



**Hypertension
Guideline Team**

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These guidelines should not be construed as including all proper methods of care or excluding other acceptable methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding any specific clinical procedure or treatment must be made by the physician in light of the circumstances presented by the patient.

Essential Hypertension

Patient population: Adults age 18 and older (non-pregnant).

Objectives: (1) Accurately diagnose hypertension. (2) Improve blood pressure (BP) control. (3) Decrease hypertension-related morbidity and mortality. (4) Encourage patient's self-involvement. (5) Provide appropriate education and follow-up. (6) Provide cost-effective care.

Key points:

■ **Diagnosis**

- Although a single, carefully taken BP reading may predict future cardiovascular risk, this risk is better identified by taking the mean BP level from recordings over several visits.
- Careful calibration of the BP monitor and thorough patient education are essential if home BP monitoring is used.
- If accurate home BP monitoring is not available or desirable, consider ambulatory BP monitoring to confirm the diagnosis for newly suspected hypertensive patients [evidence: B*].

■ **Treatment**

- For patients without diabetes or end organ damage, the target of BP therapy is less than 140/90 mm Hg [A*].
- For patients with diabetes or end organ damage (e.g. renal insufficiency, retinopathy, CHF, CAD, PVD, cerebrovascular disease), aggressive treatment of HTN provides significant improvements in clinical outcomes [A*]. Systolic goals have not been specifically defined. A target systolic blood pressure of 135 mmHg or less [D*] and diastolic BP goal of 80 mmHg or less [B*] is recommended based on trials to date.
- Treatment of SBP over 160 mmHg is important in reducing CVA and CHF risk.
- Lifestyle modifications to lower BP are important adjuncts to drug therapy [A*].
- Begin therapy with a thiazide diuretic for almost all patients and add second and third agents as needed to achieve effective BP reduction goals [A*]. Beta-blockers, ACE inhibitors, and long-acting dihydropyridine calcium channel blockers are the first choice additional agents. Other specific illnesses may guide the choice of a agent(s): especially ACE inhibitors (ARB for those unable to tolerate ACE) for patients with renal disease or diabetes with microalbuminuria or LV dysfunction, and beta-blockers for those with CAD or CHF.
- Over 70% of individuals require two or more drugs to achieve BP goals and usage of fixed combination therapy may be cost-effective. Once a day medications increase compliance and are preferred.

* Levels of evidence reflect the best available literature in support of an intervention or test:

A=randomized controlled trials; B=controlled trials, no randomization; C=observational trials; D=opinion of expert panel.

Clinical Background

**Clinical Problem
and Management Issues**

Incidence

Forty-three million United States adults have elevated hypertension, representing 24% of the U.S. adult population; 20 million have no

medication prescribed, and 12 million are on medication but not controlled. Thus, about one out of four hypertensive patients are adequately controlled. Uncontrolled hypertension results in end stage organ damage, which leads to significant mortality and morbidity.

(continued on page 5)

Table 1. Selection of Additional Antihypertensive Drug(s) Based on Concurrent Disease States

Coexisting Condition	Disease Specific Agent*	Relatively Contra-indicated Agents**	Comments
Cardiovascular			
Angina	β blocker; ACE if LV dysfunction		First generation dihydropyridine calcium channel blockers are relatively contraindicated for all coronary artery disease.
MI History	β blocker; ACE if LV dysfunction		
CHF - Systolic	ACE, β blocker; ARB if ACE not tolerated	Non-DHP CCB	β blockers should be used in very low dosages and slowly titrated.
Cardiomyopathy (Hypertrophic)	β blocker, non-DHP CCB	diuretic, ACE and ARB, α1 blocker, DHP CCB	Effects may be less with cardioselective or ISA β blockers.
Tachycardia (Supraventricular)	β blocker, non-DHP CCB		
Bradycardia/heart block		β blocker, Non-DHP CCB, α2 agonist	
Aortic/Mitral Regurgitation	ACE, DHP CCB, ARB if ACE not tolerated		
Metabolic			
Diabetes	ACE, ARB		Concerns that thiazide diuretics and β blockers may worsen glucose control and β blockers may mask hypoglycemia have largely been refuted as clinically insignificant
Gout	losartan is uricosuric	thiazide diuretics	Diuretic-induced hyperuricemia does not require treatment in the absence of gout or kidney stones.
Renal Disease			
Chronic Renal	ACE, ARB if ACE not tolerated	DHP CCB (alone)	Avoid potassium-sparing agents due to increased risk of hyperkalemia. Loop diuretics preferred if creatinine is ≥ 2.5.
GU			
Impotence	ACE (ARB if ACE not tolerated), DHP CCB		
Bilateral (or equivalent) Renal Artery Stenosis	β blocker, DHP CCB	ACE and ARB	
Pulmonary			
Reactive Airway Diseases		β blocker	
Psychiatric/CNS			
Headaches (Vascular)	β blocker, non-DHP CCB		Verapamil (not diltiazem) especially useful for cluster headaches and, to a lesser extent, migraines.
Pregnancy			
	methyldopa, β blocker (except atenolol), calcium channel blocker, labetalol, hydralazine	atenolol ACE, ARB	ACE and ARB are absolutely contraindicated.
Drug Interactions			
Cyclosporine HTN	β blocker, DHP CCB		
Lithium Usage	β blocker, DHP CCB, Non-DHP CB	Diuretics, ACE and ARB	Thiazides may increase level by 25-40%. Loop & potassium sparing have minor effects.

*** Antihypertensive Drug Classes**

Alpha 1 blocker
 Angiotensin converting enzyme inhibitor
 Angiotensin II receptor antagonist
 Beta blocker
 Centrally acting alpha-2 agonist

Abbreviations

α1 blocker
 ACE inhibitor
 ARB
 β blocker
 NA

Antihypertensive Drug Classes (cont.)

Dihydropyridine calcium channel blocker (e.g.-amlodipine, felodipine)
 Direct vasodilator
 Diuretic
 Non-dihydropyridine calcium channel blocker (e.g.-diltiazem, verapamil)

Abbreviations

DHP CCB
 NA
 NA
 Non-DHP CCB

**** May still be used under certain circumstances.**

Table 2. Antihypertensive Medications: Common Doses and Costs (UMHS Preferred Drugs in Bold)

Drug Class (generic name)	Brand Name	Usual Dosage Regimens			Cost / 30 Days*				
<u>Thiazide Diuretics</u>									
hydrochlorothiazide	generic		12.5 mg QD	25 mg QD		\$13	\$4		
chlorthalidone	generic			25 mg QD			\$5		
<u>Beta Blockers</u>									
atenolol	generic	25 mg QD	50 mg QD	100 mg QD	\$12	\$12	\$18		
	Tenormin				\$34	\$35	\$51		
metoprolol tartrate	generic		50 mg BID	100 mg BID		\$7	\$9		
	Lopressor					\$52	\$77		
propranolol	generic		40 mg BID	80 mg BID			\$7 all		
	Inderal						\$45	\$70	
nadolol	generic	40 mg QD	80 mg QD	120 mg QD	160 mg QD	\$15	\$20	\$25	\$28
	Corgard					\$52	\$71	\$92	\$103
metoprolol succinate	Toprol XL			100 mg QD	200 mg QD			\$31	\$53
labetalol	generic		100 mg BID	200 mg BID	300 mg BID	\$15	\$31	\$39	
	Trandate/Normodyne					\$36	\$54	\$72	
<u>Potassium Sparing/Thiazide Combination Diuretics</u>									
amiloride /HCTZ**	generic			5 mg/50 mg QD				\$5	
spironolactone/HCTZ	generic			25 mg/25 mg QD				\$10	
triamterene/HCTZ	generic			37.5 mg/25 mg QD				\$11	
<u>ACE Inhibitors</u>									
captopril	generic		12.5 mg BID	25 mg BID	50 mg TID	\$5	\$7	\$12	
	Capoten					\$64	\$69	\$178	
enalapril	generic	2.5 mg QD	5 mg QD	10 mg QD	10 mg BID	\$8	\$10	\$11	\$22
	Vasotec					\$25	\$32	\$34	\$68
lisinopril	generic	5 mg QD	10 mg QD	20 mg QD	40 mg QD	\$9	\$9	\$9	\$12
	Prinivil/Zestril					\$30	\$31	\$33	\$48
quinapril	Accupril		10 mg QD	20 mg QD	40 mg QD				\$32 all
moexipril	Univasc			7.5 mg QD	15 mg QD				\$26 all
benazepril	Lotensin	5 mg QD	10 mg QD	20 mg QD	40 mg QD				\$30 all
ramipril	Altace		2.5 mg QD	5 mg QD	10 mg QD	\$35	\$38		\$45
trandolapril	Mavik		1 mg QD	2 mg QD	4 mg QD				\$26 all
fosinopril	Monopril		10 mg QD	20 mg QD	40 mg QD				\$36 all
perindopril	Aceon			4 mg QD	8 mg QD			\$33	\$50
<u>ACE Inhibitor / Diuretic Combinations</u>									
lisinopril/HCTZ	Prinzide/Zestoretic	10 mg/12.5 mg QD	20 mg/12.5 mg QD	20 mg/25 mg QD		\$34	\$37	\$38	
benazepril/HCTZ	Lotensin HCT	5 mg/6.25 mg QD	10 mg/12.5 mg QD	20 mg/12.5 mg QD				\$29 all	
fosinopril/HCTZ	Monopril HCT		10 mg/12.5 mg QD	20 mg/12.5 mg QD				\$36 all	
quinapril/HCTZ	Accuretic	10 mg/12.5 mg QD	20 mg/12.5 mg QD	20 mg/25 mg QD				\$32 all	

Table 2. Antihypertensive Medications: Common Doses and Costs, continued

Drug Class (generic name)	Brand Name	Usual Dosage Regimens				Cost / 30 Days*			
<u>Angiotensin Receptor Blockers</u>									
valsartan	Diovan		80 mg QD	160 mg QD			\$42	\$46	
losartan	Cozaar	50 mg QD	100 mg QD	50 mg BID		\$43	\$59	\$86	
candesartan	Atacand	8 mg QD	16 mg QD	32 mg QD		\$38	\$39	\$51	
eprosartan	Teveten	400 mg QD	600 mg QD	800 mg QD		\$28	\$37	\$56	
irbesartan	Avapro		150 mg QD	300 mg QD			\$45	\$54	
telmisartan	Micardis		40 mg QD	80 mg QD			\$42	\$46	
olmesartan	Benicar		20 mg QD	40 mg QD					\$36 all
<u>Angiotensin Receptor Blocker / Diuretic Combinations</u>									
losartan/HCTZ	Hyzaar	50 mg/12.5 mg QD	100 mg/25 mg QD			\$43	\$59		
valsartan/HCTZ	Diovan HCT	80 mg/12.5 mg QD	160 mg/12.5 mg QD			\$48	\$52		
<u>Calcium Channel Blockers</u>									
diltiazem	generic	30 mg QID	60 mg TID	60 mg QID	90 mg TID	\$13	\$14	\$18	\$19
	Cardizem					\$64	\$76	\$101	\$106
diltiazem CD	generic	120 mg QD	180 mg QD	240 mg QD	300 mg QD	\$26	\$30	\$42	\$47
	Cardizem CD					\$40	\$49	\$67	\$87
nifedipine CC	generic	30 mg QD	60 mg QD	90 mg QD		\$29	\$52	\$61	
	Adalat CC					\$40	\$72	\$84	
verapamil SR	generic				240 mg QD				\$23
	Calan SR								\$56
amlodipine	Norvasc			5 mg QD	10 mg QD		\$41	\$59	
nisoldipine	Sular	20 mg QD	30 mg QD	40 mg QD					\$33 all
felodipine	Plendil		5 mg QD	10 mg QD			\$33	\$59	
isradipine	Dynacirc		2.5 mg BID	5 mg BID			\$75	\$109	
isradipine CR	Dynacirc CR		5 mg QD	10 mg QD			\$45	\$71	
<u>Calcium Channel Blocker / ACE Inhibitor Combinations</u>									
amlodipine/benazepril	Lotrel	2.5mg/10mgQD	5mg/10mgQD	5mg/20mgQD		\$58	\$58	\$62	
trandolapril/verapamil	Tarka	1mg/240mgQD	2mg/180mgQD	2mg/240mgQD	4mg/240mgQD				\$54 all
<u>Other Diuretics</u>									
furosemide	Generic		40 mg QD	80 mg QD			\$5	\$6	
	Lasix						\$9	\$14	

Note: UMHS preferred in **bold**.

* Cost = Average wholesale price based -10% for brand products and Maximum Allowable Cost (MAC) + \$3 for generics on 30-day supply, *Amerisource Bergen item Catalog 4/03 & Blue Cross Blue Shield of Michigan Mac List, 1/15/03*

** HCTZ = hydrochlorothiazide

Rationale for Recommendations

Recommendations are made regarding:

- Diagnosis of hypertension
- Initial evaluation of newly diagnosed patient
- Treatment of hypertension
- Monitoring blood pressure control

Diagnosis of Hypertension

Blood pressure measurement. Current expert opinion is that adults who are believed to be normotensive should receive BP measurements every 2 years; however one should consider BP measurement for every adult visit.

Individuals with risk factors for hypertension should have BP measurements at least annually. Although a single, carefully taken BP reading may predict future cardiovascular risk, this risk is better identified by taking the mean BP level from recordings over several visits.

BP readings need to be performed accurately to provide useful information (Table 3). BP should be checked after 3-5 minutes of rest while the patient is not talking and the results recorded on the medical record. Patients should be informed of the readings, interpretation and necessary follow-up if indicated.

The average BP readings should be staged according to JNC VI expert opinion guidelines (Table 3). Patients with initial BP measurements of 130-139/85-89 mm Hg should have their BP measured annually. Patients with Stage 1 of 140-159/ 90-99 can undergo observation for 12 months before initiating drug therapy since BP may return to normal during that time; however lifestyle modification should be recommended. Delaying possible treatment to assure accuracy of the diagnosis of the most common degree of hypertension (stage 1) is not dangerous to the patient based on longitudinal, epidemiological evidence since the consequences of untreated hypertension are most typically related to the *duration* of sustained hypertension. If the BP average is >140/90, assessing for and correcting the reversible causes of hypertension should be considered (Table 5). Aortic regurgitation may be a cause of suspected isolated systolic hypertension.

Table 3. Classification of Office BP Readings

Category	Systolic	Diastolic
Optimal	<120	<80
<u>Normal</u>	<130	<85
<u>High Normal</u>	130-139	85-89
<u>Hypertension</u>		
• Stage 1	140-159	90-99
• Stage 2	160-179	100-109
• Stage 3	>180	>110

Home blood pressure monitoring. If home BP monitoring is used, certain conditions should be met. The patient needs to be knowledgeable of the proper technique for BP monitoring. Patients should be instructed to take their BP at different times throughout the day, due to the diurnal variation of BP. Ideally, the readings should be mathematically averaged or the handout chart should be used to save time and improve accuracy. If the home BP readings are normal and the office BP readings remain elevated, ambulatory BP monitoring may be considered.

Ambulatory blood pressure monitoring. If accurate home BP monitoring is not available or desirable, ambulatory BP monitoring can be considered for newly suspected hypertensive patients. Ambulatory BP monitoring will identify individuals whose BP is elevated in the physician's office but is not elevated in ambulatory, non-office settings (office hypertension or "White Coat Syndrome"). Several studies have demonstrated better end-organ disease prediction of cardiovascular morbidity and mortality based on ambulatory BP monitoring than office BP monitoring.

White Coat Syndrome. Ambulatory BP monitoring may be cost effective if the medication costs of office hypertension are considered. White Coat Syndrome is often refractory to therapy, and therapy escalates drug costs. White-coat, or office, hypertension is found in 20-34% of patients with elevated BP, and excluding them from medication treatment more than offsets the cost of ambulatory BP monitoring. Normal daytime ambulatory BP average is <135/85 mmHg. It is estimated that half of patients with White Coat Syndrome will become hypertensive within 20 years. White Coat Syndrome may have clinical consequences, however the end-organ damage is not as common as in true hypertension.

Initial Evaluation of Newly Diagnosed Patients

History. Once the diagnosis of hypertension is made, the clinician should determine by history and physical examination whether the patient has evidence suggesting secondary hypertension, as well as other cardiovascular risk factors. The history should focus on the following:

- Cardiovascular review of systems, including known duration of hypertension
- Symptoms or previous personal/family history that helps to identify secondary hypertension
- Presence or absence of other cardiovascular risk factors
- Psychosocial and environmental factors that may influence BP control
- Medications being taken

Table 4. Errors in Measurement of Blood Pressure

Faulty Technique	Patient Related	No effect on BP readings
<ul style="list-style-type: none"> • Back not supported • Arm not supported • Elbow too high • Elbow too low • Missed auscultatory 	<ul style="list-style-type: none"> • Pseudo-hypertension • Atrial fibrillation • Pain or anxiety • Acute smoking • Acute caffeine • Acute ethanol • Talking during BP reading 	<ul style="list-style-type: none"> • Menstrual phase • Chronic caffeine ingestion • Phenylephrine nasal spray • Cuff self-inflation • Examinee and examiner discordance in sex or race • Thin shirtsleeve under cuff • Bell vs diaphragm of stethoscope • Room temperature
Faulty BP Equipment		
<ul style="list-style-type: none"> • Gauge inaccurate • Cuff not correct size 		

Physical examination. Based on expert opinion, the JNC VI recommendations for the physical examination of hypertensive patients are:

- Two or more BP measurements separated by 2 minutes with the patient either supine or seated
- Verification in the contralateral arm
- Weight (possibly height and waist circumference)
- Fundoscopic examination for arteriolar narrowing, nicking, hemorrhages, exudates, etc.
- Neck examination for carotid bruits, distended veins, or enlarged thyroid
- Heart/lung examination
- Abdominal examination for renal bruits, aortic aneurysm
- Extremity examination for pedal pulses and edema
- Neurological assessment

Laboratory tests and diagnostic procedures.

Essential hypertension. Consider the following tests before therapy is initiated [*D**, *expert opinion*]:

- | | |
|-----------------|---------------|
| • Potassium | • Urinalysis |
| • Blood glucose | • Lipid panel |
| • Creatinine | • EKG |
| • Calcium | |

Secondary and/or complicated hypertension. Consider other testing and/or referral when secondary hypertension or complicated hypertension (does not respond to usual measures, pre-existing controlled hypertension becomes uncontrolled, sudden onset of hypertension, and/or malignant hypertension) is suspected. History and the above laboratory screening may be helpful in detection.

Secondary hypertension and complicated hypertension etiologies include:

- Renovascular hypertension
- Primary hyperaldosteronism
- Aortic coarctation
- Cushing’s syndrome
- Pheochromocytoma

Risk Stratification. The risk of cardiovascular disease in patients with hypertension is determined not only by the

level of BP but also by the presence or absence of target organ damage:

- | | |
|---|---|
| <ul style="list-style-type: none"> ▪ LVH ▪ CHF ▪ angina ▪ nephropathy (microalbuminuria or proteinuria) ▪ peripheral arterial disease ▪ retinopathy | <p>Other risk factors:</p> <ul style="list-style-type: none"> ▪ smoking ▪ dyslipidemia ▪ diabetes ▪ older >60years old ▪ men & postmenopausal women ▪ family history of premature cardiovascular disease |
|---|---|

History of:

- MI
- CABG
- CVA
- TIA

Patients without risk factors or target organ damage (TOD) and high normal BP should have lifestyle modification recommended. Drug therapy is recommended for all patients with Stage 2-3 hypertension and all patients with either more than one risk factor, diabetes, or any TOD.

Treatment of Hypertension

Treatment Goal. Clinical trial data reviewed by the Joint National Committee VII support reducing SBP to < 140 mm Hg and DBP to < 90 mm Hg. A sustained decrease in SBP of 10 mm Hg or DBP of 5-6 mm Hg for patients with hypertension decreases the chance of stroke by 35-40% and decreases the chance of coronary heart disease by 20-25%.

Diabetes or end organ damage. Persons with diabetes mellitus or renal disease should be treated to a goal of < 135/80 [*A**]. For patients with other end organ damage (e.g. retinopathy, CHF, CAD, PVOD, cerebrovascular disease), aggressive treatment of HTN provides significant improvements in clinical outcomes [*A**]. Systolic goals have not been specifically defined, but the data suggests that a target systolic blood pressure of 135 mmHg or less may be appropriate. Diastolic BP goal should be 80 mmHg or less [*B**] based on trials to date.

Lifestyle modifications. Patients with Stage I hypertension and no other factors can also be recommended

a trial of lifestyle modification for up to 12 months. Clinical trials have shown that lifestyle modifications can lower BP [A*]. Lifestyle modifications are best initiated and sustained through an educational partnership between the patient and a multidisciplinary health care team. While team members may vary by clinical setting, behavior-change strategies should include nutrition, exercise, and smoking cessation services.

Stress reduction. Some trials have shown evidence of reduced blood pressure after some stress management techniques. Interpretation of these data are controversial and await further clarification.

Weight reduction and maintenance. A significant number of individuals who are both overweight and hypertensive can lower their BP with weight reduction. The effect is usually evident in the early stages of weight loss and frequently occurs with only a ten pound reduction in weight.

Modification of dietary sodium. The current recommendation is to lower sodium intake to less than 2.4 grams per day. Encourage patients to lower their sodium intake by not adding salt to their food or in cooking; limiting processed, convenience, or fast foods; and reading food labels for sodium content. Water softeners contribute sodium to the water, which in some cases may be significant.

Moderation of alcohol intake. Patients should not exceed a daily alcohol intake of 1 ounce of ethanol. This amount is contained in 2 ounces of 100 proof whiskey, 8 ounces of wine, or 24 ounces of beer [B*].

Adequate physical activity. Regular aerobic physical activity may be beneficial for both the prevention and treatment of hypertension and may enable weight loss, improve functional health status, and diminish mortality and risk for cardiovascular disease. Thirty to forty-five minutes of brisk walking three or four times weekly is adequate, inexpensive, and effective. Resistive isotonic activities are not recommended to lower BP in hypertensive patients when done as the only form of exercise training.

Tobacco avoidance. All smokers should be offered assistance in smoking cessation and strongly advised to quit.

Potassium. High dietary potassium may protect against hypertension development, and hypokalemia may exacerbate hypertension and induce ventricular arrhythmia. Potassium sparing diuretics and ACE inhibitors retain potassium and magnesium whereas simple potassium chloride replacement does not contain magnesium.

Other dietary factors. Calcium supplementation may result in a very small reduction in blood pressure (systolic - 1.27 mm Hg; diastolic -0.24 mm Hg). There is no

definitive data to suggest magnesium supplementation lowers blood pressure. Dietary fats have no effect on blood pressure. Acute caffeine ingestion may elevate blood pressure; however, tachyphylaxis to chronic ingestion attenuates this effect. Garlic has not been shown in level A or B trials to be an effective agent for hypertension; some lower level studies have suggested a possible beneficial effect in some patients but this needs further study. A diet low in sodium and saturated fats, and high in vegetables, fruits, and low fat dairy products has been shown to lower blood pressures (the “DASH” diet) [A*].

Drug therapy. Because hypertension is a chronic disease, the choice of which medication(s) to prescribe has long term implications. Data from a very large multicenter RCT supported by smaller studies demonstrate that low-dose thiazide diuretics are as good as any other class of agents in reducing coronary adverse outcomes, and superior in secondary outcomes such as stroke and CHF. This finding holds true in all subgroups including diabetics, those with existing heart disease, African-Americans, patients with hyperlipidemia, and the elderly. Most patients will require two or more drugs to achieve control, and a few will not tolerate thiazides. The choice of additional or alternative medication should be individualized to achieve the target BP and the following goals:

- Once daily administration
- Reduction in CV complications demonstrated in clinical trials
- Choice of agent(s) that also treat concurrent conditions
- Least potential disruptive side-effects based on concurrent conditions or lifestyles
- Least expensive (both in pharmaceutical and laboratory monitoring costs)
- Fixed combination therapy can be more cost-effective and may improve compliance. Some patients may benefit from beginning with fixed combination therapy (e.g.- Stage 2-3 hypertension or patients resistant to monotherapy in the past).

All agents *within* a class have similar physiological action, except the calcium channel blockers and beta blockers that have sub-classes with different physiological effects. If monotherapy is not effective in reaching the BP goal, the addition or substitution of a different class with different physiological action is indicated. Combining medications from the same class is not effective. Table 2 shows costs of drug treatment using various antihypertensive agents.

Diuretics, beta blockers, ACE inhibitors, and long-acting dihydropyridine CCBs have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality. The ALLHAT study was a large multicenter direct comparison RCT designed to determine if the older or newer agents are more effective in prevention of cardiovascular morbidity and mortality. It compared

Table 5. Reversible Causes of Sustained Elevated Blood Pressure Readings

<p>Medications:</p> <ul style="list-style-type: none"> • NSAIDs * • oral contraceptive agents • glucocorticoid or mineralocorticoid steroids <p>* interferes with antihypertension meds</p>	<p>Medications (continued):</p> <ul style="list-style-type: none"> • appetite suppressants • anti-depressants • MAO inhibitors • cyclosporin • erythropoietin 	<p>Lifestyle factors</p> <ul style="list-style-type: none"> • alcohol > 2 drinks/day • sedentary lifestyle <p>Illicit drugs:</p> <ul style="list-style-type: none"> • cocaine • amphetamines • anabolic steroids 	<p>Diet:</p> <ul style="list-style-type: none"> • High sodium (esp. elderly or African-American) <p>Associated Conditions:</p> <ul style="list-style-type: none"> • Sleep apnea • Alcoholism
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treatment starting with a thiazide diuretic, an ACE inhibitor, a long-acting dihydropyridine CCB, and an alpha-blocker. Beta blockers and centrally-acting agents were used as the second step drugs; almost three fourths of patients required two or more drugs and beta blockers were the most commonly used second agent. The alpha blocker arm was discontinued early because of an excess of adverse outcomes. The other agents performed equally in primary outcome (coronary endpoints), but the thiazide was superior in secondary outcomes (stroke and CHF). This finding was consistent across age and race, and in all subgroups including patients with diabetes, coronary disease, and hyperlipidemia.

Diuretics. Thiazide diuretics are the preferred initial treatment for almost all patients with hypertension. Loop diuretics are preferred for individuals with renal impairment (serum creatinine ≥ 2.5 mg/dl) and individuals allergic to thiazide diuretics. Higher dosages of thiazide diuretics have shown only minimal improvement on BP control. Consequently, the maximum suggested dosage of thiazide diuretics has been lowered in order to avoid metabolic side-effects. The range of hydrochlorothiazide is 6.25mg to 25 mg each morning.

Side effects. Thiazide diuretics increase the frequency of sexual dysfunction in men. Thiazides cause a short-term increase in LDL cholesterol; however, long-term trials have shown minimal change and outcome studies show no clinical impact. Thiazide diuretics have a minimal effect on glycemic control of diabetics. They can increase uric acid, and related attacks of gout Hypokalemia is uncommon at usual (12.5-25 mg) doses but occurs relatively often at doses of 50 mg or more.

Loop diuretics are useful for preload reduction, which contributes to hypertension in renal-impaired individuals. Hypokalemia is less common due to the renal impairment, but should still be monitored. Loop diuretics may not be as likely as thiazide diuretics to cause gout.

Beta blockers have been shown to reduce cardiovascular morbidity and mortality in controlled clinical trials for both diastolic and isolated systolic hypertension and have been shown to be equally effective as captopril in diabetes in UKPDS, however the blood pressure control in this trial was not adequate by today's

standard. Beta blockers are least effective in patients with low renin levels (elderly, African American); it is not clear whether outcome benefits are less for these groups, however. Beta blockers are definitively indicated for patients with coronary disease or CHF unless specific contraindications or documented intolerance exists.

Side effects. Fatigue and impotence are uncommon side effects at the recommended low doses. Beta-1 blockers produce the same dramatic reduction in angiotensin II levels as ACE inhibitors, and the two agents together have an additive effect. Though beta blockers may raise triglycerides and lower HDL cholesterol, these effects have not been found to be clinically significant in outcome studies.

Angiotensin converting enzyme (ACE) inhibitors as a class have similar actions and side effects, with the only major difference being duration of action. ACE inhibitors reduce BP with generally few side effects and slow the decline of renal function in most diseases. Ramipril was shown in the HOPE trial to decrease cardiovascular events and the new onset of diabetes in hypertensive and normotensive individuals with at least one cardiovascular risk factor.

Side effects. Angioedema is a rare side effect (0.1%), which may be life-threatening and may occur at any point in the treatment. Renal impairment may occur in patients with bilateral renal artery stenosis or unilateral renal artery stenosis with a single kidney. All in this class induce cough equally, which may be disabling enough with some patients to result in the need to discontinue the drug; cough occurs more often in women. **This class is contraindicated in pregnancy.**

Angiotensin II receptor antagonists (ARB) are designed to displace angiotensin II (AII) from its type 1 receptors. Losartan and irbesartan have been shown in randomized, double-blind trials with diabetics with microalbuminuria or azotemia to decrease the development of frank proteinuria or progression to renal failure requiring dialysis or transplantation (INDT, IRMA, REENAL studies).

Side effects. Angioedema has been rarely reported with Losartan, but has occurred in patients with prior angioedema on ACE inhibitors. Losartan has a uricosuric effect that is unique compared to others in this class. Losartan may be less efficacious compared to others in this group at lowering BP and should be used twice a day. **This class is contraindicated in pregnancy.**

Calcium channel blocking agents. There are three classes of calcium channel blocking agents based on different calcium channel receptors, all with different physiological effects and side effects. In contrast to beta-blockers, calcium channel blockers are most effective in patients with low renin states.

The agents in the dihydropyridine class (e.g. nifedipine) are especially potent vasodilators. The first generation, or short-acting, dihydropyridine agents are to be avoided in the treatment of hypertension, especially after myocardial infarction, due to possible increased cardiovascular morbidity/mortality. The second generation dihydropyridine agents (e.g. amlodipine, felodipine) have more sustained duration, making single daily dosing possible. A long-acting dihydropyridine agent was found to be successful in preventing cardiovascular mortality/morbidity in the ALLHAT trial but was inferior to thiazide in noncardiac endpoints. Amlodipine was not effective in preventing diabetic nephropathy compared to irbesartan in patients with diabetic proteinuria (INDT study).

Side effects. A class side effect is edema formation, usually around the eyes or ankles, as a consequence of excessive arteriolar or pre-capillary vasodilation, and is more pronounced in the second generation dihydropyridine agents. These agents should be avoided as a single agent for patients with microalbuminuria, as they will worsen protein loss, but may be used in combination with ARB or ACE inhibitors. The second generation dihydropyridine agents may be used in patients with angina; however, some feel that it only should be used when combined with a beta blocker. Nifedipine may be useful in hypertensive patients with aortic regurgitation.

Diltiazem and verapamil should also be avoided in the first 24-48 hours of a myocardial infarction. These agents may be beneficial in the treatment of hypertension with atrial fibrillation and/or hypertrophic cardiomyopathy and may be used alone in patients with hypertension and angina due to the lack of reflex tachycardia. Verapamil has more pronounced bradycardia effects and often results in constipation.

Peripheral alpha blockers are more likely to result in orthostatic hypotension. As a class they may improve benign prostatic hypertrophy. However, there are reports of urinary incontinence in women. The shorter acting agents (e.g. prazosin and terazosin) are more likely to exhibit a first dose effect of syncope due to orthostatic

hypotension, which may also occur in the first few days of therapy or with rapid increased dosages. This class lowers serum lipids. The ALLHAT study showed a 25% increase in CV events in the doxazosin vs. chlorthalidone group and, as a result, this arm of the study was terminated prematurely. **Alpha blockers should not be used as initial therapy but may be added to a thiazide or other outcome-improving agent for additional BP control or when prostatism treatment is desired.**

Centrally-acting alpha-2 agonists are less often used due to their side-effects and because, while they lower BP effectively, they have no evidence of outcome benefit. Methyldopa has many compliance-limiting side effects, including orthostatic hypotension, decreased alertness, and depression. Clonidine and guanabenz can be extremely effective, especially in patients with renin-dependent disease.

Side effects. May induce bradycardia; dry mouth and sedation are common. Rebound hypertension has never been documented in proper clinical trials.

Direct vasodilators induce reflex tachycardia and thus should be combined with a beta blocker or non-dihydropyridine calcium channel blocker. Due to an increased fluid retention, they should also be combined with a diuretic. These agents have not been shown to reduce left ventricular hypertrophy.

Hydralazine may produce a lupus erythematosus-like syndrome; the syndrome is extremely rare when the daily dose is less than 200 mg. Headache, palpitations, anorexia, nausea and at least twice daily dosing requirements limit the usefulness of this drug.

Minoxidil is effective in treating the severest forms of hypertension although it is used less frequently today because ACE inhibitors and calcium channel blockers may be as effective. The most limiting side effects have been hypertrichosis and fluid accumulation in serous cavities, including the pericardium.

Monitoring Blood Pressure Control

There are no studies determining what is appropriate monitoring of BP and follow-up. The following is a consensus opinion of the task force.

Blood pressure measurement. All patients who have been diagnosed with hypertension should be taught the technique of home BP monitoring, assuming that there are no cognitive deficiencies that would preclude the technique. The handout about the purchase and proper technique maybe used. Patients should purchase an electronic, digital home BP cuff. The proper size should be indicated to the patient from the healthcare provider. Automatic and non-automatic electronic monitors are equally effective, with the non-automatic being cheaper but

more labor intensive. Patients should be instructed to take their BP daily, upon awakening and before dinner (other times as necessary), until the BP is controlled to the targeted range discussed above. After BP control is achieved, BPs may be obtained monthly. The BP readings should be recorded on a BP monitoring sheet and sent or brought to the physician. The wrist and finger units, although easy to use, are not reliable for monitoring blood pressure.

Stage 1 or 2 hypertension. Stage 1 hypertension may be controlled with lifestyle modification instead of medications, unless the patient has significant risk factors and/or target organ damage. If the BP remains elevated at stage 1 levels, the patient should be monitored at 3-6 month intervals, and medication therapy should be started before target organ damage develops. The disadvantage to waiting longer for lifestyle management to be successful is that many patients will be lost to follow-up and not achieve blood pressure control.

If medication is utilized to lower the BP in stage 1 or 2 hypertension, it may take months to control the BP adequately without adverse effects. Sometimes initial combination therapy with a thiazide plus an additional agent is useful, if the hypertension is greater than stage 1 or the patient has reported resistance to prior therapy. Additionally, patients that are felt to possibly less compliant may achieve better control with initial combination therapy. The patient should have a follow-up office visit to assess BP control, adverse medication effects, patient adherence, and new target organ damage within 1 month of initiating therapy. If after 1-3 months the BP does not reach the targeted goal:

- 1) Insure that the patient is believed to be taking the medication as prescribed
- 2) Insure that the dose of the medication is adequate
- 3) Add a second drug from another class if necessary to reach goal

Most patients will require two or more medications to reach goal. Fixed dosage combination antihypertensive medications may simplify therapy and improve adherence, but generic individual agents are usually less costly. If blood pressure is uncontrolled after persistent attempts to do so, or multiple (>3) drugs are needed referral to a hypertensive specialist should be considered. Intolerance to multiple medications may be an indication of overtreated hypertension due to a significant white coat effect. Ambulatory or home BP monitoring may then be helpful.

Stage 3 hypertension. For Stage 3 hypertension there are no guidelines. Office visits every week would be prudent for Stage 3 hypertension. Symptomatic Stage 3 hypertension may need hospitalization if new end-organ damage is evident, or the criteria of hypertensive emergency are met (i.e. - dissecting aneurysm, myocardial infarction, pregnancy, stroke). For symptomatic Stage 3

hypertensive patients, consider urinalysis to detect casts and hematuria, CBC to detect hemolytic anemia from vasculitis, and fundoscopic examination to look for papilledema.

Once BP is controlled, office visits every 3-6 months are appropriate. At any time, for any stage of hypertension, consultation with a clinician skilled in the management of hypertension should be considered if BP cannot be controlled adequately, patient compliance is poor, or there is difficulty identifying exacerbating conditions or medications.

Special Populations

Hypertension and Pregnancy. The use of anti-hypertensives in pregnancy must consider fetal well-being. Treating uncomplicated Stage I or II hypertension is often not necessary in otherwise low-risk women with normal renal function and no other target organ disease. These women should be closely followed during pregnancy. Pre-eclampsia or other pregnancy-induced hypertension should be treated by a physician experienced in managing these diseases.

Women considering pregnancy who are hypertensive and require treatment, should be on anti-hypertensive medication ideally three to six months prior to conception. The drug with the longest experience and probably still most commonly used is methyldopa. Problems with this medication include frequent side effects and the need to dose multiple times a day. Beta-blockers other than atenolol (which may be associated with intrauterine growth retardation) are relatively popular and the first choice by some. Labetalol, diuretics, and calcium channel blockers are also acceptable to use. ACE inhibitors and ARBs are contraindicated in pregnancy. In order of preference in treating significant hypertension during pregnancy are: 1) methyldopa, 2) beta-blocker with or without diuretic (avoiding atenolol), 3) labetalol, 4) calcium channel blocker [D*].

Related National Guidelines

This guideline is consistent with the sixth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure, updated with results of major trials subsequently. (See annotated references.)

Strategy for Literature Search

Preliminary evidence was identified using literature considered relevant by the National High Blood Pressure Education Program:

Annotated References

A search of more recent literature was conducted on Medline prospectively using the major keywords of: *hypertension, human adults, English language, clinical trials, guidelines, and published since 1/1/99*. Terms used for specific topic searches within the major key words included: *alpha 1 blocker, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonist, beta blockers (selective and non-selective), calcium channel blockers (dihydropyridine and non-dihydropyridine forms), centrally acting alpha-2 agonist, diuretics (thiazide and non-thiazide, loop, potassium-sparing, vasodilator, avoidance (alcohol, stress, tobacco), blood pressure monitoring (ambulatory, home), dietary (caffeine, calcium, garlic, magnesium, onion, potassium, sodium), disease-based management (brain, cardiac, eye, kidney, peripheral vascular), and exercise..* Detailed search terms and strategy available upon request.

The search was conducted in components each keyed to a specific causal link in a formal problem structure (available upon request). The search was supplemented with very recent information available to expert members of the panel, including abstracts from recent meetings and results of clinical trials. Negative trials were specifically sought. The search was a single cycle. Conclusions were based on prospective randomized clinical trials if available, to the exclusion of other data; if randomized controlled trials were not available, observational studies were admitted to consideration. If no such data were available for a given link in the problem formulation, expert opinion was used to estimate effect size.

Disclosures

The University of Michigan Health System endorses the Guidelines of the Association of American Medical Colleges and the Standards of the Accreditation Council for Continuing Medical Education that the individuals who present educational activities disclose significant relationships with commercial companies whose products or services are discussed. Disclosure of a relationship is not intended to suggest bias in the information presented, but is made to provide readers with information that might be of potential importance to their evaluation of the information.

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The 6th report of the Joint National Committee on detection, evaluation, and treatment of high blood pressure. NHLBI, 1997.

The 6th report of the Joint National Committee (JNC VI) was approved by the National High Blood Pressure Education Program Coordinating Committee. This report was derived from a combination of evidence review and consensus, and provides guidelines for the primary prevention and control of high blood pressure.

Burt VL Whelton P Roccella EJ Brown C Cutler JA Higgins M Horan MJ Labarthe D. Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988-1991: Hypertension (1995 Mar) 25(3):305-13.

Prevalence awareness, treatment, and control rates for high blood pressure are reported from the 1988-1991 National Health and Nutrition Examination Survey (NHANES III). These are the first new data in more than a decade in this area.

Hansson L. Lindholm LH. Ekbom T. Dahlof B. Lanke J. Schersten B. Wester PO. Hedner T. de Faire U. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study, Lancet. 354(9192):1751-6, 1999 Nov 20

Examines effects of anti hypertensives in the elderly.

Hansson L. Zanchetti A. Carruthers SG. Dahlof B. Elmfeldt D. Julius S. Menard J. Rahn KH. Wedel H. Westerling S. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group, Lancet. 351(9118):1755-62, 1998 Jun 13.

Established that lowering blood pressure below the traditional 140/90 is safe, and offers outcome benefit to patients in risk groups B & C (those with diabetes mellitus, target organ damage, or multiple risk factors).

The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, Ramipril, on cardiovascular events in high-risk patients, N Engl J Med 2000; 342:145-153, Jan 20, 2000

Conclusions Ramipril significantly reduces the rates of death, myocardial infarction, and stroke in a broad range of high-risk patients who are not known to have a low ejection fraction or heart failure.

Lasagna L. Diuretics vs alpha-blockers for treatment of hypertension: lessons from ALLHAT. Antihypertensive

and Lipid-Lowering Treatment to Prevent Heart Attack Trial, JAMA. 283(15):2013-4, 2000 Apr 19.

Alpha blocker treatment arm of ALLHAT was discontinued because of excess adverse outcomes compared to ACE I, though blood pressure improvements were equivalent.

Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group, JAMA. 265(24):3255-64, 1991 Jun 26.

Demonstrated improvement in CHF, stroke, and MI among elderly with isolated systolic hypertension, using hydrochlorothiazide as the basis of therapy and adding other agents as needed

Major Outcomes in High Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or calcium Blocker vs Diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, JAMA 288:2981-2997, 2002.

The ALLHAT trial was the first large-scale trial to directly compare active treatments against one another in realistic primary treatment settings. It demonstrated thiazide-, ACE-, and long-acting CCB-based treatments (using β -blockers as the most common second drug) to be equal in CAD outcomes, with thiazide superior in CHF and in stroke rates. More than 2/3 of patients needed two or more drugs to achieve control.

Table 5. Standardized Blood Pressure Measurement

Types of Measuring Devices

- **Aneroid manometer** could be used. However, the deflated cuff should read exactly zero, and it should be calibrated at least yearly, unless used frequently and then yearly.
- **Electronic manometers** should be calibrated twice a year if used weekly, or once a year if used less often.
- **The cuff** should be the appropriate size for the measured arm, and each cuff should have markers to note the proper selection.

Proper Technique

1. **Prior activity.** Ideally, the patient should not have eaten, smoked, ingested caffeine or alcohol, or exercised in the past 1 hour.
2. **Preparation.** The patient should sit with their back supported and feet on the floor (not seated on the exam table) for 5 minutes before the 1st blood pressure is taken.
3. **First visit: bilateral measures.** The blood pressure should be measured at least once in each arm (at the patient's first visit) to assure that there is no difference in blood flow (i.e., should be < 10 mm Hg difference), and if there is a significant difference, the higher pressure should be used thereafter.
4. **Cuff. Improper cuff size is the most common source of measurement error.** The arm should be bare, and the cuff should be fitted securely so that the bladder midline is over the brachial artery and the lower edge of the cuff is 1 inch above the antecubital fossa.
5. **Gauge.** The gauge should be at eye level.
6. **Arm.** The patient's arm should be supported, and the stethoscope or measurement point should be at heart level.
7. **Inflation.** Inflate the cuff at least 30 mm Hg above the systolic reading and deflate at a maximum of 2-3 mm per second or a maximum of 2 mm per pulse beat between the Korotkoff sounds.
8. **Measurement.** Record the systolic reading at the first sound heard Korotkoff phase I and the diastolic reading as the last sound heard Korotkoff phase V. If there is a muffling of the sound, this should also be recorded Korotkoff phase IV (e.g.- 150/50/0).
9. **Repeated measurement.** Take the patient's pulse while waiting to repeat a second measurement after 1-2 minutes. If the measurement is performed immediately after walking into the room and the reading is normal, it should be recorded and repeated in 1-2 minutes. If the blood pressure is elevated immediately after walking into the room, it should not be recorded and the blood pressure should be repeated after 5 minutes of rest. At least two readings should be taken, and if the readings vary by more than 5 mm Hg diastolic, the readings should be repeated until there is less variability.
10. **Other recorded information.** The arm used, position of the patient, and the size of the cuff (when non-standard cuff size used) should be recorded.
11. **Inform.** Inform the patient of the readings.