first for monotherapy or, when dual drug therapy is initiated, be included in the 2-drug combination therapy. Table 3 displays preferences for antihypertensive agents based on the presence of selected CVD comorbidities, unless absolutely contraindicated.

Antihypertensive Therapies

Lifestyle modifications should be initiated in all patients with HTN, whether pharmacotherapy is planned. BP can be brought to goal in the majority of patients if antihypertensive medications are correctly dosed or combined. As BP is brought to goal, attention should be specifically directed to long-term adherence to therapy.

The contemporary approach to the pharmacological management of HTN should be mindful of the many therapy options that exist. The presence of concomitant medical conditions should bear on the manner in which HTN is treated either because of concomitant conditions or because of compelling indications for the use of specific drug classes. The ALLHAT provides some insight into the relative ability of various antihypertensive drug classes to prevent HF and CVD in hypertensive blacks with the metabolic syndrome.¹⁴⁴ Although no ALLHAT treatment group attained average in-study SBP levels as low as the ISHIB goal for hypertensive black patients with target organ injury, preclinical CVD, or overt CVD (<130/80 mm Hg), the primary end point of combined CVD and stroke was more effectively prevented in blacks with chlorthalidone than with either lisinopril or doxazosin, and risk of end-stage renal disease was lower in the chlorthalidone group than in the lisinopril group. Chlorthalidone was also superior to lisinopril, doxazosin, and amlodipine in preventing HF. At 4-year follow-up, SBP was lower in the chlorthalidone group by 4.0, 3.4, and 1.4 mm Hg, respectively, compared with the lisinopril, doxazosin, and amlodipine groups.¹⁴⁴

A stepped-care approach to the treatment of HTN entails the sequenced addition of medications on a pro forma basis, usually using a thiazide-type diuretic or a β -blocker as first-line therapy. Increasingly, however, 2-drug therapy is now recommended when the desired BP goal is >15/10 mm Hg higher than the existing BP. Two-drug therapy can be given as individual monotherapies or as a single pill fixed-dose combination. Two-drug regimens have generally contained a thiazide-type diuretic; however, the combination of a CCB with either an ACE inhibitor or an ARB has been shown equally efficacious in BP lowering but with demonstrated superiority (CCB+ACE) for hard clinical outcomes compared with the same ACE inhibitor plus a thiazide-type diuretic.⁴⁸

Dose-response effects exist for all classes of antihypertensive drugs, but BP responses to dose titration are most evident with diuretics, sympatholytic agents, α -blockers, and CCBs. A major consideration in the pharmacodynamic dose-response relationship for an antihypertensive medication is that of counterregulatory mechanisms (ie, increase in cardiac output, peripheral vasoconstriction, and salt/water retention) activated by BP lowering.

Thiazide-type diuretics (chlorthalidone 12.5 to 25.0 mg/d; HCTZ 25.0 to 50.0 mg/d) are very useful in the treatment of HTN either as monotherapy or when administered adjunctively. Diuretics are extremely useful in stage 1 HTN (SBP 140 to 159 mm Hg or DBP 90 to 99 mm Hg), because they lower BP as efficaciously as most other drug classes as long as there is adequate kidney function (eGFR \approx 45 mL/min per 1.73 m² or higher for HCTZ, down to low to mid 30s for

chlorthalidone). Blacks and the elderly usually respond well to diuretic monotherapy but not necessarily better than nonblack or younger patients do. HCTZ is the most commonly used diuretic in HTN therapeutics in the United States. This relates, in part, to the fact that virtually all diuretic-based, fixed-dose antihypertensive combinations that include a thiazide or thiazide-like diuretic contain HCTZ. Loop diuretics do not reduce BP as well as thiazide-type compounds when given as single-drug therapy, particularly if dosed once daily, unless the eGFR is significantly reduced.

Both efficacy and outcome data that strongly support the use of diuretic therapy in the elderly are available from the Systolic Hypertension in the Elderly Program^{29,145} and, in blacks, from ALLHAT.²⁶ The thiazide-type diuretic used in both the Systolic Hypertension in the Elderly Program and ALLHAT was chlorthalidone, a compound that differs from HCTZ in that it has a much longer half-life and has been shown to more efficiently decrease BP.¹⁴⁶ Chlorthalidone also effectively lowers BP and decreases the incidence of pressure-related complications down to an eGFR lower than that at which HCTZ loses its effectiveness.¹⁴⁵ Thus, we favor the use of chlorthalidone over HCTZ in most situations.

The aldosterone antagonists spironolactone and eplerenone have been used with or without a thiazide-type diuretic in the treatment of HTN and, most recently, as add-on therapy for resistant HTN.¹⁴⁷ On a milligram-for-milligram basis, eplerenone is a less potent BP-lowering agent than spironolactone, and BP lowering with 50 mg of spironolactone twice daily is 1.3 to 2.0 times greater than with eplerenone dosed 50 mg twice daily (or 100 mg once daily).¹⁴⁸ Eplerenone has been studied in blacks with HTN, and its BP-lowering effect as monotherapy is comparable to that observed in white patients; moreover, in blacks, it is clearly superior to the monotherapy response with the ARB losartan.¹⁴⁹ The potassium-sparing diuretics amiloride and triamterene also effectively lower BP in blacks with HTN when given alone or coadministered with spironolactone.^{150,151}

The add-on effect of spironolactone occurs within days to weeks, persists for months, and is independent of race/ethnicity, plasma aldosterone values, and urinary aldosterone excretion. When spironolactone (12.5 to 50.0 mg/d) was added to a regimen of a diuretic, ACE inhibitor, or ARB, a mean fall in BP of 21/10 mm Hg (6 weeks) and 25/12 mm Hg (6 months) occurred.¹⁵² The benefit of aldosterone blockade in the overall population of patients with resistant HTN suggests that aldosterone excess (relative or absolute) may be a more widespread cause of resistant HTN than was previously believed. Eplerenone has a more favorable adverse effect profile than spironolactone and is not associated with the same degree of gynecomastia. Use of either eplerenone or spironolactone can be accompanied by significant degrees of hyperkalemia.

ACE inhibitors or ARBs are recommended as alternative monotherapy options in the treatment of HTN in blacks. The rationale for their lower tier monotherapy recommendation is because they have consistently achieved lesser average reductions in BP relative to that observed with monotherapy using either a diuretic or CCB. In the ACE inhibitor- or ARB-treated patient who does not reach goal BP with

monotherapy, addition of either a diuretic or CCB either as add-on therapy or in a fixed-dose combination substantially augments the BP lowering. The BP-lowering effect of an ACE inhibitor or an ARB is also significantly enhanced with the addition of a CCB. Results from head-to-head comparison trials support the comparable antihypertensive efficacy and tolerability of the various ACE inhibitors and ARBs (with the possible exception of losartan) when given at equipotent doses.

Joint administration of ACE inhibitors and ARBs is not generally recommended (see Table 5). The rationale for this is the fact that, in a study of high-risk coronary artery disease patients, renal outcomes were worse, CVD outcomes did not improve, and discontinuation rates because of hypotensive symptoms were greater relative to monotherapy with either drug class, despite the few millimeters of mercury of additional BP reduction with combined therapy.¹⁵³ Cough and angioedema are class effect phenomena with ACE inhibitors that occur more frequently in blacks than in whites¹⁵⁴; thus, the occurrence of either of these adverse events prohibits the use of any ACE inhibitor (particularly in the case of angioedema). Cough is not seen with ARB therapy, and angioedema is an uncommon occurrence. Recently, the direct renin inhibitor aliskiren has become available. The ability of this drug to reduce BP in patients with HTN is similar to (or slightly better than) that seen with standard therapeutic doses of various ACE inhibitors or ARBs.¹⁵⁵ Treatment experience with aliskiren monotherapy in blacks shows that the magnitude of average BP reduction is significantly smaller in blacks than in whites for both SBP and DBP. Based on the mechanism of action of aliskiren and the phenotypic characteristics of many black patients with HTN, there is little reason to believe that this compound would work under circumstances in which an ACE inhibitor or ARB has failed. Neither cough nor angioedema occurs with direct renin inhibition.

All of the patient subtypes are to some degree responsive to CCB monotherapy, including the elderly and low-renin, salt-sensitive, diabetic and black hypertensive patients. CCBs have a steep dose-response curve for BP reduction. CCBs are also useful as add-on therapy when combined with an ACE inhibitor or ARB as a fixed-dose combination therapy (eg, benazepril plus amlodipine, felodipine plus enalapril,trandolapril plus verapamil, or amlodipine plus valsartan or olmesartan), as well as with thiazide diuretics.

Of note, dihydropyridine CCBs (eg, amlodipine) should not be used as monotherapy in hypertensive patients with CKD and proteinuria. The nondihydropyridine CCBs verapamil and diltiazem are preferred over dihydropyridine CCBs if monotherapy with a CCB is used in the CKD patient with proteinuria (or if RAS blockade cannot be used in a complex drug regimen [bilateral renal artery stenosis]); however, the negative renal effects of dihydropyridine CCB monotherapy in the CKD patient with proteinuria seem to be negated with the concurrent administration of RAS blockade.¹⁵⁶

The efficacy and adverse effect profiles of β -blockers are both compound and delivery system dependent. Although β -blockers have important primary roles in the treatment of angina pectoris, systolic and diastolic forms of HF, and in the

postmyocardial infarction patient, they have limited usefulness as monotherapy in certain subsets of hypertensive patients, including blacks, the elderly, and those with diabetes mellitus.⁴ This limited use, together with the poor CVD outcomes that have been observed with β -blockers, has clearly shifted the use of these compounds to lower tier status other than for select circumstances. Much of the debate on the proper place of β -blockers in the management of HTN has focused on how effective (or not) the cardioselective β -blocker atenolol is in the treatment of HTN and in providing specific outcome benefits. Also, it is not currently known whether vasodilating β -blockers such as carvedilol or nebivolol will result in similar or different clinical outcomes in comparison with the older β -blockers.¹⁵⁷

α_1 -Adrenergic-blocking drugs (α_1 blockers) reduce BP comparably to other major drug classes and are also effective therapies for benign prostatic hypertrophy.⁴ α -Blockers further reduce BP when combined with nearly all antihypertensive drug classes and are useful add-on drug therapies in contemporary treatment regimens of patients with resistant HTN. These drugs are the only antihypertensive drug class that improves lipid profiles and reduces insulin resistance; however, the latter 2 properties are not associated with a specific outcome benefit.

Direct vasodilators, such as hydralazine and minoxidil, are poor therapeutic choices as single-drug therapy because of their activation of counterregulatory responses (ie, salt and water retention and activation of the sympathetic nervous system) and, in the case of hydralazine, because it must be administered 3 times daily; thus, these compounds are used primarily as late add-on therapy in the setting of severe HTN.

HTN Therapeutics in Special Situations

Practical Tips for Lowering BP in Resistant HTN

Resistant HTN has been defined as the lack of BP control on ≥ 3 adequately dosed drugs of different classes (including a diuretic) or controlled BP on ≥ 4 agents inclusive of a diuretic. The rising numbers of Americans with HTN and subsequent resistant HTN have been attributed to the rapidly increasing prevalence of comorbidities, such as obesity, type 2 diabetes mellitus, and CKD.^{158–160} Treatable causes of resistant HTN should be sought and addressed or eliminated to the greatest degree feasible. These include OSA and use of modalities that raise BP (high-salt/low-potassium diet, excessive alcohol intake, nonsteroidal antiinflammatory agents, decongestants, cocaine, etc). Table 6 displays recommendations for attaining BP control in patients with resistant HTN including the use of a diuretic that is appropriate to the level of kidney function. Impedance cardiography appears to be a useful therapeutic decision aid. Three-month HTN control rates in HTN specialist¹⁶¹ and primary care¹⁶² have been higher when drug selections have been guided by hemodynamic abnormalities.

HTN Therapy in Diabetes Mellitus

The interpretation of the Action to Control Cardiovascular Risk in Diabetes Study results¹⁶³ has reignited debate regarding the optimal BP target for persons with diabetes mellitus. The Action to Control Cardiovascular Risk in Diabetes Study

Table 6. Therapeutic Recommendations for Lowering BP in Resistant HTN

Scrutinize current drug regimen to

- Remove drugs (eg, NSAIDs) that can attenuate BP lowering
- Identify exposures (eg, excessive alcohol, high sodium) that undermine pharmacological BP lowering

Review current antihypertensive drug regimen to

- Avoid undesirable therapeutic combinations that are poorly tolerated and/or minimally effective (see Table 5)
- Include ≥ 1 diuretic that is appropriate for the level of kidney function
- Consider adding a second diuretic with a complementary mechanism of action (eg, chlorthalidone+spironolactone)
- Ensure that ≥ 1 CCB is in the treatment regimen
- If systolic heart function is normal (ejection fraction $\geq 50\%$), consider the simultaneous use of a DHP and a non-DHP CCB

If available, use noninvasively measured vascular function to guide therapeutic selections

Consider referral to a hypertension specialist

DHP indicates dihydropyridine; NSAID, nonsteroidal anti-inflammatory drug.

compared 2 levels of SBP lowering, <140 mm Hg (standard) and <120 mm Hg (intensive), on the primary composite end point of nonfatal myocardial infarction, nonfatal stroke, and death from CVD causes.¹⁶³ At 4.7 years, the primary end point was nonsignificantly lower (12%) in the intensive-treatment group. Nevertheless, up to a 27% reduction in the primary end point may have been missed because the event rate was lower than projected. The annual rates of any stroke and nonfatal stroke were 41% ($P=0.01$) and 37% ($P=0.03$) lower, respectively, in the intensive-treatment group, and there was less macroalbuminuria in the intensive group (6.6% versus 8.7%; $P=0.009$). There was, however, more hypotension (0.70% versus 0.04%), hypokalemia (2.1% versus 1.1%), and eGFR <30 mL/min per 1.73 m² (4.2% versus 2.2%) in the intensive group.¹⁶³

In the placebo-controlled Appropriate Blood Pressure Control in Diabetes normotensive study,³⁴ patients with type 2 diabetes mellitus and BP $<140/90$ mm Hg were randomized to moderate BP control (DBP: 80 to 89 mm Hg; placebo) or intensive BP control (DBP: 10 mm Hg lower than baseline; active drug therapy). Baseline BP averaged 137/84 and 136/84 mm Hg, respectively, in the 2 treatment groups. Over ≈ 5 years, there was less progression of retinopathy and proteinuria and fewer strokes in the intensive-control group (BP averaged 128/75 mm Hg) compared with the moderate-control group (BP averaged 137/81 mm Hg).³⁴ In the Appropriate Blood Pressure Control in Diabetes hypertensive study³³ in patients with type 2 diabetes mellitus and DBP ≥ 90 mm Hg who were randomized to either intensive BP control (DBP: <75 mm Hg) or moderate BP control (DBP: 80 to 89 mm Hg), fewer overall deaths (5.5% versus 10.7%; $P=0.037$) occurred in the intensive BP control group. In the Hypertension Optimal Treatment Study,³⁷ there were fewer CVD events and myocardial infarctions and lower CVD mortality in the diabetic subgroup randomized to the ≤ 80 -mm Hg treatment arm compared with the ≤ 90 -mm Hg treatment arm. Thus, the totality of evidence, including the absence of substantive harm from aggressive BP lowering,

was persuasive enough to leave unchanged the goal BP ($<130/80$ mm Hg) for nephropathy-, retinopathy-, and stroke-prone blacks with diabetes mellitus and HTN.

Indigent Patients With HTN

Indigent blacks consume inadequate amounts of fruits and vegetables and also engage in less physical activity than recommended.¹⁶⁴ Consumption of a diet high in fruits and vegetables may be difficult because of limited availability and, when available, because of higher cost in their usual shopping venues. Teaching social problem solving in food selection to indigent patients can assist with adoption of a Dietary Approaches to Stop Hypertension-type diet.¹⁶⁵ Medications used in indigent patients must be effective, tolerable, and affordable. Pi-by-no programs now offered by major pharmacy chains offer improved and lower cost access to effective pharmaceuticals. However, generic formularies typically offer a restricted range of antihypertensive agents. In addition, patient-in-need programs, although at times difficult to use, can provide branded pharmaceuticals from pharmaceutical companies at no cost. Patients use multiple strategies to secure their medications, even those with drug benefit plans, such as requesting generic medications because of lower copays, pill splitting, and seeking community health center-based support for access to prescriptions at lower costs.¹⁶⁶ However, the substitution of generics for more expensive branded antihypertensive drugs does not invariably increase adherence.¹⁶⁷ Furthermore, clinicians should remember that out-of-pocket costs may increase at the end of the contract year. The annual dollar limit, or cap, on managed care plans, including Medicaid and Medicare Part D, is another barrier to medication access. Pi-by-no long-acting CCBs, chlorthalidone, reserpine, and spironolactone, will be key antihypertensive agents when assembling a low-cost, efficacious antihypertensive drug regimen. Reserpine, an often-maligned antihypertensive agent, is cheap, long acting, and highly effective. It can be used with minimal adverse effects when prescribed at a low dose (0.10 to 0.25 mg/d).^{4,168} The risk of rebound HTN is lower than with clonidine because of its long duration of action. Importantly, reserpine combines very effectively with diuretic agents.¹⁶⁸

Summary

HTN in blacks remains a vexing public health and clinical problem. This updated ISHIB consensus statement provides a comprehensive overview of HTN in blacks together with specific strategies for successfully approaching BP lowering and target-organ protection in black patients. We have placed a major emphasis on the comprehensive assessment and appropriate risk stratification of individual blacks with HTN. It is our belief that an increased understanding of HTN in blacks, along with implementation of the specific strategies detailed in this document, will lead to better BP control and improved outcomes for blacks with HTN. Irrespective of the pharmacological agents used, the practitioner must persistently monitor BP, change medications as needed, and reinforce comprehensive lifestyle changes to ensure attainment and persistent maintenance of BP below target levels.

Appendix

Table. Outcomes by Race in Drug Treatment Cardiovascular/Renal Clinical Outcomes Trials

| Trial/Year (Reference No.) | No. (%) of Blacks | Design (1° End Point [EP]) | Rx Groups | BP Δ SBP/DBP, mm Hg* | Results | Results Reported in Blacks |
|---------------------------------|-------------------------|--|--|---|--|---|
| Placebo controlled | | | | | | |
| RENAAL 2001, 2006 (20,21) | 230 (15) | RDB (composite of ESRD, creatinine doubling, or death) | PLCB vs ARB | 2/0 | Sig \downarrow 1° EP, ESRD (28% \downarrow), creatinine doubling, and HF with ARB | NS 17% \downarrow in ESRD |
| IDNT 2001 (42) | 288 (13) | RDB (composite of ESRD, creatinine doubling, or death) | PLCB vs CCB PLCB vs ARB | 3/3 4/3 | \downarrow 1° EP and creatinine doubling with ARB only | NR |
| HOPE 2000 (41) | 175 (1.8) | RDB (composite of MI, stroke, or CV death) | PLCB vs ACEI | 3/1 | Sig \downarrow 1° EP, CV death, MI, stroke; revascularization, HF and total mortality with ACEI | NR |
| Syst-Eur 1997 (31) | Eastern Europe | RDB (CVA) | CCB vs PLCB | 10/5 | \downarrow CVA, HF+MI, CVD | None |
| CAPT-DM 1993 (30) | 15 (3.7) | RDB (Creatinine doubling) | PLCB vs ACEI | 2/4 | \downarrow in 1°EP, ESRD+death, proteinuria | NR |
| SHEP 1991 (29) | 657 (13.9) | RDB (CVA) | PLCB vs THZD+BB | 12/4 | \downarrow CVA, CHD, MI, CVD | NR |
| Active comparisons | | | | | | |
| Outcomes by BP goal | | | | | | |
| AASK 2002 (15) | 1094 (100) | RDB, 3x2 factorial (Δ GFR slope and time to ESRD or death or threshold GFR \downarrow) | MAP 102–107 vs <92 mm Hg | 13/7 | NS difference | Same |
| PROGRESS 2001 (43) | Australia, Asia, Europe | RDB (CVA) | PLCB vs ACEI PLCB vs ACEI+THZD | 5/3 12/5 | \downarrow CVA and CVD with ACEI+THZD only | NR |
| ABCD 1998, 2000 (32,33) | 65 (13.8) | RDB (Δ creatinine clearance) | DBP 80–89 vs <75 mm Hg | 6/8 | NS difference | NR |
| UKPDS 38 1998, 1998 (35,36) | 87 (7.6) | PROBE (composite diabetic complications, CVD, renal) | BP <85/105 vs <150/85 | 10/5 | \downarrow diabetic complications, diabetic mortality, stroke, microvascular with low BP goal | NR |
| HOT 1998 (37) | 582 (3.1) | PROBE (composite CVD+CVA) | DBP \leq 90 vs DBP \leq 85 vs DBP \leq 80 mm Hg | 2/2 | NS difference except \downarrow CVD in diabetics at lowest goal | NR |
| HDFP 1979 (18,19) | 4846 (44.3) | Random allocation (all-cause mortality) | Usual care vs stepped care | .../6 | 17% \downarrow mortality with stepped care | 19% to 28% \downarrow mortality with stepped care |
| VA Cooperative 1970 (17) | 380 (41.3) | RDB (Composite CVD) | THZD/ reserpine/ hydralazine vs PLCB | 31/19 | \downarrow CVD | Similar to whole cohort |
| VA Cooperative 1967 (16) | 77 (53.8) | RDB (composite CVD) | THZD/ reserpine/ hydralazine vs PLCB | 43/28 | \downarrow CVD | Similar to whole cohort |
| Drug class comparisons | | | | | | |
| ACCOMPLISH 2008 (48) | 1416 (12.3) | RDB (composite of CV death, nonfatal MI, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, coronary revascularization) | ACEI+CCB vs ACEI+THZD | 1/1 | Sig \downarrow 1°EP, MI, coronary revascularization, composite of CV events, composite of CV death with ACEI+CCB | NR |
| ASCOT-BPLA 2005, 2008 (46,47) | ~960 (5) | PROBE (fatal CHD/nonfatal MI) | BB vs CCB | 3/2 | \downarrow mortality, CHD, CVD, CVA, PVD with CCB | NR |
| ALLHAT 2000, 2002, 2005 (24–26) | 15 094 (35.6) | RDB (fatal CHD/nonfatal MI) | THZD vs α -blocker THZD vs CCB THZD vs ACEI | 2/0 overall; 4/0 in blacks 1/1 2/0; 4/1 in blacks | \downarrow HF, CVA and CVD with THZD \downarrow HF with THZD \downarrow HF, CVA, CVD with THZD | Similar to whole cohort, similar to whole cohort \downarrow HF, CVA, CHD, CVD with THZD |
| VALUE 2004, 2006 (27,28) | 639 (2.7) | RDB (fatal CHD/ nonfatal MI) | CCB vs ARB | 2/2 overall; 4.5/2.0 in blacks | \downarrow CHD with CCB | Similar to whole cohort |
| CONVINCE 2003 (45) | 1122 (6.8) | RDB (Composite CVD) | CCB vs BB/THZD | 0/0 | \downarrow HF with BB/THZD | NR |
| ANBP-2 2003 (44) | Australia | PROBE (composite CVD) | THZD vs ACEI | 0/0 | \downarrow CVD males only | NR |
| LIFE 2002, 2004 (22,23) | 533 (6.0) | RDB (composite CVD) | BB vs ARB | 1/0 | \downarrow 1°EP, CVA with ARB | \downarrow 1°EP with BB |

(Continued)

Table. Continued

| Trial/Year (Reference No.) | No. (%) of Blacks | Design (1° End Point [EP]) | Rx Groups | BP Δ SBP/DBP, mm Hg* | Results | Results Reported in Blacks |
|-----------------------------|-------------------|---|--|-----------------------|--|----------------------------|
| AASK 2002 (15) | 1094 (100) | RDB (Δ GFR slope and 1° time to composite ESRD or death or threshold GFR ↓) | BB vs CCB BB vs ACEI CCB vs ACEI | 2/0 0/1 2/1 | ↓ composite, ESRD, GFR threshold with ACEI vs CCB and BB | Same |
| IDNT 2001 (42) | 228 (13) | RDB (composite ESRD or creatinine doubling or death) | PLCB vs CCB PLCB vs ARB CCB vs ARB | 3/3 4/3 1/0 | ↓ 1°EP and creatinine doubling with ARB vs CCB | NR |
| NORDIL 2000 (40) | Sweden | PROBE (composite CVD) | BB/THZD vs CCB | 3/0 | NS difference | NR |
| CAPPP 1999 (38) | Finland/Sweden | PROBE (Composite CVD) | BB/THZD vs ACEI | 3.3/... | ACEI not superior to BB/THZD | NR |
| STOP-2 1999 (39) | Sweden | PROBE (Composite CVD) | CCB or ACEI vs BB or HCTZ | 0/0 | CCB and ACEI not superior to BB/HCTZ | NR |
| UKPDS 39 1998, 1998 (35,36) | 87 (7.6) | PROBE (composite diabetic complications, CVD, renal) | BB vs ACEI | 1/2 | NS difference | NR |
| ABCD 1998, 2000 (32,33) | 65 (13.8) | RDB (Δ creatinine clearance) | CCB vs ACEI | NS | ↓ CHD, nonfatal MI with ACEI | NR |

AASK indicates African American Study of Kidney Disease and Hypertension Study Group; ABCD, Appropriate Blood Pressure Control in Diabetes; ACCOMPLISH, Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension; ACEI, ACE inhibitor; ANBP-2, Second Australian National Blood Pressure Study; ASCOT-BPLA, Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm; BB, β-blocker; CAPPP, Captopril Prevention Project; CAPT-DM, Captopril Diabetes Mellitus; CONVINCE, Controlled Onset Verapamil Investigation of Cardiovascular End Points; CVA, cerebrovascular accident; ESDR, end-stage renal disease; GFR, glomerular filtration rate; HDPF, Hypertension Detection and Follow-Up Program; HOPE, Heart Outcomes Prevention Evaluation; HOT, Hypertension Optimal Treatment; IDNT, Irbesartan Diabetic Nephropathy Trial; LIFE, Losartan Intervention for End Point Reduction in Hypertension; MI, myocardial infarction; NORDIL, Nordic Diltiazem Study; NR, not reported; NS, not significant; PLCB, placebo; PROBE, prospective, randomized, open-label, blinded-end point; PROGRESS, Perindopril Protection Against Recurrent Stroke Study; PVD, peripheral vascular disease; RDB, randomized, double-blind; RENAAL, Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan; SHEP, Systolic Hypertension in the Elderly Program; Sig, significant; STOP-2, Swedish Trial in Old Patients With Hypertension-2; Syst-Eur, Systolic Hypertension in Europe; THZD, thiazide diuretic; UKPDS, United Kingdom Prospective Diabetes Study; VA Coop, Veterans Administration Cooperative Study Group on Antihypertensive Agents; VALUE, Valsartan Antihypertensive Long-term Use Evaluation.

*Data show the difference in BP (control group—experimental group).

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