

CLINICAL STRATEGIES FOR OPTIMAL HYPERTENSION MANAGEMENT

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ABSTRACT

In the United States, approximately 25% of the adult population older than 40 years has hypertension. Americans have a 90% chance of developing hypertension during their lifetime, with the disease prevalence increasing sharply with the population's advancing age. Regardless of the stage at which hypertension is discovered, lifestyle modifications offer first-line treatment for most patients because they can effectively reduce cardiovascular risk and lower blood pressure, and may reduce the number and dosage of antihypertensive medications required by patients on drug therapy. Clinical implementation of the recommendations of the Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, along with public health approaches such as reducing calories, saturated fat, and salt and increasing physical activity, promote a downward shift in the population distribution of blood pressure trends and provide an important opportunity to interrupt and prevent the continuing costly cycle of managing hypertension and its complications. This article additionally reviews the principles of hypertension care in special patient populations. In particular, hypertension in patients with diabetes mellitus deserves special attention because of the associated increased risk for macrovascular and microvascular complications leading to the increased incidence of coronary events, blindness, and other devastating clinical outcomes.

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The prevalence of hypertension in a representative sample of patients from the National Health and Nutritional Examination Survey (NHANES III, phases 1 and 2) reveals that in the United States approximately 25% of the adult population older than age 40 years has hypertension. The prevalence of hypertension increases sharply with the population's advancing age, as illustrated by data from the Framingham Heart Study's long-term follow-up indicating that an American's lifetime risk of developing hypertension is 90%.^{1,2} Appropriate antihypertensive treatment can effectively reduce cardiovascular morbidity and mortality by approximately 25% among patients age 60 years and older who have hypertension.³

JNC-7 RECOMMENDATIONS FOR HYPERTENSION MANAGEMENT

Hypertension rarely produces clinical symptoms in its early stages, thus patients usually do not learn they have this potentially devastating condition unless it is identified during routine clinical screening. Therefore, clinicians must measure blood pressure at all health-care visits for all patients and must maintain a high level of clinical suspicion for hypertension among those patients with significant risk factors.

The recent release of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) offers a workable blueprint for improving hypertension detection and treatment in any practice setting. Several new features distinguish these recommendations from previous guidelines. Because these new features are described in detail elsewhere in this monograph, they are only summarized in this article. As in previous guidelines, lifestyle modifications comprise first-line treatment for hypertension for most patients in most cases. Thiazide-type diuretics, alone

or in combination with agents from other drug classes, now represent initial drug therapy for most patients. Certain high-risk conditions are identified as “compelling indications” for treatment with specific antihypertensive drug classes or combinations of agents. Based on the findings of several large population studies, clinicians recognized that most patients with hypertension require therapy with 2 or more antihypertensive agents to achieve blood pressure targets. The Figure shows a treatment algorithm from the JNC-7 guidelines that incorporates these new recommendations and key messages for comprehensive treatment of primary hypertension.⁴

The JNC-7 recommendations focus on increased cardiovascular risk because of hypertension and emphasize effective ways to achieve target blood pressure in patients with hypertension as a means of reducing cardiovascular disease among Americans. The increased risk of cardiovascular death associated with systolic and diastolic hypertension has been demonstrated in several large population studies, including the Multiple Risk Factor Intervention Trial (MRFIT), which evaluated cardiac disease and other health outcomes in some 350 000 men screened from 1973 to 1975.^{5,6} The result is an enormously powerful database that allows a close look at the relationship of systolic blood pressure (SBP) and diastolic blood pressure (DBP), independently, to coronary heart disease (CHD) mortality risk.

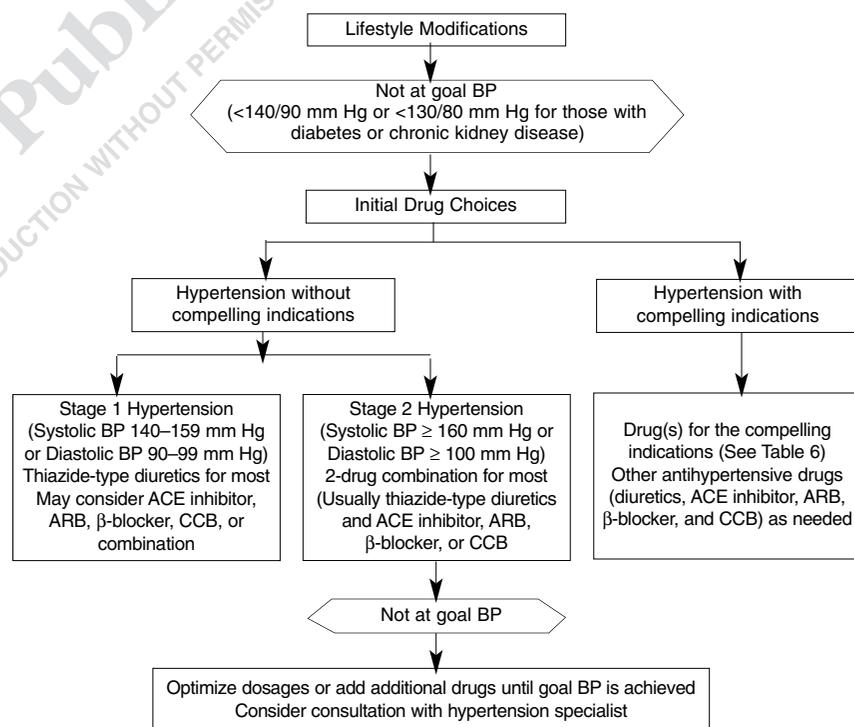
Overall, there were 7150 deaths caused by CHD during 11.6 years of follow-up in MRFIT. As compared to the subjects in the bottom decile of blood pressure distribution (SBP <112; DBP <71), those patients in the top decile (SBP ≥151; DBP ≥98) were at a significantly increased risk for death from CHD. The relationship of rising blood pressure to cardiovascular risk was continuous and graded and was steeper for SBP versus DBP. Average blood pressure levels of the MRFIT cohort were SBP 130 mm Hg and DBP 84 mm Hg. Optimal

SBP (the level with the lowest death rate) was less than 120 mm Hg.

LIFESTYLE MODIFICATIONS: PREVENTING AND MANAGING HYPERTENSION

Lifestyle modifications can effectively reduce cardiovascular risk and lower blood pressure, may reduce the number and dosage of antihypertensive medications required by patients on drug therapy, and can prevent or delay the onset of hypertension in some patients with risk factors for the disease. Therefore, the adoption of healthy lifestyles by children and adults is an indispensable part of the management and prevention of hypertension.⁴ When clinicians instruct patients about lifestyle modification, they must emphasize that a healthy lifestyle is a key element in

Figure. Algorithm for Treatment of Hypertension



ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BP = blood pressure; CCB = calcium channel blocker.

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hypertension management in patients treated with or without drug therapy (Figure; Table).^{4, 7-14}

PHARMACOTHERAPY

INITIAL COMBINATION THERAPY

The JNC-7 recommendations also acknowledge evidence from clinical trials, such as the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), which demonstrate that most patients with hypertension require at least 2 antihypertensive drugs to reach target blood pressure levels.^{3,15-21} The addition of a second antihypertensive agent with a different mechanism of action should be initiated when adequate doses of an initial agent fail to achieve target blood pressure goals. Furthermore, combination therapy should be considered as initial therapy for patients who are more than 20 mm Hg above their SBP target and more than 10 mm Hg above their DPB target; one agent should be a thiazide-type diuretic unless otherwise indicated.^{4,15}

TREATMENT OF PATIENTS WITH CONCOMITANT RISK FACTORS

THE METABOLIC SYNDROME AND TYPE 2 DIABETES MELLITUS

Patients who are overweight and exhibit hypertension, dyslipidemia, and decreased insulin sensitivity, characteristic of the metabolic syndrome, are at a significantly increased risk for complications related to hypertension. These patients sustain 2- to 3-fold increases in CHD, stroke, and chronic kidney disease incidence, and 4- to 5-fold increases in cardiovascular mortality compared to control populations.²²⁻²⁴ Therefore, patients with the metabolic syndrome have a high probability of requiring treatment with multiple agents and specific treatment combinations, as described in JNC 7.

Type 2 diabetes mellitus is one of the risk factors for heart disease that comprise the metabolic syndrome. Although aggressive attention to all cardiovascular risk factors is important, hypertension in patients with diabetes mellitus deserves special attention because of the increased associated risk for diabetic macrovascular and microvascular compli-

cations that lead to an increased risk of coronary events.²⁵ Many studies of different antihypertensive agents have been performed in patients with diabetes mellitus, and extensive data regarding the role of calcium channel blocking agents, β -blocking agents, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) now exist.

The primary care clinician is in an ideal position to address concerns associated with hypertension and its treatment in patients with diabetes mellitus before the onset of nephropathy and other diabetic microvascular complications. Thiazide diuretics play an important role overall in the first-line therapy of patients with hypertension who are at risk for coronary disease. In patients with diabetes mellitus, ACE inhibitors are the cornerstone of antihypertensive pharmacotherapy. In patients who do not tolerate ACE inhibitors, the substitution of an ARB is an alternative. An ARB is less likely to be associated with a cough or some other adverse effect as compared to an ACE inhibitor.

Table. Lifestyle Modifications to Prevent and Manage Hypertension

Modification	Recommendation	Approximate Systolic BP Reduction, Range
Weight reduction	Maintain normal body weight (BMI, 18.5–24.9)	5–20 mm Hg/10-kg weight loss ^{7,8}
Adopt DASH eating plan	Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat	8–14 mm Hg ^{2,10}
Dietary sodium reduction	Reduce dietary sodium intake to no more than 100 mEq/L (2.4 g sodium or 6 g sodium chloride)	2–8 mm Hg ^{9,11}
Physical activity	Engage in regular aerobic physical activity, such as brisk walking (at least 30 minutes per day, most days of the week)	4–9 mm Hg ^{12,13}
Moderation of alcohol consumption	Limit consumption to no more than 2 drinks per day (1 oz or 30 mL ethanol [eg, 24-oz beer, 10-oz wine, or 3-oz 80-proof whiskey]) in most men and no more than 1 drink per day in women and lighter-weight persons	2–4 mm Hg ⁴

BMI = body mass index; BP = blood pressure; DASH = Dietary Approaches to Stop Hypertension.

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Lifestyle modifications are warranted in all patients with diabetes mellitus because they provide myriad benefits regarding other clinical disorders associated with the metabolic syndrome.

Appropriate medical therapy of hypertension in patients with diabetes mellitus can alter disease progression significantly. Therefore, the careful gathering of family history, examination, and laboratory analysis is of the utmost importance to the early identification of patients at risk, and close follow-up to ensure compliance and effective treatment is warranted. A patient's lack of response to medical therapy or signs of end-organ damage, such as left ventricular hypertrophy, nephropathy, or coronary disease, suggest that specialty consultation should be considered.

CORONARY ARTERY DISEASE

Findings from the recent Comparison of Amlodipine versus Enalapril to Limit Occurrences of Thrombosis trial demonstrate that patients with coronary artery disease and normal baseline blood pressure measurements (SBP approximately 130 mm Hg; DBP <100 mm Hg) benefited further from the addition of amlodipine or enalapril to their therapy. The 2 patient groups were evaluated regarding the incidence of cardiovascular death, nonfatal myocardial infarction, resuscitated cardiac arrest, coronary revascularization, hospitalization for angina pectoris, hospitalization for congestive heart failure, fatal or nonfatal stroke or transient ischemic attack, and a new diagnosis of peripheral vascular disease. Amlodipine showed a higher reduction in subsequent cardiac events than enalapril; the drug may also produce a slower progression of atherosclerosis (as evaluated through intravascular ultrasound) than would the addition of enalapril. Based on these findings, the optimal target SBP in patients with coronary artery disease should be less than 130 mm Hg.^{26,27}

ADVANCED AGE

More than 66% of Americans older than 65 years of age have hypertension. Significantly, older Americans also have the lowest rates of blood pressure control of any age group.⁴ Treatment of older patients (including those patients with isolated systolic hypertension) should follow the same principles as outlined for the general care of hypertension. Lower initial drug doses may be necessary to avoid medication adverse effects, and multiple drugs may be needed to reach blood pressure targets in older patients.

Fortunately, nonpharmacologic interventions for hypertension offer safe, effective treatment in older patients. In a clinical trial of lifestyle modification involving 875 men and women aged 60 to 80 years, the restriction of salt by 2 g daily combined with weight reduction significantly decreased the need for antihypertensive medications in 50% of the subject group and completely eliminated the need for antihypertensive agents in 40% of all study participants.²⁸

MINORITY POPULATIONS

Of all ethnic groups, hypertension control rates are lowest among patients of Mexican and Native-American heritage.⁴ The prevalence and severity of hypertension are increased among African Americans, who also often demonstrate somewhat reduced responses to monotherapy with β blockers, ACE inhibitors, or ARBs versus diuretics or calcium channel blockers. However, these differences in treatment response are largely eliminated by combination therapy that includes adequate doses of diuretic agents.⁴

RENAL DISEASE

Considerable data have suggested a positive association between ACE inhibitor therapy and renal protection. Results of a recent meta-analysis of 11 trials involving 1860 patients with nondiabetic renal disease demonstrate that antihypertensive regimens, including ACE inhibitors, are more effective than other regimens in slowing the progression of nondiabetic renal disease in patients with hypertension.²⁹ In this analysis, patients assigned to receive treatment with ACE inhibitors demonstrated a mean decrease in urinary protein excretion that was 0.46 g/day greater than that among control groups (95% confidence interval [CI], 0.33–0.59 g/day). Furthermore, as compared with control groups, the relative risk for end-stage renal disease among patients treated with ACE inhibitors was 0.69 (95% CI, 0.51–0.94).

STROKE

The ALLHAT investigation did not demonstrate a difference in the primary study endpoints of myocardial infarction and fatal CHD or in mortality, despite significantly improved blood pressure control among patients treated with chlorthalidone as compared to patients receiving lisinopril (an ACE inhibitor).¹⁵ However, statistically there were significant differences in secondary outcomes, including stroke incidence. In

particular, treatment with chlorthalidone reduced the stroke rate by 15% in the overall study population and was associated with a mean improvement of SBP of 4 mm Hg. However, the increased stroke incidence of 15% for all study participants treated with an ACE inhibitor versus a diuretic was dramatically affected by the inclusion of African-American patients, who experienced a 40% greater stroke event-rate during treatment with ACE inhibitors. Significantly, when African Americans were exempted from the analysis, no difference was noted in the stroke event-rate among patients treated with these 2 classes of antihypertensive agents. Chlorthalidone was significantly better at reducing heart failure than lisinopril or amlodipine. The key message from ALLHAT is that blood pressure control is most important. Many patients who receive an ACE inhibitor or an ARB will require a low dose of a diuretic to achieve their desired blood pressure. The use of an ACE inhibitor or ARB is associated with a lower risk of patients developing diabetes mellitus in the future.

The Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial is a prospective, multinational, double-blind, randomized, controlled clinical trial evaluating cardiovascular outcomes in high-risk patients with hypertension who are receiving valsartan versus amlodipine, both with or without the addition of hydrochlorothiazide.³⁰ The VALUE trial enrolled more than 15 000 participants and is one of the largest trials investigating whether various antihypertensive agents have differing effects on cardiovascular outcomes.³¹ The study evaluated the hypothesis that among patients with hypertension who are at high risk for cardiovascular events and are receiving equivalent levels of hypertension control, the ARB valsartan would be superior to the calcium channel blocker amlodipine in reducing cardiovascular morbidity and mortality. At the conclusion of the trial, no difference was noted between the groups receiving valsartan or amlodipine regarding the main outcome of cardiac disease (a composite of cardiac mortality and morbidity). However, during the early phases of the trial, amlodipine treatment lowered blood pressure quicker and more effectively than the valsartan regimen.

In a period of 0 to 3 months, patients' SBP was 4 mm Hg lower with amlodipine compared to valsartan. This blood pressure differential was associated with a stroke event-rate that was lower among patients treated with amlodipine, although this intergroup difference was undetectable 6 months into the trial.

However, the disparity in blood pressure control in the comparator groups in the VALUE trial makes it difficult to interpret the study results. Unequal blood pressure reductions likely account for the reduced incidence of myocardial infarction and stroke seen in patients receiving amlodipine, particularly early in the study when these differences were greatest. In addition, a dramatic decrease in the risk for new-onset diabetes noted in the high-risk patients receiving valsartan suggests that the drug's benefits extend beyond control. Overall, these findings emphasize the importance of prompt, effective control in patients at high risk for stroke and other cardiovascular events associated with inadequately controlled hypertension.

CONCLUSIONS

Regardless of the stage at which hypertension is discovered, lifestyle modifications comprise first-line treatment for most patients, can effectively reduce cardiovascular risks and lower blood pressure, and may reduce the number and dosage of antihypertensive medications required by patients on drug therapy. Public health approaches (eg, reducing calories, saturated fat, and salt in processed foods and increasing community and school opportunities for physical activity) can achieve a downward shift in the population distribution of blood pressure trends, thus potentially reducing morbidity, mortality, and the lifetime risk of hypertension. These public health measures offer an attractive opportunity to interrupt and prevent the continuing costly cycle of managing hypertension and its complications. Hypertension in patients with diabetes mellitus deserves special care because of the associated increased risk for diabetic macrovascular and microvascular complications that lead to increased risk of coronary events, blindness, and other devastating clinical outcomes.

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