IMPROVING CARDIOVASCULAR HEALTH OUTCOMES THROUGH THE USE OF EVIDENCE-BASED MEDICINE

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The risk of cardiovascular (CV) and renal complications begins at a relatively low blood pressure (BP), and this risk is associated with such disorders as metabolic syndrome. When comparing older antihypertensive agents with newer agents, for the most part no significant differences have been seen in rates of CV events. However, rapidly controlling BP is critical to reduce event rates, particularly rates of stroke. Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers consistently decrease the rate of onset of type 2 diabetes. (*Ethn Dis*. 2005;15[suppl 2]:S2-23–S2-26)

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INTRODUCTION

The goals of therapy for hypertension are to reduce cardiovascular disease (CVD) and renal morbidity and mortality. For the general population, the goal is <140/90 mm Hg and for patients with diabetes or chronic kidney disease (CKD) and proteinuria >1 gm the goal is <130/80 mm Hg. Complicated hypertension is accompanied by one or more additional risk factors, eg, coronary artery disease (CAD), diabetes, metabolic syndrome, CKD, microalbuminuria, or proteinuria that augment CVD risk. Certain hypertensive populations are at increased risk as well, such as Blacks, Hispanics, and the elderly. Unfortunately, according to the NHANES 2000 report, hypertension control rates remain unsatisfactory at 34% for the goal of <140/90 mm Hg. In the diabetic population, where the goal is lower, the control rate is only 12%.

HIGH NORMAL BLOOD PRESSURE IS NOT BENIGN

The Framingham database has demonstrated that as systolic blood pressure (SBP) increases beyond 117 mm Hg, a progressive increase is seen in risk of cardiovascular (CV) events, including CV death, myocardial infarction (MI), stroke, and congestive heart failure (CHF). From SBP 120 to 139 mm Hg risk increases 2.5 fold for women and 1.6 fold for men. JNC 7 emphasized that starting at 115/75 mm Hg, CVD risk doubles with every 20/10 mm Hg increase in blood pressure (BP).[1] At higher risk are persons with metabolic syndrome, in which one of the criteria for definition is BP ≥135/85 mm Hg (see Table 1 for ATP III definition of metabolic syndrome). Metabolic syndrome increases coronary heart disease (CHD) and stroke risk 2–3 fold, CVD mortality by 4–5 fold, CKD (glomerular filtration rate [GFR]<60 mL/min) by 2.6 fold and microalbuminuria (30–300 mg/gm creatinine) by 1.9 fold.[3] The overall prevalence of metabolic syndrome is estimated to be approximately 24%; however, in persons age 60 years and older, the prevalence is 44 %. The highest prevalence in the United States is among Mexican Americans. Lifestyle modification is critical as a therapeutic approach as there are numerous benefits. For example, for every 10 kg weight loss, a 5–20 mm Hg reduction is seen in SBP; dietary sodium reduction lowers SBP by 2–8 mm Hg; regular physical activity lowers SBP by 4–9 mm Hg; and moderation of alcohol consumption lowers SBP by 2–4 mm Hg.[1] One of the new concepts in JNC 7 is the inclusion of the BP classification of prehypertensive, which encompasses individuals with SBP between 120–139 mm Hg or DBP between 80–89 mm Hg. For this group, lifestyle modification is indicated without active pharmacotherapy unless a compelling indication exists for an individual drug class. JNC 7 also emphasized the importance of lifestyle modification as an adjunct to pharmacologic treatment of hypertension in all classes of BP elevation.

RECENT HYPERTENSION TRIALS WITH "OLD" VERSUS "NEW" DRUGS

A number of clinical trials have documented the benefit of antihypertensive

Table 1. ATP III criteria for the metabolic syndrome

Risk Factors	Defining Level
Abdominal obesity	Waist
Men	>40 inches
Women	>35 inches
Triglycerides	≥150 mg/dL
HCL-cholesterol	
Men	40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/≥85 mm Hg
Fasting glucose	≥110 mg/dL

The diagnosis of metabolic syndrome depends on the presence of ≥3 of the above risk factors. Modified from reference 2.

Table 2. Head-to-head antihypertensive drug comparisons

CAPPP[7]	Captopril Prevention Project (captopril vs diuretic/β-blocker)
STOP-2[8]	Swedish Trial in Old Patients with Hypertension-2 (ACE inhibitors/CCBs vs diuretics/β-blockers)
NORDIL[9]	Nordic Diltiazem Study (diltiazem vs diuretic/β-blocker)
INSIGHT[10]	International Nifedipine GITS Study (nifedipine GITS vs diuretic/β-blocker)
ALLHAT[11]	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (chlorthalidone vs lisinopril or amlodipine)
CONVINCE[12]	Controlled Onset Verapamil Investigation of Cardiovascular End Points (verapamil-COER vs diuretic/β-blocker)
LIFE[13]	Losartan Intervention For Endpoint Reduction in Hypertension (losartan vs diuretic/β-blocker)
VALUE[6]	Valsartan Antihypertensive Long-term Use Evaluation Trial (valsartan vs amlodipine)

therapies to reduce CV morbidity and mortality when an active treatment arm is compared with placebo (eg, SHEP, SYS-EUR).[4,5] However, more recently, head-to-head comparisons of different classes of antihypertensive agents have largely failed to demonstrate significant differences in the primary cardiovascular endpoint or outcome. The recent hypertension trials are listed in Table 2. In these trials, the older drug was usually a β-blocker and/or diuretic. The one exception was the VALUE trial, where the angiotensin-receptor blocker (ARB) valsartan was compared to the dihydropyridine calcium channel blocker (CCB) amlodipine.[6]

The LIFE trial is an exception to the trials listed above because it showed a significant difference in the primary outcome of the study, which compared the angiotensin receptor blocker losartan with the β-blocker atenolol in >9000 high-risk hypertensive persons with left ventricular hypertrophy. Blood pressure control was not significantly different during the approximately 4 years of follow-up in this trial. The primary composite endpoint, which included CV death, stroke, and MI, had an adjusted risk reduction of 13%, P=.021 with losartan compared with atenolol. This favorable outcome was driven by the 25% risk reduction in stroke by losartan compared to atenolol. Among the 600 US Black patients enrolled in the trial, the primary composite endpoint favored atenolol, which is opposite to the result seen in US Whites in the trial and the study population as a whole. No explanation for the difference in results is apparent. An additional outcome of the trial was a 24% reduction in new onset of diabetes with losartan compared with atenolol. Similar reductions were seen in the ALLHAT trial with lisinopril compared with amlodipine. These observations, along with retrospective analyses from at least 10 other trials, support a specific mechanism whereby angiotensin-converting enzyme (ACE) inhibitors and ARBs block the ability of angiotensin II to oppose the action of insulin, which results in reduction in new onset of diabetes.

Randomized controlled trials in the general population have documented the beneficial effects of ACE inhibition when given with other medications to improve outcomes in heart failure, post MI, post stroke, high cardiovascular risk, and CKD (diabetic and nondiabetic).[1] Unfortunately, many randomized clinical trials enrolled few Blacks or African Americans, which has led to erroneous interpretation of the efficacy of using certain agents in Black Americans. For example the SOLVD trial was interpreted as lack of efficacy of ACE inhibitors in Blacks with heart failure because mortality was higher in the prevention and treatment limbs of the study. Mortality rate in Blacks was twice as high as that in Whites in the prevention trial and 20% higher in the treatment trial.[14] A subsequent analysis of the prevention arm of the trial reported that enalapril was equally effective in Black and White participants.[15] Factors that influenced the outcome of the trial include that hypertension was the cause of heart failure in more Black participants, while CAD was the cause in more Whites.

A total of 800 Black participants were enrolled in the trial, compared to ≈6000 Whites. In addition, the ACE inhibitor dose was probably suboptimal in Blacks because the BP change in Black participants was significantly less than that seen in White participants. Multiple barriers prevent enrollment of Black Americans; these barriers are related to lack of access to health care, negative experiences with the healthcare system, lack of education, lack of physician referral for enrollment, distrust of medical research, patient adherence issues, transportation, and inconvenience, to name a few. These barriers may be overcome as evidenced by the recent AASK and ALLHAT trials.[11,16]

The AASK trial was the landmark outcome trial that documented the benefit of ACE inhibition in Blacks.[16] This trial evaluated the efficacy of treatment with an ACE inhibitor, ramipril; a β-blocker, metoprolol; or a CCB, amlodipine to delay progression of kidney disease in patients with mild to moderate CKD (GFR was 46 mL/min/

1.73m^2) secondary to hypertensive nephrosclerosis. The AASK trial enrolled 1094 patients (mean age 54 years and 61% men) and demonstrated that ramipril slowed the decline in renal function to a significantly greater degree than did amlodipine or metoprolol. Moreover, ramipril decreased clinical events (a 50% decline in GFR or an absolute decline of 25 mL/min/1.73m^2; end-stage renal disease or death) by 38% compared with amlodipine and by 22% compared with metoprolol for the entire study population. Of interest is the fact that the median urinary protein-to-creatinine ratio was 0.11, and the ratio exceeded 0.22 in approximately one third of the participants. A urinary protein-to-creatinine ratio $>$0.22 corresponds to urinary protein excretion of $\approx$300 mg/day, a value identifying significant and dipstick-positive proteinuria. In this group with urinary protein-to-creatinine ratio $>$0.22, the ramipril effects were even more profound, with a 46% reduction of clinical events compared to the reduction seen with amlodipine. Previous studies in non-Black populations have documented that ACE inhibition, compared with the effect of other classes of antihypertensive agents, is associated with renal protection, but the level of urinary protein has typically exceeded 500 mg/day.[17] The AASK trial is unusual in that the level of proteinuria associated with hypertensive nephrosclerosis is relatively low by comparison to the level of proteinuria seen with other forms of kidney disease (eg, diabetic nephropathy), yet renal protection with ramipril was clearly apparent. Significantly greater proteinuria is associated with greater risk of renal disease progression and risk of cardiovascular disease events.[18,19] Ramipril was more effective than amlodipine or metoprolol at reducing urinary protein excretion. No differences in blood pressure were seen throughout the trial to account for the beneficial effects of ramipril. Multiple drugs were required to achieve goal blood pressures in this trial, and most patients required high doses of a loop diuretic. No differences in CV event rates were noted in this trial among the three comparator drugs because the trial did not enroll enough patients to identify a difference in CV outcomes. The AASK trial is to date the only trial that has definitively established the efficacy of blocking the renin-angiotensin-aldosterone system in Black Americans for target tissue protection independent of blood pressure reduction.

The ALLHAT trial did not provide any evidence for a greater benefit of ACE inhibition, as occurred with the AASK trial.[11] This trial, which enrolled the largest number of Black Americans of any trial, did not take into account the pathophysiology of hypertension (hypertension in Black Americans has a volume-dependent component).[20] The ALLHAT trial was structured to assess the efficacy of treatment with different classes of agents (chlorthalidone, amlodipine, lisinopril, or doxazosin) on the combined incidence of fatal coronary heart disease and nonfatal myocardial infarction. However, this trial was limited in that Blacks on lisinopril had poorer blood pressure control because relatively low doses were used in the absence of a diuretic or CCB. This limitation may have negatively influenced the secondary outcomes (stroke and heart failure) that were significantly reduced in favor of the diuretic. This study enrolled 42,400 patients 55 years and older with hypertension and at least one additional CHD risk factor; 35% of the subjects were Black Americans, and 36% had type 2 diabetes. The doxazosin limb of the trial was discontinued prior to the trial's end because the doxazosin-treated patients developed excessive heart failure compared with the chlorthalidone-treated patients.

The ALLHAT trial did not demonstrate a difference in the primary outcome rates of MI and fatal CHD (the primary study endpoints) or in mortality, despite significantly better BP control in the chlorthalidone-treated group compared with the lisinopril-treated participants. Despite this equivalency in primary outcome, the authors of the trial recommended chlorthalidone (the thiazide diuretic) over the other two drug agents (the ACE inhibitor and the CCB) to prevent major CV events. This recommendation was in part driven by the fact that the thiazide diuretics are inexpensive compared to the comparator antihypertensive agents.

Statistically significant differences in secondary outcomes influenced the final recommendations of the ALLHAT investigators. Specifically, chlorthalidone reduced stroke rate by 15% in the overall study population and was associated with an additional 4 mm Hg reduction of SBP compared to the diuretic. Better BP control was observed with the diuretic and CCB compared to the ACE inhibitor throughout the 5-year duration of the study. This higher stroke event rate of 15% for the whole group of participants with the ACE inhibitor as compared to the diuretic was driven by the inclusion of the Black participants (35% of the study population) who experienced a 40% greater stroke event rate with the ACE inhibitor. When Blacks were excluded from the analysis, no difference in the stroke event rate was seen with these two classes of antihypertensive agents. Chlorthalidone was also significantly better at reducing heart failure than was lisinopril or amlodipine. Given the known differential pathophysiologic mechanism of hypertension in Black subjects one would anticipate that use of an ACE inhibitor without an accompanying diuretic, significant sodium restriction, or CCB would result in poorer BP control, which was documented. The trial design, which used an ACE inhibitor without an accompanying diuretic in a large number of subjects with salt-dependent hypertension, anticipated that the ACE inhibitor limb of the trial would have had poorer BP control and a greater number of CV complications (stroke and heart failure), which was

demonstrated. Given these considerations, ALLHAT did not support the recommendation that ACE inhibition should be used as initial therapy in patients with hypertension despite the fact that other clinical trial data support the use of ACE inhibitors as initial therapy in patients with diabetes with or without nephropathy, non-diabetic renal disease, status post-MI, or heart failure.

The VALUE trial represents the most recent large hypertension trial and helps interpret the results of the ALLHAT trial with respect to the higher stroke event rate in Black Americans.[6] The study evaluated the hypothesis that among hypertensive patients at high risk for CV events, with equivalent levels of BP control, the ARB valsartan would be superior to the CCB amlodipine for reduction of CV morbidity and mortality. The study enrolled >15,000 participants. For the primary composite endpoint (total composite cardiac morbidity and mortality) no difference between the two agents was observed at the completion of the trial. However, during the early phases of the trial, the amlodipine treatment regimen lowered BP more quickly and effectively then the valsartan regimen. From 0–3 months, the SBP was 3.8 mm Hg lower with amlodipine compared with valsartan. This BP differential was associated with a stroke event rate that was higher with valsartan, an effect that had dissipated by six months into the trial. From then until the completion of the trial, BP control was ≈2 mm Hg better with amlodipine. This study made the novel observation that reducing BP quickly at the beginning of a trial will maximally benefit study participants. This finding had not been demonstrated previously and represented an unexpected outcome of the trial. This finding has important relevance to the interpretation of the higher stroke event rate in the ALLHAT trial in the Black American group.

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