

Hypertension: Current Management Strategies

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Background: Hypertension affects 50 million persons in the United States and is the most common reason for office visits and prescriptions. This report reviews the epidemiology, diagnosis, and treatment of this condition and provides special attention to concomitant risk factors and issues of adherence.

Methods: A literature search was performed using MEDLINE files dating back to 1986. The key words were "hypertension," "antihypertensive agents," "patient compliance," "cardiovascular risk factors," "isolated systolic hypertension," and "JNC." Additional references were accessed by cross-referencing the bibliographies of the articles obtained in this search.

Results and Conclusions: Effective therapeutic pharmacologic and nonpharmacologic management of hypertension, including stage 1 as reclassified by the Fifth Report of the Joint National Committee (JNC-V), can greatly reduce mortality for patients. Despite extensive national efforts, 35 percent of hypertensive patients remain unknown, and only 7 percent have their hypertension adequately controlled. Any additional cardiovascular risk factors compound the risk of adverse outcome and can be adversely affected by treatment. JNC-V recommendations regarding equally effective pharmacologic agents are flexible but controversial. The favorable cardioprotective effects of angiotensin-converting enzyme inhibitors, calcium channel blockers, α -blockers, and α - β -blockers often make them a more appropriate choice than diuretics or β -blockers. Practical techniques for improving patient adherence to treatment regimens are also important and should begin when the diagnosis of hypertension is made. (J Am Board Fam Pract 1994; 7:202-17.)

Hypertension is the most common reason for a physician office visit in the United States.¹ As many as 50 million persons in this country are receiving treatment for hypertension or have had elevated blood pressure diagnosed. Hypertension is also the leading indication for the use of prescribed drugs.²

Hypertension has been reclassified by the Joint National Committee (JNC-V) on Detection, Evaluation, and Treatment of High Blood Pressure based on impact on risk (Table 1).³ Treatment of elevated blood pressure decreases the associated mortality and morbidity, and control of hypertension has contributed substantially to the 57 percent and 50 percent decline in mortality from stroke and coronary heart disease, respectively, from 1972 to 1990 (Figure 1).³ The purpose of this article is to review the epidemiology, work-up, and treatment options for this condition.

Prevalence

The prevalence of hypertension depends on the composition of the population studied and the definition used for the study. Nevertheless, it is commonly believed that about 50 million persons in the United States have hypertension. The incidence rates increase approximately 5 percent for every 10 years of age. High blood pressure stage 1, previously termed *mild* is the most common form in adults and is responsible for a large proportion of the excess morbidity and mortality.^{2,3}

The Framingham Study reported that 50 percent of a white suburban population had blood pressures of 140/90 mmHg or more. The percentages for African-Americans, those with a genetic history of hypertension, the elderly, the obese patient, and those who consume excessive amounts of alcohol were higher. Figure 2 reflects the prevalence of hypertension based on race, age, and sex.⁴

Efforts through the National High Blood Pressure Education Program have reduced the number of untreated cases of hypertension in the last 20 years. If the 140/90 mmHg criterion is used, 35 percent of those with elevated blood pressure are estimated to be unknown and their conditions, therefore, untreated. In 1991, 49 percent of those known to have hypertension were

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Table 1. Classification of Blood Pressure for Adults Aged 18 Years or Older.*

Category	Systolic (mmHg)	Diastolic (mmHg)
Normal	<130	<85
High normal	130-139	85-89
Hypertension†		
Stage 1 (mild)	140-159	90-99
Stage 2 (moderate)	160-179	100-109
Stage 3 (severe)	180-209	110-119
Stage 4 (very severe)	≥210	≥120

*Not taking antihypertensive drugs and not acutely ill.

†Based on the average of two or more readings taken at each of two or more visits following an initial screening.

taking antihypertensive medications, and about 21 percent of those whose hypertension was being treated had their condition satisfactorily under control,³ which means that only 10 percent of those known to have hypertension, or 7 percent of all hypertensive individuals, are under adequate control (Table 2).

Etiology

In 90 to 95 percent of cases the underlying cause of hypertension is unknown and labeled essential (or primary). Of the 5 to 10 percent of treatable secondary cases of hypertension, the cause almost always results from problems within the renal or endocrine system. The pathophysiology of hypertension is multifaceted and heterogenous. An elevation of blood pressure can result from an increase in either cardiac output or total peripheral resistance or both. The primary hemodynamic abnormality in essential hypertension is elevated systemic peripheral resistance^{5,6} (Figure 3).

Although population studies have revealed heredity as a factor in primary hypertension, many environmental factors have also been hypothesized regarding its development. Sodium handling, chloride channels, membrane cation flux, and modulation responses all have been theorized as contributing to hypertension. The increased vascular resistance can be caused by structural thickness or functional vasoconstriction caused by an increase in intracellular calcium.²

The Framingham cohort had a 70 percent association of newly acquired hypertension with obesity.⁷ Glucose intolerance, insulin resistance, and hyperinsulinemia also are associated with both obesity and hypertension.⁸ As much as 10 percent of hypertension in men has been attributed to alcohol. In small quantities, alcohol could raise the blood pressure; in larger quantities, it can be responsible for serious hypertension.^{2,3}

Risk Factors

Hypertension increases cardiovascular morbidity and mortality two- to fourfold. Risk is proportional to the degree of systolic blood pressure or diastolic blood pressure elevation at any age in either sex. Considerable risk accrues even for those with high normal blood pressures.⁹ Women and whites, however, tolerate hypertension better than men and African-Americans. Genetic, pathophysiological, and socioeconomic factors all contribute to decreased hypertension control in the African-American population.¹⁰

Systolic blood pressure elevations are more a determinant of cardiovascular risk than are diastolic blood pressure elevations for the entire adult age range (Figure 4).¹¹ These conditions present together are even more devastating. The relative risk of death for systolic blood pressures ≥160 mmHg and diastolic blood pressures ≥100 mmHg is increased by more than 3.4 times in both men and women aged 35 to 64 years.¹²

The associated atherogenic risk factors of increased total cholesterol to high-density lipoprotein (HDL) -cholesterol ratio, smoking, impaired

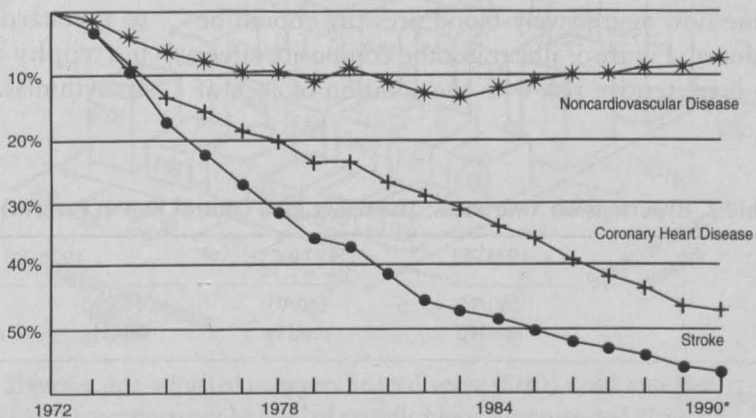


Figure 1. Percentage of decline in age-adjusted mortality rates since 1972.

*Provisional data for 1990.

Source: National Center for Health Services data calculated by the National Heart, Lung and Blood Institute.

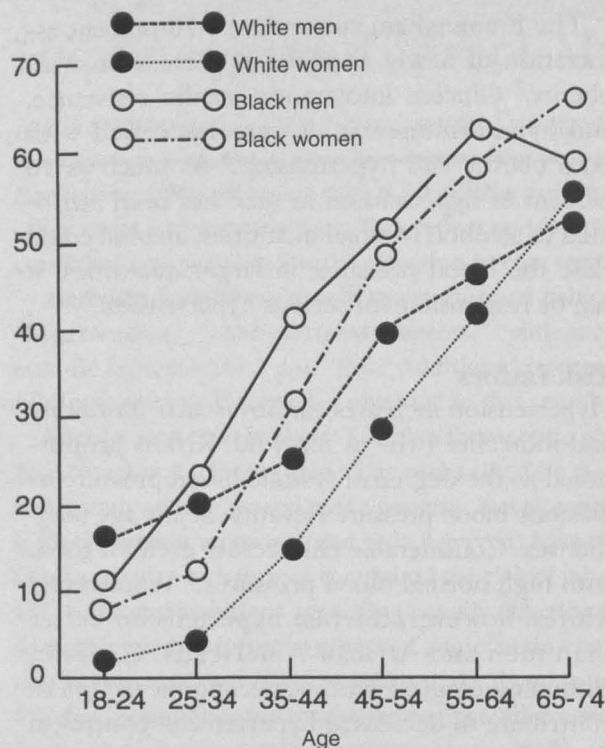


Figure 2. Percentage of population with hypertension: United States 1976-1980.

Source: National Center for Health Services Advance Data, Vital and Health Statistics of the National Center for Health Statistics, Department of Health and Human Services.

glucose tolerance, obesity, sedentary lifestyle, and electrocardiogram (ECG) abnormalities (specifically, left ventricular hypertrophy) escalate the risk independently. The JNC-V has recommended that cardiovascular risk from all cardiovascular and metabolic abnormalities, not just diastolic blood pressure and systolic blood pressure, be assessed in the hypertensive patient to determine how aggressively blood pressure should be reduced. Figure 5² illustrates the composite effect on hypertensive risk with the addition of each of

these variables.¹³ Left ventricular hypertrophy, measured by electrocardiography or echocardiography, has emerged as the most important risk factor for adverse outcomes among hypertensive patients,^{14,15} especially for those with "borderline hypertension" as described in the Tecumseh Blood Pressure Study.¹⁶

The Lipid Research Clinics Coronary Primary Prevention Trial was able to effect a 24 percent reduction in definite coronary heart disease deaths and a 19 percent reduction in nonfatal myocardial infarctions.¹⁷ Trial results showed that for every 1 percent reduction in cholesterol level, a 2 percent decrease in coronary heart disease could be achieved.¹⁸ Smokers with serum cholesterol levels and systolic blood pressure levels in the highest quintiles had coronary heart disease death rates 20 times greater than nonsmokers with low cholesterol and systolic blood pressure levels. While hypertension should be detected as early as possible, it is important that the associated risk factors be treated even earlier.

Natural History of Untreated Hypertension

Hypertension is a progressive and potentially lethal disease. Before effective treatment existed, hypertension contributed to a life span reduction of 10 to 20 years. Even those whose hypertension is in the stage 1 category will develop end organ damage within an untreated decade. Almost 60 percent of the excess mortality risk occurs in the previously defined mild hypertensive category of 90 to 105 mmHg diastolic readings,¹⁹ with heart disease being the most common cause of death. Most of these deaths are related to myocardial infarction, left ventricular hypertrophy with congestive heart failure, or arrhythmias.²⁰

Table 2. Hypertension Awareness, Treatment, and Control Rates (Percent).

	1971-72	1974-75	1976-80		1988-91	
	160/95 mmHg	160/95 mmHg	140/90 mmHg	160/95 mmHg	140/90 mmHg	160/95 mmHg
Aware	51	64	54	73	65	84
Treated	36	34	33	56	49	73
Controlled						
Treated	16	20	11	34	21	55
Known					10	40
All					7	34

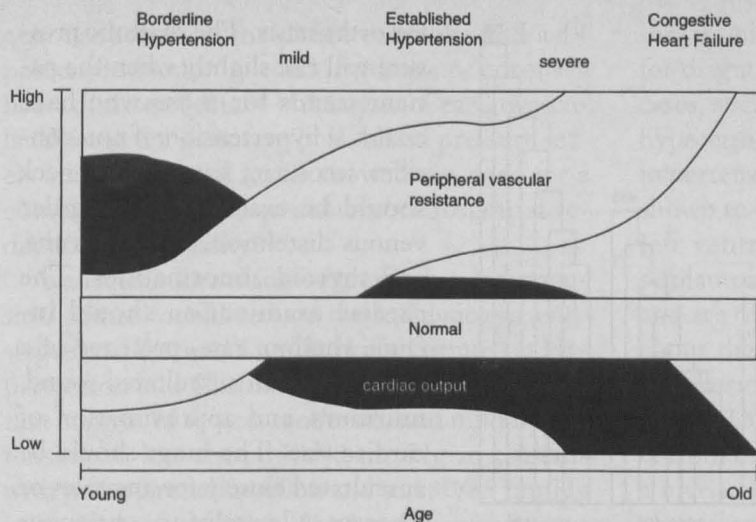


Figure 3. Changing hemodynamics of essential hypertension with age.
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Retinal hemorrhagic changes occur rapidly and can leave irreparable damage; sclerotic changes, on the other hand, are usually slow but can be equally debilitating. Cerebral vascular manifestations of hypertension are transient ischemic attacks or strokes. End-stage renal disease attributed to hypertension, particularly in African-Americans, the elderly, and those who have diabetes, has increased annually in the last decade and is now second to diabetes as a major category of morbidity. Arteriosclerotic changes in the hypertensive patient are most severe in the kidney, and albuminuria is a signal of renal damage. Hypertensive nephrosclerosis accounts for 40 percent of end-stage renal disease in African-Americans and 25 percent in whites, an association having been found between elevated blood pressure level and declining renal function.^{21,22} Peripheral vascular disease is another common complication of hypertension.

Isolated Systolic Hypertension
 Blood pressure, particularly systolic, tends to increase progressively with age. Isolated systolic

hypertension is a common problem, especially in the seventh decade of life. An independent cardiovascular risk factor, it affects approximately 3 million persons in the United States. It is associated with increased morbidity and mortality in those aged more than 65 years.²³

The Systolic Hypertension in the Elderly Program results have shown that proper treatment of isolated systolic hypertension is effective in lowering morbidity and mortality. Treatment, as reported in this study, decreased stroke incidence 36 percent and myocardial infarction or coronary deaths 27 percent, with a combined 32 percent reduction of all

cardiovascular events.²⁴ We have learned that isolated systolic hypertension should be treated, even in patients older than 80 years of age.²⁵ The Swedish Trial in Old Patients with Hypertension confirmed that treating combined hypertension in the elderly is beneficial.²⁶

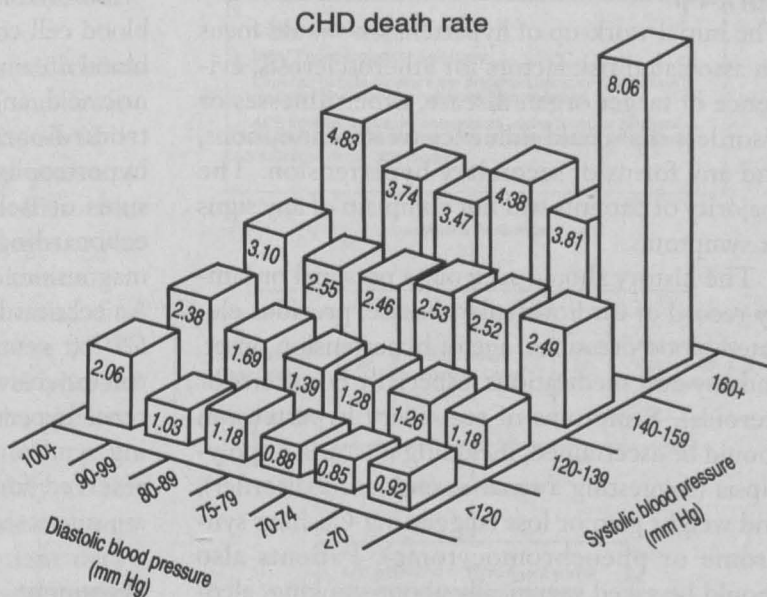


Figure 4. Age-adjusted coronary heart disease (CHD) death rate per 10,000 person-years by level of systolic blood pressure and diastolic blood pressure for men screened in the Multiple Risk Factor Intervention Trial.

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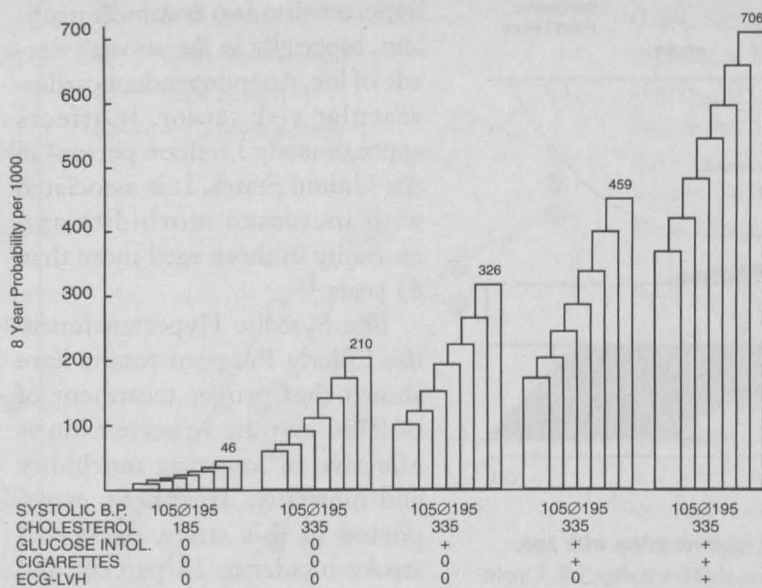


Figure 5. The 8-year risk of cardiovascular disease for men aged 40 years in Framingham according to progressively higher systolic blood pressures (in mmHg) at specified levels of other risk factors.

BP = blood pressure, INTOL = intolerance, ECG-LVH = electrocardiogram-left ventricular hypertrophy.

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Work-Up

The initial work-up of hypertension should focus on associated risk factors for atherosclerosis, evidence of target organ disease, other illnesses or disorders that could influence treatment options, and any forms of secondary hypertension. The majority of patients will not complain of any signs or symptoms.

The history should seek out a personal or family record of cardiovascular disease, previous elevated blood pressures, age of hypertension onset, and any new medications (especially hormones or steroids). Symptoms of secondary hypertension should be ascertained, including nocturia or polydipsia (suggesting a renal or endocrine disorder), and weight gain or loss (suggesting Cushing syndrome or pheochromocytoma). Patients also should be asked specifically about smoking, alcohol intake, drug use, diabetes mellitus, dyslipidemia, and dietary intake of sodium, cholesterol, and saturated fats.

The physical examination should be thorough, yet directed. Blood pressures should be checked in both supine and standing positions to evaluate

for orthostasis. The diastolic pressure will rise slightly when the patient stands for those who have essential hypertension; if not, consider secondary causes. The neck should be examined for jugular venous distention, carotid bruits, and thyroid abnormalities. The cardiac examination should include rhythm, rate, presence of a third or fourth auscultated sound, murmurs, and approximation of cardiac size. The lungs should be auscultated closely for any rales or wheezes. A lateralizing continuous systolic-diastolic abdominal bruit could indicate renal artery stenosis.²⁷ The abdomen should be palpated for hepatomegaly, renal masses, and aortic enlargements. The extremities should be examined for edema, tone, and pulses. The neurologic examination should include checking for arteriovenous diameter ratio changes, exudates, hemorrhages, and papilledema in the fundus.

Laboratory studies should include a complete blood cell count; a urinalysis; a lipid profile; and blood urea nitrogen, creatinine, glucose, calcium, uric acid, and potassium measurements. An electrocardiogram could disclose left ventricular hypertrophy, axis deviation, and any previous signs of ischemia. An initial chest radiograph, echocardiogram, and measurements of serum magnesium and phosphorus levels are optional. An echocardiogram is more sensitive and specific for left ventricular hypertrophy but currently is too expensive for routine use. Special studies for renal hypertension, pheochromocytoma, Cushing syndrome, and aortic coarctation should be reserved for patients in whom these diagnoses are suspected.^{2,3,19}

Treatment

A National Heart, Lung and Blood Institute meta-analysis of randomized trials reported an 11 percent reduction in total mortality with blood pressure control, a reduction primarily attributed to a decline in incidence of fatal strokes.²⁸ A continuation of the meta-analysis showed a 42 per-

cent reduction in incidence of stroke and a 14 percent reduction in total incidence of coronary heart disease events.^{29,30} Analysis of cardiovascular disease in relation to both blood pressure levels and cholesterol levels showed the need for a combined reduction to achieve a substantial reduction in morbidity.³¹

Available information suggests that hypertension control could reduce the incidence of end-stage renal disease. The Working Groups on Hypertension and Chronic Renal Failure concluded that control of severe, moderate, and mild hypertension to less than 140/90 mmHg in patients with normal renal function and to 130/85 mmHg in patients with established renal impairment can be beneficial.²¹ Studies also have shown that regression of cardiovascular structural changes can be achieved with long-term antihypertensive treatment.³²

Hypertension treatment can range from non-pharmacologic to monopharmacologic therapy to the use of multiple drugs with adjunctive treatments. For stage 1 and 2 hypertension, a period of lifestyle modifications (reduction or cessation of associated risk factors, exercise, modification of sodium intake to 2 g daily, reduction of alcohol intake to 1 oz or less per day, relaxation or bio-feedback, and weight loss) might be the only treatment necessary.³³

The report of the United States Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure recommends individualized treatment of diastolic blood pressures between 90 and 94 mmHg for those at high risk, i.e., men, smokers, and patients with target organ damage, diabetes mellitus, hyperlipidemia, or other major risk factors for cardiovascular disease.^{3,10} A persistent diastolic pressure of 95 mmHg or greater seems to be the level wherein therapy has been shown to provide the greatest protection.³⁴

Because blood pressure can vary widely within 1 patient, it is important to take multiple readings (at least three) before making treatment decisions, unless the initial level is moderately to severely elevated. Anyone can have labile blood pressure; thus, the term *labile hypertension* is meaningless. Most home readings are 5 to 10 mmHg lower than office readings. On the other hand, "white coat hypertension" can lead to a serious misclassification.³⁵ Ambulatory blood pres-

sure monitoring for 24 hours is sometimes helpful for diagnostic and treatment decisions in difficult cases, such as drug resistance, nocturnal changes, hypotensive episodes while treated, and episodic hypertension. Ambulatory monitoring has been shown to be the best predictor of those at risk for left ventricular hypertrophy.^{36,37} Inexpensive, semiautomatic home devices are readily available and are often worthwhile in reaching conclusions about the effectiveness of treatment or the need for pharmacologic treatment.³⁸

The latest recommendations, shown in Figure 6, from the Joint Committee are flexible and yield a myriad of options. Nevertheless, this treatment algorithm fails to capture what is in the JNC-V text. Special indications, concomitant diseases or risk factors, drug interactions, and so on, very fre-

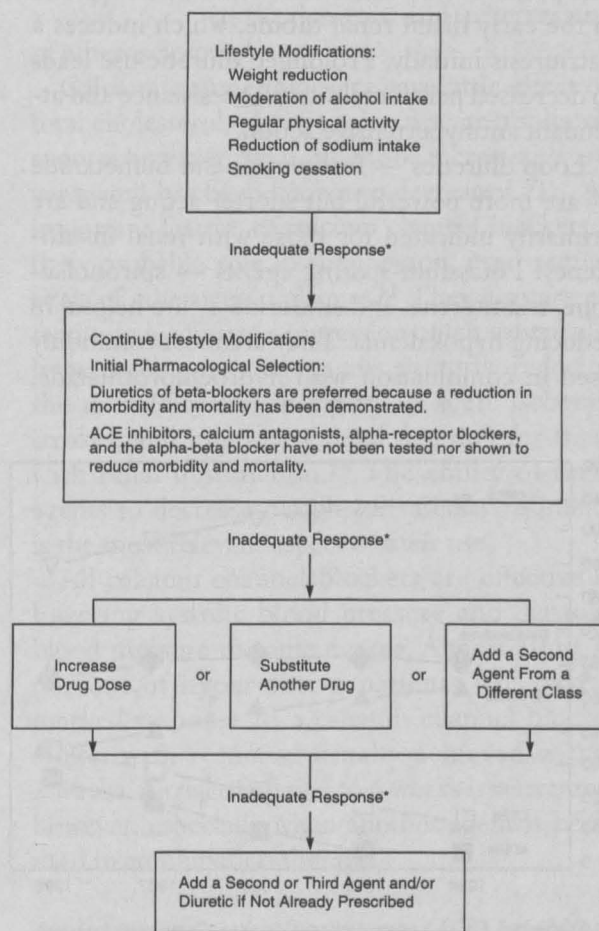


Figure 6. Treatment algorithm for hypertension.

*Response means the patient achieved goal blood pressure or is making considerable progress toward this goal.

ACE = angiotensin-converting enzyme.

Source: The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure.

quently make the calcium antagonists, angiotensive converting enzyme (ACE) inhibitors, α -blockers, and the α - β -blockers a more appropriate choice than the "preferred" diuretics and β -blockers. All are effective in lowering blood pressure about 10 percent in most patients who have mild to moderate hypertension, with relatively little difference in efficacy between the various available drugs. Small differences in efficacy might be less important than differences in quality of life and cost. Changes in the relative frequency of usages in different categories are shown in Figure 7.²

Diuretics

Thiazides have been a proven cornerstone of hypertension therapy for years and continue to be effective. The mechanism of action is through competitive inhibition of sodium reabsorption in the early distal renal tubule, which induces a natriuresis initially. Prolonged diuretic use leads to decreased peripheral vascular resistance and attendant antihypertensive action.

Loop diuretics — furosemide and bumetanide — are more powerful but shorter acting and are primarily indicated for those with renal insufficiency. Potassium-sparing agents — spironolactone, triamterene, and amiloride — are helpful in reducing hypokalemia. They are most commonly used in combination with hydrochlorothiazide.

The diuretic dosage effectiveness curve is relatively flat; thus, small doses usually can be used. Hydrochlorothiazide doses of 12.5 mg are often as effective as 50 mg. Rarely are doses higher than 50 mg needed.

The use of diuretics as first-line therapy has diminished because of their extensive side effects and aggravation of associated risk factors.⁷ There is evidence that they produce changes in serum lipids, glucose, potassium, and uric acid levels. The adverse pharmacologic effects on lipid metabolism have been shown to persist for many years,³⁹ but in other studies they persisted only 1 year.⁴⁰ The data on this entire subject are controversial.⁴¹ Both the Multiple Risk Factor Intervention Trial and Hypertension Detection and Follow-Up Program studies suggested that in patients with abnormal electrocardiograms, a higher coronary disease mortality rate resulted for those treated with diuretics, presumably from hypokalemic-induced ventricular ectopy.^{19,42} Diuretics also fail to reverse left ventricular hypertrophy and aggravate insulin resistance.⁴³ Figure 8 shows the pathogenetic profile for the side effects of diuretics.²

Diuretics are particularly effective for African-American, elderly, and other low-renin hypertensive patients. Most of the available data on the long-term treatment benefit for hypertension have been with diuretic therapy. Many of the reported adverse metabolic effects of diuretics might be of limited clinical importance.⁴⁴ For this reason and because they are inexpensive, JNC-V gave diuretics a preferred status.^{3,45} Diuretics should be avoided in patients with gout and used with caution in those with diabetes, hyperlipidemia, a low salt intake, or preexisting volume depletion.⁴⁶

β -Blockers

β -Adrenergic inhibitors are the second most widely used drugs after diuretics and have also been proved to reduce morbidity and mortality. The mechanism of action of β -blockers without intrinsic sympatholytic activity is competitive with β -adrenergic stimulants for receptor sites, which then leads to decreases in the heart rate, cardiac output, and renal blood flow. This group also inhibits vasoconstriction, thus decreasing peripheral resistance. These β -blockers have an adverse effect on lipid metabolism and carbohydrate tolerance. They are relatively contra-

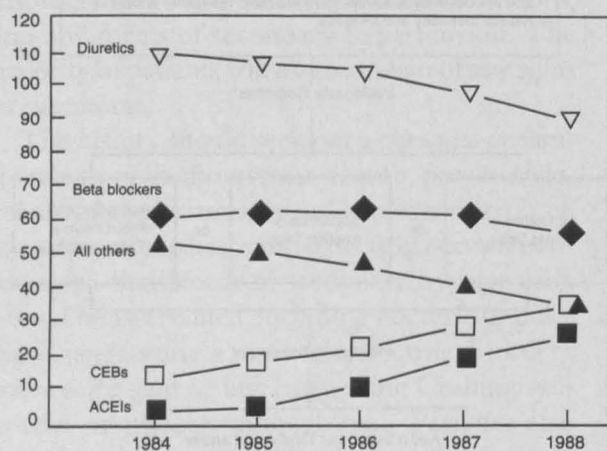


Figure 7. Numbers of prescriptions (in millions) written for antihypertensive drugs in the United States from 1984 to 1988.

CEBs = channel calcium (entry) blockers, ACEIs = angiotensin-converting enzyme inhibitors.

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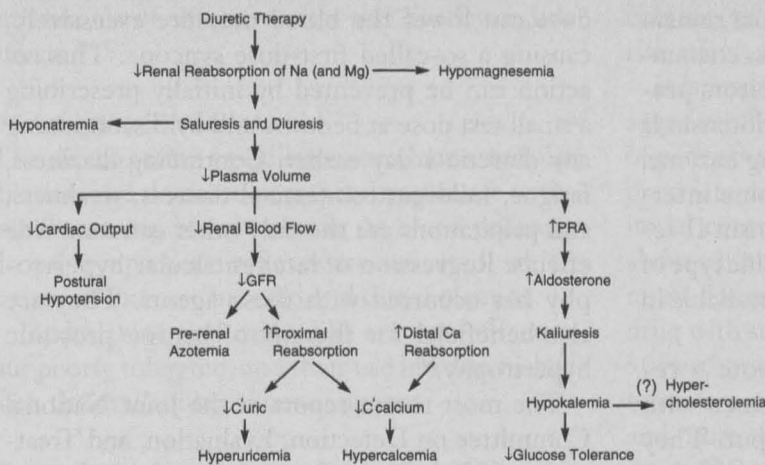


Figure 8. Mechanisms by which chronic diuretic therapy might lead to various complications.

Na = sodium, Mg = magnesium, GFR = glomerular filtration rate, Ca = calcium, C¹ = clearance.

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indicated in patients with diabetes mellitus, hyperlipidemia, active peripheral vascular disease, depression, asthma, and congestive heart failure.

The β -blockers that have intrinsic sympatholytic activity possess some sympathomimetic activity and work with less reduction in heart rate and cardiac output. They have a favorable effect on serum lipids, in contrast to other β -blockers that reduce HDL cholesterol and increase triglycerides and low-density lipoprotein (LDL) cholesterol.⁴⁷ Edema is more likely in those taking β -blockers with intrinsic sympatholytic activity.²

β -Blockers are particularly useful in patients who have left ventricular hypertrophy, anxiety, tachycardia, angina, migraine, or glaucoma. In addition, they provide some protection against the recurrence of a myocardial infarction or sudden death.^{2,48}

Calcium Channel Blockers

Calcium channel blockers are a heterogeneous group of compounds that substantially lower blood pressure in hypertensive patients. The calcium channel blockers can be used as monotherapy or in combination with other agents. They should be considered as first-line therapy because of their blood pressure response, tolerance, side-effect profile, and relative lack of adverse metabolic effects.

Calcium channel blockers cause arterial and arteriolar vasodilatation by interfering with the transmembrane flow of calcium through proposed voltage-dependent channels. Dihydropyridine causes a more potent and rapid reflex sympathetic stimulation than does verapamil or diltiazem, which can lead to flushing, headaches, and edema. Verapamil has the greatest negative inotropic effect, can delay cardiac conduction, and can cause constipation. Diltiazem has effects somewhat in between the others.⁴⁹ The exact role of calcium in hypertension has not been defined,⁵⁰ but the calcium ion plays a critical role in the genesis and progression

of atherosclerosis.⁵¹

Calcium channel blockers have little effect on total cholesterol, glucose tolerance, or insulin response; however, HDL might be increased,⁵² and verapamil has been known to decrease LDL. An important feature of calcium channel blockers is their probable role in suppression, even regression, of atherogenic plaques.⁵³ They also are effective in leading to a regression of left ventricular hypertrophy, treating angina pectoris, reducing the morbidity and mortality in acute ischemic strokes, and improving renal function for those with renal dysfunction.⁵⁴ The ability of these agents to decrease peripheral vascular resistance is the most relevant aspect of their use.

All calcium channel blockers are effective in lowering systolic blood pressure and diastolic blood pressure to some degree. Almost 50 to 75 percent of hypertensive patients will have a marked response to a calcium channel blocker alone, with response usually achieved within 2 weeks. A trial of up to 4 to 6 weeks is warranted, however, especially when another agent is being used in combination therapy.

Angiotensin Converting Enzyme (ACE) Inhibitors

The mechanism of action of the ACE inhibitors is not entirely known, but they appear to act through the suppression of the renin-angiotensin aldosterone system. The degree of blood pressure reduction achieved is positively correlated with

plasma renin activity, but ACE inhibitors remain effective even in low renin states, such as encountered in the elderly.⁵⁵ The ACE inhibitors prevent conversion of angiotensin I to angiotensin II by inhibiting the angiotensin-converting enzyme. Local vascular, renal, and catecholamine interactions also can occur. Type I angiotensin II receptor antagonists are a new, more specific type of inhibitor that is promising but not yet available in the United States.⁵⁶

In general, ACE inhibitors promote a reduction in peripheral vascular resistance with possible improvement in cardiac output. They have been shown to reduce left ventricular hypertrophy. These features make the ACE inhibitors an ideal agent for hypertensive patients with congestive heart failure and have been shown to improve survival.⁵⁷ In addition, ACE inhibitors seem to increase renal blood flow, preserve the glomerular filtration rate, and reduce proteinuria. They might have a beneficial renal effect, particularly in diabetic patients with nephropathy. Other studies have reported slowing of progressive renal failure in patients receiving ACE inhibitors.⁵⁸

ACE inhibitors are an excellent first-line choice of pharmacologic therapy.^{2,59} From the many options available, most are principally metabolized by the kidney. Exceptions include fosinopril and ramipril, which have dual excretions in the liver and kidney. In combination therapy ACE inhibitors are also important, particularly for postmyocardial infarction congestive heart failure. When starting therapy with ACE inhibitors, the patient's renal status requires careful monitoring, particularly for those who have preexisting renal disease. Side effects with ACE inhibitors include rash, taste disturbance, cough, neutropenia, and proteinuria.

α-Blockers

α-Adrenergic receptor blockers are adrenergic inhibitors that act on the arterial smooth muscle receptors, blunting vasoconstriction and inducing peripheral vasodilation with minimal reflex stimulation of cardiac output. They are an effective treatment for all forms of hypertension.

α-Blockers have no known adverse metabolic effects. In fact, they seem to be lipid protective, lowering total cholesterol and triglyceride levels and raising HDL-cholesterol levels.⁴¹ The initial

dose can lower the blood pressure excessively, causing a so-called first-dose syncope. This reaction can be prevented by initially prescribing a small test dose at bedtime and by discontinuing any diuretic 1 day earlier. Continuing dizziness, fatigue, mild gastrointestinal distress, weakness, and palpitations are the only other common side effects. Regression of left ventricular hypertrophy has occurred with these agents. They are also beneficial for therapy of benign prostatic hypertrophy.⁶⁰

The most recent report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure lists α-blockers as first-step pharmacologic agents.³ Others, such as Dzau,⁶¹ have previously considered them the preferred drug for selected patients in the individualized approach to initial therapy.

α-β-Blockers

Labetalol is a nonselective β-adrenergic receptor blocker and is also highly selective for α-adrenergic receptors.² This combined effect reduces vascular resistance while preserving cardiac output. Orthostatic hypotension is the most frequent adverse side effect.

Central-acting Adrenergic Inhibitors

Central-acting adrenergic inhibitors are α(2)-receptor agonists that act at the vasomotor centers in the brain, resulting in a decrease in sympathetic outflow and peripheral resistance. Cardiac output is decreased slightly.

Methyldopa, clonidine, guanabenz, and guanfacine are used less frequently than they once were and are usually second-line drugs for those who tolerate or escape sedation. These drugs can be helpful for patients who do not tolerate or respond well to other drugs.²

Peripheral-acting Adrenergic Inhibitors

Peripheral-acting adrenergic inhibitors work both in the central nervous system and upon the peripheral neurons. Some act as competitive inhibitors of α-receptors and others as blockers of β-receptors.

This class of drugs can be effective in treating hypertension. Reserpine is relatively inexpensive and is frequently used with a diuretic. Guanethidine is now considered primarily to be a last-option drug. Guanadrel, a drug similar to guan-

ethidine, is of shorter action and has fewer side effects.²

Direct-acting Vasodilators

The direct-acting vasodilators produce arteriolar dilation and decrease peripheral resistance without increasing blood volume. As blood pressure drops, sympathetic reflexes are activated, which causes an increase in renin and catecholamine.

Hydralazine and minoxidil are very effective but poorly tolerated, and their use has diminished with the availability of newer agents.²

Therapeutic Strategies

Individualized care is touted by most authors on the subject today, and stepped care has been abandoned. Profiling patients based on their demographics and associated medical conditions provides valuable information.

A recent six-drug study by the Department of Veterans Affairs of hypertensive men, of which 48 percent were African-American, showed that diltiazem therapy had the greatest success in reaching the blood pressure goal, with race and age having an important effect on response. Captopril was best for young men but was least effective in African-American patients. Systolic blood pressure was most responsive to hydrochlorothiazide and clonidine. Atenolol was most effective in older white patients. In general, prazosin was the least effective and clonidine the least tolerated.⁴⁰

Physicians can ascertain whether a drug is effective and well tolerated through trial and error by carefully monitoring the patient.² An n-of-1 trial technique offers a practical opportunity to individualize therapy. The choice is based on an analysis of results observed after the sequential administration of two or three monotherapies, which are interrupted by 2-week washout periods.⁵⁶ Sex of the patient has not been shown to affect drug responsiveness.³ Antihypertensive drugs can worsen some concomitant diseases or cardiovascular risk factors. JNC-V has given diuretics and β -blockers preferred status on the basis of documented reduction of morbidity and mortality. Nevertheless, the calcium antagonists, ACE inhibitors, and α -adrenergic receptor blockers have important, proven benefits that apply to a great percentage of hypertensive patients.^{43,47} Table 3 provides a comprehensive summary of

choices, side effects, contraindications, coronary risk effect, and indications.

It is important to select the initial hypertensive agent carefully because approximately 50 percent of patients will continue to take that drug. An appropriate strategy is "dose low and go slowly." If initial control is hard to achieve, opinions differ about whether it is advisable to prescribe the maximum dosage of a first drug or to add a second drug with submaximum doses of both. More than 50 percent of patients can have their mild or moderate hypertension managed with monotherapy, and more than 90 percent are managed with two drugs.⁶² Reducing the amount of medication after 1 year of normotensive readings is advisable; as many as 15 percent of hypertensive patients taking medications will be able to eliminate drug therapy altogether. The criteria for step-down therapy in mild essential hypertension are youth, normal body weight, low salt intake, no alcohol consumption, low pretreatment blood pressure, successful therapy without medication, and no (or minimal) signs of target organ damage.⁶³

J-Curve

There has been considerable debate on the importance and clinical appreciation of the J-curve. Some studies have found an increase in coronary events if the diastolic pressure is lowered below 85 to 90 mmHg. Most authors, however, agree that the actual low point of the J-curve has not been clearly defined and that the goal should still be a diastolic target of 85 to 90 mmHg, depending on therapy tolerance and response.^{2,64,65}

Adherence

Concern about patient adherence to treatment regimen should begin as soon as the diagnosis of hypertension is confirmed.⁶⁶ Nonadherence is a major problem, contributing greatly to the 93 percent of patients who are inadequately controlled. Development of an effective treatment plan requires that patients and physicians reach an understanding and an informed agreement about the problem, the treatment, and respective roles of physician and patient. In this way patient ideas, feelings, and expectations are incorporated into the treatment planning and will contribute to adherence.⁶⁷⁻⁶⁹ It is important to be aware how side effects from antihypertensive medications, such as sexual dysfunction, can interfere

Table 3. Antihypertensive Agents, Dosage, and Profiles

Antihypertensive Agents	Daily Dose Range	Side Effects	Relative Contraindications	Coronary Risk Factors	Indications
Calcium Channel Blockers					
Diltiazem (Cardizem, Dilacor)	120-480 mg	Nausea, edema, headache, flushing	Hypersensitivity, CHF	Favorable	Angina
Verapamil (Calan, Isoptin, Verelan)	120-180 mg	Edema, headache, bradycardia	Heart block, CHF	↓	↓
Dihydropyridines:					
Amlodipine (Norvasc)	2.5-10 mg	Nausea, edema, headache, flushing	Hypersensitivity, CHF	↓	↓
Felodipine (Plendil)	5-20 mg	↓	Aortic stenosis CHF	↓	↓
Isradipine (DynaCirc)	5-10 mg	↓	Hypersensitivity, CHF	↓	↓
Nicardipine (Cardene)	60-120 mg	↓	Hypersensitivity, CHF	↓	↓
Nifedipine (Adalat, Procardia)	30-180 mg	↓	Heart block, CHF	↓	↓
ACE Inhibitors					
Benazepril (Lotensin)	10-40 mg	Fatigue, cough, dizziness, dysgeusia, rash	Hypersensitivity, renal disease	Favorable	CHF
Captopril (Capoten)	25-150 mg	↓	↓	↓	↓
Enalapril (Vasotec)	5-20 mg	↓	↓	↓	↓
Fosinopril (Monopril)	10-80 mg	↓	↓	↓	↓
Lisinopril (Prinivil, Zestril)	10-40 mg	↓	↓	↓	↓
Quinapril (Accupril)	10-80 mg	↓	↓	↓	↓
Ramipril (Altace)	2.5-20 mg	↓	↓	↓	↓
Diuretics					
Chlorthalidone (Hygroton)	12.5-50 mg	Hypokalemia, biochemical changes	Diabetes, gout, hyperlipidemia	Unfavorable	CHF
Hydrochlorothiazide (Esidrix, Hydrodiuril, Oretic)	6.25-50 mg	↓	↓	↓	↓
Furosemide (Lasix)	20-160 mg	↓	↓	↓	↓
Hydrochlorothiazide + triamterine (Dyazide, Maxide)	1/2-2 tablets	↓	↓	↓	↓
Indapamide (Lozol)	2.5-5 mg	↓	↓	↓	↓
α-Blockers					
Doxazosin (Cardura)	1-16 mg	Syncope, dizziness, weakness	Postural hypotension	Favorable	Hyperlipidemia, BPH
Prazosin (Minipress)	2-20 mg	↓	↓	↓	↓
Terazosin (Hytrin)	1-20 mg	↓	↓	↓	↓

Continued

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Table 3. Continued.

Antihypertensive Agents	Daily Dose Range	Side Effects	Relative Contraindications	Coronary Risk Factors	Indications
β-Blockers					
Atenolol (Tenormin)	25–100 mg	Bronchospasm, CHF, fatigue, bradycardia	Asthma, IDDM, CHF, COPD	Mixed: dyslipidemia, cardioprotective	Angina, tachycardia, post-MI, migraine
Betaxolol (Kerlone)	10–60 mg	↓	↓	↓	↓
Carteolol (Cartrol)	2.5–10 mg	↓	↓	↓	↓
Metoprolol (Lopressor)	50–300 mg	↓	↓	↓	↓
Nadolol (Corgard)	40–320 mg	↓	↓	↓	↓
Propranolol (Inderal)	40–480 mg	↓	↓	↓	↓
With intrinsic sympatholytic activity:					
Acebutolol (Sectral)	200–800 mg	Dyspnea, edema, fatigue, dizziness	↓	↓	↓
Penbutolol (Levatol)	20–80 mg	↓	↓	↓	↓
Pindolol (Visken)	10–60 mg	↓	↓	↓	↓
Timolol (Blocarden)	20–60 mg	↓	↓	↓	↓
α-β-Blockers					
Labetalol (Normodyne, Trandate)	200–1200 mg	Hypotension, fatigue, bronchospasm, edema	Asthma, IDDM, CHF	Neutral	Hypertensive emergency
Central α Agonists					
Clonidine (Catapres)	0.2–1.2 mg	Patch dermatitis, rebound hypertension, sedation	Depression	Favorable	
Guanabenz (Wytensin)	8–32 mg	Sedation, fatigue, dry mouth	Hypersensitivity	↓	Addictive disease treatment
Guanfacine (Tenex)	1–3 mg	Sedation, fatigue, dry mouth	Hypersensitivity	↓	Addictive disease treatment
Methyldopa (Aldomet)	500–3000 mg	Liver dysfunction, autoimmune diseases	Liver disease	↓	Addictive disease treatment Pregnancy
Peripheral Inhibitors					
Guanadrel (Hylorel)	10–75 mg	Orthostatic hypotension, diarrhea	Impotence	Mixed	CNS sedation
Guanethidine (Ismelin)	10–150 mg	Orthostatic hypotension, diarrhea	Impotence, CHF	↓	Treatment failure
Reserpine (Serpalon, Serpasil)	0.05–0.25 mg	Sedation, nasal congestion	Depression	↓	Cost consideration
Vasodilators					
Hydralazine (Apresoline)	50–400 mg	Headache, tachycardia, edema	CHF, lupus	Mixed	Pregnancy
Minoxidil (Loniten)	5–100 mg	Headache, tachycardia, edema	CHF hirsutism	↓	Third step

↓ = as above, CHF = congestive heart failure, BPH = benign prostatic hypertrophy, IDDM = insulin dependent diabetes mellitus, COPD = chronic obstructive pulmonary disease, MI = myocardial infarction, CNS = central nervous system.

with a patient's quality of life and lead to nonadherence.⁷⁰

Prolonged trials have dropout rates as great as 20 to 40 percent, and as many as 50 percent of patients have dropped out after 1 year. It has been shown that one-half of the side effects were actually present *before* the patients began taking the medication. In the Hypertension Detection and Follow-up Program, new symptoms occurred in only 14.3 percent of patients. Thus, it is important to be specific not only about the symptoms, but also about their timing and severity.⁷¹

Practical techniques for improving patient adherence include monitoring no-shows, watching for poor therapeutic response, and questioning the patient directly. Early attention to patient convenience for appointments, simplification of treatment regimens, and cost is important. Missed appointments need to be noticed and a reminder system developed.^{66,72} Table 4 lists factors in treatment choice.⁷³ Table 5 outlines strategies to overcome adherence issues.

Conclusions

Hypertension is an extremely common condition and a major cardiovascular risk factor. The National High Blood Pressure Education Program was launched 20 years ago to help solve a massive public health problem. Prevention of hypertension through healthier lifestyles and the detection, evaluation, and treatment of hypertension are laudable and deserve active support from physicians and all health professionals.

Effective therapeutic management can reduce mortality for patients, including those who have mild hypertension. Some nonpharmacologic interventions are also effective, particularly weight and sodium reduction.⁷⁴ Initial drug therapy should be individualized according to the patient

Table 4. Factors Affecting Choice of Antihypertensive Agents.

Antihypertensive effects
Safety
Patient acceptance
Cost
Number of doses per day
Need for laboratory follow-up
Mechanism of action
Potential interaction with other drugs
Additional salutary effects

Table 5. Strategies for Improving Patient Adherence to Treatment.

Adherence Issues	Strategies
Ignorance about problem	Teaching, repetition
Adverse behavior	Motivate patient change
Forgetfulness	Cue pill taking to other activities
Denial	Supportive exploration
Want cure	Control goal stressed
Communication barriers	Respectful, empathetic physician
Inadequate social support resources	Significant other, community
Expense	Cost-effective choices
Office waiting time	Drop-in follow-up visits
Complicated schedule	Once or twice daily medication
Side effects	Dosage, education, change
Poor follow-up	Appointment reminder system

profile, concomitant diseases or cardiovascular risk factors, and adherence issues. Only 20 percent of men have no other risk factor. Even though stroke reduction has been dramatic, coronary risk reduction has been less noteworthy when blood pressure has been lowered with thiazide diuretics or β -blockers.⁷⁵

The favorable cardioprotective effects of new classes of drugs, including ACE inhibitors, calcium channel blockers, α -blockers, and α - β -blockers are reasons for optimism that therapy with these agents will diminish cardiovascular morbidity and mortality.⁷⁶ Multiple pharmacologic agents are available that are equally effective in lowering blood pressure but have different effects on individual patients.⁷⁷ The choice of the drug must be carefully, and sometimes intuitively, made with a rational and deliberate attempt to monitor each patient closely for an adequate response, the presence of side effects, and ongoing therapeutic adherence.

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