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Research Needs to Improve Hypertension Treatment and Control in African Americans

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Summary

Additional targeted research and customized training programs could spearhead strategies for elimination of the disparities in prevalence and control of high BP between African Americans and the remainder of the US general population.

Keywords

Hypertension; African Americans; prevention; treatment

Introduction

This report presents findings of an ad hoc working group assembled by the National Heart, Lung, and Blood Institute (NHLBI) to assess research needs to improve prevention, treatment and control of hypertension among African Americans. Non-Hispanic Blacks (African American and Black will be used for US and international studies, respectively) tend to have an earlier onset, higher prevalence, and disproportionately high risk of complications for hypertension compared to non-Hispanic Whites and Mexican Americans.[1]

Surveillance and measurement of BP

Surveys identify substantial variation in mean blood pressure (BP) among populations of African origin.[2] In high income countries, including the US, mean BP and prevalence of hypertension is higher in adults self-described[3–6], observer reported[7, 8] or otherwise identified[9, 10] as being black or having darker skin color.[11] However, the relationship between African origin and BP is absent or only minimally apparent in reports from middle-income countries.[12–14] Research to clarify reasons for this variability may contribute to understanding of hypertension-related racial disparities in the US.

In US National Health and Nutrition Examination Survey (NHANES) reports, crude and age-adjusted prevalence of hypertension (systolic BP ≥140 mm Hg, diastolic BP ≥90 mm Hg, or taking antihypertensive medication) in adults has remained fairly constant at about 30% since 1999–2000.[3, 4] The corresponding prevalence estimate for African Americans is about 40%, and has also remained reasonably stable.

In African Americans, hypertension awareness and treatment rates are higher but control rates lower compared to non-Hispanic Whites (85.7% vs. 82.7% for awareness, 77.4% vs. 76.7% for treatment, and 49.5% vs. 53.9% for control in NHANES 2011–2012).[4] The lower prevalence of BP control is present despite use of more BP lowering medications, including thiazide diuretics.[15] This contrasts with clinical trial experience, where differences in BP control rates by race/ethnicity are modest or absent, particularly during chlorthalidone-based

treatment.[16] High levels of BP control, including in African Americans, have been attained in large organizations with system-wide hypertension treatment and control programs.[17, 18]

Research is needed to optimize hypertension prevention and treatment in African Americans. US regional cohort studies including the Bogalusa Heart Study, REasons for Geographic and Racial Differences in Stroke (REGARDS) Study, and Jackson Heart Study provide opportunities to study psychosocial factors, lifestyle habits, and medication beliefs in African Americans – all of which are potential targets for research. Investigation of African Americans with a normal BP despite exposure to environmental factors that predispose to high BP is also important.

Pathophysiology and genetic basis of hypertension in Blacks

With the exception of *APOL 1* variants in patients with chronic kidney disease (CKD), genome-wide association studies have yielded limited insights into racial disparities in CVD morbidity and mortality, including hypertension.[19] Given the likelihood that multiple genes are involved, environmental, behavioral and psychosocial factors probably play a more important role than genetics in the higher prevalence of hypertension in African Americans.[19]

Lifestyle change and other nonpharmacological interventions

Nonpharmacological interventions, including reduced sodium and increased potassium intake, weight loss, increased physical activity, and healthy diets such as the Dietary Approaches to Stop Hypertension (DASH) lower BP in adult African Americans.[20, 21] However, the body of evidence is limited, especially for randomized controlled trials (RCTs). In efficacy trials, dietary sodium reduction[22], potassium supplementation[23] and the DASH diet[24] resulted in greater lowering of BP in African Americans compared to Whites. There has been limited study of the basis for these differences.[25] Few Black participants have been included in RCTs that have demonstrated a beneficial effect of reduced alcohol consumption on BP[26] and observational analyses suggest African Americans may not derive the same CVD reduction benefits as Whites from consumption of modest quantities of alcohol.[27]

Gradual but progressive reductions in sodium added to food products represents the least onerous nonpharmacological intervention and offers great potential for success.[28] Models for culturally appropriate evidence-based lifestyle modification may provide a good template for lifestyle change in African Americans.[29]

Potassium supplementation shows particular promise in African Americans[23] and those consuming excessive amounts of sodium, but it has not been tested sufficiently in long term RCTs. More research is needed to understand its efficacy, alone and in combination with reduced sodium, in lowering BP and in mitigating thiazide-related increases in serum glucose in African Americans[30] as well as documenting its long-term safety in African Americans and other populations with a high prevalence of reduced kidney function or receiving treatments that impair renal excretion of potassium.

Psychosocial factors

Psychosocial factors, including personality trait, responses to environmental and other stressors, anxiety, hostility, and anger are associated with high BP. In African Americans, stress related to perceived discrimination and residence in a stress-prone neighborhood have been strongly correlated with hypertension.[31, 32]

Major clinical outcomes in hypertension treatment trials

During the 1970s – 1980s, similar benefits were noted in African Americans and Whites for first-step antihypertensive therapy with thiazide or thiazide-type diuretics compared with placebo or usual care. The 1990s ushered in an era of comparative efficacy and effectiveness trials. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) included more than 15,000 African Americans in a long-term comparison of first-step therapy with a thiazide-type diuretic and three other agents.[33] There was no evidence of superiority for prevention of CVD during first step therapy with the angiotensin converting enzyme inhibitor (ACE-I) lisinopril, calcium channel blocker (CCB) amlodipine or α-receptor blocker doxazosin, compared with the thiazide-type diuretic chlorthalidone. Chlorthalidone was superior to amlodipine, lisinopril and doxazosin for prevention of new-onset heart failure (HF) in both African Americans and Whites. In African Americans, chlorthalidone was more effective than lisinopril for prevention of stroke, likely due in part to a greater reduction in BP. Despite similar treatment-related reductions in BP by race, a lack of protection against stroke was reported with the angiotensin receptor blocker (ARB) losartan compared to the β-blocker atenolol in 533 Black (523 African American) Losartan Intervention For Endpoint reduction in hypertension (LIFE) clinical trial participants.[34]

Hydrochlorothiazide, the most commonly used diuretic in the US, may have a different level of efficacy than chlorthalidone.[35] In ALLHAT, there was no difference in the effect of treatment assignment on incidence of HF across race groups during the randomized treatment phase. When post-trial follow-up (mean of 8.8 years) was included, the hazard ratio for HF associated with randomization to amlodipine compared to chlorthalidone remained significantly higher in African Americans, but not in other race subgroups.

African Americans develop end stage renal disease (ESRD) at a rate three times higher than Whites, constituting 13% of the US general population but more than 32% of patients receiving dialysis for kidney failure. In the African American Study of Kidney Disease and Hypertension (AASK), antihypertensive treatment with the ACE-I ramipril in patients with non-diabetic CKD was superior to the β-blocker metoprolol or CCB amlodipine in slowing progression of CKD despite a 3 mm Hg higher achieved SBP compared to amlodipine.[36] However, in ALLHAT, first-step therapy with the ACE-I lisinopril was not superior to chlorthalidone or amlodipine-based therapy in preventing ESRD in African American participants.[37] These results should be reconciled across the spectrum of renal disease. Despite a mean SBP/DBP of 133/78 mm Hg and use of ACE-I in >80% during long-term follow-up (≥7 years) in 1,094 AASK participants, 54% experienced a doubling of serum creatinine, ESRD or death.[38] There is urgent need for more effective treatments in African Americans with hypertension and CKD.

African Americans have higher levels of albuminuria compared to Whites.[39] In AASK, the effect of a lower BP goal on renal and CVD outcomes was inconclusive but there was a suggestion of renal disease benefit in participants with proteinuria.[36, 40] This should be explored in other BP lowering trials with a substantial number of African Americans, such as the Systolic Blood Pressure Intervention Trial (SPRINT).[41] RCT evidence for the role of renin angiotensin system (RAS) inhibitors in African Americans with albuminuria is inconclusive. Dual RAS inhibition, with ACE-I and ARB agents, lowered BP and albuminuria more than either drug alone in the Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial (ONTARGET), but was associated with increased risk for acute kidney injury, renal disease progression, syncope, and hypotensive events.[42] Unfortunately, the subgroup with African ethnicity was small (2.4% of the study sample). Similar findings were noted in a subsequent meta-analysis.[43] In the REGARDS study, the association of albuminuria with stroke risk was stronger for African Americans compared to Whites.[44] However, there are few data evaluating whether albuminuria modifies the effect of BP interventions on stroke, HF or mortality risk among African Americans.

In observational studies, the risk of stroke associated with a unit higher level of SBP is greater in African Americans compared with Whites.[45] However, in SPRINT, there was no significant interaction between race (Black versus Non-Black) and treatment effect for the composite primary outcome, which included both ischemic and hemorrhagic stroke.[41]

Higher visit-to-visit BP variability (VVV) is associated with increased risk for coronary heart disease, stroke, HF and mortality.[46] African Americans have higher VVV compared to Whites, which may be due to abnormal autonomic function, baroreflex function, or altered sodium excretion.[46] Whether VVV should be a therapeutic target or inform drug selection is unknown. African Americans also have a high prevalence of nocturnal hypertension (SBP/DBP ≥ 120/70 mm Hg) and non-dipping BP.[47] The underlying mechanisms are poorly understood but self-reported experiences of racism and perceived ethnic discrimination are possibilities.[32, 48, 49] Studies comparing the effects of antihypertensive drugs with a longer compared to shorter half-life (e.g. chlorthalidone compared to hydrochlorothiazide), bedtime dosing with antihypertensive medication, and non-pharmacologic interventions on diurnal patterns of BP are warranted in African Americans with hypertension.

Resistant hypertension is common in African Americans and associated with an increased risk of target organ damage[50]. Novel approaches to prevention and treatment of resistant hypertension are warranted. Few clinicians prescribe chlorthalidone for treatment of hypertension, even in patients with resistant hypertension.[51] In ALLHAT, the benefits of once daily chlorthalidone (12.5 – 25 mg/d) for first-step drug therapy of hypertension were even more compelling for African Americans compared to Whites.[33] Research on ways to increase use of properly dosed chlorthalidone for initial treatment of hypertension, particularly in African Americans, is needed. The optimal approach to achieving BP control, especially with a BP target like that used in SPRINT, may be to initiate combination rather than monotherapy. Some guidelines emphasize the value of diuretics and CCBs when treating Blacks.[21, 52] However, the International Society of Hypertension in Blacks (ISHIB) recommends a combination of CCB and RAS blocker as initial drug therapy in African Americans with stage 2 hypertension, with use of combined thiazide and RAS blocker only

if there is volume overload.[1] This is based on evidence from a single RCT, Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH)[53], with no separate results for the 1,416 African American participants. The thiazide diuretic used in ACCOMPLISH (hydrochlorothiazide) was relatively short-acting, and its dosage was roughly equivalent to half that of the longer-acting thiazide-type diuretic (chlorthalidone) used in ALLHAT and at most half that which has been shown to reduce CVD events in other RCTs. Identification of optimal combination therapy in African Americans with hypertension remains an important unanswered research question.

Genetic determinants of the effects of antihypertensive therapy

Most genetic studies in hypertension have focused on predictors of elevated BP. A logical next step is to extend genetic and pharmacogenetic studies to major CVD and renal outcomes. GenHAT, an ALLHAT genetics substudy, provides an opportunity to explore a racially diverse population that includes about 15,000 African Americans with treated hypertension.[54] Fewer than 500 African American participants have been studied for Gene-Treatment interactions in GWAS studies.[55–57] Lack of data specific to African Americans has the potential to create a new disparity in the era of precision medicine. Partnerships with Federally Qualified Health Centers and other community-based organizations that predominantly serve African Americans, and use of datasets from RCTs with a substantial number of African Americans could remedy this underrepresentation in genomic research.

Pharmacogenomics of hypertension outcomes may benefit from adapting proof of concept studies conducted in other fields, where treatment effects have differed by race. One approach would be to use genetically defined African ancestry for study risk of hypertension-related disorders and their modification by antihypertensive treatment. Many non-diabetic African Americans with CKD, low level or absent proteinuria and hypertension have genetically mediated primary glomerulosclerosis associated with *APOL1 variants*.[58] In these patients, intensive anti-hypertensive treatment with ACE-I does not appreciably slow loss of kidney function.[59] Others, who present in a similar fashion have arteriolar nephrosclerosis on kidney biopsy.[58] There is controversy regarding the extent to which anti-hypertensive therapy slows progression of arteriolar nephrosclerosis-associated CKD. *APOL1* variant genotyping of participants from ALLHAT and other studies with a large number of African Americans might be informative.

Individuals with recent African ancestry may inherit *APOL1* G1 and G2 renal-risk-variants. Both variants are rare in non-African populations but approximately 40% of African Americans with ESRD have *APOL1*-associated nephropathy and *APOL1* renal-risk variants predict progression of CKD.[59] Additionally, these risk variants are associated with earlier failure of renal allografts transplanted from deceased African American compared to White donors.[60] In the Atherosclerosis Risk in Communities (ARIC) study, a majority of African Americans with and without *APOL1* risk genotypes in the general population experienced a similar rate of decline in glomerular filtration rate. *APOL1* genotypes in ARIC were associated with a significant risk for adverse renal outcomes but they only explained a minority of kidney outcomes. Compared to African Americans at high risk for CKD, the

ARIC findings do not support general population screening for *APOL1* in African Americans.[61]

Intervention approaches and BP outcomes in quality improvement clinical trials

Considerable research has focused on quality of hypertension care in African Americans, elimination of the race-related gap in BP control and the higher rates of stroke and premature mortality in African Americans[62]. Much of this has focused on RCTs testing interventions that target patients, providers, clinics, health systems, or some combination of these groups.[63] Team-based interventions that assign responsibilities to a health professional other than the primary care physician provide a potent and cost-effective strategy for improving BP control.[64, 65] They seem to be as effective in African Americans as in others but more scrutiny is needed. There is also need to determine the ideal composition of hypertension care teams, the best strategies for interaction and communication, and the most efficient and cost-effective utilization of individual team members. Team-care delivered in non-traditional locations, including community pharmacies, patient homes, barber shops, faith-based organization and workplaces, shows promise but the cost-effectiveness and sustainability of these approaches need study.

Technology, including telemanagement, is highly effective, especially when combined with home BP monitoring and web-based management[66] but has been insufficiently studied in African Americans.

Medication adherence in patients with hypertension is an important concern, especially in African Americans[67]. Practitioners want better and more practical methods for detection and management of poor adherence, particularly in patients with apparent treatment resistant hypertension. In-person, telephone, and web-based motivational counseling all show promise[68], as does provider training in patient-centered communication skills[69] but additional research is needed to identify the value and durability of these interventions on change in lifestyle and clinically meaningful outcomes.

With a rapidly changing clinical practice environment, clinician attitudes[70] and uncertainty[71] may be equally important compared to level of knowledge. The quality of BP assessments for decision making in clinical practice is important but poorly studied, especially in practices that predominantly serve African Americans. There is need to understand the extent to which practitioners, including those predominantly caring for African Americans, adhere to recommendations for accurate BP measurement and the barriers that limit adherence to BP measurement recommendations.

Recent comparative effectiveness quality improvement trials incorporate implementation research methods.[72] However, there is need for greater attention to hypertension implementation and dissemination research in African Americans.[73] Especially needed are studies of how specific activities and strategies affect integration of evidence-based interventions into routine health care. Likewise, there is need to study factors necessary for adoption and implementation of evidence-based interventions ready for widespread use.

Barriers to hypertension control in African Americans exist at multiple levels including factors related to individual patients; family and social support systems; health care providers; organization and practice settings where care occurs; the local community environment; and local, state, and national health policy. Research is needed to test interventions that target three or more levels, such as interventions that link community, system and team-level approaches to individual provider- and patient-level programs of care.

Performance measures in clinical settings

National Committee for Quality Assurance Healthcare Effectiveness Data and Information Set (HEDIS) measures are commonly used in federal quality reporting programs. The current HEDIS measure for BP control utilizes the most recent clinic BP reading. If multiple readings are available, the lowest value can be selected. This approach has substantial potential for ascertainment bias[74], and fails to account for differences in difficulty controlling hypertension based on patient characteristics. In RCTs that target specified BP goals, attention is paid to guideline recommendations for measurement of BP and not all patients in the intervention arm reach the goal BP.[41] Research is needed to understand whether use of a RCT BP target as a performance metric in clinical practice is safe and beneficial.[75] Such an approach has potential to result in a higher proportion of patients having a lower BP compared to experience in RCTs.

BP is higher and more resistant to treatment in African Americans.[50] Providers who treat African Americans may be penalized by use of the current HEDIS BP performance indicator. Similarly, there may be a disincentive for accurate reporting of BPs. Alternative measures, including change in BP over time, should be considered. Reliance on office-based BP performance measures ignores the impact of nocturnal and masked hypertension, which are common in African Americans, and may contribute to overall disparities in CVD.[47, 76] Incorporation of home BP readings into performance measures may be warranted but requires a change in electronic medical records reporting and validation studies. Hypertension in adolescents is an emerging contributor to race-related disparities in hypertension control. African American adolescents have markedly higher rates of uncontrolled BP compared to their White counterparts.[77]

Quality improvement initiatives based on use of performance measures have the potential to close racial inequalities in BP control. However, substantial gaps remain in collection of race and ethnicity data, and few governmental organizations or health systems report data on racial/ethnic disparities in BP control.

Building the Workforce Capacity

Existing models suggest workforce diversity is an important element in reducing health disparities, but little is known about diversity of the workforce committed to hypertension disparities research. Most training programs are focused on academic scholarship and devote insufficient attention to skills needed to address racial disparities by measurement of social determinants associated with hypertension; application of health services research methods to explore burden and mechanisms of racial disparities; or selection of clinical outcomes in

event-based RCTs and BP outcomes in quality improvement trials that are especially relevant in African Americans. This highlights the need for interdisciplinary training programs that incorporate social and behavioral sciences, environmental factors and expertise in health policy. Existing programs, particularly training cores within larger programs, should be evaluated for success in developing early stage investigators committed to hypertension disparities research. Workgroups designed to facilitate training related to hypertension in African Americans should be explored in large ongoing multisite observational studies such as CARDIA and MESA and in multicenter RCTs such as SPRINT. Databases from completed RCTs with continued participant follow-up, such as ALLHAT, and ACCORD also provide opportunities for mentored learning and exploration of issues related to high BP in African Americans. Hypertension training programs need to bridge instruction related to etiology and translation of research findings to application in clinical practice and formulation of health policy. Further, they need to focus on developing multi-sectorial partnerships that intervene at the environmental, housing, educational and behavioral levels, including the built environment and access to better quality and affordable foods that are low in sodium and saturated fat. There is need for NIH workshops that target scientific inquiry within the topic of disparities in hypertension - similar to the Office of Behavioral and Social Sciences (OBSSR) Summer Institute on RCTs. Programs should foster development of professional networks for trainees and young investigators through networking and cross-institutional training while recognizing the importance of role models in the early stages of career development. Given the importance of clinical practice to dissemination and implementation of research results, training programs should include practicing clinicians who do not plan to make research the main focus of their career.

Conclusions

Despite remarkable progress in recent decades, African Americans continue to have a disproportionately high prevalence of hypertension and risk of BP-related complications compared to non-Hispanic Whites. A list of research needed to improve prevention, treatment and control of hypertension in African Americans is provided in the supplement and includes studies related to surveillance of hypertension; the environmental, social and psychosocial determinants of high BP; genetic and pharmacogenomic studies of BP-related cardiovascular and renal disease; non-pharmacological and drug intervention trials; and dissemination and implementation of evidence-based strategies for hypertension control in clinical and public health practice. In addition, there is need for customized training programs to develop the next generation of scholars who will address racial disparities in prevalence and control of high BP.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Novelty and Significance

What is new?

- African Americans have a disproportionately high prevalence of hypertension and risk of BP-related CVD and renal disease.
- Despite use of more BP-lowering medications, hypertension is less well controlled in African Americans compared to the US general population.
- We report findings of a NHLBI Working Group that was tasked with identification of research needs to improve prevention, treatment and control of hypertension in African Americans.

What is relevant?

- Research needs were identified related to surveillence; the environmental, social, and psychosocial determinants of high BP; genetic and pharmacogenetics studies; non-pharmacological and drug intervention studies; and best approaches to dissemination and implementation of evidence-based strategies for control of hypertension.
- The Working Group also indentified need for customized training programs to develop the next generation of scholars who will address racial disparities in prevalence and control of high BP.