



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.

Essential Hypertension

Patient population: Adults age 18 and older.

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 aspects and recommendations:

Diagnosis

- Although a single, carefully taken blood pressure (BP) reading may predict future cardiovascular risk, for clinical purposes this risk is better identified by taking the mean BP level from recordings over several visits.
Home and ambulatory blood pressure monitoring helps improve BP control, and identifies "white coat" and "masked" hypertension [IIA]\*.
If home BP monitoring is used, careful calibration of the BP monitor and thorough patient education are essential.
Individuals with mean BP > 135/80 should be screened for diabetes [IB].

Treatment

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

\* Strength of recommendation:

I= generally should be performed; II = may be reasonable to perform; III = generally should not be performed.

Levels of evidence for the most significant recommendations

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.

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

<b>Coexisting Condition</b>	<b>Disease Specific Agent*</b>	<b>Relatively Contra-indicated Agents**</b>	<b>Comments</b>
<b>Cardiovascular</b>			
Angina	β blocker; ACEI if LV dysfunction		Short-acting DHP CCBs are relatively contraindicated for all coronary artery disease.
MI History	β blocker, ACEI		
CHF – Systolic	ACEI, β blocker; ARB if ACEI not tolerated, aldosterone inhibitor	Non-DHP CCB, alpha blocker	HYD and nitrate if ACEI and ARB not tolerated β blockers should be used in very low dosages and slowly titrated.
Cardiomyopathy (Hypertrophic)	β blocker, non-DHP CCB	diuretic, ACEI & ARB, α1 blocker, DHP CCB	Effects may be less with cardioselective βblockers
Tachycardia (Supraventricular)	β blocker, non-DHP CCB		
Bradycardia/heart block		β blocker, Non-DHP CCB, α2 agonist	
Aortic/Mitral Regurgitation	ACEI, DHP CCB, ARB if ACEI not tolerated		
<b>Metabolic</b>			
Diabetes	ACEI, ARB		Concerns that thiazide diuretics and βblockers may worsen glucose control and βblockers may mask hypoglycemia have largely been refuted as clinically insignificant
Gout	losartan is uricosuric		Diuretic-induced hyperuricemia does not require treatment in absence of gout or kidney stones.
<b>Renal Disease</b>			
Chronic Renal	ACEI, ARB if ACEI not tolerated	DHP CCB (alone)	Avoid potassium-sparing agents due to increased risk of hyperkalemia. Loop diuretics preferred if creatinine is $\geq 2.5$ (GFR < 30 ml/min).
<b>GU</b>			
Impotence	ACEI (ARB if ACEI not tolerated), DHP CCB		
Bilateral (or equivalent) Renal Artery Stenosis	β blocker, DHP CCB	ACEI and ARB	
<b>Pulmonary</b>			
Reactive Airway Diseases			β blockers should be started at low dose and slowly titrated.
<b>Psychiatric/CNS</b>			
Headaches (Vascular)	β blocker, non-DHP CCB		Verapamil (not diltiazem) useful for cluster headaches and, to lesser extent, migraines.
<b>Pregnancy</b>			
	methyldopa, β blocker (except atenolol and propranolol), calcium channel blocker, labetalol, hydralazine	atenolol, propranolol ACEI, ARB	ACEI and ARB are absolutely contraindicated.
<b>Drug Interactions</b>			
Cyclosporine HTN	β blocker, DHP CCB		
Lithium Usage	β blocker, DHP CCB, Non-DHP CB	Diuretics, ACEI and ARB	Thiazides may increase level by 25-40%. Potassium sparing diuretics have minor effects.

**\* Antihypertensive Drug Classes**

Alpha 1 blocker  
 Angiotensin converting enzyme inhibitor  
 Angiotensin II receptor antagonist  
 Beta blocker  
 Centrally acting alpha-2 agonist  
 Dihydropyridine calcium channel blocker (e.g.-amlodipine, felodipine)

**Abbreviations**

α1 blocker  
 ACEI  
 ARB  
 β blocker  
 NA  
 DHP CCB

**Antihypertensive Drug Classes (cont.)**

Direct vasodilator  
 Diuretic  
 Hydralazine  
 Isosorbide Dinitrate  
 Non-dihydropyridine calcium channel blocker (e.g.-diltiazem, verapamil).

**Abbreviations**

NA  
 NA  
 HYD  
 ISDN  
 Non-DHP CCB

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

**Table 2. Antihypertensive Medications: Common Doses and Costs**

Drug Class (generic name)	Brand Name	Usual Dosage Regimens			Cost / 30 Days*		
<u>Thiazide Diuretics</u>							
hydrochlorothiazide	generic	12.5mg.daily	25mg daily	50 mg daily	\$8	\$4	\$5
chlorthalidone	generic			25 mg daily			\$8
<u>Potassium Sparing/Thiazide Combination Diuretics</u>							
amiloride /HCTZ**	generic			5 mg/50 mg daily			\$4
triamterene/HCTZ	generic			37.5 mg/25 mg daily			\$5
spironolactone/HCTZ	generic			25 mg/25 mg daily			\$11
<u>ACE Inhibitors</u>							
captopril	generic	12.5 mg BID	25 mg BID	50 mg TID	\$4	\$4	\$6
	Capoten				\$97	\$105	\$270
benazepril	generic	5 mg daily	10 mg daily	20 mg daily			\$6 all
	Lotensin			40 mg daily			\$44 all
quinapril	generic	10 mg daily	20 mg daily	40 mg daily			\$9 all
	Accupril						\$50 all
lisinopril	generic	5 mg daily	10 mg daily	20 mg daily	\$6	\$7	\$8
	Prinivil/Zestril			40 mg daily	\$39	\$40	\$43
enalapril	generic	2.5 mg daily	5 mg daily	10 mg daily	\$6	\$7	\$7
	Vasotec			10 mg BID	\$41	\$54	\$60
fosinopril	generic	10 mg daily	20 mg daily	40 mg daily			\$11 all
	Monopril						\$43 all
trandolapril	generic	1 mg daily	2 mg daily	4 mg daily			\$21 all
	Mavik						\$38 all
moexipril	Univasc		7.5 mg daily	15 mg daily		\$46	\$48
ramipril	Altace	2.5 mg daily	5 mg daily	10 mg daily	\$54	\$57	\$67
perindopril	Aceon		4 mg daily	8 mg daily		\$60	\$73
<u>ACE Inhibitor / Diuretic Combinations</u>							
benazepril/HCTZ	generic	5 mg/6.25 mg daily	10 mg/12.5 mg daily	20 mg/12.5mg daily			\$8 all
	Lotensin HCT						\$44 all
lisinopril/HCTZ	generic	10 mg/12.5 mg daily	20 mg/12.5 mg daily	20 mg/25 mg daily	\$9	\$11	\$9
	Prinzide/Zestoretic				\$45	\$49	\$50
fosinopril/HCTZ	generic	10 mg/12.5 mg daily	20 mg/12.5 mg daily	20 mg/12.5 mg daily			\$29 all
	Monopril HCT						\$43 all
quinapril/HCTZ	generic	10 mg/12.5 mg daily	20 mg/12.5 mg daily	20 mg/25 mg daily			\$31 all
	Accuretic						\$50 all

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**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>									
telmisartan	Micardis		40 mg daily	80 mg daily		\$59	\$64		
olmesartan	Benicar		20 mg daily	40 mg daily		\$56	\$65		
valsartan	Diovan		80 mg daily	160 mg daily		\$64	\$69		
irbesartan	Avapro		150 mg daily	300 mg daily		\$60	\$72		
candesartan	Atacand		8 mg daily	16 mg daily	32 mg daily	\$57	\$57	\$77	
eprosartan	Teveten		400 mg daily	600 mg daily		\$65	\$82		
losartan	Cozaar		50 mg daily	100 mg daily	50 mg BID	\$60	\$81	\$119	
<u>Angiotensin Receptor Blocker / Diuretic Combinations</u>									
valsartan/HCTZ	Diovan HCT		80 mg/12.5 mg daily	160 mg/12.5 mg daily		\$69	\$75		
telmisartan/HCTZ	Micardis HCC	40 mg/12.5 mg daily	80 mg/12.5 mg daily	80 mg/25 mg daily		\$64	\$70	\$79	
candesartan/HCTZ	Atacand HCT		16 mg/12.5 mg daily	32 mg/12.5 mg daily		\$77	\$79		
losartan/HCTZ	Hyzaar	50 mg/12.5 mg daily	100 mg/25 mg daily			\$61	\$84		
olmesartan/HCTZ	Benicar HCT	20 mg/12.5 mg daily	40 mg/12.5 mg daily	40 mg/25 mg daily		\$68	\$76	\$86	
eprosartan/HCTZ	Teveten HCT		600 mg/12.5 mg daily	600 mg/25 mg daily				\$87 all	
<u>Calcium Channel Blockers</u>									
<u>Non-DHP</u>									
verapamil SR	generic			240 mg daily				\$13	
	Calan SR							\$79	
diltiazem	generic	30 mg QID	60 mg TID	60 mg QID	90 mg TID	\$10	\$11	\$13	\$13
	Cardizem					\$103	\$76	\$101	\$106
diltiazem CD	generic	120 mg daily	180 mg daily	240 mg daily	300 mg daily	\$23	\$26	\$36	\$40
	Cardizem CD					\$67	\$81	\$116	\$150
	Dilacor								
<u>DHP (dihydropyridines)</u>									
amlodipine	generic			5 mg daily	10 mg daily			\$13	\$17
	Norvasc							\$59	\$80
felodipine	generic			5 mg daily	10 mg daily			\$37	\$66
	Plendil							\$46	\$82
nifedipine CC	generic		30 mg daily	60 mg daily	90 mg daily	\$25	\$43	\$67	
	Adalat CC					\$42	\$75	\$87	
	Procardia XL								
nisoldipine	Sular		20 mg daily	30 mg daily	40 mg daily	\$77	\$84	\$84	
isradipine	generic			2.5 mg BID	5 mg BID				\$102 all
isradipine CR	Dynacirc CR			5 mg daily	10 mg daily			\$77	\$118

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

<b>Drug Class (generic name)</b>	<b>Brand Name</b>	<b>Usual Dosage Regimens</b>					<b>Cost / 30 Days*</b>		
<u>Calcium Channel Blocker / ACE Inhibitor Combinations</u>									
amlodipine/benazepril	generic	2.5mg/10mg daily	5mg/10mg daily	5mg/20mg daily		\$64	\$65	\$68	
	Lotrel					\$88	\$89	\$94	
trandolapril/verapamil	Tarka	1mg/240mg	2mg/180mg	2mg/240mg	4mg/240mg	all daily			\$83 all
<u>Aldosterone Antagonists</u>									
spironolactone	generic		25 mg daily	50 mg daily			\$9	\$16	
	Aldactone						\$26	\$45	
eplerenone	Inspra		50 mg daily	50 mg BID			\$123	\$246	
<u>Beta Blockers</u>									
atenolol	generic		25 mg daily	50 mg daily	100 mg daily		\$5	\$5	\$6
	Tenormin						\$48	\$49	\$73
metoprolol tartrate	generic			50 mg BID	100 mg BID			\$6	\$7
	Lopressor						\$84	\$125	
propranolol	generic (IR)			40 mg BID	80 mg BID				\$7 all
	generic (ER)		60 mg daily	80 mg daily	120 mg daily		\$32	\$36	\$45
	Inderal LA						\$104	\$121	\$151
labetalol	generic		100 mg BID	200 mg BID	300 mg BID		\$13	\$16	\$20
	Trandate/Normodyne						\$42	\$56	\$72
nadolol	generic		40 mg daily	80 mg daily	160 mg daily		\$12	\$17	\$34
	Corgard						\$84	\$104	NA
metoprolol succinate	generic (XL)			100 mg daily	200 mg daily			\$31	\$43
	Toprol XL							\$43	\$69
nebivolol	Bystolic		2.5 mg daily	10-20 mg daily	40 mg daily		\$51	\$51-102	\$203
carvedilol	generic		3.125 BID	12.5-25 mg BID	25 BID				\$12 all
	Coreg								\$133 all
	Coreg CR	10mg daily	20 mg daily	40 mg daily	80 mg daily				\$117 all
<u>Vasodilators</u>									
Isosorbide dinitrate	generic		10 mg TID	20 mg TID	40 mg TID		\$6	\$7	\$14
Hydralazine	generic		25 mg TID	50 mg TID	100 mg TID		\$26	\$34	\$58
Methyldopa	generic		25 0mg TID	500 mg TID	1000 mg TID		\$17	\$28	\$52
<u>Alpha Blockers</u>									
Doxazosin	generic		1mg daily	2mg daily	4mg daily		\$5	\$5	\$6
	Cardura						\$43	\$43	\$46
terazosin	generic		1mg daily	2mg daily	5mg daily				\$7 all
	Hytrin								\$64 all
Prazosin	generic		1mg BID	2mg BID	5mg BID		\$11	\$19	\$29
	Minipress						\$40	\$56	\$95

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

<b>Drug Class (generic name)</b>	<b>Brand Name</b>	<b>Usual Dosage Regimens</b>		<b>Cost / 30 Days*</b>	
<u>Renin Inhibitors</u>					
aliskiren	Tekturna	150 mg daily	300mg daily	\$70	\$88
<u>Other Diuretics</u>					
Torsemide (Furosemide –generic or Lasix – has no blood pressure indication, only volume control.)	Demadex	5 mg daily	10 mg daily	\$32	\$36

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, 11/08, and Michigan Department of Community Health M.A.C. manager, 11/08.

\*\* HCTZ = hydrochlorothiazide

**Table 3. Errors in Measurement of Blood Pressure**

<p><b>Faulty Technique</b></p> <ul style="list-style-type: none"> <li>• Back not supported</li> <li>• Arm not supported</li> <li>• Elbow too high</li> <li>• Elbow too low</li> <li>• Missed auscultatory</li> <li>• Feet not on ground</li> </ul> <p><b>Faulty BP Equipment</b></p> <ul style="list-style-type: none"> <li>• Gauge inaccurate</li> <li>• Cuff not correct size</li> </ul>	<p><b>Patient Related</b></p> <ul style="list-style-type: none"> <li>• Pseudo-hypertension</li> <li>• Atrial fibrillation</li> <li>• Pain or anxiety</li> <li>• Acute smoking</li> <li>• Acute caffeine</li> <li>• Acute ethanol</li> <li>• Talking during BP reading</li> </ul>	<p><b>No effect on BP readings</b></p> <ul style="list-style-type: none"> <li>• Menstrual phase</li> <li>• Chronic caffeine ingestion</li> <li>• Phenylephrine nasal spray</li> <li>• Cuff self-inflation</li> <li>• Examinee and examiner discordance in sex or race</li> <li>• Bell vs diaphragm of stethoscope</li> <li>• Room temperature</li> <li>• Thin shirtsleeve under cuff (growing evidence, not universally endorsed)</li> </ul>
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**Table 4. Classification of Office BP Readings**

<b>Category</b>	<b>Systolic</b>	<b>Diastolic</b>
Normal	<120	and <80
Prehypertension	120-139	or 80-89
Hypertension		
• Stage 1	140-159	or 90-99
• Stage 2	≥160	or ≥100

**Table 5. Reversible Causes of Sustained Elevated Blood Pressure Readings**

<p><b>Medications:</b></p> <ul style="list-style-type: none"> <li>• NSAIDs *</li> <li>• oral contraceptive agents</li> <li>• glucocorticoid or mineralocorticoid steroids</li> </ul> <p>* interferes with antihypertensive medications</p>	<p><b>Medications (continued):</b></p> <ul style="list-style-type: none"> <li>• appetite suppressants</li> <li>• anti-depressants</li> <li>• MAO inhibitors</li> <li>• cyclosporin</li> <li>• erythropoietin</li> </ul>	<p><b>Lifestyle factors</b></p> <ul style="list-style-type: none"> <li>• alcohol &gt; 2 drinks/day</li> <li>• sedentary lifestyle</li> </ul> <p><b>Illicit drugs</b></p> <ul style="list-style-type: none"> <li>• cocaine</li> <li>• amphetamines</li> <li>• anabolic steroids</li> </ul>	<p><b>Diet</b></p> <ul style="list-style-type: none"> <li>• High sodium (esp. elderly or African-American)</li> </ul> <p><b>Associated Conditions</b></p> <ul style="list-style-type: none"> <li>• Sleep apnea</li> </ul>
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## Rationale for Recommendations

Recommendations are organized under headings for:

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

### Diagnosis of Hypertension

**Performing BP measurement.** BP readings need to be performed accurately to provide useful information. BP in the office should be checked after 5 minutes of sitting quietly in a chair, with feet on the floor, and arm supported at the heart level, and the results recorded on the medical record. Caffeine, exercise, and smoking should be avoided for at least 30 minutes prior to measurement. (See Appendix for detail about devices and proper technique.) Patients should be informed of the readings, interpretation and necessary follow-up if indicated.

**Frequency of BP screening.** Frequency depends on patient risk status regarding hypertension.

- If normotensive, at least every 2 years (current expert opinion). However one should consider BP measurement for every adult visit.
- If risk factors, at least annually.

Although a single, carefully taken BP reading may predict future cardiovascular risk, risk is better identified by taking the mean BP level from recordings over several visits.

**HTN classification and follow-up assessment.** The average initial BP readings should be staged according to JNC VII (7) expert opinion guidelines (Table 4).

For prehypertension (120-139 / 80-89 mm Hg), measure BP annually.

If the BP average is  $\geq 140/90$ , consider assessing for and correcting the reversible causes of hypertension (Table 5). Aortic regurgitation may be a cause of isolated systolic hypertension.

**BP monitoring.** BP can be monitored at home in two ways.

- Home blood pressure monitoring (HBPM) – Patient or caregiver records blood pressures at home with a blood pressure cuff. It is inexpensive, but requires knowledge of proper technique. Upper arm BP cuffs are preferred, since wrist and finger monitors are not reliable. Proper technique and calibration of home BP cuffs should be checked at the clinic.
- Ambulatory blood pressure monitoring (ABPM) – Automated cuff sent home from the clinic, worn for a pre-specified period of time (usually 24 hours). It is expensive, but is reliable and has been shown to be an independent predictor of cardiovascular morbidity and mortality when added to office based BP measures.

HBPM and ABPM identify patients whose BP at clinic visits differs from BP outside the office. They may also be useful in resistant hypertension.

- White coat hypertension (WCH) refers to patients with elevated BP at office visits, but normal BP outside the office. This condition is common (>20% of patients with elevated BP) and may result in overtreatment if unrecognized. Both HBPM and ABPM can help identify WCH. Documentation of WCH results in decreased drug cost, with no change in LV mass, cardiovascular outcomes, or well being. WCH may carry a higher long term risk of hypertension, but at least one study has not shown an increase in risk.
- Masked hypertension refers to patients with target BP at clinic, but elevated home BP. This condition may be nearly as common as WCH. These patients may have LVH or other target organ damage despite normal office BP. Both HBPM and ABPM can help identify masked hypertension, resulting in more aggressive medication regimens and improved cardiovascular outcomes.

Currently, reimbursement for ABPM by Medicare is covered only for suspected WHC, defined by 3 or more office visit BPs  $>140/90$  mm Hg, at least two documented BPs outside the office  $<140/90$  mm Hg, and no evidence of target organ damage.

### 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

**Physical examination.** Based on expert opinion the JNC VII 7 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
- Body mass index (BMI), calculated by weight (kg)/[height (m)]<sup>2</sup> (possibly waist circumference)
- Funduscopic examination for arteriolar narrowing, nicking, hemorrhages, exudates, etc.
- Neck examination for carotid bruits, distended veins, or enlarged thyroid
- Heart/lung examination

- Abdominal examination for enlarged kidneys, masses, distended bladder, 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. Screening for diabetes is particularly important.

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

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:

- Chronic or acute kidney disease
- Renovascular hypertension
- Sleep apnea
- Medications or illicit drugs
- Chronic kidney disease
- Renovascular disease
- Primary aldosteronism
- Coarctation of the aorta
- Chronic steroid therapy and Cushing's syndrome
- Pheochromocytoma
- Thyroid or parathyroid disease

Medications and other reversible causes are described further in Table 5.

**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:

Current diagnoses:

- LVH
- CHF
- Angina
- Stroke or TIA
- Chronic kidney disease (includes microalbuminuria and proteinuria)
- Peripheral arterial disease
- Retinopathy

History of:

- MI
- CABG
- CVA
- TIA

Other risk factors:

- Smoking
- Obesity (BMI $\geq$ 30 kg/m<sup>2</sup>)
- Physical inactivity
- Dyslipidemia
- Diabetes
- Estimated GFR < 60 mL/min)
- Age (>55 for men, >65 for women)
- Family history of premature cardiovascular disease (men <55 or women <65) disease

## Treatment of Hypertension

**Treatment BP goal.** The goal depends on the presence of other risk factors.

Goal if no risk factors. Clinical trial data reviewed by the Joint National Committee VII 7 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 risk of stroke by 35-40% and decreases the chance of coronary heart disease by 20-25%.

Goal if diabetes or end organ damage. The goals for blood pressure treatment in diabetes have been evaluated in several randomized trials.

For diastolic blood pressure, a target of 80 mmHg provides marked benefits. Caution is suggested when diastolic BP falls below 60 mmHg or less. Mortality increased when patients with diabetes had diastolic BP below 70.

Systolic blood pressure has not been evaluated as rigorously. For patients with elevated blood pressure and other end organ damage (e.g. retinopathy, CHF, CAD, PVOD, cerebrovascular disease), aggressive treatment of HTN provides significant improvements in clinical outcomes. Few studies have targeted or achieved systolic pressures below 140 mmHg. However, the available data suggest that a systolic target of 135 mmHg is reasonable, and more aggressive control may be warranted, particularly in patients with renal disease. Some organizations, including the National Committee of Quality Assurance, which establishes the Health Plan Employer Data and Information Set (HEDIS), the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, and the American Diabetes Association promote a systolic pressure below 130 mmHg, but there are no data from randomized controlled trials to support this. More aggressive control may be warranted, particularly in patients with renal disease.

**Treatment selection.** While lifestyle modification is always recommended, the addition of medications depends on disease severity and other risk factors.

Patients with prehypertension but without risk factors or target organ damage (TOD) should have lifestyle modification recommended.

Patients with Stage 1 hypertension and no other risk factors can be recommended for a trial of lifestyle modification for up to 12 months. With recent evidence suggesting that early treatment to goal blood pressure levels may attenuate the expression of hypertension and improve clinical outcomes, more experts are recommending both medication

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and lifestyle modification initially, with plans to reduce or eliminate drug therapy as lifestyle goals are achieved.

Patients with Stage 2 hypertension or with either diabetes, or any TOD should have drug therapy in addition to lifestyle modification. Initial combination therapy with a thiazide plus an additional agent is useful (or other combinations). Additionally, patients that are felt to have resistance to prior therapy or possibly less compliant may achieve better control with initial combination therapy.

**Lifestyle modifications.** Clinical trials have shown that lifestyle modifications can lower BP. 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.

Weight reduction and maintenance. Many 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 and 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.

Adequate physical activity. Regular aerobic physical activity may be beneficial for both prevention and treatment of hypertension. It 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 and effective. Resistive isotonic activities as sole exercise are not recommended to lower BP in hypertensive patients.

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. 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 replace magnesium.

Other dietary factors. Calcium supplementation may result in a very small reduction in BP (systolic -1.27 mm Hg; diastolic -0.24 mm Hg). No definitive data suggest magnesium supplementation lowers blood pressure. Dietary fats have no effect on blood pressure. Acute caffeine ingestion may elevate BP; however, tachyphylaxis to chronic ingestion attenuates this effect. 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).

**Drug therapy.** Hypertension is a chronic disease. Thus, the choice of which medication(s) to prescribe has long term implications.

Drug selection. Data from a very large multicenter RCT supported by smaller studies demonstrate that moderate-to-high dose thiazide diuretics (chlorthalidone 25 mg/day or its equivalent of HCTZ, about 50mg/day) are as good as any other class of agents in reducing cardiovascular adverse outcomes, and superior in secondary outcomes such as stroke and CHF. 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 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 for 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 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. 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, in moderate to high doses, 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.

Existence of other risk factors, co-morbidities, and concern for untoward drug effects may influence initial drug selection. ACE inhibitors, ARB's, and CCB's may be initial options. Beta blockers are not preferred as initial therapy in the elderly. Recent meta-analyses suggest that beta blockers may be less effective in stroke reduction when compared to other classes of antihypertensive therapy. Beta blocker usage for HTN may be deferred unless CAD or CHF exists.

It is not yet clear whether specific drug combinations impart superior clinical outcomes (e.g., ACEI/CCB vs. ACEI/diuretic; ACEI/ARB vs. ACEI or ARB). Currently, the ACEI/ARB combination is not recommended for lowering BP but has been found to improve outcomes in hypertensive subjects with certain forms of kidney disease and heart failure.

**Diuretics. Thiazide diuretics are the preferred initial treatment for most patients with hypertension.** Although the trials that showed a decrease in cardiovascular morbidity and mortality used moderate to high dose diuretics, higher dosages of thiazide diuretics have shown only minimal improvement in 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 12.5mg to 50 mg each morning. The most studied thiazide is chlorthalidone, though hydrochlorothiazide is the predominant prescription thiazide in the USA.

*Side effects.* Thiazide diuretics increase the frequency of sexual dysfunction in men and women and initially may cause interruptions in daily routine for micturition. Thiazides cause a short-term increase in LDL cholesterol; however, long-term trials have shown minimal change and outcome studies show no clinical impact. Thiazides slightly increase risk for diabetes (ALLHAT). While small changes in LDL and glycemic control are not contraindications, the clinical impact of these metabolic aberrations has yet to be elucidated. Thiazides can increase uric acid and precipitate 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. These diuretics are preferred for individuals with renal impairment (serum creatinine  $\geq$  2.5 mg/dl) and individuals allergic to thiazide diuretics. Loop

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

Angiotensin converting enzyme (ACE) inhibitors. As a class, ACE-inhibitors 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. The renoprotective effect may be augmented when combined with angiotensin receptor blocker. Ramipril was shown in a randomized controlled trial to decrease cardiovascular events in hypertensive and normotensive individuals with systolic heart failure over placebo. However, newer trials have not shown renin-angiotensin blockade to be superior to other medications in decreasing morbidity and mortality. Onset of diabetes was not prevented by ramipril in a study directly addressing this issue.

*Side effects.* Angioedema is a rare side effect (0.1-0.7%), which may be life-threatening and may occur at any point in the treatment. The incidence may be higher in African Americans. Although renal artery stenosis per se is not a contraindication for ACE therapy, 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) displace angiotensin II (AII) from its type 1 receptors. Losartan and irbesartan have been shown in randomized, double-blind trials in diabetics with microalbuminuria or azotemia to decrease the development of frank proteinuria or progression to renal failure requiring dialysis or transplantation. In patients who have systolic heart failure and are intolerant to an ACEI because of cough, ARBs are recommended.

*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 (i.e. increases excretion of uric acid, lowering concentration in blood) 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 (CCB) agents. There are three classes of calcium channel blocking agents based on different classes of calcium channel receptors, all with different physiological effects and side effects: verapamil, diltiazem, and dihydropyridines. All long acting DHP CCB's have

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been shown to reduce blood pressure and cardiovascular events.

Of the dihydropyridine CCB's, the longer-acting agents (e.g. amlodipine, felodipine, nisoldipine) make single daily dosing possible. These drugs provide the most reliable and significant blood pressure reduction in most patient subtypes. They are particularly effective in stroke reduction and have been shown to reduce overall CVD risk. The short-acting agents are not indicated for hypertension.

Some effects with specific diseases include:

- *Acute coronary syndrome.* Short-acting dihydropyridines should be avoided in the first 24-48 hours of an acute coronary syndrome.
- *Chronic kidney disease.* Dihydropyridines should be avoided as a single agent for patients with microalbuminuria, as they will worsen protein loss and renal function, but may be used in combination with ARB or ACE inhibitors.
- *Chronic CAD.* Verapamil has shown to be as effective as a beta-blocker in patients with CAD or remote history of MI. The second generation dihydropyridine agents may be used in patients with angina; however, some feel that they only should be used when combined with a beta blocker. All CCB's can be used in hypertensive patients with chronic CAD to reduce anginal episodes
- *Aortic regurgitation.* Nifedipine may be useful in hypertensive patients with aortic regurgitation.

*Side effects.* Edema may occur and is more pronounced with the dihydropyridine agents.

Bradycardia is a side effect of verapamil and diltiazem, but renders them useful agents in the treatment of atrial fibrillation/SVT). Verapamil has more pronounced bradycardia effects and often results in constipation. Verapamil and diltiazem may increase risk for statin myopathy (cytochrome 3A4 inhibition).

Aldosterone inhibitors. Spironolactone and eplerenone are used in certain conditions associated with hypertension, such as resistant hypertension, hyperaldosteronism, and potassium wasting. However, when used in patients with chronic kidney disease, or concurrently with potassium sparing agents (ACEI, ARB, triamterene), they carry significant risk for **life-threatening hyperkalemia**. Combination therapy is generally restricted to patients with systolic heart failure, and requires close follow-up. Gynecomastia and breast pain are common side effects with spironolactone, causing discontinuation in about 10%.

Beta blockers have been shown to reduce cardiovascular morbidity and mortality in controlled clinical trials for both diastolic and isolated systolic hypertension. However, one study showed that diuretics are superior to beta-blockers for stroke reduction, and another showed that losartan is superior to beta blocker for

CVD reduction. The results of three meta analyses suggest that other anti-hypertensive agents are superior to most beta-blockers for initial therapy. In particular, atenolol has poorer outcomes when compared to other beta-blockers (an excess stroke risk of 17%). Beta blockers are indicated for patients with coronary disease or CHF unless specific contraindications or documented intolerance exists. Certain beta blockers (e.g., carvedilol) also have alpha blocking properties and are useful for maintenance therapy of heart failure.

*Side effects.* Occasionally fatigue and uncommonly impotence are 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.

Renin inhibitors are a novel way of blocking the renin-angiotensin-aldosterone system (RAAS). The first drug in this class is aliskiren. The drug has been shown to lower blood pressure alone or in combination with other antihypertensives, but its effects on clinical outcomes is unknown. Aliskiren should be used as a fourth line agent in patients who have failed standard therapy.

*Side Effects.* As with other RAAS agents, aliskiren can cause an increase in serum creatinine and potassium especially is used in combination with an ACE inhibitor or ARB. **This class is contraindicated in pregnancy.**

Peripheral alpha blockers. **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.**

*Side effects:* Alpha blockers may cause first dose syncope, so are generally started at bedtime and slowly titrated up in dose. They may cause fluid retention and edema. The ALLHAT study showed a 25% increase in cardiac events in the doxazosin vs. chlorthalidone group.

Centrally-acting alpha-2 agonists are less often used due to their side-effects. They have no evidence of outcome benefit. Methyldopa remains a first line agent in pregnancy.

*Side effects.* May induce bradycardia; dry mouth and sedation are common. Rebound hypertension may occur with sudden discontinuation of clonidine.

Direct vasodilators. These drugs are fourth line agents for essential hypertension and should be used in patients who have failed standard therapy. Direct vasodilators induce reflex tachycardia and thus should be combined with a beta blocker or non-dihydropyridine calcium channel blocker. Due to increased fluid retention, they should also

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be combined with a diuretic. These agents have not been shown to reduce left ventricular hypertrophy. They are third or fourth line agents, sometimes useful in refractory hypertension.

Hydralazine may produce a lupus erythematosus-like syndrome; the syndrome is extremely rare when the daily dose is less than 200 mg. Side effects include headache, palpitations, anorexia, and nausea. At least twice daily dosing requirements limit the usefulness of this drug. Hydralazine has shown benefit in CHF when combined with a nitrate.

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. Side effects include hypertrichosis and fluid accumulation in serous cavities, including the pericardium.

### Monitoring Blood Pressure Control

No studies demonstrate the most appropriate monitoring of BP and follow-up. The following is a consensus opinion of the guideline team.

**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. A handout about the purchase and proper technique may be used. Patients should purchase an electronic, digital home BP cuff. The proper cuff size should be indicated to the patient by the healthcare provider. Automatic (self-inflating) 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, BP 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.

**Prehypertension.** Follow at least annually.

**Stage 1 hypertension.** Once antihypertensive therapy is initiated, most patients should return for follow-up and adjustment of medications at monthly intervals or less until the BP goal is reached. At each visit, BP control, adverse medication effects, patient adherence, and new target organ damage should be assessed. If after 1-3 months the BP does not reach the targeted goal:

- 1) Ensure that the patient is believed to be taking the medication as prescribed.
- 2) Ensure that the dose of the medication is adequate.

- 3) Reconsider reversible causes.
- 4) Add a second drug from another class if necessary to reach goal.

After BP is at goal and stable, follow-up visits can usually be at 3- to 6-month intervals. A randomized controlled trial showed that for stable patients that patient outcomes were equivalent for follow-up intervals of 3 and 6 months. Serum potassium and creatinine should be monitored at least 1-2 times/year. Monitoring for microalbuminuria may also be useful.

**Stage 2 hypertension.** Follow-up is generally similar to that for medical therapy for Stage 1 hypertension, except more frequent visits may be necessary, e.g., more frequently than monthly intervals initially to adequately control BP.

**Additional considerations.** 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, consider referral to a hypertension specialist.

Intolerance to multiple medications may be an indication of over-treated hypertension due to a significant white coat effect. Ambulatory or home BP monitoring may then be helpful.

**Controlled BP.** 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.

**Resistant hypertension.** Resistant hypertension is the failure to reach goal BP in patients who are adhering to full doses of an appropriate 3-drug regimen that includes a diuretic. After excluding potential identifiable causes of hypertension (Table 5), clinicians should explore reasons why the patient is not at the goal BP. Particular attention should be paid to diuretic type and dose in relationship to renal function. Consultation with a hypertension specialist should be considered if goal BP cannot be achieved.

## Special Considerations

**Hypertension and Pregnancy.** The use of anti-hypertensives in pregnancy must consider fetal well-being. Treating uncomplicated Stage 1 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. Medications for treating significant hypertension during pregnancy, in order of preference, are:

- 1) Methyldopa – the drug with the longest experience and probably still most commonly used. Problems with this medication include frequent side effects and the need to dose multiple times a day.
- 2) Beta-blocker with or without diuretic (avoiding atenolol, which may be associated with intrauterine growth retardation) – are relatively popular and the first choice of some.
- 3) Labetalol
- 4) Calcium channel blockers

Diuretics are also acceptable to use.

Contraindicated in pregnancy are ACE inhibitors, ARBs, and renin inhibitors.

**Ongoing diabetes screening.** While screening for diabetes is recommended when a mean BP > 135/80 is first identified, for patients with hypertension an optimal interval for subsequent screening for diabetes is not known. The American Diabetes Association (based on expert opinion) recommends screening at 3-year intervals.

### Related National Guidelines

This guideline is consistent with the 7th report of the Joint National Committee on Prevention, 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 in the 7th report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (see annotated references). That report utilized literature searches of the preceding reports and added a systematic search of literature from January 1997 through April 2003.

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 from 1/1/03 through 5/1/07.* 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 (direct), avoidance (alcohol, stress, tobacco), blood pressure monitoring (ambulatory, home), dietary (caffeine, calcium, garlic, magnesium, onion, potassium, sodium), exercise, disease-based management (stroke, coronary artery disease, cardiac, heart failure, arterial fibrillation, peripheral vascular disease, diabetes, chronic kidney disease, metabolic syndrome), and resistant hypertension..* 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

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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1997: Steven Yarows, MD, FACP, William Barrie, MD, Christine Birmingham, RN, Steven Erickson, PharmD, Kenneth Jamerson, MD, Christopher Wise, PhD, Philip Zazove, MD.

2003: William Barrie, MD, Janice Stumpf, PharmD, Kenneth Jamerson, MD, Philip Zazove, MD; Lee Green, MD (consultant).

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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  $\beta$ -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.

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CHARM - Pfeffer MA, Swedberg CB, Held P, et al. Effects of candesartan on mortality and morbidity in patient with chronic heart failure: the CHARM-Overall programme. Lancet 2003; 362:759.

Candesartan was well tolerated and significantly reduced cardiovascular deaths and hospital admissions for heart failure.

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Effect of  $\beta$ -blockers is less than optimum compared to other antihypertensive drugs (e.g., 16% higher risk of stroke). Beta-blockers should not be considered first-line therapy to treat primary hypertension and should not be used as reference drugs in future randomized trials

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

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## APPENDIX. 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 1<sup>st</sup> 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.