Hypertension

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Hypertension

- Brief History of Hypertension Guidelines
- Burden of Hypertension
- Diagnosis of Hypertension
  - White Coat Hypertension & Masked Hypertension
- Secondary Hypertension
- Management of Hypertension
  - Non Pharmacological
  - Pharamcological
- Hypertension & Co- Morbidities
- Hypertensive Crises
- Resistant Hypertension

Brief history of Hypertension Guidelines

Hypertension Guidelines Brief History

JNC 1
1976

Panel: Experts in	
HTN	14
PCP	6
Geriatricians	2
Cardiology	2
Nephrology	3
Nursing	1
Pharmacology	2
Clinical Trials	6
EBM	3
Epidemiology	1
Informatics	4
Clinical Guidelines	4

JNC 6
1997

JNC 6 Category	SBP/DBP
Optimal	<120/80
Normal	120–129/80–84
Borderline	130–139/85–89
Hypertension	≥140/90
Stage 1	140–159/90–99
Stage 2	160–179/100–109
Stage 3	≥180/110

JNC 7
2003

Classification of Blood Pressure (BP)*

Category	SBP mmHg		DBP mmHg
Normal	<120	and	<80
Prehypertension	120–139	or	80–89
Hypertension, Stage 1	140–159	or	90–99
Hypertension, Stage 2	≥160	or	≥100

* See *Blood Pressure Measurement Techniques* (reverse side)
Key: SBP = systolic blood pressure DBP = diastolic blood pressure

JNC 8
2014

	Goal BP
Age ≤ 60 yrs	< 140/90
Age ≥ 60 yrs	<150/90
DM	<140/90
CKD	<140/90

Hypertension Guidelines History

JNC 7 2003

EVALUATION

Classification of Blood Pressure (BP)*

Category	SBP mmHg		DBP mmHg
Normal	<120	and	<80
Prehypertension	120–139	or	80–89
Hypertension, Stage 1	140–159	or	90–99
Hypertension, Stage 2	≥160	or	≥100

* See *Blood Pressure Measurement Techniques* (reverse side)
Key: SBP = systolic blood pressure DBP = diastolic blood pressure

Diagnostic Workup of Hypertension

- Assess risk factors and comorbidities.
- Reveal identifiable causes of hypertension.
- Assess presence of target organ damage.
- Conduct history and physical examination.
- Obtain laboratory tests: urinalysis, blood glucose, hematocrit and lipid panel, serum potassium, creatinine, and calcium. Optional: urinary albumin/creatinine ratio.
- Obtain electrocardiogram.

Assess for Major Cardiovascular Disease (CVD) Risk Factors

- Hypertension
- Obesity (body mass index ≥30 kg/m²)
- Dyslipidemia
- Diabetes mellitus
- Cigarette smoking
- Physical inactivity
- Microalbuminuria, estimated glomerular filtration rate <60 mL/min
- Age (>55 for men, >65 for women)
- Family history of premature CVD (men age <55, women age <65)

Assess for Identifiable Causes of Hypertension

- Sleep apnea
- Drug induced/related
- Chronic kidney disease
- Primary aldosteronism
- Renovascular disease
- Cushing's syndrome or steroid therapy
- Pheochromocytoma
- Coarctation of aorta
- Thyroid/parathyroid disease

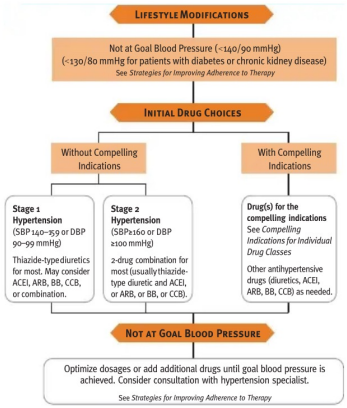
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Heart, Lung, and Blood Institute

TREATMENT

Principles of Hypertension Treatment

- Treat to BP <140/90 mmHg or BP <130/80 mmHg in patients with diabetes or chronic kidney disease.
- Majority of patients will require two medications to reach goal.

Algorithm for Treatment of Hypertension



Blood Pressure Measurement Techniques

Method	Notes
In-office	Two readings, 5 minutes apart, sitting in chair. Confirm elevated reading in contralateral arm.
Ambulatory BP monitoring	Indicated for evaluation of "white coat hypertension." Absence of 10–20 percent BP decrease during sleep may indicate increased CVD risk.
Patient self-check	Provides information on response to therapy. May help improve adherence to therapy and is useful for evaluating "white coat hypertension."

Causes of Resistant Hypertension

- Improper BP measurement
- Excess sodium intake
- Inadequate diuretic therapy
- Medication
  - Inadequate doses
  - Drug actions and interactions (e.g., nonsteroidal anti-inflammatory drugs (NSAIDs), illicit drugs, sympathomimetics, oral contraceptives)
  - Over-the-counter (OTC) drugs and herbal supplements
- Excess alcohol intake
- Identifiable causes of hypertension (see reverse side)

Compelling Indications for Individual Drug Classes

Compelling Indication	Initial Therapy Options
Heart failure	THIAZ, BB, ACEI, ARB, ALDO ANT
Post myocardial infarction	BB, ACEI, ALDO ANT
High CVD risk	THIAZ, BB, ACEI, CCB
Diabetes	THIAZ, BB, ACEI, ARB, CCB
Chronic kidney disease	ACEI, ARB
Recurrent stroke prevention	THIAZ, ACEI

Key: THIAZ = thiazide diuretic, ACEI= angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, BB = beta blocker, CCB = calcium channel blocker, ALDO ANT = aldosterone antagonist

Strategies for Improving Adherence to Therapy

- Clinician empathy increases patient trust, motivation, and adherence to therapy.
- Physicians should consider their patients' cultural beliefs and individual attitudes in formulating therapy.

The National High Blood Pressure Education Program is coordinated by the National Heart, Lung, and Blood Institute (NHLBI) at the National Institutes of Health. Copies of the JNC 7 Report are available on the NHLBI Web site at http://www.nhlbihin.gov or from the NHLBI Health Information Center, P.O. Box 30105, Bethesda, MD 20824-0105; Phone: 301-592-8573 or 240-629-3255 (TTY); Fax: 301-592-8563.

Principles of Lifestyle Modification

- Encourage healthy lifestyles for all individuals.
- Prescribe lifestyle modifications for all patients with prehypertension and hypertension.
- Components of lifestyle modifications include weight reduction, DASH eating plan, dietary sodium reduction, aerobic physical activity, and moderation of alcohol consumption.

Lifestyle Modification Recommendations

Modification	Recommendation	Avg. SBP Reduction Range†
Weight reduction	Maintain normal body weight (body mass index 18.5–24.9 kg/m²).	5–20 mmHg/10 kg
DASH eating plan	Adopt a diet rich in fruits, vegetables, and low fat dairy products with reduced content of saturated and total fat.	8–14 mmHg
Dietary sodium reduction	Reduce dietary sodium intake to ≤100 mmol per day (2.4 g sodium or 6 g sodium chloride).	2–8 mmHg
Aerobic physical activity	Regular aerobic physical activity (e.g., brisk walking) at least 30 minutes per day, most days of the week.	4–9 mmHg
Moderation of alcohol consumption	Men: limit to ≤2 drinks* per day. Women and lighter weight persons: limit to ≤1 drink* per day.	2–4 mmHg

* 1 drink = 1/2 oz or 15 mL ethanol (e.g., 12 oz beer, 5 oz wine, 1.5 oz 80-proof whiskey).
† Effects are dose and time dependent.

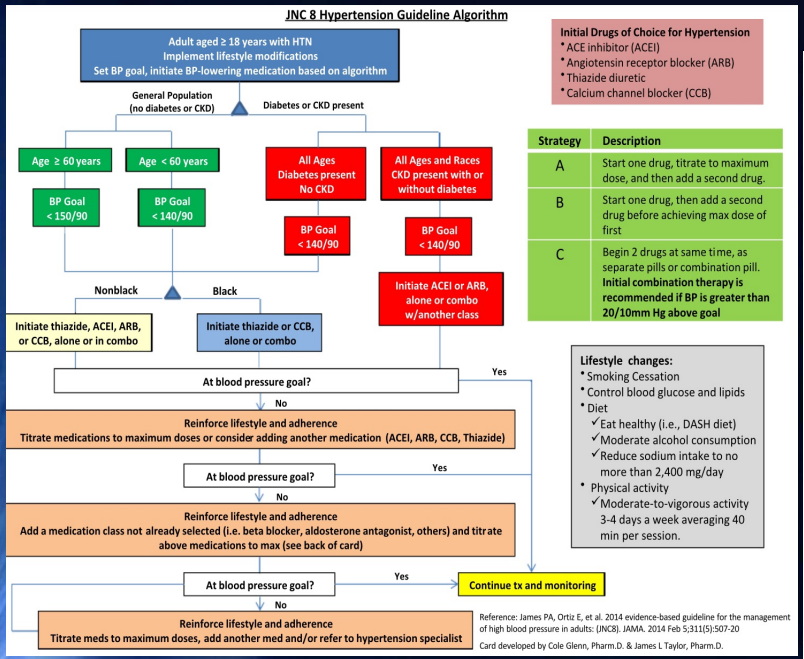
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Heart, Lung, and Blood Institute
National High Blood Pressure Education Program

NIH Publication No. 03-5231
May 2003

Hypertension Guidelines History

JNC 8 2014

JNC 8 Hypertension Guideline Algorithm



Initial Drugs of Choice for Hypertension
- ACE inhibitor (ACEI)
- Angiotensin receptor blocker (ARB)
- Thiazide diuretic
- Calcium channel blocker (CCB)

Strategy	Description
A	Start one drug, titrate to maximum dose, and then add a second drug.
B	Start one drug, then add a second drug before achieving max dose of first
C	Begin 2 drugs at same time, as separate pills or combination pill. **Initial combination therapy is recommended if BP is greater than 20/10mm Hg above goal**

Lifestyle changes:
- Smoking Cessation
- Control blood glucose and lipids
- Diet
  - ✓Eat healthy (i.e., DASH diet)
  - ✓Moderate alcohol consumption
  - ✓Reduce sodium intake to no more than 2,400 mg/day
- Physical activity
  - ✓Moderate-to-vigorous activity 3-4 days a week averaging 40 min per session.

Reference: James PA, Ortiz E, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: (JNC8). JAMA. 2014 Feb 5;311(5):507-20

Card developed by Cole Glenn, Pharm.D. & James L Taylor, Pharm.D.

Hypertension Treatment

Compelling Indications	
Indication	**Treatment Choice**
Heart Failure	ACEI/ARB + BB + diuretic + spironolactone
Post –MI/Clinical CAD	ACEI/ARB AND BB
CAD	ACEI, BB, diuretic, CCB
Diabetes	ACEI/ARB, CCB, diuretic
CKD	ACEI/ARB
Recurrent stroke prevention	ACEI, diuretic
Pregnancy	labetolol (first line), nifedipine, methyldopa

Beta-1 Selective Beta-blockers – possibly safer in patients with COPD, asthma, diabetes, and peripheral vascular disease:
- metoprolol
- bisoprolol
- betaxolol
- acebutolol

Drug Class	Agents of Choice	Comments
Diuretics	HCTZ 12.5-50mg, chlorthalidone 12.5-25mg, indapamide 1.25-2.5mg triamterene 100mg *K+ sparing* – spironolactone 25-50mg, amiloride 5-10mg, triamterene 100mg furosemide 20-80mg twice daily, torsemide 10-40mg	Monitor for hypokalemia Most SE are metabolic in nature Most effective when combined w/ ACEI Stronger clinical evidence w/chlorthalidone Spironolactone - gynecomastia and hyperkalemia Loop diuretics may be needed when GFR <40mL/min
ACEI/ARB	*ACEI*: lisinopril, benazapril, fosinopril and quinapril 10-40mg, ramipril 5-10mg, trandolapril 2-8mg *ARB*: candesartan 8-32mg, valsartan 80-320mg, losartan 50-100mg, olmesartan 20-40mg, telmisartan 20-80mg	SE: Cough (ACEI only), angioedema (more with ACEI), hyperkalemia Losartan lowers uric acid levels; candesartan may prevent migraine headaches
Beta-Blockers	metoprolol succinate 50-100mg and tartrate 50-100mg twice daily, nebivolol 5-10mg, propranolol 40-120mg twice daily, carvedilol 6.25-25mg twice daily, bisoprolol 5-10mg, labetalol 100-300mg twice daily,	Not first line agents – reserve for post-MI/CHF Cause fatigue and decreased heart rate Adversely affect glucose; mask hypoglycemic awareness
Calcium channel blockers	*Dihydropyridines*: amlodipine 5-10mg, nifedipine ER 30-90mg, *Non-dihydropyridines*: diltiazem ER 180-360 mg, verapamil 80-120mg 3 times daily or ER 240-480mg	Cause edema; dihydropyridines may be safely combined w/ B-blocker Non-dihydropyridines reduce heart rate and proteinuria
Vasodilators	hydralazine 25-100mg twice daily, minoxidil 5-10mg terazosin 1-5mg, doxazosin 1-4mg given at bedtime	Hydralazine and minoxidil may cause reflex tachycardia and fluid retention – usually require diuretic + B-blocker Alpha-blockers may cause orthostatic hypotension
Centrally-acting Agents	clonidine 0.1-0.2mg twice daily, methyldopa 250-500mg twice daily guanfacine 1-3mg	Clonidine available in weekly patch formulation for resistant hypertension

Hypertension Guidelines History

	JNC 8[1]	NICE[2]	JSH[3]	ESH/ESC[4]	CCS[5]
General	<140/90 (<60 years old)	<140/90	<130/85	<140/90	<140/90
Diabetes	<140/90	NR	<130/80	<140/85	<130/80
CKD	<140/90	<130/80	<130/80	<140/90	<140/90
MI	NR	NR	<130/80	<140/90	<140/90
Stroke	NR	<130/80	<140/90	<140/90	<140/90
Elderly	<150/90 (≥60 years old)	<150/90 (≥80 years old)	<140/90	<140/90 (<80 years old)	<150/90 (≥80 years old)

CKD=chronic kidney disease; CCS=Canadian Cardiovascular Society; ESC=European Society of Cardiology; ESH=European Society of Hypertension; JNC 8=Eighth report of the Joint National Committee; JSH=Japanese Society of Hypertension; MI=myocardial infarction; NICE=National Institute for Health and Care Excellence; NR=not reported

Hypertension Guidelines History

American Heart Association.

AMERICAN COLLEGE of CARDIOLOGY

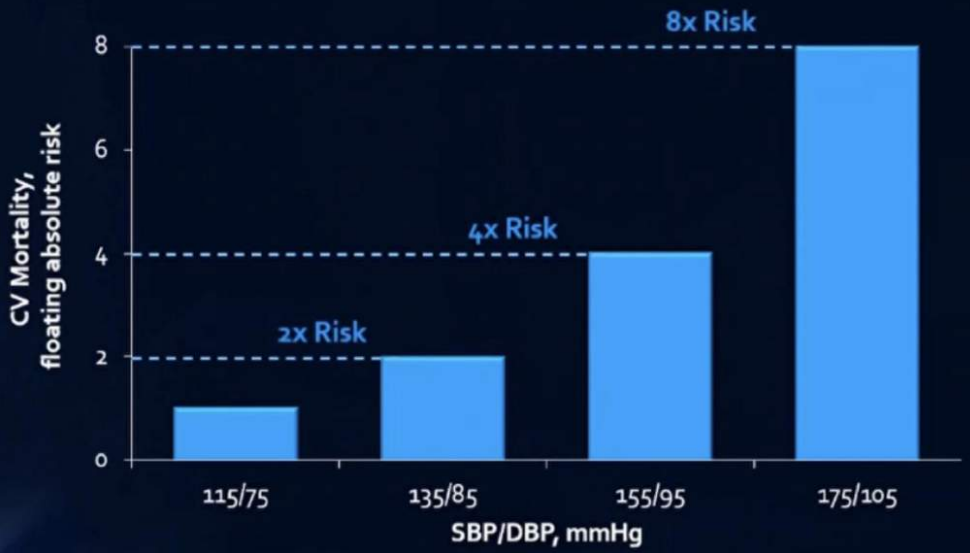
BLOOD PRESSURE CATEGORY	SYSTOLIC mm Hg (upper number)		DIASTOLIC mm Hg (lower number)
NORMAL	LESS THAN 120	and	LESS THAN 80
ELEVATED	120 – 129	and	LESS THAN 80
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 1	130 – 139	or	80 – 89
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 2	140 OR HIGHER	or	90 OR HIGHER
HYPERTENSIVE CRISIS (consult your doctor immediately)	HIGHER THAN 180	and/or	HIGHER THAN 120

ESC European Society of Cardiology

Hypertension disease staging	Other risk factors, HMOD, or disease	BP (mmHg) grading			
		High normal SBP 130-139 DBP 85-89	Grade 1 SBP 140-159 DBP 90-99	Grade 2 SBP 160-179 DBP 100-109	Grade 3 SBP ≥180 or DBP ≥110
Stage 1 (uncomplicated)	No other risk factors	Low risk	Low risk	Moderate risk	High risk
	1 or 2 risk factors	Low risk	Moderate risk	Moderate to high risk	High risk
	≥3 risk factors	Low to Moderate risk	Moderate to high risk	High Risk	High risk
Stage 2 (asymptomatic disease)	HMOD, CKD grade 3, or diabetes mellitus without organ damage	Moderate to high risk	High risk	High risk	High to very high risk
Stage 3 (established disease)	Established CVD, CKD grade ≥4, or diabetes mellitus with organ damage	Very high risk	Very high risk	Very high risk	Very high risk

Burden of Hypertension

Effect of Hypertension on Risk of Cardiovascular Death



*Based on observational studies, risk was present in all age groups 40–89 years
BP=blood pressure; CV=cardiovascular; DBP=diastolic blood pressure; IHD=ischemic heart disease; SBP=systolic blood pressure

Chobanian AV, et al. *Hypertension*. 2003;42:1206-1252.

What is the big deal about BP Control?

Analysis of 5 major observational studies demonstrated that small differences in SBP resulted in significant risk difference in developing complications:[1]

SBP by 5 mmHg →
- Stroke mortality by 14%
- CHD mortality by 9%
- All-cause mortality by 7%

A meta-analysis of 61 prospective randomized studies involving 12.7 million person-years demonstrated that modest SBP reduction was associated with significant risk reduction in developing complications:[2]

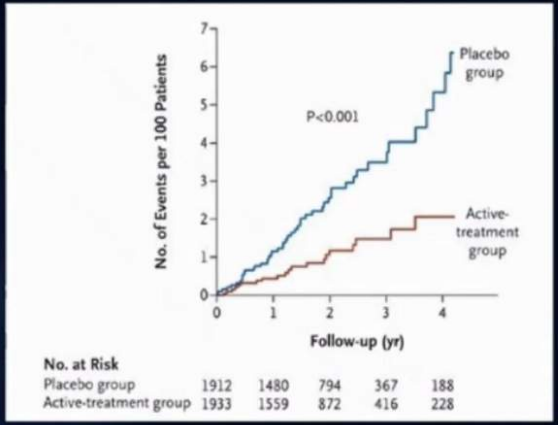
SBP by 2 mmHg →
- Stroke mortality by 10%
- IHD mortality by 7%

CHD=coronary heart disease; IHD=ischemic heart disease; SBP=systolic blood pressure

1. Stalmer R. *Hypertension*. 1991;17(Suppl1):I16-I20.
2. Lewington S, et al. *Lancet*. 2002;360:1903-1913.

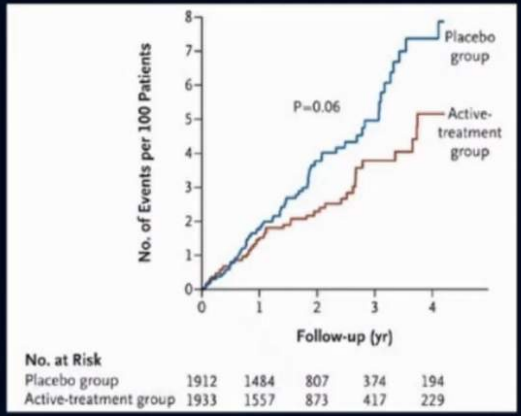
Treatment works !!

HF



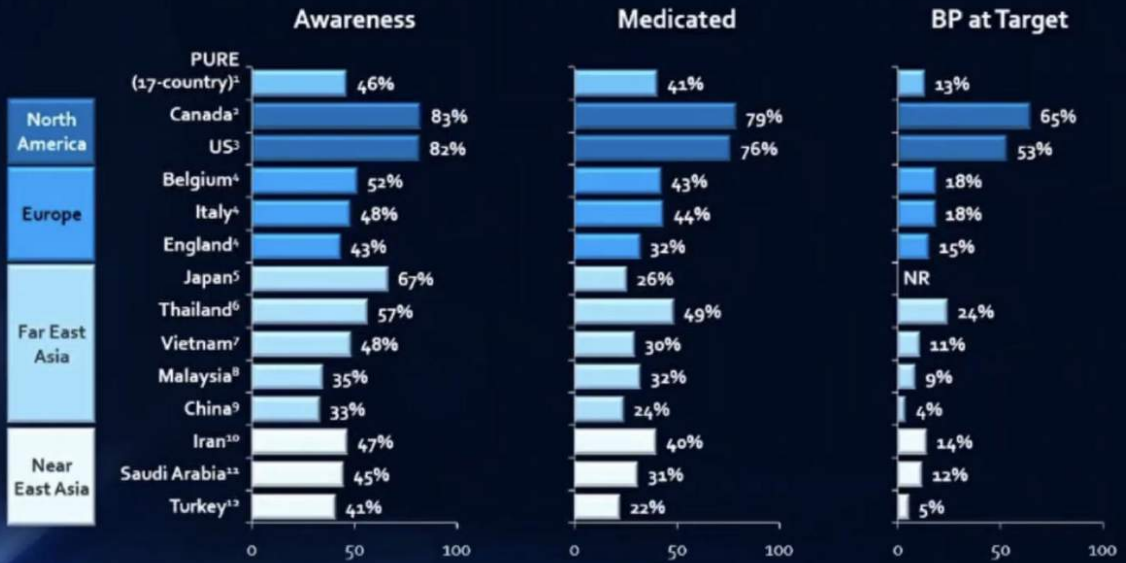
1. Kostis et al. SHEP Cooperative Research Group. JAMA 1991;270: 212–6.

CVA

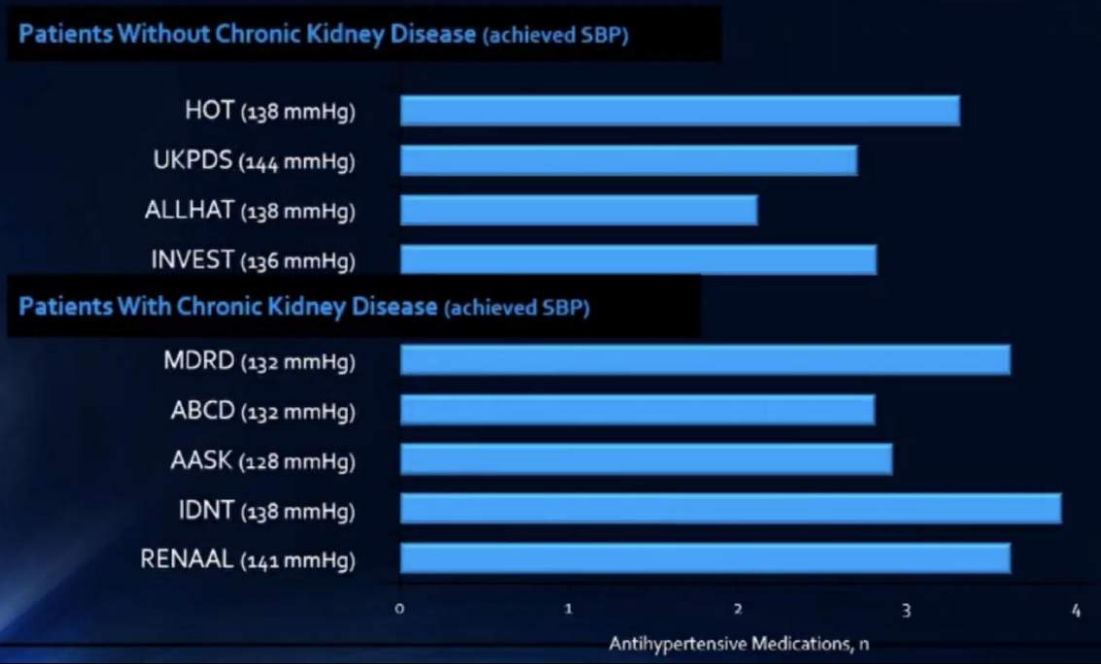


2. Beckett et al. HYVET. N Engl J Med 2008;358:1887–98.

Among Adults with Hypertension: Awareness, Treatment, and At Target



Number of Medications Needed to Achieve Goal Systolic Blood Pressure



Diagnosis of Hypertension

Diagnosis of Hypertension

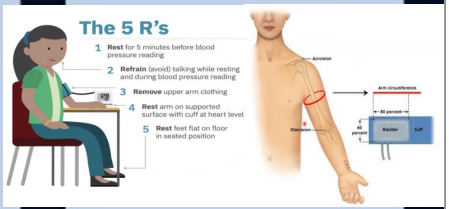
- **Guidelines for Proper Technique for measurement of BP**

Posture

- Patient sit quietly for 3-5 minutes before taking the measurement
- Support the arm at heart level during measurement
- BP should be measured in both arms, with the arm with the higher pressure being used to make future measurements
- Initially, check for postural changes by taking readings after five minutes supine, then immediately and two minutes after standing; this is particularly important in patients over age 65 years, diabetics, or those taking antihypertensive drugs
- Sitting pressures are recommended for routine follow-up; the patient should sit quietly with the back supported for five minutes and the arm supported at the level of the heart

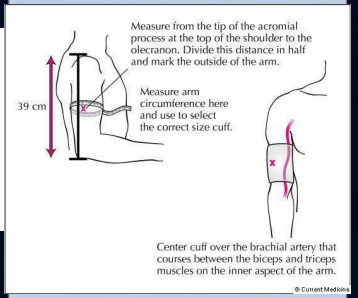
Circumstances

- No caffeine during the hour preceding the reading, and no smoking during the preceding 30 minutes
- No exogenous adrenergic stimulants, such as phenylephrine in decongestants or eye drops for pupillary dilatation
- A quiet, warm setting
- Home readings should be taken upon varying circumstances



Equipment

- Cuff size
  - The length of the bladder should be 80%, and the width of the bladder should be at least 40% of the circumference of the upper arm
- Manometer
  - Aneroid gauges should be calibrated every six months against a mercury manometer



For the diagnosis of hypertension, take three readings at least one week apart

Technique

- Number of readings
  - Take at least two readings on each visit, separated by as much time as possible; if readings vary by more than 5 mmHg, take additional readings until two consecutive readings are close
- If the arm pressure is elevated, take the pressure in one leg, particularly in patients under age 30 years
- Performance
  - Inflate the bladder quickly to 20 mmHg above the systolic pressure as estimated from loss of radial pulse
  - Deflate the bladder by 3 mmHg per second
  - Record the Korotkoff phase V (disappearance) as the diastolic pressure except in children in whom use of phase IV (muffling) may be preferable
  - If the Korotkoff sounds are weak, have the patient raise the arm, open and close the hand 5 to 10 times, and then inflate the bladder quickly
- Note the pressure, patient position, arm, and cuff size: eg, 140/90, seated, right arm, large adult cuff

Diagnosis of Hypertension

- Types of BP Measurements

CENTRAL ILLUSTRATION: Clinic, Home, and Ambulatory Blood Pressure Measurements

	Clinic Measurements	Home BP Monitoring	Ambulatory BP Monitoring
Description	• BP measured in a medical setting • Patient should be seated, resting quietly with their back supported and feet flat on the floor	• BP measured while seated at home, resting quietly with back supported and feet flat on the floor • BP readings obtained in the morning and evening	• BP measured during routine activities • 48 to 72 readings obtained over 24 hours
Strengths	• Associated with cardiovascular outcomes • Only method that has been used to guide treatment in large outcome trials	• Strong association with cardiovascular outcomes • Detects white coat and masked hypertension	• Strong association with cardiovascular outcomes • Detects white coat and masked hypertension • BP measured at work and at night (i.e., during sleep)
Weaknesses	• Less precise as only 1 or 2 BP measurements typically obtained • Many factors affect the accuracy of readings • Requires training and frequent re-training of staff	• Patients may not correctly measure and report their BP • Requires patient training and re-training • Many home devices are not validated	• Not tolerated by some patients • Equipment is not widely available • Requires two clinic visits: to set up and return the device

Muntner, P. et al. J Am Coll Cardiol. 2019;73(3):317-35.

Diagnosis of Hypertension

- **Ambulatory (ABPM) and Home BP Monitoring (HBPM)**
  - Very useful for patients with white coat hypertension
  - Ideally be attained in all patients with resistant hypertension
  - If out-of-office readings are at or below the desired target, while office readings remain elevated, home or office readings may be used to guide medication adjustments.
  - Ambulatory monitoring is also a better predictor than office blood pressure measurements of cardiovascular morbidity (ie, end-organ damage) and mortality in patients with resistant hypertension
  - Goal is an average of Systolic BP < 135 mmHg and Diastolic BP < 85 mmHg

Diagnosis of Hypertension:

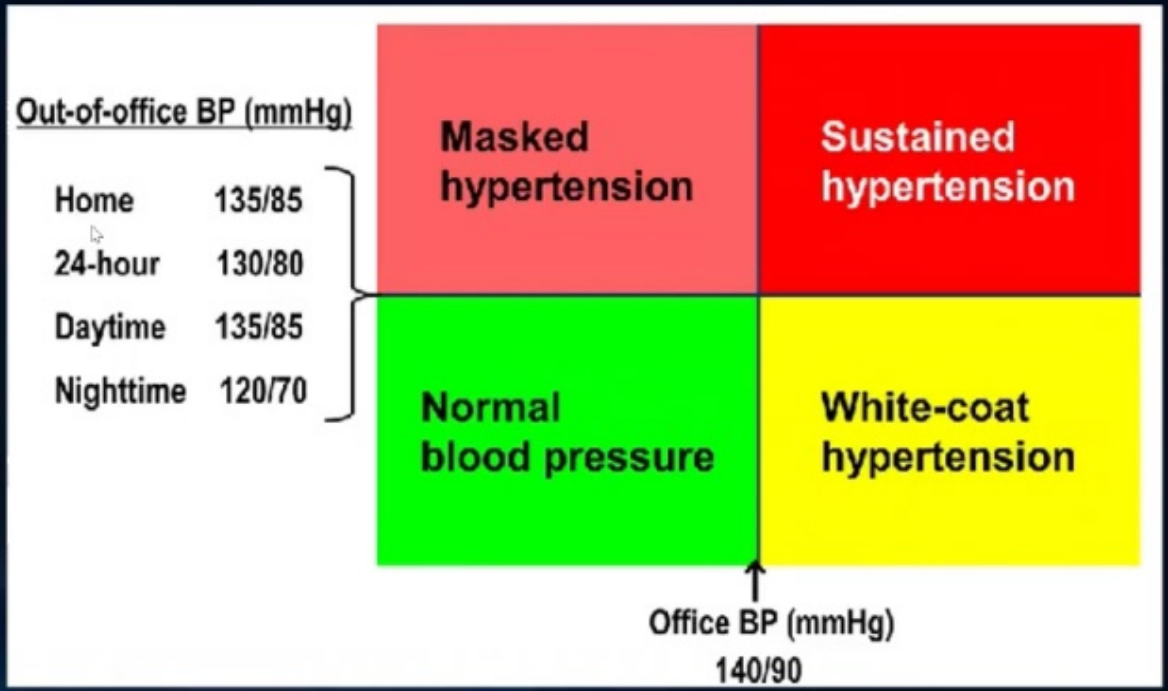
Corresponding Values of Systolic BP/Diastolic BP for Clinic, Home (HBPM), Daytime, Nighttime, and 24-Hour Ambulatory (ABPM) Measurements.

Clinic	HBPM	Daytime ABPM	Nighttime ABPM	24-Hour ABPM
120/80	120/80	120/80	100/65	115/75
130/80	130/80	130/80	110/65	125/75
140/90	135/85	135/85	120/70	130/80
160/100	145/90	145/90	140/85	145/90

Whelton PK, et al. Hypertension. Nov. 2017.

Diagnosis of Hypertension

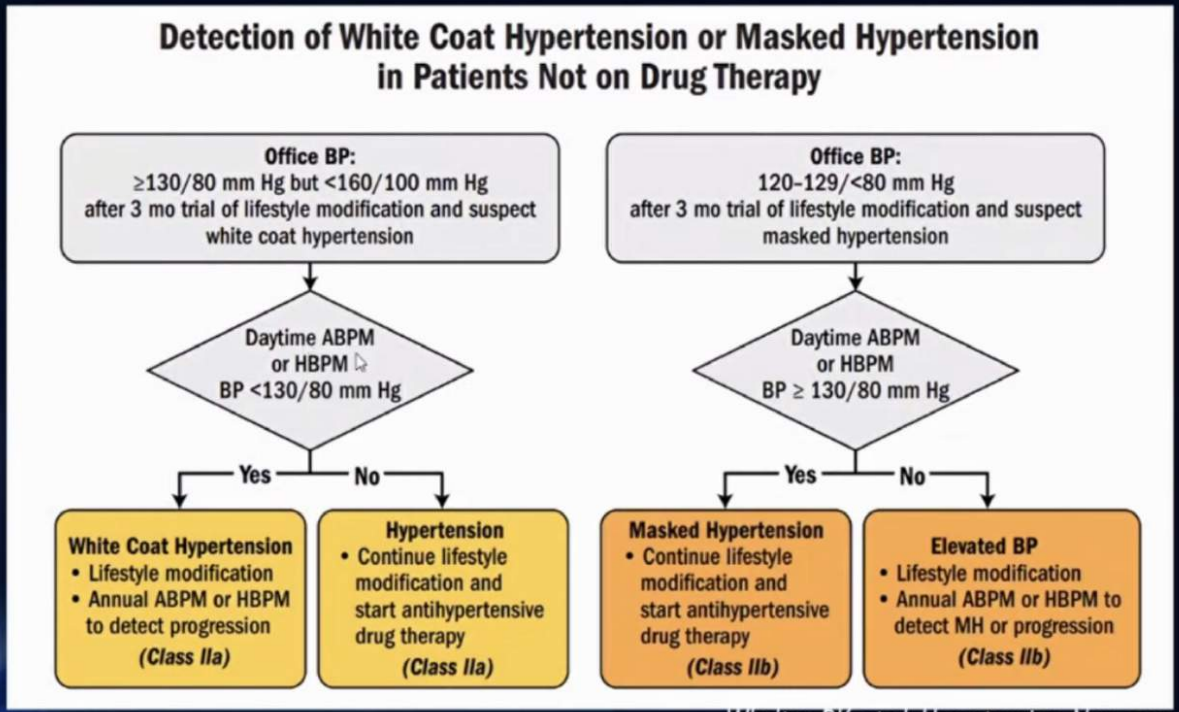
Diagnosis of Hypertension:



Diagnosis of Hypertension:

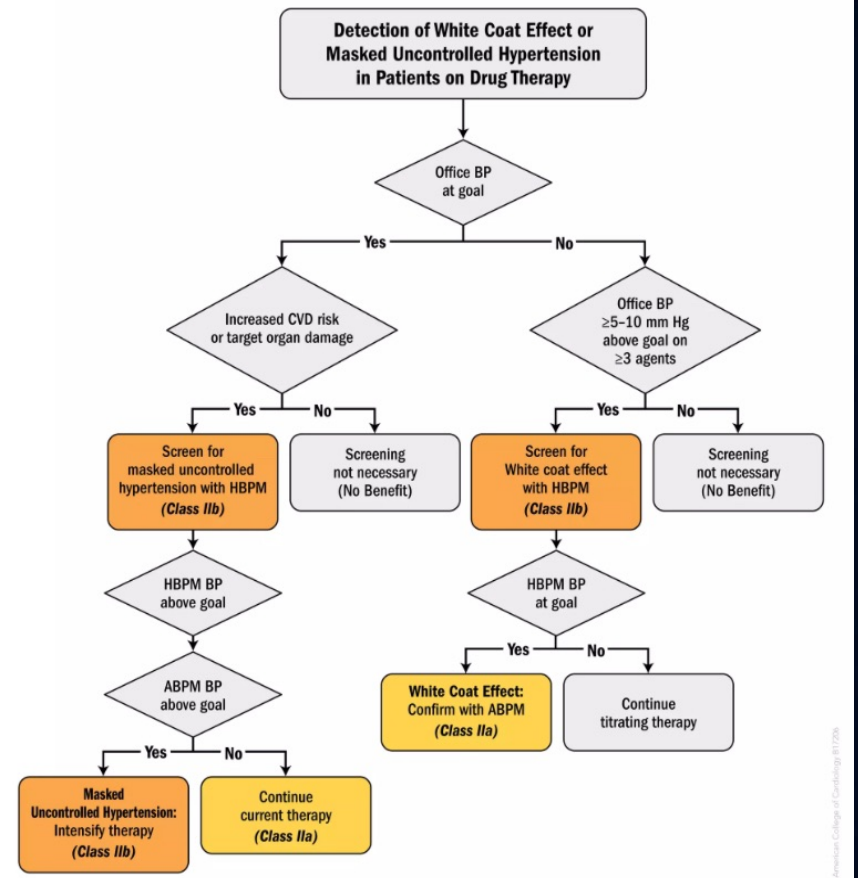
	Office/Clinic/Healthcare Setting	Home/Nonhealthcare/ABPM Setting
Normotensive	No hypertension	No hypertension
Sustained hypertension	Hypertension	Hypertension
Masked hypertension	No hypertension	Hypertension
White coat hypertension	Hypertension	No hypertension

Diagnosis of Hypertension:



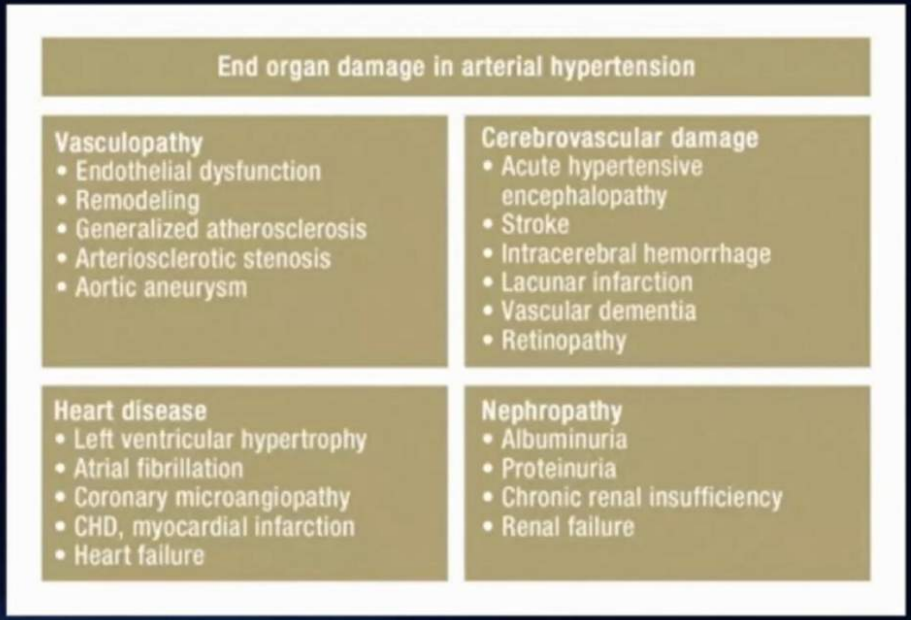
Whelton PK, et al. Hypertension. Nov. 2017

Diagnosis of Hypertension:

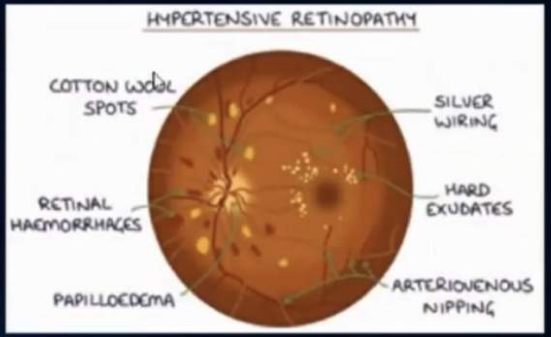


Diagnosis of Hypertension:

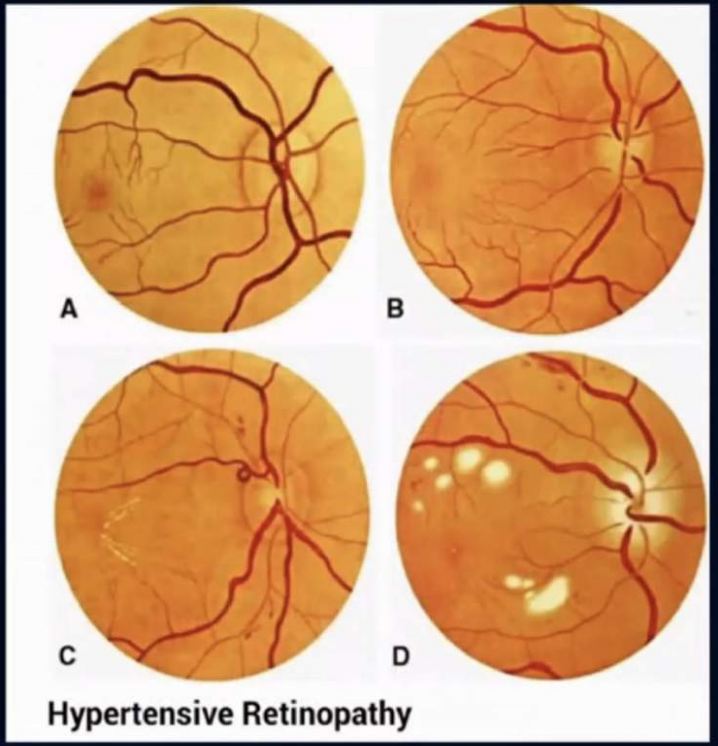
Primary Work up



Diagnosis of Hypertension:



Grade	Classification
Grade I	Mild generalized retinal arteriolar narrowing or sclerosis
Grade II	Definite focal narrowing and arteriovenous crossings Moderate to marked sclerosis of the retinal arterioles Exaggerated arterial light reflex
Grade III	Retinal hemorrhages, exudates and cotton wool spots Sclerosis and spastic lesions of retinal arterioles
Grade IV	Severe grade III and papilledema



Diagnosis of Hypertension:

Primary
Work up

BP check is advised routinely every 5 years

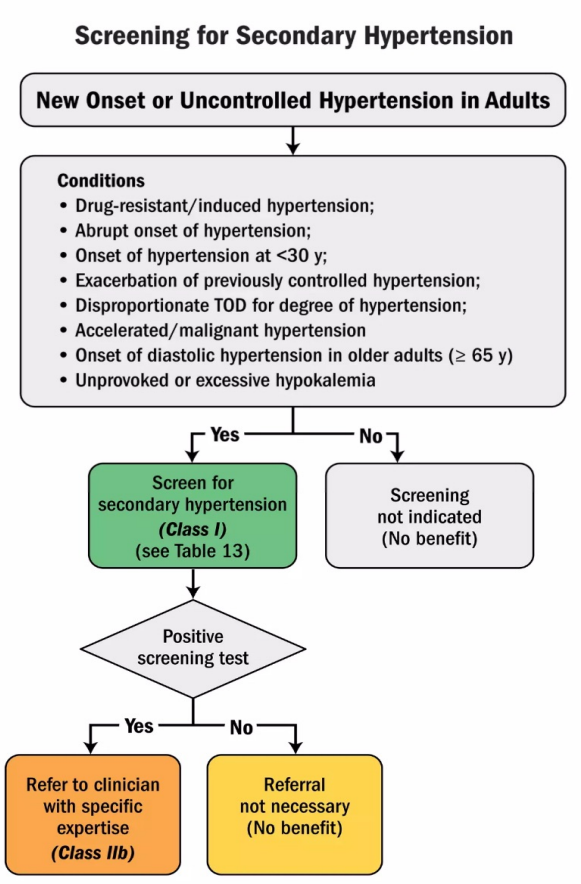
Basic Testing	Fasting blood glucose*
	Complete blood count
	Lipid profile
	Serum creatinine with eGFR*
	Serum sodium, potassium, calcium*
	Thyroid-stimulating hormone
	Urinalysis
	Electrocardiogram
Optional Testing	Echocardiogram
	Uric acid
	Urinary albumin to creatinine ratio

*May be included in a comprehensive metabolic panel

Whelton PK, et al. Hypertension. Nov. 2017

Diagnosis of Hypertension:

Secondary Work up



Secondary Hypertension

Secondary Hypertension

Common causes
Renal parenchymal disease
Renovascular disease
Primary aldosteronism
Obstructive sleep apnea
Drug or alcohol induced
Uncommon causes
Pheochromocytoma/paraganglioma
Cushing's syndrome
Hypothyroidism
Hyperthyroidism
Aortic coarctation (undiagnosed or repaired)
Primary hyperparathyroidism
Congenital adrenal hyperplasia
Mineralocorticoid excess syndromes other than primary aldosteronism
Acromegaly

Whelton PK, et al. Hypertension. Nov. 2017.

Secondary Hypertension

	Prevalence	Clinical Indications	Physical Exam	Screening Tests	Additional/ Confirmatory Tests
Common Causes					
Renal parenchymal disease	1%–2%	Urinary tract infections; obstruction, hematuria; urinary frequency and nocturia; analgesic abuse; family history of polycystic kidney disease; elevated serum creatinine; abnormal urinalysis	Abdominal mass (polycystic kidney disease); skin pallor	Renal ultrasound	Tests to evaluate cause of renal disease
Renovascular disease	5%-34%*	Resistant hypertension; hypertension of abrupt onset or worsening or increasingly difficult to control; flash pulmonary edemam (atherosclerotic); early onset hypertension, especially in women (fibromuscular hyperplasia)	Abdominal systolic-diastolic bruit; bruits over other arteries (carotid – atherosclerotic or fibromuscular dysplasia), femoral	Renal Duplex Doppler ultrasound; MRA; abdominal CT	Bilateral selective renal intraarterial angiography
Primary aldosteronism	8%–20%†	Resistant hypertension; hypertension with hypokalemia (spontaneous or diuretic-induced); hypertension and muscle cramps or weakness; hypertension and incidentally discovered adrenal mass; hypertension and obstructive sleep apnea; hypertension and family history of early onset hypertension or stroke	Arrhythmias (with hypokalemia); especially atrial fibrillation	Plasma aldosterone/ renin ratio under standardized conditions (correction of hypokalemia and withdrawal of aldosterone antagonists for 4–6 wk)	Oral sodium loading test (prior to 24 h urine aldosterone) or IV saline infusion test with plasma aldosterone at 4 h of infusion. Adrenal CT scan, Adrenal vein sampling. Trial of mineralocorticoid receptor blockers§
Obstructive sleep apnea‡	25%–50%	Resistant hypertension; snoring fitful sleep; breathing pauses during sleep; daytime sleepiness	Obesity, Mallampati class III–IV; loss of normal nocturnal BP fall	Berlin Questionnaire (8); Epworth Sleepiness Score (9); overnight oximetry	Polysomnography
Drug- or alcohol-induced‖	2%–4%	Sodium-containing antacids; caffeine; nicotine (smoking); alcohol; NSAIDs; oral contraceptives; cyclosporine or tacrolimus; sympathomimetics (decongestants, anorectics); cocaine, amphetamines and other illicit drugs; neuro psychiatric agents; erythro-poiesis stimulating agents; clonidine withdrawal; herbal agents (MaHuang, ephedra)	Fine tremor, tachycardia, sweating (cocaine, ephedrine, MAO inhibitors); acute abdominal pain (cocaine)	Urinary drug screen (illicit drugs)	Response to withdrawal of suspected agent

Whelton PK, et al. Hypertension. Nov. 2017.

Secondary Hypertension

	Prevalence	Clinical Indications	Physical Exam	Screening Tests	Additional/ Confirmatory Tests
Uncommon Causes					
Pheochromocytoma/ paraganglioma	0.1%–0.6%	Resistant hypertension; paroxysmal hypertension or crisis superimposed on sustained hypertension; "spells", BP lability, headache, sweating, palpitations, pallor; positive family history of pheochromocytoma/ paraganglioma; adrenal incidentaloma	Skin stigmata of neurofibromatosis (café-au-lait spots; neurofibromas); orthostatic hypotension	24-h urinary fractionated metanephrines or plasma metanephrines under standard conditions (30' supine position with indwelling IV cannula)	CT or MRI scan of abdomen/pelvis
Cushing's syndrome	<0.1%	Rapid weight gain, especially with central distribution; proximal muscle weakness; depression; hyperglycemia	Central obesity, "moon" face, dorsal and supraclavicular fat pads, wide (1 cm) violaceous striae, hirsutism	Overnight 1 mg dexamethasone suppression test	24-h urinary free cortisol excretion (preferably multiple); midnight salivary cortisol
Hypothyroidism	<1%	Dry skin; cold intolerance; constipation; hoarseness; weight gain	Delayed ankle reflex; periorbital puffiness; coarse skin; cold skin; slow movement; goiter	Thyroid stimulating hormone; free thyroxine	None
Hyperthyroidism	<1%	Warm, moist skin; heat intolerance; nervousness; tremulousness; insomnia; weight loss; diarrhea; proximal muscle weakness	Lid lag; fine tremor of the outstretched hands; warm, moist skin	Thyroid stimulating hormone, free thyroxine	Radioactive iodine uptake and scan
Aortic coarctation (undiagnosed or repaired)	0.1%	Young patient with hypertension (<30 y of age)	BP higher in upper extremities compared to lower extremities; absent femoral pulses; continuous murmur over patient's back, chest, or abdominal bruit; left thoracotomy scar (postoperative)	Echocardiogram	Thoracic and abdominal CT or MRA
Primary hyperparathyroidism	Rare	Hypercalcemia	Usually none	Serum calcium	Serum parathyroid hormone

Whelton PK, et al. Hypertension. Nov. 2017.

Secondary Hypertension

Causes of Secondary Hypertension with Clinical Indications and Diagnostic Screening Tests *(3 of 3)*

	Prevalence	Clinical Indications	Physical Exam	Screening Tests	Additional/ Confirmatory Tests
Uncommon Causes *(continued from previous page)*					
Congenital adrenal hyperplasia	Rare	Hypertension and hypokalemia; virilization (11-beta-hydroxylase deficiency [11-beta-OH]) incomplete masculinization in males and primary amenorrhea in females (17-alpha-hydroxylase deficiency [17-alpha-OH])	Signs of virilization (11-beta-OH) or incomplete masculinization (17-alpha-OH)	Hypertension and hypokalemia with low or normal aldosterone and renin	11-beta-OH: elevated deoxycorticosterone (DOC), 11-deoxycortisol and androgens 17-alpha-OH: decreased androgens and estrogen; elevated deoxycorticosterone and corticosterone
Mineralocorticoid excess syndromes other than primary aldosteronism	Rare	Early onset hypertension; resistant hypertension; hypokalemia or hyperkalemia	Arrhythmias (with hypokalemia)	Low aldosterone and renin	Urinary cortisol metabolites; genetic testing
Acromegaly	Rare	Acral features, enlarging shoe, glove or hat size; headache, visual disturbances; diabetes mellitus	Acral features; large hands and feet; frontal bossing	Serum growth hormone ≥1 ng/mL during oral glucose load	Elevated age- and sex-matched IGF-1 level; MRI scan of the pituitary

*Depending on the clinical situation (hypertension alone, 5%; hypertension starting dialysis, 22%; hypertension and peripheral vascular disease, 28%; hypertension in the elderly with congestive heart failure, 34%).

†8% in general population with hypertension; up to 20% in patients with resistant hypertension.

‡Although obstructive sleep apnea is listed as a cause of secondary hypertension, RCTs on the effects of continuous positive airway pressure on lowering BP in patients with hypertension have produced mixed results

§May treat patients with resistant hypertension with a MRA whether or not primary aldosteronism is present.

Table 13

Secondary Hypertension

Agent	Possible Management Strategy
Alcohol	• Limit alcohol to ≤1 drink daily for women and ≤2 drinks for men
Amphetamines (e.g., amphetamine, methylphenidate dexmethylphenidate, dextroamphetamine)	• Discontinue or decrease dose • Consider behavioral therapies for ADHD
Antidepressants (e.g., MAOIs, SNRIs, TCAs)	• Consider alternative agents (e.g., SSRIs,) depending on indication • Avoid tyramine containing foods with MAOIs
Atypical antipsychotics (e.g., clozapine, olanzapine)	• Discontinue or limit use when possible • Consider behavior therapy where appropriate • Lifestyle modification (Section 6.2) • Consider alternative agents associated with lower risk of weight gain, diabetes mellitus, and dyslipidemia (e.g., aripiprazole, ziprasidone).
Caffeine	• Generally limit caffeine intake to <300 mg/d • Avoid use in patients with uncontrolled hypertension • Coffee use in patients with hypertension associated with acute increases in BP; long-term use not associated with increased BP or CVD
Decongestants (e.g., phenylephrine, pseudoephedrine)	• Use for shortest duration possible and avoid in severe or uncontrolled hypertension • Consider alternative therapies (e.g., nasal saline, intranasal corticosteroids, antihistamines) as appropriate
Herbal supplements (e.g., Ma Huang [ephedra], St. John's wort [with MAO inhibitors, yohimbine])	• Avoid use
Immunosuppressants (e.g., cyclosporine)	• Consider converting to tacrolimus, which may be associated with less effects on BP
Oral contraceptives	• Use low-dose (e.g., 20–30 mcg ethinyl estradiol) agents or a progestin-only form of contraception and/or consider alternative forms of birth control where appropriate (e.g., barrier, abstinence, IUD) • Avoid use in women with uncontrolled hypertension
NSAIDs	• Avoid systemic NSAIDs when possible • Consider alternative analgesics (e.g., acetaminophen, tramadol, topical NSAIDs,) depending on indication and risk
Recreational drugs (e.g., "bath salts" [MDPV], cocaine, methamphetamine, etc.)	• Discontinue and/or avoid use
Systemic corticosteroids (e.g., dexamethasone, fludrocortisone, methylprednisolone, prednisone, prednisolone)	• Avoid or limit use when possible • Consider alternative modes of administration (e.g., inhaled, topical) when feasible
Angiogenesis inhibitor (eg. bevacizumab) and tyrosine kinase inhibitors (eg. sunitinib, sorafenif)	• Initiate or intensify antihypertensive therapy

Whelton PK, et al. Hypertension. Nov. 2017.

Management of Hypertension

Management of Hypertension:

Know your Goal

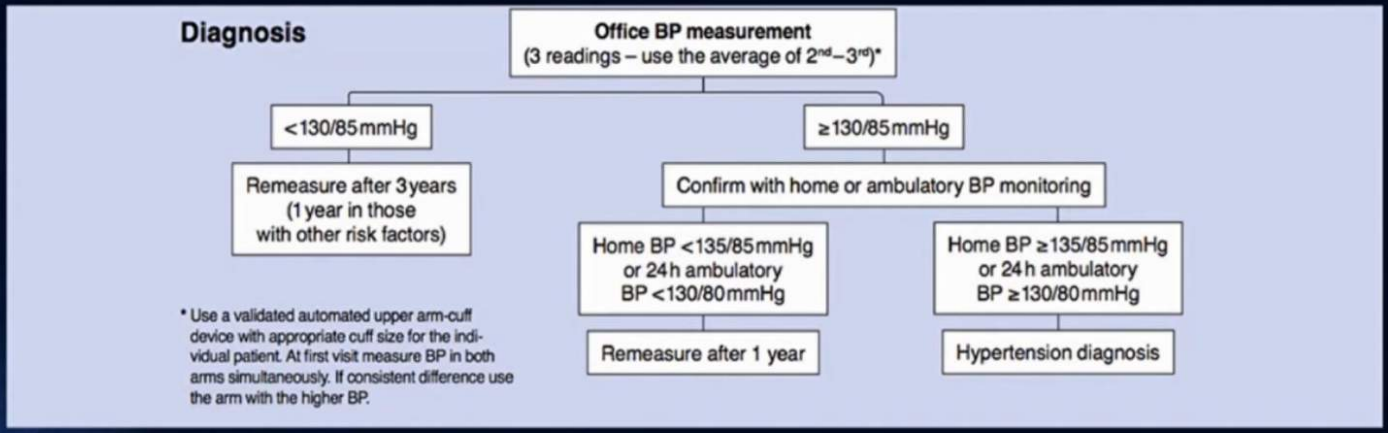
ACC/AHA Guidelines

BP Category	Systolic	Diastolic	10 yrs CVD Risk	Rx	Goal BP
Normal	< 120	<80		Lifestyle Modification	√
Elevated	120-129	<80		Non Pharm. Rx	√
Stage 1	130-139	80-89	<10%	Non Pharm. Rx	
			>10% T2DM CRI	+ BP Medications	< 130/80
Stage 2	>140	>90		+ BP Medications	< 130/80

Management of Hypertension:

Management of Hypertension

ISH 2020 Recommendations



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Management of Hypertension

ISH 2020 Recommendations

Evaluation

History & Physical Exam
- Exclude drug-induced hypertension
- Evaluate for organ damage
- Consider additional CV risk factors
- Assess total cardiovascular risk
- Search for symptoms/signs of secondary hypertension
- Check adherence

Lab Tests
- Serum sodium, potassium & creatinine, uric acid
- Lipid profile & glucose
- Urine dipstick
- 12 lead ECG

Additional Tests
- If necessary for suspected organ damage or secondary hypertension

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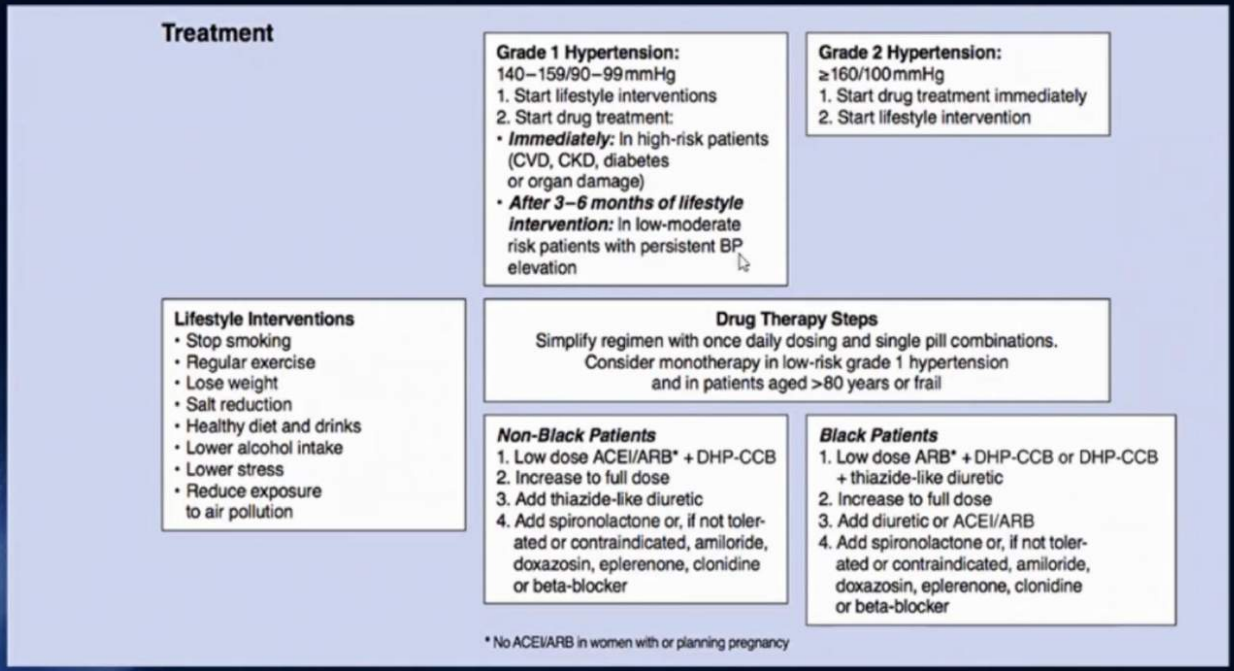
Management of Hypertension

ISH 2020 Recommendations



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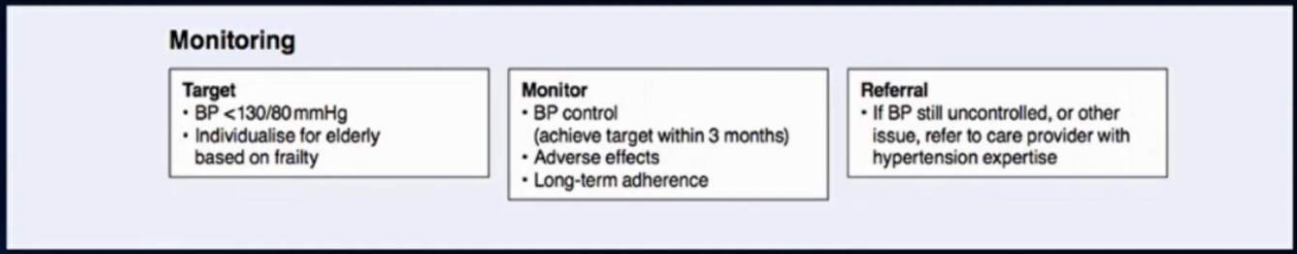
Management of Hypertension

ISH 2020 Recommendations



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Management of Hypertension

Non Pharmacological Interventions

	Nonpharmacologic Intervention	Dose	Approximate Impact on SBP	
			Hypertension	Normotension
Weight loss	Weight/body fat	Ideal body weight is best goal but at least 1 kg reduction in body weight for most adults who are overweight. Expect about 1 mm Hg for every 1 kg reduction in body weight.	-5 mm Hg	-2/3 mm Hg
Healthy diet	DASH dietary pattern	Diet rich in fruits, vegetables, whole grains, and low-fat dairy products with reduced content of saturated and trans l fat	-11 mm Hg	-3 mm Hg
Reduced intake of dietary sodium	Dietary sodium	<1,500 mg/d is optimal goal but at least 1,000 mg/d reduction in most adults	-5/6 mm Hg	-2/3 mm Hg
Enhanced intake of dietary potassium	Dietary potassium	3,500–5,000 mg/d, preferably by consumption of a diet rich in potassium	-4/5 mm Hg	-2 mm Hg
Physical activity	Aerobic	• 120–150 min/wk • 65%–75% heart rate reserve	-5/8 mm Hg	-2/4 mm Hg
	Dynamic Resistance	• 90–150 min/wk • 50%–80% 1 rep maximum • 6 exercises, 3 sets/exercise, 10 repetitions/set	-4 mm Hg	-2 mm Hg
	Isometric Resistance	• 4 x 2 min (hand grip), 1 min rest between exercises, 30%–40% maximum voluntary contraction, 3 sessions/wk • 8–10 wk	-5 mm Hg	-4 mm Hg
Moderation in alcohol intake	Alcohol consumption	In individuals who drink alcohol, reduce alcohol† to: • Men: ≤2 drinks daily • Women: ≤1 drink daily	-4 mm Hg	-3 mm Hg

Management of Hypertension

Pharmacological Interventions

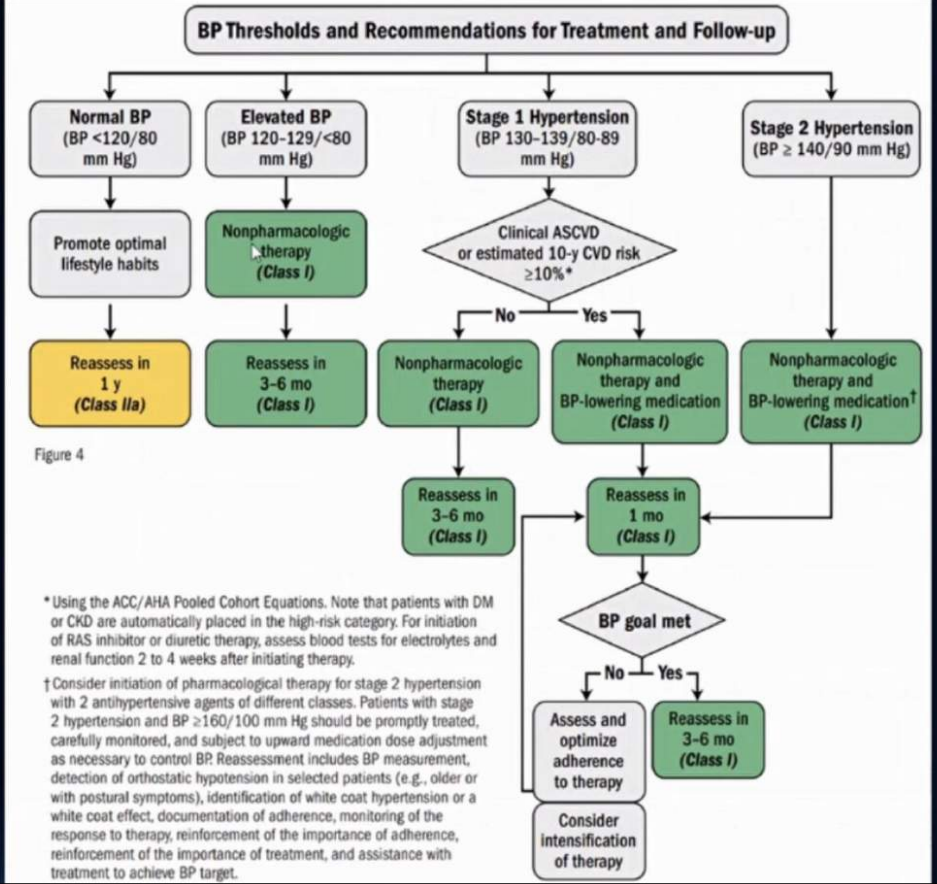


Figure 4

*Using the ACC/AHA Pooled Cohort Equations. Note that patients with DM or CKD are automatically placed in the high-risk category. For initiation of RAS inhibitor or diuretic therapy, assess blood tests for electrolytes and renal function 2 to 4 weeks after initiating therapy.

†Consider initiation of pharmacological therapy for stage 2 hypertension with 2 antihypertensive agents of different classes. Patients with stage 2 hypertension and BP ≥160/100 mm Hg should be promptly treated, carefully monitored, and subject to upward medication dose adjustment as necessary to control BP. Reassessment includes BP measurement, detection of orthostatic hypotension in selected patients (e.g., older or with postural symptoms), identification of white coat hypertension or a white coat effect, documentation of adherence, monitoring of the response to therapy, reinforcement of the importance of adherence, reinforcement of the importance of treatment, and assistance with treatment to achieve BP target.

Management of Hypertension:

- **Choice of Initial Medication:**
  - Thiazide diuretics
  - CCBs
  - ACE inhibitors or ARBs

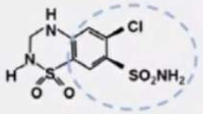
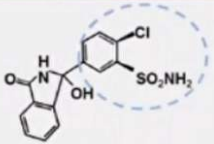
- Use **two** 1st line agents in patients with:
  - Stage 2 hypertension
  - Average BP >20/10 mm Hg above their BP target

Anti-Hypertensive Medications

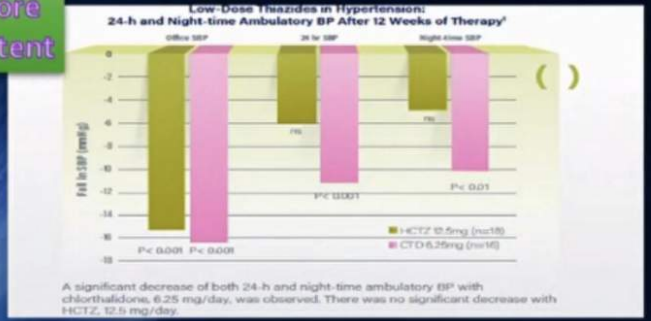
Class	Drug	Usual Dose, Range (mg per day)*	Daily Frequency	Comments
Primary Agents				
Thiazide or thiazide-type diuretics	**Chlorthalidone**	12.5–25	1	• Chlorthalidone preferred based on prolonged half-life and proven trial reduction of CVD • Monitor for hyponatremia and hypokalemia, uric acid and calcium levels. • Use with caution in patients with history of acute gout unless patient is on uric acid-lowering therapy.
	Hydrochlorothiazide	25–50	1	
	Indapamide	1.25–2.5	1	
	Metolazone	2.5–10	1	
ACE Inhibitors	**Benazepril**	10–40	1 or 2	• Do not use in combination with ARBs or direct renin inhibitor • Increased risk of hyperkalemia, especially in patients with CKD or in those on K+ supplements or K+-sparing drugs • May cause acute renal failure in patients with severe bilateral renal artery stenosis • Do not use if history of angioedema with ACE inhibitors. • Avoid in pregnancy
	Captopril	12.5–150	2 or 3	
	Enalapril	5–40	1 or 2	
	Fosinopril	10–40	1	
	Lisinopril	10–40	1	
	Moexipril	7.5–30	1 or 2	
	Perindopril	4–16	1	
	Quinapril	10–80	1 or 2	
	Ramipril	2.5–10	1 or 2	
	Trandolapril	1–4	1	
ARBs	**Azilsartan**	40–80	1	• Do not use in combination with ACE inhibitors or direct renin inhibitor • Increased risk of hyperkalemia in CKD or in those on K+ supplements or K+-sparing drugs • May cause acute renal failure in patients with severe bilateral renal artery stenosis • Do not use if history of angioedema with ARBs. Patients with a history of angioedema with an ACEI can receive an ARB beginning 6 weeks after ACEI discontinued. • Avoid in pregnancy
	Candesartan	8–32	1	
	Eprosartan	600–800	1 or 2	
	Irbesartan	150–300	1	
	Losartan	50–100	1 or 2	
	Olmesartan	20–40	1	
	Telmisartan	20–80	1	
	Valsartan	80–320	1	
CCB—dihydropyridines	**Amlodipine**	2.5–10	1	• Avoid use in patients with HFrEF; amlodipine or felodipine may be used if required • Associated with dose-related pedal edema, which is more common in women than men
	Felodipine	5–10	1	
	Isradipine	5–10	2	
	Nicardipine SR	5–20	1	
	Nifedipine LA	60–120	1	
	Nisoldipine	30–90	1	
CCB—nondihydropyridines	**Diltiazem SR**	180–360	2	• Avoid routine use with beta blockers due to increased risk of bradycardia and heart block • Do not use in patients with HFrEF • Drug interactions with diltiazem and verapamil (CYP3A4 major substrate and moderate inhibitor)
	Diltiazem ER	120–480	1	
	Verapamil IR	40–80	3	
	Verapamil SR	120–480	1 or 2	
	Verapamil-delayed onset ER (various forms)	100–480	1 (in the evening)	

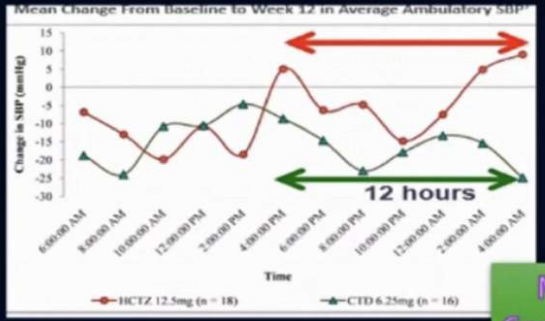
Table is continued in the next two pages

Why Chlorthalidone (CLD) as Thiazide like diuretic?

Properties	Hydrochlorothiazide (HCTZ)	Chlorthalidone (CLD)
Classification	Benzothiadiazine (thiazide) diuretic	Thiazide-like diuretic
Chemical Structure*		
Half-Life	6–9 hours	40 hours
Inhibition of Carbonic Anhydrase		1–3 orders of magnitude stronger on several carbonic anhydrase isozymes

More Potent





More Consistent

Carter BL, et al. Hypertension. 2004;43:4-9.
Kurtz TW. Hypertension. 2010;56:335-337.

Anti-Hypertensive Medications

Class	Drug	Usual Dose, Range (mg per day)*	Daily Frequency	Comments
Secondary Agents				
Diuretics—loop	**Bumetanide**	0.5–4	2	• Preferred diuretics in patients with symptomatic HF. Preferred over thiazides in patients with moderate-to-severe CKD (e.g., GFR <30 mL/min)
	Furosemide	20–80	2	
	Torsemide	5–10	1	
Diuretics—potassium sparing	**Amiloride**	5–10	1 or 2	• Monotherapy agents minimally effective antihypertensives • Combination therapy of potassium sparing diuretic with a thiazide can be considered in patients with hypokalemia on thiazide monotherapy • Avoid in patients with significant CKD (e.g., GFR <45 mL/min)
	Triamterene	50–100	1 or 2	
Diuretics—aldosterone antagonists	**Eplerenone**	50–100	12	• Preferred agents in primary aldosteronism and resistant hypertension • Spironolactone associated with greater risk of gynecomastia and impotence compared to eplerenone • Common add-on therapy in resistant hypertension • Avoid use with K+ supplements, other K+-sparing diuretics or significant renal dysfunction • Eplerenone often requires twice daily dosing for adequate BP lowering
	Spironolactone	25–100	1	
Beta blockers—cardioselective	**Atenolol**	25–100	12	• Beta blockers are not recommended as first-line agents unless the patient has IHD or HF • Preferred in patients with bronchospastic airway disease requiring a beta blocker • Bisoprolol and metoprolol succinate preferred in patients with HFrEF • Avoid abrupt cessation
	Betaxolol	5–20	1	
	Bisorolol	2.5–10	1	
	Metoprolol tartrate	100–400	2	
	Metoprolol succinate	50–200	1	
Beta blockers—cardioselective and vasodilatory	**Nebivolol**	5–40	1	• Induces nitric oxide-induced vasodilation • Avoid abrupt cessation
Beta blockers—noncardioselective	**Nadolol**	40–120	1	• Avoid in patients with reactive airways disease • Avoid abrupt cessation
	Propranolol IR	160–480	2	
	Propranolol LA	80–320	1	
Beta blockers—intrinsic sympathomimetic activity	**Acebutolol**	200–800	2	• Generally avoid, especially in patients with IHD or HF • Avoid abrupt cessation
	Carteolol	2.5–10	1	
	Penbutolol	10–40	1	
	Pindolol	10–60	2	

Table is continued in the next page

Anti-Hypertensive Medications

Class	Drug	Usual Dose, Range (mg per day)*	Daily Frequency	Comments
Secondary Agents *(continued from previous page)*				
Beta blockers—combined alpha- and beta-receptor	**Carvedilol**	12.5–50	2	• Carvedilol preferred in patients with HFrEF • Avoid abrupt cessation
	Carvedilol phosphate	20–80	1	
	Labetalol	200–800	2	
Direct renin inhibitor	**Aliskiren**	150–300	1	• Do not use in combination with ACE inhibitors or ARBs • Aliskiren is very long acting • Increased risk of hyperkalemia in CKD or in those on K+ supplements or K+ sparing drugs • May cause acute renal failure in patients with severe bilateral renal artery stenosis • Avoid in pregnancy
Alpha-1 blockers	**Doxazosin**	1–8	1	• Associated with orthostatic hypotension, especially in older adults • May consider as second-line agent in patients with concomitant BPH
	Prazosin	2–20	2 or 3	
	Terazosin	1–20	1 or 2	
Central alpha1-agonist and other centrally acting drugs	**Clonidine oral**	0.1–0.8	2	• Generally reserved as last-line due to significant CNS adverse effects, especially in older adults • Avoid abrupt discontinuation of clonidine, which may induce hypertensive crisis; clonidine must be tapered to avoid rebound hypertension
	Clonidine patch	0.1–0.3	1 weekly	
	Methyldopa	250–1000	2	
	Guanfacine	0.5–2	1	
Direct vasodilators	**Hydralazine**	250-200	2 or 3	• Associated with sodium and water retention and reflex tachycardia; use with a diuretic and bet a blocker • Hydralazine associated with drug-induced lupus-like syndrome at higher doses • Minoxidil associated with hirsutism and requires a loop diuretic. Can induce pericardial effusion
	Minoxidil	5–100	1 -3	

Hypertension & Co-Morbidities

Hypertension & Co- morbidties

Heart Failure with Reduced Ejection Fraction (HFrEF)

Recommendations for Treatment of Hypertension in Patients with Heart Failure with Reduced Ejection Fraction (HFrEF)

Referenced studies that support recommendations are summarized in online Data Supplement 34

COR	LOE	Recommendations
I	C-EO	1. Adults with HFrEF and hypertension should be prescribed GDMT* titrated to attain a BP less than 130/80 mm Hg.
III: No Benefit	B-R	2. Nondihydropyridine CCBs are not recommended in the treatment of hypertension in adults with HFrEF.

Whelton PK, et al. Hypertension. Nov. 2017.

Hypertension & Co- morbidties

Heart Failure with Preserved Ejection Fraction (HF*p*EF)

Recommendations for Treatment of Hypertension in Patients with Heart Failure with Preserved Ejection Fraction (HF*p*EF)

Referenced studies that support recommendations are summarized in online Data Supplement 35, 36

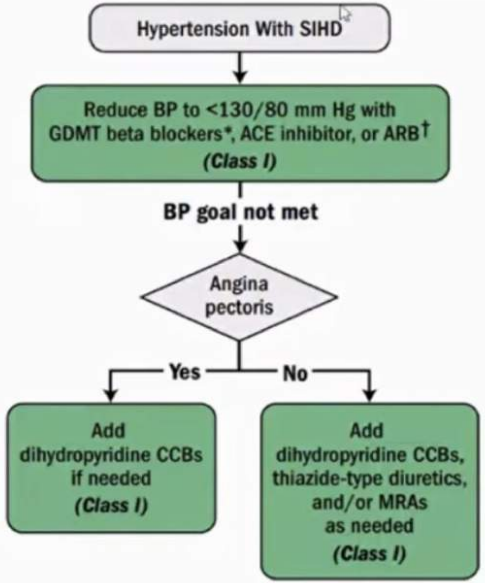
COR	LOE	Recommendations
I	C-EO	1. In adults with HF*p*EF who present with symptoms of volume overload, diuretics should be prescribed to control hypertension.
I	C-LD	2. Adults with HF*p*EF and persistent hypertension after management of volume overload should be prescribed ACE inhibitors or ARB and beta blockers titrated to attain systolic BP less than 130 mm Hg.

Whelton PK, et al. Hypertension. Nov. 2017.

Hypertension & Co-morbidties

Whelton PK, et al. Hypertension. Nov. 2017.

Management of Hypertension in Patients with Stable Ischemic Heart Disease (SIHD)

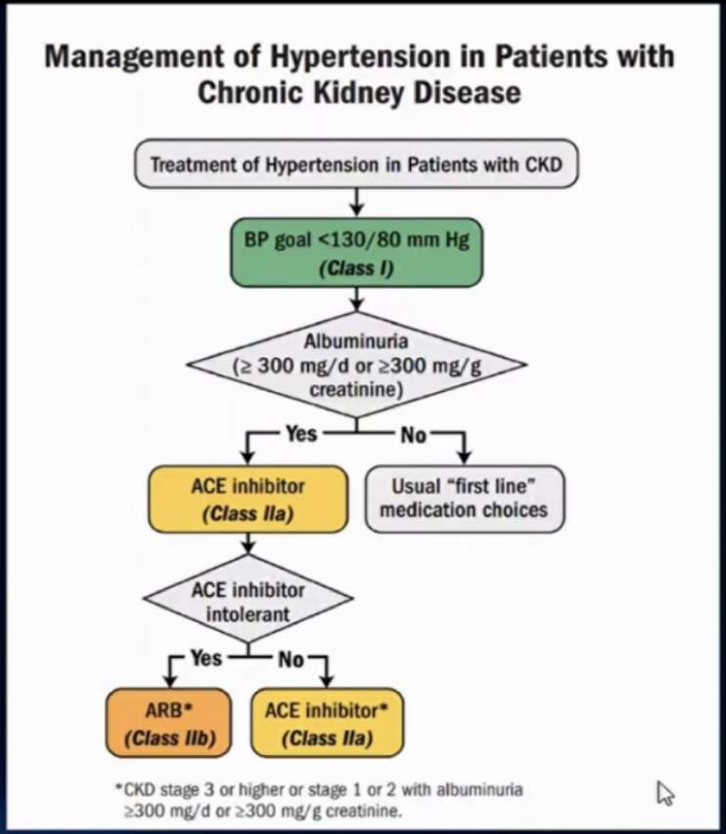


* GDMT beta blockers for BP control or relief of angina include carvedilol, metoprolol tartrate, metoprolol succinate, nadolol, bisoprolol, propranolol, and timolol. Avoid beta blockers with intrinsic sympathomimetic activity. The beta blocker atenolol should not be used because it is less effective than placebo in reducing cardiovascular events.

† If needed for BP control.

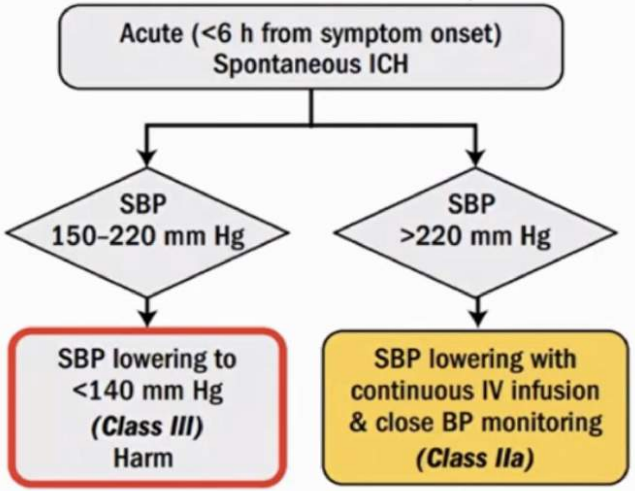
Hypertension & Co-morbidties

Whelton PK, et al. Hypertension. Nov. 2017.



Hypertension & Co-morbidties

Management of Hypertension in Patients with Acute Intercerebral Hemorrhage



Whelton PK, et al. Hypertension. Nov. 2017.

Hypertension & Co-morbidties

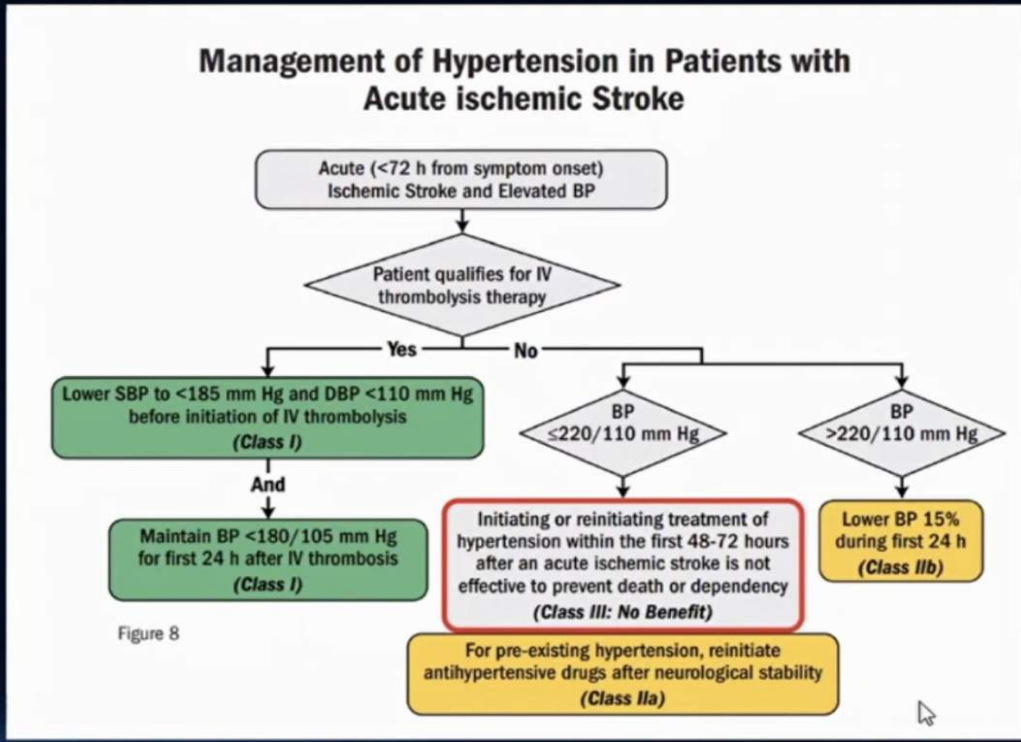


Figure 8

Whelton PK, et al. Hypertension. Nov. 2017.

Hypertension & Co-morbidties

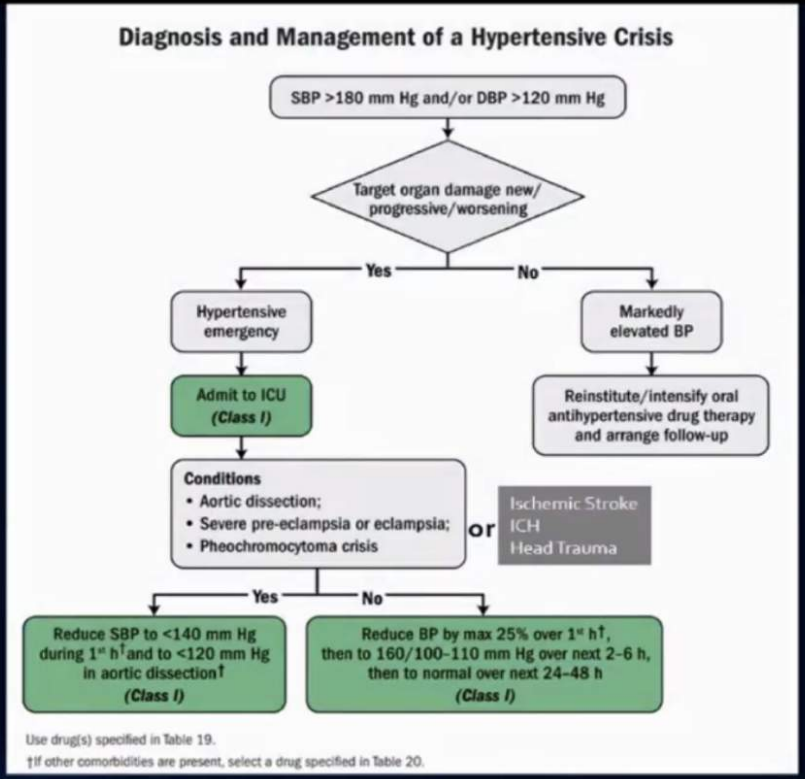
Whelton PK, et al. Hypertension. Nov. 2017.

Hypertension & Co- morbidties

- Diabetes Mellitus
  - All first-line classes of antihypertensive agents (i.e., diuretics, ACE inhibitors, ARBs, and CCBs) are useful and effective.
  - ACE inhibitors or ARBs may be considered in the presence of albuminuria
- Atrial Fibrillation
  - ARB can be useful for prevention of recurrence of AF
- Aortic Regurgitation
  - Avoid Bradycardia
- Aortic Disease
  - Beta blockers

Hypertensive Crises

Hypertensive Crises



Whelton PK, et al. Hypertension. Nov. 2017.

Hypertensive Crises Medications

Agent	Drugs	Usual Dose Range	Comments
CCB-dihydropyridines	**Nicardipine**	Initial 5 mg/h, increasing every 5 min by 2.5 mg/h to maximum 15 mg/h.	Contraindicated in advanced aortic stenosis; no dose adjustment needed for elderly.
	Clevidipine	Initial 1–2 mg/h, doubling every 90 s until BP approaches target, then increasing by < double every 5–10 min; maximum dose 32 mg/h; maximum duration 72 h.	Contraindicated in pts with soybean, soy product, egg, and egg product allergy and in pts with defective lipid metabolism (e.g., pathological hyperlipidemia, lipoid nephrosis or acute pancreatitis). Use low-end dose range for elderly pts.
Vasodilators-nitric oxide dependent	**Sodium nitroprusside**	Initial 0.3–0.5 mcg/kg/min; increase in increments of 0.5 mcg/kg/min to achieve BP target; maximum dose 10 mcg/kg/min; duration of treatment as short as possible. For infusion rates ≥4–10 mcg/kg/min or duration >30 min, thiosulfate can be coadministered to prevent cyanide toxicity.	Intra-arterial BP monitoring recommended to prevent "overshoot". Lower dosing adjustment required for elderly. Tachyphylaxis common with extended use. Cyanide toxicity with prolonged use can result in irreversible neurologic changes and cardiac arrest.
	Nitroglycerin	Initial 5 mcg/min; increase in increments of 5 mcg/min every 3–5 min to a maximum of 20 mcg/min.	Use only in pts with acute coronary syndrome and/or acute pulmonary edema. Do not use in volume-depleted pts.
Vasodilators-direct	**Hydralazine**	Initial 10 mg via slow IV infusion (maximum initial dose 20 mg); repeat every 4–6 h as needed.	BP begins to decrease within 10–30 min and the fall lasts 2–4 h. Unpredictability of response and prolonged duration of action do not make hydralazine a desirable first-line agent for acute treatment in most pts.
Adrenergic blockers beta1 receptor selective antagonist	**Esmolol**	Loading dose 500–1,000 mcg/kg/min over 1 min followed by a 50 mcg/kg/min infusion. For additional dosing, the bolus dose is repeated and the infusion increased in 50 mcg/kg/min increments as needed to a maximum of 200 mcg/kg/ min.	Contraindicated in pts with concurrent beta-blocker therapy, bradycardia and/or decompensated HF Monitor for bradycardia. May worsen HF. Higher doses may block beta2 receptors and impact lung function in reactive airway disease.
Adrenergic blockers-combined alpha1 and nonselective beta receptor antagonist	**Labetalol**	Initial 0.3–1.0 mg/kg dose (maximum 20 mg) slow IV injection every 10 min or 0.4–1.0 mg/kg/h IV infusion up to 3 mg/kg/h. Adjust rate up to total cumulative dose of 300 mg. This dose can be repeated every 4–6 h.	Contraindicated in reactive airways disease or chronic obstructive pulmonary disease. Especially useful in hyperadrenergic syndromes. May worsen HF and should not be given in pts with 2nd or 3rd degree heart block or bradycardia.
Adrenergic blockers-non-selective alpha receptor antagonist	**Phentolamine**	IV bolus dose 5 mg. Additional bolus doses every 10 min as needed to lower BP to target.	Used in hypertensive emergencies induced by catecholamine excess (pheochromocytoma, interactions between monamine oxidase inhibitors and other drugs or food, cocaine toxicity, amphetamine overdose or clonidine withdrawal).
Dopamine1-receptor selective agonist	**Fenoldopam**	Initial 0.1–0.3 mcg/kg/min; may be increased in increments of 0.05–0.1 mcg/kg/min every 15 min until target BP is reached. Maximum infusion rate 1.6 mcg/kg/min.	Contraindicated in pts at risk for increased intraocular pressure (glaucoma) or intracranial pressure and those with sulfite allergy.
Angiotensin converting enzyme inhibitor	**Enalaprilat**	Initial 1.25 mg over a 5 min period. Doses can be increased up to 5 mg every 6 h as needed to achieve BP target.	Contraindicated in pregnancy and should not be used in acute MI or bilateral renal artery stenosis. Mainly useful in hypertensive emergencies associated with high plasma renin activity. Dose not easily adjusted. Relatively slow onset of action (15 min) and unpredictability of BP response.

Whelton PK, et al. Hypertension. Nov. 2017.

Resistant Hypertension

Definitions

- Uncontrolled HTN
- Resistant HTN
- Refractory HTN
- Apparent Resistant HTN
- True Resistant HTN
- Pseudo-Resistant HTN

Definitions

- Uncontrolled Hypertension:
- BP not meeting goal BP

Definitions

- Resistant Hypertension:
- Blood pressure that remains above goal in spite of concurrent use of three antihypertensive agents of different classes
- If tolerated, one of the three agents should be a diuretic
- All agents should be prescribed at optimal doses
  - 50 % or more of the maximum recommended antihypertensive dose
- Resistant hypertension may be in both systolic and diastolic but *isolated systolic hypertension is common*

Definitions

- Refractory Hypertension:
- ***Resistant hypertension*** that cannot be controlled, even with ***maximal*** medical therapy with ***≥ 4 drugs*** with complementary mechanisms given at maximal level under the ***care of a hypertension specialist***.

- Refractory hypertension patients also have significantly higher heart rates despite more beta blocker use
- Diminished responses to spironolactone therapy

- Treatment failure may be due to neurologic mechanisms (? sympathetic overactivity)

Definitions

- Apparent Resistant Hypertension:
- Uncontrolled BP despite being prescribed ≥ 3 HTN meds
- Controlled BP on ≥ 4 HTN meds

- This could be:
  - True Resistant Hypertension
  - Pseudo-Resistant Hypertension

Definitions

- True Resistant Hypertension:
- Uncontrolled BP despite
  - Being **compliant** with an antihypertensive regimen
  - Regimen includes three or more drugs including a diuretic and each at optimal doses
  - Uncontrolled blood pressure confirmed by 24-hour ambulatory blood pressure monitoring

Definitions

- Pseudo-Resistant Hypertension:
- Uncontrolled hypertension that appears resistant but is actually attributable to other factors

- 5 most common causes:
  - Inaccurate measurement of blood pressure
  - Poor adherence to antihypertensive therapy
  - Suboptimal antihypertensive therapy
    - Diuretic and two or more additional drugs each at 50 percent or more of the maximal recommended antihypertensive dose
  - Poor adherence to lifestyle and dietary approaches to lower blood pressure such as a reduced sodium intake
  - White coat hypertension

Definitions

- White Coat Hypertension:
- AKA: Isolated clinic or office hypertension
- **Office** readings that averages to be uncontrolled and **reliable out-of-office** readings that averages to be controlled.

- Prevalence:
  - 20-30% of patients
  - 37-44% in Apparent Resistant HTN patients

- Tend to have less severe target organ damage and appear to be at less CV Risk
- Having the BP in the office taken by a nurse or technician, rather than the clinician, may minimize the white coat effect

Epidemiology

- Prevalence:
  - 8.9% among Hypertensive patients
  - Number of resistant HTN is increasing. Possible reasons include:
    - Increases in the average age
    - Increases in the average weight

Risk Factors

PATIENT RELATED

- Higher baseline BP (particularly systolic)
- Presence of LVH
- Older age
- Obesity
- African-American race
- Chronic kidney disease
- Diabetes

POTENTIALLY REVERSIBLE

- Suboptimal therapy
- Lifestyle and diet
- Medications
- Extracellular volume expansion
- Secondary causes of hypertension
- OSA

Risk Factors

- Suboptimal therapy
- Lifestyle and diet
  - Obesity
  - High-salt diet
  - Physical inactivity
  - Heavy alcohol intake
- Extracellular volume expansion
  - Renal insufficiency
  - Sodium retention due to therapy with vasodilators
  - Ingestion of a high-salt diet (which can be assessed by measuring sodium excretion in a 24-hour urine collection)

Risk Factors

- Medications
  - Can raise BP or reduce the response to antihypertensive drugs
  - Most commonly implicated agents are:
    - NSAIDs
      - NSAIDs can interfere with the antihypertensive effect of virtually any agent, except calcium channel blockers
    - Sympathomimetics
      - Diet pills
      - Decongestants
      - Amphetamine-like stimulants
      - Cocaine
    - Alcohol
    - Glucocorticoids
    - Estrogen-containing contraceptives
    - Erythropoietin
    - Herbal preparations (ephedra or ma huang)
    - Natural Licorice
    - Calcineurin inhibitors (cyclosporine and tacrolimus)
    - Antidepressants

Risk Factors

- Secondary causes of hypertension
  - Should be considered in al patients with resistant HTN
  - More common:
    - Primary aldosteronism
    - Renal artery stenosis
    - Chronic kidney disease
    - Obstructive sleep apnea
  - Less common:
    - Pheochromocytoma
    - Cushing's syndrome
    - Hyperparathyroidism
    - Aortic coarctation

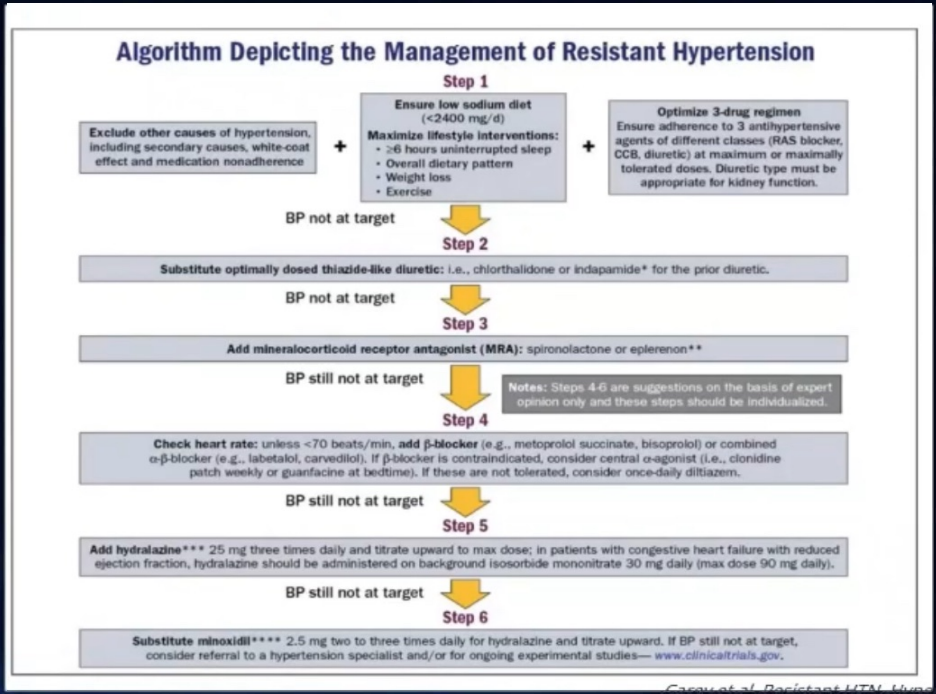
Risk Factors

- Primary Aldosteronism
  - 10-20% of patients with resistant hypertension
  - Unexplained hypokalemia is the major clue (>50% of patients with proven primary hyperaldosteronism are normokalemic)
- Renal Artery Stenosis
  - common cause
  - 2 forms:
    - Atherosclerotic disease
    - Fibromuscular dysplasia
- Chronic kidney disease
  - As renal function declines, there is an increasing need for additional antihypertensive medications
  - Diuretics play a central role
  - "Dry weight" defined as the weight at which further fluid loss leads to either symptoms (fatigue, orthostatic hypotension) or decreased tissue perfusion as evidenced by an otherwise unexplained elevation in the blood urea nitrogen and/or serum creatinine concentration

Risk Factors

- Obstructive sleep apnea
  - Severity of sleep apnea correlates with the severity of hypertension
  - Screen for OSA in Resistant HTN with following risk factors:
    - Obesity
    - Loud snoring
    - Daytime sleepiness
  - Treatment of OSA with positive airway pressure provides a usually modest antihypertensive benefit among patients with hypertension.

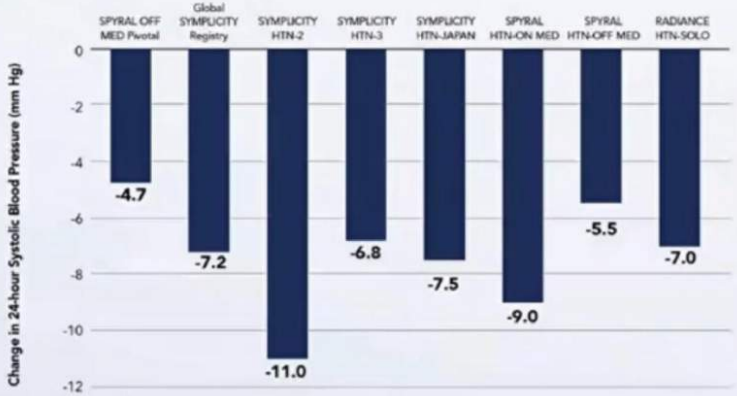
Management of Resistant Hypertension



Carey et al. Resistant HTN. Hypertension 2018;72:e53-e90.

Renal Denervation

Blood pressure reductions (mm Hg) among patients treated with renal denervation in randomized trials and the Global SYMPLICITY Registry.



Note: Global SYMPLICITY Registry, SYMPLICITY HTN-2, 3 and JAPAN trials involve treatment with SYMPLICITY Flex catheter (Medtronic CardioVascular, Santa Rosa, CA); SPYRAL ON and OFF MED and SPYRAL OFF-MED Pivotal Trial, SYMPLICITY Spyral catheter (Medtronic CardioVascular); RADIANCE HTN-SOLO, Paradise RDN system (ReCor Medical, Palo Alto, CA).

Kandzari D. Cardiology Magazine. June 2020.

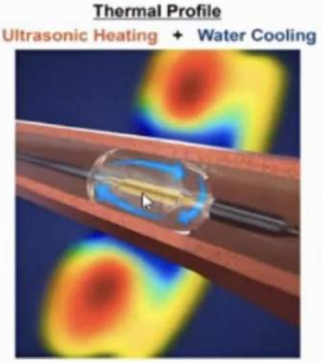
Renal Denervation

RADIANCE HTN TRIO

Renal Denervation

RADIANCE HTN TRIO

- Ring of ablative energy (depth of 1-6 mm) to interrupt renal nerve traffic
- Arterial wall protected by water circulating through balloon
- 2-3 sonications lasting 7 seconds each are delivered to each main renal artery



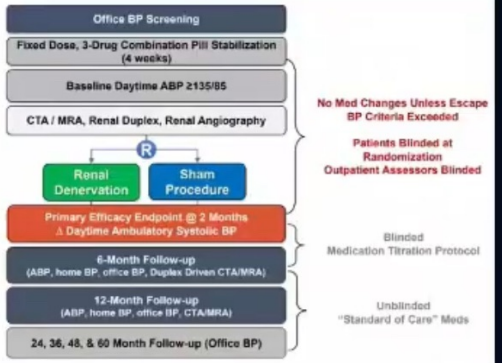
Source: ACC.21 Presentation Slides for RADIANCE-HTN TRIO: Endovascular Ultrasound Renal Denervation to Treat

Renal Denervation

RADIANCE HTN TRIO

Key Entry Criteria:

- Office BP ≥140/90 on 3+ anti-HTN meds
- Daytime ABP ≥135/85 on a fixed-dose, 3-drug combination pill
- Age 18-75 years
- No secondary hypertension aside from OSA
- No CV or cerebrovascular events within the prior 3M
- No Type I or uncontrolled Type II diabetes
- eGFR ≥40 mL/min/m^2
- Eligible renal artery anatomy

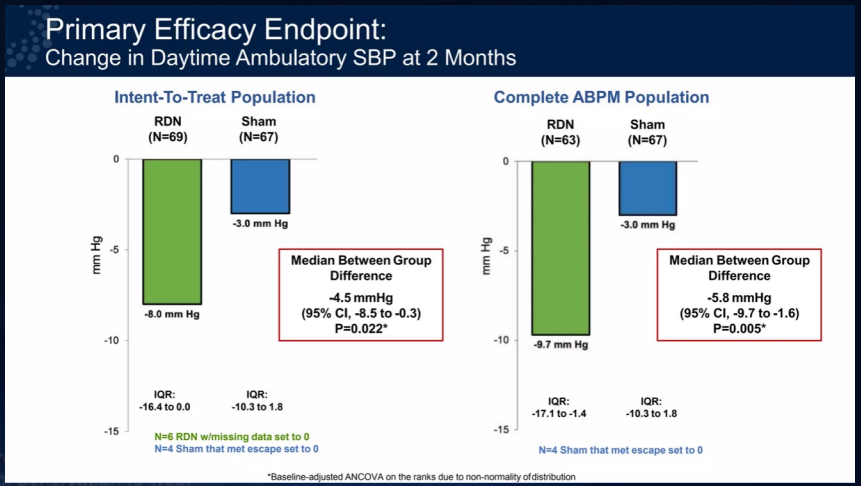


Source: ACC.21 Presentation Slides for RADIANCE-HTN TRIO: Endovascular Ultrasound Renal Denervation to Treat

Renal Denervation

RADIANCE HTN TRIO

Primary Efficacy Endpoint:
Change in Daytime Ambulatory SBP at 2 Months



*Baseline-adjusted ANCOVA on the ranks due to non-normality of distribution

Thank You