ASHP Therapeutic Position Statement on the Treatment of Hypertension

Statement of Position

The American Society of Health-System Pharmacists (ASHP) supports aggressive measures to achieve optimal blood pressure control in patients with hypertension. A substantial body of scientific evidence has conclusively shown that optimal blood pressure control will reduce the development and progression of heart disease, cerebrovascular disease, and chronic kidney disease (CKD). Optimal blood pressure control is defined as less than 130/80 mm Hg for patients with diabetes mellitus or CKD and less than 140/90 mm Hg for all other patients. All patients with hypertension should be educated about the long-term effects of the disease and the goals of therapy.

ASHP promotes the rational selection of antihypertensive medications to achieve optimal blood pressure control. Selection of antihypertensive medications should be directed by evidence that demonstrates improved outcomes and balanced by drug-related variables (e.g., efficacy and safety), patient-related variables (e.g., comorbidities and recent blood pressure readings), and system-related variables (e.g., drug cost and availability). ASHP recognizes that a wealth of evidence supports the use of thiazide diuretics, either alone or in combination with other antihypertensive agents, as the initial pharmacologic treatment of hypertension in the majority of patients. Most patients will require two or more medications to achieve optimal blood pressure control. In addition, ASHP advocates continuous lifestyle modification to help achieve blood pressure goals.

ASHP encourages all health systems to develop strategies to identify and treat patients with hypertension and help patients achieve optimal blood pressure control. Strategies should include a collaborative, systemwide approach by all health care professionals.

Background

Hypertension is a chronic disease that affects more than 50 million Americans and more than 1 billion people worldwide.[1] The risk of hypertension increases with age. Data from the National Health and Nutrition Examination Survey (NHANES) indicate that 7.2% of people age 18–39 years have hypertension, compared with 65.4% of people over 60 years of age.[2] Approximately 90% of people age 50–65 years will develop hypertension by the time they reach 80–85 years of age.[3] Clearly, hypertension is a prominent health problem that will grow as the U.S. population ages.

Hypertension is a key risk factor for cardiovascular and cerebrovascular morbidity and mortality.[4,5] Both systolic blood pressure (SBP) and diastolic blood pressure (DBP) have a strong and continuous influence on cardiovascular risk.[6] The risk of cardiovascular mortality from ischemic heart disease or stroke doubles with each 20/10-mm Hg increment in blood pressure greater than 115/75 mm Hg.[7] The consequences of uncontrolled hypertension, such as heart failure, stroke, and CKD, significantly affect patients' quality of life and health care costs.[8,9] Data from the Framingham Heart Study indicate that the 10-year cumulative incidence of myocardial infarction (MI), stroke, or heart failure is 10.1% for men and 4.4% for women with an SBP between 130 and 139 mm Hg or a DBP of 85–89 mm Hg.[4] By comparison, 5.8% of men and women with an SBP of <120 mm Hg and 1.9% with a DBP of <80 mm Hg will have an MI, stroke, or heart failure.

Hypertension is the second leading cause of CKD. In one large epidemiologic study of 332,544 men, the relative risk (RR) of developing end-stage renal disease was 1.8 times higher for each 16-mm Hg increase in SBP.[10] In another study, the five-year risk of developing a serum creatinine concentration of >2.0 mg/dL was significantly related to increases in DBP.[11]

Optimal Blood Pressure Control

Strategies to control hypertension are paramount for preventing irreversible complications of the disease. Results from numerous landmark, placebo-controlled, clinical trials have corroborated epidemiologic evidence. Several medications that lower blood pressure will reduce morbidity and mortality related to hypertension, including stroke, MI, and CKD.[12–14] For example, in the Systolic Hypertension in the Elderly Program (SHEP) study, 4736 hypertensive patients were randomized to a thiazide-diuretic-based treatment regimen or placebo.[14] During 4.5 years of follow-up, the average SBP was 12 mm Hg lower in the treatment group compared with the placebo group. The RR of stroke in the treatment group was 0.69 (95% confidence interval [CI], 0.51–0.95; $p = 0.02$). Similarly, the combined endpoint of nonfatal MI and fatal coronary heart disease (CHD) was reduced by 27% in the treatment group.

In 2003, the Joint National Committee (JNC) published the seventh edition of its guidelines for the prevention, detection, evaluation, and treatment of high blood pressure (JNC-7).[15,16] In this guideline, high blood pressure is defined as an SBP of >140 mm Hg or a DBP of >90 mm Hg, with the goal of treatment to lower the blood pressure below this threshold. For patients with diabetes mellitus or CKD, optimal blood pressure control is defined as a SBP of <130 mm Hg or a DBP of <80 mm Hg. The JNC-7 definitions for optimal blood pressure control are consistent with recommendations by the National Kidney Foundation[17] and the American Diabetes Association.[18]

While definitions for hypertension and blood pressure control have been established for many years, the rate of optimal blood pressure control remains poor. Data from the third NHANES showed that blood pressure was controlled in only 22.7% of patients with hypertension between 1991 and 1994 and that this rate increased to only 31% between 1999 and 2000.[2] Disturbingly, more than 40% of hypertensive patients in the most recent NHANES were not receiving pharmacologic treatment.

The relatively low rate of blood pressure control among the general population contrasts with the high percentage of patients who achieved blood pressure goals in clinical trials

and some managed care organizations. According to the 2003 National Committee for Quality Assurance (NCQA) State of Health Care Quality Report, the top 10% of managed care plans achieved blood pressure control rates of 64–68%.[19] Similarly, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the largest hypertension trial conducted to date, blood pressure control was achieved in over 60% of patients, regardless of treatment group.[20] These data suggest that it is possible to obtain blood pressure control in a majority of patients, but they do not make clear what strategies can be universally applied to achieve this goal. It is likely that changes in the care delivery system are needed.

Methods for Achieving Optimal Blood Pressure Control

Patient and Provider Education. In the JNC-7 guidelines, a new classification scheme for hypertension was developed (Table 1).[15] Based on data regarding the lifetime risk of hypertension, "prehypertension" was added as a new category to these guidelines. This category identifies those patients at high risk for developing hypertension. The prehypertension category is intended to increase awareness and early identification of hypertension by clinicians and patients. To augment this effort, the National High Blood Pressure Education Program (NHBPEP), coordinated through the National Heart, Lung, and Blood Institute, has developed professional, patient, and public education programs. The "Know Your Numbers" campaign is designed to help patients understand their blood pressure measurement, the consequences of high blood pressure, and what they can do to prevent or control high blood pressure. Information about NHBPEP can be found at www.nhlbi.nih.gov/about/nhbpep. These materials are not copyright protected, and health care professionals are encouraged to use them as part of their ongoing patient-education efforts.

Initial Antihypertensive Therapy. There is an immense body of literature regarding the pharmacologic treatment of hypertension. As a result, there is ongoing debate about which pharmacologic treatment regimen is the best for a specific patient. ALLHAT provided substantial data regarding the initial selection of antihypertensive therapy.[20] The trial compared four medications that represented commonly prescribed classes of antihypertensive agents for the initial treatment of hypertension: chlorthalidone (thiazide diuretic), doxazosin (α-blocker), lisinopril (angiotensin-converting-enzyme [ACE] inhibitor), and amlodipine (calcium channel blocker [CCB]). The trial included an equal number of men and women, as well as a high degree of representation from various age, ethnic, racial, and socioeconomic groups. In addition, a large number of patients with diabetes mellitus and other cardiovascular risk factors participated in the trial. In 2000, the doxazosin-treated group was discontinued prematurely due to a higher rate of cardiovascular events compared with the other treatment groups.[21]

In 2002, the final results were published for the chlorthalidone-, lisinopril-, and amlodipine-treated groups, which included 33,357 participants who were followed for an average of 4.9 years.[20] There was no difference between the treatment groups in the primary outcome of combined fatal CHD and nonfatal MI. However, patients receiving amlodipine had a significantly higher rate of heart failure compared with the chlorthalidone-treated group (RR, 1.38; 95% CI, 1.25–1.52). Also, the lisinopril group had significantly higher rates for combined cardiovascular disease (RR, 1.10; 95% CI, 1.05–1.16), stroke (RR, 1.15; 95% CI, 1.02–1.30), and heart failure (RR, 1.19; 95% CI, 1.07–1.31), compared with the chlorthalidone group. The use of amlodipine or lisinopril did not confer a significant benefit over chlorthalidone in any subgroup, including those with diabetes mellitus or heart failure. SBP was significantly lower in the chlorthalidone-treated group compared with patients receiving lisinopril and amlodipine by 1 and 2 mm Hg, respectively. Experts have debated whether chlorthalidone is truly superior or if the blood pressure difference accounted for the findings.[22] Nonetheless, chlorthalidone was more effective at lowering blood pressure in these patients, of whom 35% were black and almost 50% were women.

Shortly after the ALLHAT results were released, the authors of the Second Australian National Blood Pressure (ANBP-2) study came to a different conclusion regarding the best initial choice for the treatment of hypertension.[23] In ANBP-2, enalapril was found to be significantly better than hydrochlorothiazide at preventing cardiovascular events and all-cause mortality among 6083 patients. But the results were positive only in men (RR, 0.83), despite the fact that 51% of study participants were women. In contrast to ALLHAT, the ANBP-2 studied a population that was relatively healthy and more than 90% Caucasian. The ALLHAT population included many patients with several cardiovascular risk factors, and more than 50% of participants were non-Caucasians.

Several other large clinical trials have compared newer antihypertensive agents, including CCBs[24–27] and ACE inhibitors,[23,28] with the thiazide diuretics, and these agents did not demonstrate superiority over thiazide diuretics. A meta-analysis of 42 trials including 192,478 patients compared initial antihypertensive therapy with diuretics to therapy with β-blockers, CCBs, ACE inhibitors, and angiotensin-receptor blockers (ARBs).[29] The analysis examined multiple endpoints, including CHD, heart failure, stroke, and cardiovascular mortality. Diuretics were equal or superior to all other antihypertensive agents, regardless of the cardiovascular or cerebrovascular endpoint.

Table 1.
Classification of Blood Pressure for Adults[a]

Category	Systolic Blood Pressure (mm Hg)	Qualifier	Diastolic Blood Pressure (mm Hg)
Normal	<120	And	<80
Prehypertension	120–139	Or	80–89
Stage 1 hypertension	140–159	Or	90–99
Stage 2 hypertension	≥160	Or	≥100

[a]Reprinted from reference 15.

While scientific evidence supports the use of thiazide diuretics as initial treatment for hypertension, there is debate concerning which thiazide to use.[30] A posthoc analysis of the Multiple Risk Factor Intervention Trial (MRFIT) suggested that chlorthalidone may have a mortality benefit over hydrochlorothiazide.[31,32] However, no clinical trial has prospectively evaluated potential differences in the efficacy or safety of the thiazide diuretics for the treatment of hypertension. Based on the wealth of data supporting the use of thiazide diuretics in a wide variety of patient populations, coupled with their low cost and ease of use, the JNC-7 recommends use of thiazide diuretics as the preferred initial antihypertensive agent for the majority of patients.[15]

While previous guidelines have recommended β-blockers as first-line agents for the treatment of hypertension, recent studies have also raised doubts about the routine use of β-blockers, especially atenolol, in the absence of compelling indications (Table 2).[15] In one large meta-analysis, patients who received β-blockers had significantly more cardiovascular events than those treated with diuretics.[29] Results from the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) trial also questioned the utility of β-blockers as first-line agents for hypertension.[33] In this randomized controlled study of 9193 patients, there was a significant reduction in both fatal and nonfatal strokes in the losartan-treated group compared with patients receiving atenolol. A second meta-analysis that examined the use of β-blockers for the treatment of hypertension reported that the RR of stroke was 16% greater for patients receiving β-blockers versus other drugs.[34] Atenolol demonstrated the most unfavorable difference for risk of stroke. The authors believed that this finding may not be limited to atenolol but may apply to other β-blockers. Based on these findings, β-blockers are no longer recommended as first-line agents unless the patient has a compelling indication for their use in a specific comorbid condition.

Combination Antihypertensive Therapy. A majority of patients will require two or more antihypertensive agents to achieve optimal blood pressure control.[35] More than 60% of patients enrolled in ALLHAT required two or more medications to control blood pressure.[36] Similarly, more than 50% of patients in the UK Prospective Diabetes Study (UKPDS) and Hypertension Optimal Treatment (HOT) trial required two or more medications to achieve their target blood pressure.[37,38] Therefore, achieving goal blood pressure in a timely manner may require combination antihypertensive therapy. Appropriately selected combination therapies act synergistically to produce greater reductions in blood pressure at lower doses.[39] In a meta-analysis of 354 clinical trials of hypertensive patients using thiazides, β-blockers, ACE inhibitors, CCBs, and ARBs, low-dose, combination antihypertensive therapy produced additive reductions in blood pressure.[40] The JNC-7 guidelines recommend initiating two antihypertensive agents for patients whose SBP is 20 mm Hg above their goal or whose DBP is 10 mm Hg above their goal.[16] In most cases, combination drug regimens should include a thiazide diuretic.

Evidence from previous clinical trials suggests that certain antihypertensive medication classes may have special benefits for patients with specific comorbidities. The JNC-7 guidelines list several comorbidities for which a compelling indication exists to select a specific class of antihypertensive medication. For patients with a compelling indication, recommendations for antihypertensive drug selection are provided (Table 2).[15] For most patients with a compelling indication, combination therapy with a thiazide diuretic and one or more recommended antihypertensive drugs will be required to achieve optimal blood pressure control.

While ALLHAT provided convincing evidence to support the initial use of a thiazide diuretic for the treatment of hypertension, it did not provide guidance regarding the most appropriate second-line choice for patients without a compelling indication. While many experts continue to debate the "best" antihypertensive regimen, a series of papers published by Staessen and colleagues[41–43] suggests that the characteristics of individual antihypertensive medications may be less important than simply lowering blood pressure. All antihypertensive medications can safely and effectively lower blood pressure. Therefore, the most appropriate second-line choice for patients without compelling indications should be based on patient-related variables, such as allergies, previous response, and adherence issues, as well as system-related variables, such as cost and availability.

Lifestyle Modifications. Recommended lifestyle strategies include weight loss for overweight patients, a heart-healthy diet, reduced sodium intake, limited alcohol consumption, increased physical activity, and cessation of tobacco use (Table 3). Strong evidence supports the use of these lifestyle-modification interventions to prevent and control high blood pressure. During an 18-month trial, 181 patients were randomly assigned to weight loss, dietary sodium reduction, or usual care.[44] Patients in the weight-loss group who lost 3.5 kg had a 5.8-mm Hg reduction in SBP compared with the usual-care group. Similarly, patients in the dietary-sodium-reduction group had a 3.3-mm Hg reduction in SBP compared with those receiving usual care. The effects of diet and sodium reduction on blood pressure were also evaluated in the Dietary Approaches to Stop Hypertension (DASH) study.[45,46] SBP was significantly reduced when the sodium

Table 2.
Compelling Indications for Individual Drug Classes[a]

	Recommended Drugs[c]					
Compelling Indication[b]	Diuretic	BB	ACEI	ARB	CCB	Aldo-ANT
Heart failure	X	X	X	X		X
Postmyocardial infarction		X	X			X
High coronary disease risk	X	X	X		X	
Diabetes mellitus	X	X	X	X	X	
Chronic kidney disease			X	X		
Recurrent stroke prevention	X		X			

[a]Reprinted from reference 15.
[b]Compelling indications for antihypertensive drugs are based on benefits from outcome studies or existing clinical guidelines; the compelling indication is managed in parallel with the blood pressure.
[c]BB = β-blocker, ACEI = angiotensin-converting-enzyme inhibitor, ARB = angiotensin-receptor blocker, CCB = calcium channel blocker, AldoANT = aldosterone antagonist.

Table 3.
Lifestyle Modifications to Control High Blood Pressure[a]

Modification	Recommendation
Weight reduction	Lose 5–10% of body weight if overweight or maintain normal body weight (body mass index, 18.5–24.9 kg/m^2).[43]
Heart healthy diet (DASH)[b]	Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat.[44,45]
Dietary sodium reduction	Reduce dietary sodium intake to no more than 100 mmol per day (2.4 g sodium or 6 g sodium chloride).[44–47]
Moderation of alcohol consumption	Limit consumption to no more than 2 drinks (e.g., 24 oz beer, 10 oz wine, or 3 oz 80-proof alcohol) per day in most men and no more than 1 drink per day in women and lighter-weight persons.[48]
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 minutes per day, most days of the week).[49]
Tobacco cessation	Strategies to address tobacco cessation should be instituted for all patients who use tobacco.[50]

[a]Adapted from reference 15.
[b]DASH = Dietary Approaches to Stop Hypertension.

content was reduced from a high to moderate level as well as from a moderate to low level. Further, patients who followed the DASH diet had a significantly lower SBP than did patients following the control diet. Hypertensive patients who followed the DASH diet and consumed low-sodium foods had an 11.5-mm Hg decrease in SBP compared with patients receiving the control diet and high-sodium foods.

Changes in physical activity and alcohol consumption have also been shown to affect blood pressure. In a meta-analysis of 54 randomized controlled trials, aerobic exercise significantly reduced SBP by 3.8 mm Hg and DBP by 2.5 mm Hg.[49] Areduction in alcohol consumption was also associated with significant reductions in SBP (–3.3 mm Hg) and DBP (–2.0 mm Hg) according to a meta-analysis of 15 trials.[48] Finally, for overall cardiovascular risk reduction, strategies to facilitate tobacco cessation should be instituted for all patients who use tobacco. Readers are referred to the Surgeon General's clinical practice guidelines for treating tobacco use and dependence.[50] A comprehensive lifestyle-modification approach was prospectively evaluated in a recent clinical trial involving 810 patients.[51] Patients who were randomized to receive the comprehensive lifestyle interventions had a significant reduction in SBP (–4.3 mm Hg) compared with patients who did not receive information regarding lifestyle changes. Collectively, data from these studies form the basis for the current recommendations for lifestyle modifications (Table 3). Clinicians should strive to initiate these strategies in all patients with hypertension and prehypertension.

Collaborative Systems of Care. Despite a wealth of information regarding the benefits of lifestyle modifications and the availability of many effective medications to control blood pressure, the majority of patients do not achieve optimal blood pressure control. Even patients who have access to health care and frequent physician contact often have poorly controlled blood pressure.[52] A recent survey of patients and physicians explored the barriers to controlling hypertension.[53] Results indicated that patient factors such as medication adherence, patient acceptance, and regimen complexity accounted for only 9% of the barriers to adequate antihypertensive therapy. The primary barrier to achieving optimal blood pressure control identified in this study was apparent physician satisfaction with the degree of blood pressure control achieved. In another study, antihypertensive medication was adjusted only 43% of the time when the patient's recorded SBP exceeded 165 mm Hg.[54] These data strongly suggest that poor blood pressure control is most frequently the result of clinical inertia and inadequate systems of care. In addition, the effectiveness of antihypertensive medications can be diminished by the concurrent use of other medications.[55] Recognizing and addressing potential drug–drug and drug–disease interactions may require reengineering the system of care.

Failure to initiate and adjust medication for the treatment of hypertension and to reinforce lifestyle modifications is common in clinical practice.[15] A number of approaches for overcoming clinical inertia and facilitating the optimal management of patients with hypertension have been evaluated. Paper-based and computerized decision-support systems that provide reminders to clinicians to adjust therapy when treatment goals have not been reached, order laboratory tests, and schedule follow-up appointments are one effective strategy.[56] System approaches implemented by managed care organizations to increase adherence to clinical practice guidelines, including chart audits with provider feedback, have achieved rates of optimal blood pressure control similar to the rates observed in clinical trials.[57] Multidisciplinary approaches to managing patients with hypertension have also been shown to improve the rate of optimal blood pressure control.[15] Nurses, pharmacists, dieticians, physician assistants, optometrists, and dentists can provide repetitive messages to patients that reinforce the need for medication and lifestyle changes to achieve optimal blood pressure control. Pharmacist- and nurse-managed hypertension clinics based in physician offices, managed care organizations, hospitals, and community pharmacies can contribute to better blood pressure control.[15,58] In addition, the advantages of self-monitoring beyond convenience include improved medication compliance and blood pressure control.[59] Lay community health workers improve outreach to underserved populations and augment efforts to screen, identify, refer, and educate patients.[60] Lastly, cultural differences between patients and health care practitioners can cause communication barriers and lead to misunderstandings, mistrust, and disparities in the delivery and outcomes of care.[61] Clinicians and health care systems must adopt strategies to become culturally proficient, actively exploring methods to identify and meet the needs of the communities they serve.

Summary

ASHP recognizes that a wealth of evidence supports the use of thiazide diuretics, either alone or in combination with other antihypertensive agents, as the initial pharmacologic treatment of hypertension in the majority of patients. Hypertension is a major cause of morbidity and mortality. The adverse health effects of hypertension can be minimized by achieving optimal blood pressure control. Unfortunately, blood pressure remains poorly controlled in millions of Americans. Numerous clinical trials have unequivocally demonstrated the benefits of treating hypertension with medications and lifestyle modifications. ASHP supports aggressive measures to identify, treat, and achieve optimal blood pressure control through the rational selection of antihypertensive medications, promotion of continuous lifestyle modification, and use of collaborative, systemwide strategies.

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