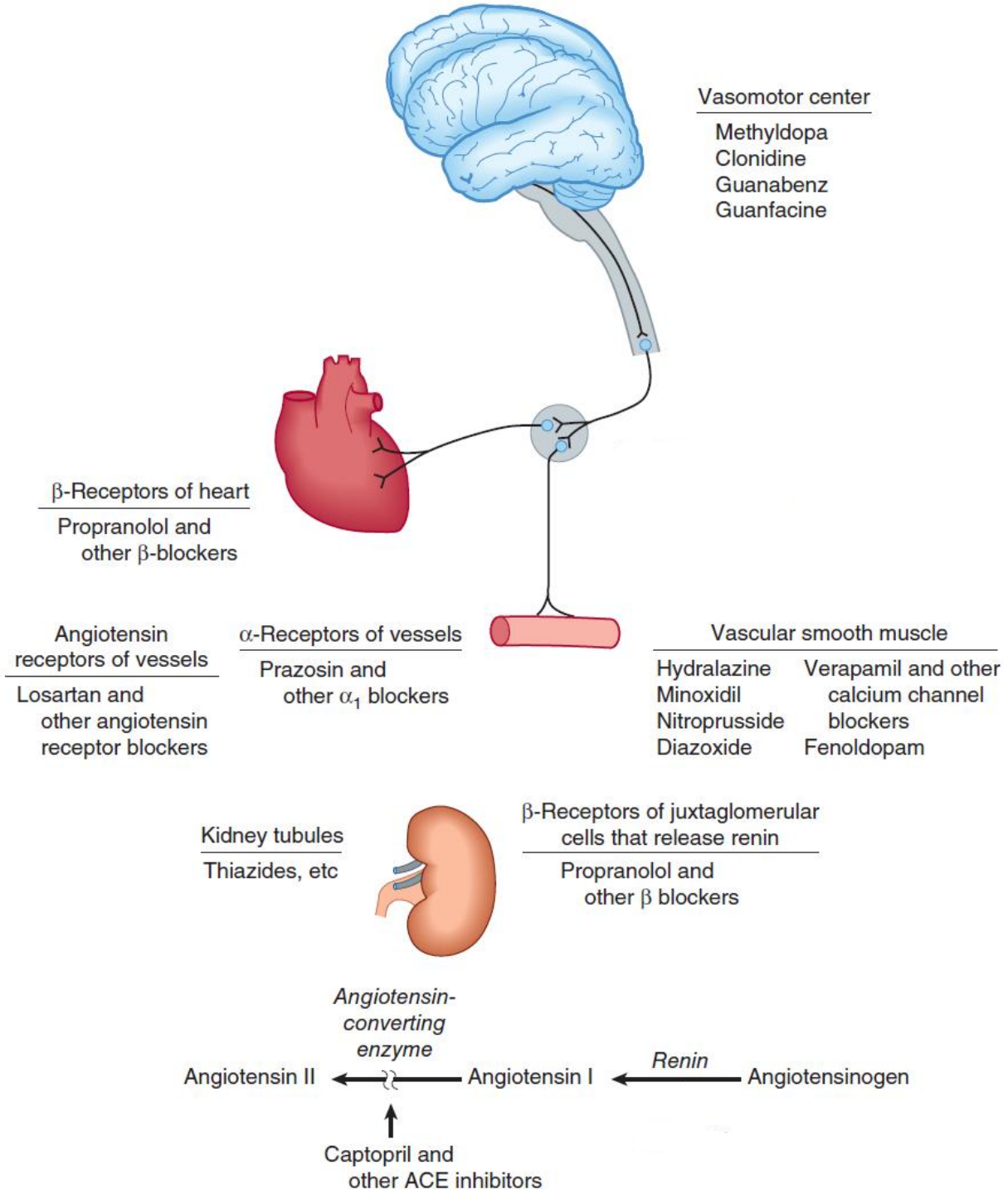
Sites of Action of the Major Classes of Antihypertensive Drugs



Antihypertensive Agents (Class Notes)

I. Diuretics • MOA: ↑ urine volume → ↓ blood volume → ↓ BP

A. Thiazides → block Na/H_2O reabsorption in distal tubule (5-10% Na/H_2O reabsorption)

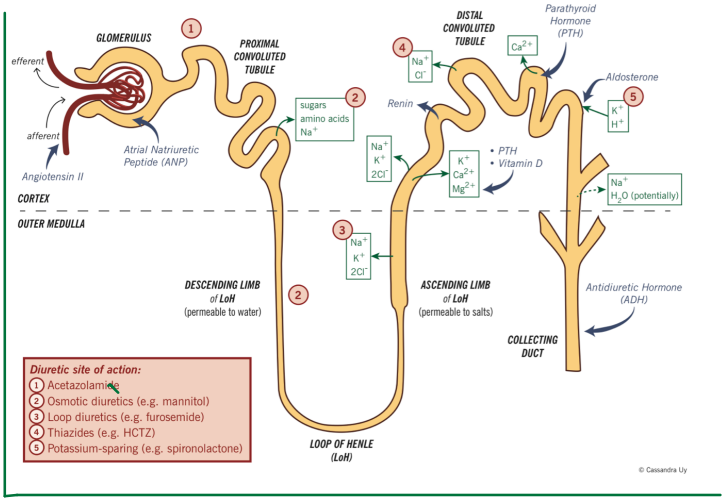
(1) HCTZ (Hydrodiuril) 12.5 – 50 mg caps/tabs

(2) Chlorthalidone (Diuril)

- longer DOA than HCTZ

(3) Metolazone (Zaroxolyn)

- works on the proximal tubule
- may be combined w/ Loop diuretic to enhance effects



B. Loop Diuretics

- block Na/H_2O reabsorption in the ascending Loop of Henle (20-25% Na/H_2O reabsorption)

(1) Furosemide (Lasix)

(2) Bumetanide (Bumex)

- when CrCl < 30 ml/min, Loop diuretics are indicated, since thiazide diuretics are not effective in renally impaired patients

C. K^+ Sparing Diuretics

(1) Spironolactone (Aldactone) – also an aldosterone antagonist

- may cause gynecomastia/impotence in men

(2) Triamterene (Dyrenium)

D. Side Effects

(1) Hypokalemia — Prevent/Treat with the following:

ⓐ K-Sparing Diuretics w/ Thiazides

Examples: Dyazide & Maxzide (HCTZ + Triamterene)

(b) KCl Supplements

Examples: KDur 20mEq/40mEq SR tabs
KCl 10% Liquid (immediate absorption)

(c) KCl IV infusion (KCl riders)

Example: KCl 20mEq in NS 250ml IVPB
infuse over 2 hours

(2) Hypomagnesemia – Prevent/Treat w/ Mg supplements

Examples: Magnesium Oxide 400mg tabs } PO
Slo-Mg 84mg SR tabs }
Magnesium sulfate 1-2 GM IVPB } IV
infuse over 1-2 hours

(3) Hypocalcemia with Loop Diuretics
(Note: Thiazides are calcium-sparing)

- Prevent/Treat with calcium supplements

TUMS ($CaCO_3$) 800-1200 mg PO daily

Calcium Gluconate 1-2 GM IVPB over 1-2 hours

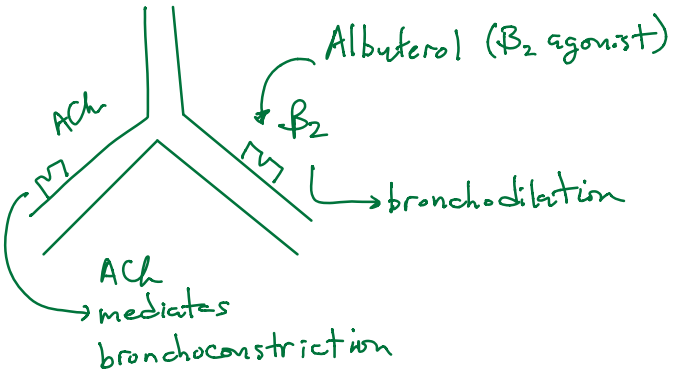
II. Beta-Blockers
- Non-selective beta-blockers block β_1, β_2
- Selective beta-blockers block β_1

A. Non-Selective Beta-Blockers

Propranolol (Inderal)

- use with caution in patients with COPD/asthma since propranol blocks β_2 receptors in the airways and competes with albuterol (β_2 agonist) for β_2 receptor sites.
- propranolol also blocks β_2 receptors in the liver in diabetics

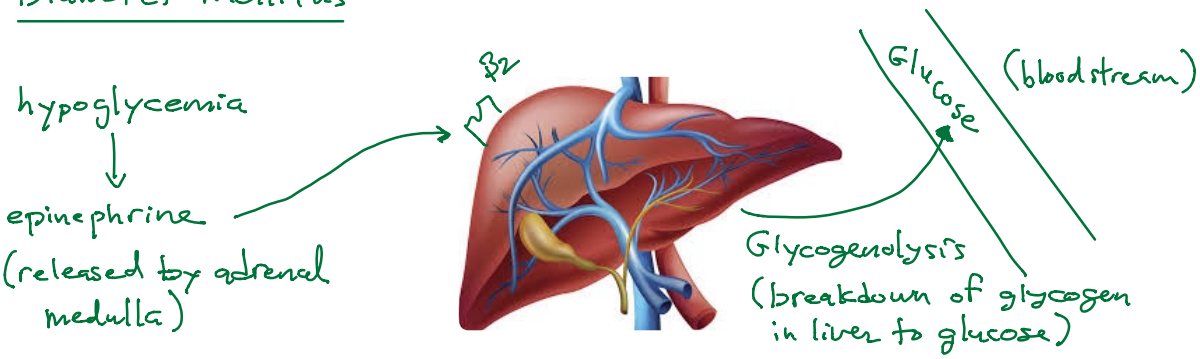
COPD/Asthma



Duoneb
= albuterol + ipratropium
(β_2 agonist) (ACh blocker)

inhalational bronchodilator which stimulates β_2 and block ACh receptors in bronchioles

Diabetes Mellitus



- During hypoglycemic episodes, Epi is released into the bloodstream by the adrenal medulla to stimulate β_2 receptors in the liver to initiate glycogenolysis. Non-selective beta-blockers block glycogenolysis and prevent glucose replacement during hypoglycemic episodes.
- Note: "ALL" beta-blockers (ie., selective and non-selective) will mask the sympathetic signs & symptoms (caused by Epi) during hypoglycemia in diabetics.

B. Selective β_1 - Blockers

(1) Metoprolol
- metoprolol tartrate (Lopressor) (BID dosing)
- metoprolol succinate (Toprol XL) (Once daily dosing)

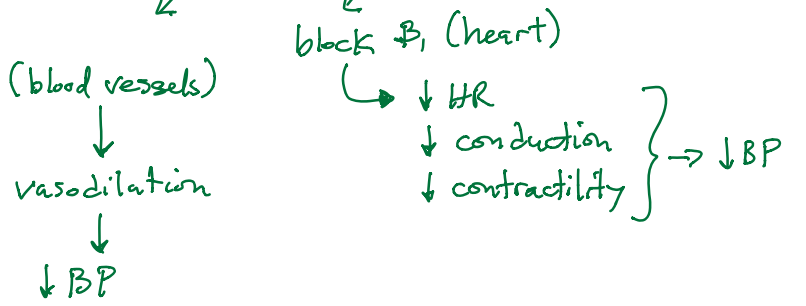
(2) Atenolol (Tenormin)

III. Alpha-Beta Blockers (combined α_1 and β_1/β_2 blockers)

(1) Labetalol (Trandate)

(2) Carvedilol (Coreg)

Note: Nonselective beta blocking



IV. Alpha-1 Blockers (block α-1 receptors → vasodilation → ↓ BP)

(1) Prazosin (Minipres)

(2) Doxazosin (Cardura)

(3) Terazosin (Hytrin)

Side Effects

Orthostatic Hypotension → Vertigo → Syncope

(therefore, terazosin is dosed once daily at bedtime (QHS))

V. ACE-Inhibitors

(1) Captopril (Capoten)

(2) Enalapril (Vasotec)

(3) Lisinopril (Prinivil, Zestril)

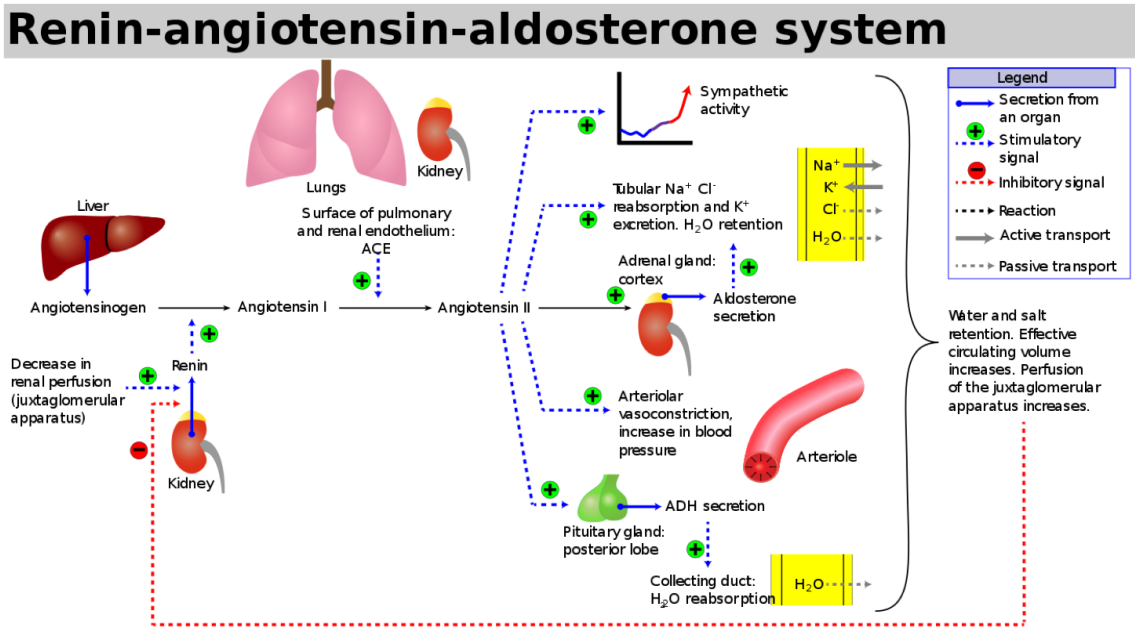
Side Effects

Hyperkalemia
Cough
Angioedema

Caution

ACE-I's & ARB's are contraindicated during pregnancy

Mechanisms of Action of ACE-I's and ARB's



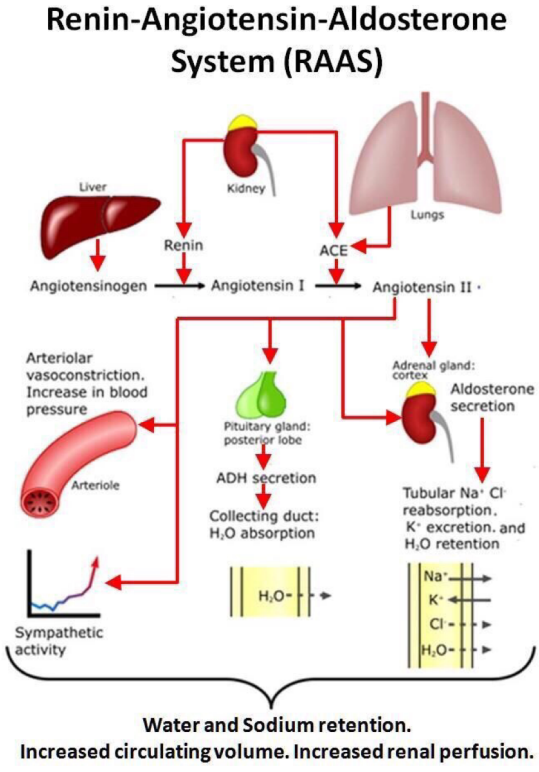
VI. Angiotensin II Receptor Blockers (ARB's)

(1) Losartan (Cozaar)

(2) Valsartan (Diovan)

Caution: ACE-I's & ARB's are contraindicated in pregnancy.

Note: If switching from ACE-I to ARB (due to cough or angioedema), allow a 6-week washout period before starting an ARB.



VII. Calcium Channel Blockers

A. Dihydropyridines
- Amlodipine (Norvasc)
- Nifedipine (Procardia)

↳ block calcium influx into vascular smooth muscle
↓
vasodilation → ↓BP

- may cause reflex tachycardia (+++) in response to baroreceptor stimulation (aortic bodies and carotid sinuses)

B. Nondihydropyridines
- Diltiazem (Cardizem)
- Verapamil (Calan, Isoptin)

↳ block calcium influx into cardiac muscle → ↓ myocardial contractility → ↓BP
and nodal tissue → { ↓ HR ; ↓ conduction velocity (AV node) } → ↓ BP

- verapamil & diltiazem may also be used to treat SVT (supraventricular tachycardia) and atrial fibrillation
- verapamil should be used with caution in patients with heart failure because it can reduce contractility (i.e., negative inotropic effect) in a "weak" heart.

Effects	Nifedipine (Procardia)	Diltiazem (Cardizem)	Verapamil (Calan, Isoptin)
vasodilation	(+++)	(+)	(+/-)
reflex tachycardia	(+++)	(+)	0
AV block (negative inotrope)	0	(+)	(+++)

Note: 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 (decreased contractility) on the heart.

VIII. Centrally-Acting Alpha-2 Agonists

(1) Clonidine (Catapres)

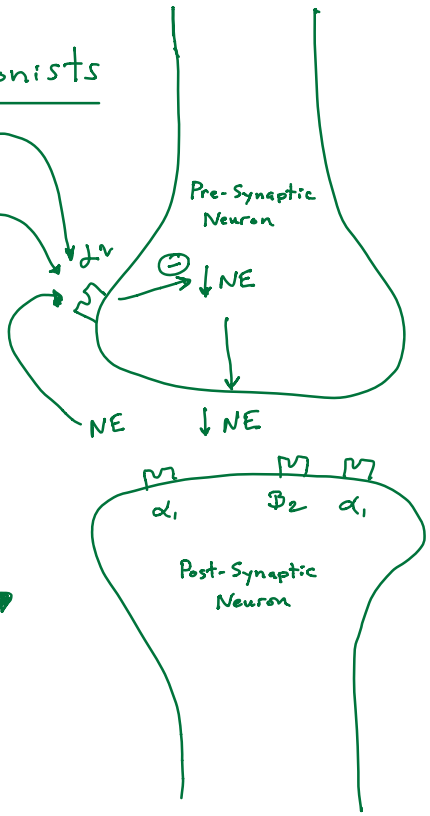
(2) Methyldopa (Aldomet)

stimulating presynaptic α_2 receptors in vasomotor and cardiac centers decreases norepinephrine (NE) release and decreases sympathetic outflow to the heart and blood vessels

↳ ↓ HR

↳ vasodilation

↓ BP



Medulla Oblongata

ARAS (consciousness)	Cardiac Center
Respiratory Center	Vasomotor Center

Note: #1 side effect of centrally-acting α_2 agonists is: sedation/drowsiness

IX. Direct-Acting Vasodilators

(1) Hydralazine (Apresoline)

(2) Minoxidil (Loniten)

} Potent Vasodilators

- Direct-acting diuretics are 3rd-4th line agents in the stepped-care treatment of HTN

↓↓ BP → ↓ renal blood flow → ↑ renin → Na/H_2O retention (treat with diuretic)

↓↓ BP → ↓↓ BP

↓↓ BP → baroreceptors → reflex tachycardia (treat with β-blocker)

Antihypertensive Agents Used for Hypertensive Urgencies/Emergencies

① Labetolol (Normadyne, Trandate) (IV)

α_1, β_1, β_2 blocks

Typical order:
Labetolol 10-20 mg IV Q6H prn SBP > 160-170

② Enalapril (Vasotec) (IV)

ACE-Inhibitor

Typical order: Enalapril 0.625-1.25 mg IV Q6H prn SBP > 160-170

③ Clonidine (Catapres) (PO)

Centrally-Acting α_2 Agonist

Typical order: Clonidine 0.1 mg PO Q6-8H prn SBP > 160-170

④ Hydralazine (IV)

Direct-Acting Vasodilator

Typical Order: Hydralazine 10-20 mg IV Q4-6H prn SBP > 160-170

⑤ Nicardipine (Cardene) (IV)

Calcium Channel Blocker (Dihydropyridine)

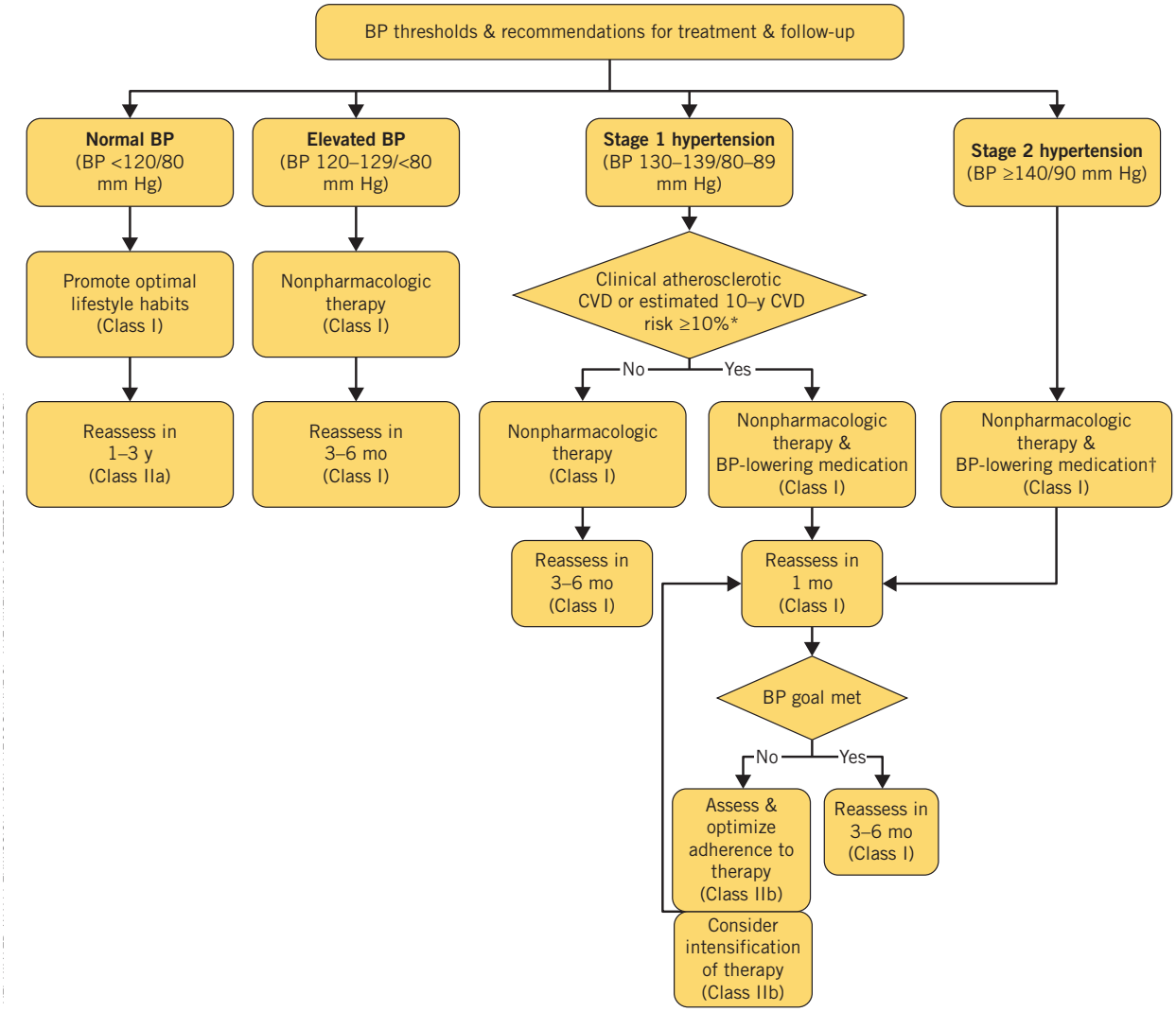
Typical Order:
5-15 mg/hr infusion for SBP > 185/DBP > 110 indicated for Stroke

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, increase the dose of the initial drug OR add a 2nd drug from a different class.

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

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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

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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

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Interdependent and Interacting Factors in Blood Pressure Regulation