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Hypertension Treatment in Blacks: Discussion of the U.S. Clinical Practice Guidelines

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Abstract

Blacks are especially susceptible to hypertension(HTN) and its associated organ damage leading to adverse cardiovascular, cerebrovascular and renal outcomes. Accordingly, HTN is particularly significant in contributing to the black-white racial differences in health outcomes in the US. As such, in order to address these health disparities, practical clinical practice guidelines (CPGs) on how to treat HTN, specifically in blacks, are needed. This review article is a timely addition to the literature because the most recent U.S. CPG more explicitly emphasizes race into the algorithmic management of HTN. However, recent clinical research cautions that use of race as a proxy to determine therapeutic response to pharmaceutical agents may be erroneous. This review will address the implications of the use of race in the hypertension CPGs. We will review the rationale behind the introduction of race into the U.S. CPG and the level of evidence that was available to justify this introduction. Finally, we will conclude with practical considerations in the treatment of HTN in blacks.

Keywords

Hypertension; minorities; African Americans; blacks

Race has only recently been introduced as a branch-point in the clinical practice guideline algorithm for hypertension(HTN) designed to assist decision making in the treatment of HTN in the U.S[1]. This paradigm shift in the treatment of HTN in blacks has provoked an element of controversy reminiscent of the introduction of race-based heart failure (HF) therapy with the hydralazine/nitrate drug, Bidil™[2]. Specifically, the recommendation

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regarding the use of ace-inhibitors/angiotensin receptor blockers (ACEIs/ARBs) for treatment of HTN in blacks has been controversial. There has been concern that the unintended consequence of this recommendation may be that blacks whose HTN would benefit from the introduction to an ACEI/ARB may not be offered this option.

Given that HTN disproportionately affects the black population in the US[3], blacks have been relatively under-represented in US HTN trials. Even though the earliest Veteran Administration Cooperative Studies[4, 5] enrolled a relatively high proportion of blacks (>40%), these were smaller scale trials that do not represent modern day HTN therapy. Since these earlier trials, the more contemporary HTN trials have enrolled lower proportions of blacks (< 20%)[6–8]. It was only with the enrollment of a substantial proportion of blacks (35%) in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) that the HTN guideline committees had good quality data on blacks with HTN with which to make recommendations/statements.

Morbidity and Mortality Related to HTN in Blacks

The stark disparity in over-all mortality between whites and blacks is largely a result of the disparate burden of HTN in black communities. As much as 30% of all deaths in HTN black men and 20% of all deaths in hypertensive black women might be attributable to high blood pressure(BP)[9]. HTN- related disease is especially severe in blacks[10, 11] and while there are similar treatment rates amongst the different racial/ethnic groups, HTN control rates are worse in blacks[3]. Several factors may contribute to the difficulty in achieving control in blacks:

- **a.** Higher prevalence of comorbid diseases (such as chronic kidney disease/CKD, diabetes mellitus/DM, obesity)[11]
- **b.** Higher baseline BP levels[12]
- **c.** Higher levels of physical inactivity[11]

Despite these complexities, HTN in blacks is a condition that is modifiable with appropriate management. It is therefore imperative that clinical practice guidelines (CPGs)focused on management of HTN in blacks be practical for health care providers in order to impact the public health of this high-risk group.

Personalizing HTN Therapy Based on its Etiology in Blacks

Personalized management of HTN has been an explicit goal dating back to Joint National Committee (JNC)I[13]. Personalized medicine strives for “treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations”[14].

The foundation of primary “essential” HTN for the most part actually does not differ among the different racial/ethnic groups. In all populations, HTN is a quantitative trait that is diagnosed when elevated BP exceeds an arbitrary cut-off[15]. Therefore, HTN is a result of the progressive accumulation of a quantitative trait. Numerous heterogeneous

(hypertensinogenic) factors contribute to this quantitative trait[15]; some of these factors have a biologic basis, but to a large degree the trait is a result of exposure to sociocultural, environmental and behavioral factors[16] (Figure 1). Genetic factors certainly do play a role but it has been difficult to tease out the ethnic/racial intricacies because of the polygenetic nature leading to the expression of elevated BP[17]. It is for this reason that many believe that these polygenetic variations are as significant within specific racial/ethnic groups as between different racial/ethnic groups. With this in mind, many theorize that pharmaceutical therapy logically should be more homogeneous for all racial/ethnic groups with the personalized aspect of therapy focusing specifically on sociocultural, environmental and behavioral aspects.

Low-Renin Physiology in Blacks

The most recognized biological profile associated with HTN in blacks is the low renin physiology[18]. This physiology is associated with a salt-sensitive phenotype with excess effective circulating volume being the mechanism of HTN. This finding has been used to lend credence to the current strategy of using specific anti-HTN classes in blacks that address volume issues [ie. dihydropyridine calcium channel blockers (DHP-CCB) and diuretics]. While it appears that blacks tend to have a higher prevalence of low renin physiology than other racial/ethnic groups, caution must be taken to avoid the presumption that the distribution of renin activity in blacks is limited to the lower activity levels[18]. Furthermore, it should be appreciated that the low renin physiology cited usually refers to systemic renin activity, which has been shown to be often discordant with tissue renin activity[19], which is arguably more important in terms of organ damage (eg intra-renal renin activity). Therefore, even though BP lowering may not be as robust with the “anti-renin” drugs (ie ACEIs/ARBs/Beta-blockers), the tissue-protective benefits should certainly be considered in the treatment of blacks in an effort to not only improve BP control but to achieve the ultimate goal of reducing the risk of organ damage.

Introduction of Race into U.S. HTN CPGs

Race-based therapy in medicine has been gaining prominence in the new century and remains controversial[2, 17, 20]. The Report From the Panel Members Appointed to the Eighth JNC (henceforth referred to as ‘JNC 8’) only recently introduced race as a branch-point in the actual treatment algorithm in 2013. Prior to JNC 8, even though race was discussed within the text of previous JNC iterations, race was not a branch-point in published algorithms (Table 1).

The British Hypertension Society was the first major society to explicitly factor race in its 2004 CPG decision-making algorithm; advocating for CCBs and diuretics in blacks[21]. It is important to note that the ALLHAT trial was not cited as a clinical trial to support their statement. A couple of years later, in a joint initiative with the major UK guideline society (NICE UK), the use of race in HTN treatment algorithms was reinforced, this time using ALLHAT as a supporting trial[22].

The Role of the International Society of HTN in Blacks (ISHIB)

ISHIB has been at the forefront for advocating for effective treatment of HTN in blacks. ISHIB released their initial consensus statement in 2003[23] and followed up with an update in 2010[24]. The release of their statement was exceptional in that it recognized that blacks with HTN suffered an inordinate burden of high-risk features that necessitated earlier and more aggressive treatment, independent of BP levels. The ISHIB statement is remarkable in that recommendations are not only based on absolute BP levels, but rather focuses on the absolute cardiovascular (CV) risk. This statement reflects recognition that risk reduction for CV events is related to 2 important factors: a) absolute baseline CV risk, and b) the magnitude of BP lowering.

JNC 8: Treatment of HTN In Blacks

JNC 8 was the first iteration of the US guidelines that allowed for use of any one of the 3 anti-HTN classes (thiazide-type diuretics, DHP CCB or ACEI/ARBs) as first line in the general nonblack population. However, initial anti-HTN treatment in blacks with HTN was limited to a diuretic or CCB (moderate recommendation; weak recommendation in blacks with DM). ACEI/ARBs are recommended as first-line agents in blacks only with comorbid CKD (moderate recommendation); the two most important trials cited in the introduction of race in the algorithmic treatment of HTN are Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) and African American Study of Kidney and Hypertension (AASK).

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

ALLHAT was a trial conducted in patients with HTN and at least 1 other CHD risk factor in the United States, Canada, Puerto Rico, and the US Virgin Islands. A large proportion (35%) of the 33,357 participants were black. ALLHAT was designed to compare the newer classes of anti-HTN agents, DHP-CCBs and ACEI, to the older diuretic (chlorthalidone). The primary outcome of incident coronary heart disease (CHD) events was actually not significantly different between the diuretic, CCB and ACEI arms. Therefore, based on the primary end-point analysis, ALLHAT was considered to be a null study. However, stroke incidence was a pre-specified secondary end-point. There was a 40% higher incidence of stroke in participants randomized to the ACEI lisinopril arm (versus the chlorthalidone arm). Incident stroke rates were virtually identical for both ACEI and diuretic arms in the nonblack participants, meaning that the entire overall difference between chlorthalidone and lisinopril could be accounted for by the dramatic 40% greater event rate in black patients randomized to lisinopril. This stroke outcome in the ALLHAT trial has had an inordinate influence on HTN guidelines given that it was a subgroup analysis of a secondary outcome in a CHD trial. In addition, the stepped-therapy treatment algorithm of the trial was not representative of recommended algorithmic guidelines in contemporary practice. The vast majority of trial participants required more than the first-line agent to achieve BP control to goal. While current clinical practice would recommend either a diuretic or CCB to be added to the ACEI arm, the ALLHAT algorithm design prohibited this practice. Instead, anti-HTN

therapy was intensified with the most common second line anti-HTN, atenolol[25]. Therefore, ALLHAT was essentially an atenolol-backed trial because it was the usual 2nd line for all 4 arms and most participants required > 2 medications in order to reach the goal BP of the trial. With this in mind, it is not surprising that when compared to more favorable stepped therapy combinations, outcomes in the ACEI arm were less favorable. An initial combination of lisinopril and atenolol is simply not an appropriate regimen in any uncomplicated HTN patient, particularly a black patient.

African American Study of Kidney and Hypertension (AASK)

AASK was a long awaited trial because blacks are particularly at risk for CKD secondary to HTN. The AASK trial included 1,094 self-identified African-Americans with HTN, and CKD (mostly HTN nephropathy). Patients were randomized to therapy with ramipril or amlodipine. Even though BP lowering was more impressive w/amlodipine, ACEI was more effective in reducing risk of worsening CKD, especially if proteinuria is present. This finding introduced the concept that despite lesser BP lowering properties, ACEIs does have a vital role in management of HTN in blacks. This suggests that aside from BP lowering, we should recognize pleomorphic effects of ACEIs[26, 27] that could result in improved outcomes in blacks even if BP lowering is not as impressive[28].

Target BP levels in the Algorithm of HTN Treatment in Blacks

JNC 8 has been criticized for loosening its targets in high-risk HTN patients. The JNC 8 committee, in a close vote, recommended to raise the threshold and target of therapy in the population with HTN > 60 years of age. This recommendation was not unanimous amongst the members of JNC 8 with one of the reasons cited that blacks may be especially effected by this recommendation[29]. While the recommendation only applied to the population > 60 years of age without comorbid DM/CKD, it has been recognized that blacks have a higher prevalence of high-risk conferring comorbidities/biomarkers that differ from DM/CKD [eg. left ventricular hypertrophy (LVH)]. These factors independently modify the risk for subsequent CV disease, and their presence or absence should be considered when determining BP targets.

The liberalization of systolic BP goals in a certain group of the general population with HTN may have the unintended effect of reducing the gains in improvement of CV and renal outcomes in blacks over the past few decades. Risk reduction in all populations is not only dependent on achieving the goal BP but also on the percent improvement in BP achieved compared to baseline. Furthermore, blacks have been shown to benefit from lower BP goals. The AASK trial compared a traditional BP target to a more intensive target (mean BP was 130/78 mm Hg in the intensive-control group and 141/86 mm Hg in the traditional) with blacks with proteinuria having more favorable renal outcomes with the lower target.

The release of the recent Systolic Blood Pressure Intervention Trial (SPRINT) study, has once again swung the pendulum towards targeting BPs lower than 140/90. As a result of a concerted effort by the National Institute of Health to improve recruitment of minorities in their clinical trials, blacks populated approximately a third of the SPRINT trial. Analysis by

race (blacks vs non-blacks) was pre-specified in the protocol. There were no racial differences in the observed benefit from the intensive treatment arm in SPRINT. The importance of a substantial representation of Blacks in SPRINT was evident because blacks indeed did have different characteristics with blacks tending to be younger and achieving poorer BP control.

Practical Recommendations

Consider Reducing the Target BP for Initiation of Anti-HTN Therapy in Elderly Blacks

The International Society of Hypertension in Blacks advocates for lower BP target because of the high CV risk that disproportionately is found in elderly blacks as compared to whites. Even in the absence of DM and CKD, elderly blacks tend to have a higher prevalence of ominous biomarkers, such as LVH[30, 31]. An important aspect of CV risk reduction is the degree of BP lowering achieved. We would advocate that the higher systolic target of 150 mmHg only be considered in blacks >= 80 years of age.

Use of Single-Pill Combination Therapy

A major flaw of trials used in HTN guidelines is that the older trials used antiquated stepped-therapy techniques to intensify anti-HTN therapy as opposed to the more common contemporary practice of initiating therapy with a combination of medications. The landmark trial demonstrating the CV benefits of early combination therapy (single pill combination) was ACCOMPLISH[8]. There was somewhat of a representation of blacks in this trial (12 %) and despite use of ACEI in blacks, outcomes when used in combination with amlodipine or hydrochlorothiazide were similar to whites.

We advocate for single-pill combination therapy based on the fact that the vast majority of blacks with HTN will need > 1 anti-HTN agent to achieve BP goal < 140/90. Furthermore, the likely lowering of BP goal targets will further necessitate the use of multiple agents.

Where available, use of ARB in the single-pill combination formulation, as opposed to ACEI, may be preferable. ISHIB recommends ARBs over ACEIs because of the higher incidence of angioedema in blacks. The JNC 7 committee also noted that ACEI induced cough was more common in blacks.

Where available, use of CCBs in the single-pill combination formulation may be preferable because of the higher prevalence of DM in blacks and the potential for diuretics to worsen the glycemic profile. However, blacks are also at higher risk for HF, and diuretics are clearly superior to CCBs in that respect.

Remaining Controversies

Should We Consider Early Treatment of Elevated BP Before Current Recommended Thresholds for Treatment?

Despite the absence of outcomes studies in blacks with pre-HTN (systolic BP ≥ 130 – 140 mmHg), there is some data that suggests that blacks would benefit from early therapy of elevated BPs in the pre-HTN zone. It should be appreciated that the transition from preHTN

to HTN is accelerated in blacks. Effective treatment of blacks for HTN disease may entail early treatment prior to the BP threshold espoused by the JNC 8 guidelines. It has been suggested that risk levels for cerebrovascular events do not return to the low levels of normotensive once HTN develops, even if the HTN becomes controlled[32].

Discussion

HTN guidelines will be altered in the near future due to the results of the SPRINT trial with a likely lowering of the BP treatment targets. The potential harms/benefits of using ACEI in blacks will be difficult to address using SPRINT data. We believe the emphasis on using combination therapy will result in most participants being on ACEIs/ARBs as part of their regimen. At baseline, the frequency of ACEI/ARB use was similar in blacks and non-blacks[33]. These modern day trials tend to emphasize combination therapy even in relatively low risk patients[34]. In so doing, most participants will be on ACEI/ARBs since they are included in the overwhelming majority of combination strategies.

We should be cautious with recent attempts at race-based pharmacologic therapy of CV disease, including hypertension. HTN is a complex phenotype that is expressed variably based on exposure to certain sociocultural, environmental and behavioral influences. It is tempting to assign a higher degree of relevance to genetic/biological factors than may be warranted. While it is vital to focus on the disproportionately high mortality/morbidity of HTN in blacks, the use of race as a proxy for pharmaceutical efficacy remains very controversial indeed.

Practically, most blacks with HTN will eventually need at least 2 complementary classes of anti-HTN to attain control to target BP levels. An ACEI/ARB is an essential component to the vast majority of combination therapy options. In effect, this eliminates the debate regarding use of ACEI/ARBs and provides optimal therapy for the majority of blacks with HTN.

Abbreviations

ACEI	Angiotensin converting enzyme inhibitors
ARB	Angiotensin receptor blocker
BP	Blood pressure
CCB	Cacium channel blocker
CHD	Coronary heart disease
CKD	Chronic kidney disease
CPGs	Clinical practice guidelines
CV	Cardiovascular
DHP-CCB	Dihydropyridine calcium channel blockers

DM	Diabetes mellitus
HF	Heart failure
HTN	Hypertension or Hypertensive
JNC	Joint National Committee
LVH	Left ventricular hypertrophy

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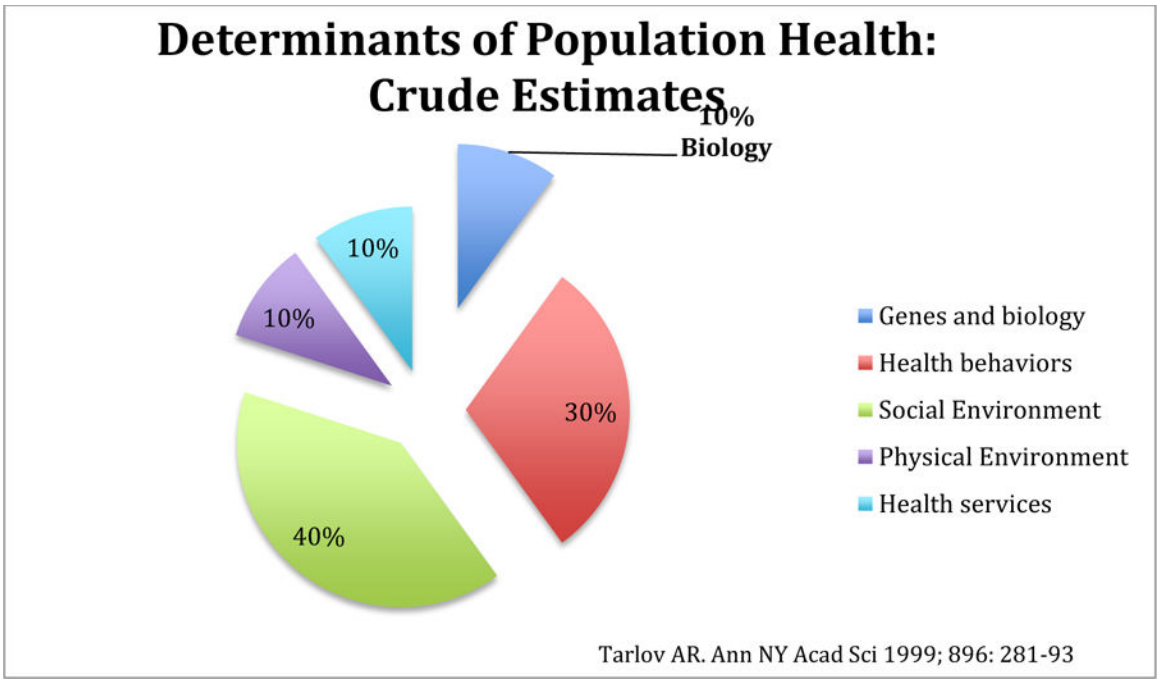

Figure 1.
Determinants of Population Health emphasizing the relatively minor contribution of genes and biology (crude estimates)

Table 1

Chronological History of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) Recommendations With Regards to Race

JNC iteration	Year of Publication	Statement on Black Race	Supporting Evidence Cited
JNC 1 [1]	1977	No race-specific recommendations	n/a
JNC 2 [2]	1980	No race-specific recommendations	n/a
JNC 3 [3]	1984	In the text of the guideline, mentions that black hypertensive patients may respond somewhat better to diuretics than to beta-blockade	No citations
JNC 4 [4]	1988	In the text of the guideline, mentions that, with regard to mono-therapy, black hypertensive may respond more effectively to diuretics. Blacks tend not respond as well to beta-blockade or ACE-I as do whites. However, combinations of beta-blockers or ACE-I with diuretics are equally effective in black and white hypertensive patients. Similar BP lowering responses have been noticed with calcium channel blockers, centrally acting alpha-2 agonists, peripheral alpha-1 antagonists, and combined alpha/beta - blockers	No citations
JNC 5 [5]	1993	In the text of the guideline, mentions that diuretics should be the agent of first choice for blacks with hypertension because of their proven effectiveness in clinical trials. For whites, beta-blockers are also an option for first line therapy. Mono-therapy with beta-blockers or ACE-Is is less effective in blacks. More black patients will require multidrug therapy.	No citations
JNC 6 [6]	1997	In the text of the guideline, mentions that diuretics should be the agent of first choice in blacks because of their proven effectiveness in clinical trials. Beta-blockers can also be considered as mono-therapy for whites. Mono-therapy with beta-blockers or ACE inhibitors is less effective in blacks. However, in combination with diuretics, these drugs are effective multi-drug therapy.	Citations [7, 8]
JNC 7 [9]	2003	Diuretics are recommended as first line agents in all hypertensives. JNC 7 mentions that diuretics are more effective at BP lowering in blacks than beta-blockers, ACE-I or ARBs. However, blacks with diseases such as chronic kidney disease and myocardial infarction benefit from ACE-I and beta-blockers. Consider the use of combination drug therapy that includes a thiazide type diuretic	Citations [10–14]
JNC 8 [15]	2014	First time that race is explicitly introduced as a branch-point in the treatment algorithm. For uncomplicated primary hypertension, ACE-I or ARBs are not recommended as monotherapy. Diuretics or calcium channel blockers are recommended for monotherapy in blacks without CKD. In blacks with CKD and proteinuria, ACE-I should be used early in the treatment regimen because of the incidence of end-stage renal disease in blacks. The indication for ACE-Is in blacks with CKD, but without proteinuria, is less clear. Regardless, combination therapy should be considered in therapeutic efforts.	Citations [11, 16]

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