Pharmacotherapy 1

Hypertension

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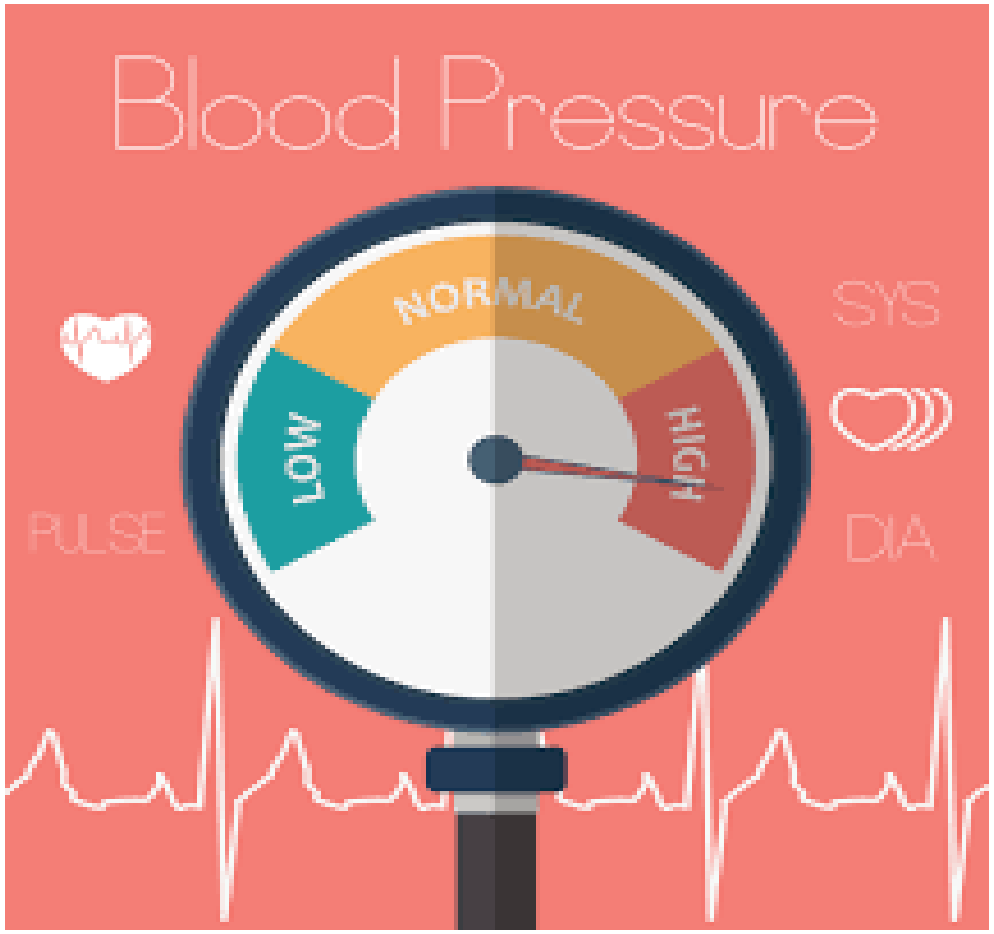
Topic outline:

- ✓ Definition
- ✓ Epidemiology
- ✓ Etiology
- ✓ Pathophysiology
- ✓ Clinical Presentation
- ✓ Diagnostic Considerations
- ✓ Treatment - Goals of Therapy
- ✓ Non-pharmacologic Therapy
- ✓ Pharmacotherapy
- ✓ Individual Antihypertensive Agents
- ✓ Compelling Indications
- ✓ Special Populations
- ✓ Team-Based Collaborative Care
- ✓ Monitoring the Pharmacotherapy Plan
- ✓ Resistant Hypertension
- ✓ Hypertensive Urgencies and Emergencies

Hypertension (HTN): sustained elevation of arterial blood pressure (BP)

- ✓ One of the most significant risk factors for cardiovascular (CV) disease.
- ✓ Screening, early detection, and control of hypertension → decreased risk of stroke, myocardial infarction (MI), and heart failure (HF)
- ✓ But in Jordan, preventive and interventional programs are limited and not well structured and organized with shortage of recent data on HTN prevalence, awareness, control, and its risk factors



➢ Epidemiology

Prevalence:

- ✓ Almost one-third of Jordanian adults have hypertension (33.8% among men and 29.4% among women-2017 study)
- ✓ An overall estimated prevalence of hypertension in adults in Arab countries is 29.5%.
- ✓ An overall worldwide hypertension prevalence of 26% in the adult population

Awareness rate:

- ✓ 57.7% of men and 62.5% of women are aware of hypertension in Jordan (2017 study, was 39.8% and 51.8%, respectively, in 2009)
- ✓ varied from 18% to 79.8% with an overall rate of 46% in Arab countries
- ✓ 25 to 75% worldwide (almost half to two-thirds of patients in developed countries)

➢ Epidemiology

Controlled HTN:

- ✓ Almost one-third (30.7% of men and 35.1% of women) of Jordanian adults on antihypertensive medications (% were 17.4% and 18.6%, respectively, in 2009) - possible reasons for the poor HTN control in Jordan:
  - inadequate management of hypertension,
  - not using evidence-based practices, and
  - poor adherence to medication.
- ✓ Patients in Jordan aged ≥50 years were more likely to have hypertension, to be aware of the disease and to have better control compared to younger patients.
- ✓ In Arab countries: 8% to 44%.
- ✓ The low control rate was also seen in USA and European countries.

➢ Epidemiology

Complications:

- ✓ The complications of hypertension account for 9.4 million deaths worldwide/yr
- ✓ It is estimated that up to 1.58 billion adults will suffer from complications of hypertension by 2025, worldwide.
- ✓ Approximately one in three adult (age 20 years or older) Americans have elevated BP.
- ✓ Among hypertensive patients, 54.1% are at their goal BP, 76.5% are treated, and 82.7% are aware they have hypertension.
- ✓ The overall incidence is similar between men and women.

Table 1: Number of deaths from selected causes by age groups: Jordan MoH, 2009

Cause of death	Under 1 year	1-4 years	5-14 years	15-24 years	25-44 years	45-64 years	65 years and over	Not stated	Total
Diseases of the circulatory system (I00-I99)	**5**	**12**	**8**	**25**	**231**	**1343**	**3675**	**19**	**5318**
Acute rheumatic fever and chronic rheumatic heart diseases (I00-I09)	0	0	0	1	0	0	5	0	6
Hypertensive diseases (I10-I15)	0	1	1	1	24	219	771	6	1023
Ischaemic heart diseases (I20-I25)	2	0	1	9	126	643	1218	10	2009
Acute myocardial infarction (I21-I22)	1	0	1	5	93	416	715	6	1237
Other ischaemic heart diseases (I20,I23-I25)	1	0	0	4	33	227	503	4	772
Pulmonary heart disease and disease of pulmonary circulation (I26-I28)	0	0	0	3	16	30	81	0	130
Heart failure (I50)	2	7	2	3	15	95	330	3	457
Other forms of heart disease (I30-I49,I51)	1	3	0	3	15	24	32	0	78
Cerebrovascular diseases (I60-I69)	0	1	3	5	24	314	1197	0	1544
Atherosclerosis (I70)	0	0	0	0	1	2	9	0	12
Aortic aneurysm and dissection and other aneurysms (I71-I72)	0	0	0	0	6	8	17	0	31
Other diseases of the circulatory system (I73-I99)	0	0	1	0	4	8	15	0	28

➢ Etiology

Essential (or primary) HTN

- ✓ Over 90% of individuals with high BP have essential HTN
- ✓ HTN results from unknown pathophysiologic etiology (cannot be cured, can be controlled)
- ✓ Genetic factors may play a role in the development of essential HTN

Secondary HTN

- ✓ Less than 10% of patients - either a comorbid disease or a drug (or other product) is responsible for elevating BP (Table 2)
- ✓ Patients have a specific cause of their HTN → can be cured
- ✓ Removing the offending agent (when feasible) or treating/correcting the underlying comorbid condition should be the first step in management

Table 33-1: Secondary causes of hypertension

Diseases	Chronic kidney disease, Cushing's syndrome, Coarctation of the aorta, Obstructive sleep apnea, Parathyroid disease, Pheochromocytoma, Primary aldosteronism, Renovascular disease, Thyroid disease
Drugs associated with hypertension (For some patients, the addition of these agents can be the cause of elevated BP or can exacerbate underlying hypertension. Identifying a ***temporal relationship*** between starting the suspected agent and developing elevated BP is most suggestive of drug-induced BP elevation).	Amphetamines, Corticosteroids (cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone), Calcineurin inhibitors (cyclosporine, tacrolimus), Decongestants (pseudoephedrine, phenylephrine), Ergot alkaloids (bromocriptine, dihydroergotamine, methysergide), Erythropoiesis-stimulating agents (erythropoietin, darbepoetin), Estrogen-containing oral contraceptives, Nonsteroidal anti-inflammatory drugs-cyclooxygenase-2 selective (celecoxib) and nonselective, Others: desvenlafaxine, venlafaxine, bupropion

Table 2: Secondary causes of hypertension

Situations related to drug use	β-blocker or centrally acting α-agonists (when abruptly discontinued), β-blocker without α-blocker first when treating pheochromocytoma, use of a monoamine oxidase inhibitor (isocarboxazid, phenelzine, tranylcypromine) with tyramine-containing foods or certain drugs
Street drugs and other products	Cocaine and cocaine withdrawal, Ephedra alkaloids, Nicotine and withdrawal, anabolic steroids, narcotic withdrawal, ergot-containing herbal products, St. John's wort
Food substances	Sodium, Ethanol, Licorice

➢ Pathophysiology

Arterial BP

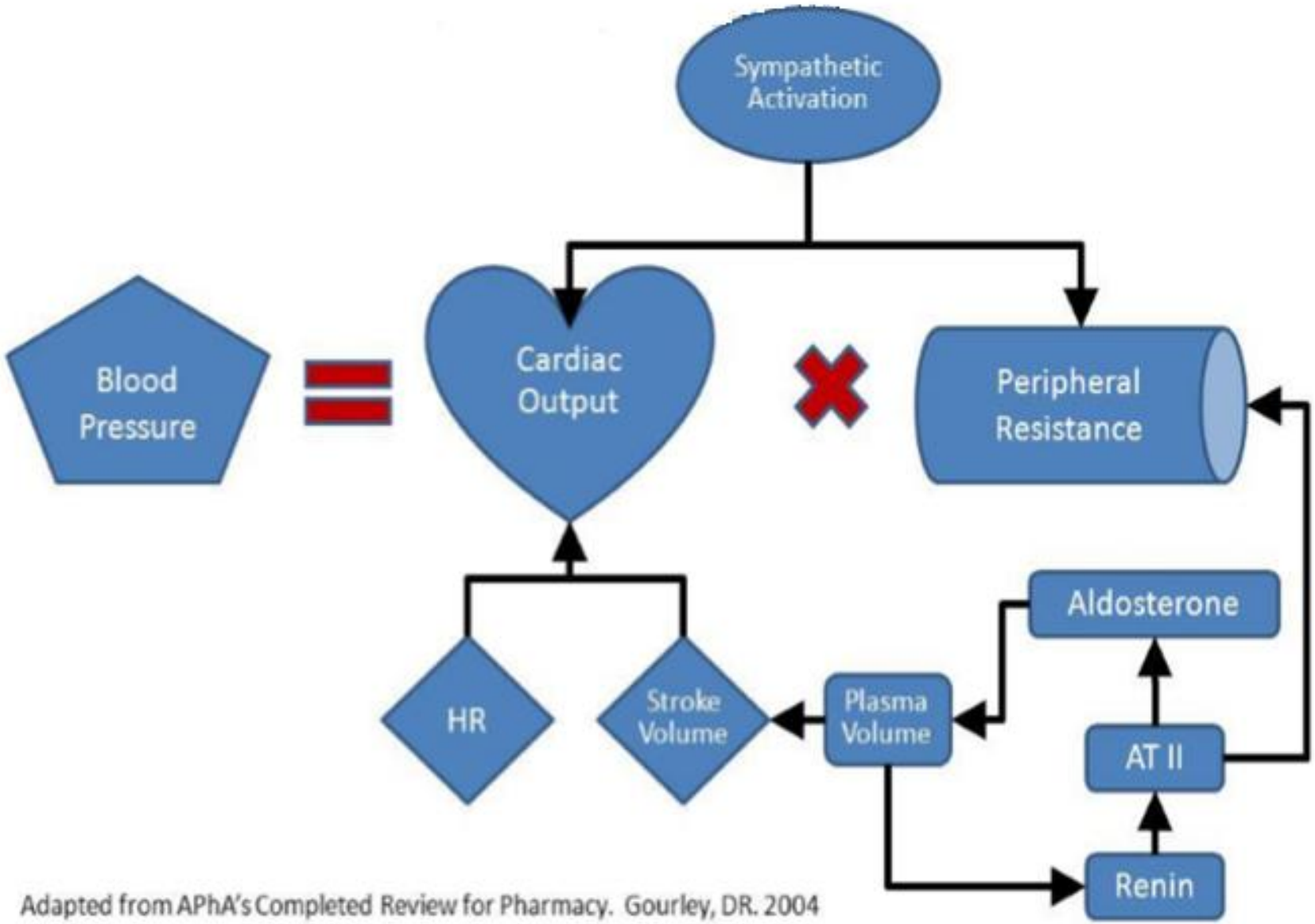
- ✓ Arterial BP is the pressure in the arterial wall measured in mm Hg.
- ✓ Two arterial BP values: systolic BP (SBP) and diastolic BP (DBP)
- ✓ SBP represents the peak value, which is achieved during cardiac contraction.
- ✓ DBP is achieved after contraction when the cardiac chambers are filling, and represents the minimum value.
- ✓ Mean arterial pressure (MAP) is the average pressure throughout the cardiac cycle of contraction. It is sometimes used clinically to 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, the MAP is calculated by using the following equation:

$$MAP = (SBP \times 1/3) + (DBP \times 2/3)$$

- ✓ Arterial BP is mathematically defined as the product of cardiac output (CO) and total peripheral resistance (TPR) according to the following equation:

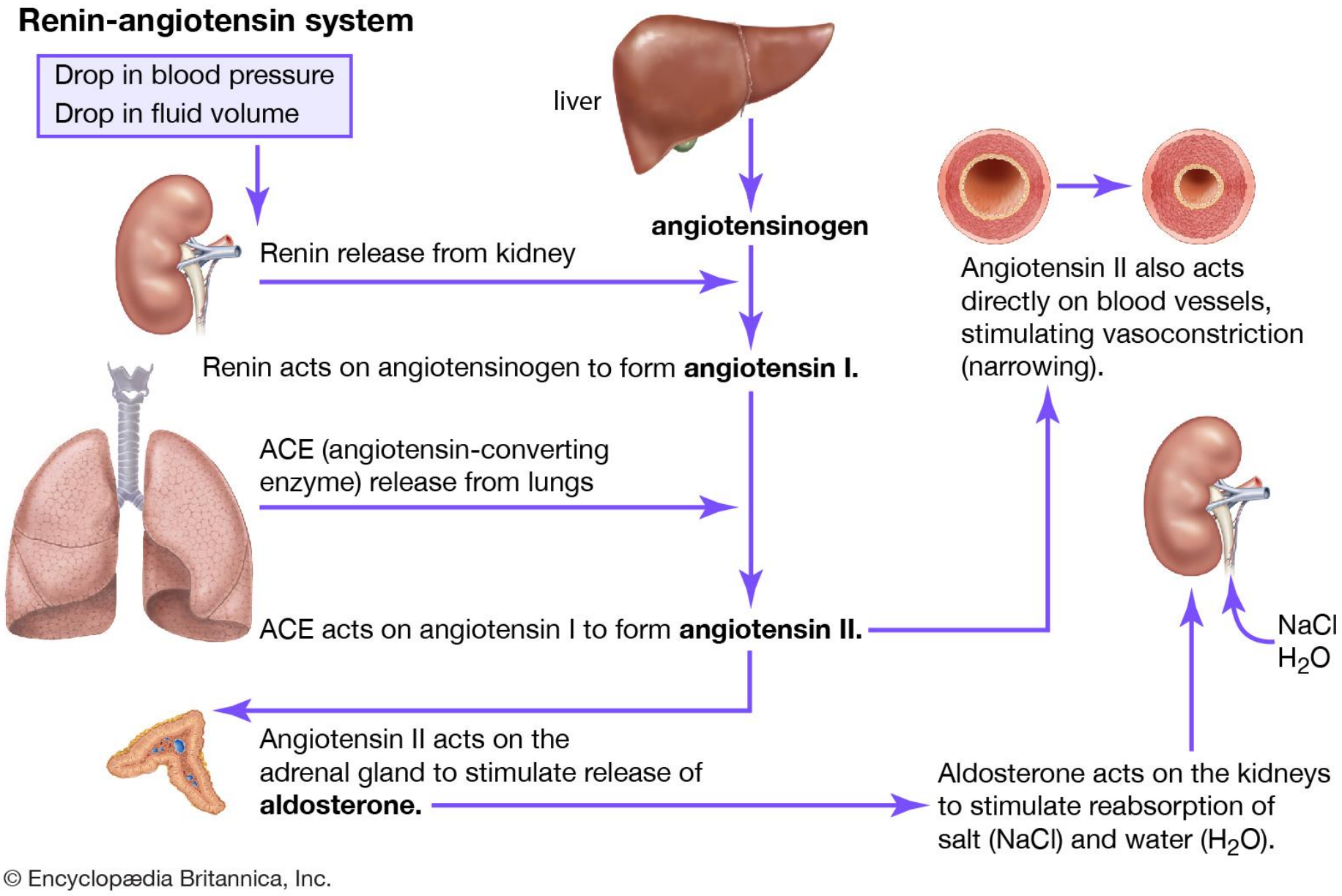
$$BP = CO \times TPR$$

- ✓ CO is the major determinant of SBP, whereas TPR largely determines DBP.
- ✓ CO is a function of stroke volume, heart rate (HR), and venous capacitance.
- ✓ An increase in CO normally results in a compensatory decrease in TPR; likewise, an increase in TPR results in a decrease in CO.

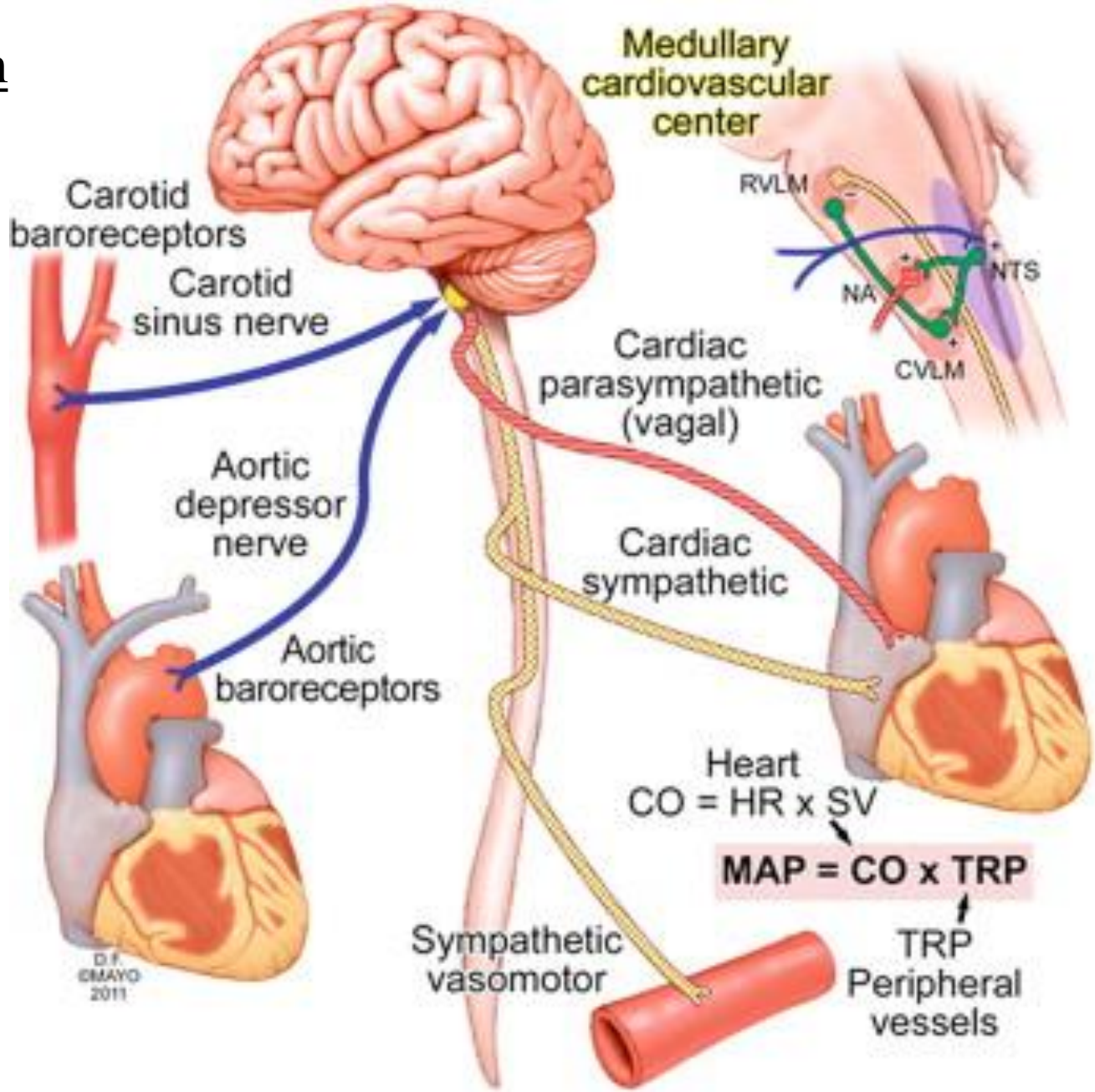


Adapted from APhA's Completed Review for Pharmacy. Gourley, DR. 2004

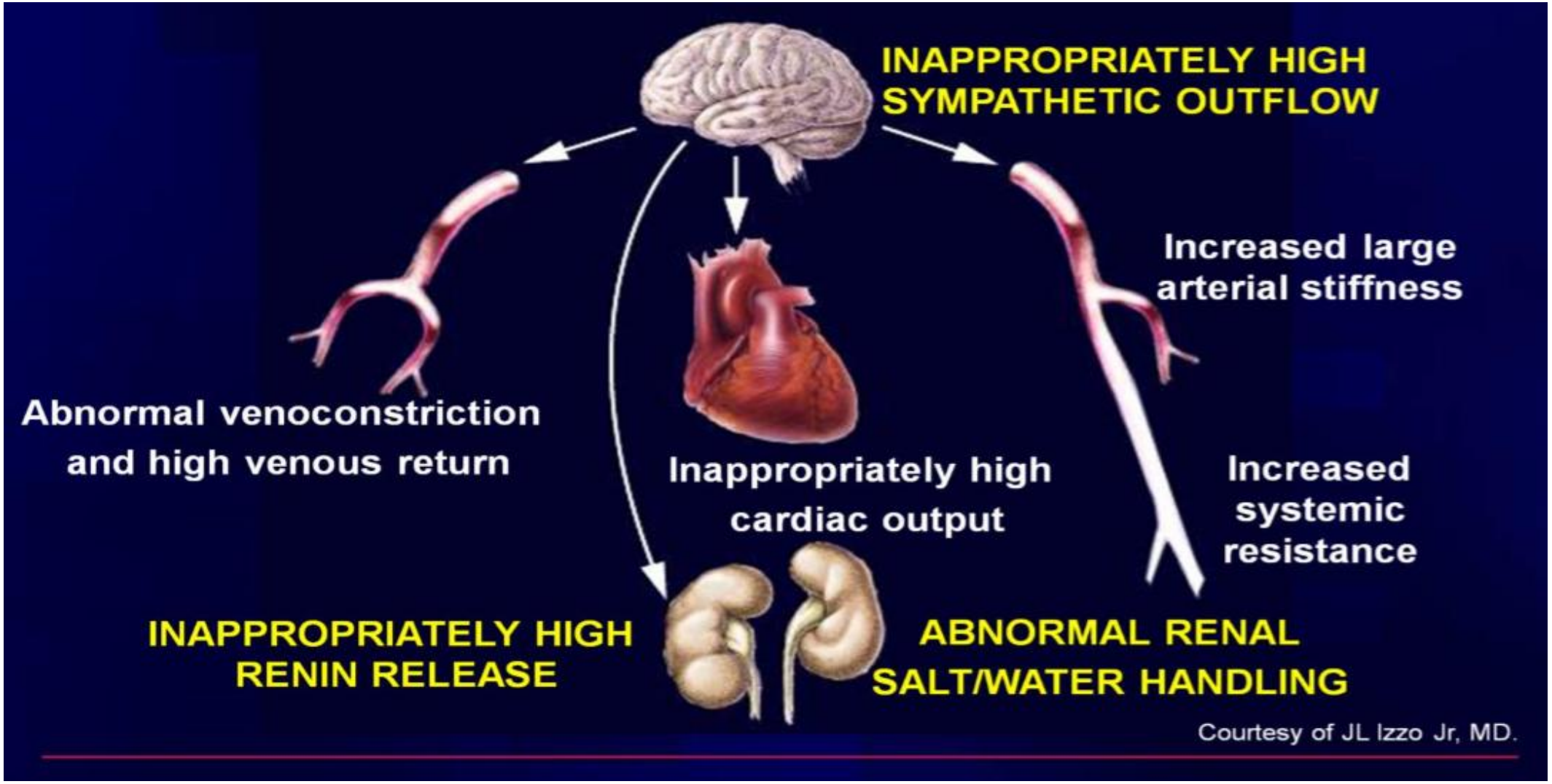
Hormonal Regulation



Neuronal Regulation



Different systems are physiologically interrelated. A defect in one component (pathologic disturbances) may alter normal function in another. Therefore, cumulative abnormalities may explain the development of essential hypertension.



➢ Clinical Presentation

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

- Age (greater than or equal to 55 years for men, greater than or equal to 65 years for women)
- Diabetes (type 1 or type 2)
- Dyslipidemia
- Albuminuria
- Family history of premature CV disease
- Overweight (BMI 25-29.9 kg/m^2) or Obesity (BMI ≥30 kg/m^2)
- Physical inactivity
- Tobacco use

Symptoms: usually none related to elevated BP.

Signs: previously elevated BP values.

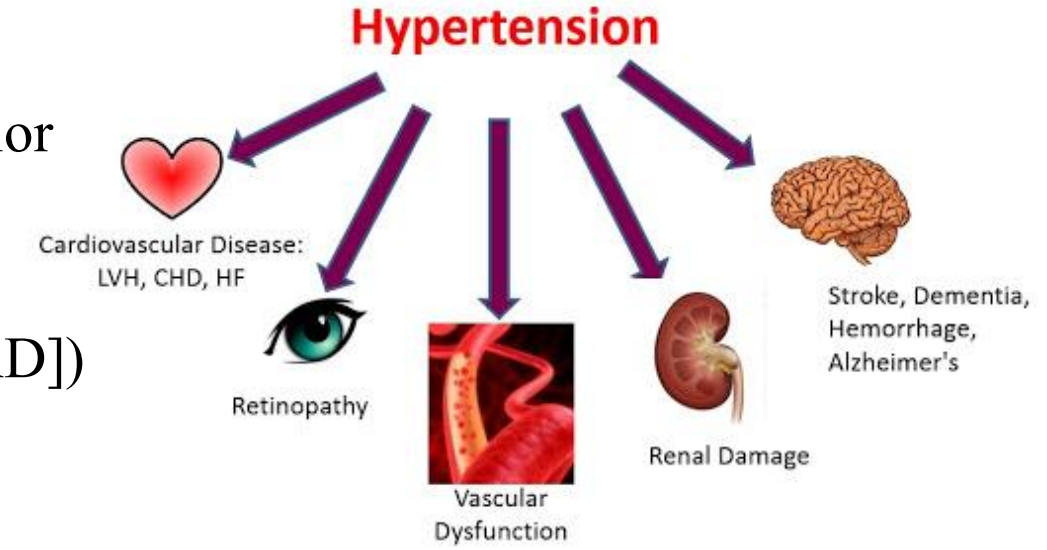
Routine laboratory tests: BUN, serum creatinine, fasting lipid panel, fasting blood glucose, serum electrolytes (sodium, potassium), hemoglobin and hematocrit, and spot urine albumin-to-creatinine ratio.

May have normal values and still have hypertension.

Abnormal values consistent with either additional CV risk factors or hypertension-related damage.

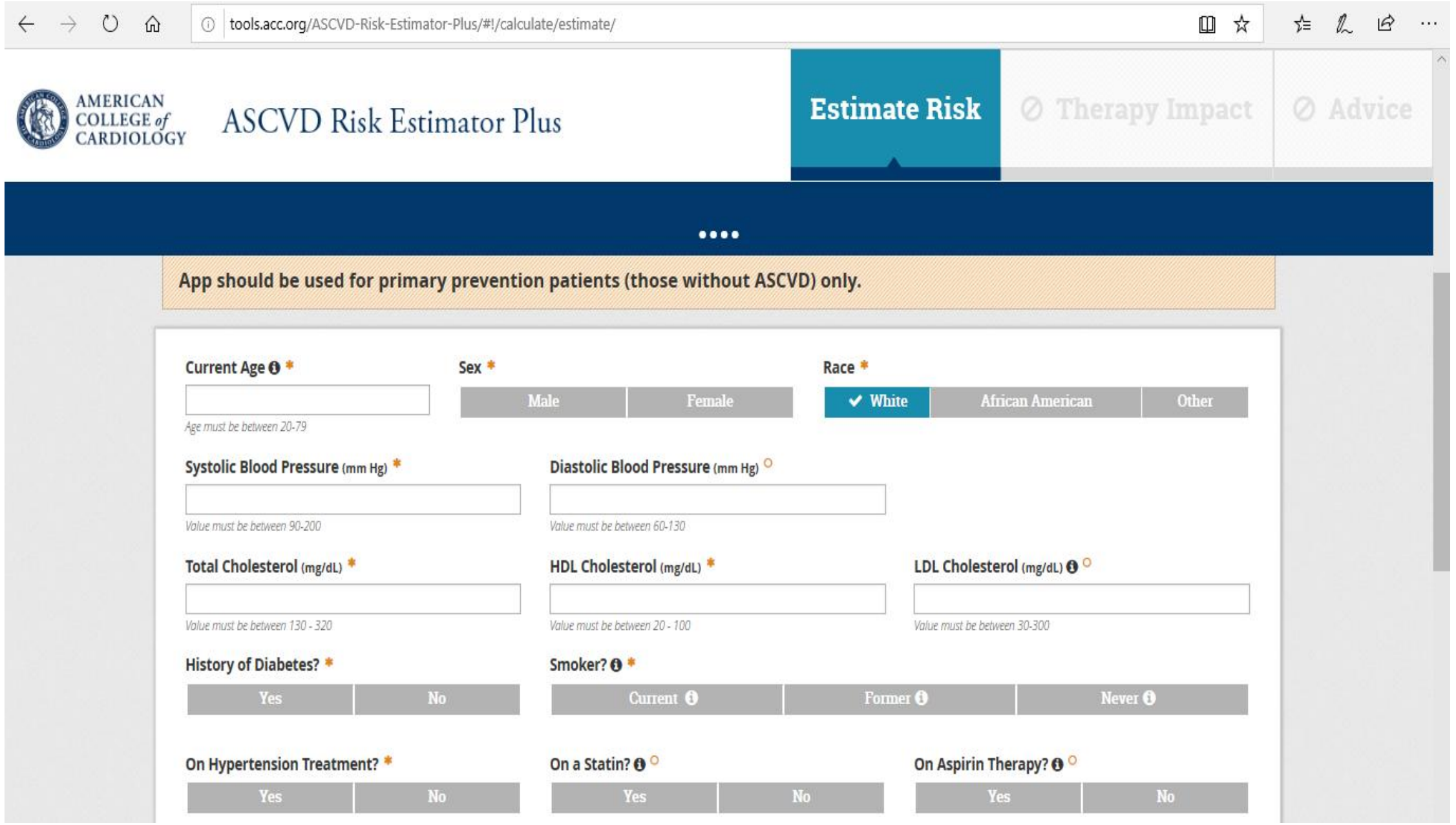
Hypertension-related complications: (PMH or diagnostic findings)

- Brain (stroke, transient ischemic attack, dementia)
- Eyes (retinopathy)
- Heart (left ventricular hypertrophy [LVH], angina, prior MI, prior coronary revascularization, HF)
- Kidney (chronic kidney disease [CKD])
- Peripheral vasculature (peripheral arterial disease [PAD])

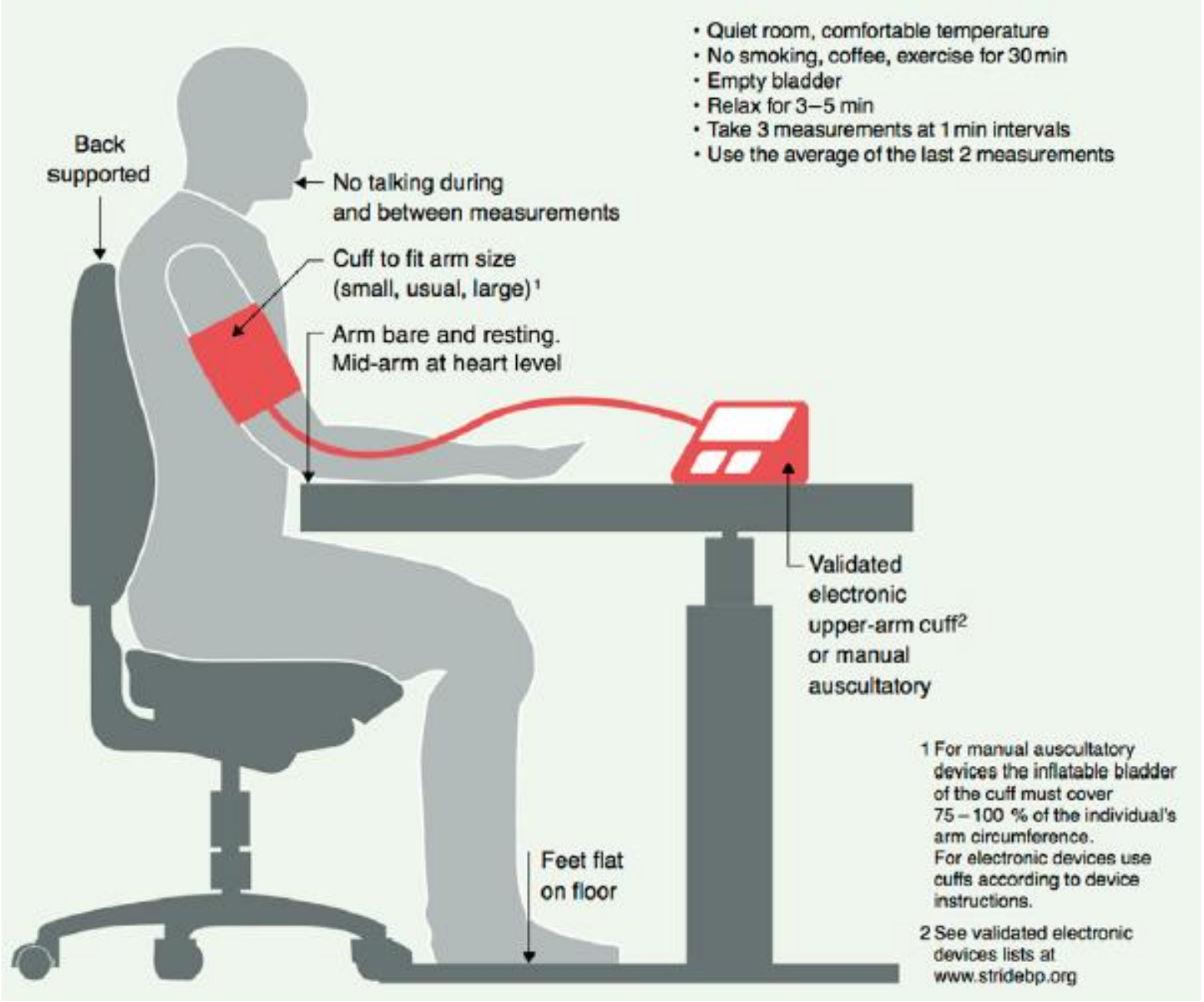


➢ Diagnostic considerations

- ✓ Hypertension is called the silent killer because most patients do not have symptoms.
- ✓ The primary physical finding is elevated BP.
- ✓ The diagnosis of hypertension cannot be made based on only one elevated BP measurement.
- ✓ The average of two or more measurements taken during two or more clinical encounters is required to diagnose hypertension.
- ✓ Outside of clinical setting measurements (ambulatory and self-BP monitoring) are recommended for diagnostic confirmation before starting antihypertensive therapy.
- ✓ For patients without a history of CAD, noncoronary atherosclerotic vascular disease (ASCVD), LV dysfunction, or DM, it is also important to estimate future risk of CV disease and clinical ASCVD.
- ✓ The 10-year risk of clinical ASCVD (defined as coronary death or nonfatal MI, or fatal or nonfatal stroke) can be found at: http://tools.acc.org/ASCVD-Risk-Estimator/


tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/
AMERICAN COLLEGE of CARDIOLOGY
ASCVD Risk Estimator Plus
Estimate Risk
Therapy Impact
Advice
App should be used for primary prevention patients (those without ASCVD) only.
Current Age *
Age must be between 20-79
Sex *
Male
Female
Race *
White
African American
Other
Systolic Blood Pressure (mm Hg) *
Value must be between 90-200
Diastolic Blood Pressure (mm Hg)
Value must be between 60-130
Total Cholesterol (mg/dL) *
Value must be between 130 - 320
HDL Cholesterol (mg/dL) *
Value must be between 20 - 100
LDL Cholesterol (mg/dL)
Value must be between 30-300
History of Diabetes? *
Yes
No
Smoker? *
Current
Former
Never
On Hypertension Treatment? *
Yes
No
On a Statin?
Yes
No
On Aspirin Therapy?
Yes
No

How to measure BP



✓ Inaccuracies with the manual BP measurements result from:

1. Inherent biologic variability of BP (environmental temperature, the time of day, meals, physical activity, posture, alcohol, nicotine, and emotions)
2. Inaccuracies related to suboptimal technique
3. The white coat effect (~15% to 20% of patients): BP values rise in a clinical setting but return to normal in nonclinical environments using home or ambulatory BP (ABP) measurements.
4. Masked hypertension: a decrease in BP occurs in the clinical setting (home BP is hypertensive, while the in-office BP is normotensive or substantially lower than that at home) - may lead to under treatment or lack of treatment for hypertension.
5. Variations between individuals measuring BP due to differences in hearing or technique

- ✓ In the clinic setting, standard BP measurement procedures (eg, appropriate rest period, correct technique, correct cuff size) are often not followed, which results in poor estimation of true BP.
- ✓ Due to various human factors related to manual measurements of BP, use of oscillometric devices is generally preferred.

➢ Natural Course of Disease

- ✓ Essential hypertension is usually preceded by *elevated* BP values.
- ✓ BP values may *fluctuate* between elevated and normal levels for a period.
- ✓ As the disease progresses, BP elevation becomes *chronic*.
- ✓ Hypertension-associated *complications*

➢ Treatment

<u>Overall goal of treatment:</u>
reduce associated morbidity and mortality from CV events (eg, coronary events, cerebrovascular events, HF, kidney disease).

The specific selection of antihypertensive drug therapy should be based on evidence demonstrating CV event reduction.

Surrogate target* (BP goals):

- ✓ Treating patients to achieve a desired target BP value is a surrogate goal of therapy.
- ✓ Reducing BP to goal is associated with a lower risk of hypertension-associated complications.
- ✓ Targeting a goal BP value is how clinicians evaluate response to therapy.
- ✓ It is the primary method used to determine the need for titration and regimen modification.

*: a laboratory measurement or physical sign used in therapeutic trials as a direct measure of how a patient feels, functions, or survives and is expected to predict the effect of the therapy.

Desired Outcomes: Goal BP for Chronic Treatment

Most patients (including patients with clinical ASCVD [secondary prevention], diabetes, or CKD; primary prevention patients regardless of 10-year ASCVD risk score):

- <130/80 mm Hg

Older ambulatory, community dwelling patients:

- SBP <130 mm Hg

Institutionalized older patients, those with high disease burden and comorbidities, or limited life-expectancy:

- Consider a relaxed SBP goal of at least <150 mm Hg; <140 mm Hg in some patients if tolerated
- Use a team-based decision process weighing patient preferences, risks, and benefits

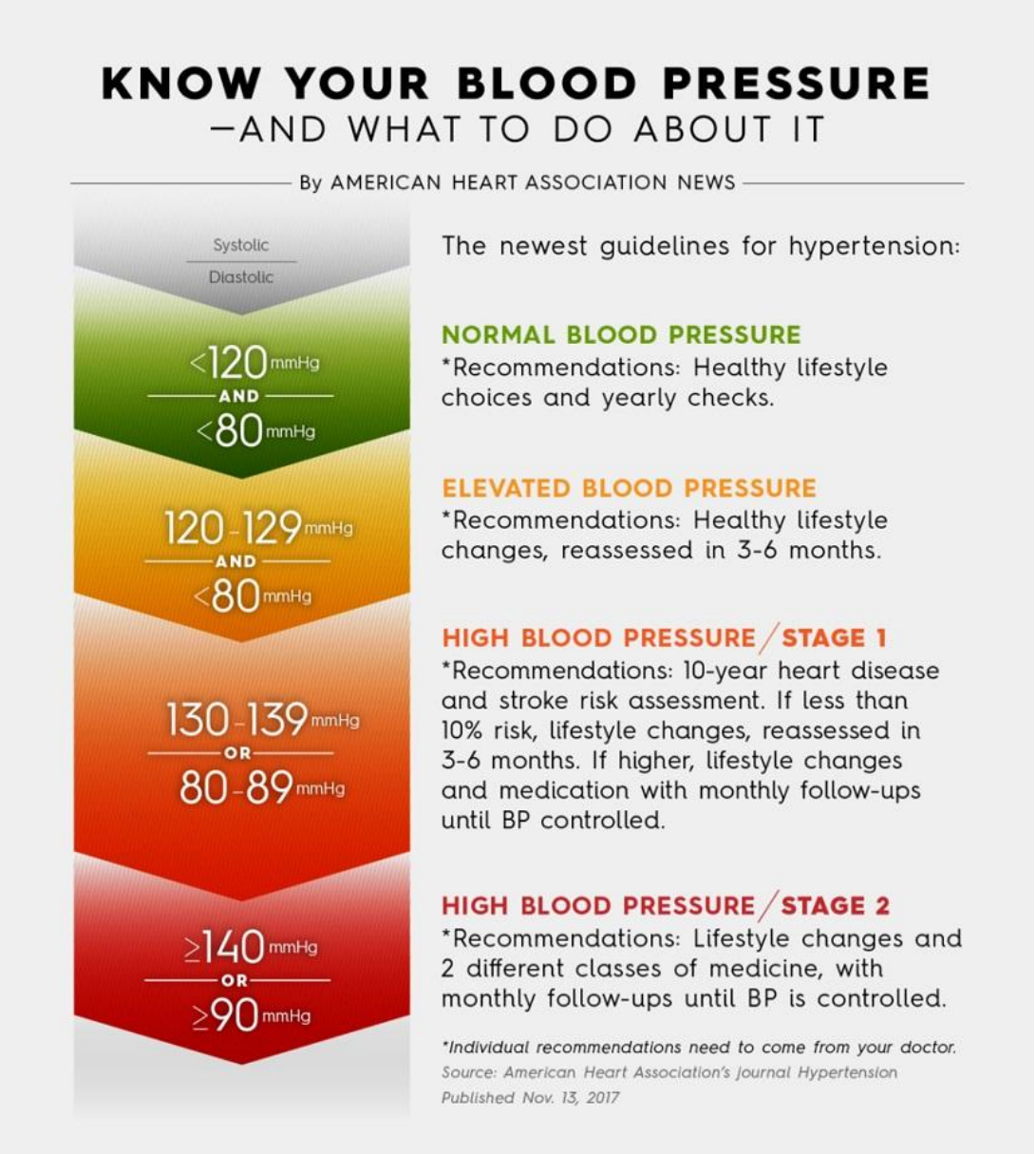
Updated slide

Classification of Blood Pressure in Adults (Age ≥18 Years)[a]

a: Classification is determined based on the average of two or more properly measured seated BP values from two or more clinical encounters.

Out-of-office measurements should be used to confirm the diagnosis.

If SBP and DBP values yield different classifications, the highest category is used for the purpose of determining a classification.



➢ Nonpharmacologic Therapy

- ✓ They should never be used as a replacement for antihypertensive drug therapy for patients who are not at goal BP, especially in those with additional CV risk factors or hypertension-associated complications.

- ✓ They can provide small to moderate reductions in SBP.

Lifestyle modifications to prevent & manage HTN with approximate SBP reduction (**mm Hg**)*

- Weight loss: BMI=18.5-24.9 kg/m^2 ---**5-20**/10-kg weight loss
- DASH-type dietary patterns: diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat -----**8-14**
- Reduced salt intake: 1.5 g/day sodium, or 3.8 g/day sodium chloride -----**2-8**
- Aerobic physical activity: 3-4 sessions/wk,~ 40 min/session------**4-9**
- Moderation of alcohol intake: ≤2 drink equivalents/day in men & ≤1 drink equivalent/day in women and lighter weight persons** -----**2-4**

*: Effects of implementing these modifications are time- and dose-dependent and could be greater for some patients.

**: One drink equivalent is equal to approximately 45 mL of 80-proof distilled spirits (eg, whiskey), an approximately 150 mL glass of wine (12%), or approximately 350 mL of beer.

Cigarette smoking

- ✓ Smoking is a major modifiable risk factor for CV disease.
- ✓ Hypertensive smokers should be counselled regarding the additional health risks that result from smoking.
- ✓ The potential benefits that cessation can provide should be explained to encourage cessation.

General approach to treatment

- ✓ All patients should be placed on lifestyle modifications after a diagnosis of hypertension.
- ✓ Lifestyle modification alone is appropriate for patients with elevated BP.
- ✓ Patients with additional CV risk factors or those with hypertension-associated complications will typically need antihypertensive drug therapy in addition to lifestyle modifications.
- ✓ The choice of initial antihypertensive drug therapy depends on the degree of BP elevation and presence of compelling indications.
- ✓ Most patients with stage 1 HTN should be initially treated with a first-line antihypertensive drug or the combination of two.
- ✓ Combination drug therapy is recommended for patients with more severe BP elevation (stage 2 HTN), using preferably two first-line antihypertensive drugs.

➢ Pharmacotherapy

- ✓ An ACEI, ARB, CCB, or thiazide are preferred first-line antihypertensive agents for most patients (evidence demonstrates CV event reduction).
- ✓ β-Blocker therapy should be reserved to either treat a specific compelling indication or used in combination with one or more of the aforementioned first-line antihypertensive agents for patients without a compelling indication.
- ✓ Other antihypertensive drug classes are considered alternative drug classes that may be used in select patients after first-line agents (see the tables below).

TABLE 10–2 First-Line and Other Common Antihypertensive Agents

Class/Subclass/Drug (brand name)	Usual Dose Range (mg/day)	Daily Frequency
Angiotensin-converting enzyme inhibitors		
Benazepril (Lotensin)	10–40	1 or 2
* Captopril (Capoten)	12.5–150	2 or 3
* Enalapril (Vasotec)	5–40	1 or 2
Fosinopril (Monopril)	10–40	1
* Lisinopril (Prinivil, Zestril)	10–40	1
Moexipril (Univasc)	7.5–30	1 or 2
Perindopril (Aceon)	4–16	1
Quinapril (Accupril)	10–80	1 or 2
* Ramipril (Altace)	2.5–10	1 or 2
Trandolapril (Mavik)	1–4	1
Angiotensin II receptor blockers		
Azilsartan (Edarbi)	40–80	1
* Candesartan (Atacand)	8–32	1 or 2
Eprosartan (Teveten)	600–800	1 or 2
Irbesartan (Avapro)	150–300	1
Losartan (Cozaar)	50–100	1 or 2
Olmesartan (Benicar)	20–40	1
Telmisartan (Micardis)	20–80	1
* Valsartan (Diovan)	80–320	1
Calcium channel blockers		
Dihydropyridines		
* Amlodipine (Norvasc)	2.5–10	1
* Felodipine (Plendil)	5–20	1
Isradipine (DynaCirc)	5–10	2
Isradipine SR (DynaCirc SR)	5–20	1
Nicardipine sustained-release (Cardene SR)	60–120	2
Nifedipine long-acting (Adalat CC, Procardia XL)	30–90	1
Nisoldipine (Sular)	10–40	1

TABLE 10–2 First-Line and Other Common Antihypertensive Agents

Class/Subclass/Drug (brand name)	Usual Dose Range (mg/day)	Daily Frequency
Nondihydropyridines		
Diltiazem sustained-release (Cardizem SR)	180–360	2
* Diltiazem sustained-release (Cardizem CD, Cartia XT, Dilacor XR, Diltia XT, Tiazac, Taztia XT)	120–480	1
Diltiazem extended-release (Cardizem LA)	120–540	1 (morning or even
Verapamil sustained-release (Calan SR, Isoptin SR, Verelan)	180–480	1 or 2
Verapamil controlled-onset extended-release (Covera HS)	180–420	1 (in the evening)
Verapamil chronotherapeutic oral drug absorption system (Verelan PM)	100–400	1 (in the evening)
Diuretics		
Thiazides		
Chlorthalidone (Hygroton)	12.5–25	1
* Hydrochlorothiazide (Esidrix, HydroDiuril, Microzide, Oretic)	12.5–50	1
* Indapamide (Lozol)	1.25–2.5	1
Metolazone (Mykrox)	0.5–1	1
Metolazone (Zaroxolyn)	2.5–10	1

TABLE 10–2 First-Line and Other Common Antihypertensive Agents (*Continued*)

Class/Subclass/Drug (brand name)	Usual Dose Range (mg/day)	Daily Frequen
Triamterene (Dyrenium)	50–100	1 or 2
Triamterene/hydrochlorothiazide (Dyazide)	37.5–75/25–50	1
Loops		
* Bumetanide (Bumex)	0.5–4	2
* Furosemide (Lasix)	20–80	2
Torsemide (Demadex)	5–10	1
Potassium sparing		
Amiloride (Midamor)	5–10	1 or 2
* Amiloride/hydrochlorothiazide (Moduretic)	5–10/50–100	1
β-Blockers		
Cardioselective		
* Atenolol (Tenormin)	25–100	1
Betaxolol (Kerlone)	5–20	1
Bisoprolol (Zebeta)	2.5–10	1
* Metoprolol tartrate (Lopressor)	100–400	2
* Metoprolol succinate extended-release (Toprol XL)	50–200	1
Nonselective		
Nadolol (Corgard)	40–120	1
* Propranolol (Inderal)	160–480	2
Propranolol long-acting (Inderal LA, InnoPran XL)	80–320	1
Timolol (Blocadren)	10–40	1

TABLE 10–2 First-Line and Other Common Antihypertensive Agents (*Continued*)

Class/Subclass/Drug (brand name)	Usual Dose Range (mg/day)	Daily Frequen
Intrinsic sympathomimetic activity		
Acebutolol (Sectral)	200–800	2
Carteolol (Cartrol)	2.5–10	1
Penbutolol (Levatol)	10–40	1
Pindolol (Visken)	10–60	2
Mixed α- and β-blockers		
* Carvedilol (Coreg)	12.5–50	2
Carvedilol phosphate (Coreg CR)	20–80	1
* Labetalol (Normodyne, Trandate)	200–800	2
Cardioselective and vasodilatory		
* Nebivolol (Bystolic)	5–20	1

TABLE 10–3 Alternative Antihypertensive Agents

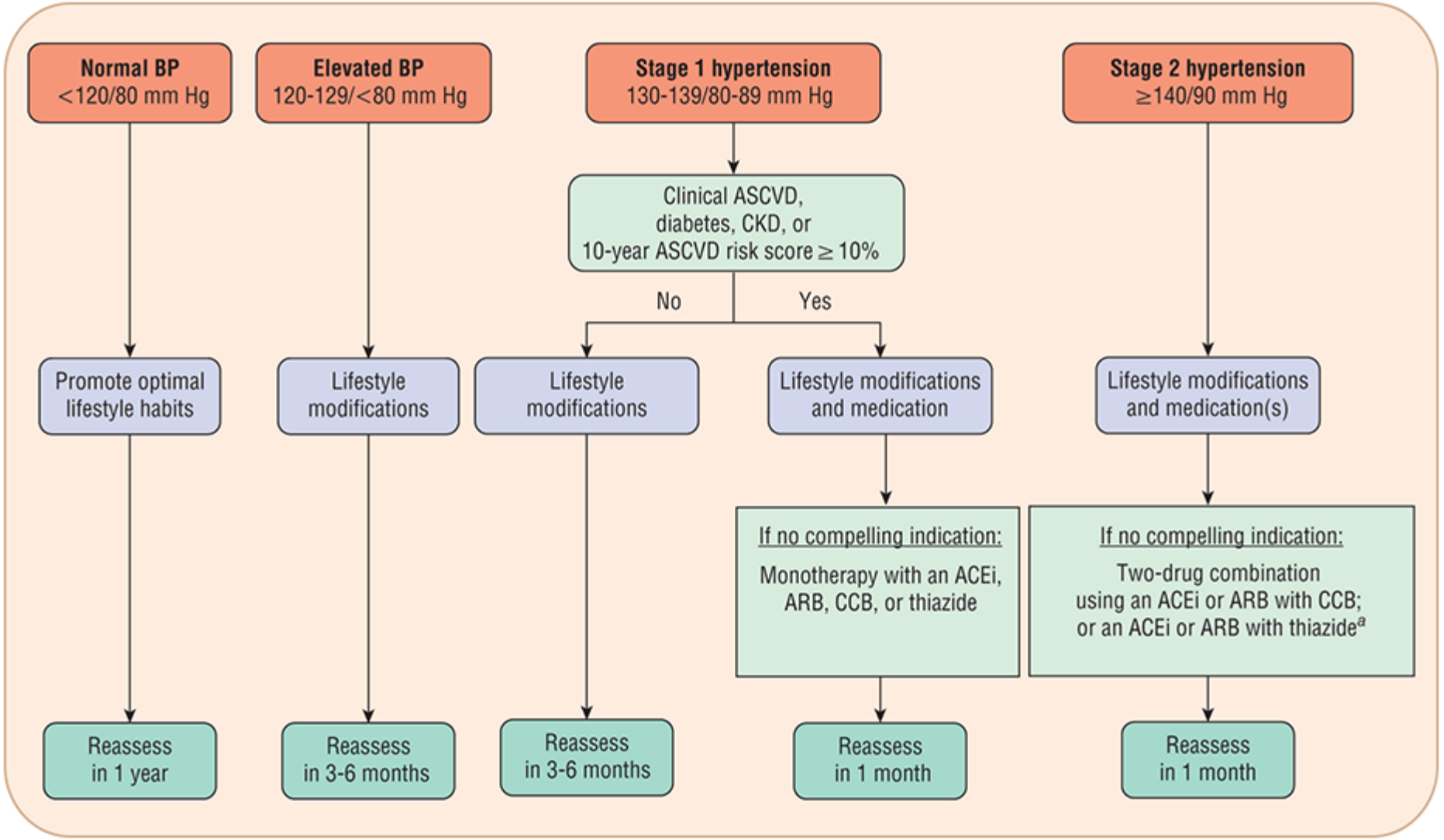
Class Drug (Brand Name)	Usual Dose Range (mg/day)	Daily Frequency
α_1-Blockers		
* Doxazosin (Cardura)	1–8	1
Prazosin (Minipress)	2–20	2 or 3
Terazosin (Hytrin)	1–20	1 or 2
Direct renin inhibitor		
Aliskiren (Tekturna)	150–300	1
Central α_2-agonists		
Clonidine (Catapres)	0.1–0.8	2
Clonidine patch (Catapres-TTS)	0.1–0.3	1 weekly
* Methyldopa (Aldomet)	250–1,000	2
Peripheral adrenergic antagonist		
Reserpine (generic only)	0.05–0.25	1
Direct arterial vasodilators		
Minoxidil (Loniten)	10–40	1 or 2
* Hydralazine (Apresoline)	20–100	2 to 4

Updated slide

FIGURE 33-2 Algorithm for treatment of elevated BP and hypertension based on BP category at initial diagnosis.

a: Monotherapy with an ACEi, ARB, CCB, or thiazide is appropriate in patients presenting in Stage 2 hypertension if they are at high risk for orthostatic hypertension or are very elderly.

(ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.)



Source: Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, Lisa M. Holle, Jennifer Cocohoba, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 13th Edition*

➢ Individual Antihypertensive Agents

✓ Angiotensin-converting enzyme inhibitors

- By blocking the ACE, vasodilation and a decrease in aldosterone occur.
- An ACEI also blocks degradation of bradykinin and stimulates the synthesis of other vasodilating substances (prostaglandin E2 and prostacyclin).
- Increased bradykinin enhances the BP-lowering effects of an ACEI, but also is responsible for the side effect of a dry cough.
- An ACEI may effectively prevent or regress LVH by reducing direct stimulation by angiotensin II on myocardial cells.

There are many evidence-based uses for an ACEI:

- Patients with HFrEF (reduces CV morbidity and mortality)
- Decrease progression of CKD
- Patients with diabetes and hypertension (CV disease and kidney benefits)
- A regimen with a thiazide in recurrent stroke prevention (reduced risk of secondary stroke)
- In CHD and post-MI with β-blocker therapy (reduce CV risk)

Updated slide

- ACEI therapy is generally well tolerated.
- They can increase potassium serum concentrations. While this increase is usually small, **hyperkalemia** is possible. Monitor serum potassium and creatinine within 4 weeks of starting or increasing the dose of an ACEI.

GFR does decrease in patients when started on an ACEI or ARB. This is attributed to the inhibition of angiotensin II vasoconstriction on the efferent arteriole. Either modest elevations of less than or equal to 35% **(for baseline creatinine values ≤3 mg/dL)** or absolute increases less than 1 mg/dL do not warrant changes. If larger increases occur, ACEI therapy should be stopped or the dose reduced.

New slide

Modest elevations of ≤ 35% (for baseline Cr. ≤3 mg/dL) or absolute increases <1 mg/dL do not warrant changes:

- Result ≤ limits (long-term kidney protection) → Continue ACEi
- Result ≥ limits (possible renal artery stenosis/dehydration/diuretic overuse/NSAIDs use) → Stop ACEi/lower dose

Different starting points of baseline Cr:

Low Baseline (Healthy Kidneys) → Watch **% increase**

- **Example:** Cr 0.8 → 1.5 mg/dL **Absolute:** +0.7 (Passes <1.0 rule) **Percentage:** +88% (Fails ≤35% rule) → Stop/lower dose

Moderate Baseline (Early CKD like 2-2.5 mg/dL) → Watch **% increase** (but % or absolute value can be used)

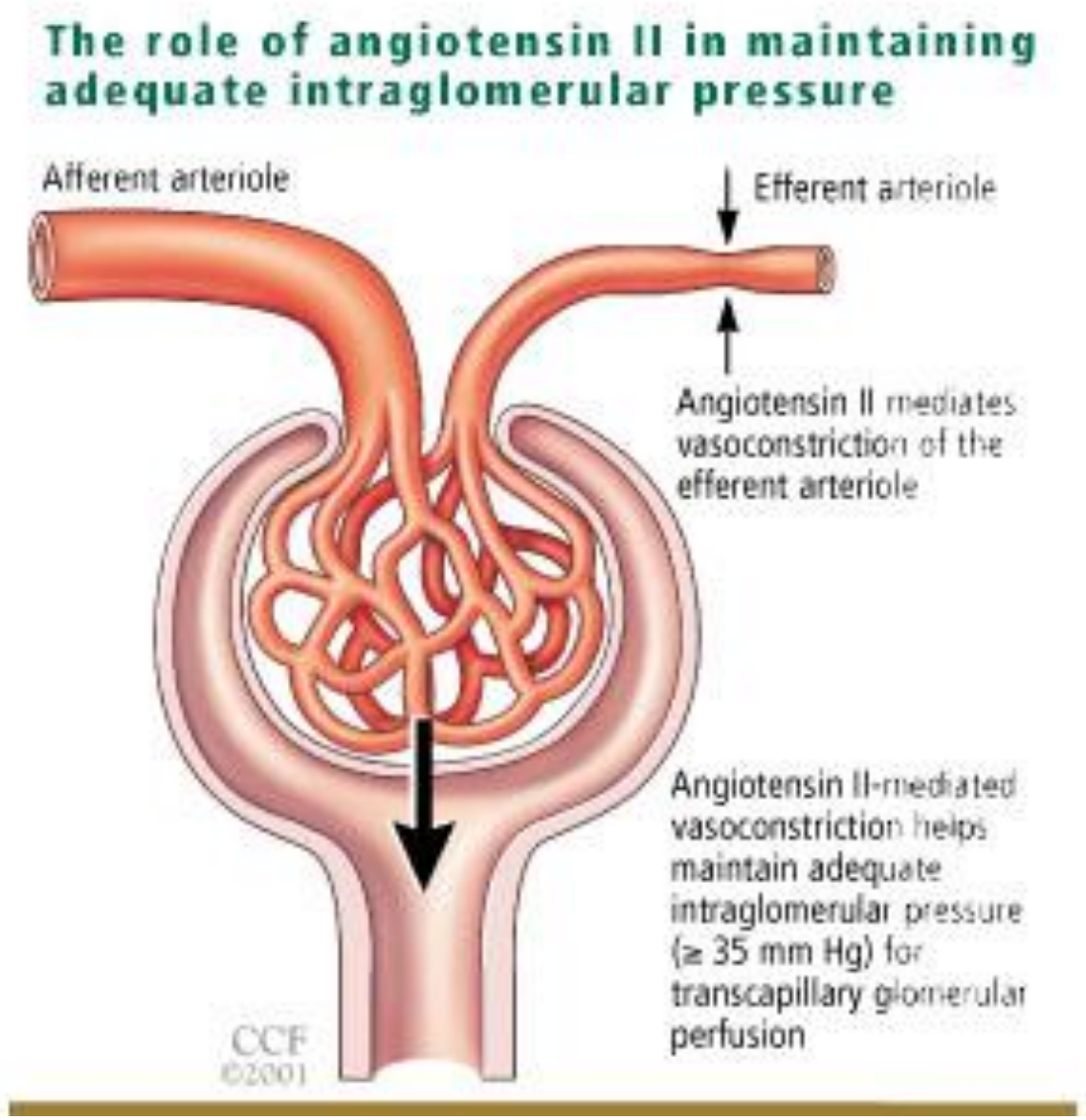
- **Example:** Cr 2.0 → 2.6 mg/dL **Absolute:** +0.6 (Passes <1.0 rule) **Percentage:** +30% (Passes ≤35% rule) → Continue ACEi

High Baseline (Advanced CKD Cr at 3 mg/dL) → Watch **Absolute increase**

- **Example:** Cr 3.0 → 4.05 mg/dL **Absolute:** +1.05 (Fails <1.0 rule) **Percentage:** +35% (Passes ≤35% rule) → Stop/lower dose → (some consider 1 absolute increase the max allowed)

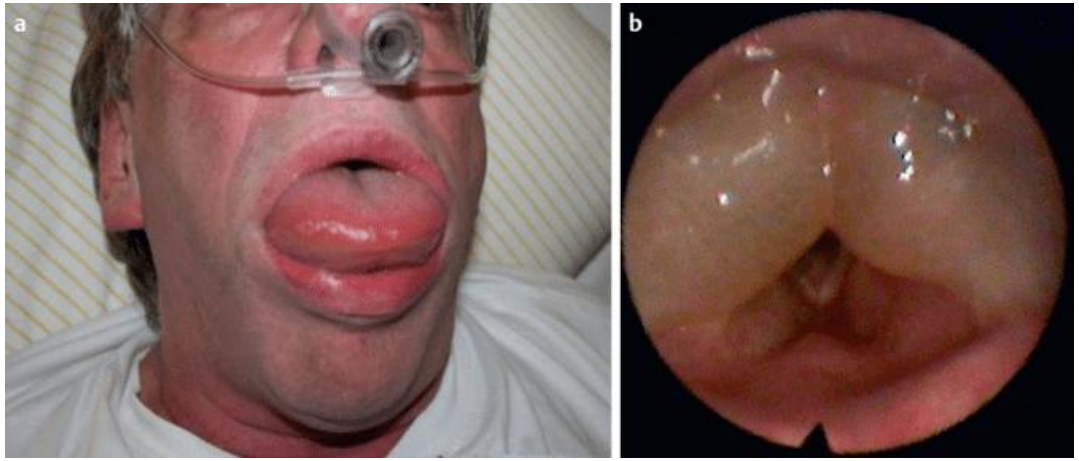
- The most worrisome adverse effect of ACEI therapy is **acute kidney failure**.

Bilateral renal artery stenosis or unilateral stenosis of a solitary functioning kidney renders patients dependent on the vasoconstrictive effect of angiotensin II on the efferent arteriole of the kidney, thus explaining why these patients are particularly susceptible to acute kidney failure from an ACEI. Slow titration of the ACEI dose and rational kidney function monitoring can minimize risk and allow for early detection of those with renal artery stenosis.

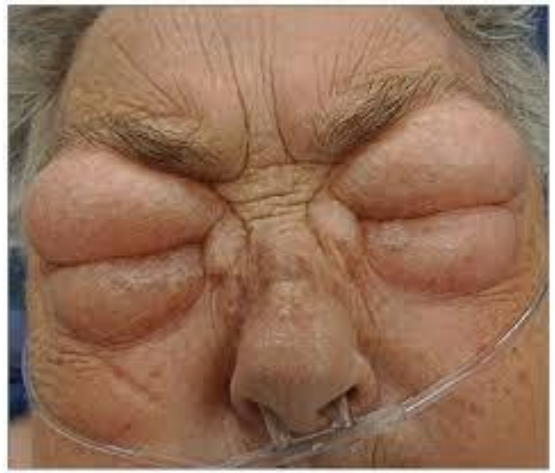


- **<u>Angioedema</u>** is a serious potential complication of ACEI therapy.

Symptoms include lip and tongue swelling and possibly difficulty breathing. Drug withdrawal is appropriate for treating patients with angioedema. However, angioedema associated with laryngeal edema and/or pulmonary symptoms requires additional treatment like emergent intubations to support respiration. A history of angioedema, even if not from an ACEI, precludes use of another ACEI (it is a contraindication). Cross-reactivity between an ACEI and an ARB is very low and does not appear to be a significant concern (an ARB can be used in a patient with a history of ACEI-induced angioedema when it is needed) → BUT clinicians should monitor for repeat occurrence, since idiopathic angioedema may still occur.

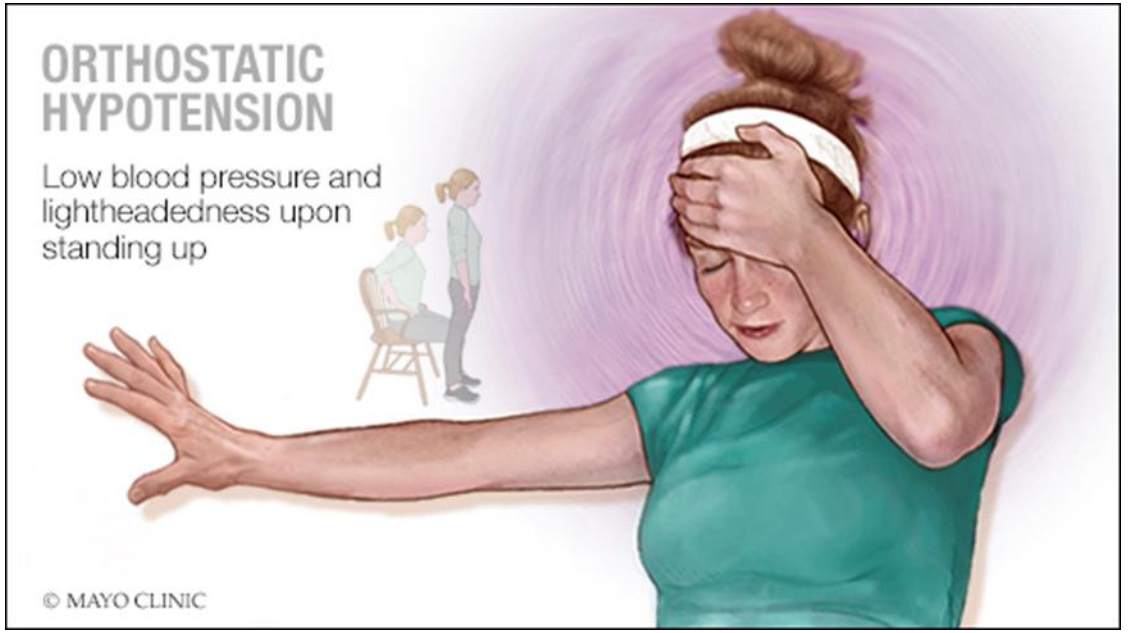


ACEI-induced angioedema of the tongue and the larynx



- A persistent **dry cough** develops in up to 20% of patients treated with an ACEI (inhibition of bradykinin breakdown).

- Starting doses of an ACEI should be low, with even lower doses for patients at risk for **orthostatic hypotension**. Patients who are sodium or volume depleted, in a HF exacerbation, very elderly, or on concurrent vasodilators or thiazide therapy are at high risk for this effect. It is important to start with half the normal dose of an ACEI for all patients with these risk factors and to use slow dose titration.



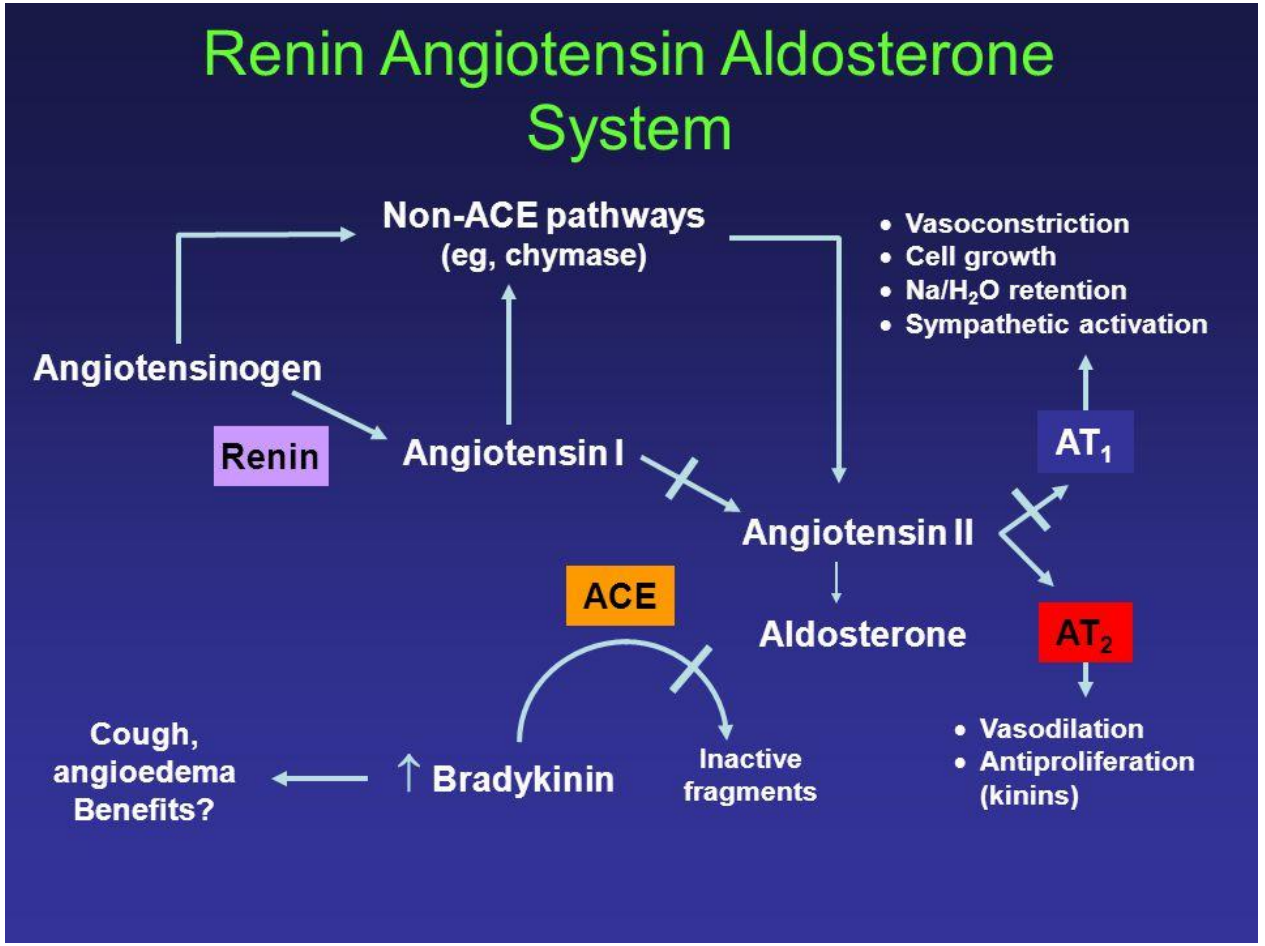
- An ACEI, as well as an ARB or direct renin inhibitor, are absolutely contraindicated in pregnancy. Female patients of childbearing age should be counseled regarding effective forms of birth control.

✓ ARB

- Angiotensin II is generated by two enzymatic pathways: the RAAS, which involves ACE, and an alternative pathway that uses other enzymes such as chymase (tissue ACE).

- An ACEI inhibits only the effects of angiotensin II produced through the RAAS, whereas ARBs inhibit angiotensin II from all pathways.

- ARB therapy directly blocks the AT1 receptor that mediates the known effects of angiotensin II in humans (vasoconstriction, aldosterone release, sympathetic activation, and constriction of the efferent arterioles of the glomerulus).



- An ARB does not block the breakdown of bradykinin so, some of the beneficial effects of bradykinin, such as vasodilation, and regression of myocyte hypertrophy and fibrosis, are not present with ARB therapy.

- The CV event-lowering benefits of ARB therapy are similar to ACEI therapy in hypertension.

- The combination of an ACEI with an ARB had no additional CV event lowering but was associated with a higher risk of side effects (renal dysfunction, hypotension) so do not use an ACEI with an ARB.

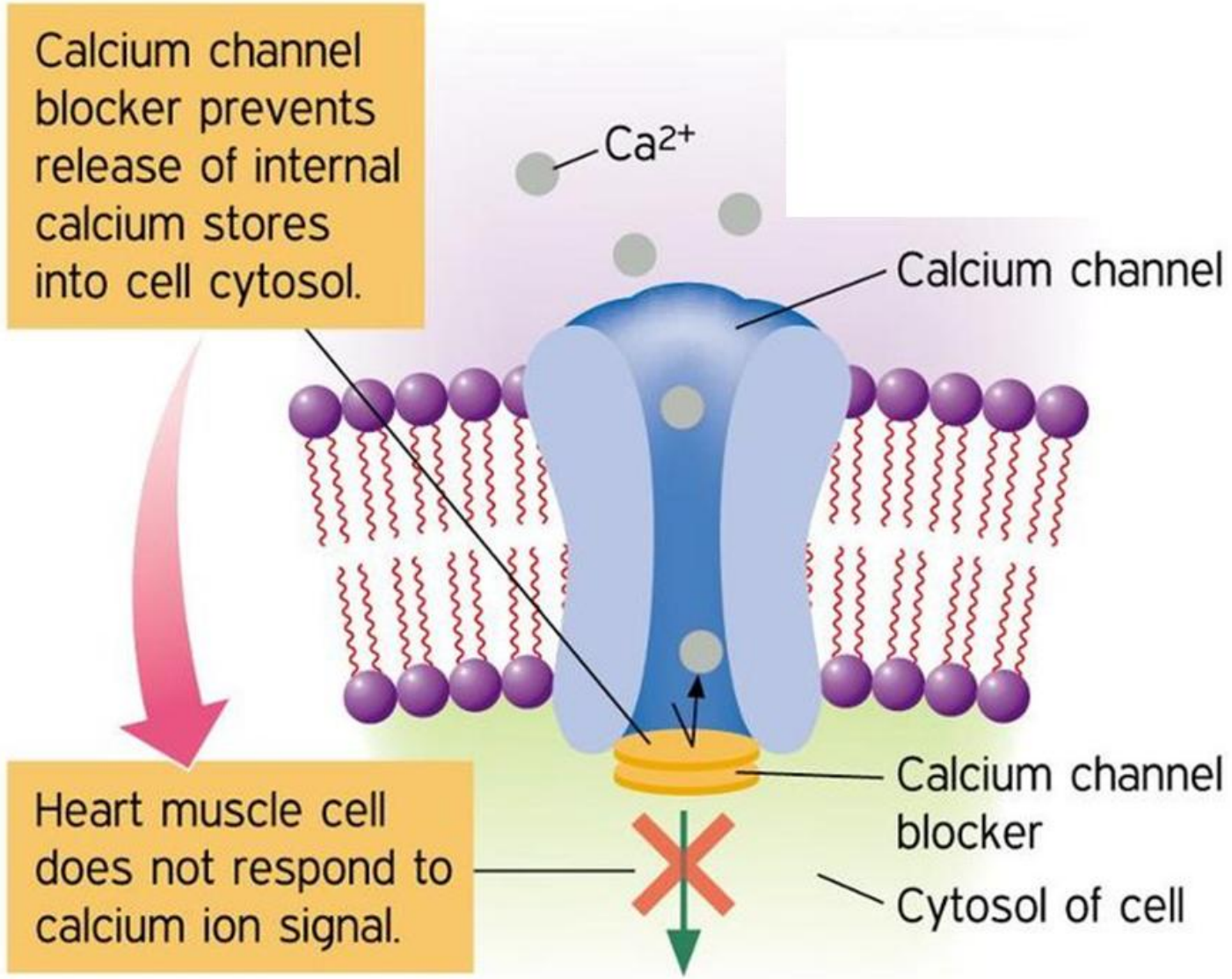
- Same precautions that apply to ACEI therapy :

- may cause hyperkalemia in patients with CKD or in those receiving a potassium-sparing diuretic, aldosterone antagonist, ACEI, or direct renin inhibitor
- can cause acute kidney failure in patients with severe bilateral renal artery stenosis or severe stenosis in artery to solitary kidney
- do not cause a dry cough like an ACEI may
- do not use in pregnancy
- starting dose should be reduced 50% in patients who are on a thiazide, are volume depleted, or are very elderly due to risks of hypotension

✓ CCB

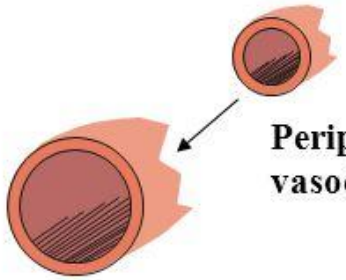
- Contraction of cardiac and smooth muscle cells requires an increase in free intracellular calcium concentrations from the extracellular fluid.

- CCBs work by inhibiting influx of calcium across the cell membrane which leads to coronary and peripheral vasodilation.

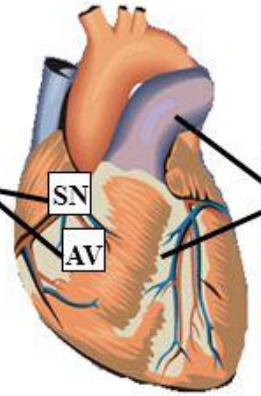


Differential effects of different CCBs on CV cells

Dihydropyridines: Selective vasodilators



Peripheral vasodilation

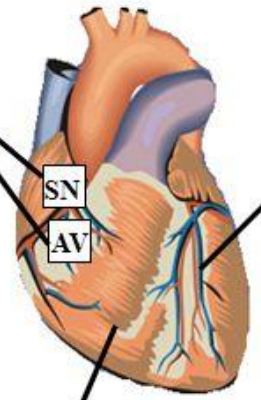


Potential reflex increase in HR, myocardial contractility and O_2 demand

Coronary VD

Non -dihydropyridines: equipotent for cardiac tissue and vasculature

Heart rate moderating



Peripheral and coronary vasodilation

Reduced inotropism

- The two subclasses, dihydropyridines and nondihydropyridines, are pharmacologically very different from each other.
- Antihypertensive effectiveness is similar with both subclasses, but they differ in other pharmacodynamic effects.
- Nondihydropyridines (verapamil and diltiazem) decrease HR and slow AV nodal conduction.
- Similar to a β-blocker, these drugs may also treat supraventricular tachyarrhythmias (eg, atrial fibrillation).
- Verapamil produces negative inotropic & chronotropic effects that can precipitate or cause systolic HF.
- Diltiazem also has these effects but to a lesser extent than verapamil.
- All CCBs (except amlodipine and felodipine) have negative inotropic effects.
- Dihydropyridines may cause a baroreceptor-mediated reflex tachycardia because of their potent peripheral vasodilating effects.

- This effect appears to be more pronounced with the first-generation dihydropyridines (eg, nifedipine) and is significantly diminished with the newer agents (eg, amlodipine) and when given in sustained-release dosage forms.

- Dihydropyridines do not alter conduction through the AV node and thus are not effective agents in supraventricular tachyarrhythmias.

Dihydropyridine CCB

- Dihydropyridine CCBs are very effective in older patients with isolated systolic hypertension.

- Immediate-release nifedipine has been associated with an increased incidence of adverse CV effects, is not approved for treatment of HTN, and should not be used to treat HTN.

- Side effects with dihydropyridines include dizziness, flushing, headache, gingival hyperplasia, peripheral edema, mood changes, and various GI complaints. Side effects due to vasodilation (dizziness, flushing, headache, peripheral edema) occur more frequently with all dihydropyridines than with the non-DHP because they are less potent vasodilators.

Nondihydropyridine CCB

- Diltiazem & verapamil can cause cardiac conduction abnormalities as bradycardia or AV block.
- These problems occur mostly with high doses or when used for patients with preexisting abnormalities in the cardiac conduction system.
- HF has been reported due to negative inotropic effects.
- Both drugs can cause anorexia, nausea, peripheral edema, and hypotension.
- Verapamil causes constipation in about 7% of patients. This side effect also occurs with diltiazem, but to a lesser extent.
- Verapamil and to a lesser extent diltiazem can cause drug interactions due to their ability to inhibit the cytochrome P450 3A4 isoenzyme system.
- This inhibition can increase serum concentrations of other drugs that are metabolized by this isoenzyme system (eg, cyclosporine, digoxin, lovastatin, simvastatin, tacrolimus, theophylline).

- Verapamil and diltiazem should be given very cautiously with a β-blocker because there is an increased risk of heart block with these combinations.

- When a CCB is needed in combination with a β-blocker for BP lowering, a dihydropyridine should be selected because it will not increase risk of heart block.

- The hepatic metabolism of CCBs, especially felodipine, nicardipine, nifedipine, and nisoldipine, may be inhibited by ingesting large quantities of grapefruit juice (≥ 1 quart [946.35 mL] daily).

✓ Thiazide and other Diuretics

- Thiazides, loops, potassium sparing agents, and aldosterone antagonists.
- A thiazide is the preferred type of diuretic for HTN and is considered a first-line therapy option in most patients with HTN (is very effective in lowering BP).
- Loops are more potent agents for inducing diuresis, but they are not ideal antihypertensive agents unless relief of edema is also needed.
- Loops are sometimes needed over a thiazide for HTN in patients with CKD when estimated GFR is < 30 mL/min/1.73 m^2, especially when edema is present.
- Potassium-sparing diuretics are very weak antihypertensive agents when used alone and provide minimal additive effect when used in combination with a thiazide or loop diuretic.
- Their primary use is in combination with another diuretic to counteract the potassium-wasting properties of the other diuretic agent.

- Aldosterone antagonists (spironolactone and eplerenone) may be technically considered potassium-sparing agents but are more potent as antihypertensives. However, they are viewed as an independent class due to evidence supporting compelling indications.

- The drop in BP seen when diuretics are first started is caused by an initial diuresis.

- Diuresis causes reductions in plasma and stroke volume, which decreases CO and BP.

- This initial drop in CO causes a compensatory increase in PVR.

- With chronic diuretic therapy, extracellular fluid and plasma volume return to near pretreatment values. However, PVR decreases to values that are lower than the pretreatment baseline. This reduction in PVR is responsible for chronic antihypertensive effects.

- Diuretics should ideally be dosed in the morning if given once daily and in the morning and late afternoon when dosed twice daily to minimize risk of nocturnal diuresis.

- With chronic use, thiazides, potassium-sparing diuretics, and aldosterone antagonists rarely cause a pronounced diuresis.

- Side effects of a thiazide include hypokalemia, hypomagnesemia, hypercalcemia, hyperuricemia, hyperglycemia, dyslipidemia, and sexual dysfunction.

- Loop diuretics may cause the same side effects. Although the effect on serum lipids and glucose is not as significant, hypokalemia is more pronounced, and hypocalcemia may occur.

- Hypokalemia and hypomagnesemia may cause muscle fatigue or cramps. Also, serious cardiac arrhythmias can occur in patients with severe hypokalemia and hypomagnesemia. Patients at greatest risk include those with LVH, coronary disease, post-MI, a history of arrhythmia, or concurrently receiving digoxin.

- Hyperuricemia can precipitate gout. This side effect may be especially problematic for patients with a previous history of gout and is more common with thiazides.

- High doses of thiazide and loop diuretics may increase fasting glucose and serum cholesterol values. These effects, however, usually are transient and often unimportant.

- Potassium-sparing diuretics can cause hyperkalemia, especially in patients with CKD or diabetes and in patients receiving concurrent treatment with an ACEI, ARB, direct renin inhibitor, or potassium supplements.

- Hyperkalemia is especially problematic for the newest aldosterone antagonist eplerenone. This agent is a very selective aldosterone antagonist, and its propensity to cause hyperkalemia is greater than with the other potassium-sparing agents and even spironolactone. Due to this increased risk of hyperkalemia, eplerenone is contraindicated for patients with an estimated CrCl <50 mL/min, elevated serum creatinine (>1.8 mg/dL in women, >2 mg/dL in men), and type 2 diabetes with microalbuminuria

- Spironolactone may cause gynecomastia in up to 10% of patients, this occurs rarely with eplerenone. Avoid spironolactone in patients with CKD (estimated CrCl <30 mL/min).

✓ β-Blocker

- β-Blocker therapy has negative chronotropic and inotropic effects that reduce CO.
- β-receptors are also located on the surface membranes of juxtaglomerular cells, and a β-blocker inhibits these receptors and thus the release of renin.
- The ability of a β-blocker to reduce plasma renin and thus angiotensin II concentrations may play a major role in their ability to reduce CV risk.
- β-Blockers that possess a greater affinity for β1-receptors than for β2-receptors are cardioselective.
- Cardioselective β-blocker therapy is not likely to provoke bronchospasm and vasoconstriction.
- Insulin secretion and glycogenolysis are mediated by β2-receptors. Blocking β2-receptors may reduce these processes and increase blood glucose or blunt recovery from hypoglycemia.

- Cardioselective β-blockers (eg, atenolol, bisoprolol, metoprolol, and nebivolol) have clinically significant advantages over nonselective agents (eg, propranolol and nadolol), and are preferred when using a β-blocker to treat HTN.

- Cardioselective agents are safer than nonselective agents for patients with asthma or diabetes.

- Cardioselectivity is a dose-dependent phenomenon; at higher doses, cardioselective agents lose their relative selectivity for β1-receptors and block β2-receptors as effectively as they block β1-receptors. The dose at which cardioselectivity is lost varies from patient to patient.

- Propranolol is the most lipophilic drug and atenolol is the least lipophilic. It is thought that higher lipophilicity is associated with more CNS side effects (dizziness and drowsiness).

- The lipophilic properties can provide better effects for non-CV conditions such as migraine headache prevention, essential tremor, and thyrotoxicosis.

- Most side effects of β-blocker therapy are extensions of their ability to antagonize β-receptors.
- β-Blockade in the myocardium can be associated with bradycardia, atrioventricular conduction abnormalities (eg, 2nd- or 3rd-degree heart block), and the development of acute HF.
- The decrease in HR may benefit certain patients with atrial arrhythmias (atrial fibrillation).
- β-Blocker therapy usually only produce HF if used in high initial doses for patients with preexisting LV dysfunction or if started in these patients during an acute HF exacerbation.
- Blocking β2-receptors in arteriolar smooth muscle may cause cold extremities and may aggravate intermittent claudication or Raynaud's phenomenon as a result of decreased peripheral blood flow.
- Abrupt cessation of β-blocker can produce unstable angina, MI, or even death in patients with coronary disease. Abrupt cessation may also lead to rebound hypertension (a sudden increase in BP to or above pretreatment values). To avoid this, β-blockers should always be tapered gradually over 1 to 2 weeks before eventually discontinuing the drug.

- For patients without coronary disease, abrupt discontinuation may present as tachycardia, sweating, and generalized malaise in addition to increased BP.
- Like a thiazide, β-blocker therapy has been shown to increase serum cholesterol and glucose values, but these effects are transient and of little clinical significance.
- Nebivolol is considered a third-generation β-blocker.
- Similar to carvedilol and labetalol, this β-blocker results in vasodilation.
- Nebivolol causes vasodilation through release of nitric oxide.
- The long-term clinical benefits of the nitric oxide effects seen with nebivolol are currently unknown, but this might explain a lower risk of β-blocker-associated fatigue, erectile dysfunction, and metabolic side effects (eg, hyperglycemia) with this agent.

Clinical controversy… β-blocker versus first-line agents

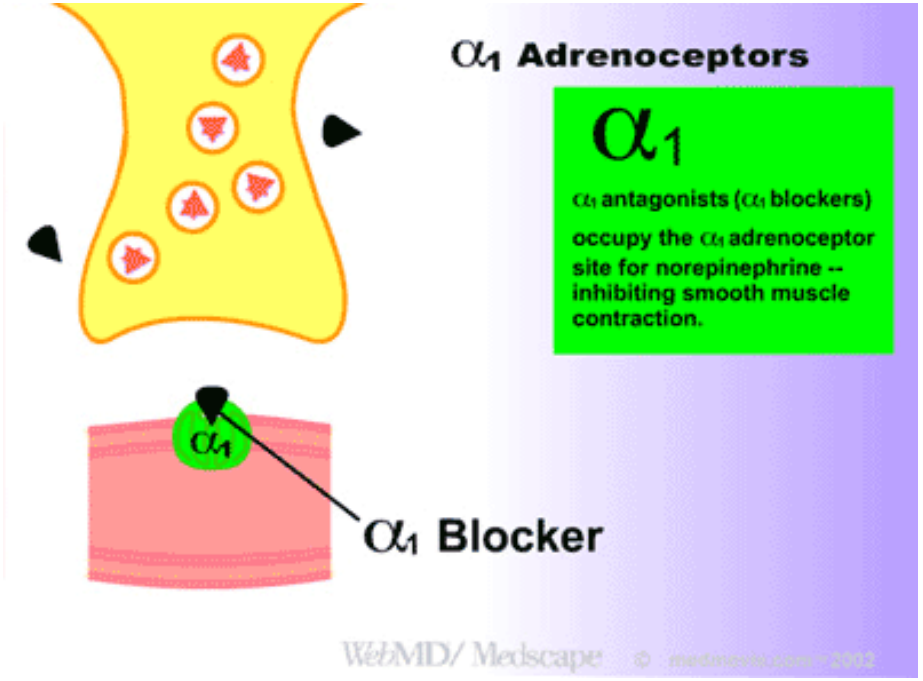
- ✓ Clinical trial data cumulatively suggest that treatment with a β-blocker may not reduce CV events (less CV event reduction benefits) to the extent that an ACEI, ARB, CCB, or thiazide does.
- ✓ Meta-analyses data evaluating β-blockers and their ability to reduce CV events have limitations:
- Most studies that were included used atenolol as the β-blocker studied.
- It is possible that atenolol is inferior (only β-blocker that reduces CV events less than first-line classes).
- These studies used once-daily atenolol, which may be inadequate based on its short half-life (6 to 7 hours).
- Immediate-release forms of carvedilol (6-10 hrs)& metoprolol (3-7 hrs) are dosed at least twice daily.
- It is possible the findings of β-blocker-based therapy may not reduce CV events as well as the other agents might only apply to atenolol & these findings may be a result of using atenolol once daily instead of twice.
- ✓ β-blocker-based antihypertensive therapy does not increase risk of CV events
- ✓ β-blocker-based therapy reduces risk of CV events compared with no antihypertensive therapy
- ✓ Add-on role after first-line agents to reduce BP in patients with HTN but without compelling indications.

✓ Alternative Agents

Primary role: additional BP lowering in patients already treated with combination of first-line agents

❖ **α1-Blocker:** Prazosin, terazosin, and doxazosin are selective α1-receptor blockers.

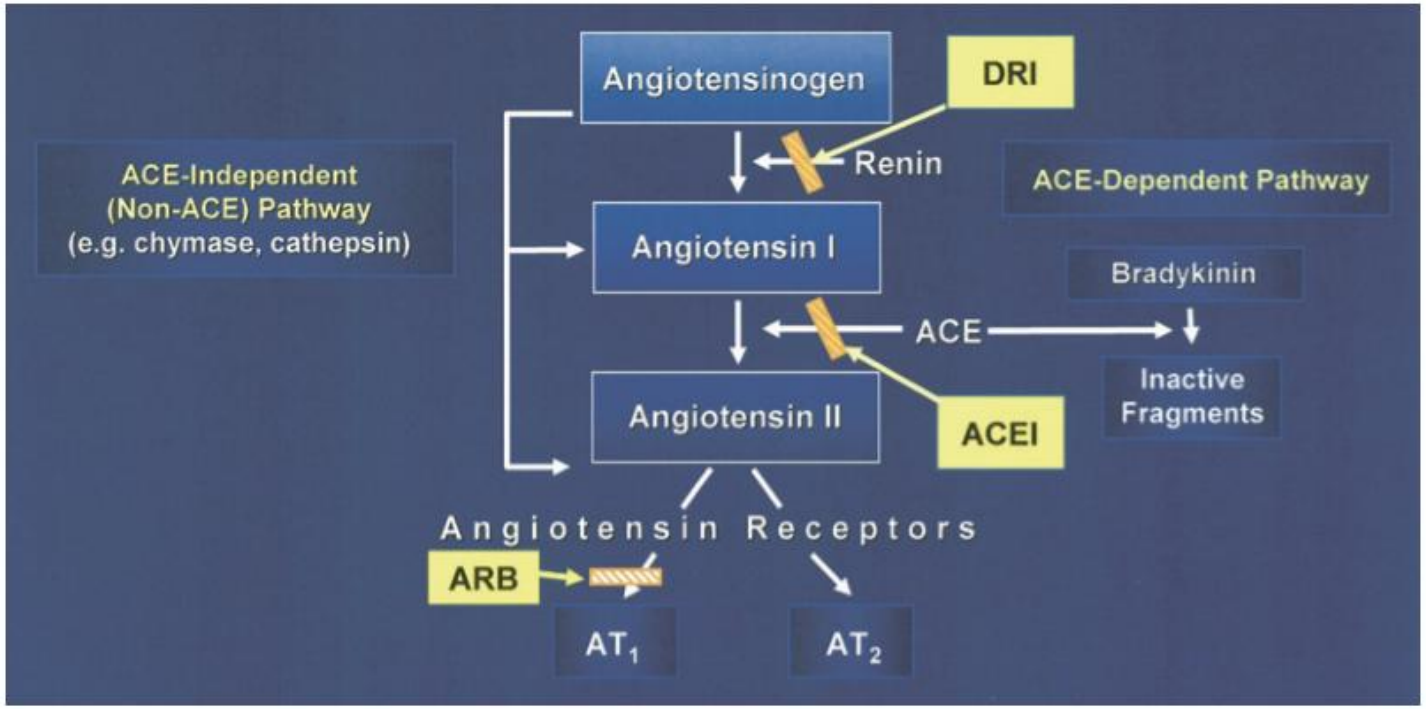
- inhibit the uptake of catecholamines in smooth muscle cells of the peripheral vasculature resulting in vasodilation and BP lowering.
- can provide symptomatic benefits in men with benign prostatic hypertrophy (causing relaxation and decreased resistance to urinary outflow)



- A potentially severe side effect: “first-dose” phenomenon characterized by transient faintness, palpitations, & even syncope within 1-3 hours of the first dose (also happen after dose increases) → can be avoided by taking the first dose & subsequent first increased doses at bedtime.
- should be used very cautiously in elderly patients →may increase the risk of falls (orthostatic hypotension and dizziness may persist with chronic administration)
- cross BBB (lassitude, vivid dreams, and depression)
- may cause priapism & sodium & water retention (recommended with a thiazide)

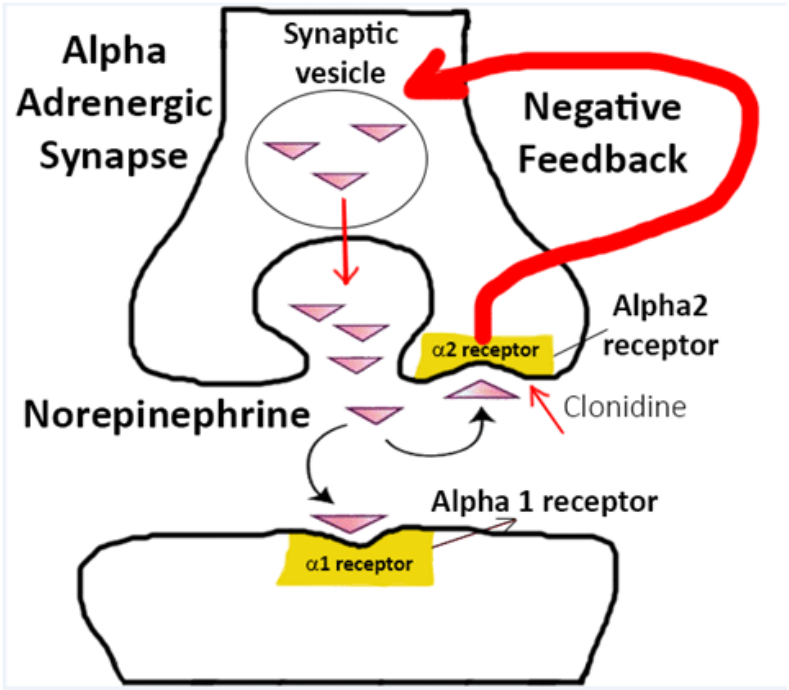
❖ **Aliskiren:** is a direct renin inhibitor.

- blocks the RAAS at its point of activation (reduced plasma renin activity and BP lowering)
- It has a 24-hour half-life, and provides 24-hour antihypertensive effects with once-daily dosing.
- It has a very limited role in the management of HTN.
- It should not be used in combination with an ACEI or an ARB (higher risk of serious adverse effects without providing additional reduction in CV events).
- Cautions and adverse effects: should never be used in pregnancy (teratogenic effects of using other drugs that block the RAAS system), angioedema, increases in serum creatinine and serum potassium values



❖ **Central α2-Agonist:** Clonidine, guanabenz, guanfacine, and methyldopa

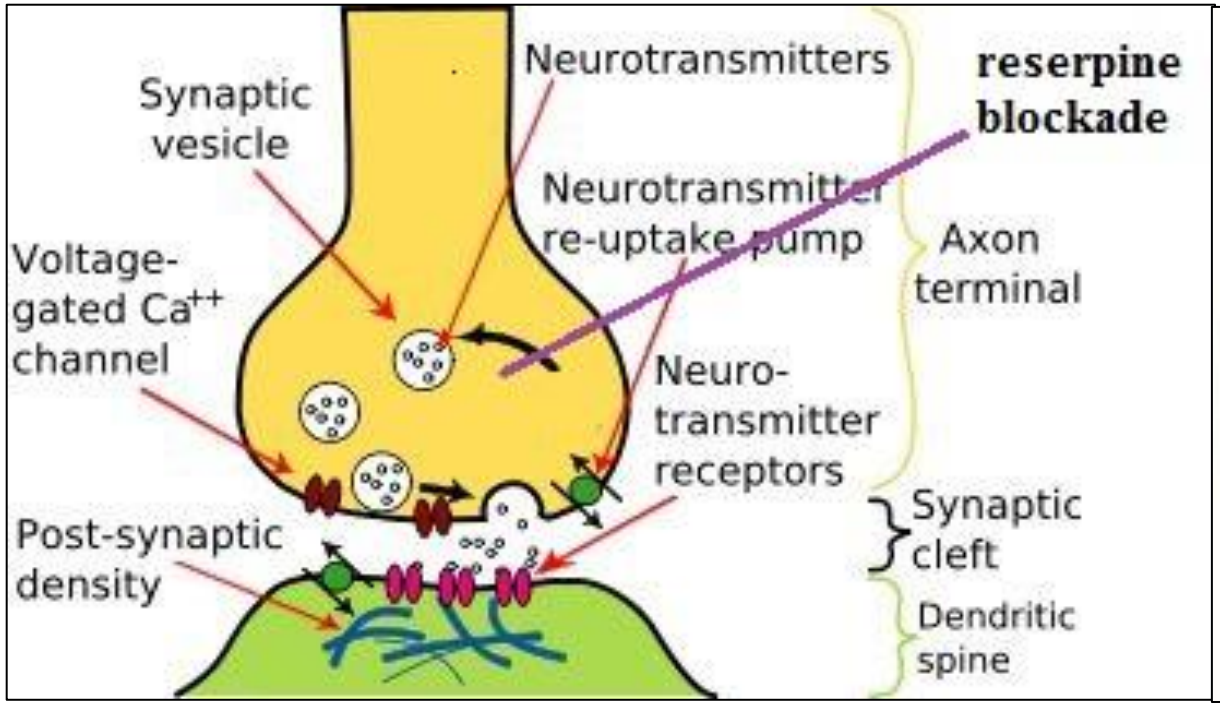
- Lower BP primarily by stimulating α2-adrenergic receptors in the brain (reduces sympathetic outflow from the vasomotor center in the brain and increases vagal tone)
- It is also believed that peripheral stimulation of presynaptic α2-receptors may further reduce sympathetic tone.
- Decrease HR, CO, TPR, plasma renin activity, and baroreceptor reflexes.
- Clonidine is often used in resistant hypertension, & methyldopa is commonly used for pregnancy-induced hypertension.
- Chronic use results in sodium and water retention especially with methyldopa.
- Low doses of clonidine (and guanfacine or guanabenz) can be used to treat hypertension without the addition of a thiazide. Methyldopa should be given in combination with a thiazide.

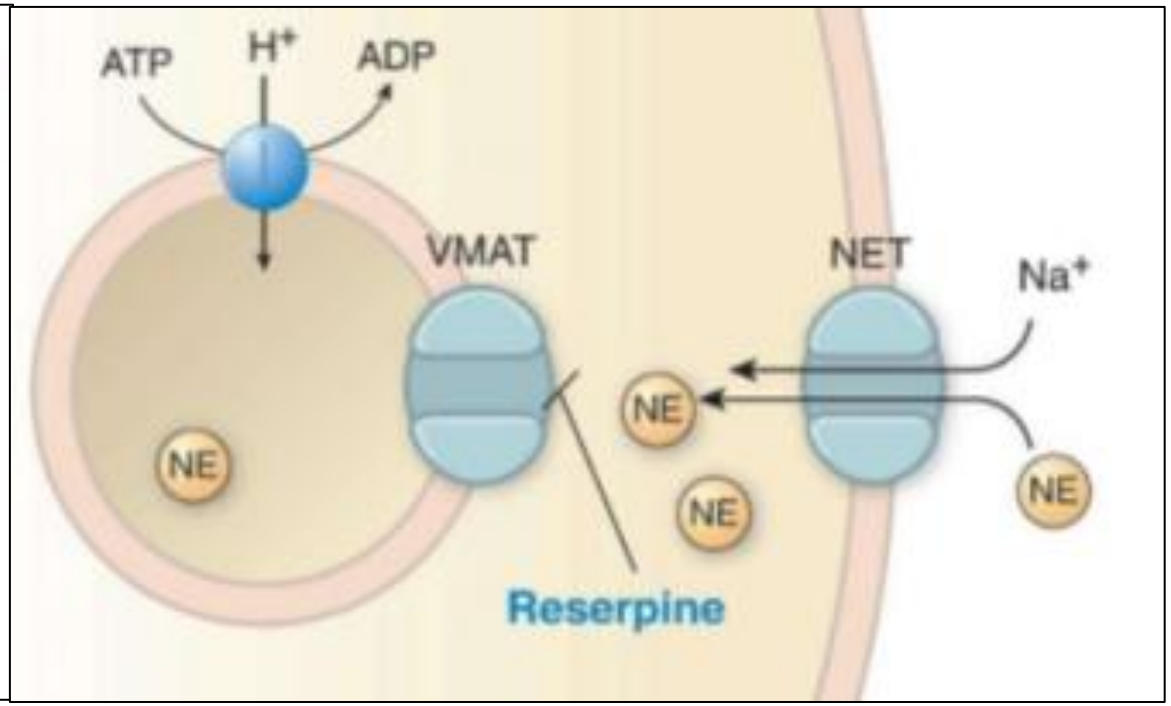


- The incidence of orthostatic hypotension and dizziness is higher than with other antihypertensive agents, so they should be used very cautiously in the elderly.
- Abrupt cessation of a central α2-agonist may lead to rebound hypertension (secondary to a compensatory increase in norepinephrine release after abrupt discontinuation).
- For patients who are receiving concomitant β-blocker therapy, the β-blocker should be gradually discontinued first several days before gradual discontinuation of clonidine.

❖ Reserpine

- Reserpine lowers BP by depleting norepinephrine from sympathetic nerve endings and blocking transport of norepinephrine into its storage granules.
- Norepinephrine release into the synapse following nerve stimulation is reduced and results in reduced sympathetic tone, PVR, CO, and BP.





❖ **Direct Arterial Vasodilator:** Hydralazine and minoxidil

- Directly relax arteriolar smooth muscle resulting in vasodilation and BP lowering
- Activation of baroreceptors results in a compensatory increase in sympathetic outflow, which leads to an increase in heart rate, CO, and renin release.
- Tachyphylaxis can develop resulting in a loss of hypotensive effect with continued use.
- The compensatory baroreceptor response can be counteracted by concurrent use of a β-blocker.
- All patients receiving hydralazine or minoxidil long-term for HTN should first receive both a thiazide and a β-blocker.
- Direct arterial vasodilators can precipitate angina in patients with underlying coronary disease unless the baroreceptor reflex mechanism is blocked with a β-blocker.
- Minoxidil is a more potent vasodilator than hydralazine (the compensatory increases in HR, CO, renin release, and sodium retention are even more dramatic).
- Due to significant water retention, a loop diuretic is often a more effective antihypertensive than a thiazide in patients treated with minoxidil.

➢ Alternative Drug Treatments

- Direct renin inhibitor, α-blocker, central α2-agonist, adrenergic inhibitor, and arterial vasodilator are effective in lowering BP but they either do not have compelling outcome data showing reduced morbidity and mortality in hypertension, or have poor tolerability and adverse effects that significantly limit their use.

- Alternative agents are generally reserved for patients with resistant hypertension or as add-on therapy with multiple other first-line antihypertensive agents.