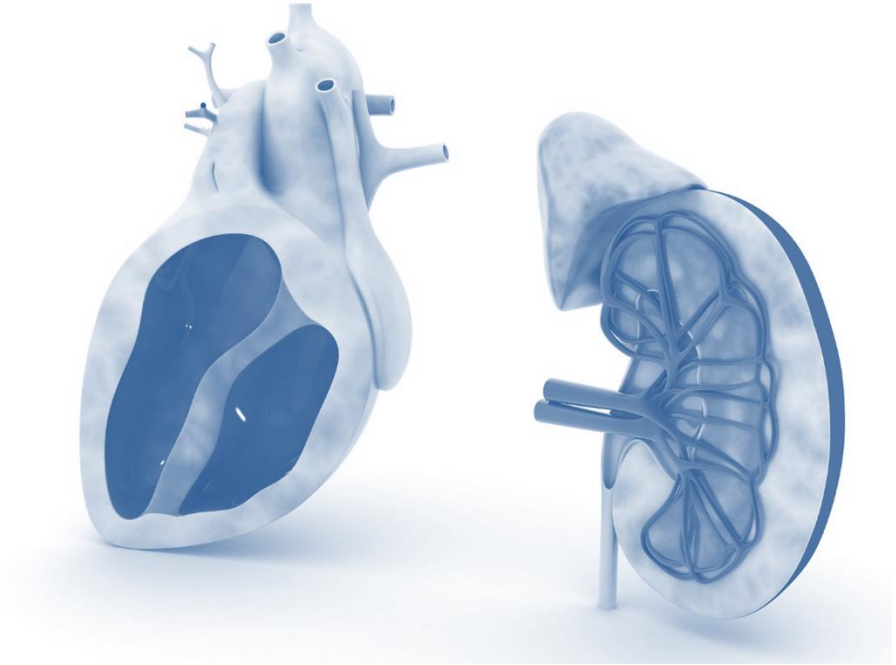
Pharmacotherapeutics III (Cardiology/Nephrology) PHAR 565



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Chapter 2:
HYPERTENSION (HTN)

Learning Objectives

- Understand the pathophysiology of HTN
- Recognize the importance of HTN and preventing its complications
- Identify the different treatment modalities of HTN
- Learn how and what to monitor
- Recommend an appropriate treatment plan
- Discuss management of hypertensive crises
- Provide appropriate patient education
- Describe the role of the pharmacist in the management of hypertensive patients

Outline

- Introduction
- Epidemiology
- Etiology
- Definitions
- Diagnosis
- Pathophysiology
- Clinical presentation
- Complications
- Treatment guidelines
- Overview of hypertensive agents
- Hypertensive crises
- Hypertension in pregnancy

Guideline

- **2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults**
  - **A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines**

Introduction

- Blood pressure:
  - Pressure of the blood against the walls of the arteries
  - Results from two forces:
    - Force created by the heart as it pumps blood into the arteries and through the circulatory system
    - Force of the arteries as they resist the blood flow

Introduction

- HTN:
  - Common disease
  - Defined as persistently elevated arterial blood pressure (BP)
  - Widely prevalent and accounts for significant morbidity and mortality
  - Prevalence differs based on age, sex, and ethnicity

Epidemiology

- Worldwide
  - Leading risk factor for cardiovascular diseases (CVD) and mortality
  - Over 1 billion individuals
  - Over 7 million deaths per year

- Prevalence and control of HTN In Lebanon
  - Prevalence 31.2%
  - 75% of the Lebanese aged >65 years have HTN
  - 60 % of hypertensive patients are receiving medical therapy
  - Of those treated 50% have controlled HTN on therapy

- BP ↑ with age
  - Lifetime risk of developing HTN among those ≥ 55 years who are normotensive is 90%

Etiology

- **Essential or Primary HTN:**
  - Cause is unknown
  - Majority of patients: up to 95%
  - Genetic factors
    - Many affecting sodium balance
    - Some altering nitric oxide release, excretion of aldosterone, other adrenal steroids, and angiotensinogen

Etiology

Secondary HTN: Identifiable cause

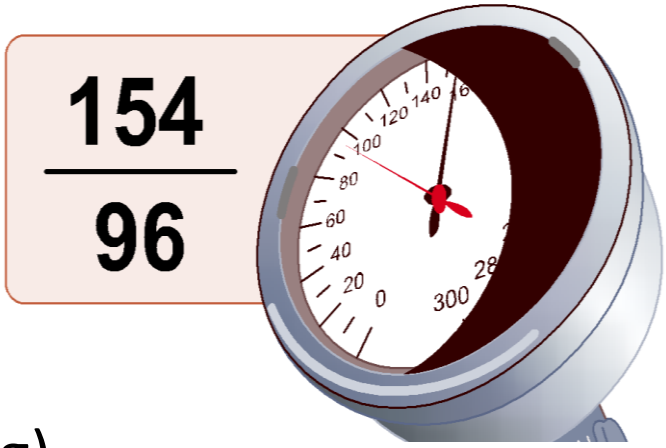
➔ < 10% of patients

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

Drug-induced

- Steroids
- Amphetamine (sibutramine)
- Estrogen and COC
- Oral decongestants
- Erythropoiesis stimulating agents (erythropoietin)
- NSAIDs
- Cyclosporine
- Some antidepressants (MAOI, venlafaxine)
- Alcohol (chronic)
- Licorice
- Others

Definitions



- Arterial BP
  - Pressure in the arterial wall (mm Hg)
  - Systolic BP (SBP)
    - Achieved during cardiac contraction (peak value)
    - Represents the cardiac output
    - First Korotkoff sound
  - Diastolic BP (DBP)
    - Achieved after contraction when the cardiac chambers are filling (nadir value)
      - During ventricular relaxation
    - Represents peripheral vascular resistance of blood vessels
    - Fifth or last Korotkoff sound

Definitions

- Mean Arterial blood pressure (MABP) or Mean Arterial Pressure (MAP)
  - Product of cardiac output and total peripheral resistance
    - **MABP or MAP = CO × TPR**
  - Average pressure throughout the cardiac cycle of contraction
    - 2/3 of the time is spent in diastole and 1/3 in systole
    - **MABP or MAP = (SBP × 1/3) + (DBP × 2/3)**

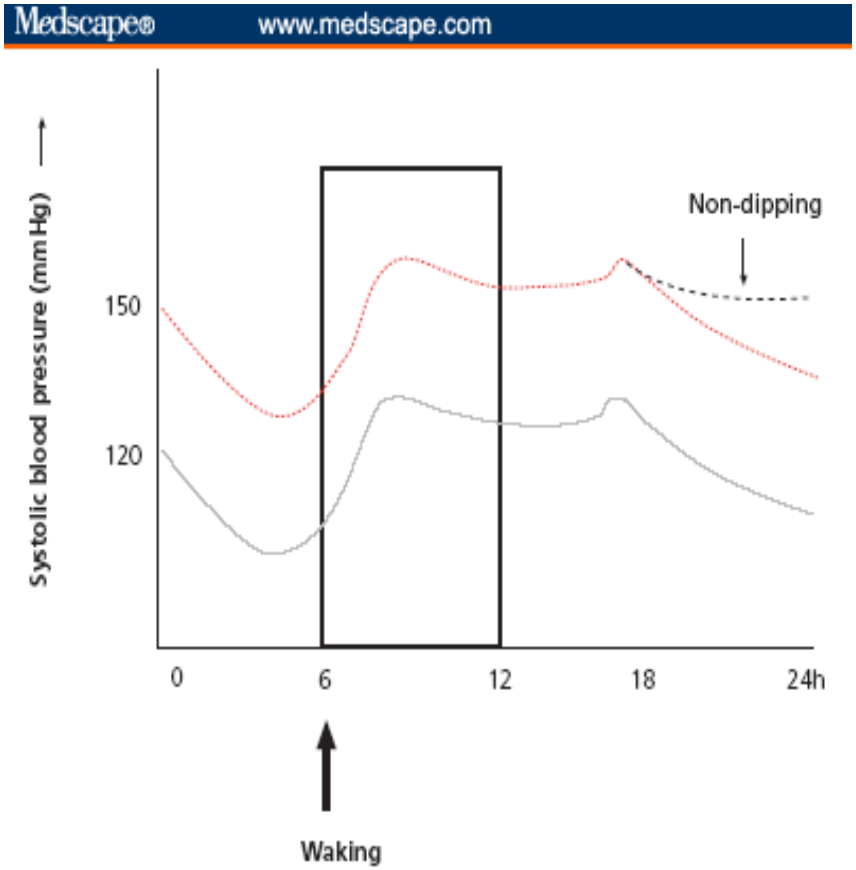
- Cardiac output (CO)
  - Function of stroke volume (SV), heart rate (HR), and venous capacitance
  - **CO = HR x SV**

- Pulse pressure (P_{pulse})
  - Measure of arterial wall tension
  - **P_{pulse} = SBP – DBP**

- Mid BP
  - Sum of SBP and DBP, divided by 2
  - **Mid BP = (SBP + DBP) / 2**

Definitions

- Circadian rhythm of BP
  - A rise (up to 20/15 mmHg) in BP from the time of waking or before (about 6 am)
  - Highest levels of BP occur after 10 am with a peak around noon but often with a plateau extending to 6 pm
  - A decline in BP of 10-20% in the late evening and on going to sleep
  - A nadir in BP at about 3 am



Definitions

- <u>"Office" or "white-coat" HTN</u>
  - Describes patients who have consistently elevated BP values measured in a clinical environment
    - In the presence of a health care professional (e.g., physician's office)
  - Yet when measured elsewhere or with 24-hour ambulatory monitoring, BP is not elevated
    - Distract the patient with something else
    - Ask patient to take it at home
      - Home Blood Pressure Measurement (HBPM)

Definitions

- Hypertensive Crises
  - BP values are markedly elevated
    - SBP>180 mm Hg &/or DBP>120 mm Hg
  - Classified as:
    - Hypertensive emergency
      - With acute or progressive target-organ damage
    - Hypertensive urgency
      - Without acute or progressive target-organ damage

Diagnosis

- HTN
  - Elevation in Systolic BP, Diastolic BP, or both

- Diagnosis
  - Obtain a medical history and physical examination
  - Obtain a family history
  - Office BP is recommended for screening and diagnosis of HTN
  - Diagnosis is based on **at least two BP measurements per visit** and on **at least two visits**
  - Palpation of the pulse at rest to determine
    - Heart rate and to search for arrhythmias

Diagnosis

- Diagnosis
  - Suspicion of white-coat HTN
    - Diagnose using out-of-office BP measurement
    - ABPM (ambulatory BPM) or HBPM (Home BPM)
  - Out-of-office BP should be considered to:
    - Confirm the diagnosis of HTN, identify the type of HTN
    - Detect hypotensive episodes
    - Evaluation of vertigo and dizziness needed
  - Detection of orthostatic hypotension
    - Measure BP at first visit ➔ 1 and 3 mins after assuming a **standing** position in:
      - Elderly subjects & diabetic patients

Accurate BP Measurement

Key Steps for Proper BP Measurements	Specific Instructions
Step 1: Properly prepare the patient	1. Have the patient relax, sitting in a chair (feet on floor, back supported) for >5 min. 2. The patient should avoid caffeine, exercise, and smoking for at least 30 min before measurement. 3. Ensure patient has emptied his/her bladder. 4. Neither the patient nor the observer should talk during the rest period or during the measurement. 5. Remove all clothing covering the location of cuff placement.
Step 2: Use proper technique for BP measurements	1. Use a BP measurement device that has been validated and ensure that the device is calibrated periodically. 2. Support the patient's arm (e.g., resting on a desk). 3. Position the middle of the cuff on the patient's upper arm at the level of the right atrium (the midpoint of the sternum). 4. Use the correct cuff size 5. Either the stethoscope diaphragm or bell may be used for auscultatory readings

Accurate BP Measurement

Key Steps for Proper BP Measurements	Specific Instructions
Step 3: Take the proper measurements needed for diagnosis and treatment of elevated BP/hypertension	1. At the first visit, record BP in both arms. Use the arm that gives the higher reading for subsequent readings. 2. Separate repeated measurements by 1–2 min.
Step 4: Properly document accurate BP readings	1. Record SBP and DBP. 2. Note the time of most recent BP medication taken before measurements.
Step 5: Average the readings	Use an average of ≥2 readings obtained on ≥2 occasions to estimate the individual's level of BP.
Step 6: Provide BP readings to patient	Provide patients the SBP/DBP readings both verbally and in writing.

Pathophysiology

- Primary HTN:
  - Pathophysiology: heterogeneous
  - Ultimately exerts its effects through the two primary determinants of blood pressure:
    - Cardiac output
    - Peripheral resistance

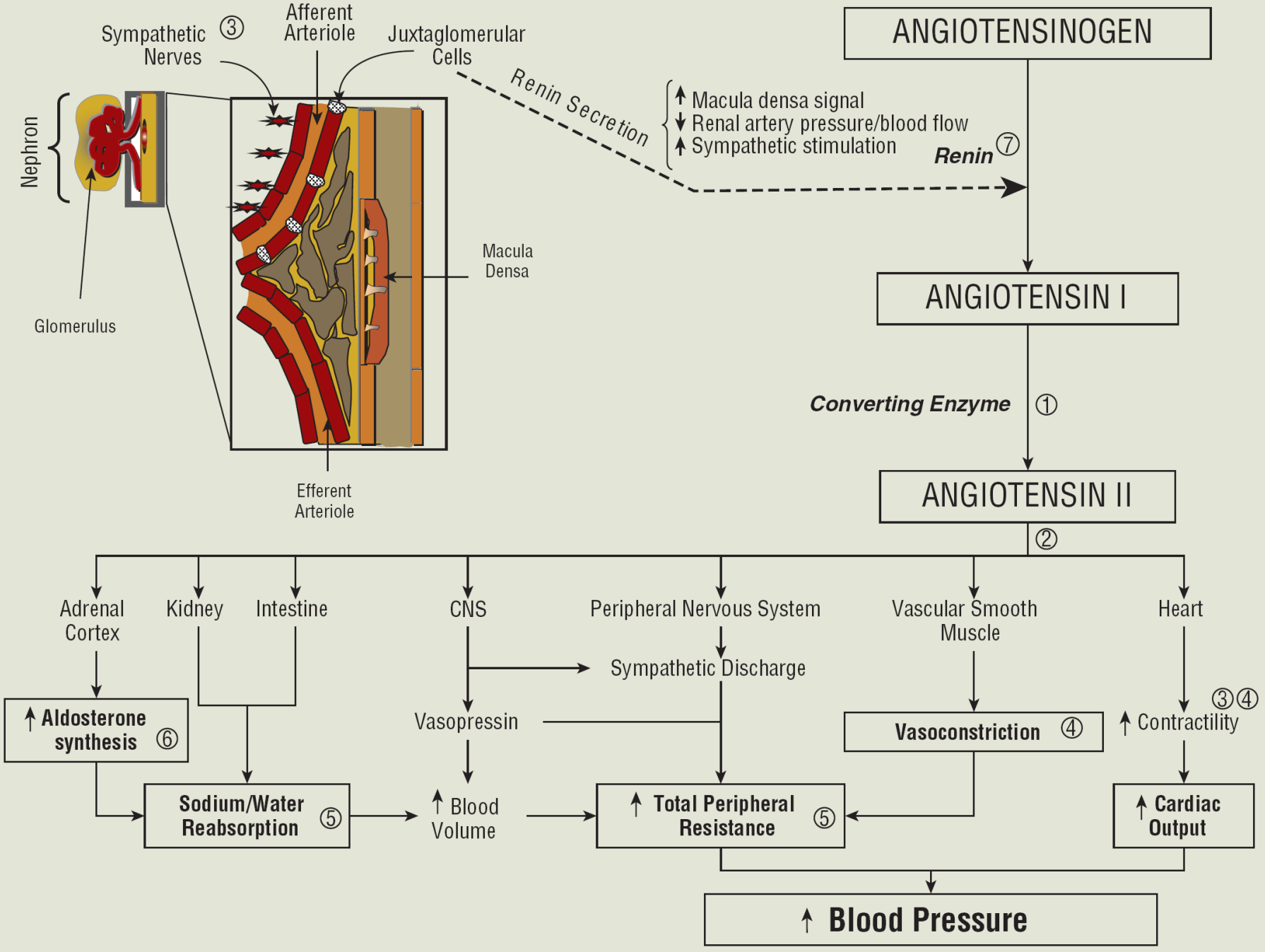
- Involves the following:
  1. **Humoral system**
  2. **Neuronal regulation**
  3. **Vascular endothelial mechanisms**
  4. **Electrolytes and other chemicals**

Pathophysiology

1. **Humoral system**
   A. Renin-angiotensin-aldosterone system (RAAS)
   B. Natriuretic hormone
      - Secreted by atrial heart muscle cells
        – Atrial natriuretic peptide (ANP) is thought to block the active transport of Na^+ out of arteriolar smooth muscle cells → ↑ intracellular Na^+ → ultimately ↑ vascular tone and BP
   C. Insulin resistance and hyperinsulinemia
      - The exact mechanism is unknown
        – ↑ renal Na^+ retention
        – Enhanced sympathetic nervous system activity
        – ↑ intracellular calcium → ↑ vascular resistance

Pathophysiology

2. **Neuronal regulation**
   - Stimulation of α- and β-receptors
   - Baroreceptors less responsive to changes in BP
     - Blunted in elderly and diabetic
3. **Vascular endothelial mechanisms**
   - Deficiency in vasodilation substances
     - Prostacyclin, Bradykinin, Nitric oxide (intrinsic deficiency)
   - Excess vasoconstricting substances
     - Angiotensin II, Endothelin I
4. **Electrolytes and other chemicals**
   - ↑ serum Na^+
   - ↑ intracellular calcium
     - Lack of dietary Ca^{2+} hypothetically can disturb the balance between intracellular and extracellular Ca^{2+}→ ↑ intracellular Ca^{2+}
     - Dietary calcium supplementation results in a modest BP reduction in patients with HTN


Sympathetic Nerves ③
Afferent Arteriole
Juxtaglomerular Cells
Nephron
Glomerulus
Macula Densa
Efferent Arteriole
Renin Secretion
↑ Macula densa signal
↓ Renal artery pressure/blood flow
↑ Sympathetic stimulation
Renin ⑦
ANGIOTENSINOGEN
ANGIOTENSIN I
Converting Enzyme ①
ANGIOTENSIN II
②
Adrenal Cortex
Kidney
Intestine
CNS
Peripheral Nervous System
Vascular Smooth Muscle
Heart
↑ Aldosterone synthesis ⑥
Sodium/Water Reabsorption ⑤
Vasopressin
↑ Blood Volume
Sympathetic Discharge
↑ Total Peripheral Resistance ⑤
Vasoconstriction ④
↑ Contractility ③④
↑ Cardiac Output
↑ Blood Pressure

Clinical Presentation/Risk Factors

- Most patients are asymptomatic (Silent Killer)
  - Symptoms are secondary to HTN-induced organ damage
- CVD Risk Factors Common in Patients With HTN

Modifiable Risk Factors	Relatively Fixed Risk Factors
Current cigarette smoking, secondhand smoking	CKD
Diabetes mellitus	Family history
Dyslipidemia / hypercholesterolemia	Increased age
Overweight/obesity	Low socioeconomic Low educational status
Physical inactivity/low fitness	Male sex
Unhealthy diet	Obstructive sleep apnea
	Psychosocial stress

Complications

- HTN-Induced Target-Organ Damage
  - Eyes (retinopathy)
  - Peripheral vasculature (peripheral arterial disease)
  - Brain (stroke*, transient ischemic attack)
  - Heart (left ventricular hypertrophy, angina/MI*, heart failure)
  - Kidney (Nephropathy, chronic kidney disease*)

* Are the primary causes of CV morbidity and mortality in patients with HTN

Treatment

GUIDELINE:
2017
ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

Classification: BP Categories in Adults

BP* Category	SBP		DBP
Normal	<120 mm Hg	and	<80 mm Hg
Elevated	120–129 mm Hg	and	<80 mm Hg
Hypertension			
Stage 1	130–139 mm Hg	or	80–89 mm Hg
Stage 2	≥140 mm Hg	or	≥90 mm Hg

*BP indicates blood pressure (based on average of ≥ 2 careful readings obtained on ≥2 occasions)

Note: Individuals with SBP and DBP in 2 categories should be designated to the higher BP category

BP Thresholds and BP Goals for Patients with HTN

Clinical Condition	BP Threshold mm Hg*	BP Goal mm Hg
General		
Clinical CVD or 10-year ASCVD Risk ≥ 10%	≥ 130/80	< 130/80
No clinical CVD and 10-year ASCVD Risk < 10%	≥ 140/90	< 130/80
Older persons (>65 years of age; non-institutionalized, ambulatory, community living adults)	≥ 130/80 (SBP)	< 130/80 (SBP)

* BP lowering medication is recommended at this threshold

Case-based Learning: Case 1

A 40-year-old African American woman has a BP measurement of 150/110 mm Hg when she first arrives for a routine physical examination by a medical assistant. She has no previous history of hypertension. She is extensively interviewed and examined, and has no signs of acute or chronic hypertension-associated end-organ damage.

Her physician measures her BP again 20 minutes later, and it is 142/98 mm Hg (140/100 mm Hg when repeated).

Her most recent fasting lipid panel was also normal, and her 10-year ASCVD risk score is 1.2%. She is instructed to measure her BP at home twice each morning. After 2 weeks, her average home BP is 138/96 mm Hg.

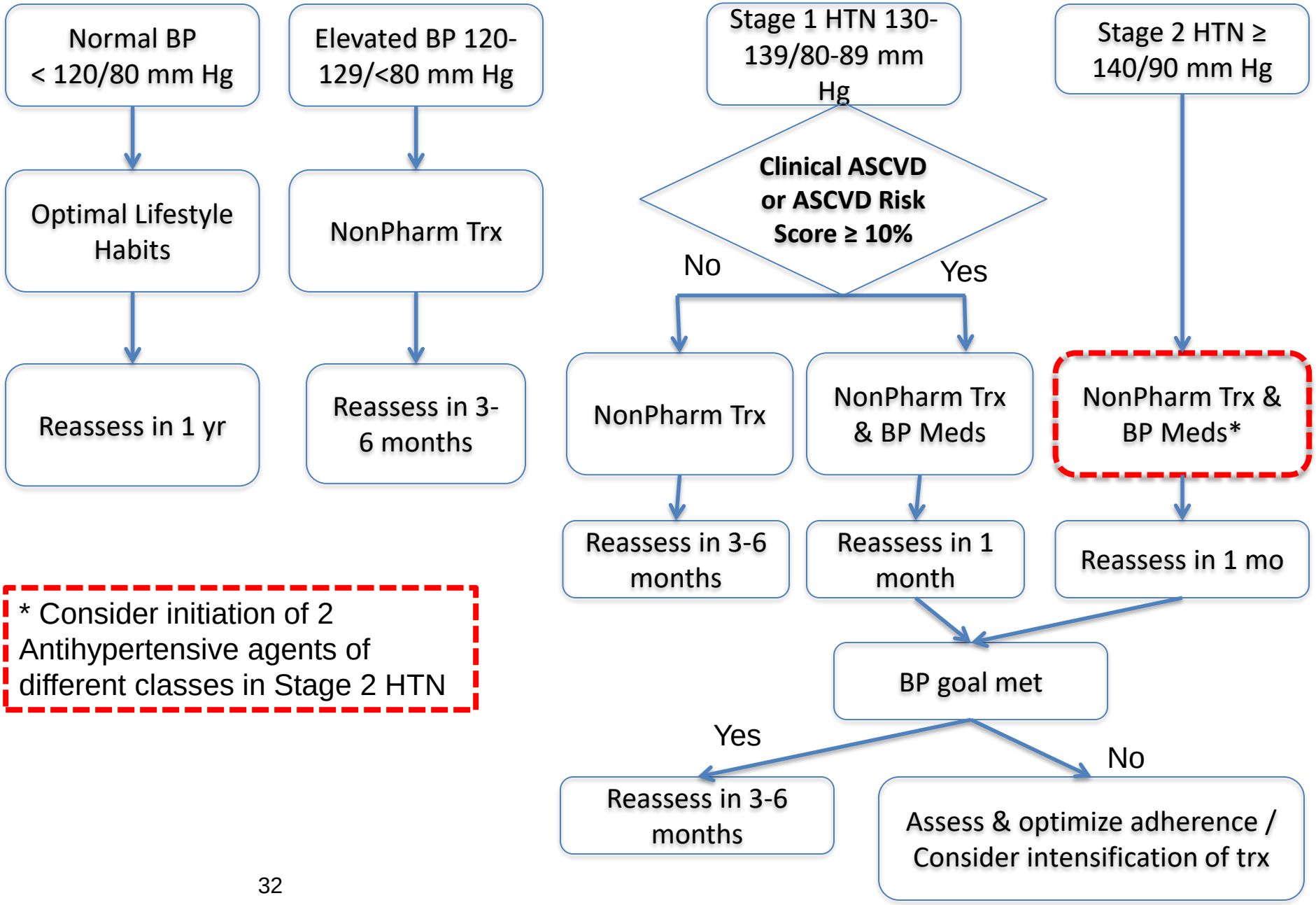
Case 1 Questions

Q1. Which is an accurate clinical assessment of her present situation?

A. White coat hypertension
B. Elevated blood pressure
C. Stage 1 hypertension
D. Stage 2 hypertension

Q2. Which is the appropriate BP goal in this patient?

2017 ACC/AHA HTN Treatment Algorithm



Non-pharmacologic Approaches

Weight loss	Weight loss in overweight or obese (1-kg reduction in body wt for overweight)	
Heart-healthy diet	DASH (Dietary Approaches to Stop HTN) diet	Diet rich in fruits, vegetables, whole grains, and low-fat dairy products, low saturated fats
Sodium reduction	Optimal goal is <1500 mg/d, but aim for at least a 1000-mg/d reduction	
Potassium supplementation	Dietary Potassium supplementation (aim for 3500–5000 mg/d), unless contraindicated due to CKD or use of drugs that reduce potassium excretion	
Increased physical activity	Structured exercise program of 90-150 min/wk	
Limit Alcohol intake	Limit alcohol to no more than 2 standard drinks per day for men and 1 standard drink per day for women	

Antihypertensive Therapy Recommendations

Without Compelling Indications

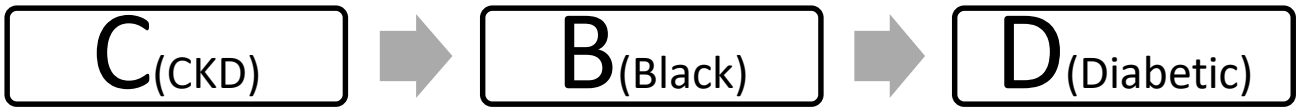
First-line agents
ACEI, ARB, CCB and/or thiazide

Stage 1 (BP ≥ 130/80 mm Hg)	• Antihypertensive monotherapy
Stage 2 (BP ≥ 140/90 mm Hg and average BP > 20/10 mm Hg above goal)	• Start with antihypertensive combination therapy • As separate medications or fixed dose combinations

Antihypertensive Therapy Recommendations

Without Compelling Indications

- Special population-based recommendations
  - Black
    - Choice of meds
      - Black without diabetes or with diabetes ➔ Thiazide or CCB
      - Black and CKD ➔ ACE Inhibitor or ARB
        - » **Treatment is a priority regardless of race or diabetes**
          - **ACE Inh or ARB improve kidney outcome**



  - Pregnancy
    - Methyldopa, nifedipine, and/or labetalol
    - Avoid ACEi, ARB, & ARA

Antihypertensive Therapy Recommendations: Compelling Indications

Clinical Condition	1st line Drug	BP Threshold mm Hg*	BP Goal mm Hg
DM	Thiazide, CCB, ACEi, or ARB	≥ 130/80	< 130/80
DM with Albuminuria	ACEi or ARB	≥ 130/80	< 130/80
CKD (Stage 3 or higher or stage 1 or 2 with albuminuria)	ACEi or ARB	≥ 130/80	< 130/80
HTN after Kidney transplant	CCB	≥ 130/80	< 130/80
HF with reduced EF	• Beta Blocker, ACEi, or ARB, ARA • Avoid NDHP CCBs	≥ 130/80	< 130/80
HF with preserved EF	Beta Blocker, ACEi, or ARB	≥ 130/80	< 130/80
Stable ischemic heart dss	Beta Blocker, ACEi, or ARB	≥ 130/80	< 130/80
Stable ischemic heart disease with angina	Beta Blocker, CCB (DHP)	≥ 130/80	< 130/80
Secondary stroke prevention	Thiazide, ACEi, or ARB	≥ 140/90	< 130/80
PAD	Thiazide, CCB, ACEi, or ARB	≥ 130/80	< 130/80
Afib prevention	ARB	Depends on comorbid diseases	
Aortic dss	Beta Blocker		

* BP lowering medication is recommended at this threshold

Case 1 Questions - Continued

Q3. Which is an appropriate plan for her at this time?

Q4. If the patient suffers also from chronic kidney disease, would you choose the same antihypertensives you selected in the previous question?

Case-based Learning: Case 2

Majeed is a 72-year-old man who resides in Mount Lebanon and has a past medical history of hypertension for 10 years. His BP today is 148/82 mm Hg (152/84 mm Hg when repeated), heart rate is 70 beats/min, serum creatinine is 1.2 mg/dL (eGFR 58 mL/min/1.73 m^2), and potassium is 4.3 mEq/L. He is adherent to benazepril 40 mg daily and amlodipine 10 mg daily.

- Weight: 93 kg
- Height: 201 cm
- BMI: 32 kg/m^2
- Smokes one-half pack cigarettes daily
- Consumes two ethanol-containing drinks weekly.

Case 2 Questions

Q5. Is Majeed's blood pressure controlled? If not, what is his goal blood pressure and what is the most appropriate medication to add to his antihypertensive regimen?

Q6. Which lifestyle changes should be adopted by Majeed to help him in further lowering his BP?

Resistant HTN

Confirm Treatment Resistance

- Office BP ≥ 130/80 mm Hg
- **AND**
- Patient prescribed ≥ 3 BP medications (ACEi or ARB + Thiazide + CCB) at optimal doses including a diuretic if possible
- **OR**
- Office BP <130/80 mm Hg receiving > 4 BP medications

Exclude Pseudoresistance

- **Ensure accurate office BP measurement**
- Assess for non-adherence to BP medications
- Obtain home or ambulatory BP readings to exclude white coat effect

Identify and reverse contributing lifestyle factors

- Obesity, physical inactivity, alcohol, high salt, low fiber diet

D/C or minimize interfering substances

- NSAIDs, Sympathomimetics, stimulants, COCs, licorice, ephedra

Screen for secondary causes of HTN

- Primary aldosteronism, CKD, renal artery stenosis, pheochromocytoma, obstructive sleep apnea

Treatment approaches

- Maximize diuretic therapy
- **Add a mineralocorticoid receptor antagonist**
- Add other BP medications with different mechanism of action (beta blocker, alpha 2 agonist, alpha 1 antagonist, or direct vasodilator…)
- Use a loop diuretic in patients with CKD or receiving potent vasodilator (e.g. minoxidil)

Strategies to Dose Antihypertensive Drugs

Strategy	Description	
A	Start one drug, titrate to maximum dose, and then add a second drug and titrate up to the maximum recommended dose of the second drug to achieve goal BP.	• If goal BP is not achieved with 2 drugs, select a third drug from the list (thiazide-type diuretic, CCB, ACEI, or ARB), **avoiding the combined use of ACEI and ARB.** Titrate the third drug up to the maximum recommended dose to achieve goal BP.
B	Start one drug and then add a second drug before achieving maximum dose of the initial drug then titrate both drugs up to the maximum recommended doses of both to achieve goal BP.	
C	Begin with 2 drugs at the same time, either as 2 separate pills or as a single pill combination (Stage 2 HTN)	

Combination Therapy

Common Fixed Dose Combinations				
ACEi + Thiazide	**ARB + Thiazide**	**ACEi + CCB**	**ARB + CCB**	**ARB + CCB + Thiazide**
Captopril + HCTZ	Losartan + HCTZ	Enalapril + Lercanidipine	Valsartan + Amlodipine	Losartan + Amlodipine + HCTZ
Enalapril + HCTZ	Valsartan + HCTZ	Perindopril + Amlodipine	Olmesartan + Amlodipine	Valsartan + Amlodipine + HCTZ
Lisinopril + HCTZ	Irbesartan + HCTZ	Enalapril + Nitrendipine	Telmisartan + Amlodipine	Olmesartan + Amlodipine + HCTZ
Perindopril + Indapamide	Candesartan + HCTZ		Irbesartan + Amlodipine	
Ramipril + HCTZ	Telmisartan + HCTZ		Losartan + Amlodipine	
Quinapril + HCTZ	Olmesartan + HCTZ			
Zofenopril + HCTZ				

Pharmacologic Treatment

Primary Agents	Secondary Agents
• Thiazide or thiazide-like diuretics • ACE Inhibitors • ARBs • CCB— dihydropyridines • CCB— nondihydropyridines	• Diuretics—loop • Diuretics— potassium sparing • Diuretics— aldosterone antagonists • Beta blockers— cardioselective • Beta blockers— cardioselective and vasodilatory • Beta blockers— noncardioselective • Beta blockers— intrinsic sympathomimetic activity • Beta blockers— combined alpha- and beta-receptor • Direct renin inhibitor • Alpha-1 blockers • Central Alpha2- agonists and other centrally acting drugs • Direct vasodilators

Antihypertensive Drugs Dosing

Class	Drug	Usual Dose, Range (mg/d)	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	

Antihypertensive Drugs Dosing

Class	Drug	Usual Dose, Range (mg/d)	Daily Frequency	Comments
Primary Agents				
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. • May cause dry cough • 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	2.5–20	1 or 2	
	Trandolapril	1–4	1	

Antihypertensive Drugs Dosing

Class	Drug	Usual Dose, Range (mg/d)	Daily Frequency	Comments
Primary Agents				
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	

Antihypertensive Drugs Dosing

Class	Drug	Usual Dose, Range (mg/d)	Daily Frequency	Comments
Primary Agents				
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	2.5–10	1	
	Isradipine	5-10	2	
	Lercanidipine	10–20	1	
	Nicardipine SR	60-120	2	
	Nifedipine LA	60–120	1	
	Nisoldipine	17-34	1	
	Nitrendipine	20	1	
CCB—nondihydropyridines	Diltiazem ER	120–480	1	• 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)
	Verapamil SR	120–480	1 or 2	

Antihypertensive Drugs Dosing

Class	Drug	Usual Dose, Range (mg/d)	Daily Frequency	Comments
Secondary Agents				
Diuretics— loop	Bumetanide	0.5-2	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	30-80	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	1 or 2	• 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	

Antihypertensive Drugs Dosing

Class	Drug	Usual Dose, Range (mg/d)	Daily Frequency	Comments
Secondary Agents				
Beta blockers (BBs)—cardioselective	Atenolol	25–100	1 or 2	• 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	
	Bisoprolol	2.5–10	1	
	Metoprolol succinate	50–200	1	
BBs — Cardioselective & vasodilatory	Nebivolol	5—40	1	• Induces nitric oxide-induced vasodilation • Avoid abrupt cessation
BBs — Noncardioselective	Nadolol	40–120	1	• Avoid in patients with reactive airways disease • Avoid abrupt cessation
	Propranolol LA	80–320	1	
BBs — intrinsic sympathomimetic activity	Acebutolol	200-800	2	• Generally avoid, especially in patients with IHD or HF • Avoid abrupt cessation
	Penbutolol	10-40	1	
	Pindolol	10-60	2	
BBs — 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	

Antihypertensive Drugs Dosing

Class	Drug	Usual Dose, Range (mg/d)	Daily Frequency	Comments
Secondary Agents				
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	1–16	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 Alpha2-agonists 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	100-200	2 or 3	• Associated with sodium and water retention and reflex tachycardia; use with a diuretic and beta 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	

Case-based Learning: Case 3

A 55-year-old man with hypertension and no other chronic medical problems is currently treated with hydrochlorothiazide 50 mg daily, irbesartan 300 mg daily, carvedilol 25 mg twice daily, and amlodipine 10 mg daily. His BP is 144/96 mm Hg (146/94 mm Hg when repeated). He is adherent to all of these medications and with lifestyle modifications. Serum creatinine is 1.2 mg/dL, potassium is 3.7 mEq/L, and all other laboratory values are normal.

Q7. What is the patient diagnosed with at this stage? What agent do you recommend to add to his regimen?

Hypertensive Crises

Hypertensive urgency

Hypertensive emergency

Hypertensive Crises

- Possible causes:
  - Non-compliance
  - Pheochromocytoma
  - Renal vascular disease
  - Glomerulonephritis
  - Head injury
  - Severe burns
  - Eclampsia
  - Abrupt drug withdrawal
  - Drug-drug or drug-food interactions
  - Others

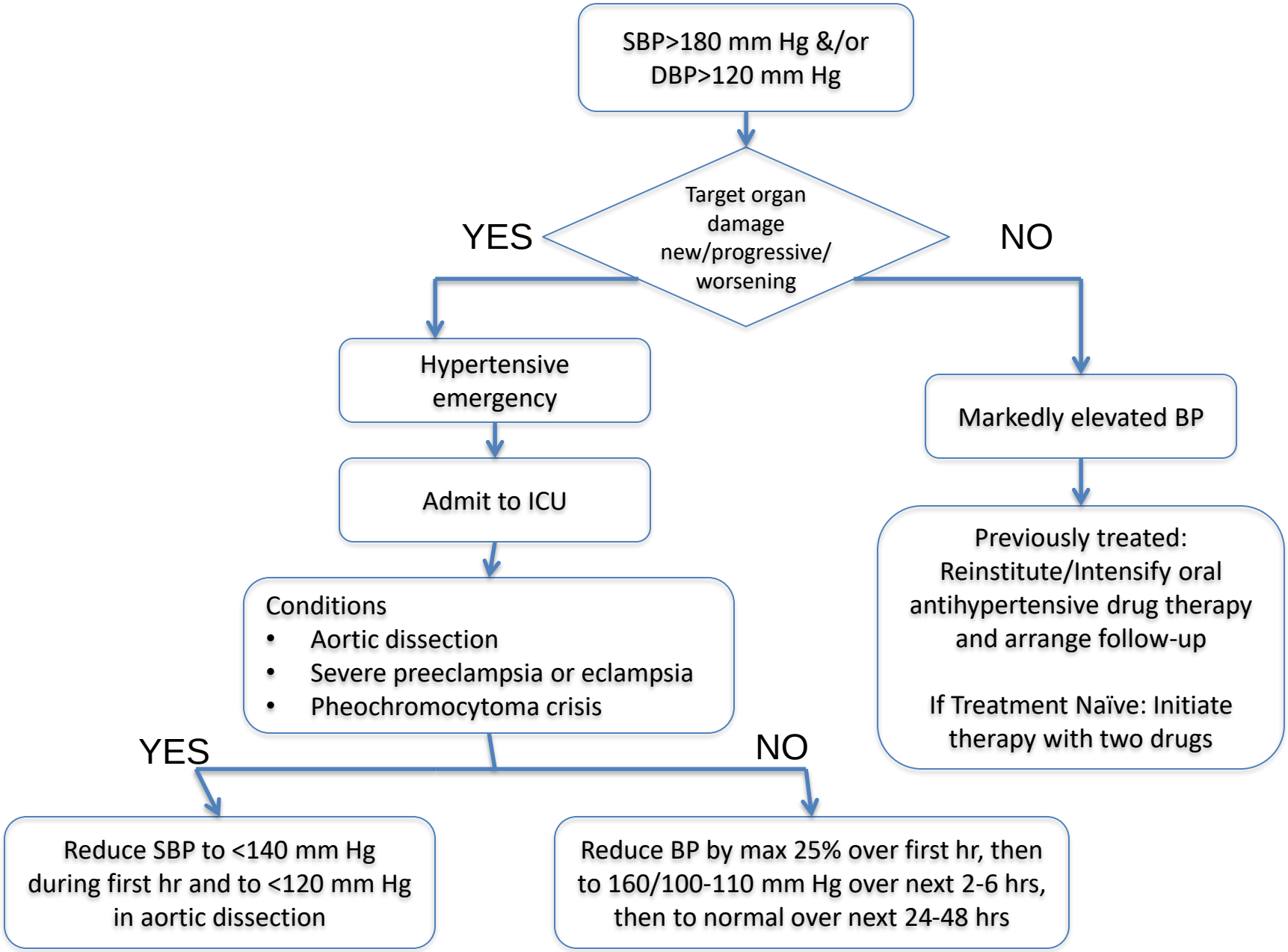
Hypertensive Crises

- Can lead to acute organ damage
  - CNS: Motor or sensory defects, dizziness, confusion encephalopathy, weakness, Intracranial hemorrhage
  - Eyes: ocular hemorrhage or fundoscopic changes, blurred vision, loss of sight
  - Heart: Acute left ventricular failure with pulmonary edema, peripheral edema, angina, aortic dissection, heart rate, 3rd or 4th heart sound, heart murmurs, arrhythmias
  - Kidney: renal failure/ insufficiency
  - Peripheral arteries: absence, reduction, or asymmetry of pulses, cold extremities, ischemic skin lesions.

- Rate of BP lowering should be individualized
  - If overly aggressive lowering in BP

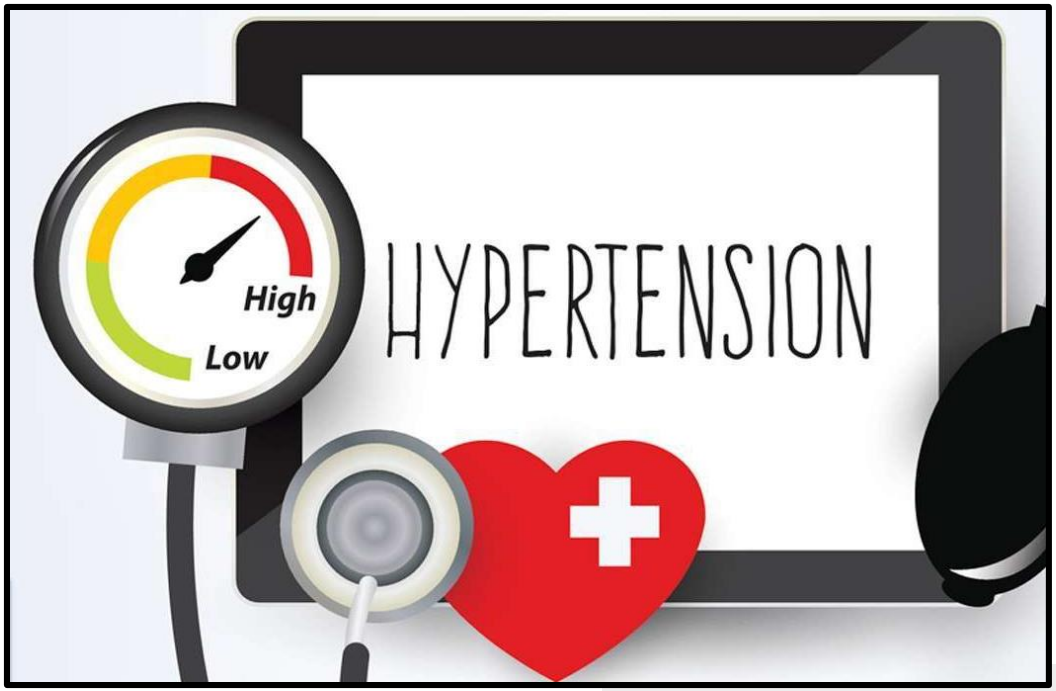
    → Risk organ ischemia or infarction: cerebrovascular accidents, MI, acute kidney failure

Algorithm for Management of a Hypertensive Crisis



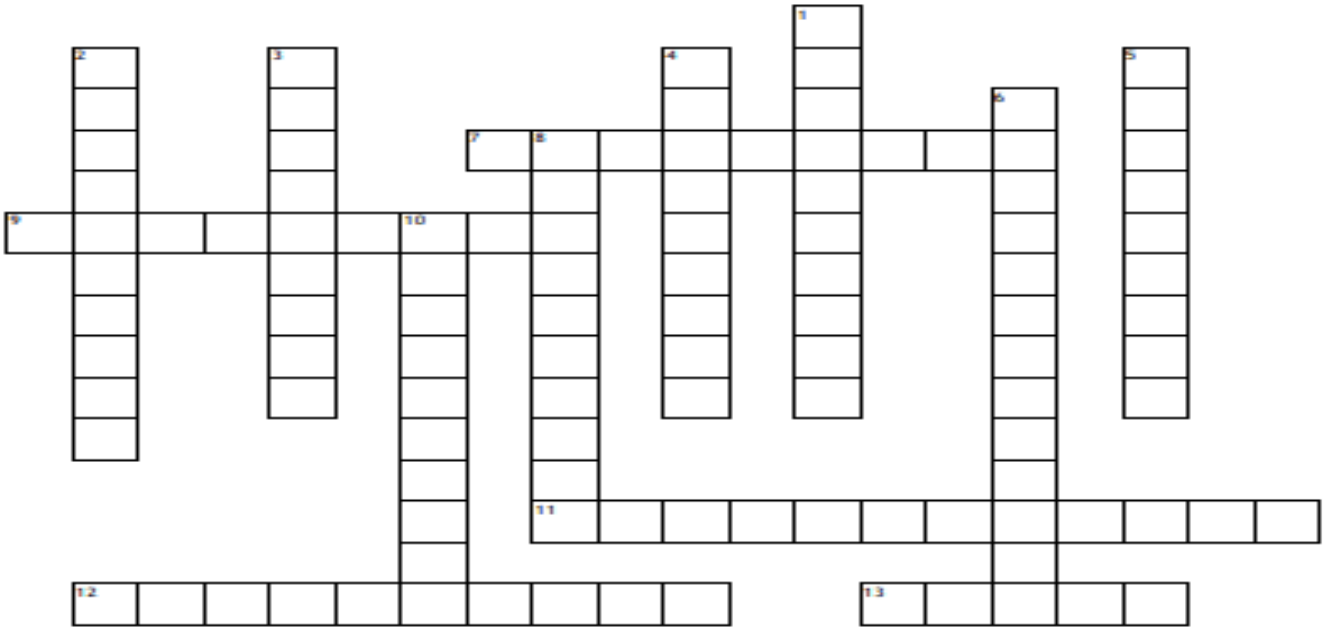
Hypertensive Crises: EMERGENCY Treatment based on Organ Damage (FYI)

Comorbidity	Preferred Drug(s)*		Comorbidity	Preferred Drug(s)*
Acute aortic dissection	Esmolol Labetalol Nicardipine Nitroprusside		**Eclampsia or preeclampsia**	Hydralazine Labetalol Nicardipine
Acute pulmonary edema	Clevidipine Nitroglycerin Nitroprusside		**Perioperative hypertension**	Clevidipine Esmolol Nicardipine Nitroglycerin
Acute coronary syndromes	Esmolol Labetalol Nicardipine Nitroglycerin		**Acute sympathetic discharge or catecholamine excess states (e.g., pheochromocytoma, post-carotid endarterectomy status)**	Clevidipine Nicardipine Phentolamine
Acute renal failure	Clevidipine Fenoldopam Nicardipine		**Acute ICH**	Labetalol Nicardipine Esmolol
Acute heart failure	Nitroglycerin Enalaprilat		**Acute ischemic stroke**	Labetalol Nicardipine



Let's Game It Out

Hypertension Crossword



Across

7. Severe hypertension with end-organ damage is known as hypertensive.....

9. Blood pressure that requires at least 4 drugs to be controlled

11. Hypertension is considered as a "silent killer" because it is frequently.....

12. The most potent loop diuretic

13. ACEs and ARBs are NOT preferred first line in this group of people

Down

1. A preferred agent in primary aldosteronism and resistant hypertension

2. A beta blocker that is preferred to be used in hypertensive patients having heart failure with reduced ejection fraction

3. It is crucial to monitor serum creatinine and ..... levels in patients treated with a combination of aldosterone receptor antagonist and an ACEI/ARB

4. An antihypertensive agent that should be avoided in hypertensive patients having heart failure with reduced ejection fraction

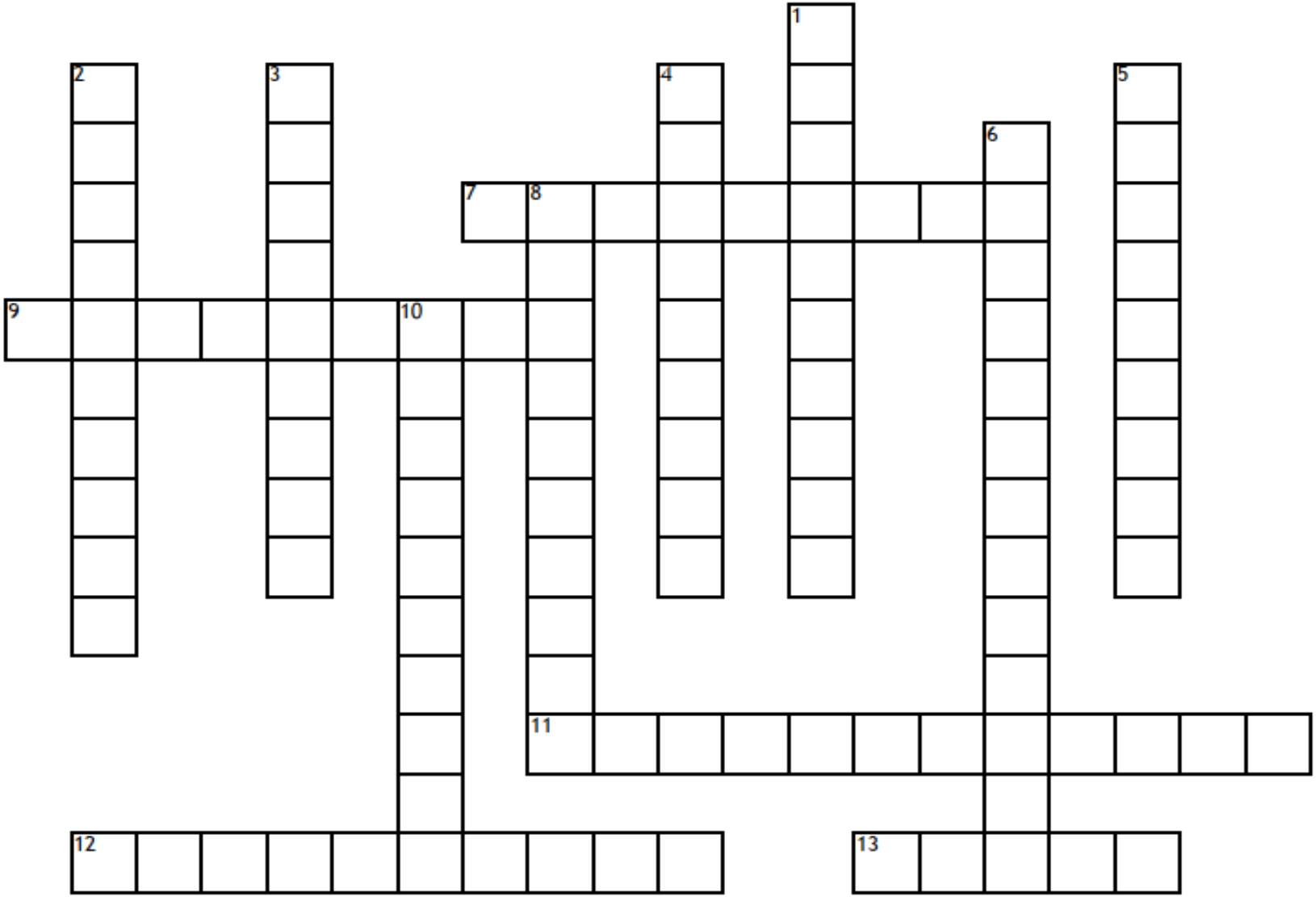
5. An antihypertensive agent that may cause acute renal failure in patients with severe bilateral renal artery stenosis

6. A side effect associated with the use of chlorthalidone

8. A safe antihypertensive agent to be used in pregnant females

10. Life threatening side effect of ACE-Inhibitors and ARBs

Hypertension Crossword



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Hypertension Word Search

D L D K P Y Z Q Z C K M B C K J S R E Y C X R T
E D I M E S O R U F E E S L Z W H Y A L K N H F
H D L Y B N X O Z T M Z F P H P J P Y W S L O Z
G Y N U G C F F M W U A H L Z Q N R C D K Y Q H
Z O E M Y V R L T S L I X V O Q E V W K J Q F L
Z F W R R U Y G U L O T H S D L B N P B M U C C
F C V L B K I Q I G V L S Y S T O L I C Y R M Y
I T Y U Y W C S S I E I T K A Q T R F W E I W B
U Z B O H T I J X Y K D N G X H Y Y P L G A R C
K H U V Q N E V P Y O A N R B I N Y L O K K A I
G F H Z O L A T A Q R H M E W R I I D Y T R O N
M K J P C E I M B V T W N L B A K Y E A D E H H
M J R Q N U T E E T S O K S O T Y V I I K B M W
J I N I V T C Z W D T F V J N D F Y A D L U B M
L F B F X V X L S C E I B E L I I C C X X L X N
G K X J C V W Y A J B O L E N L O P D N V I P B
V R Z Y M U W L J M U I I S R U U A I R E Q F M
X U P W B V O A D I S W H G T I N T D N L G O V
Q R S E L N D S K H D L S P N A X I Q M E X R Y
D F B P O N M Q P G F O U B A A E Q Z V F R G U
S R J R N O D I V X C T U E F V L U Y Y Z J I Y
Z R I S T N A T R A S E D N A C Q P Q C M D F J
K P Y M V U F A L I S K I R E N L B Q K N T W T
S I J U D E N O D I L A H T R O L H C H L A Q K

stroke volume
amlodipine
spironolactone
diltiazem
cardiac output
systolic
chlorthalidone
metoprolol
lisinopril
angioedema
urgency
furosemide
silent killer
candesartan
aliskiren

Thank you
Questions?