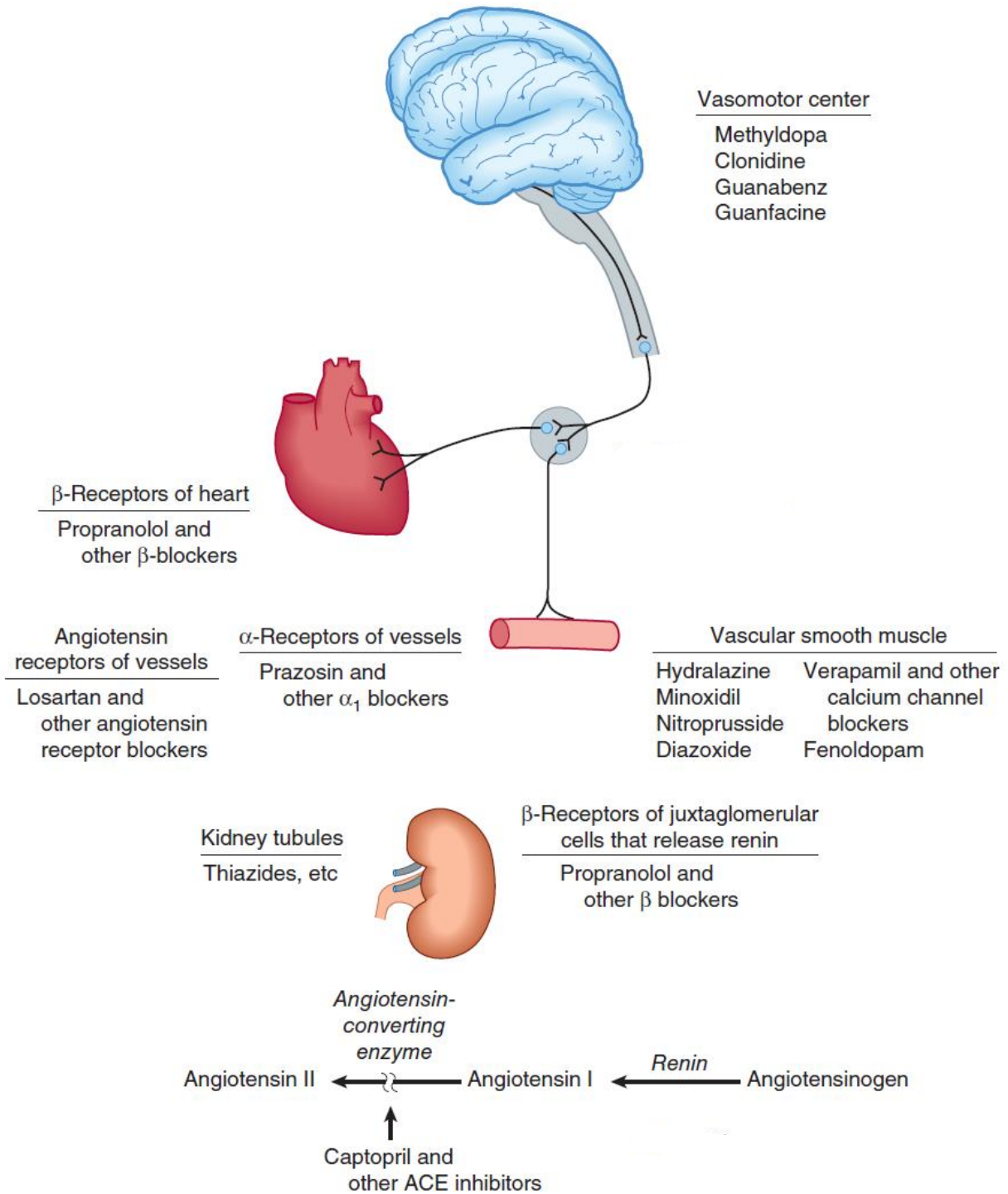


Sites of Action of the Major Classes of Antihypertensive Drugs



Antihypertensive Agents

I. Diuretics

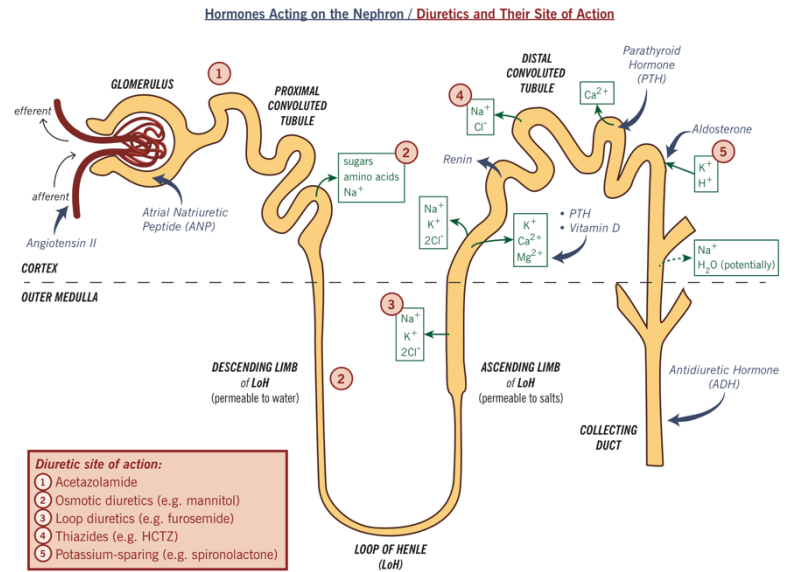
- MOA: Diuretics increase urine volume → decrease blood volume → decrease blood pressure.

A. Thiazide Diuretics: Hydrochlorothiazide (HCTZ)

- Thiazide diuretics block Na/H₂O reabsorption in distal tubule, which accounts for approx. 5-10% of Na/H₂O reabsorption by the nephron.

B. Loop Diuretics: Furosemide (Lasix)

- Loop diuretics block Na/H₂O reabsorption in the ascending Loop of Henle, which accounts for 20-25% of Na/H₂O reabsorption by the nephron.
- When CrCl < 30 ml/min, Loop diuretics are indicated, since thiazide diuretics are not effective in renally impaired patients.



C. Potassium-Sparing Diuretics (K-Sparing Diuretics): Triamterene (Dyrenium) and Spironolactone (Aldactone)

D. Side Effects of Thiazide and Loop Diuretics

(1) Hypokalemia

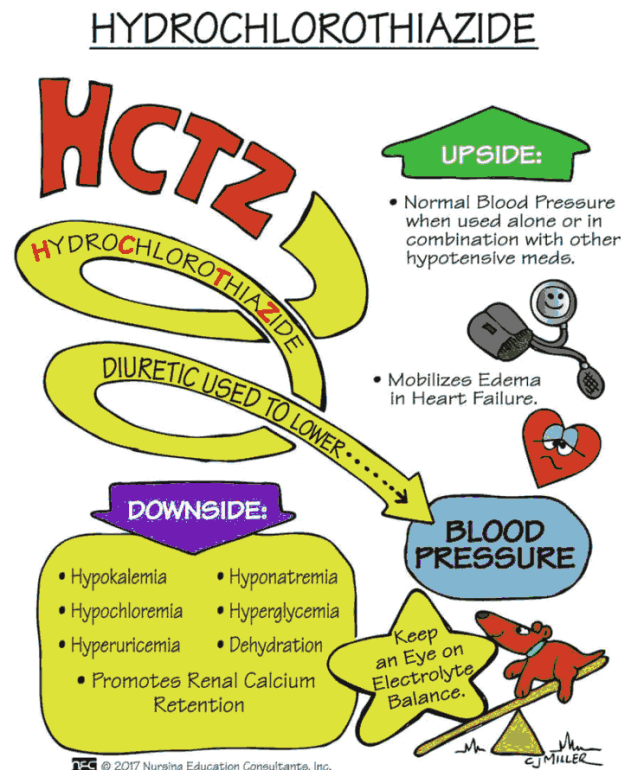
- Hypokalemia may be prevented or treated with the following options:
 - (a) K-Sparing Diuretics → Example: Dyazide (HCTZ + Triamterene)
 - (b) KCl Supplements → Example: K-Dur 20 mEq / 40 mEq SR tablets

(2) Hypomagnesemia

- Hypomagnesemia may be prevented or treated with magnesium supplementation.
- Examples: Magnesium Oxide 400 mg tablets and Slo-Mag 84 mg SR tablets

(3) Hypocalcemia with Loop Diuretics

- Note: Thiazides are calcium-sparing.
- Hypocalcemia may be prevented or treated with calcium supplementation.
- Example: TUMS (calcium carbonate) 800-1000 mg PO daily.



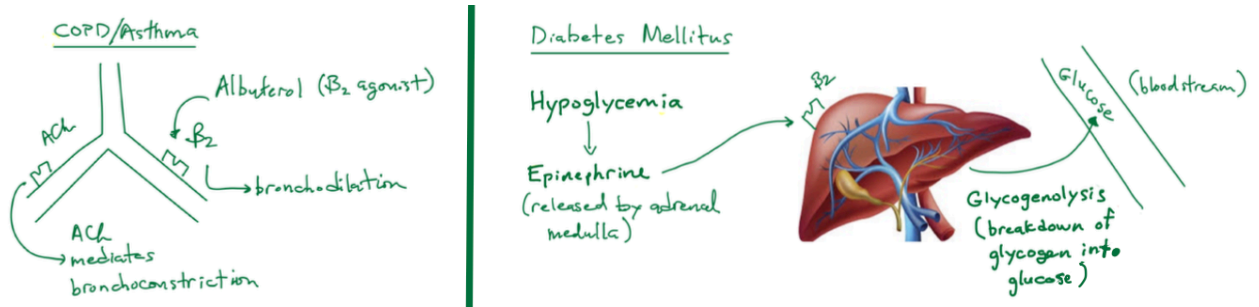
II. Beta Blockers

A. Selective Beta-1 Blockers: Metoprolol (Lopressor, Toprol XL)

- Selective beta-1 blockers are also called “cardioselective” beta blockers.

B. Non-Selective Beta Blocker: Propranolol (Inderal)

- Avoid propranolol in patients with COPD/asthma, since propranolol blocks beta-2 receptors in the airways and competes with albuterol (beta-2 agonist) for beta-2 receptor sites.
- Propranolol also blocks beta-2 receptors in the liver → blocks glycogenolysis → prevents glucose replacement in diabetics during hypoglycemic episodes.
 - During hypoglycemic episodes, epinephrine (Epi) is released into the bloodstream by the adrenal medulla to stimulate beta-2 receptors in the liver to initiate glycogenolysis. Non-selective beta-blockers block glycogenolysis and prevent glucose replacement during hypoglycemic episodes in diabetics.
 - Cautionary Note: All beta blockers (i.e., selective and non-selective) will mask the signs and symptoms of hypoglycemia in diabetics.

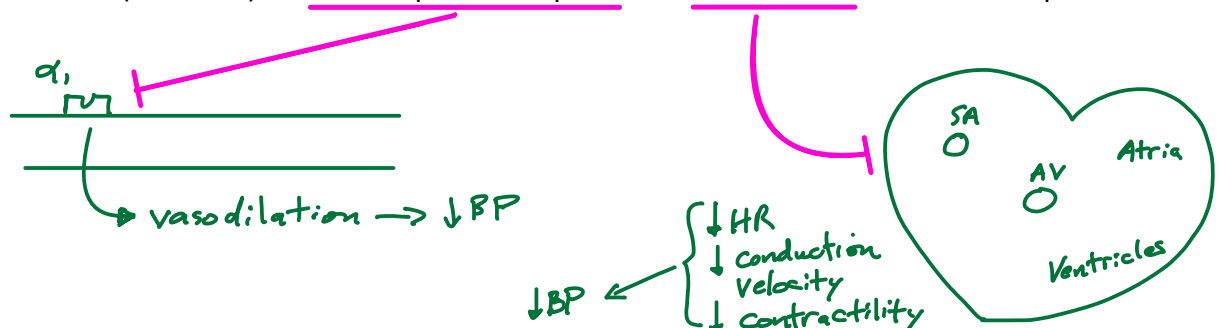


III. Alpha-1 Blockers: Terazosin (Hytrin)

- Terazosin blocks alpha-1 receptors on blood vessels → vasodilation → decreases BP.
- Side Effect: orthostatic hypotension → vertigo → syncope
- Terazosin is dosed once daily at bedtime (QHS) to prevent orthostatic hypotension.

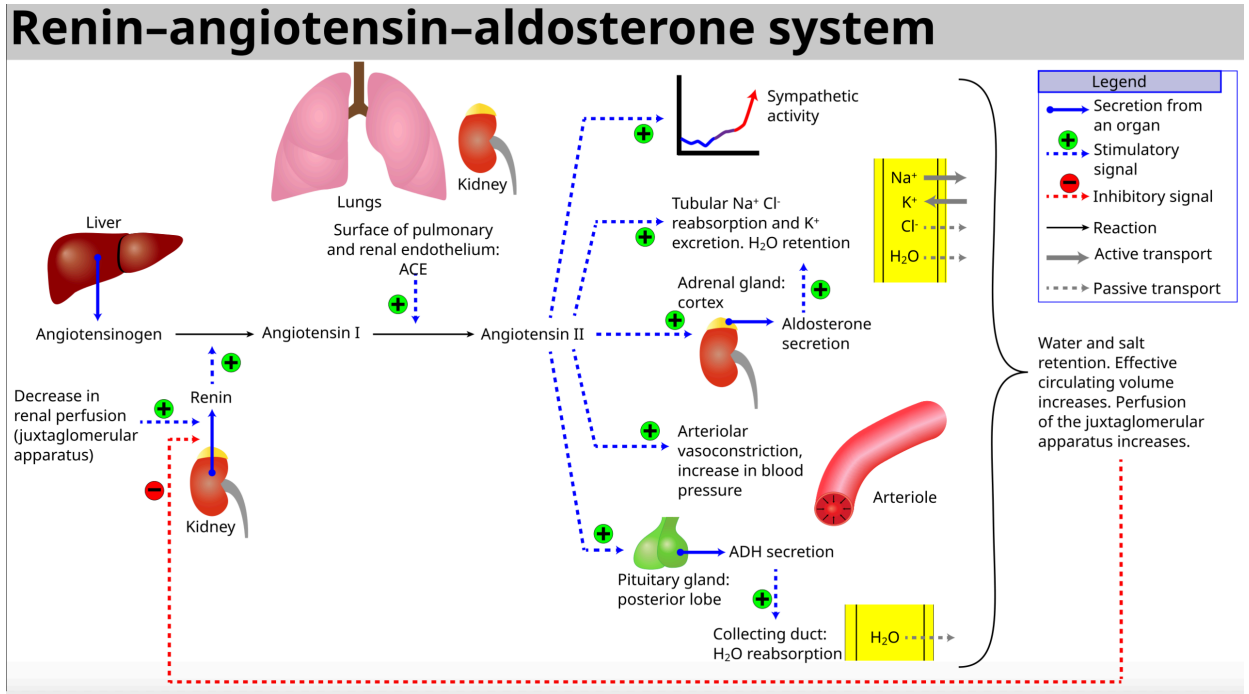
IV. Alpha-Beta Blockers: Labetalol (Trandate)

- Labetalol (Trandate) → blocks alpha-1 receptors and blocks beta-1 & beta-2 receptors.



V. ACE-Inhibitors (ACEi): Lisinopril (Zestril, Prinivil)

- Side Effects: (1) hyperkalemia, (2) cough, and (3) angioedema.
- Caution: ACEi's are contraindicated in pregnancy.

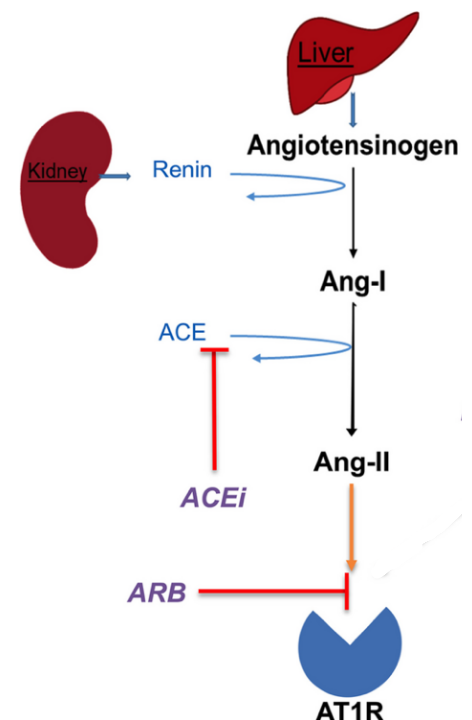


VI. Angiotensin-II Receptor Blockers (ARB): Losartan (Cozaar)

- Side Effects: (1) hyperkalemia
(2) cough
(3) angioedema

Note: The incidence of cough and angioedema is significantly less frequent with ARB's than with ACEi's.

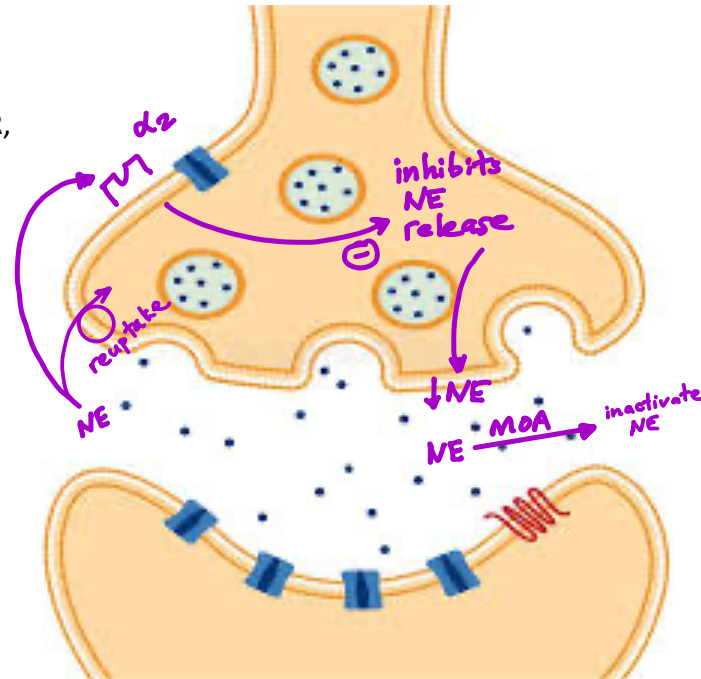
- When switching from an ACEi to an ARB due to cough or angioedema, allow a 6-week washout period before starting an ARB.
- Caution: ARB's and ACEi's are contraindicated in pregnancy.



VII. Centrally-Acting Alpha-2 Agonists: Clonidine (Catapres)

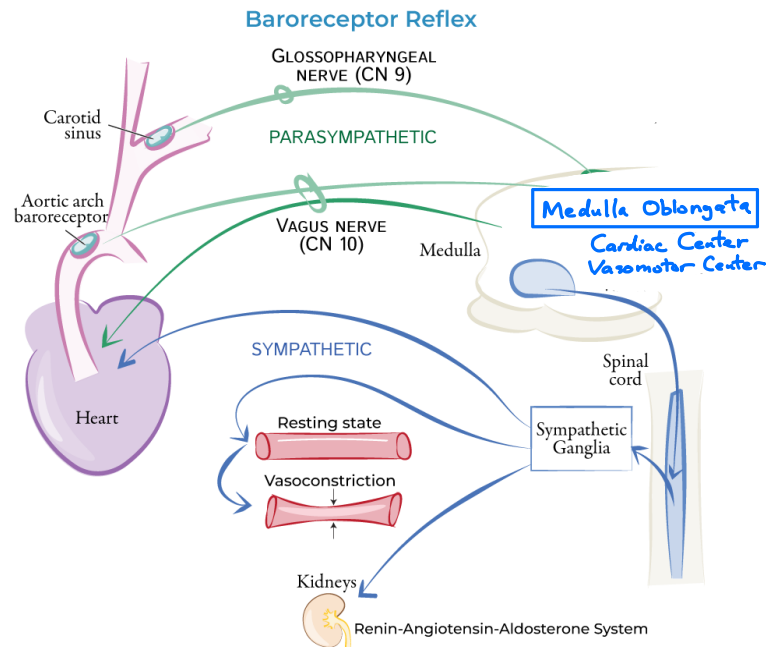
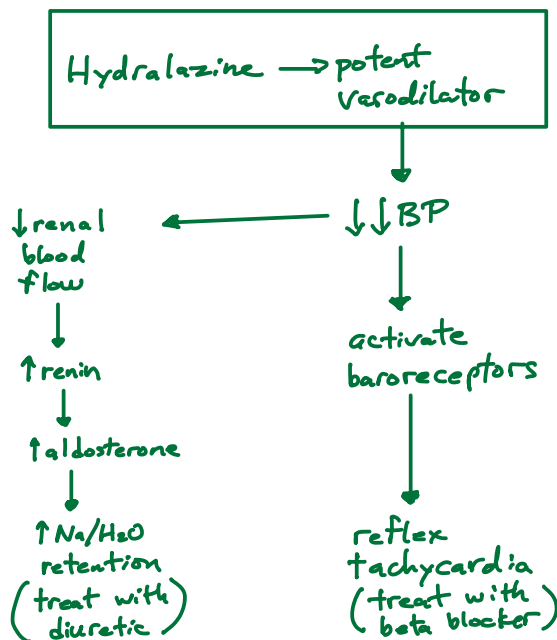
- Clonidine stimulates presynaptic alpha-2 receptors in the cardiac and vasomotor centers → decreases NE release → decreases sympathetic outflow to the heart (decreases HR, conduction velocity, force of contraction) and blood vessels (i.e., vasodilation) → decreases blood pressure.
- Side Effect: sedation / drowsiness

MEDULLA OBLONGATA	
ARAS (consciousness)	Cardiac Center
Respiratory Center	Vasomotor Center



VIII. Direct-Acting Vasodilators: Hydralazine (Apresoline)

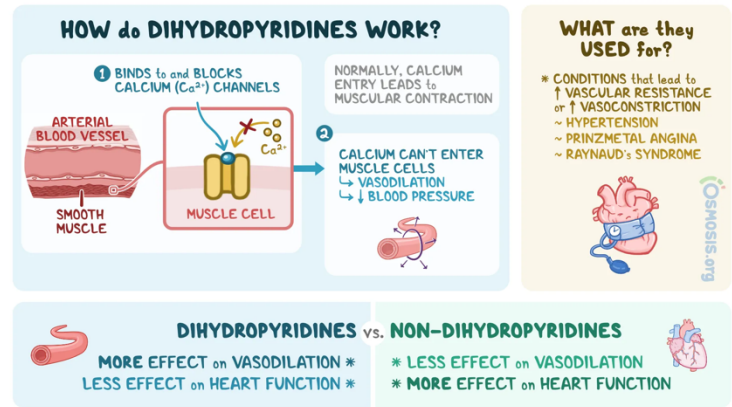
- Hydralazine is a 3rd or 4th-line agent in the stepped-care treatment of hypertension, since direct-acting vasodilators are very potent vasodilators.
- Side Effects: reflex tachycardia and Na/H₂O retention.



IX. Calcium Channel Blockers (CCB)

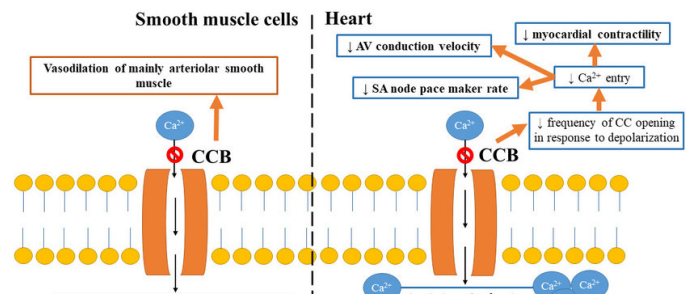
A. Dihydropyridines: Nifedipine (Procardia)

- Nifedipine blocks calcium influx into vascular smooth muscle → vasodilation → decrease blood pressure.
- Nifedipine may cause reflex tachycardia (+++) in response to baroreceptor stimulation in the aortic bodies and carotid sinuses.



B. Non-Dihydropyridines: Diltiazem (Cardizem) and Verapamil (Calan)

- Non-dihydropyridine CCB's → block calcium influx into cardiac muscle → decrease myocardial contractility → decrease blood pressure
- Non-dihydropyridine CCB's → block calcium influx into nodal tissue → decrease HR (SA node) and decrease conduction velocity (AV node) → decrease blood pressure
 - Since non-dihydropyridine CCB's inhibit nodal tissue, they may also be used to treat atrial fibrillation and SVT (supraventricular tachycardia).



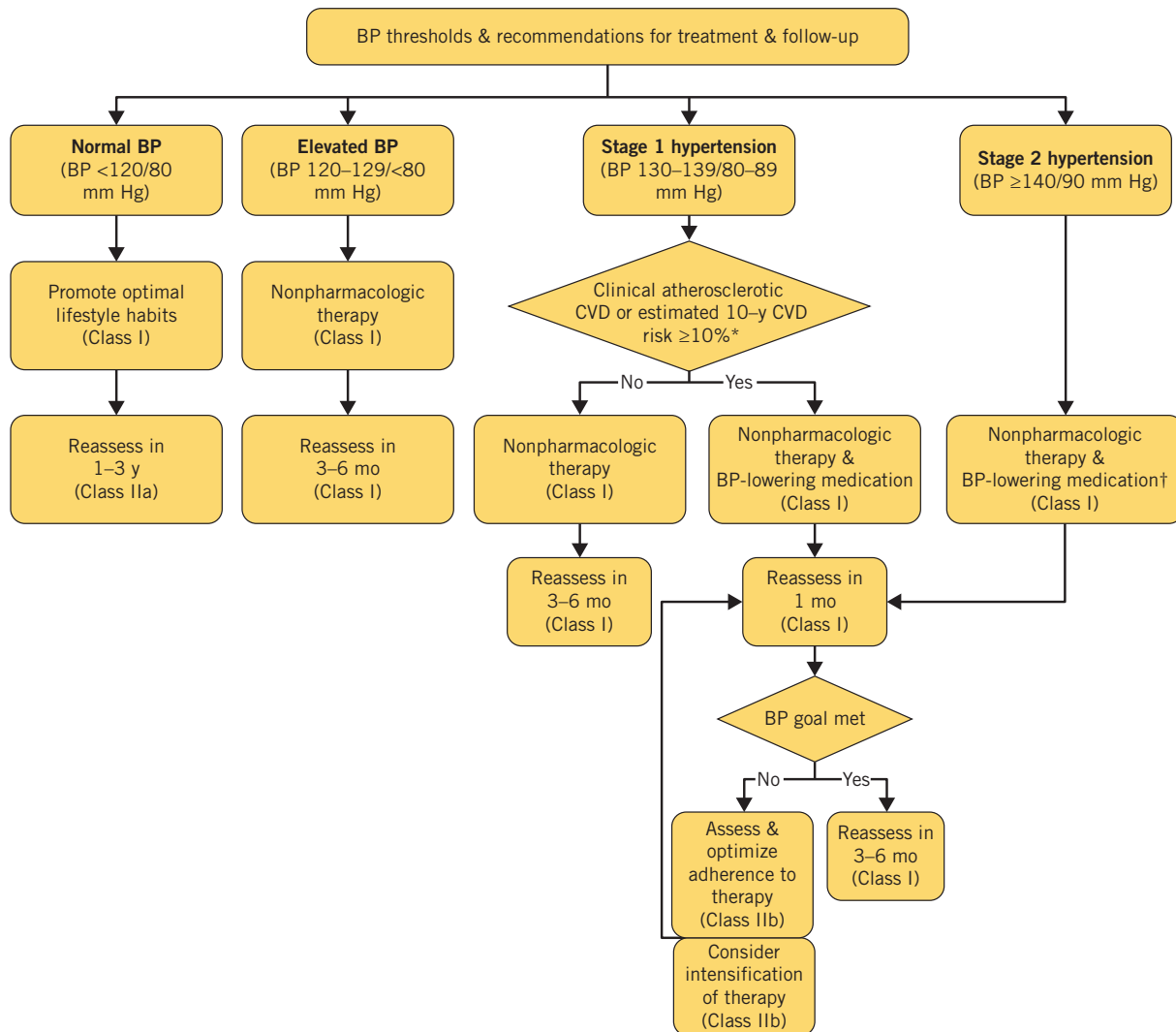
- Verapamil should be used with caution in patients with heart failure since it may reduce contractility in an already "weakened heart."

- Nifedipine has the greatest potency (+++) for vasodilation and reflex tachycardia.
- Verapamil has the greatest potency (+++) for AV blocking effect and causing a negative inotropic effect (i.e., decreased contractility) on the heart.

EFFECTS	Nifedipine (Procardia)	Diltiazem (Cardizem)	Verapamil (Calan)
Vasodilation	(+++)	(+)	(+/-)
Reflex Tachycardia	(+++)	(+)	0
Negative Inotropic	0	(+)	(+++)

ACC/AHA: Clinical Practice Guidelines (2017)

TABLE 1. Comparing BP classifications ^{4,7}			
If the patient's systolic and diastolic BPs fall into different categories, classify the patient's hypertension according to the highest category.			
Systolic BP (mm Hg)	Diastolic BP (mm Hg)	2017 guideline	JNC 7
<120	<80	Normal	Normal
120-129	<80	Elevated	Prehypertension
130-139	80-89	Stage 1 hypertension	Stage 1 hypertension
140-159	90-99	Stage 2 hypertension	Stage 2 hypertension
≥160	≥100		Stage 2 hypertension



INITIAL TREATMENT RECOMMENDATIONS

- In the absence of specific compelling indications: ACE-I or ARB, CCB, and thiazide diuretic.
- General non-black population, including those with diabetes, initial pharm treatment should include: ACE-I or ARB, CCB, and thiazide diuretic.
- General black population, initial treatment should include: CCB and thiazide diuretic.
- All patients with CKD and HTN, initial tx should include: ACE-I or ARB → improve kidney outcomes
- In all hypertensive patients, if goal BP is not reached within a month of initiating treatment, increase the dose of the initial drug OR add a 2nd drug from a different class. *OR discontinue 1st drug and select a drug from a different class (MOA)*

Oral Antihypertensive Drugs (1 of 3)

Class	Drug	Usual Dose, Range (mg per day)*	Daily Frequency	Comments
Primary Agents				
Thiazide or thiazide-type diuretics	Chlorthalidone	12.5-25	1	<ul style="list-style-type: none"> • Chlorthalidone preferred based on prolonged half-life and proven trial reduction of CVD • Monitor for hyponatremia and hypokalemia, uric acid and calcium levels. • Use with caution in patients with history of acute gout unless patient is on uric acid-lowering therapy.
	Hydrochlorothiazide	25-50	1	
	Indapamide	1.25-2.5	1	
	Metolazone	2.5-10	1	
ACE Inhibitors	Benazepril	10-40	1 or 2	<ul style="list-style-type: none"> • Do not use in combination with ARBs or direct renin inhibitor • Increased risk of hyperkalemia, especially in patients with CKD or in those on K+ supplements or K+-sparing drugs • May cause acute renal failure in patients with severe bilateral renal artery stenosis • Do not use if history of angioedema with ACE inhibitors. • Avoid in pregnancy
	Captopril	12.5-150	2 or 3	
	Enalapril	5-40	1 or 2	
	Fosinopril	10-40	1	
	Lisinopril	10-40	1	
	Moexipril	7.5-30	1 or 2	
	Perindopril	4-16	1	
	Quinapril	10-80	1 or 2	
	Ramipril	2.5-10	1 or 2	
ARBs	Azilsartan	40-80	1	<ul style="list-style-type: none"> • Do not use in combination with ACE inhibitors or direct renin inhibitor • Increased risk of hyperkalemia in CKD or in those on K+ supplements or K+-sparing drugs • May cause acute renal failure in patients with severe bilateral renal artery stenosis • Do not use if history of angioedema with ARBs. Patients with a history of angioedema with an ACEI can receive an ARB beginning 6 weeks after ACEI discontinued. • Avoid in pregnancy
	Candesartan	8-32	1	
	Eprosartan	600-800	1 or 2	
	Irbesartan	150-300	1	
	Losartan	50-100	1 or 2	
	Olmesartan	20-40	1	
	Telmisartan	20-80	1	
	Valsartan	80-320	1	
CCB—dihydropyridines	Amlodipine	2.5-10	1	<ul style="list-style-type: none"> • Avoid use in patients with HFrEF; amlodipine or felodipine may be used if required • Associated with dose-related pedal edema, which is more common in women than men
	Felodipine	5-10	1	
	Isradipine	5-10	2	
	Nicardipine SR	5-20	1	
	Nifedipine LA	60-120	1	
	Nisoldipine	30-90	1	
CCB—nondihydropyridines	Diltiazem SR	180-360	2	<ul style="list-style-type: none"> • Avoid routine use with beta blockers due to increased risk of bradycardia and heart block • Do not use in patients with HFrEF • Drug interactions with diltiazem and verapamil (CYP3A4 major substrate and moderate inhibitor)
	Diltiazem ER	120-480	1	
	Verapamil IR	40-80	3	
	Verapamil SR	120-480	1 or 2	
	Verapamil-delayed onset ER (various forms)	100-480	1 (in the evening)	

Table is continued in the next two pages



Oral Antihypertensive Drugs (2 of 3)

Class	Drug	Usual Dose, Range (mg per day)*	Daily Frequency	Comments
Secondary Agents				
Diuretics—loop	Bumetanide	0.5–4	2	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Monotherapy agents minimally effective antihypertensives Combination therapy of potassium sparing diuretic with a thiazide can be considered in patients with hypokalemia on thiazide monotherapy Avoid in patients with significant CKD (e.g., GFR <45 mL/min)
	Triamterene	50–100	1 or 2	
Diuretics—aldosterone antagonists	Eplerenone	50–100	12	<ul style="list-style-type: none"> Preferred agents in primary aldosteronism and resistant hypertension Spironolactone associated with greater risk of gynecomastia and impotence compared to eplerenone Common add-on therapy in resistant hypertension Avoid use with K⁺ supplements, other K⁺-sparing diuretics or significant renal dysfunction Eplerenone often requires twice daily dosing for adequate BP lowering
	Spironolactone	25–100	1	
Beta blockers—cardioselective	Atenolol	25–100	12	<ul style="list-style-type: none"> 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	100–400	2	
	Metoprolol succinate	50–200	1	
Beta blockers—cardioselective and vasodilatory	Nebivolol	5–40	1	<ul style="list-style-type: none"> Induces nitric oxide-induced vasodilation Avoid abrupt cessation
Beta blockers—noncardioselective	Nadolol	40–120	1	<ul style="list-style-type: none"> Avoid in patients with reactive airways disease Avoid abrupt cessation
	Propranolol IR	160–480	2	
	Propranolol LA	80–320	1	
Beta blockers—intrinsic sympathomimetic activity	Acebutolol	200–800	2	<ul style="list-style-type: none"> Generally avoid, especially in patients with IHD or HF Avoid abrupt cessation
	Carteolol	2.5–10	1	
	Penbutolol	10–40	1	
	Pindolol	10–60	2	

Table is continued in the next page



Oral Antihypertensive Drugs (3 of 3)

Class	Drug	Usual Dose, Range (mg per day)*	Daily Frequency	Comments
Secondary Agents (continued from previous page)				
Beta blockers—combined alpha- and beta-receptor	Carvedilol	12.5-50	2	<ul style="list-style-type: none"> • Carvedilol preferred in patients with HFrEF • Avoid abrupt cessation
	Carvedilol phosphate	20-80	1	
	Labetalol	200-800	2	
Direct renin inhibitor	Aliskiren	150-300	1	<ul style="list-style-type: none"> • Do not use in combination with ACE inhibitors or ARBs • Aliskiren is very long acting • Increased risk of hyperkalemia in CKD or in those on K⁺ supplements or K⁺ sparing drugs • May cause acute renal failure in patients with severe bilateral renal artery stenosis • Avoid in pregnancy
Alpha-1 blockers	Doxazosin	1-8	1	<ul style="list-style-type: none"> • Associated with orthostatic hypotension, especially in older adults • May consider as second-line agent in patients with concomitant BPH
	Prazosin	2-20	2 or 3	
	Terazosin	1-20	1 or 2	
Central alpha1-agonist and other centrally acting drugs	Clonidine oral	0.1-0.8	2	<ul style="list-style-type: none"> • Generally reserved as last-line due to significant CNS adverse effects, especially in older adults • Avoid abrupt discontinuation of clonidine, which may induce hypertensive crisis; clonidine must be tapered to avoid rebound hypertension
	Clonidine patch	0.1-0.3	1 weekly	
	Methyldopa	250-1000	2	
	Guanfacine	0.5-2	1	
Direct vasodilators	Hydralazine	250-200	2 or 3	<ul style="list-style-type: none"> • 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	

*Dosages may vary from those listed in the FDA approved labeling (available at <http://dailymed.nlm.nih.gov/dailymed/index.cfm>).

Adapted with permission from Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA. 2003; 289:2560-72

Table 18



