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Review Article

Pharmacotherapy of Hypertension: A Review

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ABSTRACT
Systemic hypertension is a major risk factor for cardiovascular disease and is present in 69% of patients with a first myocardial infarction, in 77% of patients with a first stroke, in 74% of patients with chronic heart failure, and in 60% of patients with peripheral arterial disease. Double-blind, randomized, placebo-controlled trials have found that antihypertensive drug therapy reduces cardiovascular events in patients aged younger than 80 years and in patients aged 80 years and older in the Hypertension in the Very Elderly Trial. Although the optimal blood pressure treatment goal has not been determined, existing epidemiologic and clinical trial data suggest that a reasonable therapeutic blood pressure goal should be <140/90 mm Hg in patients younger than 80 years and a systolic blood pressure of 140-145 mm Hg if tolerated in patients aged 80 years and older. Non-pharmacologic lifestyle measures should be encouraged both to prevent development of hypertension and as adjunctive therapy in patients with hypertension. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, calcium channel blockers, and diuretics have all reduced cardiovascular events in randomized trials. The choice of specific drugs depends on efficacy, tolerability, presence of specific comorbidities, and cost.

Keywords: *Hypertension, diuretics, beta blockers*

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INTRODUCTION
Hypertension , also known as high blood pressure , is a long term medical condition in which the blood pressure in the arteries is persistently elevated.[1] High blood pressure usually does not cause symptoms.[2] Long term high blood pressure, however, is a major risk factor for coronary artery disease, stroke, heart failure, peripheral vascular disease,vision loss, and chronic kidney disease.[3,4]

High blood pressure is classified as either primary (essential) high blood pressure or secondary high blood pressure.[5] About 90–95% of cases are primary, defined as high blood pressure due to nonspecific lifestyle and genetic factors.[5,6] Lifestyle factors that increase the risk include excess salt, excess body weight, smoking, and alcohol.[2,5] The remaining 5–10% of cases are categorized as secondary high blood pressure, defined as high blood pressure due to an identifiable cause, such aschronic kidney disease, narrowing of the kidney arteries, an endocrine disorder, or the use of birth control pills.[5] Blood pressure is expressed by two measurements, the systolic and diastolic pressures, which are the maximum and minimum pressures, respectively.[2] Normal blood pressure at rest is within the range of 100–140 millimeters mercury (mmHg) systolic and 60–90 mmHg diastolic.[7] High blood pressure is present if the resting blood pressure is persistently at or above 140/90 mmHg for most adults.[5] Different numbers apply to children.[8] Ambulatory blood pressure monitoring over a 24-hour period

appears more accurate than office best blood pressure measurement.[1,5]

Hypertension is an important worldwide public-health challenge because of its high frequency and concomitant risks of cardiovascular and kidney disease.[9] It has been identified as the leading risk factor for mortality, and is ranked third as a cause of disability-adjusted life-years.[10] The World Health Organization has concluded that hypertension is the major factor responsible for the most deaths worldwide (12.8% per year or more than seven million).[1] More than a quarter of the world's adult population-totalling nearly one billion (26%) had hypertension in 2000, and because a larger proportion of the world's population is expected to be older in 2025, this proportion has been projected to increase to 1.56 billion ($29% prevalence by that time). However, there is considerable variation among countries and geographic regions for the reported prevalence of hypertension (≈5% to 70%) and hypertension control rates (≈5% to 58%).[10,11] The prevalence of hypertension increases with advancing age; for example, about 50% of people between the ages of 60 and 69 years old have hypertension, and the prevalence is further increased beyond age 70.[12] Although hypertension is more prevalent in economically developed countries, the larger population of developing countries results in a considerably larger absolute number of individuals affected. Hypertension is a heterogeneous medical condition. In most patients (over 90% of individuals) it results from unknown pathophysiologics etiology (essential or primary hypertension). However a small percentage of patients (10%) have a specific cause of their hypertension (secondary hypertension). While essential hypertension cannot be cured, it can be controlled. Although it has frequently been indicated that the causes of essential hypertension are not known, this is only partially true because we have little information on genetic variations or genes that are over-expressed or under-expressed as well as the intermediary phenotypes that they regulate to cause high BP.[13] A number of factors increase BP, including 1) obesity, 2) insulin resistance, 3) high alcohol intake, 4) high salt intake (in salt-sensitive patients), 5) aging and perhaps 6) sedentary lifestyle, 7) stress, 8) low potassium intake, and 9) low calcium intake.[14,15]

Furthermore, many of these factors are additive, such as obesity and alcohol intake. Causes of secondary hypertension includes concurrent medical conditions or are endogenously induced (chronic kidney disease, cushing's syndrome, coarctation of the aorta, obstructive sleep apnea, Parathyroid disease, pheochromocytoma, primary aldosteronism, renovascular disease, thyroid disease).[4] In most of these cases, renal dysfunction resulting from chronic kidney disease or renovascular disease is the most common secondary cause.[16] If the cause of secondary hypertension can be identified, hypertension in these patients can be cured. Hypertension is an important risk factor for cardiovascular morbidity and mortality[17]. The large numbers of clinical trials have demonstrated the benefits of blood pressure control with drugs to reduce cardiovascular morbidity and mortality[18]. Despite the availability of effective antihypertensive, it is estimated that in the developed countries only 25-30% of the patients have their blood pressure controlled adequately[19]. A part of this uncontrolled blood pressure is caused by true treatment resistant hypertension as a result of genetic differences[20]. Adherence to treatment is another important cause of this uncontrolled blood pressure[21]. In one study demonstrated that non-adherence substantially contributed to uncontrolled blood pressure.[22] The problem of poor adherence is of major concern to all stakeholders in the health care system. This is because the risk of poor adherence increases with the duration and complexity of treatment regimens and both long duration and complex treatment are inherent to chronic illnesses. Adherence is the single most important modifiable factor that compromises treatment outcome. The best treatment can be rendered ineffective by poor adherence. The perspective is that an understanding of basic behavioural principles and models of behavioural change is relevant to adherence to treatment for all chronic medical conditions, and more helpful than a disease-specific approach to the issue. The effectiveness of adherence interventions based on behavioural principles has been demonstrated in many therapeutic areas. like include hypertension[23].

Definition and Prevalence

Resistant hypertension is defined as blood pressure (BP) that remains above goal in spite of use of three antihypertensive medications in effective doses, usually including a diuretic1. Patients who are intolerant of diuretics and have uncontrolled BP on regimens of 3 drugs from other classes are also considered to have resistant hypertension. The BP goal is <140/90 mm Hg in the general population of hypertensives and

<130/80 mm Hg in hypertensive patients with diabetes or chronic kidney disease (CKD) (glomerular filtration rate <60 ml/min/1.73m^2; serum creatinine >1.5 mg/dl in men or >1.3 mg/dl in women; albuminuria >300 mg/24-hr or >200 mg/g creatinine)[24]. Similarly, patients who require 4 or more medications to control their BP are considered to have resistant hypertension. Factors that predispose to antihypertensive treatment resistance include population characteristics, such as increased life expectancy, higher obesity rates and decreased physical activity, as well as provider characteristics, including inadequate attention to systolic BP (SBP) elevations and the more aggressive BP goals recommended by recent guidelines. The various contributing factors (Table 1) and secondary causes related to resistant hypertension (Table 2) are discussed in this review.

Epidemiology

It is estimated that approximately 30% of the population (50 million Americans) has high BP (140/90 mm Hg).[25,26] Estimates from the National Health and Nutrition Examination Survey from 1999–2000 indicate that the prevalence is 30.1% and 27.1% among men and women, respectively.[25] This represents a significant increase of 5.6% in women from 1988 to 2000, whereas the prevalence in men has remained unchanged. Prevalence rates are highest in non Hispanic blacks (33.5%), followed by non-Hispanic whites (28.9%) and Mexican-Americans (20.7%). BP values increase with age and hypertension is very common in the elderly.

The lifetime risk of developing hypertension among those 55 years of age and older who are normotensive is 90%.[27] Most patients have prehypertension BP values before they are diagnosed with hypertension, and most hypertension diagnoses occur between the third and fifth decades of life. Up to the age of 55 years, more men than women have hypertension. From the ages of 55 to 74 years, slightly more women have hypertension than men, with this sex difference becoming greater in the very elderly (75 years). In the older population (age: 60 years), the prevalence of hypertension is 65.4% (estimated in 2000), which is significantly higher than the 57.9% prevalence estimated in 1988.[25]

Etiology

Hypertension is a heterogeneous medical condition. In most patients it results from unknown pathophysiologic etiology (essential or primary hypertension).While this formof hypertension cannot be cured, it can be controlled. A small percentage of patients have a specific cause of their hypertension (secondary hypertension). There are many potential secondary causes that are either concurrent medical conditions or are endogenously induced. If the cause of secondary hypertension can be identified, hypertension in these patients potentially can be cured.

Pathophysiology[28,31]

A clear understanding of arterial BP and regulation is needed to manage hypertension appropriately and to understand antihypertensive drug therapy mechanistically. Multiple factors that control BP are potential contributing components in the development of hypertension. These include malfunctions in either humoral (i.e., the renin-angiotensin-aldosterone system [RAAS]) or vasodepressor mechanisms, abnormal neuronal mechanisms, defects in peripheral autoregulation, and disturbances in sodium, calcium, and natriuretic hormone. Many of these factors are cumulatively affected by the multifaceted RAAS, which ultimately regulates arterial BP. It is probable that none of these factors is solely responsible for hypertension; however, most antihypertensives specifically target thesemechanisms and components of the RAAS.

Classification

The JNC7 classification of BP in adults (age 18 years) is based on the average of two or more properly measured BP readings from two or more clinical encounters[27]. It includes four categories, with normal values considered to be an SBP of less than 120 mm Hg and a DBP of less than 80mmHg. Prehypertension is not considered a disease category but identifies patients whose BP is likely to increase into the classification of hypertension in the future. There are two

stages of hypertension, and all patients in these categories warrant drug therapy. Hypertensive crises are clinical situations where BP values are greater than 180/120mmHg.[31,33] They are categorized as either a hypertensive emergency or hypertensive urgency. *Hypertensive emergencies* are extreme elevations in BP that are accompanied by acute or progressing target-organ damage. Examples of acute target-organ injury include encephalopathy, intracranial hemorrhage, acute left ventricular failure with pulmonary edema, dissecting aortic aneurysm,

unstable angina, and eclampsia or severe hypertension during pregnancy. Hypertensive emergencies require an immediate but gradual

reduction in BP over a period of several minutes to several hours using intravenous antihypertensive agents. A reasonable goal is to gradually
lower DBP to <110 mm Hg.[31] Abrupt BP reductions should be avoided. Hypertensive urgencies are high elevations in BP without acute or progressing target-organ injury. These situations require BP reductions with oral antihypertensive agents to stage 1 values over a period of several hours to several days.

Nonpharmacologic Therapy

All patients with prehypertension and hypertension should be prescribed lifestyle modifications. Modifications that have been shown to lower BP . These approaches are recommended by the JNC71 and provide small to moderate reductions in SBP. Aside from lowering BP in patients with known hypertension, lifestyle modification can decrease the progression to hypertension in patients with prehypertension BP values.[54] In a number of hypertensive patients with relatively good BP control while on single antihypertensive drug therapy, sodium reduction and weight loss may allow withdrawal of drug therapy.[55,56] A sensible dietary program is one that is designed to reduce weight gradually for overweight and obese patients and one that restricts
sodium intake with only moderate alcohol consumption. Successful implementation of dietary lifestyle modifications by clinicians requires aggressive promotion through reasonable patient education, encouragement, and continued reinforcement. Patients may better understand the rationale for dietary intervention in hypertension if they are provided the following observations and facts:

1. Hypertension is two to three times more prevalent in overweight as compared with lean persons.
2. Over 60% of hypertensive persons are overweight
3. Weight loss, even as little as 10 pounds, can decrease BP significantly in hypertensive overweight individuals.[57]
4. Abdominal obesity is associated with the metabolic syndrome, which is a precursor to hypertension and insulin-resistance syndrome that may progress to type 2 diabetes, dyslipidemia, and ultimately, cardiovascular disease.[42]
5. Diets rich in fruits and vegetables and low in saturated fat have been shown to lower BP in hypertensive individuals.[58,59]
6. Although some hypertensive patients are not salt-sensitive, most people experience some degree of SBP reduction with sodium restriction.[60,61] The DASH eating plan is a diet that is rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat.

Pharmacologic Therapy

There are nine different antihypertensive drug classes. Diuretics, β-blockers, ACE inhibitors, angiotensin II receptor blockers, and calcium channel blockers are considered primary antihypertensive agents . Several of these classes (i.e., diuretics, β-blockers, and calcium
channel blockers) have subclasses where significant differences in mechanism of action, clinical use, or side effects or evidence from outcomes studies exist. β-Blockers, central α2-agonists, adrenergic inhibitors, and vasodilators are considered alternative drug classes that may be used in select patients after primary agents . Evidence-based medicine is a conscientious, explicit, and judicious use of current best evidence to make decisions about the care of individual patients. Evidence-based practice in hypertension involves selecting specific agents based on outcomes data demonstrating a reduction in hypertension-associated target-organ damage or cardiovascular morbidity and mortality. Scientific evidence demonstrating simply BP lowering, tolerability, or costs never should be the sole justification for selecting drug therapy. When considering these factors, the most useful agents are diuretics, ACE inhibitors, angiotensin II receptor blockers, β-blockers, and calcium channel blockers. The JNC7 drug therapy recommendations are discussed
throughout this section and are founded based on evidence-based medicine principles

Hypertension in Children and Adolescents[62]

Detecting hypertension in children requires special attention to BP measurement, and detection is based on age-determined percentiles for excessive BP.[62] Hypertensive children often have a family history of high BP, and many are overweight. Unlike hypertension in adults, secondary hypertension ismuchmore common in children and adolescents. An appropriate work-up for secondary causes is essential if elevated BP is identified. Kidney disease (e.g., pyelonephritis,
glomerulonephritis, renal artery stenosis, and renal cysts) is the most common cause of secondary hypertension in children. Pheochromocytoma and coarctation of the aorta also can produce secondary hypertension. Medical or surgical management of the

underlying disorder
usually normalizes BP. Treatment recommendations are provided in the 1996 National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents.[62] Nonpharmacologic treatment is the cornerstone of therapy for essential hypertension. The goal is to reduce the BP to below the 95th percentile for age. Diuretics, β-blockers, and ACE inhibitors are very effective. ACE inhibitors and ARBs are contraindicated in sexually active girls owing to potential teratogenic effect and in those who might have bilateral renal artery stenosis or unilateral stenosis in a solitary kidney. Longacting dihydropyridineCCBs have been successfully used in children, but long-term safety is unknown.

INDIVIDUAL ANTIHYPERTENSIVE AGENTS[27,31]

Diuretics [36-38,63,64,65]

Diuretics, preferably a thiazide, are fist-line agents for most patients with hypertension.1 The best available evidence justifying this recommendation is from ALLHAT.[63] Moreover, when combination therapy is needed in hypertension to control BP, a diuretic is recommended as
one of the agents used.[27] Four subclasses of diuretics are used in the treatment of hypertension: thiazides, loops, potassium-sparing agents, and aldosterone antagonists Potassium-sparing diuretics are weak antihypertensive agents when used alone but provide
an additive effect when used in combination with a thiazide or loop diuretic. Moreover, they counteract the potassium- and magnesiumlosing properties of the other diuretic agents. Aldosterone antagonists (spironolactone) technically may be considered potassium-sparing agents but are more potent antihypertensives with a slow onset of activity (up to 6 weeks with spironolactone). However, they are viewed by the JNC7 as an independent class because of evidence supporting compelling indications. The exact hypotensive mechanism of action of diuretics is not known but has been well hypothesized. The drop in BP seen when diuretics
are first started is caused by an initial diuresis. Diuresis causes reductions in plasma and stroke volume, which decreases cardiac output and BP. This initial drop in cardiac output causes a compensatory increase in peripheral vascular resistance.With chronic diuretic therapy,
extracellular fluid and plasma volume return to near pretreatment values. However, peripheral vascular resistance decreases to values that are lower than the pretreatment baseline. This reduction in peripheral vascular resistance is responsible for chronic antihypertensive
effects. Thiazide diuretics have additional actions that may further explain their antihypertensive effects. Thiazides mobilize sodium and water from arteriolar walls. This effect would lessen the amount of physical encroachment on the lumen of the vessel created by excessive accumulation of intracellular fluid. As the diameter of the lumen relaxes and increases, there is less resistance to the flow of blood, and peripheral vascular resistance drops further. High dietary sodium intake can blunt this effect, and a low salt intake can enhance this effect. Thiazides also are postulated to cause direct relaxation of vascular smooth muscle. This theory is based on the known mechanism of action of diazoxide, which is a direct vasodilator that is structurally related to thiazide diuretics. Thiazides are the preferred type of diuretic for treating hypertension. In patients with adequate kidney function (estimated GFR > 30 mL/min), thiazides are the most effective diuretics for lowering BP. As kidney function declines, a more potent diuretic is needed to counteract the associated increase in sodium and water retention. In this case, a loop diuretic (e.g., furosemide dosed twice daily) should be considered. Diuretics ideally should be dosed in the morning if given once daily and in the morning and afternoon if dosed twice daily to minimize the risk of nocturnal dieresis.

Angiotensin-Converting Enzyme Inhibitors [66,67,68,69,70]

ACE inhibitors are considered second-line therapy to diuretics in most patients with hypertension.1 The ALLHAT demonstrated less heart failure and stroke with chlorthalidone versus lisinopril.[63] This difference in stroke is consistent with another outcomes trial, the
Captopril Prevention Project (CAPPP).[70] However, other outcome studies have demonstrated similar, if not better, outcomes with ACE inhibitors versus thiazide diuretics.[66,67] In the elderly, one study found that they were at least as effective when compared with diuretics and beta blockers,[69] and another study found that they were more effective.[67] In addition, ACE inhibitors have many roles for patients with hypertension and coexisting conditions. Nonetheless, most clinicians will agree that if ACE inhibitors are not first-line therapy in most patients

with hypertension, they are a very close second to diuretics..ACEis distributed in many tissues and is present in several different cell types, but its principal location is in endothelial cells. Therefore, the major site for angiotensin II production is in the blood vessels, not the kidney. ACE inhibitors block the conversion of angiotensin I to angiotensin II. This latter substance is a potent vasoconstrictor that also stimulates aldosterone secretion. ACE inhibitors also block the degradation of bradykinin and stimulate the synthesis of other vasodilating substances, including prostaglandin E2 and prostacyclin. The observation that ACE inhibitors lower BP in patients with normal plasma rennin activity suggests that bradykinin and perhaps tissue production of ACE are important in hypertension. Increased bradykinin enhances the BP-lowering effects of ACE inhibitors but also is responsible for the side effect of dry cough. ACE inhibitors effectively prevent or regress LVH by reducing the direct stimulation by angiotensin II onmyocardial cells. The JNC7 lists six compelling indications for ACE inhibitors, indicating many evidence-based uses for this drug class .

_ Angiotensin II Receptor Blockers [71]

Angiotensin II is generated by two enzymatic pathways: the RAAS, which involves ACE, and an alternative pathway that uses other enzymes such as chymases. ACE inhibitors inhibit only the effects of angiotensin II produced through the RAAS, whereas ARBs inhibit
angiotensin II from all pathways. It is unclear howthese differences affect tissue concentrations of ACE. Because of these differences, ACE inhibitors only partially block the effects of angiotensin II. ARBs directly block the angiotensin II type 1 (AT1) receptor that mediates the
known effects of angiotensin II in humans: vasoconstriction, aldosterone release, sympathetic activation, antidiuretic hormone release, and constriction of the efferent arterioles of the glomerulus. They do not block the angiotensin II type 2 (AT2) receptor. Therefore, beneficial
effects of AT2 receptor stimulation (i.e., vasodilation, tissue repair, and inhibition of cell growth) remain intact when ARBs are used. Unlike ACE inhibitors, ARBs do not block the breakdown of
bradykinin. Therefore, some of the beneficial effects of bradykinin such as vasodilation (which can enhance BP lowering), regression of myocyte hypertrophy and fibrosis, and increased levels of tissue plasminogen activator are not present with ARB therapy. ARBs have outcomes data showing long-term reductions in progression of target-organ damage in patients with hypertension and certain compelling indications. In patients with type 2 diabetes
and nephropathy, progression of nephropathy has been shown to be reduced significantly with ARB therapy. Some benefits appear to be independent of BP lowering, suggesting that the unique benefits of ARBs are explained pharmacologically by effects on the efferent
arteriole. For patients with systolic heart failure, the CHARM studies showed that ARB therapy reduces the risk of cardiovascular events when added to a stable regimen of a diuretic, ACE inhibitor, and _-blocker or as alternative therapy in ACE inhibitor–intolerant
patients.

β-Blockers [66,72,63]

β-Blockers have been used in several large outcome trials in hypertension. They were recommended previously as first-line agents along with diuretics in most patients. However, in most of these trials, diuretics were the primary agents, and β-blockers were added on for additional BP lowering. Therefore, they are now considered appropriate first-line agents when there are compelling indications (after myocardial infarction or high coronary disease risk) and are evidenced-based as additional therapy for other compelling indications (heart failure
and diabetes). Numerous trials have shown reduced cardiovascular risk when β-blockers are used following a myocardial infarction, during acute coronary syndrome, or in chronic stable angina. Although once considered contraindicated in heart failure, multiple studies have shown that carvedilol and metoprolol succinate reduce mortality in patients with systolic heart failure who are treated with a diuretic and an ACE inhibitor. Atenolol was even used in type 2 diabetes in the
UKPDS studies and showed comparable, if not better, cardiovascular risk reduction when compared with captopril. Several mechanisms of action have been proposed for
α-adrenoceptor blockers (β-blockers), but none of them alone has been shown to be associated consistently with a reduction in arterial BP. β-Blockers have negative chronotropic and inotropic cardiac effects that reduce cardiac output,which explains some of the antihypertensive
effect. However, cardiac output falls equally in

patients treated with β-blockers regardless of BP lowering. Additionally, β-blockersNwith intrinsic sympathomimetic activity (ISA) do not reduce cardiac output, yet they lower BP and decrease peripheral resistance. β-Adrenoceptors are also located on the surface membranes of juxtaglomerular cells, and β-blockers inhibit the release of renin. However, there is a weak association between plasma renin concentrations and antihypertensive efficacy of β-blocker therapy. Some patients with low plasma renin concentrations do respond to β-blockers. NTherefore, additional mechanisms also must account for the antihypertensive effect of β-blockers. However, the ability of β-blockers to reduce plasma renin and thus angiotensin II concentrations may play a major role in their ability to reduce cardiovascular risk. Pharmacokinetic differences among β-blockers relate to firstpass metabolism, serum half-lives, degree of lipophilicity, and route of elimination. Propranolol and metoprolol undergo extensive first-pass metabolism, so the dose needed to attain β-blockade with either drug varies from patient to patient. Atenolol and nadolol have relatively long half-lives and are excreted renally. The dose of these agents may need to be reduced in patients with moderate to severe chronic kidney disease.

Calcium Channel Blockers [39,66]

CCBs are not first-line agents but are very effective antihypertensive agents, especially in African-American patients. They have compelling indications in high coronary disease risk and in diabetes. However, with these compelling indications, they are in addition to or in replacement of other antihypertensive drug classes. Some data indicated that dihydropyridines may not provide as much protection against cardiac events when compared with "conventional" therapy (diuretics and β-blockers) or ACE inhibitors in uncomplicated hypertension.[66] Since only heart failure was higher with amlodipine versus chlorthalidone in ALLHAT, differences between agents are small.[63] In patients with hypertension and diabetes, ACE inhibitors appear to be more cardioprotective than dihydropyridines.[68] Studies with thenondihydropyridine CCBs diltiazem and verapamil are limited, but the NORDIL study found diltiazem to be equivalent to diuretics and β-blockers in reducing cardiovascular events.[66] It is possible that these differences (beneficial with diltiazem and neutral with dihydropyridines) may relate to the sympathetic stimulation that can occur with dihydropyridines. Dihydropyridine CCBs are very effective in older patients with isolated systolic hypertension. The Syst-Eurwas a placebo-controlled trial that demonstrated that a long-acting dihydropyridine CCB reduced the risk of cardiovascular events markedly in isolated systolic hypertension.[15] In previous guidelines, isolated systolic hypertension was a compelling indication for a long-acting dihydropyridine CCB. The JNC7 does not list isolated systolic hypertension differently from any other form of hypertension, and diuretics remain first-line therapy. However, a long-acting dihydropyridine CCB may be considered as add-on therapy if a thiazide diuretic is not controlling BP in a patient with isolated systolic hypertension and no other compelling indications. This is especially relevant if the patient is older with SBP elevation. Contraction of cardiac and smooth muscle cells requires an increase in free intracellular calcium concentrations from the extracellular fluid. When cardiac or vascular smooth muscle is stimulated, voltage-sensitive channels in the cell membrane are opened, allowing calcium to enter the cells. The influx of extracellular calcium into the cell releases stored calcium from the sarcoplasmic reticulum.

α1-Blockers[73]

Prazosin, terazosin, and doxazosin are selective α1-receptor blockers. They work in the peripheral vasculature and inhibit the uptake of catecholamines in smooth muscle cells, resulting in vasodilation and BP lowering. Doxazosin was one of the original treatment arms of the ALLHAT. However, it was stopped prematurely when statistically more secondary end points of stoke, heart failure, and cardiovascular events were seen with doxazosin compared with chlorthalidone.[73]

There were no differences in the primary end point of fatal coronary heart disease and nonfatal myocardial infarction. These data suggest that thiazide diuretics are superior to doxazosin (and probably other α1-blockers) in preventing cardiovascular events in patients with hypertension. Therefore, α1-blockers are alternative agents that should be used in combinationwith one ormore primary antihypertensive agent(s). α1-Blockers can provide symptomatic benefits in men with benign prostatic hypertrophy. These agents block postsynaptic 1-adrenergic receptors located

on the prostate capsule, causing relaxation and decreased resistance to urinary outflow. However, they should be used only in addition to other standard antihypertensive agents.

Central α2-Agonists

Clonidine, guanabenz, guanfacine, and methyldopa lower BP primarily by stimulating α2-adrenergic receptors in the brain. This stimulation reduces sympathetic outflow from the vasomotor center in the brain and increases vagal tone. It is also believed that peripheral stimulation of presynaptic α2-receptors may further reduce sympathetic tone. Reduced sympathetic activity, together with enhanced parasympathetic activity, can decrease heart rate, cardiac output, total peripheral resistance, plasma renin activity, and baroreceptor reflexes.

Although guanabenz and guanfacine are used rarely in clinical practice, clonidine is often used in resistant hypertension, andmethyldopa is a first-line agent for hypertension in pregnancy..

Chronic use of centrally acting α-agonists results in sodium and water retention,which ismost prominent with methyldopa. Low doses of clonidine (and guanfacine or guanabenz) can be used to treat hypertension without the addition of a diuretic. However, methyldopa should be given with a diuretic to avoid the blunting of antihypertensive effect that happens with prolonged use, except in pregnancy. Sedation and dry mouth are common side effects that typically improve

with chronic use of low doses. As with other centrally acting antihypertensives, depression can occur. The incidence of orthostatic hypotension and dizziness is higher than with other antihypertensive agents, so they should be used very cautiously in the elderly.

Reserpine

Reserpine lowers BP by depleting norepinephrine from sympathetic nerve endings and blocking transport of norepinephrine into its storage granules. Norepinephrine release into the synapse following nerve stimulation is reduced and results in reduced sympathetic tone, peripheral vascular resistance, and BP. Reserpine also depletes catecholamines from the brain and the myocardium, which may lead to sedation, depression, and decreased cardiac output. Reserpine has a slowonset of action and long half-life that allows for once daily dosing. However, it may take 2 to 6 weeks before the maximal antihypertensive effect is seen. Reserpine can cause significant sodium and water retention. It should be given in combination with a diuretic (preferably a thiazide). Reserpine's strong inhibition of sympathetic activity results in increased parasympathetic activity.

This effect explainswhy side effects such as nasal stuffiness, increased gastric acid secretion, diarrhea, and bradycardia can occur. Depression has been reported, which is a consequence of central nervous system depletion of catecholamines and serotonin. Depression may manifest as sadness, loss of appetite or self-confidence, gradual loss of energy, erectile dysfunction, or early-morning awakening. The initial reports of depression with reserpine were in the 1950s and are not consistent with current definitions of depression. Regardless, reserpine-induced depression is likely dose-related, and very high doses (above 1 mg daily) were used frequently in the 1950s. Depression is minimal when doses between 0.05 and 0.25 mg daily are used. With these low doses, the rate of depression is equal to that seen with β-blockers, diuretics, or placebo.[36] Reserpinewas used as a third-line agent in many of the landmark clinical trials that have documented its benefit in treating hypertension, including the VA Cooperative trials and, most important, the SHEP trial.[36] An analysis of the SHEP data found that reserpine was very well tolerated. The combination of a diuretic and reserpine is very effective at lowering BP, and this is a very inexpensive antihypertensive regimen.

Direct Arterial Vasodilators

The antihypertensive effects of hydralazine and minoxidil are caused by direct arteriolar smooth muscle relaxation. They exert little to no venous vasodilation. By decreasing arterial BP, they also reduce impedance to myocardial contractility. Both agents cause potent reductions in perfusion pressure that activates the baroreceptor reflexes. Activation of baroreceptors results in a compensatory increase in sympathetic outflow, which leads to an increase in heart rate, cardiac

output, and renin release. Consequently, tachyphylaxis can develop, resulting in a loss of hypotensive effect,with continued use. This compensatory baroreceptor response can be counteracted by concurrent use of a β-blocker. All patients receiving these drugs long term for hypertension generally should receive both a diuretic and a β-blocker first. Direct arterial vasodilators can precipitate angina in patients with underlying coronary artery disease unless the baroreceptor reflex mechanism is completely blocked with a β-blocker. Clonidine can be used in patients who have contraindications to β-blockers. The side effect of sodium and water

retention is significant with these drugs and can be minimized with diuretic therapy (preferably thiazides).

One side effect unique to hydralazine is a dose-dependent druginduced lupus-like syndrome. Hydralazine is eliminated by hepatic *N*-acetyltransferase. This enzyme displays genetic polymorphism, and slow acetylators are especially prone to develop drug-induced lupus with hydralazine. This syndrome is more common in women and is reversible on discontinuation. Drug-induced lupus may be avoided by using less than 200 mg hydralazine daily. Other side

effects of hydralazine include dermatitis, drug fever, peripheral neuropathy, hepatitis, and vascular headaches. For these reasons, hydralazine has limited usefulness in the treatment of hypertension. However, it is still used with isosorbide dinitrate in patients with heart

failure (especially African-Americans) and is useful in patients with severe chronic kidney disease and kidney failure. Minoxidil is a more potent vasodilator than hydralazine. Therefore,

the compensatory increases in heart rate, cardiac output, rennin release, and sodium retention are even more dramatic. Sodium and water retention can be so severe with minoxidil that heart failure can be precipitated. It is even more important to coadminister a β-blocker and a diuretic with minoxidil. A loop diuretic is often more effective than a thiazide diuretic in patients treated with minoxidil. A troublesome side effect of minoxidil is hypertrichosis. Increased hair growth

occurs on the face, arms, back, and chest. This drug-induced hirsutism ceases with discontinuation of the drug. Other minoxidil side effects include pericardial effusion and a nonspecific T-wave change on the electrocardiogram. Minoxidil generally is reserved for very difficult to control hypertension and patients requiring hydralazine that experience drug-induced lupus.

Other Agents

Guanethidine and guanadrel are postganglionic sympathetic inhibitors. They deplete norepinephrine from postganglionic sympathetic nerve terminals and inhibit the release of norepinephrine in response to sympathetic nerve stimulation, thus resulting in reduced cardiac output and peripheral vascular resistance. Orthostatic hypotension is common because reflex-mediated vasoconstriction is blocked. Otherggr common side effects include erectile dysfunction, diarrhea, and weight gain. Long-term norepinephrine depletion leads to postsynaptic receptor supersensitivity. Therefore, concomitant use of tricyclic antidepressants and sympathomimetics may provoke acute severe hypertensive episodes. Because of these complications, these drugs have little to no role in the current management of hypertension

Pharmacoeconomic Considerations: The cost of effectively treating hypertension is substantial. However, these costs can be offset by savings thatwould be realized by reducing cardiovascular morbidity and mortality. Cost related to treating other forms of target-organ damage (e.g., myocardial infarction and endstage kidney failure) can drive health care costs up substantially. The cost per life-year saved fromtreating hypertension has been estimated to be $40,000 for younger adults and even less for older adults. Treatments that cost less than $50,000 per life-year saved generally are considered favorable by health economists. Drug costs can account for over 70%of the total cost of hypertensivecare. One model for calculating the cost-effectiveness of various initial monotherapies formild tomoderate hypertension found that the cost of life-year saved ranged from $10,900 with a generic β-blocker to $72,100 with a brand-name ACE inbhitor.109 In a cost-minimization study that included the cost of drug acquisition, supplemental drugs, laboratory tests, clinic visits, and complications, the total costs of treating hypertension were $895 for -blockers, $1043 for diuretics, $1165 for α-agonists, $1243 for ACE inhibitors, $1288 for -blockers, and $1425 for CCBs.[74] Another cost-minimization analysis found that 86 middle-aged or 29 elderly hypertensive patients would need to be treated to prevent one myocardial infarction, stroke, or death. The excess cost of preventing one event with a CCB or ACE inhibitor instead of a diuretic or β-blocker was $89,000 to $341,000 for a middle-aged patient and $30,000 to $115,000 for an elderly patient. Depending on the agent chosen, the added cost would be $200 to $800 per year. Acomparative analysis in hypertensive patients aged 65 and older from a state prescription drug assistance program demonstrated that 40% of patients were prescribed pharmacotherapy that was not necessarily recommended by the JNC7 guidelines.[75] If these 40% had drug therapy modifications made to follow evidence-based treatment, a reduction in costs of $11.6 million would have been realized in the 2001 calendar year based on discounted prices. This was

projected to increase to $20.5 million using usual Medicaid pricing limits It therefore is crucial to identify ways to reduce the cost of care without increasing the morbidity and mortality associated with uncontrolled hypertension.Using evidence-based pharmacotherapy will save costs not only by using the most effective agents. Thiazide diuretics are recommended as first-line therapy in most patients and are very inexpensive. Just using thiazides, either as monotherapy or in combination, is appropriate under almost all circumstances and aspects of hypertension management. When needed, using other generic primary antihypertensive agents (e.g., atenolol or metoprolol for β-blockers and lisinopril or enalapril for ACE inhibitors) that can be administered once daily should be considered.

Hypertensive Urgencies And Emergencies [27,31,33]

Hypertensive urgencies and emergencies both are characterized by the presence of very elevated BP, greater than 180/120 mm Hg (see "Classification" in the "Arterial Blood Pressure" section). However, the need for urgent or emergent antihypertensive therapy should be determined based on the presence of acute or immediately progressing target-organ injury but not elevated BP alone. Urgencies are not associated with acute or immediately progressing target-organ injury,
whereas emergencies are. A common error with hypertensive urgency is overly aggressively
antihypertensive therapy. This treatment likely has been perpetrated by the classification terminology *urgency*. Hypertensive urgencies ideally are managed by adjusting maintenance therapy by adding a new antihypertensive and/or increasing the dose of a present medication. This is the preferred approach to these patients because it provides a more gradual reduction in BP. Very rapid reductions in BP to goal values should be discouraged because of potential risks.
Since autoregulation of blood flow in chronically hypertensive patients occurs at a much higher range of pressures than in normotensive persons, the inherent risks of reducing BP too precipitously include cerebrovascular accidents, myocardial infarction, and acute kidney
failure. All patients with hypertensive urgency should be reevaluated within no more than 7 days (preferably after 1 to 3 days). Acute administration of a short-acting oral antihypertensive agent (captopril, clonidine, or labetolol), followed by careful observation for several hours to ensure a gradual reduction in BP, is an option for hypertensive urgency. However, there are no data supporting this approach as being absolutely needed. Oral captopril is one of the
agents of choice and can be used in doses of 25–50 mg at 1- to 2-hour intervals. The onset of action of oral captopril is 15 to 30 minutes, and a marked fall in BP is unlikely to occur if no hypotensive response is observed within 30 to 60 minutes. For patients with hypertensive
rebound following withdrawal of clonidine, 0.2 mg clonidine can be given initially, followed by 0.2 mg hourly until the DBP falls below 110 mm Hg or a total of 0.7 mg clonidine has been administered. A single dose may be all that is necessary. Labetolol can be given in a dose of 200–400 mg, followed by additional doses every 2 to 3 hours. Oral or sublingual immediate release nifedipine has been used in the office setting, nursing homes, and hospitals for acute BP lowering but is potentially dangerous. This approach produces a rapid reduction in BP. Immediate-release nifedipine should never be used for hypertensive urgencies because of reports of severe adverse events such as myocardial infarctions and strokes.[107]
Hypertensive emergencies are those rare situations that require immediate BP reduction to limit newor progressing target-organ damage (see "Classification" in the "Arterial Blood Pressure" section). Hypertensive emergencies generally require parenteral therapy, at least initially, with one of the agents. The goal in hypertensive emergencies is not to lower BP to less than 140/90 mm Hg; rather, a reduction in mean atrial pressure (MAP) of up to 25% within minutes to hours is the initial target. If the BP is then stable, BP can be reduced toward 160/100–110 mm Hg within the next 2 to 6 hours. Precipitous drops in BP may lead to end-organ ischemia or infarction.

Combination Antihypertensive Therapy: Starting therapy with a combination of two drugs is now recommended in patients far from their BP goal, for patients in whom goal achievement may be difficult (i.e., those with diabetes or chronic kidney disease and African-Americans), or in patients with multiple compelling
indications for different antihypertensive agents. However, combination therapy is often needed to control BP in patients already on therapy, and most patients require two or more agents.[27,53]
Combination regimens for hypertension should include a diuretic, preferably a thiazide. If a diuretic was not the first drug added, it should be the second agent as add-on therapy. This method will provide additional BP lowering because

most patients respond well to a two-drug regimen that includes a diuretic. Clinicians should anticipate the need for three drugs to control BP in patients with aggressive BP goals (diabetes and chronic renal disease).

Diuretics, when combined with several agents (especially an ACE inhibitor, ARB, or β-blocker), can result in additive antihypertensive effects that are independent of reversing fluid retention. BP lowering from certain antihypertensive agents can activate the RAAS as a compensatory mechanism to counteract BP changes and regulate fluid loss. Most alternative antihypertensive agents (e.g., reserpine, arterial vasodilators, and centrally acting agents) need to be given with a diuretic to avoid sodium and water retention. Many fixed-dose combination products are available commercially, and some are generic . Most of these products contain a thiazide diuretic and have multiple dose strengths available. Individual dose titration is more complicated with fixed-dose combination products, but this strategy can reduce the number of daily tablets/capsules and can simplify regimens to improve adherence. This alone may increase the likelihood of achieving or maintaining goal BP values. Depending on the product, some may be less expensive to patients and to health systems.

Clinical Monitoring

Patients should be monitored for signs and symptoms of progressive target-organ disease . A careful history for chest pain (or tightness), palpitations, dizziness, dyspnea, orthopnea, headache, sudden change in vision, one-sided weakness, slurred speech, and loss of balance should be taken to assess the likelihood of cardiovascular and cerebrovascular hypertensive complications. Other clinical monitoring parameters that may be used to assess target-organ disease includes changes in funduscopic findings, LVH regression on electrocardiogram or echocardiogram, proteinuria, and changes in kidney function. These parameters should be monitored periodically because any sign of deterioration requires immediate assessment and follow-up. Clinic-based BP monitoring remains the standard for managing hypertension. BP response should be evaluated 2 to 4 weeks after initiating or making changes in therapy.With some agents, monitoring BP 4 to 6 weeks later may better represent steady-state BP values (reserpine) or in the case of ACE inhibitors may minimize the risk of adverse effects. Once goal BP values are attained, assuming no symptoms of acute target-organ disease, BP monitoring can be done every 3 to 6 months. More frequent evaluations are required in patients with a history of poor control, nonadherence, progressive target-organ damage, or symptoms of adverse drug effects. Self-measurements of BP or automatic ambulatory BP monitoring can be useful clinically to establish effective 24-hour control. This type of monitoring may become the standard of care in the future, but the JNC7 recommends that ambulatory BP monitoring only be used in select situations such as suspected white coat hypertension. If patients are measuring their BP at home, it is important that they measure during the early morning hours for most days and then at different times of the day on alternative days of the week. Patients should be monitored routinely for adverse drug effects. These side effects typically should occur 2 to 4 weeks after starting a new agent or increasing the dose, and laboratory tests should be repeated every 6 to 12 months in stable patients. Additional monitoring may be needed for other concomitant diseases, if present (e.g., diabetes, dyslipidemia, and gout). The occurrence of an adverse drug event may require dosage reduction or substitution with an alternative antihypertensive agent.

CONCLUSION

Hypertension is a relatively asymptomatic disease, and antihypertensive agents are not without adverse side effects. Therefore, it is imperative to assess patient adherence on a regular basis. Identification of nonadherence should be followed up with appropriate patient education and counseling. Once daily regimens are preferred in most patients to improve adherence. Although some practitioners may believe that aggressive treatment will have a negative impact on quality of life, several studies have found that most patients actually feel better once their BP is controlled. Patients on antihypertensive therapy should be questioned periodically about changes in their general health perception, energy level, physical functioning, and overall satisfaction with their treatment. At the present time, there is inadequate information to recommend any herbal therapy as a treatment strategy for hypertension. Lifestyle modifications always should be recommended and encouraged continually in patients engaging in such endeavors.

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