Clinical Hypertension and Vascular Diseases
Series Editor: William B. White

Keith C. Ferdinand *Editor*

Hypertension in High Risk African Americans

Current Concepts, Evidence-based Therapeutics and Future Considerations

Humana Press

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ISBN 978-1-4939-2009-9 ISBN 978-1-4939-2010-5 (eBook)
DOI 10.1007/978-1-4939-2010-5
Springer New York Heidelberg Dordrecht London

Library of Congress Control Number: 2014954130

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Preface

Hypertension is the most commonly diagnosed and treated chronic condition in the outpatient setting. High blood pressure is a powerful risk for cardiovascular and renal disease and is disparate in US blacks in prevalence and complications. This text is designed to highlight important epidemiological data, target organ manifestations, and the evidence basis for potentially the most effective means to prevent and control this deadly condition in African Americans.

Nevertheless, the optimal approach to developing best practices must entail more than a recitation of recent guidelines. While graded, evidence-based guidelines are necessary to identify optimal treatment of patients, in most circumstances clinicians also remain appreciative of the viewpoints of experts in this field. These opinions add to and supplement guidelines, which are actually never assumed to be a replacement for clinical judgment. In the final analysis, patient care must be applied on a one-on-one approach, reflecting the unique circumstances presented by that patient. As a result, especially considering the often-insufficient inclusion of African Americans and other racial/ethnic minorities in many large randomized clinical trials, while clinicians must hopefully utilize outcome evidence to guide therapy, the expert opinions contained in this text also may assist in treating their high-risk African American patients. Hence, understanding the concepts in this compendium for effective treatment of hypertension in African Americans is a necessary step to decreasing and eventually eliminating disparities in cardiovascular diseases.

In the final analysis, this dual approach may best curtail the unfortunate and unnecessary premature morbidity and mortality due to hypertension prevalence in blacks and associated cardiorenal metabolic and atherosclerotic cardiovascular disease (CVD) events.

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Chapter 1
Overview

Samar A. Nasser

This text is designed to support effective practices for clinicians, including physicians, nurse practitioners and cardiac nurse specialists, pharmacists, physician assistants, nutritionists, and others who treat high-risk African Americans. Pharmacologic therapy is usually necessary, but alone has not been sufficient to treat hypertension. Furthermore, the Institute of Medicine (IOM) has recognized five main environmental factors as prominent underpinnings for the widespread burden of hypertension in the United States [1]. Particular dietary patterns, nutrient intake, and levels and types of physical activity can play a major role in cardiovascular disease (CVD) prevention and treatment through effects on modifiable CVD risk factors (i.e., blood pressure [BP] and lipids). As it relates to hypertension in African Americans, the recent 2013 American College of Cardiology/American Heart Association (AHA/ACC) Guideline on Lifestyle Management to Reduce Cardiovascular Risk may be used to achieve appropriate BP prevention and control [1]. First of all, the new guidelines advise adults to engage in aerobic physical activity 3–4 sessions per week involving moderate- to vigorous-intensity physical activity with an average 40 min per session to lower BP. In addition, the evidence supports consuming a dietary pattern that emphasizes the intake of vegetables, fruits, and whole grains; includes low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils, and nuts; and limits the intake of sweets, sugar-sweetened beverages, and red meats. Furthermore, the recommendation for overall heart healthy eating patterns is additionally expanded to include lowering sodium intake in those who need to control blood pressure.

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K.C. Ferdinand (ed.), *Hypertension in High Risk African Americans*, Clinical Hypertension and Vascular Diseases, DOI 10.1007/978-1-4939-2010-5_1

The first chapter after this overview presents a better understanding of epidemiology, awareness, prevalence, and control by Brent M. Egan and Daniel T. Lackland. The evidence is clear that progress has been made in identifying and treating hypertension in African Americans. However, effective control at levels which will eliminate disparities in CVDs remains elusive. This broad, up-to-date first chapter reconfirms that hypertension is a significant dilemma for African Americans with multiple forms of higher and premature target organ damage, including stroke, cardiovascular, and renal complications of hypertension than in other race/ethnicity groups. Moreover, Egan and Lackland point out that African Americans are at greater risk for treatment-resistant hypertension than Caucasians. Although the reasons for the significant hypertension-related racial disparities in elevated blood pressure remain unclear, there is an undebatable urgency to identify African American men and women with excess hypertension risk. The wise clinician uses all tools available, and Egan and Lackland review both pharmaceutical and non-pharmaceutical effective therapies for African American hypertensive patients. As later detailed in this text by Angela Brown and David Kountz, adherence is generally lower in African Americans as compared with Caucasian hypertensive patients, involving multiple factors that must be addressed to ensure decreasing or eliminating disparities.

Moreover, this text provides extensive attention to the effective implementation and importance of therapeutic lifestyle control (TLC), which is the cornerstone of hypertension treatment. Hygiene measures are essential to advance patient care in hypertension and CVD. In view of the powerful impact of lifestyle on hypertension prevalence and control, the subsequent chapter by Margaret Scisney-Matlock addresses the essential need to not only prescribe medications to control the risks of uncontrolled hypertension in African Americans but to concurrently address lifestyle modifications. Particular dietary patterns, nutrient intake, and levels and types of physical activity can play a major role in CVD prevention and treatment through effects on modifiable CVD risk factors (i.e., BP and lipids). TLC involves beneficial lifestyle modifications, which are especially important components of care for high-risk populations, including many African Americans with hypertension. This text reviews data supporting effective utilization of TLC in US African Americans. Moreover, the evidence supports wider implementation in all populations of various lifestyle approaches to curb cardiovascular morbidity and potentially mortality [2].

Therefore, to identify and refine methods to utilize TLC in patients with hypertension, the chapter by Margaret Scisney-Matlock and colleagues discusses the benefits of the approaches they have developed. Scisney-Matlock and colleagues provide a comprehensive review of the Women's and Men's Hypertension Experiences and Emerging Lifestyles Intervention (WHEEL-1), an evidence-based approach to implementing TLC. Their techniques [3] are especially effective in African American women with hypertension. The program developed in Michigan several years before current lifestyle guidelines were promulgated offers support and advice to adults who would benefit from BP lowering. The WHEEL-1 methods laid the groundwork for the translation of a theoretically derived cognitive-behavioral intervention to clinical practice, with a focus upon relationships between

cognitive representations of disease- and health-related behavior, hypertension treatment regimens, and dietary approaches to reduce blood pressure. It provides techniques particularly useful for women from racially and geographically diverse backgrounds.

Throughout several chapters in the text, various authors also propose further implementation of healthy dietary patterns, such as the Dietary Approaches to Stop Hypertension (DASH) [4] dietary pattern, and lower sodium intake. Most of the general community would benefit from no more than 2,400 mg of sodium per day, but despite ongoing debate and controversy, there is strong and consistent clinical trial evidence that reducing sodium intake further lowers BP, and this lowering effect has been demonstrated in adults with hypertension (HTN) and pre-HTN, independent of gender, ethnicity, or age. There is evidence from well-controlled feeding studies as well as studies in which participants were counseled to lower sodium that reducing sodium intake has an effect on BP independent of changes in weight. Moreover, lower sodium intake may prevent progression from pre-HTN to HTN and promote hypertension control, possibly associated with a lower risk of CV events.

This text is designed to address disparities in hypertension and CVD, specifically in African Americans, and supports the work of the Million Hearts® (MH) initiative [5]. The MH encourages widespread adoption and use of standardized treatment protocols for improving BP control, and despite the clear importance of TLC, pharmacotherapy, often with multiple medications, is usually necessary for effective HTN control.

1.1 Community Programs

The one-on-one application of evidence-based medicine and appropriate individualized care is essential to control hypertension for any given patient. Nevertheless, the chapter "Community Programs for Hypertension: A Means of Identification and Intervention in the Highest Risk Population" by Joseph Ravenell and Olugbenga Ogedegbe provides a brief history and present-day evidence for using community-wide approaches to explore hypertension control programs [6]. Ravenell and Ogedegbe especially note that community-based hypertension programs have long been recognized as additional pathways to achieve BP control, particularly among high-risk populations such as African American men who tend to under-utilize primary care settings. In the 1960s, the fight to reduce suffering from hypertension started with the recognition by the first National Health Examination Survey, conducted from 1960 to 1962, that there was a significant prevalence of hypertension among adults, particularly among African Americans [7]. In their historical overview, the authors point to the 1970s as a period of a rapid expansion of hypertension control efforts nationwide and specifically the establishment of the National High Blood Pressure Education Program (NHBPEP) in 1972 [8]. Subsequently, multiple, culturally relevant community venues for hypertension screening evolved.

For instance, in the African American community, churches are pillars that provide information and services in a familiar nonthreatening setting. Furthermore, health is approached in an environment that is outside a mainstream health-care system, which often times is viewed with suspicion. Moreover, in churches, health promotion embraces and recognizes the culture of their communities.

The authors respectfully describe the early efforts in Baltimore, Maryland, with Elijah Saunders and Waine B. Kong [9], and other pioneering programs, such as the Healthy Hearts Community Prevention Project, led by Keith and Daphne Ferdinand in New Orleans, Louisiana [10]. More recent, peer-reviewed published data is found in the work of Ron Victor, Ravenell, and colleagues from the Barber-Assisted Reduction in Blood Pressure in Ethnic Residents (BARBER-1) study, involving African American-owned barbershops in Dallas, Texas [11]. This cluster-randomized, barbershop-based trial demonstrated that the shops in the intervention arm had significantly greater BP control among hypertensive customers compared to the control shops (absolute group difference in control rate = 8.8 %, $P = 0.04$). The importance of BARBER-1 is that it appears to be the first completed randomized barbershop-based hypertension trial in the peer-reviewed literature.

Important contemporary outreach work in communities is also described, specifically the Men's Health Initiative, led by the chapter authors. This program is comprised of three studies: (1) the *M*ulti-Intervention Study to *I*mprove Colorectal Cancer *S*creening and *t*o *E*nhance *R*isk Reduction in *B*lack Men (MISTER B), (2) the Faith-based Approaches in the Treatment of Hypertension and Prevention of Colorectal Cancer (FAITH-CRC), and (3) the New York University Prevention Research Center Comparative Effectiveness Program. This ambitious broad approach to communities in the New York City area, to date, has recruited over 1,100 men and screened over 6,000 African American men over age 50 years at 100 faith-based organizations and 90 black-owned barbershops. The authors anticipate completing the trials in 2015. Not only do Ravenell and Ogedegbe describe past and ongoing community efforts but also call for continued refinements in community-based intervention. They conclude with a plea to develop and maintain effective programs past the length of funded studies, building true relationships with community-driven programs to help continue curbing the comorbid effects of hypertension on these disparate populations.

1.2 Hypertension and Risk of Stroke

Hypertension-related target organ damage and cardiovascular morbidity and mortality are disproportionately high in Africans Americans. Therefore, any comprehensive text on hypertension in African Americans must recognize the unacceptably high burden of stroke, especially in younger US African Americans. The chapter entitled "Stroke and Hypertension in High-Risk African Americans" by Virginia J. Howard, Megan E. Ruiter Petrov, Tanya Dudenbostel, and Stephen P. Glasser presents a clear, thoughtful, up-to-date description of the epidemiology of stroke and its relationship to hypertension in African Americans.

Stroke is preventable in most cases, although it remains a leading cause of death [12]. There has been progress, and an overall decline of stroke mortality in the past 50 years, an unacceptable disparity persists, as Howard and her colleagues detail. Stroke prevalence is consistently higher in African Americans than any other US race/ethnic group, and to curtail these disparities, two major risks factors must be controlled and/or prevented to reverse the excess black/white disparity attributable to hypertension and diabetes [13]. Perhaps even more important as a risk factor for stroke than for coronary heart disease (CHD), hypertension in African Americans has higher prevalence, and less control than in Caucasians. In their excellent comprehensive description of current data, the authors demonstrate that the impact of uncontrolled hypertension on stroke risk is three times greater for African Americans than Caucasians. Furthermore, for primary providers and hypertension specialists, ambulatory BP monitoring may assist in detailing a variety of abnormalities, more prevalent in US African Americans, including masked hypertension, the nocturnal BP pattern, and circadian BP variability. The chapter on stroke is absolutely essential reading for anyone interested in understanding the excess risk in African Americans, potential reasons for excess risk, and areas where interventions are needed to reduce the unequal burden of stroke. Their conclusion is clear: a main path for the reduction of stroke in African Americans is *via* the prevention, detection, and control of high blood pressure.

1.3 Hypertensive Target Organ Damage

Of the most lethal, yet often underappreciated, risks associated with hypertension in African Americans are left ventricular hypertension (LVH) and its associated sequelae. In the chapter "Manifestations of Left Ventricular Hypertrophy and Coronary Heart Disease: The Contribution of Hypertension and the Paradox in Blacks," Tochukwu M. Okwuosa and Kim A. Williams explore the epidemiology and pathophysiology underlying the link of hypertension and LVH. The authors note LVH robustly predicts CVD events (including myocardial infarction [MI], sudden death, stroke, congestive heart failure, and overall CVD mortality). This increased risk is found independent of traditional cardiovascular risk factors, including hypertension, diabetes, smoking status, and dyslipidemia. A major independent predictor of cardiovascular mortality, LVH, and increased left ventricular (LV) mass is more prevalent in African Americans compared with whites [14]. Moreover, LVH and increased LV mass are responses to the greater workload associated and promote CVD as a powerful, independent risk factor for CVD death. For clinicians, it is important to recognize nuances in LVH diagnosis based on the electrocardiogram (ECG) versus magnetic resonance imaging (MRI). Recognition of LVH by ECG has low sensitivity, but high specificity, especially in African Americans, for detecting cardiac MRI-defined LVH, whose high level of accuracy and reproducibility represent the new gold standard. Nevertheless, beyond diagnosis, patients with LVH have worse outcomes and prognosis, regardless of imaging modality employed.

This worsened prognosis of LVH includes heart failure, sudden death, and unrecognized MI. Accordingly, with LVH, African American race may be associated with 130 % increased risk of developing new heart failure relative to non-African American race [15]. Optimal therapeutic approaches to treatment of LVH remains uncertain, based on outcome studies, but perhaps renin system modulation, often considered less effective as monotherapy for BP reduction in African Americans, may assist with controlling LVH and its sequelae.

1.4 Heart Failure and Hypertension in African Americans

Elizabeth Ofili and colleagues detail the widespread prevalence and associated morbidity and mortality associated with heart failure (HF). Although, overall, a growing and major cardiovascular problem, specifically hospitalization for HF is a major contributor to poor cardiovascular outcomes and economic burden and the primary diagnosis in over one million hospitalizations annually [16]. In consideration of HF as the most common Medicare diagnosis-related group (DRG), numbers and costs are expected to grow considerably, since 1 in 5 Americans will be >65 years of age by 2050, and HF prevalence is highest in this age group [17]. African Americans have the highest risk for HF, and it affects approximately 3 % of the African American population. Notably, the duration and severity of hypertension directly correlate with HF incidence. This chapter tackles some of the theory and clinical data on variation in HF etiology and drug response that appear more common in African Americans. Building on data from retrospective analysis of various HF studies using the combination of isosorbide dinitrate and hydralazine in patients, the African American Heat Failure Trial (AHEFT) confirmed the potential benefit of correction of nitric oxide bioavailability, using a combination of fixed dose isosorbide dinitrate (ISDN) and hydralazine (Hyd). The authors further note that the results of the AHEFT support the recent American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Guidelines recommending ISDN/Hyd in addition to standard therapy for African Americans with HF/preserved ejection fraction (EF) currently receiving angiotensin-converting enzyme inhibitors (ACEI) and beta-blockers (BBs) (Class I, Level A) and for patients with HF who are unable to tolerate ACEIs and angiotensin receptor blockers (ARBs) (Class IIa, Level B) [18].

1.5 Atrial Fibrillation and Hypertension in African Americans

The relationship of atrial fibrillation and hypertension in African Americans is unclear, and even paradoxical. Atrial fibrillation (AF) has been repeatedly reported to be less prevalent in African Americans compared to Caucasians, even though

hypertension, more common in African Americans, is one of the most important risk factors for AF [19]. Therefore, the lower occurrence of AF in African Americans compared to Caucasians remains at odds with the high or higher rates of AF risk factors in African Americans [20]. Authors Elsayed Z. Soliman and Ronald J. Prineas address factors involved in the AF paradox in the chapter "Hypertension and Atrial Fibrillation in African Americans." The number and interplay of factors explaining the paradox are numerous and complex and complicated by the lack of data on the racial/ethnic distribution of AF subtypes, especially paroxysmal AF. Long-term studies are needed to examine AF in younger age groups (<45 years) for black/white differences in prevalence and incidence and the differential effects of risk factors for AF over longer periods of time to determine the true "life cycle" of AF.

Overall, African Americans are at particularly higher risk for stroke and stroke mortality compared to Caucasians, and AF carries a more than fivefold increase in stroke incidence. Nevertheless, despite such a strong association between AF and stroke, it is incompletely understood why African American race/ethnicity has been repeatedly associated with less AF. Such a paradox mandates rethinking the epidemiology of AF and revising the current knowledge of the racial/ethnic distribution of AF. There remains the possibility of racial/ethnic differences in AF patterns (i.e., African Americans may have more paroxysmal AF, a pattern difficult to detect, or Caucasians have more chronic AF, a pattern easier to detect). However, the suggestion that African Americans might have higher prevalence of asymptomatic or paroxysmal AF (or whites have more chronic AF) is based on "clues" not "evidence" and the African American AF paradox provides a compelling case for more investigation of AF in African Americans.

1.6 Cardiometabolic Renal Syndrome in African Americans

In the chapter "Cardiorenal Metabolic Syndrome and Diabetes in African Americans: Adding to the Risk of Hypertension," Ankur Jindal, Adam Whaley-Connell, and James Sowers describe the multiple risk factors that constitute the cardiometabolic renal syndrome (CRS). These include abdominal obesity, atherogenic dyslipidemia (elevated serum triglycerides and apolipoprotein B, increased small low-density lipoprotein [LDL] particles, and a reduced level of high density lipoprotein [HDL] cholesterol), raised blood pressure, dysglycemia, and kidney disease (glomerular filtration rate [GFR] less than 60 and/or albuminuria).

The terminology of CRS recognizes that renal involvement in the form of proteinuria/albuminuria is frequently present in people with the metabolic syndrome, and this constellation of findings (CVD, renal disease and metabolic abnormalities). Considering the fact that African Americans are more likely to manifest renal disease at an earlier age, they are more often classified as having CRS rather than being identified as simply having the metabolic syndrome. Importantly, although hypertension is a clinical and public health problem in African Americans,

diabetes and obesity add to the risk conferred by hypertension and increase the mortality and morbidity with earlier and more severe kidney disease. Often in conjunction with heart disease, African Americans are more likely to manifest the CRS than other populations in the United States. Treatment considerations should include healthy diet and lifestyle modifications, which are important components in the pathogenesis of hypertension and the CRS in African Americans.

There is an increase in obesity and physical inactivity in African Americans, especially in females, although the dyslipidemia profile consistent with ATP3 metabolic syndrome (MetS) (high triglycerides, low HDL-C) may be less common than expected in African Americans. Furthermore, overweight status and obesity may be risk factors for MI and ischemic heart disease regardless of the presence or absence of the conventional metabolic syndrome identifying individuals [21]. Regardless, in high-risk African Americans, the concept of CRS is a better predictor of CVD risk than the conventional MetS definition.

1.7 Chronic Kidney Disease and End-Stage Renal Disease

Chronic kidney disease (CKD) is prevalent and disparate in African Americans. Hypertension, along with diabetes, is a major contributor to the unacceptably high rates of end-stage renal disease (ESRD) in African Americans. Myra Kleinpeter details the evidence that CKD is a major risk for CVD. She also confirms that effective blood pressure control is essential to control this risk in the future. The primary risk factors of obesity, hypertension, insulin resistance, hyperglycemia, dyslipidemia, CKD, as well as associated adverse behaviors of physical inactivity, smoking, and unhealthy eating habits concurrently impact the prevalence of metabolic syndrome among various racial/ethnic groups; however, metabolic syndrome disproportionately affects African Americans, Hispanics, American Indians/Alaskan Natives, and perhaps other minorities such as Americans of Asian Indian (South Asian), East Asian, and Middle Eastern descent [22].

1.8 Central Aortic Pressure and Arterial Compliance in African Americans

In the chapter "Central Aortic Pressure, Arterial Compliance: Emerging Tools to Identify and Guide Therapy for High-Risk African American Patients," Yonghong Huan, Debbie L. Cohen, and Raymond R. Townsend discuss mechanisms explaining the possible greater degree of arterial stiffness in African Americans.

Accordingly, reduced concentrations of vitamin D and higher systolic and pulse pressure in some studies have been associated with greater arterial stiffness in several studies in both men and women. Higher blood pressures are also associated with higher pulse wave velocity (PWV) in adolescent African Americans when

compared to Caucasian populations [23]. Additionally, preliminary work suggests that about 20 % of the PWV phenotype is heritable, but identifying specific genes, particularly in African American populations, is still in a discovery phase. One physiologic method, the β_2 receptor, when stimulated by isoproterenol, reduces PWV in Caucasians but not African Americans, indicating a blunting of the response to vasodilatory influences. As in other populations, the presence of diabetes is associated with increased PWV in African American adolescents compared with whites.

Although a growing body of cross-sectional evidence indicates that there are differences, generally in an adverse direction, in central arterial pressure, arterial stiffness, and PWV in Africans and African Americans, when compared with Caucasians, the importance of such differences, and their susceptibility to modulation by lifestyle, drug, or both interventions, await support from clinical trial evidence. Overall, most of the central pressure data on African Americans and those of African descent are cross-sectional in nature and typically show that measures of central pressure are higher in African Americans and those of African descent when compared with other race/ethnicities. The findings are usually not apparent from knowledge of the brachial BP alone.

1.9 Resistant Hypertension

Resistant hypertension may be defined as a failure to achieve a guideline-driven BP of less than 140/90 mmHg, utilizing maximally tolerated doses of at least three antihypertensive drugs, one of which must be a diuretic appropriate for kidney function [24]. Perhaps even more so in African Americans, persons with resistant hypertension, with blood pressures that are more difficult to control, have a high absolute cardiovascular and renal risk and higher prevalence of target organ damage. Several resistant hypertension risk factors are common with African American race/ethnicity, including obesity (especially in women), type 2 diabetes, and CKD. For clinicians with a significant African American patient population, there is a clinical need for additional tools to control resistant hypertension and potentially decrease cardiovascular and renal disease and heart failure [25].

In consideration of these factors, the chapter “Renal Denervation Therapy and Baroreceptor Activation Therapy: Emerging Tools for Treating Resistant Hypertension” by Peter D. Hart, George Bakris, and colleagues explores the background, brief history, and potential clinical utility of novel interventions to curtail the ravages of hypertension. Recent technical advances targeting the renal sympathetic nerves (i.e., renal denervation therapy [RDT]) and the baroreceptors in the carotid sinuses (i.e., baroreflex activation therapy [BAT]) are promising tools in the armamentarium treating resistant hypertension. Although results from the Simplicity HTN-2 and Rheos Pivotal trials on efficacy and safety of RDT and BAT indicate these therapies can safely reduce BP in patients with resistant hypertension, neither intervention as of early 2014 has been approved in the United States by the Food and Drug Administration (FDA) for use outside appropriately designed clinical trials [26].

Currently, renal denervation should be considered only in patients whose BP cannot be controlled by a combination of lifestyle modification and optimal pharmacologic therapy, tailored according to current guidelines [27]. It is inconclusive whether renal denervation may be useful in less severe forms of hypertension or in other conditions characterized by heightened renal sympathetic nerve activity (e.g., heart failure, metabolic syndrome, arrhythmias, and CKD). Currently, long-term safety and efficacy of renal denervation are being collected in national and international registries [28]. Ultimately, the widespread adoption of renal denervation will depend on results of well-designed trials, experiences in clinical practice, and the clinical reassurance that patient referral for the procedure will be effective, safe, and durable over time. Nevertheless, while renal denervation is still investigational in the United States, internationally it has shown significant acceptance and use.

1.10 Integration of a Team Approach to Hypertension Treatment

This text would be inadequate if it did not include evidence on the effectiveness of teamwork and best practices in promoting adherence and control. Angela L. Brown and David Kountz recognize that effective adherence is definitively linked to adherence. They offer insights on how to better understand and decrease this high hurdle to effective care. For many decades, the scope of practice for pharmacists has often been confined to retail, community, or institutional settings; however, more recently there has been a shift of the scope of practice for pharmacists to provide much needed education to patients about the medications and to incorporate technological advances into the field of pharmacology [29]. Kevin Sneed clarifies the progress of a pharmacist in therapeutic medicine in the chapter "Integration of a Team Approach to Hypertension Treatment." In his chapter, Sneed describes a much needed role for pharmacists as providers to discuss safe and effective medication use by patients, especially given the inclination towards polypharmacy in patients with chronic diseases, such as hypertension.

Most hypertension guidelines and practice algorithms tout multiple medications to manage hypertension in patients, sometimes after a trial with TLC. Effective utilization of medications is best based upon evidence-based medication regimens, stemming from randomized controlled trials. Pharmacological treatment, while likely necessary in treating hypertension, can become complex with multiple unrecognized drug–drug interactions.

Furthermore, Sneed describes how pharmacists are well positioned to significantly contribute to increasingly utilized technology-driven evolution of health care. The ability to effectively document clinical interactions directly into the electronic medical record will improve communication between pharmacists, physicians, and other providers. By developing collaborative protocols to establish clinical workflows and communication strategies, clinical pharmacists may be a valued member of the health-care team. Utilization of technology by patients will truly create a

patient-centered approach to health care. Health information technologies, designed and implemented in conjunction with clinical pharmacists, have a great potential to remove the silos and barriers between health practitioners that have existed for many decades.

1.11 Therapeutic Considerations in African American Hypertensives

The 2014 American College of Cardiology (ACC)/American Heart Association (AHA)/Centers for Disease Control and Prevention (CDC) Science Advisory for effective BP control approach encourages simple, evidence-based treatment protocols, clarifying titration intervals and treatment options and expanding the types of staff that can assist in timely follow-up with patients [30]. Their suggestions along with protocols embedded in electronic health records serve as clinical decision supports at the point of care so no opportunities are missed to achieve control. Although a variety of evidence-based hypertension treatment protocols are available, the authors in this text contribute proposed expert opinions to treat African Americans, often more difficult to control patients. The MH website and recent AHA/ACC/Centers for Disease Control Science Advisory on effective high BP control are very useful resources, but it should be noted therein that health-care professionals should always consider the individual clinical circumstances of each person, and hypertension protocols are not a substitute for professional medical advice.

1.12 Practical Pearls and Best Pharmacologic Treatment

Despite the benefits of therapeutic lifestyle interventions to prevent and control high blood pressure, most high-risk African American patients, as true in all high-risk individuals, need expert and appropriate pharmacological care. The centerpiece of this text is therefore the suggested approaches clinicians can embrace for effectively the complications of uncontrolled hypertension in their patients.

Elijah Saunders, John Flack, and others propose combination therapy in most high-risk African Americans, often as first step in pharmacotherapy. Saunders has established a lengthy record of research and clinical care on hypertension in high-risk African Americans. His practical approach to the adequate treatment and control of hypertension in African Americans considers multiple factors, including various pathophysiological and nonphysiological factors. While reviewing the treatment of hypertension included in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) and the International Society of Hypertension in Blacks (ISHIB) consensus report [31, 32], Saunders highlights the importance of factoring in hypertension-related morbidities, target organ injury, and other comorbidities such as diabetes,

obesity, and dyslipidemia into care. His chapter, "Practical Pearls in the treatment of Hypertension in Blacks," builds on the recommendations of the earlier JNC 7 and antecedent ISHIB consensus statement. Although there are several newer 2013 and 2014 hypertension guidelines, the expert opinion views of Saunders offers a comprehensive means for clinicians to treat their African American patients and refine their practices. His insights on important aspects of various classes of medications and reflections on the risk stratification and treatment algorithm of hypertension in African Americans adopted from the 2010 ISHIB Consensus report are worthwhile for practical, effective pharmacotherapy. Since at least two-thirds of hypertensive patients will require more than one drug to achieve goal blood pressure, Saunders promotes the effective and appropriate use of combination pharmacotherapy.

In addition to the extensive research and experience of Saunders, Flack has long been a leader in identifying best practices in high-risk African Americans. In the chapter "Hypertension in African Americans," Flack, Ference, and Levy detail the aspects of salt sensitivity and non-dipping nocturnal BP as common intermediate BP phenotypes. In addition, the authors note vitamin D deficiency is pervasive in African Americans. Although it remains a controversial and increasingly debated approach, supplementation with vitamin D appears to lower BP in this population. Flack addresses the ongoing debate on the impact of excessive vitamin D deficiency in African Americans relative to Caucasians, starting in childhood. Although, as the authors note, the IOM has established the level of 20 ng/mL (50 nmol/L) as vitamin D sufficiency based on the level deemed sufficient to maintain bone health, the potential impact on low vitamin D levels and supplementation on hypertension in African Americans may be less easily defined.

Flack and others note there are several BP as well as physiological phenotypic *tendencies* in African Americans compared to Caucasians, but further suggest these racial differences/tendencies, in most instances, are quantitative rather than qualitative. For example, the lack of nocturnal decline in BP and salt sensitivity are two intermediate BP phenotypes potentially linked to hypertension in African Americans. However, they point out that these intermediate phenotypes are modifiable and may be influenced by multiple environmental and lifestyle exposures.

Non-dipping nocturnal BP in African Americans appears more prevalent in African Americans than Caucasians and a possible source of higher 24-h BP burden, especially the higher nighttime BP levels. The authors propose non-dipping of BP is not a truly genetic manifestation but also has been linked to high levels of dietary sodium intake, low levels of dietary potassium intake, and augmented activity of the sympathetic nervous system and also CKD, type 2 diabetes mellitus, older age (above 40 years), and obesity. Interestingly, sleep-disordered breathing, often with obesity, has also been linked to non-dipping of BP. Moreover, African Americans are disproportionately salt sensitive, operationally defined as a rise or fall in BP with dietary sodium exposure, more so than their Caucasian counterparts with similar levels of BP. Nevertheless, rather than a genetic, immutable factor, salt sensitivity may be affected by potassium bicarbonate supplementation and differences in renal function.

Similar to the chapter of clinical pearls from Saunders, Flack and others offer views on past guidelines and reports as they affect strategies for lowering hypertension in African Americans. Notably, the majority of hypertensive across races will require more than one antihypertensive agent to achieve BP control, and which combination of medications maybe more important versus which single medication should be employed.

1.13 The Impact of Recent Cardiovascular Risk Guidelines in the Management of High-Risk Patients with Hypertension

Finally, in the development of this text, multiple cardiovascular guidelines and reports have been recently published that may inform clinical practice in the management of high-risk African Americans. A brief review of these recommendations may supplement and support the evidence and expert opinion reported by the authors of various chapters.

1.13.1 Lifestyle

As previously noted, the 2013 Guideline on Lifestyle proposes significant benefit from BP lowering a dietary pattern that emphasizes intake of vegetables, fruits, and whole grains; includes low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils, and nuts; and limits intake of sweets, sugar-sweetened beverages, and red meats [1]. Limiting sodium intake may be effective in assisting with BP control in many African Americans with hypertension, and decreasing caloric intake is essential to curb excess body weight, a potent HTN risk factor and contributor to the CRS. Additionally, a limit on sodium intake to no more than 2,400 mg of sodium/day is advised; however with further reduction in sodium intake to 1,500 mg/day, there is a more significant reduction in BP. Finally, by reducing sodium intake by at least 1,000 mg/day, even if the desired daily sodium intake is not achieved, there is a significant reduction in BP and a reduction in CVD events by about 30 %. In adults 30–80 years of age with or without HTN, counseling to reduce sodium intake by an average of 1,150 mg/day reduced BP by 3–4/1–2 mmHg. The best option is to combine the DASH dietary pattern with the lower sodium intake. When all food was supplied to adults with BP 120–159/80–95 mmHg and both body weight and sodium intake were kept stable, the DASH dietary pattern, when compared to a typical American diet of the 1990s, lowered BP by 5–6/3 mmHg.

In adults with BP of 120–159/80–95 mmHg, modifying the DASH dietary pattern by replacing 10 % of calories from carbohydrates with the same amount of

either protein or unsaturated fat (8 % monounsaturated and 2 % polyunsaturated) lowered systolic BP by 1 mmHg compared to the DASH dietary pattern. Among adults with BP 140–159/90–95 mmHg, these replacements lowered systolic BP by 3 mmHg relative to DASH.

African Americans, especially black women, may have lower rates of recreational activity. Generally speaking, adults should be advised to engage in aerobic physical activity to lower BP at least 3–4 sessions a week, lasting on average 40 min per session and involving moderate- *to* vigorous-intensity physical activity. Among adult men and women at all BP levels, including individuals with HTN, aerobic physical activity decreases systolic and diastolic BP, on average by 2–5 mmHg and 1–4 mmHg, respectively. Typical interventions shown to be effective for lowering BP include aerobic physical activity of, on average, at least 12 weeks duration, 3–4 sessions per week, lasting on average 40 min/session and involving moderate- to vigorous-intensity physical activity.

1.13.2 Assessing CVD Risk Associated with Obesity

The 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults is clearly relevant in African Americans [33]. When assessing the risk for CVD and/or the presence of obesity-related comorbidities, diabetes risk assessment is critical and includes a history, physical examination, and clinical and laboratory assessments, including BP, fasting blood glucose, and fasting lipid panel. A waist circumference measurement is recommended for those with a body mass index (BMI) 25 < 35 kg/m^2 to provide additional information on risk. It is not necessary to measure waist circumference in patients with BMI >35 because the waist circumference will likely be elevated and it will add no additional risk information. The Panel recommends, by expert opinion, using the current cut points (>88 cm or >35 in for women and >102 cm or >40 in for men) as indicative of increased cardiometabolic risk. Additionally, the Panel recommends by expert opinion that intensive management of CVD risk factors associated with obesity (hypertension, dyslipidemia, prediabetes, or diabetes) or other obesity-related medical conditions (e.g., sleep apnea) be instituted if they are found, regardless of weight loss efforts.

In overweight or obese adults with elevated CVD risk (including type 2 diabetes and hypertension), there is a dose–response relationship between the amount of weight loss achieved at up to 3 years by lifestyle intervention (alone or combined with orlistat) and the lowering of BP. At a 5 % weight loss, a weighted mean reduction in systolic and diastolic BP of approximately 3 and 2 mmHg, respectively, is observed. At <5 % weight loss, there are more modest and more variable reductions in BP. A 5 % mean weight loss difference achieved over 4 years by intensive lifestyle intervention in overweight or obese adults with type 2 diabetes is associated with a lower prevalence of patients who are prescribed antihypertensive medications compared with controls.

Using current BMI cut points, the relative risk of fatal CVD was higher in obese Caucasian women than in obese African American women compared to normal weight women. This is a paradox, especially since African American women in particular are more obese and have comorbid hypertension and diabetes.

1.14 Dyslipidemia Guidelines

Although this text is focused on hypertension, the wise clinicians do not isolate major risk factors, and potentially overlook one area, while focusing on another. By more accurately identifying higher-risk individuals for statin therapy, the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults focuses statin therapy on those most likely to benefit [34]. Statin treatment based on estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk avoids the overtreatment of lower-risk groups such as younger, non-Hispanic Caucasian women who, despite moderate elevations in LDL-C, are typically not at significantly increased risk for ASCVD in the next 10 years in the absence of substantial risk factor burden. However, ignoring the increased ASCVD risk in African American women and men might result in the undertreatment of some individuals who are at significantly higher ASCVD risk at the same LDL-C level.

In adults with diabetes, statin therapy reduced the relative risk (RR) for CVD by a similar magnitude for subgroups of diabetic men and women, aged <65 and >65 years; treated hypertension; BMI <25, >25 to <30, and >30; systolic blood pressure <160 and >160 mmHg; diastolic blood pressure <90 and >90 mmHg; current smokers and nonsmokers; estimated GFR <60, >60 to <90, and >90 mL/min/1.73 m^2; and predicted annual risk for CVD <4.5 %, >4.5 % to <8.0 %, and >8.0 %.

1.15 Hypertension Guidelines

Jackson Wright is widely published in the field of treating high-risk African Americans and has been central to recent US guideline development [35]. His viewpoints are often beyond accepted dogma and question and investigate what exactly are the best approaches in high-risk African Americans. According to a 2014 guideline report from members appointed to the Eighth Joint National Committee (JNC 8) for the management of high blood pressure, the main objective of hypertension treatment is to attain and maintain goal BP [36]. If the BP goal is not reached within a month of treatment, the initial drug dose should be increased or another class of antihypertensive agents should be added (i.e., thiazide diuretic, calcium channel blocker [CCB], ACEI, or ARB). While monitoring and reassessing BP, adjustment to the regimen should be made until BP goal is reached. If goal BP cannot be reached with two drugs, then a third drug should be added and titrated.

If the BP goal is not attained after this point, then a referral to a hypertension specialist may be indicated.

Consistent with JNC 8, there is strong evidence to support treating hypertensives aged ≥60 years to a BP goal of <150/90 mmHg and hypertensives of 30 through 59 years of age to a diastolic goal of <90 mmHg. Furthermore, the panel recommends a BP of <140/90 mmHg for those younger than 60 years for a systolic goal or in those younger than 30 years for a diastolic goal [35]. The same thresholds and goals are recommended for hypertensive adults with diabetes or nondiabetic CKD as for the general hypertensive population younger than 60 years. There is moderate evidence to support initiating drug treatment with an ACEI, ARB, CCB, or thiazide-type diuretic in the nonblack hypertensive population, including those with diabetes. In the black hypertensive population, including those with diabetes, a CCB or thiazide-type diuretic is recommended as initial therapy, which is also supported by the clinical practice guidelines by the American Society of Hypertension (ASH) and the International Society of Hypertension (ISH) [37]. There is moderate evidence to support initial or add-on antihypertensive therapy with an *ACEI* or ARB in persons with CKD to improve kidney outcomes.

According to the clinical practice guidelines by the ASH and the ISH, in patients >80 years old, the suggested threshold for starting treatment is at levels ≥150/90 mmHg. Thus, the target of treatment should be <140/90 mmHg for most patients but <150/90 mmHg for older patients (unless these patients have CKD or diabetes, when <140/90 mmHg can be considered). In patients with stage 2 hypertension (BP ≥160/100 mmHg), drug treatment should be started immediately after diagnosis, usually with a combination of two drugs, without waiting to see the effects of lifestyle changes.

Further guidance provided by the 2014 AHA/ACC/CDC Science Advisory suggested developing, disseminating, and implementing an effective hypertension treatment algorithm as a critical part of a multilevel, systematic approach to controlling hypertension. The advisory suggests how the algorithm could facilitate clinical decision-making, provide a default approach with proven benefits, and engage multiple providers in a coordinated manner.

It is the intent of the authors to point out best practices and enlighten the interested reader. Knowledge of drugs is insufficient to provide high-quality care. Therapeutic lifestyle changes, public health programs, and a better appreciation of the complexities of caring for high-risk African Americans will hopefully lead to further progress in modern, effective treatment.

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Chapter 2
Epidemiology Awareness, Prevalence, and Control: Newest Findings on Hypertension in Blacks

Daniel T. Lackland and Brent M. Egan

2.1 Introduction

The racial disparities in hypertension and hypertension-related disease outcomes have been related to mortality and morbidity risks compared with their white counterparts. These excess risks from elevated blood pressure have a dramatic effect on life expectancy for African American men and women which is significantly less than for Caucasian Americans. Stroke risks are twofold greater for African Americans [1]. In addition, the age of onset of diseases such as stroke is significantly earlier for African Americans compared to Caucasians. This race-age interaction impacts the hypertension-related disease risks. For example, a 45-year-old African American man residing in the Southeast has the stroke risk of a 55-year-old white man in the Southeast and a 65-year-old white man residing in the Midwest [1]. While high blood pressure affects all segments of the population, high blood pressure rates are more prevalent among African American men and women [2]. The increased prevalence and relative risks constitute significant population attributable risks [3]. Specifically, the population attributable risk for hypertension and 30-year mortality among white men was 23.8 % compared with 45.2 % among black men and 18.3 % for white women compared with 39.5 % for black women. These excess disease risks have been long recognized and reported from the Evans County Heart Study [4] and the Charleston Heart Study [5] which were both

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K.C. Ferdinand (ed.), *Hypertension in High Risk African Americans*, Clinical Hypertension and Vascular Diseases, DOI 10.1007/978-1-4939-2010-5_2

initiated in 1960 specifically to study these racial disparities in cardiovascular disease in adults. Similarly, the Bogalusa Heart Study [6] assessed the racial differences in children and young adults. More recently, the Jackson Heart Study [7] has been established to assess cardiovascular risk factors in this population. Further, the REasons for Geographic and Racial Differences in Stroke (REGARDS) study has further documented and confirmed the racial and geographic differences in awareness, treatment, and control of hypertension [8]. With these large epidemiology studies, high blood pressure has been a common significant factor associated with the excess disease burden for African Americans [9].

2.2 Blood Pressure and Hypertension Levels

Nearly one-third of the adult population in the United States are considered to have hypertension with elevated blood pressure (≥140/90 mmHg) and/or being treated with antihypertensive medication. The prevalence of hypertension is higher in both middle-aged and older African Americans compared with non-Hispanic whites [10, 11]. As presented in Fig. 2.1, data from the National Health and Nutrition Examination Survey (NHANES) show the racial disparities with black men and women having significantly higher rates of hypertension than white men and women

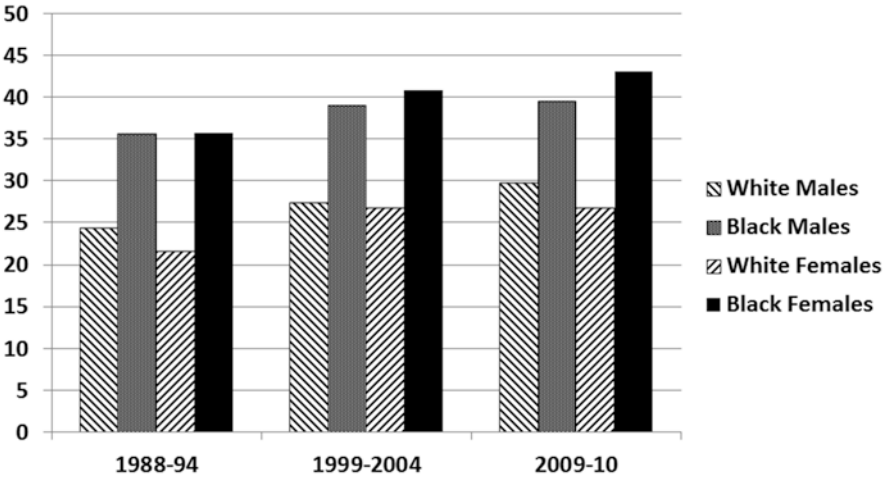

Fig. 2.1 Prevalence of hypertension (percent of adult population) US 1988–1994 and 1999–2004. Adapted from Lackland DT. Racial Differences in Hypertension: Implications for High Blood Pressure Management. American Journal of the Medical Sciences 2014; Cutler JA, Sorlie PD, Wolz M, Thom T, Fields LE, Roccella EJ. Trends in Hypertension Prevalence, Awareness, Treatment, and Control Rates in United States Adults Between 1988–1994 and 1999–2004. Hypertension. 2008;52:818–827; and Guo F, He D, Zhang W, Walton G. Trends in prevalence, awareness, management, and control of hypertension among United States adults 1999 to 2010. J AM Coll Cardiol 2012;60:599–606

[12, 13]. The prevalence rates increased for all four race-sex groups from the 1988–1994 period to the 2009–2010 period. However, the racial disparities in hypertension prevalence remained consistent over the time periods. These racial differences are evident at all ages. Blacks are found to develop hypertension at an earlier age than whites. An assessment of US children aged 8–17 years found systolic blood pressures to be 2.9 and 1.6 mmHg higher in black boys and girls compared with age-matched white boys and girls [14]. With the consistent racial differences at all ages, it is evident that disparities in hypertension represent a lifetime consideration [15–17].

2.3 Hypertension Awareness, Treatment, and Control

While large-scale clinical trials have consistently demonstrated that the control of elevated blood pressure significantly reduces the risk for major cardiovascular disease, stroke, and end-stage renal disease outcomes, a substantial portion of hypertensive patients do not achieve blood pressure control [15]. Data from the National Health and Nutrition Examination Survey suggest that blood pressure is controlled for less than two-thirds of all patients on antihypertensive medications [12, 18]. African Americans demonstrated poorer blood pressure control compared with Caucasians. Figure 2.2 presents the hypertension control rates for all four race-sex

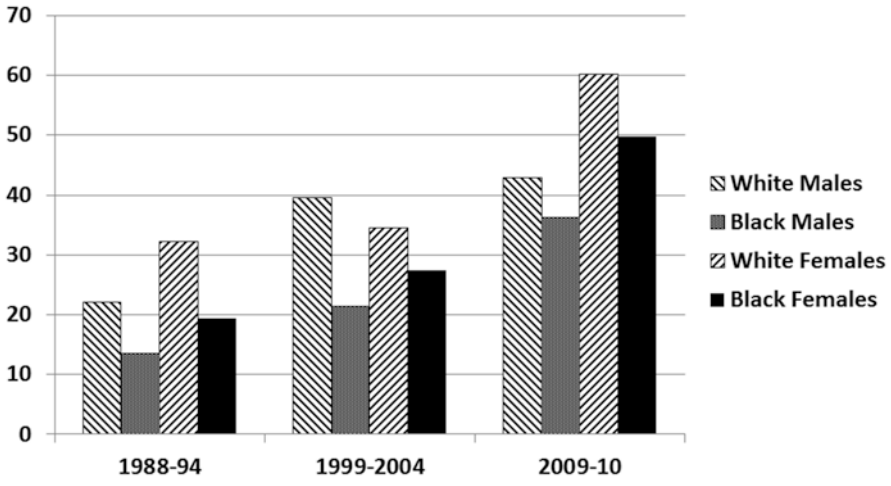

Fig. 2.2 Percent of hypertensive adult population with controlled blood pressure levels. US 1988–1994, 1999–2004, and 2009–2010. Adapted from Lackland DT. Racial Differences in Hypertension: Implications for High Blood Pressure Management. American Journal of the Medical Sciences (in press) Cutler JA, Sorlie PD, Wolz M, Thom T, Fields LE, Roccella EJ. Trends in Hypertension Prevalence, Awareness, Treatment, and Control Rates in United States Adults Between 1988–1994 and 1999–2004. Hypertension. 2008;52:818–827; and Guo F, He D, Zhang W, Walton G. Trends in prevalence, awareness, management, and control of hypertension among United States adults 1999 to 2010. J AM Coll Cardiol 2012; 60:599–606

groups from 1988 to 2010. While the high blood pressure control rates improved from the 1988–1994 period to the 2009–2010 period for all four race-sex groups, the racial disparities remained consistent. These findings of disparities in hypertension control are consistent with other studies [8, 11, 12, 19, 20]. The racial differences in control rates cannot be attributed to differences in rates of awareness and treatment [8, 9, 11, 12, 15, 18, 21]. Rates of awareness of hypertension as well as treatment patterns of antihypertensive therapy are similar for both race groups and even better among black men and women compared to white men and women. Results from the REasons for Geographic And Racial Differences in Stroke study (REGARDS) study indicate that efforts to raise awareness of prevalent hypertension among blacks apparently have been successful (31 % greater odds in blacks relative to whites), and efforts to communicate the importance of receiving treatment for hypertension have been successful (69 % greater odds among blacks relative to whites) [8].

Dietary factors including sodium and potassium, while different for blacks and whites, do not explain the racial disparities in hypertension. The Dietary Approaches to Stop Hypertension (DASH) diet with sodium restriction found better BP reduction for African Americans than Caucasians, indicating that black individuals may respond differently than whites [22, 23]. Similarly, treatment of elevated blood pressure with antihypertensive medications and different medications may produce different effects in African Americans and whites. Calcium channel blockers and diuretics have been proposed as being particularly effective for African Americans with hypertension [24–26]. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have not been shown to be as effective in black populations compared with white populations [25–27]. Similarly, ACE inhibitors, ARBs, and β-blockers have been reported to be less effective in blacks with heart failure compared with white patients [28]. However, it is important to consider sample size and confounders as well as study design when interpreting these results.

2.4 Hypertension Risks

The higher hypertension prevalence at earlier ages and more severe blood pressure levels correlate with the higher disease risks for blacks compared with whites. The risk ratios for stage 1 (≤140/90 mmHg) and stage 2 (≥160/95 mmHg) hypertension are presented in Table 2.1 for the four race-sex groups and 30-year all-cause mortality [3]. The risk ratios are significant for all but are greater for black men and women. Likewise, the risk ratios are higher in the more severe blood pressure levels for all four race-sex groups with higher risks for black men and women compared with white men and women [3, 29]. The disparities of higher prevalence and greater risks from high blood pressure are most evident with the population attributable risks which are nearly twice as great for black men and women (Table 2.2).

Table 2.1 Thirty-year mortality risk ratios and 95 % CI for elevated blood pressure (140/90 mmHg and greater) adjusting for age, socioeconomic status, smoking, high cholesterol, and diabetes (the Charleston Heart Study and Evans County Heart Studies, 1960)

	White males	White females	Black males	Black females
140/90	1.6 (1.2, 2.0)	1.4 (1.1, 2.0)	2.1 (1.3, 3.1)	2.0 (1.2, 2.8)
160/95	1.8 (1.3, 2.2)	2.0 (1.2, 2.6)	2.4 (1.5, 3.5)	2.4 (1.6, 3.2)

Adapted from Lackland, D.T.; Keil, J.E.; Gazes, P.C.; Hames, C.G.; Tyroler, H.A. Outcomes of black and white hypertensive individuals after 30 years of follow-up. Clinical and Experimental Hypertension 17:1091–1105, 1995

Table 2.2 Thirty-year population attributable risks for hypertension and all-cause mortality (the Charleston Heart Study and Evans County Heart Study, 1960)

White males	23.8 %
White females	18.3 %
Black males	45.2 %
Black females	39.5 %

Adapted from Lackland, D.T.; Keil, J.E.; Gazes, P.C.; Hames, C.G.; Tyroler, H.A. Outcomes of black and white hypertensive individuals after 30 years of follow-up. Clinical and Experimental Hypertension 17: 1091–1105, 1995

Table 2.3 Hazard ratio and 95 % CI for stroke and 10-mmHg systolic blood pressure differential racial susceptibility (the REasons for Geographic And Racial Disparities in Stroke Study)

Whites	Blacks
1.08 (1.0–1.16)	1.25 (1.14–1.35)

Adapted from Howard G, Lackland DT, Kleindorfer DO, Kissela BM, Moy CS, Judd SE, Safford MM, Cushman M, Glasser SP, Howard VJ. Racial Differences in the Impact of Elevated Systolic Blood Pressure on Stroke Risk. JAMA Intern Med. 2013;173(1): 46–51

In addition to hypertension risk from categories, the racial disparity is also evident in blood pressure level. Table 2.3 shows results from REGARDS and an impact of a 10-mmHg higher level of systolic blood pressure for white and black participants [30]. In the total cohort, there was a 14 % increased risk of stroke associated with a 10–mm Hg higher SBP (hazard ratio [HR], 1.14; 95 % CI, 1.08–1.21). However, racial differences in this association were identified (P-value for interaction, 0.02) with an 8 % increase in whites (HR, 1.08; 95 % CI, 1.00–1.16) and a 24 % increase in blacks (HR, 1.24; 95 % CI, 1.14–1.35) [30]. These disparities in risks remained evident after long-term follow-up of the Hypertension Detection and Follow-up Study [31].

2.5 Factors Associated with Racial Disparities

While the disparities in blood pressure levels, hypertension prevalence and control, and high blood pressure risks are evident, the factors associated with the race differences are less evident. However, several parameters are proposed that may contribute to the disparities [32].

Though salt intake affects blood pressure in most individuals and populations, racial differences in intake as well as handling of sodium and potassium have been consistently reported [33]. While the prevalence of salt sensitivity was similar for African American and Caucasian women, the magnitude of blood pressure increase was different [34]. Blood pressure increases were greater in African Americans, with a positive association of salt sensitivity associated with Na Ca2 intake and the ratios of Na to K and Ca2 to Mg2 [34].

Racial differences in body mass index have long been recognized and suggestive of disparities in blood pressure level and hypertension prevalence. African Americans have been identified with higher rates of obesity and overweight at different age groups [35, 36]. However, while body mass affects blood pressure level in both race groups, anthropometric measurements do not explain all of the disparities in high blood pressure levels [33, 35, 36].

Resistant and refractory hypertensions are defined as uncontrolled blood pressure despite the use of three or more antihypertensive agent classes or controlled blood pressure with four or more agents [37]. Refractory hypertension represents the extreme phenotype of hypertension treatment failure and is defined as the use of five or more antihypertensive classes of medication with a systolic blood pressure of greater than or equal 140 mmHg and/or diastolic blood pressure of greater than or equal 90 mmHg [38]. The prevalence ratio for refractory hypertension when compared with individuals with resistant hypertension was 3.00 (1.68–5.37) for African Americans [38].

Likewise, there are numerous other factors with significant racial differences that could affect the disparities in hypertension including social determinants, access to care, fetal/early life origins, and differential treatment response [32, 39–42].

2.6 Implications

The racial disparities in hypertension and hypertension risks have significant implications for high blood pressure prevention, management and control programs and strategies, as well as gaps in research. Decades of hypertension control efforts have been attributed in part to the decline in stroke mortality identified for the past decades [43]. While clinical guidelines and prevention strategies recognize the racial disparities in risks from hypertension [44, 45], the evidence from clinical trials and clinical studies is often inadequate and insufficient with regard to high-risk populations such as African Americans [46]. Likewise, there remain evidence gaps

for the factors associated with the disparities. Thus, the evidence-based guidelines for prevention, treatment, and management of hypertension inadequately address the excess risk of high blood pressure for African Americans. The opportunity is great for the implementation of research epidemiological studies and clinical trials focused on the assessment of the racial disparities in blood pressure levels and hypertension risks. These results could be used to implement strategies to close the racial disparity gap in high blood pressure risks. The adjusted relative risk of stroke, for example, is more than twice as high in hypertensive blacks as compared with hypertensive whites [30]. As a result, effective antihypertensive therapy is particularly important in these patients [47].

2.7 Considerations for the Treatment of High Blood Pressure

The disparities in hypertension prevalence and adverse outcomes have prompted the consideration of treatment specific to the differences. For example, recommendations from the International Society on Hypertension in Blacks suggest antihypertensive therapy for blacks without target organ damage or concomitant cardiovascular diseases at blood pressures greater than 135/85 mmHg and, for those at higher risk, at blood pressures greater than 130/80 mmHg [48]. In addition, monotherapy is deemphasized in favor of combination therapy for blacks with high blood pressure [48]. However, there is not a consensus on this need for earlier treatment and the use of combination therapy for black hypertensive [49]. But there is consensus on the need for widespread and effective therapy of blacks with hypertension, novel methods to enhance screening, and patient education to increase hypertension control in this population [50]. The choice of therapy in black hypertensive patients depends on the presence or absence of comorbid conditions as well as the efficacy of the treatment employed to attain goal blood pressure [51].

2.7.1 Choice of Therapy

While the general treatment and management considerations are similar for all patients with hypertension, some specific recommendations focus on black patients with high blood pressure. Based on the excess disease burden, combination therapy can be a first-line therapy for blacks with hypertension [49]. In addition, African Americans are at greater risk for treatment-resistant hypertension than white patients often requiring a four-drug combination [51]. Black patients who have moderate to advanced chronic kidney disease (estimated glomerular filtration rate <45 mL/min/1.73 m^2) or a baseline serum potassium >4.6 meq/L have an increased risk for hyperkalemia, which requires monitoring for serum potassium that may affect how the blood pressure is treated [51].

2.7.2 Nonpharmacologic Therapy

Nonpharmacologic therapies including dietary salt restriction, weight loss in obese patients, avoidance of excess alcohol, and exercise are the major modes of therapy recommending for high blood pressure interventions among African Americans [52, 53]. While nonpharmacologic interventions have not been well studied in the African American population, current data suggest that the major components of nonpharmacologic therapy are similarly or more effective in black patients as compared with white counterparts [54]. For example, a trial of black hypertensives found 4 weeks of a low-sodium diet was associated with a reduction in the blood pressure from 159/101 to 151/98 mmHg [55]. Likewise, a randomized study of black men with hypertension assessed antihypertensive therapy alone with added regular exercise (45 min of stationary cycling three times per week) which was begun after the blood pressure was under control with treatment [55]. The exercise group showed an additional average of 5 mmHg reduction in blood pressure and regression of left ventricular hypertrophy [55].

2.7.3 Pharmaceutical Therapy

Different classes of antihypertensive therapy have shown efficacy levels specific for African Americans with high blood pressure. Several studies have shown calcium channel blockers to have proven efficacy in blacks [25, 56–58]. For example, a comparative study of black men and women found that dihydropyridine calcium channel blocker provided a statistically greater reduction in blood pressure and control rate of hypertension than a diuretic, a nondihydropyridine calcium channel blocker, or an ACE inhibitor [57]. In a subset of black participants in the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial which assessed hypertensive high-risk individuals, the patients assigned to combination therapy with ACE-calcium channel blocker showed better cardiovascular outcomes than ACE-diuretic combination [49, 58].

A number of comparative studies have demonstrated that African American hypertensive patients respond well to diuretic therapy, with greater blood pressure reduction than monotherapy with an ACE inhibitor, an ARB, or a beta-blocker [59–63]. This increased efficacy of diuretics (with concurrent salt restriction) suggesting the role for volume is consistent with the observation that blacks have a higher frequency of salt sensitivity than whites (as defined by a rise in blood pressure with salt loading and/or decline of blood pressure with salt restriction) [54].

African Americans with high blood pressure have a smaller blood pressure reduction than white patients in response to ACE inhibitors, ARBs, and most beta-blockers when given as monotherapy [57, 63]. One finding addressing this disparity indicating baseline plasma renin activity as modestly but not significantly lower in the black patients compared to white [27]. Black patients required two to four times

the dose of ACE to achieve the same reduction in blood pressure. This occurred despite no differences between the groups in plasma drug levels or in the degree of ACE inhibition at the same dose suggesting that the hypertension is not as angiotensin II dependent in blacks.

While African American patients are generally more responsive to calcium channel blockers than to monotherapy with ACE inhibitors, benefits are identified for combinations with ACE inhibitors in black patients with chronic kidney disease [64, 65].

2.7.4 Adherence

Adherence is generally lower in black as compared with white hypertensive patients [20, 66]. A variety of factors can reduce compliance with antihypertensive therapy including health literacy [66]. Several intervals have been successfully implemented to improve adherence for African American hypertensive patients. Peer-based education is very effective to increase adherence and control among blacks. The BARBER-1 randomized trial of urban black-owned barbershops found that hypertension control rates were significantly increased with barbers measuring blood pressures for the black male patrons and motivation to follow up with physicians [50]. In another trial of black hypertensive patients with hypertension, significantly improved blood pressure was identified in a video that conveyed the personal stories of other black patients with hypertension [67].

Single-pill combination therapy is another method to improve adherence. Such approaches may be particularly beneficial in black patients with hypertension. In a retrospective cohort assessment of hypertensive patients, single-pill combination therapy was associated with greater blood pressure control at one year than two-pill combination therapy or monotherapy [37]. The difference in control rates comparing single-pill with two-pill combinations was larger among blacks (63 versus 51 %) than among whites (73 versus 67 %) [68].

2.8 Summary

Hypertension is a major problem for blacks with higher incidence and prevalence of hypertension-related outcomes including stroke and cardiovascular and renal complications of hypertension than in other race/ethnicity groups and likely reflects the higher prevalence, earlier onset, and greater severity of hypertension in black patients than other race/ethnicity groups. The prevalence of hypertension is evident for all age groups. Black patients are at greater risk for treatment-resistant hypertension than white patients. The reasons for the significant racial disparities in elevated blood pressure and hypertension-related outcomes risk remain unclear. However, the implications of the disparities of hypertension for prevention and

clinical management are substantial identifying African American men and women with excess hypertension risk. These risks have prompted different clinical treatment considerations and warranting interventions focused on these differences. In addition, focused research to identify the factors attributed to these disparities in risk burden is an essential need to address the evidence gaps. Both pharmaceutical and non-pharmaceutical therapies and strategies are effective for black hypertensive patients. Adherence is generally lower in black as compared with white hypertensive patients with different factors reducing compliance with antihypertensive therapy such as peer-based education and single-pill combination antihypertensive therapy.

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Chapter 3
Therapeutic Lifestyle Changes to Decrease Unhealthy Eating Patterns and Improve Blood Pressure in African Americans

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3.1 Importance of Non-pharmacological Treatment to Improve Hypertension Management

Prevention and effective control of high blood pressure is critical, and hypertension management is often difficult even with intensive pharmacological therapy. Although the majority of adults with hypertension, over 74 million in the United States, including over two million new cases per year, are given prescription medications to control high levels of blood pressure, many have not reduced their blood pressure to less than 140/90 mmHg [17]. Shimbo et al. [29] suggest that once hypertension is resistant, requiring upwards to five antihypertensive agents, non-pharmacological treatment alone is almost always not effective. Nevertheless, the effectiveness of therapeutic lifestyle changes (TLC) can be substantial, with varying estimates for blood pressure reductions with TLC reported in The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines (JNC 7, [5]). Previous comprehensive reviews have documented the efficacy of TLC, barriers to lifestyle changes, and strategies to overcome barriers in African Americans [25]. This previously published comprehensive review of effective TLC for control of blood pressures illustrated the need for systematic coordination of patient, provider, and community roles. Moreover, this report illustrates the relationship of salient factors associated with barriers to behavior change which impact sustained effects of TLC in African Americans.

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K.C. Ferdinand (ed.), *Hypertension in High Risk African Americans*, Clinical Hypertension and Vascular Diseases, DOI 10.1007/978-1-4939-2010-5_3

Furthermore, evidence-based TLC for improving blood pressure includes maintenance of normal weight or weight reduction, physical activity for at least 30 min a day, limiting daily sodium (salt) intake to 2,300 mg or less, increasing potassium intake, limiting alcohol consumption to no more than one or two drinks a day, and the consumption of a diet rich in fruits, vegetables, and low-fat dairy products such as the Dietary Approaches to Stop Hypertension (DASH) eating pattern [5]. The recommendations from a 2010 Institute of Medicine's report, *A population based policy and systems change approach to prevent and control hypertension*, suggest that hypertension is being ignored and healthcare providers should create an environment for health-promoting behaviors, including recommending the DASH diet to impact both individual and population blood pressure control. In consideration of these facts, there must be a clear concordance between the treatment approaches for physical, psychological, and cultural characteristics of a given group used to reach its members to enhance receptivity, acceptance, and effectiveness of applying health information and programs.

Similarly, Hedayati et al.'s [11] systematic review of literature on lifestyle modifications on reducing blood pressure reported that effectiveness was shown for DASH diet, dietary sodium restriction, weight loss, and DASH diet in combination with exercise and weight loss. In addition, Sacks et al. [24] reported that a low sodium diet (1,500 mg) results in better reduction of blood pressure than both the DASH diet and reduced sodium intake diet alone. Green et al. [10] also suggested self-measurement of blood pressure is effective for improving blood pressure. Subsequently, a systematic review of 72 randomized clinical trials [9] identified self-monitoring as the only effective intervention compared to professional health education and appointments.

Particularly for hypertension control in African Americans, the important question now is not what non-pharmacological treatment will work to reduce blood pressure, but rather how to motivate an individual to sustain TLC [8]. Clearly, no treatment is effective unless the patient is motivated to follow it. However, a promising solution for this major problem may lie within a recent report from the Institute of Medicine entitled "Public Health Priorities to Reduce and Control Hypertension in the U.S. Population," prepared by Centers for Disease Control and Prevention. Focusing on evidence-based approaches to increase progress in blood pressure reduction and hypertension control, recommendations include behavioral and lifestyle interventions—reducing sodium intake, increasing consumption of fruits and vegetables, and increasing physical activity. The report also suggested that healthcare providers increase their compliance with evidence-based guidelines. This document coupled with goals from Healthy People 2020 national health agenda that proposes technologically based approaches to provide health-related information to close the gap for health disparities should guide implementation of effective interventions to improve blood pressure. Additionally, Webb et al. [36] suggest effective interventions should demonstrate characteristics for replication, such as the theoretical basis or predictors of the intervention, the cognitive and behavioral change techniques developed for the intervention, and the mode of delivery for the intervention.

Disparate hypertension prevalence and severity, along with higher rates of diabetes, lead to increased morbidity and mortality for heart disease and stroke. Carefully planned, framed, and researched interventions must be tested and implemented. Nearly 80 % of African American women who are 60 years or older have hypertension, and women as a group, once over the age of 59, have a higher prevalence of hypertension than men of the same age. It is possible that some providers would be less likely to offer African American women a dietary intervention, although previous studies have shown DASH diet education and related interventions were effective among African American participants [22, 27].

Davis et al. [7] also conducted a systematic review of interventions targeting patients with cardiovascular disease, finding evidence that sodium restriction in African Americans is somewhat effective in controlling blood pressure. Other studies have confirmed that healthy dietary changes and increased physical activity were beneficial [33]. Nevertheless, a significant number of patients, especially African Americans, may have limited access to healthcare professionals and lack of trust in their health providers, choose to stop seeking treatment, experience side effects from treatment, endure family pressures, and may have lack of support to engage in self-care and inadequate information and medical care [25]. Moreover, in some cases, particularly after prescription medication is started, the role of healthy diet and TLC is not viewed as a central issue for control or treatment for hypertension. The high incidence of uncontrolled hypertension in middle-aged and older African American women may be linked to chronic noncompliance or failing to follow medical regimens including both pharmacological therapy and dietary recommendations. It is certain that without the exploration of the role between dietary modification and hypertension control, hypertension will not be managed effectively.

3.2 Dietary Approaches to Stop Hypertension

To address this critical issue of the hypertension-dietary pattern linkage, an expert panel several years ago clearly outlined some simple dietary guidelines for patients with hypertension [21]. These recommendations were similar to those reported in the landmark DASH study, a controlled-feeding clinical trial utilizing a portion-controlled eating plan, lower in fat and higher than usually consumed in the USA in vegetables, fruits, and low-fat dairy products, with an approximately 2,300 mg sodium limitation [2]. The data from DASH support a healthy dietary pattern and other specific lifestyle behavior modifications such as (a) losing weight, (b) limiting alcohol consumption, (c) engaging in aerobic/physical activity/exercise, (d) limiting sodium intake to 2.3 g a day and limiting cholesterol and total fat intake, and (e) increasing (dietary and supplementary) potassium intake. This randomized, multicenter feeding study was conducted at four different clinical sites, with subjects consuming daily 4–5 servings of fruit, 7–8 servings of grains, 4–5 servings of vegetables, 2–3 servings of low-fat dairy products, 2 or fewer servings of meat, 4–5 servings of nuts and beans, and limited fats and sweet food.

Baseline characteristics of participants in the original DASH trial were as follows: the mean age of participants was 45 years, 60 % were African American, 82 % had a college education, 48 % were married, 22 % had been taking medication, and 6 % had ceased medication taking before enrollment in the study; mean systolic blood pressure (SBP) was 132 mmHg (24 % with Stage 1 systolic hypertension), and mean diastolic blood pressure was 85 mmHg (14 % with Stage 1 diastolic hypertension). Results of DASH diet for those with normal blood pressure ($n=326$) showed significant drops of 5.5 mmHg (systolic) and 3 mmHg (diastolic) within a week and remained stable over the study's 6 weeks. For those with high blood pressure ($n=133$) over 140 mmHg (systolic) or 90 mmHg (diastolic), a more dramatic drop in BP, on average of 11.4/5.5 mmHg, was observed. These reductions were the same as achieved using one standard BP medication. One conclusion is that the DASH diet may lower the number of medications required for effective blood pressure management and, if the condition is mild, may eliminate the need altogether. The results of subsequently conducted DASH diet-related studies on blood pressure improvement are compelling, however with the exception of the PREMIER Trial (Lin et al. 2007), reporting less than 5.0 mmHg SBP reduction after 6 months. The difference may have been associated with participants required to purchase their own food. The major purpose of PREMIER was to report on the adherence of DASH diet compared to an established diet that did not specify the servings of fruits and vegetables [17].

On the other hand, the ENCORE Study [4] reported on significant effects of DASH diet alone and in combination with exercise and weight loss on blood pressure and cardiovascular biomarkers in men and women with high blood pressure. The ENCORE trial demonstrated after 8 weeks that the effects of DASH diet alone showed reduction of SBP of −11 mmHg, with −16 mmHg reduction shown for DASH diet and weight loss. Hedayati et al. [11] reviewed the literature on non-pharmacological treatment recommendations on blood pressure and reported that the ENCORE trial showed for those with uncontrolled blood pressure >140/90 and minority population even greater reductions. It was important to note that the ENCORE trial was guided with social cognitive theory (SCT) for framing the importance of a specific action plan, information, and follow-up to behavioral change.

The support for utilizing the DASH diet is significant because it may be as effective as exercise, weight loss and sodium reduction, or the traditional TLC for improving blood pressure [30]. In addition, several health organizations (American Heart Association and American Dietetic Association) strongly recommend this heart healthy combination dietary approach as a perfect antidote to unhealthy eating habits and for prevention, treatment, and management of hypertension as well other chronic diseases including type 2 diabetes.

The down side for DASH diet is lack of concordance with adherence [19], with fewer than 20 % of patients maintaining adherence to DASH. In consideration of dismal, unhealthy eating habits of adults with hypertension, medical regulatory agencies, such as the State of Michigan Department of Community Health, have

issued the Michigan Quality Improvement Consortium Guideline for improving blood pressure. The guideline requires health providers to include as part of a comprehensive hypertension treatment plan lifestyle modification including weight reduction (BMI <25), reduction of dietary sodium to less than 2.4 mg/day, DASH diet, aerobic physical activity > on most days of the week, tobacco avoidance, increased dietary potassium and calcium, moderation of alcohol consumption, and the use of self-blood pressure monitoring. Reports of barriers from patients from the State in 2012 indicate that progress in providing DASH as a TLC for controlling hypertension may be hindered because of lack of providers and food deserts.

Similarly, the implementation of DASH diet in clinical practice has been suboptimal as a means to provide feasible, cost-effective approaches. Two areas of concern have been identified. First, there is evidence that poor compliance with taking one antihypertensive medication to treat and control hypertension is similar to the results following DASH. Therefore, clinicians may consider it easier to recommend taking one antihypertensive agent than to provide information and follow-up for DASH diet, despite side effects and quality of life issues associated with BP medication and the potentially high cost of medication. One systematic review article [11] concluded that blood pressure control for African Americans cannot be sustained without dietary modification and healthier eating habits that limit sodium and saturated fat intake.

Secondly, there are online DASH programs developed for employee-based health promotion benefits, which show promise for providing information to track DASH adherence and promote an improvement in blood pressure and weight. However, the reviewed online programs [20] did not meet the standard criteria established for an effective computer-mediated intervention for clinical practice relying on self-reported blood pressure and weight changes. Specifically, as it relates to African Americans, there is a failure to address cultural relevance for minorities, and these programs are not developed for information exchange with the healthcare provider. Moreover, interventions are required to further expand previous investigations to address a critical gap in hypertension research and provide knowledge to sustain effective non-pharmacological treatment or lifestyle modification behaviors to improve blood pressure and unhealthy eating habits. The objective is to provide the knowledge to set goals for the motivation and self-confidence to ensure TLC involving DASH diet for diverse populations.

To this end, Webb et al. [36] advocate describing the theoretical basis or predictors of the intervention, the cognitive and behavioral change techniques developed for the intervention, and the mode of delivery for the intervention. Thus, a theoretically derived intervention and comprehensive strategies that incorporate DASH diet are needed to effectively guide prevention and treatment of hypertension. Perhaps, in the future, more clinicians will adopt features of effective interventions, such as the computerized cognitive-behavioral intervention, the Women's Hypertension Experiences and Emerging Lifestyles Intervention (WHEELS-I) Program. This approach integrates evidence-based research, understanding cognition and the impact of culture to improve TLC.

3.3 The Need for a Theoretically Driven Intervention

Identifying the theoretical basis and components of an intervention is necessary for systematic clinical implementation of TLC specifically involving DASH diet. A significant challenge among people with hypertension is the consistent adherence to healthier eating habits, and the benefits from DASH diet are the greatest for minorities who are at risk for uncontrolled blood pressure and stroke associated with unhealthy eating habits [8]. A theoretical basis that includes the role of culture will provide the evidence of why the approach for diverse populations who are recommended to follow DASH diet will acquire the critical information for setting goals to guide decisions for achieving long-term dietary behavioral changes.

Over the past four decades, SCT and self-regulation model theory (SRM) have provided a theoretical basis for developing interventions that are effective at promoting medication compliance in hypertension patients [14]. First, SCT and SRM [16] are thought to help the healthcare provider understand how memories or cognitive representations are formed after the clinical diagnosis of hypertension. Cognitive representations (CRs) are the product of the assimilation of culturally relevant perceptions that guide health-related goal and behaviors [3].

CRs exist for everything that is learned, and this information is processed to guide decisions for behavior [31], and the central nervous system coordinates all stimuli and integrates information used to adapt, function, and cope. A way to think about cognitive representations is how an individual explains experiences with anything that can be perceived from the environment, including a disease and treatment recommendations. The processing occurs on multiple levels: (1) abstract, for example, smoking is a health risk, and (2) concrete, for example, smoking is pleasurable. An individual's "appraisal" is an ongoing process of monitoring representations of treatment effectiveness, coping abilities, and disease-related outcomes. Behavior in this model is episodic and individual's CRs are dynamic and evolving overtime. Accurate and accessible CRs guide improved behavior, and assessment of CRs can explain adherence to treatment regimens.

Effective interventions to address nonadherence to TLC, such as DASH diet, must have the capacity to assess poor eating habits and provide information to fill in knowledge deficits and change preferences for incompatible health behavior CRs [15]. Lack of accessible and accurate CRs to form knowledge makes adherence with antihypertensive regimes (taking blood pressure medication and adherence to dietary modifications and exercising regularly) difficult and limits the ability of patients to address and to solve problems associated with hypertension management [28].

3.4 The Need for Cognitive and Behavioral Change Techniques for an Intervention

The cognitive change can be achieved by assessing cognitive representations of self-regulatory behavior as the first step for insight of the existing knowledge and extent of information required for behavioral change. Scisney-Matlock, in 1998, synthesized the theoretical basis for assessing self-regulatory behaviors for hypertension treatment recommendation as cognitive representations of lifestyle behaviors. This assessment approach guides the selection of the stimulus tasks manipulation or required information or tailored information that corresponds with existing cognitive representations [27]. This new knowledge is most appropriate in the form of tailored messages to learning about lifestyle modification recommendations, particularly for minority populations.

3.4.1 Using Tailored Messages to Deliver Knowledge

Cognitive science principles describe how to frame health-relevant information into tailored messages for positive integration of information with prior perceptions or cognitive representations [23]. Tailored messages complement cognitive and behavioral approaches for reinforcement, performance, repetition, and feedback for shaping cognitive representations [13]. Messages can increase CRs relating to a person's sense of control for decisions that will likely promote positive health behavior. Tailored messages are a method to convey specific textual information to increase and improve coping behaviors, decrease cognitions associated with maladaptive behaviors, and reframe inaccurate disease schemata through a self-regulation process [32, 34]. Scisney-Matlock et al. [27] suggested the use of tailored messages to provide health-related information for enhancing dietary adherence for reducing fat and increasing consumption of more fruits and vegetables. Results showed significant improvement in the daily consumption of fruits and vegetables for minorities who reported significantly lower eating of fruits and vegetables.

According to Krantz and Manuck [12], there is an imputed direct effect of framed messages on blood pressure [24]. This notion suggests that if cognitive representations (CRs) are shaped and built from messages provided by environmental cues, then a process called "sensory intake" or "attentive observation" is activated. This response, which was outlined by Smith, is theorized to elicit a specific pattern of physiological reactivity that results in decreased emotional arousal and motor activity, decreased heart rate and cardiac output, and vasoconstriction of skeletal muscle, skin, and viscera. Adding new tailored information based on momentary DASH cognitive representation assessment has the capacity to create and update CRs to enable an individual to selectively engage, assimilate, store, retrieve, and evaluate information for choices to reduce the disease threat.

3.5 An Emerging Conceptual Framework to Address Intervention Criteria for Theory-Based, Cognitive, and Behavioral Techniques and Mode of Delivery

In 1998, Scisney-Matlock demonstrated the problem of unhealthy eating patterns in adults with hypertension, particularly in African American women. She developed and tested the initial WHEELS intervention with print tailored messages to target high blood pressure, the leading cause of stroke in African American women and other ethnic groups. The problem of unhealthy eating and direct association to hypertension is complex and very difficult for providing evidence-based treatment and at the same time ensuring cultural sensitivity among healthcare providers as they strive for congruency between best and effective practices and treatment adherence behavior in minority patients. Leventhal et al.'s [16] self-regulation model was used to guide the identification of concepts for an emerging conceptual framework to explain the relationship of cognitive processes/representations (CRs) to self-regulatory behavior, including adherence with antihypertensive regimes.

The conceptual framework is based on the assumption that the active cognitive process to form the representations from perceptions of an object, situation or event, or disease, and the parallel process of coping strategies for problem solving and appraisal of the efficacy of the coping strategies. This framework is grounded in cognitive and behavioral theories to permit the integration of three principal concepts: (a) information from assessment of illness cognition or cognitive representations [16], (b) integration of tailored messages based on cognitive representation assessment to provide the critical health-related information from Tversky and Kahneman [34], and (c) involvement in self-care activities from Leventhal [13]. What is unique about the framework is the intent of the patient to express their view of routine self-care practices and to have immediate access to new relevant knowledge for creating and updating of self-regulatory cognitive representations permitting problem solving and evaluation of information regarding choices to reduce disease threat. Although this framework was instructive for a basis of a cognitive-behavioral intervention for systematic implementation of DASH diet in clinical practice, it was soon discovered that there was a need to transform this print-based program to computer-mediated intervention.

3.6 Testing of WHEELS-I Pilot Study

The purpose of this pilot study tested in November 2009 to August 2010 was to evaluate the efficacy of a computerized cognitive-behavioral intervention, the Women's Hypertension Experiences and Emerging Lifestyles Intervention (WHEELS-I), on blood pressure and healthier dietary habits. WHEELS-I Program incorporates previously tested non-pharmacological treatment recommendations with African American women for lifestyle strategies, e.g., the DASH diet (developed by the National Institute of Heart, Lung and Blood [21]). The revised

intervention was refined to include self-appraisal responses for four self-regulation model components: goal setting, DASH diet cognitive representation assessment, DASH adherence, and self-blood pressure measurement.

The WHEELS-I Program, a theoretically derived cognitive-behavioral intervention, incorporates a computer-mediated approach to promote self-regulatory behaviors for DASH diet. It is hypothesized that WHEELS-I Program shapes self-perceptions or cognitive representations of enduring memories of DASH diet representations that form the knowledge to guide goal setting to prompt lifestyle self-care activities and improve blood pressure in women with hypertension. Such improvement in accurate and accessible DASH diet representations (DDCRs) after assessing DDCRs and reading DASH tailored messages is expected to motivate an individual to set DASH diet goals to guide decisions for healthier eating habits over time and lower blood pressure towards therapeutic levels in a culturally diverse population of hypertensive women [26]. The four central research questions are as follows.

1. Is WHEELS-I Program associated with (a) blood pressure reduction at 1 and 3 months follow-up compared with the control group?
2. Is there an improvement in the pattern of DASH diet cognitive representations, from pre- to post-WHEELS-I at 1 and 3 months follow-up compared with the control group?
3. Is there an improvement in the pattern of DASH diet adherence, from pre- to post-WHEELS-I Program at 1 and 3 months follow-up?
4. Is exposure to WHEELS-I after 1 year associated with improved blood pressure, healthier eating habits, and overall improvement of hypertension (assessed by focus group results and clinic electronic medical records)?

3.7 Sample and Sampling Stratification Plan

The sample was to consist of no less than 64 women; 80 women were recruited ranging in age from 30 to 85 years, who were being treated for hypertension with prescription medication and not currently participating in a weight loss program and meeting study criteria. The sample was recruited from two outpatient clinics and mailed invitation from a health insurers' database. Each volunteer meeting the study criteria was randomly assigned to two possible stratified groups as shown in the Table 3.1. The significant effect sizes from a sample with adequate power from 32 for each experimental (WHEELS-I Program) and control groups would provide more confidence that true differences exist as recommended by Cohen [6]. A power analysis revealed a sample size of 64 would have 80 % power to detect a medium-sized effect with an alpha = 0.05.

The study was IRB approved, and in August 2008, 600 WHEELS Survey booklets were mailed (300 African Americans), 125 were returned as undeliverable, 74 people declined to participate, and 110 usable booklets were returned. Of these, 108 consented to follow up (98 %); 53 were African American. The majority of the

Table 3.1 Sample for WHEELS-I pilot study

Random group assignment	Treatment assignment	Recruitment condition	
		Mailed invitation from database	Face to face
Groups		*N*	*N*
I. Experimental group	WHEELS	16	16
II. Control group	Pre-post test	16	16
Subtotals		32	32

sample (55 %) stated that they had a computer and Internet access. E-mail invitations were sent to patients who met inclusion criteria. The remaining participants were recruited from two outpatient services with the help of the provider and advanced nurse practitioners. After consent was obtained, research assistants scheduled appointments to obtain baseline measures of data.

The inclusion criteria were (1) female; (2) clinical diagnosis of Stage 1 or 2 hypertension, with at least one antihypertensive medication prescribed for 6 months; (3) age 30 or older; (4) no history of heart attack, stroke, or TIA; (5) no secondary diagnosis of advanced cardiac, respiratory, or renal disease; (6) normal or corrected hearing and vision; and (7) sufficient command of the English language to complete questionnaires. Exclusion criteria were (1) recent DASH diet counseling; (2) a history of mental illness, neurological disorder, stroke, cardiovascular accident, renal disease, insulin-dependent diabetes, alcoholism, or substance abuse; (3) pregnant or planning a pregnancy; (4) participation in clinical trial for hypertension; and (5) current enrollment in specific fee-for-service program for lifestyle changes (e.g., weight watchers). After initial screening, individuals meeting study criteria were randomly assigned using minimization balanced listing to the experimental or control groups.

3.7.1 Procedures for Home Blood Pressure Measurements

At the first appointment after enrollment in the study, all volunteers were instructed in the technique of self-measurement of blood pressure with the Omron automatic blood pressure monitor (model 790IT). Blood pressures were measured once in the evening, between 5 P.M. and 11 P.M., if possible. To facilitate intervention compliance, volunteers are asked to send evidence of their daily home blood pressure monitoring as part of the WHEELS-I protocol. Home blood pressure results will not be analyzed as a major outcome variable for this pilot study; however, it is expected that blood pressure self-measurement will build the association between healthier eating and control of blood pressure [2].

3.7.2 Study Measures

Measures were gathered from all volunteers at baseline, 30 and 90 days for the study. Demographic data were collected in the WHEELS Survey booklet at baseline on individual characteristics including age, race, marital status, menopausal state, support for hypertension regimes (meal preparation and procurement of medications), educational level, occupation, income level, and employment status. Other measures included self-efficacy, food habits, quality of life indicators, and medication compliance

Clinic blood pressures were measured using the standard automated devices endorsed by the University of Michigan Clinical Research Center and at the clinics. Repeated measurement of blood pressure levels was obtained for baseline and 30 and 90 days for each subject at each data collection time point in the sitting positions using the guidelines developed by the American Heart Association [1]. Medical records were reviewed for previous blood pressure measurements and in order to determine changes at 1 year for a subset of subjects.

Receipt reliability to assess WHEELS-I Program intervention engagement was measured by logins over the study period as discussed by Moore et al. [20]. Receipt reliability for this study was calculated by dividing the total number of messages sent to participants by the number of times users clicked on links to open Web-based surveys over the 8 weeks of the study. A 50 % login percentage was expected to establish reliability of the computer system.

Adherence to the DASH diet was assessed using responses to survey questions about consuming fruit, vegetables, low-fat dairy, limited sodium, lean meat, grains, and limited sweets. The number of "yes" responses from the 56 daily evening survey items was used to calculate adherence percentages. A 50 % "yes" response level was anticipated to establish effectiveness of the WHEELS-I to promote healthier eating habits.

3.7.3 Sample Characteristics and Data Analysis Procedures

A total of 73 cases were used for data analysis at 30 days, and 67 cases remained in the study at 90 days, and 92 % of all data were used for statistical analyses. While two volunteers were identified as outliers, due to higher systolic and diastolic blood pressures, they were included in the data analyses. The majority of the participants at baseline measures ($N=80$) were over 56 years of age and married, and over 40 % of the sample had a college education. One-way ANOVAs and *t*-test were used to determine whether systolic/diastolic blood pressures, weight, DASH diet adherence, and DASH diet cognitive representations differed by demographic characteristics and group assignment at baseline assessment. Results revealed no significant differences by race for SBP and weight at baseline African American women compared to Caucasian American women. Results of data analyses revealed no

significant differences at baseline assessment on sociodemographic variables: age, race, educational level, and marital status according to group assignment. Sample characteristics by group assignment can be viewed in Table 3.2.

3.7.4 Results of Pilot Study

The pilot study's specific aims and major hypotheses that WHEELS-I would demonstrate greater improvement in SBP and DASH diet cognitive representations post intervention. The research questions, hypotheses, and results are presented below as follows. Results for diastolic blood pressures are not reported.

Research Question 1 Is WHEELS-I Program associated with (a) blood pressure reduction at 1 and 3 months follow-up compared with the control group?

Hypothesis 1 The WHEELS-I Program, cognitive-behavioral intervention (CBI), will lower blood pressure assessed by clinic measures, showing greater improvements and lower BP at 30 and 90 days in the experimental group (CBI) than in the control group (CG).

Results: No significant differences were found in the clinic SBP baseline measures (mean, 136 mmHg) (SD = 17.71) between the CBI and CG. Repeated measures ANOVA with SBP measures by group—no sphericity assumption violation—demonstrated that the mean scores at baseline 1 and 3 months post intervention were statistically significantly different (F (4.585, 2) = 510.229, $p = 0.012$). For CBI group, paired t-test for SBP at 1 and 3 months was significantly different ($p = 0.000$ and $p = 0.004$), −9.1 mmHg (SD = 14.66) and −8.22 (SD = 16.80) compared to 2.26 (SD = 15.23) and −0.40 (SD = 13.14) for CG. Women in CBI with baseline SBP >140/90 showed SBP mmHg reductions of −13.09 (SD = 12.89) and −13.04 (SD = 13.04) at 1 and 3 months. No significant differences were revealed between groups for weight loss; modest reductions of −1.1 and −1.4 lb were shown for CBI compared to −0.76 and −0.86 for CG.

Table 3.2 Descriptive summary by characteristic for experimental and control group assignment

Characteristic	Experimental ($n = 43$)	Control ($n = 34$)	Total sample ($n = 77$)
Age (years)			
Mean/SD	52.80/8.08	60.50/11.74	56.24/10.74
Race			
Caucasian American woman	$n = 12$ (27.9 %)	$n = 5$ (14.7 %)	$n = 17$ (23.1 %)
African American woman	$n = 31$ (72.1 %)	$n = 29$ (85.3 %)	$n = 60$ (76.9 %)
Education			
Less than HS	$n = 4$ (9.3 %)	$n = 12$ (35.3 %)	$n = 16$ (19 %)
Some college	$n = 13$ (30.2 %)	$n = 13$ (38.2 %)	$n = 26$ (31 %)
College degree	$n = 26$ (60.5 %)	$n = 9$ (26.5 %)	$n = 36$ (42.9 %)

Research Question 2 Is there an improvement in the pattern of DASH diet cognitive representations, from pre- to post-WHEELS-I Program at 1 and 3 months follow-up compared with the control group?

Hypothesis 2 The WHEELS-I Program, cognitive-behavioral intervention (CBI), will lead to improved scores for the DASH diet cognitive representation scores (DDCR) at 3 months, showing greater improvements in the experimental group than in the control group.

Results: This hypothesis was supported with analysis of data to evaluate the impact of a cognitive-behavioral intervention on DDCR scores using repeated measures ANOVAs with group (experimental versus control) as a between-subjects factor and time of measurement (pretest and at 90 days post) as a within-subjects factor. The results of differences between experimental group and control groups revealed there was more improvement in the DDCR score for the experimental group than for the control group.

Table 3.3 shows the trend for changes in DASH diet cognitive representations over the study period. These findings are consistent with previously published reports demonstrating a positive and significant improvement in healthier eating patterns after exposure to DASH diet information guided by a theory-based cognitive-behavioral intervention.

Research Question 3 Is there an improvement in the pattern of DASH diet adherence, from pre- to post-WHEELS-I at 1 and 3 months follow-up?

Table 3.3 Repeated measures mean values at baseline and 8 weeks for DDCR scores by group assignment for selected food groups

DDCR outcome measure	Experimental group $n=36$ Mean	Control group=25 Mean	Sig at 0.05 level
	Mean	Mean	
Veggie servings			
Baseline	2.8	3.0	$p=0.03$
8 weeks	3.8	3.3	
Whole grain servings			
Baseline	2.8	2.7	$p=0.05$
8 weeks	3.5	2.7	
Nuts, bean servings			
Baseline	2.8	3.0	$p=0.05$
8 weeks	3.8	3.3	
Limiting sodium 2,300 mg			
Baseline	3.5	3.7	$p=0.01$
8 weeks	4.6	3.9	

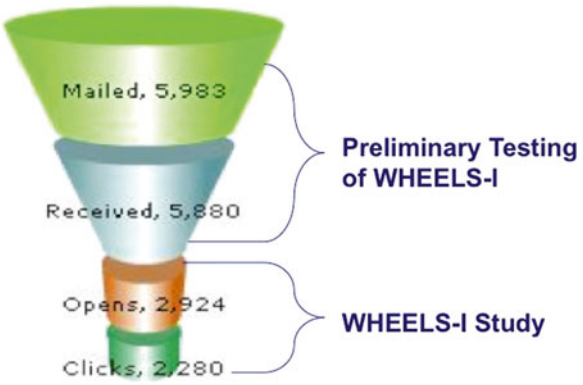

Fig. 3.1 Conversion pipeline for intervention engagement

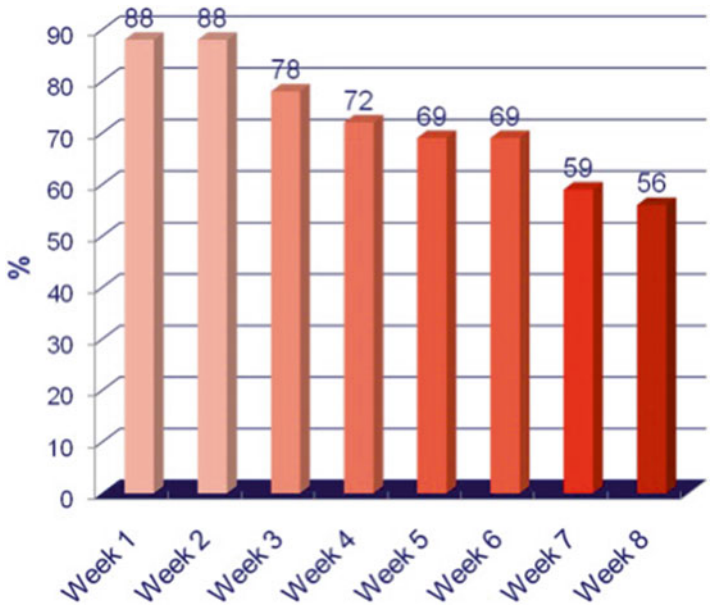

Fig. 3.2 Percentage of logons for messages sent for WHEELS-I Program

The WHEELS-I Program reliably delivered morning and evening e-mail messages which were linked to Web-based rapid response surveys. Intervention engagement was demonstrated by the number of logins to open Web-based surveys and number of clicks documented as responses to questions about self-care activities (Fig. 3.1). There were high levels of intervention engagement, based on 2,924 messages opened and 2,280 clicks in the rapid response surveys. As Fig. 3.2 illustrates there was sustained intervention engagement of more than 50 % over the 8 weeks of data collection.

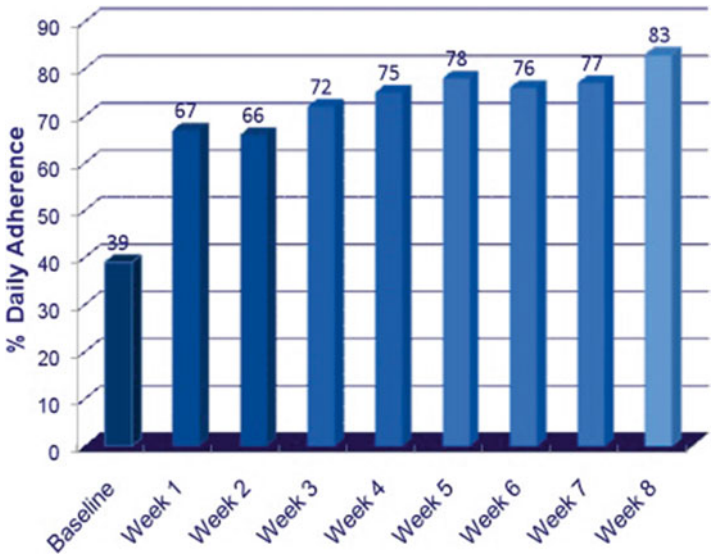

Fig. 3.3 Average percentage of weekly adherence to dietary approaches to stop hypertension diet over 8 weeks

3.7.5 Computer Assessment of DASH Diet Adherence Over 8 Weeks

Self-appraisal response of adherence to DASH diet recommendations as assessed by computer momentary assessment, based on data downloaded from the rapid response surveys, showed a positive trend (Fig. 3.3) for greater adherence after the first 4 weeks, although morning messages were terminated. The radar plot (Fig. 3.4) shows the trend for improvement over time for food groups thought to be consumed for fruit, vegetables, low-fat dairy, whole grain products, and sodium. One major shortcoming of the DASH diet is the daily recommendation for 2,300 mg sodium limitation versus 1,500 mg as recommended by Sacks et al. [24].

Research Question 4 Is exposure to WHEELS-I after 1 year associated with improved blood pressure, healthier eating habits, and overall improvement of hypertension (assessed by focus group results)?

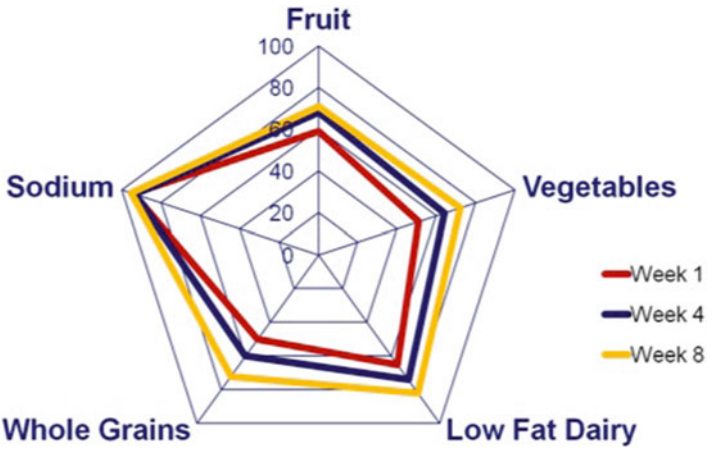

Fig. 3.4 Adherence to dietary approaches to stop hypertension diet for selected food groups over 8 weeks

3.7.5.1 Focus Group Sub-study Results

The purpose of this sub-study is to examine qualitative data from women who participate in focus groups to determine the effectiveness and benefits of WHEELS-I Program.

Methods: After Institutional Board Review approval, younger and middle-aged women who were recruited by a certified nurse practitioner from their point of treatment and randomly assigned to the WHEELS-I Program were invited to participate. Scisney-Matlock developed the interview questions and probes for the focus group sub-study and trained two Ph.D. prepared certified advanced nurse practitioners to moderate the sessions. African American women ($N = 14$) exposed to WHEELS-I Program participated in two focus group sessions yielding 4 h of tape-recorded dialogue for transcription and analysis. Repeated measures of blood pressure and weight at baseline, 30 and 90 days, were analyzed for focus group participation.

Results: Focus group qualitative data analyzed from transcribed statements revealed major themes for effectiveness, challenges, and benefits. Comments indicated that the WHEELS-I Program was effective in improving blood pressure and promoting healthier eating habits with the DASH diet. Analysis of data conducted with repeated ANOVAs showed significant difference in blood pressure for groups who were exposed to WHEELS-I Program with or without focus group participation. The focus group WHEELS-I Program showed more weight loss at 90 days post than the other two groups.

Detailed Qualitative Focus Group Results

A total of 4 h of insightful feedback about their experiences with the 2-month WHEELS-I Program was examined to address this question. The participant's statements clearly articulated their opinions regarding experiences in the study. As with any focus group, the goal is for the participants to interact with one another after introduction of the topic question. The following is a summary of focus group experiences with the WHEELS-I Program.

Impressions

From the moderator's summary, participants often responded to one another when answering the interview questions, as if the moderator was not present. The women spoke highly of the WHEELS-I Study and verbalized both challenges and positive aspects, and experiences, during their participation in the study.

3.7.5.2 Effectiveness and Benefits

The program was effective at increasing knowledge and awareness of what hypertension is, what affects it negatively and positively, and what patients can personally do to control their blood pressure.

3.7.5.3 Challenges

One of the identified challenges identified by the groups was incorporating the recommended amount of "whole grain" required with the DASH diet. Participants verbalized the recommended servings of grains "were a lot to eat" and they had to be "creative" when selecting foods in the category. Participants also verbalized problems with identifying enough foods in the grain category that they liked and would eat. Even an oatmeal raisin cookie was counted as a grain because a few women did not eat hot cereal. Most verbalized eating hot cereal every morning or eating sliced bread as one way of meeting the daily grain requirement.

Exercising on a regular basis was also identified by participants as a challenge. Some participants stated "did n't want to do it" and there were "hair issues." Other participants indicated that illness during the study interfered with their ability to exercise.

3.8 Effects of WHEELS-I Program on Blood Pressure

The results of this study have provided evidence of the significant experimental effect of the cognitive-behavioral intervention designed for this research on reducing blood pressure over time. Results of this study demonstrated changes in SBP that were clinically and statistically significant for the WHEELS-I Program- experimental group compared with the control group. This finding was sustained after 1 year for those who participated in the focus groups demonstrating compelling evidence for impact of this technological innovation. The results showed greater trends in reduction of SBP consistent with those provided by Appel et al. [2], that is, systolic and diastolic reductions of 5.5 and 3 mmHg for normotensive. For women with uncontrolled blood pressure assigned to the experimental group, a more impressive pattern of SBP reduction emerged at 30 and 90 days ($M = -13.0$, SD = 12.89; $M = -13.0$, SD = 15.7) than for the control group ($M = -1.72$, SD = 16.54 and $M = -8.44$, SD = 13.16). These results were impressive when compared to effects of DASH on SBP from large NIH funded clinical trials even with all DASH diet food and drinks provided in feeding studies [2] as well as ENCORE trial results [4].

An analysis of differences of reduction in SBPs in the experimental group showed 73.8 % versus 36.7 % for the control group. There was less reduction in SBP and benefit for the control group. There is some evidence that the effects of a CBI may be expected to contribute another 2.5–3.0 mmHg SBP reduction. Therefore, adding a CBI such as WHEELS-I Program to DASH diet is more effective for lowering blood pressure among women who were required to select, purchase, and prepare meals according to DASH diet recommendations. The benefits for reduction in blood pressure are attributed to the cognitive-behavioral intervention that was designed to provide critical knowledge and a novel approach using a computer to deliver e-mail messages linked to computer momentary assessment self-appraisal surveys to provide critical information and reinforce positive health-promoting lifestyle dietary behaviors.

3.9 Differences in Responses to WHEELS-I Program by Race/Ethnic Identity

Analyses of data for this study when categorized by race/ethnic identity (Caucasian American women and African American women) revealed significant differences for blood pressure reduction for both Caucasian American women and African American women assigned to WHEELS-I Program/experimental group ($p = 0.016$ and $p = 0.025$, respectively). However by study end, African American women showed nearly twice the level of reduction for SBP as Caucasian American women, demonstrating net mean differences of –5.72 mmHg versus –9.17 mmHg,

respectively. This finding suggested post CBI; SBP was lowered towards therapeutic levels for African American women and closer to national blood pressure report levels reported for Caucasian American women. Results showed that at baseline mean SBP for African American women was 136 mmHg and at study end with WHEELS-I Program was 127.69 mmHg versus 149.50 mmHg at baseline and 142.82 mmHg with CBI at study end for Caucasian American women. More research needs to address the differences in responses for African American women and Caucasian American women. Research investigating these relationships could significantly address the goals and objectives of the Healthy People 2020 Agenda [35] to narrow the gap in health status due to hypertension between minorities and other groups in the United States.

The results also showed that time is required to allow for a more gradual improvement over time for mean DDCR scale scores for healthier eating pattern in African American women in the WHEELS-I Program than for Caucasian American women. For example, for gains in cognitive representations of low-fat dairy products and corresponding reductions in mean SBPs, African American women, at Time 1 ($M = 2.70$; SBP = 136 mmHg), Time 2 ($M = 4.42$; SBP = 128 mmHg), and Time 3 ($M = 3.66$; SBP = 127 mmHg), than for Caucasian American women, at Time 1 ($M = 3.30$; SBP = 149 mmHg), Time 2 ($M = 4.45$; SBP = 139 mmHg), and Time 3 ($M = 4.18$; SBP = 142 mmHg). Thus, the greatest improvement and changes in the women's perceived value of and adherence to guidelines of the DASH diet occurred differentially for these women. Fifty six morning messages may be required for the African American women as suggested during the focus groups. Moreover, one of the more interesting findings was the sustained DASH adherence after the morning messages stopped showing that log-ins for messages and clicks for Web-based surveys far exceeded the acceptable criteria of 50 % for satisfactory intervention engagement level according to Moore et al. [20].

The result reported for the focus groups was 100 % African American women who were exposed to WHEELS-I Program and recruited by a certified advanced nurse practitioner in their community clinic. As anticipated, the impact of the computer-mediated WHEELS-I Program was effective and beneficial for this sample as evidenced by qualitative and quantitative data analysis results. An interesting finding emerged when the entire study sample was compared on the impact of WHEELS-I Program according to recruitment method, that is, a mailed invitation versus face to face from two clinics. This significant difference in blood pressure at study end suggests there is an important role regarding a certified advanced nurse practitioner for subject recruitment, retention, and intervention engagement. Focus group comments suggested the WHEELS-I Program should be made available to all patients with hypertension and may be improved by providing the morning messages over the entire 56 days of the study as opposed to 28 days that the WHEELS-I Program participants experienced.

3.10 Implications for Theory and Further Research

The design of the methodological approach through which cognitive representations of dietary behaviors were measured in this study informs us about adherence with medical regimes. This work supports theoretical evidence that healthcare providers can use cognitive representations to convey health information that is consistent with patients' needs and update a person's cognitive representations in order to guide behavioral changes [13]. Assessing maladaptive cognitive representation for DASH diet and providing a mechanism for increasing critical knowledge to manage hypertension more effectively. Testing of the SRM-guided WHEELS-I Program suggests that some new knowledge is available to use as a foundation for defining an accurate cognitive knowledge structure. The computer assessment of DASH diet cognitive representations can classify the extent of the knowledge deficit or "problem space" as a basis to predict the dose of tailored messages. As such, we have a proposition to set forward hypotheses to examine whether information, integration, and involvement as proposed by the conceptual framework predict long-term changes in response to hypertension lifestyle recommendations.

The findings from this research suggest that this cognitive-behavioral intervention employing sending tailored messages is a powerful reinforcement for learning and memory, as some information becomes internalized close in time to when reading e-mail messages and responding to Web-based rapid response surveys. The most interesting finding was the striking differences in reduction of blood pressure at 30 days post WHEELS-I Program of −11.10 mmHg versus −2.70 mmHg for those assigned to the experimental group who spent more time reading the morning messages than for those who spent less time. Results also revealed that for African American women the dramatic differences according to time spent reading AM messages showing decreases of −10.0 and −11.7 mmHg at 30 and 90 days post WHEELS-I Program for those spending more time compared to +1.11 and +3.44 mmHg for those spending less time engaged. The statistical conversion pipeline for logons and clicks for Web-based surveys suggests that the computer-mediated approach for sending e-mail messages is reliable at the 50 % compliance criterion for logons and must be considered in future studies to gain greater understanding of the effects of dose effect for providing computer health information programs.

3.11 Potential for Improvement of Quality of Life

The subjects' positive evaluation of the study, few dropouts, and finding from focus groups suggests that this approach is promising for overall improvement of quality of life. Perhaps the interactive nature of the intervention, in reading and responding to the messages, is what made subjects feel as though their input and behavior were truly important factors pertaining to the outcome of their health. When information is just "provided" to people without an opportunity to see and track how they are

changing (mentally—as they did with self-blood pressure measurement), it may be harder to continue and to maintain expected dietary modifications. However, the one major complaint from the women concerning the study centered on wanting to see more results; specifically, they wanted some evidence of weight loss from all of "this effort." We need to know more about how these women go about selecting foods and reading labels to reduce problem eating areas and when the set point was achieved for learning this new information.

The results demonstrated that specific DASH diet tailored messages have the potential to clarify dietary adherence decisions as well as identify those messages that may not be useful. More comprehensive tailored messages should be developed from the results of this research to address the three more problematic lifestyle dietary challenges for overweight adults. This includes managing modifications involving sweets/sugar and salt/sodium and having large portions of red meat.

3.12 Significance and Recommendations for Future Research

The major impact is the relevance and effectiveness of this dietary program for diverse populations. This is the only study that tests the minimum number of self-regulatory components with a diverse population in treatment for hypertension. The key to sustained intervention engagement appears to be related to recruitment at the point of care. The more engaged were those recruited from the physician-advanced nurse team provider as compared to those recruited through mail invitation from their health insurer database. Little research is available on the role of the advanced nurse practitioner to administer computer-mediated interventions for hypertension management. One sidelight of this study was the role of morning messages to prompt goal setting for one DASH diet food group; another was the ways that reading tailored messages is reflected in responses for DASH diet adherence behaviors. More research will determine reasons for less engagement, but greater DASH diet adherence, during the last 4 weeks of the study, was a very positive finding.

3.13 Conclusion

The WHEELS-I Program is a small step towards addressing the 2010 Institute of Medicine's Report to take hypertension seriously and for researchers to create an environment for patients to successfully reduce their blood pressure. The computer-mediated surveys are developed to capture a momentary assessment of dietary habits over time, for patients to become motivated to adjust their eating goals to accomplish long-term behavior changes. WHEELS-I is unlike any other program designed to provide critical DASH information; it was created to guide

behavioral changes using tailored information based on existing mental representations of eating-related knowledge, attitude, and skills for healthier eating patterns. Findings from our recent research studies and recent epidemiological studies show that a reduction in the SBP can translate to 50 % and 30–40 % reductions in the risk of dying from stroke and coronary heart disease. If we can reduce blood pressure in the African American population to that of the Caucasian population, this would abrogate approximately 2,500 annual deaths from stroke and would narrow the health disparity gap for uncontrolled BP between African Americans and Caucasians.

The continuing challenge is to develop more research with the purpose of testing the effectiveness of the WHEELS-I Program and the DASH diet to reduce uncontrolled hypertension and poor nutrition and improve responsiveness among diverse populations. It is anticipated that a research proposal can be developed from the results of this study to generate and test hypotheses in order to address the following goals with middle-aged women from diverse backgrounds in treatment for hypertension who are randomly assigned to experimental and control groups.

1. Explore development of mobile iPhone application to provide WHEELS-I Program to all patients with prehypertension and for those diagnosed with hypertension.
2. Assess the relationship of health-sustaining behaviors to DASH diet adherence, such as medication taking and home monitoring of blood pressure.
3. Design the WHEELS-I Program to offer 1,500 mg sodium and 1,200 calories to ensure optimal blood pressure reduction and weight loss.
4. Determine the role of WHEELS-I Program as associated with cardiac reactivity and self-blood pressure measurement.

This study has provided new knowledge of how to respond to the diverse needs of clinical populations with hypertension. The strengths of efforts to shape and refine CRs related to DASH diet with goals and messages aimed at reducing nonadherence showed more improvement by African American women than for Caucasian American women in general. This is a very important finding since research has not explained reasons for the earlier onset and greater prevalence of hypertension and greater nonadherence with DASH diet among minority populations. Thus, the WHEELS-I Program cognitive-behavioral intervention developed and pilot tested resulted in the following outcomes for women with uncontrolled HTN: (a) producing positive blood pressure reactivity, (b) adding critical information for increasing general knowledge of hypertension and for enhancing specific dietary behaviors, and (c) decreasing maladaptive cognitive representations of dietary behavior.

Acknowledgements This project was supported and funded by Blue Cross Blue Shield Foundation of Michigan, University of Michigan, School of Nursing and Office of the Senior, Vice-Provost Academic Affairs. A debt of gratitude is owed to the women who volunteered to participate in the research study and to Kenneth Jamerson, M.D.; Susan Steigerwalt, M.D.; Stephanie Lucas, M.D.; Shelia Crowley, A.R.N.P.; and Robin Nwankwo, R.D., M.P.H.

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Chapter 4
Community Programs for Hypertension: A Means of Identification and Intervention in the Highest-Risk Population

Joseph E. Ravenell and Gbenga Ogedegbe

The prevalence rate of hypertension among blacks in the United States currently exceeds 41 % and is among the highest in the world. Black men in particular have the greatest burden of death from hypertension (HTN), with death rates from hypertension being three times greater for black men compared to whites [1]. A major reason for the disproportionate morbidity and mortality from HTN and its complications in blacks is suboptimal blood pressure (BP) control. In fact, the disparity in hypertension control between blacks and whites accounts for nearly 8,000 excess cardiovascular deaths annually for African Americans [2]. Widespread hypertension control requires the engagement of patients and physicians and other clinical providers alike, and the involvement of individuals, health systems, and communities to facilitate two critical processes: (1) identification of individuals who have hypertension or at risk for developing hypertension and (2) therapeutic intervention to lower blood pressure and prevent complications of uncontrolled hypertension. Community-based hypertension programs have long been recognized as means to achieve these two requisite steps to achieve blood pressure control [3], particularly among high-risk populations such as black men who tend to underutilize primary care settings [4, 5]. In this chapter, we will briefly review the history of community-based hypertension control efforts and highlight selected community-based strategies from the peer-reviewed literature that have aimed to address blood pressure control in hypertensive African Americans.

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K.C. Ferdinand (ed.), *Hypertension in High Risk African Americans*, Clinical Hypertension and Vascular Diseases, DOI 10.1007/978-1-4939-2010-5_4

4.1 Community-Based Strategies to Control Hypertension: Historical Perspective

The 1960s began a new chapter in the fight to reduce suffering from hypertension. The first National Health and Nutrition Examination Survey, conducted from 1960 to 1962, demonstrated the significant prevalence of hypertension among adults and particularly among blacks [6]. As a result, the 1970s saw a rapid expansion of hypertension control efforts nationwide, including the establishment of the National High Blood Pressure Education Program (NHBPEP) in 1972 [7]. The mission of the NHBPEP was to coordinate initiatives such as screenings and education. NHBPEP was organized as a coalition of federal agencies, national organizations, state health departments, and community-based programs. The urgency of these efforts were intensified by the results of the VA Cooperative Trials published in 1967, 1970, and 1972 which demonstrated the unimpeachable morbidity and mortality benefits of antihypertensive therapy in adults with hypertension [8–10].

In light of the emerging epidemiology of hypertension and clinical trial evidence of the efficacy of treatment, several independent programs also picked up the mantle of screening the masses for hypertension. Some of the early programs explored using neighborhood medical clinics for mass screening [11]. Such clinic-based programs, however, were felt to be ineffective, as only 1–10 % of the target population was reached through these traditional medical venues [11, 12]. Other programs conducted blood pressure screenings at various community venues such as shopping centers, schools, YMCAs, and health fairs. Among the first programs were the Community Hypertension Evaluation Clinic (CHEC) Program [13] and the Atlanta Community High Blood Pressure Program conducted in 1970 [11, 12]. The CHEC program screened over 1 million Americans in a 2-year period from 1973 to 1975 using nonclinical community sites and partnering with community-based organizations. Engaging community volunteers to assist, this program included a 2-day event in New Orleans in which over 30,000 adults were screened and over 9,000 found to be hypertensive and referred for medical follow-up [14]. This project's use of community volunteers who assisted the health professionals to implement the screening is an early example of the community health worker model for hypertension. The Atlanta Community program was based in a nearly 100 % black, middle-class community and tested, among 6,000 individuals, four screening methods: (1) screening at a hospital-based location, (2) community venues within walking distance from the residences of the selected community members, (3) door-to-door home visits for blood pressure screening, and (4) mobile vans parked in high-traffic areas. The latter two were found to be most efficient screening modalities, while the hospital-based screening proved least efficient. This finding validated the value of nonclinical community venues for reaching hypertensive African Americans and set the stage for subsequent projects that would use community venues that have special cultural relevance for African Americans.

The aforementioned community screening programs sought to achieve both the identification and intervention aspects of improving blood pressure control, by

referring adults found to be hypertensive for medical follow-up. Unfortunately, only 50–60 % of those referred actually followed up with a physician [12, 14]. Clearly, these programs were very successful in achieving the first step of identification. However, the question of how to leverage the success of screening to address hypertension once identified in high-risk individuals remained an outstanding question to be addressed in subsequent programs and studies.

4.2 Pioneering Culturally Relevant Community Venues for Hypertension Screening: The African American Church

Virtually every neighborhood in North America has at least one church [15, 16]. In urban black communities, 65–80 % of persons attend church regularly and 55 % are involved in church-related activities [17]. Churches are a pillar of black communities and often provide information and services in a familiar nonthreatening setting to individuals who may not trust the mainstream health-care system because of differences in attitudes or health beliefs and thus often succeed where outside health professionals cannot [18–20]. Given their history of volunteerism and preexisting social networks to facilitate the adoption and maintenance of health behaviors, churches are an ideal site for health promotion and disease prevention programs [21, 22]. This makes churches a valuable delivery channel for evidence-based behavior change programs [23], particularly for black men given their historically low participation in clinical trials. Many pastors believe health and spirituality are linked and are interested in participating in health-related programs [24, 25]. The National Black Health Providers Task Force on High Blood Pressure Education and Control advocates the use of churches as a setting for the delivery of health promotion programs [19], and the role of church-based health promotion programs on behavior change is well documented [18, 21, 22, 26]. Disease prevention programs targeted at healthy behaviors have been evaluated in churches, including increased fruit and vegetable intake, adoption of physical activity, weight loss, and smoking cessation [27–34]. One of the first programs to organize African American churches for interventions as hypertension detection and control centers was the pioneering effort in Baltimore, Maryland, by the Urban Cardiology Research Center and the Association of Black Cardiologists, led by Drs. Elijah Saunders and B. Waine Kong [20]. With support from the National Heart, Lung, and Blood Institute, the investigators partnered with the American Heart Association (AHA) to train and certify church volunteers to measure blood pressure. The investigators note that in 1978, the certifying of lay health workers to measure blood pressure was “a revolutionary concept” and was a first for the AHA. Over 500 volunteers were trained to measure blood pressure.

Another pioneering effort in churches was the Healthy Hearts Community Prevention Project, led by Drs. Keith and Daphne Ferdinand in New Orleans,

Louisiana [35]. Inspired by the efforts in Baltimore, and also funded by NHLBI, the Healthy Heart Community Prevention Project was an outgrowth of the National Medical Association's (NMA) Healthy People 2000 Program, whose focus was to reduce excessive morbidity and mortality from preventable/treatable chronic diseases. The HHCPP had three components: a barbershop-based hypertension project (described below), a church-based component, and a practice-based component focused on providers. The church-based component, entitled "Give God a Hand," offered health education in various churches throughout New Orleans. The ministers gave "healthy heart sermons," which related health to church and religious text. Specifically, these were planned sermons focused on global cardiovascular risk reduction, including high blood pressure, hyperlipidemia, smoking, and exercise.

4.3 Pioneering Culturally Relevant Community Venues for Hypertension Screening: Barbershops

The black-owned barbershop is an ideal community site for health promotion interventions targeting hypertensive black men [35–39]. Black-owned barbershops are a major small business enterprise in urban centers across the United States [39]. With more nearly 20,000 sites across the United States, the black-owned barbershop is a popular secular site where black men of all socioeconomic strata gather frequently and feel comfortable discussing important issues in their lives [39]. Therefore, black barbers are influential peers with a long history of shaping public opinion [35–39]. Previous studies indicate that the average customer has had the same barber for over a decade and visits the same barber for a haircut every week or two [40]. Thus, barbershops constitute an existing and unique community setting and peer network that can be utilized to improve cardiovascular health in the black male community.

The pioneers for church-based hypertension programs also led the way for using barbershops as hypertension control centers. The barbershop component of HHCPP—inspired by a barbershop screening program implemented by Drs. Saunders and Kong in Baltimore—was entitled "Cut Your Pressure." [35] Volunteers taught beauticians and barbers how to check blood pressures over 10 h of training using the American Red Cross and the American Heart Association guidelines. The trainees who demonstrated the ability to check blood pressures appropriately according to consensus guidelines and qualified as "specialists" took sphygmomanometers back to their salons and barbershops to measure the blood pressures of their customers. They were also familiarized with various NIH publications regarding cholesterol and dietary guidelines. The purpose of partnering with barbershops was to reach areas where working class and lower socioeconomic status clients reside who traditionally may not be exposed to advocates of risk factor modification.

More recently, Victor, Ravenell, and colleagues performed the Barber-Assisted Reduction in Blood Pressure in Ethnic Residents (BARBER-1) study in black-owned barbershops in Dallas, Texas [41]. This cluster-randomized, barbershop-based trial was developed in response to epidemiologic data from the Dallas Heart Study (DHS), a population-based study that enrolled over 3,000 black volunteers [42]. The DHS found a hypertension control rate of 17 % among black men and that black men were least likely to have a primary care doctor. The intervention under study was similar to the HHCPP Cut Your Pressure program, wherein barbers were trained to measure blood pressure of their clientele at every visit, and to refer hypertensive customers to medical care. The barbers were trained to measure blood pressure according to consensus guidelines [43] using well-validated state-of-the-art blood pressure monitors and were trained to counsel their hypertensive customers according to a well-established behavior change theoretical framework and a previously validated teaching aid known as "role model stories." [41, 44] In this NHLBI-funded community-based trial, 17 barbershops were randomized to either the barber-based, "enhanced" intervention or a comparison group, which received standard printed educational materials about hypertension. In the enhanced intervention, barbers continually monitored their customers' BP, delivered health messages targeted at risk perception and social norms about seeking medical care, and provided social support. The primary outcome was change in the hypertension control rate among hypertensive customers from baseline to 10 months. At the end of the study, the shops in the intervention arm had significantly greater blood pressure control among hypertensive customers compared to the control shops (absolute group difference in control rate = 8.8 %, $P = 0.04$). To our knowledge, the BARBER-1 is the one completed randomized barbershop-based hypertension trial in the peer-reviewed literature. The results are promising, demonstrating that a program of continuous BP monitoring and peer-based health messaging in a barbershop can (1) be implemented by barbers rather than research personnel [40] and (2) improve BP control in the barbershop compared to printed educational materials [41]. One of the major advantages to this barbershop-based model is the built-in follow-up, because men are visiting the barbershop regardless for haircuts. While this advantage addresses one of the major challenges to previous community-based efforts (i.e., the inability to intervene due to poor follow-up), further research needs to investigate the long-term sustainability of partnering with barbers to improve hypertension control.

4.4 Current and Ongoing Community-Based Efforts

Thanks in large measure to the success of the studies and programs described above, there are new and promising ongoing community-based programs and trials aimed at improving hypertension control among high-risk African Americans, which will be reviewed here.

4.4.1 The Black Barbershop Health Outreach Program

The Black Barbershop Health Outreach Program (BBHOP) was established by Dr. Bill Releford in 2007 and was designed to educate, screen, and refer patrons in barbershops nationwide for needed care related to diabetes and hypertension [45]. The BBHOP has conducted barbershop-based screening with coordinated referrals targeting persons with undiagnosed hypertension and diabetes in order to institute early intervention.

The program was designed to identify partner barbershops in cities across the country and recruit 2-person teams of volunteers consisting of a medically trained personnel (i.e., physician, registered nurse, paramedic, or health professions student under supervision) and lay community volunteers. Although final outcomes are not available in the published peer-review literature, this program has reportedly screened more than 30,000 men in over 500 barbershops in 38 cities with a goal to screen more than 500,000 men by the year 2014 [46].

4.4.2 The New York University Men's Health Initiative

Barbershops and churches hold special appeal for community-based intervention trials, as they are cultural institutions that draw a large and loyal male clientele and provide an open forum for discussion of numerous topics, including health, with influential peers. A focus on community-based settings is particularly important among black men, a group that is less likely to access primary care health-care settings [41]. Building on the promising results of barbershop-based and church-based initiatives described earlier in the chapter, we propose that, given their historical significance as trusted community settings [39], the barbershop and the church are not only valuable delivery channels for evidence-based interventions for hypertension but may be a useful setting to address cancer prevention as well [4].

The Men's Health Initiative, led by the authors, is comprised of three studies: (1) the Multi-Intervention Study to Improve CRC Screening and to Enhance Risk Reduction in Black Men (MISTER B), (2) the Faith-based Approaches in the Treatment of Hypertension and Prevention of Colorectal Cancer (FAITH-CRC), and (3) the NYU Prevention Research Center Comparative Effectiveness Program. The Men's Health Initiative will leverage these studies to examine the efficacy and effectiveness of lifestyle counseling, patient navigation (PN), and the combination of lifestyle counseling and PN for black men. The intervention will be implemented in two community-based settings, black-owned barbershops and faith-based institutions, both of which have important cultural and social significance in the target population. This project will enable comparisons and evaluation of the impact of three different strategies to improve HTN control and CRC screening delivered in churches versus the impact of these strategies delivered in barbershops. Additionally, we will estimate and compare the long-term morbidity and mortality impact of BP

improvement and CRC screening using PN intervention alone, lifestyle intervention alone, and both. We aim to enroll 1420 black men over age 50 with uncontrolled hypertension who have not been previously screened for colorectal cancer. For illustrative purposes, we will describe the procedures for one of the studies (the MISTER B trial) in more detail below, as it exemplifies a successful strategy for combining outreach with important community-based research.

MISTER B was designed to evaluate the effect of two interventions on BP reduction and colorectal cancer (CRC) screening among 480 self-identified black men aged ≥50 years with uncontrolled HTN and in need of CRC screening: (1) a lifestyle intervention delivered through telephone-based motivational interviewing (MINT) to reduce blood pressure and (2) a culturally tailored patient navigation (PN) intervention delivered by community health workers to promote CRC screening [4]. We hypothesize that among enrolled participants, (1) those randomized to the lifestyle MINT intervention will have lower BP compared to those randomized to the patient navigation intervention at 6 months and (2) those randomized to the patient navigation intervention will have higher CRC screening rates compared to those randomized to the lifestyle intervention at 6 months.

MISTER B is a two-parallel arm randomized controlled trial that will compare the effect of a MINT lifestyle intervention and a culturally targeted PN intervention on improvement of BP and CRC screening among black men aged >50 with uncontrolled HTN who are eligible for CRC screening.

This innovative research design will allow each intervention to serve as the control for each other. Specifically, the MINT arm will be the control condition for the PN arm, and vice versa, in that the MINT intervention arm will receive usual counseling for colon cancer screening, and the PN arm will receive usual counseling about appropriate lifestyle changes to improve BP. We believe this novel, simultaneous testing of two community-based interventions *in a randomized fashion* is an economical and yet rigorous strategy that enhances the acceptability of the project to the community because all participating men will receive a potentially beneficial intervention (i.e., no one receives a "placebo"). The MINT intervention will be conducted by trained research assistants, while the PN intervention will be delivered by trained community health workers. The interventions were chosen because they are similarly high-impact public health problems for black men and are conducive to community-based delivery in a population that is underrepresented in primary care clinical settings.

MISTER B is being conducted in black-owned barbershops throughout New York City. Barbershops are recruited through word of mouth and by neighborhood tour accompanied by cold recruitment. Participants are recruited from barbershops that have agreed to participate in the study. For this purpose, we park an all-purpose mobile health van at the barbershop storefronts. Barbers in the participating barbershops refer potentially eligible customers to the van or to a blood pressure measuring station. Following the determination of eligibility, consent procedures, and completion of baseline self-report and psychosocial measures, participants are randomized to either the MINT lifestyle intervention or the CRC patient navigation intervention.

4.4.3 MINT Lifestyle Intervention

Motivational Interviewing (MINT) is an empirically tested, client-centered counseling approach designed to motivate people for change by helping them recognize and resolve the discrepancy between their present behavior and future personal goals and values [47, 48]. Several behavioral intervention trials that have included black men [26, 27, 30–32] have demonstrated the potential efficacy of MINT in this population. The content of the intervention is based on established hypertension treatment guidelines, which recommends weight loss (if overweight), limiting sodium and alcohol intake, smoking cessation, medication adherence, regular physical activity, and eating a low-fat diet that is rich in fruit and vegetables [43]. As such, all participants will be given the NIH/NHLBI *Your Guide to Lowering Blood Pressure* booklet as well as NIH/NHLBI DASH diet booklet titled *Facts about the DASH Eating Plan* and guided through the topics by the research assistant during the baseline session. The methodology, structure, and the content of the MINT counseling sessions will be patterned after our recently completed and successful practice-based trial [49].

The MINT sessions will focus on individual needs to tailor intervention strategies to the participant's personal context including social support, specific behavior change goals, problem-solving, and maintaining motivation during challenging situations. The men randomized to this group will receive four sessions of MINT sessions on lifestyle behaviors.

4.4.4 Patient Navigation Intervention

This intervention is patterned after the standard New York City Department of Health and Mental Hygiene (NYC DOHMH) patient navigation (PN) protocol [50] and culturally targeted to black men. It is widely accepted in the health promotion literature that interventions are more effective when they are culturally appropriate. The goals of the intervention are to (1) educate participants about CRC screening tests, (2) address participants' concerns about CRC screening, and (3) help participants overcome barriers to screening. Participants randomized to this arm will receive at least two planned sessions with trained patient navigators (PN) to assist them with completion of their choice of CRC screening modality.

The primary outcomes are (1) within-patient change in systolic and diastolic BP from baseline to 6 months and (2) CRC screening rates as determined by colonoscopy report from the primary care provider at 6 months.

4.4.5 Current Status of the Men's Health Initiative

To date, over 1,100 men have been recruited to the Men's Health Initiative, and we have screened over 6,000 black men over age 50 at 100 faith-based organizations and 90 black-owned barbershops. We anticipate completing the trials in 2015.

4.5 Seniors Centers as Hypertension Control Centers: The Counseling Older Adults to Control Hypertension (COACH) Trial

Despite the proven efficacy and compelling evidence of the beneficial effects of therapeutic lifestyle changes (TLC) on BP reduction in large clinical trials conducted in academic research settings, its effectiveness in community-based settings remains unclear. This is particularly true among elderly patients who tend to have an abysmally low rate of BP control, especially minority elders, who share a greater burden of hypertension (HTN)-related outcomes including heart failure, stroke, and end-stage kidney disease compared to whites. The COACH trial is a randomized controlled trial that evaluates the effect of a senior center-based comprehensive therapeutic lifestyle intervention (MINT-TLC) versus a control condition (CC), on BP reduction [51]. We hypothesize that minority elders randomized to MINT-TLC will exhibit at 12 months a greater BP reduction, increased intake of fruits and vegetables, higher levels of physical activity, higher percent change in weight, reduced 24-h urinary sodium excretion, and a higher proportion of seniors with adequate BP control. Two hundred and fifty African American seniors (age >60 years) with poorly controlled HTN (BP > 140/90 mmHg) will be enrolled from community-based senior centers affiliated with the New York City Department for the Aging. Seniors in the CC condition will receive a single brief advice session on TLC and print versions of NHLBI publications *Your Guide to Lowering Blood Pressure* and *Facts about the DASH Eating Plan*. Seniors in the MINT-TLC group will attend weekly group classes for 10 weeks (intensive phase), followed by monthly individual motivational interviewing (MINT) sessions for 3 months (extended phase), and then bimonthly individual booster MINT sessions for 6 months (maintenance phase). MINT-TLC is designed to help participants make appropriate TLC and develop skills to maintain these changes long term. MINT-TLC will be delivered by trained research personnel. The primary outcome is within-patient change in BP from baseline to 12 months. The secondary outcomes are levels of targeted therapeutic lifestyle behaviors and proportion of seniors with adequate BP control at 12 months (BP < 140/90 mmHg). All outcomes will be assessed in person at baseline and 12 months by using well-validated procedures and measures. BP will be assessed with an automated digital BP monitor. Therapeutic lifestyle behaviors will be assessed with NCI's brief fruit/vegetable and fat dietary assessment questionnaires and the 7-day physical activity recall. The long-term goal is to refine MINT-TLC and integrate it into routine senior center hypertension monitoring programs as a result of the data obtained, thus maximizing the likelihood of its translation into standard practice.

4.6 Conclusions

Community-based programs to address hypertension control remain essential for addressing health disparities among high-risk African-Americans. A critical issue for future study is sustainability of community-based interventions. It is important to maintain effective programs past the length of funded studies, thereby maintaining the trust of communities and continuing to address health disparities beyond the scope of individual research studies. Research into the efficacy of developing sustainable community-based methods to address health disparities in black communities is essential.

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Chapter 5
Stroke and Hypertension in High-Risk African Americans

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5.1 Introduction to Stroke Epidemiology with a Focus on African Americans

Stroke is primarily an "end-organ" outcome of atherosclerotic and hypertensive diseases and embolic disease usually arising from the heart or aorta. The most common type of stroke is ischemic stroke, the result of cerebral vessel occlusion from the accumulation of arteriosclerotic plaque or thrombi that develop in remote blood vessels and migrate to the smaller cerebral arteries, resulting in the death of brain tissue. The less common type of stroke is hemorrhagic, due to bleeding from a ruptured vessel within the brain [parenchymal or intracerebral hemorrhage (ICH)] or around the brain [subarachnoid hemorrhage (SAH).] It is estimated that 87 % of all strokes are ischemic, 10 % ICH, and 3 % SAH [1] with ischemic stroke having an overall lower risk of fatality than either ICH or SAH [2]. In 2010, stroke was the fourth leading cause of death in the United States (USA), followed by diseases of the heart, cancer, and chronic lower respiratory diseases [1]. Moreover, it is estimated that 6.8

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K.C. Ferdinand (ed.), *Hypertension in High Risk African Americans*, Clinical Hypertension and Vascular Diseases, DOI 10.1007/978-1-4939-2010-5_5

million Americans have had a stroke (4.3 % black males, 4.7 % black females compared to 2.4 % white males, 2.9 % white females), and each year approximately 795,000 (45,000 black males, 60,000 black females, 325,000 non-Hispanic white males, 365,000 non-Hispanic white females) will have a new or recurrent stroke [1]. Based on US Census population distributions by age and racial/ethnicity for 2010 and forecasts through 2050 combined with available data on stroke incidence rates, it is projected that the number of incident strokes will increase by about 2.25 times, with the distribution about 56 % white, 24 % Hispanic, and 12 % black, with the remainder other races [3]. Beyond the personal and family impacts associated with stroke, the total direct medical stroke-related costs are significant and are projected to increase dramatically between 2012 and 2030, from $71.55 billion annually to $183.1 billion [4].

Stroke death rates rise steeply with age—but stroke is not just an "old person's disease." It is estimated that about 15 % of all ischemic strokes occur in adults aged 18–44 [5]. To eliminate the effects of different age distributions of population groups, rates are commonly age adjusted, but this can mask important age differences. Age-adjusted US stroke death rates per 100,000 were higher in men than women in 2010 except for the oldest age group (85+) (Table 5.1).

Since the 1950s there has been such an overall decline in stroke death rates that it has been called one of the top ten public health achievements of the twentieth century [6]. However, the age-adjusted death rates remained consistently higher in blacks than whites through this period (Fig. 5.1). The current US stroke death rates are higher in blacks than in whites in each age–sex group except for those 85+ (Table 5.1). The relative excess in deaths from stroke among blacks is highest below age 65 (e.g., a black-to-white mortality ratio of 2.8 among men aged 45–54), but the black-to-white mortality ratio decreases with age in both sexes. As shown in Fig. 5.2, other racialethnic groups have lower reported stroke mortality than whites. Stroke death rates are lowest in American Indians/Alaska Natives (26.5–29.8 per 100,000 in 2010). Stroke death rates are similar in Hispanic and Asian/Pacific Islanders and generally lower than in whites. (Note, though, that the race groups of white, black,

Table 5.1 Death rates per 100,000 population for stroke, according to age and sex, for blacks and whites, and black-to-white mortality ratio, 2010

	Men			Women		
	Black	White	B–W mortality ratio	Black	White	B–W mortality ratio
45–54	33.6	12.2	2.8	26.7	9.1	2.9
55–64	83.2	29.0	2.9	51.3	20.6	2.5
65–74	182.6	83.3	2.2	126.2	66.8	1.9
75–84	398.0	288.3	1.4	347.2	280.2	1.2
85+	804.5	903.2	.9	1,001.5	1,052.8	1.0

Notes: Race groups include persons of Hispanic and non-Hispanic origins.
Source: Centers for Disease Control and Prevention, National Center for Health Statistics. *Health, United States, 2012*: With Special Feature on Emergency Care. Hyattsville, Maryland, 2013. Accessed Sept 21, 2013, at http://www.cdc.gov/nchs/hus/diseases.htm

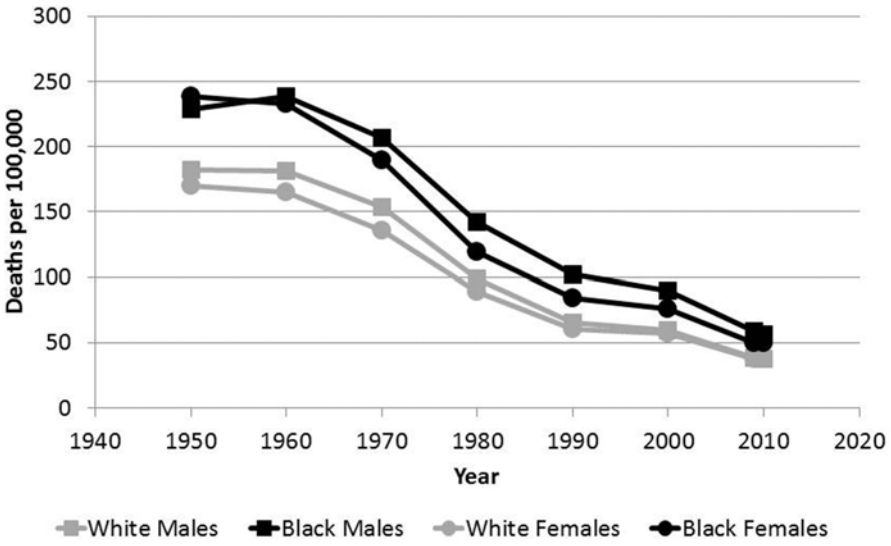

Fig. 5.1 Age-adjusted stroke death rates, for blacks and whites, by sex, USA, 1950–2010. Age-adjusted stroke death rates, for black–white, age, sex, 1950–2010. (**a**) Race groups include persons of Hispanic and non-Hispanic origins. (**b**) Underlying cause of death coded according to different revisions of International Classification of Disease (ICD): 1950, 6th revision; 1960, 7th revision; 1970, 8th revision; 1980–1990, 9th revision; 1999 onward, 10th revision. (**c**) Age-adjustment calculated using the 2000 standard population. Prior to 2001. Age-adjusted rates calculated using standard million proportions based on rounded population numbers. With 2001 data onward, unrounded population numbers used. (**d**) *Source*: Centers for Disease Control and Prevention, National Center for Health Statistics. *Health*, *United States*, *2012*: With Special Feature on Emergency Care. Hyattsville, Maryland, 2013. Accessed Sept 21, 2013 at http://www.cdc.gov/nchs/hus/diseases.htm

Asian/Pacific Islander, and American Indian/Alaska Native include persons of Hispanic and non-Hispanic origin and the Hispanic category includes persons across all race groups. Also, death rates are known to be underestimates for Asian/Pacific Islanders and American Indians/Alaska Natives for whom data may be inadequate.)

Black–white differences in mortality by stroke subtypes have also been reported, with higher rates of mortality from all subtypes among blacks compared with whites [7], but there are well-known inaccuracies and incomplete coding of death certificates including the fact that a majority of stroke deaths in the USA are coded as "stroke, not specified as hemorrhage or infarction [8, 9].

Much of what is known about the epidemiology of racial/ethnic differences in stroke at the national level comes from mortality statistics since the USA has not had a national record keeping system for reporting nonfatal strokes [10]. The first reports and concerns about the black–white disparity in the burden of stroke were reported in the 1970s based on mortality statistics from the 1940s to 1950s [11, 12]. Shortly thereafter this disparity was supported by incidence data from three

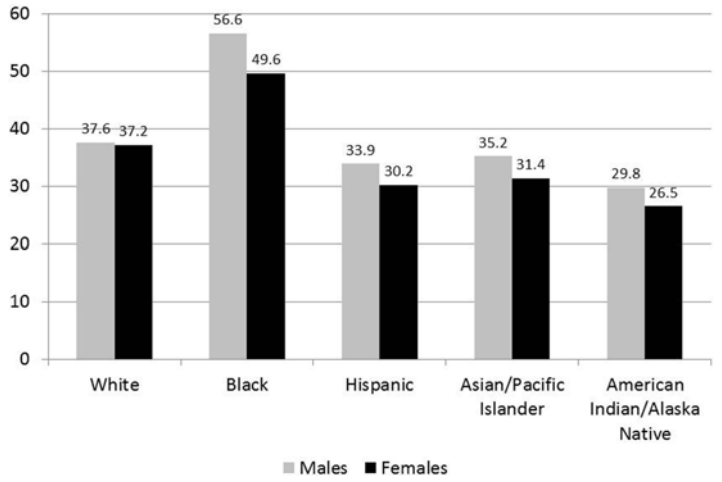

Fig. 5.2 Age-adjusted death rates (per 100,000) for stroke by racialethnicity, 2010. Age-adjusted stroke death rates, for 2010, by racialethnicity. (**a**) Race groups of white, black, Asian/Pacific Islander, and American Indian/Alaska Native include persons of Hispanic and non-Hispanic origins. Persons of Hispanic origin may be of any race. Death rates for American Indian/Alaska Native and Asian/Pacific Islander and Hispanic are known to be underestimates. (**b**) Underlying cause of death coded according to International Classification of Disease (ICD) 10th revision. (**c**) Age-adjustment calculated using the 2000 standard population. (**d**) *Source*: Centers for Disease Control and Prevention, National Center for Health Statistics. Health, United States, 2012: With Special Feature on Emergency Care. Hyattsville, Maryland, 2013. Accessed Sept 21, 2013, at http://www.cdc.gov/nchs/hus/diseases.htm

population-based cohort studies initiated during the 1960s [13–15]. More current epidemiologic studies of stroke incidence including the National Health and Nutrition Examination Survey (NHANES) Epidemiologic Follow-up Study, the Atherosclerosis Risk in Communities (ARIC), the Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS), the Northern Manhattan Stroke Study (NOMASS), and the REasons for Geographic And Racial Differences in Stroke (REGARDS) study also provide evidence to support this pattern—that the burden of stroke is consistently higher for blacks than whites for both ischemic and hemorrhagic stroke.

Furthermore, similar to stroke mortality, the greatest black–white disparity in stroke incidence is at younger ages [16–24]. In the national REGARDS study, the highest black-to-white sex-adjusted incidence rate ratio (IRR) for all stroke was for the youngest age group, 45–54 years (4.02; 95 % CI, 1.23–13.11), with IRRs monotonically lower in each older age group [23]. Data from the GCNKSS show that while blacks have a higher incidence of all stroke types, young and middle-aged blacks (ages 45–54 and 55–64) have a higher risk of incident SAH and ICH than whites of the same age [19, 24]. Stroke at younger ages has a disproportionately higher economic impact due not only to the individual's lost productivity from morbidity and premature mortality but also caregivers' lost productivity.

Ischemic strokes can be further classified into cardioembolic, large-vessel, small-vessel lacunar infarcts, other, or underdetermined. Within the GCNKSS, small-vessel strokes and undetermined strokes were about twice as common among blacks than whites, and large-vessel strokes were 40 % more common in blacks than whites, with a trend towards more cardioembolic strokes in blacks than whites [25]. In the ARIC study, after multivariable adjustment, blacks had a threefold higher-risk ratio for lacunar stroke compared to whites, but no black–white differences were found in incidence of non-lacunar or cardioembolic strokes [26]. There are less data related to recurrent stroke, but some studies have shown a higher rate of recurrent stroke for blacks compared to whites [27–29]. However, studies of patients with acute ischemic stroke have found lower or similar in-hospital mortality for blacks compared to whites [29–31].

In addition, stroke is one of the leading causes of disability in the USA [32], and there are racial/ethnic disparities in stroke-related disability. At stroke onset, blacks present with more severe deficits [33, 34]. Based on combined data from 2 years (2000 to 2001) of the National Health Interview Survey, among noninstitutionalized persons with self-reported stroke, 49.6 % of blacks compared to 33.8 % of whites reported stroke as one of the health conditions that limited their activities. After adjustment for age and sex, black stroke survivors were significantly more likely than whites to report limitations on all 12 of various activities queried and more likely to report using special equipment [35].

5.2 Black–White Disparities in the Impact of Stroke Risk Factors (with a Focus on Hypertension)

Epidemiologic studies not only provide insights to black–white differences in stroke incidence across a broad age spectrum and in different regions of the USA, but some also provide insights into the risk factors potentially contributing to the excess stroke risk in blacks compared to whites. Higher prevalence of hypertension and diabetes in blacks is the most consistently documented risk factors that contribute to the excess stroke incidence risk in blacks [16, 17, 36]; however, they explain only approximately 30–50 % of the excess [17, 37].

A report from the first NHANES Follow-up Study showed that the combined risk factors of age, sex, education, blood pressure treatment group (normotensive, controlled hypertensive, hypertensives receiving medication, hypertensives not receiving medication), systolic blood pressure, diabetes, history of heart disease, Quetelet index (i.e., body mass index), hemoglobin, and magnesium explained approximately one-third of the excess stroke risk among blacks who were 35–74 years of age at baseline [17]. There was also an interaction with age, similar to what was found in the earlier Evans County, Georgia, study [13], indicating that even after adjustment for these risk factors, blacks aged 35–44 were at substantially increased risk for stroke, but racial differences above age 64 were smaller or nonexistent.

Limitations of the NHANES report include the use of administrative data (medical records, death certificates) for stroke events, lack of smoking status, and less complete follow-up for blacks [17].

The ARIC cohort study that included four geographical areas of the USA (only two had sufficient numbers of blacks) with physician adjudication of potential stroke cases over an average follow-up period of 7.2 years showed that the addition of educational status to the variables of age, sex, hypertension, and diabetes decreased the black-to-white ischemic stroke incidence rate ratio by one-third, from 1.57 (95 % CI: 1.18–2.09) to 1.38 (95 % CI: 1.01–1.89), although the potential age interaction was not examined [18]. A report from the population-based incident stroke case–control study of NOMASS compared the prevalence, odds ratios (ORs), and etiological fraction (EF) of stroke risk factors across whites, blacks, and Caribbean Hispanics in the same community of northern Manhattan [38]. (Using the prevalence and OR, the etiological fraction is an estimate of the proportion of strokes attributable to a specific risk factor and provides information on proportion of population at risk of stroke that could be reduced with elimination or control of the specific risk factor.) The EF and prevalence of hypertension were highest in both blacks (prevalence 62 %, EF 37 %) and Caribbean Hispanics (prevalence 58 %, EF 32 %) compared to whites (prevalence 43 %, EF 25 %). A significantly greater prevalence of diabetes was also seen in blacks and Caribbean Hispanics compared to whites, and physical inactivity was a strong stroke risk factor for all three race–ethnic groups [38].

REGARDS is a population-based national cohort study of 30,239 community-dwelling individuals, aged 45 or older at enrollment in January 2003–October 2007, designed to advance the understanding of racial and geographic differences in stroke mortality and cognitive functioning [39]. The cohort is 55 % women, 45 % men, 42 % blacks, 58 % whites, 56 % residents of stroke belt states (Alabama, Arkansas, Georgia, Louisiana, Mississippi, North Carolina, South Carolina, and Tennessee), and 44 % residents of the other 40 continental USA. Participants or their proxies are contacted every 6 months by telephone to identify potential strokes or deaths, and follow-up is ongoing with physician adjudication of medical records from suspected stroke events. More details regarding the study design and methods are provided elsewhere [23, 39, 40]. In cross-sectional analyses from REGARDS, the black–white differences in estimated 10-year stroke risk by the Framingham Stroke Risk Score (FSRS) were calculated for participants without a self-reported history of stroke or transient ischemic attack (TIA) [41]. The components of the FSRS include age, sex, systolic blood pressure (SBP), use of antihypertensive medications, current smoking status, history of heart disease, diabetes, left ventricular hypertrophy (LVH), and atrial fibrillation [42, 43]. Blacks had a higher age- and sex-adjusted mean (standard deviation) FSRS than whites, 11.3 % (11.8) vs. 9.7 % (10.1) in whites. This represented a substantially worse risk factor profile in all but two of the risk factors of the FSRS—history of heart disease and atrial fibrillation that were less common in blacks. Consistent with other studies, the biggest difference between blacks and whites was in diabetes and hypertension [41].

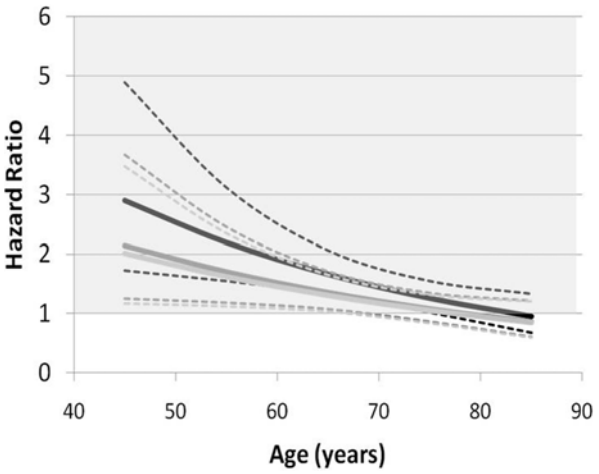

Fig. 5.3 Estimated black-to-white hazard ratio as a function of age and covariate adjustment. Darkest lines show hazard ratio and 95 % confidence limits after adjustment for sex, medium dark lines show hazard ratio and 95 % confidence limits after further adjustment for Framingham stroke risk factors, and lightest lines show hazard ratio and 95 % confidence limits after further adjustment for SES factors

Using an approach similar to that used with the NHANES follow-up data [17], in REGARDS, blacks were found to be at higher risk of stroke than whites after adjusting for variables in the FSRS as well as socioeconomic status (SES), defined by annual household income and education [37]. Similar to the findings from NHANES, after adjustment for the Framingham risk factors, there was substantial attenuation of the black excess risk after adjustment for SES factors. Forty percent of the analysis sample of 25,714 participants was black. Blacks were younger and had higher prevalence of antihypertensive medication use, diabetes, LVH, and smoking and lower SES than whites. The hazard ratio for incident stroke in blacks compared to whites at different ages is shown in Fig. 5.3. At ages ≤65, where the black–white disparities in stroke risk are the greatest, the Framingham risk factors accounted for approximately 40 % of the excess risk in blacks; with the inclusion of the SES factors, this increased to approximately 50 % [37].

Analyses to establish which of the risk factors contributed to this reduction in black–white differences showed that SBP had the greatest effect, explaining approximately 50 % of the effect of the combined risk factors. The next largest contributing factors were use of antihypertensive medications and diabetes, each accounting for approximately 25–33 % of the combined risk factor effect [37]. While the FSRS factors and SES adjustment accounted for approximately one-half of the black–white excess stroke risk, the other half must be attributable to other sources or factors. The REGARDS investigators suggest that the other potential contributors to the black–white disparity in stroke risk could be arising from (1) a racial difference in the impact of risk factors, with the presence of risk factors having a larger impact

in blacks than whites; (2) residual confounding from incomplete assessment of these traditional risk factors, where, for example, characterizing hypertension with systolic blood pressure and medication use fails to capture other aspects such as the duration of hypertension or diurnal variations in blood pressure; (3) "novel" risk factors such as inflammation, psychosocial factors, etc.; and (4) measurement error in the predictive factors in the model [37].

Further work in REGARDS examined black–white differences in the impact of SBP on the risk of stroke for three age groups (<65, 65–74, ≥ 75) and three levels of SBP (<120, 120–139, and 140–159 mmHg, with too few white participants having SBP above 160 mmHg to assess racial differences) [44]. Elevated SBP was found to be associated with higher risk of stroke in blacks than whites, and the differences were found to be greatest in the lowest age category of 45–64 years and among those with more severe hypertension (i.e., SBP 140–159 mmHg): black-to-white hazard ratio (HR) = 1.38, 95 % CI, 0.94–2.02 for SBP 120–139 mmHg, and HR = 2.38, 95 % CI, 1.19–4.72 for SBP 140–159. These differences were not substantially modified after adjustment for other traditional stroke risk factors [44]. Multiple studies have shown that while blacks are more likely than whites to be aware of their hypertension and to be treated for it, they are less likely than whites to have their hypertension under control [45–48]. Thus, this differential control appears to be a significant contributor to the black–white disparity in incident stroke risk and reinforces the contention that improvement in the control of hypertension at all levels and at all ages would reduce or could even eliminate this disparity [49].

Accordingly, it has been estimated that among persons with hypertension who have a stroke, approximately 90 % of the strokes are attributable to uncontrolled hypertension [50]. In the recent Secondary Prevention of Small Subcortical Stroke (SPS3) trial, an international multisite 2×2 factorial design trial of two levels of SBP control and two regimens of antiplatelet therapy in which both normotensive and hypertensive patients with recent lacunar stroke were randomized, non-Hispanic black participants were more likely to report a history of hypertension prior to stroke, have uncontrolled hypertension at time of enrollment, and be taking more antihypertensive medications than the other racialethnic groups [51]. Reasons for uncontrolled treated hypertension are multifactorial, and some are similar across race–ethnic groups, i.e., age, medication nonadherence, not receiving regular medical care, treatment-resistant hypertension, and lack of healthy behaviors such as physical activity, etc., but persons of African ancestry are more likely to have treatment-resistant hypertension and specific associated pathophysiology of hypertension, i.e., low-renin hypertension, etc., that require targeted evaluation and management [52, 53]. Failure to diagnose and treat the different underlying comorbidities or contributors of hypertension in blacks has been suggested as a major contributor to the black–white stroke disparity [54]. Therefore, especially in blacks, it is recommended that physicians take an individualized approach to assess and manage blood pressure (BP) levels, including changing medications and incorporating advice related to lifestyle changes [55–57]. This is true in relation to both primary and secondary prevention strategies and regardless of stroke subtypes [26, 51, 58].

5.3 Other Hypertension-Related Stroke Risk Factors in Blacks

Ambulatory BP monitoring has uncovered a variety of abnormalities that may predict stroke and that are more prevalent in blacks. These include masked hypertension, the nocturnal BP pattern, and circadian BP variability [59]. These could represent other potential explanations for the higher stroke risk among blacks in general, but clearly more studies of these associations are needed.

5.3.1 Prehypertension

It is well known that BP in the prehypertensive ranges, defined by the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) as a BP of 120–139-mmHg systolic and/or 80–89-mmHg diastolic, is associated with the future development of frank hypertension (HTN). In the modern era, overall stroke events have declined, and statins are in higher use; therefore, stroke risks conferred by prehypertension are not well established. In a meta-analysis of 12 prospective cohort studies (518,520 participants), an association was found of higher values of baseline prehypertension (SBP 130–139 mmHg or DBP 84–89 mmHg) with incident stroke, but since many of the included studies were from Japan and China, only the racialethnic comparison between Asians vs. non-Asians was conducted [60]. Similarly, in a meta-analysis of 16 randomized clinical trials (70,664 participants) of antihypertensive medications in persons with prehypertension (average SBP 120–140 mmHg and DBP <90 mmHg), there was a 22 % statistically significant reduction in incident strokes with antihypertensive treatment compared to placebo [61], but again, no data were reported for black–white comparisons. In a report on stroke risk in 22,748 black and white participants in REGARDS, during 4.5 years of follow-up 715 incident strokes occurred, and for each 10-mmHg increase in SBP (from a SBP of >120 mmHg), there was an 8 % increase in stroke risk for whites but a 24 % increase for blacks. The hazard ratio was 0.87 for normotensive participants, 1.38 for those with prehypertension, and 2.38 for those with stage 1 hypertension [44].

The possibility of excess stroke risk in subjects with prehypertension has pathophysiologic plausibility, and this is particularly so for blacks. Several alterations in cardiovascular structure and function have been reported to precede the finding of frank hypertension including left ventricular hypertrophy (LVH) in children and young adults of hypertensive parents, more LVH in blacks generally, diastolic filling abnormalities in normotensive individuals predisposed to hypertension, endothelial dysfunction as a precursor to the finding of hypertension, and increased arterial stiffness in normotensive subjects predisposed to develop hypertension [62]. In a study of subjects with confirmed prehypertension, carotid intimal–medial thickness

was increased compared to subjects who were normotensive [63]. All of these aforementioned pathophysiologic changes have been reported more frequently and at younger ages in blacks vs. whites.

5.3.2 Pulse Pressure

Pulse pressure (PP) is an indirect measure of arterial stiffness and is an indicator of the stiffness predominantly of large arteries, especially the aorta. SBP and DBP increase with age in a parallel manner until about age 60 years, after which SBP continues to rise and DBP begins to decrease. This age-related phenomenon results in the large increase in PP after age 60 years and an increase in the prevalence of isolated systolic hypertension (ISH). As a result, PP may be a key blood pressure measure in older individuals and may be an important risk factor for cardiovascular disease, including stroke, myocardial infarction, and death. Increased PP (as well as other measures of arterial stiffness) occurs earlier in blacks compared to whites representing yet another explanation for the greater burden of stroke in African Americans [64]. A report from the Third NHANES (1988–1994) found higher pulse pressures among racial and ethnic minorities than among non-Hispanic whites and among males than females [65]. Whereas the superiority of pulse pressure as a cardiac risk predictor in hypertension is strong, the relationship between pulse pressure and stroke is weaker [66–69]. In the ARIC study, after multivariable adjustment, SBP was found to have the greatest contribution to risk prediction for stroke, and this was true separately for blacks ($n=3,428$) as well as whites ($n=9,912$) [68]. Analyses from REGARDS ($N=27,680$, 40 % black) found that while PP was positively associated with incident stroke, this association was attenuated after multivariable adjustment that included SBP, DBP, and mean arterial pressure [69].

5.3.3 Masked Hypertension

In previous studies that have reported on the prevalence of masked hypertension in all-African American populations, an alarmingly high prevalence of 70 % in the African American Study of Kidney Disease (AASK) cohort study and 58 % in a small cohort study were reported among individuals with normal clinic BP [70, 71]. A meta-analysis of 28 studies ($N=25,605$ subjects) that used a standardized definition of masked hypertension reported an average prevalence of 16.8 % (95 % CI: 13.0–20.5 %) and 19 % (95 % CI: 16.1–23.6 %) for adults across all racialethnic groups [72]. In a more recent meta-analysis of eight studies (also unfortunately not stratified by race) that included 7,961 subjects, when compared with normotensives, the overall adjusted HR for any CVD outcome (including stroke in seven of studies) was 0.96 (95 % CI: 0.65–1.42) for white-coat hypertension, 2.09 (95 % CI: 1.55–2.81) for masked hypertension, and 2.59 (95 % CI: 2.0–3.35) for sustained

hypertension [73]. Apart from use of different definitions, prevalence estimates vary depending on subject characteristics and populations studied. Factors suggested as contributing to masked hypertension include cigarette smoking, alcohol use, physical activity, diabetes, and occupational and psychological stress [74]. One suggested explanation for the probable higher prevalence of masked hypertension in African Americans is diminished endothelial function (also described to be more common in African Americans) [71, 75, 76].

In a population-based study from Japan, a comparison of normotensive subjects and those with masked hypertension showed an increased risk of stroke (HR, 2.17; 95 % CI, 1.31–3.60) but not of cardiovascular mortality (HR, 1.88; 95 % CI, 0.95–3.72) [77]. Other studies have reported only combined CVD events or all-cause mortality [59, 74].

Since masked hypertension is more common in blacks, this could represent another potential explanation for the higher stroke risk among blacks in general, but clearly more studies of this association are needed. The take-home message is that office BP may not be sufficient to predict the presence of masked hypertension, and this further reinforces the importance of ambulatory BP monitoring to help identify individuals with high BP who do not present as such at doctors' office visits. These individuals may require some kind of intervention, whether it be nonpharmacological or pharmacological.

5.3.4 Circadian Blood Pressure Variability

The "dipper" versus "non-dipper" classification was first introduced in 1988 when a retrospective analysis suggested that non-dipping hypertensive subjects had a higher risk of stroke than the majority of subjects with a dipping pattern [78]. Since, a non-dipping nocturnal pattern has been associated with cerebral, renal, and cardiovascular target organ involvement [79]. Moreover, nocturnal BP has been suggested to be an independent risk factor for CVD outcome over and above all other measures of BP [80, 81] especially in patients with severe CHF [82], renal insufficiency [83], obstructive sleep apnea [84], and stroke [85]. For example, in the Dublin Outcome Study, for each 10-mmHg increase in mean nighttime SBP, CVD mortality risk increased by 21 % [80]. Diminished nocturnal blood pressure dipping is more prevalent among African Americans than whites [86] and has been proposed as one reason why African Americans are at higher risk for target organ damage and stroke than are members of other racialethnic groups [87].

A meta-analysis of 18 studies involving 2,852 African Americans, African immigrants, Afro-Caribbeans living in the United Kingdom, Native South Africans, European Americans, and Europeans was conducted to identify the overall effect of race on circadian blood pressure patterns. Separate analyses were conducted on effect sizes for differences between participants of African and European descent in daytime and nighttime systolic and diastolic blood pressure and nocturnal dip in systolic and diastolic blood pressure. Results of overall meta-analyses indicate that

subjects of African descent experience higher levels of systolic and diastolic blood pressure, and these differences were significantly greater at night than during the day ($p<0.05$) [86]. In a longitudinal study of blood pressure variability in 297 African Americans and 344 European Americans with an average age of 14 years at the initial visit. African–Americans showed higher values of blood pressure variability ($p<0.05$) than European Americans [88]. While the role of short-term and long-term blood pressure variability as a predictive factor is still under investigation, as noted above, some studies point out its predictive value for target organ damage and stroke.

5.3.5 Recurrent Stroke and Medication Adherence

As previously noted, there are limited data on recurrent stroke, but rates appear to be highest among blacks compared to other racialethnic groups [89]. One suggested component to this is poor medication adherence to secondary prevention treatment. Notwithstanding the increased risk for recurrent stroke, multiple studies have reported lower rates of primary and secondary stroke prevention therapy use among minorities [89–92]. Studies have found that among stroke survivors, blacks were more likely than whites to have cost-related medication nonadherence, even after adjusting for demographic differences, comorbidities, and prescription drug coverage [93]. The role of race as it relates to medication adherence is not clear. Since stroke is but one of a number of related vascular issues (e.g., myocardial infarction, vascular-related causes of death), understanding medication adherence is critical for determining meaningful strategies to provide the secondary preventative care that would have a large public health and economic impact by avoiding costly recurrent vascular events.

5.3.6 Chronic Kidney Disease

Chronic kidney disease (CKD), defined as reduced glomerular filtration rate (GFR), is a cause and consequence of hypertension. CKD is an established risk factor for coronary heart disease (CHD), and a reduced estimated glomerular filtration rate (eGFR) has been associated with a higher risk of CHD events and death independent from traditional risk factors [1]. A reduced estimated glomerular filtration rate (eGFR) has also been associated with a higher risk for fatal and nonfatal stroke, but the aggregate literature is not consistent [94, 95] and there are limited data on measures of kidney function and stroke risk in blacks. In an examination of the association of eGFR and urinary albumin excretion (measured as albumin-to-creatinine ratio, ACR) with incident stroke in REGARDS, a higher ACR was found to be independently associated with higher stroke risk in black, but not white participants [95]. An editorial accompanying the paper suggests that albuminuria could be an

important new marker for uncontrolled hypertension in blacks, reemphasizing the need for diagnosis of the underlying pathophysiology of the hypertension and an individualized approach to managing BP levels to reduce stroke risk in blacks [54].

5.3.7 Left Ventricular Hypertrophy

Long-standing or severe hypertension increases cardiac workload and promotes left ventricular hypertrophy (LVH). A higher prevalence of left ventricular (LV) hypertrophy and LV dysfunction in blacks [96–98] may partially contribute to their greater incidence of stroke compared to whites. Whether LVH is defined echocardiographically or electrocardiographically, LVH has been associated with risk of ischemic stroke and is included in the Framingham stroke risk function as well as the ARIC one [99]. In 10-year follow-up of a general population cohort from Japan, both Cornell product (CP) and Sokolow–Lyon (SL)-defined LVH were found to be predictors of stroke after adjustment for risk factors [100], but it has been shown that the use of ECG-defined LVH for detecting increased LV mass index varies by race [97, 101]. REGARDS showed SL-LVH present in approximately 6 % of whites and 14 % of blacks, and it was associated with a 40 % (95 % CI: 9–81 %) increase in stroke risk [37]. While LVH is more than twice as prevalent in blacks than whites, the relatively low prevalence implies that it only accounts for a relatively small proportion (11–19 %) of the total impact of the traditional risk factors on the black–white difference in stroke risk between ages 45 and 65 [37]. As summarized in a review article, although there is indirect evidence that hypertension control can modify stroke risk, the mechanisms for the effect of LVH on risk of ischemic stroke are uncertain and further studies are required [99].

5.4 Sleep Disorders as a Risk Factor for Stroke Among Blacks

There is burgeoning evidence that suggests sleep disorders, particularly sleep-disordered breathing (SDB) (that includes obstructive sleep apnea (OSA), the most common type of SDB) as well as self-reported sleep disruptions and sleep duration, are related to incident stroke [102–104]. The prevalence of OSA is estimated to be 30–40 % in persons with hypertension and may be even higher in persons with resistant hypertension, especially if they are obese [105]. A meta-analysis of studies (of mostly older individuals) published between 1995 and 2006 suggests that SDB and OSA are significantly more prevalent and more severe among African Americans than whites [106]. A recent single-site study with a younger sample found that age, sex, and body mass index were effect modifiers of racialethnic differences in SDB. Specifically, African American males <39 years old or between the ages 50

and 59 were more likely to have severe SDB than white males, and the relationship was attenuated when body mass index was included in the model [107].

SDB, as measured by the apnea–hypopnea index, or the frequency of apneas (cessations in breathing ≥10 s) and hypopneas (decreased respiration rate and depth) per hour, is prospectively and independently linked to incident stroke [102–104]. Reigning hypotheses for why ethnic group differences are apparent in OSA prevalence and severity are craniofacial morphology differences that may alter upper airway mechanics [108], differences in the neurochemical control of breathing [109], and disparities in healthcare access and presentation for treatment [106, 110]. All of these factors may jointly contribute to disparities in OSA between African American and whites that may ultimately lead to disparities in stroke events as well.

Self-reported short and long sleep durations are also independent risk factors for stroke [111–114]. A meta-analysis conducted on studies from 1997 to 2009 reported the relative risks of stroke in short sleepers (<6 h) and long sleepers (≥9 h) were 15 and 65 % greater than 7–8-h sleepers, respectively [115], and later studies continue to demonstrate these associations between extremes in sleep duration and subsequent stroke [116–120]. However, only a few studies on the sleep duration–stroke relationship had samples of African Americans [111, 112, 117], two of which did not have samples with proportions representative of the US population. The one study with a representative African American sample was cross-sectional in design [117]. In each of these studies, the sleep duration–stroke relationship was independent of racial/ethnicity. However, racial/ethnicity may still be a factor considering a substantial literature demonstrating that African Americans have both shorter objectively measured (via overnight polysomnography or wrist actigraphy) and self-reported sleep duration [121]. Epidemiologic studies also find that African Americans are more likely than whites to report both short and long habitual sleep durations [122, 123]. Further inquiry is needed to ascertain whether the preponderance of stroke among African Americans may be partially explained by differences in sleep duration.

5.5 Clinical Trials of Hypertension Treatment and Stroke Outcomes in Blacks

High blood pressure is the most well-established modifiable risk factor for ischemic and hemorrhagic stroke in terms of strength and consistency of findings [124, 125]. It is also the most important risk factor in terms of percentage of strokes caused and potential for effective management. Randomized clinical trials (RCTs) have provided conclusive evidence that antihypertensive treatment is effective in preventing first and recurrent stroke overall and in blacks separately [59, 124, 126, 127]. A 1993 meta-analysis included five RCTs that reported data by race groups and found no difference in pooled odds ratio for reduction in stroke for blacks compared

to whites, 32 % reduction for blacks compared to 37 % for whites [126]. A 2004 systematic review of the blood pressure lowering efficacy of monotherapy from 30 trials studying 53 interventions with eight classes of antihypertensive drugs in 20,006 blacks, aged 18 to >80 years, in the USA, Africa, and the Caribbean included data from four trials that reported morbidity and mortality outcomes in blacks; two reported stroke-only outcomes: SHEP (Systolic Hypertension in the Elderly Program) and ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) [128]. In the SHEP trial with stroke as the primary outcome, in 658 (14 %) blacks, compared to placebo, the active chlorthalidone-based treatment reduced stroke in black women (RR 0.36, 95 % CI: 0.16, 0.83) but not in black men (RR 0.98, CI: 0.39, 2.44) [128]. More recently, ALLHAT included 11,792 (35 %) blacks with race (black vs. nonblack) a prespecified subgroup; fatal and nonfatal stroke was a preplanned secondary outcome. The subgroup findings by race were generally similar to the overall results with the exception of the stroke outcome. Overall, blacks had significantly higher rates of stroke (6.5 % vs. 5.3 %, $p<0.001$) than nonblacks, but there was no adjustment for the many differences in baseline characteristics between the two groups [127]. In the comparison of lisinopril with chlorthalidone, there were different treatment effects by race for BP reduction ($p<0.001$ for interaction) and stroke ($p=0.01$). Compared to chlorthalidone, lisinopril increased stroke in blacks (RR 1.40, 95 % CI: 1.17–1.68), but not in nonblacks (RR 1.00, 95 % CI: 0.85–1.17). As the ALLHAT investigators note, the difference in effect on stroke between the two race groups is likely attributable, in part, to the BP differences [127]. The Secondary Prevention of Small Subcortical Stroke (SPS3) trial evaluated two regimens targeted to reducing blood pressure <130 vs. 130–149 mmHg in patients with recent, symptomatic, MRI-confirmed lacunar stroke. Lowering of systolic blood pressure to a target of less than 130 mmHg resulted in nonsignificant reductions in all stroke, disabling or fatal stroke, and major vascular events, but a significant reduction in intracerebral stroke. Blacks constituted 16 % (432 participants) of the SPS3 population, and they demonstrated no differences in stroke occurrence compared to the overall trial population [129].

ALLHAT is one of only a few hypertension trials with a sizable number of blacks and adjudicated stroke outcomes. The current NIH-funded SPRINT (Systolic Blood Pressure Intervention Trial), a 2-arm, multicenter, randomized trial to determine if a treatment program to reduce SBP to a lower goal than currently recommended will reduce cardiovascular risk (including stroke), recently completed enrollment with approximately 30 % blacks (2,800) (ClinicalTrials.gov NCT01206062). While there have been many meta-analyses and systematic reviews of hypertension trials that do include stroke either as a separate outcome or part of a composite endpoint, most do not include a summary of stroke results by race groups. With the knowledge that blacks with hypertension have a higher morbidity and mortality from stroke than any other racialethnic group in the USA (also among the highest in the world), and there are differences in the effectiveness of hypertension medications in lowering and controlling BP in blacks compared to nonblacks, it is imperative that RCTS be designed and targeted for inclusion of a substantial number of black participants. In addition, studies need to be directed towards whether goal BPs should be the same across all racialethnic groups [130].

5.6 Conclusions

Stroke is a leading cause of death, but it is preventable. Despite the significant decline in overall stroke mortality in the USA over the past 50 years, stroke mortality rates have remained consistently higher in blacks than for any other racialethnic group. Consistent evidence supports that approximately half of the excess black-to-white disparity in stroke risk is attributable to traditional stroke risk factors, primarily systolic blood pressure and diabetes. Recently the pace of scientific investigations into the reasons for this disparity has increased. In addition to the well-documented higher prevalence of hypertension in blacks, evidence supports that blacks are less likely to have their blood pressure controlled than whites. This lack of control has a potent effect, as recent data show that the impact of uncontrolled hypertension on stroke risk is three times greater for blacks than whites. With this and other knowledge of the causes, interventions can be designed and implemented to reduce the unequal burden of stroke. In addition to work previously funded by institutes within the US National Institutes of Health including NINDS, NHLBI, NIA, and NIMHD, new funding initiatives by the NINDS are targeted to use this knowledge to develop "high-impact" interventions to address stroke disparities among racial/ethnic minorities, rural, and disadvantaged socioeconomic groups [131]. The prevention, detection, and control of high blood pressure appear to be the cornerstones of the reduction of stroke risk in high-risk African Americans.

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Chapter 6
Manifestations of Left Ventricular Hypertrophy and Coronary Heart Disease: The Contribution of Hypertension and the Paradox in Blacks

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Abbreviations

AA	African American
ACE	Angiotensin-converting enzyme
ANP	Atrial natriuretic peptide
BMI	Body mass index
BNP	Brain natriuretic peptide
CAC	Coronary artery calcium
CAD	Coronary artery disease
CHD	Coronary heart disease
CHF	Congestive heart failure
CV	Cardiovascular
CVD	Cardiovascular disease
ECG	Electrocardiography
EDV	End-diastolic volume
LIFE	Study Losartan Intervention for Endpoint Reduction Study
LV	Left ventricle
LVH	Left ventricular hypertrophy
LVM	Left ventricular mass
MI	Myocardial infarction
MRI	Magnetic resonance imaging

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K.C. Ferdinand (ed.), *Hypertension in High Risk African Americans*, Clinical Hypertension and Vascular Diseases, DOI 10.1007/978-1-4939-2010-5_6

NHANES	National Health and Nutrition Examination Survey
RWT	Relative wall thickness
SPECT-MPI	Single-photon emission computed tomography–myocardial perfusion imaging
US	United States

6.1 Introduction

Cardiovascular disease—the leading cause of morbidity and mortality in the United States—is significantly more prevalent in black men and women compared with any other racial/ethnic group within the United States [1]. It is a major contributor to the reduced life expectancy observed in AAs [2]. Compared with any other race/ethnic group in the United States, AAs have the highest incidence of stroke, heart failure, sudden death, and CVD in general—with an earlier age of onset [3, 4]. Moreover, they exhibit the highest overall prevalence of hypertension and out-of-hospital coronary deaths, with highest mortality rates from hypertension, heart failure, stroke, and sudden cardiac death. It is noteworthy that the high rate of CVD and CHD observed in AAs appears to be out of proportion to risk burden, and various mechanisms have been proposed for this disparity.

Left ventricular hypertrophy is defined as increased LV mass. Specifically, the definition of LVH employs a categorical cut point, where LVH is defined as LV mass above the 97.5th percentile of the LV mass distribution in normotensive individuals [5]. Population studies from the 1960s were the first to link ECG-defined LVH with cardiovascular events [6, 7]. Since then, LVH has been shown to robustly predict CVD events [including myocardial infarction (MI), sudden death, stroke, congestive heart failure, and overall CVD mortality [8–10]], independent of traditional cardiovascular risk factors, including hypertension, diabetes, smoking status, and dyslipidemia [8, 11]. In addition, LVH is a major independent predictor of cardiovascular mortality, and AAs are known to have higher left ventricular mass compared with whites [12–14].

LVH by both ECG and echo is more prevalent in AAs compared with whites [12–14], and in AAs, LVH is an independent predictor of CHD/CVD survival [11, 13, 15] and appears to be more important than multivessel CAD and left ventricular systolic dysfunction in predicting survival in this population [13]. In children, AA race predicted LV mass independent of BMI [16]. Furthermore, LVH is an independent predictor of CHD/CVD survival in AAs [13, 15] and appears to be more important than single-vessel CAD, but similar to multivessel CAD in predicting survival in this population [13]. As such, LVH has been cited as a major player in black-white differential in CVD survival.

6.2 Mechanism of Left Ventricular Hypertrophy

LVH is an abnormal increase in the left ventricular myocardial mass and is usually caused by adaptation to chronically elevated workload on the heart. This elevated work load may result from increased afterload (as in aortic stenosis or chronic hypertension), which leads to concentric LVH, or volume overload (as in mitral or aortic regurgitation) leading to eccentric LVH [17, 18]. Coronary artery disease also leads to LVH as normal myocardium, in response to increased wall stress, attempts to compensate for ischemic or infarcted myocardial tissue. In essence, a large myocardial infarction leads to volume overload in the non-infarcted myocardium, leading to cardiac dilation with eventual increase in LV mass [18–20]. Nonetheless, both forms of LVH are usually accompanied by complex changes in genetic programming, including re-expression of immature fetal cardiac genes (e.g., those that encode energy or motor unit regulation and those that encode components of hormonal pathways, e.g., ANP or ACE) and variable/blunted expression of other genes [18]. This causes changes in signaling pathways, eventually leading to hypertrophy and increased connective tissue (particularly collagen) deposition, resulting in poor lusitropic function.

6.3 The Left Ventricular Hypertrophy Paradox

The LVH paradox [21] lies in the fact that increased LV mass is considered possibly as a response to greater workload associated with hypertension and a useful adaptation to chronic increase in myocardial stress. On the other hand, LVH appears to promote further CVD and is regarded as a powerful, independent risk factor for CV death. The proposed mechanisms for this paradox are the following [21, 22]: that LVH possibly integrates the effects of a myriad of factors integrated over time, that LVH is limited as an adaptive process and the initial advantages of parietal stress reduction are overridden with time by myocyte growth and chamber remodeling, and that there is a clear difference between the mechanisms of physiological and pathological LVH to begin with. The actual mechanism for this paradox remains to be fully elucidated.

6.4 Diagnosis of Left Ventricular Hypertrophy

The diagnosis of LVH can be made by ECG, echocardiography, or cardiac MRI. ECG as an LVH diagnostic modality (criteria shown in Table 6.1) has the advantage of being widely available and cheap with high specificity for LVH detection, but exhibits very poor sensitivity in the detection of LVH [17, 23]. The specificity of ECG diagnosis of LVH is about the same or higher in whites compared with AAs, but has

Table 6.1 Sensitivities and specificities for commonly used electrocardiographic criteria for the diagnosis of left ventricular hypertrophy in African Americans compared with the general population

Name	Criteria	Overall sensitivity	Overall specificity	Sensitivity in AAs	Specificity in AAs
Sokolow-Lyon voltage	SV1 + RV5/V6 ≥ 3.5 mV and/or RaVL ≥ 1.1 mV; sometimes ≥ 1.3 mV (13 mm) is used	26 %	92.6 %	36.7 %	86.8 %
Gender-specific Cornell voltage	SV3 + RaVL >2.8 mV (for men) and >2.0 mV (for women)	15.1 %	97.3 %	18.7 %	96.6 %
Romhilt-Estes point score[a]	Partition values ≥ 5 points (definite LVH) and ≥ 4 points (probable LVH)	5.7 % for definite LVH	99.1 % for definite LVH	7.3 % for definite LVH	98.8 % for definite LVH
Framingham ECG score	Presence of a strain pattern and at least 1 of the following voltage criteria: RI + SIII ≥ 2.5 mV, SV1/V2 + RV5/V6 ≥ 3.5 mV, the S wave on the right precordial lead ≥ 2.5 mV, and the R wave on the left precordial lead ≥ 2.5 mV	7 %	99.2 %	11.3 %	98.7 %
Left ventricular strain	Presence of isolated ST-T wave ischemic abnormalities as per Novacode 5.5 or 5.6	10.7 %	97 %	14.7 %	95.7 %
Cornell voltage product	(RaVL + SV3)*QRS duration ≥ 243,600 μVms	14.8 %	97.3 %	14.7 %	96.8 %
Sokolow-Lyon voltage product	(SV1 + RV5/RV6)*QRS duration ≥ 371,000 μVms	12.5 %	98.4 %	18.7 %	97.7 %

[a]Romhilt-Estes points: any limb R wave or S wave ≥ 2.0 mV (20 mm), 3 points; ST-T wave changes typical of LVH, 1 point if taking digitalis and 3 points if not taking digitalis; left atrial abnormality, 3 points; left axis deviation ≥ −30°, 2 points; QRS duration ≥ 90 ms, 1 point; intrinsicoid deflection in V5 or V6 ≥ 50 ms (0.05 s), 1 point

†Sensitivities and specificities determined from Jain et al. 2010 [27]

higher sensitivity in AAs likely due to higher LV mass indexes in those with LVH [24, 25]. Obesity appears to reduce the sensitivity of ECG-defined LVH [17, 23], in addition to fluid and air [17]. In general, the Sokolow-Lyon and 12-lead voltage criteria have been shown to overestimate, while the Cornell voltage has

underestimated the presence and severity of LVH in AA compared with white individuals [26]. ECG showed low sensitivity but high specificity for detecting MRI-defined LVH, with the highest sensitivity being observed in AAs compared with other racial/ethnic groups [27].

On the other end of the spectrum is cardiac MRI, described as the gold standard for the detection of LVH due to its high level of accuracy and reproducibility [17, 27]. The use of cardiac MRI for the detection of LVH is however limited to research purposes due to associated relative high costs and limited availability [17].

The most commonly employed modality and test of choice for the detection of LVH is echocardiography. This is widely available, is not too expensive, and has acceptable sensitivity and specificity for the detection of LVH relative to cardiac MRI and necropsy findings [17, 28]. This test uses the LV end-diastolic diameter, posterior wall thickness, and septal wall thickness in calculating LV mass. The resulting values can be indexed to body surface area or height in the determination of standardized LV mass values. The LIFE study proposed mass index cutoff values of >104 g/m^2 in women and >116 g/m^2 in men. The formula for calculation of LV mass by 2D echocardiography is

$$\mathrm{LVM} = 0.8 \times \left[1.04 \times \left(\mathrm{LVIDd} + \mathrm{LVPWT} + \mathrm{IVST} \right)^3 - \mathrm{LVID}^3 \right]$$

where LVIDd is LV internal diameter in diastole; LVPWT, LV posterior wall thickness; and IVST, intraventricular septal wall thickness.

LVH is further categorized by calculating the relative wall thickness of the LV by the formula (2 × PWTd)/LVIDd. Based on this formula, LVH is categorized as concentric LVH (increase in LV mass with RWT ≥0.42), eccentric LVH (increased LV mass with RWT ≤0.42), and concentric remodeling (normal LV mass with RWT ≥0.42) [29]. Normal LV mass is defined as LVM ≤95 g in females and ≤115 g in males. In actuality, the definition of LVH is dependent on the method by which LV mass is indexed—to body surface area, height^2 [21]. Using these LV mass cut points, a somewhat different classification of LVH was recently proposed: "eccentric non-dilated" (normal LVM/EDV and EDV), "eccentric dilated" (increased EDV, normal LVM/EDV), "concentric non-dilated" (increased LVM/EDV with normal EDV), and "concentric dilated" (increased LVM/EDV and EDV), and compared to patients with normal LV mass and non-dilated LV cavity [30]. For this study, the eccentric non-dilated group had higher LV stroke volume, Cornell voltage product, and systolic blood pressure, and were less likely to be AA [30].

6.5 Predictors of Left Ventricular Hypertrophy

The left ventricle grows from infancy to adulthood, although indexing LV mass for height improves cardiac risk prediction than body size indexes [31]. Sex also influences LV mass, in that post puberty, LV mass indexed to body surface area is about

10–20 % higher in men compared with women [32, 33]. Obesity, older age, systolic blood pressure [22], and preexisting CAD are strong and independent predictors of increased LV mass/LVH [34]. Of all these risk factors, obesity/increased BMI leads to increased relative wall thickness [35] and appears to be the strongest predictor of LV mass and LVH [35, 36]. Similarly, in a study of AA adolescents, elevated blood pressure and obesity were independent predictors of LVH [37]. In fact, using cardiac MRI for LVH diagnosis, the study by Drazner et al. showed that, at the highest levels of systolic blood pressure and BMI, BMI becomes as important as SBP being associated with significantly high prevalence of LVH. In the Bogalusa Heart Study, childhood obesity was the only consistent and significant determinant of LVH [38]. Other described predictors of increased LV mass include alcohol [21]. In the Framingham Heart Study, participants less than 30 years of age exhibited a 6 % LVH prevalence, compared with the 43 % prevalence in those 70 years of age or older [5]. Whether LVH results in heart failure independent of other mechanisms remains to be determined. Nonetheless, compared with patients who did not develop CHF, hypertensive patients who developed CHF were older, more likely to be black, current smokers, and diabetic [39].

6.6 Prevalence of Left Ventricular Hypertrophy

Irrespective of race/ethnicity, women generally have higher prevalence of LVH compared with men [23, 40]. In a meta-analysis of black and white men and women with hypertension, the overall prevalence of LVH was 35.6 % [41]. The prevalence of LVH diagnosed by echocardiography in the Framingham Heart Study (a population of white men and women) was 14.2 % in men and 17.6 % in women [23]. In the ARIC cohort of 1,616 black men and women, the prevalence was 39 % by conservative echocardiographic criteria for LVH (34 % concentric remodeling, 30 % concentric hypertrophy, and 12 % eccentric hypertrophy) [42]. In a population of 4,967 participants, the prevalence of LVH assessed by MRI was ~8 %. For this cohort, LVH was present in 39 % of AAs, compared with 26 % of white participants [27]. Another MRI cohort showed that LVH was 2–4 times more prevalent in AA than white men and women (depending of the definition of LVH) [40]. In the HyperGEN study which included 1,060 AAs and 580 whites with baseline hypertension, AAs were 1.8 times more likely to have LVH (indexed to height) and 2.5 times more likely to have LVH (indexed to BSA), compared to whites [43]. Nonetheless, other studies suggest that when indexed for body surface area, the prevalence of LVH defined by echocardiographic criteria is about the same in both races, although AAs have higher mean wall thickness values [35, 44]. This is particularly true in populations free of hypertension. In a population of young, healthy adults free of CVD or CVD risk factors, the prevalence of LVH was similar in white and AAs, although relative wall thickness was significantly greater in AAs relative to whites [45]. In another population of mildly hypertensive men and women (mean blood pressure 140/91 mmHg), LVH indexed to body surface area and height was

greater in women (20 % vs. 45 %) than men (13 % vs. 24 %), respectively. However, AAs had higher wall thickness but similar LV mass values compared with non-blacks [46]. Among hypertensive AA patients with kidney disease, the prevalence of echocardiographic LVH was as high as 69 % in the African American Study of Kidney Disease Cohort [25].

6.7 Markers of Left Ventricular Hypertrophy

LV mass and LVH appear to be influenced by genetic factors. Studies have shown that LVH predicted incident hypertension, independent of baseline blood pressure, in initially normotensive individuals free of other CVD/CVD risk factors [47, 48]. This suggests that the mechanism of LVH is likely not simply a structural adaptation to cardiovascular insults such as hypertension, but could rather represent a constellation of genetic adaptive changes. In general, monozygotic twins have significantly similar LV masses relative to dizygotic twins [49, 50]. In the Framingham twin studies, LV mass heritability ranged from 24 to 32 % [51]. In a study of 22 AA normotensive twin pairs, the intraclass correlation for monozygotic twins was 0.90 ($p<0.01$), while it was 0.33 ($p=$NS) for dizygotic twins, thus supporting the heritability of LV mass [50]. In fact, the genetic influence on LV mass appears to be more obvious in AAs relative to their white counterparts as was observed in the HyperGEN study which showed better sibling correlations of LV mass and geometry in hypertensive AAs more than whites [52]. In genome-wide association studies, certain single-nucleotide polymorphisms such as those linked with the ACE insertion/deletion polymorphism have been linked with LVH. In addition, prior linkage, candidate gene, and genome-wide association studies have identified certain LVH risk loci; but these only explain a fraction of the phenotypic variation associated with genetic risk of LVH [53–55]. One study of whole exon sequencing identified 5 genes as being associated with LV mass indexed to height. Of these, the THBS1, which encodes an adherence glycoprotein promoting matrix preservation in pressure overload LVH, showed 34 % expression in hypertrophied cells ($p=0.0003$), a variant of which was significantly associated with LV mass indexed to height ($p=4\times10^{-6}$) [56]. Nonetheless, the specific genes and functional variants contained in the chromosomal regions associated with LVH have not yet been identified [33].

Some studies have associated certain biomarkers with LVH. In the Dallas Heart Study of 2,413 participants, individuals with LVH who had either elevated troponin T or N-terminal proBNP had a greater than fourfold higher risk for heart failure or CV death after multivariable adjustment for CV risk factors, renal function, and LV mass, relative to those who had lower to normal levels of biomarker and without LVH [57]. After examining 39 candidate biomarkers, one of 1,193 blacks belonging to hypertensive sibships found higher circulating levels of natriuretic peptides, adrenomedullin, endothelin, and osteoprotegerin to be independently associated with increased LV mass, likely mainly due to their association with eccentric hypertrophy [58]. Serum troponin levels were not examined in this study.

6.8 Prognosis of Left Ventricular Hypertrophy

Patients with LVH have worse outcomes and prognosis, regardless of imaging modality employed in the diagnosis of LVH. ECG LVH provided the first insight into worsened prognosis of LVH, including heart failure, sudden death, and unrecognized myocardial infarction [59–61]. In one study of patients with LVH, black race was associated with 130 % increased risk of developing new heart failure relative to nonblack race [62]. In another predominantly AA population, LVH and hypertension were two independent factors associated with non-ST elevation myocardial infarction [63].

Data from the Framingham Heart Study showed that echocardiographically determined LVH is associated with increased risk of cardiovascular death (RR of 1.73 in men and 2.12 in women) and all-cause mortality (RR 1.49 in men and 2.01 in women) [8]. When compared by ethnic groups, the NHANES data showed that the adjusted hazard ratio for 10-year cardiovascular mortality was 2.30 in AAs, 2.11 in Latinos, and 1.42 in whites, while the 10-year total mortality was 1.41 in AAs, 1.15 in Latinos, and 1.19 among whites. This suggests higher rates of events among AAs relative to other ethnic groups [15]. In a predominantly black population, LV mass as estimated by echocardiography was a strong prognosticator, independent of ejection fraction and obstructive coronary disease [64]. In general, black race is associated with greater relative wall thickness which by itself carries a bad prognosis for worsened CV outcome [35]. LVH has also been associated with higher risk of strokes [44].

Among patients with LVH, worsened prognosis was observed among those with CAD and [65] concentric LVH [66]. Concentric LVH has been shown to be more prevalent in AAs and is associated with worse prognosis [67]. In one study of black participants, LVH independently accounted for 37 % of the attributable risk fraction for death, while the attributable risk fractions were 1 %, 22 %, and 9 % for single-vessel disease, multivessel disease, and ventricular dysfunction, respectively [13]. On the other hand, LVH regression by ECG or echocardiographic criteria has been associated with improved cardiovascular outcomes [68–70].

6.9 Left Ventricular Hypertrophy and Testing for Coronary Heart Disease

6.9.1 Nuclear Imaging and Stress

Some prior studies have suggested false-positive perfusion defects (particularly in the anterior and inferior walls of the left ventricle) with SPECT-MPI perfusion imaging [71], while other studies have disputed this information [72]. However, myocardial SPECT has been shown to accurately prognosticate the risk of cardiac events in patients with LVH beyond their clinical and historical variables [73] and is

also able to differentiate LVH from normal geometry in participants free of myocardial ischemia [74]. In one study [75], LVH increased the specificity of TID for severe CAD, relative to those without LVH. In patients with severe CAD, LVH had an additive influence on the incidence of TID and increased the incidence from 21 % without LVH to 75 % with LVH ($p < 0.006$) [75].

6.9.2 Subclinical Atherosclerosis

LVH has been shown to be significantly positively associated with CAC score in AAs, but not whites [76]. In another study of white and black young adults from the Bogalusa Heart Study [77], LVH was shown to be associated with widened pulse pressure, increased arterial stiffness, and decreased arterial compliance. Increased LV mass has been significantly associated with increased carotid IMT in various studies [78–80] and also associated with carotid plaque formation and progression [81]. The LVH pattern associated with increased IMT is usually concentric [82]. This is the same pattern that is more prevalent in AAs and associated with worsened prognosis.

6.9.3 Echo and Stress Echo

In a population of patients with CAD, wall motion abnormalities occurred less frequently in those with LVH (odds ratio for normal wall motion is 2.86), compared with individuals with normal LV wall thickness [83]. Conversely, another study showed that the sensitivity and specificity of stress echo for the diagnosis of CAD was similar in participants with LVH as in those without LVH [84, 85]. When broken down by LVH subtypes however, stress echo demonstrated lower sensitivity for the diagnosis of LVH in participants identified as having concentric LVH [85]. In a study of 548 AA patients, LVH was an independent predictor of cardiovascular events in AA patients with a normal stress echo [86].

6.10 Management of Left Ventricular Hypertrophy

LVH appears to respond reasonably well to therapy—the goal of therapy being the treatment of the underlying condition, particularly hypertension. To this end, a small study of 309 urban AA men showed that intense antihypertensive therapy was linked to lower LV mass at 36 months of follow-up, compared with less intense blood pressure treatment [87]. Furthermore, a regression in LV mass was observed for previously untreated hypertensive blacks who underwent effective antihypertensive therapy over a period of 12 months [88]. More recently, a study of 103

persons of African descent showed reductions in LV mass index ($p<0.01$) and relative wall thickness ($p<0.05$) with 13 months of therapy targeting 24-h blood pressure control [89].

Nevertheless, the most effective treatment modality to cause LVH regression in blacks remains in question. A meta-analysis of 80 studies examining different treatment modalities on regression of LVH showed that ARBs were the most effective medications for LVH regression with a 13 % decrease in LV mass, after adjustment of treatment duration. Furthermore, calcium channel blockers reduced LV mass by 11 %, ACE inhibitors by 10 %, diuretics by 8 %, and beta blockers by 6 % [90]. These findings are not necessarily surprising given that the renin-angiotensin-aldosterone hormonal axis has been implicated in the pathway for fibrosis in patients with LVH. Unfortunately, the number of AAs included in the meta-analysis and the proportion with significant response to the therapy described were not noted in this study.

Treatment of LVH has also been linked to improved cardiovascular outcome. To this end, the LIFE study showed that the treatment of hypertension, with resulting ECG LVH regression and reduced LV mass by echocardiography, were each associated with significant reductions in cardiovascular mortality, myocardial infarction, and stroke, irrespective of the blood pressure achieved and treatment modality employed [70, 91]. This suggests a possible role for the treatment of blood pressure with the goal of LVH regression on ECG or LV mass decrease on echocardiography, similar to the use of hemoglobin A1c to target diabetes treatment [17]. On the other hand, a LIFE sub-study of CV risk reduction in hypertensive black patients with LVH showed that while there was no substantial difference between atenolol and losartan in blood pressure control among black patients, atenolol was more effective at CV risk reduction and losartan caused more ECG-defined LVH regression in these patients [92].

6.11 Conclusions

Left ventricular hypertrophy is an important and independent predictor of cardiac events. In African Americans, the prevalence of LVH is higher and carries a worse prognosis. Since African Americans are also more prone to adverse events from CVD, it stands to reason that LVH has a possible role to play in the higher prevalence of cardiovascular events in this population. One study has examined this possibility for CHD and has found that LVH does not predict coronary events beyond traditional cardiovascular risk factors in African Americans compared with their white counterparts [93]. Nonetheless, current data are inconclusive as to whether LVH leads to systolic heart failure, partly because the incidence of systolic heart failure in AAs with preexisting hypertension is not known. Whether LVH predicts CVD risk as a whole in African Americans relative to whites also remains to be determined. Identification of specific genetic variants associated with LVH in African Americans might play a role in enabling this risk prediction. In any case,

clinicians should be aware of the importance of LVH as a valuable prognostic tool in African Americans (as well as persons of other races) and the associations with significant improvement in prognosis with LVH regression. This suggests that clinicians could possibly regard LVH as an indispensable risk marker for cardiac disease identification and its regression as a useful treatment goal linked to better prognosis.

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Chapter 7
Heart Failure Morbidity, Mortality, and Its Relationship to Hypertension

Elizabeth O. Ofili, Rigobert Lapu Bula, Adesoji Oderinde, and Adefisayo Oduwole

7.1 The Burden of Heart Failure: A Growing Cardiovascular Diagnosis with Persistent Disparities

Heart failure (HF) remains a significant cardiovascular problem, with increasing incidence and prevalence rates: Adult Americans over 40 years of age have a 20 % lifetime risk of developing heart failure [1, 2]. Approximately five million people in the USA have HF, and over 650,000 new cases of HF are diagnosed each year [3–5]. HF incidence increases with age: from 20 per 1,000 among individuals 65–69 years of age to greater than 80 per 1,000 for individuals who are over 85 years of age [4].

Hospitalization for HF is a major contributor to poor cardiovascular outcomes and economic burden of the disease: HF is the primary diagnosis in over one million hospitalizations annually [3]. Patients hospitalized for HF are at high risk for rehospitalization, with a 30-day readmission rate of 25 % [6]. The total cost of HF care in the USA exceeds $30 billion annually, with over half of these costs spent on hospitalizations [3]. Costs for HF has consumed 5.4 % of the US healthcare budget, since 1991. HF is the most common Medicare diagnosis-related group (DRG) and accounts for more Medicare dollars spent compared to other diagnoses [3, 7]. These numbers and costs are expected to grow considerably, since 1 in 5 Americans will be >65 years of age by 2050, and HF prevalence is highest in this age group [8].

The absolute mortality rates for HF remain high, at 50 % within 5 years of diagnosis. The rate of sudden cardiac death in HF patients is 6–9 times the rate of the general population [9–12].

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K.C. Ferdinand (ed.), *Hypertension in High Risk African Americans*, Clinical Hypertension and Vascular Diseases, DOI 10.1007/978-1-4939-2010-5_7

There are persistent disparities in the epidemiology and mortality of HF: Blacks have the highest risk for HF; HF affects approximately 3 % of the black population in the USA compared to 2 % of nonblacks [13, 14]. In the Atherosclerosis Risk in Communities (ARIC) population study, white women had the lowest incidence, and black men had the highest incidence of HF, per 1,000 person-years. Similarly prevalence of HF is much higher among blacks, compared with whites: 4.5 % and 3.8 % for black men and women respectively, compared with 2.7 % and 1.8 % for white men and women. Blacks in the ARIC study have a greater 5-year mortality rate than whites [14].

7.2 Hypertension and Comorbid Risk Factors Have a Causal Role in Heart Failure Morbidity and Mortality

Data from ARIC and other longitudinal cohort studies have demonstrated that the duration and severity of hypertension correlate with HF incidence: For example, in the Framingham study, the cumulative incidence of HF over 15 years was three and six times higher in individuals with stages 1 and 2 hypertension, respectively, compared to those with normal blood pressure [9, 10].

A review of several major HF clinical trials (V-HeFT I, V-HeFT II, SOLVD, US Carvedilol, BEST, MERIT-HF) revealed divergence in the underlying etiology of left ventricular dysfunction (LVD) by race: Hypertension-based HF was documented in 50–80 % of blacks enrolled in these clinical trials, compared with 40–50 % of nonblacks. Coronary artery disease (CAD) was more prevalent among nonblacks (50–80 %), compared with 40–50 % prevalence rate for blacks that were enrolled in these HF clinical trials [15, 16].

In an analysis of 1,200 patients hospitalized over a 12-month period in a large urban teaching hospital serving predominantly black patients, we found over 98 % prevalence rate of hypertension, with 59 % having poorly controlled blood pressure (over 140/90 mmHg at the time of heart failure hospitalization). Comorbid risk factors contributing to recurrent hospitalization in this patient population include left ventricular hypertrophy (61 %), CAD (52 %), and diabetes (42 %) [17].

As is the case for US blacks, hypertension contributes to HF morbidity in sub-Saharan Africa. The Sub-Saharan Africa Survey of Heart Failure (THESUS-HF) was a prospective, multicenter, observational survey of 1,006 patients with AHF admitted to 12 university hospitals in 9 countries. Hypertension was the predominant risk factor for acute decompensation and was prevalent in 45 % of black African patients [18].

In addition to the high prevalence of hypertension noted in numerous HF registries, there is an alarming trend showing high rates of obesity among HF patients [19, 20]. The disproportionate burden of hypertension, obesity, and diabetes among blacks are likely significant contributors to HF disparities [17].

7.3 From Hypertension to Heart Failure: A Structural and Functional Cardiovascular Continuum

HF is a heterogeneous clinical syndrome that can result from any structural or functional disorder that impairs the contractile function of the heart. The diagnosis of HF is made when structural or functional impairment of ventricular filling or ejection of blood is accompanied by the clinical syndrome of dyspnea and fatigue with or without fluid retention. A wide spectrum of LV functional abnormalities is seen in heart failure, ranging from normal LV size and preserved ejection fraction (EF) to severe LV dilatation, with or without markedly reduced EF. EF provides a framework for HF classification; most clinical trials select patients based on EF: HFrEF (HF-reduced EF) refers to HF with EF less than 40 %. Patients with HFrEF have been most well studied in clinical trials and there are evidence-based therapies for HFrEF [1]. HF-preserved EF (HFpEF) describes the syndrome of HF accompanied by EF over 40 % and is usually associated with diastolic dysfunction as measured by echo Doppler indices. This group likely represents a heterogeneous patient population, with varying responses to evidence-based therapies. There remains a significant therapeutic gap, with virtually no outcome-driven evidence-based therapy for HFpEF [1].

The structural and functional progression from hypertension to heart failure may represent a continuum that is characterized by varying degrees of cardiovascular remodeling, including LV hypertrophy, with or without cardiac enlargement, and with preserved or reduced EF [21–26].

HF has long been considered to be an advanced stage of a progressive deterioration in myocardial function that occurs over many years after the initial insult to the heart. The presence of comorbid conditions such as CAD, hypertension, obesity, and diabetes may accelerate remodeling and progressive LV dysfunction [17]. There appears to be a variable period of latent remodeling of the myocardium, the coronary arteries, and the microvasculature, during which patients are generally asymptomatic [21, 22].

Early in the course of hypertensive heart disease, hemodynamic and neurohormonal compensatory mechanisms enable the hypertrophic myocardium to maintain a normal cardiac output. Over time, myocardial pressure/volume loop shifts to a less efficient curve, leading to progressive diastolic filling abnormality and increased left ventricular diastolic pressure. Persistent neurohormonal and beta-adrenergic activation lead to increased salt and water retention, increased systemic vasoconstriction, progressive cardiovascular remodeling, and, eventually, symptomatic HF [21–26]. Patients may move between these structural and functional stages with treatment or clinical deterioration.

In addition to the renin-angiotensin-aldosterone (RAAS) and beta-adrenergic systems, nitric oxide plays an important role in cardiovascular remodeling. Nitric oxide (NO) is an endogenous vasodilator produced by the endothelium in epicardial vessels as well as the coronary microvasculature. NO also modulates cell growth (hypertrophy) and postinfarction remodeling [27–30]. Hypertension and comorbid

risk factors in hypertensive heart disease, promote oxidative stress, through superoxide production and reactive oxygen species (ROS). In the presence of superoxide and other ROS, NO is converted to peroxynitrite, which impairs relaxation of the endothelium, leading to endothelial dysfunction [29]. The relative contribution of RAAS and NO in the structural and functional remodeling in HF, has implications for therapeutic approaches [30].

7.4 Nitric Oxide-Mediated Hypertrophy and Microvascular Dysfunction: An Intermediate HF Penotype? [31–33]

In order to further elucidate the pathophysiology of nitric oxide-mediated vascular remodeling in hypertension, we studied a population-based cohort of African-American hypertensives: We performed brachial artery ultrasound and flow-mediated dilation (FMD) in 187 patients with hypertension (mean age 49 years) and 132 race-matched subjects without hypertension (mean age 45 years). We observed a reduction in FMD in African-Americans with hypertension consistent with impaired endothelial function. We found that the mean FMD was lower in those with hypertension, 7 % (range 5–19 %), compared with participants without hypertension, 16 % (range 5–28 %; $p<0.001$). After controlling for age, FMD inversely correlates with systolic blood pressure ($r=0.29$, $p<0.001$), diastolic blood pressure ($r=0.35$, $p<0.002$), and mean blood pressure ($r=0.40$, $p<0.0001$) [31, 32]. These studies represent the largest population-based sample of African-Americans with carefully phenotyped FMD indices of endothelial function (ref AJC). We further explored the possible link between endothelium-dependent vasodilatory function and hypertension-induced left ventricular remodeling (LVH). Hypertensive subjects with LVH had lower FMD compared with those without LVH (5.4 % vs. 12.8 %, $p<0.01$). Furthermore, the presence of concentric LVH identified the group with the lowest FMD consistent with marked impairment in vascular endothelial function [32, 33].

Using myocardial contrast echocardiography and dipyridamole infusion as a vasodilator, in a subset of participants, we examined the coronary vasodilatory flow reserve by measuring the ratio of myocardial subendocardial to subepicardial flow (a flow ratio less than 1.0 suggests myocardial ischemia). LVH was associated with reduced myocardial flow ratio: 0.9 compared with 1.4 in participants without LVH. Although not statistically significant, this finding is consistent with abnormal coronary vasodilatory flow reserve and microvascular dysfunction. These findings also suggest that nitric oxide deficiency and abnormal nitroso-redox balance may play a critical and ongoing role in the progressive remodeling of LV dysfunction, including hypertensive heart disease. LVH with associated NO-mediated microvascular dysfunction may therefore represent an intermediate phenotype in the continuum from hypertension to heart failure [32, 33].

7.5 Hypertensive Heart Disease and LVH Are Associated with Non-Q Wave Myocardial Infarction in Patients Who Are Hospitalized with Acute Chest Pain Syndromes and Found to Have Normal Coronary Arteries [34]

In a retrospective analysis of 700 patients (75 % African-Americans) undergoing cardiac catheterization for the evaluation of acute chest pain and suspected myocardial ischemia, we identified 179 patients who had normal coronary arteries or only luminal irregularities (less than 10 % luminal obstruction). The presence of LVH on echocardiography and uncontrolled hypertension were important predictors of acute Myocardial infarction (MI) in this cohort. Acute MI occurred in 17 of 88 (19 %) patients with LVH compared with none of the 28 patients without LVH ($p < 0.02$). The mean systolic blood pressure was significantly higher in patients with acute MI compared with the nonacute MI group ($p < 0.03$). Other clinical variables, such as diastolic blood pressure, cigarette smoking, and a history of hypertension, were not predictive of acute MI.

These data further suggest that the hypertensive phenotype characterized by LVH predisposes to acute myocardial ischemia, even in the absence of significant epicardial CAD, presumably due to nitric oxide-mediated microvascular dysfunction and subendocardial ischemia. These clinical data support the potential NO-mediated mechanism identified in our population-based cohort studies described in the preceding section, as well as other clinical and laboratory studies of remodeling in hypertension, progressive LV dysfunction, and HF. [35, 36]

7.6 Implication of NO-Mediated LV Remodeling in the Therapeutic Approach to HF in African-Americans: The African-American Heart Failure Trial (A-HeFT) [37, 38, 42]

Retrospective analysis of HF studies using the combination of isosorbide dinitrate and hydralazine in patients with HFrEF in Veterans Administration Heart Failure Trial (V-HeFT) I and V-HeFT II suggested benefits in blacks; however, the findings were not conclusive [39–41].

The African-American Heart Failure Trial (A-HeFT) was designed to test the hypothesis that correction of NO bioavailability, using a combination of fixed-dose hydralazine and isosorbide dinitrate (FDC HYD/ISDN), will improve HF outcomes among self-identified African-American patients. A-HeFT enrolled 1,050 patients with NYHA Class III–IV HF receiving optimized guideline-based care, including BBs, ACE-Is, and/or ARBs. Participants were randomized in a double-blind protocol to FDC HYD/ISDN vs. “placebo”; the placebo arm was optimized neurohormonal therapy and standard HF care. Indeed the “placebo” arm of A-HeFT received

the highest rates of evidence-based therapy of any HF trial: diuretics, 90 %; ACE inhibitors, 70 %; ARBs, 17 %; beta-blockers, 74 % (carvedilol, 56 %); digoxin, 60 %; and spironolactone, 39 %. The primary outcome of A-HeFT was a composite score of mortality, hospitalization, and quality of life (QOL). The survival benefit of FDC HYD/ISDN over "placebo" led to early termination of the study after only 3 years. With a median follow-up period of 10 months, FDC HYD/ISDN in combination with neurohormonal blockade reduced mortality by 43 %. The first hospitalization for HF was a component of the primary composite score in A-HeFT. Over an average follow-up period of 10 months (range, 0–18), 215 patients were hospitalized—130 patients (24.4 %) in the placebo group and 85 (16.4 %) in the FDC HYD/ISDN group ($P=0.001$). The risk of first HF hospitalization was reduced by 39 % with FDC HYD/ISDN compared to placebo (hazard ratio 0.61, 95 % confidence interval 0.46–0.80, $P<0.001$). The treatment effect appeared early, approximately 50 days after starting treatment when no mortality difference was seen, and remained significant throughout the study. A similar beneficial effect of FDC HYD/ISDN was observed in all the subgroups analyzed including age (younger or older than 65 years), gender, ischemic HF etiology, baseline blood pressure (systolic BP >126 mmHg or <126 mmHg), presence of diabetes mellitus, history of chronic renal insufficiency, and baseline medication usage.

The findings were very impressive and unprecedented in a HF trial, particularly considering that the "placebo" arm was very well treated and optimized on standard therapy.

The findings on hospitalization and health-related quality of life (HRQOL) are especially relevant to current efforts to reduce health resource utilization; [44] in addition to costs to the healthcare system, HF rehospitalization exerts a tremendous toll on HRQOL [45–47]. On average, HF patients have a 30-day readmission rate of 25 %. HF thus commonly leads to a revolving door of rehospitalizations and progressive deterioration of HRQOL [45–47]. In A-HeFT, adding FDC HYD/ISDN to standard therapy improved HRQOL based on the Minnesota Living with Heart Failure (MLHF) questionnaire [38]. Currently approved HF medications such as ACE-Is, ARBs, and beta-blockers have not shown similar outcomes for HRQOL. Other than FDC HYD/ISDN, the only other evidence-based therapies shown to improve HRQOL are cardiac resynchronization therapy (CRT) and certain disease management and educational approaches [1].

7.7 Do the Clinical Outcomes Observed in A-HeFT Support Potential Benefit of FDC HYD/ISDN in HFrEF, Regardless of Race?

A-HeFT survival curves were similar for both treatment and placebo cohorts until approximately 6 months [38], possibly indicating that progressive LV remodeling is a significant factor underlying death and hospitalization in the placebo group. Subsequently, an echocardiographic sub-analysis of the A-HeFT population

determined that FDC HYD/ISDN therapy improved LV structure and function [43]. Echocardiographic data and blood BNP levels were obtained at baseline and 6 months after randomization. Measurements of LVEF ($n=666$) and LV internal dimension at end-diastole (LVIDD, $n=678$) were available at baseline and at 6 months. All echocardiograms were analyzed by the same cardiologist in blinded fashion. Although equivalent at baseline, by 6 months, mean LVEF was significantly increased with FDC HYD/ISDN ($P=0.0025$ vs. placebo) and LVIDD significantly decreased ($P=0.0062$). Mean changes in LVEF and LVIDD from baseline to 6 months were also significantly greater with FDC HYD/ISDN ($P=0.0025$ and $P=0.0062$ vs. placebo). Mean BNP was significantly decreased after 6 months' therapy with FDC HYD/ISDN ($P=0.005$ vs. placebo), and the mean decrease in BNP at month 6 was also significantly greater ($P=0.05$), consistent with a sustained, favorable effect on LV structure and function. The echocardiographic substudy of A-HeFT confirmed that the effect of FDC HYD/ISDN on LV remodeling was the likely mechanism of the mortality, hospitalization, and HRQOL benefits shown in A-HeFT. These conclusions were further bolstered by a separate analysis that evaluated A-HeFT outcomes by baseline blood pressure [48]. A-HeFT participants with baseline systolic blood pressure (SBP) equal to or below the median (126 mmHg) had features of more severe HF. Baseline SBP equal to or below the median was an independent risk factor for death (hazard ratio [HR] 2.09; 95 % confidence interval [CI] 1.02–4.29) or first hospitalization for HF (HR 1.66; 95 % CI 1.18–2.34). These latter findings are consistent with worse HF and more extensive remodeling in A-HeFT participants with systolic blood pressure (SBP) below the median. FDC HYD/ISDN treatment was associated with a 67 % decrease in mortality in participants with SBP below the median (HR 0.33, 95 % CI 0.13–0.85) and a 48 % decrease in mortality in participants with an SBP above the median (HR 0.52, 95 % CI 0.15–1.80) (interaction $p=0.59$). Similarly, the effects of FDC HYD/ISDN on mortality or first hospitalization for HF in participants with SBP below the median (HR 0.61, 95 % CI 0.39–0.92) and above the median (HR 0.60, 95 % CI 0.35–1.02) did not differ (interaction $p=0.98$).

These findings suggest that HF patients with an extensive remodeling phenotype, similar to participants in the A-HeFT study, could potentially benefit from FDC HYD/ISDN added to optimized standard therapy.

7.7.1 Ten Years After A-HeFT: Persistent Underutilization of FDC HYD/ISDN in Eligible Patients with HF

The findings and the weight of the evidence support the clinical use of FDC HYD/ISDN in the care of patients with symptomatic HF. Based on the results of A-HeFT, the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines recommend hydralazine and isosorbide dinitrate in addition to standard therapy for African-Americans with HFrEF currently receiving ACE-Is and BBs (Class I, Level A) and for patients with HF who are unable to tolerate ACE-Is and ARBs (Class IIa, Level B) [1].

Despite the impressive clinical trial evidence and strong guideline recommendation, the combination of hydralazine and isosorbide dinitrate therapy remains woefully underutilized in eligible black patients with HF. The potential morbidity and mortality costs of such underutilization are best reflected in comparing current HF therapies using the "number needed to treat" in order to prevent cardiac events: ACE-Is and ARBs are guideline-recommended treatment for heart failure, and the relative risk reduction (RRR) in mortality is 17 % with a number needed to treat (NNT) for 36 months of 26. For BBs, the RRR is 34 % and the NNT is 9, and for FDC HYD/ISDN the RRR is 43 % and the NNT is 7 [49]. In the OPTIMIZE-HF study, 5,108 black patients hospitalized with HF and an EF <40 %, only 4.5 % of eligible patients were prescribed nitrates and hydralazine at hospital discharge [50]. In a study including 17,775 black patients hospitalized with HF, only 26.4 % were treated with nitrates and hydralazine [51].

In a more recent observational study, analysis of 54,622 patients admitted with HFrEF and discharged home from 207 hospitals participating in the Get With The Guidelines (GWTG)–Heart Failure registry from April 2008 to March 2012 was conducted to assess prescription, trends, and predictors of use of combination hydralazine and isosorbide dinitrate among eligible patients [52]. Among 11,185 African-American patients eligible for combination hydralazine and isosorbide dinitrate therapy, only 2,500 (22.4 %) received the therapy at discharge. In the overall eligible population, 5,115 of 43,498 (12.6 %) received combination hydralazine and isosorbide dinitrate at discharge. Treatment rates increased over the study period from 16 to 24 % among African-Americans and from 10 to 13 % among the entire HFrEF population. Considering that this latter analysis involved participating hospitals in the GWTG-HF registry, who are more likely to optimize care based on the hospitals' investments in GWTG tools, it is very unlikely that other hospitals across the country would approach this level of utilization of combination hydralazine and isosorbide dinitrate in eligible patients. Data from the IMPROVE-HF study in outpatient cardiology practices treating patients with HF supports this conclusion: The median use of nitrates and hydralazine in black patients with reduced EF was 0 % and the mean was 7.3 % [53].

Together, these findings show that 10 years after A-HeFT, the use of FDC HYD/ISDN in eligible patients with HFrEF remains substantially low during hospitalization, low in the transition from the hospital to the outpatient setting, and low during longitudinal follow-up in outpatient practices.

More importantly in patients without prior FDC HYD/ISDN therapy, only 8.5 % had the therapy initiated during the hospitalization, and only 3.6 % had the therapy initiated at the time of discharge. The opportunity and strategy to initiate FDC HYD/ISDN therapy in eligible patients during hospitalization or at the time of discharge is likely to result in increased utilization, as has been shown for other cardiovascular therapies such as lipid lowering therapies in acute coronary syndromes.

If the currently untreated patients in the current patient population with HF eligible for treatment with FDC HYD/ISDN were treated, more than 6,650 lives could potentially be saved each year [49]. Potential strategies to increase utilization of evidence-based HF treatments include educational outreach focused on ACGME

training programs and expansion of hospitals participating in GWTG. Incorporation of treatment with FDC HYD/ISDN as a core performance measure for HF [54], with appropriate documentation of contraindication for its use as well as further educating primary care physicians and cardiologists, might help to bridge this persistent and substantial gap between the evidence base and clinical practice of clinical use of FDC HYD/ISDN in African-American patients with HFrEF.

7.8 Conclusion

Heart failure continues to exert a clinical and economic burden on patients, the health system, and society. As the population continues to age, heart failure can be expected to exert an even greater toll on the quality of life of affected patients and their families. As a critical call to action, the cardiology community must address the substantial gap between clinical practice and the evidence base for heart failure care, especially among African-American patients who continue to suffer a disproportionate burden of mortality, morbidity, and worse HRQOL.

Acknowledgement Dr Ofili is supported by the National Institutes of Health, Grant Numbers: U54MD008149; 8 U54 MD007588; U54MD008173; and U54MD008173 from the National Institute on Minority Health and Health Disparities (NIMHD) and Grant Number UL1TR000454 from the National Center for Advancing Translational Sciences (NCATS) of the National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health (NIH) NIMHD or NCATS.

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Chapter 8
Hypertension and Atrial Fibrillation in African Americans

Elsayed Z. Soliman and Ronald J. Prineas

8.1 Epidemiology of Atrial Fibrillation (AF) in Blacks

8.1.1 Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice. Over 2.3 million adults in the USA have AF, and the number is expected to more than double in the next few decades [1]. Approximately two-thirds of all emergency department visits with a primary diagnosis of AF result in hospital admissions, and 35 % of all hospital admissions for arrhythmia are attributable to AF [2, 3]. During the past 20 years, hospital admissions for AF have increased by 66 % [4]. The high healthcare resource utilization rates of AF patients have imposed a substantial cost burden on the healthcare system. In 2001, the total annual costs for treatment of AF were estimated at US$6.65 billion [5]. Planning and budgeting for future healthcare expenditure imposed by AF require clear understanding of the epidemiology of AF in the rapidly growing nonwhite races/ethnicities in the USA.

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K.C. Ferdinand (ed.), *Hypertension in High Risk African Americans*, Clinical Hypertension and Vascular Diseases, DOI 10.1007/978-1-4939-2010-5_8

8.1.2 Atrial Fibrillation in Blacks vs. Whites

The few studies which addressed the risk of AF in blacks vs. whites consistently suggest that blacks have lower prevalence/incidence of AF compared to whites.

In the Cardiovascular Health Study (CHS) [6], 5,201 adults ≥65 years old (≈95 % white, 5 % African American) were examined annually on four occasions between June 1989 and May 1993. Participants with a pacemaker or AF at baseline ($n=357$) were excluded. New cases of AF were identified from three sources: annual self-reports, annual ECGs, and hospital discharge diagnoses. Among 4,844 participants, 304 developed a first episode of AF during an average follow-up of 3.28 years, for an incidence of 19.2 per 1,000 person-years. The incidence was slightly lower in blacks than in whites (12.0 vs. 19.5 per 1,000 person-years, respectively; $P>.10$). In a multivariate Cox proportional hazards model including age and traditional cardiovascular risk factors, black race was associated with lower risk of incident AF (HR (95 % CI), 0.47 (0.22, 1.01)) compared with white race. This relationship was stronger in participants without cardiovascular disease at baseline (HR (95 % CI), 0.21 (0.05, 0.86)).

Data from the Atherosclerosis Risk in Communities (ARIC) Study confirm the CHS results. ARIC investigators [7] studied the incidence of AF in 15,792 (≈27 % blacks) men and women 45–65 years of age at baseline from four communities in the USA since 1987. AF cases were identified from electrocardiograms (ECGs) conducted at baseline and three follow-up visits and from hospitalizations and death certificates through the end of 2004. During follow-up, 1,085 new cases of AF were identified (196 in blacks, 889 in whites). Crude incidence rates of AF were 6.7, 4.0, 3.9, and 3.0 per 1,000 person-year in white men, white women, black men, and black women, respectively. Compared to whites, blacks had a 41 % (95 % CI, 8–62 %) lower age- and sex-adjusted risk of being diagnosed with AF. The cumulative risk of AF at 80 years of age was 21 % in white men, 17 % in white women, and 11 % in black men and women.

Other data sources further support a lower rate of AF in blacks compared to their white counterparts. A cross-sectional study of 1.89 million (≈85 % whites, 4 % blacks) adults aged 20 years or older who were enrolled in a large health maintenance organization in California confirms that AF is more common in whites. Among persons aged 50 years or older, prevalence of AF was higher in whites than in blacks (2.2 % vs. 1.5 %; $P<.001$). In this study, AF prevalence was ascertained using hospital and outpatient diagnosis codes and an ECG database [1].

In the US National Hospital Ambulatory Medical Care Survey, rates of visits to an emergency department with AF as the primary diagnosis were higher in whites than in blacks (9 vs. 5 per 10,000 person-years) [8]. The National Hospital Discharge Survey, which compiles data on discharges from nonfederal hospitals in the USA, also shows a higher incidence of AF hospitalizations in whites than in blacks [9].

This pattern of racial/ethnic difference in the incidence of AF has been also evidenced in patients with heart failure [10], stroke [11], and patients attending general practice clinics [12]. In the Evaluating Processes of Care and the Outcomes of

Children in Hospital (EPOCH), blacks had a 50 % lower prevalence of AF than whites even after adjustment for known risk factors for AF [10]. Also, in the Northern Manhattan Stroke Study, of those patients presenting with ischemic stroke, AF was more common in whites (29 %) than in blacks (11 %) [11].

In a large study of 664,754 US veterans [13], the prevalence of AF (based on data from hospital discharges and outpatient clinic visits) was 5.7 % in whites, 3.4 % in blacks, 3.0 % in Hispanics, 5.4 % in native Americans/Alaskans, 3.6 % in Asians, and 5.2 % in Pacific Islanders ($p<0.001$). Racial/ethnic differences remained after adjustment for demographic and clinical characteristics. The major limitation of this study was that it included only males.

In the Southern Community Cohort Study (SCCS) which included participants aged >65 years receiving Medicare coverage from 1999 to 2008 ($n=8,836$), AF was diagnosed in 1,062 participants over an average of 5.7 years of Medicare coverage. AF prevalence was significantly lower among blacks (11 %) than whites (15 %) ($p<0.0001$). Odds ratios for blacks compared to whites persisted after adjustment for AF cardiovascular risk factors (odds ratio 0.64, 95 % confidence interval 0.55–0.73) [14].

A meta-analysis that included ten studies totaling 1,031,351 participants, including some of the studies as noted earlier, demonstrated that African American race/ethnicity was associated with less AF prevalence as compared to Caucasian race (odds ratio 0.51, 95 % CI 0.44 to 0.59). In subgroup analyses, African American race/ethnicity was significantly associated with a lower prevalence of AF in the general population, those hospitalized or greater than 60 years old, postcoronary artery bypass surgery patients, and patients with heart failure [15].

8.1.3 Methodological Considerations in the Estimated Black/White Differences in AF

The racial/ethnic distribution of AF should be interpreted in the context of the limited methodology to detect AF as well as the untested assumption that the ability to diagnose AF is similar across different racial/ethnic groups.

Previous studies used self-report and/or short-term ECG recording for AF ascertainment and, very infrequently, a 24-h ambulatory ECG (Holter) recording. All have limitations in detection of AF cases. These "unavoidable" limitations are mainly related to certain inherent characteristics of AF that make accurate AF ascertainment difficult. AF is often asymptomatic. As many as 30 % of AF patients are unaware of their condition [16], and 25 % of those with AF-associated stroke have no prior diagnosis of AF [17, 18]. These observations support the contention that self-report has low sensitivity to detect AF. Additionally, the fibrillation pattern is paroxysmal in 30 % of patients with stroke and may not appear in a single ECG recording [17–19]; hence, the sensitivity of short-term ECG recording is also low. Twenty-four-hour Holter monitoring enables detection of previously unrecognized AF in 2 % of stroke patients, a higher proportion than detected using a standard

12-lead ECG. Furthermore, extending the ECG recording time from 24 to 72 h increases the detection of paroxysmal AF in stroke patients from 1.2 to 6.1 % [18–22]. Although using long-term ECG recording would provide better prevalence/incidence estimates, cost and complexity have been obstacles to use of Holter monitoring in large epidemiologic studies.

8.2 Hypertension and Atrial Fibrillation

8.2.1 Hypertension and Other AF Risk Factors in Blacks and Whites

There are well-defined risk factors identified repeatedly for association with prevalent AF and prediction of incident AF, with hypertension being the always included AF risk factor and predictor.

The main risk factors identified to date include hypertension, systolic blood pressure, age, male sex, prolonged PR interval, and heart failure identified in combining three cohorts from the CHS, the Framingham Heart Study (FHS), and the Age, Gene/Environment Susceptibility-Reykjavik (AGES) in 13,538 combined white and 874 black participants 45–95 years of age followed 5 years for incident AF [23]. Together, however, these risk factors only explain 64 % of risk with similar levels for blacks (66 %) and whites (68 %) [23].

From a 10-year follow-up of the ARIC cohort, AF predictors included age, white race, male sex, systolic blood pressure, diastolic blood pressure, antihypertensive medication, body mass index (BMI) $\geq$30, height $\geq$173 cm, waist circumference, high-density lipoprotein cholesterol (HDL-C) $<$ 40 mg/dL, triglycerides $>$ 200 mg/dL, heart rate, PR interval $>$ 200 ms, ECG left ventricular hypertrophy, ECG left atrial enlargement, diabetes, coronary artery disease (CAD), and heart failure [24].

In a case control population-based study [25], 433 patients with AF and 899 controls from a healthcare system, where all were treated for hypertension, the level of blood pressure mattered beyond the diagnosis of hypertension in determining AF onset. So using the average of the last three clinic visits, 17.2 % (CI 4.3–28.3 %) of incident AF was attributable to systolic blood pressure $\geq$ 140 mmHg compared to systolic blood pressure of 120–129 mmHg. Moreover, increased pulse pressure has been shown to be a risk factor for AF beyond systolic and diastolic blood pressure in a clinical trial population [26].

Chronic kidney disease (CKD), another morbidity commonly linked to hypertension, is also a risk factor for AF [27]. Risk factors for AF in CKD are different from those in the general population and include age, male sex, smoking, history of heart failure, and history of cardiovascular disease. However, race, hypertension, diabetes, body mass index, physical activity education, C-reactive protein, total serum cholesterol, and alcohol intake were not risk factors for AF in CKD [27].

The relationships of AF risk factors to blacks and whites were examined in the SCCS using linkage to Social Security, Medicare, and Medicaid files for 8,836 persons with AF which found that traditional risk factors for AF applied similarly in blacks and whites and did not explain the different occurrence of AF in the two racial/ethnic groups [14].

Also, among heart failure patients, the AF difference between blacks and whites was not explained by risk factors for AF, adjusting for hypertension, CAD, prior heart failure, cardiomyopathy, hyperthyroidism, mitral stenosis, chronic obstructive airway disease, valvular repair, diabetes, coronary artery bypass graft surgery, and coronary angioplasty [28].

In CHS, all examined risk factors were similar in blacks and whites except that left ventricular wall thickness was more strongly associated with AF in blacks (per 0.2 cm, blacks HR 1.72 [95 % CI, 1.18–1.43]). More notably, no other risk factors for AF were more weakly associated with AF in blacks than in whites [29].

The possible increased risk of AF from hypertension in blacks than whites noted above was refuted in an ARIC cohort study [24] that showed left ventricular hypertrophy (generally associated with hypertension) increased the risk of incident AF in whites but not blacks. Factors associated with progression from a first episode of AF to permanent AF included increase in BMI (adjusted for other risk factors), but hypertension, diabetes, and blood pressure levels had no such effect among Group Health members aged 30–84 years with 1,385 incident cases of AF in the time period 2001–2004 [30].

Serum uric acid, another risk factor for AF, was associated with AF in blacks but not in whites which is counter to the lesser prevalence of AF yet higher serum uric acid in blacks. The higher uric acid in blacks is related to the greater prevalence of the SLC2A9 gene which in turn is related to the reabsorption of uric acid in the proximal tubule [31].

8.2.2 Differential Effect of Hypertension in Blacks and Whites as a Risk Factor for AF

Hypertension is well demonstrated to be more common in blacks than whites and it has also been identified in some studies as the most common antecedent to AF [32]. Left ventricular hypertrophy on echocardiography is significantly increased in patients with AF and is probably a result of hypertension [33].

In a study of 234 normotensive patients and 84 hypertensive patients, the P-wave parameters of P-wave duration and P-wave voltage were similar in both blacks and whites who were normotensive [32]. Thus, hypertensive blacks had a greater increase in these parameters than white hypertensives, suggesting that hypertension was a greater risk for blacks than whites. However, in a study of hospital patients presenting with AF, heart failure and hypertension were the two most common comorbid conditions for 1,346 (6 %) patients with AF from 29,694 general patients

at Henry Ford Hospital from 1989 to 1991 [34]. And in that study hypertension was the most common antecedent for AF, and left ventricular hypertrophy by ECG (Cornell voltage) increased the risk of 10-year incident AF in whites ($n = 10,682$) but not in blacks. This effect of hypertension via left ventricular hypertrophy development was also observed to be greater in whites than blacks in ARIC where ECG left ventricular hypertrophy [Cornell voltage] increased the risk of 10-year incident AF in 10,682 whites but not in 6,506 blacks [24].

8.3 The Paradox of Atrial Fibrillation in Blacks

The increased prevalence of AF risk factors in blacks compared to whites contradicts with the reported low prevalence in blacks, the AF paradox [35–37]. Notably, blacks also are at particularly higher risk for stroke with 2–5 times the risk of incident stroke and 2–4 times the risk of stroke mortality compared to whites [38, 39]. Results from the Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS) [38] show that the excess stroke-related mortality in blacks is due to higher stroke incidence rates, rather than higher mortality rates after stroke. Therefore, conventional wisdom suggests that disparities in stroke risk factors may explain, at least in part, the disparity in stroke incidence between these races/ethnicities. In this context, AF should be playing a role given its strong association with stroke [40–45]. AF carries a more than fivefold increase in stroke incidence, a relative risk that is the highest of the traditional risk factors for incident stroke [40]. The rate of ischemic stroke among patients with AF is about 5 % per year, 2–7 times that of people without AF [41–43], and one of every six strokes occurs in a patient with AF [44]. With such a strong association between AF and stroke, it is incompletely understood why black race/ethnicity has been repeatedly reported to have less AF despite having higher stroke rates and higher AF/stroke risk factors. Such a paradox mandates rethinking the epidemiology of AF and revising the current knowledge of the racial/ethnic distribution of AF.

8.3.1 Possible Explanations for the AF Paradox in Blacks

There are several hypotheses which are forwarded in an attempt to unravel the paradox of less AF in blacks despite multiple AF risks factor in high or higher prevalence. At this stage, efforts to explain the AF paradox in Blacks would be merely speculative.

8.3.1.1 Limited Methodology to Detect AF in Population Studies

First of all, as noted earlier, most of the methods of AF detection in population studies do not take into account the paroxysmal/intermittent nature of AF in most cases. It could be argued, however, that a limited AF detection method with a low

sensitivity would equally underdiagnose AF in blacks and whites; thus, the proportionate distribution of AF between these two groups would not be affected. If this is true, the proportionate difference in AF (i.e., relative risk) between blacks and whites should be similar regardless of the method of AF detection. However, this is not the case according to results from the *RE*asons for *G*eographic *A*nd *R*acial *D*ifferences in *S*troke (REGARDS) study in which the relative risk of AF in blacks vs. whites was changing by changing the level of the sensitivity of the AF detection method [46].

The REGARDS study investigators conducted an analysis on 18,833 black and white participants from a number of US states. Levels of sensitivity to detect AF, from presumed least to most sensitive, were created for combinations of self-report (SR) and ECG methods, as follows: (a) both SR and ECG required, (b) ECG alone, (c) SR alone, and (d) either SR or ECG. For the four methods used to detect AF, the strength of association between black race and AF progressively decreased with increasing test sensitivity (ORs, 0.20, 0.40, 0.70, and 0.71 respectively). As concluded by the authors, the association of lower prevalence of AF with black race/ethnicity was inversely related to the sensitivity of the method used to detect AF; as test sensitivity increased, the association became attenuated. Seeing that different methods yield different relative rates of AF between whites and blacks violates the assumption that the ability to diagnose AF is similar across different racial/ethnic groups. Therefore, it is possible that differential under-ascertainment of AF in blacks is playing a role in the paradox of AF. The question then would be, why such a differential under-ascertainment of AF in blacks?

8.3.1.2 Differential Distribution of AF "Subtypes"

It would be appropriate to think that the ability to accurately estimate the incidence/prevalence of AF in any population would be dependent on the proportion of individuals with the difficult-to-detect AF patterns such as paroxysmal and asymptomatic AF. In other words, if groups differ in the prevalence of paroxysmal or asymptomatic AF, detection of AF by ECG or self-report will differ across groups. At present, no data on racial/ethnic differences in the prevalence/incidence of AF subtypes have been published. However, using data from the ARIC studies, the racial/ethnic distributions of variables derived from P-wave morphology (P-wave indices) were used as surrogates for racial/ethnic distribution of future AF (which would include paroxysmal and chronic AF) [37]. The results of this study showed that whereas AF was significantly less common in blacks compared with whites (0.24 % vs. 0.95 %, $P<0.0001$), similar to what has been reported in previous studies, blacks had significantly higher and more abnormal values of P-wave indices after adjusting for common cardiovascular risk factors (odds ratios for different P-wave indices ranged from 2.1 to 3.1, $p<0.001$). Notably also, P-wave indices were significantly and independently associated with AF and ischemic stroke in both blacks and whites. The ARIC investigators concluded that there is a disconnect between the racial/ethnic distribution of P-wave indices and the racial/ethnic

distribution of ECG-diagnosed AF, probably because the former, unlike the latter, do not suffer from low sensitivity. With the assumption that the racial/ethnic distributions of P-wave indices could be used as surrogates for the racial/ethnic distribution of AF (which was confirmed in this study), these results support the contention that blacks might actually have a higher prevalence of AF that might have been missed by previous studies owing to limited methodology. Interestingly, the metabolic syndrome has been reported to be an independent risk factor for paroxysmal AF [OR (95 % CI), 2.8 (1.3, 6.2); $P<0.01$] [47]. Although blacks generally do not have higher rates of metabolic syndrome [48], findings further raise the possibility that blacks may have more paroxysmal AF than whites. These suggestions, however, need further confirmation. Nevertheless, these "hypothetical" suggestions accord with and might explain, at least in part, the AF paradox in blacks.

8.3.1.3 Differential Access to Healthcare

One of the possible explanations of less prevalent AF in US blacks could be related to the poorer access of blacks to medical care [49] which might have led to underdetection of AF by self-report in blacks. However, this would not explain the lower rates of ECG-detected AF observed in epidemiologic studies [37].

8.3.1.4 Survival Bias

Differential mortality between blacks and whites could be another explanation. Total and cardiovascular disease mortality is higher among blacks than whites [50], which in turn could lead to lower AF incidence in the former group if the increased mortality affected disproportionably individuals susceptible to developing AF. In this regard, it has been shown that post-myocardial infarction mortality is higher among blacks than whites (35 % vs. 30 % among patients admitted to the hospitals for coronary revascularization) [51], increasing the proportion of myocardial infarction survivors, and hence patients at higher risk of AF, among whites. Also, among 20,962 black and white participants from the REGARDS study, the prevalence of AF by ECG among men ≥ 65 years of age was 5.2 % in white and 1.8 % in black—a clear excess of AF in whites than blacks, mirroring the many studies cited above. However, for those 45 to 64 years, the prevalence by race was reversed for men: white 0.4 % and black 1.0 % [52]. These results support the notion of a survival bias, whereas the blacks with AF die earlier than whites so that older populations reflect AF survivors only, giving a false view of the relative AF occurrence in the two racial/ethnic groups. These results also reflect an earlier report from 17,974 adults aged 20 years and older in an 18-month period in the Kaiser Permanente healthcare system that showed the prevalence of AF was greater in whites than blacks for those older than 50 years but that the prevalence of AF for those 50–59 years was 0.5 % in both blacks and whites [1]. Nonetheless, despite the notable

racial/ethnic differences in survival, the magnitude of difference is not enough to explain a 50 % lower cumulative risk of AF among blacks as shown in the ARIC study [7].

8.3.1.5 Biological Factors

Biological differences between blacks and whites might have resulted in differential impact of AF risk factors with whites being more susceptible to AF risk factors. For example, in the CHS, white men had on average a larger left atrium than their black counterparts [53], and a larger left atrium was associated with an increased risk of AF [6]. It may be possible that larger left atrium in whites results in a more "chronic" AF that is easily detected in this racial/ethnic group compared to blacks.

8.3.1.6 Differential Impact of AF Risk Factors

Is it possible that blacks are less affected or whites are more affected by AF risk factors? If true, this may explain why AF is less common in blacks despite having more risk factors. Evidence from current studies, however, contradicts this assumption. Results from the ARIC study show that overall cardiovascular risk is associated with AF in both whites and blacks [54, 55]. In the CHS cohort, most risk factors for AF were not more weakly associated with AF in blacks than in whites [29]. Even more, in the SCCS, the associations with hypertension and diabetes were somewhat stronger among blacks [14]. Overall, these data make the differential impact of risk factors an unlikely explanation of the AF paradox since traditional risk factors for AF seem to have at least similar impact in both whites and blacks.

8.3.1.7 Genetic Differences

A meta-analysis using data from the ARIC and CHS studies revealed that every 10 % increase in European ancestry increases the risk of AF by 13 % (hazard ratio, 1.13; 95 % confidence interval, 1.03–1.23; $P=0.007$). After adjustment for potential confounders, European ancestry remained a predictor of incident AF in each cohort alone, with a combined estimated hazard ratio for each 10 % increase in European ancestry of 1.17 (95 % confidence interval, 1.07–1.29; $P=0.001$) [56]. These findings are in accord with the reported low prevalence of AF in blacks but clearly do not explain the AF paradox. Nevertheless, these data should be interpreted in the context of the methods of AF detection that were used in ARIC and CHS which expectedly will miss paroxysmal/intermittent AF, and therefore these results are mainly applicable to chronic AF. If the prevalence of AF patterns differ across races, as previously suggested, it would be hard to put these results in the context of explaining AF paradox in blacks.

In consideration of the current evidence, it seems there is no convincing explanation for the paradox of AF in blacks. There is a need, however, to exclude the possibility of racial/ethnic differences in AF patterns, i.e., blacks have more paroxysmal AF (a pattern difficult to detect) or whites have more chronic AF (a pattern easier to detect). There is no doubt that the suggestion that blacks might have higher prevalence of asymptomatic or paroxysmal AF (or whites have more chronic AF) is based on "clues," not "evidence"—at least for now. Nevertheless, such a suggestion provides a compelling explanation for the paradox of AF in blacks.

8.4 Concluding Remarks

- AF has been repeatedly reported to be less in blacks compared to whites.
- High blood pressure, which is more common in blacks, is one of the most important risk factor for AF.
- The magnitude of AF risk associated with high blood pressure and other AF risk factors seems to be similar in blacks and whites.
- The lower occurrence of AF in blacks compared to whites remains at odds with the high or higher rates of AF risk factors in blacks (*the AF paradox*).
- The number and interplay of factors supporting, refuting, or explaining the paradox are many and complex—with no one final answer.
- The inability to explain the paradox of AF in blacks is complicated by lack of data on the racial/ethnic distribution of AF subtypes, especially paroxysmal AF.
- Examining AF in younger age groups (<45 years) for black/white differences in prevalence and incidence and the differential effects of risk factors for AF between race/ethnic groups requires larger studies over longer periods of time to determine the true "life cycle" of AF.

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Chapter 9
Cardiorenal Metabolic Syndrome and Diabetes in African Americans: Adding to the Risk of Hypertension

Ankur Jindal, Adam Whaley-Connell, and James R. Sowers

9.1 Introduction

Hypertension is a significant public health concern affecting approximately one third of US adults and costing about 131 billion USD annually in direct medical costs [1]. It is projected that the costs associated with hypertension will triple over the next two decades [2]. There has been an increased scrutiny of blood pressure control in the United States with an increase in the portion of the population that has met target blood pressure from only 31 % of people with hypertension in 1999–2000 to 53.3 % in 2009–2010 [3, 4]. In this context, there has been a recent surge in interest in blood pressure control, especially in vulnerable populations such as in the African American community who are at high risk for cardiovascular disease (CVD) and kidney complications.

Hypertension disproportionately affects African Americans. The National Center for Health Statistics (NCHS) estimates that 40 % of non-Hispanic blacks and 27 %

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K.C. Ferdinand (ed.), *Hypertension in High Risk African Americans*, Clinical Hypertension and Vascular Diseases, DOI 10.1007/978-1-4939-2010-5_9

of non-Hispanic whites are hypertensive [4]. Non-Hispanic blacks are more aware of their hypertension and are more likely to be on treatment compared to the general US population [4]. The Centers for Disease Control and Prevention (CDC) data suggests that hypertension is not only more prevalent; it develops earlier in African Americans and disproportionately affects African American women. Data from other population-based studies also suggests that non-Hispanic blacks are more likely to have hypertension, diabetes, and hypercholesterolemia, or all three comorbidities collectively. This population is more likely to have renal disease in conjunction with heart disease and metabolic abnormalities, e.g., the cardiorenal metabolic syndrome (CRS) (Fig. 9.1, Table 9.1) [5]. Data from the National Health and Nutrition Examination

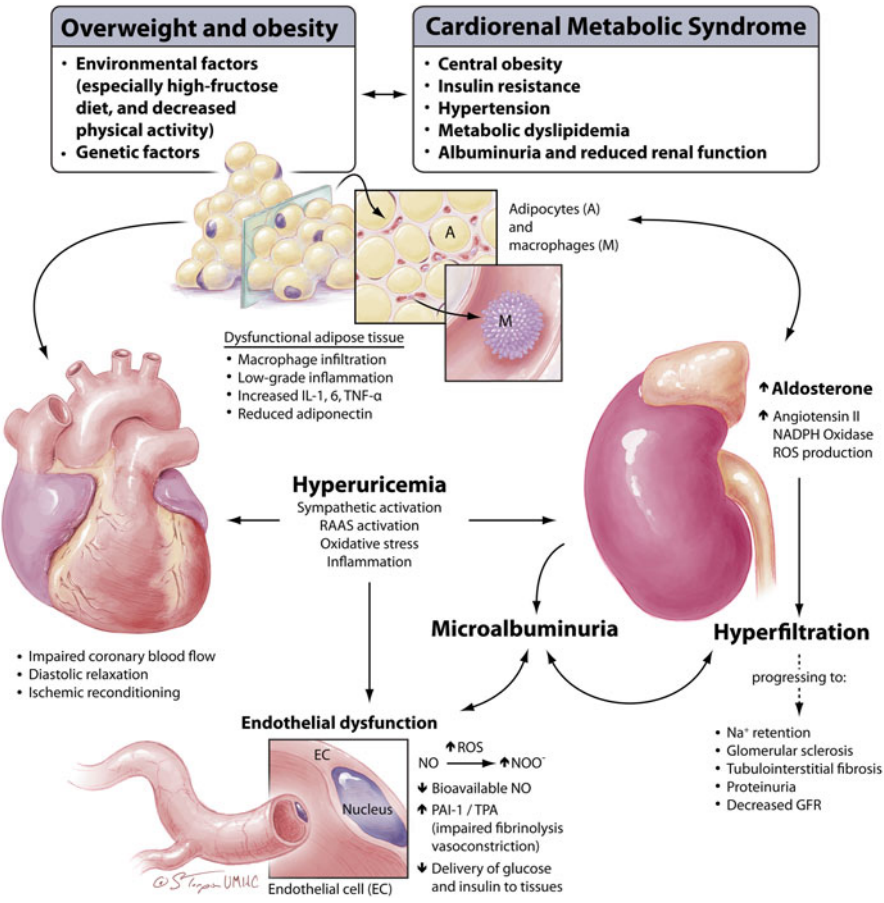

Fig. 9.1 The interrelationship between adiposity and maladaptive changes in the heart and kidney in CRS. *GFR* glomerular filtration rate, *IL* interleukin, *PAI* plasminogen activator inhibitor, *RAAS* renin-angiotensin-aldosterone system, *ROS* reactive oxygen species, *TNF* tumor necrosis factor, *TPA* tissue plasminogen activator. Sowers JR, Whaley-Connell A, Hayden MR: The role of overweight and obesity in the cardiorenal syndrome. Cardiorenal Med (2011) 1(1):5–12. Copyright © 2011 Karger Publishers, Basel, Switzerland

Table 9.1 Defining different forms of CRS [13]

CRS general definition
A complex pathophysiological disorder of the heart and kidneys where acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ
CRS type I (acute CRS)
Abrupt worsening of cardiac function (e.g., acute cardiogenic shock or acute decompensation of chronic heart failure) leading to kidney injury
CRS type II (chronic CRS)
Chronic abnormalities in cardiac function (e.g., chronic heart failure) causing progressive chronic kidney disease
CRS type III (acute renocardiac syndrome)
Abrupt worsening of renal function (e.g., acute kidney failure or glomerulonephritis) causing acute cardiac disorder (e.g., heart failure, arrhythmia, or pulmonary edema)
CRS type IV (chronic renocardiac syndrome)
Chronic kidney disease (e.g., chronic glomerular disease) contributing to decreased cardiac function, cardiac hypertrophy, and/or increased risk of adverse cardiovascular events
CRS type V (secondary CRS)
Systemic condition (e.g., diabetes mellitus or sepsis) causing both cardiac and renal dysfunction

Survey (NHANES) supports that important ethnic and racial disparities exist with regard to awareness and treatment of hypertension, with lower rates of blood pressure control among non-Hispanic blacks compared to non-Hispanic whites [3]. Target blood pressure of <130/80 mmHg was observed in 43 % of non-Hispanic white diabetics and 30 % of non-Hispanic black diabetic subjects in the REasons for Geographic And Racial Differences in Stroke (REGARDS) study, a national population-based, longitudinal cohort study of 30,228 adults [6]. A recent retrospective analysis of 51,772 hypertensive subjects and a retrospective longitudinal cohort study involving veterans both confirmed that disparities exist with regard to hypertension therapy and control in the population, with relatively poor control evident in the non-Hispanic black diabetics, compared to non-Hispanic white diabetics [7, 8].

The high prevalence of hypertension and the associated increases in morbidity and mortality make hypertension in African Americans a public health concern. Herein, we will review the importance of hypertension in the African American community in the context of the CRS. We have emphasized the CRS classification rather than the metabolic syndrome, as the latter underrepresents the African American population. Indeed, this population has more renal disease and relatively less metabolic dyslipidemia and central (visceral) obesity than Americans of European and Asian descent.

9.2 Cardiorenal Metabolic Syndrome

Metabolic syndrome is prevalent across different population and ethnic groups and is predictive of macrovascular disease [9]. The World Health Organization (WHO) consultation group proposed the first working definition of metabolic syndrome to

aid its diagnosis in clinical practice. The WHO consultation group emphasized the role of insulin resistance (IR) and considered demonstration of IR mandatory for the clinical diagnosis of metabolic syndrome [9]. Many other organizations have proposed alternative criteria since IR is difficult and impractical to measure in clinical practice. Though IR appears to play a central role in the pathogenesis of metabolic syndrome, other factors associated with IR, like central obesity and an atherogenic dyslipidemia, are easy to measure or demonstrate in clinical practice. The knowledge about CVD risk factors and interaction between different organ systems is far from complete. Renal involvement in the form of proteinuria/albuminuria is frequently present in people with the metabolic syndrome, and this constellation of findings (CVD, renal disease, and metabolic abnormalities) has been recognized as the CRS [10–13]. Data from a cross-sectional study by Chen et al. shows a positive relationship between the metabolic syndrome and risk for chronic kidney disease (CKD) and microalbuminuria. The study further shows that the risk for CKD increases progressively with increasing components of the metabolic syndrome [10]. There is some suggestion that nonalcoholic fatty liver disease (NAFLD) might be a component of metabolic syndrome or the CRS as well.

The CRS has been defined differently by different organizations, but in all cases it is a cluster of cardiac, renal, and metabolic risk factors that are found together more often than can be explained by chance alone [11–13]. These risk factors, either alone or in combination, predict risk for development of type 2 diabetes as well as CVD [11–13]. The risk factors that constitute the CRS include abdominal obesity, atherogenic dyslipidemia (elevated serum triglycerides and apolipoprotein B, increased small low-density lipoprotein [LDL] particles, and a reduced level of high-density lipoprotein [HDL] cholesterol), raised blood pressure and dysglycemia, and kidney disease (GFR less than 60 and/or albuminuria) [11, 12]. The data regarding prevalence of CRS is inconsistent due to differences in diagnostic criteria and study designs, but it is clear that the prevalence is age and ethnicity dependent and is increasing among US adults.

Most recently, CRS has been defined as a complex pathophysiological disorder of the heart and kidneys where acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ [13]. CRS has been subclassified into five categories based on the primary and secondary pathology, acuity of primary pathology, and cardiorenal involvement due to systemic disease like diabetes mellitus [13]. A recent study involving 494 individuals of African descent has shown that overweight and obesity are associated with increased GFR, filtration fraction, and high prevalence of glomerular hyperfiltration [14]. These changes in renal function can potentially translate into progressive renal disease, in the presence of inflammatory, immunological, and oxidative insults [12]. Because African Americans are more likely to manifest renal disease at an earlier age, they are more often classified as having CRS than being classified as simply having a metabolic syndrome.

Both the distribution and the degree of body fat have important metabolic and clinical implications. It is known that central obesity, i.e., excess fat in the abdominal area, has a stronger association with an adverse CRS profile than peripheral obesity, i.e., excess fat in the gluteofemoral area [15]. Visceral fat is thought to be

Table 9.2 Cardiometabolic risk factors associated with increased CVD risk

Hypertension
Central obesity
Insulin resistance
Endothelial dysfunction
Microalbuminuria
Low HDL levels
High triglyceride levels
High small, dense LDL cholesterol particle levels
Increased fibrinogen levels
Increased inflammatory markers like CRP
Decreased plasminogen activator levels
Absent nocturnal dipping of blood pressure and heart rate
Salt sensitivity

Adapted from Sowers et al. Hypertension and Diabetes: An Update (Book: Hypertension A companion to Braunwald's Heart Disease)

strongly associated with IR, hypertension, dyslipidemia, and other CRS risk factors [15–18]. Visceral adipose tissue is considered metabolically active and its contribution to cardiometabolic risk (Table 9.2) is thought to stem from the secretion of vasoactive substances and growth factors [18]. The metabolic activity of other abdominal fat depots is an area of active study [19–21]. Data from a cross-sectional study, involving 3,001 participants from Framingham Heart Study, suggests that both subcutaneous and visceral adipose tissue are associated with metabolic risk factors and an adverse CRS risk profile [18]. Some researchers have reported that deep abdominal subcutaneous adipose tissue is strongly associated with IR and other aspects of CRS [16]. However, others have reported that subcutaneous abdominal fat may have a CRS or cardiometabolic protective role [15].

In the Jackson Heart Study involving 2,477 persons, data showed that both visceral and subcutaneous adipose tissue are associated with CRS risk in African Americans, though the association of visceral adipose tissue with components of the CRS was stronger. While both visceral and subcutaneous adipose tissues correlate well with body mass index (BMI), African Americans generally have less visceral adipose tissue compared to European Americans of similar BMI [17]. Thus using waist circumference and metabolic dyslipidemia as components of a metabolic syndrome underrepresents African Americans who have relatively earlier and more severe renal disease [11–13].

9.3 Role of High-Fructose Corn Syrup in CRS

Over the last few decades, the consumption of high-fructose corn syrup (HFCS), a major portion of non-calorie-free sweeteners in diet foods, has increased precipitously in the United States. It has been estimated that the average annual intake of

HFCS may be close to 62.4 lb per person [22]. Metabolism of fructose leads to increased degradation of nucleotides and consequently increased synthesis of uric acid. Intake of HFCS has been linked to albuminuria and renal dysfunction; it has been proposed that this might stem from increased uric acid production [12]. Analyses of data from the ARIC study showed that sugar-sweetened soda consumption is associated with increased prevalence of hyperuricemia and kidney disease, though a cause and effect relationship could not be established [12, 22].

The unique role of HFCS in obesity and CRS has been debated. It is clear that the use of HFCS has increased over time and has paralleled the increase in prevalence of obesity and CRS, which has been attributed to the effects of HFCS and increased calorie intake. Accumulating data suggests that increased intake of sugar-sweetened soda may be driving the epidemic of obesity, hypertension, CRS, and diabetes [12].

9.4 CRS in African Americans

Analyses of data from the NHANES (1988–1994) provide some interesting insights into the demographics of CRS and suggest that CRS is less prevalent in African Americans (21.6 %) compared to Mexican Americans (31.9 %) and Caucasians (23.8 %). Even though the prevalence of the metabolic syndrome is similar in males and females, African American women had a 57 % higher prevalence than African American men [23]. This lower prevalence of CRS in African Americans by ATP 3 criteria is counterintuitive and raises concerns for underdiagnoses of the metabolic syndrome in African American populations, especially obesity, hypertension, IR, CVD, and CVD risk factors which are more prevalent in the African American population [24–26]. It has been observed that dyslipidemia of IR (high triglyceride levels and low HDL levels) is less prevalent among African Americans and that IR does not adversely affect the lipid profile in African Americans. As hypertriglyceridemia and low HDL levels are diagnostic criteria for the metabolic syndrome, this disparity in the lipid profile by virtue of the variable effect of IR on lipoprotein lipase activity can potentially explain the lower prevalence or potential underdiagnoses of CRS in this population subgroup [25, 26]. These findings raise questions regarding the applicability of diagnostic criteria for CRS in the African American population.

9.5 Obesity and Hypertension Link in African Americans

Hypertension is more prevalent in African Americans that are obese. It affects ~42 % of obese American adults compared to 15 % of nonobese adults [27]. Obesity is an important predictor, risk factor, and driving force for increasing the prevalence of hypertension [27]. The associations between obesity and mortality have been questioned especially whether obesity increases mortality independent of other

associated risk factors. The search for the ideal weight range or BMI is ongoing. While some investigators have found a curvilinear relationship between adiposity and mortality, others have argued against such a relationship [28–32]. The increased mortality in the very lean population is considered artifactual and stems from the failure to account for confounding factors such as smoking and subclinical disease [33]. Regardless of the shape of the curve, literature supports a strong predictive relationship between high BMI and cardiovascular mortality [29]. Data also suggests that the association between increased BMI and mortality might not be as strong in blacks as in whites [29]. Data from a cross-sectional study involving a nationally representative sample of adults showed that overweight and obesity are strongly associated with increased prevalence of hypertension and type 2 diabetes in African Americans [34]. Data analyses from two large prospective cohort studies, Nurses' Health Study and Health Professionals Follow-Up Study, showed that the incidence of diabetes, hypertension, and heart disease increases with excess weight [35]. In the studied population, the risk for developing these conditions increased with escalating severity of obesity [35].

Data from collaborative analyses of 57 prospective studies of 894,576 participants showed a 30 % increase in all-cause mortality for every 5 kg/m^2 increase in BMI above 22.5–25 kg/m^2 range [32]. BMI was positively associated with multiple vascular risk factors including systolic and diastolic blood pressure (DBP). The association with blood pressure was nearly linear such that 5 kg/m^2 higher BMI was associated with 5 mmHg higher systolic blood pressure (SBP) [32]. Even though the association between obesity and hypertension has been observed for a long time, the significance of such association has been neglected until much later. Understanding the association has been cluttered by trivial explanations like inaccurate indirect blood pressure measurements related to large arm circumference, etc. [36, 37]. Data from the Framingham Study provides prospective evidence of the existence of complex associations between obesity and hypertension [36].

Data from the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study suggests that higher values of traditional cardiovascular risk factors, like total serum cholesterol, triglycerides, and blood glucose, are seen in people with progressively higher BMI and waist circumference. Higher values of BMI and waist circumference were also associated with increased blood pressure and erratic blood pressure variability in the studied population [38]. Similarly data from the Insulin Resistance Atherosclerosis Family Study (IRAS) suggest visceral adipose tissue is associated with a higher prevalence of hypertension in African American women independent of total body adiposity [39]. A meta-analysis of 21 cohort studies including 302,296 healthy subjects and a total of 18,000 coronary heart disease events during the follow-up period was conducted. The data from analyses showed that a five-unit increase in BMI was associated with a 29 % increase in risk of CHD. The investigators further found that even though adverse effects of obesity on blood pressure and cholesterol levels explained increased risk partially, there was a substantial increase in the risk independent of the effect of blood pressure and cholesterol [40]. Data from the Framingham study highlighted the association between excess weight, even in the overweight category, and the risk for development of CVD and CVD risk factors [41].

9.6 Hypertension and Diabetes in African Americans

The CDC estimates 4.9 million (i.e., 18.7 %) African Americans aged 20 years or older have diabetes, a major cause of stroke and heart disease in US population. Hypertension and diabetes coexist while hypertension increases the CVD and nephropathy burden associated with diabetes [42]. Data from United Kingdom Prospective Diabetes Study (UKPDS) and Multiple Risk Factor Intervention Trial (MRFIT) suggests that type 2 diabetes is an independent CVD risk factor, and it adds to the CVD risk conferred by hypertension [43]. Hypertension in Diabetes Study (HDS) is a cross-sectional study, designed to study the benefits of tight blood pressure control in subjects with type 2 diabetes and to compare the angiotensin-converting enzyme (ACE) inhibitor and beta blocker therapy in this cohort. Data from this study showed that hypertension is more prevalent in people with type 2 diabetes and it is often unrecognized and undertreated. Hypertensive diabetics often have other CVD risk factors and a higher prevalence of macrovascular complications than normotensive diabetics [44]. The data further highlighted that hypertension itself is an important risk factor for cardiovascular mortality and morbidity in subjects with type 2 diabetes [45]. The hypertensive diabetic subjects were found to be at increased risk for diabetes-related death and fatal or nonfatal morbid events such as myocardial infarction, angina, nonfatal strokes, amputation, or blindness [45].

Analyses of data from UKPDS showed that better glycemic control can decrease mortality related to diabetes complications and underscored the role of hyperglycemia in diabetes complications. A risk reduction of 21 % for diabetes-related deaths, 14 % for myocardial infarction, and 37 % for microvascular disease was observed for every one-unit reduction in updated mean HbA_{1c} in subjects with type 2 diabetes [46].

Observational analyses of data from UKPDS suggest that strong associations exist between elevated blood pressure and risk of microvascular and macrovascular diabetic complications in subjects with type 2 diabetes [47]. These associations were independent of glycemia, lipid concentrations, and albuminuria. The data further showed that for every 10 mmHg reduction in updated mean SBP, there was a 12–19 % reduction in the risk for microvascular and macrovascular diabetic complications [47].

9.7 Benefits of Blood Pressure Control in African American Diabetics

Inadequate blood pressure control appears to affect the African American population disproportionately. Apart from pathophysiological factors, multiple non-physiologic factors have been linked to this trend. The involvement of many heterogeneous and subjective variables like individual medical beliefs and patient

interactions with providers appears to complicate the seemingly simple pharmacologic therapy. Factors like nonadherence to therapy, inability to follow prescription instruction, mistrust for the healthcare system, beliefs regarding curability of hypertension, and symptomatic treatment of hypertension contribute to inadequate blood pressure control in African Americans [48].

The adverse outcomes in African Americans with hypertension have been attributed to an excessive prevalence of hypertension, disproportionate prevalence of severe hypertension, poor long-term control, and high frequency of comorbid conditions (type 2 diabetes, CKD, and target organ injury) [48]. Analyses of data from 73,913 patients enrolled in 31 intervention trials, which amounted to 295,652 patient-years of exposure, showed that for every 5 mmHg reduction in SBP or 2 mmHg reduction in DBP, the stroke risk decreased by 13 % [49].

9.8 Blood Pressure Control Targets in Black Diabetics with Hypertension

Even though nephropathy is well established in the role of blood pressure control for prevention of CVD, optimal blood pressure parameters for diabetics have been debated. Report of the Joint National Committee on Prevention of High Blood Pressure (JNC 7) recommended a blood pressure target of 130/80 or lower in people with type 2 diabetes. These recommendations are based on expert opinion rather than irrefutable data from high-quality studies. These blood pressure targets need to be reanalyzed in light of emerging data (Table 9.3).

Table 9.3 Treatment goals according to risk categories as recommended by ISHIB [48]

Risk category	Recommended treatment	Goal BP
Primary prevention		
BP ≥ 135/85 mmHg without target organ damage[a], preclinical CVD[b] or CVD[c]	Lifestyle modification (up to 3 months without drugs) + drug therapy	<135/85
Secondary prevention/target organ damage		
BP ≥ 130/80 mmHg with target organ damage[a], preclinical CVD[b], and/or presence of CVD[c]	Lifestyle modification + drug therapy	<130/80

This table has been adapted from the management of high blood pressure in blacks, an update from the ISHIB consensus statement

[a]Target organ damage is defined as albumin: creatinine > 200 mg/g, estimated glomerular filtration rate < 60 mL/min/1.73 m^2, or electrographic or echocardiographic evidence of left ventricular hypertrophy

[b]Indicators of preclinical CVD include metabolic syndrome, Framingham risk score > 20 %, prediabetes, or T2DM

[c]CVD include systolic or diastolic heart failure, CHD/post MI, peripheral arterial disease, stroke, transient ischemic attack, and/or abdominal aortic aneurysm

In Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study, 4,733 participants with diabetes were randomly assigned to intensive blood pressure therapy or standard blood pressure therapy. SBP <120 was targeted for the intensive group and mean SBP 119.3 mmHg was achieved. For the standard group, SBP 140 was targeted, and mean SBP 133.5 mmHg was achieved. Primary outcome defined as first occurrence of major cardiovascular event (a composite of nonfatal MI, nonfatal stroke, or cardiovascular death) was not significantly different between the two groups [50]. Rates of total stroke and nonfatal stroke were slightly lower in the intensive treatment group compared to standard therapy group, but this came at a cost of increased adverse events such as hypotension (0.7 % versus 0.04 %), hyperkalemia (04 % versus 0.04 %), and renal failure (0.2 % versus 0.04 %) [50].

In UKPDS, 1,148 subjects with type 2 diabetes were randomly allocated to tight blood pressure control (<150/85) or liberal blood pressure control (<180/105) and followed for a median of 8.4 years. The blood pressure achieved in the two groups was 144/82 and 154/87 respectively. Tight control of blood pressure was associated with 32 % (95 % CI, 6–51 % $P=0.019$) risk reduction for deaths related to diabetes and 44 % (95 % CI, 11–65 % $P=0.019$) risk reduction for strokes [51].

Results from Appropriate Blood Pressure Control in Diabetes (ABCD) trial, a prospective randomized controlled trial, showed a decreased incidence of incipient and overt diabetic nephropathy, slower progression of retinopathy, and decreased occurrence of cerebrovascular events with intensive blood pressure control compared to more liberal blood pressure control in diabetic subjects with baseline blood pressure less than 140/90. Mean blood pressure achieved in the intensive group and moderate group was 128/75 and 137/81 respectively [52].

Data from a meta-analysis of 13 randomized controlled trials, involving 37,736 subjects with type 2 diabetes, impaired fasting glucose, or impaired glucose tolerance, suggests potential cerebrovascular benefits of intensive blood pressure control (SBP <130) compared to less aggressive blood pressure control (SBP <140). Similar benefits were not seen for cardiac, renal, and retinal outcomes with lower blood pressure targets [53]. Another meta-analysis further showed that for every 5 mmHg reduction in SBP or 2 mmHg reduction in DBP, there was a 13 % reduction in risk for stroke, in diabetics [49].

Benefits of early detection and treatment of hypertension in diabetics and general population cannot be overemphasized. Unfortunately data regarding treatment parameters are inconsistent and there is discord between the trial data and expert opinion. Over time, the clinical guidelines for the treatment of hypertension have been modified in light of available data, and many societies are now suggesting more liberal blood pressure parameters for patients with diabetes that provide some latitude based on patient characteristics and risk factors. An SBP target <140 is optimal for most patient with type 2 diabetes.

9.9 Risk Stratification

Hypertension is a known risk factor for CVD. Studies suggest that continuous associations exist between vascular disease and blood pressure, even in normal range to SBP and DBP as low as 115 and 75 respectively [54]. The risk is modified by presence of comorbidities and other CVD risk factors, and hence the risk stratification is an important initial step in evaluation of a patient with hypertension. International Society on Hypertension in Blacks (ISHIB) recommends the use of Framingham 10-year CHD risk score to aid risk stratification in African Americans [48]. Active participation by patients in their treatment and blood pressure surveillance might increase compliance and help achieve target blood pressure. Home blood pressure monitoring helps involve patients in their care and can aid clinical decision making. Opportunity should be taken to identify and treat other modifiable risk factors.

Diet and lifestyle appear to play an important role in the pathogenesis of hypertension in African Americans. Sedentary lifestyle, excess calorie consumption, and obesity have been implicated in the pathogenesis of hypertension in African Americans [48]. Thus lifestyle modification seems to be a logical initial therapeutic modality and should be implemented in all patients with hypertension. It should be implemented as an initial therapeutic modality in low-risk patients, with blood pressure >115/75 to 145/90 for primary prevention. Even after initiation of pharmacological therapy for hypertension, comprehensive lifestyle modification should be encouraged [48].

9.10 Summary

Hypertension is an important clinical and public health problem in African Americans and African American diabetics. Diabetes and obesity add to risk conferred by hypertension and increase the mortality, morbidity, and costs associated with obesity. Because African Americans have earlier and more severe kidney disease, often in conjunction with heart disease, they are more likely to manifest the CRS than other populations in the United States. Diet and lifestyle appear to play an important role in the pathogenesis of hypertension and the CRS in African Americans. Hypertension is underappreciated and undertreated in African Americans, though hypertension awareness appears to have increased over time. Aggressive treatment of hypertension to SBP goal of at least <140 mmHg will help decrease the vascular disease burden and mortality associated with hypertension in African Americans with type 2 diabetes and/or obesity.

Acknowledgements This research was supported by the NIH (R01 HL73101-01A1 and R01 HL107910-01 to JRS) and the Veterans Affairs Merit System 0019 (JRS). The authors would like to thank Brenda Hunter for her editorial assistance.

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Chapter 10
Central Aortic Pressure, Arterial Compliance: Emerging Tools to Identify and Guide Therapy for High-Risk African American Patients

Yonghong Huan, Debbie L. Cohen, and Raymond R. Townsend

10.1 Introduction

African Americans have significantly higher burden of hypertension and associated cardiovascular morbidity and mortality [1]. About 30 % of deaths in African Americans are attributable to hypertension [2]. Peripheral brachial BP by conventional sphygmomanometry has remained the gold standard for measuring BP for over a century. Elevated peripheral brachial BP has been recognized as a major risk factor for cardiovascular disease (CVD), and reduction of peripheral brachial BP has been shown to reduce cardiovascular events [3]. However, peripheral brachial BP does not always reflect the central aortic BP, which is intuitively more relevant for the pathogenesis of CVDs. While the mean and diastolic BP remain almost constant from the aortic root to peripheral brachial artery, the systolic BP and pulse pressure (the difference between the systolic and diastolic BP) are amplified from the aortic root to the peripheral brachial artery with increasing distance. The amplification of systolic and pulse BP is mainly a function of the timing and magnitude of wave reflections and can be profoundly affected by many factors including age, gender, height, heart rate, aortic stiffness, and antihypertensive medications. Central aortic BP and arterial compliance can now be assessed using noninvasive applanation tonometry [4, 5]. Emerging data suggest that measurements of central aortic BP and arterial compliance are better and more robust predictors of cardiovascular outcomes than traditional peripheral brachial BP [6]. Measuring central aortic BP and arterial compliance will likely become an increasingly important part of routine clinical assessment of BP and related cardiovascular risks and treatment effects, especially in high-risk African Americans.

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K.C. Ferdinand (ed.), *Hypertension in High Risk African Americans*, Clinical Hypertension and Vascular Diseases, DOI 10.1007/978-1-4939-2010-5_10

10.2 Risk of Hypertension, Cardiovascular-Kidney Disease in African Americans

The prevalence of hypertension in African Americans in the United States is among the highest in the world, and it continues to increase [7]. Comparing 1988–1994 with 1999–2002, the prevalence of hypertension in adults increased from 35.8 to 41.4 %. It was particularly high among African American women at 44.0 % [7]. Compared with Caucasians, African Americans develop hypertension earlier in life and with much higher average BP and more target organ damage related to hypertension including LVH [2]. As a result, African Americans have a 1.3 times greater rate of nonfatal stroke, a 1.8 times greater rate of fatal stroke, and a 1.5 times greater rate of death attributable to CVD compared with Caucasians.

The mortality rates related to hypertension are much higher for both African American males and females when compared to Caucasians [7]. The 2009 overall death rate related to hypertension was 18.5 per 100,000 population. However, the death rates related to hypertension were 51.6 and 38.3 per 100,000 for African American males and females, respectively, compared to 17.0 and 14.4 per 100,000 for their respective Caucasian counterparts.

Within the black community, rates of hypertension vary substantially [8, 9]. Analysis from the REasons for Geographic And Racial Differences in Stroke study (REGARDS) suggests that efforts to raise awareness of prevalent hypertension among blacks have been successful (31 % greater odds in blacks relative to whites), and the efforts to communicate the importance of receiving treatment for hypertension have also been successful (69 % greater odds among blacks relative to whites); however, substantial racial disparities remain with regard to the control of BP to less than 140/90 mmHg, with the odds of control being 27 % lower in blacks than in whites. In contrast, geographic disparities in hypertension awareness, treatment, and control were minimal [10].

African Americans have higher rates of CVD, which remains the leading cause of death in African Americans. In African Americans, CVD develops approximately 5 years earlier and has higher mortality rates when compared to Caucasians of the similar age [11, 12]. Although mortality from CVD has declined over the last 30 years, the decline is less in African Americans when compared to Caucasians [13]. The overall rate of death attributable to CVD was 236.1 per 100,000 population in 2009 [7]. However, the rates were much higher at 387.0 and 267.9 per 100,000 for African American males and females, respectively, when compared to 281.4 and 190.4 per 100,000 for their respective Caucasian counterparts [7].

Stroke is the third leading cause of death in the United States. Although stroke rates have been declining, stroke-related death rates remain higher in African Americans than in Caucasians. Compared to Caucasians 35–54 years of age, young African Americans have a 2–3 times greater risk of ischemic stroke and African American men are more likely to die from a stroke [14].

The Meharry-Hopkins physician cohort study analyzed predictors of CVD in African and Caucasian physicians [15]. Hypertension was shown to be the best

predictor of cardiac events in African Americans. Hypertension-related mortality is higher in African Americans than for other populations and African Americans also have a higher prevalence of additional CVD risk factors compared to Caucasians of similar socioeconomic status [7, 12]. Synergistic interactions among multiple risk factors in African Americans result in greater risk of CVD [16]. Diabetes is very prevalent in African Americans with increased mortality rates when compared to Caucasians. There is also an increased incidence of hyperlipidemia and obesity in African Americans [17]. Other reasons for the higher rates of CVD in African Americans have been attributed to increases in peripheral vascular resistance, increased salt sensitivity, and decreased circulating renin [18–20].

African Americans are also at greater risk of developing progressive chronic kidney disease (CKD) and end stage renal disease (ESRD) than other racial group [21]. In combined data from NHANES 3 and USRDS, the prevalence of CKD was similar among African Americans and Caucasians, but the risk of CKD progression was fivefold higher in African Americans [22]. This has been demonstrated in a number of trials. The MRFIT trial showed that African Americans had faster progression of CKD than Caucasians despite similar BP control [23]. However, this is an older study and was done before the use of ACE inhibitors and lower BP goals. In the more recent AASK trial, African Americans with hypertensive CKD again showed progressive CKD despite the use of RAAS blockade and achievement of lower BP goals of 130/80 mmHg [24]. In this study, the 10-year cumulative incidence of doubling of serum creatinine, developing ESRD or death was 54 %, and it was similar for patients randomized to the standard or lower BP goal. When this data was analyzed using ambulatory BP data, it was shown that many of these patients had masked hypertension which may account for CKD progression despite adequate in-office BP control [25].

A meta-analysis has shown that African Americans contribute disproportionally to the number of patients reaching ESRD [26]. ESRD has a four times higher incidence in African Americans than other races [27]. Findings from multiple studies now suggest the excess burden of ESRD among African Americans is due to rapid progression of CKD to ESRD rather than an excess of CKD or a higher prevalence of hypertension or diabetes [22, 28, 29]. Possible explanations for the progressive CKD to ESRD in African Americans may be masked hypertension with seemingly good office BP control and possible genetic variations predisposing African Americans to CKD progression. A significant association between African ancestry and nondiabetic ESRD has been demonstrated, and this association has not been shown to be present in diabetic ESRD [30, 31]. African Americans with risk variants of APOL1 (gene that codes apolipoprotein L1) have been linked to higher risk of hypertension-attributable kidney disease [32, 33]. Some of the increased risk of progression of CKD to ESRD has also been attributed to lower socioeconomic status and poorer access to health care [21, 34, 35]; however, the risk remains greater than that of Caucasians even when these factors are accounted for [36, 37].

In summary African Americans have significantly higher burden of hypertension and related cardiovascular-kidney disease. African Americans tend to develop hypertension at a younger age, and have more severe hypertension and greater risk

of end-organ damage and overall mortality. CVD is more prevalent in African Americans and has a higher mortality. The reasons for the greater risk of CVD in African Americans include longer duration and more severe hypertension, greater 24-h BP burden at any given level of causal BP [19], lower socioeconomic status and poorer access to health care [35], and higher prevalence of coexisting risk factors including diabetes, smoking, obesity, and physical inactivity compared to Caucasians. African Americans also have greater age-adjusted risk of ESRD, mostly attributed to an increased rate of progression of CKD to ESRD. Even when accounting for other factors such as higher prevalence of hypertension, lower socioeconomic status, and poorer access to health care, the rate of CKD progression remains higher in African Americans when compared to Caucasians. Genetic factors and the presence of masked hypertension may play a significant role in the greater risk of CKD progression [33]. Due to this excess risk of hypertension, CVD, CKD, and ESRD in African Americans, it is important to identify new tools to better assess BP burden and related cardio-renal risks and to help guide therapy in this high-risk population.

10.3 Measuring Central Aortic Pressure and Arterial Compliance Using Applanation Tonometry

Central aortic pressure can be determined by capturing arterial pressure wave forms. The arterial pressure wave forms are the summation of the forward transmissions of the cardiac pressure impulses and backward reflections generated by the peripheral vascular system at the interface between large arteries (conduit) and small (resistant) arteries. The shape of arterial pressure wave forms depends largely on three key factors including the (1) amplitude and duration of the ventricular ejection (note: duration is affected by heart rate), (2) the amplitude of the reflected wave, and (3) the velocity of the reflected wave from the periphery. Under normal physiological condition, the reflected waves return to the central arteries in very late systole or early diastole during the same cardiac cycle, which augments the coronary perfusion. However, the cardiac systolic pressure and workload are increased and the coronary perfusion is decreased when the reflected waves return earlier in systole due to increased pulse wave velocity (PWV), proximal site of wave reflection, or longer ejection time.

In addition, as the forward pressure waves travel farther from the aortic root and closer to the peripheral reflecting sites, the reflected waves are more likely to augment systolic and pulse pressures. Therefore, systolic and pulse pressures are amplified from the aortic root to the peripheral brachial artery due to the wave reflection while diastolic and mean pressures remain relatively constant. This amplification phenomenon is most pronounced in younger people with healthy large (conduit) arteries leading to high brachial systolic and pulse pressures [38]. Therefore, despite being a strong traditional predictor of cardiovascular risk, peripheral brachial BP does not accurately represent central aortic pressure which is intuitively more relevant to the true BP burden experienced by the major organs.

PWV remains the gold standard in measuring arterial stiffness [39]. Increasing PWV due to stiffening of the aorta is mostly seen with aging [40] and observed in isolated systolic hypertension in elderly and sustained systolic-diastolic hypertension in middle age, as well as populations with type 2 diabetes, CKD, or ESRD [41, 42].

Central systolic blood pressure increases with age [43]. Before age 50 years, the increase in central systolic pressure is primarily due to greater amplitude of wave reflection. After age 50 years, the increase in central systolic pressure is mostly due to systolic augmentation related to wave reflection returning earlier because of increasing PWV [38]. Slower heart rates lead to longer ejection time and increase the possibility of augmenting systolic pressure as the wave reflection returning earlier during the cardiac cycle. Small statures also lead to earlier return of the wave reflection because sites of reflection are closer to the aorta.

Central aortic pressure wave forms are easily estimated through a mathematical transformation of the radial or carotid arterial pressure wave forms captured by noninvasive applanation tonometry [44]. Figure 10.1 shows how the arterial wave

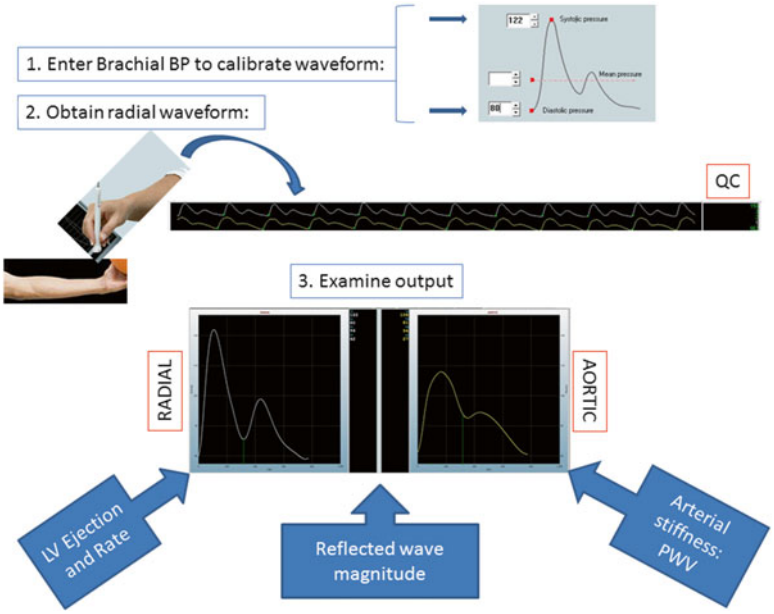

Fig. 10.1 To obtain central pressures, once the software program (in this example the SphygmoCor program) is running and demographics have been filled in, the actual study begins with entering the systolic and the diastolic BP to calibrate the radial artery wave form as step 1. After instructing the software to capture data, the probe is placed over the radial artery, usually of the right hand, and 10 s worth of stable data is obtained as shown by the strip with repeated wave forms as step 2. The end of that panel shows a variety of QC data which can be used to accept or repeat the wave form. The output is shown as step 3, with an ensemble radial waveform on the left and an algorithm-derived aortic waveform on the right. These waveforms represent a composite of forces that govern wave transmission as shown by the boxed arrows, including the nature and rate of left ventricle (LV) ejection, the magnitude of wave reflection, and the pulse wave velocity which is related to arterial stiffness

forms are captured and information on central aortic pressure wave forms are obtained. Central aortic systolic, diastolic, mean, and pulse pressures can easily be obtained from the contour and the peak/trough values of the central aortic pressure wave forms. Augmentation of central aortic pressure can be quantified as the amount of pressure added to the systolic pressure peak due to the wave reflection. The ratio of the augmentation pressure portion to the total central pulse pressure is termed as augmentation index and expressed as percentage. The augmentation index is sometimes "normalized" to a heart rate of 75 bpm. Compared to carotid artery, radial artery applanation tonometry is more comfortable for the patients and easier to use in the clinical settings.

Aortic PWV can be determined by capturing arterial wave forms from two sites, typically carotid and femoral, and measuring the distance between the two sites and time required for the waves to travel [5]. Compared to ultrasonography or magnetic resonance image-based approach, applanation tonometry is easier to use and less expensive and time consuming.

10.4 Value of Measuring Central Arterial Pressure and PWV in African Americans

Most of the knowledge about the value of central aortic pressure measurements in African Americans comes from cross-sectional studies involving normotensive and hypertensive study participants. In studies of healthy African Americans, a higher augmentation index and relatively higher central systolic pressure (less amplification of systolic pressure from the central aorta to the brachial artery) are observed, compared with subjects of European ancestry [45]. In adolescent African Americans, the relationships of central systolic and pulse pressure to left ventricular mass were stronger than the relationships of conventional brachial systolic and pulse pressure [46]. In native Africans in South Africa, a study of 635 subjects using tonometry to assess central pressure profiles showed that the ratio of sodium to potassium intake significantly predicted the augmentation index, as well as office and central pulse pressure [47]. Thus, sodium intake, a modifiable factor, could be leveraged to improve cardiovascular risk through anticipated beneficial effects on central and peripheral pulse pressures.

In a substudy of African Americans with stage 2 hypertension, we found that treatment with an aliskiren/HCTZ combination approach, compared with amlodipine alone, produced similar reduction in brachial BP (office and 24 h), but a significantly greater reduction of central systolic pressure that was 30 mmHg in the aliskiren/HCTZ group compared with 21 mmHg in the amlodipine group [48]. Beta blockers have fallen out of favor as an initial antihypertensive choice because of concerns about less effective stroke prevention, particularly in older people, compared with other agents that reduce BP to the same degree. This was shown in the Conduit Artery Function Evaluation (CAFÉ) study [49], where treatment with an atenolol-based regimen had a higher central systolic (and central pulse pressure)

profile despite nearly identical degrees of brachial BP reduction with an amlodipine-based regimen, though this was undertaken almost exclusively in white Europeans. The use of beta-blockade in African Americans has a similarly higher central systolic pressure compared to African Americans not treated by beta-blockade despite similar brachial BP [50].

In the largest meta-analysis of central pressure profiles undertaken to date, ethnic differences in central augmentation indices were evident when comparing Africans (from South Africa) with Europeans, American Indians, Chinese, and Andean Hispanic cohorts [51]. In this report of 10,550 adults, the authors examined the central augmentation index findings in a healthy reference sample of 3,497 subjects. They observed that central augmentation indices in healthy African men averaged about 37 % compared with values ranging from 22 to 30 % in other ethnic groups. Similarly, African women had central augmentation indices that averaged about 55 % compared with values of 32–50 % in other ethnic groups. This study also derived ethnic-specific normative equations that incorporated measures of age, gender, height, and heart rate.

In summary, most of the central pressure data on African Americans and those of African descent are cross-sectional in nature. They typically show that measures of central pressure are higher in African Americans and those of African descent when compared with other ethnicities, which is usually not apparent from knowledge of the brachial BP alone.

Most of what is known about the value of PWV measurements in African Americans also comes from cross-sectional studies involving normotensive and hypertensive study participants. Studies of healthy African American subjects have observed higher PWV when compared with subjects of European ancestry [45]. In the Chronic Renal Insufficiency Cohort (CRIC) study, we noted that PWV values were about 0.5 m/s higher in African Americans compared with participants who designated their race as white, after adjusting for differences in mean arterial pressure [52].

In one of the few longitudinal studies of arterial stiffness, investigators of the Study of Women's Health Across the Nation (SWAN) examined PWV twice (separated by 2.3 years) in 99 African Americans and 204 Caucasian women [53]. In both groups of these middle-aged women, baseline systolic pressure and waist circumference measures were the strongest factors associated with greater 2-year progression of aortic PWV after adjustments for age and cardiovascular and psychosocial risk factors. In African American women only, the diastolic pressure, LDL-C, and, to a lesser extent, glucose levels were associated with greater PWV progression.

Mechanisms proposed to explain the greater degree of arterial stiffness in African American populations are reduced concentrations of vitamin D [45], and higher systolic and pulse pressure which in some studies is associated with greater arterial stiffness in men [54] and in other studies with both men and women [55]; higher blood pressures are also associated with higher PWV in adolescent African Americans [56] especially when compared to Caucasian populations. Additionally, preliminary work suggests that about 20 % of the PWV phenotype is heritable, but identifying specific genes, particularly in African American populations, is still in a

discovery phase [57]. The β_2 receptor, when stimulated by isoproterenol, reduces PWV in Caucasians but not African Americans, indicating a blunting of the response to vasodilatory influences [58]. As in other populations [59], the presence of diabetes is associated with increased PWV in African American adolescents. When compared with adolescent Caucasian diabetics, PWV was 0.75 m/s faster in the African American subjects [60]. In this same study, both the Caucasian and the African American adolescents had pronounced effects of age, obesity, and blood pressure on PWV. However, in the African Americans, there was no modifying effect of HDL cholesterol as there was in the Caucasian adolescents nor did the duration of diabetes matter in the African Americans whereas it was significantly related to PWV in the Caucasians. Another mechanism invoked to explain the higher PWV in African Americans is aerobic fitness. In a study of 33 African Americans compared with 215 Caucasians, maximal oxygen uptake on treadmill testing was significantly higher in Caucasians compared with African American subjects, while BMI was lower in the Caucasians [61]. The aortic PWV was significantly lower in the Caucasian group by 0.9 m/s. When carefully matched for BMI and maximal oxygen use, the differences in PWV disappeared, arguing for an influence of aerobic fitness on PWV.

10.5 Summary

A growing body of cross-sectional evidence indicates that there are differences, generally in an adverse direction, in central arterial pressure, arterial stiffness, and PWV in Africans and African-Americans, when compared with Caucasians. The importance of such differences and their susceptibility to modulation by lifestyle, drug, or both interventions await support from clinical trial evidence.

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Chapter 11
Renal Denervation Therapy and Baroreceptor Activation Therapy: Emerging Tools for Treating Resistant Hypertension

Peter D. Hart, Priyanka Gosain, and George Bakris

11.1 Introduction

Resistant hypertension is defined as failure to achieve a guideline-driven blood pressure (BP) of less than 140/90 mmHg in patients who are adherent to maximally tolerated doses of at least three antihypertensive drugs, one of which must be a diuretic appropriate for kidney function [1, 2]. Persons with resistant hypertension have a high absolute cardiovascular and renal risk [3]; higher prevalence of target organ damage and blood pressures that are more difficult to control [4].

The prevalence of resistant hypertension among US adults continues to rise. Population-based studies published recently indicate that the prevalence of resistant hypertension ranges from 3 to 10 % of people with hypertension in the USA [5]. This translates to 2.5–8 million people, raising a major concern that despite the improvement in BP control rates observed in the past decade, prevalence of resistant hypertension continues to increase. The reasons for this observation include the association between resistant hypertension and risk factors such as African-American ethnicity, obesity, advanced age, diabetes, and chronic kidney disease

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K.C. Ferdinand (ed.), *Hypertension in High Risk African Americans*, Clinical Hypertension and Vascular Diseases, DOI 10.1007/978-1-4939-2010-5_11

(CKD) [6]. Presence of these independent risk factors makes hypertension more difficult to control and substantially increases cardiovascular and renal disease [7].

The prognosis of resistant hypertension is not adequately defined. Indirect published data indicate that resistant hypertension is associated with poor prognosis. Major cohort studies show that increased risk of stroke, myocardial infarction, congestive cardiac failure, and kidney failure is directly linked to the extent of BP elevation [8, 9]. Additionally, there is published evidence that resistant hypertension usually occurs in patients with high cardiovascular risks, e.g., age >55 years, obesity, diabetes, and CKD [10–12].

Patients with resistant hypertension are more likely to have hypertension-associated target organ damage including left ventricular hypertrophy (LVH), microalbuminuria, retinopathy, and thickening of the carotid intima vessels. Indeed, cross-sectional studies of large cohorts of hypertensive patients showed that resistant hypertension is associated with higher comorbidity, more target organ damage, and higher rates of cardiovascular disease than in patients without resistant hypertension [13, 14].

The extent to which cardiovascular morbidity and mortality related to resistant hypertension is reduced by optimal blood pressure control is controversial [15]. However, major outcome studies support the notion that higher baseline blood pressure and larger decreases in blood pressures with treatment are associated with marked reduction in hypertension-associated target organ damage [16].

Despite the availability of numerous effective BP lowering agents—seven drug classes and over 120 different medications, including fixed dose combinations—36 million (48 %) of the 75 million adults in the USA with hypertension do not reach goal blood pressure [17]. A majority of these patients have resistant hypertension and its prevalence especially among African Americans continues to rise as populations around the world age and become more obese.

A leading contributing factor for this lack of adequate BP control is failure to inhibit the sympathetic nervous system (SNS) optimally, which plays an important role in chronic BP elevation. Adrenergic overdrive in younger people and altered sympathetic and parasympathetic balance in older people trigger elevated BP and its consequences such as LVH and metabolic abnormalities. Pharmacologic inhibition of the SNS with centrally active α2-adrenergic receptor drugs such as α-methyldopa and clonidine effectively decreases BP in most people with this problem, but these drugs elicit intolerable side effects thereby limiting their use [17]. Alternative device therapies are now being explored to rectify this problem.

Recent technical advances targeting the renal sympathetic nerves, i.e., renal denervation therapy (RDT), and increased sympathetic activity of the carotid sinuses, i.e., baroreceptor activation therapy (BAT), have renewed interest in invasive therapy for resistant hypertension. Both procedures have firm pathophysiological background in experimental and clinical studies. This chapter will review the basis, main features, efficacy, and safety of these two emerging tools—RDT and BAT in patients with resistant hypertension.

11.2 Renal Denervation Therapy

11.2.1 Role of Renal Nerves in the Development and Progression of Hypertension

The afferent and efferent renal sympathetic nerves have been intimately linked with the pathophysiology of hypertension in both animal and human experimental models [18]. Renal afferent nerves are activated in response to various stimuli, such as renal ischemia, renal parenchymal injury, and hypoxia. These nerves send signals to the posterior hypothalamus and directly influence central sympathetic outflow, which innervates the heart, the peripheral vasculature, and the kidney itself. The stimulation of these nerves causes an increase in cardiac contractility, heart rate, and rhythm. They also control intravascular circulating blood volume through alterations in tone of the splanchnic storage vessels and have a role in regulation of salt and water reabsorption through efferent renal innervation [19].

The efferent renal sympathetic nerves supply the juxtaglomerular apparatus, the renal tubules, and the renal blood vessels [20]. These exclusively noradrenergic nerves show a graded response to stimulation, starting with an initial increase in renin secretion rate (β-1 adrenoreceptors), followed by an increase in proximal tubular sodium reabsorption (β-1), and with continued stimulation, a direct α-1 adrenergic-mediated increase in renal vascular resistance [21, 22]. The increase in efferent activity in patients with hypertension has been demonstrated by the increased rate of "norepinephrine spillover," which uses a radiotracer dilution method to quantify the amount of norepinephrine that is in excess after neuronal uptake, and can therefore be measured in the circulation. The effects of efferent stimulation cause a rightward shift of the pressure-natriuresis curve and thus lead to progression and sustenance of hypertension [23].

Increased sympathetic drive has been implicated particularly in hypertension secondary to obesity and renal insufficiency [24]. Some studies have also shown a heightened sympathetic activity in the African-American male population, independent of other comorbidities [25, 26]. Therefore, a reduction of excessive central sympathetic activity by removal of afferent signals to the hypothalamus and the removal of the renal nerves affecting the response to these signals is a therapeutically attractive target in the treatment of patients with resistant hypertension.

11.2.2 Surgical Denervation Studies in Man

Surgical sympathectomy was used in humans since the early 20th century. The surgery classically involved a splanchnicectomy [27] and/or removal of lumbar and thoracic sympathetic ganglia [27–29]. In general, more extensive procedures were used for the younger patients who were more symptomatic, and smaller operations were reserved for the elderly [28]. Although there are no studies that compared

these surgeries with randomized control cohorts on medical therapy, there is indisputable evidence of marked improvement in blood pressure recordings in patients with severe hypertension treated in this way [27–31].

Despite the favorable effect on blood pressure, these surgeries were associated with myriad adverse effects related to the effects of the sympathectomy and to the surgery itself. Patients suffered severely limiting post-procedure hypotension [28, 29]. Some patients reported vasospasm of the hands and intercostal neuralgia [28, 29]. Most men who underwent lumbar sympathectomy were rendered impotent [29]. Other long-term effects predictably included bowel and bladder dysfunction [31]. The surgery required the chest to be opened and this was associated with the common occurrence of pleural effusion and lung collapse [28]. There was also a substantial reported mortality of about 7 % associated with this major surgery [28]. With the advent of antihypertensive medications, this technique was abandoned in the early 1970s [32].

Another classical approach has been to block the sympathetic system with drugs. Ganglion-blockers were used in the past and fell out of favor due to their adverse effects. More recently antiadrenergic drugs are being used, but only as second- and third-line antihypertensive agents, as they have undesirable side effect profiles and are not as effective as other available pharmacologic therapy.

11.2.3 Catheter-Based Renal Denervation

Early clinical studies with catheter-based, selective renal sympathetic denervation in patients with resistant hypertension have demonstrated clinically significant, sustained reductions in blood pressure-Symplicity HTN-1 [40] and Symplicity HTN-2 [39]. The SYMPLICITY HTN-3 is an ongoing RCT that will enroll 530 patients in various centers throughout the USA and rigorously determine the efficacy and safety of RDT in the treatment of resistant hypertension [33].

11.2.3.1 Procedure

Two types of catheters are available for renal sympathetic denervation, the Symplicity catheter (Ardian Inc., Palo Alto, CA) and the PARADISE catheter (ReCor Medical, Ronkonkoma, NY). Also, some investigators have used the standard radio frequency ablation catheter and achieved similar results [34, 35]. Another new catheter, the EnligHTN multielectrode system (St. Jude Medical Inc., St. Paul, Minnesota), is being investigated [36] in the ARSENAL (Safety and Efficacy Study of Renal Artery Ablation in Resistant Hypertension Patients) study in Greece and Australia. Other catheters using radio frequency or ultrasound techniques are being used in various ongoing trials [37].

After establishing access to the renal artery via the femoral artery, the catheter is advanced to the distal section of one renal artery. Low power (<8 W) radio frequency energy is delivered to the endothelial layer through an electrode for an average of 2 min. This leads to transmural lesions and damage to the sympathetic fibers traveling in the adventitia of the arterial wall. The catheter is then pulled back and radio frequency energy applied five or six times longitudinally and circumferentially in the artery. This is repeated in the contralateral renal artery.

While the procedural technique remains essentially the same, the three specialized catheters have subtle differences in their design. The PARADISE catheter uses ultrasound energy and has a balloon that enables cooled fluid to circulate during the energy delivery process to keep the artery wall cool, minimizing damage to nontarget tissues. The energy used with this catheter is higher than the Symplicity catheter (25 W compared with approximately 8 W). Similar to the Symplicity catheter, the EnligHTN catheter uses radio frequency ablation. However, the multielectrode basket design of the EnligHTN catheter allows for simultaneous energy delivery to four sites along the endoluminal surface of the artery. This has the potential benefit of reducing renal denervation procedural time. This may translate into a reduction in procedural pain, a side effect of renal denervation using the Symplicity catheter.

11.2.3.2 Efficacy

The efficacy of this procedure in lowering blood pressure has been demonstrated in two large randomized controlled trials: the Symplicity HTN-2 that enrolled 106 patients, 52 cases (54 controls) and the trial by Ukena and colleagues with 37 cases (9 controls) [38, 39]. Encouraging evidence was also observed in several case series, the largest of which enrolled 153 patients [40]. Ukena and colleagues showed a decrease in blood pressure of −31/−9 mmHg at 3 months (compared with 0/+1 in the control group) (Table 11.1) [38]. The Symplicity HTN-2 investigators reported an absolute decrease of −32/−12 mmHg at 6 months (compared with +1/0 in the control group) and −28/−9 mmHg at 1 year follow-up (Table 11.1) [39]. The earliest blood pressure reduction was reported immediately after the procedure and at 2 weeks [41]. In his case series, Krum followed patients for 1 year and showed a sustained decrease of −27/−17 mmHg [42]. Other case series have reported similar reductions in blood pressure. The Symplicity HTN-1 investigators reported the longest follow-up of 2 years and demonstrated a sustained decrease of blood pressure of −32/− 14 mmHg from baseline (Table 11.1) [40]. In a large systematic review, out of 128 patients with available follow-up, 48 (37 %) achieved a systolic BP of <140 mmHg [43].

There is also some preliminary data that shows the efficacy of renal nerve denervation in reducing LVH and improving diastolic parameters in patients with resistant hypertension [44].

Table 11.1 Selected studies of renal denervation therapy in resistant hypertension

Study/location/ funding source	Design	Patient characteristics	Intervention	Follow-up duration	Change in SBP/ DBP (mmHg)	Adverse effects
Ukena [38]	Randomized controlled trial	Ethnicity: NR; women: 32 %; mean age: 59.1 ± 9.4; BMI: 31.8 ± 5.2; DM: 43 %; eGFR: 70 ± 24; diuretics: 89 %; average number of antihypertensive medications: 5.9 ± 1.4	Patients recruited from Symplicity HTN-2 trial. Method of denervation not specified separately	3 m: No loss to follow-up reported	3 m: −31/−9	None reported
Location: Germany	*N* (cases) = 37					
Funding source: Not declared	*N* (controls) = 9	Ethnicity: NR; women: 21 %; mean age: 64.9 ± 6.4; BMI: 30.2 ± 4.6; DM: 22 %; eGFR: 64.5 ± 16; diuretics: 78 %; average number of antihypertensive medications: 5.0 ± 1.2		3 m: No loss to follow-up reported	3 m: 0/−1	

Symplicity HTN-2 [39]	Randomized controlled trial	Caucasian: 98 %; women: 35 %; mean age: 58 ± 12; BMI: 31 ± 5; DM: 40 %; eGFR: 77 ± 19; diuretics: 89 % (aldosterone antagonist: 17 %); average number of antihypertensive medications: 5.2 ± 1.5	4–6 ablations on bilateral renal arteries, duration of ≤2 min at a maximum power of 8 W. Heparin used to maintain activated clotting time of >250 s	6 m: 49	6 m: −32/−12	Intra-procedural bradycardia requiring atropine (7)
Location: Australia	*N* (cases) = 52				12 m: −28.1/−9.7	Femoral artery pseudoaneurysm (1)
Funding source: Ardian Inc.						Low BP requiring decrease in number of drugs (1)
						UTI (1)
						TIA (1)
						Angina requiring stent (1)
						Hypertensive emergency (3)
	N (controls) = 54	Caucasian: 96 %; women: 50 %; mean age: 58 ± 12; BMI: 31 ± 5; DM: 28 %; eGFR: 86 ± 20; diuretics: 89 % (aldosterone antagonist: 17 %); average number of antihypertensive medications: 5.2 ± 1.5		6 m: 51	6 m: +1/0	TIA (2)
						Angina requiring stent (1)
						Hypertensive emergency (2)
Krum [42]	Case–control	Non-Caucasian: 4 %; women: 44 %; mean age: 58 ± 9; BMI: NR; DM: 31 %; eGFR: 81 ± 23; diuretics: 96 %; average number of antihypertensive medications: 4.7 ± 1.5	Six ablations on bilateral renal arteries with a maximum duration of 2 min and energy of 8 W. Heparin used to maintain activated clotting time of >250 s	1 m: 41	1 m: −14/−10	Renal artery dissection requiring stent placement (1)
Location: Australia	*N* (cases) = 45			3 m: 39	3 m: −21/−10	Femoral artery pseudoaneurysm (1)
Funding source: Ardian Inc.				6 m: 26	6 m: −22/−11	
				9 m: 20	9 m: −24/−11	
				12 m: 9	12 m: −27/−17	

(continued)

Table 11.1 (continued)

Study/location/ funding source	Design	Patient characteristics	Intervention	Follow-up duration	Change in SBP/ DBP (mmHg)	Adverse effects
Hering [52]	Case series	Ethnicity: NR; women: 40 %; mean age: 61 ± 9; BMI: 33 ± 8; DM: 73 %; eGFR: 31.2 ± 8.9; diuretics: 100 %; average number of antihypertensive medications: 5.6 ± 1.3	Average of 9.9 ± 1.5 ablation treatments using a predetermined treatment protocol as in Symplicity HTN-1 trial	3 m: 15	1 m: −34/−14	None reported
Location: Australia	*N* = 15			6 m: 8	3 m: −25/−11	
Funding source: National Health and Research				12 m: 5	6 m: −32/−15	
Council of Australia and the Victoria Government's					12 m: −33/−19	
Operational Infrastructure Support Program						
Symplicity HTN-1 [40]	Case series	Non-Caucasian: 5 %; women: 39 %; mean age: 57 ± 11; BMI: NR; DM: 31 %; eGFR: 83 ± 20; diuretics: 95 % (aldosterone blocker: 22 %); average number of antihypertensive medications: 5.1 ± 1.4	4–6 ablations on bilateral renal arteries, duration of ≤2 min at a maximum power of 8 W. Heparin used to maintain activated clotting time of > 250 s	1 m: 138	1 m: −20/−10	Renal artery dissection requiring stent placement (1)
Location: Australia, Europe and the USA	*N* = 153			3 m: 135	3 m: −24/−11	Femoral artery pseudoaneurysm/hematoma (1)
Funding source: Ardian Inc.				6 m: 86	6 m: −25/−11	Bilateral flank pain—persistent for few months (1)
				12 m: 64	12 m: −23/−11	Bilateral flank/ back pain—transient (3)
					24 m: −32/−14	Transient dizziness (6)

BMI body mass index, *eGFR* estimated glomerular filtration rate, *DM* diabetes mellitus, *NR* not reported, *UTI* urinary tract infection, *TIA* transient ischemic attack

11.2.3.3 Home-Based BP Measurement and Ambulatory Blood Pressure Monitoring

Symplicity HTN-2 investigators reported a significant decrease in home-based blood pressure measurements (−20/−12 mmHg). A significant decrease in ambulatory blood pressure measurements was also reported: −11/−7 mmHg (Symplicity HTN-2) [39] and −11 mmHg [42].

Some studies, however, did not demonstrate a decrease in ambulatory blood pressure monitoring (ABPM) even though significant changes were reported in clinic measurement of BP [45].

Norepinephrine spillover is a marker of the effectiveness of efferent renal denervation. Krum and colleagues reported a 47 % decrease in renal norepinephrine spillover in ten patients in the intervention group [42]. Simonetti reported no change in urine catecholamines [46].

11.2.3.4 Decrease in Number of Medications

Even though most studies to date demonstrate a significant decrease in blood pressure readings, this has not completely translated into a decrease in the use of pharmacologic therapy in treated patients. In most studies, the average number of antihypertensive medications being used by patients with resistant hypertension is five. While some studies have reported a decrease in the use of antihypertensive medications in 10–25 % of the treated patients [40, 44, 47, 48], others showed no change in the preexisting antihypertensive regimens [34, 38, 49].

There is no data on the efficacy of this technique specifically in the African American population. Most studies have not reported the ethnicity of the study population. Of those that have reported ethnicity, a very small number of patients were non-Caucasian. However, the sympathetic system has been implicated at least in part in causing and sustaining hypertension in African Americans [25, 26] and therefore, study results are probably valid in this population.

11.2.3.5 Effect on Quality of Life

A recent analysis of effects on quality of life after RDT showed that there was significant increase in the vitality, social function, role emotion, and mental health domains. There were also improvement in the depression scores, particularly with regard to symptoms of sadness, tiredness, and libido. The magnitude of BP reduction was not associated with the change in quality of life [50].

11.2.4 Safety

From the available data and follow-up, it appears that this procedure is relatively safe, with no reported long-term adverse effects.

The periprocedural adverse events have included pseudoaneurysm formation [38, 40, 44, 47] and renal artery dissection in a few patients [40, 44]. These were repaired and did not lead to any long-term consequences. A minority of patients complained of back and/or flank pain during and immediately after the procedure [40, 41, 47]. Post-procedural hypotension and intra-procedural bradycardia occurred in some patients [47, 51]. There were no changes in renal artery anatomy or development of clinically significant stenosis on follow-up computed tomographic angiography and magnetic resonance imaging studies.

In Symplicity HTN-1, all patients had normal baseline renal function. Of 153 patients, follow-up estimated glomerular filtration rate (eGFR) was available at 24 months for 10 patients (6.5 %) and showed a mean reduction of eGFR by 16 mL⁄min⁄1.73 m^2 [40]. However, no significant change in serum creatinine, development of CKD Stage IV, or the requirement for dialysis was reported. Hering and colleagues conducted this procedure in 15 patients with CKD and a mean baseline eGFR of 31.2 ± 8.9 mL⁄min⁄1.73 m^2, and no significant change in eGFR, serum creatinine, or proteinuria was reported (Table 11.2) [52].

11.2.5 Limitations

In all the interventional trials, only renal arteries with an anatomy favorable to catheter-based therapy (minimal length of 20 mm and minimal diameter of 4 mm) were included [43]. Therefore, until new data or new techniques become available, patients must be selected after careful imaging of the renal arteries. Additionally, there is no test to evaluate whether renal denervation was successful immediately following the procedure. Hence, one must wait weeks to months to evaluate the success of the procedure.

Additionally, the available studies have not fully evaluated the 24-h ambulatory blood pressure response; SYMPLICITY HTN-3 will correct this problem. Lastly, hypertension in patients with renal insufficiency has been shown to be linked to sympathetic overdrive. However, these patients were excluded in the larger randomized control trials, even though some smaller studies have been done in this subset [52]. Based on current data, this technique is not approved for patients with moderate renal insufficiency; however, there are case series emerging in the European Union in patients on hemodialysis showing promising results.

Table 11.2 Selected studies of baroreceptor activation therapy in resistant hypertension

Study/location/funding source	Design	Patient characteristics	Intervention	Follow-up duration: *N*	Decrease in blood pressure (SBP/DBP) (mmHg)	Adverse effects
Rheos Feasibility Trial [67]	Case series	Ethnicity: NR; Women: 40 %; Mean age: 50 ± 13; Average number of anti-hypertensive medications: 6 ± 1	Rheos system; activated one month after implantation	3 months: 10	3 m: −22/−18	No adverse events
Location: United States	*N* = 10				12 m: −35/−16	
Funding: CVRx, Inc., Minneapolis, MN						
DEBUT-HT [68]	Case series	African American: 0 %; Women: 42 %; Mean age: 54 ± 9; BMI: 32 ± 6; DM: 31 %; Renal insufficiency: NR; Diuretics: 100 %; Average number of antihypertensive medications: 5	Rheos system; device activated 1 month after implantation. At each follow up visit, therapy was individualized with the programmer to achieve optimal BP reduction.	3 m: 37	3 m: −21/−12	Infection (3)
Location: Europe, multicentre	*N* = 45			1 y: 26	1 y: −30/−20	Perioperative stroke with minimal residual effects (1)
Funding source: CVRx, Inc., Minneapolis, MN				2 y: 17	2 y: −33/−22	Injury to the hypoglossal nerve (1)
				4 y: 18	3 y: −40/−21	
					4 y: −53/−30	Moderate pulmonary edema that resolved within 6 days (1)
						Device movement, requiring re-implantation (1)

(continued)

Table 11.2 (continued)

Study/location/funding source	Design	Patient characteristics	Intervention	Follow-up duration: *N*	Decrease in blood pressure (SBP/DBP) (mmHg)	Adverse effects
Rheos Pivotal Trial [70]	Randomized control trial	African Americans: 17 %; Women: 36 %; Mean age: 53.7 ± 10.5; BMI: 32.6; DM: 31 %; Renal insufficiency: NR; Diuretics: 96 %; Average number of antihypertensive medications: 5.2 ± 1.6	Subjects received either BAT (Group A) for the first 6 months or delayed BAT initiation following the 6-month visit (Group B)	6 m: 181	6 m: SBP-26	Surgical complication, 13 (4.8 %)
	Group A			12 m: 180	12 m: SBP-35	Nerve injury with residual
	N = 181					Deficit, 13 (4.8 %)
						Transient nerve injury, 12 (4.4 %)
						Respiratory complication, 7 (2.6 %)
						Wound complication, 7 (2.6 %)
						Hypertensive crisis (Group A) 9 (5 %)
						Hypertensive crisis (Group B) 7 (8.3 %)
	Group B	African Americans: 21 %; Women: 45 %; Mean age: 52.4 ± 9.8; BMI: 32.2; DM: 35 %; Renal insufficiency: NR; Diuretics: 92 %; Average number of antihypertensive medications: 5.2 ± 1.8		6 m: 84	6 m: SBP-17	Hypertension-related stroke, 6 (2.3 %)
	N = 84			12 m: 84	12 m: SBP-33	

BMI body mass index, *eGFR* estimated glomerular filtration rate in mL/min/1.73 m^2, *DM* diabetes mellitus

11.3 Baroreceptor Activation Therapy (BAT)

11.3.1 Role of Baroreceptor Activation in Development and Progression of Hypertension

The carotid sinus baroreceptors, located at the bifurcation of the common carotid artery, play an important role in the control of both short- and long-term fluctuation in blood pressure. They are mechanoreceptors that respond to vascular distention. Stimulation of the stretch-sensitive afferent nerves in the carotid sinus by either elevated BP or increased intravascular volume triggers the baroreceptor signal that travels from the carotid sinus nerve through the glossopharyngeal nerve (CN IX) to the nucleus tractus solitarius in the medulla. This leads to an inhibition of sympathetic output, decrease in heart rate and cardiac contractility, and subsequently reduction of blood pressure [53].

Arterial baroreceptors were initially thought to play little or no role in chronic long-term control of sympathetic activity and blood pressure [54, 55]. However, Lohmeier et al. [56, 57] elegantly showed that prolonged baroreceptor activation in an animal model of obesity-induced hypertension reduced arterial pressure and plasma norepinephrine as well as whole-body norepinephrine spillover rates. Thus, baroreceptor activation may chronically suppress the sympathetic activation associated with obesity and help blunt the increases in BP associated with this condition. Additionally, baroreflex activation may exert an inhibitory effect on renin excretion via sustained reduction in renal sympathetic nerve activity (RSNA) [58]. Lohmeier's group also showed that the chronic BP lowering effect of baroreflex activation was reduced by 75 % in angiotensin-II-induced hypertension, demonstrating that long-term antihypertensive effects of baroreflex activation are diminished in the presence of high circulating angiotensin-II levels [59]. This observation emphasizes the importance of baroreflex-induced suppression of renin secretion, likely via decreased RSNA, and subsequent enhancement of pressure natriuresis. These elegant preclinical animal studies have provided detailed insight into the mechanisms responsible for long-term lowering of blood pressure during prolonged baroreceptor activation. It seems likely that carotid baroreflex activation initially lowers blood pressure by suppression of central sympathetic outflow, but chronic lowering of blood pressure requires suppression of RSNA, decreased renin release, increase in sodium excretion, and maintenance of sodium balance [60]. Additionally, it is likely that other mechanisms beyond renal sympatho-inhibition may be involved [61, 62].

Lastly, hypertensive patients with risk factors such as African American ethnicity, older age, obesity, and sleep apnea commonly have increased sympathetic activity and resistant hypertension. Thus, increased sympathetic activity may have a hitherto unappreciated role in the pathogenesis of resistant hypertension. Clearly, if this hypothesis is correct, suppression of central and renal nerve sympathetic activity by baroreceptor activation should translate into blood pressure decreases among

patients with resistant hypertension. When and how BAT will be fully introduced in hypertension clinical practice may depend on factors such as extent of blood pressure reduction, device invasiveness, battery life, adverse outcome, long-term safety profile, patient selection, and lifetime treatment costs.

11.3.2 Early Baroreceptor Activation Devices

The feasibility of reversing hypertension by carotid sinus nerve stimulation dates back to the 1950s. Carlsten et al. demonstrated that electrical stimulation of the carotid sinus nerve was associated with decreased mean arterial pressure and heart rate [63]. Subsequently, Bilgutay et al. implanted an electrical stimulator (called "baropacer") in a severely hypertensive patient (BP 260/165 mmHg) and noted a prompt decrease in BP to 150/90 mmHg [64]. Subsequently, in 1965, Schwartz et al. tested the device in 8 patients with BP >190/110 mmHg for a duration of 5 months to 2.5 years [63]. In all patients BP decreased by an average of −48/42 mmHg and six patients discontinued oral antihypertensive drugs altogether. However, these early devices had major limitations that precluded their use in clinical practice. They were bulky, implantation was very invasive, and due to the inability to individualize dose, most patients developed postural hypotension and bradycardia. Local nerve and soft tissue irritation from implantation of the stimulator and frequent adjustment of electrical stimulation frequency caused these devices to fall out of favor [65].

11.3.3 Rheos BAT System Device

The resurgence of carotid sinus stimulator therapy began with the observation that even with the numerous oral antihypertensive agents currently available, prevalence of resistant hypertension in the developed countries continues to rise. The Rheos hypertension system (CVRx, Minneapolis, MN) is a new implantable carotid baroreceptor stimulator specifically being used to treat patients with resistant hypertension. The device consists of an implantable pulse generator, bilateral carotid leads, and a programmer system. The generator has a battery and circuit system that activates the carotid sinus receptors with variable amounts of energy in a temporally varying pattern through the carotid leads. The programmer system is computer based and allows noninvasive communication with and control of the generator via radio frequency coupling. The device is surgically implanted by open bilateral carotid exposure and perivascular lead implantation. The procedure is done under narcotic anesthesia to preserve the carotid reflex for assessment of optimal lead placement [65, 66].

11.4 BAT Efficacy and Safety

Clinical trials in the USA and Europe have been done to assess feasibility, efficacy, and safety of BAT in patients with resistant hypertension.

The Rheos Feasibility Trial was a US-based case series that studied ten patients with resistant hypertension after receiving BAT [67]. Eligibility criteria was SBP >160 mmHg despite receiving maximal doses of three or more antihypertensive drugs including a diuretic. Patients with secondary causes of hypertension, baroreflex dysfunction, and known carotid disease were excluded. Dose–response testing at 0–6 V was assessed prior to discharge at monthly intervals, and the device was activated after 1 month of implantation. Of the study participants, 40 % were African American, and 40 % were women, with an average age of 50 ± 13 years. At baseline, office BP was 180 ± 29/114 ± 19 and after 3 months, SBP (−22 mmHg, $p = 0.01$) and DBP (−18 mmHg, $p = 0.007$) decreased. No episodes of symptomatic hypotension, bradycardia, heart blocks, or adverse renal events were reported (Table 11.2).

Another important case series was the Device-Based Therapy in hypertension Trial (DEBuT-HT), a multicenter European study to evaluate the efficacy and safety of BAT in patients with severe hypertension [68]. Eligibility, exclusion criteria, and study protocols were similar to the Rheos Feasibility Trial with an average of five antihypertensive drugs including diuretics (100 %). Forty-five patients were enrolled in the study and 18 successfully completed 4 years of follow-up. All were Europeans, 42 % were women with an average age of 54 ± 9 years, average BMI 32 ± 6, and 31 % had diabetes mellitus. Of note, at each follow-up visit, therapy was individualized with the programmer to achieve optimal BP reduction. At baseline, office BP was 179 ± 29/105 ± 22 mmHg and after 3 months SBP decreased −21 mmHg ($p < 0.001$) and DBP decreased −12 mmHg ($p < 0.001$). Sustained and statistically significant SBP/DBP decreases were observed at follow-up of −30/20 mmHg at 1 year, −40/−21 mmHg at 3 years, and −53/−30 mmHg at 4 years (Table 11.2). In total 72 % of patients achieved a 30 mmHg sustained decrease in SBP at 3 years [69]. This trial demonstrated that BAT was effective in lowering BP and maintained optimal BP levels in patients with resistant hypertension. In terms of safety profile, adverse events were mostly procedure related (16 %) and only one device-related event was recorded.

The recently published prospective randomized control study, Rheos Pivotal Trial [70] also evaluated the efficacy and safety of BAT in patients with resistant hypertension. Two hundred and sixty-five patients with resistant hypertension were implanted with the Rheos system and after 1 month randomized (2:1) to receive active BAT for the first 6 months (Group A) or delayed BAT, initiation following the 6-month visits (Group B). Resistant hypertension was defined as office BP ≥160/80 mmHg and 24-h ambulatory SBP ≥135 mmHg despite at least 1 month of maximally tolerated therapy with ≥3 antihypertensive drugs including a diuretic. The five co-primary end points were (1) clinically significant reduction of office SBP at 6 months, (2) sustained responder rate at 12 months, (3) procedure safety, (4) device safety, and (5) BAT safety. Ninety-nine percent (264/265) of patients

completed an average duration of 21 months of BAT with the Rheos system. Of the patients studied, 17 % were African American and 36 % were women. The average age was 53 ± 10 years, average BMI was 32.6, 31 % had diabetes, and the average number of antihypertensive drugs was five. Baseline office SBP and DBP for Groups A and B were 169 ± 26/101 ± 17 mmHg and 168 ± 24/100 ± 14 mmHg respectively. The trial did not meet two of the five pre-specified co-primary end points in short-term efficacy and safety.

Early BAT (Group A) reduced SBP by −26 mmHg at 6 months and −35 mmHg at 12 months, while delayed BAT (Group B) reduced SBP by −17 mmHg and −33 mmHg at similar time points, respectively. After a follow-up of 1 year, 81 % of the study participants had SBP reduction of 10 mmHg compared to baseline. Additionally, 63 % of the patients achieved SBP <140 mmHg with an average SBP reduction of 44 mmHg (Table 11.2).

Seven deaths (2.65 %) were reported during the study and none were adjudicated as procedure- or device-related occurrences. The main procedure-related side effects were associated with carotid sinus lead placement. Nerve injury, transient (4.4 %), or permanent (4.8 %) was reported at the time of implant.

After completion of the Rheos Pivotal Trial, patients participated in an open-label non-randomized follow-up study to assess long-term efficacy and safety of BAT [71]. Seventy-six percent of the implanted patients qualified as clinically significant responders and an additional 10 % were indeterminate. Among long-term responders (average follow-up 28 ± 9 months), the mean blood pressure decrease was −35/16 mmHg. Number of antihypertensive drugs that were reduced at 12 months in the Rheos Pivotal Trial remained lower during the follow-up period. Additionally, among responders, 55 % achieved goal systolic blood pressures (<140 or <130 mmHg in diabetes and kidney disease). This level of blood pressure reduction was sustained over the long-term follow-up of 22–53 months.

11.4.1 Limitations

Major limitations of the Rheos Pivotal Trial and other BAT studies include the need for surgical placement, bilaterally, of the electrodes around the carotid bifurcation. The new NEOS device that requires only unilateral placement and is smaller has rectified this problem. Hence, the procedure time has been reduced by more than 50 % and no overnight stay is required. Unlike RDT, patients with advanced kidney disease may have this procedure. Moreover, the procedure provides immediate response as to whether blood pressure will be reduced when the battery is activated and voltage increased. These results have been published and are highly reproducible [67, 70].

Taken together, current evidence indicates that BAT is safe, efficacious, and worthy of continued study in resistant hypertension. Procedure-, device-, and BAT-related adverse events occur predominantly in the short term, but longer-term follow-up data over 2 years does not have major side effects noted. Recent clinical

evaluation and validation of second generation, minimally invasive BAT system, such as the Barostim Neos, have begun in Europe and the USA. Clearly, lessons learned from the Rheos Pivotal study and ongoing studies with the Barostim Neos may provide great efficacy and safety and establish its role in the management of patients with resistant hypertension.

11.5 Summary and Conclusions

Experimental and clinical studies summarized in this chapter provide insight into the mechanisms that account for chronic reduction of blood pressure during suppression of central and renal nerve sympathetic activity. They present novel alternative approaches for BP treatment in patients with resistant hypertension. Results of published data to date indicate that these emerging therapies—RDT and BAT—enhance blood pressure control, reduce left ventricular mass, and improve metabolic profile in patients with resistant hypertension.

RDT has been shown to be efficacious and safe in lowering BP in carefully selected patients with resistant hypertension. However, published studies have some methodological limitations, and longer-term randomized control studies such as the ongoing SYMPLICITY HTN-3 trial will provide more robust data on the efficacy and safety of RDT including 24-h ABPM on all patients' pre- and post-procedure.

The recent feasibility trials showed that BAT is efficacious and safe in patients with resistant hypertension. Unlike the previous Rheos device, the new NEOS device being currently studied and awaiting FDA approval requires unilateral implantation, reduces time for insertion, and is an outpatient procedure. It may be better suited for patients with resistant hypertension who have CKD, as this is not an exclusion criterion unlike renal denervation. Moreover, a recent long-term follow-up of patients who received the device documented no adverse effects on kidney function [72]. It is noteworthy that few African American patients were enrolled in studies with both these devices, thus limiting the applicability and generalizability of this procedure to this group of patients who are disproportionately affected by resistant hypertension.

Selection of patients with resistant hypertension for RDT and BAT studies has so far been based on SBP >160 mmHg while taking a minimum of three antihypertensive medications including a diuretic. It seems too early to recommend which therapy—RDT or BAT—is better for optimal BP control and who might be an ideal candidate for which procedure. It is reasonable, however, to predict that hypertensive patients with risk factors for exaggerated sympathetic nerve activity such as African-Americans, those who are obese, older age, and have sleep apnea may substantially benefit from these novel device therapies. Additionally, it is clear that although RDT and BAT may not eliminate the need for prescribing antihypertensive medications, these procedures will enhance people's ability to reduce their blood pressure such that their risk for stroke and kidney disease progression as well as cardiovascular mortality is reduced.

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Chapter 12
Practical Approaches to Promote Adherence and Improve Blood Pressure Control in Black Patients

Angela L. Brown and David Kountz

12.1 Terminology

Adherence—the extent to which a person's behavior—taking medications, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider [1].

Compliance—the extent to which the patient's behavior coincides with the clinical prescription; differs from adherence in that patient's agreement is not required [1, 2].

Concordance—the process of discussion between the health care professionals and patients to reach agreement about the treatment plan and the patient's use of prescribed medicines [2].

Persistence—the length of time during which the patient continues to be engaged with the prescribed dosing regimen [2].

12.2 Introduction

Although significant gains have been made in improving blood pressure control rates in African American patients, cardiovascular morbidity and mortality still remain disproportionately high in the African American (AA) population compared

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K.C. Ferdinand (ed.), *Hypertension in High Risk African Americans*, Clinical Hypertension and Vascular Diseases, DOI 10.1007/978-1-4939-2010-5_12

with whites [3, 4]. Patient adherence to recommended therapy is a key factor in addressing the disparities in blood pressure control and hypertension-related complications and in closing the gaps. However, developing strategies to increase adherence, and ultimately improve blood pressure control rates and outcomes, requires an understanding of the complex interplay of the behavioral factors and belief systems that effect how patients interact with the health care system.

12.3 Background

The prevalence of hypertension in blacks in the USA is among the highest in the world [3]. Data from NHANES 2007 to 2010 showed that blood pressure control rates for non-Hispanic blacks was 47.6 % compared with 54.9 % for non-Hispanic whites [3]. Uncontrolled blood pressure in blacks when compared to whites results in a 1.3 times greater rate of nonfatal stroke, 1.8 times greater rate of fatal stroke, 1.5 times greater rate of death attributable to heart disease, and 4.2 times greater rate of end-stage renal disease [3]. However, clinical trial data has shown that treating hypertension has been associated with mean reductions in the incidence of stroke by 35–40 %, myocardial infarction by 20–25 %, and heart failure by greater than 50 % [5]. Overall, the cost (direct and indirect) related to hypertension and its complications in 2009 were $51 billion, and are estimated to reach $343 billion by 2030 [3].

12.4 Adherence to Medical Therapy

Patient adherence to high blood pressure therapy recommendations and persistence with therapy are key factors in high blood pressure control [2]. Poor adherence to long-term therapy results in failure to achieve blood pressure targets, exacerbations of disease, increased hospitalizations and emergency department visits, adverse health outcomes, and increased preventable health care costs [1, 3, 6].

Despite published treatment guidelines and the availability of effective and well-tolerated antihypertensive agents, 65 % of patients with hypertension are prescribed the indicated care based on a random telephone sample of 1,973 hypertensive adults (identified from 6,712 sampled) in US metropolitan areas [7].

Rates for patient adherence to pharmacotherapy range from 35 to 97 %, with most studies reporting a range of 50–70 % [1, 8]. This variance is due to differences in patient groups and unreliable measurement methods. Traditional methods, like pill counts, questionnaires, diaries, and plasma drug concentrations, have been shown to overestimate adherence [8].

Estimates of drug therapy persistence at 1 year after initiation vary between 16 and 50 % [8–11]. In a longitudinal database study containing histories of 4,783 hypertensive patients, only 50 % of patients were persistent with therapy and 10 %

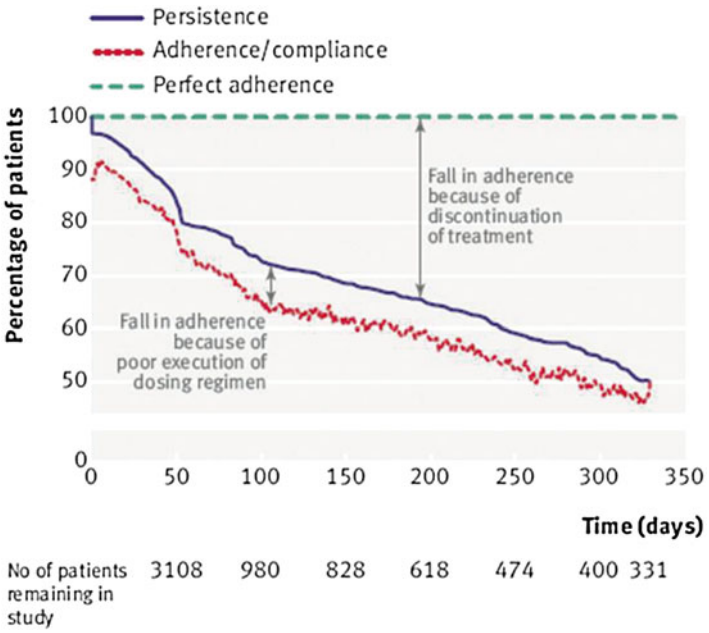

Fig. 12.1 Time course of adherence/compliance parameters (execution, persistence). From Vrijens B, Vincze G, Kristano P, et al. Adherence to prescribed anti-hypertensive drug treatments: longitudinal study of electronically compiled dosing histories. BMJ 2008;336;1114-1117. Figure copied from Hill MN, Miller NH, DeGeest S on behalf of the American Society of Hypertension Writing Group. ASH position paper: Adherence and persistence with taking medication to control high blood pressure. J Clin Hypertens (Greenwich). 201;12:757-764

of the doses prescribed were omitted each day while on treatment (nonexecution) [8] (Fig. 12.1) [2]. Among those who continue therapy, missed doses are common, with forgetfulness being the most common reason cited [12, 13].

In a cross-sectional survey of 178 respondents, persistence was related to a higher perceived need, fewer side effect concerns, higher perceived disease severity, and better knowledge about the medication [11].

Evidence has consistently shown that better medication adherence in patients with hypertension has led to decreased systolic and diastolic blood pressures and improved outcomes [14]. Using the characteristics of patients in the Anglo-Scandinavian Cardiac Outcomes Trial Lipid-Lowering Arm (ASCOT-LLA), Cherry et al. created a simulated patient model to assess the cost, morbidity, and mortality benefit of "ideal" over "real-world or typical" adherence in patients with hypertension and hyperlipidemia. The data demonstrated that the relative risk of myocardial infarction, angina, and stroke nearly doubled (13.3 vs. 25 events per 100 patient years over 3 years) in patients who were nonadherent compared to those with ideal adherence [15]. Multiple clinical trials, e.g., Multiple Risk Factor Intervention Trial (MRFIT), Systolic Hypertension in the Elderly Program (SHEP),

Hypertension Detection and Follow-up Program (HDFP), and the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), have demonstrated that improved blood pressure control and outcomes can be achieved with good adherence to medical therapy in various outpatient settings [2].

12.5 Key Factors Related to Patient Adherence

Patient adherence to medical therapy assumes that the patient has the knowledge, motivation, skills, and resources required to follow the recommendations of the health care provider [2]. The factors that effect patient adherence are multifactorial and extend beyond the common belief that patients are solely responsible for taking their prescribed treatment [1]. Other factors that affect patient behavior represent the complex interplay between patients, health care providers, and health care systems [2].

Patient and provider education were the focus of early studies of interventions to improve blood pressure control. The hypothesis was that increasing patient knowledge of the importance of controlling high blood pressure would lead to improved adherence and persistence [2]. These studies, however, also revealed that psychosocial and behavioral factors like patient attitudes, beliefs, and social support, in addition to tailored strategies to simplify therapeutic regimens and remind patients to take the medications as prescribed, were just as important as the direct education efforts [2]. As a result, the National High Blood Pressure Education Program (NHBPEP) and early Joint National Committee (JNC) reports focused on public awareness of high blood pressure and the physician's role in high blood pressure management by providing education through management guidelines and therapeutic strategies. These early programs did not substantially address the providers' need for resources that would enable them to develop counseling skills, improve communication, and foster the physician–patient relationship to build trust as methods to improve adherence [2].

The World Health Organization (WHO) report on long-term adherence identifies five key factors that contribute to poor adherence and persistence to medical therapy. The WHO Multidimensional Adherence Model [1] includes:

1. Social and economic factors
2. Condition-related factors
3. Therapy-related factors
4. Patient-related factors
5. Health care system and health care team-related factors

The data to support this model was derived from a body of literature encompassing epidemiology, clinical trials, behavioral science and health services research, and systematic reviews [2]. This model also provides a framework for developing strategies and interventions directed at poor adherence.

12.6 Socioeconomic and Sociodemographic Factors

Social and economic factors have a significant effect on adherence. Some of these factors include: lower socioeconomic status, poverty, illiteracy, low level of education, unemployment, lack of effective social support networks, unstable living conditions, long distance from treatment centers, high cost of medications and care, lack of transportation, cultural and lay beliefs about illness and treatment, and family dysfunction [1].

Sociodemographic factors like race/ethnicity, gender, and age are reported to be predictors of adherence but are less well-characterized in the literature.

Previous data suggest that adherence rates are much lower in blacks in comparison to whites [16]. The role of race/ethnicity in adherence and persistence with antihypertensive medications was assessed in a retrospective exploratory study of 51,772 hypertensive adult subjects using an electronic medical record database [17]. Blacks and Hispanics were found to have the lowest odds of adherence (0.46 and 0.58, $P<0.001$) and persistence (0.70 and 0.70, $P<0.001$) compared to white subjects. Analysis also demonstrated that lower odds of adherence and persistence in both groups were associated with younger age and less chronic disease when compared with whites and other nonwhite groups [17].

Similarly, a cross-sectional analysis of 176 subjects in public and private clinics utilizing the Medication Event Monitoring System for 30 days showed that AA ethnicity compared to Hispanic ethnicity (OR = 0.36), female sex (OR = 0.38), and receiving care in a publicly funded clinic verses a private clinic (OR = 0.45) was associated with lower adherence. There was no association with age in this cohort [18].

Barriers related to adherence based on sex differences are not well described. In a cross-sectional analysis of data from the Cohort Study of Medication Adherence among Older Adults (CoSMO) ($N=2,194$), the overall prevalence of low medication adherence did not differ according to sex ($P=0.21$) [19]. However, women who were nonadherent were more likely to report dissatisfaction with communication with their health care provider (OR = 1.75 women, 1.16 men; $P=0.13$) and depressive symptoms (OR = 2.29 women, 0.93 men; $P=0.11$). On the other hand, factors associated with nonadherent men were sexual dysfunction (OR = 2.03 men, 1.28 women; $P=0.04$) and increased BMI (OR = 3.23 men, 1.23 women; $P=0.07$) [19]. The relationship of BMI with adherence has not been previously shown, but few studies have looked at this relationship.

Several studies have specifically looked at antihypertensive medication adherence in AA men, a group that tends to have lower levels of blood pressure control and worse outcomes compared to other groups. In the Veteran's Study to Improve the Control of Hypertension (569 subjects, 42 % AA, 59 % white), 63 % of AA men compared to 50 % of white men were found to have inadequate blood pressure control (OR = 1.70, $P<0.003$) [20]. Based on self-report, AA men were 81 % more likely to be nonadherent but were also more likely to perceive high blood pressure as serious [20]. The findings of this study are significant because access to care in the Veteran's Affairs system is generally equal regardless of race or income [21].

Adherence is essential to the well-being of elderly patients, as the number of elderly with chronic conditions continues to increase. Nonadherence has been associated with unnecessary complications that led to disability and early death [1]. The prevalence of cognitive and functional impairment in this population increases the risk of poor adherence [1]. Studies, however, have been inconsistent in confirming older age as a predictor of nonadherence. Some data show greater nonadherence in younger aged groups suggesting that they may not perceive their treatment regimens as necessary due to less disease burden [17].

In a retrospective cohort study of 168,522 Medicare Part D enrollees with hypertension, adherence was 67.8 % for blacks, 69.3 % for Hispanics, and 81.5 % for whites [6]. In the multivariate model, blacks had 47 % lower odds of adherence and Hispanics 42 % lower than whites. These data also suggest that improved cost and access (as through Medicare Part D) may not adequately reduce ethnic disparities in antihypertensive medication adherence [6].

In general, demographic factors, such as sex, income, and education level, have not consistently predicated or correlated with medication adherence in hypertensive AAs [22]. However, there is a trend of less adherence in younger AAs [22].

Studies evaluating the relationship between social support and adherence have shown variable results [22, 23]. Different methodologies of assessing adherence have been used (e.g., electronic cap method or self-report) and may contribute to the discrepancy.

12.7 Patient-Related Factors

Patient-related factors associated with adherence represent the resources, knowledge, attitudes, beliefs, perceptions, and expectations of the patient [1]. Patients hold differing beliefs about prescribed medications that affect whether they are adherent and/or persistent. Adherence is increased when patients have a higher perception of need for the therapy, fewer side effect concerns, greater understanding of disease severity, and greater knowledge about the medication [11].

In a Wall Street Journal Online/Harris Interactive nationwide poll of 2,507 adults, patients gave a number of reasons for not taking their medications. These included forgetfulness (>50 %); no symptoms or symptoms disappeared, wanted to save money, considered drug ineffective, and didn't think drug was needed (each ~ 33 % respectively); side effects (28 %); drug prevented other activities (25 %); and no prescription refill reminder, problem getting prescription filled, confused by number of drugs prescribed, and could not open bottle (each 20 % or less) [24].

Self-efficacy is a key patient-related factor that refers to the level of confidence a patient has in their ability to adhere to their medications [22], and it has consistently been associated with medication adherence in hypertensive AA patients. Schoenthaler et al. examined the relationship of self-efficacy, depression, and medication adherence in 167 hypertensive AA patients using self-report questionnaires in primary care clinics, and demonstrated that increased self-efficacy was associated

with better medication adherence [25]. The results also suggested that poor adherence would decrease by 23 % for every one unit increase in self-efficacy ($P=0.010$). Similarly, Elder et al. showed similar results in a cross-sectional study of 235 Southern AA men where those with higher self-efficacy scores were more likely to have better adherence (OR = 1.08) [26].

Secondary analyses of a subset of patients in the CAATCH trial (Counseling African Americans to Control Hypertension) assessed the patient, provider, and health system factors associated with medication adherence among hypertensive black men ($N=253$) [21]. Fifty-four percent (54 %) of black men followed in a community/migrant health center were nonadherent. Using hierarchical regression analysis, the variance factors that predicted adherence were patient-related factors—age, self-efficacy, and depression—with little contribution from provider-related ($P<0.001$) or health care system-related factors ($P<0.001$) [21]. Men who were less adherent were of younger age and had more depressive symptoms based on the Patient Health Questionnaire Depression Module (PHQ-9), whereas higher scores of self-efficacy were associated with more adherence. These data are consistent with previous studies that have documented associations between self-efficacy, depression, and adherence in AA men. However, the findings are inconsistent with some studies that have shown insurance status, income, social support, and comorbidity as associative factors for adherence in AA men.

Culturally specific beliefs play a role in lower medication adherence among black individuals [17, 27]. Krousel-Wood et al. showed in a cross-sectional study of 2,180 older blacks and whites (mean age 75.0 ± 5.6 years) that the use of complementary and alternative medicine, including health foods and supplements, was associated with lower adherence to antihypertensive medications among blacks, but not whites (OR = 1.56 and 0.95, respectively, $P=0.069$ for the interaction) [28]. Other associations related to culture have also been described. For example, in a cross-sectional study of hypertension in Chinese immigrants in northern California, nonadherence was associated with lower perceived disease susceptibility (OR = 3.8), higher perceived benefit of Chinese herbs (OR = 2.2), lower perceived benefit of Western medications for HTN (OR = 2.78), and longer length of stay in the USA (OR = 2.5) [17]. Therefore, strategies to improve medication-taking behavior and outcomes must be developed in a culturally appropriate manner.

12.8 Condition-Related Factors

Two of the most important factors contributing to poor adherence related to antihypertensive therapy are the fact that hypertension is typically asymptomatic and the lifelong nature of the disease [1]. Condition-related factors represent the illness-related demands faced by the patient, e.g., severity of symptoms, severity of disease, availability of effective treatments, and other comorbidities.

The effect of depression on adherence is well documented in the literature [22, 25, 28]. In a cross-sectional study of 371 adults (60 % nonwhite) with CVD or

CVD-risk equivalent, nearly 1 in 5 participants was classified as depressed based on the screening method used in the INTERHEART study [29]. Univariate analysis showed that depression (OR = 2.5, $P < 0.05$) and feeling sad or blue for at least 2 weeks were associated with nonadherence [29]. A proposed reason for the association with depression may be the documented relationship between psychosocial risk factors for CVD, such as depression, stress, and low social support, and decreased compliance with preventive self-care behaviors [30]. In addition, alcohol abuse may be a concomitant factor. The combination of depression and alcohol abuse may modify the adherent behavior [1] and has been associated with medication nonadherence in black men [31]. Therefore, it is important to screen for depression and other lifestyle factors, like alcohol use, as a way of identifying nonadherent patients.

12.9 Therapy-Related Factors

The most notable therapy-related factors are those related to the complexity of the medical regimen, duration of treatment, side effects, frequency of treatment changes, and the medical support to deal with these issues [1]. The literature is relatively limited in this area in regard to AAs with hypertension and the effects on adherence. In the Veteran's Study to Improve the Control of Hypertension, only increased urination was related to poor blood pressure control (OR = 1.63 in AA men compared to whites) [20]. AA men were more likely prescribed diuretics compared with whites (61 % vs. 49 %, $P < 0.006$), which may have contributed to poorer adherence and worse control. The availability of health care provider support to deal with side effects in a manner that may impact adherence has not been addressed in any study [32].

12.10 Health Care Team-Related Factors

The importance of health care team-related factors as they affect the relationship between the patient and the provider cannot be understated. These include lack of knowledge and training for health care providers, overworked providers, lack of incentives and feedback on performance, short consultation times, and lack of knowledge on adherence and effective interventions for improvement [1].

The quality of the patient–provider relationship, communication, and trust contributes to favorable adherence patterns in AAs. In studies where patients reported that their provider's communication was non-collaborative, medication adherence was reduced [22], and when physician communication was rated poorly, the risk of nonadherence was 19 % higher [2]. Additional studies have shown that nonadherent patients were more uncomfortable questioning their provider about their health than adherent patients [33].

Trust remains an important issue for AAs based on the historical context of mistreatment and racial discrimination [26, 34]. Racial and ethnic minorities are more prone to distrust the health care system than whites. Southern AAs are more likely than are whites to report perceived racial barriers to care, and AA men are more likely than are AA women to report perceived discrimination, which are both associated with poorer medical adherence and delays in seeking health care. In a cross-sectional study of 993 participants with hypertension [820 AA (585 women, 235 men) and 173 white], trust, medication adherence, and blood pressure control were evaluated in the subset of AA men. Logistic regression models showed that AA men with higher levels of general trust in the medical system were more likely to self-report better adherence (OR = 1.06, $P = 0.027$) [26].

12.11 Health Care System

Health care system factors are related to how patient care is delivered and include the regulatory climate under which health care systems operate [22]. Factors that contribute to poor medical adherence include poorly developed health services with inadequate or nonexistent reimbursement by health insurance plans, poor medication distribution systems, weak capacity of the system to educate patients and provide follow-up, and inability to establish community support and self-management capacity [1].

Several studies (not all directly related to hypertension outcomes) have looked at the effect of strategies to address some of the health care system barriers that impede medication adherence.

The effect of eliminating out-of-pocket costs, or full prescription coverage, on medication adherence and cardiovascular outcomes in patients after myocardial infarction was evaluated in a cluster randomized, controlled policy study. Patients were randomly assigned to full prescription coverage ($N = 2{,}845$) or to usual prescription coverage ($N = 3{,}010$) based on randomization of their plan sponsor ($N = 1{,}494$ full coverage and $N = 1{,}486$ usual coverage) [35]. Compared with usual prescription coverage, rates of adherence to prescribed medications were 4–6 percentage points higher in the full-coverage group ($P < 0.001$). Although patient costs were reduced for drugs and other services ($P < 0.001$) [35], the elimination of co-payments did not increase total spending ($P = 0.68$).

The effects of a pharmacist-led intervention that targeted medication management and adherence counseling to improve blood pressure control in patients with diabetes mellitus in two high-performing health care systems were evaluated in a multisite cluster, randomized pragmatic trial. Although the mean systolic blood pressure (SBP) of patients in the intervention arm ($N = 1{,}797$) was 2–4 mmHg lower immediately after the intervention than that of those in the control arm ($N = 2{,}303$), the mean SBP decrease from 6 months after the intervention was similar in magnitude (~9 mmHg) in both arms [36]. This strategy had been applied in previous clinical trials; however, the lack of difference in the current study suggests that this intervention may be difficult to implement in the real-world clinical setting.

Higher levels of adherence have been identified in Medicare Part D recipients; however, predictors of low adherence include nonwhite race, greater comorbidity, more medications, and increased number of unique prescribers [2]. In a telephone survey of 202 hypertensive subjects (mean age 77.4 years, 64.8 % black) from four urban primary care practices, those who were not aware of the Medicare Part D coverage plan were 50 % less likely to be adherent than those who were aware of the plan ($P<0.05$) [37]. An observational study to evaluate the effect of Medicare Part D coverage gap on medication use in patients with hypertension and hyperlipidemia demonstrated that patients with no Part D gap coverage or with generic-only gap coverage were less likely to fill prescriptions, had more continuous medication gaps, and were less likely to adhere to appropriate medication schedules [38].

Reducing out-of-pocket costs (ROPC) involves program and policy changes that make cardiovascular disease preventive services more affordable. Services include medications, behavioral counseling, and behavioral support. Expanded treatment coverage and lowering or eliminating patient out-of-pocket expenses can reduce costs [39]. Based on evidence from 14 studies to assess the effectiveness of ROPC (three studies with outcomes specific for medication adherence), the Community Preventive Services Task Force recommends ROPC for medication to control high blood pressure and that ROPC should be combined with other interventions such as team-based care accompanied by medication counseling and patient education [39].

Value-based insurance design (VBID) programs rely on the concept that associations between medical adherence and positive health care outcomes represent cause-and-effect relationship that can be replicated through interventions targeted at medication adherence [40]. The model establishes cost sharing according to a medication's or service's clinical value instead of its acquisition cost [41]. Co-payments can be set lower for medications deemed more effective than other medications in the same class, or alternatively cost sharing can be decreased for certain populations who are most likely to benefit from improved access to treatment [42]. A retrospective pre-post data analysis evaluating VBID in a large insurer database showed improvements in adherence and disease management and lower health care spending. Limited economic analyses suggest that VBID programs are cost neutral [43, 44].

12.12 Strategies to Improve Medication Adherence

Clear evidence for proven interventions to improve medication adherence in AAs is lacking due to homogeneity of most studies and lack of longitudinal data. However, extrapolation of available data suggests that multiple strategies may be effective in targeting medication adherence and blood pressure control in AAs. Effective interventions must address patient, provider, health system, and socioeconomic factors through culturally appropriate education, behavior changes, and policy changes. Figure 12.2 illustrates a model for productive interactions that improve functional and clinical outcomes [45]. This model reflects the importance of understanding the

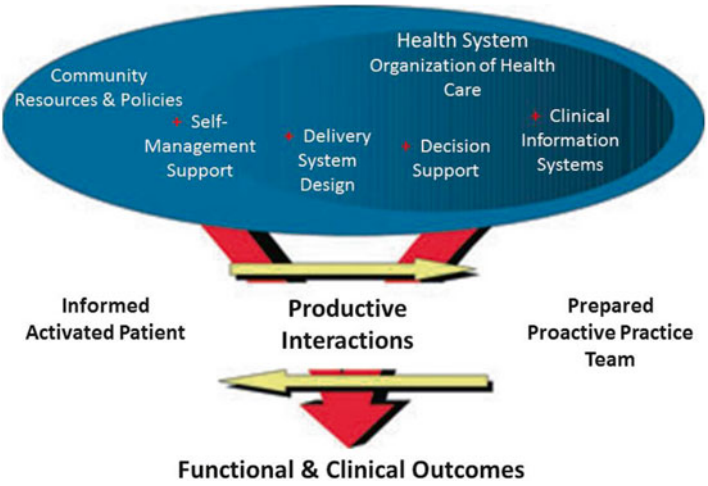

Fig. 12.2 Interventions that improve outcomes. Wagner EH, Davis C, Schaefer J, et al. A survey of leading chronic disease management programs: are they consistent with the literature? Manag Care Q. 1999;7(3):56-66. Figure copied from Hill MN, Miller NH, DeGeest S on behalf of the American Society of Hypertension Writing Group. ASH position paper: Adherence and persistence with taking medication to control high blood pressure. J Clin Hypertens (Greenwich). 201;12:757-764

complex relationship between patients, providers, and health care systems in developing strategies for improving adherence and blood pressure control.

Unlike socioeconomic and psychosocial factors that may be difficult to change, medication choice, co-payments, and access to care are potentially modifiable through system level interventions. System changes that have shown positive results include alternative and complimentary models of care like nurse-run clinics, nurse case management, team-based care, pharmacy-based counseling, and community-based monitoring and care sites with closer patient follow-up and close adherence to guidelines by providers. A comparative effectiveness review of interventions aimed to improve medication adherence for chronic health conditions in the USA revealed that blister packaging, case management, and education with behavioral support were the most effective for improving adherence to antihypertensive medication [14].

It is important to develop valid monitoring strategies beyond self-report and pill count. Newer methods like electronic medical record and e-records of pharmacy prescription refills add an important dimension. Physicians must be skilled to monitor adherence [2], and must be trained to execute adherence-enhancing interventions. The principles of motivational interviewing have been shown to facilitate a communication style that fosters a collaborative partnership with the patient (concordance) and support self-management.

Table 12.1 Practical considerations and recommendations for adherence

Focus on clinical outcomes
Initiate medications according to national guidelines
Keep the regimen simple: once-/twice-a-day dosing
Reevaluate all uncontrolled blood pressures (BPs)
Communicate with patients about taking medications as directed
Encourage self-monitoring of BP
Use technologies (e.g., e-mail) to monitor progress and maintenance of goal BPs
Empower informed activated patients
Assess patient knowledge, skills, behaviors, confidence, and barriers to adherence
Encourage problem-solving and behavior change interventions
Urge the use of pill boxes for daily use
Help patients develop a system for refilling prescriptions
Implement a team approach
Implement a collaborative model based on a team approach
Apply office practice policies and procedures to improve BP control
Support self-management and problem prevention
Advocate for health policy reform
Elevate medication adherence as a critical health care issue
Develop policies to support prevention and chronic illness management including self-management
Structure/finance health care that stimulates behavioral aspects of care in communities
Seek regulatory changes to improve the use of home BP monitors

Modified from Hill MN, Miller NH, DeGeest S on behalf of the American Society of Hypertension Writing Group. ASH position paper: Adherence and persistence with taking medication to control high blood pressure. J Clin Hypertens (Greenwich). 201;12:757-764

Table 12.1 shows four key strategies for adherence that can be integrated into effective health policies that emphasize and improve prevention and management of hypertension, in addition to other chronic illness [2].

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Chapter 13
Integration of a Team Approach to Hypertension Treatment

Kevin B. Sneed

13.1 Hypertension: Background

Hypertension is the most common chronic cardiovascular condition encountered in outpatient and ambulatory settings. According to the American Heart Association Heart Disease Statistics 2013 update, it is estimated that 33 % of US adults have hypertension [1]. This represents approximately 78 million American adults with hypertension [1]. Through significant patient education and outreach, clinical management, and general greater self-awareness, the USA has seen a marked increase in the number of people that are aware of their condition. It is estimated that approximately 82 % of adult patients are aware of their hypertension condition, and approximately 75 % of adult patients are using antihypertensive medication [1]. Despite this enhanced awareness, only 53 % of patients diagnosed with hypertension are at or below their target blood pressure goals at current recommended levels. African American awareness of hypertension has significantly improved, but the excess burden of elevated blood pressure and the subsequent consequences on health outcomes remain high [1]. Medication nonadherence is widely recognized as a major cause of patients not maintaining control of chronic cardiovascular conditions [2–4]. Other causes for patients not attaining their blood pressure goals may include socioeconomic challenges, advanced atherosclerotic vascular changes from prolonged exposure to uncontrolled cardiovascular risks, and lack of positive response to medication therapy [5]. Despite the overall causes, the necessity to find alternative and innovative methods to adequately control hypertension in Americans remains the goal of all healthcare clinicians.

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K.C. Ferdinand (ed.), *Hypertension in High Risk African Americans*, Clinical Hypertension and Vascular Diseases, DOI 10.1007/978-1-4939-2010-5_13

There are various issues associated with effectively treating hypertension in African-American populations, many of which have been well studied through an abundance of health disparities and health inequities research projects. The numerous qualitative and quantitative measures of the social determinants of health reveal the multifaceted challenges that many African-American patients encounter as they attempt to improve their cardiovascular health. At the core of improved health, as in most social interactions, is the ability to improve communication. Several researchers have examined the communication patterns between health providers and African-American patients, and it is commonly noted that interpersonal communication between patients and their clinician is very important for the successful delivery of high-quality healthcare [6–8]. Improved interpersonal communication is also noted to improve patient satisfaction, adherence to treatment recommendations, health outcomes, and an improvement in racial/ethnic disparities [6]. Other factors believed to contribute to increased hypertension prevalence among African-Americans when compared to other races include social factors, psychological factors, biological factors, and economic factors. Differences in the ability to have affordable access to care and lower socioeconomic status are also thought to contribute to ethnic and racial disparities in hypertension [5, 6].

13.2 Pharmacological Intervention: An Important Component to Hypertension Treatment

Most guidelines and published recommendations on hypertension treatment tout multiple methods to manage hypertension in patients. Recommendations for therapeutic lifestyle modifications (TLC) or non-pharmacological treatments for hypertension have traditionally included weight loss, dietary sodium restriction, increased physical activity, moderation of alcohol intake, and healthy dietary pattern [9]. As the US population ages, and communities have continued to develop more sedentary lifestyles, behavioral change modifications have not been enough to achieve normal blood pressure in most patients. Upon diagnosis of hypertension, healthcare providers usually will begin a pharmacological treatment, sometimes after a trial with therapeutic lifestyle changes (TLC). Initial pharmacological therapy will often include diuretics but may also include beta blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or calcium channel blockers (CCBs). Effective utilization of medications has always been based upon evidence-based medicine stemming from randomized controlled trials. While multiple landmark clinical trials have shown cardiovascular benefit of pharmacotherapy over the past several decades [10–12], translating similar success to large population-based hypertension clinical management strategies has proven difficult. Pharmacological treatment, while still recognized as the one of the most likely methods of treating hypertension, remains one of numerous methods that must be implemented concomitantly when treating hypertension in patients.

Table 13.1 Literature supporting pharmacists on collaborative clinical teams

	Author (year)	Title	Journal
1.	Pande, S. (2013)	The effect of pharmacist-provided non-dispensing services on patient outcomes, health service utilisation and costs in low- and middle-income countries	*Cochrane Database of Systematic Reviews*
2.	Kerby, T. J. (2012)	Adherence to blood pressure telemonitoring in a cluster-randomized clinical trial	*Journal of Clinical Hypertension*
3.	Olivier, H. E. (2012)	Implementation of a hypertension clinic using a streamlined treatment algorithm	*American Journal of Health-System Pharmacy*
4.	Carter, B. L. (2012)	The hypertension team: the role of the pharmacist, nurse, and teamwork in hypertension therapy	*Journal of Clinical Hypertension*
5.	St Peter, W. L. (2011)	Role of collaborative care models including pharmacists in improving blood pressure management in chronic kidney disease patients	*Current Opinion in Nephrology and Hypertension*
6.	Santschi, V. (2012)	[Team-based care involving pharmacists and nurses to improve the management of hypertension]	*Revue Medicale Suisse*
7.	Weber, Cynthia A. (2010)	Pharmacist-physician comanagement of hypertension and reduction in 24-h ambulatory blood pressures	*Archives of Internal Medicine*

Personalized approaches in the treatment of hypertension must be developed with population dynamics in mind if we are to achieve improved cardiovascular outcomes from hypertension management. Any strategy that is developed must also include significant strategies for racial/ethnic populations, as well as those communities that are considered to be underserved according to available primary and specialty care and application of evidence-based clinical management strategies.

Numerous studies have shown the benefits of having a pharmacist included in the clinical collaborative management of patients [13–16]. (Table 13.1) With the clinical treatment of hypertension having a significant emphasis on medication use, pharmacists can provide an important role in clinical decision-making support for health providers. With many patients being treated for hypertension also having other comorbid chronic conditions, often including type 2 diabetes, hypercholesterolemia, as well as other chronic health challenges, health practitioners must treat these various conditions with multiple medications. While polypharmacy regimens may often be needed to maintain control of chronic health conditions, particularly with hypertension, this may often lead to other complications, including potential medication interactions while treating other comorbidities, increased chances for medication nonadherence, and significant increases in the costs of medications [3, 17]. Continuous monitoring of all the medications that a patient is taking is needed during the total duration of their medication treatment. Effective communication strategies among multiple providers prescribing medications for an individual

patient should be a priority, but often are overlooked and does not occur. Having a pharmacist available to review medications, assess their effectiveness and safety, and then effectively communicate this information back to all health providers of the patient can be an effective strategy to reduce medication errors, optimize medication efficacy, and improve patient satisfaction [18–20].

13.3 Acceptance of the Changing Roles of Pharmacist Clinicians

For many decades, the scope of practice for pharmacists has often been perceived to be confined to retail community pharmacies, or institutional settings, such as hospitals [21, 22]. This limited view by some physicians concerning the scope of practice for non-physician providers has often extended beyond pharmacists [23, 24]. Nevertheless, during this time period, the pharmacist has been increasingly viewed as a widely trusted health professional, providing much-needed education to patients about the medications. The major function of the pharmacist during the past 4–5 decades has been the preparation and dispensing of medications, particularly in the community settings. Other important roles of the pharmacist included maintenance of medication inventories, regulatory oversight (usually designated by state boards of pharmacy), insurance reconciliation, and providing timely and accurate medication information to both patients and other health providers. Further, the administration, maintenance, purchasing, monitoring, and removal of pharmaceutical agents clearly represent a much-needed role with regard to safe and effective medication use by patients. The perception of "gatekeepers of medication [25, 26]" has previously been readily and thoroughly embraced by the pharmacy profession, and has been promulgated throughout pharmacy institutions providing instruction to aspiring pharmacists [22, 25, 26].

However, in recent years, a significant shift in the role of the pharmacist is beginning to unfold. Pharmacists have become far more integrated into patient management roles, particularly in institutional settings [13, 22, 27, 28]. Their participation as a valued member of healthcare teams doing rounds in hospital wards has become a routine function of the pharmacist. The resulting transformation of the pharmacist from a primarily dispensing technician to more of a patient management clinician is now more widely accepted.

The profession of pharmacy has been widely recognized as a very necessary and integral component of the healthcare system. Pharmacy as a discipline and as a profession has come to coexist very well with all of the health professions and disciplines [15, 16, 22]. Especially in the management of chronic disease states, many pharmacists are now being called upon to assist primary care providers and other specialist in the medication management of these patients. As the healthcare system in America continues to struggle to find ways and means to effectively meet the healthcare needs of citizens in our communities, there will be an increasing demand to involve the pharmacist clinicians in patient care, especially chronic conditions such as hypertension.

A 2011 report delivered to the US Surgeon General by the Chief Professional Officer, Pharmacy, detailed the significant role that pharmacists play in patient care [29]. The report was a very comprehensive and evidence-based document describing methods by which pharmacists contribute to patient care, and improve health systems outcomes through effective collaboration with other providers. Outlined in the executive summary of the report was the fact that the healthcare system is significantly challenged with regards to access, safety, quality, and cost of patient care. There was further magnification of the fact that there are projected health provider workforce shortages, particularly in primary care providers [29, 30]. Also noted was the fact that in federal healthcare facilities, pharmacists have worked collaboratively with other health professionals to manage numerous disease states through effective medication use, as well as other cognitive and clinical pharmacy services [29]. In a response letter, the Surgeon General provided a public letter of support for pharmacists to be more thoroughly recognized for their contributions to healthcare teams [31]. In the document, the Surgeon General noted "the comprehensive patient care services that pharmacists are currently providing through collaborative practice agreements in 43 states and federal healthcare settings." [31] This report was widely viewed by pharmacists across the country as a key and integral moment to achieving full health provider status in the Social Security Act, which has been a primary barrier to full integration of pharmacists into healthcare teams. Dissemination to healthcare leaders and policymakers was fully intended to provide additional momentum to recognizing pharmacists as important members of healthcare teams that provide health provisions to patients.

In addition, other organizations also recognized the importance of having pharmacists provide key health management services to patients. The American Academy of Family Physicians (AAFP) published a position paper supporting pharmacy professionals' involvement in patient care [32]. In the report's introduction, the AAFP stated recognition of the "evolving complexity and proliferation of pharmaceutical agents and the important role pharmacists play in the delivery of high-quality healthcare." [32] The paper went on to further describe the benefits of collaborative arrangements with physicians to attenuate the fragmentation of care to patients, while improving health outcomes for patients with team-based care models. The AAFP position paper concluded by supporting arrangements where the pharmacist is part of an integrated, team-based approach to care. It should also be noted that the position paper did not support independent prescription authority for pharmacist, with the belief that this could lead to further fragmentation of the American healthcare system. However, through effective communication in very thoroughly written collaborative practice agreements, prescription authority would not be seen as being independent, and would be done under the supervision and ultimate authority of the physician.

The American Public Health Association also published a policy statement supporting the role of pharmacists in public health [33]. The policy statement noted that pharmacist services should include more patient-oriented, administrative, and public health functions. Pharmacists were noted to have roles separate from dispensing medication and provided additional value to patients as an accessible resource for

Table 13.2 Health policies and literature supporting expanded pharmacists' roles

	Author	Title	Journal
1.	Leasure, E. L. (2013)	There is no "i" in teamwork in the patient-centered medical home: defining teamwork competencies for academic practice	*Academic Medicine*
2.	Howard, J. (2012)	Physicians as inclusive leaders: insights from a participatory quality improvement intervention	*Quality Management in Health Care*
3.	Gerber, B. S. (2012)	Design of a trial to evaluate the impact of clinical pharmacists and community health promoters working with African-Americans and Latinos with diabetes	*BMC Public Health*
4.	Carter, B. L. (2010)	A cluster-randomized effectiveness trial of a physician-pharmacist collaborative model to improve blood pressure control	*Circulation: Cardiovascular Quality and Outcomes*
5.	Giberson, S. (2011)	Improving Patient and Health System Outcomes through Advanced Pharmacy Practice. A Report to the U.S. Surgeon General	*Office of the Chief Pharmacist. U.S. Public Health Service*
6.	Dey, R. M. (2011)	Collaboration in chronic care: unpacking the relationship of pharmacists and general medical practitioners in primary care	*International Journal of Pharmacy Practice*

health and medication information. This accessibility was seen as extremely valuable because of the centralized placement of pharmacists in communities. The policy statement went on to further describe the necessity for public health principles to be placed in pharmacy education; it thoroughly described the levels of public health activity contributed by pharmacists and very strongly endorsed the notion that pharmacists have many functions that are aligned with those essential health services that are critical to public health (Table 13.2).

13.4 Role of Interprofessional Patient Management: The Emergence of Pharmacist Clinicians

In March of 2010, the US healthcare system underwent a major change with the passage of the Affordable Care Act (ACA). The law expanded health coverage to millions of individuals, ushered in insurance reforms, and created the platform to test various approaches to delivering new types of delivery of medical care [34–36]. With passage of the ACA, more than 30 million US residents that were currently uninsured were expected to gain insurance coverage [34]. Additionally, all US residents that currently have health insurance would be guaranteed coverage of basic and essential health benefits, as opposed to the past standards of having numerous exclusions, questionable and varied coverage, and a high prevalence of

underinsurance [34]. This landmark legislation overhauled the US healthcare system, and although controversial, it was seen as an opportunity to effectively improve the healthcare landscape across the USA.

During the same time that the ACA was being debated and passed, the US healthcare system faced a looming shortage of primary care physicians [37]. In consideration of the additional 30 million Americans expected to gain access to healthcare, the forecasted shortage of primary care physicians is seen as a possible hindrance to the effective delivery of healthcare [30, 37–39]. Nevertheless, it may be expected that advanced nurse practitioners and physician assistants will be the most logical health practitioners to meet the challenge of the forecasted primary care physician shortage [37]. Seeking answers to this looming provider shortage, policymakers, healthcare administrators, and pharmacist advocates began to question whether pharmacists can assist with the projected primary care provider shortage [16, 40, 41]. While pharmacists have performed health-related duties for decades in institutional settings and defense-related healthcare systems (Veterans Administration Hospitals; Department of Defense health institutions), because of a lack of provider status in the Social Security Act (Title XVIII (Medicare) of the Social Security Act) pharmacists do not have the ability to autonomously bill for clinical services under Medicare Part B [42]. Therefore, without recognized provider status, third-party insurance payers also do not routinely reimburse pharmacists for performing clinical services. Irregardless of clinical training at a clinical doctorate level, plus clearly demonstrated and documented proficiency in providing healthcare services, the ability for pharmacists to be reimbursed for clinical and cognitive services has been very limited. Despite intense efforts by pharmacy associations and political action groups [31–33, 43], the profession has not been successful in expanding the reimbursable scope of cognitive and clinical services provided by pharmacist.

In addition, healthcare reform has led to the development of alternative innovative models of delivering healthcare [42]. One of the most promising models of healthcare delivery is the patient-centered medical home (PCMH), which is a primary care model designed to facilitate partnerships between individual patients, health providers, and other health practitioners. The goal of the PCMH is to control costs while providing a higher level of coordinated care for the patient [44, 45]. Expected goals and outcomes for pharmacists participating in PCMH models include first-contact care, coordinated care, comprehensive care, and sustain personal relationships along with information technology support and payment reform [42]. While this model shows promise for reformed healthcare, the proper utilization and implementation of non-physician healthcare providers, including clinical pharmacist, remains to be determined.

Two of the biggest challenges in healthcare today regarding management of patients with chronic conditions are medication nonadherence and a lack of coordinated care [46]. Numerous studies and publications have shown the value of having pharmacists collaborate in multidisciplinary and interprofessional clinical models to assist in the management of chronic illnesses [14, 15, 19, 42, 47]. A meta-analysis including 15 randomized controlled trials (9,111 outpatients), which included clinical interventions conducted exclusively by pharmacists in 8 studies, and in

collaboration with physicians, nurses, dietitians, or physical therapists in 7 studies, was conducted. These meta-analyses conducted by V. Santschi and colleagues revealed that pharmacists were consistently found to have a positive impact on clinical patient outcomes when collaborating with physicians and other providers.

In a more directed prospective clinical study examining clinical collaborations between physicians and pharmacists to control blood pressure, the results were even more convincing. In a prospective, cluster-randomized, controlled clinical trial, which enrolled 179 patients with uncontrolled hypertension from five primary care clinics in Iowa City, Iowa, hypertension patients were found to achieve consistent and significantly greater reductions and high rates of blood pressure control in the intervention groups versus the control groups. Common chronic illnesses managed by clinical pharmacist include hypertension, diabetes, heart failure, hypercholesterolemia, and anticoagulation therapy [28, 48–50]. Through the use of collaborative practice agreements, pharmacists may provide cognitive management services alongside physicians and non-physician healthcare providers. As the PCMH clinical delivery model continues to gain traction, there will be less emphasis on fee-for-service reimbursement, with a subsequent increase in fees associated with increased value, with the full expectation that there will be an improved outcome profile for patients [51]. In this new healthcare model, a pharmacist may actually become a desirable healthcare provider to have as part of an interprofessional clinical team. With a different type of negotiated fee structure, the PCMH reduces reliance upon fee-for-service clinical activities, thereby making the inclusion of clinical pharmacists a reality in the new healthcare model that was clearly unattainable in previous models. African American patients with uncontrolled hypertension and other chronic comorbid conditions could potentially benefit from the developing approaches to CVD risk factor management and prevention.

Another developing healthcare model that has resulted from the ACA has been the emergence of the Accountable Care Organization (ACO) healthcare model. In the late 1990s and early 2000s, Health Maintenance Organizations (HMOs) were instituted as a cost control measure designed to place the primary care provider as a gatekeeper to the rest of the healthcare services for a patient. The fee structure was implemented using a per-member per-month payment system, with a capitated amount paid to participating providers. Ultimately, that lack of clear metrics and attainable measurable outcomes presented potential road blocks to becoming a widely used and sustainable model. With the advent of the ACO model, a very similar network of physicians, non-physician providers, and facilities are developed with the full intention of providing coordinated care for a patient. One noticeable change is that each entity in the network is at financial risk for the delivery of healthcare to patients. By placing at risk modifier attached onto improved patient outcomes, all entities within the network are now held "accountable" for improving health outcomes. At current, there are approximately 33 CMS metrics that each ACO will be measured against, including patient satisfaction and improved health outcomes. All health providers within the ACO may experience financial gains from their patients having improved health outcomes, while managing their resources

effectively and efficiently. By reducing their risk, theoretically there should be improved health at a cheaper cost that will incentivize providers to achieve the best care possible.

In the ACO model, various non-physician providers may become invaluable to attaining quality metrics necessary to gain maximum fee credits. Because of a particular emphasis on chronic illness that will most effectively be managed through medication therapy, lifestyle and behavior modification, and improved care coordination, ACO networks will very likely be willing to employ clinical pharmacists, along with healthcare coaches and patient navigators. The medication-related activities that will be required of the ACOs will be well managed by clinical pharmacists in collaboration with other primary care providers [52, 53]. And as noted by Jacobsen, physicians and medical professional organizations may be better served to abandon their long-standing opposition to non-physician practitioners and create high functioning healthcare teams that truly create patient-centered healthcare models [53].

13.5 Emerging Technologies: The Pharmacists' Roles Expand

Healthcare worldwide is in the midst of a rapid technological explosion. For example, the rapid adoption of electronic health records and other medical technologies allows health practitioners to effectively store and manage large amounts of patient-related information [54]. The utilization of electronic health records replaces the traditional paper-based patient documentation commonly used by practitioners. Health information technology (HIT) will continue to evolve over the coming decade, leading to uses beyond being electronic renderings of traditional paper documents [55, 56]. And, as HIT evolves, additional health systems supports will require specialized individuals in the areas of informatics, support systems technologists, and even compliance and ethics specialists. Health practitioners will very likely require training in these areas to maximize the capabilities of the technology, while remaining compliant with the regulatory requirements to utilize the technology. The ability to quickly and efficiently access large amounts of medical information in secure databases will allow health practitioners to identify specific disease states within their patient populations for very specified purposes. For example, the ability to identify all of the patients with hypertension in a medical system or practice will allow for quality assessments to determine if proper medical guideline standards are being followed and accomplished.

Medical applications (apps) have emerged as one of the most useful and coveted tools in the administration of healthcare [57]. Mobile health technologies utilize mobile devices such as smartphones and tablets. These technologies are now well positioned to move the delivery of healthcare to becoming more patient-centered, which has long been talked about, but slow to develop. Mobile health

Fig 13.1 iPhone as a glucometer. ACC/AHA Heart Failure Guideline, MERIT-HF, COPERNICUS, CIBIS, SOLVD, AIRE, TRACE, ValHEFT, RALES, ACC/AHA Post-MI Guideline, BHAT, SAVE, Capricorn, EPHESUS, ALLHAT, HOPE, ANBP2, LIFE, CONVINCE

technology allows providers to recommend educational and tracking applications, while allowing the patient to be a willing participant in their own healthcare [56, 58]. As mobile health technologies continue to evolve, it is very likely that practitioners will prescribe mobile apps to patients just as they prescribe medications. This "mobile app prescription" will become part of the patient's permanent electronic medical record, and assist their goals of documenting care plans for patients.

Various emerging health technologies will be available to create foundational platforms for pharmacists to be very significant contributors to the healthcare team in the future. Smartphone technology will allow patients to do remote monitoring of countless vital signs and laboratory tests that traditionally have only been performed either in medical offices or in laboratories. For example, technology already exists that allows blood glucose levels to be attained using a smartphone. Additional tests that patients will be able to perform remotely with a smartphone will include blood pressure, spirometry, dermatoscopy, and even electrocardiography (ECG). Technology even exists to be able to perform labs using smartphone technology (Fig. 13.1. iPhone as a glucometer). Patients shall be able to perform these tests, and transmit them remotely and securely to their primary care physician and all other members of the healthcare team, including the clinical pharmacist. By having access to all of this information through these emerging technologies, clinical

decision-making support mechanisms will be easily implemented by the healthcare team to allow for the provision of healthcare for patients. And the costs associated with acquiring and providing these smartphone and mobile health technologies will actually be lower than the total costs associated with having patients continually travel to physician offices and other healthcare centers to perform these very same routine vital sign activities. This will allow health systems to better control costs while improving efficiencies, which is an overall goal of healthcare reform, the Affordable Care Act, ACOs, and PCMHs.

Pharmacists are well positioned to significantly contribute to the technology-driven evolution of healthcare. The ability to effectively document clinical interactions directly into the electronic health record will improve communication between pharmacists and other providers. Creating collaborative protocols to establish clinical workflows and communication strategies will make clinical pharmacists a valued member of the healthcare team. All providers' actions will be properly documented and accessible for everybody to follow the care plan of a particular patient. Utilization of technology by patients will truly create a patient-centered approach to healthcare. The patient will be able to effectively monitor their own health remotely, and report those findings through electronic means to their entire healthcare team, which will include the clinical pharmacist. For medication-related clinical issues, the numerous health information technologies will allow prompt, effective, and evidence-based clinical decision-making support contributions by the pharmacist that will be transparent to the patient and to the entire healthcare team. Health information technologies have a great potential to remove the silos and barriers between health practitioners that have existed for many decades. But even more importantly, these mobile health technologies and smartphone applications will keep the patient actively engaged in their own healthcare, thus truly creating the patient-centered medical model that we all envision for the future of health.

Responsibility must be exercised as mobile health technologies continue to emerge with regard to underrepresented and underserved communities. It has been well documented that underrepresented and underserved populations have increased cardiovascular risks, and are more likely to succumb to medication nonadherence, socioeconomic challenges, and decreased access to healthcare [5]. Costs associated with mobile technologies will continue to decline rapidly within the current decade, and it is also expected that the cost savings associated with providing these remote technologies to patients in resource-restricted communities may be an innovative method to overcome the health disparities that have plagued healthcare not only in our country, but around the world. Having well-trained pharmacists in these newly emerging informatics technologies will be a valuable resource to increase access to healthcare for patients, while providing a high level of clinical pharmacology expertise to an expanded number of patients in all communities. Telehealth medicine will also effectively allow pharmacists to provide education and counseling concerning a patient's medication therapy anywhere the patient can receive a telecommunications signal. And as previously stated, the ability to effectively communicate these patient management interactions using an electronic medical record will keep the entire healthcare team informed of the patient counseling, education,

and recommendations made by the pharmacist. This innovative communication strategy will greatly improve coordination of care for patients in all communities. It is very evident that HIT can be a critical tool in expanding and improving population health while developing and implementing additional efficiencies in the delivery of health by the entire healthcare system or team.

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Chapter 14
Practical Pearls in the Treatment of Hypertension in Blacks

Elijah Saunders and Jude Ediae

Hypertension poses a significant morbidity and mortality problem among African Americans or blacks. A study of heart disease and stroke statistics in 2009 showed that African Americans have the highest age-adjusted prevalence of hypertension (44.4 % men and 43.9 % women) as compared to Whites (34.1 % men and 30.3 % women) and Mexican Americans (23.1 % men and 30.4 % women) [1].

It has been previously estimated that as many as 30 % of all deaths in hypertensive black men and 20 % in hypertensive black women may be as a result of uncontrolled hypertension [2]. Uncontrolled hypertension has also been clearly linked to an increased risk of stroke, left ventricular hypertrophy, chronic heart failure, and end stage renal disease especially among blacks.

There has been an increasing awareness of hypertension among blacks and Americans as a whole. It was estimated that approximately 80 % of black women and 68 % of black men were aware of hypertension according to an analysis of the 1999–2004 National Health and Nutrition Examination Survey. Despite these numbers, control of blood pressure has remained inadequate ranging from approximately 36 % in black women and 30 % in black men, which is lower when compared to their white counterparts [3].

There are various pathophysiological and nonphysiological factors linked to the etiology and control of hypertension. The pathophysiological factors include diet and lifestyle, obesity, overactivity of the renin-angiotensin system, vascular abnormalities, salt sensitivity, and secondary causes like critical renal artery stenosis, obstructive sleep apnea, and primary aldosteronism which among others are most

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K.C. Ferdinand (ed.), *Hypertension in High Risk African Americans*, Clinical Hypertension and Vascular Diseases, DOI 10.1007/978-1-4939-2010-5_14

common in blacks. Moreover, the nonphysiological factors mostly lead to inadequate treatment and control of hypertension and are usually related to patient, physician, or healthcare system factors. The patient-related factors include misconceptions and poor knowledge about the disease and its consequences, poor adherence to therapy, significant concerns about side effect to medications which ultimately leads to poor adherence, difficulty with lifestyle changes, and demographic factors like age, sex, and low socioeconomic status. Physician-related factors include a lack of knowledge about current treatment guidelines and thus nonadherence to these guidelines. Often among physicians and other healthcare providers is a failure to intensify or optimize medication regimens (therapeutic inertia) if blood pressure goals are not met and a failure to lay more emphasis on therapeutic lifestyle changes (TLC).

A practical approach to the adequate treatment and control of hypertension in blacks will involve a conscientious consideration of a number of factors which should include the various pathophysiological and nonphysiological factors alluded to earlier. Recent guidelines on treatment of hypertension which all providers should be familiar with are the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) [4] and the 2003 International Society of Hypertension in Blacks (ISHIB) consensus statement and 2010 update [5, 6]. Emphasized in these guidelines is the importance of factoring in hypertension-related morbidities, target-organ injury, and other comorbidities such as diabetes, obesity, and dyslipidemia. These clinical reviews remain important, comprehensive, practical tools to assist clinicians in treating African American patients.

For the purpose of clarity, we will summarize the JNC 7 report and the ISHIB statements, particularly as the recommendation relates to treating hypertension in blacks. The goals of blood pressure control based on the recent reports have been determined by risk stratification and broken down into two main risk strata depending on the presence or absence of target end organ injury, preclinical cardiovascular disease, and/ or cardiovascular disease (CVD). Target-organ injury is defined as the presence of microalbuminuria (albumin: creatinine ratio > 200 mg/g), chronic kidney disease (eGFR < 60 mL/min) or left ventricular hypertrophy as evidenced by electrocardiographic or echocardiographic changes. Preclinical or equivalent cardiovascular conditions include prediabetes (impaired fasting glucose [100–125 mg/dL] and/or impaired glucose tolerance [2-h post-load glucose of 140–199 mg]) or diabetes mellitus. CVD includes coronary artery disease, systolic or diastolic heart failure, peripheral arterial disease, abdominal aortic aneurysm, cerebral vascular accident, and/or transient ischemic attack.

The first risk stratum, otherwise called the *low risk stratum (primary prevention)*, basically comprises individuals without evidence of target-organ injury, preclinical CVD, and/or CVD. The recommendation is to attain a target BP <135/85 per the ISHIB report which is slightly lower than 140/90 recommended by the JNC 7 and primarily recommended for African Americans, a high risk population. The second group is the *high risk stratum (secondary prevention)* that includes individuals with

evidence of target-organ damage, preclinical CVD, and/or CVD (or its equivalent, e.g., diabetes) for which the target BP is <130/80.

Management of hypertension should ideally start with a comprehensive evaluation which includes the following:

1. Obtaining a comprehensive history which should include demographics, previous diagnosis of hypertension, age at onset, known duration, usual BP readings or range, highest known BP, treatment history, current medications including over-the-counter medications/supplements and homemade remedies, history of other previous and active chronic medical or psychiatric conditions which could influence choice of antihypertensive medications, family history of hypertension or CVD (making note of premature onset: <age 40 yrs), type 2 diabetes mellitus, CHD, CVD, or early-onset CVA (especially hemorrhagic). In addition, smoking and alcohol history including current use; substance abuse history especially amphetamines, cocaine, and phencyclidine; engagement in regular exercise or physical activity; dietary assessment; and environmental assessment including housing, neighborhood, and employment should be obtained. History should also include a review of systems looking for symptoms of complications of long-standing uncontrolled hypertension like unexplained shortness of breath, exertional chest pain/discomfort, chronic coughing, and/or leg swelling.
2. Physical examination which should include height, weight, calculation of body mass index, waist circumference, vital signs ensuring that BP is obtained using the appropriate technique, systemic examination (with particular attention to cardiovascular and pulmonary), and fundoscopy. Ankle/brachial ratio for blood pressure should be measured if symptoms suggest peripheral arterial disease.
3. Diagnostic testing which should include complete blood count, basic metabolic panel, urinalysis, spot urine for albumin:creatinine or protein:creatinine ratio, fasting lipid panel, electrocardiogram, and Framingham 10-year CHD risk score. Chest X-ray can be performed for further evaluation of chest-related symptomatology like coughing, unexplained shortness of breath. A two-dimensional echocardiogram can also be performed to evaluate for the presence of LVH when the history and 12 electrocardiograms (ECG) are suggestive of this. The presence of LVH will influence the treatment approach to achieve a lower target BP.

14.1 Treatment Approach

14.1.1 Basic Principles

A reasonable approach to the treatment of hypertension in blacks should always begin with comprehensive TLC whether or not antihypertensive drugs are concurrently initiated. Overall, TLC include dietary modifications like low salt, low fat, low cholesterol, and a high potassium diet. Additionally, weight loss, regular physical activity, smoking cessation, and limitation of alcohol intake. TLC is advocated for

all blacks with a BP ≥115/75 considering that epidemiological studies have shown that an upward incline in CVD risk begins at this point [7]. Although TLC can be difficult to implement in a sustained fashion, it should be continuously encouraged in black patients with hypertension even when BP is controlled with or without medications. The DASH trial, which used the DASH diet, included a sizeable number of black patients and demonstrated the benefits of TLC in the control of hypertension. The black patients actually had a better response to this diet than whites, although all patients benefitted [8].

In the low risk group of patients, as described in paragraph 3, who have no evidence of target-organ injury and a blood pressure <145/90, a trial for 3 months of TLC is recommended before initiating antihypertensive medications to achieve their goal BP.

14.1.2 Treatment with Antihypertensive Medications

Monotherapy with antihypertensive medications in black patients has been previously overemphasized. Clinical trials over the last two decades have shown that more than 65 % of antihypertensive patients regardless of race or ethnicity have required combination therapy (≥2 drugs) to achieve adequate BP control [4]. However there is still an important role of monotherapy as initial therapy to achieve BP control in a select group of patients based on risk stratification.

Figure 14.1 shows the recommended medication regimen based on risk stratification according to the most recent ISHIB consensus statement [6]. These recommendations are similar to the JNC 7 guidelines [4] except a slight reduction in the target BP for primary prevention which is slightly lower (135/85) per the ISHIB report than that recommended by JNC 7 (140/90).

Monotherapy, preferably with either a thiazide diuretic or calcium channel blocker (CCB), is recommended for uncontrolled BP in the low risk patients or in the high risk patients if BP is <15/10 above the goal BP. Other alternatives are renin-angiotensin system (RAS) blockers [angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), direct renin inhibitors] and beta-blockers. In high risk patients, it is recommended that a medication with a compelling indication as regards existing comorbidities is used. For example, a patient with a history of diabetes mellitus with or without evidence of proteinuria should be initially started on an RAS blocker for blood pressure control. Another situation is using a beta-blocker in a patient with CHD/history of myocardial infarction, cardiomyopathy, or heart failure assuming there are no contraindications to its use.

If BP is >15/10 above goal in the high risk stratum patients, combination therapy including drugs with a compelling indication is recommended as initial management. Preferred combination therapies are CCB + RAS blocker or thiazide + RAS blocker. Alternative combinations are thiazide + beta-blockers, thiazide + calcium channel blockers, or thiazide + aldosterone antagonist. As stated earlier, most hypertensive patients categorized as stage 2 (BP ≥ 160/100) will require at least two drugs

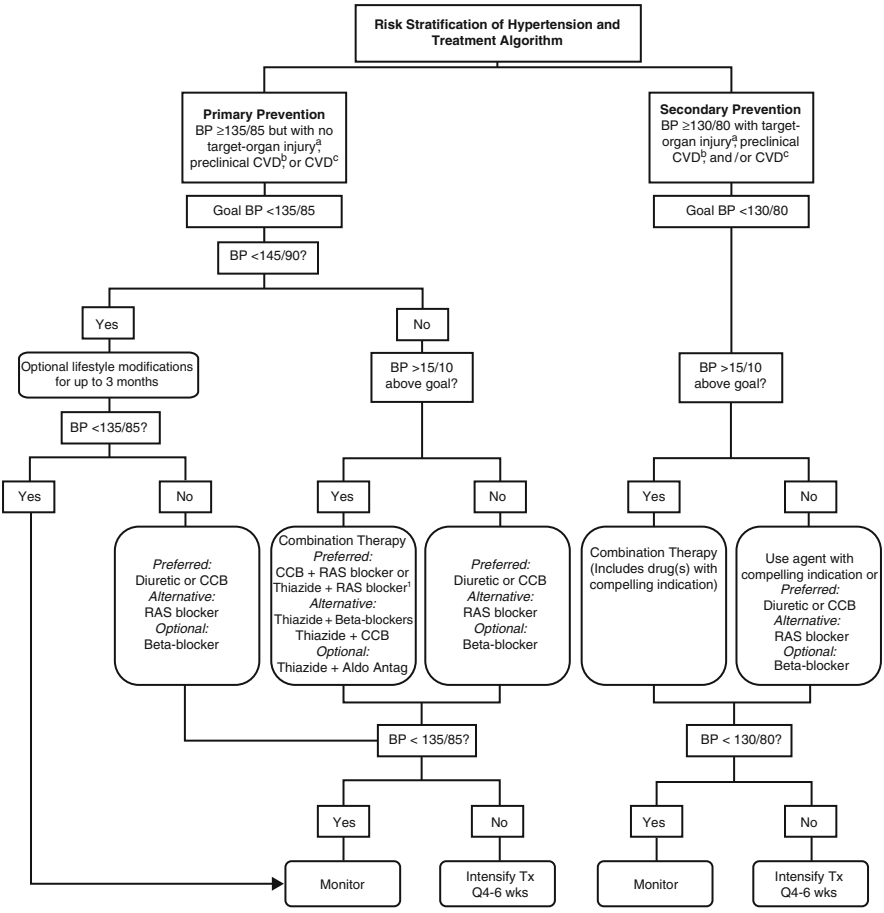

Fig. 14.1 Risk stratification and treatment algorithm of hypertension in blacks adopted from the *2010 ISHIB Consensus Statement*. Aldo Antag indicates aldosterone antagonist; *Tx* treatment. [a]Target-organ injury is defined as albumin:creatinine ratio >200 mg/g, eGFR <60 mL/min per 1.73 m^2, or electrocardiographic or echocardiographic evidence of LVH. [b]Indicators of preclinical CVD include metabolic syndrome, Framingham risk score >20 %, prediabetes (impaired fasting glucose [100–125 mg/dL] and/or impaired glucose tolerance [2-h post-load glucose >140 mg/dL]), or diabetes mellitus. [c]CVD includes HF (systolic or diastolic), CHD/postmyocardial infarction, peripheral arterial disease, stroke, transient ischemic attack, and/or abdominal aortic aneurysm. §Most effective 2-drug combinations: CCB + RAS blocker; thiazide diuretic + RAS blocker; thiazide diuretic + aldosterone antagonist; and thiazide diuretic + beta-blocker. Recommended RAS blockers are ACE inhibitors or ARBs in ACE inhibitor-intolerant patients. 1 indicates preferred combination therapy in edematous and/or volume overload states

in combination to achieve goal blood pressure. Best practice suggests starting the combination initially is recommended by most guidelines. In some cases, physician's discretion can warrant starting two drugs even for stage 1 hypertension (BP 140–160/90–100). Fixed-dose combinations (see below) lead to better adherence, less side effects, and usually less expense to the patient.

Patients should be generally followed up every 4–6 weeks after initiating therapy. Treatment should be gradually intensified if BP is not at goal. Intensification of therapy will involve gradual dose adjustments and/or adding new drugs. Up to four drugs could be required to achieve BP control for resistant hypertension which is defined as uncontrolled BP despite ≥3 adequately dosed drugs of different classes (one a diuretic) or controlled BP on ≥4 drugs and warrants referral to a hypertension specialist. In our population (of mostly black patients), we generally feel spironolactone (if not contraindicated) should be included in therapeutic regimen before calling blood pressure "resistant."

The benefits of rapid attainment of BP control are not so clear. Previous studies have demonstrated greater CVD risk reduction with more rapid control of blood pressure [9], but it appears that the greater risk reduction is mostly confounded by other patient clinical characteristics like obesity, DM, and the presence of albuminuria that portends a higher CVD risk, decreases the rate and speed of BP control, and increases the need for more intense antihypertensive drug therapy [6]. Moreover, a previous study also showed that titration of an ACE inhibitor as monotherapy every 6 weeks as compared to every 2 weeks leads to higher BP control rates with fewer serious adverse events [10]. Attention should always be placed on the occurrence of side effects and long-term adherence to therapy when initiating and optimizing antihypertensive medications. A prudent recommendation is to gradually up-titrate antihypertensive medications when BP remains above goal and to generally avoid therapeutic inertia (Fig. 14.1).

14.1.3 Combination Therapy

As alluded to above, at least 2/3 of hypertensive patients will require more than one drug to achieve goal blood pressure. The old concept of "step care" beginning with one drug, titrating to maximally tolerated dose, and then adding another is pretty much out of practice. Thus, the JNC 7 suggests if the BP is in stage 2 (>−160/100), physicians should start with two agents. ISHIB is somewhat more aggressive suggesting two drugs initially if the BP is 15/10 mm or greater above systolic/diastolic goal. Also, for stage 1 hypertension, clinical judgment can suggest starting with two drugs. For instance, for the diabetic, African American, CKD patient, and other high risk patients, starting with two drugs in fixed- or non-fixed-dose combination is recommended, even for stage 1 hypertension.

Recently, triple-drug combinations have come to the market (RAS blocker, CCB, and a diuretic). This novel approach is based upon achieving goal BP fairly soon and safely. These drugs should be used initially only after two drugs are on board and not for initial therapy for any stage of hypertension. All of these drugs have several doses of each component, so the physician can titrate till getting to the desired goal without risking serious adverse effects. Also with 2- and 3-drug combinations, compliance and adherence are improved, adverse events are minimized, and cost can be reduced.

14.1.4 Specific Antihypertensive Therapies

14.1.4.1 Thiazide and Thiazide-Like Diuretics

Two main classes of antihypertensive medications (*thiazide/thiazide-like diuretics and CCBs*) when used as monotherapy lower BP on average more than other main classes like RAS blockers or beta-blockers [5, 6].

Thiazide and thiazide-like diuretics, e.g., hydrochlorothiazide (HCTZ) 25–50 mg and chlorthalidone 12.5–25 mg, are efficacious in the treatment of hypertension in blacks either as monotherapy or in combination therapy as demonstrated by multiple clinical trials [11–14]. The thiazide diuretics act primarily by inhibiting sodium transport in the distal tubule [15, 16], the connecting segment at the end of the tubule [17], and probably the cortical collecting tubule [18, 19]. They tend to have a smaller natriuretic effect than loop diuretics because the segments which they act on reabsorb a smaller proportion of the filtered sodium load than the loop of Henle (main site action of loop diuretics, e.g., furosemide) [15, 16]. Moreover, the net diuresis may be partially limited by increased reabsorption in the cortical collecting tubule [20, 21]. At maximum doses, thiazide diuretics inhibit about 3–5 % of the filtered sodium at the most [15, 16] as compared to loop diuretics which inhibit about 20–25 % [15, 22]. These characteristics of thiazide diuretics make it less useful in the treatment of fluid overload or edematous states but effective in the treatment of uncomplicated hypertension where fluid loss is not desirable. In fluid overload states or with significant renal impairment, a combination with a loop diuretic is usually required to treat hypertension and edema or renal insufficiency.

The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a CVD clinical outcome trial that compared the efficacy of different classes of antihypertensive agents, found that ACE inhibitors (lisinopril) was less effective than a thiazide-type diuretic, chlorthalidone (and a CCB) in lowering BP and also preventing major clinical outcomes including heart failure, stroke, and coronary events in black participants [11–13]. Thiazide diuretics are very useful in stage 1 HTN (SBP 140–159 mmHg and DBP of 90–99 mmHg) as long as there is adequate kidney function (eGFR $\geq$ 45 mL/min per 1.73 m^2). Elderly patients and blacks tend to respond well to diuretic monotherapy but not necessarily better than young patients or non-blacks. There are good data that strongly support the use of thiazide diuretics in the elderly in terms of efficacy and clinical outcomes [14, 23].

Nevertheless, HCTZ is the most commonly used thiazide diuretic in the United States partly because it is included either as 12 or 25 mg dose in most antihypertensive combination therapies available. Two recent surveys showed that prescription for HCTZ outnumbers those for chlorthalidone by greater than 20-fold [24]. Ironically chlorthalidone has been shown to be more effective than HCTZ in lowering BP and preventing cardiovascular events [24, 25]. Its advantages over HCTZ include having a longer half-life (40–60 h versus 5.6–14.8 h for HCTZ) and being

more efficacious in patients with lower kidney functions (eGFR in the low to mid 30 mL/min per 1.73 m^2) when compared to HCTZ (eGFR of 45 mL/min per 1.73 m^2). A clinical study in patients with mild renal dysfunction demonstrated that chlorthalidone lowers BP and also reduces the incidence of hypertension-related complications at an eGFR lower than a point where HCTZ loses its effectiveness [23]. The incidence of hypokalemia which is a common adverse effect of thiazide diuretics was shown to be similar in both drugs when compared on a milligram-by-milligram basis [26]. The ISHIB 2010 consensus update thus favors the use of chlorthalidone over HCTZ for treating HTN in blacks [6]. The ISHIB report also recommends a dose of ≥25 mg when using HCTZ for the treatment of hypertension in blacks [6]. The rationale for this is the observation that higher CVD morbidity and mortality occurred when a lower dose of HCTZ was used in combination with benazepril as compared to amlodipine + benazepril combination in the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial [27].

Thiazide diuretics are most commonly used in combination therapy with RAS blockers and beta-blockers. Less often are they used with CCBs except with an RAS blocker in a 3-drug fixed-dose combination (see below). They are also used with the less often used peripheral- and central-acting sympathetic blocking agents like reserpine, guanabenz, methyldopa, and guanethidine. In the concept of using combination therapy, addition of a second agent does not only serve to augment BP lowering from its direct effect but also sometimes counteracts adverse physiologic perturbations that could arise from the first agent. For example, when using thiazide diuretic/RAS blocker combination, the RAS blockade will counteract the diuretic-induced hypovolemia which causes an activation of the RAS system (by counter regulatory feedback mechanism), hypokalemia, and/or glucose elevation in addition to its direct effects on the RAS system to lower blood pressure. Also beta-blockers in combination with thiazide diuretics would counteract diuretic-mediated sympathetic activation in addition to their BP lowering effects. The potential adverse effects of thiazide diuretics include hypokalemia, hyponatremia, hypomagnesemia, hyperglycemia, and hypercholesterolemia.

14.1.5 Loop Diuretics (Furosemide, Torsemide, Bumetanide)

These agents should not be ideally used as first-line single agents since they do not lower BP as well as thiazide diuretics when used as monotherapy particularly if dosed once daily. However, as stated earlier, they have a role to play when the eGFR is significantly reduced and in congestive heart failure or fluid overload states [28, 29].

14.1.6 Calcium Channel Blockers (Amlodipine, Nifedipine, Diltiazem, Verapamil, etc.)

The heterogeneous class of CCBs has also been shown in various clinical studies to be effective either as monotherapy [30, 31] or in combination therapy [27] in the treatment of hypertension. There are data also showing a decrease in hypertension-related complications (CHD, CVA, PVD) and overall mortality with the use of CCBs [27, 32]. They have also been shown to be more effective in lowering BP as monotherapy more than RAS blockers or beta-blockers in black patients. All of the subtypes of patients in terms of pathophysiology are to some extent responsive to CCBs including the low renin, salt sensitive, elderly, and black hypertensive patients. There are two major subclasses of CCBs: dihydropyridine (amlodipine, nifedipine) and non-dihydropyridine CCBs (diltiazem, verapamil).

The mechanism of action of dihydropyridine CCB involves the inhibition of calcium ions from entering the "slow channels" or select voltage-sensitive areas of vascular smooth muscle during depolarization producing vascular muscle relaxation, peripheral arterial dilatation, decreased peripheral vascular resistance, and ultimately a decrease in BP. Non-dihydropyridine CCBs act in a similar fashion and also in the myocardium producing coronary vasodilatation resulting in increased myocardial oxygen delivery in patients with vasospastic angina. They also induce reduction in heart rate. It is very important to note that dihydropyridine CCBs are not ideal as monotherapy in hypertensive patients with CKD and proteinuria as it has been shown to be much less efficacious in decreasing proteinuria and other clinical outcomes like the onset of end stage renal disease and overall mortality in African Americans (and the overall population) when compared with RAS blockers [33, 34]. However, when combined with RAS blockers, the inferior effects of dihydropyridine CCBs in patients with CKD and proteinuria are not observed [35]. CCBs are very useful in combination therapies with diuretics, ACE inhibitors, or ARB. There are multiple available fixed-dose combination therapies including amlodipine + benazepril, amlodipine + valsartan, felodipine + enalapril, and trandolapril + verapamil. The non-dihydropyridine CCBs are also effective agents in heart rate control in patients with paroxysmal or chronic atrial tachyarrhythmias and should be considered initially for BP control in such patients. A common adverse effect of dihydropyridine CCBs is peripheral edema which occurs in >10 % of patients [36]. Other adverse effects are less frequent and include palpitations, flushing, and fatigue in dihydropyridines and bradyarrhythmias with non-dihydropyridines.

14.1.7 RAS Blockers

RAS blockers (ACE inhibitors and ARBs) are also very useful agents for the treatment of hypertension. They are recommended as another monotherapy option for the treatment of hypertension in blacks. ACE inhibitors inhibit the RAS system and decrease BP by competitive inhibition of angiotensin converting enzyme thereby

preventing the conversion of angiotensin I to angiotensin II. Angiotensin II is a potent vasoconstrictor and acts on the adrenal gland to release aldosterone which causes salt and water retention. ARBs decrease BP by directly blocking angiotensin II AT_1 receptors and causing vasodilation, decreased secretion of vasopressin and aldosterone. ACE inhibitors and ARBs have been shown to be the most effective class of antihypertensives for slowing the progression of kidney disease in patients with diabetic and nondiabetic CKD including black patients [34, 37, 38].

There has been a long-standing erroneous perception that the RAS system is less active in blacks versus whites because of the tendency towards suppressed circulating renin activity in blacks [39, 40] and the lesser average BP response in blacks as compared to white hypertensive patients with ACE inhibitors when used as monotherapy [13, 41–43]. However circulating renin levels are not fully suppressed in the majority of blacks [44]. Also suppressed renin production and circulating renin levels from a high sodium intake have been associated with higher rather than lower levels of vascular angiotensin II production [45]. Moreover, there are data that suggest that there is greater activation of RAS system in healthy blacks as compared to whites [46]. In addition, the excessive rates of target-organ injury (LVH, CKD, and proteinuria) in blacks with HTN have all been linked to RAS activation [6]. Of note, when consuming a high sodium diet, blacks have shown a blunted suppression of intrarenal RAS activity as compared to whites [47], and dietary sodium intake in salt-sensitive humans suppresses urinary nitric oxide metabolites [48, 49] and augments vascular angiotensin II production [45]. These observations could probably explain why the largest differences in BP responses to ACE inhibitors between blacks and whites occur in the setting of high dietary sodium intake. As stated earlier, thiazide diuretics and CCBs have consistently achieved better results in the control of BP in blacks as compared to RAS blockers (which have showed better results in whites) when used as monotherapy. However, these observations should not be used as a standard in selecting antihypertensive therapy for patients of any race as more recent studies have showed a significant overlap between races/ethnic groups. It now seems that the greatest source of variability is within racial/ethnic group rather than between them [41, 42]. There are particular situations where an ACE inhibitor or ARB should be considered first as initial single therapy for BP control, e.g., when BP is <15/10 above goal and there is a compelling indication (DM, CKD, albuminuria). If these patients do not reach goal BP while on an ACE inhibitor or ARB monotherapy, addition of a second agent either with a CCB or thiazide diuretic is recommended [6] and usually will substantially enhance BP lowering. One may make the argument that RAS blockade should be a mandatory component of any antihypertensive regimen in blacks because it is a high risk population with pathophysiology at the tissue level as noted above, suggesting a major role the RAS system may play in this population. Of note, a randomized double-blind study (sited earlier) with a sizeable number of black participants (12.3 %) comparing the combination of an ACE inhibitor + CCB versus ACE inhibitor + thiazide diuretic showed comparable BP lowering effects with both combinations but significantly less CVD clinical outcomes (MI, coronary revascularization, composite of cardiovascular mortality) with ACE inhibitor + CCB than with ACE + thiazide

diuretics [27]. Physicians should take this into cognizance when initiating treatment for hypertension especially when starting initially with two antihypertensive drugs.

The combination of ACE inhibitors and ARBs is not recommended because of a higher risk of adverse effects, a higher rate of discontinuation of therapy despite a negligible amount of BP reduction [50].

Cough and angioedema are adverse effects mostly seen with ACE inhibitors and tend to occur more frequently in blacks than in whites [51] and preclude the use of these agents especially with angioedema. Cough does not occur with ARB and angioedema is uncommon so it is reasonable to try an ARB in the place of an ACE inhibitor with the occurrence of these adverse reactions.

14.1.8 Aliskiren

Aliskiren, a direct renin inhibitor, has recently become available and appears to have similar or slightly better efficacy in controlling BP when compared to various ACE inhibitors or ARBs at standard therapeutic doses [52]. Some clinical trials have shown improvement in BP control in stage 2 hypertension (systolic BP $\geq$160 and diastolic $\geq$100) in African American patients when using aliskiren in combination therapy as compared to amlodipine monotherapy [53, 54]. Neither cough nor angioedema occurs with aliskiren based on its mechanism of action. However, there has been recent FDA advisories on the use of this drug with an ARB in diabetic patients or patients with renal disease based on a recent study showing increased cardiovascular and renal events in these group of patients [55]. Another recent study also showed the addition of this drug to standard therapy in patients with heart failure and decreased LVEF did not reduce CV death or heart failure hospitalizations as compared to placebo and standard therapy and even resulted in more adverse events [56].

14.1.9 β-Blockers

β-blockers (atenolol, bisoprolol, nadolol, carvedilol, nebivolol, propranolol) are another important class of antihypertensive drugs used in blacks. They are particular useful in patients with concomitant ischemic heart disease; nonischemic, dilated, or obstructive cardiomyopathy; heart failure; and certain cardiac arrhythmias. They are also useful in patients with hyperkinetic circulation (tachycardia and palpitations), anxiety states, migraine, and essential tremors. β-blockers are also referred to as β-adrenergic blocking agents, β-adrenergic antagonist, and β-antagonists in the literature. The antihypertensive effects of β-blocker were first demonstrated in the mid-1960s with pronethalol and propranolol [57, 58]. Subsequently propranolol was approved as the first beta-blocker used in the treatment of hypertension. β-blockers are highly heterogeneous probably because of variations in their

aromatic ring structure which confers unique pharmacological properties to the different types. These variations in structure translate to differences in pharmacokinetic properties including variations in gastrointestinal absorption, degree of first-pass hepatic phenomenon, lipid solubility, protein binding, volume of distribution, penetration into the central nervous system, concentration in the myocardium, and renal clearance which ultimately translate to variations in clinical effects [59]. Hence some β-blockers have a higher degree of intrinsic sympathomimetic activity, membrane stabilizing effect, β-1 receptor selectivity, and α-1 adrenergic blocking effect. These properties are usually considered when selecting β-blockers for the treatment of hypertension in blacks especially with other comorbid conditions. The mechanism of action of β-blockers in lowering BP is not exactly clear but proposed mechanisms include reduction in heart rate and cardiac output, inhibition of renin release, reduction in venous return and plasma volume, reduction in peripheral vascular resistance (β-blockers with intrinsic sympathomimetic activity), improvement in vascular resistance, reduction in norepinephrine release, and central nervous system inhibitory effect [59, 60].

The use of β-blockers as first-line agents or monotherapy in the treatment of hypertension is controversial. β-blockers have been generally viewed to be not very effective as monotherapy or first-line agents in the absence of a compelling indication for treatment of hypertension in blacks and other subsets of patients like the elderly and those with diabetes mellitus. Ironically, JNC 7 [4] recommends that β-blockers should be considered as first-line agents for the treatment of hypertension. These recommendations were based on large clinical trials showing a reduction in morbidity and mortality in patient on β-blockers although most of these benefits were related to secondary prevention of cardiovascular complications in patients with established disease as opposed to primary prevention [4]. Also in support of this recommendation are available trial data of large scale meta-analyses as stated in the most recent European guidelines on the treatment of hypertension [61], showing that there were no significant differences in the efficacy to reduce blood pressure between diuretics, β-blockers, CCBs, ACE inhibitors, and ARBs. There are clinical scenarios where the use of β-blockers as monotherapy is indicated and reasonable, e.g., in a patient with a history of ischemic heart disease and mild hypertension when a single antihypertensive agent will achieve BP control. β-Blockers are also very useful in combination or as add-on therapy for the treatment of hypertension. The antihypertensive effects of β-blockers can be enhanced with the coadministration of a diuretic [59], and combinations with HCTZ and chlorthalidone have been approved and are available for the treatment of hypertension. They can also be useful as add-on therapy in the setting of vasodilatation-induced tachycardia from medications like hydralazine, minoxidil, and dihydropyridine calcium channel blockers [62].

Selection of β-blockers as a second agent or add-on therapy for hypertension should also be guided by the existence of other comorbidities and the effects of β-blockers of these other medical conditions. β1 selective blocking agents, such as metoprolol, atenolol, bisoprolol, acebutolol, esmolol, and nebivolol, when used in low doses, inhibit cardiac β-1 receptors but have less influence on the bronchial and

vascular receptors making them a better choice of antihypertensives in patients with reactive airway disease. However, in higher doses (e.g., >50 mg of metoprolol/day), these agents also block β-2 receptors [59].

Nebivolol is a β-1 selective blocker with additional vasodilator actions approved for the treatment of hypertension. Its vasodilator actions are apparently related to an enhancement of nitric oxide activity. There are some data suggesting that blacks with CVD may have a lower bioavailability of NO due to more endothelial dysfunction. A study done by Mason et al. showed that nebivolol was able to restore nitric oxide bioavailability in the endothelium of blacks [60]. We published a study on the efficacy and tolerability of nebivolol in hypertensive African Americans [61] which showed that this drug had antihypertensive efficacy in blacks comparable to the general population when given in monotherapy. In addition, its tolerability was comparable to placebo. Of note, sexual dysfunction which is a common adverse effect with β-blockers and a cause of decreased compliance with therapy was rarely observed with nebivolol in this study and should be considered in patients with such complaints. Other reports have also demonstrated its efficacy as monotherapy and in combination therapy for the treatment of hypertension [62, 63].

It appears that variation in the pharmacological properties of various β-blockers have a significant impact on their clinical effects in patients with diabetes as demonstrated in the GEMINI (the Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives) trial [64]. This study compared the effects of carvedilol versus metoprolol tartrate on glycemic control in participants with hypertension and diabetes already receiving RAS blockers and found that carvedilol improved insulin sensitivity and glycemic control and reduced progression to microalbuminuria with equivalent BP lowering effects when compared to metoprolol. Based on this study, carvedilol may be a better β-blocker for diabetics when used in combination with RAS blockers for the treatment of hypertension.

β-Blockers should be used with caution in patients with reactive airway disease (asthma and chronic obstructive pulmonary disease) as they can precipitate an exacerbation especially in high doses. β-Blockers with high β-1 selectivity, such as nebivolol, may be safer under these circumstances. β-Blockers should be avoided in greater than first-degree heart block and as a new medication in patients with acute decompensated systolic heart failure. They should also be used with caution in patients with insulin-dependent diabetes mellitus because they can worsen glucose intolerance, mask the symptoms of hypoglycemia, and prolong recovery from hypoglycemia [65]. β-Blockers may also alter plasma lipids by reducing the level of high density lipoprotein and increase triglycerides [59]. β-Blockers with intrinsic sympathomimetic activity and/or α-blocking vasodilator activity have minimal or no effects on plasma lipids [59].

Extended-release formulations of metoprolol, carvedilol, nebivolol, and propranolol which allow for once-daily dosing are also available and might be a better option for patients with compliance issues.

14.1.10 Other Antihypertensive Therapies

Aldosterone antagonists (spironolactone and eplerenone) have also been used for treating hypertension in blacks in combination with or without a thiazide diuretic therapy. They have also been demonstrated to be effective as an add-on therapy for the treatment of resistant hypertension [66]. As monotherapy the antihypertensive effect of eplerenone has been shown to be similar between whites and blacks [67]. In the same study, it was also shown to be clearly superior to the ARB losartan in terms of BP lowering when used as monotherapy. Eplerenone, however, is a less potent antihypertensive than spironolactone when compared on a milligram-to-milligram basis. At equivalent doses of 50 mg twice daily (or 100 mg of eplerenone), spironolactone is a 1.3–2 times more potent than eplerenone [68].

The use of both medications is associated with hyperkalemia and gynecomastia although eplerenone is associated with a lesser degree of gynecomastia. Potassium-sparing diuretics (amiloride and triamterene) are also effective in lowering BP in blacks with hypertension when given alone or in combination with spironolactone [69, 70]. We tend not to call patients "resistant" until they have been given a trial of spironolactone added to their 3-drug regimen. Because these patients are on RAS blockers, one must watch for hyperkalemia, especially in those who have renal impairment.

α1 Adrenergic inhibitors (adrenergic blocking agents) used in the treatment of benign prostatic hypertrophy are also effective antihypertensive agents and comparable to other classes [4]. They are most useful in combination therapy and can be combined with all other drug classes for hypertension. They are also useful as add-on therapy for resistant hypertension.

Centrally acting adrenergic inhibitors such as clonidine are occasionally used as add-on therapies in patient with severe/resistant hypertension [71]. Combination of this class with α-adrenergic blockers could lead to significant orthostatic hypotension which is a common cause of falls and syncope, especially in the elderly. Orthostatic hypotension and significant bradycardia can also result when clonidine is combined with β-adrenergic blockers; hence, these combinations should generally be avoided. We believe these agents should be reserved for hypertensive urgencies and can keep many patients out of the ER. Because they are short acting, it is not practical to use clonidine orally for chronic therapy except in the slow-release topical patch form.

Direct vasodilators such as hydralazine and minoxidil are not ideal therapeutic choices as monotherapy because their use precipitates the activation of counter regulatory mechanisms which includes the activation of the sympathetic nervous system and salt and water retention. They are reserved for late adjunctive therapy in patients with severe hypertension. Hydralazine is also dosed three times daily which makes it difficult to use and leads to noncompliance issues.

14.1.10.1 Resistant Hypertension

Resistant hypertension is defined as the lack of BP control with ≥3 antihypertensive medications from different classes (including a diuretic) with adequate dosage or controlled BP while on ≥4 different antihypertensive medications including a diuretic. As stated above, we prefer giving a trial on spironolactone in patients who can tolerate it before calling the patient "resistant." The increasing prevalence of resistant hypertension among Americans has been attributed to the increasing incidence of comorbidities like type 2 diabetes mellitus, obesity, and chronic kidney disease [72–74] and other lifestyle factors including excessive alcohol intake, excessive dietary sodium intake, and cocaine and amphetamine misuse [71]. Some medications have also been implicated in causing difficult to control hypertension and they include nonsteroidal anti-inflammatory drugs, oral contraceptives, sympathomimetic-like nasal decongestant, and some diet pills, among others. There are also secondary causes to consider like primary hyperaldosteronism, obstructive sleep apnea, renal artery stenosis, pheochromocytoma, Cushing's syndrome, and thyroid disease. Management of resistant hypertension has been extensively discussed in a previous chapter.

14.2 Future Directions

In the early 1950s, thoracolumbar surgical sympathetic denervation was shown to be beneficial in the treatment of essential hypertension even before the availability of effective and diverse pharmacological therapy. However, this treatment was associated with significant morbidities which curtailed any widespread clinical acceptance [75]. The theory at that time was that extensive surgical sectioning of the sympathetic nerves resulted in the removal of systemic vasoconstriction and thus a reduction in BP. Subsequently, preclinical studies using animal models showed that selective renal denervation resulted in BP lowering [76], suggesting that the sympathetic nerves in the kidneys played a significant role in the pathogenesis of hypertension. This was the basis of the Simplicity Hypertension 1 and 2 trials [77–79] which evaluated the efficacy of renal sympathetic denervation using a minimally invasive catheter (Simplicity catheter system) to ablate the renal nerves by applying short bursts of radiofrequency energy along the length of the main renal arteries for the treatment of drug-resistant hypertension. Both studies had their limitations but showed positive and very encouraging results. The Simplicity Hypertension 1 trial [77, 78] was a non-randomized "proof-of-principle" multicenter cohort study. The Simplicity Hypertension 2 [79] was a prospective randomized controlled trial, but its limitations included a lack of ambulatory blood pressure monitoring, patient's nonadherence and incomplete records, and also non-blinding of patients or staff who measured the BP response to renal denervation. These methodological flaws will hopefully be addressed by the Simplicity Hypertension 3 trial which is currently in progress. Perhaps, in the future, along with the combination of appropriate

TLC and pharmacotherapy, devices for resistant hypertension, including renal nerve denervation and carotid baroreceptor stimulation, may assist with optimal BP control and diminish the morbidity and mortality associated with hypertension in blacks in the United States.

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Chapter 15
Hypertension in African Americans

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15.1 Introduction

Hypertension in African Americans has long been considered a distinct clinical entity. There are several blood pressure (BP) as well as physiological phenotypic *tendencies* in African Americans compared to whites that seemingly distinguish the African American hypertensive from other racial and ethnic groups. Nevertheless, racial differences/tendencies, in most instances, are quantitative rather than qualitative. The focus of this chapter is not to present an encyclopedic armada of facts and data. Rather, the approach taken will be to provide an overview of hypertension in African Americans in such a way that will help connect the dots into a unifying hypothesis

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K.C. Ferdinand (ed.), *Hypertension in High Risk African Americans*, Clinical Hypertension and Vascular Diseases, DOI 10.1007/978-1-4939-2010-5_15

regarding the origins of the excess of hypertension and pressure-related target-organ injury. Inordinate focus will also be placed on modifiable exposures (e.g., dietary sodium, vitamin D deficiency) and interventions that have the potential to lower the risk of hypertension, lower BP, and improve BP control in those afflicted with hypertension and to mitigate the emergence of pressure-related target-organ complications and adverse clinical events (e.g., stroke, heart failure). Data from non-African American human populations and relevant animal models will be strategically discussed to show concurrence as well as disagreement with data derived from African Americans. These data will also be used to fill in gaps in our understanding of human physiology when specific data are not available in African American populations.

15.2 Pre-hypertension and Hypertension Prevalence

Higher rates of pressure-related CVD-renal complications at incrementally higher BP levels have been observed beginning at BP levels well within the normal range. Accordingly, Fig. 15.1 displays the sex-specific age-adjusted prevalence of

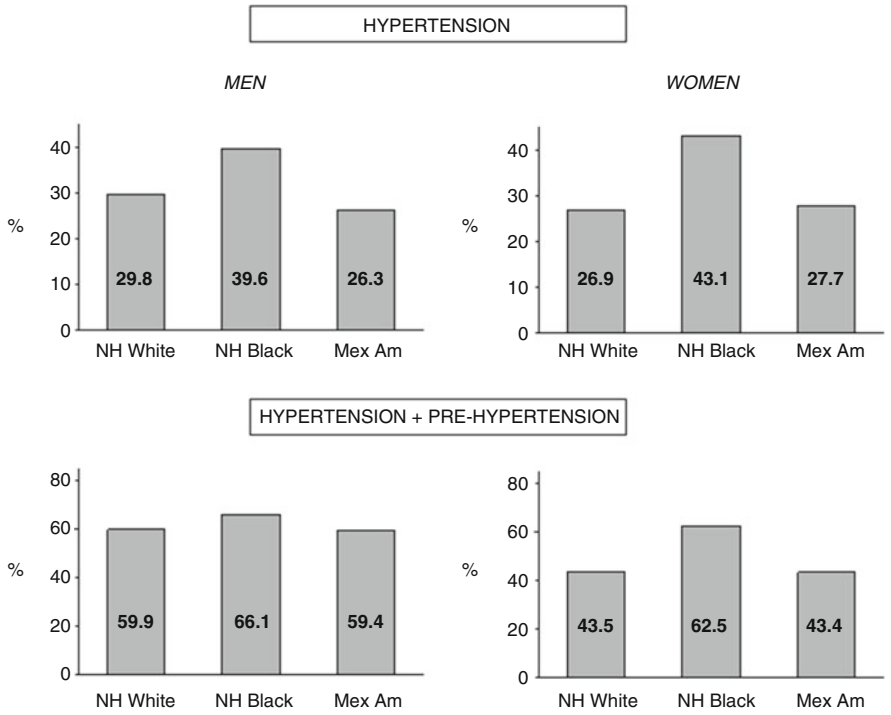

Fig. 15.1 Age-adjusted prevalence of pre-hypertension and hypertension amongst the major race-ethnicity groups in the United States, NHANES 2009–2010. Adapted from Guo, F., et al., *Trends in prevalence, awareness, management, and control of hypertension among United States adults, 1999 to 2010*. J Am Coll Cardiol, 2012. 60(7): p. 599-606. Hypertension defined as SBP ≥140 mmHg or DBP ≥90 mmHg or taking antihypertensive medication. Pre-hypertension defined as SBP ≥120 mmHg or DBP ≥80 mmHg but not meeting criteria for hypertension

pre-hypertension as well as hypertension in the three major race-ethnicity groups in the United States [1]. Rates of pre-hypertension are similar across race-ethnicity groups. However, hypertension prevalence is higher in African American men and women relative to sex-matched whites and Mexican Americans. Hypertension prevalence is slightly higher in African American women than men. Almost two-thirds of African American men and women have either hypertension or pre-hypertension.

15.3 Hypertension Awareness, Management, and Control

Table 15.1 displays the age-adjusted prevalence of hypertension awareness, management, and control to <140/90 mmHg amongst those under management. African American men are more aware of their hypertension and more likely to be under management than white men. Nevertheless, white men under management are much more likely than African American men to have attained BP control. African American men do better than Mexican American men in all categories. African American women have similar awareness and slightly higher rates of management than white women. However, white women under management are much more likely to attain control than African American women. African American women

Table 15.1 Age-adjusted awareness, management, and control of hypertension in the United States

	Awareness %	
	Men	Women
NH white	68.9	80.2
NH black	82.7	81.5
Mex Am	62.0	67.0
	Management %	
NH white	64.7	80.4
NH black	72.6	85.8
Mex Am	55.6	66.6
	Control in management %	
NH white	65.0	74.8
NH black	49.7	57.9
Mex Am	38.5	59.7

Adult hypertensives, NHANES 2009–2010
Adapted from Guo, F., et al., *Trends in prevalence, awareness, management, and control of hypertension among United States adults, 1999 to 2010*. J Am Coll Cardiol, 2012. 60(7): p. 599-606
Awareness was having been told of hypertension diagnosis and management was taking antihypertensive medication or adopting lifestyle modifications

Table 15.2 Age- and sex-specific differences in average systolic blood pressure between blacks with hypertension and non-Hispanic whites with hypertension

	SBP Δ, mmHg (B–W)	
Age category, (years)	Men	Women
25–34	+1	+14
35–44	+7	+13
45–54	+9	+10
55–64	+10	+4
65–74	+3	+4
≥75	+9	+1
Mean Δ, mmHg	+6.5	+8

Adapted from Fiscella, K. and K. Holt, *Racial disparity in hypertension control*: *tallying the death toll*. Ann Fam Med, 2008. 6(6): p. 497-502

are more likely than Mexican American women to be aware of their diagnosis and to be under management but are equally likely to have attained control once under management.

In NHANES 1999–2002 blood pressure was higher in all age categories in African American compared to white hypertensives [2]. In men, BP averages 6.5 mmHg higher and amongst women 8.2 mmHg higher than their sex-matched non-Hispanic white hypertensive counterparts. However, these differences are distinctly different across the age-span in men and women (Table 15.2). Given that the magnitude of differences is much greater amongst younger women, these data suggest that, over the lifespan, African American women are at much greater incremental risk for pressure-related complications than are African-American men relative to their sex-matched non-Hispanic white counterparts. The potential impact of the aforementioned racial disparity in BP control is staggering. Fiscella and Holt [2] estimated that elimination of the racial disparity in BP would, in African American hypertensives, reduce the number of annual deaths from heart disease by 5,480 and from stroke by 2,190. They made no attempt to quantify the impact of eliminating this BP control disparity on morbid events.

15.4 Epidemiology of Pressure-Related Target-Organ Injury and Cardiovascular-Renal Events

Relative to whites, African Americans experience more functional and anatomic vascular abnormalities, even within the normotensive range of BP [3–6]. African Americans also have strikingly higher rates of pressure-related complications such as stroke, heart failure, and chronic kidney disease (CKD)/end-stage renal disease (ESRD) [7–9] than any other racial/ethnic group in the United States. Hypertension accounts for a considerable amount of premature mortality in Africans American as

20–30 % of deaths in African American hypertensives can be attributed to elevated BP [10]. Importantly, the risk for pressure-related target-organ complications as well as adverse clinical events begins and incrementally escalates at progressively higher BP levels well below conventional BP thresholds for diagnosing hypertension.

15.5 Blood Pressure Phenotypes of African Americans

The lack of nocturnal decline in BP and salt sensitivity are two intermediate BP phenotypes that have been repeatedly linked to the African American hypertensive. Both intermediate phenotypes are modifiable as they appear to be influenced by multiple environmental and lifestyle exposures.

15.5.1 Non-dipping Nocturnal Blood Pressure

Epidemiological observations have determined that nighttime BP level is more closely correlated with CVD risk than either 24 h ambulatory BP or daytime BP. BP normally falls 10–20 % during nighttime hours; non-dipping BP is when the nocturnal (midnight–6 AM) BP falls less than 10 % from daytime levels. African Americans have been observed to more often be non-dippers than whites [11]. Plausibly the higher 24 h BP burden, especially the higher nighttime BP levels, play a role in the excess-pressure-related risk in African Americans relative to whites. Non-dipping of BP has been linked to high levels of dietary sodium intake, low levels of dietary potassium intake, and augmented activity of the sympathetic nervous system [12] as well as to chronic kidney disease (CKD) [13], type 2 diabetes mellitus [14], older age [past 40 years] [15], and obesity [16]. Non-dipping of BP has been specifically demonstrated in salt-sensitive African American adolescents [17]. Interestingly, rapid weight loss over 1 month in obese subjects more than 30 % above ideal body weight restores the normal nocturnal decline in BP [16]. Sleep-disordered breathing, a condition frequently coexisting with obesity, has also been linked to non-dipping of BP [18]. Thus, a plethora of conditions, some modifiable and some linked to one another, known to be more common in African Americans than whites, have been linked to non-dipping BP, a high-CVD risk intermediate BP phenotype.

15.5.2 African Americans Are Disproportionately Salt Sensitive

Salt sensitivity can be operationally defined as a rise in BP when dietary sodium exposure increases and/or a reduction in BP when dietary sodium intake is selectively reduced. Both normotensive and hypertensive African Americans manifest

salt sensitivity more so than their white counterparts with similar levels of BP [19, 20]. Salt sensitivity in hypertensive African Americans has been linked to BP non-dipping [21]. Non-dipping of BP is a modifiable BP phenotype as nighttime BP falls more on a low- compared to high sodium diet [21]. This observation seems consistent with the hypothesis that an attenuated or lack of nocturnal decline in BP may be explained by impaired renal natriuresis and that BP remains high as a compensatory mechanism to augment renal sodium elimination.

Intuitively, because sodium is known to expand plasma volume (PV), it has been tempting to search for PV expansion in African Americans relative to whites. Nevertheless, dietary sodium expands PV and increases cardiac output only *transiently* in salt-sensitive individuals [22, 23]. It does not appear that BP elevations in salt-sensitive African Americans can be attributed to PV expansion as the magnitude of PV expansion does not differ between those who are and who are not salt sensitive. Rather, it appears that salt-sensitive African American normotensives experience a paradoxical rise in both systemic vascular resistance (SVR) and renal artery resistance with a reduction in renal blood flow whereas non-salt-sensitive African Americans actually manifest a fall in SVR with no changes in renal arterial resistance or renal blood flow in response to dietary sodium loading [23, 24]. The rise in BP during dietary sodium augmentation in salt-sensitive African Americans is directly linked to the magnitude of salt-induced renal dysfunction [25]. There is also strong experimental evidence from this same group that asymmetrical dimethylarginine (ADMA) mediates the rise in SVR and BP during dietary salt loading of normotensive African Americans as changes in both were highly correlated with the rise in ADMA [24].

Salt sensitivity should not be conceptualized as a BP phenotype that one carries from birth to the grave. There is good evidence that dietary exposures modify the expression of salt sensitivity in both African Americans and whites. Potassium bicarbonate supplementation prevents the pressor response to dietary sodium chloride loading in normotensive salt-sensitive African Americans and also prevented a rise in renal filtration fraction [25]. These same investigators also have shown that supplementation of potassium to 70 mmol/day suppressed moderate salt sensitivity to a similar degree in African American and white normotensives and supplementation of potassium to 120 mmol/day abolished moderate salt sensitivity and markedly attenuated severe salt sensitivity in African Americans [20].

15.5.3 Dietary Sodium and Potassium Intakes of African Americans

Most adult Americans consume dietary sodium far in excess of the amount needed for normal physiological functioning. Dietary recommendations for dietary sodium intake vary between less than 1,500 mg/day (65 mmol/day) [26, 27] and 2,300 mg/day (100 mmol/day) [28]. The median intake of dietary sodium from food and

beverages (exclusive of added dietary sodium) is 3,161 mg/day (138 mmol/day) in African Americans, 3,423 mg/day (149 mmol/day) in whites, and 3,251 mg/day (141 mmol/day) in Mexican Americans. Virtually all African Americans consume more than 1,500 mg/day and 85.6 % consume more than 2,300 mg/day [29]. Dietary potassium intake is important because it has been shown to blunt/prevent the pressor effect of dietary sodium intake in African Americans [20]. Low dietary potassium intake has been identified as a risk factor for stroke in animal models [30] and has also been linked epidemiologically to stroke risk in humans [31]. Finally, in western diets foods rich in sodium tend to be low in potassium and vice versa. The majority of adult Americans consume inadequate amounts of potassium. The IOM and the US Department of Health and Human Services/US Department of Agriculture have recommended that all Americans augment their intake of potassium-rich foods (fruits and vegetables) to achieve an intake of ≥4,700 mg/day (120 mmol/day). Usual daily intakes of potassium for whites, African Americans, and Mexican Americans are, respectively, 2,712 mg/day (69 mmol/day), 2,193 mg/day (56 mmol/day), and 2,586 mg/day (66 mmol/day). Thus, achieving recommended dietary targets for sodium and potassium will require significant changes to the diets of all Americans and especially amongst African Americans.

15.6 Is Vitamin D Important in the Excess Hypertension in African Americans?

Low vitamin D (25 OH D) levels are much more common in African Americans than amongst either whites or Mexican Americans [32–34]. This is likely attributable to dark skin reducing the conversion of 7-dehydrocholesterol to vitamin D_3 in the skin and greater obesity, especially amongst women. Perhaps importantly, the emergence of excessive vitamin D deficiency in African Americans relative to whites has its origins in childhood [34–36]; thus, many adult African Americans with low levels of vitamin D have likely been vitamin D deficient for many decades.

The Institute of Medicine has established the level of 20 ng/mL (50 nmol/L) as vitamin D sufficiency based on the level deemed sufficient to maintain bone health. Approximately two-thirds of African American men and women in the National Health and Nutrition Examination Survey (2001–2006) had vitamin D levels ≤16 ng/mL [37]. Thus, the data supporting strikingly disproportionate vitamin D inadequacy in African Americans is compelling.

Cross-sectional [34, 38] epidemiological studies have linked depressed vitamin D levels to higher levels of BP. In addition, longitudinal epidemiological data [39] also show that vitamin D levels relate inversely to risk for incident hypertension. It has been estimated from NHANES hypertension prevalence data that ~50 % of the excess hypertension in non-Hispanic blacks relative to whites can be attributed to the racial disparity in vitamin D blood levels [34]. Furthermore, there is strong biological plausibility that vitamin D impacts physiological systems important in the regulation, both directly and indirectly, of blood pressure (BP), vascular tone as

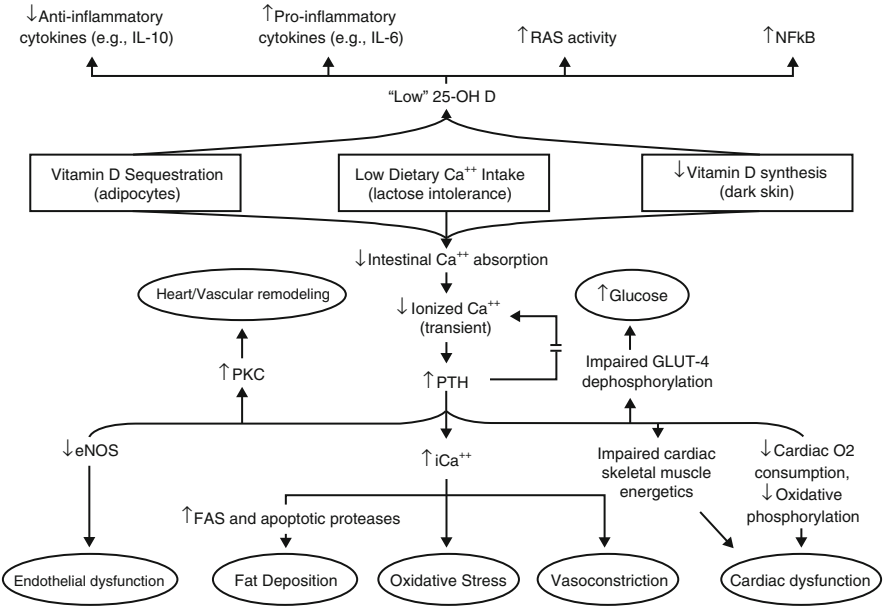

Fig. 15.2 Apoptotic proteases—u-calpain and Ca^{2+}/calpain-dependent capase-12. *Ca++* calcium, *eNOS* endothelial nitric oxide, *FAS* fatty acid synthase, *GLUT* glucose transporter, *IL* interleukin, *NFkB* nuclear factor kappa beta, *PKC* protein kinase c, *PTH* parathyroid hormone, *RAS* renin-angiotensin system

well as of pressure-related target-organ damage/dysfunction (Fig. 15.2). Accordingly, our group has shown that vitamin D levels are inversely related to urinary nitric oxide (NO) metabolites in healthy normotensive African Americans [40]. Mice lacking vitamin D receptors or 1-alpha-hydroxylase show striking activation of the renin-angiotensin system and increased BP levels; accordingly, 1,25 $(OH)_2D$, the active form of vitamin D, suppresses renin gene transcription [41–43]. In aggregate these data demonstrate the physiological plausibility of vitamin D having a role in the excess hypertension observed in African Americans relative to whites.

There are human experimental data demonstrating that raising vitamin D levels in African American lowers BP, especially systolic BP. A recently reported 3-month study by Forman and coworkers [44] administered vitamin D in doses of 1,000, 2,000, or 4,000 IU/day and placebo to African Americans with average baseline BP of 122/78 mmHg; the difference in clinic cuff BP change between placebo and the respective treatment groups was −2.4, −4.0, and −4.7 mmHg during 3-month supplementation periods during winter months. There was a statistically insignificant trend toward greater SBP reductions in participants with baseline vitamin D level <20 ng/mL compared to those with ≥20 ng/mL. Interestingly, there was no detectable effect of vitamin D on diastolic blood pressure (DBP). Importantly, this proof of concept study did not require pretreatment documentation of vitamin D deficiency

which, from our ongoing work in this area, has a significant influence on BP response (personal communication J Flack); that is, African American hypertensives with the lowest levels (<15 ng/mL) of vitamin D have the greatest reduction of BP during vitamin D supplementation.

15.7 Hypertension Therapy in African Americans

It is important to establish the framework upon which the following treatment recommendations have been based. First, it is impossible to formulate a comprehensive approach to the therapy of hypertension in African Americans solely on the basis of data derived specifically in this hypertension-prone demographic group. Second, though prospective randomized clinical trial endpoint data represent the highest quality data upon which to make recommendations, such trials do not adequately address all of the relevant clinical decisions that must be made; therefore, other data must be considered such as the magnitude of inherent population risk for pressure-related complications that we seek to prevent or, at a minimum, forestall as well as the current effectiveness of BP treatment in the population subgroup. Third, we consider it highly unlikely that there is an inherently different fundamental relationship between BP and CVD-renal disease in African Americans in comparison to whites. Nevertheless, there are well-documented differences between these two populations in the timing of onset of pressure-related subclinical vascular complications as well as in the risk for adverse clinical complications once traditional BP thresholds for the diagnosis of hypertension have been breached. Thus, though the overall fundamental relationship is likely the same, the risk for the onset of preventable pressure-related complications, both subclinical and clinical, appears to be shifted to lower levels of BP in African Americans. Finally, our recommendations have been significantly influenced by the emerging data strongly suggesting that the frankly intuitive notion of lifetime risk of CVD is related to the duration of elevated BP levels [45]. It has long been established that higher BP levels track over time. That is, that higher BP levels early in life portend even higher BP levels later in life. A biologically plausible explanation for this is that the degree of vascular injury that likely significantly underpins the age-related rise in BP is incrementally greater at incrementally higher BP levels, even within the so-called normal BP range. Accordingly, treating more modest BP elevations than we have traditionally done is a logical approach to attenuating, or possibly even preventing, the age-related rise in BP at a time prior to prominent pressure-related vascular injury and target-organ dysfunction. Moreover, BP control can be obtained with much less medication prior to significant pressure-related vascular injury than after its onset.

15.7.1 What Should the Goal BP Be in African Americans?

In the first update of the International Society on Hypertension in Blacks (ISHIB) consensus statement [46], we proposed a target BP <135/85 mmHg for African Americans without clinically manifest target-organ injury, preclinical CVD, or overt CVD (Table 15.3). In hypertensives with one or more of these conditions, the target BP <130/80 mmHg was put forth. The rationales for these recommendations were the following: (1) African Americans manifest subclinical pressure-sensitive vascular injury at BP levels well below the conventional BP threshold (140/90 mmHg) for diagnosing hypertension; (2) once the BP threshold for hypertension has been breached, the risk for pressure-related complications is multiples of that observed in whites; (3) the existence of human data showing reductions of BP-related complications in hypertensive cohorts with baseline BP as low as 110 mmHg [47]; (4) clear population-based evidence of lesser BP control and therefore inadequate treatment of hypertensive African Americans relative to whites [2]; (5) the lack of evidence of substantive harm in more recent, large-scale hypertension trials with aggressive BP targets; and (6) high-risk comorbidities (e.g., prediabetes, metabolic syndrome) merit lower than usual BP levels. It was also hoped that the recommended lower BP target would, at a minimum, improve BP control rates at the conventional threshold of <140/90 mmHg.

As proposed in the ISHIB 2010 consensus update [46], a target BP for low-risk African Americans of <135/85 mmHg can be justified on the basis of the *totality* of evidence; these are individuals without evidence of target-organ injury, preclinical CVD, or CVD. In African Americans with these conditions, a BP of <130/80 mmHg is recommended. Some of the high-risk comorbidities noted in Table 15.3 do not have randomized clinical trial data to directly support specific BP targets.

Table 15.3 ISHIB risk stratification scheme

Secondary prevention, BP >130/80
• Target-organ injury
– Albumin : creatinine >200 mg/g
– EGFR <60 mL/min/1.73 m^2
– EKG or Echo LVH
• Preclinical CVD
– Framingham risk score >20 %
– Prediabetes
– Diabetes mellitus
• CVD
– Heart failure
– Coronary heart disease/postmyocardial infarction
– Peripheral arterial disease
– Stroke/transient ischemic attack
– Abdominal aortic aneurysm

EGFR estimated glomerular filtration rate, *EKG* electrocardiogram, *CVD* cardiovascular disease

Nevertheless, their presence confers high CVD risk thereby making BP lowering even more critical. Lifestyle modifications, in particular reduction in dietary sodium intake (~2 g/day), increased aerobic activity, weight loss, and limiting alcohol intake (2 drinks/day in men, 1 drink/day in women), seem prudent. Increased intake of a potassium-rich diet (fruits and vegetables) is also prudent in at-risk as well as in frankly hypertensive African Americans. Lifestyle modifications should be encouraged when BP exceeds 115/75 mmHg. Moreover, lifestyle modifications should be continued after initiating drug therapy. Checking vitamin D levels is also recommended as is supplementation in those deficient (<20 ng/mL) to maintain vitamin D levels at least above this level.

15.7.1.1 Strategies for Lowering Blood Pressure in Hypertensive African Americans

The majority of hypertensives of all races will require >1 antihypertensive drug to achieve BP control. This is especially true amongst African Americans. In the updated ISHIB 2010 consensus statement, we proposed favoring the use of either a diuretic or calcium antagonist when BP was <145/90 or <10/5 mmHg above goal BP if there is no compelling indication for another antihypertensive drug class(es). The sole rationale was that control of BP to less than target levels without the need for additional drugs would be more likely with these drug classes; we explicitly avoided proposing black race, per se, as a sole criterion upon which to base selection of antihypertensive drug monotherapy. However, when BP was >15/10 mmHg above goal, combination therapy should be initiated. The recommended favored drug combination was a calcium antagonist plus an ACE (or ARB in ACE-intolerant patients) given the greater CVD risk reduction in the ACCOMPLISH trial of high-risk hypertensives with the combination of benazepril plus amLodipine compared to benazepril plus hydrochlorothiazide [48]. In patients with edema and/or volume overload, combination therapy with a thiazide diuretic plus an ACE inhibitor (or ARB in ACE-intolerant patients) was the preferred combination therapy. Therapeutic inertia should be avoided. That is, when BP is elevated, no therapeutic changes are made. Nevertheless, there is little reason to up-titrate long-acting antihypertensive drugs sooner than every four weeks or so.

15.7.2 BP Goals in High-Risk African Americans: Focus on Diabetes Mellitus and Chronic Kidney Disease

15.7.2.1 Diabetes Mellitus

Several groups have promulgated relaxed BP targets for high-risk hypertensive patients such as those with diabetes guidelines under the mantra that “no data exists” to support the target <130/80 mmHg [49, 50]. The ACCORD study [50], for

example, has been interpreted as a negative study (mean follow-up 4.7 years) because the underpowered primary composite endpoint (nonfatal myocardial infarction, nonfatal stroke, or CVD death), which trended in the direction of benefit (hazards ratio 0.88; 95 % confidence interval [CI], 0.73–1.06, $p=0.20$), was not significantly reduced in the <120 mmHg systolic group (versus <140 mmHg); however, there was an impressive reduction in the pre-specified secondary endpoint of stroke (hazards ratio 0.59; 95 % confidence interval 0.39–0.89, $p=0.010$) in the low BP group. There was no demonstrable benefit of the low BP target on either progression of diabetic retinopathy in ACCORD. On the other hand, in the Appropriate Blood Pressure Control in Diabetes (ABCD) trial (average follow-up 5.3 years) in diabetic persons with baseline BP <140/90 mmHg (average BP 136.4/84.4) randomized patients to intensive (DBP 10 mmHg lower than baseline DBP) versus moderate (80–89 mmHg) control [51]; clinical benefit was shown when treating before the BP threshold of 140/90 mmHg. BP averaged 128/75 mmHg versus 137/81 mmHg in the two groups. There were fewer strokes ($p=0.03$), less progression of diabetic retinopathy ($p=0.019$), less conversion of normoalbuminuria to microalbuminuria ($p=0.012$) as well as less conversion of microalbuminuria to overt albuminuria ($p=0.028$) in the intensive compared to moderate control group. Thus, a prospective human study in persons with diabetes all of whom had baseline BP <140/90 mmHg, the ADA-recommended BP threshold for initiating treatment, has shown multiple clinical benefits.

Therefore when making recommendations for BP targets in African Americans with diabetes mellitus, a stroke-prone population with a stroke-risk enhancing condition, as well as considering the greater prevalence of diabetic retinopathy (38.8 % versus 26.4 %) and vision-threatening diabetic retinopathy (9.3 % versus 3.2 %) [pressure-sensitive conditions] in African Americans compared to whites [52], the BP target <130/80 mmHg seems justified. Though there is conflicting data in regard to retinopathy between the ACCORD and ABCD studies, similar to the conflicting data on the benefits of angiotensin converting enzyme inhibitors in persons with diabetes between the HOPE (clinical benefit demonstrated) [53] and ALLHAT studies (no clinical benefit demonstrated) [54], the prudent recommendation is to prefer the strategy that has shown clinical benefit in the absence of undue harm. That is exactly the approach taken in the ISHIB consensus statement. To date, despite conflicting evidence on the benefit of ACE inhibitors in hypertensive persons with diabetes, no authorative group has rescinded their recommendation of ACE inhibitors as a preferred therapy in this population. This stands in direct contradistinction to their aversion for recommending low BP therapeutic targets (<130/80 mmHg).

15.7.2.2 Chronic Kidney Disease

In nondiabetic CKD there is a substantial body of long-term data from the African American Study of Kidney Disease (AASK) specific in nondiabetic nephropathy available [55, 56]. The AASK trial enrolled nondiabetic African American men and women aged 18–70 years with iothalamate-determined glomerular filtration rates

between 20 and 65 mL/min/1.73 m^2 into a 3×2 factorial trial; the three drug arms were amlodipine, metoprolol, and ramipril, and the two levels of BP control were a target mean arterial pressure ≤92 mmHg and 102–107 mmHg. Participants were followed a minimum of 3 years up to as long as 6.4 years during the trial phase. Blood pressure averaged 128/78 or 12/8 mmHg lower in the lower BP group. The main study outcome measures, rate of change in GFR slope, and the clinical composite of a reduction in GFR by ≥50 % (or ≥25 mL/min/1.73 m^2), ESRD, or death were not different by randomized BP stratum. The ramipril group experienced a 22 % (95 % confidence interval, 1–38 %, $p=0.04$) and 38 % (95 % confidence interval, 14–56 %, $p=0.004$) lower rate of the composite clinical endpoint relative to the metoprolol and amLodipine groups, respectively [56]. Notably, during the trial the lower BP group experienced significantly less progressive change in proteinuria ($p<0.001$) than the higher BP group though 4 years; also, amlodipine was associated with a greater rise in proteinuria than the other two drug groups ($p<0.001$). No difference in GFR slope was observed between the randomized drug groups. At the conclusion of the AASK trial, participants were invited to enter into a long-term cohort study phase where the BP target was <130/80 mmHg and the primary outcome was the clinical composite of doubling of serum creatinine level, development of ESRD, or death [55]. Follow-up ranged from 8.8 to 12 years. During the cohort phase, BP averaged 131/78 mmHg in the low BP group and 134/78 mmHg in the higher BP group. In both study phases combined, the risk for the primary clinical composite was insignificantly lower in the entire study cohort (hazard ratio 0.91, $p=0.27$); however, when study outcomes were stratified on the pre-specified level of baseline proteinuria (protein/creatinine ratio ≤0.22 versus >0.22), the hazard ratio was 0.73 ($p=0.01$). The two secondary endpoints, doubling of serum creatinine or ESRD development as well as ESRD or death, were both reduced to a greater extent in the lower BP group. The clinical benefit in the heaviest proteinuria group was evident during the trial phase ($p=0.04$) when the BP difference was greatest and was borderline significant during the cohort phase ($p=0.07$) when the BP difference was much smaller between the two groups.

The findings of the AASK study and their interpretation are informative. First, in nondiabetic CKD pharmacological blockade of the renin-angiotensin system (RAS) was proven superior to alternative therapeutic approaches in African Americans similar to findings in whites. On the other hand, the AASK randomized treatment groups did not mimic contemporary clinical practice where RAS blockade would be combined with calcium antagonists. Second, the benefit of more aggressive BP lowering was evident during the trial though only in the group with the heaviest proteinuria. Interestingly, during the course of the trial, the marker that subsequently predicted benefit from aggressive BP treatment, proteinuria, progressed significantly less in the low BP group compared to the higher BP group. Thus, as in whites, African Americans with nondiabetic CKD benefit from preferential pharmacological RAS blockade. There was clinical benefit of aggressive BP treatment (mean arterial pressure ≤92 mmHg corresponding to <130/80 mmHg) for preventing clinical CKD in African Americans with significant proteinuria. It is clearly a reasonable interpretation of the AASK data to continue to recommend a target BP

<130/80 mmHg for African Americans with nondiabetic nephropathy and significant proteinuria. A less certain, though arguably reasonable, recommendation is simply to treat all African Americans with nondiabetic nephropathy to <130/80 mmHg. Though trials are not available testing specific low BP targets in diabetic nephropathy, for reasons other than nephropathy in African Americans, the <130/80 mmHg target is recommended.

Similar to BP targets in diabetes, there have been calls for relaxing the BP target in CKD to <140/90 mmHg. However, there have been no such calls for abandoning the recommendation for the use of RAS blockers in nondiabetic CKD despite their lack of overall benefit in the ALLHAT trial in CKD irrespective of diabetes status [57]. Again, in the setting of conflicting data it seems prudent to side with the strategy that has demonstrated human protection in at least some studies in the absence of undue harm. Nevertheless, the fact that battle lines have been drawn over the level of BP control while there has been near total silence regarding the benefits of RAS blockade in both diabetes and CKD signifies the selective and uneven interpretation of human endpoint data in our field.

15.8 Summary

Hypertension in African Americans remains an important clinical and public health problem. The totality of the evidence highlights the devastating toll on this population from the high prevalence of hypertension, the inordinate severity of the hypertension, and the inadequate BP control relative to their white counterparts. The presence of risk-enhancing comorbidities such as prediabetes, diabetes, and chronic kidney disease stealthily increases the absolute level of CVD risk at any given BP level in African Americans. Multifaceted lifestyle modifications—dietary sodium reduction, augmented potassium intake, aerobic exercise, weight loss, and moderation of alcohol intake—are all prudent measures both for the prevention as well as adjunctive treatment of established hypertension. More aggressive strategies for dealing with BP elevations, including initiating antihypertensive treatment at levels below conventional (140/90 mmHg) thresholds, are eminently defendable. Selective evidence-based medicine zealotry appears to be a powerful driving force behind the misguided and likely harmful efforts to relax BP targets in the high-risk conditions of diabetes and CKD. Such recommendations will disproportionately and deleteriously impact African Americans because of the excessive prevalence of these conditions in African Americans and also because these conditions are accompanied by an enhanced risk for pressure-sensitive complications such as progressive, vision-threatening retinopathy and stroke. The data from the AASK study very strongly justify the BP target of <130/80 mmHg amongst African Americans with nondiabetic CKD and urine protein/creatinine ratios >0.22.

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Chapter 16
New Guideline Recommendations on Hypertension: Preventing CVD and Renal Disease with Applications to Blacks

Gabriel Thornton and Jackson T. Wright Jr.

A number of unique features distinguish hypertension in Blacks from other populations, and attempts to address these features have been incorporated into multiple national and international guidelines. Although there remains a significant lack of data, over the past decade several clinical outcome trials with sufficient sample size of Blacks have been completed. The results of these trials have informed these guideline recommendations and resulted in several common themes. However, differences in the interpretation of the trial results as well as differences in the methodology used to develop the guidelines have led to significant differences in recommendations. The objective of this chapter is to compare both the recommendations and the evidence base and rationale forming the basis for current recommendations for the treatment of hypertension in Black-hypertensive populations. Guidelines selected for review are those that specifically indicate recommendations in Black populations or that reviewed studies conducted in Black-hypertensive patients though not specifically making recommendations by race. In patients requiring the use of BP lowering medications for concomitant disorders (e.g., coronary heart disease, heart failure, proteinuric chronic kidney disease) in addition to treating hypertension, the focus of the chapter will be on recommendations for lowering elevated blood pressure assuming the addition of the agents specifically indicated for the treatment of non-blood pressure-related disorders.

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K.C. Ferdinand (ed.), *Hypertension in High Risk African Americans*, Clinical Hypertension and Vascular Diseases, DOI 10.1007/978-1-4939-2010-5_16

16.1 International Society on Hypertension in Blacks [1]

This is the only guideline specifically prepared to address the evaluation and treatment recommendations for hypertension in Black populations. It was developed as a *consensus* document by acknowledged experts and investigators in this area. These expert members reviewed the available treatment and prevention guidelines, publications of hypertension clinical trials undertaken solely in Blacks or with sizeable number of Blacks, reporting either pre-specified or post hoc analyses. The methodology for rating the quality of data and strength of evidence for the recommendations was not described. Where data were not available in Black patients, data from randomized trials in non-Blacks were considered.

The International Society on Hypertension in Blacks (ISHIB) guidelines recommended treatment based on two risk stratification profiles: (1) primary prevention defined by a BP ≥135/85 mmHg but without evidence of target organ damage, clinical CVD, or preclinical CVD and (2) secondary prevention included those with BP ≥130/80 mmHg, eGFR <60 mL/min/1.73 m^2, macroalbuminuria, LVH by electrocardiogram or echocardiogram, clinical CVD (i.e., heart failure, overt coronary heart disease/postmyocardial infarction, peripheral vascular disease, stroke or transient ischemic attack, or aortic aneurysm), or "preclinical CVD" defined by the presence of the metabolic syndrome, Framingham risk >20 %, diabetes, or impaired fasting glucose.

The ISHIB guideline recommended that Black patients meeting criteria for primary prevention should be treated to a BP goal of <135/85 mmHg and those with criteria for secondary prevention treated to a goal of <130/80 mmHg. Thus, the BP defining need for BP treatment (hypertension) would be reduced from 140/90 to 135/80 mmHg, and because of the risk profile in the population, the majority of Black patients would require antihypertensive treatment to a BP <130/80 mmHg. While no direct evidence was available to support these BP targets, the investigators extrapolated from observational studies [2, 3], clinical outcome trials [4, 5], and a surrogate outcome study [6]. They also extrapolated the elevated risk in Blacks associated with increased cardiovascular risk factors as the indication for the lower BP goal of <130/80 mmHg.

Thiazide-type diuretics and calcium channel blockers are both recommended for initial therapy. For BP greater than 15/10 above the recommended goal, initial therapy with two or more agents is recommended. Based largely on the results from the ACCOMPLISH trial [7], a CCB/RAS inhibitor regimen was recommended over a THZ/RAS inhibitor regimen for combination therapy unless treatment of volume overload or edema is indicated.

16.2 American Heart Association (AHA) and American Stroke Association (ASA) Statements on the Management of Hypertension

The AHA has issued several types of publications on the management of cardiovascular disease. Since 2007, two types of publications have been issued on the management of hypertension. These documents have been in the form of either a "scientific

statement" or "science advisory" representing consensus recommendations authored by experts selected by the AHA after review of the current literature. *Scientific statements* have the objective to "increase knowledge and awareness by healthcare professionals of effective, state of the art science related to the causes, prevention, detection, or management of cardiovascular disease or stroke." *Science advisories* are developed to "provide a rapid, clear and consistent AHA and ASA positioning on scientific issues. Advisories are statements on an evolving, prominent scientific issue of great interest to the public and health professionals." While both forms are consensus documents, they do undergo external peer review and are reviewed and approved by the AHA Scientific Advisory and Coordinating Committee, the highest scientific body of the AHA/ASA. In addition, another consensus document on the management of hypertension in the elderly was developed in collaboration with the American College of Cardiology and other professional organizations (see below). These documents need to be distinguished from AHA practice guidelines that must adhere to the policies and procedures outlined by the ACC/AHA Guidelines Task Force available at that time. These procedures are currently under revision as part of the new partnership between the AHA and ACC with the NHLBI to develop future guidelines [8, 9].

16.2.1 AHA Treatment of HTN in the Prevention and Management of Ischemic Heart Disease: A Scientific Statement from the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention [10]

In 2007 the American Heart Association (AHA), in conjunction with the American College of Cardiology Foundation (ACCF), developed a scientific statement on the treatment of hypertension in the prevention and management of ischemic heart disease. This scientific statement is proposed recommendations on systolic and diastolic blood pressure targets, identify the most effective pharmacologic therapy for primary and secondary prevention of ischemic heart disease, and evaluated whether the beneficial effects of these treatments are due to more than just the blood pressure lowering itself. In addition, the writing group provided recommendations for antihypertensive drug treatment in patients with stable coronary artery disease (CAD) as well as those with acute coronary syndromes, including non-ST-elevation myocardial infarction (NSTEMI), unstable angina, and ST-elevation myocardial infarction (STEMI).

The Task Force on Practice Guidelines at the time was responsible for establishing the overall policy and identifying nominees for writing committee members. Members of the Task Force writing committee were senior cardiologists or other experts in the field of cardiovascular research who generally had served on previous

Table 16.1 AHA/ACCF scientific statement classification of recommendations and evidence grading [11]

Classification of recommendations
Class I: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective
Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment
Class IIa: Weight of evidence/opinion is in favor or usefulness/efficacy
Class IIb: Usefulness/efficacy is less well established by evidence
Class III: Conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful
Level of evidence
Level of Evidence A: Data derived from multiple randomized clinical trials or meta-analysis
Level of Evidence B: Data derived from a single randomized trial or nonrandomized studies
Level of Evidence C: Only consensus opinion of experts, case studies, or standard of care

guideline writing committees. A research analyst was appointed to do a preliminary review of relevant literature search results, and the writing committee had the final determination of which articles would be used to prepare the scientific statement. The recommendation and level of evidence was rated according to the most recent Task Force on Practice Guidelines (Table 16.1).

For primary prevention, BP lowering to <140/90 mmHg was recommended in all, and <130/80 mmHg in individuals with diabetes mellitus, chronic renal disease, CHD, and clinical CVD and in patients with a Framingham risk score of ≥10 % (class IIa recommendation, level B evidence). They further recommended that BP should be lowered slowly in those with elevated DBP, and in those with CHD and evidence of myocardial ischemia, lowering DBP <60 mmHg should be done with caution (level C evidence). Initial drug treatment should use an ACE inhibitor (or ARB), calcium channel blocker (CCB), or thiazide diuretic, supplemented by a second drug if control is inadequate. Despite reference to the ALLHAT, the panel recommended no difference in initial drug selection by race.

In patients with hypertension, CHD, and chronic stable angina, beta-blockers were considered drugs of choice due to their ability to alleviate ischemic symptoms via negative inotropic and chronotropic effects. Beta blocker use in patients with angina, prior MI, and HF is given a class I, level A evidence recommendation, whereas their use in secondary prevention in low-risk patients is given class IIa recommendation. Nondihydropyridine CCBs were recommended as substitutes for beta-blockers in this setting. ACE inhibitor or ARB use in patients with CHD with concomitant diabetes mellitus and/or LV systolic dysfunction was viewed a class I ACC/AHA recommendation.

In hypertensive patients with heart failure diuretics, ACE inhibitors or ARBs, beta-blockers, and aldosterone antagonists were recommended as first-line, but beta-

blockers were recommended as second-line in the absence of heart failure or CHD (class IIa, level B evidence). The use of hydralazine and isosorbide dinitrate was recommended to be added to the regimen of a diuretic, ACE inhibitor or ARB, and beta-blocker in Black patients with heart failure (class 1, level B of evidence) [11].

16.2.2 ACCF/AHA 2011 Expert Consensus Document on Hypertension in the Elderly [12]

This document was drafted in 2011 by the American College of Cardiology and the American Heart Association in collaboration with the American Academy of Neurology, American College of Physicians, American Geriatrics Society, American Society of Hypertension, American Society of Nephrology, American Society of Preventive Cardiology, Association of Black Cardiologists, and the European Society of Hypertension for the treatment of hypertension in patients age ≥65 years. The methodology for this set of recommendations was based on consensus of a panel of acknowledged experts in a number of disciplines from the represented professional organizations after review of available literature. Evidence was selected from randomized controlled trials, reviews, and observational studies conducted in human subjects, some of which included sizeable numbers of African-American participants. After a literature search result using multiple keyword search terms was distributed to the panel, the evidence was reviewed, the document prepared, and consensus of the panel and approval of represented organizations obtained. The specific methodology for rating the quality of data and strength of evidence for the recommendations was not described.

Except for octogenarians, the recommended blood pressure goals in the elderly were just as aggressive as those recommended for younger adults. It advised the initiation of blood pressure medications starting with the lowest dose and gradual increases to achieve a systolic blood pressure <140 mmHg, if tolerated. A goal BP of <130/80 mmHg was recommended for those with heart failure, chronic kidney disease, and coronary artery disease. Thiazide diuretics were recommended as the initial drug of choice without compelling indications to use an alternative class of drugs. For blood pressure >20/10 mmHg above goal, a 2-drug regimen was advised. ACE inhibitors or ARBs were recommended as drugs of choice in patients with chronic kidney disease with evidence of proteinuria (>300 mg/day). Alpha blockers were to be avoided due to excess cardiovascular events compared to thiazide diuretics evidenced in ALLHAT and increased risk of orthostatic hypotension in the elderly.

In those >80 years old, the panel believed the data on the harms and benefits of aggressive blood pressure management were less robust. Therefore, they recommended initiating drug treatment with single-drug therapy to achieve an SBP between 140 and 145 mmHg if tolerated and to avoid SBP <130 or DBP <65 mmHg to reduce the risk of organ hypoperfusion. They noted the data from HYVET and post hoc subgroup analyses from other randomized controlled trials

showing that patients over 80 years of age have reduced cardiovascular risk and mortality from blood pressure medications, but without a consistent reduction in cognitive decline that is associated with hypertension. They noted that ACCOMPLISH [7, 13] and INVEST [14, 15] showed no difference in effects of antihypertensives in patients older than 80 compared to younger patients, but ACCORD BP found no additional benefit and noted increased drug-related adverse events in older patients [16].

In Blacks with uncomplicated hypertension, thiazide diuretics were recommended based on the results from ALLHAT. Calcium channel blockers were also recommended for their ability to lower blood pressure, CHD, and stroke events. The SHEP trial [17] also showed increased benefit in older Blacks with chlorthalidone-based treatment versus placebo. Medications targeting the renin-angiotensin system (including beta-blockers) appear to be less effective, unless combined with a diuretic or CCB. However, the AASK trial showed renoprotective benefits of ACE inhibitors compared to amlodipine and metoprolol succinate in Black patients with CKD.

16.2.3 A Science Advisory from the American Heart Association, the American College of Cardiology, and the Centers for Disease Control and Prevention. An Effective Approach to High Blood Pressure Control [18]

In 2013, the American Heart Association, the American College of Cardiology, and the Center for Disease Control published a "science advisory" focusing on the need for a systems approach to high blood pressure management in adults using algorithms from best practice models such as Kaiser Permanente and the Veterans Administration Medical Centers that have shown a track record for success at hypertension control [18]. The writing group comprised representatives from several managed care organizations, the AHA, and the Centers for Disease Control. Expert peer review was conducted by the AHA Office of Science Operations as per all AHA Scientific Statements and guidelines. Recommendations were based on data from previous hypertension management guidelines produced by various organizations including the AHA, the ACC, the CDC, the European Society of Hypertension (ESH), and Kidney Disease: Improving Global Outcomes (KDIGO).

This document recommends that most individuals have a blood pressure goal of <140/90; however, lower targets are suggested for special populations which include African-Americans, the elderly, diabetics, those with chronic kidney disease, and patients with left ventricular dysfunction. The exact goal for blood pressure in these populations is not specified in the document.

Patients presenting with stage 1 hypertension (defined as systolic blood pressure 140–159 or diastolic blood pressure 90–99) should receive a trial of lifestyle modification, and a thiazide diuretic should be "considered." A follow-up blood pressure is recommended at 3 months of diagnosis, and those not at their blood pressure goal

should have a thiazide diuretic or other antihypertensive provided. If they are already on medications, then the doses should be titrated or additional medications added to their regimen until they have reached their target pressures. In those with stage 2 hypertension (defined as systolic blood pressure >160 or diastolic blood pressure >100), lifestyle modification as well as a 2-drug therapy with a thiazide diuretic and another medication is recommended, depending upon the patient's comorbidities. Blood pressure should be reassessed every 2–4 weeks until at goal. Recommendations for specific agents are similar to previously published guidelines. Beta-blockers and ACE inhibitors are recommended in those with coronary artery disease, and ACE inhibitors or ARBs, beta-blockers, aldosterone antagonists, and thiazide diuretics recommended in the presence of heart failure. Diabetics and those with kidney disease should receive ACE inhibitors or ARBs.

16.3 KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease [19]

In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO), an international nonprofit foundation associated with the National Kidney Foundation, published its updated evidence-based guidelines for the management of patients with non-dialysis-dependent chronic kidney disease (GFR category 1–4) [19, 20]. The writing group was composed of experts in internal medicine, nephrology, hypertension, epidemiology, and endocrinology. They were supported by guideline methodologists under contract at the Tufts Medical Center. The writing group reviewed randomized controlled trials (RCTs), systematic reviews, and meta-analyses involving patients with CKD as well as selected RCTs including populations at increased cardiovascular risk that did not specifically have a diagnosis of CKD. Summary tables and evidence profiles were constructed to assess the quality of the evidence led by the methodologists. Recommendations were formulated by the panel and graded according to the strength of the recommendation as well as the quality of the evidence on which they are based (see Table 16.2).

In CKD patients with proteinuria, the work group recommended the use of ACE inhibitors and angiotensin receptor blockers as first-line medications for hypertension, "regardless of race or ethnicity." However, in those with CKD without albuminuria or proteinuria, there is no specific recommendation regarding the use of ACE inhibitors or ARB medications. Furthermore, they noted that no randomized controlled trials were available to support a clear second- or third-line agent for hypertension requiring multidrug therapy. In addition, no compelling evidence is available supporting the use of any specific class of antihypertensive in the absence of significant proteinuria. Diuretics, particularly thiazide diuretics, compliment ACEIs/ARB when used in combination, and they are generally favored in the treatment of hypertensive patients with renal dysfunction. The combined use of renin-

Table 16.2 KDIGO nomenclature and description for rating guideline recommendations [20]

Grade[a]	Patients	Clinicians	Policy
Level 1 "We recommend"	Most people in your situation would want the recommended course of action and only a small proportion would not	Most patients should receive the recommended course of action	The recommendation can be evaluated as a candidate for developing a policy or a performance measure
Level 2 "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined

Grade	Quality of evidence	Meaning
A	High	We are confident that the true effect lies close to that of the estimate of the effect
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that is a substantial different
C	Low	The true effect may be substantially different from the estimate of the effect
D	Very low	The estimate of effect is very uncertain and often will be far from the truth

Within each recommendation, the strength of recommendation is indicated as *level 1*, *level 2*, or *not graded*, and the quality of the supporting evidence is shown as *A*, *B*, *C*, or *D*. Implications

angiotensin system (RAS) blockers failed to show a benefit on nephropathy progression in the ALTITUDE and ONTARGET trials [21, 22]. These combinations were also associated with more adverse effects without a significant cardiovascular outcome benefit. Neither of these trials had significant numbers of Black participants.

The writing group recommended that both diabetic and nondiabetic adults with CKD and urine albumin excretion <30 mg/24 h with hypertension be treated to a goal blood pressure less than or equal to 140/90 mmHg (Grade 1B). Goal BP ≤130/80 mmHg was recommended in those with higher levels of proteinuria (30–300 mg/24 h (Grade 2D) or >300 mg/24 h Grade 2C)), respectively. While the writing group suggested more aggressive blood pressure treatment in those with higher level of proteinuria, they also noted that the quality of evidence available for that

recommendation is inadequate and based primarily on expert opinion. In fact, use of ACE inhibitors or ARBs in nondiabetic patients received a grade of 2D, suggesting that there is no clear indication for a specific antihypertensive agent in these patients. These recommendations differ from many previous guidelines that advocated the use of RAS blocking medications, mainly ACE inhibitors and ARBs, in all CKD patients above GFR category 5 regardless of the level of proteinuria with a goal blood pressure of <130/80 mmHg. More evidence in the form of RCTs with significant power will be required to further investigate appropriate target blood pressures and the effects of specific antihypertensive agents.

16.4 NICE 2011 HTN Guidelines [23, 24]

The National Clinical Guideline Center of the NICE publishes these hypertension guidelines in the United Kingdom and they were developed for providers working in the British National Health Service. First published in 2004 with updates in 2006 and 2011, this was one of the first hypertension guidelines to utilize a true systematic evidence review with pre-specified criteria for collecting and reviewing the available evidence. Questions to be addressed were drafted and literature search conducted. The titles and abstracts from the literature search were reviewed using a pre-specified checklist and review criteria for initial screening. Potentially relevant studies were identified and the full papers reviewed by research staff against the pre-specified inclusion and exclusion criteria to identify studies that were useful for the development of the guideline document. Evidence tables were then used to draft the evidence (Table 16.3). The evidence tables were then used to draft evidence statements for the questions and finally the recommendations drafted from the evidence statements. An independent Guideline Review Panel oversees the updating of the document. Beginning in 2006, specific questions on drug therapy in black "Africans/Afro-Caribbean s" were addressed.

Unique to the NICE guidelines is the recommendation in the 2011 update for either ambulatory blood pressure monitoring (ABPM) or home blood pressure monitoring (HBPM) to establish the diagnosis of hypertension before initiating antihypertensive therapy and as an adjunct to clinic BP measurements to monitor response to treatment. NICE recommends antihypertensive drug treatment for all hypertensive patients less than 80 years with stage 1 hypertension and one of the following: target organ damage, established CVD, renal disease, diabetes, or a 10-year cardiovascular risk equivalent to or greater than 20 % and everyone with stage 2 hypertension. Recommended goal clinic blood pressure is <140/90 mmHg (<135/85 mmHg using ABPM or HBPM measurements) for those under the age of 80 and <150/90 (145/85 using ambulatory or home blood pressure measurements) for people aged 80 years and older.

An ACE inhibitor or ARB is recommended for hypertensive patients less than 55 years with stage 1 hypertension. Based on the results from the ALLHAT, a calcium channel blocker (CCB) is recommended for those over age 55 or of African descent

Table 16.3 National Institute for Health and Care Excellence (NICE) Hypertension Guidelines [23]

Other risk factors, asymptomatic organ damage or disease	Blood pressure (mmHg)			
	High normal	Grade 1 HT	Grade 2 HT	Grade 3 HT
	SBP 130–139 or DBP 85–89	SBP 140-159 or DBP 90–99	SBP 160-179 or DBP 100–109	SBP ≥180 or DBP ≥110
No other RF	• No BP intervention	• Lifestyle changes for several months	• Lifestyle changes for several weeks	• Lifestyle changes
		• Then add BP drugs targeting <140/90	• Then add BP drugs targeting <140/90	• Immediate BP drugs targeting <140/90
1–2 RF	• Lifestyle changes	• Lifestyle changes for several weeks	• Lifestyle changes for several weeks	• Lifestyle changes
	• No BP intervention	• Then add BP drugs targeting <140/90	• Then add BP drugs targeting <140/90	• Immediate BP drugs targeting <140/90
≥3 RF	• Lifestyle changes	• Lifestyle changes for several weeks	• Lifestyle changes	• Lifestyle changes
	• No BP intervention	• Then add BP drugs targeting <140/90	• BP drugs targeting <140/90	• Immediate BP drugs targeting <140/90
OD, CKD stage 3 or diabetes	• Lifestyle changes	• Lifestyle changes	• Lifestyle changes	• Lifestyle changes
	• No BP intervention	• BP drugs targeting <140/90	• BP drugs targeting <140/90	• Immediate BP drugs targeting <140/90
Symptomatic CVD, CKD stage ≥4 or diabetes with OD/RFs	• Lifestyle changes	• Lifestyle changes	• Lifestyle changes	• Lifestyle changes
	• No BP intervention	• BP drugs targeting <140/90	• BP drugs targeting <140/90	• Immediate BP drugs targeting <140/90

BP blood pressure, *CKD* chronic kidney disease, *CV* cardiovascular, *CVD* cardiovascular disease, *DBP* diastolic blood pressure, *HT* hypertension, *OD* organ damage, *RF* risk factors, *SBP* systolic blood pressure

(Moderate quality evidence). Thiazide diuretics were not recommended for initial therapy by the NICE guidelines because of the data from the NICE meta-analyses suggesting an association with an increased risk of diabetes. If CCB cannot be tolerated due to side effects or intolerance, then a thiazide-like diuretic is recommended. The document recommends chlorthalidone or indapamide as first-line agents over hydrochlorothiazide (HCTZ). However, those already well controlled on HCTZ or another thiazide agent could continue that treatment. If therapy is started with a beta-blocker and a second agent is needed, a CCB was again recommended over a thiazide diuretic. Based on the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) Trial [7], a CCB in combination with either an ACE inhibitor or ARB was recommended as the preferred drug combination if target BP was not met with a single agent. This recommendation was given a quality rating of "Moderate." In Black patients, an ARB was recommended over an ACE inhibitor. This recommendation is based on subgroup analyses from ALLHAT which showed an increased incidence of angioedema in Blacks [25]. If a three-drug regimen is required, the combination of an ACE inhibitor or ARB, CCB, and a thiazide-like diuretic should be used as per 2006 recommendations. The management of hypertension in patients with diabetes mellitus and chronic kidney disease was discussed in separate NICE guideline documents.

16.5 2013 European Society of Hypertension/European Society of Cardiology Guidelines for the Management of Arterial Hypertension [26]

These guidelines are published approximately every 6 years using consensus methodology by experts selected by these societies based upon their expertise and freedom from conflicts of interests. Each panel member is assigned a specific writing task to be reviewed by three other panel members and the two guideline chairs, each appointed by the two societies. Quality of evidence and strength of the recommendation is graded as shown in Table 16.4. The guideline is then reviewed by 42 outside reviewers, half from each society.

Similar to other recent guidelines, a clinic BP of 140/90 is both the threshold for the initiation of antihypertensive drug treatment and the goal for BP control in patients <80 years old. Other than the recommendation for the use of thiazide-type diuretics and CCBs as initial therapy, no other specific recommendations in Black hypertensive patients were indicated.

Table 16.4 2014 US Guideline Recommendations [28]

Recommendation 1
In the general population 60 years of age or older, initiate pharmacologic treatment to lower BP at systolic blood pressure (SBP) ≥150 mmHg or diastolic blood pressure (DBP) ≥90 mmHg and treat to a goal SBP <150 mmHg and goal DBP <90 mmHg (*strong recommendation—Grade A*)
Corollary recommendation: In the general population 60 years of age or older, if pharmacological treatment for high BP results in lower achieved SBPs (e.g., <140 mmHg) and treatment is well tolerated and without adverse effects on health or quality of life, treatment does not need to be adjusted (*expert opinion—Grade E*)
Recommendation 2
In the general population less than 60 years of age, initiate pharmacologic treatment to lower BP at DBP ≥90 mmHg and treat to a goal DBP <90 mmHg (*for ages 30–59 years*, *strong recommendation—Grade A*; *for ages 18–29 years*, *expert opinion—Grade E*)
Recommendation 3
In the general population less than 60 years of age, initiate pharmacologic treatment to lower BP at SBP ≥140 mmHg and treat to a goal SBP <140 mmHg (*expert opinion—Grade E*)
Recommendation 4
In the population 18 years of age or older with chronic kidney disease, initiate pharmacologic treatment to lower BP at SBP ≥140 mmHg or DBP ≥90 mmHg and treat to goal SBP <140 mmHg and goal DBP <90 mmHg (*expert opinion—Grade E*)
Recommendation 5
In the population age 18 years and older, with diabetes, initiate pharmacologic treatment to lower BP at SBP ≥140 mmHg or DBP ≥90 mmHg and treat to a goal SBP <140 mmHg and goal DBP <90 mmHg (*expert opinion—Grade E*)
Recommendation 6
In the general non-Black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB) (*moderate recommendation—Grade B*)
Recommendation 7
In the general Black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or CCB (*for general Black population*: *moderate recommendation—Grade B*; *for Blacks with diabetes*: *weak recommendation—Grade C*)
Recommendation 8
In the population age 18 years or older with chronic kidney disease (CKD) and hypertension, initial (or add-on) antihypertensive treatment should include an ACEI or ARB to improve kidney outcomes. This applies to all CKD patients with hypertension regardless of race or diabetes status (*moderate recommendation—Grade B*)
Recommendation 9
The main objective of hypertension treatment is to attain and maintain goal BP. If goal BP is not reached within a month of treatment, increase the dose of the initial drug or add a second drug from one of the classes in Recommendation 6 (thiazide-type diuretic, CCB, ACEI, or ARB). Continue to assess BP and adjust the treatment regimen until goal BP is reached. If goal BP cannot be reached with two drugs, add and titrate a third drug from the list provided. Do not use an ACEI and an ARB together in the same patient. If goal BP cannot be reached using only the drugs in Recommendation 6 because of a contraindication or the need to use more than three drugs to reach goal BP, antihypertensive drugs from other classes can be used. Referral to a hypertension specialist may be indicated for patients in whom goal BP cannot be attained using the above strategy or for the management of complicated patients where additional clinical consultation is needed (*expert opinion—Grade E*)

16.6 Clinical Practice Guidelines for the Management of Hypertension in the Community: Statement by the American Society of Hypertension and the International Society of Hypertension [27]

This guideline was drafted by experts from the represented societies based upon their review of the current literature purely as consensus document. Though the authors are acknowledged experts in their respective areas, no details on the methodology for developing the guidelines were provided. While "Suggested Reading" is provided, no specific evidence or even references are provided for most recommendations. Recommended BP threshold for initiating antihypertensive medications and the target BP is above and below 140/90 mmHg, respectively, for ages up to 80 years old. The epidemiology and recommendations for the treatment of hypertension in Black populations is specifically addressed by this guideline. CCBs and thiazide-type diuretics are recommended as initial therapy in Black patients with and without diabetes in the absence of CKD. ACEIs and ARBs are recommended with CKD.

16.7 2014 Evidence-Based Guideline for the Management of Blood Pressure in Adults [28]

The most recent US guideline was the result of a rigorous attempt to revamp guideline development procedures to produce an unbiased methodical evidence-based guideline and the infrastructure for periodic updating and expansion. The authors were originally selected by the NHLBI, and the guideline was to be one of five integrated guidelines (others dealing with cardiovascular risk assessment, cholesterol lowering, obesity management, and lifestyle management). These guidelines were to be based on a systematic review of the literature to address the needs of primary care providers in caring for patients by providing a coordinated set of recommendations with the strongest evidence for reducing adverse cardiovascular outcomes. Ease of implementation was also considered a priority. Training in developing guidelines that facilitate ready implementation in the primary care setting was provided to all five guideline panels early in the development process, and an implementation working subgroup of the panels was initially established but not maintained.

The methodology for developing the hypertension guideline was designed to be consistent with the recommendations by the Institute of Medicine using a modified Delphi technique for developing consensus among experts [29, 30]. After selection, the panel elected to review the evidence and focus recommendations on three questions:

1. In adults with hypertension, does initiating antihypertensive pharmacologic therapy at specific BP thresholds improve health outcomes?
2. In adults with hypertension, does treatment with antihypertensive pharmacologic therapy to a specified BP goal lead to improvements in health outcomes?
3. In adults with hypertension, do various antihypertensive drugs or drug classes differ in comparative benefits and harms on specific health outcomes?

The intent was to initially focus on the above three questions deemed to be of highest priority to providers and later expand to other questions. Health outcomes of interest included:

- Overall CVD or CKD-related mortality
- Myocardial infarction, stroke, and hospitalized heart failure
- Revascularization (coronary and other revascularization)
- ESRD, doubling of creatinine level, or halving of glomerular filtration rate
- Surrogate outcomes were not considered.

Racial and ethnic subgroups were pre-specified as being of interest as well as subgroups with diabetes, coronary artery disease, peripheral vascular disease, heart failure, previous stroke, CKD, gender, smokers, and older age. The panel limited its evidence review to randomized controlled trials containing a sample size of >100 and a duration of at least a year. Other types of studies were not considered nor were meta-analyses or systematic reviews though the studies included in those analyses were included if they met review criteria. Studies published between January 1, 1966, and August 2013 were considered. Studies published between January 1, 1966 and December 31, 2009 were initially reviewed by an external methodology team who rated the studies for quality and summarized the data into evidence tables for review by the panel. Only those studies rated "fair" or "good" by the external methodologists were reviewed by the full panel to develop the evidence statements and subsequent recommendations. In August 2013, another literature search for studies published between December 2009 and August 2013 was conducted using the same MeSH terms as the original search. Evidence quality and strength of recommendations were rated by the panel using the criteria in Table 16.5.

Table 16.4 summarizes the recommendations of the 2014 guidelines, and Table 16.6 compares the recommendations with other guideline recommendations. Important features of the guideline include the recommendation of a goal BP of <140/90 mmHg in the general adult population <age 60 as well as those with diabetes and those with CKD up to age 70 (expert opinion-Grade E). In patients >age 70 with CKD, no recommendation was made on a specific BP target.

In the general adult population ≥age 60, a BP of <150/90 is recommended (strong recommendation-Grade A). There was no full agreement by the panel regarding evidence supporting the recommendation for a <150 SBP target in patients >age 60 years without diabetes or CKD. This recommendation caused a great deal of discussion and ended with the acknowledgement that there was a significant minority of panel members that recommended against raising the target from <140 mmHg, especially in Blacks, those with multiple risk factors, and those with clinical CVD (e.g., stroke).

The principal concerns were:

1. The recommendation to raise the SBP target to <150 mmHg in the >60 age group would over time reduce the intensity of antihypertensive treatment in a very large population at high cardiovascular (CVD) risk. In 2011–2012, more than half of

Table 16.5 Grading of evidence and recommendation strength for 2014 US Guideline

Type of evidence	Strength of evidence grade
• Well-designed, well-executed randomized controlled trials (RCTs) that adequately represent populations to which the results are applied and directly assess effects on health outcomes	High
• Meta-analyses of such studies	
• RCTs with minor limitations affecting confidence in, or applicability of, the results, including minor flaws in design or execution;	Moderate
• Well-designed, well-executed nonrandomized controlled studies and well-designed, well-executed observational studies	
• Meta-analyses of such studies	
• RCTs with major limitations	Low
• Nonrandomized intervention studies and observational studies with major limitations affecting confidence in, or applicability of, the results	
• Uncontrolled clinical observations without an appropriate comparison group (e.g., case series, case reports)	
• Physiological studies in humans	
• Meta-analyses of such studies	
Grading for Recommendation Strength	
Grade	Definition
A	Strong
B	Moderate
C	Weak
D	Recommendation against
E	Expert opinion

the 72 million hypertensives in the United States were ≥age 60 [31, 32]. Although the prevalence (65–67 %) of hypertension in this age group has not changed between 1999 and 2010, the percentage with adequate BP control has dramatically increased from 27.4 % (1999–2000) to 50.5 % (2011–2012) (in addition to 82.2 % now taking antihypertensive medications) [31, 33]. Furthermore, NHANES data from 2001 to 2008 show that among treated and untreated hypertensive adults 60 years and older, median SBP levels were 136 mmHg and 152 mmHg, respectively [34]. Moreover, SBPs have been decreasing in this age group over the past five decades [35]. Thus, a new target of <150 mmHg would likely lead to higher BP level in the treated hypertensive population and suggest that nearly half of the untreated hypertensive patients in this age range should not be treated with antihypertensive medications since the average SBP in this group is only slightly above 150 mmHg.

2. The higher goal would even apply to some of the highest cardiovascular risk groups such as African Americans, hypertensive patients with multiple CVD risk factors other than DM or CKD, and patients with clinical CVD. Compared

Table 16.6 Comparison of guideline recommendations for management of hypertension in Blacks

Guideline	Evidence review methodology	BP target in general adult population	BP target in high CVD risk groups	BP target in CKD and DM	Initial drug preference in general adult Black population
JNC-7	Consensus	<140/90 mmHg	<140/90 mmHg	<130/80 mmHg	THZ
AHA/ACC HTN in stable CHD (2007)	Consensus	<140/90 mmHg	<140/90 mmHg (DBP >60 mmHg)		ACEI/ARB/CCB/THZ (no preference for 1^0 prevention)
ISHIB (2010)	Consensus	<135/85 mmHg	<130/80 mmHg	<130/80 mmHg	Diuretic or CCB RAS/CCB over RAS/THZ unless edema or ⇑ volume
NICE (2011)	Systematic review	Age <80:<140/90	Age <80:<140/90	<140/90	THZ or CCB
		Age ≥80: <150/90	Age ≥80:<150/90		
AHA/ACC HTN in elderly (2011)	Consensus	Age <80: ≤140/90 mmHg	(CHD only <130/80 mmHg)	<130/80 mmHg	THZ or CCB
		Age ≥80: SBP 140–145/90			
NKF-KDOQI (2012)		<140/90		140/90	
ESH/ESC (2013)		Age <80:<140/90	Age <80:<140/90	<140/90	THZ or CCB
		Age ≥80: <150/90	Age ≥80: 150/90		
2014 US guideline	Systematic review	Age <60:<140/90	Age <60:<140/90	<140/90	THZ or CCB
		Age ≥60:<150/90	Age ≥60:<150/90		

Table 16.7 US CVD death rates for individuals less than and older than 65 years

Condition (cause of death by underlying cause)	Age <65 or ≥65 years	1989–1998 yearly average death rate per 100,000	1999–2010 yearly average death rate per 100,000	1989–1998 average annual % change in age-adjusted death rates (AAPC (%))	1999–2010 average annual % change in age-adjusted death rates (AAPC (%))
Coronary heart disease	<65	36	30	−3.6	−3.4
Coronary heart disease	≥65	1,312	1,038	−2.7	−5.6
Stroke	<65	9	7	−1.3	−2.3
Stroke	≥65	436	356	−0.9	−5.3

Age-adjusted to the 2000 US standard population—analysis from CDC Wonder by Dr. Michael Mussolino, NHLBI, Epidemiology Branch

to those <age 65, those over age 65 have a 35-fold increase in CHD mortality and 40-fold higher risk of stroke (Table 16.7).

3. The evidence to raise the SBP target from 140 to 150 mmHg in this subgroup was insufficient. While the objective was to produce evidence-based recommendations, the higher goal in those >age 60 was made despite the lack of convincing evidence that the risk/benefit of treatment differed by this age grouping at these SBP goals. The panel reports finding A-level evidence that reducing SBP to <150 mmHg was beneficial in those >age 60 (actual achieved SBPs were close to 140 mmHg, 143 mmHg, and 144 mmHg, respectively) [36, 37]. It reports finding no qualifying evidence showing to support any SBP target in those <60.
4. It also lacked consistency with the lack of qualifying evidence supporting the panel's other recommendations for a SBP target of <140 mmHg in groups such as in those age <60 years and in those ≥60 years with DM or CKD with similar level of evidence.
5. The higher goal in individuals over age 60 (especially Blacks) has the potential to reverse the decades long decline in CVD, especially stroke mortality. CVD, especially stroke, mortality has been decreasing in the United States, which is largely attributed to the decrease in blood pressure [35].

Thus, because of the overall evidence and the decline in CVD mortality, the minority panel concluded that the evidence for raising a BP target in high risk populations should be at least as strong as the evidence required to lower the recommended BP target, but the current evidence was insufficient. Likewise, other recent guideline groups reviewing the similar evidence have recommended 140 mmHg goal, particularly in those ≤80 years [23, 26, 38].

Recommendations for drug selection included either a thiazide diuretic (THZ), calcium channel blocker (CCB), angiotensin converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB) as an initial agent of choice in the general adult non-Black population including those with diabetes (moderate recommendation-Grade B). A THZ or CCB was recommended over an ACEI or ARB in the general

adult Black population (moderate recommendation-Grade B). In Black patients with diabetes, the same agents were preferred; however, the strength of evidence was graded less by the panel (weak recommendation-Grade C). While the evidence from ALLHAT clearly supported the diuretic over the RAS, the lower evidence rating was due to the weaker evidence for the CCB versus ACEI comparison. The CCB for preference over an ACEI consisted of the presence of 46 % of Blacks with diabetes in ALLHAT and the post hoc analysis by race of patients with the metabolic syndrome (of whom almost 70 % of Blacks had diabetes).

16.8 Summary

There is consistency in the guidelines that thiazide diuretics or CCBs should be the initial drugs of choice in Black hypertensives or included in regimens containing inhibitors of the renin-angiotensin system or beta-blockers. This is the recommendation of consensus or systematic review-based guidelines from around the world. Either ACE inhibitors or ARBs should obviously be included in regimens for patients with CKD or heart failure, as well as beta-blockers in patients with CHD regardless of race or ethnicity. All guidelines recommend additional agents added until patients achieve their BP goal. In Black hypertensives, despite the recommendations of the 2014 US guideline, it is inconceivable that a BP target higher than 140/90 mmHg should be considered, especially in the group >age 60 at highest risk.

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K.C. Ferdinand (ed.), *Hypertension in High Risk African Americans*, Clinical Hypertension and Vascular Diseases, DOI 10.1007/978-1-4939-2010-5