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Therapy of Hypertension in African Americans

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Abstract

Hypertension in African Americans is a major clinical and public health problem because of the high prevalence and premature onset of elevated blood pressure (BP) as well as the high burden of co-morbid factors that lead to pharmacological treatment resistance (obesity, diabetes mellitus, depressed glomerular filtration rate, and albuminuria). BP control rates are lower in African Americans, especially men, than in other major race/ethnicity-sex groups; overall control rates are 29.9% for non-Hispanic Black men. Optimal antihypertensive treatment requires a comprehensive approach that encompasses multifactorial lifestyle modifications (weight loss, salt and alcohol restriction, and increased physical activity) plus drug therapy. The most important initial step in the evaluation of patients with elevated BP is to appropriately risk stratify them to allow determination of whether they are truly hypertensive and also to determine their goal BP levels. The overwhelming majority of African American hypertensive patients will require combination antihypertensive drug therapy to maintain BP consistently below target levels. The emphasis is now appropriately on utilizing the most effective drug combinations for the control of BP and protection of target-organs in this high-risk population. When BP is >15/10 mmHg above goal levels, combination drug therapy is recommended. The preferred combination is a calcium antagonist/angiotensin-converting enzyme inhibitor or, alternatively, in edematous and/or volume overload states, a thiazide diuretic/angiotensin-converting inhibitor.

Hypertension in African Americans is a major clinical and public health problem because of the high prevalence and premature onset of elevated blood pressure (BP) in this population.[1] Moreover, the common occurrence of pressure-related target-organ injury (e.g. left ventricular hypertrophy, heart failure) and the high prevalence of risk-augmenting co-morbidities such

as diabetes mellitus and chronic kidney disease in African Americans markedly increase the likelihood of pressure-related morbidity and mortality in this group at any given BP level.[2] These issues result in the long-term exposure of large proportions of African Americans to higher than optimal BP and disproportionate development of associated consequences.

BP control rates are lower in African Americans, especially men, than in other major race/ethnicity-sex groups; overall control rates are 29.9% for non-Hispanic Black men.[3] Even amongst drug-treated African Americans with hypertension, only 45% have been reported to attain BP control.[4] Hypertension places an exceptionally high toll on the African American population, accounting for approximately 30% and 20% of all deaths, respectively, in African American men and women[5] and 15% of the overall racial difference in potential life-years lost.[6] Thus, enhancing BP control rates represents a profoundly important strategy for the improvement of health status and reduction of pressure-related racial health disparities (e.g. heart failure, retinopathy, stroke) that disproportionately afflict the African American population.

1. Pathogenesis of Hypertension

There are no unique risk factors 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. The pathophysiological perturbations discussed in sections 1.1–1.4 represent tendencies that occur more commonly in African Americans than in Whites.

1.1 Obesity

Obesity contributes significantly to hypertension risk in all populations, particularly racial and ethnic minorities. Obesity is more prevalent in both African Americans and Hispanics, particularly in women, compared with Whites.[7] More importantly, nearly one in six African American women are considered extremely obese (body mass index [BMI] >40 kg/m^2); this prevalence is almost 4-fold higher than that of either White or Hispanic women. There are also marked ethnic and age-based differences in the rate of weight accumulation with an earlier onset of obesity in African Americans versus Hispanics (for women) and Whites (for men).

Obesity-related physiological effects that contribute to the intermediate BP phenotype include enhanced sympathetic activity,[8] altered salt sensitivity (see also section 1.2),[9,10] and resistance to antihypertensive drug therapy.[11,12] Additionally, obesity appears to be a plausible mediator of chronic renal injury[10,13] and is a known contributor to sleep-disordered breathing.

1.2 Salt Sensitivity

Salt sensitivity is disproportionately manifest in African Americans, particularly among those with hypertension. Salt sensitivity can conceptually be defined as a rise in BP occurring during salt administration and/or a fall in BP occurring when salt is restricted. The excess prevalence of salt sensitivity among African Americans relates to the increased frequency of obesity in this population. It has been demonstrated in both Caucasians and African Americans that obesity is linked to salt sensitivity[14,15] and that weight loss ameliorates salt sensitivity, at least among overweight Caucasian adolescents.[14] Low dietary potassium intake in all likelihood substantively contributes to salt sensitivity as high levels of potassium intake can nearly ameliorate the pressor effect of salt in salt-sensitive African Americans.[16] Salt sensitivity has been linked to a lesser fall in nocturnal BP as well as to microalbuminuria and other pressure-related target-organ injury. Salt sensitivity has also been linked to higher antihypertensive medication requirements.

1.3 Renin-Angiotensin System

There has been pervasive interpretation of the tendency toward lower circulating renin levels and a lesser average BP reduction in response to monotherapy with renin-angiotensin system (RAS) antagonist drugs (e.g. ACE inhibitors) compared with diuretics in African Americans as being indicative of a relative inactive RAS system. Low circulating renin levels, however, have been linked to augmented vascular production of angiotensin II,[17] and normotensive, healthy African Americans have been shown to have more, not less, activation of the RAS system than Whites.[18] Circulating aldosterone levels are also higher in African Americans than in Whites.

The exact role of the RAS system in African Americans has not been defined. However, given the pattern of excessive RAS system-dependent target-organ injury (e.g. left ventricular hypertrophy, chronic kidney disease/proteinuria) in African Americans, it is likely that the importance of the RAS system has been overly discounted in this population.

1.4 Vascular Function

Endothelium-dependent and endothelium-independent vascular responses are abnormal in African Americans com-

pared with Whites.[19,20] There are potentially explanatory data suggesting that the bioavailablity of nitric oxide, the main determinant of endothelium-dependent vascular function, is lower in African Americans than in Whites even though African Americans have much higher endothelial-derived nitric oxide synthase (eNOS) activity.[21] It appears that the synthesis of oxygen radicals, mostly via uncoupled eNOS and lesser amounts via NADPH (nicotinamide adenosine dinucleotide phosphate) oxidase, raises levels of oxidative stress and accelerates nitric oxide destruction, which leads to reduced nitric oxide bioavailability/activity in African Americans.[21]

2. Resistant Hypertension

African American patients with hypertension have been routinely characterized as a difficult to treat population subgroup. Control of BP to less than target levels (<140/90 mmHg) in African Americans with hypertension occurs less often than in their White counterparts.[3] It also appears that African Americans with hypertension manifest more of the individual characteristics/co-morbidities (i.e. albuminuria, depressed kidney function, obesity, target-organ injury, diabetes, and severe BP elevations) that have been linked to antihypertensive drug resistance and therefore lesser overall attainment of hypertension control.[11,22] However, whether such poor BP control reflects true resistant hypertension or a confluence of other contributory factors such as therapeutic inertia, patient non-compliance, or socioeconomic status is unclear. Nevertheless, the prevalence of resistant hypertension (BP above goal levels while taking three adequately dosed antihypertensive medications of different drug classes, one of which is a diuretic, or BP below goal levels while taking at least four antihypertensive drugs of different classes, one of which is a diuretic) is more common in African Americans than in Whites.[23]

3. Hypertension Therapeutics in African Americans

Optimal treatment of hypertension requires a comprehensive approach that encompasses multifactorial lifestyle modifications (weight loss, salt and alcohol restriction, and increased physical activity) plus drug therapy. There is ample evidence from major diet intervention studies that calcium-replete diets high in fruits and vegetables as well as low in sodium lower BP to a similar magnitude to single-drug antihypertensive drug therapy.[24,25] The recently updated consensus statement on the treatment of hypertension in African Americans from the International Society on Hypertension in Blacks (ISHIB) recommends comprehensive lifestyle modifications in all African Americans with BP >115/75 mmHg.[23] This is the BP level above which epidemiological cardiovascular disease risk begins its upward inflection, essentially doubling for each 20/10 mmHg increment of BP.

3.1 Risk Stratification

The most important initial step in the evaluation of patients with elevated BP is to appropriately risk stratify them to allow determination of whether they are truly hypertensive and also to determine their goal BP levels.

Table I contrasts the most commonly used JNC 7 (Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) risk stratification scheme with the newly devised risk stratification scheme in the updated ISHIB consensus statement on the treatment of hypertension in African Americans.[23] The most important difference is that in the ISHIB scheme, the target BP for the lowest risk or primary prevention hypertension stratum has been lowered to <135/85 mmHg (from 140/90 mmHg) and the high-risk or secondary prevention group that contains the two co-morbidities in the JNC 7 report (chronic kidney disease and diabetes) has been expanded to include other risk-enhancing co-morbidities such as pre-diabetes, metabolic syndrome, left ventricular hypertrophy, and heart failure; the goal BP, however, remains <130/80 mmHg in the latter group. In the ISHIB consensus statement it was suggested that BP be lowered well below target levels in an effort to maintain BP persistently below goal levels.[23]

3.2 Antihypertensive Drug Therapy in African Americans

The historical focus of drug therapy of hypertension in African Americans has centered on the relative BP-lowering efficacy of single drug classes. However, the majority of African American hypertensive patients will not be controlled to below goal BP levels consistently over the long term with single-drug therapy. Thus, even if a single drug class is more effective than another, *per se*, in its magnitude of BP lowering, BP will often remain above the goal level.

In African Americans, monotherapy with a thiazide diuretic or a calcium channel antagonist has consistently lowered BP more effectively than β-adrenoceptor antagonists (β-blockers), ACE inhibitors, and angiotensin II type 1 receptor antagonists (angiotensin receptor blockers [ARBs]).[27,28] In addition, the less effective RAS antagonists and β-blockers have tended to lower BP, on average, more effectively in Whites than in African Americans.[27-29] Nevertheless, the focus on the relative

Table I. Comparison of blood pressure risk stratification

Parameter	Risk stratification scheme	
	JNC 7[26]	ISHIB[23]
High risk group		
Criteria	Diabetes and/or CKD[a]	Target-organ damage[b], pre-clinical CVD[c], and/or presence of CVD[d]
Goal BP (mmHg)	<130/80	<130/80
Low risk group		
Criteria	All other hypertensives	All other hypertensives
Goal BP (mmHg)	<140/90	<135/85

a Estimated glomerular filtration rate <60 mL/min/1.73 m^2 and/or albumin : creatinine ratio >200 mg/g.

b Estimated glomerular filtration rate <60 mL/min/1.73 m^2, albumin : creatinine ratio >200 mg/g, and/or electrocardiographic or echocardiographic evidence of left ventricular hypertrophy.

c Metabolic syndrome, Framingham risk score >20%, pre-diabetes mellitus (impaired fasting glucose [100–125 mg/dL] and/or impaired glucose tolerance [2-hour post glucose load 140–199 mg/dL]) or diabetes.

d Heart failure (systolic or diastolic), coronary heart disease/post-myocardial infarction, peripheral arterial disease, stroke, transient ischemic attack, and/or abdominal aortic aneurysm.

CKD = chronic kidney disease; **CVD** = cardiovascular disease; **ISHIB** = International Society on Hypertension in Blacks (ISHIB); **JNC 7** = Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

merits of single-drug therapy has diverted attention from a strategy that is essential for the long-term control of BP. That is, the prescription of combination antihypertensive drug therapy to individuals who have a high pre-treatment probability of needing more than single-drug therapy to attain their goal BP level. In addition, as we[29] and Sehgal[30] have shown, BP responses to ACE inhibitor monotherapy is much more varied within race than between race, and race-specific BP response distributions, though shifted toward a lesser average BP response in African Americans, mostly overlap.

3.2.1 Combination Antihypertensive Drug Therapy

The overwhelming majority of African American hypertensive patients will require combination antihypertensive drug therapy to control their BP, i.e. to achieve BP levels consistently below target goals. There are no discernible racial/ethnic differences in BP response to two-drug antihypertensive therapy if at least one of the drugs is either a diuretic or a calcium channel antagonist. According to the ISHIB consensus statement, a reasonable guide to whether two-drug antihypertensive drug therapy is needed is BP levels consistently >15 mmHg systolic and/or 10 mmHg diastolic above goal targets;[23] the JNC 7 report, on the other hand, is slightly more conservative, recommending two-drug combination drug therapy when BP is >20/10 mmHg above goal levels.[26]

Highly effective two-drug antihypertensive drug therapy combinations (table II) share several important characteristics. That is, virtually all of them contain either a diuretic or a calcium channel antagonist, most commonly in conjunction with a RAS antagonist. This approach to combination therapy works to effectively lower BP through a combination of direct effects (from the respective agents themselves) and a relative offsetting of potentially deleterious physiologic response mechanisms such

Table II. Highly effective two-drug antihypertensive drug therapy combinations[23]

Thiazide or thiazide-like diuretic[a,b] plus
RAS antagonist[c]
Aldosterone antagonist
Amiloride
β-Adrenoceptor antagonist
Calcium channel antagonist
Calcium channel antagonist plus
RAS antagonist
Thiazide or thiazide-like diuretic
β-Adrenoceptor antagonist
Aldosterone antagonist
Dual calcium channel antagonist blockade
Amlodipine plus a non-dihydropyridine[d] calcium channel antagonist

a Hydrochlorothiazide.

b Chlorthalidone.

c ACE inhibitor, angiotensin II type 1 receptor antagonist (angiotensin receptor blocker), or direct renin inhibitor.

d Verapamil or diltiazem.

RAS = renin-angiotensin-aldosterone system.

Table III. Relatively ineffective antihypertensive two-drug class combinations[23][a]

ACE inhibitor + ARB
β-Adrenoceptor antagonist + ACE inhibitor or ARB
β-Adrenoceptor antagonist + central adrenergic inhibitor (e.g. clonidine)
α-Adrenoceptor antagonist + central adrenergic inhibitor

a Also, β-adrenoceptor antagonists plus non-dihydropyridine calcium channel antagonists should be avoided because both drugs have negative inotropic and chronotropic effects on the myocardium.

ARB = angiotensin II type 1 receptor antagonist (angiotensin receptor blocker).

as diuretic-mediated sympathetic activation.[31] In addition, RAS blockade counteracts class-specific adverse consequences including diuretic-induced hypokalemia and glucose level elevations and calcium channel antagonist-induced peripheral edema.

Despite seemingly beneficial individual drug effects, there are a number of antihypertensive drug class combinations that are relatively ineffective and should be avoided (table III). Such ineffectiveness is largely attributable to a redundancy in the target of antihypertensive therapy (as with the combined use of ACE inhibitors and ARBs or peripheral- and central-acting adrenergic inhibitors), but may also result from an indirect reduction of BP-lowering effects. When co-morbidities such as coronary artery disease or heart failure are present, however, compelling indications may exist (table IV) that necessitate the use of medication combinations (e.g. an ACE inhibitor with a β-blocker) that, from the perspective of BP control, are considered suboptimal.

As with any approach, attainment of clinical benefit is somewhat dependent on patient adherence. This can be especially challenging with multiple-drug regimens, which has prompted the development of and recommendations for the greater use of single-pill, fixed-dose combinations. Use of single-pill combination therapies appear to be associated with better compliance and, as shown in a cross-sectional study of primary-care practices in Canada, better BP control.[32] A focused study of fixed-drug combination antihypertensives in African Americans, however, has yet to be conducted.

3.2.2 Therapeutic Algorithm for Treatment of Hypertension in African Americans

Figure 1 displays the ISHIB therapeutic algorithm for African American patients with hypertension.[23] There are several points in this algorithm that merit being highlighted.

First, we suggest an optional comprehensive lifestyle-only intervention period when individuals in the primary prevention stratum have BP that is <10/5 mmHg above their goal level. For individuals in the primary prevention group with BP >15/10 mmHg above their goal level, combination drug therapy is recommended, preferably with a calcium channel antagonist plus an ACE inhibitor unless the patient presents with edema or volume overload. In this situation, a thiazide diuretic plus an ACE inhibitor is preferred. ARBs should be substituted for ACE inhibitors in ACE-inhibitor intolerant patients. The ACCOMPLISH (Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension) trial supported the superiority of amlodipine plus benazepril combination therapy over hydrochlorothiazide (HCTZ) plus benazepril combination therapy for the prevention of cardiovascular disease morbidity and mortality;[33] personal communication with the principal investigator of the ACCOMPLISH trial confirmed the superiority of this combination in the sizeable Black cohort (n = 1416). Thus, the ISHIB consensus statement recommends a calcium channel antagonist

Table IV. Recommendations for antihypertensive drugs by co-morbidity

Co-morbidity	ACEI	ARB	Aldo antag	β-Blocker	CCB	Diuretic
CHD/angina	✓	•		✓	✓	•
CKD	✓	✓	Ø[a]		•	•
Diabetes mellitus/prediabetes	✓	✓		•	•	
Heart failure	✓	✓	✓	✓	Ø[b]	•
High vascular disease risk	✓	✓				•
Post-MI	✓	✓	✓	✓		
Recurrent stroke prevention	✓	✓				•

a If estimated glomerular filtration rate is <50 mL/min/1.73 m^2, eplerenone only; use spironolactone with caution; periodically check serum potassium levels.

b Non-dihydropyridine CCBs (diltiazem, verapamil) are contraindicated in patients with systolic heart failure.

ACEI = ACE inhibitor; **Aldo antag** = aldosterone antagonist; **ARB** = angiotensin II type 1 receptor antagonist (angiotensin receptor blocker); **CCB** = calcium channel antagonist (blocker); **CHD** = coronary heart disease; **CKD** = chronic kidney disease; **MI** = myocardial infarction; ✓ indicates compelling indication (proven benefit); • indicates likely benefit or safety proven; Ø indicates contraindication.

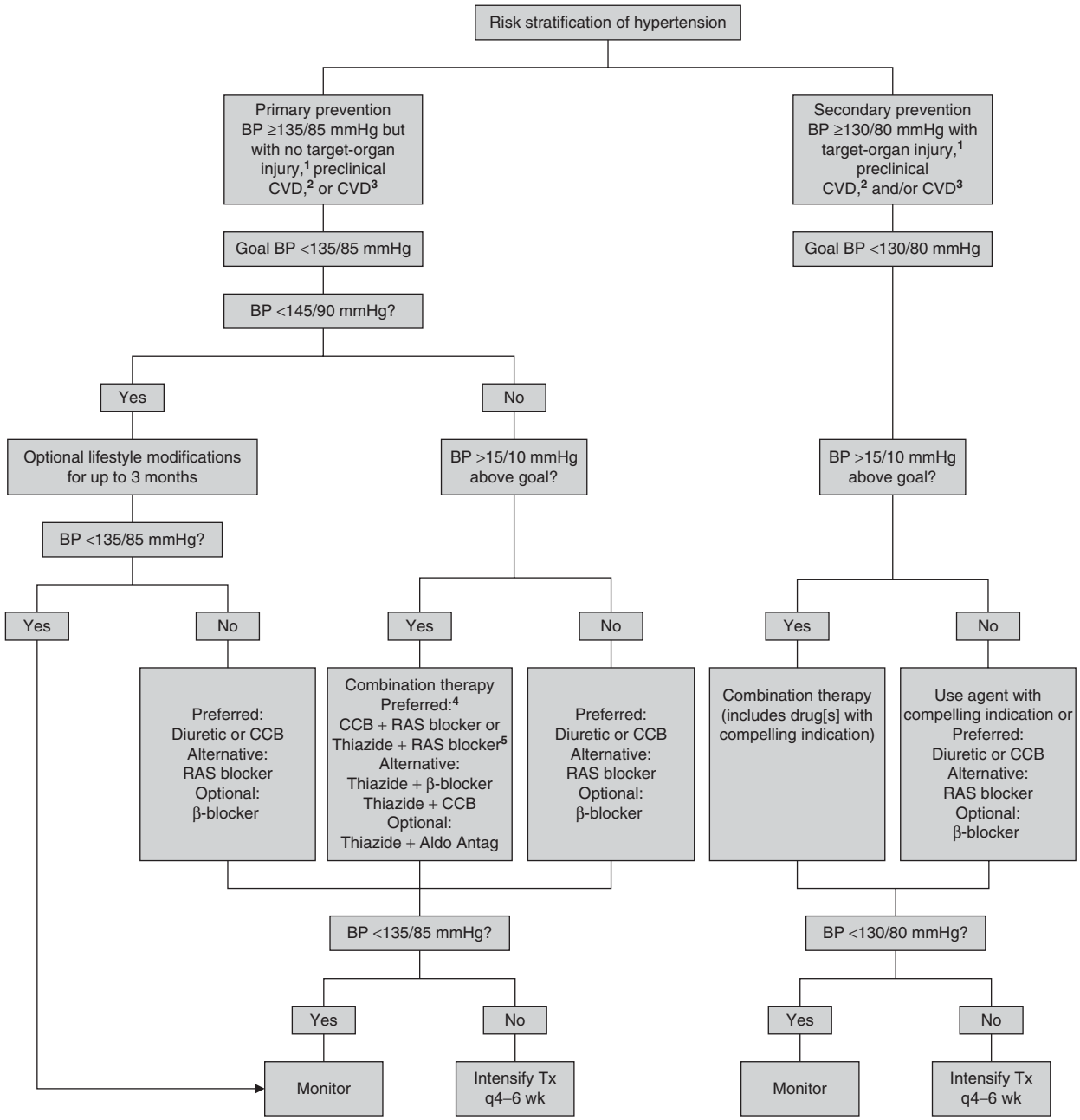

Fig. 1. The International Society on Hypertension in Blacks (ISHIB) risk stratification and treatment algorithm for African Americans[23] with hypertension. **1** Target organ damage is defined as albumin : creatinine ratio >200 mg/g, estimated glomerular filtration rate <60 mL/min/1.73 m^2, or electrocardiographic or echocardiographic evidence of left ventricular hypertrophy. **2** Indicators of preclinical cardiovascular disease (CVD) include metabolic syndrome, Framingham risk score >20%, prediabetes mellitus (impaired fasting glucose [100–125 mg/dL] and/or impaired glucose tolerance [2-hour post-load glucose ≥140 mg/dL]) or diabetes. **3** CVD includes heart failure (systolic or diastolic), coronary heart disease (CHD)/postmyocardial infarction, peripheral arterial disease, stroke, transient ischemic attack, and/or abdominal aortic aneurysm. **4** Most effective two-drug combinations: calcium channel antagonist (CCB) + renin-angiotensin system (RAS) antagonist (RAS blocker); thiazide diuretic + RAS antagonist; thiazide diuretic + aldosterone antagonist; and thiazide diuretic + β-adrenoceptor antagonist (β-blocker). Recommended RAS antagonists are ACE inhibitors or angiotensin II type 1 receptor antagonists (angiotensin receptor blockers) in ACE inhibitor-intolerant patients. **5** Preferred combination therapy in edematous and/or volume overload states. **Aldo Antag** = aldosterone antagonist; **q4–6 wk** = every 4–6 weeks; **Tx** = treatment.

plus ACE inhibitor as the preferred two-drug combination therapy. Nevertheless, there are some interpretational caveats. The diuretic used in ACCOMPLISH was HCTZ, not chlorthalidone, and the initial HCTZ dose was 12.5 mg/day. In addition, BP lowering was ~1 mmHg lower in the amlodipine plus benazapril group.

A second important aspect of the therapeutic algorithm relates to how African American race, *per se*, was used to favor the use of a thiazide diuretic or calcium channel antagonist in the primary prevention stratum when BP is <10/5 mmHg above goal levels. Importantly, African American race was not considered alone but rather was considered in combination with other patient-level information to establish the preference for these monotherapies. The rationale for this recommendation was that a single antihypertensive drug would be more likely to control BP to below target levels if either of these two monotherapies was used.

Finally, the ISHIB treatment algorithm is comprehensive but intentionally is not proscriptive. Tiered therapeutic recommendations are given with the belief that the therapeutic algorithm should avoid rigidly suffocating clinical judgment. Thus, we tended to make therapeutic recommendations in descending order of desirability using the rank-order of preferred, alternative, and optional.

3.2.3 Role of Diuretics in the Management of Hypertension in African Americans

Diuretics have and will continue to play a prominent role in the successful management of hypertension in African Americans. However, the reason for this is not that African Americans manifest with plasma volume expansion despite the repeatedly documented greater prevalence of salt sensitivity amongst hypertensive African Americans (see section 1.2). In fact, in experimental models of animal and human hypertension, salt-induced hypertension only leads to transient plasma volume expansion. However, over the long term, BP elevations are maintained via increased systemic vascular resistance and plasma volume tends to fall to lower than normal levels.[34] Interestingly, thiazide diuretics initially lower plasma volume, although, over time, plasma volume returns toward baseline levels (albeit with a lower than baseline BP) and systemic vascular resistance falls.[35,36]

The long-held debate regarding diuretics has been whether other antihypertensive agents are more protective against the emergence of pressure-related target-organ injury and undesirable clinically manifest complications (e.g. myocardial infarction). Indeed, in many hypertension clinical trials superiority has not been demonstrated for non-diuretic antihypertensive drug classes either for BP lowering or for target-organ protection.[11,25]

However, several of the important reasons to use diuretics in hypertension management are typically not the primary focus of clinical trials. That is, since most hypertensive patients, especially African Americans, will require combination drug therapy, diuretics represent a cheap and highly efficacious way to augment the BP-lowering effect of all non-diuretic antihypertensive drug classes. In fact, it is not routinely possible to effectively lower BP with complex (>2) drug regimens without the use of at least one diuretic appropriate to the level of kidney function (table V). In our extensive clinical experience in managing hypertension in African Americans with complex drug regimens, we have found the use of more than one diuretic may be necessary to attain long-term BP control. Thus, we often use the combination of chlorthalidone or HCTZ plus an aldosterone antagonist (spironolactone, eplerenone) or amiloride in hypertensive patients with uncontrolled BP – as long as the estimated glomerular filtration rate is not depressed. Except in special situations, it is wise to avoid aldosterone antagonists, amiloride, and other potassium-sparing diuretics when the estimated glomerular filtration rate is <50 mL/min/1.73 m^2. In patients with kidney function that is depressed below the level (estimated glomerular filtration rate <45 mL/min/1.73 m^2) at which HCTZ is predictably ineffective at conventional doses who need dual diuretic therapy, we use a loop diuretic plus low dose of metolazone. Alternatively, in patients with estimated glomerular filtration rates of 30–45 mL/min/1.73 m^2, the combination of chlorthalidone plus a loop diuretic represents another effective option for dual diuretic therapy.

Table V. Recommended diuretic(s) according to the level of kidney function

eGFR (mL/min/1.73 m^2)	Single diuretic	Dual diuretics
>45	Chlorthalidone HCTZ	Chlorthalidone or HCTZ plus an aldosterone antagonist or amiloride
30–44	Chlorthalidone Loop diuretic[a] Metolazone	Chlorthalidone plus a loop diuretic Metolazone plus a loop diuretic
<30	Loop diuretic Metolazone	Metolazone plus a loop diuretic

a If furosemide is used, dosing should be at least twice daily unless it is being combined with the long-acting thiazide-like diuretic metolazone or chlorthalidone.

eGFR = estimated glomerular filtration rate; **HCTZ** = hydrochlorothiazide.

In the most recent revision of the ISHIB consensus statement on the management of hypertension in African Americans,[23] we clearly favored the use of chlorthalidone over HCTZ for multiple reasons. Chlorthalidone more potently lowers BP than HCTZ on a mg per mg basis and also lowers BP more effectively than HCTZ – especially at night.[37] In addition, chlorthalidone in conventional dosages (~25 mg/day) effectively lowers BP in patients with an estimated glomerular filtration rate (mL/min/1.73 m^2) as low as the early 30s versus the mid 40s for conventionally dosed (~25 mg/day) HCTZ. However, the majority of the single-pill antihypertensive drug combinations that include a diuretic typically combine HCTZ rather than chlorthalidone with non-diuretic antihypertensive agents. Thus, one commonly encountered downside to the prescription of chlorthalidone instead of HCTZ is a greater pill burden. A cautionary note is, in our experience, the greater occurrence of intravascular volume depletion with chlorthalidone than with HCTZ. Thus, patients should be periodically monitored for pre-renal azotemia. Accordingly, when we see patients with uncontrolled BP already taking HCTZ, we typically switch them to chlorthalidone unless they are already manifesting signs of intravascular volume depletion (high normal to elevated serum bicarbonate levels [contraction alkalosis] and/or a rise in blood urea nitrogen [BUN] and creatinine levels consistent with pre-renal azotemia). Our rationale for this is that the major reason for using chlorthalidone over HCTZ is for the attainment of better BP control. However, a medication switch should not be undertaken to attain BP control when there is a high pre-substitution likelihood that this switch may cause harm. There is also concern regarding the greater likelihood of hypokalemia when using chlorthalidone rather than HCTZ; however, within the daily dosing range of 12.5 to 25 mg/day, the magnitude of hypokalemia with chlorthalidone and HCTZ is roughly equivalent.[38] However, the risk of hypokalemia is markedly reduced when chlorthalidone is used in combination with either a potassium-sparing diuretic (aldosterone antagonist or amiloride) or a RAS antagonist.

There is no drug class that has obviated the need for the use of diuretics, especially in patients requiring complex drug regimens. Appropriate utilization of these agents is absolutely essential for the successful control of BP in many patients. The major concern regarding whether diuretic and non-diuretic antihypertensive agents are superior to one another is not totally unimportant but is dwarfed by the necessity of understanding how to use diuretics most effectively in combination with non-diuretic antihypertensive drugs. Diuretics enhance the BP-lowering efficacy of all non-diuretic drugs.

3.3 Race-Specific Therapeutic Caveats

Given the high levels of pre-treatment salt sensitivity in African Americans (see section 1.2) and the salt-retaining effects of many antihypertensive drugs, and the high prevalence of obesity in hypertensive African Americans, comprehensive lifestyle modifications inclusive of reductions in dietary sodium and weight loss in overweight patients should be considered a mainstay of treatment. Advocating higher intake of dietary potassium (in patients without depressed kidney function) has been shown to lessen salt sensitivity,[39,40] restore the normal nocturnal decline in BP that is often absent or attenuated in African Americans,[41] and, in experimental animal models, to dilate the arterial vasculature.[42,43]

The clinician should be aware that angioedema occurs more commonly in African Americans than Whites during ACE inhibitor treatment.[44] Furthermore, angioedema can initially occur many months to years after the initiation of treatment. Thus, African American patients treated with ACE inhibitors should be warned about this potentially life-threatening side effect (although, in most instances, presentation is relatively benign). We habitually ask all of our patients, especially African Americans, during follow-up clinic visits about the interval occurrence of angioedema. Angioedema does not typically occur as a consequence of ARB or direct renin inhibitor therapy. Nevertheless, it should be remembered that some patients taking these therapies may experience angioedema attributable to other causes. In patients experiencing either angioedema or cough with ACE inhibitors, we have routinely switched them to ARBs without incident.

3.4 Treating Hypertension in Patients with Limited Financial Means

The landscape of hypertension management has changed significantly over the last several years. A number of drug classes – ARBs, ACE inhibitors, calcium channel antagonists, β-blockers – now have generic agents that effectively lower BP. These drug classes, when used with the long-available thiazide diuretics, comprise highly effective BP-lowering combinations. The subsequently discussed agents are highly effective antihypertensive drugs and are also often available for a few dollars per month at major pharmacy chains.

A major and often overlooked drug class that is typically used as add-on drug therapy is that of the aldosterone antagonists. Spironolactone is the prototypical agent in this class that has been used to dramatically lower BP in patients with resistant hypertension.[45] Eplerenone, the other aldosterone

antagonist, is also available as a generic product, although is not available as cheaply as spironolactone. Eplerenone is also not as potent as spironolactone on a mg per mg basis but is less likely to cause breast tenderness, gynecomastia in men, or menstrual irregularities in women. Aldosterone antagonists are highly effective BP-lowering agents in African Americans.[2,45] Amiloride, an inhibitor of the epithelial sodium channel, lowers BP effectively and safely alone as well as in combination with spironolactone in hypertensive African Americans.[46] Arguably, these agents are significantly underutilized in the treatment of hypertension in African Americans.

Central adrenergic inhibitors such as clonidine are commonly used as add-on therapy to complex drug regimens. Nevertheless, the side-effect profile is limiting and, in patients prone to abruptly stopping their antihypertensive medication(s), rebound hypertension is a distinct possibility, particularly when oral rather than transdermal clonidine is used. Reserpine in dosages lower than 0.1 mg/day is an effective central adrenergic inhibitor with a much longer half-life than clonidine. Thus, reserpine should be much less likely to result in rebound hypertension with abrupt discontinuation.

The need to put together effective antihypertensive drugs for patients with limited means will be necessary if BP control is to be attained in selected segments of the diverse African American population.

4. Conclusions

Hypertension treatment in African Americans, as well as for non-African Americans, has evolved over the years. The emphasis is now appropriately on utilizing the most effective drug combinations for the control of BP and protection of target-organs in this high risk population. In recognition of the high prevalence of subclinical vascular injury even in normotensive African Americans with above optimal BP, and the human clinical trial data suggesting benefit from BP levels below the conventional 140/90 mmHg threshold, the ISHIB consensus statement recommends a reduction in the BP target, even for the lowest risk African Americans, to <135/85 mmHg. To achieve this, however, optimal management of hypertension in African Americans will require the use of comprehensive lifestyle modifications and individualized drug therapeutics in combination.

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