

*JNC 7 Express*

The Seventh Report  
of the Joint National  
Committee on  
Prevention,  
Detection,  
Evaluation, and  
Treatment of  
High Blood Pressure



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Heart, Lung, and Blood Institute





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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES  
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## PREFACE

Since the “Sixth Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 6)” was released in 1997, new knowledge has come to light from a variety of sources. The National High Blood Pressure Education Program Coordinating Committee (NHBPEP CC), which represents 46 professional, voluntary, and Federal organizations, has periodically reviewed the emerging findings during its biannual meetings. Eventually, a critical mass of information accumulated that generated much demand for a seventh report. My decision to appoint a JNC 7 Committee was predicated on four reasons: (1) publication of many new hypertension observational studies and clinical trials; (2) need for a new, clear, and concise guideline that would be useful for clinicians; (3) need to simplify the classification of blood pressure; and (4) clear recognition that the JNC reports were not being used to their maximum benefit.

Dr. Aram Chobanian was selected as the JNC 7 chair because, like his predecessors, he is well versed in hypertension, yet independent of these major studies. The JNC 7 Executive Committee and writing teams were selected entirely from the NHBPEP CC because they are recognized as experts in their disciplines by their peers. Dr. Chobanian and his colleagues set—and met—a goal of completing and publishing this work in 5 months because of the urgency of applying the new information to improve hypertension prevention and treatment.

This has been a remarkable accomplishment, but the task of NHBPEP CC numbers is far from over. They and many others are now charged with disseminating the JNC 7 report, because none of this—neither the research studies nor the recommendations—will matter, unless the JNC 7 is applied. To facilitate its application, the JNC 7 will be produced in two versions. A “JNC 7 Express” has been developed for busy clinicians. A longer version to be published later will provide for a broader and more detailed review of the recommendations. Additional professional and patient education tools will support implementation of the JNC 7 recommendations.

Dr. Chobanian has our deep appreciation for leading the JNC 7 Executive and Coordinating Committee members in developing this new report. I feel confident that this represents a landmark document and that its application will greatly improve our ability to address a very important public health problem.



Claude Lenfant, M.D.  
Director  
National Heart, Lung, and Blood Institute  
Chair  
National High Blood Pressure Education  
Program



## ABSTRACT

The “Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure” provides a new guideline for hypertension prevention and management. The following are the report’s key messages:

- In persons older than 50 years, systolic blood pressure greater than 140 mmHg is a much more important cardiovascular disease (CVD) risk factor than diastolic blood pressure.
- The risk of CVD beginning at 115/75 mmHg doubles with each increment of 20/10 mmHg; individuals who are normotensive at age 55 have a 90 percent lifetime risk for developing hypertension.
- Individuals with a systolic blood pressure of 120–139 mmHg or a diastolic blood pressure of 80–89 mmHg should be considered as prehypertensive and require health-promoting lifestyle modifications to prevent CVD.
- Thiazide-type diuretics should be used in drug treatment for most patients with uncomplicated hypertension, either alone or combined with drugs from other classes. Certain high-risk conditions are compelling indications for the initial use of other antihypertensive drug classes (angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers).
- Most patients with hypertension will require two or more antihypertensive medications to achieve goal blood pressure (<140/90 mmHg, or <130/80 mmHg for patients with diabetes or chronic kidney disease).
- If blood pressure is >20/10 mmHg above goal blood pressure, consideration should be given to initiating therapy with two agents, one of which usually should be a thiazide-type diuretic.
- The most effective therapy prescribed by the most careful clinician will control hypertension only if patients are motivated. Motivation improves when patients have positive experiences with, and trust in, the clinician. Empathy builds trust and is a potent motivator.
- In presenting these guidelines, the committee recognizes that the responsible physician’s judgment remains paramount.





## INTRODUCTION

For more than three decades, the National Heart, Lung, and Blood Institute (NHLBI) has coordinated the National High Blood Pressure Education Program (NHBPEP), a coalition of 39 major professional, public, and voluntary organizations and seven Federal Agencies. One important function is to issue guidelines and advisories designed to increase awareness, prevention, treatment, and control of hypertension (high blood pressure (BP)). Since the publication of the “Sixth Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 6)” released in 1997,<sup>1</sup> many large-scale clinical trials have been published. The decision to appoint a JNC 7 committee was based on four factors: (1) publication of many new hypertension observational studies and clinical trials; (2) need for a new, clear, and concise guideline that would be useful for clinicians; (3) need to simplify the classification of blood pressure; and (4) clear recognition that the JNC reports were not being used to their maximum benefit. This JNC report is presented in two separate publications: a current, succinct, practical guide and a more comprehensive report to be published separately, which will provide a broader discussion and justification for the current recommendations. In presenting these guidelines, the committee recognizes that the responsible physician’s judgment is paramount in managing patients.

## METHODOLOGY

Since the publication of the JNC 6 report, the NHBPEP Coordinating Committee (CC), chaired by the director of the NHLBI, has regularly reviewed and discussed the hypertension clinical trials at its biannual meetings. In many instances, the principal investigator of the larger studies has presented the information directly to the CC. The committee’s presentations and reviews are summarized and posted on the NHLBI Web site.<sup>2</sup> In agreeing to commission a new report, the Director requested that the CC members provide in writing a detailed rationale explaining the necessity to update the guidelines and to describe the critical issues and concepts to be considered for a new report. The JNC 7 chair was selected, plus a nine-member Executive Committee appointed entirely from the NHBPEP CC membership. The NHBPEP CC served as members of five writing teams, each of which was cochaired by two Executive Committee members. The concepts identified by the NHBPEP CC membership were used to develop the report outline. A timeline was developed to complete and publish the work in 5 months. Based on the identified critical issues and concepts, the Executive Committee identified relevant Medical Subject Headings (MeSH) terms and keywords to further review the

scientific literature. These MeSH terms were used to generate MEDLINE searches that focused on English language peer-reviewed scientific literature from January 1997 through April 2003. Various systems of grading the evidence were considered, and the classification scheme used in the JNC 6 report and other NHBPEP clinical guidelines was selected<sup>3,4</sup> which classifies studies in a process adapted from Last and Abramson.<sup>5</sup> The Executive Committee met on six occasions, two of which included meetings with the entire NHBPEP CC. The writing teams also met by teleconference and used electronic communications to develop the report. Twenty-four drafts were created and reviewed in a reiterative fashion. At its meetings, the Executive Committee used a modified nominal group process to identify and resolve issues. The NHBPEP CC reviewed the penultimate draft and provided written comments to the Executive Committee. In addition, 33 national hypertension leaders reviewed and commented on the document. The NHBPEP CC approved the JNC 7 report.

## CLASSIFICATION OF BLOOD PRESSURE

Table 1 provides a classification of BP for adults ages 18 and older. The classification is based on the average of two or more properly measured, seated BP readings on each of two or more office visits. In contrast to the classification provided in the JNC 6 report, a new category designated prehypertension has been added, and stages 2 and 3 hypertension have been combined. Patients with prehypertension are at increased risk for progression to hypertension; those in the 130–139/80–89 mmHg BP range are at twice the risk to develop hypertension as those with lower values.<sup>6</sup>

## CARDIOVASCULAR DISEASE RISK

Hypertension affects approximately 50 million individuals in the United States and approximately 1 billion worldwide. As the population ages, the prevalence of hypertension will increase even further unless broad and effective preventive measures are implemented. Recent data from the Framingham Heart Study suggest that individuals who are normotensive at age 55 have a 90 percent lifetime risk for developing hypertension.<sup>7</sup>

The relationship between BP and risk of CVD events is continuous, consistent, and independent of other risk factors. The higher the BP, the greater is the chance of heart attack, heart failure, stroke, and kidney disease. For individu-

**Table 1. Classification and management of blood pressure for adults\***

BP CLASSIFICATION	SBP* MMHg	DBP* MMHg	LIFESTYLE MODIFICATION	INITIAL DRUG THERAPY	
				WITHOUT COMPELLING INDICATION	WITH COMPELLING INDICATIONS (SEE TABLE 8)
<b>NORMAL</b>	<120	and <80	Encourage		
<b>PREHYPERTENSION</b>	<b>120–139</b>	or 80–89	Yes	No antihypertensive drug indicated.	Drug(s) for compelling indications.‡
<b>STAGE 1 HYPERTENSION</b>	<b>140–159</b>	or 90–99	Yes	Thiazide-type diuretics for most†. May consider ACEI, ARB, BB, CCB, or combination.	Drug(s) for the compelling indications.‡ Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed.
<b>STAGE 2 HYPERTENSION</b>	<b>≥160</b>	or ≥100	Yes	Two-drug combination for most† (usually thiazide-type diuretic and ACEI or ARB or BB or CCB).	

DBP, diastolic blood pressure; SBP, systolic blood pressure.

Drug abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium channel blocker.

\* Treatment determined by highest BP category.

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

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

als 40–70 years of age, each increment of 20 mmHg in systolic BP (SBP) or 10 mmHg in diastolic BP (DBP) doubles the risk of CVD across the entire BP range from 115/75 to 185/115 mmHg.<sup>8</sup>

The classification “prehypertension,” introduced in this report (table 1), recognizes this relationship and signals the need for increased education of health care professionals and the public to reduce BP levels and prevent the development of hypertension in the general population.<sup>9</sup> Hypertension prevention strategies are available to achieve this goal. (See “Lifestyle Modifications” section.)

## BENEFITS OF LOWERING BLOOD PRESSURE

In clinical trials, antihypertensive therapy has been associated with reductions in stroke incidence averaging 35–40 percent; myocardial infarction, 20–25 percent; and heart failure, more than 50 percent.<sup>10</sup> It is estimated that in patients with stage 1 hypertension (SBP 140–159 mmHg and/or DBP 90–99 mmHg) and additional cardiovascular risk factors, achieving a sustained 12 mmHg reduction in SBP over 10 years will prevent 1 death for every 11 patients treated. In the presence of CVD or target organ damage, only 9 patients would require such BP reduction to prevent a death.<sup>11</sup>

**Table 2. Trends in awareness, treatment, and control of high blood pressure in adults ages 18–74\***

	NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY, PERCENT			
	II (1976–80)	III (PHASE 1) 1988–91)	III (PHASE 2) 1991–94)	1999–2000
Awareness	51	73	68	70
Treatment	31	55	54	59
Control†	10	29	27	34

\* High blood pressure is systolic blood pressure (SBP)  $\geq 140$  mmHg or diastolic blood pressure (DBP)  $\geq 90$  mmHg or taking antihypertensive medication.

† SBP  $< 140$  mmHg and DBP  $< 90$  mmHg.

Sources: Unpublished data for 1999–2000 computed by M. Wolz, National Heart, Lung, and Blood Institute; JNC 6.<sup>1</sup>

## BLOOD PRESSURE CONTROL RATES

Hypertension is the most common primary diagnosis in America (35 million office visits as the primary diagnosis).<sup>12</sup> Current control rates (SBP  $< 140$  mmHg and DBP  $< 90$  mmHg), though improved, are still far below the Healthy People 2010 goal of 50 percent; 30 percent are still unaware they have hypertension. (See table 2.) In the majority of patients, controlling systolic hypertension, which is a more important CVD risk factor than DBP except in patients younger than age 50<sup>13</sup> and occurs much more commonly in older persons, has been considerably more difficult than controlling diastolic hypertension. Recent clinical trials have demonstrated that effective BP control can be achieved in most patients who are hypertensive, but the majority will require two or more antihypertensive drugs.<sup>14,15</sup> When clinicians fail to prescribe lifestyle modifications, adequate antihypertensive drug doses, or appropriate drug combinations, inadequate BP control may result.

## ACCURATE BLOOD PRESSURE MEASUREMENT IN THE OFFICE

The auscultatory method of BP measurement with a properly calibrated and validated instrument should be used.<sup>16</sup> Persons should be seated quietly for at least 5 minutes in a chair (rather than on an exam table), with feet on the floor, and arm supported at heart level. Measurement of BP in the standing position is indicated periodically, especially in those at risk for postural hypotension. An appropriate-sized cuff (cuff bladder encircling at least 80 percent of the arm) should be used to ensure accuracy. At least two measurements should be made. SBP is the point at which the first of two or more sounds is heard

(phase 1), and DBP is the point before the disappearance of sounds (phase 5). Clinicians should provide to patients, verbally and in writing, their specific BP numbers and BP goals.

## AMBULATORY BLOOD PRESSURE MONITORING

Ambulatory blood pressure monitoring (ABPM)<sup>17</sup> provides information about BP during daily activities and sleep. ABPM is warranted for evaluation of “white-coat” hypertension in the absence of target organ injury. It is also helpful to assess patients with apparent drug resistance, hypotensive symptoms with antihypertensive medications, episodic hypertension, and autonomic dysfunction. The ambulatory BP values are usually lower than clinic readings. Awake, individuals with hypertension have an average BP of more than 135/85 mmHg and during sleep, more than 120/75 mmHg. The level of BP measurement by using ABPM correlates better than office measurements with target organ injury.<sup>18</sup> ABPM also provides a measure of the percentage of BP readings that are elevated, the overall BP load, and the extent of BP reduction during sleep. In most individuals, BP decreases by 10 to 20 percent during the night; those in whom such reductions are not present are at increased risk for cardiovascular events.

## SELF-MEASUREMENT OF BLOOD PRESSURE

BP self measurements may benefit patients by providing information on response to antihypertensive medication, improving patient adherence with therapy,<sup>19</sup> and in evaluating white-coat hypertension. Persons with an average BP more than 135/85 mmHg measured at home are generally considered to be hypertensive. Home measurement devices should be checked regularly for accuracy.

## PATIENT EVALUATION

Evaluation of patients with documented hypertension has three objectives: (1) to assess lifestyle and identify other cardiovascular risk factors or concomitant disorders that may affect prognosis and guide treatment (table 3); (2) to reveal identifiable causes of high BP (table 4); and (3) to assess the presence or absence of target organ damage and CVD. The data needed are acquired through medical history, physical examination, routine laboratory tests, and other diagnostic procedures. The physical examination should

**Table 3. Cardiovascular risk factors**

MAJOR RISK FACTORS
Hypertension*
Cigarette smoking
Obesity* (body mass index $\geq 30$ kg/m <sup>2</sup> )
Physical inactivity
Dyslipidemia*
Diabetes mellitus*
Microalbuminuria or estimated GFR <60 mL/min
Age (older than 55 for men, 65 for women)
Family history of premature cardiovascular disease (men under age 55 or women under age 65)
TARGET ORGAN DAMAGE

**Heart**

- Left ventricular hypertrophy
- Angina or prior myocardial infarction
- Prior coronary revascularization
- Heart failure

**Brain**

- Stroke or transient ischemic attack

Chronic kidney disease

Peripheral arterial disease

Retinopathy

GFR, glomerular filtration rate.

\* Components of the metabolic syndrome.

include an appropriate measurement of BP, with verification in the contralateral arm; examination of the optic fundi; calculation of body mass index (BMI) (measurement of waist circumference also may be useful); auscultation for carotid, abdominal, and femoral bruits; palpation of the thyroid gland; thorough examination of the heart and lungs; examination of the abdomen for enlarged kidneys, masses, and abnormal aortic pulsation; palpation of the lower extremities for edema and pulses; and neurological assessment.

### Laboratory Tests and Other Diagnostic Procedures

Routine laboratory tests recommended before initiating therapy include an electrocardiogram; urinalysis; blood glucose and hematocrit; serum potassium, creatinine (or the corresponding estimated glomerular filtration rate [GFR]), and calcium;<sup>20</sup> and a lipid profile, after 9- to 12-hour fast, that includes high-density lipoprotein cholesterol and low-density lipoprotein cholesterol, and triglycerides. Optional tests include measurement of urinary albumin excretion or albumin/creatinine ratio. More extensive testing for identifiable causes is not indicated generally unless BP control is not achieved.

**Table 4. Identifiable causes of hypertension**

Sleep apnea
Drug-induced or related causes (see table 9)
Chronic kidney disease
Primary aldosteronism
Renovascular disease
Chronic steroid therapy and Cushing's syndrome
Pheochromocytoma
Coarctation of the aorta
Thyroid or parathyroid disease

### Goals of Therapy

The ultimate public health goal of antihypertensive therapy is the reduction of cardiovascular and renal morbidity and mortality. Since most persons with hypertension, especially those age  $\geq 50$  years, will reach the DBP goal once SBP is at goal, the primary focus should be on achieving the SBP goal.

Treating SBP and DBP to targets that are  $<140/90$  mmHg is associated with a decrease in CVD complications. In patients with hypertension and diabetes or renal disease, the BP goal is  $<130/80$  mmHg.<sup>21,22</sup>

### Lifestyle Modifications

Adoption of healthy lifestyles by all persons is critical for the prevention of high BP and is an indispensable part of the management of those with hypertension. Major lifestyle modifications shown to lower BP include weight reduction in those individuals who are overweight or obese,<sup>23,24</sup> adoption of the Dietary Approaches to Stop Hypertension (DASH) eating plan<sup>25</sup> which is rich in potassium and calcium,<sup>26</sup> dietary sodium reduction,<sup>25-27</sup> physical activity,<sup>28,29</sup> and moderation of alcohol consumption. (See table 5.)<sup>30</sup> Lifestyle modifications reduce BP, enhance antihypertensive drug efficacy, and decrease cardiovascular risk. For example, a 1,600 mg sodium DASH eating plan has effects similar to single drug therapy.<sup>25</sup> Combinations of two (or more) lifestyle modifications can achieve even better results.

### Pharmacologic Treatment

There are excellent clinical outcome trial data proving that lowering BP with several classes of drugs, including angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers (BBs), calcium channel blockers (CCBs), and thiazide-type diuretics, will all reduce the complications of hypertension.<sup>10,31-37</sup> Tables 6 and 7 provide a list of commonly used antihypertensive agents.

Thiazide-type diuretics have been the basis of antihypertensive therapy in most outcome trials.<sup>37</sup> In these trials, including the recently published Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),<sup>33</sup> diuretics have been virtually unsurpassed in preventing the cardiovascular complications of hypertension. The exception is the Second Australian National Blood Pressure trial which reported slightly better outcomes in White men with a regimen that began with an ACEI compared to one starting with a diuretic.<sup>36</sup> Diuretics enhance the antihypertensive efficacy

**Table 5. Lifestyle modifications to manage hypertension\*\*†**

MODIFICATION	RECOMMENDATION	APPROXIMATE SBP REDUCTION (RANGE)
Weight reduction	Maintain normal body weight (body mass index 18.5–24.9 kg/m <sup>2</sup> ).	5–20 mmHg/10 kg weight loss <sup>23,24</sup>
Adopt DASH eating plan	Consume a diet rich in fruits, vegetables, and lowfat dairy products with a reduced content of saturated and total fat.	8–14 mmHg <sup>25,26</sup>
Dietary sodium reduction	Reduce dietary sodium intake to no more than 100 mmol per day (2.4 g sodium or 6 g sodium chloride).	2–8 mmHg <sup>25–27</sup>
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 min per day, most days of the week).	4–9 mmHg <sup>28,29</sup>
Moderation of alcohol consumption	Limit consumption to no more than 2 drinks (1 oz or 30 mL ethanol; e.g., 24 oz beer, 10 oz wine, or 3 oz 80-proof whiskey) per day in most men and to no more than 1 drink per day in women and lighter weight persons.	2–4 mmHg <sup>30</sup>

DASH, Dietary Approaches to Stop Hypertension.

\* For overall cardiovascular risk reduction, stop smoking.

† The effects of implementing these modifications are dose and time dependent, and could be greater for some individuals.

of multidrug regimens, can be useful in achieving BP control, and are more affordable than other antihypertensive agents. Despite these findings, diuretics remain underutilized.<sup>39</sup>

Thiazide-type diuretics should be used as initial therapy for most patients with hypertension, either alone or in combination with one of the other classes (ACEIs, ARBs, BBs, CCBs) demonstrated to be beneficial in randomized controlled outcome trials. The list of compelling indications requiring the use of other antihypertensive drugs as initial therapy are listed in table 8. If a drug is not tolerated or is contraindicated, then one of the other classes proven to reduce cardiovascular events should be used instead.



**Table 6. Oral antihypertensive drugs\***

CLASS	DRUG (TRADE NAME)	USUAL DOSE RANGE IN MG/DAY (DAILY FREQUENCY)
Thiazide diuretics	chlorothiazide (Diuril)	125–500 (1)
	chlorthalidone (generic)	12.5–25 (1)
	hydrochlorothiazide (Microzide, HydroDIURIL <sup>†</sup> )	12.5–50 (1)
	polythiazide (Renese)	2–4 (1)
	indapamide (Lozol <sup>†</sup> )	1.25–2.5 (1)
	metolazone (Mykrox)	0.5–1.0 (1)
	metolazone (Zaroxolyn)	2.5–5 (1)
Loop diuretics	bumetanide (Bumex <sup>†</sup> )	0.5–2 (2)
	furosemide (Lasix <sup>†</sup> )	20–80 (2)
	torseamide (Demadex <sup>†</sup> )	2.5–10 (1)
Potassium-sparing diuretics	amiloride (Midamor <sup>†</sup> )	5–10 (1–2)
	triamterene (Dyrenium)	50–100 (1–2)
Aldosterone receptor blockers	eplerenone (Inspra)	50–100 (1–2)
	spironolactone (Aldactone <sup>†</sup> )	25–50 (1–2)
Beta-blockers	atenolol (Tenormin <sup>†</sup> )	25–100 (1)
	betaxolol (Kerlone <sup>†</sup> )	5–20 (1)
	bisoprolol (Zebeta <sup>†</sup> )	2.5–10 (1)
	metoprolol (Lopressor <sup>†</sup> )	50–100 (1–2)
	metoprolol extended release (Toprol XL)	50–100 (1)
	nadolol (Corgard <sup>†</sup> )	40–120 (1)
	propranolol (Inderal <sup>†</sup> )	40–160 (2)
	propranolol long-acting (Inderal LA <sup>†</sup> )	60–180 (1)
	timolol (Blocadren <sup>†</sup> )	20–40 (2)
Beta-blockers with intrinsic sympathomimetic activity	acebutolol (Sectral <sup>†</sup> )	200–800 (2)
	penbutolol (Levitol)	10–40 (1)
	pindolol (generic)	10–40 (2)
Combined alpha- and beta-blockers	carvedilol (Coreg)	12.5–50 (2)
	labetalol (Normodyne, Trandate <sup>†</sup> )	200–800 (2)

**Table 6. Oral antihypertensive drugs\* (CONTINUED)**

CLASS	DRUG (TRADE NAME)	USUAL DOSE RANGE IN MG/DAY (DAILY FREQUENCY)
ACE inhibitors	benazepril (Lotensin <sup>†</sup> )	10–40 (1–2)
	captopril (Capoten <sup>†</sup> )	25–100 (2)
	enalapril (Vasotec <sup>†</sup> )	2.5–40 (1–2)
	fosinopril (Monopril)	10–40 (1)
	lisinopril (Prinivil, Zestril <sup>†</sup> )	10–40 (1)
	moexipril (Univasc)	7.5–30 (1)
	perindopril (Aceon)	4–8 (1–2)
	quinapril (Accupril)	10–40 (1)
	ramipril (Altace)	2.5–20 (1)
	trandolapril (Mavik)	1–4 (1)
Angiotensin II antagonists	candesartan (Atacand)	8–32 (1)
	eprosartan (Tevetan)	400–800 (1–2)
	irbesartan (Avapro)	150–300 (1)
	losartan (Cozaar)	25–100 (1–2)
	olmesartan (Benicar)	20–40 (1)
	telmisartan (Micardis)	20–80 (1)
	valsartan (Diovan)	80–320 (1)
Calcium channel blockers— non-Dihydropyridines	diltiazem extended release (Cardizem CD, Dilacor XR, Tiazac <sup>†</sup> )	180–420 (1)
	diltiazem extended release (Cardizem LA)	120–540 (1)
	verapamil immediate release (Calan, Isoptin <sup>†</sup> )	80–320 (2)
	verapamil long acting (Calan SR, Isoptin SR <sup>†</sup> )	120–360 (1–2)
	verapamil—Coer (Covera HS, Verelan PM)	120–360 (1)
Calcium channel blockers— Dihydropyridines	amlodipine (Norvasc)	2.5–10 (1)
	felodipine (Plendil)	2.5–20 (1)
	isradipine (Dynacirc CR)	2.5–10 (2)
	nicardipine sustained release (Cardene SR)	60–120 (2)
	nifedipine long-acting (Adalat CC, Procardia XL)	30–60 (1)
	nisoldipine (Sular)	10–40 (1)

**Table 6. Oral antihypertensive drugs\* (CONTINUED)**

CLASS	DRUG (TRADE NAME)	USUAL DOSE RANGE IN MG/DAY (DAILY FREQUENCY)
Alpha <sub>1</sub> -blockers	doxazosin (Cardura) prazosin (Minipress <sup>†</sup> ) terazosin (Hytrin)	1–16 (1) 2–20 (2–3) 1–20 (1–2)
Central alpha <sub>2</sub> -agonists and other centrally acting drugs	clonidine (Catapres <sup>†</sup> ) clonidine patch (Catapres-TTS) methyldopa (Aldomet <sup>†</sup> ) reserpine (generic) guanfacine (generic)	0.1–0.8 (2) 0.1–0.3 (1wkly) 250–1,000 (2) 0.05 <sup>‡</sup> –0.25 (1) 0.5–2 (1)
Direct vasodilators	hydralazine (Apresoline <sup>†</sup> ) minoxidil (Loniten <sup>†</sup> )	25–100 (2) 2.5–80 (1–2)

\* These dosages may vary from those listed in the “Physicians’ Desk Reference.”<sup>38</sup>

† Are now or will soon become available in generic preparations.

‡ A 0.1 mg dose may be given every other day to achieve this dosage.

**Table 7. Combination drugs for hypertension**

COMBINATION TYPE*	FIXED-DOSE COMBINATION, mg†	TRADE NAME
ACEIs and CCBs	Amlodipine/benazepril hydrochloride (2.5/10, 5/10, 5/20, 10/20) Enalapril maleate/felodipine (5/5) Trandolapril/verapamil (2/180, 1/240, 2/240, 4/240)	Lotrel Lexxel Tarka
ACEIs and diuretics	Benazepril/hydrochlorothiazide (5/6.25, 10/12.5, 20/12.5, 20/25) Captopril/hydrochlorothiazide (25/15, 25/25, 50/15, 50/25) Enalapril maleate/hydrochlorothiazide (5/12.5, 10/25) Lisinopril/hydrochlorothiazide (10/12.5, 20/12.5, 20/25) Moexipril HCl/hydrochlorothiazide (7.5/12.5, 15/25) Quinapril HCl/hydrochlorothiazide (10/12.5, 20/12.5, 20/25)	Lotensin HCT Capozide Vaseretic Prinzide Uniretic Accuretic
ARBs and diuretics	Candesartan cilexetil/hydrochlorothiazide (16/12.5, 32/12.5) Eprosartan mesylate/hydrochlorothiazide (600/12.5, 600/25) Irbesartan/hydrochlorothiazide (150/12.5, 300/12.5) Losartan potassium/hydrochlorothiazide (50/12.5, 100/25) Telmisartan/hydrochlorothiazide (40/12.5, 80/12.5) Valsartan/hydrochlorothiazide (80/12.5, 160/12.5)	Atacand HCT Teveten/HCT Avalide Hyzaar Micardis/HCT Diovan/HCT
BBs and diuretics	Atenolol/chlorthalidone (50/25, 100/25) Bisoprolol fumarate/hydrochlorothiazide (2.5/6.25, 5/6.25, 10/6.25) Propranolol LA/hydrochlorothiazide (40/25, 80/25) Metoprolol tartrate/hydrochlorothiazide (50/25, 100/25) Nadolol/bendrofluthiazide (40/5, 80/5) Timolol maleate/hydrochlorothiazide (10/25)	Tenoretic Ziac Inderide Lopressor HCT Corzide Timolide
Centrally acting drug and diuretic	Methyldopa/hydrochlorothiazide (250/15, 250/25, 500/30, 500/50) Reserpine/chlorothiazide (0.125/250, 0.25/500) Reserpine/hydrochlorothiazide (0.125/25, 0.125/50)	Aldoril Diupres Hydropres
Diuretic and diuretic	Amiloride HCl/hydrochlorothiazide (5/50) Spironolactone/hydrochlorothiazide (25/25, 50/50) Triamterene/hydrochlorothiazide (37.5/25, 50/25, 75/50)	Moduretic Aldactone Dyazide, Maxzide

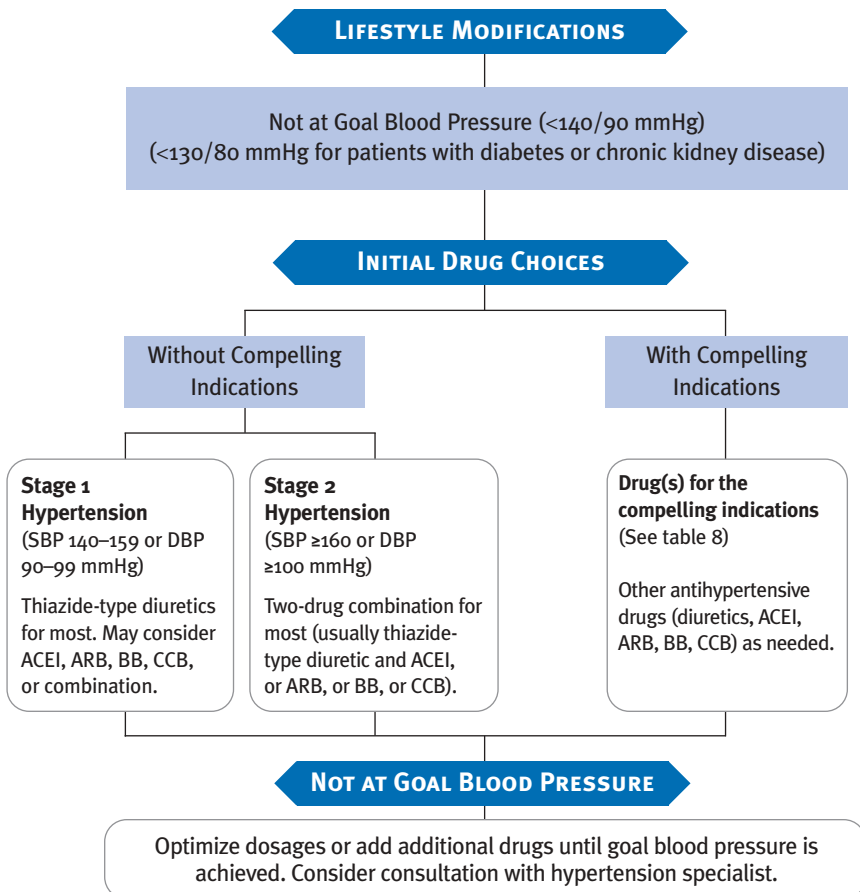
\* Drug abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium channel blocker.

† Some drug combinations are available in multiple fixed doses. Each drug dose is reported in milligrams.

## Achieving Blood Pressure Control in Individual Patients

Most patients who are hypertensive will require two or more antihypertensive medications to achieve their BP goals.<sup>14,15</sup> Addition of a second drug from a different class should be initiated when use of a single drug in adequate doses fails to achieve the BP goal. When BP is more than 20/10 mmHg above goal, consideration should be given to initiating therapy with two drugs, either as separate prescriptions or in fixed-dose combinations. (See figure 1.) The initiation of drug therapy with more than one agent may increase the likelihood of achieving the BP goal in a more timely fashion, but particular caution is advised in those at risk for orthostatic hypotension, such as patients with diabetes, autonomic dysfunction, and some older persons. Use of generic drugs or combination drugs should be considered to reduce prescription costs.

Figure 1. Algorithm for treatment of hypertension



DBP, diastolic blood pressure; SBP, systolic blood pressure.

Drug abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium channel blocker.

## Followup and Monitoring

Once antihypertensive drug therapy is initiated, most patients should return for followup and adjustment of medications at approximately monthly intervals until the BP goal is reached. More frequent visits will be necessary for patients with stage 2 hypertension or with complicating comorbid conditions. Serum potassium and creatinine should be monitored at least 1–2 times/year.<sup>60</sup> After BP is at goal and stable, followup visits can usually be at 3- to 6-month intervals. Comorbidities, such as heart failure, associated diseases such as diabetes, and the need for laboratory tests influence the frequency of visits. Other cardiovascular risk factors should be treated to their respective goals, and tobacco avoidance should be promoted vigorously. Low-dose aspirin therapy should be considered only when BP is controlled, because the risk of hemorrhagic stroke is increased in patients with uncontrolled hypertension.<sup>61</sup>

### SPECIAL CONSIDERATIONS

The patient with hypertension and certain comorbidities requires special attention and followup by the clinician.

#### Compelling Indications

Table 8 describes compelling indications that require certain antihypertensive drug classes for high-risk conditions. The drug selections for these compelling indications are based on favorable outcome data from clinical trials. A combination of agents may be required. Other management considerations include medications already in use, tolerability, and desired BP targets. In many cases, specialist consultation may be indicated.

#### Ischemic Heart Disease

Ischemic heart disease (IHD) is the most common form of target organ damage associated with hypertension. In patients with hypertension and stable angina pectoris, the first drug of choice is usually a BB; alternatively, long-acting CCBs can be used.<sup>1</sup> In patients with acute coronary syndromes (unstable angina or myocardial infarction), hypertension should be treated initially with BBs and ACEIs,<sup>49</sup> with addition of other drugs as needed for BP control. In patients with postmyocardial infarction, ACEIs, BBs, and aldosterone antagonists have proven to be most beneficial.<sup>50,52,53,62</sup> Intensive lipid management and aspirin therapy are also indicated.

**Table 8. Clinical trial and guideline basis for compelling indications for individual drug classes**

COMPELLING INDICATION*	RECOMMENDED DRUGS†						CLINICAL TRIAL BASIS‡
	DIURETIC	BB	ACEI	ARB	CCB	ALDO ANT	
Heart failure	•	•	•	•		•	ACC/AHA Heart Failure Guideline, <sup>40</sup> MERIT-HF, <sup>41</sup> COPERNICUS, <sup>42</sup> CIBIS, <sup>43</sup> SOLVD, <sup>44</sup> AIRE, <sup>45</sup> TRACE, <sup>46</sup> ValHEFT, <sup>47</sup> RALES <sup>48</sup>
Postmyocardial infarction		•	•			•	ACC/AHA Post-MI Guideline, <sup>49</sup> BHAT, <sup>50</sup> SAVE, <sup>51</sup> Capricorn, <sup>52</sup> EPHEBUS <sup>53</sup>
High coronary disease risk	•	•	•		•		ALLHAT, <sup>33</sup> HOPE, <sup>34</sup> ANBP2, <sup>36</sup> LIFE, <sup>32</sup> CONVINCe <sup>31</sup>
Diabetes	•	•	•	•	•		NKF-ADA Guideline, <sup>21,22</sup> UKPDS, <sup>54</sup> ALLHAT <sup>33</sup>
Chronic kidney disease			•	•			NKF Guideline, <sup>22</sup> Captopril Trial, <sup>55</sup> RENAAL, <sup>56</sup> IDNT, <sup>57</sup> REIN, <sup>58</sup> AASK <sup>59</sup>
Recurrent stroke prevention	•		•				PROGRESS <sup>35</sup>

\* Compelling indications for antihypertensive drugs are based on benefits from outcome studies or existing clinical guidelines; the compelling indication is managed in parallel with the BP.

† Drug abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; Aldo ANT, aldosterone antagonist; BB, beta-blocker; CCB, calcium channel blocker.

‡ Conditions for which clinical trials demonstrate benefit of specific classes of antihypertensive drugs.

## Heart Failure

Heart failure (HF), in the form of systolic or diastolic ventricular dysfunction, results primarily from systolic hypertension and IHD. Fastidious BP and cholesterol control are the primary preventive measures for those at high risk for HF.<sup>40</sup> In asymptomatic individuals with demonstrable ventricular dysfunction, ACEIs and BBs are recommended.<sup>52,62</sup> For those with symptomatic ventricular dysfunction or end-stage heart disease, ACEIs, BBs, ARBs and aldosterone blockers are recommended along with loop diuretics.<sup>40–48</sup>

## Diabetic Hypertension

Combinations of two or more drugs are usually needed to achieve the target goal of <130/80 mmHg.<sup>21,22</sup> Thiazide diuretics, BBs, ACEIs, ARBs, and CCBs are beneficial in reducing CVD and stroke incidence in patients with diabetes.<sup>33,54,63</sup> ACEI- or ARB-based treatments favorably affect the progression of diabetic nephropathy and reduce albuminuria,<sup>55,56</sup> and ARBs have been shown to reduce progression to macroalbuminuria.<sup>56,57</sup>

## Chronic Kidney Disease

In people with chronic kidney disease (CKD), as defined by either (1) reduced excretory function with an estimated GFR below 60 ml/min per 1.73 m<sup>2</sup> (corresponding approximately to a creatinine of >1.5 mg/dL in men or >1.3 mg/dL in women),<sup>20</sup> or (2) the presence of albuminuria (>300 mg/day or 200 mg albumin/g creatinine), therapeutic goals are to slow deterioration of renal function and prevent CVD. Hypertension appears in the majority of these patients, and they should receive aggressive BP management, often with three or more drugs to reach target BP values of <130/80 mmHg.<sup>59,64</sup> ACEIs and ARBs have demonstrated favorable effects on the progression of diabetic and nondiabetic renal disease.<sup>55–59,64</sup> A limited rise in serum creatinine of as much as 35 percent above baseline with ACEIs or ARBs is acceptable and is not a reason to withhold treatment unless hyperkalemia develops.<sup>65</sup> With advanced renal disease (estimated GFR <30 ml/min 1.73 m<sup>2</sup>, corresponding to a serum creatinine of 2.5–3 mg/dL), increasing doses of loop diuretics are usually needed in combination with other drug classes.

## Cerebrovascular Disease

The risks and benefits of acute lowering of BP during an acute stroke are still unclear; control of BP at intermediate levels (approximately 160/100 mmHg) is appropriate until the condition has stabilized or improved. Recurrent stroke rates are lowered by the combination of an ACEI and thiazide-type diuretic.<sup>35</sup>

## Other Special Situations

### Minorities

BP control rates vary in minority populations and are lowest in Mexican Americans and Native Americans.<sup>1</sup> In general, the treatment of hypertension is similar for all demographic groups, but socioeconomic factors and lifestyle may be important barriers to BP control in some minority patients. The prevalence, severity, and impact of hypertension are increased in African Americans, who also demonstrate somewhat reduced BP responses to monotherapy with BBs, ACEIs, or ARBs compared to diuretics or CCBs. These differential responses are largely eliminated by drug combinations that include adequate doses of a diuretic. ACEI-induced angioedema occurs 2–4 times more frequently in African American patients with hypertension than in other groups.<sup>33</sup>

### Obesity and the metabolic syndrome

Obesity (BMI  $\geq$ 30 kg/m<sup>2</sup>) is an increasingly prevalent risk factor for the development of hypertension and CVD. The Adult Treatment Panel III guideline



for cholesterol management defines the metabolic syndrome as the presence of three or more of the following conditions: abdominal obesity (waist circumference >40 inches in men or >35 inches in women), glucose intolerance (fasting glucose  $\geq 110$  mg/dL), BP  $\geq 130/85$  mmHg, high triglycerides ( $\geq 150$  mg/dL), or low HDL (<40 mg/dL in men or <50 mg/dL in women).<sup>66</sup> Intensive lifestyle modification should be pursued in all individuals with the metabolic syndrome, and appropriate drug therapy should be instituted for each of its components as indicated.

### **Left ventricular hypertrophy**

Left ventricular hypertrophy (LVH) is an independent risk factor that increases the risk of subsequent CVD. Regression of LVH occurs with aggressive BP management, including weight loss, sodium restriction, and treatment with all classes of antihypertensive agents except the direct vasodilators hydralazine, and minoxidil.<sup>1,67</sup>

### **Peripheral arterial disease**

Peripheral arterial disease (PAD) is equivalent in risk to IHD. Any class of antihypertensive drugs can be used in most PAD patients. Other risk factors should be managed aggressively, and aspirin should be used.

### **Hypertension in older persons**

Hypertension occurs in more than two-thirds of individuals after age 65.<sup>1</sup> This is also the population with the lowest rates of BP control.<sup>68</sup> Treatment recommendations for older people with hypertension, including those who have isolated systolic hypertension, should follow the same principles outlined for the general care of hypertension. In many individuals, lower initial drug doses may be indicated to avoid symptoms; however, standard doses and multiple drugs are needed in the majority of older people to reach appropriate BP targets.

### **Postural hypotension**

A decrease in standing SBP >10 mmHg, when associated with dizziness or fainting, is more frequent in older patients with systolic hypertension, diabetes, and those taking diuretics, venodilators (e.g., nitrates, alpha-blockers, and sildenafil-like drugs), and some psychotropic drugs. BP in these individuals should also be monitored in the upright position. Caution should be used to avoid volume depletion and excessively rapid dose titration of antihypertensive drugs.

### **Dementia**

Dementia and cognitive impairment occur more commonly in people with hypertension. Reduced progression of cognitive impairment may occur with effective antihypertensive therapy.<sup>69,70</sup>

## **Hypertension in women**

Oral contraceptives may increase BP, and the risk of hypertension increases with duration of use. Women taking oral contraceptives should have their BP checked regularly. Development of hypertension is a reason to consider other forms of contraception. In contrast, menopausal hormone therapy does not raise BP.<sup>71</sup>

Women with hypertension who become pregnant should be followed carefully because of increased risks to mother and fetus. Methyldopa, BBs, and vasodilators are preferred medications for the safety of the fetus.<sup>72</sup> ACEI and ARBs should not be used during pregnancy because of the potential for fetal defects and should be avoided in women who are likely to become pregnant. Preeclampsia, which occurs after the 20th week of pregnancy, is characterized by new-onset or worsening hypertension, albuminuria, and hyperuricemia, sometimes with coagulation abnormalities. In some patients, preeclampsia may develop into a hypertensive urgency or emergency and may require hospitalization, intensive monitoring, early fetal delivery, and parenteral antihypertensive and anticonvulsant therapy.<sup>72</sup>

## **Hypertension in children and adolescents**

In children and adolescents, hypertension is defined as BP that is, on repeated measurement, at the 95th percentile or greater adjusted for age, height, and gender.<sup>73</sup> The fifth Korotkoff sound is used to define DBP. Clinicians should be alert to the possibility of identifiable causes of hypertension in younger children (i.e., kidney disease, coarctation of the aorta). Lifestyle interventions are strongly recommended, with pharmacologic therapy instituted for higher levels of BP or if there is insufficient response to lifestyle modifications.<sup>74</sup> Choices of antihypertensive drugs are similar in children and adults, but effective doses for children are often smaller and should be adjusted carefully. ACEIs and ARBs should not be used in pregnant or sexually active girls. Uncomplicated hypertension should not be a reason to restrict children from participating in physical activities, particularly because long-term exercise may lower BP. Use of anabolic steroids should be strongly discouraged. Vigorous interventions also should be conducted for other existing modifiable risk factors (e.g., smoking).

## **Hypertensive urgencies and emergencies**

Patients with marked BP elevations and acute target-organ damage (e.g., encephalopathy, myocardial infarction, unstable angina, pulmonary edema, eclampsia, stroke, head trauma, life-threatening arterial bleeding, or aortic dissection) require hospitalization and parenteral drug therapy.<sup>1</sup> Patients with markedly elevated BP but without acute target organ damage usually do not require hospitalization, but they should receive immediate combination oral

antihypertensive therapy. They should be carefully evaluated and monitored for hypertension-induced heart and kidney damage and for identifiable causes of hypertension. (See table 4.)

### **Additional Considerations in Antihypertensive Drug Choices**

Antihypertensive drugs can have favorable or unfavorable effects on other comorbidities.

#### **Potential favorable effects**

Thiazide-type diuretics are useful in slowing demineralization in osteoporosis. BBs can be useful in the treatment of atrial tachyarrhythmias/fibrillation, migraine, thyrotoxicosis (short term), essential tremor, or perioperative hypertension. CCBs may be useful in Raynaud's syndrome and certain arrhythmias, and alpha-blockers may be useful in prostatism.

#### **Potential unfavorable effects**

Thiazide diuretics should be used cautiously in patients who have gout or who have a history of significant hyponatremia. BBs should generally be avoided in individuals who have asthma, reactive airways disease, or second or third degree heart block. ACEIs and ARBs should not be given to women likely to become pregnant and are contraindicated in those who are. ACEIs should not be used in individuals with a history of angioedema. Aldosterone antagonists and potassium-sparing diuretics can cause hyperkalemia and should generally be avoided in patients who have serum potassium values more than 5.0 mEq/L while not taking medications.

## **IMPROVING HYPERTENSION CONTROL**

### **Adherence to Regimens**

Behavioral models suggest that the most effective therapy prescribed by the most careful clinician will control hypertension only if the patient is motivated to take the prescribed medication and to establish and maintain a health-promoting lifestyle. Motivation improves when patients have positive experiences with and trust in their clinicians. Empathy both builds trust and is a potent motivator.<sup>75</sup>

Patient attitudes are greatly influenced by cultural differences, beliefs, and previous experiences with the health care system.<sup>76</sup> These attitudes must be understood if the clinician is to build trust and increase communication with patients and families.

Failure to titrate or combine medications, despite knowing the patient is not at goal BP, represents clinical inertia and must be overcome.<sup>77</sup> Decision support systems (i.e., electronic and paper), flow sheets, feedback reminders, and involvement of nurse clinicians and pharmacists can be helpful.<sup>78</sup>

The clinician and the patient must agree upon BP goals. A patient-centered strategy to achieve the goal and an estimation of the time needed to reach goal are important.<sup>79</sup> When BP is above goal, alterations in the plan should be documented. BP self-monitoring can also be useful.

Patients' nonadherence to therapy is increased by misunderstanding of the condition or treatment, denial of illness because of lack of symptoms or perception of drugs as symbols of ill health, lack of patient involvement in the care plan, or unexpected adverse effects of medications. The patient should be made to feel comfortable in telling the clinician all concerns and fears of unexpected or disturbing drug reactions.

The cost of medications and the complexity of care (i.e., transportation, patient difficulty with polypharmacy, difficulty in scheduling appointments, and life's competing demands) are additional barriers that must be overcome to achieve goal BP.

All members of the health care team (e.g., physicians, nurse case managers, and other nurses, physician assistants, pharmacists, dentists, registered dietitians, optometrists, and podiatrists) must work together to influence and reinforce instructions to improve patients' lifestyles and BP control.<sup>80</sup>

### **Resistant Hypertension**

Resistant hypertension is the failure to reach goal BP in patients who are adhering to full doses of an appropriate three-drug regimen that includes a diuretic. After excluding potential identifiable hypertension (see table 4), clinicians should carefully explore reasons why the patient is not at goal BP. (See table 9.) Particular attention should be paid to diuretic type and dose in relation to renal function. (See "Chronic Kidney Disease" section.) Consultation with a hypertension specialist should be considered if goal BP cannot be achieved.

**Table 9. Causes of resitant hypertension**

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Improper BP Measurement

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Volume Overload and Pseudotolerance

- Excess sodium intake
  - Volume retention from kidney disease
  - Inadequate diuretic therapy
- 

Drug-Induced or Other Causes

- Nonadherence
  - Inadequate doses
  - Inappropriate combinations
  - Nonsteroidal anti-inflammatory drugs; cyclooxygenase 2 inhibitors
  - Cocaine, amphetamines, other illicit drugs
  - Sympathomimetics (decongestants, anorectics)
  - Oral contraceptives
  - Adrenal steroids
  - Cyclosporine and tacrolimus
  - Erythropoietin
  - Licorice (including some chewing tobacco)
  - Selected over-the-counter dietary supplements and medicines (e.g., ephedra, ma haung, bitter orange)
- 

Associated Conditions

- Obesity
  - Excess alcohol intake
- 

Identifiable Causes of Hypertension. (See table 4.)

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**PUBLIC HEALTH CHALLENGES AND COMMUNITY PROGRAMS**

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Public health approaches, such as reducing calories, saturated fat, and salt in processed foods and increasing community/school opportunities for physical activity, can achieve a downward shift in the distribution of a population's BP, thus potentially reducing morbidity, mortality, and the lifetime risk of an individual's becoming hypertensive. This becomes especially critical as the increase in BMI of Americans has reached epidemic levels. Now, 122 million adults are overweight or obese, which contributes to the rise in BP and related conditions.<sup>81</sup> The JNC 7 endorses the American Public Health Association resolution that the food manufacturers and restaurants reduce sodium in the food supply by 50 percent over the next decade. When public health intervention strategies address the diversity of racial, ethnic, cultural, linguistic, religious, and social factors in the delivery of their services, the likelihood of their acceptance by the community increases. These public health approaches can provide an attractive opportunity to interrupt and prevent the continuing costly cycle of managing hypertension and its complications.



## EVIDENCE CLASSIFICATION

The studies that provided evidence supporting the recommendations of this report were classified and reviewed by the staff and the Executive Committee. The classification scheme is from the JNC 6 report.<sup>2</sup>

- M** Meta-analysis; use of statistical methods to combine the results from clinical trials
- RA** Randomized controlled trials; also known as experimental studies
- RE** Retrospective analyses; also known as case-control studies
- F** Prospective study; also known as cohort studies, including historical or prospective followup studies.
- X** Cross-sectional survey; also known as prevalence studies
- PR** Previous review or position statements
- C** Clinical interventions (nonrandomized)





## STUDY ABBREVIATIONS

AASK	African American Study of Kidney Disease and Hypertension
ACC/AHA	American College of Cardiology/American Heart Association
AIRE	Acute Infarction Ramipril Efficacy
ALLHAT	Antihypertensive and Lipid-Lowering Treatment To Prevent Heart Attack Trial
ANBP2	Second Australian National Blood Pressure Study
BHAT	$\beta$ -Blocker Heart Attack Trial
CIBIS	Cardiac Insufficiency Bisoprolol Study
CONVINCE	Controlled Onset Verapamil Investigation of Cardiovascular End Points
COPERNICUS	Carvedilol Prospective Randomized Cumulative Survival Study
EPHESUS	Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study
HOPE	Heart Outcomes Prevention Evaluation Study
IDNT	Irbesartan Diabetic Nephropathy Trial
LIFE	Losartan Intervention For Endpoint Reduction in Hypertension Study
MERIT-HF	Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure
NKF-ADA	National Kidney Foundation-American Diabetes Association
PROGRESS	Perindopril Protection Against Recurrent Stroke Study
RALES	Randomized Aldactone Evaluation Study
REIN	Ramipril Efficacy in Nephropathy Study
RENAAL	Reduction of Endpoints in Non Insulin Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan Study
SAVE	Survival and Ventricular Enlargement Study
SOLVD	Studies of Left Ventricular Dysfunction
TRACE	Trandolapril Cardiac Evaluation Study
UKPDS	United Kingdom Prospective Diabetes Study
ValHEFT	Valsartan Heart Failure Trial



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