Hypertension is a major cause of disproportionate cardiovascular disease morbidity and mortality in African Americans. Increasingly, medical management is required to be based on the best peer-reviewed evidence versus individual preferences. The 2010 International Society of Hypertension in Blacks (ISHIB) Consensus Statement contained controversial recommendations: lower target blood pressure levels for primary and secondary prevention; chlorthalidone as preferred thiazide-like diuretic; combination therapy with blood pressure >15/10 mmHg above goal; and the preferential use of long-acting calcium channel blocker/renin-angiotensin system blocker regimen when needed. However, accompanying editorial and other critics have suggested the ISHIB document was less than evidence-based and flawed in several of its salient positions. Steadfast utilization of scientific data alone to form recommendations may decrease the potential to help clinicians and patients make appropriate decisions. The ISHIB report methodology was transparent in its broad-based approach, using relevant studies, with and without adequate black cohorts, and non-randomized epidemiologic data. There is a definite place for expert opinions in managing black patients with hypertension to curtail the unacceptable, disproportionately high levels of associated death and disability. Judgment will be required to synthesize optimal treatment of blacks with hypertension.

**Keywords**
Hypertension, blacks, African-Americans, International Society of Hypertension in Blacks (ISHIB), guidelines, consensus report

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In 2003, the International Society of Hypertension in Blacks (ISHIB) published its "Management of High Blood Pressure in African Americans: Consensus Statement of the Hypertension in African Americans Working Group of the International Society of Hypertension in Blacks," the first major consensus statement on this critical area of cardiovascular care. This report has been extensively endorsed as an important, authoritative source of recommendations for managing hypertension in black patients. More recently, the 2010 "Management of High Blood Pressure in African Americans: An Update of the ISHIB Consensus Statement" was issued and published in *Hypertension: Journal of the American Heart Association*. Some of the major recommendations in this recent ISHIB Consensus Statement include: comprehensive lifestyle modifications should be recommended if blood pressure (BP) is >115/75 mmHg; lower goals or target BP levels for both primary and secondary prevention, which should be viewed as ceilings, not floors; chlorthalidone is the preferred thiazide-like diuretic versus hydrochlorothiazide (HCTZ); significant emphasis is placed on hypertension treatment in special situations, such as limited financial resources and resistant hypertension; and combination therapy is necessary in most patients.
The 2010 International Society of Hypertension in Blacks Consensus Statement

Table 1: International Society of Hypertension in Blacks 2010 Consensus Statement Major Recommendations

| Situation                                                                 | International Society of Hypertension in Blacks Recommendation                  |
|--------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| Blood pressure ≥115/75 mmHg                                             | Comprehensive lifestyle modifications                                          |
| Primary prevention without manifest target-organ injury, preclinical CVD, or a history of CVD | Goal <130/85 mmHg                                                              |
| Secondary prevention, evidence of blood pressure-related target-organ damage, preclinical CVD, or previous history of CVD | Goal <130/80 mmHg                                                              |
| Blood pressure >15/10 mmHg above goal                                    | Combination therapy is necessary in most patients with blood pressure >15/10 mmHg above goal, preferentially with a long-acting calcium channel blocker (CCB)/renin–angiotensin system |
| Thiazide-like diuretic                                                   | Chlorthalidone                                                                  |

CVD = cardiovascular disease. Source: Flack, et al., 2010.6

with BP >15/10 mmHg above goal, perhaps preferentially with a long-acting calcium channel blocker (CCB)/renin–angiotensin system (RAS) blocker regimen (see Table 1).1

In black patients for primary prevention, who do not manifest target-organ injury, preclinical CVD, or a history of CVD, the 2010 ISHIB document modestly lowered the target BP from <140/90 to <135/85 mmHg. This report, for secondary prevention, contends that with evidence of target-organ damage, preclinical CVD, or a history of CVD, BP levels should be maintained consistently below the target level of 130/80 mmHg. Patients in this secondary prevention group were expanded beyond the Joint National Committee Seventh Report (JNC 7) inclusion of diabetes mellitus and renal disease to include: proteinuria (albuminuria: spot urine albumin:creatinine ratio >200 mg/g), depressed renal function (estimated glomerular filtration rate [eGFR] <60 ml/min/1.73 m²), electrocardiographic (or echocardiographic) evidence of left ventricular hypertrophy (LVH); metabolic syndrome; a Framingham risk score corresponding to >20 % 10-year coronary heart disease (CHD) risk; the presence of ‘pre-diabetes’ (glucose intolerance [two-hour post-load glucose ≥140 mg/dl] or impaired fasting glucose [100–125 mg/dl]); diabetes mellitus; and/or overt clinical CVD.5 However, an accompanying editorial by Wright et al., “New Recommendations for Treating Hypertension in Black Patients: Evidence and/or Consensus” and other critics have suggested that the issued 2010 ISHIB document was less than evidence-based and, to some extent, flawed in several of its salient positions.

Evidence-based Guidelines and Recommendations—The Superior Approach to Clinical Decision-Making?

While in past eras, clinicians have diagnosed and prescribed or administered treatments according to their own viewpoints, in more recent years, the development of various guidelines and working group recommendations require objective evaluation of the published medical literature and evidence-based medicine to inform clinical care. This application of current best evidence from healthcare research is now considered the expected way for clinicians to diagnose and treat conditions in their patients.

In the near future, perhaps, practicing medicine by only using clear evidence to guide clinical care may be the norm, and actually mandated by the medical profession, regulatory agencies, and even third-party payers. The Institute of Medicine (IOM) maintained in its 2009 Roundtable on Evidence-based Medicine that, by “2020, 90 percent of clinical decisions will be supported by accurate, timely, and up-to-date information and will reflect the best available evidence.” The institute declared that patients should expect, at a minimum, this level of performance, using existing resources and emerging tools to track and stimulate progress.7 Nevertheless, a careful reading of the more recent IOM 2011 report, “Clinical Practice Guidelines We Can Trust,” reveals a more nuanced approach to the mandate for evidence-based recommendations. This IOM document notes that clinicians often are faced with difficult decisions and considerable uncertainty and must not only rely on scientific literature, but also on their “knowledge, experience, and patient preferences, to inform their decisions.”8

Moreover, even the paradigms of evidence-based guidelines do not demand strict adherence to only peer-reviewed evidence to determine appropriate care. The National Heart, Lung, and Blood Institute (NHLBI) describes clinical guidelines as “systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances.”9 However, the NHLBI confirms that the final guideline pronouncements should be based on recommendations by expert parties, as well as evidence-based medicine per se.

Building on the modern evidence-based medicine approach to clinical therapies, the more recent American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines for various areas of cardiovascular therapies have attempted to more expertly refine and define the levels of evidence base for their present and emerging statements. The ACCF/AHA practice guidelines are described as having been developed through a rigorous methodological approach with the review and consideration of the available medical literature. They are intended to assist clinicians in clinical decision-making by describing a range of generally acceptable approaches to define practices that meet the needs of most patients in most circumstances by categorizing the recommendations into a classification system. Regarding levels of evidence, the ACCF/AHA list a three-staged approach (see Table 2). First is level A: recommendation based on evidence from multiple randomized trials or meta-analyses; then B: recommendation based on evidence from a single randomized trial or non-randomized studies; and lastly level C: recommendation based on expert opinion, case studies, or standards of care.10

The recommendations are also classified from Class I to III (see Table 3). First is Class I: conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective.
# Hypertension

## Table 2: Level of Evidence

| Level of Evidence | Recommendations |
|-------------------|----------------|
| A                 | Recommendation based on evidence from multiple randomized trials or meta-analyses |
| B                 | Recommendation based on evidence from a single randomized trial or non-randomized studies |
| C                 | Recommendation based on expert opinion, case studies, or standards of care |

Source: Greenland, et al., 2010.

## Table 3: Classes of Recommendations in Guidelines

| Class of Recommendation | Recommendation |
|-------------------------|----------------|
| Class I                 | Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective |
| Class II                | Conditions for which there is conflicting evidence and/or divergence of opinion about the usefulness/efficacy of a procedure |
| • IIA                   | Weight of evidence is in favor of usefulness/efficacy |
| • IIB                   | Usefulness/efficacy is less well established by evidence/opinion |
| Class III               | Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful |

Source: Greenland, et al., 2010.

Subsequently, there is class II: conditions for which there is conflicting evidence and/or divergence of opinion about the usefulness/efficacy of a procedure or treatment (class IIA: weight of evidence is in favor of usefulness/efficacy, and class IIB: usefulness/efficacy is less well established by evidence/opinion). The final category is class III: conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful. Class I, the highest level for a recommendation, takes into consideration very strong evidence and strong expert experience. A less rigorous level of recommendation, class II, is divided into two subgroups, IIA and IIB. Class IIA has some evidence supporting a therapy which is not that strong, while Class IIB has evidence that is less well established and anecdotal. The need to avoid certain ineffectual or harmful therapies fulfills the ancient admonition of *primum non nocere*. Hence, Class III describes therapy that is not useful and is, in fact, harmful.

While grading data sources appears to be the most recent and widely respected means of incorporating evidence into guidelines, the American Association of Clinical Endocrinologists (AACE) reproves the ACCF/AHA guideline grading system, stating that while it is a highly detailed methodology, it is non-intuitive and confusing. Moreover, despite the widely touted different levels of evidence as stated, one detailed review of data from all ACC/AHA practice guidelines issued from 1984 to September 2008 revealed that the highest levels of evidence are often not actually incorporated into final proposed guidelines for patient care. As ascertained from the peer-reviewed report, only 314/2,711 (11.6 %) of final therapeutic recommendations were classified as level of evidence A. Even more remarkably, as much as 1,246/2,711 (46.0 %) were classified as level of evidence C. Recommendations with level of evidence A are appropriately deemed Class I. However, only 245/1,305 (18.8 %) of Class I recommendations were deemed level A. In addition, contrary to the supposed scientific rigor with which these ACCF/AHA major reports were promulgated, most new recommendations were actually Class II.

### The 2010 International Society of Hypertension in Blacks Working Group’s Methodology—The Art and Science of Medicine

The 2010 ISHIB report used not only rigorous evidence from clinical trial data specifically regarding blacks, but also a broad range of additional sources: other hypertension guidelines and clinical trials involving hypertension treatment in individuals with important comorbidities, such as diabetes and chronic kidney disease (CKD), even if specific data for AAs were not reported. The unintended consequence of overly strict and unyielding utilization of scientific data alone to form recommendations may diminish the utility of guidelines and not actually maximize their potential to help clinicians and patients make appropriate decisions about healthcare. An appropriate understanding of present guidelines for clinical care is to consider their recommendations not as fixed protocols that must be blindly followed, but as approaches that recognize and support a responsible clinician’s judgment. Hence, individual treatment plans should be tailored to the specific needs and circumstances of the patient.

The ISHIB working group is transparent in this broad-based approach and does not mislead clinicians in describing its methodology, using relevant studies in hypertension and CVD treatment and prevention. Clinical trials, with at least one solely in blacks, and with and without appreciable AA subgroups, were considered, along with non-randomized data from epidemiological studies. Preferentially, the data from randomized hypertension trials reporting clinical endpoints were sought, especially those with high proportions of, or exclusively in, blacks. For example, in the Antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT), the Collaborative Research Group reported major outcomes in high-risk hypertensive patients randomized to regimens based on an angiotensin-converting enzyme inhibitor (ACEI) (lisinopril), a CCB (amlodipine), or a diuretic (chlorothalidone), with ample numbers of blacks. A total of 33,357 participants were studied, aged 55 years or older, with hypertension and at least one other CHD risk factor, from 623 North American centers. There was a substantial contribution to the results from the approximately 35 % black subpopulation. In the ALLHAT black cohort there was significantly less BP lowering with the lisinopril regimen, and also a 40 % increase in stroke versus whites, with a greater incidence of angioedema.

Ideally, a consensus report on treatment in blacks in the US would be based only on studies solely in AAs or with a large black representation in the trial. For instance, the African-American study of kidney disease and hypertension (AASK) trial first confirmed the effect of BP lowering and antihypertensive drug class on the progression of hypertensive kidney disease, with important data on the benefit of ramipril, an ACEI. A total of 1,094 AAs aged 18 to 70 years with hypertensive renal disease...
(glomerular filtration rate [GFR] 20–65 ml/min/1.73 m²) were enrolled in AASK from 21 clinical centers throughout the US. The ACEI-based therapy with ramipril appeared to be more effective than therapy with a β-blocker (metoprolol) or dihydropyridine CCB (amlodipine) in slowing GFR decline and risk reductions in the clinical composite outcomes.15 Nevertheless, the remarkable results from the AASK trial in only one self-identified black cohort are not widely replicated regarding other effects of antihypertensive medications in AAs. Therefore the ISHIB panel places a clear emphasis on interpretation of BP and clinical endpoint data and comprehensive assessment of the totality of the evidence. Blacks in the US have high rates of associated end-organ damage and support the definite emphasis on clinical trials involving hypertensive treatment in individuals with significant comorbidities, such as diabetes mellitus and CKD, even when black participation was suboptimal or absent.

**Criticisms of the International Society of Hypertension in Blacks 2010 Report**

Many criticisms have been made of the 2010 ISHIB Statement and an accompanying editorial posed several questions regarding the appropriateness of the conclusions. In this editorial, Wright et al. stated that lowering the target BP from <140/90 to <135/85 mmHg for primary prevention and also, even more problematically, including the expanded conditions beyond diabetes mellitus and renal disease to <130/80 mmHg for secondary prevention appears both arbitrary and unfounded. This editorial also disputes the recommendation for the initiation of multiple drugs in those with ≥15 mmHg above their target systolic BP and/or ≥10 mmHg above their target diastolic BP, and strongly questions the support of the RAS inhibitor/CCB combination as superior to other RAS/diuretic regimens.16 The Avoiding cardiovascular events through combination therapy in patients living with systolic hypertension (ACCOMPLISH) trial tested the hypothesis that treatment with an ACEI combined with amlodipine would result in better cardiovascular outcomes than treatment with the same ACEI combined with a thiazide diuretic. Combination treatment with benazepril plus amlodipine was superior to treatment with benazepril plus hydrochlorothiazide in reducing the risk of cardiovascular events and death among 11,560 high-risk patients, including a sizable representation of blacks (1,416 or approximately 12 %). Although black results were not reported separately, this study bolsters the use of CCB/RAS inhibitors as a first-step combination as compelling for the ISHIB authors.17 Other prominent hypertension scholars have a similarly cautious view of the new ISHIB report and the evidence basis for many of the recommendations.

Another notable source of consternation among critics was the lower BP goal for persons with diabetes in the final ISHIB recommendations. The ample skepticism about a lower BP goal for persons with diabetes is primarily based on the Action to control cardiovascular risk in diabetes trial (ACCORD). This landmark study funded by the NHLBI compared systolic BP goals of <140 mmHg versus <120 mmHg in diabetic hypertensive patients. Blacks represented 24 % of the overall 4,733 participants, with a mean 4.7 years follow-up. Critics of the ISHIB lower BP goal for persons with diabetes emphasize that there was no difference in the primary composite outcome consisting of non-fatal myocardial infarction, stroke, or CVD death. However, in these well-treated patients, the additional benefit on stroke has biologic plausibility, considering the greater impact on stroke reduction in hypertension outcome trials. In ACCORD, there were significant differences in the rates of total stroke (hazard ratio 0.59, 95 % confidence interval [CI] 0.39–0.89, p=0.01) and non-fatal stroke (hazard ratio 0.63, 95 % CI 0.41–0.96, p=0.03). Stroke, one of the components of the primary outcome and a pre-specified secondary outcome, should not be overlooked, especially in AAs, a group with a markedly higher prevalence of stroke-related morbidity and mortality. Moving to a higher BP goal for persons with diabetes and hypertension may lead to the unintended consequence of decreasing the number of patients subsequently controlled to the conventional goal of <140/90 mmHg.17 Overall, most clinicians agree on the importance of the National Institutes of Health-funded Systolic blood pressure intervention trial to provide a definitive test of this question in high-risk non-diabetic patients.

In addition, critics note a significant proportion of the major trials ISHIB cited did not report pre-planned subgroup analysis for blacks, or adequate AAs. For instance, the Wright et al. paper expressed disapproval of the ISHIB use of an Italian study, Cardio-Sis, of the benefits of appropriate BP control and CVD event decrease in hypertensive patients with LVH. In Cardio-Sis, a randomized open-label trial in 44 centers in Italy, 1,111 non-diabetic patients with systolic BP 150 mmHg or greater were randomly assigned to a target systolic BP of less than 140 mmHg (usual control; n=553) or less than 130 mmHg (tight control). The primary endpoint was the rate of electrocardiographic LVH two years after randomization, which occurred in 82 of 483 patients (17.0 %) in the usual-control group and in 55 of 484 patients (11.4 %) of the tight-control group (odds ratio 0.63, 95 % CI 0.43–0.91, p=0.013). The number of events was relatively small. However, the trial, although in a non-black cohort, at least partially supports more intensive BP reduction with LVH in the ISHIB statement.18 Although the study was carried out in an Italian cohort, LVH is much more common in AAs versus US whites, at all levels of BP, and is associated with an increased morbidity and even mortality. Circumstantial importance of this data for blacks was considered, highlighting a significant comorbid condition that disproportionately affects blacks and amplifies the risks of hypertensive-associated diseases. Therefore, contrary to those who reject this approach, it is not reasonable to formulate comprehensive hypertensive treatment guidelines for blacks only using data exclusively from randomized trials only or predominantly based on this population. In consideration of these obvious truths, the ISHIB group extrapolated results from randomized trials conducted in predominantly non-black populations when analogous data were not specifically available in blacks (see Table 4). Although the ISHIB group specifically addresses hypertension in blacks, regardless of self-identified race or ethnicity, each individual has unique physiologic underpinnings and environmental influences. Race, after all, is a social construct with no true scientific definition. It is used by historians, census takers, politicians, social scientists, and the general public without any specific genetic or biologic markers.14 When studies inform clinical decision-making in blacks, regardless of the population cited, it is useful to consider these data.

The wisdom and practicality of promulgating recommendations for treating hypertension in blacks, limitations notwithstanding, has been...
accepted by other recent international hypertention reports in non-US black populations. In 2011, the UK National Institute for Health and Clinical Excellence (NICE) issued a guideline which considered the best means of initial treatment of hypertension in blacks as CCBs. For the general patient, ACEIs or angiotensin receptor blockers (ARBs) are the suggested drugs for starting treatment (unless contraindicated or intolerable), but the thiazide-type diuretic is not the primary initial drug of choice for blacks. Rather, NICE suggests a CCB and a diuretic only if a CCB is contraindicated or intolerable. Chlorthalidone or indapamide are listed as the preferred diuretics over HCTZ; this mirrors the ISHIB report.21 The 2010 Canadian report suggestion is that an ACEI is not an appropriate first step in blacks. The Canadian hypertension guideline recommended the following: initial therapy to be monotherapy with a thiazide-type diuretic (grade A); β-blocker (BB) in patients <60 years old (grade B); ACEI in non-black patients (grade B); a long-acting CCB (grade B) or an ARB (grade B).22

Conclusions
There is a definite place for expert opinion in managing black patients with hypertension. Blacks in the US have high rates of associated end-organ damage, which supports the definite emphasis on clinical trials involving hypertensive treatment in individuals with significant comorbidities, such as diabetes mellitus and CKD, even when black participation was suboptimal or absent. Recognizing the need to curtail the disproportionately high levels of CVD death and disability related to hypertension, judgment will be required in the synthesis of recommendations for the treatment of blacks with hypertension. Hence, several trials with limited black representation were used to form recommendations in cohorts with disease states that disproportionately affect AAs and magnify the risks of pressure-related BP clinical sequelae, including results from several landmark comorbidities studies for CKD, stroke, and CVD.

While the 2010 ISHIB report is the target of reasoned criticism, there is ample evidence that other widely accepted evidence-based cardiovascular guidelines from highly respected major organizations have also used judgment in the creation of their treatment recommendations. Clinical medicine is both art and science. Moreover, individual clinicians and researchers will interpret a given trial differently and views of the totality of the trial evidence will vary. Overall, the ISHIB writing group advocates strategies for greater BP control and targets-organ protection for AAs with hypertension. Errors, if made, were in the effort to overcome inadequate BP control in AAs and the unacceptable, inordinate risk from pressure-related BP complications. In the final analysis, the 2010 ISHIB report is not a precise compilation of fixed rules that must be followed without reflection, but several stimulating concepts that hopefully enhance responsible clinical judgment on the management of black patients with hypertension.23

Table 4: Examples of Broad-based Evidence for Supporting 2010 Report

| Study Name | Examples of Broad-based Evidence |
|------------|----------------------------------|
| African-American study of kidney disease and hypertension (AASK) | Black-only cohort: confirmed the effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease, with important data on the benefit of ramipril |
| Antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT) | Substantial black subpopulation: major outcomes including strokes increased, and less blood pressure control in high-risk hypertensive patients randomized to an angiotensin-converting enzyme inhibitor (lisinopril), versus a calcium channel blocker (amlodipine), or a diuretic (chlorothalidone) |
| Cardio-Sis | No blacks, but an important comorbidity: usual versus tight control of systolic blood pressure in non-diabetic patients with hypertension and demonstrated benefit in reducing left ventricular hypertrophy |

Source: For AASK, Wright, et al., 2002;27 for ALLHAT, Furberg, et al., 2002;28 and for Cardio-Sis, Verdecchia, et al., 2009.29