The Hypertensive Patient In Family Practice

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Background: **Hypertension is one of the commonest reasons for visits to family physicians. Left untreated, hypertension and its sequelae can lead to serious morbidity and mortality. Most hypertensive patients have essential hypertension.**

Methods: **MEDLINE and *Index Medicus* literature searches of original studies, meta-analyses, and clinical reviews were conducted for the years 1987 to the present to review the latest recommendations on the diagnosis and treatment of hypertension. Background information from articles written before 1987, accessed from cross-reference of the more recent articles, is occasionally cited.**

Results and Conclusions: **Based on the reviewed literature, an approach to the diagnosis and treatment of hypertension for the family physician is presented with an emphasis on cost-effectiveness and nonpharmacologic treatment. Nonpharmacologic measures and lifestyle modification should always be part of the treatment plan, especially given the presence or risks of other comorbid conditions (i.e., diabetes and stroke). Coexisting conditions, side-effects, ease of adherence, cost of medication and monitoring, and anti-left ventricular hypertrophy properties should be considered in selecting a pharmaceutical agent to treat hypertension.**

Several areas of further research, particularly in the areas of cost-effectiveness and outcomes, are needed to refine further the treatment of hypertension. (J Am Board Fam Pract 1994; 7:403-16.)

Hypertension, one of the most frequent conditions seen in family practice, accounts for nearly 6 percent of outpatient visits.[1] Approximately 58 million persons in the United States have hypertension, and its prevalence increases with age.[2-5] African-Americans have an increased risk of developing hypertension and tend to do so at an earlier age and in more severe forms.[2] Hypertension and its sequelae account for a great deal of morbidity and mortality.

Definitions

Hypertension is defined as persistent elevation (based on two or more readings at two or more visits) of blood pressure above 140 mmHg systolic or 90 mmHg diastolic. The Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC-V) classifies high normal blood pressure in adults as a systolic reading of 130 to 139 mmHg or a diastolic reading of 85 to 89 mmHg. Mild hypertension is classified as a systolic blood pressure of 140 to 159 mmHg or a diastolic blood pressure of 90 to 99 mmHg. Moderate hypertension is classified as a systolic blood pressure of 160 to 179 mmHg or a diastolic blood pressure of 100 to 109 mmHg. Severe hypertension is classified as a systolic blood pressure of 180 to 209 mmHg or a diastolic blood pressure of 110 to 119 mmHg, with higher readings constituting very severe hypertension (Table 1).

Isolated systolic hypertension commonly occurs in the elderly and is defined as a persistently elevated systolic blood pressure with normal diastolic blood pressures. Isolated systolic blood pressure can be graded using the same parameters as presented in Table 1. Malignant hypertension is elevated blood pressure (usually in the severe range or higher) associated with acute end-organ findings (e.g., angina, congestive heart failure, neurologic changes).

Etiology

More than 95 percent of patients with hypertension seen in family practice have essential (primary) hypertension. The cause of essential hypertension has yet to be definitively explained. A discussion of the many suggested contributing factors, including volume or sodium overload, atrial natriuretic factor, high renin status, increased vascular tone, increased cardiac output or relative hyperadrenergic states, insulin resistance, and the ionic hypothesis, is beyond the scope of

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Table 1. Classification of Hypertension.

Classification	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)
Normal	<130	<85
High normal	130–139	85–89
Mild	140–159	90–99
Moderate	160–179	100–109
Severe	180–209	110–119
Very severe	>210	>120

this review but can be found elsewhere.[6-8] Essential hypertension could represent a spectrum of physiologic states with different contributing factors in different individuals.

Secondary causes of hypertension should be sought in pediatric and adolescent populations based on certain physical findings (e.g., decreased femoral pulses in a patient with coarctation of the aorta), in cases of sudden deterioration of previously well controlled hypertension, or in hypertension refractory to treatment, especially in patients taking multiple medications. Causes of secondary hypertension are listed in Table 2.

Methods

MEDLINE and *Index Medicus* searches of recent original studies, meta-analyses, and clinical reviews on hypertension were conducted for the years 1987 to the present. Additional background information from articles written before 1987 was accessed from cross-reference of the more recent articles. Based on this review, an approach to diagnosing and treating hypertension is presented, focusing on screening, appropriate history and physical examination, selected use of laboratory testing, use of nonpharmacologic treatments, selection of appropriate medications, and patient monitoring.

Screening for Hypertension

The increased public awareness of the importance of blood pressure is reflected in the widespread availability of community-based programs (and automated machinery) offering free or low-cost blood pressure screening. The optimal screening interval has not yet been determined, but many authorities have suggested that normotensive adults be screened every 2 years if a most recent blood pressure is less than 130/85 mmHg and annually for systolic pressures between 130 and 139 mmHg or diastolic pressures between 85 and 89 mmHg.[3,9] Higher risk individuals, such as those with a family history of hypertension, diabetic patients, overweight patients, and African-Americans, should be screened more frequently.

History and Physical Examination

The initial history and physical examination of a patient with suspected hypertension should focus on lifestyle, family history, signs and symptoms of end-organ damage, and possible secondary causes of hypertension. Table 3 lists important elements of the history, and Table 4 summarizes important areas of the physical examination.

Initial laboratory testing in the work-up of suspected hypertension is somewhat individualized. Routine testing includes a complete blood count; urinalysis; measurements of blood urea nitrogen, creatinine (renal status), glucose, electrolyte levels (particularly potassium); and a lipid panel

Table 2. Selected Causes of Secondary Hypertension.

Endocrine
- Pheochromocytoma
- Hyperthyroidism (usually systolic)
- Hyperaldosteronism
- Hyperparathyroidism
- Cushing disease
- 17-α-Hydroxylase deficiency
- 11-β-Hydroxylase deficiency
- Acromegaly

Renal
- Renal artery stenosis
- Fibromuscular dysplasia
- Glomerulonephritis, acute and chronic
- Collagen vascular disease or arteritis
- Diabetic nephropathy
- Polycystic kidney disease

Medications
- Glucocorticoids
- Mineralocorticoids
- Anabolic steroids
- Oral contraceptives
- Antihypertensive medication withdrawal syndromes
- Monoamine oxidase inhibitors
- Sympathomimetics
- Cyclosporins

Substance Abuse
- Alcohol abuse
- Caffeine*
- Tobacco*
- Cocaine

Other
- Pregnancy
- Coarctation of the aorta
- Increased intracranial pressure

*Effects are usually transient.

Table 3. Areas of History for Hypertensive Patients.

System or Area	Signs, Symptoms, and History
Central nervous system	Headache, change in mental status, focal deficits, visual changes, nausea, vomiting, history of transient ischemic attack or stroke
Cardiac	Chest pain, palpitations, arrhythmia, edema, orthopnea, paroxysmal nocturnal dyspnea
Pulmonary	Shortness of breath, dyspnea on exertion, asthma, chronic obstructive pulmonary disease
Abdomen	Aneurysm, liver disease
Renal	Prostatic enlargement, urinary obstructive symptoms, hematuria, glomerulonephritis, chronic disease
Endocrine	Diabetes, thyroid, adrenal, cholesterol
Medication	See Table 2
Family	Coronary artery disease before age 60 years, hypertension, stroke, thyroid disease, obesity, lipid disorders, peripheral vascular disease, kidney disease (polycystic disease)
Social	Tobacco, alcohol, drugs, stresses (includes "white coat syndrome"), dietary habits (fat, salt), exercise habits

(total cholesterol, high-density and low-density cholesterol, and triglycerides). Many experts continue to recommend a base-line electrocardiogram (ECG), although its sensitivity for left ventricular hypertrophy is poor. An ECG can be safely omitted in a young person who has no history of cardiac problems and no signs of end-organ damage on initial physical examination and laboratory work-up. Optional tests include a chest radiograph if there is evidence of cardiomegaly, congestive heart failure, or pulmonary disease; a thyroid profile; renal imaging (sonography or angiography); and measurement of plasma renin levels, urine vanillymandelic acid, metanepherine, and urinary 17-hydroxyketosteroids. An echocardiogram is the best test for evaluating suspected left ventricular hypertrophy; however, routine echocardiography for left ventricular hypertrophy has not been found to be cost-effective or to improve the outcomes of treated patients. Pending further research, an echocardiogram should be reserved for patients needing examination for other cardiac conditions (valvular disease, ejection fraction) or when the result of the echocardiogram will cause an important change in the treatment regimen.

24-Hour Ambulatory Blood Pressure Monitoring

As many as 21 percent of borderline or mildly hypertensive patients can have "white coat syndrome," or elevated blood pressures in a medical setting only.[10] Continuous (24-hour) blood pressure monitoring has been suggested as a means of evaluating the blood pressure of these truly normotensive patients before instituting treatment.[11] Ambulatory blood pressure monitoring provides a more accurate picture of the hypertensive burden to the patient than do random measurements in a physician's office and can thus help determine which patients need treatment. Ambulatory blood pressure monitoring can also help the physician judge the efficacy of treatment. Continuous ambulatory blood pressure monitoring is expensive, and no studies have shown it to be superior to random frequent patient self-measurement with a calibrated blood pressure cuff. Several relatively inexpensive, easy-to-use, accurate, digital blood pressure cuffs are commercially available. Asking patients to check their pressures regularly at home also involves the patient more directly in care. Calibration of the patient's cuff can be checked by simultaneous comparison of blood pressure readings against an office sphygmomanometer on a regular basis.

Continuous ambulatory blood pressure monitoring might be useful when discrepancies exist between blood pressure measurements and physical findings (persistently normal blood pressure

Table 4. Physical Examination of Hypertensive Patients.

System	Physical Findings
Vital signs	Blood pressure (standing or sitting and recumbant, both arms), weight, pulse
Fundi	Loss of previously noted venous pulses, arteriovenous narrowing or nicking, hemorrhages, exudates, papilledema
Neck	Thyromegaly, bruits, jugular venous distension, carotid pulses
Heart	Rhythm, rate, point of maximum impulse, murmur, rubs, gallops, clicks
Lungs	Rales, rhonchi, wheezes, dullness to percussion
Abdomen	Pulsatile mass, femoral pulses, obesity, organomegaly, bruits
Extremities	Cyanosis, clubbing, edema, pulses
Neurological	Focal motor or sensory deficits, reflexes, tremor

and end-organ damage without other cause), when evaluating possible medication-related syncopal events, when home blood pressure readings are unreliable, or for confirming treatment-resistant hypertension before instituting a more invasive investigation for secondary causes.[3,11] These situations are rare in practice, however.

Why Treat Hypertension?

Regardless of age and whether a stepped-care approach (diuretics or β-blockers as first-line treatment) or an individualized approach is used, control of systolic and diastolic hypertension can decrease the incidence of fatal and nonfatal cerebrovascular accidents and decrease overall cardiovascular mortality.[12-15] Control of hypertension can prevent progression to more severe hypertension and slow the progression of renal failure, congestive heart failure, retinopathy, and peripheral vascular disease. Some recent trials and meta-analyses suggest that control of hypertension can also decrease the incidence of fatal or nonfatal myocardial infarction,[16] although these findings have not yet been widely reproduced.

When to Start Treatment

Counseling about lifestyle modification can begin with the first reading of mildly elevated blood pressure. Persistently mild hypertension can be safely treated with a trial of nonpharmacologic measures for 3 to 6 months. Failure of nonpharmacologic treatment or more severe degrees of hypertension warrant institution of pharmacologic treatment, but nonpharmacologic measures should remain an integral part of the treatment plan.

Treatment of secondary hypertension is directed at the underlying cause.

Considerations in Developing a Hypertension Treatment Plan

Lifestyle and risk factor modification, concurrent medical conditions, ease of medical regimen adherence, cost of medication and monitoring, and effect of medication on left ventricular hypertrophy are all considerations when individualizing a hypertension treatment plan.

Lifestyle and Risk Factor Modification

Counseling about weight loss, diet, tobacco use, alcohol use, exercise, and medical and recreational drug use should be an integral and continual part of every hypertension treatment plan. Lifestyle modification is safe and cost-effective and has beneficial effects in the prevention and treatment of many other conditions. Weight loss has consistently been the most effective nonpharmacologic treatment for obese hypertensive patients. A 10-kg weight loss could result in up to a 15-mmHg decrease in systolic blood pressure and a 13-mmHg decrease in diastolic blood pressure; reductions in blood pressure can occur with as little as 4.5 kg (10 pounds) of weight loss.[17] Nutritional counseling should be directed toward a healthy diet, with attention to cholesterol and saturated fat intake. Sodium restriction (less than 2.5 g/d) can decrease blood pressure, especially in elderly and African-American patients, and is helpful in those with fluid retention or congestive heart failure.[2,3,18-20]

Exercise seems to have a lowering effect on blood pressure independent of weight loss, although the mechanism is unclear. A written exercise prescription, therefore, should be a part of the treatment plan. An enjoyable activity of moderate intensity (60 to 85 percent of the patient's age-specific maximum heart rate or to the point of just being able to maintain a conversation), continuous for at least 30 minutes, repeated at least 3 times a week should be recommended.[3,21-23] Less strenuous exercise of longer duration can also have beneficial effects.[3,21,22,24] The exercise plan should be tailored to the patient's specific likes and should accommodate coexisting conditions (such as degenerative arthritis). Patients who have cardiac risks or are of advanced age might need exercise stress testing before participation in vigorous exercise.

Coexisting Medical Conditions

Comorbid medical conditions influence the choice of pharmaceutical agent. One medication can be used as treatment for several conditions (e.g., β-blockers or calcium channel blockers for hypertension and angina, α_1-blockers for hypertension and symptoms of benign prostatic hypertrophy). Similarly, other medical conditions might contraindicate (absolutely or relatively) the use of a particular medication (e.g., β-blockers and asthma). Medications being taken for coexisting conditions could adversely interact with antihypertensive medication (e.g., diuretics and ibuprofen). The patient's lipid status and glucose

tolerance often influence the choice of medication. Tables 5, 6, and 7 list other useful indications, contraindication, and interactions by class of medication.

Ease of Adherence to Medical Regimen

Patients adhere best to a medical regimen when medication dosage is once or twice daily.[25,26] Side effects (and so-called quality-of-life issues) also affect patient adherence to the suggested pharmaceutical regimen. When choosing an antihypertensive agent, discuss common side effects with the patient and inquire about side effects at follow-up visits. Table 8 outlines dosage frequencies for selected medications, and Table 9 lists common side effects by class.

Cost of Medication and Monitoring

Cost will also affect adherence for patients who pay all or a major portion of prescription costs. To control health care costs, medication cost and the cost of monitoring are important even for those patients whose insurance covers pharmaceuticals.

Table 5. Lipid Effects of Antihypertensive Agents, by Class.

Antihypertensive Class	Lipid Effects
Diuretic	Short-term increase in low-density lipoprotein and total cholesterol (reverts to base line long term) Increase triglycerides
β-Blocker	Increase triglycerides Those without intrinsic sympathomimetic activity decrease high-density lipoprotein levels
Angiotensin-converting enzyme inhibitor	Neutral
Calcium channel blocker	Neutral (some data suggest verapamil and nifedipine could increase high-density lipoprotein levels)
α_1-Blocker	Increase high-density lipoprotein levels Decrease low-density lipoprotein and total cholesterol Might decrease triglycerides
Central agents	Neutral (though might decrease low-density lipoprotein and total cholesterol levels) Methyldopa might decrease high-density lipoprotein levels
Direct vasodilator	Neutral
Peripheral antiadrenergic	Neutral

Table 6. Effect of Antihypertensive Agents on Glucose Tolerance.

Class	Effect on Glucose Tolerance
Diuretic	Decreased insulin sensitivity
β-Blocker	Decreased insulin sensitivity Block insulin release Can mask symptoms of hypoglycemia
Angiotensin-converting enzyme inhibitor	Can improve glucose tolerance
Calcium channel blocker	Neutral
α_1-Blocker	Can improve glucose tolerance
Central agents	Neutral
Direct vasodilator	Neutral
Peripheral antiadrenergic	Neutral

Many brand name antihypertensive medications have time-tested, safe, and effective generic substitutes. Within a given class of medications, cost can vary substantially. The cost of laboratory monitoring (e.g., potassium checks for patients on diuretics) also needs to be considered. Table 8 provides some price comparisons between medications, and Tables 5, 6, and 9 list common metabolic effects by antihypertensive class.

Left Ventricular Hypertrophy

Left ventricular hypertrophy is a strong and worrisome risk factor for development of congestive heart failure, myocardial infarction, ventricular arrhythmia, and sudden death.[10,27-29] The newer classes of antihypertensive agents (calcium channel blockers, angiotensin-converting enzyme inhibitors, α_1-adrenergic blockers) are highly effective in slowing and reversing left ventricular hypertrophy. One recent study[30] suggests that contrary to earlier studies, even diuretics possess properties that counteract left ventricular hypertrophy. Large studies controlling for age, sex, other risk factors, and degree of blood pressure control are needed to compare the effects of the different classes of antihypertensive medications on left ventricular mass and cardiac outcome. Until then, the potential effect of a medication on left ventricular hypertrophy is an important theoretical consideration when choosing an antihypertensive medication. Table 10 lists relative effects against left ventricular hypertrophy by class.

Table 7. Antihypertensive Medication Choices by Patient Characteristics and Concurrent Medical Conditions.

Characteristic or Condition	Diuretic	β-Blocker	Angiotensin-converting Enzyme Inhibitor	Calcium Channel Blocker	α_1-Blocker	Centrally Acting Agent	Direct Vasodilator
Athletes	With caution	Avoid	Recommended	Recommended	—	—	—
African-American	Recommended	Less effective	Less effective	Recommended	—	—	—
Elderly	Recommended	Less effective	Less effective	Recommended	With caution	—	—
Angina	—	Recommended; avoid agents with intrinsic sympathomimetic activity	—	Recommended	—	—	—
Atrioventricular block	—	Avoid	—	Avoid verapamil, diltiazem	—	—	—
Benign prostatic hypertrophy	With caution	—	—	—	Recommended	—	—
Congestive heart failure	Recommended	Avoid	Recommended	Avoid verapamil, diltiazem	—	—	Hydralazine recommended
Depression	—	With caution	—	—	—	Avoid	—
Diabetes	With caution	With caution	Recommended	Recommended	—	Recommended	—
Diabetic nephropathy	—	—	Recommended	Recommended	Recommended	Recommended	—
Edema or fluid retention	Recommended	—	—	With caution	—	—	Avoid
Gout	With caution	—	—	—	—	—	—
Hyperlipidemia	With caution	With caution	Recommended	Recommended	Recommended	Caution with methyldopa	—
Known left ventricular hypertrophy	With caution	—	Recommended	Recommended	Recommended	Recommended	Avoid
Migraine headache	—	Recommended	—	Recommended	—	—	—
Osteoporosis	Thiazides recommended	—	—	—	—	—	—
Post-myocardial infarction	—	Recommended	Recommended	—	—	—	—
Peripheral vascular disease or Raynaud syndrome	—	Avoid	Recommended	Recommended	—	—	—
Pregnancy	With caution	With caution	Avoid	With caution	—	Methyldopa recommended	Hydralazine recommended
Reactive airways	—	Avoid	Recommended	Recommended	Recommended	Recommended	—
Renal insufficiency	Recommend loop diuretics, avoid potassium-sparing diuretics	—	With caution	Recommended	Recommended	Recommended	—
Sexual dysfunction	Avoid	Avoid	Recommended	Recommended	Recommended	Avoid	Avoid
Supraventricular tachycardia	—	Recommended	—	Recommended; avoid verapamil, diltiazem in patients with Wolff-Parkinson-White syndrome	—	—	—

Table 8. Dosage Frequency and Cost of Selected Antihypertensive Agents by Category.

Category	Examples	Dosage Frequency*	Cost†	Notes
Diuretics				
Thiazides	Chlorothiazide	qd–bid	$	Useful in combination with most other classes
	Chlorthalidone	qd	$	Other thiazides less commonly used
	Hydrochlorothiazide	qd	$	Use with caution in sulfa-allergic patients
	Indapamide	qd	$$$$	
	Metolazone	qd	$$$$	
Potassium-sparing	Amiloride	qd–bid	$	Commonly used with and found in combination with thiazides
	Spironolactone	bid–tid	$	Can deplete total body potassium slowly with time
	Triamterene	qd–bid	$	
Loop	Bumetanide	bid	$$$	More effective in patients with renal insufficiency
	Ethacrynic acid	bid	$$$	
	Furosemide	bid	$	
β-Blockers	Acebutolol (1,3,5,7)	qd–bid	$$$$$	1. Hydrophilic
	Atenolol (1,3,7)	qd	$$$$–$$$$$	2. Lipophillic (more likely to produce CNS side effects)
	Betaxolol (1,3,7)	qd	$$$$$	3. β_1 Receptor selective at low dose
	Bisoprolol (3,+/-1)	qd	$$$$$	4. Nonselective
	Carteolol (4,5,+/-1)	qd	$$$$$	5. Intrinsic sympathomimetic activity (ISA)
	Labetalol (2,4,6)	bid	$$$$$	6. α_1 Receptor blockade
	Metoprolol (3,7,+/-1)	qd-bid	$$$$–$$$$$	7. Membrane stabilizing activity (mild antiarrhythmic properties)
	Naldolol (1,4)	qd	$$$$$	
	Penbutolol (4,5,+/-1)	qd	$$$$$	Labetolol more effective in African-Americans than other β-blockers
	Pindolol (2,4,5)	bid	$$$$$	
	Propranolol (2,4,7)	qd–bid	$–$$$$$	All β-blockers can potentiate angina in patients with coronary artery disease if abruptly discontinued
	Timolol (2,4)	bid	$$$$$	
Angiotensin-converting enzyme inhibitors	Benazepril	qd–bid	$$$$$	Can cause hyperkalemia in patients with renal insufficiency or with potassium-sparing diuretics
	Captopril	bid–tid	$$$$$	
	Cilazapril	qd–bid	$$$$$	
	Enalapril	qd–bid	$$$$$	
	Fosinopril	qd–bid	$$$$$	
	Lisinopril	qd–bid	$$$$$	
	Perindopril	qd–bid	$$$$$	
	Quinapril	qd–bid	$$$$$	
	Ramipril	qd–bid	$$$$$	
	Spirapril	qd–bid	$$$$$	

Table 8. Dosage Frequency and Cost of Selected Antihypertensive Agents by Category. *(Continued)*

Category	Examples	Dosage Frequency*	Cost†	Notes
Calcium channel blockers	Amlodipine	qd	$$$$$	Diltiazem and verapamil are less potent peripheral vasodilators
	Diltiazem	qd–tid	$$$$$	
	Felodipine	qd	$$$$$	
	Isradipine	bid	$$$$$	
	Nicardipine	tid	$$$$$	
	Nifedipine	qd (SR) or tid	$$$$$	
	Verapamil	qd or bid (SR) bid–tid (generic)	$$–$$$	
α_1-Blockers	Doxazosin	qd	$$$$$	Give first dose at bedtime to avoid postural hypotensive effects
	Prazosin	bid–tid	$$$–$$$$	
	Terazosin	qd	$$$$$	
Centrally acting agents	Clonidine	bid, patch one weekly	$–$$$$	Malignant hypertension can occur with abrupt withdrawal
	Guanabenz	bid	$$$$$	
	Guanfacine	qd	$$$$$	
	Methyldopa	bid	$–$$	
Direct vasodilators	Hydralazine	bid–qid	$	Concomitant treatment with β-blocker and diuretic needed
	Minoxidil	qd–bid	$$$–$$$$	Can cause reflex tachycardia and sodium or fluid retention
Peripheral Antiadrenergics	Guanadrel	bid	$$$$$	Rarely used; can cause severe orthostatic hypotension; has relatively poor side-effect profile
	Guanethidine	qd	$$$–$$$$	
	Reserpine	qd	$	

*Dosed as monotherapy, can be prescribed less frequently in combination with other agents.
†Average wholesale price for 30 days supply based on 1993 Red Book: pharmacy's fundamental reference resource. $=<$5/mo, $$=$5–$10/mo, $$$=$10–$20/mo, $$$$=$20–$40/mo, $$$$$=>$40/mo. Price range listed for generic substitution where applicable, brand names more expensive.
qd=once daily, bid=twice daily, tid=three times daily; qid=four times daily.
CNS=central nervous system, ISA=intrinsic sympathomimetic activity, SR=sustained-release preparation.

Table 9. Classes of Antihypertensive Agents: Mechanism of Action, Common Side Effects, and Precautions.

Classification	Mechanism	Common Side Effects	Precautions
Diuretics	Sodium excretion Decrease plasma volume Decrease extracellular fluid volume Indapamide decreases peripheral resistance Spironolactone is a weak aldosterone antagonist	Sexual dysfunction Cramps Altered taste Weakness Leukopenia Dehydration	Potentiate digoxin toxicity Potentiate ventricular arrhythmia and increase risk of sudden death in patients with left ventricular hypertrophy Potentiate renal insufficiency when used with non-steroidal anti-inflammatory agents Nonsteroidal anti-inflammatory agents antagonize the effect of diuretics Hyponatremia Hypokalemia (can occur with long-term use of potassium-sparing agents as well) Hyperkalemia (potassium-sparing agents) Hypomagnesemia Hyperuricemia
β-Blockers	Decrease pulse rate and contractility Decrease cardiac output Decrease plasma renin activity Labetalol acts as a vasodilator	Depression Increase antinuclear antibodies Postural hypotension (labetalol) Psoriasis Fatigue Erectile dysfunction Loss of libido Can precipitate bronchospasm Dyspnea on exertion Rare hepatotoxicity (labetalol) Can worsen symptoms of Raynaud phenomenon or peripheral vascular disease	Can precipitate congestive heart failure or heart block Can mask symptoms of hypoglycemia Can precipitate angina if abruptly withdrawn in patients with coronary artery disease
Angiotensin-converting enzyme inhibitors	Block formation of angiotensin II Decrease aldosterone Increase prostaglandin E_2 Increase bradykinin Vasodilators, especially renal efferent arteriole	Cough Rash Loss of taste Angioedema Dependent edema Cholestasis	Can potentiate renal failure in patients with bilateral renal artery stenosis Can improve or worsen proteinuria in diabetic renal disease Hyperkalemia

Table 9. Classes of Antihypertensive Agents: Mechanism of Action, Common Side Effects, and Precautions. *(Continued)*

Classification	Mechanism	Common Side Effects	Precautions
Calcium channel blockers	Smooth muscle relaxation Vasodilatation, especiallly renal afferent arteriole Minor inhibition of platelet aggregation	Edema Headache Constipation Flushing Atrioventricular block (verapamil, diltiazem) Palpitations, tachycardia (less with verapamil, diltiazem)	Diltiazem and verapamil increase serum digoxin levels Verapamil and diltiazem are negatively ionotropic and can precipitate atrioventricular block or congestive heart failure Verapamil contraindicated in patients with Wolff-Parkinson-White syndrome
α_1-Blockers	Vasodilation via blockade of postsynaptic α_1 adrenergic receptors	First-dose orthostasis Lightheadedness Edema Palpitations, tachycardia Headache	First dose given at bedtime to avoid orthostasis Tachyphylaxis can occur with prazosin
Centrally acting agents	α_2 Receptor agonist (reduces norepinepherine outflow) Methyldopa acts as false neurotransmitter	Orthostasis Sedation Fatigue Dry mouth Depression Hepatitis (methyldopa) Hemolytic anemia (methyldopa)	Taper gradually and avoid sudden withdrawal to avoid risk of rebound malignant hypertension
Direct vasodilators	Arteriolar smooth muscle relaxant Vasodilatation	Reflex tachycardia Headache Hirsuitism (minoxidil) Orthostasis Tachyphylaxis (hydralazine) Flushing Drug-induced lupus (hydralazine) Fluid retention	First dose at bedtime Use with β-blocker and diuretic Some patients rapidly metabolize hydralazine (rapid acetylators) Sodium and fluid retention
Peripheral anti-adrenergics	Ganglionic blockade inhibiting catecholamine release	Diarrhea Orthostasis	First dose at bedtime Not used as monotherapy

A Stepped-Care Approach within Individualized Treatment

Although treatment of hypertension relies on an individual approach to the patient, some general guidelines can be offered. Step 1 of treatment always includes risk factor and lifestyle modification. When drug treatment is necessary, most of the above considerations can be satisfied using diuretics, β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, or α_1-blockers as first-line monotherapy or in combinations. Because of side effects, centrally acting agents are commonly relegated to second-line treatment. Direct vasodilators and peripheral antiadrenergic medications are rarely used, although there is little reason to change these medications in patients with well-controlled blood pressure who tolerate them.

Treating Acutely High Blood Pressures in the Office Setting

Patients who have malignant hypertension are best managed in the inpatient setting with parenteral agents. Often, however, patients will come to a physician's office or emergency department with acute, severe elevations of blood pressure without acute end-organ signs. Many clinicians choose to care for these patients as outpatients with oral agents (Table 11), several hours of observation, regimen evaluation, and close follow-up. There is no definitive data on the best way to care for the patient with asymptomatic accelerated blood pressure; it is unclear whether acute treatment affects patient outcomes, what level of pressure elevation should trigger treatment, and what the end points of acute treatment should be. Further studies are needed to address these areas.

Table 10. Antihypertensive Agents Effective Against Left Ventricular Hypertrophy, by Class.

Effect	Class
3+	Angiotensin-converting enzyme inhibitors Calcium channel blockers α_1-Blockers Central agents (except methyldopa)
2+	β-Blockers without intrinsic sympathomimetic activity Methyldopa
0	β-Blockers with intrinsic sympathomimetic activity Diuretics* Peripheral antiadrenergics Direct vasodilators†

*Some data suggest diuretics might have a 1–2+ effect against left ventricular hypertrophy.
†Can worsen left ventricular hypertrophy.

Table 11. Oral Medication for Outpatient Treatment of Accelerated Hypertension.*

Medication	Dosage
Nifedipine	10–20 mg orally or sublingually, followed by 10 mg in 30 minutes (can cause rapid decrease in blood pressure and precipitate angina)
Furosemide	20–40 mg orally or intravenously every hour
Minoxidil	2.5–5 mg every 2–3 hours
Captopril	25–50 mg orally every hour
Clonidine	0.1–0.2 mg orally every hour (maximum 0.6 mg)
Labetolol	200–400 mg orally every 2–3 hours

*If initial attempts to decrease blood pressure with a particular agent are unsuccessful, the medication can be continued or a different agent substituted.
Note: See text for discussion.

Goals of Treatment

All antihypertension treatment regimens should emphasize a healthy lifestyle and modification of risk factors for coronary artery disease, diabetes, hyperlipidemia, and stroke. The ideal medication regimen should be effective, well tolerated, simple, and cost effective and should cause a minimal financial burden to the patient. Consistent systolic pressures less than 140 mmHg and diastolic pressures less than 90 mmHg are desirable.

The J-curve Phenomenon

Cerebrovascular morbidity and mortality have been shown to be directly proportional to the level of diastolic blood pressure. Several recent studies have raised concern that decreasing the diastolic blood pressure below 80 to 85 mmHg could lead to an increase in deaths from cardiac ischemia,[12,29] creating a J-shaped morbidity and mortality curve (decreasing morbidity and mortality from high diastolic pressures until a level of 80 to 85 mmHg, with increasing mortality as the diastolic pressure is further decreased). Methodological problems exist with many of these studies, including retrospective design and not controlling for preexisting coronary artery disease.[12] Some analyses,[29] however, indicate that despite

these flaws, the increased risk persists, although whether the risk is due to the effects of treatment or other factors is unclear. Large, prospective, well-designed studies controlling for age, sex, preexisting coronary artery disease, and risk factors are needed to determine whether excess reduction of blood pressure increases the incidence of coronary morbidity and mortality. Nevertheless, it seems reasonable that pending the outcome of well-controlled studies, a target treatment diastolic pressure in the 80 to 85 mmHg range will achieve most of the documented decrease in adverse events without increased risk.

Combination Therapy

Many patients can control their hypertension with single-drug therapy. Occasionally, however, combinations of antihypertensive agents are needed to achieve adequate blood pressure control. Combination therapy has the theoretic advantage of synergistic and additive medication effects, often at lower doses and with fewer side effects. Combination therapy should be chosen with attention to coexisting medical conditions (Table 7). Table 12 lists combinations of antihypertensive medications that can be useful in certain circumstances.

Thiazide and potassium-sparing diuretics are often found in combination (e.g., triamterene-hydrochlorothiazide). Because this combination often alleviates the need for potassium supplementation, it could be considered as monotherapy. Other fixed-dose antihypertensive combinations are commercially available, but they are usually more expensive than the sum of the individual components. These fixed-dose combinations should be used only after titration of the individual components has been achieved and if concerns about patient adherence override the additional cost.

Follow-up of Controlled Hypertensive Patients

Hypertensive patients should be seen at regular intervals (from every few days to 3 months, depending on severity) until target pressures are achieved and consistent. Once controlled, most patients with hypertension can be cared for on 3- to 12-month intervals. Reliable patients who have no side-effects and who monitor their own blood pressures at home are good candidates for yearly follow-up.

Follow-up visits should include at least two blood pressure readings, weight measurement, questions about regimen adherence and side effects, instructions on lifestyle modification and home readings, a brief physical examination, and routine laboratory monitoring as determined by coexisting conditions and medication (if any) used.

Refractory or Suddenly Deteriorating Hypertension

Table 13 lists common causes of refractory or deteriorating hypertension in previously stable hypertensive patients. If the patient has normal findings on physical examination, these conditions should be considered before doing an invasive work-up for secondary causes of hypertension.

Table 12. Selected Useful Antihypertensive Combinations.

Combination	Useful Situations	Notes
Thiazide diuretics and potassium-sparing diuretics	Same as diuretics	Often eliminates need for potassium supplementation Inexpensive generic forms available
β-Blockers and calcium channel blockers	Angina	Caution in patients with congestive heart failure or decreased left ventricular function
Diuretics and angiotensin-converting enzyme inhibitors	Congestive heart failure	Avoid potassium-sparing diuretics
β-Blockers and angiotensin-converting enzyme inhibitors	Postmyocardial infarction	β-Blockers improve survival, angiotensin-converting enzyme inhibitors decrease risk of congestive heart failure
Angiotensin-converting enzyme inhibitors and calcium channel blockers	Mild renal insufficiency	Angiotensin-converting enzyme inhibitors dilate renal efferent arteriole, calcium channel blockers dilate afferent arteriole (reduces "intrarenal" hypertension)

Stopping or Reducing Medication

After 6 to 12 months of good control and with close supervision, many patients will be able to reduce gradually or stop taking antihypertensive medications.[31,32] Motivated patients who were initially mildly hypertensive, who have low blood pressures on medication, who have lost excess weight, who optimally use lifestyle and risk factor modification, and who are taking a low dose of only one medication are good candidates. Continued use of nonpharmacologic measures and close follow-up at gradually increasing intervals of up to 1 year are important, as many of these patients will eventually need to restart or increase their medication. Most antihypertensive medications, especially centrally acting agents and β-blockers in those with coronary artery disease, should be tapered rather than stopped abruptly.

Conclusion

Usually an asymptomatic condition, hypertension is one of the most common clinical entities seen in family practice. Treatment has been shown to decrease morbidity and mortality from cerebrovascular disease and renal disease and to improve outcome for retinal disease. Findings from a careful history and physical examination and results of an individualized targeted laboratory work-up can distinguish essential hypertension from secondary causes. All treatment regimens should address lifestyle and risk factor modification. Pharmaceutical regimens should be well tolerated, cost effective, easy to follow, and individualized to the patient. Follow-up should stress lifestyle issues, adherence, and side effects. Additional readings concerning management, pharmacotherapy, and assessment of hypertension[33-42] are provided in the bibliography. Further studies are needed to determine the role of the newer antihypertensive medications that work against left ventricular hypertrophy to decrease coronary events, to elucidate further the J-curve phenomenon, to assess the treatment of asymptomatic accelerated hypertension, and to examine the most cost-effective outcomes-based strategies for treating hypertension.

Table 13. Causes of Refractory or Deteriorating Hypertension.

Nonadherence to (pharmacologic) regimen
Sudden withdrawl of antihypertensive medications (particularly central agents)
Insufficiency dose of antihypertensive medication
Drug-drug interactions (e.g., diuretics and nonsteroidal anti-inflammatory agents)
Effects of newly added drugs (steroids, oral contraceptives)
Increasing obesity
Increasing alcohol use
Volume overload
Renal failure or insufficiency
"White coat syndrome"
Renovascular occlusion

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