What's New in Hypertension Treatment Guidelines

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Epidemiology

Hypertension is a prevalent chronic health condition leading to increased morbidity and mortality. The estimated cost of hypertension in 2007 was $43.5 billion dollars. Based on the National Health and Nutrition Survey (NHANES), the 2005-2008 prevalence of hypertension in the US is 33.5% in U.S. adults or an estimated 76 million persons. Hypertension prevalence is nearly equal is men and women. This represents an increase in the prevalence from 23.9% in 1988-1994. Similarly, awareness of hypertension increased over this period to greater than 80%. Blood pressure control to <140/<90 rose from 1988–1994 to 2007–2008 (27.3% to 50.1%, P=0.006), while the average blood pressure level in hypertensive patients fell from 143.0/80.4 to 135.2/74.1, P=0.02/<0.001. Better blood pressure control from 1988–94 and 2007–08 reflected improvements in awareness (69.1% to 80.7%, P=0.03), treatment (54.0% to 72.5%, P=0.004) and the proportion of treated patients controlled (50.6% to 69.1%, P=0.006). [1]

Comparisons of NHANES data by race/ethnicity demonstrate the continued disparity in the prevalence of hypertension with the highest prevalence among African Americans which is among the highest in the world at 44%. It is encouraging to note that awareness is highest among African Americans. Prevalence is lowest in Hispanic Americans. Treatment rates are increasing in all 3 ethnic represented in NHANES, however Hispanics lag significantly behind non-Hispanic Whites and African Americans, (p=0.006). The overall trend shows an improvement in the overall control rates in all ethnicities, yet the control rates remain poorest in African Americans in every age stratum. In

comparisons across age stratum, hypertension prevalence is highest in the age group >60 years old (58% among women and 53% among men). Awareness increased over the past 20 years among all age strata with no differences between the middle age group (age 40-59 years old) and older age group (age > 60 years old) at nearly 80 % while the younger group lags significantly behind at nearly 65% ($p<0.001$). The treatment rate is highest among the older group followed by the middle age and lowest in the youngest age group. Interestingly, although the control rate among those treated is best in the youngest age group, the overall control rate is best in the middle age and older groups at 50%, compared to 40% in the younger group. ($p<0.002$) [2] Presumably, these patterns are a reflection of the increased utilization of healthcare services by older persons which may increase awareness and treatment. However younger people are likely to have different phenotypes of hypertension which may be more responsive to therapy than older persons.

Diagnosis and Classification

The proper technique of measurement of blood pressure is essential to ensuring proper diagnosis and classification. The recent trend in increasing overweight has lead to changes in the devices needed to assess blood pressure for most patients. Whereas, previously a standard cuff (arm circumference 27-34 cm) was most often used, currently more often a large adult cuff (arm circumference 35-44 cm) is necessary. Even larger arms require thigh size cuffs for proper measurement (arm circumference 45-52 cm). Since it is important to occlude arterial flow, the bladder of the cuff must encompass approximately 46% of the circumference of the upper arm and 80% of the distance from the shoulder to the elbow (a length to width ratio of 2:1). If the cuff is too small the readings will likely overestimate the true measurement. See Table 1 [3,4] Blood pressure is often measured with an automated oscillometric device. These devices have been

studied extensively and have been shown to correlate more strongly with 24 hour ambulatory blood pressure than manual blood office blood pressure. [5] There are multiple devices available commercially. Many are tested and graded using protocols by the American Association of Medical Instruments (AAMI), British Hypertension Society (BHS) and the European Society of Hypertension (EHS). This information is available on the www.dableducational.org website.

Table 1.

Instructions for taking blood pressure

1. Have the patient relax for at least 5 minutes before taking the blood pressure.
Feet should be on the floor, with the back supported.
2. The patient's arm should be supported (ie, resting on a desk) for the measurement.
3. Blood pressure should be checked in both arms with the patient sitting.
Note which arm gives the higher reading. This arm (the higher arm) should then
be used for all other (standing, lying down) future readings.
4. Measure the blood pressure in the sitting, standing, and lying positions.
5. Use the correct cuff size and note if a larger or smaller than normal cuff size is used.
6. Record systolic (onset of first sound) and diastolic (disappearance of sound) pressures.
7. DO NOT round off results to zeros or fives: record exact results to nearest even number.

Table 2
Blood pressure cuff size criteria

Arm Circumference	Cuff Size
27–34 cm	Regular
35–44 cm	Large
45–52 cm	Thigh

What Is Hypertension?:
Classification of Hypertension
JNC 7 Definitions

Blood Pressure (mm Hg)		Category
Systolic	Diastolic	
<120	and <80	Normal
120-139	or 80-89	Prehypertension
140-159	or 90-99	Stage 1 hypertension
≥160	or ≥100	Stage 2 hypertension

Chobanian AV, et al. *Hypertension* 2003;42:1206-52

Ambulatory Blood Pressure

Ambulatory blood pressure monitoring is a helpful tool in the assessment of hypertension. Furthermore ambulatory blood pressure and home blood pressure is more strongly associated with target organ damage and CVD than office blood pressure. [6,7,8] The key clinical implications for its use are white coat hypertension, masked hypertension, autonomic dysfunction, orthostatic hypotension, symptomatic episodes, nocturnal dipping status and refractory hypertension.

Prehypertension

An estimated 29.8% of US adults have prehypertension as of 1999-2006. Prehypertension has been associated with increased risk of cardiovascular events in the Framingham study with age. The 6 year event rates for major CVD were 1.5% in prehypertensives who were <60 years old, 4.9% in those 60-79 years of age, and 19.8% in those ≥80 years of age. [9] In the Framingham study, the progression rate from prehypertension to hypertension rate varies by blood pressure level and age. In individuals aged 35-64 years old, with blood pressures of <120/80 mm Hg- 12 progression to hypertension in 4 years is estimated to be 5.3%; for those with blood pressures 120-129 mm Hg or 80- 84 mm Hg the rate is 17.6%; while those with blood pressures 130-139 mm Hg or 85-89 mm Hg the rate is 37.3%. In older individuals who are aged 65-94 years old, the 4 year incidence of hypertension were 16%, 25% and 49% respectively for these categories of blood pressure. [10] More recently, however the Trial of Preventing Hypertension (TROPHY) Study demonstrated that in the placebo arm of this trial of prehypertensives with baseline blood pressures of 130-139 and/or 85-89 the 4 year incidence of hypertension was 63%. [11] Prehypertensives tend to have additional risk factors early in the development of hypertension. [12,13,14]

Barriers to Blood Pressure Control

Good blood pressure control is dependent on multiple factors. These consist of factors in several domains: patient, physician, physiologic, and the healthcare delivery system. It is important to characterize each of these in the proper context in order to make adjustments to improve control. The first domain is the patient, who is the least common denominator in this complex system. The task of the patient is to be "adherent" with the therapy which is prescribed. Adherence is described in most literature as taking therapy at least 80% of the time. In studies of pharmacy databases, hypertension medication refills begin to decline after the first 6 months of therapy. [15] In a recent follow-up of 18,809 newly diagnosed hypertensives, the best predictors of high adherence was concurrence of other conditions such as diabetes, dyslipidemia, obesity, and combination therapy. Compared to low adherers, the high adherence group had a decreased risk of cardiovascular events (HR 0.62; 95%CI 0.41-0.96; p=0.32) [16] Patient adherence seems to be improved with minimizing the number of tablets per day. In a recent study of hypertensives, adherence to therapy increased by reducing the number of tablets per day from nearly 40% at 3 tablets per day to nearly 70% at 1 tablet daily. [17] Yet once daily therapy is also met with challenges in adherence and persistence to therapy. In a database of 4783 patients taking once daily antihypertensive therapy, persistence with therapy at one year was approximately 50% and 43% of the patients missed 3 consecutive days of medications per month. [15] A second component of patient behavior is education which is an important determinant of patient behavior. In a patient survey of their comprehension of hypertension, when asked whether they needed to take medications without symptoms, a 23% of patients answered "no". [18] This highlights the need for greater education for hypertensive patients.

The second domain of barriers to control is the role of the physician in reaching blood pressure goals. In the JNC7 report, Chobanian refers to the concept of "treatment inertia" which is the failure

of physicians to titrate medications despite the clear need to do so. This is highlighted in the STITCH trial which demonstrated that a stepped algorithm of treatment was more successful in getting patients to goal than usual care when physicians are left to make their own decisions about which drugs to select and when to titrate the dose. [19]

The third domain of barriers to blood pressure control is physiologic causes. Among them, is the assumption that a patient has white coat hypertension. This garners a significant amount of attention since it provides a sound reason not to titrate medication for both patients and physicians. However the burden of proof is on the healthcare provider to be sure that the diagnosis is accurate. The prevalence of white coat hypertension is estimated to be 15-20%. The diagnosis is confirmed with ambulatory blood pressure monitoring or home blood pressure monitoring. The definition of white coat hypertension is blood pressure in the office >140/90 mm Hg and out of office blood pressure < 135/85 mm Hg. [20,21] Other considerations which affect control are the various physiologic underpinnings of phenotypes of hypertension which may dictate the responses to various drug classes. For example, elderly persons are more likely to have poorly compliant blood vessels which are the characteristics of isolated systolic hypertension. [22] Their systolic blood pressures tend to be very elevated while diastolic blood pressure may be normal or quite low. While African Americans often present with low renin hypertension and high salt sensitivity, one should not assume that these are the only relevant factors to consider in the

Characteristics Associated with Resistant Hypertension
Older Age
Obesity
Excessive Salt intake
Chronic Kidney Disease
Diabetes
Left Ventricular Hypertrophy
Black Race
Female Gender
Residence in Southeastern U.S.

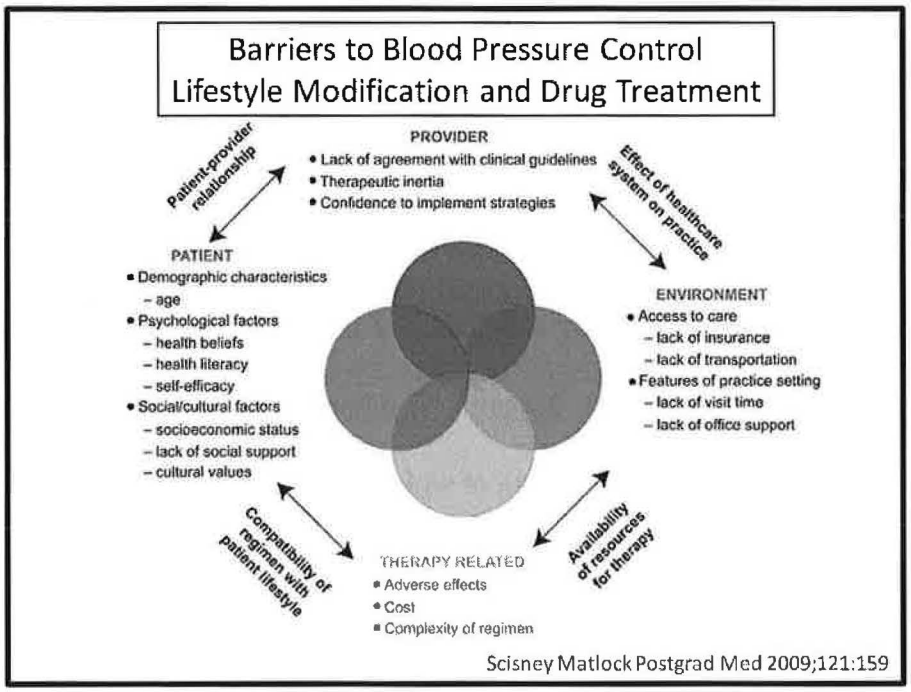
treatment paradigm. [23, 24] Clearly the greatest recent challenge in hypertension is the concurrence of obesity and hypertension. This introduces measurement error due to arm size and improper cuff sizing, as well as the complex effects of overweight and obesity on blood pressure. [24]

Secondary Hypertension Causes
Renal Artery Stenosis
Primary hyperaldosteronism
Renal Parenchymal Disease
Obstructive Sleep Apnea
Pheochromacytoma
Hyperparathyroidism
Hypercalcemia
Cushing's Disease
Aortic Coarctation
Intracranial Tumor
Thyroid Disease
Polycystic Ovarian Syndrome
Carcinoid Syndrome
Other
Herbal drugs
Alcohol consumption
Recreational drug Use

In assessing the failure to achieve blood pressure control, it is important to consider the possibility of secondary hypertension. One must ask the question of whether this is "resistant hypertension". Resistant hypertension has been defined as blood pressure which is uncontrolled on 3 agents of different classes at moderate doses, and ideally one of which includes a diuretic. [27] The most common cause of secondary hypertension is renovascular hypertension followed by hyperaldosteronism, obstructive sleep apnea, and renal parenchymal disease. Some of the less common secondary causes are pheochromacytoma, Cushing's disease, hyperparathyroidism, aortic coarctation, and intracranial tumor (see Secondary Hypertension Causes table). [27,28] These causes should be considered as possible causes when blood pressure control is not successful with 3-4 agents from different classes.

The fourth domain of barriers to blood pressure control is the healthcare system. The most vulnerable individuals to the ravages of hypertension are the individuals who do not have access to healthcare. Since both prehypertension and early hypertension, frequently do not have symptoms, we

rely on screening mechanisms to detect hypertension. The use of emergency services alone is an inadequate source of preventive care. Furthermore, the education needs of the patient can scarcely be met in the time allotted to primary care providers by current the healthcare system. [29] The increased prevalence of overweight and the burden that it places on the management of hypertension must be offset by assistance from the healthcare system such as dietary and lifestyle advice. The DASH diet has been shown to be effective for blood pressure reduction in whites and African Americans, however the success is limited by factors such as external support systems. [30] The failure to reach blood pressure goals bears a great financial burden, but more importantly the human cost is far greater.

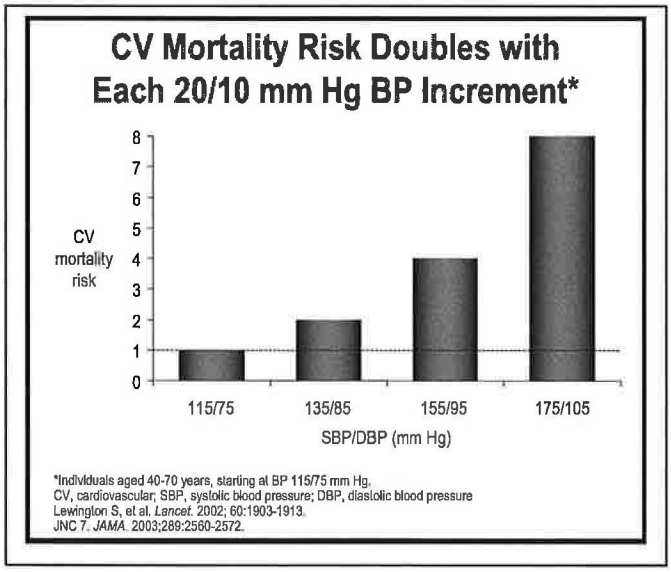


Major Guidelines

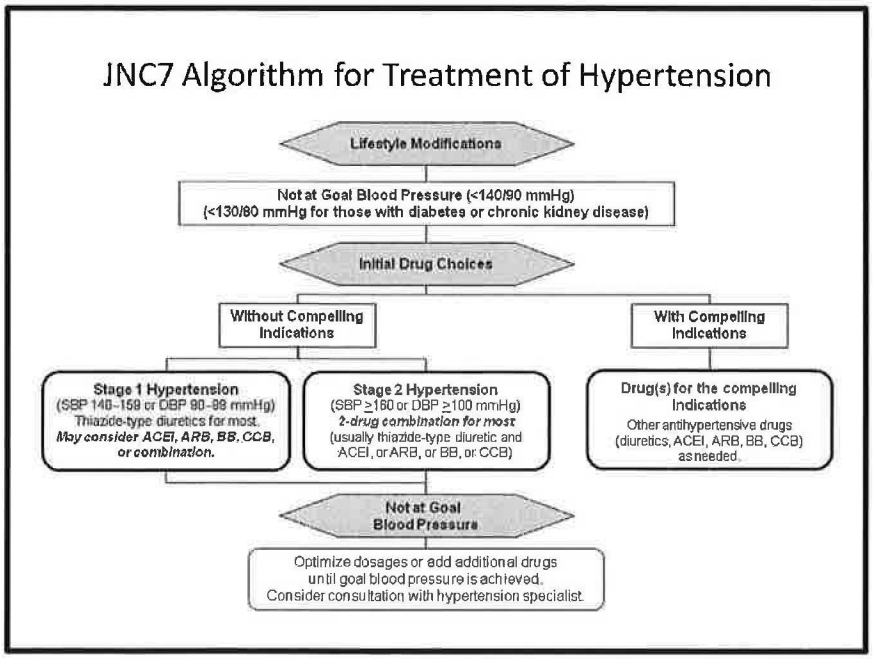
Although there are several sets of guidelines governing hypertension treatment, the guidelines from the NHLBI (National High Blood Pressure Education Program) Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of Blood Pressure (JNC7) were published in 2003. [3] These guidelines are broad and are intended to assist clinicians with diagnosing and managing most patients. However there are other sets of guidelines and consensus statements which have a more targeted focus for various smaller groups. Each group reviews the data relative to the specific population which they are addressing, thus the recommendations may differ to some

extent from the more global recommendations of the JNC. The JNC 8 is currently under revision and is expected to be presented in May 2011 with publication thereafter. The comments in this manuscript are therefore are speculations only about its content.

A brief review of the 2003 JNC 7 recommendations:



The purpose of the JNC reports is to improve the awareness, diagnosis, evaluation and treatment of hypertension. To that extent, linking the stages of blood pressure to the recommendations for follow-up and treatment is appropriate for implementation of the guidelines. The 2003 change to define prehypertension as blood pressures of 120-139/80-90 mm Hg caused some debate about the plausibility of such a class. The rationale for the "prehypertension" stage is that the cardiovascular risk associated with blood pressure begins to increase from the level of 115 mm Hg systolic and 75 mm Hg diastolic particularly for individuals aged 40-70 years old. Cardiovascular mortality increases 2-fold for every 20mm Hg in systolic and 10mm Hg in diastolic blood pressure. [31] There is significant evidence of



the hypertensive process beginning prior to the diagnosis of hypertension at >140/90 mm Hg.

The second major point introduced in JNC 7 was the concept of combination therapy as initial treatment for patients with stage 2 hypertension. Prior to that combination therapy was reserved for uncontrolled patients who were on therapy already. The new paradigm of initiating with combination therapy, successfully lead to improvement in blood pressure control over the past 7 years. In the treatment strategy, thiazide diuretics remained as a component of the recommendation for most patients and beta blockers taking a less dominant position. Other options were equally presented as treatment options. (see figure). The JNC 7 blood pressure goals were set at <140/90 mmHg for uncomplicated hypertension and <130/80 mmHg for diabetes and renal disease patients.

The third major point was to increase the focus on systolic blood pressure in persons older than 50 years old as it is clearly bears a stronger relationship to cardiovascular disease outcomes. This was also successful in shifting not only healthcare providers to focus on systolic blood pressure but also drug companies and the FDA to look at systolic blood pressure.

The fourth major point was to increase awareness of the pervasiveness of hypertensive risk in the US. The risk of developing hypertension to individuals who survive to age 55 is greater than 90%. [32]

AHA Perspective/Hypertension Management and BP Goals
Summary of Main Recommendations

Area of concern	BP Target (mm Hg)	Lifestyle † modification	Specific Drug Indications
General CAD prevention	<140/90	Yes	Any effective antihypertensive drug or combination‡
High CAD risk*	<130/80	Yes	ACEI or ARB *or* CCB *or* thiazide *or* combination
Stable angina	<130/80	Yes	*B*-blocker *and* ACEI or ARB
UA/NSTEMI	<130/80	Yes	*B*-blocker *and* ACEI or ARB §
STEMI	<130/80	Yes	*B*-blocker *and* ACEI or ARB §
LVD	<120/80	Yes	ACEI or ARB *and* *B*-blocker *and* aldo antagonist *and* thiazide or loop diuretic *and* hydral/nitrate (blacks)

*diabetes, CKD, CAD or equivalent
† weight loss if appropriate, healthy diet, exercise, smoking cessation and alcohol moderation
‡ evidence supports ACEI or ARB, CCB, or thiazide as first-line
§ if anterior MI is present, if HTN persists, if LVD or HF is present, if diabetic
adapted from Rosendorff C, et al. *Circulation* 2007;115:2761

Since the publication of the JNC 7 in 2003, the American Heart Association High Blood Pressure Council reviewed the data on high risk patients for heart disease and vascular disease with hypertension and published updated recommendations for this population. These recommendations were more aggressive in the treatment goals for patients with high risk. [33]The justification for these more aggressive goals was based on smaller trials in specific populations rather than larger traditional trials. [34]

Published Guidelines Have Set Lower Treatment Goals

JNC 7 / ADA / NKF / AACE Guidelines for Hypertension and Patients at High Risk

Condition	mmHg
Essential hypertension	<140/90
Diabetes mellitus	<130/80
Chronic renal disease	<130/80
High-risk* hypertension	<130/80

ADA=American Diabetes Association.
NKF=National Kidney Foundation.
AACE=American Association of Clinical Endocrinology.

*History of CVD event, stroke, transient ischemic attack, evidence of target-organ damage (e.g., left ventricular hypertrophy, microalbuminuria), CHD, or high-risk for CHD (e.g., metabolic syndrome).

Chobanian AV et al. *JAMA*. 2003;289:2560–2572. Arauz-Pacheco C et al. *Diabetes Care*. 2003;26(suppl):S80–S82. Torre Endocrin Pract 2006;12:193. Bakris GL et al. *Am J Kidney Dis*. 2000;36:646–661

Other guidelines such as the American Association of Clinical Endocrinology (AACE), American Diabetes Association (ADA), National Kidney Foundation (NKF) and the World Health Organization (WHO) have been published. These guidelines have been largely similar to JNC 7 in blood pressure goals and treatment recommendations. [35-38](see figure)

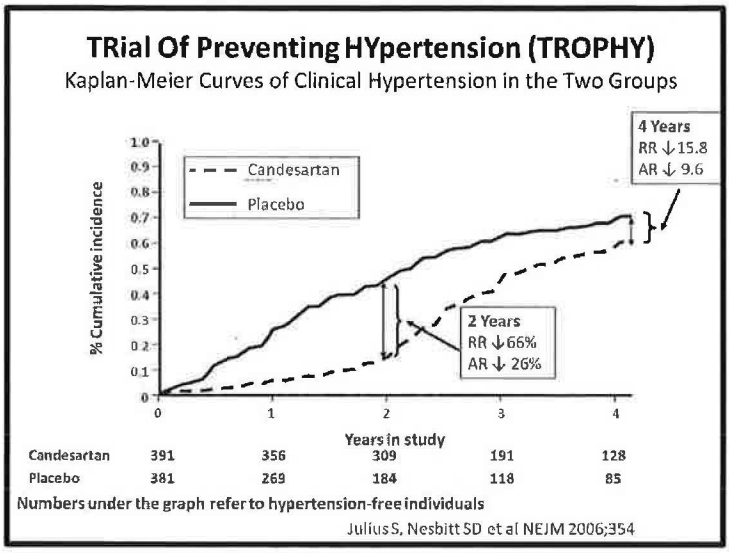
Drug Treatment Standards

	WHO/ISH	JNC 7	2003 ISHIB
Initiate TX Uncomplicated HTN	140/90 *(previously 160/90; currently 160/100 in UK)*	140/90	140/90
Initiate Combination TX- Uncomplicated		160/100	155/100
Initiate TX Complicated HTN & Goal	130/80 *(140/90 for women & elderly and in UK)*	130/80	130/80
Initiate Combination TX- Complicated HTN		150/90	145/90

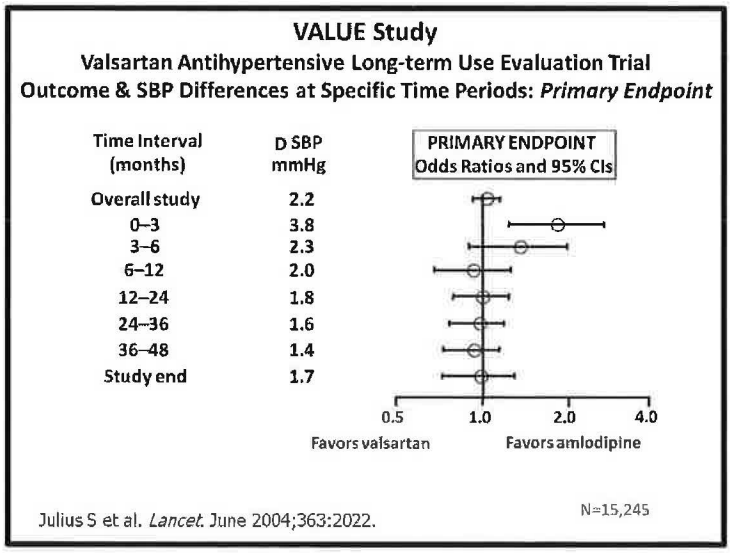
Drug Choice Recommendations

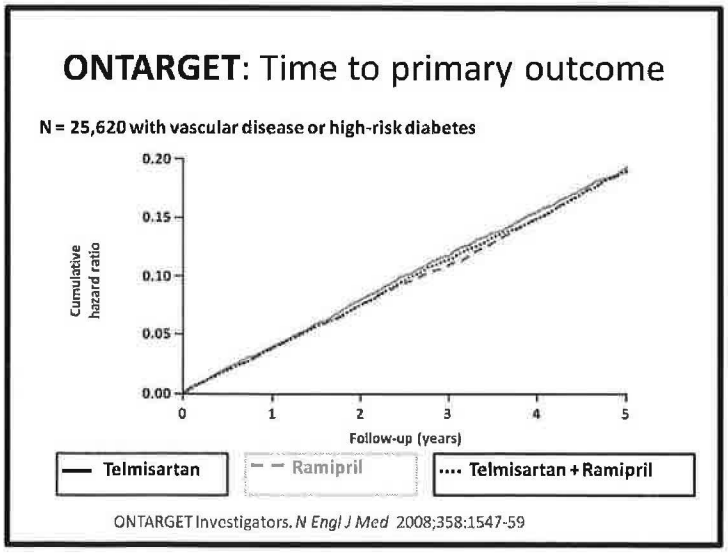
	WHO/ISH	JNC 7	2003 ISHIB
Uncomplicated HTN	*Thiazide* as initial agent	*Thiazide* as initial agent May use ACE, ARB, Beta-B, CCB	May initiate diuretic, ACE, ARB, Beta-B, CCB
Combination TX- Uncomplicated	*Not uniformly recommended*	Diuretic + (ACE, Beta-B, ARB) or ACE/CCB	Diuretic + (ACE, Beta-B, ARB) or ACE/CCB
Complicated HTN	*Treat according to the compelling condition similarly according to all guidelines.*		

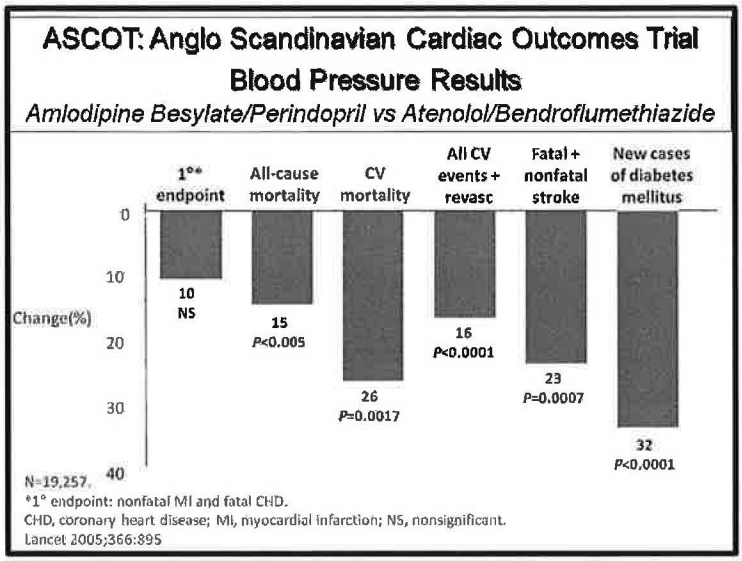
New Findings and Current Controversies in Hypertension



As the new treatment guidelines are being written, the charge of the expert panel is to review the newest data from both large and small clinical trials, epidemiologic trends and the success or failure of previous recommendations to make new recommendations for specific populations. [39] Some of the most novel trials published in hypertension since the JNC 7 guidelines are: the TROPHY, VALUE, ONTARGET/Transcend, ACCOMPLISH, ASCOT, HYVet, and ACCORD. The TROPHY Study had implications for the safety and plausibility of treating lower levels of blood pressure. The results of TROPHY demonstrated that candesartan safely reduced the 4 year incidence of hypertension compared to placebo in prehypertensives. [11] The VALUE study was designed to detect the difference between valsartan and amlodipine on cardiovascular outcomes

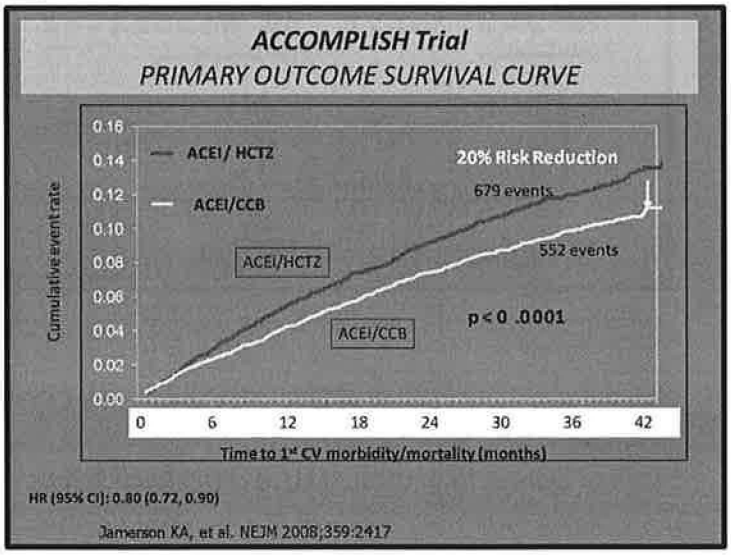




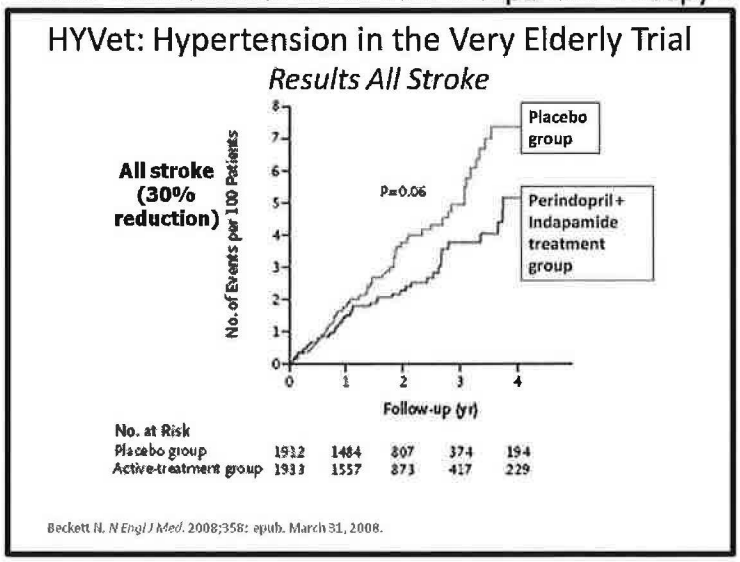


however no difference was detected in the overall trial. The most important point observed in the study was the importance of aggressive treatment of blood pressure to reach goals of therapy and the effect that can be observed in cardiovascular outcomes. [40]

The ONTARGET/Transcend trial has implications regarding the use of combination therapy of angiotensin receptor blockers and angiotensin converting enzyme inhibitors (ACEI) as these therapies have shown equivocal reduction in cardiovascular events as monotherapy or combination therapy. [41,42]



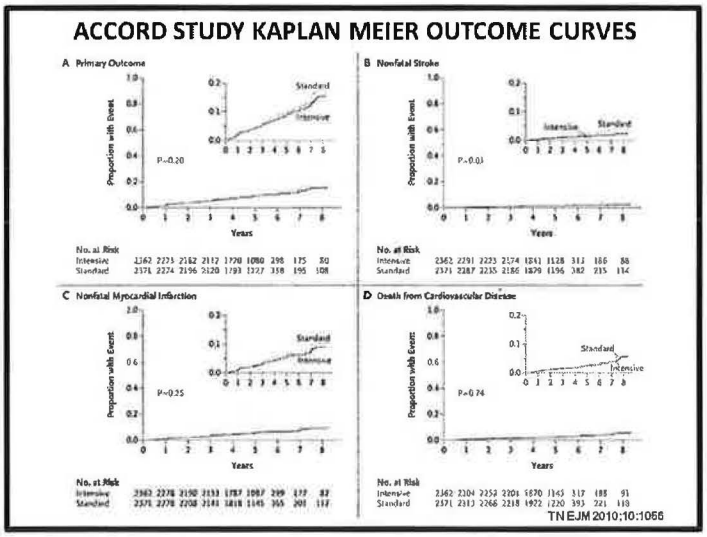
Both ACCOMPLISH and ASCOT have important implications regarding combination therapies which consist of RAS blockade/calcium channel blocker (CCB) as both trials have shown superiority of these combinations above their comparator therapy of RAS blockade/diuretic and beta blocker/diuretic respectively, in preventing cardiovascular events in high risk patients. [43,44]



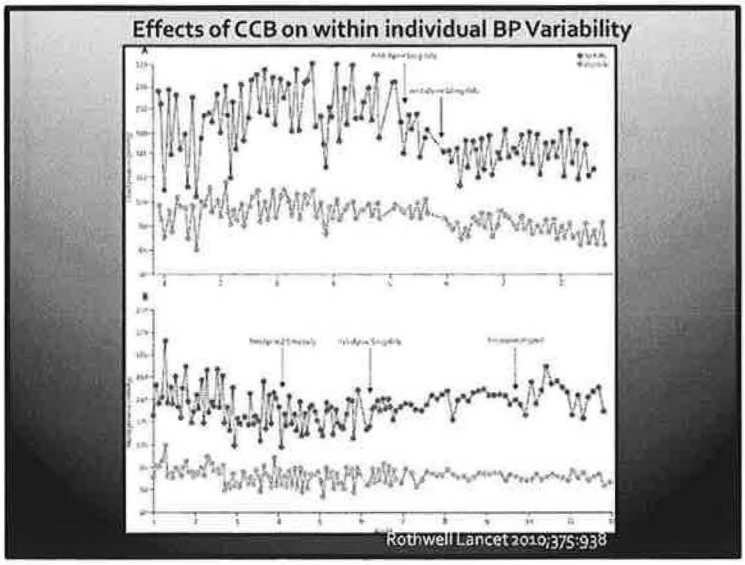
The HYVet trial is an important trial that has studied hypertension treatment in very elderly persons and has confirmed the value and

safety of treatment with ACEI/diuretics to a blood pressure of SBP< 150 mmHg in patients who are older than 80 years old in preventing cardiovascular events. [45]

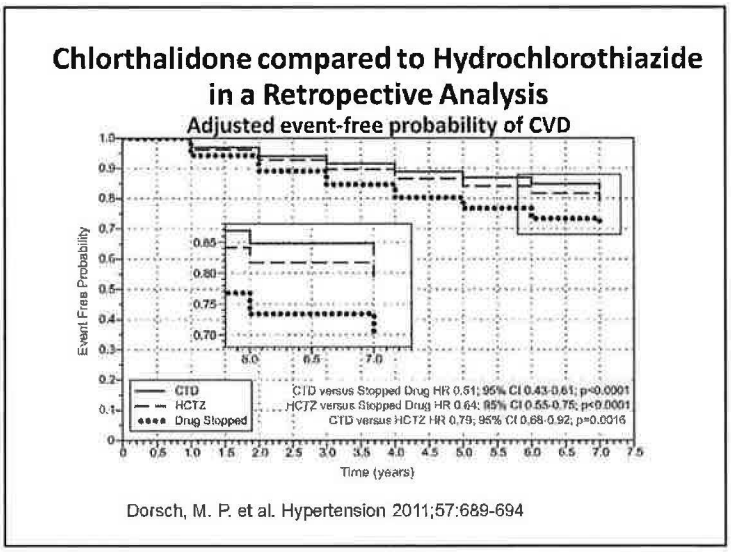
The most controversial issue is that of "how low should blood pressure be lowered". The ACCORD trial result raises questions with the previously held concept that "lower is better" without regard for a specific level. The ACCORD trial was conducted to study whether a low blood pressure goal of SBP <120 mmHg was more advantageous than the usual goal of SBP <140 mmHg in reducing cardiovascular outcomes in diabetic hypertensives. [46] The trial showed no difference between these goals in the primary outcome however there was an improvement in the secondary outcome of stroke with the lower goal (SBP<120 mm Hg). The result of ACCORD however is not clear cut since there were issues of lack of power to demonstrate a difference between the two blood pressure goals and disagreement between the cardiac outcomes versus the stroke outcome. In addition baseline blood pressure of the ACCORD population was a SBP 139 mmHg. These new findings are some of the key points of discussion for changes in the upcoming JNC 8.



Another important finding from analyses of data from several clinical trials and observational follow up studies is that the variability in blood pressure is great, and more frequent measurements are more



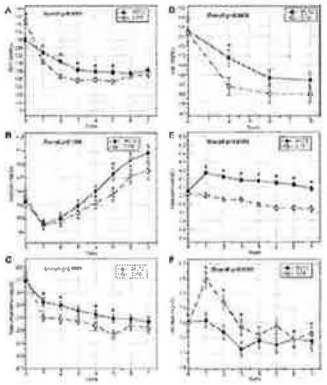
predictive of outcomes than a single blood pressure. However within an individual, high visit to visit variability in blood pressure is indicative of high risk of stroke and cardiovascular events independent of mean systolic blood pressure. [47-49] Thus the second controversial issue is whether office blood pressure is the only important measurement to assess? This issue is important for prediction of risk. The utility of home blood pressure and ambulatory blood pressure monitoring may become more important in the management of outpatient hypertension. The concept of variability in blood pressure is relevant to the selection of treatment options as well. A recent analysis of the ASCOT trial data shows that CCB reduces the variability in systolic blood pressure better than beta blocker in a dose dependent manner. [48] Furthermore that CCB is superior to all other classes in their ability to reduce the variability in blood pressure. [47] This may contribute to the unexplained superiority of RAS blocker/CCB combination therapy compared to RAS blocker/diuretic in the ACCOMPLISH Study and of RAS blocker/CCB compared to beta blocker/diuretic in the ASCOT trial. These concepts have not been tested as of yet.



There has been considerable question surrounding the use of thiazide diuretics in the past several years since JNC7. In the ALLHAT trial, chlorthalidone was the major comparator drug. The JNC 7 however did not specify chlorthalidone as being superior to other thiazide diuretics. Currently, the most commonly prescribed thiazide diuretic is hydrochlorthiazide. There are no clinical trials of direct comparisons of chlorthalidone to hydrochlorthiazide on cardiovascular events. However in the absence of a randomized, controlled clinical end point trial directly comparing chlorthalidone

and HCTZ, the data from an observational cohort analysis by Dorsch et al is another important piece of available data repository. This report is the first analysis of the relative impact of chlorthalidone and HCTZ on pressure-related cardiovascular disease (CVD) end points available in the published literature. Importantly, they reported a highly significant 21% lower risk of CVD among those taking chlorthalidone compared with those taking HCTZ over a median follow-up of 6 years. Although these data are collected in patients who were taking higher doses of both drugs than most often currently prescribed, this data is the most instructive information available. There are clear differences between hydrochlorthiazide and chlorthalidone, such as the longer half-life of chlorthalidone (45-60 hours versus 8-15 hours) and higher potency of chlorthalidone compared to hydrochlorthiazide (1.5-2.0 times higher). In addition, there were differential effects on metabolic parameters such as potassium, cholesterol and uric acid but not glucose. [50,51] Thus chlorthalidone may be proposed as a better thiazide diuretic however this is not without potential metabolic effects. A definitive trial would be most helpful to resolve the clinical question efficacy on cardiovascular endpoint reduction and the benefit risk ratio.

Effects of Chlorthalidone vs Hydrochlorothiazide on Metabolic Variables over time



Dorsch, M. P. et al. Hypertension 2011;57:689-694

Hypertension

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Learn and Live.

Management of High Blood Pressure in Blacks: An Update of the International Society on Hypertension in Blacks Consensus Statement

John M. Flack, Domenic A. Sica, George Bakris, Angela L. Brown, Keith C. Ferdinand, Richard H. Grimm, Jr, W. Dallas Hall, Wendell E. Jones, David S. Kountz, Janice P. Lea, Samar Nasser, Shawna D. Nesbitt, Elijah Saunders, Margaret Scisney-Matlock, Kenneth A. Jamerson

on behalf of the International Society on Hypertension in Blacks Hypertension

Hypertension 2010;56;780-800; originally published online Oct 4, 2010;

ISHIB Consensus Statement

The recently published 2010 International Society on Hypertension in Blacks (ISHIB) Consensus Statement on Management

of High Blood Pressure in Blacks is an update to the initial consensus statement published in 2003. The primary focus of the statement is to address prevention, diagnosis, risk stratification, and clinical management of hypertension and cardiovascular renal risk reduction in black patients with hypertension. The major points of the previous statement were to greater focus to combination therapy in Black patients utilizing the threshold of 15/10mm Hg above goal to guide the initiation of combination therapy; and to emphasize the importance of RAS blockade in the treatment of hypertensive disease in Black patients. Notably the 2003 ISHIB consensus statement was consistent with the JNC 7 goals of blood pressure therapy (<140/90 for uncomplicated hypertension and <130/80 for diabetes and renal disease). The major difference in the 2003 ISHIB statement and the JNC7 recommendations was the threshold of 15/10 mm Hg above goal for combination therapy initiation versus the 20/10 mm Hg threshold recommended by the JNC7. [3,52]

The current trends described above in the epidemiology of hypertension show that hypertension awareness of hypertension among African Americans is commensurate with the general population yet treatment rates are still significantly lower in African Americans. More importantly, these patients are frequently not reaching the current goals of therapy. [2] This highlights the need for the 26 year old organization, ***ISHIB*** (*International Society on Hypertension in Blacks*) to continue the work of promoting education in healthcare providers, research in academia, and lay person education on the hypertension in Blacks. The 2010 Consensus statement update is a major component of ISHIB's campaign on education over the past 5 years.

The Consensus panel consisted of 15 members with expertise in hypertension research and treatment in African Americans. These recommendations are the "consensus" of this group after a review of literature including large and smaller clinical trials and retrospective analyses which have included African Americans. In addition, other guidelines in special populations, a review of

epidemiology trends, and expert opinion were considered. Given the paucity of clinical trials with large sample sizes of African Americans, it is impractical to limit our conclusions to these trials alone. In the Consensus statement, the epidemiology, unique physiologic differences, non-physiologic factors affecting blood pressure, secondary hypertension and diagnostic evaluation of hypertension is discussed however in this protocol, the focus will be limited to the major treatment recommendations.

Major Recommendations of the 2010 ISHIB Consensus Statement

1. Treatment recommendations should be based on risk stratification. Two main risk strata are proposed: ***Primary prevention*** risk stratum includes individuals with no evidence of target organ damage; no preclinical CVD (Framingham risk <20%; no metabolic syndrome; no impaired fasting glucose (glucose 100-125mg/dL) and/or impaired glucose tolerance, no diabetes mellitus; no CVD (CHD/CHF/MI/ peripheral arterial disease/stroke/ TIA and/or abdominal aortic aneurysm). The goal for primary prevention should be ≤135/85 mmHg. ***Secondary prevention*** risk stratum includes all individuals with target organ disease, preclinical CVD (Framingham risk >20%; no metabolic syndrome; no impaired fasting glucose (glucose 100-125mg/dL) and/or impaired glucose tolerance, no diabetes mellitus) and CVD (includes CHD/CHF/MI/ peripheral arterial disease/stroke/ TIA and/or abdominal aortic aneurysm). The goal for treatment should be ≤130/80 mmHg.

ISHIB Consensus Statement Treatment Goals According to Risk Category or Stratum

Risk Category	Recommendation	Goal BP
Primary Prevention BP ≥135/85 mmHg without target-organ damage,† preclinical CVD,‡ or CVD§	Lifestyle Modification* (up to 3 months without drugs) + Drug Therapy	<135/85 mmHg
Secondary Prevention/ Target-Organ Damage BP ≥130/80 mmHg with target-organ damage,† preclinical CVD,‡ and/or the presence of CVD§	Lifestyle Modification + Drug Therapy	<130/80 mmHg

*Up to 3 months of comprehensive lifestyle modification without drugs if BP <145/90 mmHg without target-organ damage or other risk-enhancing comorbidities.
†Target-organ damage is defined as albumin:creatinine ratio >200 mg/g, estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m², or electro- or echocardiographic evidence of left ventricular hypertrophy (LVH).
‡Indicators of preclinical CVD: metabolic syndrome, Framingham risk score >20%, prediabetes (impaired fasting glucose [100-125 mg/dL] and/or impaired glucose tolerance [2-hr postload glucose of 140-199 mg/dL]), diabetes mellitus.
§CVD includes heart failure (systolic or diastolic), CHD/post-myocardial infarction, peripheral arterial disease, stroke, transient ischemic attack, and/or abdominal aortic aneurysm.

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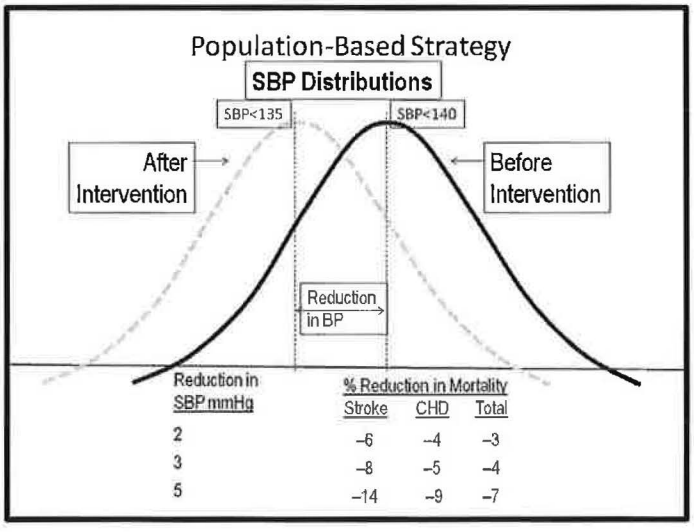
The rationale for the change in the goal of treatment to a lower goal is based primarily on the recognition that the need for

blood pressure control in African Americans is great while the success of reaching the modest goal for a large component of the population is limited. The need for blood pressure control in this population is best demonstrated by looking at the target organ damage in African Americans with hypertension. First, in the Dallas Heart Study, Drazner observed the excess prevalence of left ventricular hypertrophy among African Americans at nearly every blood pressure level above systolic blood pressure above 120 mm Hg whether regardless of the method of adjustment. [54] Secondly, microalbuminuria is a simple measure of target organ damage. Microalbuminuria is increased among prehypertensives above normotensives and remains elevated even higher in hypertensives despite blood pressure control. This trend is consistent in Whites as well. [55] The impact of blood pressure on outcomes such as stroke, renal disease and cardiovascular disease is significant. Although stroke is generally declining, the ethnic disparity remains striking. In the African American Antiplatelet Stroke Prevention Study in which 1085 stroke patients were surveyed, 87% were known to be hypertensive and 48% of the remaining patients had blood pressures above 140/90 mmHg. Only 30% of the known hypertensives were controlled. [56] In the ARIC study of 14,448 men and women aged 45 to 64 years old, African Americans had a 3-fold higher multivariate-adjusted risk ratio of lacunar stroke compared to whites. The population attributable fraction for hypertension in ARIC was 35% for all ischemic stroke. [57] Furthermore the risk of endstage renal disease is 4.2 times greater in African Americans than in Whites. [58] In a study of an age adjusted analysis of the leading causes of death in the U.S. from 1990-1998 and 1999-2006, although the 4 leading causes of death are declining but the racial disparity is not changing. [59]

There are limited data from clinical trials surrounding the issue of the ideal blood pressure goal for primary prevention. The treatment goal for primary prevention has declined over the past 30 years from no systolic goal in 1980's to <160 in 1988, then to <140 by 1993. [60,61] Much of the logic for selecting the threshold of 140 was from the observations from epidemiologic data such as the MRFIT trial. [62] Recent trials such as the TROPHY study suggest the safety of lower blood pressure goals than 140/90 mmHg. The (TOHMS) Treatment of Mild Hypertension Study trial showed that treatment (with 1 of 5 different antihypertensive drug regimens) plus multifactorial lifestyle modification alone in men and women aged 45-69 years (20% Black) with baseline blood pressure 140/91 mmHg reduced the risk of the aggregate end point of pressure related complicated when SBP was lowered to approximately 126 mm Hg(on lifestyle & active treatment) versus 132 mm Hg(on lifestyle modification alone). (Event rate 11.1% versus 16.2 % respectively, p=0.03) [63] Similarly the Cardio-Sis trial suggests that a lower blood pressure goal is safe and also has beneficial effects on intermediate outcomes such as ECG-LVH. [64] In addition the best outcomes in the ALLHAT trial were observed in the group whose blood pressures were reduced to 134/76 mmHg at 4.9 years. [65] The ACCORD trial which was designed to answer the whether the goal of SBP <120 mm Hg is better than <140 mm Hg however the study was not able to demonstrate a difference between these goals. There were several concerns about the sample size and power which leaves this question yet



unanswered. The upcoming SPRINT trial sponsored by NHLBI will take on this question more completely.

The more compelling reason to shift the blood pressure goal for African Americans is the overwhelming risk of target organ disease and the strong relationship to blood pressure. The fact is, that only a small segment of the hypertensive African American population actually reach the goal of <140/90 mm Hg. A shift in the goal to <135/85 mm Hg will actually serve to bring a greater proportion of the population of hypertensive African Americans under blood pressure control.

2. Greater focus has been placed on multiple drug therapy especially single pill options as they improve adherence. If there are no concerns of fluid overload, the preferred 2 drug option is RAS blocker/CCB, otherwise RAS blocker/diuretic may be started. The threshold for initiating combination therapy should be when the blood pressure is 15/10 mm Hg above the goal of blood pressure.

The rationale for this recommendation is based on the results of the ACCOMPLISH trial which included 1416 blacks of the total population of 11,506 and found that ACEI/CCB was superior to ACEI/HCTZ in reducing clinical outcomes when blood pressure is equivalent in the treatment groups (131.6/73.3 vs. 132.5/74.4 mm Hg respectively). The reduction in events was 19.6% $p<0.001$. Similar reduction of outcomes was observed in the black cohort of the study. [43] Additional strength for the utilization of CCB as component of the combination therapy can be found in the recent analysis of Webb demonstrating the superiority of CCB in reducing the variability of blood pressure compared to other classes of antihypertensive agents. [47] Furthermore the ASCOT study supports the superiority of ACEI/CCB compared to beta blocker/diuretic therapy in a high risk population although this

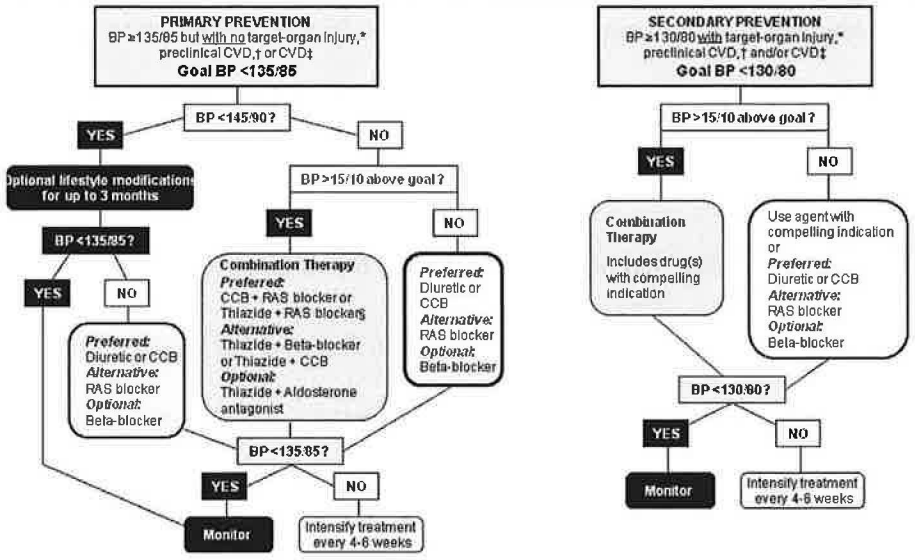
study did not include black patients. [44] The companion substudy entitled "CAFE" found that central aortic blood pressure measured non-invasively was reduced more with ACEI/CCB than beta blocker/diuretic despite equivalent peripheral blood pressure between the treatment groups. [66] It is not known whether this effect is responsible for the greater reduction in events with ACEI/CCB.

Combination therapy has been a successful tool in improving control rates since 2003 when the use was initially recommended. As described above, single pill options improve adherence. There are more combination single pill agents available currently. In the interest of promoting better adherence and higher control rates among African American patients with the overall goal of reducing mortality.

3. The treatment algorithm should encompass risk stratification, lifestyle modification and drug treatment. The Consensus statement recommends utilization of lifestyle modifications including the DASH diet. [67] See algorithm.
4. An algorithm is proposed for add on therapy in patients who are not controlled with initial monotherapy or combination therapy. See Add-on Algorithm

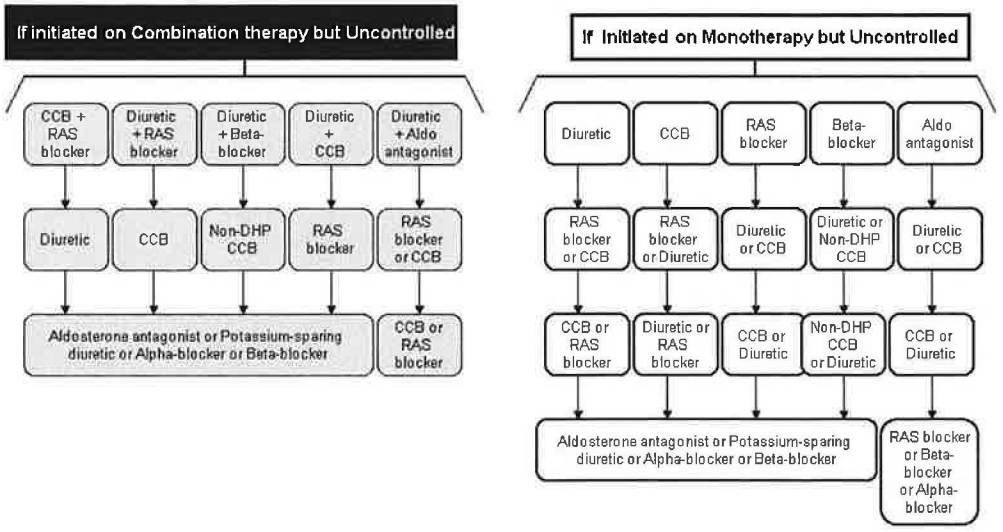
This algorithm suggests a preferable scheme for adding treatments based on the presence of selected cardiovascular co-morbidities unless absolutely contraindicated.

ISHIB 2010 Algorithm: Treatment According to Risk Stratification



NOTE: The most-effective 2-drug combinations are: CCB + RAS blocker; thiazide diuretic + RAS blocker; thiazide diuretic + aldosterone antagonist; thiazide diuretic + beta-blocker. Recommended RAS blockers are ACE inhibitors, or ARBs for patients unable to tolerate ACE inhibitors. *Target-organ injury is defined as albumin:creatinine ratio >200 mg/g, eGFR <60 mL/min/1.73 m², or electrocardiographic or echocardiographic evidence of LVH. †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-hr postload glucose ≥140 mg/dL]), or diabetes mellitus. ‡CVD includes heart failure (systolic or diastolic), coronary heart disease/post myocardial infarction, peripheral arterial disease, stroke, transient ischemic attack, and/or abdominal aortic aneurysm. §Preferred combination therapy in edematous and/or volume overload states.

Guide to Multi-Drug Therapy for Hypertension in African Americans



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Summary

Guidelines and consensus statements are helpful tools for clinicians to assist in reviewing and interpreting the literature to guide therapy decisions. Each set of guidelines is designed to address a particular population and it is important to consider this as the recommendations are implemented. The recommendations from the ISHIB Consensus Statement for African Americans with High Blood Pressure focus on improving the clinical outcomes of hypertension in this high risk population. While ISHIB's recommendations may be appropriate for this high risk group, it is unclear whether this is the best recommendation for all hypertensives. The soon to be released JNC8 will address the broader population. Some have speculated on the major questions but the answers are yet to be revealed. [68] Nevertheless, all of these consensus statements and guidelines are recommendations which do not abate the physician's ability to individualize treatment to the patient's presentation.

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