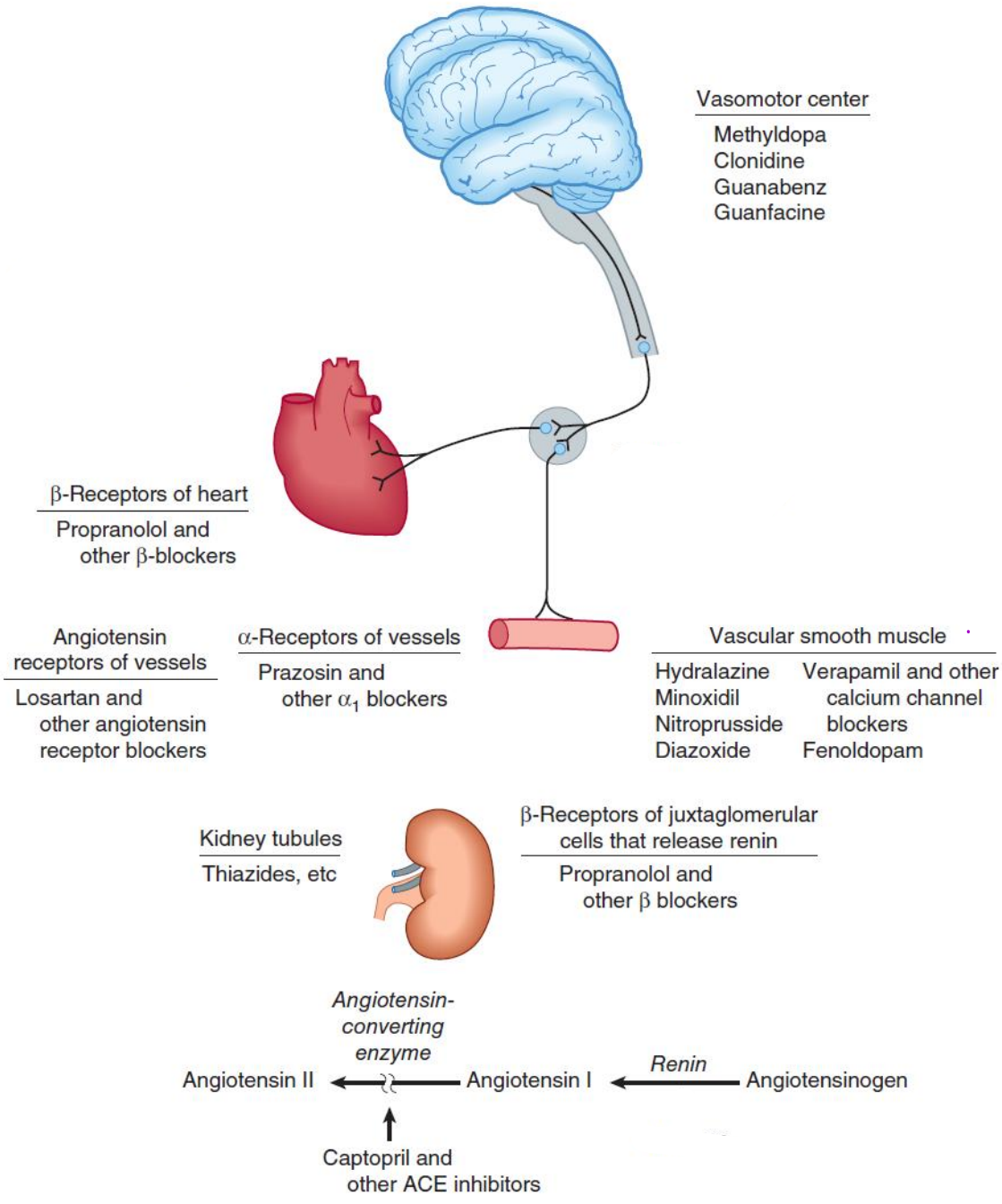
Sites of Action of the Major Classes of Antihypertensive Drugs

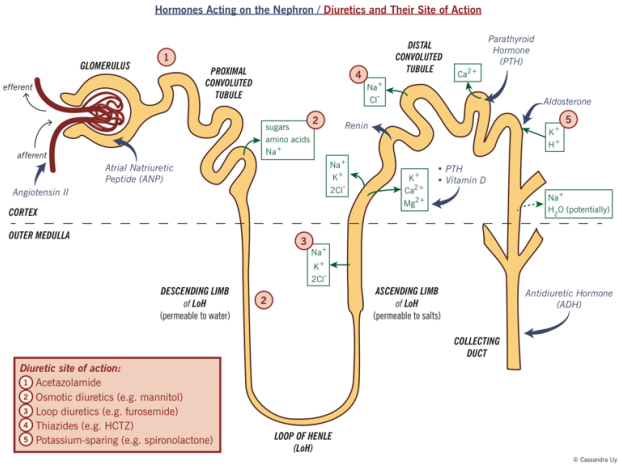


Antihypertensive Agents

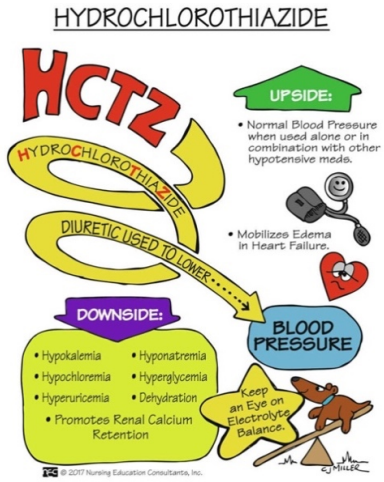
I. Diuretics

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

A. Thiazide Diuretics



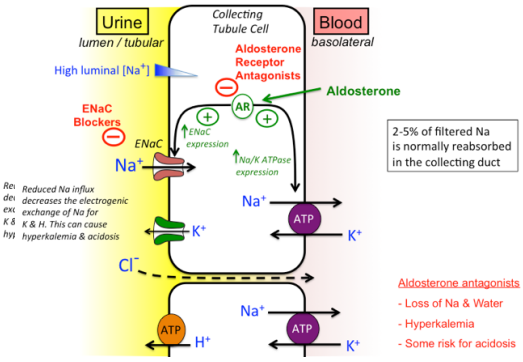
- Hydrochlorothiazide (HCTZ), chlorthalidone (Diuril), indapamide (Lozol), and metolazone (Zaroxolyn) are thiazide diuretics.
- MOA: Thiazide diuretics block Na/H_2O reabsorption in the distal tubule, which accounts for approx. 5-10% of the Na/H_2O reabsorption by the nephron.
- SEs: hypokalemia, hyponatremia, hypomagnesemia, hypercalcemia, hyperglycemia, hyperuricemia, and dehydration.
- Use with caution in patients with a history of gout unless patient is on uric acid-lowering agents, e.g., allopurinol (Zyloprim) 300 mg PO daily.



B. Loop Diuretics

- MOA: Furosemide (Lasix), bumetanide (Bumex), and torsemide (Demadex) block Na/H_2O reabsorption in the ascending Loop of Henle, which accounts for 20-25% of Na/H_2O reabsorption by the nephron.
- Bumetanide is 40 times more potent than furosemide; so, 40 mg of furosemide = 1 mg of bumetanide.
- Loop diuretics are preferred in patients with symptomatic heart failure (HF) and in patients with moderate-severe CKD (i.e., CrCl < 30 ml/min).

C. Potassium Sparing Diuretics



- Triamterene (Dyrenium), amiloride (Midamor), spironolactone (Aldactone), and Eplerenone (Inspra) are K-sparing diuretics.
- Spironolactone and eplerenone are also aldosterone antagonists.
- MOA: K-sparing diuretics block Na^+ channels (ENaC) in the late distal tubule → inhibits Na^+ reabsorption from the lumen → reduces intracellular Na^+ in tubular epithelial cells → decreases function of the Na^+/K^+ ATPase pump → retains K^+ and H^+ ion.

D. Side Effects of Thiazide and Loop Diuretics

(1) Hypokalemia may be prevented or treated with K-sparing diuretics or KCL supplementation.

Class of diuretics	*Drugs*	*Adverse drug reactions (ADRs)*
Thiazides	Hydrochlorothiazide	• ↓ K^+, Na^+, Mg^{2+} • ↑Uric acid and can trigger gout attack • ↑Ca^{2+} • ↑LDL, total cholesterol and total triglycerides
Thiazide-like	Chlorthalidone, Indapamide	
Loop diuretics	Furosemide, Torsemide, Bumetanide	↓K^+, Na^+, Mg^{2+}, Ca^{2+} Ototoxicity Hyperuricemia Dizziness
Potassium sparing diuretics	Spironolactone, Eplerenone, Triamterene, Amiloride	Hyperkalemia Hyponatremia Gynecomastia (Spironolactone) Weakness, fatigue, dizziness

(a) K-sparing diuretics may be added to a thiazide or a Loop diuretic to prevent K^+ depletion.
- Dyazide and Maxzide-25 are brand name combination products containing HCTZ 25 mg and triamterene 37.5 mg, dosed once daily.

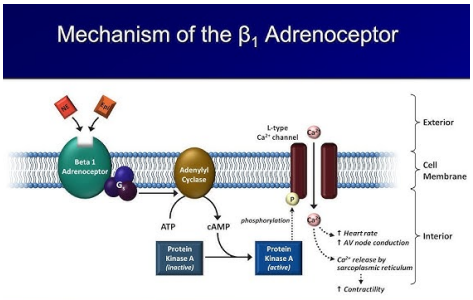
(b) KCL supplements may be separately dosed with a thiazide or a Loop diuretic to prevent and treat hypokalemia.
- K-Dur 20 mEq SR (sustained-release) tablets.
- KCl 10% liquid 20 mEq for immediate release and absorption.
- KCl IV infusions (KCL riders): KCL 40 mEq in 500 ml NS IVPB, infused over 4 hours.

(2) Hypomagnesemia may be prevented or treated with magnesium supplementation.
- Slo-Mag 84 mg SR (sustained-release) tablets.
- Magnesium oxide 400 mg immediate-release tablets.
- Magnesium Sulfate IV infusion: 1-2 grams IVPB, infused over 1-2 hours.

(3) Hypocalcemia may be prevented or treated with calcium supplementation.
- Note: Thiazide diuretics are calcium-sparing.
- Calcium carbonate (TUMS) 800-1200 mg PO daily.
- Calcium gluconate 1-2 grams IVPB, infused over 1-2 hours.

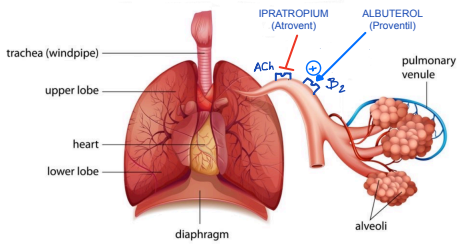
II. Beta Blockers

- MOA: Beta blockers (BB) block beta-1 receptors on the SA node, AV node, atria, and ventricles of the heart → reduce heart rate (SA node), reduce conduction velocity (AV node), and decrease myocardial contractility (atria, ventricles) → decrease blood pressure.



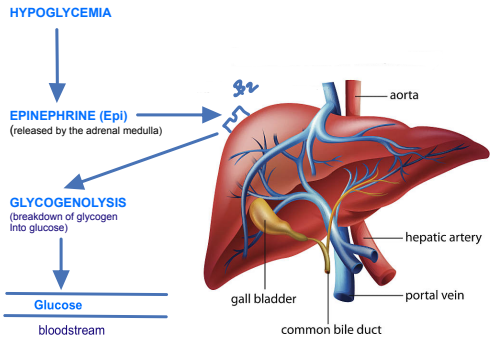
A. Selective Beta-1 Blockers: Metoprolol (Lopressor, Toprol XL) and Atenolol (Tenormin), and intravenous Esmolol (Brevibloc).
- Selective Beta-1 blockers are also called "cardioselective" beta blockers.

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 in the bronchioles → induces bronchoconstriction.



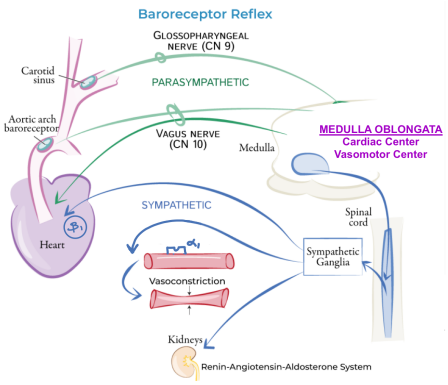
B. Non-Selective Beta Blocker: Propranolol (cont.)

- 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: Prazosin (Minipress), Doxazosin (Cardura), and Terazosin (Hytrin).

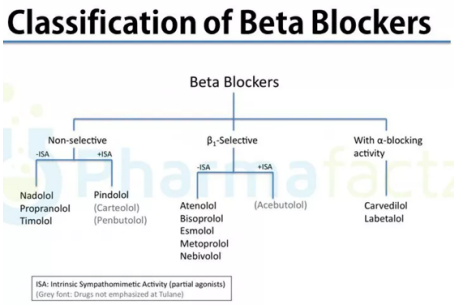
- MOA: Terazosin blocks alpha-1 receptors on blood vessels → vasodilation → decreases BP.
- SE: orthostatic hypotension → vertigo → syncope.
- Terazosin is dosed once daily at bedtime (QHS) to prevent orthostatic hypotension.
- Terazosin is also indicated for BPH (benign prostatic hyperplasia).

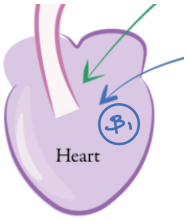


IV. Alpha-Beta Blockers: Labetalol (Trandate) and Carvedilol (Coreg).

- MOA: Labetalol (Trandate) → blocks alpha-1 receptors (blood vessels) and blocks beta-1 & beta-2 receptors.

→ blocks alpha-1 → vasodilation → decreases BP





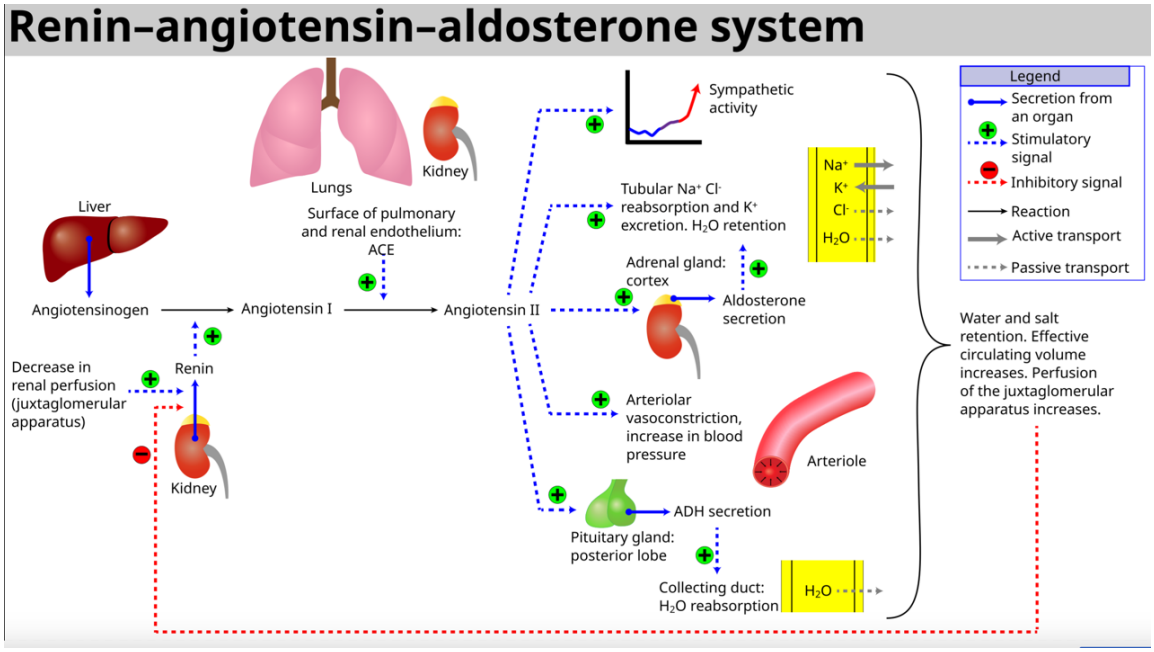
→ blocks beta-1 (SA node) → decreases HR
→ blocks beta-1 (AV node) → decreases conduction velocity
→ blocks beta-1 (atria, ventricles) → decreases contractility

→ decreases BP

V. ACE-Inhibitors (ACEi): Captopril (Capoten), Enalapril (Vasotec), and Lisinopril (Prinivil).

- MOA: ACEi's inhibit ACE → reduce conversion of A-I to A-II → reduce production of A-II

  → reduce vasoconstriction → reduce BP
  → reduce aldosterone secretion → reduce Na/H_2O reabsorption (distal tubule) → reduce BP
  → reduce ADH (vasopressin) secretion → reduce H_2O reabsorption (collecting duct) → reduce BP

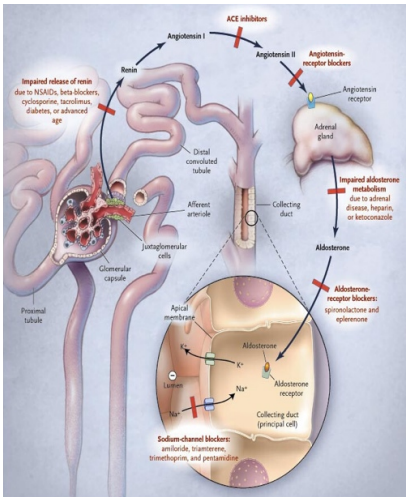


- SEs: (1) hyperkalemia, (2) cough, and (3) angioedema.
- Caution: ACEi's are contraindicated in pregnancy.

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

- MOA: ARBs block A-II receptor sites on blood vessels, adrenal cortex, and posterior pituitary gland.

  → reduce vasoconstriction → reduce BP
  → reduce aldosterone secretion → reduce Na/H_2O reabsorption (distal tubule) → reduce BP
  → reduce ADH secretion → reduce H_2O reabsorption (collecting duct) → reduce BP



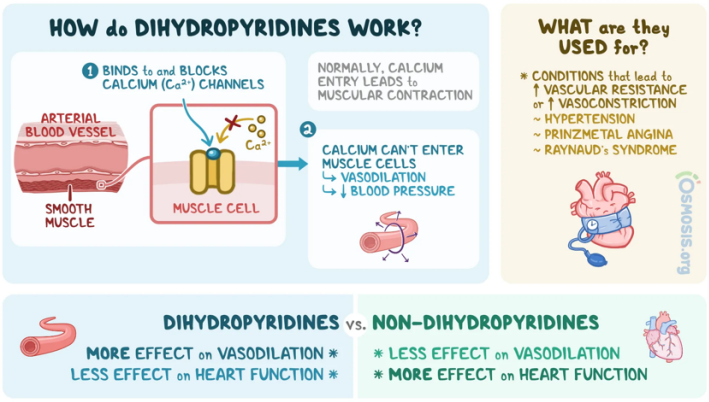
- SEs: (1) hyperkalemia, (2) cough, and (3) angioedema.

  Note: The incidence of cough and angioedema is significantly less frequent with ARBs 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: ARBs and ACEi's are contraindicated in pregnancy.

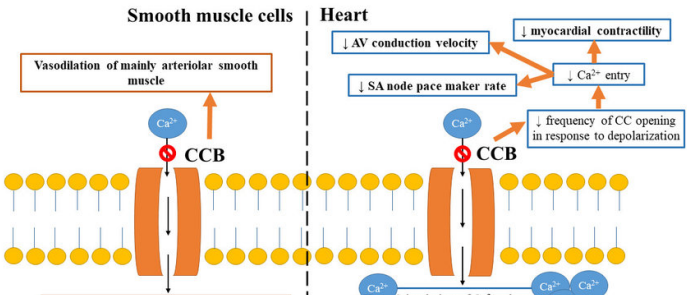
VII. Calcium Channel Blockers (CCB)

A. Dihydropyridines: Nifedipine (Procardia), Amlodipine (Norvasc), and intravenous Nicardipine (Cardene).



- MOA: Nifedipine blocks calcium influx into vascular smooth muscle → vasodilation → decreases BP.
- 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)



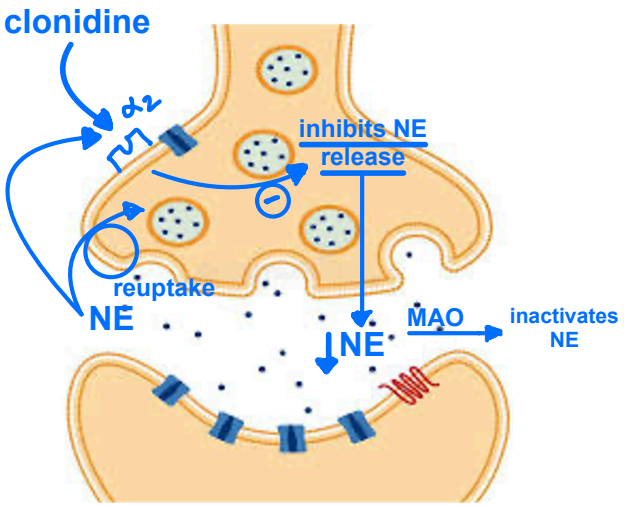
- MOA: Non-dihydropyridine CCBs block calcium influx into cardiac muscle → decrease myocardial contractility → decrease BP.
- MOA: Non-dihydropyridine CCBs block calcium influx into nodal tissue → decrease HR (SA node) and decrease conduction velocity (AV node) → decrease BP.
  - Since non-dihydropyridine CCBs inhibit nodal tissue, they may also be used to treat atrial fibrillation and SVT (supraventricular tachycardia).
  - Non-dihydropyridine CCBs, especially verapamil, should be used with caution in patients with heart failure since they 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	(+)	(+++)

VIII. Centrally-Acting Alpha-2 Agonists: Clonidine (Catapres) and Methyldopa (Aldomet).

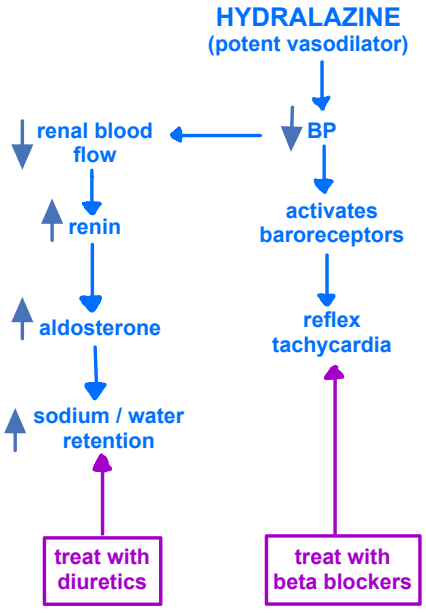
- MOA: Clonidine stimulates presynaptic alpha-2 receptors in the cardiac and vasomotor centers → decreases NE release
  → decreases sympathetic outflow to the heart (decreases HR, decreases conduction velocity, decreases myocardial force of contraction) and decreases sympathetic to blood vessels (vasodilation)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

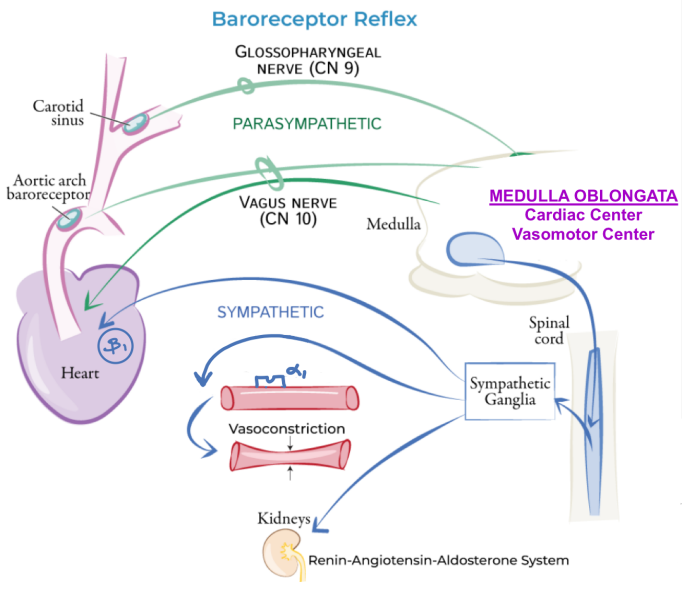


MEDULLA OBLONGATA	
ARAS (consciousness)	Cardiac Center
Respiratory Center	Vasomotor Center

IX. Direct-Acting Vasodilators: Hydralazine (Apresoline) and Minoxidil (Loniten).

- Hydralazine is a 3rd or 4th-line agent in the stepped-care treatment of hypertension, since direct-acting vasodilators are very potent vasodilators.
- SEs: reflex tachycardia and Na/H_2O retention.



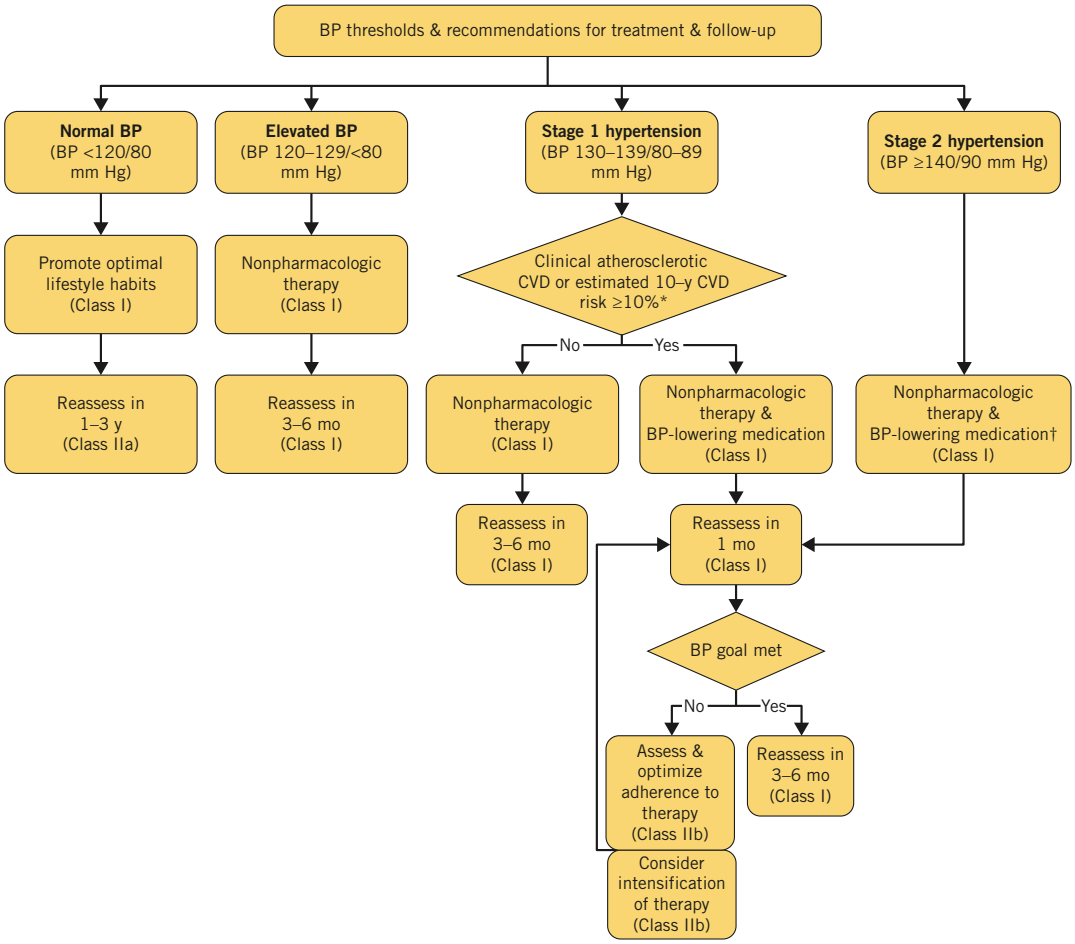


ACC/AHA: Clinical Practice Guidelines (2017)

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	
140-159	90-99	Stage 2 hypertension	Stage 1 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, you may (1) increase the dose of the initial drug OR (2) add a 2nd drug from a different class OR (3) discontinue 1st drug and select a drug from a different class.

Considerations for individualizing antihypertensive therapy

Indication or contraindication	Antihypertensive drugs
Compelling indications (major improvement in outcome independent of blood pressure)	
Heart failure with reduced ejection fraction	ACE inhibitor or ARB, beta blocker, diuretic, aldosterone antagonist*
Postmyocardial infarction	ACE inhibitor or ARB, beta blocker, aldosterone antagonist
Proteinuric chronic kidney disease	ACE inhibitor or ARB
Angina pectoris	Beta blocker, calcium channel blocker
Atrial fibrillation rate control	Beta blocker, nondihydropyridine calcium channel blocker
Atrial flutter rate control	Beta blocker, nondihydropyridine calcium channel blocker
Likely to have a favorable effect on symptoms in comorbid conditions	
Benign prostatic hyperplasia	Alpha blocker
Essential tremor	Beta blocker (noncardioselective)
Hyperthyroidism	Beta blocker
Migraine	Beta blocker, calcium channel blocker
Osteoporosis	Thiazide diuretic
Raynaud phenomenon	Dihydropyridine calcium channel blocker
Contraindications	
Angioedema	Do not use an ACE inhibitor
Bronchospastic disease	Do not use a non-selective beta blocker
Liver disease	Do not use methyldopa
Pregnancy (or at risk for)	Do not use an ACE inhibitor, ARB, or renin inhibitor (eg, aliskiren)
Second- or third-degree heart block	Do not use a beta blocker, nondihydropyridine calcium channel blocker unless a functioning ventricular pacemaker
Drug classes that may have adverse effects on comorbid conditions	
Depression	Generally avoid beta blocker, central alpha-2 agonist
Gout	Generally avoid loop or thiazide diuretic
Hyperkalemia	Generally avoid aldosterone antagonist, ACE inhibitor, ARB, renin inhibitor
Hyponatremia	Generally avoid thiazide diuretic
Renovascular disease	Generally avoid ACE inhibitor, ARB, or renin inhibitor

Antihypertensives in Pregnancy (UpToDate)

Drug	Class	Initial dose	Usual effective dose range	Maximum suggested total daily dose	Comments
Labetalol	Combined alpha and beta blocker	100 mg 2 times daily, increase by 100 mg twice daily every 2 to 3 days as needed	200 to 800 mg in 2 divided doses	2400 mg	Can cause bronchoconstriction. Avoid in patients with asthma, chronic obstructive lung disease, heart failure, bradycardia (heart rate <60 beats per minute), or greater than first-degree heart block. The dosing interval can be increased to 3 times daily if blood pressure is increased prior to the next prescribed dose.
Hydralazine **NOTE:** Due to reflex tachycardia, monotherapy with oral hydralazine is not recommended; hydralazine may be combined with methyldopa or labetalol if needed as add-on therapy	Peripheral vasodilator	Begin with 10 mg 4 times per day, increase by 10 to 25 mg/dose every 2 to 5 days	50 to 100 mg in 2 to 4 divided doses	200 mg*	
Nifedipine extended release (ER)[¶]	Calcium channel blocker	30 to 60 mg once daily as an extended release tablet, increase at 7 to 14 day intervals	30 to 90 mg once daily	120 mg	Do not administer sublingually. Based upon clinical experience of UpToDate contributors, some patients better tolerate nifedipine ER administered in 2 divided doses, which may serve to minimize its peak to trough effects (eg, instead of increasing the dose to 60 mg once daily, it may be desirable in some patients to increase to 30 mg 2 times daily).
Methyldopa	Centrally acting alpha agonist	250 mg 2 to 3 times daily, increase every 2 days as needed[Δ]	250 to 1000 mg in 2 to 3 divided doses	3000 mg	Sedation is a common side effect.

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

Table is continued in the next two pages

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

Table is continued in the next page

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

*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