Pharmaco-therapy of Hypertension

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Drug and Poison Information Center

What We Have Today

Introduction

Pathophysiology/ Etiology

Classification

Presentation

Diagnosis

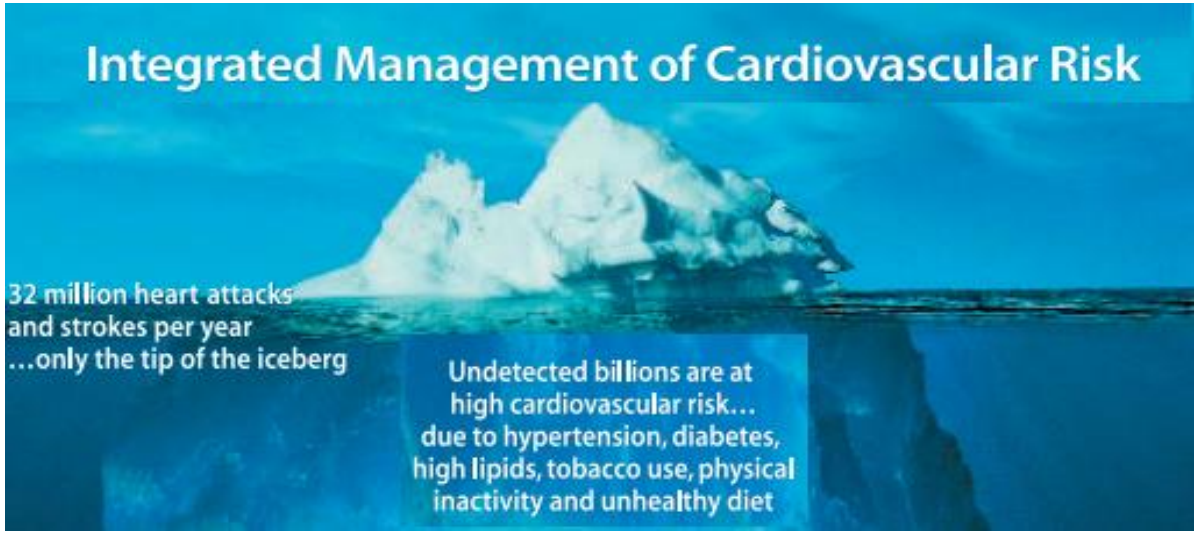
Treatment

Introduction

High Blood Pressure, The silent killer

- Biggest contributor to the global burden of disease
- In 2015, 1.13 billion adults had raised BP
- The global burden of HTN exceeds 1.4 billion people (2019)
- Increase largely in middle and low-income countries (+ lower control rate)
- HTN is controlled in less than a fifth of patients worldwide

Hypertension is called the silent killer because most patients do not have symptoms.

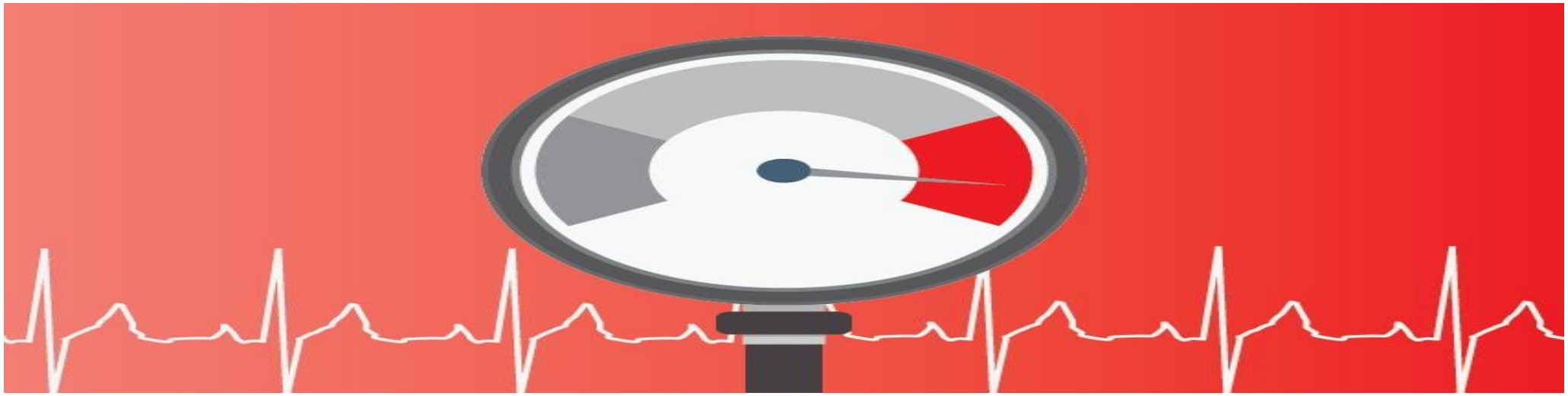


WHO report 2015

Introduction

High Blood Pressure, The silent killer

- The lifetime risk of developing hypertension among those 55 years of age and older who are normotensive is higher than 90%.
- Most patients have elevated BP before they are diagnosed with hypertension, with most diagnoses occurring between the third and fifth decades of life.



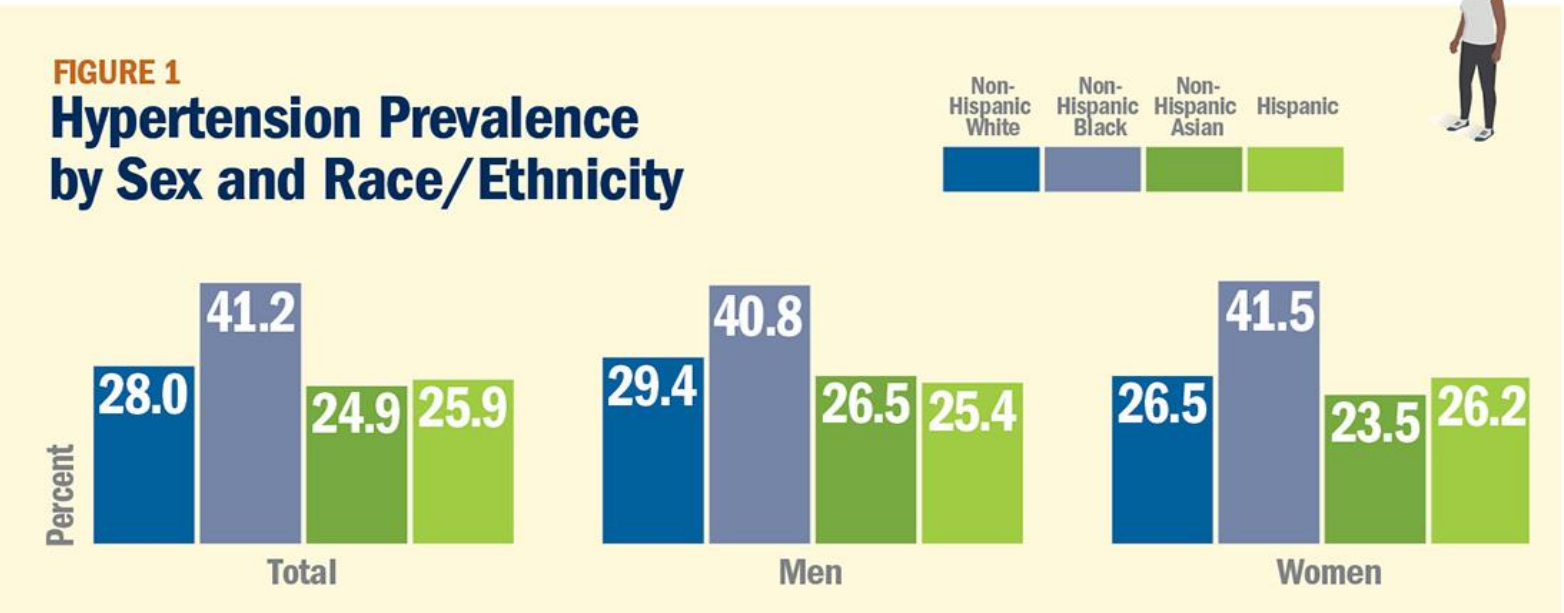
Introduction

High Blood Pressure, The silent killer

- The overall incidence of hypertension is similar between men and women, but varies depending on age

<65 years	M > F
65-74 years	M = F
>74 years	F > M

- Non-Hispanic blacks
- Non-Hispanic whites
- Non-Hispanic Asians
- Hispanic

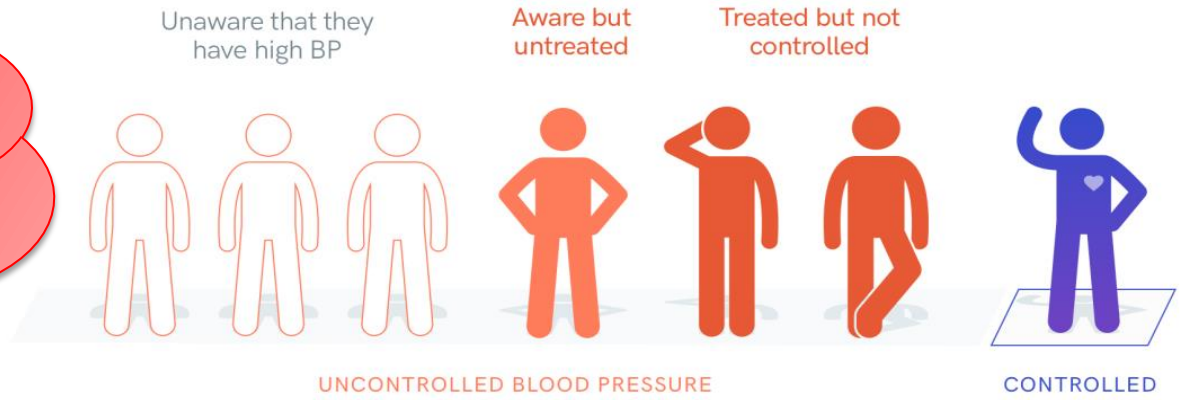


One Size Does Not Fit All: The Role of Sex, Gender, Race and Ethnicity in Cardiovascular Medicine
Oct 19, 2018 Cardiology Magazine

Introduction

High Blood Pressure, The silent killer

Globally only one of 7 people have their HTN under control



Avoid Clinical Inertia

Case

Mr. Taban
A 45 years old gentleman is your neighbor and friend
He is a fast food chef
Detection of high blood pressure in routine workplace test. (135/85 mmHg)
He denied any symptoms, except some headaches
PMH: -
FH: Father (ACS at 60)
Drug/suppl: Vitamin C
BMI: 31

Lab data	
LDL	195
HDL	30
Cr	0.9
FBS	98

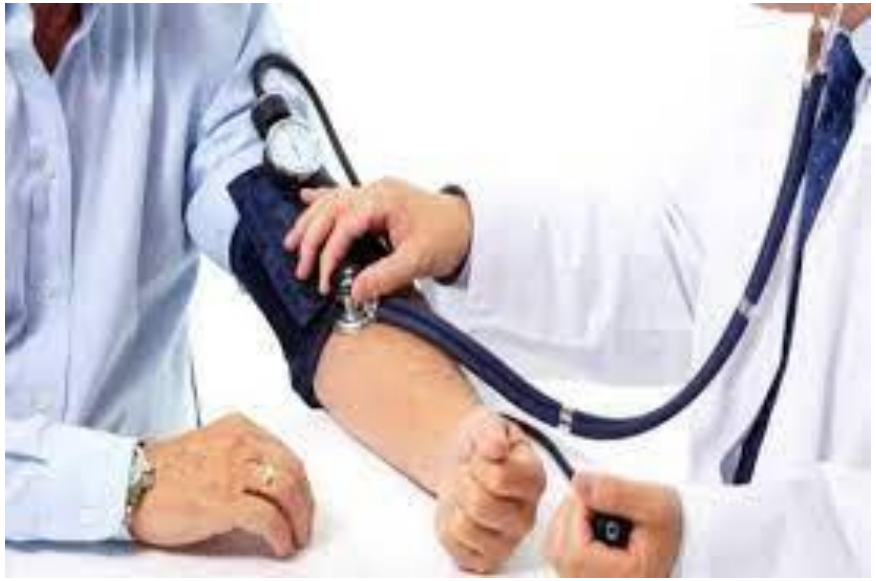
Clinical presentation

General: May appear healthy or may have additional CV risk factors

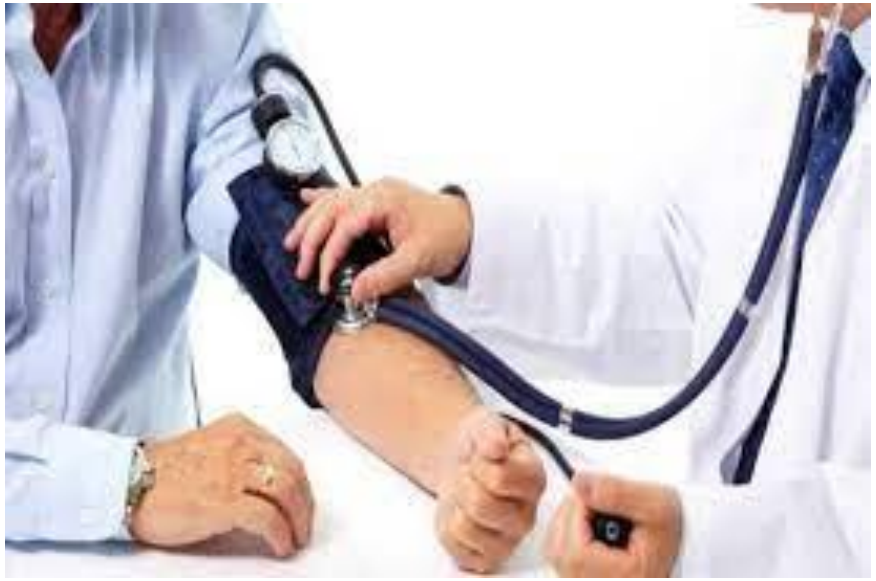
CV Risk factors	
Age (≥55 years for men, ≥65 years for women)	Diabetes (type 1 or type 2)
Dyslipidemia	Physical inactivity
Albuminuria	Overweight or obesity
Family history of premature cardiac events	Tobacco use

Symptoms: Usually none related to elevated BP.
Signs: Previous BP (SBP or DBP) values in the elevated or the HTN category

- The average of two or more BP measurements taken during two or more clinical encounters is required to diagnose hypertension.
- This BP average should be used to establish a diagnosis, and then classify the stage



In the clinic setting, standard BP measurement procedures (eg, ppropriate rest period, correct technique, right cuff size) are often not followed, which results in poor estimation of true BP.
In addition, variations may occur between individuals measuring BP.
Due to these factors, use of oscillometric devices is generally preferred.



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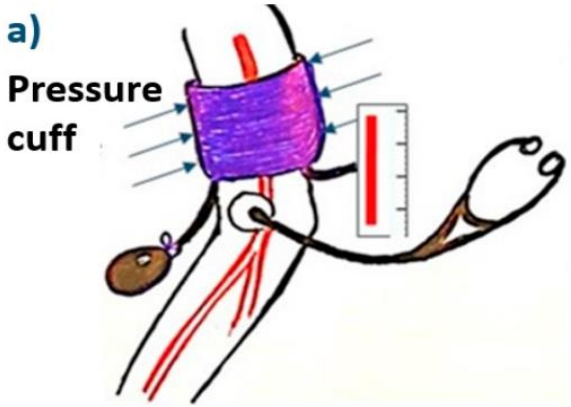
Inaccuracies with indirect measurements

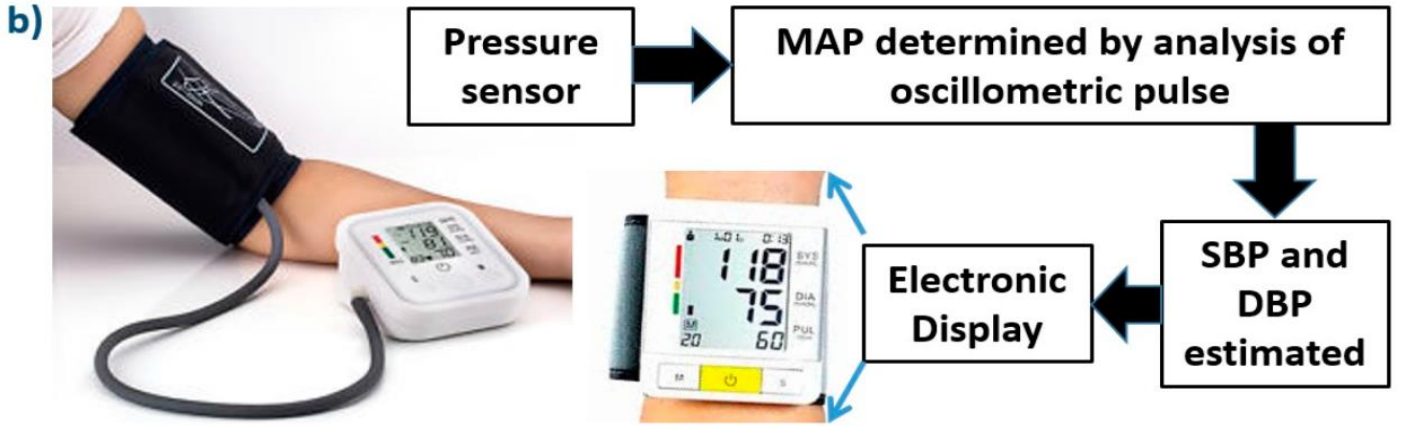
- inherent biologic variability of BP
- errors related to incorrect technique
- white coat effect

Variations in BP

- environmental temperature
- The time of day and year
- Meals
- physical activity
- Posture
- Alcohol, nicotine
- emotions



Type of Sound	Inference
No sound	Artery occluded
K-1 (clear tapping)	Systolic Pressure
K-5 (sound ceases)	Diastolic Pressure



Recommendation for Out-of-Office and Self-Monitoring of BP

References that support the recommendation are summarized in Online Data Supplement 3 and Systematic Review Report.

COR	LOE	Recommendation
I	A^{SR}	1. Out-of-office BP measurements are recommended to confirm the diagnosis of hypertension (Table 11) and for titration of BP-lowering medication, in conjunction with telehealth counseling or clinical interventions.[S4.2-1–S4.2-4]

روز	صبح		شب	
شنبه				
یکشنبه				
دوشنبه				
سه شنبه				
چهارشنبه				
پنجشنبه				
جمعه				

Measuring BP

The measurement of BP as a screening tool should be conducted at every healthcare encounter
Cuff Measurement The most common method to measure BP in clinical practice is the indirect measurement of BP using an oscillometric device or sphygmomanometry.

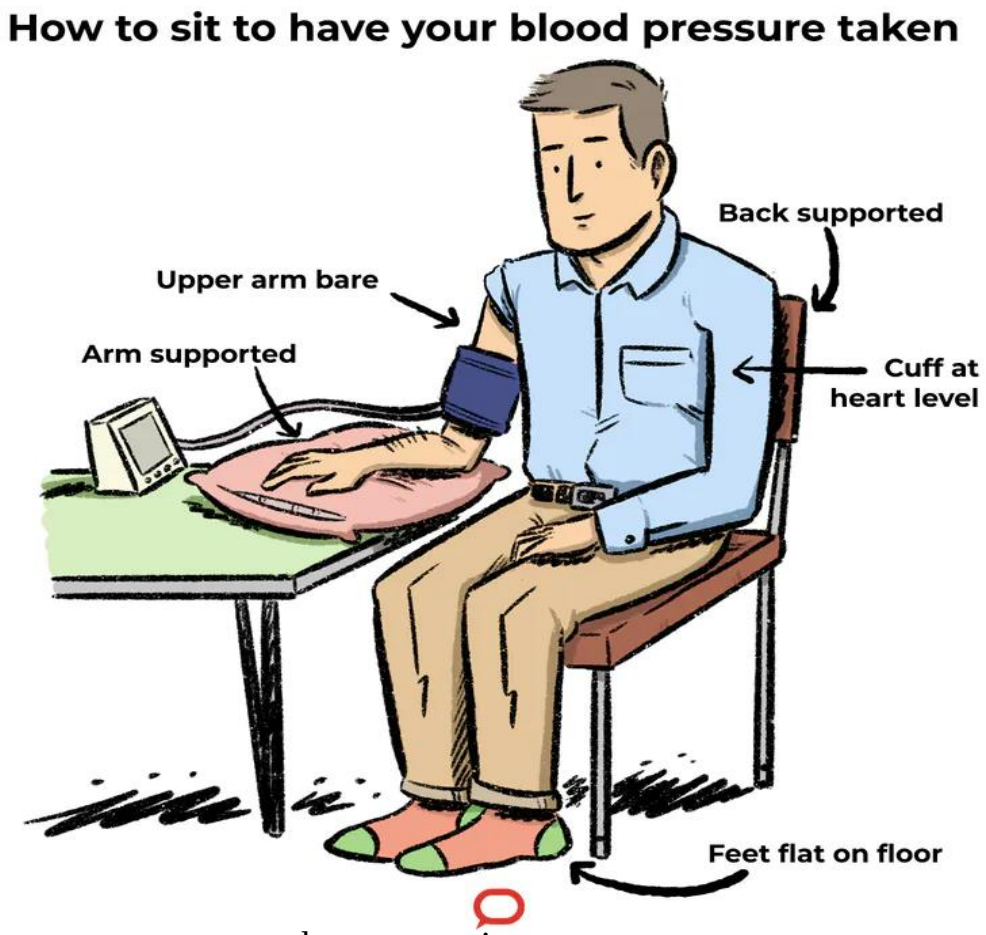


Table 8. Checklist for Accurate Measurement of BP[S4.1-3,S4.1-4]

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. 6. Measurements made while the patient is sitting or lying on an examining table do not fulfill these criteria.

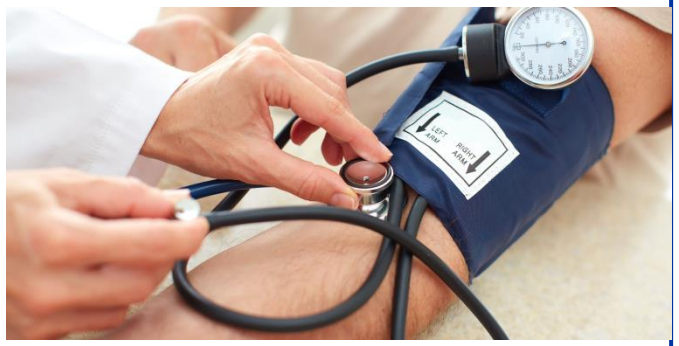
Step 2: Use proper technique for BP measurements	1. Use a BP measurement device that has been validated, and ensure that the device is calibrated periodically.* 2. Support the patient's arm (eg, resting on a desk). 3. Position the middle of the cuff on the patient's upper arm at the level of the right atrium (the midpoint of the sternum). 4. Use the correct cuff size, such that the bladder encircles 80% of the arm, and note if a larger- or smaller-than-normal cuff size is used (Table 9). 5. Either the stethoscope diaphragm or bell may be used for auscultatory readings.[S4.1-5,S4.1-6]
Step 4: Properly document accurate BP readings	1. Record SBP and DBP. If using the auscultatory technique, record SBP and DBP as onset of the first Korotkoff sound and disappearance of all Korotkoff sounds, respectively, using the nearest even number. 2. Note the time of most recent BP medication taken before measurements.

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. 3. For auscultatory determinations, use a palpated estimate of radial pulse obliteration pressure to estimate SBP. Inflate the cuff 20–30 mm Hg above this level for an auscultatory determination of the BP level. 4. For auscultatory readings, deflate the cuff pressure 2 mm Hg per second, and listen for Korotkoff sounds.
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.

روز	صبح		شب	
شنبه	135/85	130/80	125/75	128/88
یکشنبه	130/80	130/80	140/85	140/80
دوشنبه	125/75	120/80	130/75	135/85
سه شنبه	135/80	120/80	125/80	130/80
چهارشنبه	130/80	135/85	135/75	120/80
پنجشنبه	130/85	125/85	130/85	135/80
جمعه	145/95	140/85	130/85	130/85

Measuring BP

- Neither ABP nor home BP monitoring is needed for the diagnosis of hypertension, but they are recommended. These modalities can enhance the ability to identify patients with white coat and masked hypertension
- ABP monitoring may be a **stronger predictor of all-cause and CV mortality than clinic measurements**
- The 2017 ACC/AHA guideline **recommends out-of-office measurements for diagnostic confirmation and to assist in titrating antihypertensive medication**.
- **ABP monitoring may be helpful** for patients with:
    - Apparent drug resistance
    - Hypotensive symptoms while on antihypertensive therapy
    - Episodic hypertension (eg, white coat hypertension)
    - Autonomic dysfunction
    - Identifying “nondippers” whose BP does not decrease by >10% during sleep and who may portend an increased risk of hypertension-associated complications.



Guidelines

American Heart Association®

ESC European Society of Cardiology

International Society of Hypertension

2017 2018 2020

- The **SPRINT** evaluated a systolic BP goal of <120 mm Hg versus <140 mm Hg in patients with hypertension at high CV risk but without diabetes.
- The study was stopped early after a median follow-up of 3.3 years due to a significantly lower risk of the primary composite outcome (MI, other acute coronary syndromes, stroke, HF, or death from CV causes) and all cause mortality in patients treated to the lower BP goals.
- While there was an increased risk of adverse events in the intensive treatment group (eg, hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure), the significant benefits outweighed these risks.

BPLTTC

Blood Pressure Lowering Treatment Trialists' Collaboration

More than 352,000 patients

With > **352,000** patients included in the 51 collaborating trials, the BPLTTC is the largest single data resource of individual patient-level randomized clinical trial data.

48 RCT

Classification

The classification of BP in adults (age 18 years and older) is based on the average of two or more properly measured BP values from two or more clinical encounters.

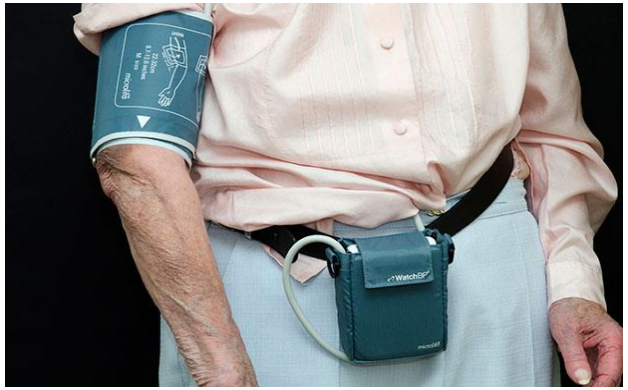
BP Category	SBP		DBP
Normal	<120 mm Hg	and	<80 mm Hg
Elevated	120–129 mm Hg	and	<80 mm Hg
Hypertension			
Stage 1	130–139 mm Hg	or	80–89 mm Hg
Stage 2	≥140 mm Hg	or	≥90 mm Hg

135/84

Elevated BP is It is not a disease category, but is associated with an increased CV risks compared to patients with normal BP.
It identifies patients whose BP is likely to progress to hypertension in the future, and thus for whom lifestyle modifications should be enacted to attenuate this progression.

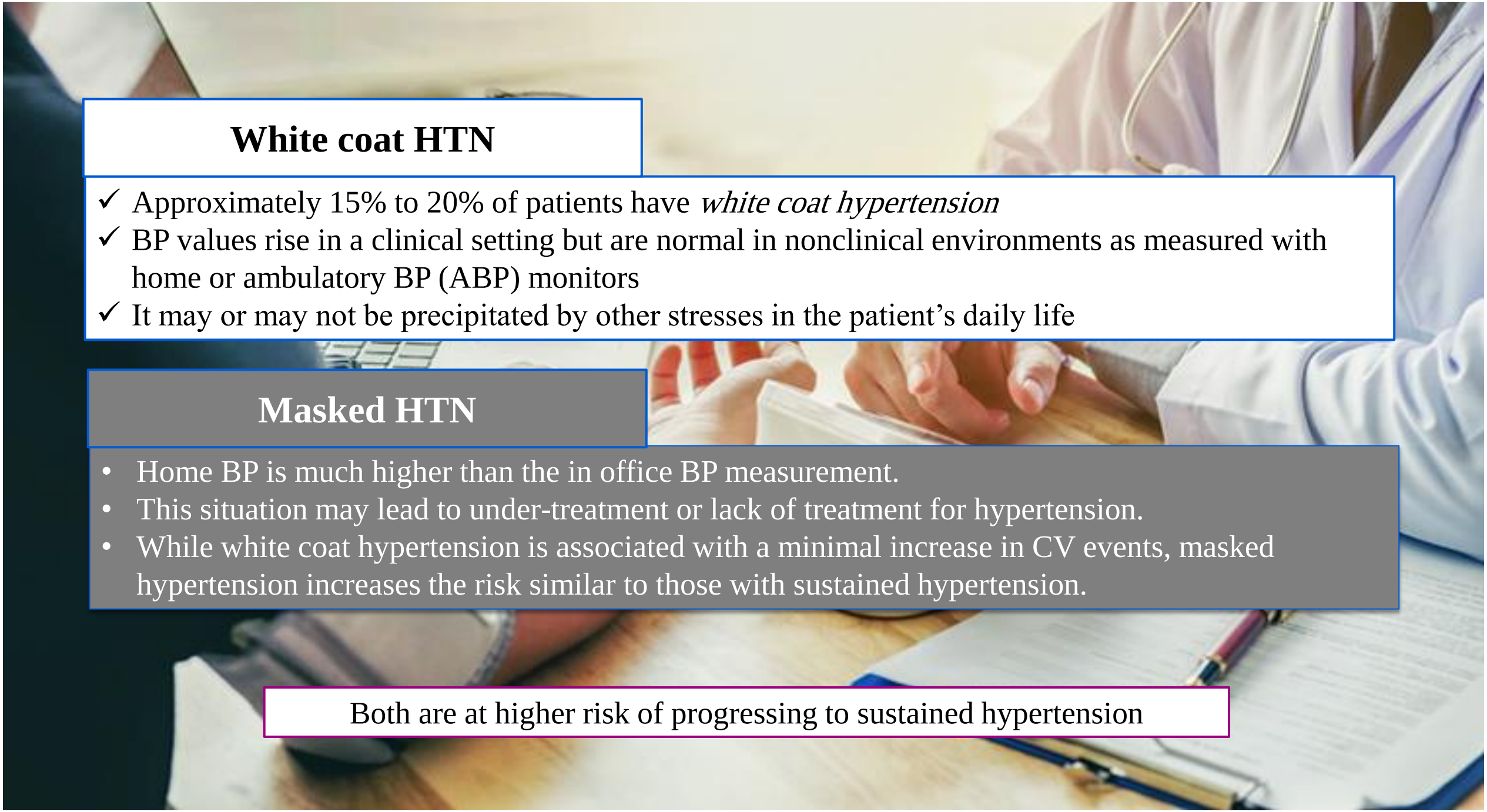
Measuring BP

Home BP monitoring values and ABP values are often lower than clinic measured values; the difference is greater in patients with stage 1 and stage 2 hypertension.



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

	Healthcare setting	Non-Healthcare setting
Normotensive	No Hypertension	No Hypertension
Sustained HTN	**Hypertension**	**Hypertension**
Masked HTN	No Hypertension	Hypertension
White coat HTN	Hypertension	No Hypertension



White coat HTN

- ✓ Approximately 15% to 20% of patients have *white coat hypertension*
- ✓ BP values rise in a clinical setting but are normal in nonclinical environments as measured with home or ambulatory BP (ABP) monitors
- ✓ It may or may not be precipitated by other stresses in the patient's daily life

Masked HTN

- Home BP is much higher than the in office BP measurement.
- This situation may lead to under-treatment or lack of treatment for hypertension.
- While white coat hypertension is associated with a minimal increase in CV events, masked hypertension increases the risk similar to those with sustained hypertension.

Both are at higher risk of progressing to sustained hypertension

Etiology

High Blood Pressure, The silent killer

Primary/Essential Hypertension

- Over 90% of HTN cases
- Numerous potential mechanisms contribute to the pathogenesis of essential hypertension, so identifying the exact underlying abnormality is not possible.
- Genetic factors play a role by affecting Na balance or other BP regulating pathways

Secondary Hypertension

- Much less common (up to 10%)
- A comorbid disease or a drug
- In most of these cases, renal dysfunction resulting from severe chronic kidney disease (CKD) or reno-vascular disease is the most common secondary cause
- Removing the offending agent or treating the underlying comorbid condition is the first step in management

Secondary causes of HTN

Diseases	CKD Renovascular diseases Thyroid disorders	Coarction of the aorta Obstructive sleep apnea Pheochromocytoma	Cushing's disease Parathyroid diseases Primary hyperaldestronism
Medications	- Amphetamines - CNIs (cyclosporin, tacrolimus) - Corticosteroids - Ergot alkaloids (ergonovin, methysergide) - Venlafaxin, desvenlafaxin	- Antivacular EGFR agent (bevacizumab, sorafenib, sunitinib) - Erythropoiesis stimulating agents (erythropoetin, darbepoetin) - Bupropion	- Decongestants (pseudoephedrine, ocular phenylephrine) - NSAIDs - Testosterone - Estrogen containing oral contraceptives
Situations	Abrupt discontinuation of B-blockers or centally acting a-agonists	B-blocker without a-blocker when treating pheochromocytoma	Use of (isocarboxazide, phenelzine, tranylcypromine) with tyramine containing foods or certain drugs
Street drugs	Methamphetamine St.John's wort	Anabolic steroids Ephedra alkaloids	Cocaine and cocaine withdrawal Ergot containing herbals
Excessive consumption of food substances		Sodium, licorice, Ethanol	

Pathophysiology

Arterial BP: pressure in the arterial wall measured in millimeters of mercury (mm Hg).
The two arterial BP values:

Systolic BP **(SBP):** peak value, achieved during cardiac contraction

Diastolic BP **(DBP):** nadir value, achieved after contraction when the cardiac chambers are filling.

Pulse pressure: (SBP-DBP), is a measure of arterial wall tension.

Mean arterial pressure (MAP): average pressure throughout the cardiac contraction cycle, represent overall arterial BP (especially in hypertensive emergency)

During a cardiac cycle, two-thirds of the time is spent in diastole and one-third in systole. Therefore:

$$MAP = \frac{1 \times SBP + 2 \times DBP}{3}$$

Pathophysiology

Arterial BP is hemodynamically generated by the interplay between blood flow and the resistance to blood flow.

BP = CO (cardiac output) × TPR (total peripheral resistance)

CO is the major determinant of SBP, TPR the largely determines DBP

CO (ml/min) = Stroke volume (ml/beat) × Heart rate (beat/min)

- Under normal physiologic conditions, arterial BP fluctuates throughout the day following a circadian rhythm
- BP decreases to its lowest values during sleep followed by a sharp rise starting a few hours prior to awakening, with the highest values occurring midmorning
- BP is also increased acutely during physical activity or emotional stress

- **SBP** is a stronger predictor of CV disease than DBP (adult > 50 yrs.); it is the most important BP parameter for most patients.
- **Isolated systolic hypertension:** SBP values are elevated and DBP values are not.
- Systolic hypertension result from pathophysiologic changes in the arterial vasculature consistent with aging.
- These changes decrease the compliance of the arterial wall and portend an increased risk of CV morbidity and mortality.
- **A wider pulse pressure reflect the extent of atherosclerotic disease in older patients and is a measure of increased arterial stiffness.**
- Higher pulse pressure values seen in those with isolated systolic hypertension are directly correlated with risk of CV mortality.

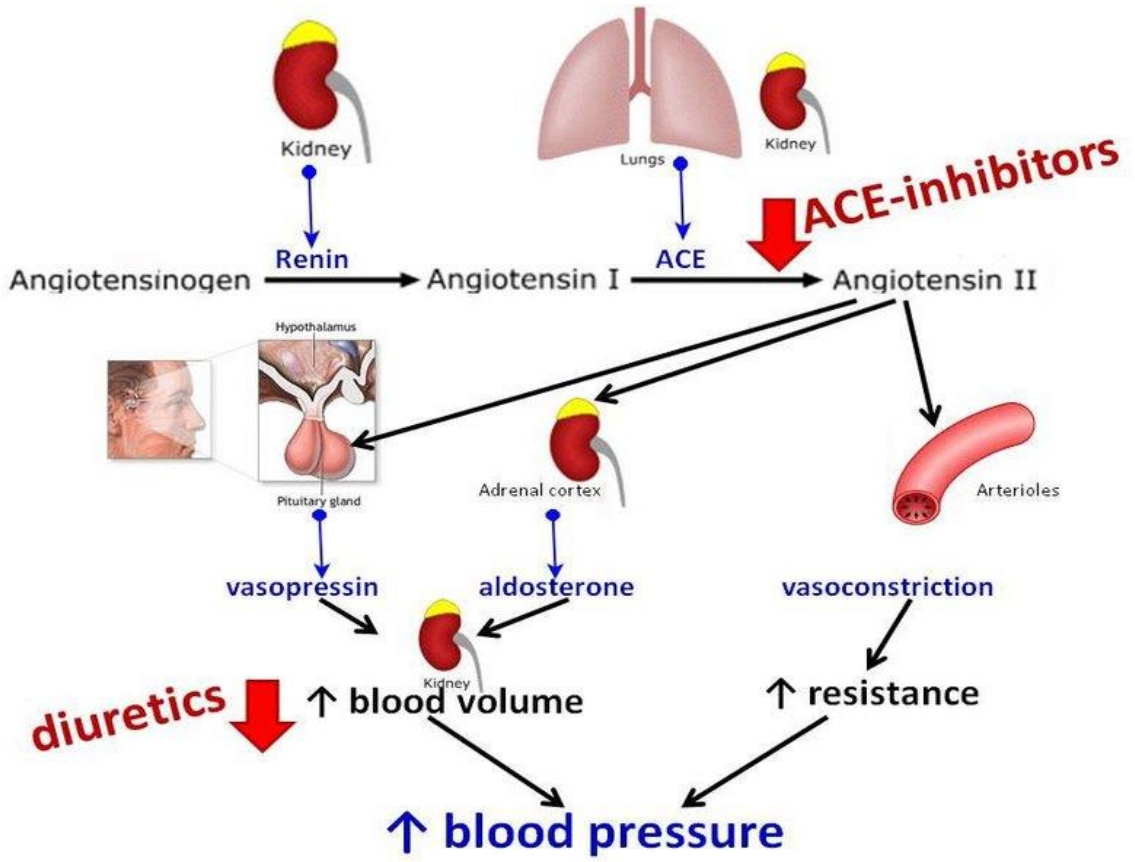
Pathophysiology

Neural Mechanisms

Renal Mechanisms

Hormonal Mechanisms

Vascular Mechanisms



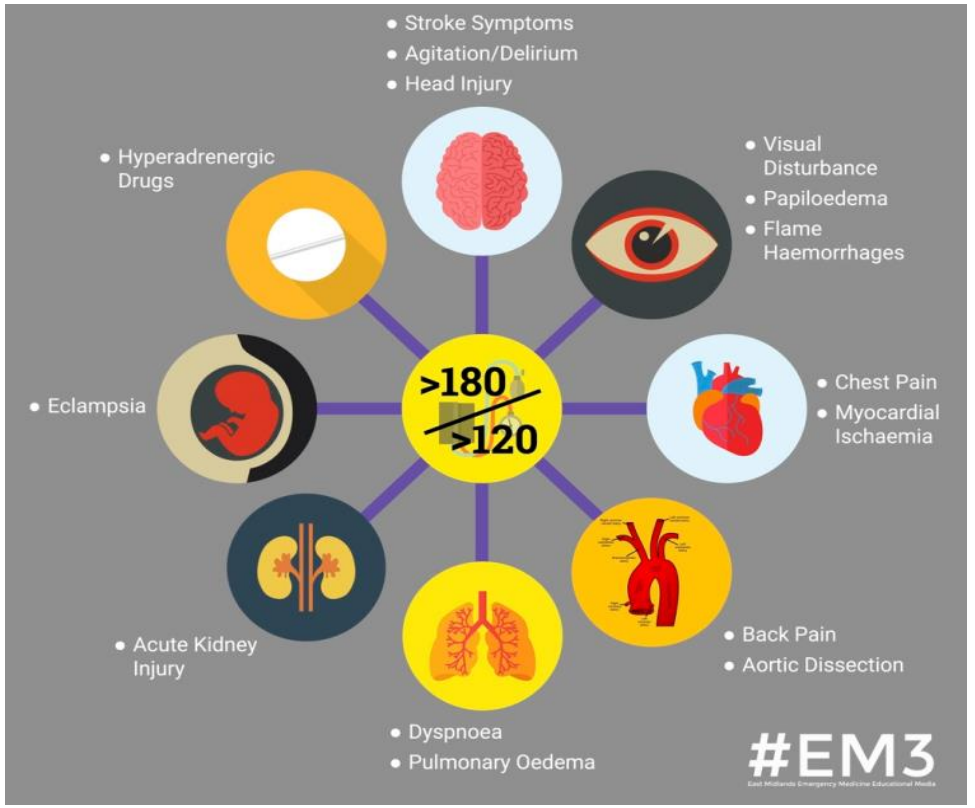
Complications

Cardiovascular risk

Retinopathy

Renal Disease

Peripheral arterial disease



Treatment

General Goal: morbidity and mortality from CV and kidney disease.

Therefore, the specific selection of antihypertensive **drug therapy should be based on evidence demonstrating a reduction in morbidity and mortality, not merely a reduction in BP.**

Surrogate Targets—Blood Pressure Goals

Guideline	Goal
2017 ACC/AHA	<130/80 for most patients
ADA	<140/90 for most patients with diabetes <130/80 for certain individuals (eg, those at high risk of ASCVD)
KDIGO	≤140/90 Hg for patients with hypertension and CKD (nondialysis) ≤130/80 for persistent albuminuria (≥30 mg urine albumin excretion/24h)

Blood Pressure Thresholds and Goals of Pharmacologic Therapy in Patients with Hypertension According to Clinical Conditions[2]

Clinical Condition(s)	BP Threshold for Antihypertensive Therapy Initiation (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; noninstitutionalized ambulatory, community-living adults)	≥ 130 (SBP)	< 130 (SBP)
Specific Conditions		
Diabetes mellitus	≥ 130/80	< 130/80
Chronic kidney disease	≥ 130/80	< 130/80
Chronic kidney disease postrenal transplantation	≥ 130/80	< 130/80
Heart failure	≥ 130/80	< 130/80
Stable ischemic heart disease	≥ 130/80	< 130/80
Secondary stroke prevention	≥ **140/90**	< 130/80
Secondary stroke prevention (lacunar)	≥ 130/80	< 130/80
Peripheral arterial disease	≥ 130/80	< 130/80

•**BP goal values for patients with diabetes** have been a subject of debate for years

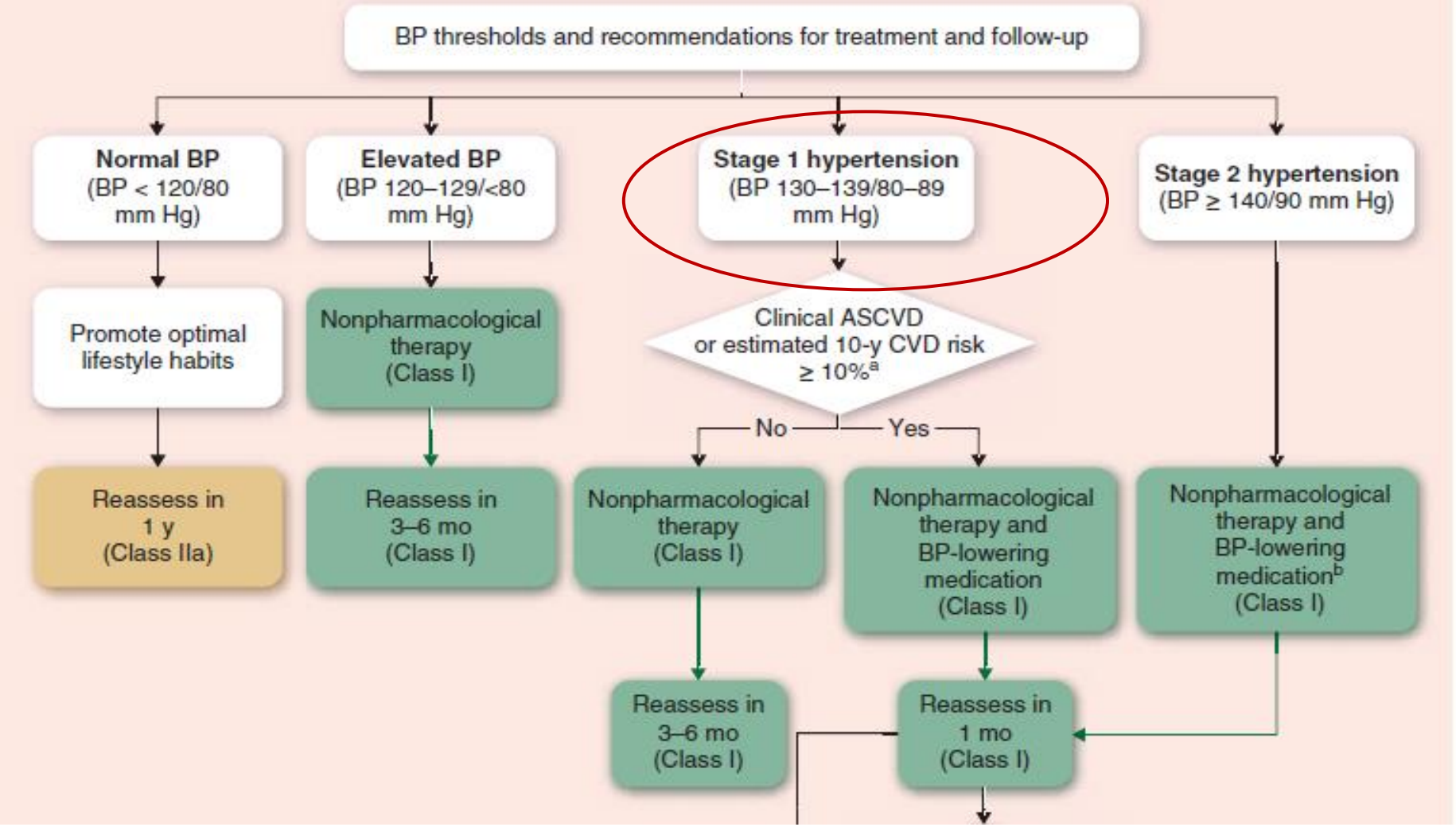
•<130/80 mm Hg

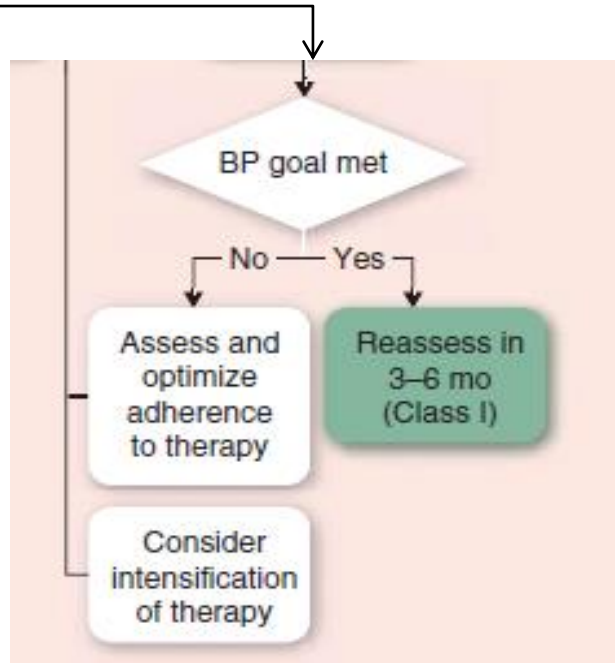
•Hypertension Optimal Treatment (HOT) study: compared DBP goals of <90 mm Hg, <85 mm Hg, or <80 mm Hg on CV outcomes

NHLBI-sponsored Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD-BP) study : no difference between SBP of <120 or SBP<140 (stroke)

ADA: <140/90 (based on ACCORD)

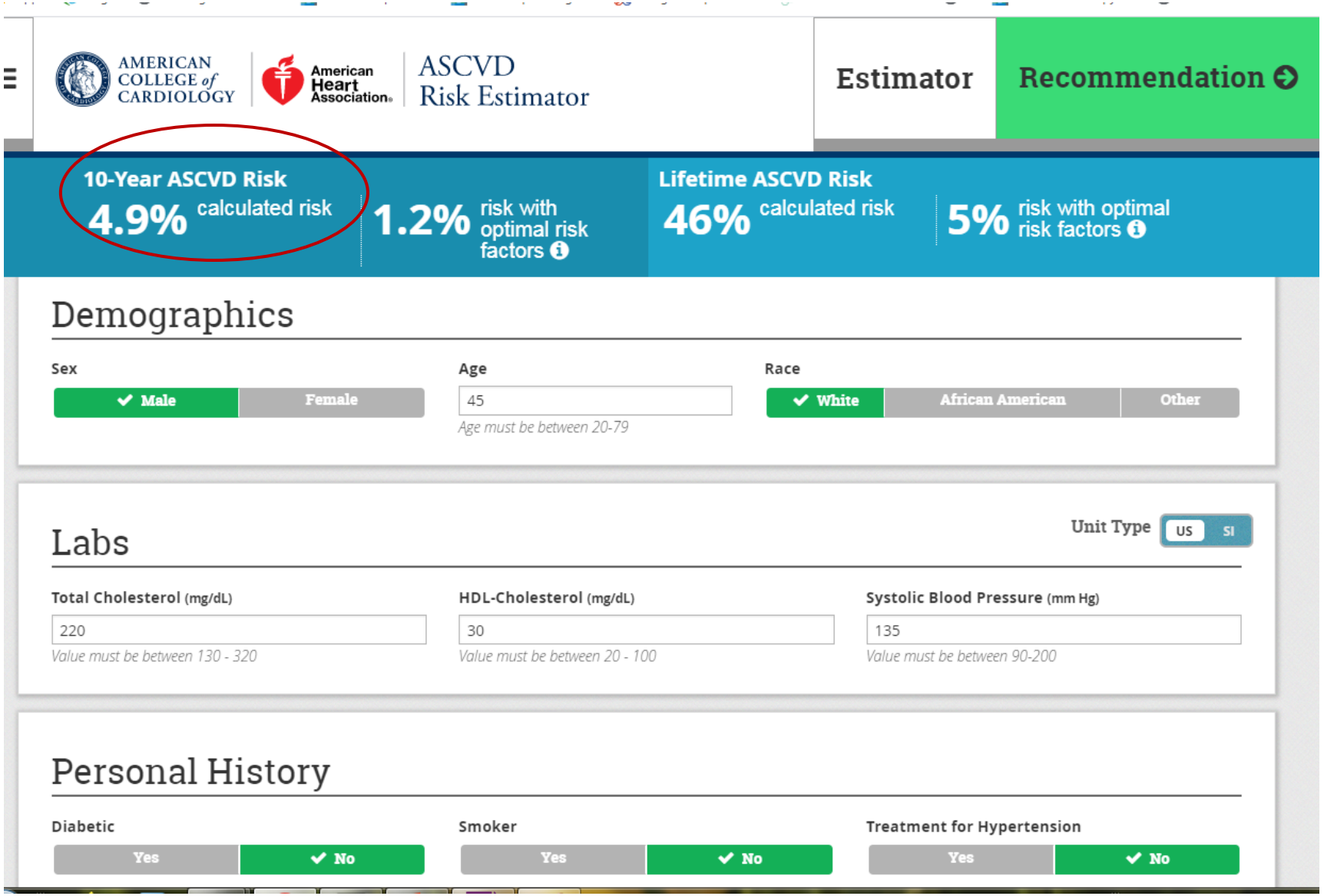
AHA: <130/80 (based on evidence-based review)

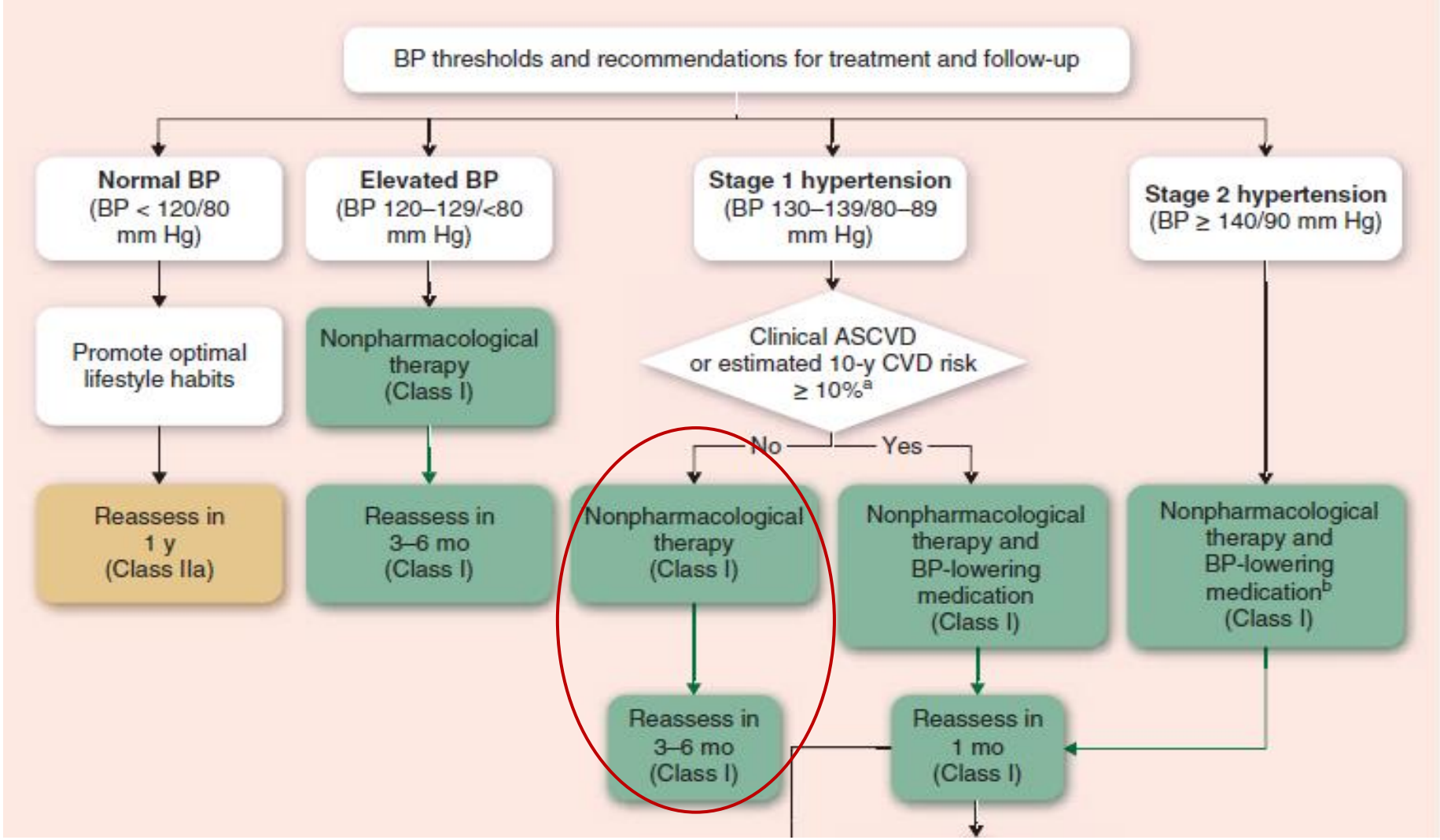


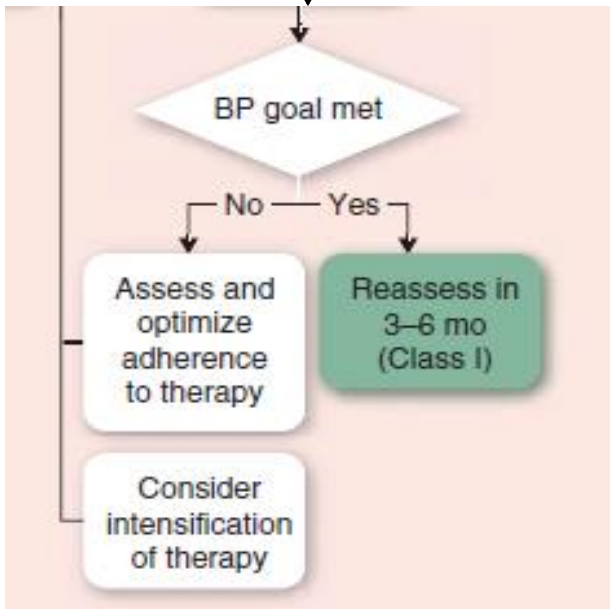


AHA/ACC 2017 HTN guideline

https://tools.acc.org/ldl/ascvd_risk_estimator/index.html#!/calculate/estimator/







AHA/ACC 2017 HTN guideline

Treatment/ non-pharmacologic

✓All patients with elevated blood pressure and hypertension should be prescribed lifestyle modifications.

✓However, they should never be used as a replacement for antihypertensive drug therapy for patients with hypertension who are not at goal BP.

✓Lifestyle modifications can provide small to moderate reductions in SBP.

✓Strict adherence to lifestyle modification can decrease the progression to hypertension in patients with elevated BP values

AHA/ACC 2017 HTN guideline

Treatment/ non-pharmacologic

Modification	Recommendation	Approximate SBP reduction	
		+ HTN	- HTN
Weight loss	Maintain normal weight (BMI: 18.5-24.9), but aim at least 1 kg reduction, 1 mm Hg/ per 1 kg weight loss	**5**	2-3
DASH dietary pattern	A diet rich in fruits, vegetables, and low fat dairy products with a reduced content of saturated and total fat	**11**	3
Reduced salt intake	Reduce as much as possible, ideally to 1.5 g/day (Na)/ 3.8 g/day (NaCl)	5-6	2-3
Physical activity	90-150 min/wk of aerobic or dynamic resistance training, (moderate to vigorous)	5-8 aerobic 4 dynamic	2-4 aerobic 2 dynamic
Moderation of alcohol	Limit consumption to less than 2 drink/day for males and less than 1 drink/day for females	4	3

AHA/ACC 2017 HTN guideline

Smoking cessation

- Smoking (tobacco or other products) is not a secondary cause of essential hypertension.
- Therefore, smoking cessation is not a recommended strategy to control BP.
- However, smoking is a major, independent, modifiable risk factor for CV disease. Patients with hypertension who smoke should be counseled regarding the additional health risks that result from smoking.
- Moreover, the potential benefits that smoking cessation can provide should be explained to encourage cessation.

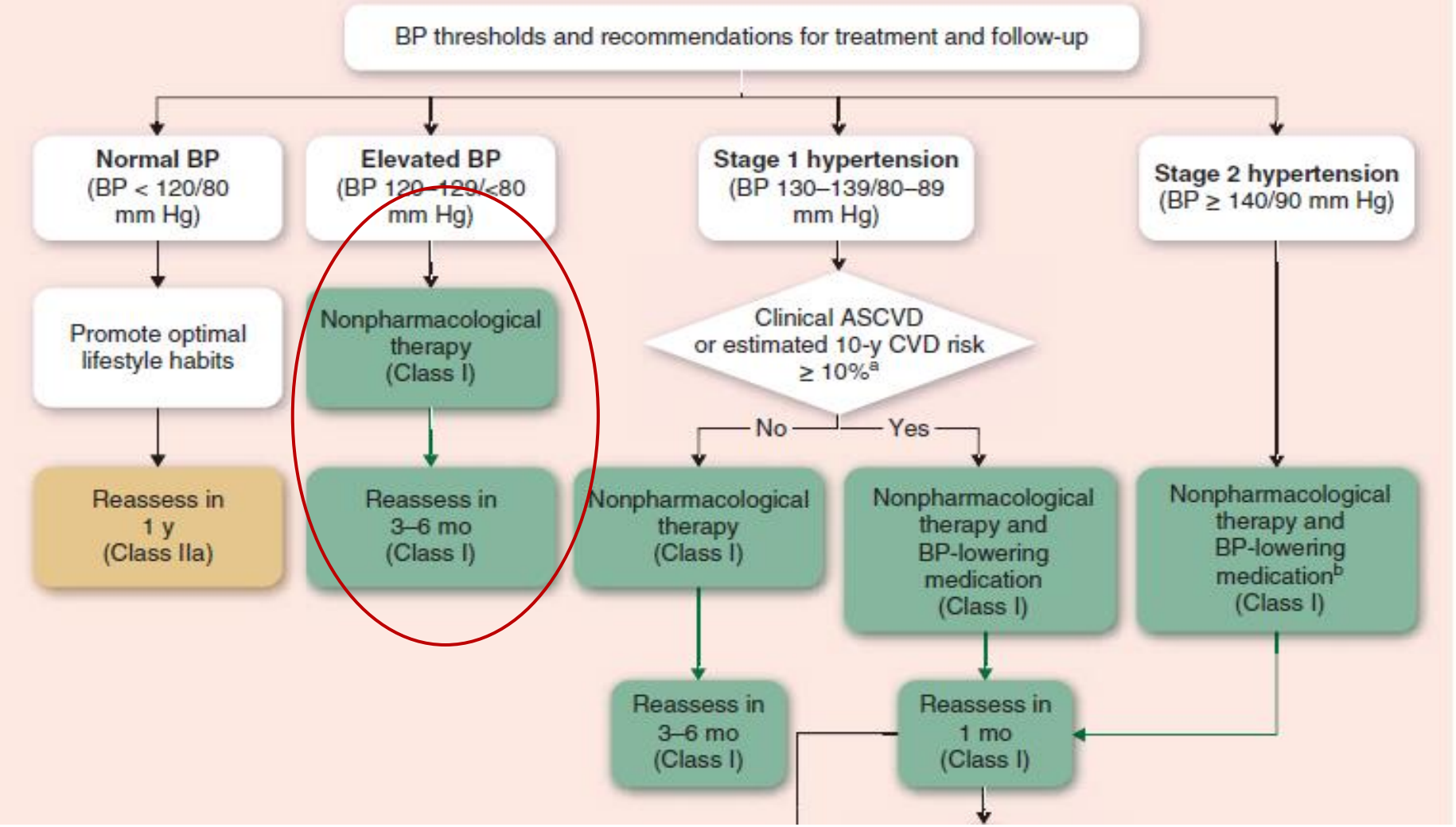
125/75

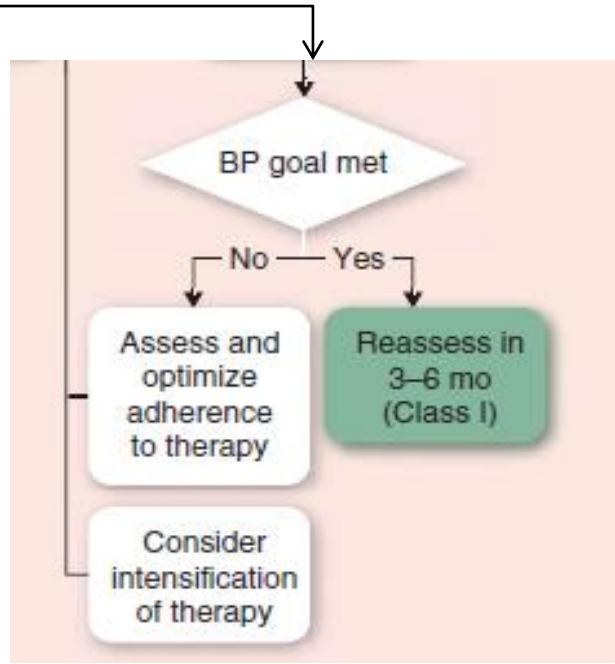
After 6 months of life style modification + Atorvastatin 20 mg daily

135/84

Lab data	
LDL	140
HDL	45
FBS	89
BMI	29

Lab data	
LDL	195
HDL	30
Cr	0.9
BMI	31



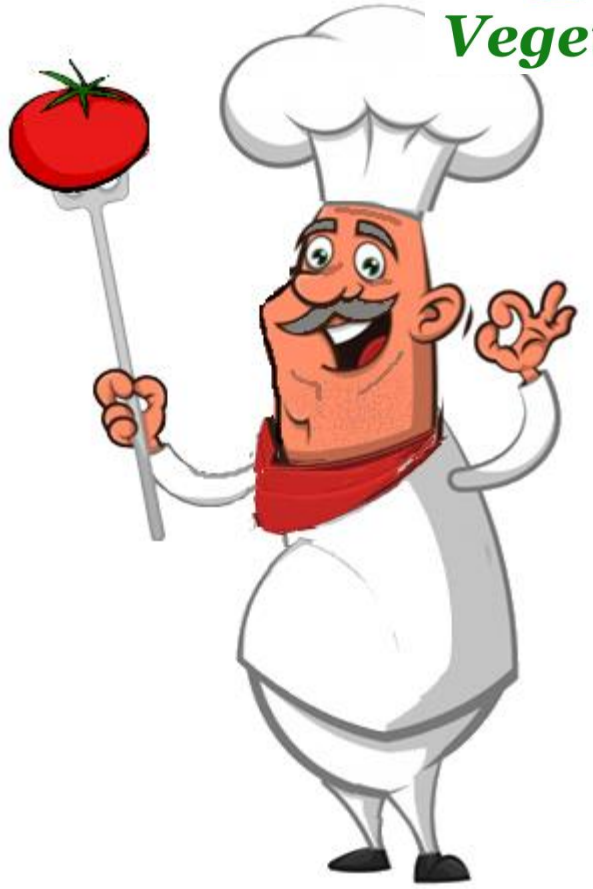


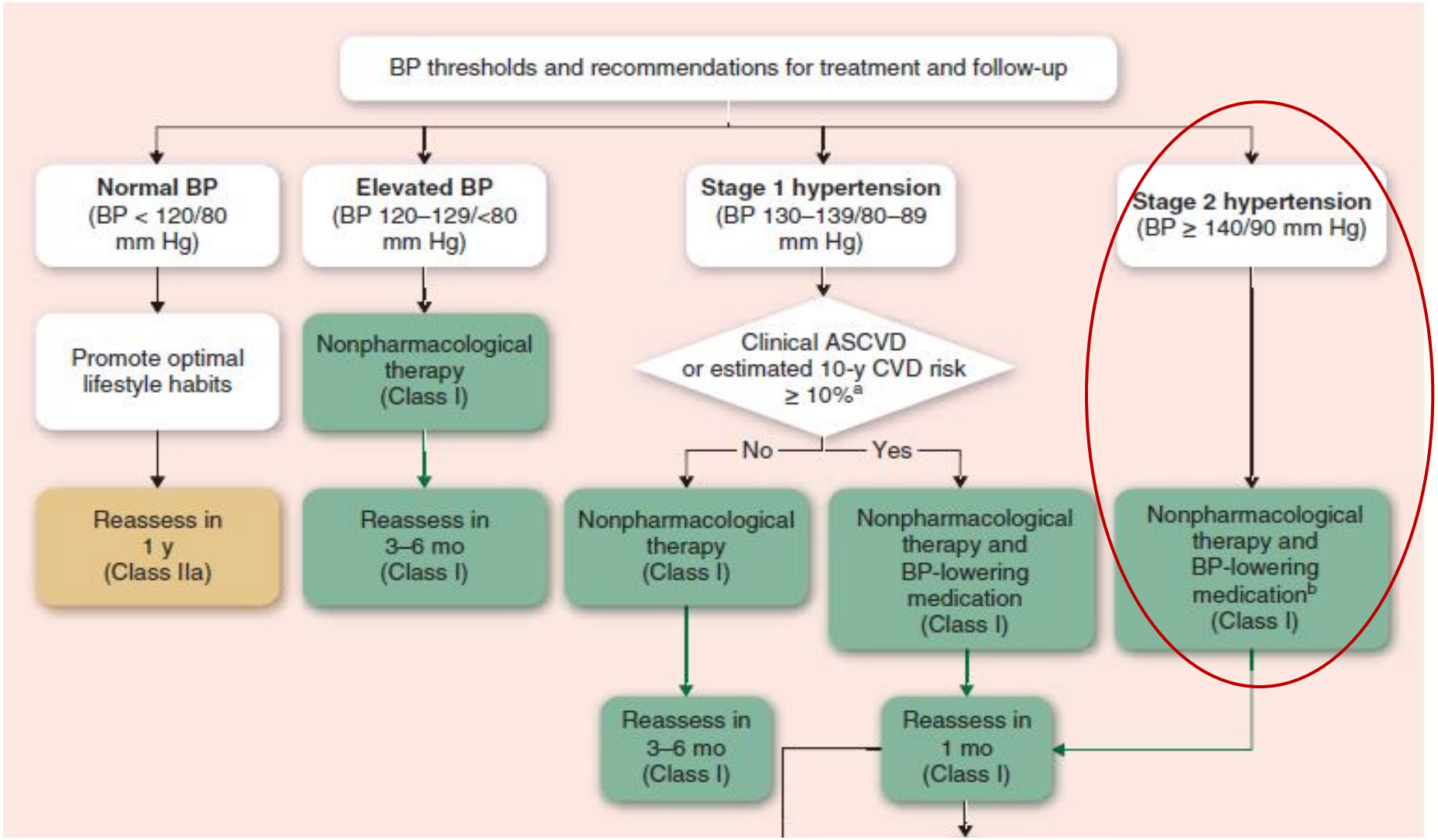
AHA/ACC 2017 HTN guideline

Case, 10 Years later

Mr. Taban
A 55 years old gentleman is your neighbor and friend
He is a vegetarian rsturant chef
Blood pressure: 150/85
He denied any symptoms, except some headaches
PMH: Dyslipidemia, goat
FH: Father (ACS at 60)
Drug/suppl: Atorvastatin 20 mg daily, Allopurinol 100 mg daily
BMI: 26

Lab data	
LDL	105
HDL	45
Cr	1
FBS	85
Uric acid	6




BP thresholds and recommendations for treatment and follow-up
Normal BP (BP < 120/80 mm Hg)
Elevated BP (BP 120–129/<80 mm Hg)
Stage 1 hypertension (BP 130–139/80–89 mm Hg)
Stage 2 hypertension (BP ≥ 140/90 mm Hg)
Promote optimal lifestyle habits
Nonpharmacological therapy (Class I)
Clinical ASCVD or estimated 10-y CVD risk ≥ 10%a
No
Yes
Reassess in 1 y (Class IIa)
Reassess in 3–6 mo (Class I)
Nonpharmacological therapy (Class I)
Nonpharmacological therapy and BP-lowering medication (Class I)
Nonpharmacological therapy and BP-lowering medicationb (Class I)
Reassess in 3–6 mo (Class I)
Reassess in 1 mo (Class I)

150/85

Treatment

The choice of initial antihypertensive drug therapy depends on the
degree of BP elevation
and
presence of compelling indications

1

A single first-line antihypertensive drug should be started as an initial therapy in most patients with newly diagnosed hypertension presenting with stage 1 hypertension.

2

Combination drug therapy, preferably with two first-line antihypertensive drugs, should be started as an initial therapy in patients with newly diagnosed hypertension presenting with more severe BP elevation (stage 2 hypertension).

AHA/ACC 2017 HTN guideline

Recommendations for Choice of Initial Monotherapy Versus Initial Combination Drug Therapy*		
COR	**LOE**	**Recommendations**
I	C-EO	1. Initiation of antihypertensive drug therapy with 2 first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 hypertension and an average BP more than 20/10 mm Hg above their BP target.
IIa	C-EO	2. Initiation of antihypertensive drug therapy with a single antihypertensive drug is reasonable in adults with stage 1 hypertension and BP goal <130/80 mm Hg with dosage titration and sequential addition of other agents to achieve the BP target.

International Society of Hypertension

Table 9. Ideal Characteristics of Drug Treatment

1.	Treatments should be evidence-based in relation to morbidity/mortality prevention.
2.	Use a once-daily regimen which provides 24-hour blood pressure control.
3.	Treatment should be affordable and/or cost-effective relative to other agents.
4.	Treatments should be well-tolerated.
5.	Evidence of benefits of use of the medication in populations to which it is to be applied.

Treatment/pharmacologic

- Overall, current clinical guidelines provide a reasonable basis for guiding the selection of drug classes for individuals based on their stage of hypertension, comorbidities, and special circumstances.

1st

ACEI

ARB

CCB

Thiazide

These agents should be used because of evidence demonstrating CV event reduction

1st

ACEI

OR

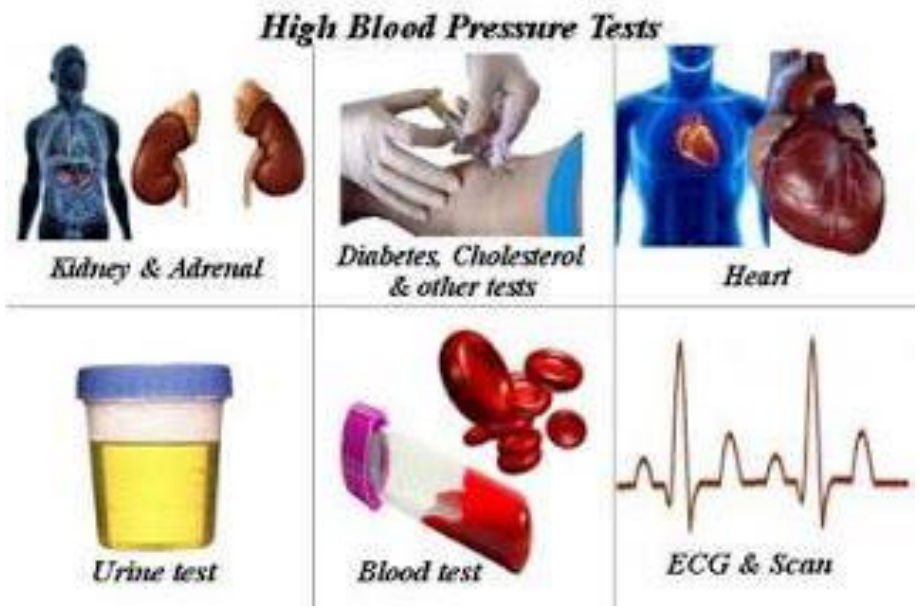
ARB

CCB

Thiazide

8.1.4. General Principles of Drug Therapy

Recommendation for General Principle of Drug Therapy References that support recommendations are summarized in Online Data Supplement 25.		
COR	**LOE**	**Recommendation**
III: Harm	A	1. Simultaneous use of an ACE inhibitor, ARB, and/or renin inhibitor is potentially harmful and is not recommended to treat adults with hypertension.[S8.1.4-1–S8.1.4-3]



Basic testing	Optimal Testing
FBS, Na, K, Ca	ECG
CBC, TSH	Uric acid
Lipid profile	Urinary albumin to creatinine ratio
Serum Cr, eGFR, UA	

Mr. Taban Lab data					
LDL	105	Na	138	WBC	8.5
HDL	45	K	4	Hgb	14.5
TG	160	Ca	8.5	Plt	200000
FBS	85	TSH	2		
Uric	6	Cr,	1		
Urine Pr	Neg.	eGFR	105		

Diuretics/ thiazides

Practical attributes of diuretics:

- Low cost
- Availability as combination agents
- Several years of experience
- Favorable outcome in clinical trials for select population

Thiazide diuretics are by far the most commonly prescribed with the greatest number of outcome-based studies supporting their use.
This type of diuretic inhibits the sodium-chloride symporter in the renal distal convoluted tubule thus increasing sodium and chloride excretion.

Contrary to the historical preference to use a thiazide as preferred for treating most patients with hypertension, they are simply one of four 1st-line options

Several recent analyses have demonstrated superiority of **chlorthalidone** over hydrochlorothiazide.
The 2017 ACC/AHA guidelines to specifically recommend chlorthalidone over other diuretics.

- Because the relationship between antihypertensive efficacy and metabolic/electrolyte-related side effects of thiazide diuretics is dose-related, attention to the differential in potency may be important.
- Metabolic effects (hyperlipidemia and hyperglycemia) and electrolyte-related effects (hypokalemia, hypomagnesemia, hyperuricemia, and hypercalcemia) increase with higher doses.
- Not exceed 25 to 50 mg/day of HCTZ **or** 25 mg/day of chlorthalidone

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	2.5–5	1	

AHA/ACC 2017 HTN guideline

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	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	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	2	

Calcium Channel Blockers

Dihydropyridine CCBs

- Nifedipine and **amlodipine**
- Has no utility for managing patients with atrial dysrhythmias but may be used safely (exception being nifedipine) in patients with reduced EF.
- Associated with edema (especially when used at higher doses)

Non-dihydropyridine CCBs

- Verapamil and diltiazem
- Electrophysiological effects, and negative chronotropic and inotropic effects.
- Block cardiac conduction through the AV node
- Management of patients with AF + Hypotension.
- Negative inotropic effects: should be avoided in HFrEF

All CCBs possess some coronary vasodilating properties
May be used in for the management of **angina**, plus their antihypertensive benefits.

Calcium Channel Blockers

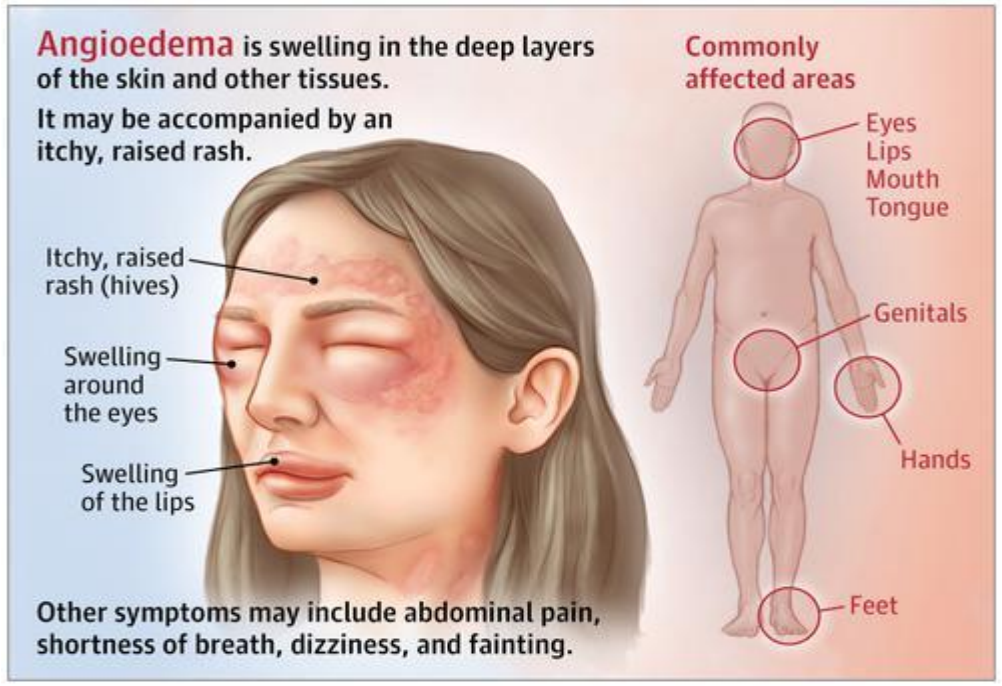
CCB—dihydropyridines	**Amlodipine**	2.5–10	1	• Avoid use in patients with HFrEF; amlodipine or felodipine may be used if required • Associated with dose-related pedal edema, which is more common in women than men
	Felodipine	2.5–10	1	
	Isradipine	5–10	2	
	Nicardipine SR	60–120	2	
	Nifedipine LA	30–90	1	
	Nisoldipine	17–34	1	

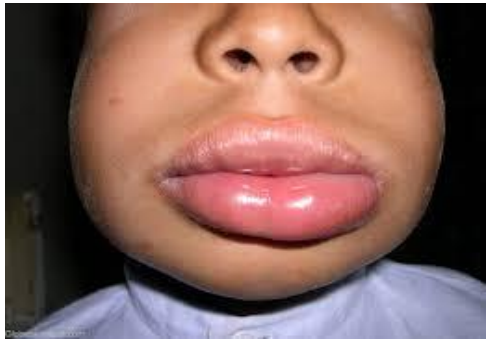
Calcium Channel Blockers

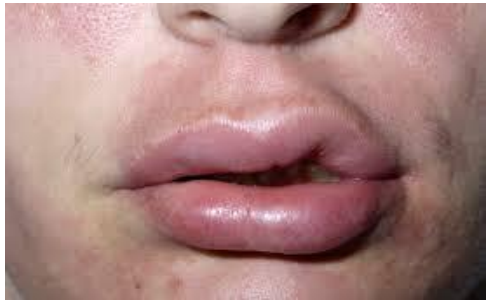
CCB–nondihydropyridines	**Diltiazem ER**	120–360	1
	Verapamil IR	120-360	3
	Verapamil SR	120–360	1 or 2
	Verapamil-delayed onset ER	100–300	1 (in the evening)

- 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)

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	2.5–20	1 or 2	
	Trandolapril	1–4	1	







- Patients with angioedema with an ACEi can receive an ARB 6 weeks after ACEi discontinuation.

JAMA, *DOI: 10.1001/jama.2018.4860*

ACE inhibitors

- ACE-Is have been **extensively studied for the treatment of hypertension**, and outcome-based trials **generally support their use for a wide array of patients.**
- These **compelling indications include their qualified role in managing patients with history of type 1 or 2 DM, HF, MI, CKD, or stroke.**.
- **ACE-Is represent appropriate choices as either first- or second-line hypertensive therapies that effectively achieve a target BP goal for most patients with or without comorbidities.**

Persistent dry cough	Caused by **accumulation of bradykinin** resulting from a direct effect of inhibiting angiotensin-converting enzyme. **If a cough jeopardizes compliance with the agent → ARB**

ACE inhibitors

AKI

- Particularly in patients with **hemodynamically significant bilateral renal artery stenosis** (or unilateral if one functioning kidney), **preexisting kidney dysfunction**, **blood dyscrasias, or angioedema.**
- Inhibition of angiotensin II synthesis through ACE inhibition (or direct blockage of the angiotensin II receptor by ARBs) **naturally would reduce the efferent renal artery tone, thereby changing the intra-glomerular pressure.**
- **Although changes in the afferent renal artery tone also occur, the overall effects usually produce a reduction in GFR with resulting decline in GFR of up to 30%.**
- Such reductions in GFR are not usually indications to discontinue use of the ACE-I; however, **continued monitoring for further decreases in GFR and consideration of dose reduction remain prudent.**
- **Alternatively, should declines in GFR exceed 30%, dose reduction or discontinuation is warranted until further evaluation can be made.**

Hyperkalemia

- Modest elevations in serum potassium (starting or increasing the dose)
- Compromised renal function, any concurrent NSAIDs, potassium supplements, or potassium-containing salt substitutes
- Hyperkalemia is rarely a reason for discontinuation of therapy
- Periodic monitoring of serum potassium

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	

ARB

- **While the pharmacologic differences between ARBs and ACE-Is are clear, the therapeutic relevance resulting from these differences remains ambiguous.**
- **Although better tolerated than ACE-Is, ARBs have not been shown to demonstrate superiority of outcomes relative to ACE-Is.**

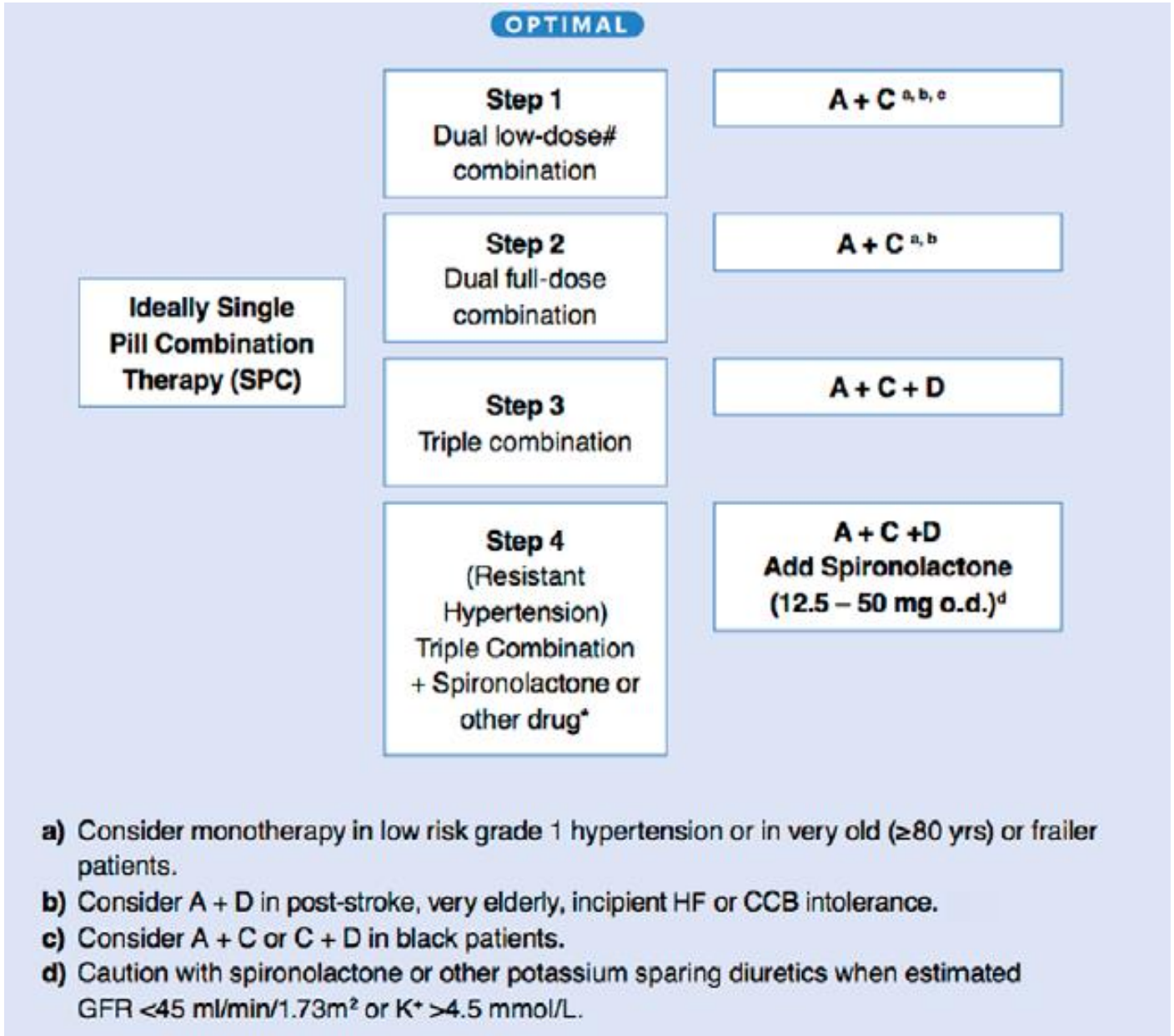
- Do not use if history of angioedema with ARBs.

- Patients with angioedema with and ACEi can receive an ARB 6 weeks after ACEi discontinuation.

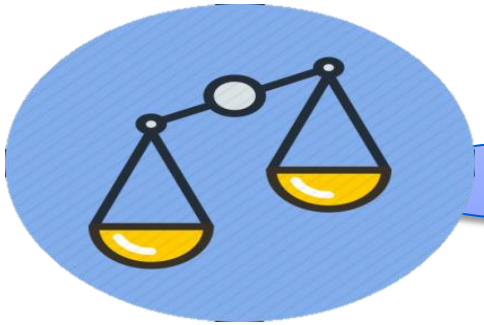
COR	LOE	Recommendations
I	C-EO	1. Initiation of antihypertensive drug therapy with 2 first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 hypertension and an average BP more than 20/10 mm Hg above their BP target.

American Society of HTN recommendation for Combination therapies

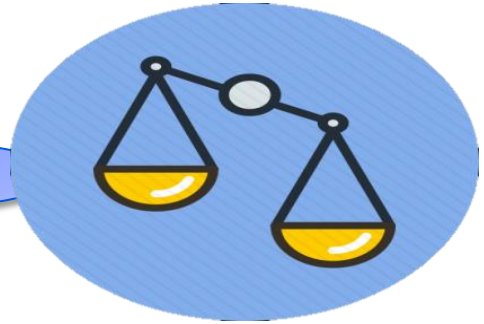
Preferred	Acceptable	Less effective
ACEi/CCB	β-blocker/thiazide	ACEi/β-blocker
ARB/CCB	CCB (dihydropyridine)/ β-blocker	ARB/β-blocker
ACEi/thiazide	CCB/thiazide	CCB (non-dihydropyridine) /β-blocker
ARB/thiazide	Thiazide/potassium sparing diuretic	Centrally acting agent/ β-blocker



International Society of Hypertension

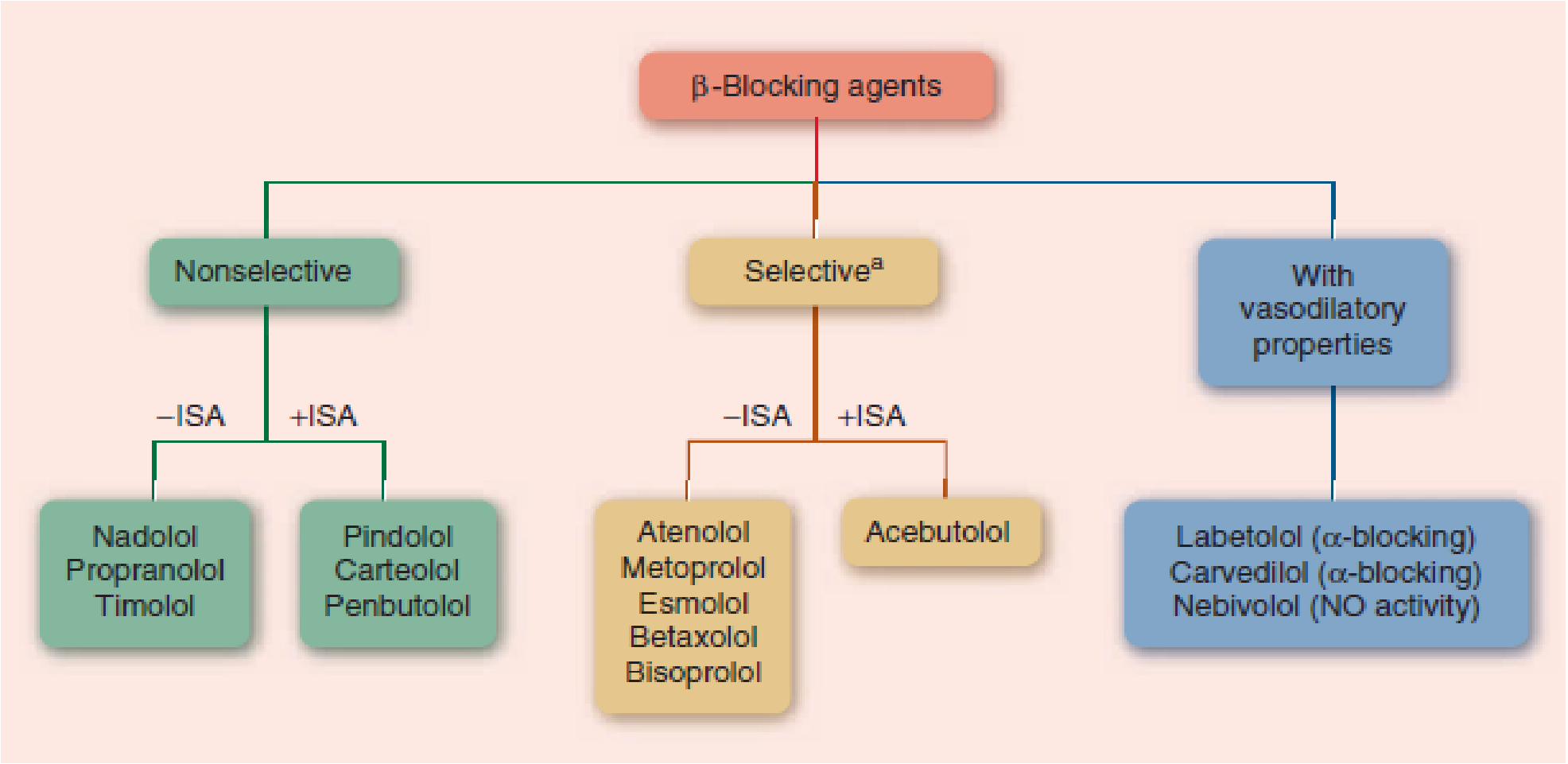


• β-Blocker Versus First-Line Agents



- Clinical trial data and meta-analyses cumulatively suggest that treatment with a **β-blocker may not reduce CV events to the extent that an ACEi, an ARB, a CCB, or particularly a thiazide does.**
- In the systematic review and network analysis conducted for the 2017 ACC/AHA guideline, β-**blockers were less effective for the prevention of stroke and CV events than diuretics.**
- **β-Blocker–based antihypertensive therapy does not increase the risk of CV events; β-blocker–based therapy reduces the risk of CV events compared with no antihypertensive therapy.**

Beta-Blockers



There are several compelling indications where specific antihypertensive drug classes have evidence showing unique benefits in patients with hypertension.

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.

AHA/ACC 2017 HTN guideline

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)

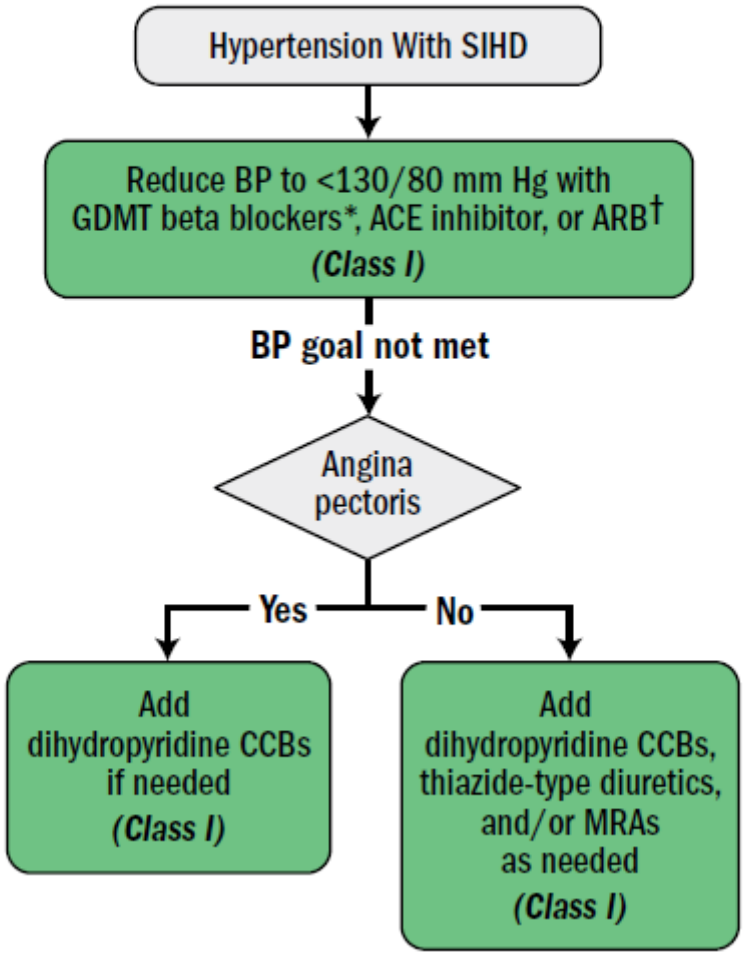
Referenced studies that support recommendations are summarized in online Data Supplement 35, 36

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 hepertension.
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.

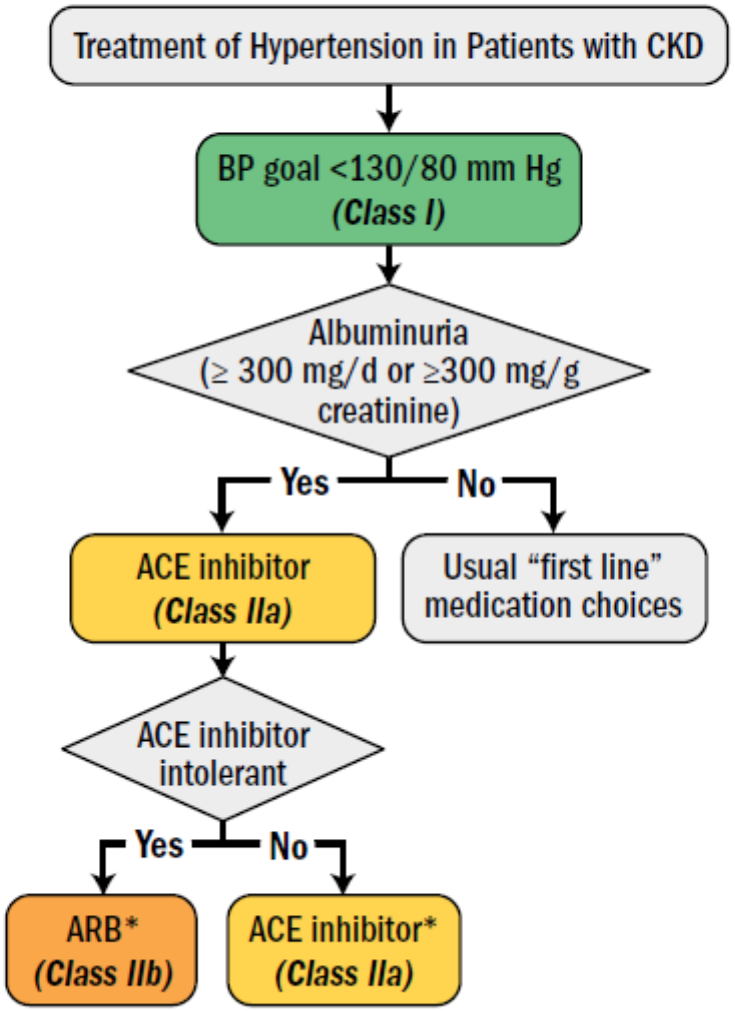
Diabetes Mellitus

Recommendations for Treatment of Hypertension in Patients With DM		
COR	**LOE**	**Recommendations**
I	SBP: B-R[SR] DBP: C-EO	1. In adults with DM and hypertension, antihypertensive drug treatment should be initiated at a BP of 130/80 mm Hg or higher with a treatment goal of less than 130/80 mm Hg.
I	A[SR]	2. In adults with DM and hypertension, all first-line classes of antihypertensive agents (i.e., diuretics, ACE inhibitors, ARBs, and CCBs) are useful and effective.
IIb	B-NR	3. In adults with DM and hypertension, ACE inhibitors or ARBs may be considered in the presence of albuminuria.

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



Management of Hypertension in Patients with Chronic Kidney Disease



*CKD stage 3 or higher or stage 1 or 2 with albuminuria

Beta-Blockers

- Use in diabetics is usually a complex decision: effects on insulin, glucose availability, and blocking the signs and symptoms of hypoglycemia against their potential for morbidity/mortality benefits for select candidates with comorbidities such as HFrEF.
- Beta-blockers, particularly non-selective (other than carvedilol, nebivolol), have a greater effect on glucose metabolism as well as other metabolic effects, and they should be used cautiously if at all with diuretics unless compelling indications exist for both.

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	

Beta blockers—cardioselective	**Atenolol**	25–100	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 tartrate	100–200	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	80–160	2	
	Propranolol LA	80–160	1	
Beta blockers—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	

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 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	

Side effects/ toxicity

•Laboratory monitoring: typically **4 weeks after starting a new agent or dose increase**, and then every **6 to 12** months in stable patients.

•Additional diseases specific monitoring might be needed depending on specific agents

•Patients treated with a MRAs should have K+ concentrations and kidney function assessed within 3 days of initiation and again at 1 week to detect potential hyperkalemia.

•The occurrence of an ADE may require dosage reduction or substitution with an alternative antihypertensive agent .

Side effects/ toxicity

TABLE 30-11 Routine Monitoring for Select Antihypertensive Agents

Class	Parameters
ACEi	BP; BUN/serum creatinine; serum potassium
ARB	BP; BUN/serum creatinine; serum potassium
β-Blocker	BP; heart rate
Calcium channel blocker	BP; heart rate
Mineralocorticoid receptor antagonist	BP; BUN/serum creatinine; serum potassium
Thiazide	BP; BUN/serum creatinine; serum electrolytes (potassium, magnesium, sodium); uric acid (for thiazides)

Disease Progression

•Patients should be monitored for signs and symptoms of HTN-associated complications.

•A careful history for ischemic chest pain (or pressure), palpitations, dizziness, dyspnea, orthopnea, headache, sudden change in vision, one-sided weakness, slurred speech, and loss of balance should be taken to determine the presence of CV and cerebrovascular disease.

•Funduscopic changes on eye exam, LVH on electrocardiogram, albuminuria, and changes in kidney function by calculating estimated GFR

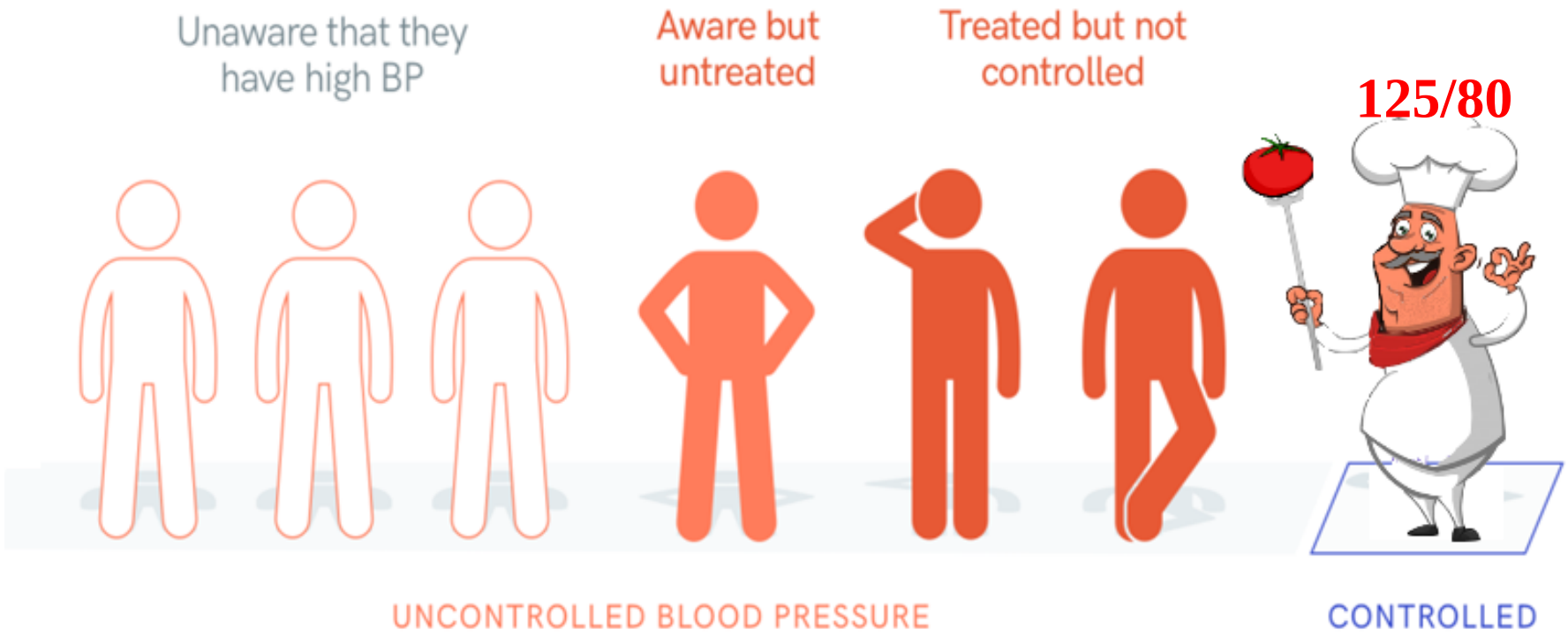
Periodic monitoring

Drugs don’t work in patients who don’t take them

- Talk with them, find the reason of non-compliance, don’t blame them, encourage them
- Simplify medications and therapy regimens
- Recommend the use of pill dispensers or reminders

Pharmacists help patients with hypertension

Studies show medical teams with pharmacists helped patients control blood pressure




Changes one small thing today and bigger changes will follow.