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TEACHERS' TOPICS

Hypertension: A Clinical Pharmacist's Synopsis of JNC 7

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Hypertension affects more than 50 million Americans. The National High Blood Pressure Education Program recently presented the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7). This report provided information to clinicians regarding the prevention and management of hypertension. The key messages of the JNC 7 Report will be conveyed in this paper. The purpose of this paper is to review the significant findings of the JNC 7 Report as well as other clinical trials in order to help pharmacy practitioners incorporate current literature into clinical practice. This paper can be used as a teaching tool to assist the instructor in presenting an overview of hypertension management. It can also be used to educate pharmacy students on the usefulness of medical literature.

Keywords: hypertension, blood pressure, drug therapy

INTRODUCTION

Despite its high prevalence, hypertension is not well controlled in the United States. According to the latest update of the National Health and Nutrition Examination Survey, NHANES III, 20% of participants aged 18 to 74 years suffered from hypertension, which is defined as having a mean systolic blood pressure (SBP) ≥ 140 mm Hg, having a mean diastolic blood pressure (DBP) ≥ 90 mm Hg, or being prescribed medication for hypertension. Of these, 30% were previously unaware of their hypertension, 18% were aware of their condition but their disease was neither treated nor controlled, 27% were being treated but their disease was not under control, and only 25% were both being treated and had their disease controlled.[1] Undiagnosed, untreated, and uncontrolled hypertension clearly places a substantial strain on the health care delivery system.[2]

It is our role as pharmacy practitioners to assist in the management of hypertension, in an effort to decrease the prevalence of undiagnosed, untreated, and uncontrolled hypertension. As pharmacists, we have the knowledge and expertise to assist health care providers in ensuring that patients are receiving the appropriate antihypertensive agent based on their medical history, response to existing or previous therapy, adverse drug reactions, and current medical literature.

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Etiology

There are 2 types of hypertension: essential and secondary. More than 90% of patients have essential hypertension.[3] It is described as high blood pressure (BP) with no identifiable cause. In contrast, secondary hypertension has an identifiable cause. Fewer than 5% of people who suffer from high blood pressure have secondary hypertension.[4] The causes of secondary hypertension can include but are not limited to renal disease, coarctation of the aorta, primary aldosteronism, Cushing's syndrome, pheochromocytoma, pregnancy, hyper- or hypothyroidism, and hyperparathyroidism. Secondary hypertension can also be drug-induced. Some medications that induce hypertension are estrogens, glucocorticoids, nonsteroidal anti-inflammatory agents, oral contraceptives, tricyclic antidepressants, venlafaxine, and oral decongestants. When a secondary cause is identified, treatment should be directed at removing the offending agent or treating the underlying condition.[4]

Clinical Presentation and Diagnosis

Typically, patients with essential hypertension are asymptomatic. Usually, the only sign of primary hypertension is an elevated blood pressure. Patients with secondary hypertension tend to complain of symptoms suggestive of the underlying condition. The diagnosis of hypertension should not be based on one elevated BP measurement. The average of 2 or more readings, taken at 2 or more visits after the initial screening, should be used to diagnose hypertension.[2] There are 3 methods of measuring blood pressure: in-office setting, ambulatory blood pressure monitoring (ABPM), and self-measure-

Table 1. Clinical Situations in Which Ambulatory Blood Pressure Monitoring May Be Helpful

- Suspected white-coat hypertension in patients with hypertension and no target organ disease
- Apparent drug resistance (office resistance)
- Hypotensive symptoms with antihypertensive medication
- Episodic hypertension
- Autonomic dysfunction

Adapted with permission from Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension*. 2003;42:1206-52.[2]

ment. The ausculatory method of blood pressure measurement should be used in an office setting. The person should be seated quietly for at least 5 minutes in a chair, their feet on the floor, and their arm supported at heart level. Caffeine, exercise, and smoking should be avoided for at least 30 minutes prior to measurement. An appropriately sized cuff (cuff bladder encircling at least 80% of the arm) should be used to ensure accuracy. Approximately 20% to 35% of patients experience blood pressures that are higher in a doctor's office than at home.[5] This phenomenon is termed "white coat" hypertension. Patients with suspected white coat hypertension should be prompted to self-measure their BP. ABPM provides multiple BP readings over a 24-hour period during the patient's daily activities and sleep.[6] Indications for the use of ABPM are listed in Table 1. Self-measurement of BP at home and work is used to assess differences between in-office and out-of-office BP, prior to considering ambulatory monitoring. For those whose out-of-office blood pressures are consistently ≤130/80 mm Hg despite an elevated office BP, and who lack evidence of target organ disease, 24-hour monitoring or drug therapy can be avoided. Self-measurement or ambulatory monitoring may be particularly helpful in assessing BP in smokers. Smoking raises BP acutely; however, BP returns to baseline approximately 15 minutes after stopping.

Routine laboratory tests that are recommended before initiating therapy include hemoglobin and hematocrit, urinalysis, serum potassium, calcium and creatinine, liver function tests, electrocardiogram, lipid profile (including high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides), plasma glucose, and serum uric acid.

There are a number of examinations that can reveal additional information regarding the progression of elevated blood pressure. A fundoscopic examination may reveal arteriolar narrowing indicative of increased peripheral vascular resistance and/or arteriovenous nicking. Retinal hemorrhages and infarcts reflect vasculitis secondary to high arterial blood pressure. Papilledema in hypertensive patients suggest a malignant stage of hypertension requiring rapid treatment. Auscultation of the heart may identify an accentuated second heart sound created by a high intra-aortic diastolic pressure.[4]

Table 2. Changes in Blood Pressure Classification in JNC7

JNC 6 Category	Blood Pressure	JNC 7 Category
Optimal	<120/80	Normal
Normal	120-129/80-84	Prehypertension
Borderline	≥130-139/85-89	Prehypertension
Hypertension	140/90	Hypertension
Stage 1	140-159/90-99	Stage 1
Stage 2	160-179/100-109	Stage 2
Stage 3	≥180/110	Stage 2

JNC 6= Sixth Report of the Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; JNC 7=Seventh Report of the JNC; SBP=systolic blood pressure; DBP= diastolic blood pressure.
Adapted with permission from Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension*. 2003; 42:1206-52.[2]

Development of JNC 7

The decision to appoint a committee for JNC 7 was based on 4 factors:

- Publication of many new hypertension observational studies and clinical trials since the last report was published in 1997;
- Need for new clear and concise guidelines that would be useful for clinicians;
- Need to simplify the classification of BP; and
- Clear recognition that JNC reports were not used to their maximum benefit.

Comparison of JNC 6 and JNC 7

In JNC 6, high normal BP was considered 130–139/85–90 mm Hg and drug therapy was indicated if the patient had target organ damage/clinical cardiovascular disease and/or diabetes (Table 2). In contrast, JNC 7 classifies 120–139/80–89 BP as prehypertensive (Table 2). Patients classified as prehypertensive are encouraged to institute lifestyle modifications. Currently, no drug therapy is required in prehypertension unless the patient has compelling indications as defined by JNC 7 (Table 3).

JNC 6 recommended a trial of lifestyle modifications for ≤ 12 months for Risk Group A or ≤ 6 months for Risk Group B depending on the risk factors prior to drug therapy in patients with Stage 1 hypertension (140–149/90–99 mm Hg). Drug therapy was not initiated in Stage 1 hypertension unless target organ damage or clinical cardiovas-

Table 3. Blood Pressure Classification in Adults (JNC 7)

BP Classification	SBP* mm Hg	DBP mm Hg	Lifestyle modification	Initial Drug Therapy: Without Compelling Indication	Initial Drug Therapy: With Compelling Indication†
Normal	< 120	and <80	Encourage	No antihypertensive drug indicated	Drug(s) for compelling indications‡
Prehypertension	120-139	or 80-89	Yes		
Stage 1 Hypertension	140-159	or 90-99	Yes	Thiazide-type diuretics for most. May consider ACEI, ARB, BB, CCB, or combinations	Drugs(s) for the compelling indications. Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed.
Stage 2 Hypertension	≥160	or ≤100	Yes	Two-drug combination for most (usually thiazide-type diuretic and ACEI or ARB, or BB, or CCB)	

*Treatment determined by highest BP category

†Initial combined therapy should be used cautiously in those at risk for orthostatic hypotension

‡Treat patients with chronic kidney disease or diabetes to BP goal of <130/80 mm Hg

JNC 7= Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, ß-blocker; CCB, calcium channel blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table 4. Blood Pressure Classification in Adults (JNC 6)

Stage of Hypertension	Risk Group A	Risk Group B	Risk Group C
	No risk factors[8]	At least one risk factor	TOD/CCD and or diabetes, with or without other risk factors
	No TOD/CCD	No diabetes, TOD/CCD	
High normal BP (130-139/85-89 mm Hg)	Lifestyle modifications†	Lifestyle modifications	Drug therapy‡/LM
Stage 1 (140-159/90-99 mm Hg)	Lifestyle modifications (≤ 12 mo)	Lifestyle modification (≤ 6 mo)	Drug therapy/LM
Stage 2 (160-179/100-109 mm Hg)	Drug therapy/LM	Drug therapy/LM	Drug therapy/LM
Stage 3 (≥180/≥110 mm Hg)	Drug therapy/LM	Drug therapy/LM	Drug therapy/LM

* Major risk factors include smoking, dyslipidemia, diabetes mellitus, age > 60 yr, men and postmenopausal women, family history of cardiovascular disease (women <65 yr, men< 55 yr)

† For patients with heart failure or renal insufficiency, or those with diabetes

‡ For patients with multiple risk factors, consider drug therapy as initial therapy

JNC 6=Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; TOD/CCD= target organ damage/clinical cardiovascular disease includes heart diseases (left ventricular hypertrophy, angina, prior myocardial infarction, poor revascularization, heart failure), stroke or transient ischemic attack, nephropathy, peripheral arterial disease, LM- lifestyle modification

Adapted from Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[59]

cular disease and/or diabetes were present. Initiation of drug therapy was recommended in all patients with Stage 2 hypertension (Table 4). JNC 7 recommends initiation of drug therapy in addition to lifestyle modifications in Stage 1 hypertension and initiation of 2 drugs in combination in Stage 2 hypertension (Table 3). The seventh report of the JNC emphasizes that the risk of cardiovascular disease, beginning at 115/75 mm Hg, doubles with each increment of 20/10 mm Hg. Observational studies involving more than 1 million individuals have indicated that death from both ischemic heart disease and stroke increased progressively and linearly from BP levels as low as 115/75 mm Hg.[7] For every 20 mm Hg systolic or 10 mm Hg diastolic increase in blood pressure, there is a doubling of mortality from both ischemic heart disease and stroke.[2] The Framingham Heart Study investigators reported the lifetime risk of hypertension to be approximately 90% for men and women who were nonhypertensive at 55 or 65

years old and survived to age 80 to 85 years.[8] JNC 7 also emphasizes that in persons older than 50 years, systolic blood pressure (SBP) greater than 140 mm Hg is a much more important cardiovascular disease (CVD) risk factor than diastolic blood pressure (DBP).[2]

Lifestyle Modifications

The impact of a healthy lifestyle has shown promise in enhancing the effectiveness of blood pressure management. Major lifestyle modifications are important in lowering blood pressure, improving drug therapy efficacy, and reducing cardiovascular risk. JNC 7 identified several approaches to modifying lifestyle habits. Recommendations include weight reduction, adopting the Dietary Approaches to Stop Hypertension (DASH) eating plan, dietary sodium reduction, engaging in physical activity, and limiting alcohol consumption.

Excess weight has been linked to the development of several comorbidities such as heart disease, diabetes, and hypertension. Body mass index (BMI) and waist circumference provides useful information to evaluate body weight. Both measurements have been useful in identifying obesity and people at high risk for health problems. BMI is a measurement that evaluates weight and height to gauge total body fat. When the BMI is 24 or less, a person is considered to have a healthy weight. A BMI of 25–29.9 is considered overweight and above 30 is obese. An enlarged waist circumference or abdominal obesity is regarded as 40-inches or greater in men and 35-inches or greater in women, according to the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).[9] Weight loss (approximately 10 lbs) reduces blood pressure or averts hypertension in overweight persons.[2]

The DASH diet includes low-fat dairy products, with a reduction in saturated fat, total fat, and cholesterol, combined with a higher content of rich fruits and vegetables. The DASH dietary pattern lowers blood pressure and, with widespread use, could reduce the number of cardiovascular events due to hypertension.[10] As people age, sodium intake plays a more important role in the development of high blood pressure. Blood pressure normally increases with age, and age-related increases in blood pressure can cause renal impairment and subsequent heightened sensitivity of blood pressure to salt ingestion. In individuals with normal blood pressure, salt restriction will result in only a small (approximately 2 mm Hg) blood pressure reduction, whereas in hypertensive individuals, salt restriction can result in reductions in systolic pressure as large as 11 mm Hg, such as those observed in the DASH study.[11] Dietary sodium should be restricted to no more than 2.4 g per day; equivalent to approximately 1 teaspoonful. Patients who adhere to the recommended amounts of sodium intake should expect systolic blood pressure reductions of 2 to 8 mm Hg.[12]

Regular physical activity reduces systolic blood pressure by approximately 4 to 9 mm Hg.[12] The overall population is encouraged to engage in at least 30-minutes of exercise 5 to 6 days a week. An exercise program may include activities such as walking, running, cycling, and aerobics.

Other approaches to lowering blood pressure include limiting alcohol consumption, reducing caffeine intake, and avoiding tobacco. Moderate to heavy alcohol intake increases the incidence of hypertension.[13] The JNC 7 Report recommends no more than 2 drinks per day (1-oz or 30-ml ethanol) for most men and no more than 1 drink per day for women and men of lighter weight.[12] Caffeine in increased amounts is thought to affect blood pressure and patients should be advised to limit intake. Increased amounts of caffeine consumption may elevate blood pressure and increase the possible risk of stroke.[14] Cigarette smoking causes an acute elevation in blood pressure, thus increasing the incidence of stroke. Tobacco avoidance can help minimize that risk and lower blood pressure.[15] Hypertensive patients who do smoke or consume caffeine regularly should avoid doing so for at least 2 hours prior to blood pressure measurement so that an accurate baseline reading can be obtained.[16]

Ample evidence supports the beneficial effects of a healthy lifestyle in the prevention and management of hypertension. Lifestyle modifications can help decrease blood pressure and enhance the overall efficacy of antihypertensive therapy.

Drug Therapy

Several clinical trials evaluating blood pressure lowering have proven that better clinical outcomes are achieved when more than one class of antihypertensive medications with different mechanisms of action are administered in combination.[17] Many patients require multiple medications, including a diuretic, aldosterone receptor antagonist, ß-blocker, angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor blocker (ARB), calcium channel blocker (CCBs), central alpha-adrenergic agonist, or alpha-adrenergic blocker to effectively control blood pressure and reduce complications.[18]

Diuretics

There are 4 types of diuretics: carbonic anhydrase inhibitors, thiazide diuretics, loop diuretics, and potassium-sparing diuretics; the latter 3 have demonstrated antihypertensive effects (Table 5). The early effect of diuret-

Table 5. Diuretics

	Drug	Trade Name(s)	Usual Total Dose Range, mg/day (Doses/day)
Thiazide and Thiazide-like			
	Chlorthalidone*	Hygroton	12.5-50 (1)
	Hydrochlorothiazide*	Hydrodiuril, Microzide, Esidrix	12.5-50 (1)
	Chlorothiazide	Diuril	125-500 (1)
	Indapamide	Lozol	1.25-5 (1)
	Metolazone	Zaroxolyn	2.5-5 (1)
		Mykrox	0.5-1.0 (1)
Loop			
	Bumetanide*	Bumex	0.5-4 (2-3)
	Ethacrynic acid	Edecrin	25-100 (2-3)
	Furosemide*	Lasix	40-240 (2-3)
	Torsemide	Demadex	5-100 (1-2)
Potassium-sparing agents			
	Amiloride*	Midamor	5-10 (1)
	Triamterene*	Dyrenium	25-100 (1)

*Generic product available
Adapted from Chobanian et al[2] and Brenner et al[55]

Table 6. Aldosterone Receptor Antagonists

Drug	Trade Name	Usual Total Dose Range, mg/day (Doses/day)
Spironolactone*	Aldactone	25-100 (1)
Eplerenone	Inspra	50-100 (1-2)

*Generic product available
Adapted from Chobanian et al[2] and Brenner et al[55]

ic therapy is related to sodium diuresis and volume depletion; peripheral vascular resistance reduction has been observed with long-term use.[19] Thiazide diuretics, the most effective treatment for hypertension, prevent cardiovascular complications, and reduce morbidity and mortality.[17] However, electrolyte abnormalities such as hyponatremia, hypokalemia, hyperglycemia, hyperuricemia, and lipid abnormalities have been observed in patients taking thiazide diuretics. Low-dose therapy can help to minimize the risks; however, close laboratory monitoring remains paramount. Loop diuretics are potent agents that produce more diuresis than thiazides. They are generally reserved to treat patients with renal insufficiency (creatinine clearance < 30 ml/min). Potassium-sparing diuretics provide an additional hypotensive effect when used in combination with loop and thiazide diuretics. They are also beneficial in preventing or correcting hypokalemia. Therapy is typically initiated at a low dose and titrated as necessary. Potassium levels should be monitored at frequent intervals. Thiazide diuretics are generally well tolerated and should be used as initial treatment for patients with uncomplicated hypertension.

Large-scale clinical trials have shown a decrease in mortality with diuretics alone and in combination with other classes of antihypertensive medications.[17,20] The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) demonstrated that thiazide diuretic (chlorthalidone) is superior to the calcium channel blocker, amlodipine (increased risk of heart failure), the angiotensin-converting enzyme-inhibitor, lisinopril (higher risk of stroke, heart failure, and angina), and the alpha-adrenergic blocker, doxazosin (higher rate of heart failure and cardiovascular disease) at preventing cardiovascular events.[17] Thiazide diuretics reduce the incidence of stroke and cardiovascular events in elderly patients with isolated systolic hypertension.[21] Most ongoing trials use thiazide diuretics as the initial drug of choice for hypertension treatment.

Aldosterone Receptor Antagonists

Aldosterone is a component of the renin-angiotensin-aldosterone system (RAAS). Angiotensin II, a potent vasoconstrictor, is a stimulator of aldosterone secretion. Inhibition of aldosterone leads to an increased excretion of sodium chloride and water, and a decreased excretion of potassium.[22] These agents can be used as monotherapy or in conjunction with other antihypertensive medications to reduce blood pressure (Table 6). They are also useful in treating patients with heart failure or myocardial

Table 7. β-blockers

	Drug	Trade Name	Usual Total Dose Range, mg/day (Doses/day)
Cardioselective (Beta-1 Blocking Activity)			
	Acebutolol†	Sectral	200-800 (1)
	Atenolol*	Tenormin	25-100 (1-2)
	Betaxolol	Kerlone	5-20 (1)
	Bisoprolol	Zebeta	2.5-10 (1)
	Metoprolol*	Lopressor	50-300 (2)
		Toprol-XL	50-300 (1)
Nonselective			
	Nadolol*	Corgard	40-320 (1)
	Penbutolol†	Levatol	10-20 (1)
	Pindolol*†	Visken	10-60 (2)
	Propranolol*	Inderal	40-480 (2)
		Inderal LA	40-480 (1)
	Timolol*	Blocadren	20-60 (2)
Alpha-β-blockers			
	Carvedilol	Coreg	12.5-50 (2)
	Labetalol*	Normodyne, Trandate	200-1,200 (2)

*Generic product available
†Intrinsic Sympathomimetic Activity (ISA)
Adapted from Chobanian et al[2] and Brenner et al[55]

infarction (MI). Gynecomastia and hyperkalemia are common adverse effects.

ß-blockers

Several mechanisms have been presented to explain the hypotensive effect of ß-blockers. Beta blockers reduce cardiac output through negative inotropic and chronotropic effects on the heart, decrease cardiac contractility, lower heart rate, reduce central release of adrenergic substances, inhibit peripheral epinephrine release, decrease renin release, diminish sympathetic reflex in response to exercise, and lower arterial pressure.[19,23,24] According to JNC 7, ß-blockers are indicated for high-risk conditions such as heart failure, postmyocardial infarction, and diabetes, and for patients at increased risk for cardiovascular disease.[2,24]

There are 3 types of ß-blockers: nonselective, cardioselective, and intrinsic sympathomimetic activity (ISA). Each demonstrate different properties (Table 7). Beta-1 receptors are primarily found in the heart, while beta-2 receptors are found in the kidneys, lungs, and peripheral arteriolar endothelium.[24] Nonselective ß-blockers respond to inhibitory activity at both beta-1 and beta-2 receptors. Cardioselective ß-blockers demonstrate beta-1 blocking activity at low doses. At higher doses, selectivity for beta-1 adrenergic receptors is diminished. Cardioselective ß-blockers are beneficial in patients with bronchospasm and diabetes. ß-blockers with ISA properties are nonselective drugs with partial agonist activity.[19] They can lower blood pressure with less effect on resting heart rate and are preferred for patients who develop symptomatic bradycardia or postural hypotension with other ß-blockers.[25]

The degree of lipophilicity should be considered in patients with renal impairment or hepatic dysfunction. ß-blockers that are more lipophilic (eg, propranolol, penbutolol, and metoprolol) will undergo extensive hepatic metabolism. Patients with liver problems may require dose adjustments. These agents penetrate the blood-brain barrier well; thus, they would be suitable for patients with migraine headaches. Less lipophilic agents (eg, atenolol, bisoprolol) are eliminated primarily through the kidneys.[3,24] Dose adjustments are necessary in patients with renal dysfunction.

Combination blockers that have selectivity for alpha-1, beta-1, and beta-2 adrenergic receptors are called α-ß-blockers. These agents lower arterial blood pressure by a mechanism similar to ß-blockers and reduce peripheral vascular resistance.[3] Common adverse effects of ß-blockers include: fatigue, insomnia, bradycardia, depression, sexual dysfunction, nightmares, decreased exercise tolerance, bronchospasm, and dyslipidemia. Generally, ß-blockers are well tolerated and suitable for most patients.

Table 8. ACE inhibitors

Drug	Trade Name(s)	Usual Total Dose Range, mg/day (Doses/day)
Benazepril	Lotensin	5-40 (1-2)
Captopril*	Capoten	25-150 (2-3)
Fosinopril	Monopril	10-40 (1-2)
Lisinopril	Prinivil, Zestril	5-40 (1)
Moexipril	Univasc	7.5-15 (2)
Quinapril	Accupril	5-80 (1-2)
Ramipril	Altace	1.25-20 (1-2)
Trandolapril	Mavik	1-4 (1)

*Generic product available
Adapted from Chobanian et al[2] and Brenner et al[55]

Angiotensin-Converting Enzyme (ACE) Inhibitors

ACE inhibitors lower blood pressure by inhibiting the angiotensin-converting enzyme that converts angiotensin I to angiotensin II, thereby producing vasodilation. They also hinder the degradation of bradykinin and decrease aldosterone secretion. ACE inhibitors cause a reduction in angiotensin II mediated intraglomerular pressure that retards the progression of renal disease, decreases proteinuria, and stabilizes renal function.[3] These agents are favorable for hypertensive diabetics, especially those patients that exhibit evidence of microalbuminuria (Table 8).[24] Patients with high renin levels often respond favorably to ACE inhibitor therapy, although patients with lower renin levels (more common in African Americans) may have partial response.[24]

The Heart Outcome Prevention Evaluation (HOPE) Study concluded that ACE inhibitors decrease the occurrence of stroke, myocardial infarction, and death; decrease progression of proteinuria in diabetics; and reduce mortality in patients at high-risk for cardiovascular events.[26] Based on these results, ACE inhibitors seem to provide similar benefit to hypertensive patients as diuretic and ß-blocker therapy. The Second Australian National Blood Pressure (ANBP-2) Trial reported slightly better outcomes in white men who were treated with an ACE inhibitor as the initial drug.[2,27] However, patients in the ALLHAT ACE-inhibitor treatment group had a significantly higher risk of stroke, heart failure, and angina compared with the diuretic group.[17]

Adverse effects that have been reported include: hyperkalemia, angioedema, dry cough, taste disturbances, skin rash, hypotension (in volume-depletion), acute renal failure (with bilateral renal artery stenosis), neutropenia, and agranulocytosis. ACE Inhibitors are contraindicated in pregnancy.[3,23,24]

Table 9. Angiotensin Receptor Blockers

Drug	Trade Name	Usual Total Dose Range, mg/day (Doses/day)
Losartan	Cozaar	25-100 (1-2)
Valsartan	Diovan	80-320 (1)
Irbesartan	Avapro	150-300 (1)
Candesartan	Atacand	8-32 (1)
Eprosartan	Tevetan	400-800 (1-2)
Olmesartan	Benicar	20-40 (1)
Telmisartan	Micardis	20-80 (1)

Adapted from Chobanian et al[2] and Brenner et al[55]

Angiotensin Receptor Blockers

Angiotensin Receptor Blockers (ARBs) produce their antihypertensive effects by interfering with the binding of angiotensin II to angiotensin-subtype-1 receptors (Table 9). This inhibition promotes vasodilation and prevents aldosterone release. Similar to ACE inhibitors, ARBs are favored in patients with heart failure, diabetes, and chronic kidney disease.[2] Even though ARBs can be considered as first-line agents, they are commonly used as second-line alternatives, especially for patients who develop an ACE inhibitor-induced cough.[2] Unlike ACE inhibitors, ARBs do not inhibit the breakdown of bradykinin. These agents delay the development of diabetic nephropathy and slow the progression of renal disease, thereby reducing renal complications.[28,29]

In the Losartan Intervention For End point (LIFE) reduction in hypertension study, the ARB treatment group was shown to decrease cardiovascular morbidity and mortality more than the ß-blocker in hypertensive patients with left ventricular hypertrophy.[30] More clinical trials are necessary to evaluate further cardiovascular outcomes.

ARBs should be avoided in pregnancy. Hyperkalemia and renal insufficiency may occur while on therapy. ARBs may be used as alternative therapy for patients who develop angioedema with ACE inhibitors. However, some reports have described cross-reactivity between ARBs and ACE inhibitors.[4]

Calcium Channel Blockers

Calcium channel blockers (CCBs) cause relaxation of cardiac and smooth muscle by blocking voltage-sensitive calcium channels, thereby reducing the entry of extracellular calcium into the cells. Vascular smooth muscle relaxation leads to vasodilation, causing a reduction in blood pressure and a decrease in peripheral resistance.[23,25] There are 2 classes of CCBs: dihydropyridines (eg, amlodipine and nifedipine) and nondihydropyridines (eg, verapamil and diltiazem) (Table 10). Dihydropyridines are considered potent vasodilators and cause minimal or no increase

Table 10. Calcium Channel Blockers

	Drug	Trade Name	Usual Total Dose Range, mg/day (Doses/day)
Non-dihydropyridines			
	Diltiazem		
	Immediate-Release	Cardizem*	120-360 (3)
	Extended-Release	Cardizem SR	120-360 (2)
		Cardizem CD, Dilacor XR, Tiazac	120-540 (1)
	Verapamil		
	Immediate-Release	Calan*, Isoptin*	80-320 (2)
	Extended-Release	Calan SR*, Isoptin SR*	120-360 (1-2)
		Verelan, Covera HS	120-360 (1)
Dihydropyridines			
	Amlodipine	Norvasc	2.5-10 (1)
	Felodipine	Plendil	2.5-20 (1)
	Isradipine	DynaCirc	5-20 (2)
		DynaCirc CR	5-20 (1)
	Nicardipine	Cardene SR	60-90 (2)
	Nifedipine	Procardia XL, Adalat CC	30-120 (1)
	Nisoldipine	Sular	20-60 (1)

*Generic product available
Adapted from Chobanian et al[2] and Brenner et al[55]

Table 11. Alpha Adrenergic Blockers

Drug	Trade Name	Usual Total Dose Range, mg/day (Doses/day)
Doxazosin	Cardura	1-16 (1)
Prazosin*	Minipress	2-30 (2-3)
Terazosin*	Hytrin	1-20 (1-2)

*Generic product available
Sources: Adapted from Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension*. 2003; 42:1206-1252; and Brenner BM, Cooper ME, DeZeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345:861-9.

in heart rate. Nifedipine, however, can cause an increase in heart rate. Non-dihydropyridines have a negative inotropic effect on the heart, slowing atrioventricular conduction and reducing heart rate. None of the CCBs affect glucose, lipids, uric acid, or electrolytes, or asthma, gout, or peripheral vascular disease.

CCBs are beneficial in treating hypertension in patients with ischemic heart disease and diabetes.[2] Avoid immediate-acting CCBs for the treatment of hypertension; the sustained-release formulations are preferential. CCBs can cause headaches, flushing, peripheral edema, constipation (especially verapamil), atrioventricular block, bradycardia, heart failure, and lupus-like rash (diltiazem).[25]

In a comparative analysis of intermediate-acting or long-acting CCBs vs other antihypertensive therapies, the combined results showed evidence that CCBs were associated with a significantly higher risk of major complications due to hypertension, including acute MI, CHF, and combined major cardiovascular events.[31] The ALLHAT study reported a 38% increase in the risk of heart failure in patients taking a CCB compared with patients taking a diuretic.[17] However, preliminary results of the International Verapamil SR/Trandolapril (INVEST) Study state that CCB-based treatment is as effective as ß-blocker therapy in reducing mortality, MI, and stroke in patients with hypertension and coronary artery disease.[32] The use of CCBs for cardiovascular benefit remains a controversial issue.

Alpha Adrenergic Blockers

Arteriolar and venous dilation occur as a result of peripheral postsynaptic alpha-adrenergic blockade. This class of medication produces postural hypotension, leading to first-dose syncope within a few hours (Table 11). Drug therapy should be initiated at bedtime at a low dose and titrated gradually. Alpha-adrenergic blockers may also cause dizziness, orthostatic hypotension, headaches, and drowsiness. Patients may experience improvements in the lipid profile (ie, a reduction in triglycerides and cholesterol and an increase in high-density lipoprotein).

In the ALLHAT study, the alpha-adrenergic blocker treatment group had a significantly higher incidence of

Table 12. Central Alpha Adrenergic Agonists and Other Centrally Acting Drugs

Drug	Trade Name	Usual Total Dose Range, mg/day (Doses/day)
Guanadrel	Hylorel	10-75 (2)
Guanethidine	Ismelin	10-150 (1)
Reserpine*	Serpasil	0.05-0.25 (1)
Clonidine*	Catapres	0.2-1.2 (2-3)
Guanabenz*	Wytensin	8-32 (2)
Guanfacine*	Tenex	1-3 (1)
Methyldopa*	Aldomet	500-3,000 (2)

*Generic product available
Adapted from Chobanian et al[2] and Brenner et al[55]

combined cardiovascular disease and heart failure. That treatment arm was stopped prior to the end of the study.[17] Alpha-adrenergic blockers should not be considered as first-line treatment for essential hypertension. These agents have been used to provide symptomatic relief for patients with benign prostatic hypertrophy.

Central Alpha Adrenergic Agonists

Central alpha adrenergic agonists inhibit sympathetic outflow through stimulation of alpha-2 receptors in the central nervous system (CNS), which produces peripheral vasodilation, thereby decreasing blood pressure. These agents are useful in refractory hypertension as adjunct therapy to other antihypertensives (Table 12). They are not indicated for first-line treatment. Due to the possibility of rebound hypertension, sudden withdrawal of therapy should be avoided. The possible side effects of these medications include sedation, drowsiness, headache, palpitation, mucosal drying, and nervousness.

Combination Therapy

Most patients will require 2 or more antihypertensive medications to achieve effective blood pressure control. The use of additional drugs from a different class should be implemented when initial therapy is inadequate. Often, diuretics are combined with ACE inhibitors, ß-blockers, CCBs, ARBs, or alpha-blockers to produce an additive effect on blood-pressure–lowering.[33] Diabetic patients usually require 2 or more drugs to reach their target blood pressure; chronic renal disease patients often require 3 or more drugs.[34,35] Multi-drug regimens or fixed-dose combinations would be advantageous in both of these high-risk conditions, as well as in other patients with several comorbidities. In fact, JNC 7 recommends starting combination therapy if patients are more than 20/10 mm Hg over their BP goal. Combination products are commercially available in a single pill (Table 13). These agents will help to simplify the medication regimen, provide additive effects, minimize adverse effects, and improve adherence.

SPECIAL CATEGORIES

Elderly Patients

Evaluating therapeutic options for older persons should be considered cautiously as this age group may have more than one comorbiditiy. Drugs with multiple indications should be used to improve medication adherence, reduce cost, prevent drug interactions, and eliminate further complications. In persons older than 50 years, systolic blood pressure of more than 140 mm Hg is a much more important cardiovascular disease risk factor than diastolic blood pressure.[2] Patients with isolated systolic hypertension (ISH) should be appropriately treated and monitored closely until blood pressure is normalized. The lowest dose needed to achieve maximal results should be used.

African-Americans

Due to the high prevalence of salt sensitivity and suppressed renin activity in African-Americans, more than one medication is usually necessary to reach blood pressure goals in this patient population.[36] African-Americans demonstrate a reduced BP response to monotherapy with ß-blockers, ACE inhibitors, or ARBs; however, with the addition of a diuretic, blood-pressure–lowering effects are improved.[17] The use of combination therapy or multiple drugs would have a significant impact in this ethnic group. The possibility of achieving appropriate antihypertensive response is highly probable with adequate treatment and lifestyle modifications.

Compelling Indications

Compelling indications include diabetes, heart failure, postmyocardial infarction, high coronary disease risk, chronic kidney disease, and recurrent stroke prevention. There are antihypertensive agents that are preferred for compelling indications (Table 14). Several clinical trials have been performed to prove therapeutic advantages for specific high-risk conditions.

Improving Blood Pressure Control

Socioeconomic status, lifestyle habits, lack of motivation, medication, and healthcare costs may all be barriers to improving blood pressure. Seeking family support, setting realistic timelines for developing a healthy lifestyle, ambulatory blood pressure monitoring, and medication adherence can be beneficial towards achieving target blood pressure goals.

Table 13. Combination Drug Therapy

Drug Combinations	Trade Name
ACE inhibitors and diuretics	
Benazepril/hydrochlorothiazide (5/6.25, 10/12.5, 20/12.5, 20/25)	Lotensin HCT
Captopril/hydrochlorothiazide (25/15, 25/25, 50/15, 50/25)	Capozide
Enalapril/hydrochlorothiazide (5/12.5, 10/25)	Vaseretic
Lisinopril/hydrochlorothiazide (10/12.5, 20/12.5, 20/25)	Prinzide, Zestoretic
Moexipril/hydrochlorothiazide (7.5/12/5, 15/25)	Uniretic
Quinapril/hydrochlorothiazide (10/12.5, 20/12.5, 20/25)	Accuretic
Angiotensin II receptor antagonists and diuretics	
Candesartan/hydrochlorothiazide (16/12.5, 32/12.5)	Atacand HCT
Eprosartan/hydrochlorothiazide (600/12.5, 600/25)	Teveten HCT
Irbesartan/hydrochlorothiazide (75/12.5, 150/12.5, 300/12.5)	Avalide
Losartan/hydrochlorothiazide (50/12.5 mg, 100/25)	Hyzaar
Telmisartan/hydrochlorothiazide (40/12.5, 80/12.5)	Micardis HCT
Valsartan/hydrochlorothiazide (80/12.5, 160/12.5)	Diovan HCT
β-blockers and diuretics	
Atenolol/chlorthalidone (50/25, 100/25)	Tenoretic
Bisoprolol/hydrochlorothiazide (2.5/6.25, 5/6.25, 10/6.25)	Ziac
Metoprolol/hydrochlorothiazide (50/25, 100 mg/25)	Lopressor HCT
Nadolol/bendroflumethiazide (40/5, 80/ 5)	Corzide
Propranolol/hydrochlorothiazide (40/25, 80/25)	Inderide
Propranolol LA/hydrochlorothiazide (80/50, 120/50, 160/50)	Inderide LA
Timolol/hydrochlorothiazide (10/25)	Timolide
Calcium channel blockers and ACE inhibitors	
Amlodipine/benazepril (2.5/10, 5 mg/10, 10/20)	Lotrel
Verapamil/trandolapril (2/180, 1/240 mg, 2/240, 4 mg/240)	Tarka
Felodipine/enalapril (5/5)	Lexxel
Other combinations	
Amiloride/hydrochlorothiazide (5/50)	Moduretic
Clonidine/chlorthalidone (0.1/15, 0.2/15, 0.3/15)	Combipres
Guanethidine/hydrochlorothiazide (10/25)	Esimil
Hydralazine/hydrochlorothiazide (25/25, 50/50, 100/50)	Apresazide
Methyldopa/chlorothiazide (250/250)	Aldochlor
Methyldopa/hydrochlorothiazide (250/15, 250/25, 500/30, 500/50)	Aldoril
Reserpine/chlorothiazide (0.125/250, 0.25/500)	Diupres
Reserpine/hydrochlorothiazide (0.125/25, 0.125/50)	Hydropres
Spironolactone/hydrochlorothiazide (25/25, 50/50)	Aldactazide
Triamterene/hydrochlorothiazide (37.5/25, 50/25, 75/50)	Dyazide, Maxzide

Adapted from Chobanian et al[2] and Brenner et al[55]

Summary

The JNC 7 Report concluded many important details regarding the management of hypertension. The following points were emphasized:

- Thiazide-type diuretics should be used in drug treatment for most patients with uncomplicated hypertension, either alone or combined with drugs from other classes. Certain high-risk conditions are compelling indications for the initial use of other antihypertensive drug classes (angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, ß-blockers, calcium-channel blockers).
- Classification of 120–139/80–89 mm Hg as prehypertensive. Patients classified as prehypertensive are encouraged to institute lifestyle modifications. Currently, no drug therapy is required in prehypertension unless the patient has compelling indications.
- Most patients with hypertension will require 2 or more antihypertensive medications to achieve

Table 14. Individual Drug Classes for High-Risk Conditions

Compelling Indications	Initial Therapy Options	Clinical Trial Basis
Heart failure	THIAZ, BB, ACEI, ARB, ALDO ANT	ACC/AHA Heart Failure Guideline,[37] MERIT-HF,[38] COPERNICUS,[39] CIBIS,[40] SOLVD,[41] AIRE,[42] TRACE,[43] ValHEFT,[44] RALES[45]
Postmyocardial infarction	BB, ACEI, ALDO ANT	ACC/AHA Post-MI Guideline,[46] BHAT,[47] SAVE,[48] Capricorn,[49] EPHESUS[50]
High CAD risk	THIAZ, BB, ACE, CCB	ALLHAT,[17] HOPE,[26] ANBP2,[27] LIFE,[30] CONVINCE[51]
Diabetes	THIAZ, BB, ACE, ARB, CCB	NKF-ADA Guideline,[34,52] UKPDS,[53] ALLHAT[17]
Chronic kidney disease	ACEI, ARB	NKF Guideline,[52] Captopril Trial,[54] RENAAL,[55] IDNT,[56] REIN,[57] AASK[35]
Recurrent stroke prevention	THIAZ, ACEI	PROGRESS[58]

AASK, African American Study of Kidney Disease and Hypertension; ACC/AHA, American College of Cardiology/American Heart Association; ACEI, Angiotensin-converting enzyme inhibitor; AIRE, Acute Infarction Ramipril Efficacy; ALDO ANT, Aldosterone Antagonist; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ANBP2, Second Australian National Blood Pressure Study; ARB, Angiotensin-receptor blocker; BB, Beta Blocker; BHAT, Beta Blocker Heart Attack Trial; CCB, Calcium Channel Blocker; CIBIS, Cardiac Insufficiency Bisoprolol Study; CONVINCE, Controlled Onset Verapamil Investigation of Cardiovascular End Points; COPERICUS, Carvedilol Prospective Randomized Cumulative Survival Study; EPHESUS, Eplerenone Post-Acute Myocardial Infarction Heart Failure and Efficacy and Survival Study; HOPE, Heart Outcomes Prevention Evaluation Study; IDNT Irbesartan Diabetic Nephropathy Trial; LIFE, Losartan Intervention For Endpoint Reduction in Hypertension Study; MERIT-HF, Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; NKF-ADA, National Kidney Foundation-American Diabetes Association; PROGRESS, Perindopril Protection Against Recurrent Stroke Study; RALES, Randomized Aldactone Evaluation Study; REIN, Ramipril Efficacy in Nephropathy Study; RENAAL, Reduction of Endpoints in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan Study; SAVE, Survival and Ventricular Enlargement Study; SOLVD, Studies of Left Ventricular Dysfunction; THIAZ, Thiazide Diuretic; TRACE, Trandolapril Cardiac Evaluation Study; UKPDS, United Kingdom Prospective Diabetes Study; ValHEFT, Valsartan Heart Failure Trial. Adapted from Chobanian et al[2]

their blood pressure goal (less than 140/90 mm Hg or less than 130/80 mm Hg for patients with diabetes or chronic kidney disease).

- If blood pressure is >20/10 mm Hg above goal blood pressure, consideration should be given to initiating therapy with 2 agents, one of which should usually be a thiazide-type diuretic.

There have been other significant findings in landmark trials that have provided insightful information about hypertension management. For instance, the ALLHAT study clearly points to thiazide diuretics as the drug of choice for uncomplicated hypertension; while the ANBP-2 study recommends ACE-inhibitors as first-line treatment. However, the information reported from the latter study is somewhat difficult to extrapolate to the general public. The ANBP-2 study had a smaller sample size and the study population did not compare with the ALLHAT. With this in mind, each clinician should understand the current guideline recommendations as well as key findings from clinical trials in order to critically evaluate the literature and make informed decisions concerning the management of hypertension.

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