9 Hypertension Management in African Americans: The AASK and Other Landmark Trial Application

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Introduction

Hypertension is a major public health challenge and affects 120 million adults in the United States. Recent hypertension trial outcomes indicate that further lowering of blood pressure below the standard target may reduce mortality [1] which is now reflected in the latest treatment guidelines that have lowered the target blood pressure to 130/80 mmHg [2]. The excess burden of hypertension among African-Americans was recognized in the early twentieth century and largely contributes to the excessive morbidity and mortality seen in this population compared to other racial/ethnic groups. It is well documented that hypertension in African-Americans is more prevalent, has an earlier onset, increased severity and results in more complications than other populations [3]. Despite treatment advances, improved access to health care, and similar control rates across most racial groups, African-Americans continue to experience high rates of hypertension attributable complications such as end stage renal disease (ESRD), heart failure and stroke. A comprehensive approach for effective management of hypertension in the African-American population is crucial to address this important health disparity. The pathogenesis, new hypertension guidelines and clinical trial outcomes related to African-Americans, specifically the African American Study of Kidney Disease and Hypertension (AASK) trial, will be discussed in this chapter. The term "African-American" or "Black" patients will refer to all people of African ancestry living in the USA.

Epidemiology

Hypertension has been recognized as the most potent risk to cardiovascular health of African Americans and is the leading cause of

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cardiovascular and end stage renal disease. The recent National Health and Nutrition Survey (NHANES) 2011–2012 [4] indicated the age-adjusted prevalence of hypertension was higher among non-Hispanic blacks (42.4%) than non-Hispanic whites (28%), non-Hispanic Asians (24.9%) or Hispanic (25.9%) adults. Relative to whites, African Americans have more blood pressure elevations above conventional hypertension thresholds (140/90 mmHg), experience earlier onset hypertension, manifest greater blood pressure elevation (>180/110 mmHg), and have more comorbid conditions such as diabetes and left ventricular hypertrophy that augment risk for poor clinical outcomes [5]. The prevalence rates of hypertension are steadily increasing in all racial groups and African women have the highest hypertension prevalence at 46.1%, compared to black men (44.9%) and non-Hispanic and Hispanic women (30%). Awareness, treatment and control rates of hypertension have increased over time in all racial groups [6]. The hypertension control rate (blood pressure < 140/90 mmHg) was higher among non-Hispanic whites (55.7%), than non-Hispanic blacks (48.5%), non-Hispanic Asian (43.5%), or Hispanic (47.4%) adults. Despite some treatment advances, hypertension attributable morbidity and mortality in African Americans remain high with 30% more nonfatal stroke, 80% more fatal stroke, 50% more cardiovascular disease, and fourfold more kidney disease compared to other populations [7, 8]. In addition, the Coronary Artery Risk Development in Young Adults (CARDIA) study, showed that African Americans have a 20-fold higher rate of incident heart failure before the age of 50 compared to White Americans, which is considered directly related to hypertension [9]. Further, Black – White differences in hypertension-related hospitalization rates increased from 2004 to 2009 with threefold higher rates among African Americans compared to White Americans [10]. Overall, hypertension is thought to account for 50% of the Black-White mortality disparity in the USA.

Pathogenesis of Hypertension

There are no unique risk factors or biomarkers for hypertension between racial/ethnic groups. However, some pathophysiological mechanisms that are etiologically linked to the development of hypertension do tend to be disproportionately prevalent in selected racial/ethnic groups. In 2017, Musemwa and Gadegbeku [11] proposed that the excess burden of hypertension in African Americans is likely due to interactions of biological, environmental, and social factors superimposed on a genetically-susceptible population (Fig. 9.1).

Roles of Genetic Contribution in the Development of Hypertension in African Americans

Multiple genetic variations with intermediate phenotypes unique to African Americans have been extensively identified, but the results are not conclusive and not linked to hypertension burden in this special population. In a recent study with more than 1000 African Americans, a genome-wide association study (GWAS) using pathway-based analysis identified two potential blood pressure regulation candidate genes associated with systolic blood pressure, SLC24A4 (sodium/potassium/calcium exchanger) and CACNA1H (a voltage-dependent calcium channel) with replication of some their findings in a West African cohort [12]. Unfortunately, these new results could not be replicated in an independent Milwaukee cohort of nearly 2500 African Americans [13]. The Continental Origins and Genetic Epidemiology Network (COGENT) performed the largest blood pressure GWAS including individuals of African (29, 000), European (69,000), and East Asian (19,000) ancestries and found common blood pressure loci across ethnic groups [14]. In contrast, the excess burden of non-diabetic kidney disease has been explained in part by genetic high risk variants in the apolipoprotein 1 (APOL1) gene among African

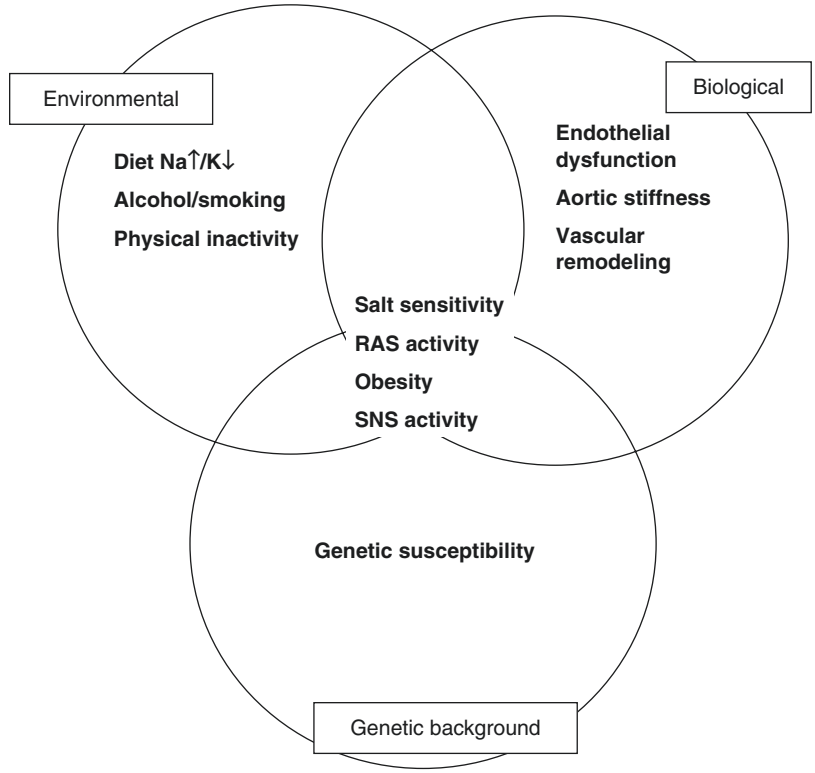

Fig. 9.1 Proposed excess burden of hypertension in African Americans. (Adapted from Ref. [12])

Americans [15, 16]. However, there is conflicting data whether the APOL1 genetic mutations are associated with the increased cardiovascular risk. APOL1 risk alleles have recently been linked to higher systolic blood pressure and earlier onset of hypertension in young African Americans prior to the decline in renal function [17], but these findings were not duplicated in the AASK trial cohort [18]. In summary, these inconclusive race-specific findings using the state-of-the-art genetic investigational tools did not find unique blood pressure regulation genes in African Americans and further research is needed to explore the complex question.

Obesity

Body mass index (BMI) positively correlates with blood pressure and is well documented in all racial/ethnic groups. Obesity is more prevalent in African Americans, particularly in African American women compared to White or Hispanic populations. In obesity, hypertension along with dyslipidemia, and insulin resistance often composes a health risk cluster: metabolic syndrome which is a significant cardiovascular risk. One in six African American women is considered to be extremely obese (BMI > 40 kg/m^2) and this prevalence is almost fourfold higher than that in white or Hispanic women [5]. Obesity impacts blood pressure through multiple mechanisms including increasing sympathetic nerve activity, salt sensitivity, and activation of renal angiotensin aldosterone system (RAAS), and glomerular hypertrophy which has been implicated in subsequent renal injury [19].

Salt-Sensitivity

Salt sensitivity is more common in normotensive and hypertensive African Americans than the general population. Higher rates of obesity

and lower oral potassium intake contribute to the excess prevalence of salt sensitivity in this population [20, 21]. Both weight loss and increases in potassium intake ameliorate salt sensitivity with a reversal of the pressor effects of sodium in salt sensitive African Americans. Importantly, salt sensitivity is linked to a reduced dipping in nocturnal blood pressure, microalbuminuria, and other pressure related target organ injury [22, 23].

Renin-Angiotensin-Aldosterone System

It is well observed that African Americans have low circulating levels of renin as well as a lower response to monotherapy with angiotensin converting enzyme (ACE) inhibitors compared to diuretics. Clinical evidence suggests that low renin levels in the circulation reflect high local tissue angiotensin II production rather than high volume status. Increased tissue angiotensin II promotes inflammation and fibrosis in the kidney leading to excess salt retention [24, 25]. In a salt-sensitive and low-renin African American population, urinary angiotensinogen, a marker of intra-renal RAAS activation, was associated with elevated blood pressure [26]. In addition, circulating the aldosterone level is increased in African Americans. Collectively, RAAS activation plays an important role in hypertension and pressure-related target organ damage that is not reflected by hormonal activity in the circulation.

Vascular Dysfunction

Enhanced peripheral vascular resistance is the primary contributor to the maintenance of hypertension. A review of vascular studies in normotensive Black and White individuals concludes that African Americans have enhanced adrenergic vascular reactivity and attenuated vasodilator response [27]. The scientific literature suggests the vasodilatory impairment is due to both endothelium-dependent and non-endothelium-dependent mechanisms. Reduced nitric oxide (NO) bioavailability largely contributes to endothelium dependent vasodilation [5]. Dysregulation of oxygen derived free radicals, and endothelin-1 may potentiate the imbalance of vasoactive hormones that leads to elevated blood pressure and vascular remodeling [28]. Recent evidence suggests that central aortic pressure better reflects the load on target organs than brachial pressure. Central pressures are more predictive of cardiovascular outcomes and may partially explain racial differences in cardiovascular outcomes despite equivalent rates of hypertension control [29, 30]. In an important recent study, healthy young black men with similar clinical characteristics as young white men, including brachial blood pressure, were found to have higher central blood pressures, enhanced augmentation of central blood pressure, increased central arterial stiffness, increased carotid intima-media thickness, and reduced endothelial function [31]. Similar findings of greater carotid arterial stiffness was observed in the Black population of the Atherosclerosis Risk in Communities (ARIC) study when compared to the White population at baseline analysis [32]. Therefore, vascular dysfunction occurs earlier and may not be clinically apparent in the African American population versus White population. The above findings regarding differences in vasculature may be an important clue to the in the cause and consequences of hypertension in African American population.

Social Behavior and Environmental Risk Factors

There are many studies linking dietary habits and other lifestyle indicators to inadequate blood pressure control in the African American population [33]. Higher prevalent rates of obesity, excess dietary intake of sodium, and inadequate dietary intake of potassium are well recognized in African Americans. Physical inactivity rates are higher among the Hispanic and African American adults compared to White

Americans. The consumption of large amounts of alcohol (>210 g/week) is associated with higher risk of hypertension in adults, but the risk is observed at low to moderate amounts (1–209 g/per week) of alcohol in black men in high stress environments and with low socioeconomic status [34]. However, a cross-sectional study of NHANES data from 2001–2006 concluded that health behaviors do not fully explain the existing racial disparities in hypertension prevalence and control rate in this special population [35].

Application of Clinical Trial Results and Guidelines to African American Hypertensive Patients

African American Study of Kidney Disease and Hypertension (AASK) Trial

The African American Study of Kidney disease and Hypertension (AASK) study [36] was the first large scale trial to investigate the effects of three different anti-hypertensive drug classes as well as the effects of two levels of blood pressure (Intensive vs Standard) on decline in kidney function in an African American hypertensive population with chronic kidney disease using a 3 × 2 factorial design. The study enrolled 1094 African Americans aged 18–70 years with hypertensive renal disease (GFR: 20–65 ml/min/per 1.73 m^2) and followed for 3–6.4 years. Open label antihypertensive agents were added to the groups to reach the blood pressure goal. In 2002, final results of the AASK trial showed the ACE inhibitor, ramipril, was better than the β blocker, metoprolol, or the dihydropyridine calcium channel blocker (CCB), amlodipine, in slowing glomerular filtration rate (GFR) decline in African American hypertensive patients with mild to moderate hypertensive kidney disease. Metoprolol was not different from the amlodipine in the clinical outcomes. Of note, there was no difference between the intensive blood pressure (MAP: 92 mmHg) and standard blood pressure (MAP: 102–107 mmHg) groups in regards to the kidney function decline and the secondary clinical composite outcome. The secondary clinical composite end point in the AASK trial comprised of a decrease in GFR ≥50%, or ≤25 ml/min/1.73 m^2, ESRD or death. The final results from the AASK trial suggest that reduction in blood pressure to levels below those currently advocated for cardiovascular risk reduction did not provide additional renal protective benefits to African Americans with hypertensive nephrosclerosis. This conclusion must be considered in the setting of the relatively limited follow up time period and that only one third of the subjects in the original AASK trial had a urinary protein excretion >220 mg/g creatinine. The low level of urinary protein excretion for the majority of subjects would argue against significant loss of kidney function over the several years of the clinical trial. In the long-term follow up, AASK trial participants were invited to enroll into cohort phase after completing trial phase in which blood pressure target was less than 130/80 mmHg in the intensive blood pressure group and all patients were followed up to 8.8–12.2 years [37]. There was no significant difference between two blood pressure groups in slowing the progression of chronic kidney disease and primary outcome which includes doubling of serum creatinine and ESRD or death. However, in patients with proteinuria ≥220 mg/g, the intensive blood pressure control provided significant renal protection in this special group of patients as compared with standard blood pressure control. Another long term (up to 14.4 years) follow up study with AASK trial participants [38] found the strict blood pressure control did not delay the onset of ESRD, but may reduce the relative risk of death in African American hypertensive patients with chronic kidney disease. Cardiovascular outcomes were also studied in AASK trial participants with mean follow up of 4.1 years. The cardiovascular events rate (cardiac death, myocardial infarction, stroke, and heart failure) was not different among the three anti-hypertensive drug classes or two blood pressure control levels. However, the AASK trial was not powered for cardiovascular

events thereby limiting conclusions regarding intensive versus standard blood pressure regimens [39]. Importantly, the final AASK trial results provide the fundamental basis for the use of ACE inhibitor in the hypertensive African American population with mild to moderate chronic kidney disease. The relative superiority of the ACE inhibitor as initial therapy in African American with non-diabetic kidney disease is ironic given the long-hold belief that CCBs were preferred anti-hypertensive agents for African Americans [40]. The AASK trial findings were consistent with renal outcomes in other populations with non-diabetic hypertensive kidney disease.

Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

ALLHAT trial was the largest hypertensive trial in recent years and this study enrolled over 33,357 hypertensive patients with age >50 years and at least one other cardiovascular risk factor from 623 North American Centers during 1994 through 2002 [41, 42] in which 35% of patients are African American. The ALLHAT trial was designed to determine whether CCB or ACE inhibitor is superior to a thiazide diuretic in reduction of cardiovascular outcomes. Other anti-hypertensive agents were added to achieve blood pressure <140/90 mmHg in all groups. The final trial results demonstrated the primary cardiovascular end points (fatal coronary heart disease and non-fatal myocardial infarction) were not different among treatment groups. The diuretic, chlorthalidone, was associated with greater reductions in blood pressure then the ACE inhibitor, lisinopril. Chlorthalidone was also associated with a relative reduction in heart failure and stroke compared with lisinopril [43]. However, the higher stroke risk relative to chlorthalidone in the lisinopril group was experienced only in African American patients and can plausibly be explained by the lesser blood pressure reduction in lisinopril treatment group, where systolic blood pressure was on average 4 mmHg higher. The blood pressure differences were likely even larger between the lisinopril and chlorthalidone treatment groups in preceding study years.

The ALLHAT design employed a rather restrictive sequence of treatment scheme, which was not practical in clinical practice since African American patients with hypertension are more required using a diuretic as add on agent for hypertension treatment which was not permitted in ALLHAT trial. In this high risk population, the ALLHAT trial also showed amlodipine was comparable to chlorthalidone and lisinopril for the renal events rate as well as for an estimated rate of decline of renal function in an elderly population. This was an unexpected result, because the dihydropridine CCBs provide good anti-hypertensive therapy but, not renal protective effects beyond those anticipated with blood pressure reduction.

Systolic Blood Pressure Interventional Trial (SPRINT)

The SPRINT trial was a latest randomized large trial to evaluate the impact of intensive blood pressure control (systolic blood pressure < 120mmHg) vs standard blood pressure control (systolic blood pressure < 140 mmHg) on the incident cardiovascular, renal and neurological outcomes in a diverse population [1]. More than 9000 non-diabetic patients with cardiovascular risk and chronic kidney were enrolled in the trial in which 30% participants are African American. The trial results revealed intensive blood pressure control reduced cardiovascular composite outcomes by 25% in the high risk patients as compared with standard treatment. These results differ from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [44] which did not see a difference with intensive blood pressure therapy in a smaller population with type 2 diabetes. A sub-analysis study [45] further revealed

similar treatment benefits exist in African American racial/ethnicity groups as compared with other racial groups with intensive blood pressure management group, although the African American population required an average of 0.3 more medications to achieve the systolic blood pressure goal of <120 mmHg. The above trials highlight the current uncertainty of the ideal blood pressure target of hypertension treatment. However, the large SPRINT trial demonstrated some beneficial outcomes and no significant harm thereby effectively opening the door for more aggressive therapy in high risk populations such as hypertensive African Americans.

International Society of Hypertension in Blacks Consensus Statement (ISHIB)

The 2010 International Society of Hypertension in Blacks (ISHIB) Consensus panel updated recommendations for more aggressive hypertension therapy than proposed by other guidelines for African American population. The ISHIB panel endorsed blood pressure target of <135/85 mmHg for primary prevention, and <130/80 for secondary prevention and initiation of lifestyle modifications at blood pressure ≥115/75 mmHg [46]. The guideline focused on the risk stratified treatment and early use of two drug combination therapy and initial therapy agents with diuretics or CCBs.

The optimal blood pressure target of hypertension treatment in general population has been debated many years, general population guidelines worldwide agree that treatment is warranted for stage 1 hypertension (blood pressure ≥140/90 mmHg) [47–51]. However, the guidelines vary in blood pressure targets in older persons in the general population (Table 9.1). The JNC 8 convened an expert panel in 2014 and recommended raising the blood pressure target in patients >60 years without diabetes and chronic kidney disease to 150/90 mmHg [52]. The newly published ACC/AHA guideline in 2017 [2] recommends to relax the blood pressure target to 130/80 mmHg in the general population regardless ages and racial/ethnicity. Those new hypertension treatment guidelines are consistent with the 2010 ISHIB Consensus panel recommendations and endorses target blood pressure is <130/80 mmHg in African American population with hypertension (Table 9.2).

Table 9.1 Comparison of initial drug therapy by race in hypertension consensus panels

Guidelines	Initial therapy in non-Blacks	Initial therapy in Blacks
ISHIB (2010)	–	Diuretics or CCB
NICE (2011)	<55 years ACEI, ARB; >55 years CCB	CCB
ESH/ESC (2013)	Any class	Diuretics or CCB
AHA/ACC/CDC (2014)	Thiazide, ACEI, ARB, CCB	–
ASH/ISH (2014)	Thiazide, ACEI, ARB, CCB	Thiazide or CCB
2014 JNC VIII	Thiazide, ACEI, ARB, CCB	Thiazide or CCB
CHEP (2016)	Thiazide, ACEI, ARB, CCB	Thiazide, CCB, ARB, BB if <60 years
AHA/ACC (2017)	Thiazide, ACEI, ARB, CCB	Thiazide, CCB, ACEI, ARB

Abbreviations: ISHB International Society of Hypertension in Blacks, *NICE* National Institute for Health and Clinical Evidence, *ESH/ESC* European Society of Hypertension/European Society of Cardiology, *AHA* American Heart Association, *ACC* American College of Cardiology, *CDC* United States Centers for Disease Control and Prevention, *ASH/ISH* American Society of Hypertension/International Society of Hypertension, *JNC VIII* the Eighth Join National Committee, *CHEP* Canadian Hypertension Education Program

Table 9.2 Blood pressure targets by hypertension consensus panels

Guidelines	Blood pressure target	Age-specific blood pressure target	Diabetes	Chronic kidney disease	Combination blood pressure threshold
ISHIB (2010)	<135/85	–	<130/80	<130/80	<15/10
NICE (2011)	<140/90	<150/90	<140/90	<140/90	–
ESH/ESC (2013)	<140/90	<140 or 150/90	<140/85	<140/90	Preferred
AHA/ACC/CDC (2014)	<140/90	<140–145/90	<140/90	<140/90	<20/10
ASH/ISH (2014)	<140/90	<150/90	<140/90	<140/90	<20/10
JNC VIII (2014)	<140/90	<150/90	<140/90	<140/90	<20/10
CHEP (2016)	<140/90	<150/90	<130/80	<140/80	<20/10
AHA/ACC (2017)	<130/80	<130/80	<130/80	<130/80	–

Age specific blood pressure targets: NICE, ESH/ESC, AHA/ACC/CDC, ASH/ISH, CHEP are for any age >80 years; 2014 JNC VIII for age >60 years
ESH/ESC, combination preferred for markedly high blood pressure or high risk patients
AHA/ACC/CDC, blood pressure goal, if tolerated
JNC VIII, if blood pressure below target and well tolerated, no need to adjust
Optional alternative
CHEP, optional

Conclusion

Despite advances in hypertension treatment, the prevalence of hypertension in African Americans is higher when compared to other racial/ethnic populations. Hypertension develops at an earlier age in African Americans than Whites and is associated with more severe hypertension related complications, including chronic kidney disease, end stage renal disease, stroke, heart failure and cardiovascular disease. Hypertension may account for 50% of the Black-White mortality disparity in the USA. Therefore, it is crucial to address the unique risks in this specific population. The pathogenesis of hypertension in African Americans is multifactorial, and a multi-pronged approach may be necessary to address hypertension control. Addressing health disparities, such as social and environmental risks, that contribute to the development of hypertension in African American patients can have an important impact on treatment. Modifiable risk factors such as salt intake, obesity, and physical inactivity should be addressed routinely during clinic visits. Based on the latest recommendations, combination drug therapy with diuretics and RAAS inhibitors is preferred in this special population. It remains to be seen whether this population has specific genetic predisposition to hypertension. Overall, the needs of African Americans are diverse, and a comprehensive treatment plan should address each of these pathogenetic mechanisms.

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