
Pharmacotherapy of Hypertension

Tessema Tsehay (B.Pharm., M.Pharm., RPh.)

INTRODUCTION

- Hypertension is defined as *persistently elevated arterial blood pressure (BP)*.
- The classification of BP in adults (age 18 years and older)

Table 6. Categories of BP in Adults*

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

*Individuals with SBP and DBP in 2 categories should be designated to the higher BP category.

BP indicates blood pressure (based on an average of ≥2 careful readings obtained on ≥2 occasions, as detailed in Section 4); DBP, diastolic blood pressure; and SBP systolic blood pressure.

Cont...

- **Hypertensive crisis** (BP >180/120 mm Hg) may be categorized as:
 - **hypertensive emergency** (extreme BP elevation with acute or progressing end-organ damage) or
 - **hypertensive urgency** (high BP elevation without acute or progressing end-organ injury).

PATHOPHYSIOLOGY

- Hypertension may result from:
 - an unknown etiology (**primary or essential hypertension**) or from
 - a specific cause (**secondary hypertension**).

Cont...

- **Secondary hypertension** (<10% of cases) is usually caused by **chronic kidney disease (CKD)** or renovascular disease.
- Other conditions are:
 - Cushing syndrome
 - Coarctation of the aorta
 - Obstructive sleep apnea
 - hyperparathyroidism
 - Pheochromocytoma
 - Primary aldosteronism and
 - Hyperthyroidism

Cont...

- **Some drugs** that may increase BP include
 - Corticosteroids
 - Estrogens
 - NSAIDs
 - Amphetamines
 - Sibutramine
 - Cyclosporine
 - Tacrolimus
 - Erythropoietin and
 - Venlafaxine

Cont...

- **Factors contributing to development of primary hypertension include:**
 - Humoral abnormalities involving the renin–angiotensin–aldosterone system (RAAS) or natriuretic hormone;
 - Disturbance in the CNS, autonomic nerve fibers, adrenergic receptors, or baroreceptors;

Cont...

- Abnormalities in renal or tissue autoregulatory processes for sodium excretion, plasma volume, and arteriolar constriction;
- **Deficiency** in synthesis of **vasodilating substances** in vascular endothelium (prostacyclin, bradykinin, and nitric oxide) OR **Excess vasoconstricting substances** (angiotensin II, endothelin) and
- High sodium intake or lack of dietary calcium.

Cont...

- **Main causes of death are:**
 - Cerebrovascular events,
 - Cardiovascular (CV) events, and
 - Renal failure
- Probability of premature death correlates with the severity of BP elevation.

CLINICAL PRESENTATION

- Patients with **uncomplicated** primary hypertension are usually **asymptomatic initially**.
- Patients with secondary hypertension may have **symptoms of the underlying disorder**.
 - Patients with **pheochromocytoma** may have headaches, sweating, tachycardia, palpitations, and orthostatic hypotension.

Cont...

- In **primary aldosteronism**, hypokalemic symptoms of muscle cramps and weakness may be present.
- Patients with **Cushing syndrome** may have weight gain, polyuria, edema, menstrual irregularities, recurrent acne, or muscular weakness in addition to classic features (moon face, buffalo hump, and hirsutism).

DIAGNOSIS

- **Elevated BP** may be the **only sign of primary hypertension** on physical examination.
- Diagnosis should be based on the **average of two or more readings taken at each of two or more clinical encounters.**
- Signs of **end-organ damage** occur primarily in the **eye, brain, heart, kidneys, and peripheral blood vessels.**

Cont...

- **Funduscopy examination** may reveal:
 - Arteriolar narrowing
 - Focal arteriolar constrictions
 - Arteriovenous nicking
 - Retinal hemorrhages and exudates, and
 - Disk edema
- Presence of **papilledema** usually indicates a **hypertensive emergency** requiring rapid treatment.

Cont...

- **Cardiopulmonary examination** may reveal:
 - Abnormal heart rate or rhythm
 - Left ventricular (LV) hypertrophy
 - Coronary heart disease or
 - Heart failure (HF)
- **Peripheral vascular examination** may reveal:
 - Aortic or abdominal bruits
 - Distended veins
 - Diminished or absent peripheral pulses or
 - Lower extremity edema

Cont...

- Patients with renal artery stenosis may have an **abdominal systolic-diastolic bruit**.
- **Baseline hypokalemia** may suggest mineralocorticoid-induced hypertension.
- **Protein, blood cells, and casts** in the urine may indicate renovascular disease.

Laboratory tests

- Blood urea nitrogen (BUN)
- Serum creatinine
- Fasting lipid panel
- Fasting blood glucose
- Serum electrolytes (sodium and potassium)
- Hemoglobin and hematocrit
- Spot urine albumin-to-creatinine ratio
- Estimated glomerular filtration rate (eGFR)
- A 12-lead electrocardiogram (ECG) should also be obtained.

Cont...

- **Laboratory tests to diagnose secondary hypertension:**
 - Plasma norepinephrine and urinary metanephrine levels for pheochromocytoma,
 - plasma and urinary aldosterone concentrations for primary aldosteronism,
 - plasma renin activity, captopril stimulation test, renal vein renin, and renal artery angiography for renovascular disease.

TREATMENT

Goals of Treatment:

- The overall goal is to reduce morbidity and mortality by the least intrusive means possible.
- The goal BP for most patients, including those with DM/CKD (nondialysis), is <130/80 mm Hg.

NONPHARMACOLOGIC THERAPY

- **Lifestyle modifications:**
 - **Weight loss** if overweight or obese,
 - Adoption of the Dietary Approaches to Stop Hypertension (**DASH**) **eating plan**
 - **Dietary sodium restriction** ideally to 1.5 g/day (3.8 g/day sodium chloride),
 - Regular aerobic **physical activity**
 - **Moderation of alcohol consumption** ??? (two or fewer drinks per day), and
 - **Smoking cessation**

Cont...

- Lifestyle modification alone is **sufficient for most patients with prehypertension**
 - but inadequate for patients with hypertension and additional CV risk factors or target organ damage.

PHARMACOLOGIC THERAPY

- **Initial drug selection depends on:**
 - The degree of BP elevation and
 - Presence of compelling indications for selected drugs.
- **Acceptable first-line options** are the following:
 - Angiotensin-converting enzyme (ACE) inhibitors,
 - Angiotensin II receptor blockers (ARBs),
 - Calcium channel blockers (CCBs), and
 - Thiazide diuretics

Cont...

- **β -Blockers** are used to either treat:
 - a specific compelling indication or
 - as combination therapy with a first-line antihypertensive agent for patients without a compelling indication

Cont...

- Most patients with stage 1 hypertension should be treated **initially with a first-line antihypertensive drug** or a two-drug combination
- **Combination therapy is** recommended for patients with stage 2 hypertension, preferably with two first-line agents.
- There are **six compelling indications** where specific antihypertensive drug classes provide unique benefits

TABLE 10-2

First-Line and Other Common Antihypertensive Agents

Class	Subclass	Drug (Brand Name)	Usual Dose Range (mg/day)	Daily Frequency
ACEi		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
ARB		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 blocker	Dihydropyridine	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 30–90	2 1
		Nifedipine long-acting (Adalat CC, Nifedical XL, Procardia XL)	10–40	1
		Nisoldipine (Sular)		
	Nondihydropyridine	Diltiazem sustained release (Cardizem SR)	180–360 120–480	2 1
		Diltiazem sustained release (Cardizem CD, Cartia XT, Dilacor XR, Diltia XT, Tiazac, Taztia XT)	120–540 180–480	1 (morning or evening)
		Diltiazem extended release (Cardizem LA)	180–420 100–400	1 or 2 1 (in the evening)
		Verapamil sustained release (Calan SR, Isoptin SR, Verelan)		1 (in the evening)
		Verapamil controlled onset, extended release (Covera-HS)		
		Verapamil chronotherapeutic oral drug absorption system (Verelan PM)		

Diuretic	Thiazide	Chlorthalidone (Hygroton)	12.5–25	1
		Hydrochlorothiazide (Esidrix, HydroDiuril, Microzide, Oretic)	12.5–50	1
			1.25–2.5	1
		Indapamide (Lozol)	2.5–10	1
		Metolazone (Zaroxolyn)		
	Loop	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–	1
			100	1 or 2
		Triamterene (Dyrenium)	50–100	1
		Triamterene/hydrochlorothiazide (Dyazide)	37.5– 75/25–50	
	Aldosterone antagonist	Eplerenone (Inspra)	50–100	1 or 2
		Spironolactone (Aldactone)	25–50	1 or 2
		Spironolactone/hydrochlorothiazide (Aldactazide)	25–50/25– 50	1

β -Blocker	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, Inderal XL, InnoPran XL)	80–320	1
		Timolol (Blocadren)	10–40	1
	Intrinsic	Acebutolol (Sectral)	200–800	2
	sympathomimetic activity	Carteolol (Cartrol)	2.5–10	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

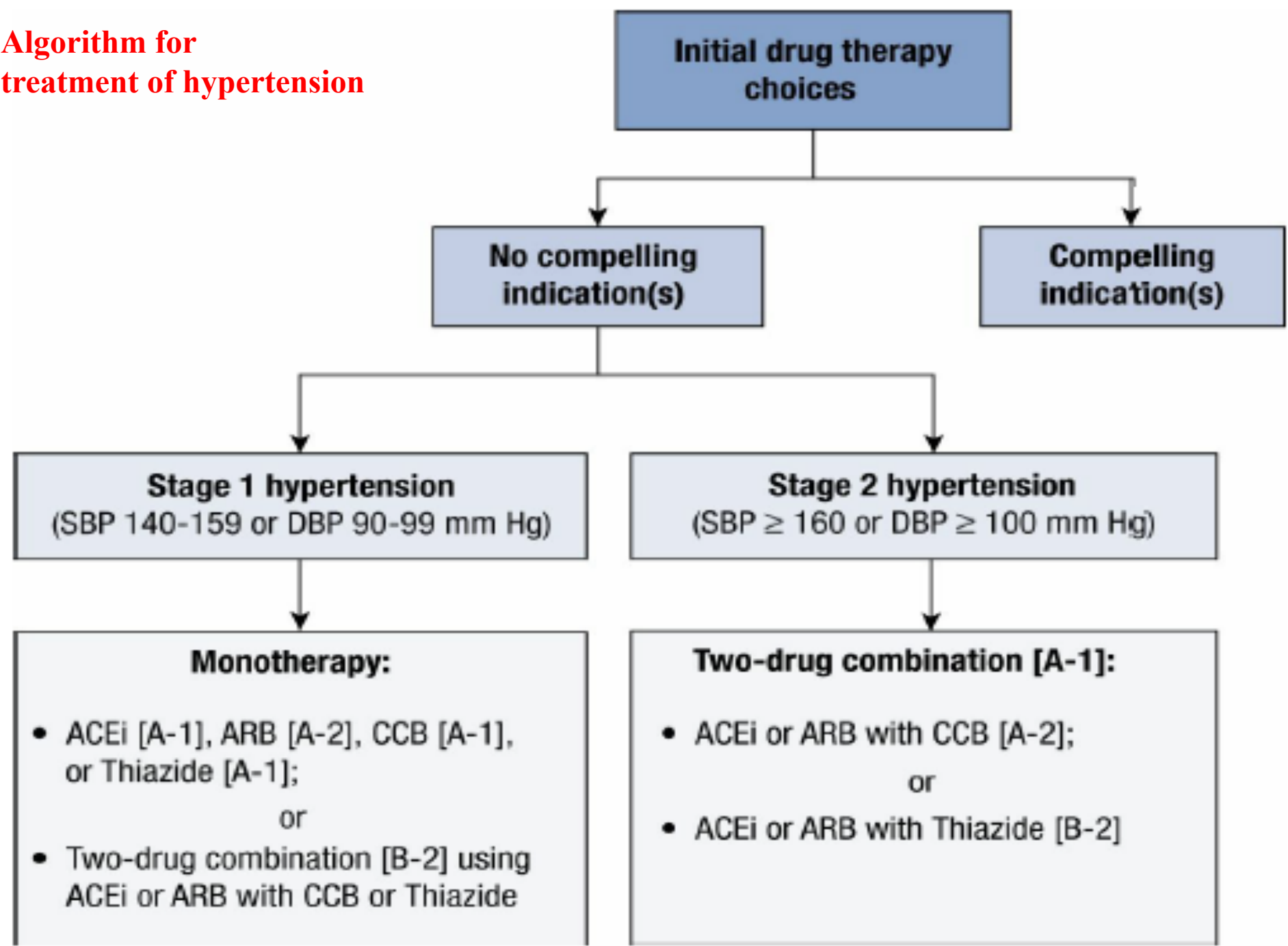
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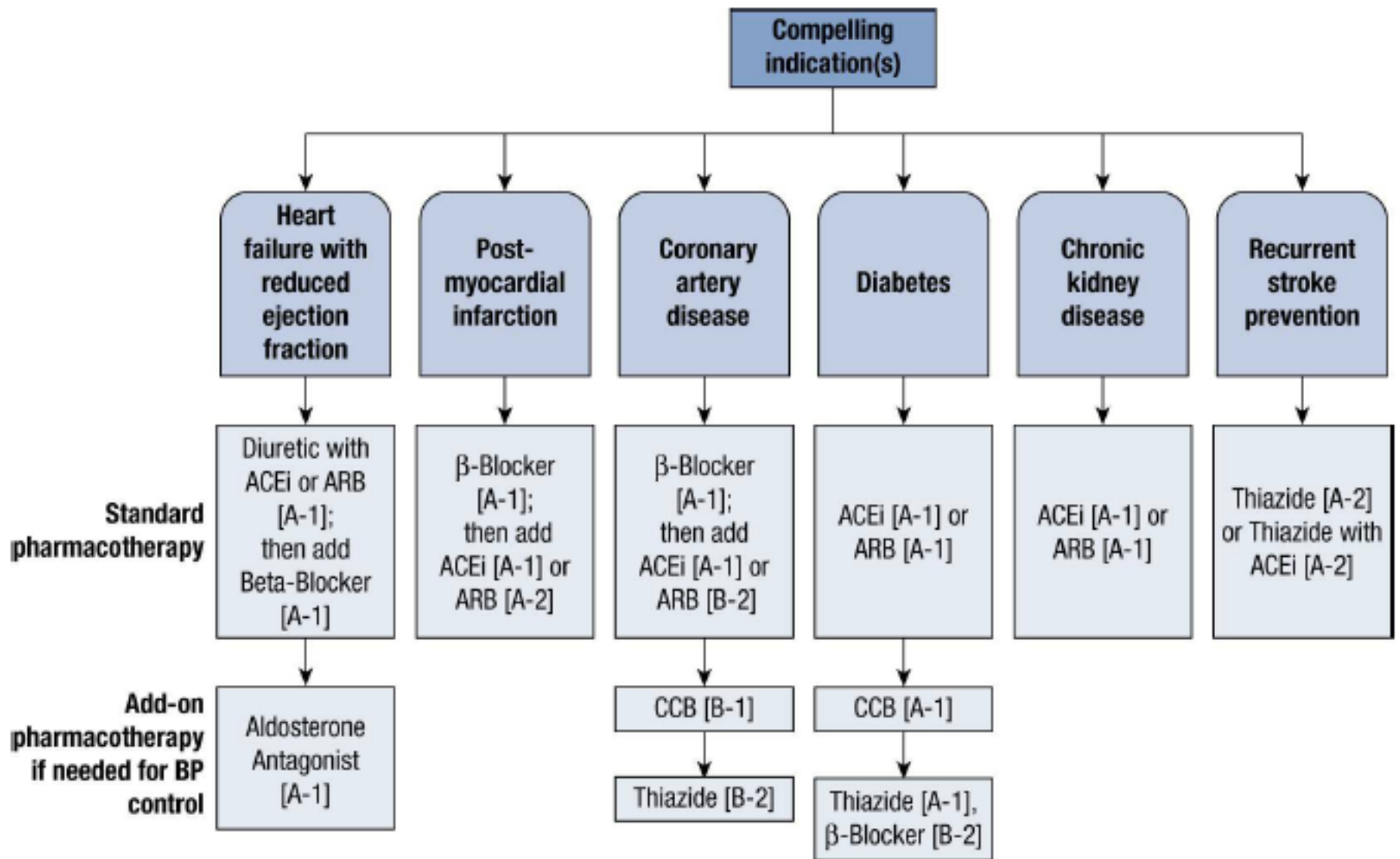
- Other antihypertensive drug classes which are **alternatives** that may be used for select patients after first-line agents are the following:
 - α 1-blockers
 - Direct renin inhibitors
 - Central α 2-agonists
 - Adrenergic inhibitors, and
 - Direct arterial vasodilators
- However, there is no compelling outcome data showing reduced morbidity and mortality in hypertension.

TABLE 10-3**Alternative Antihypertensive Agents**

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

Algorithm for
treatment of hypertension





Compelling indications for individual drug classes

MEDICATIONS

Angiotensin-Converting Enzyme Inhibitors (ACEIs)

- Are a first-line option, and if they are not the first agent used, they should be the second agent tried in most patients.
- Block conversion of angiotensin I to angiotensin II, a potent vasoconstrictor and stimulator of aldosterone secretion.
- Also block degradation of bradykinin and stimulate synthesis of other vasodilating substances, including prostaglandin E2 and prostacyclin.

Cont...

- Starting doses should be low with slow dose titration.
- Acute hypotension may occur at the onset of therapy, especially in patients who are sodium or volume depleted, in HF exacerbation, very elderly, or on concurrent vasodilators or diuretics.
- Start administering doses in such patients, using half the normal dose followed by slow dose titration.

Cont...

Hyperkalemia to ACEIs Use

- ACEIs decrease aldosterone and can **increase serum potassium concentrations**.
- Hyperkalemia occurs primarily:
 - In patients with CKD
 - In those also taking:
 - potassium supplements,
 - potassium-sparing diuretics,
 - ARBs, or a
 - direct renin inhibitor.

Cont...

- **Acute renal failure** is a rare but serious side effect; preexisting kidney disease increases risk.
- **GFR declines** in patients receiving ACEIs because of inhibition of angiotensin II vasoconstriction on efferent arterioles.
 - Serum creatinine concentrations often increase, but modest elevations (eg, absolute increases <1 mg/dL) do not warrant treatment changes.
 - **Discontinue** therapy or reduce dose if larger increases occur

Cont...

- **Angioedema** occurs in few <1% of patients.
 - Drug withdrawal is necessary, and some patients may require drug treatment and/or emergent intubation.
 - An ARB can generally be used in patients with a history of ACE inhibitor–induced angioedema, with careful monitoring.

Cont...

- A persistent **dry cough** occurs in up to **20%** of patients and is thought to be due to inhibition of bradykinin breakdown.
- ACEIs (as well as ARBs and direct renin inhibitors) are **contraindicated in pregnancy**.

Angiotensin II Receptor Blockers (ARBs)

- ARBs are a **first-line therapy option** in most patients with hypertension and reduce CV events similar to ACE inhibitors.
- The **combination** of an ACEI and ARB has **no additional CV event lowering** but is associated with a higher risk of side effects (renal dysfunction, hypotension).

Cont...

- Unlike ACEIs, ARBs **do not block bradykinin breakdown.**
 - Although this accounts for the lack of cough as a side effect, there may be negative consequences because some of the antihypertensive effect of ACE inhibitors may be due to increased levels of bradykinin.

Cont...

- **All ARBs have similar antihypertensive efficacy and fairly flat dose-response curves.**
- **Addition of a CCB or thiazide diuretic significantly increases antihypertensive efficacy.**
- **ARBs have a low incidence of side effects.**
 - **Like ACEIs, they may cause renal insufficiency, hyperkalemia, and orthostatic hypotension.**

Calcium Channel Blockers (CCBs)

- Calcium channel blockers (CCBs), including both dihydropyridine and non-dihydropyridine types, are **first-line therapy options**.
- They are also used in addition to or instead of other first-line antihypertensives for the compelling indications of **coronary artery disease and diabetes**.

Cont...

- Dihydropyridine CCBs may cause **reflex sympathetic activation**, and all agents (except amlodipine and felodipine) may have negative inotropic effects.

Cont...

- **Verapamil** decreases heart rate, slows atrioventricular (AV) nodal conduction, and produces a negative inotropic effect that **may precipitate HF** in patients with borderline cardiac reserve.
- **Diltiazem** decreases AV conduction and heart rate to a lesser extent than verapamil.

Cont...

- Diltiazem and verapamil can cause:
 - **cardiac conduction abnormalities** such as bradycardia, AV block, and HF.
- Both can cause **anorexia, nausea, peripheral edema, and hypotension.**
- Verapamil causes **constipation** in about 8% of patients.

Cont...

- Dihydropyridines cause a **baroreceptor-mediated reflex increase in heart rate** because of potent peripheral vasodilating effects.
- **Dihydropyridines** do not decrease AV node conduction and are **not effective for treating supraventricular tachyarrhythmias**.

Cont...

- Short-acting **nifedipine** may rarely increase frequency, intensity, and duration of angina in association with acute hypotension.
 - This effect may be obviated by using sustained-release formulations of nifedipine or other dihydropyridines.
- Other side effects of dihydropyridines are **dizziness, flushing, headache, gingival hyperplasia, and peripheral edema.**

Diuretics

- **Thiazides** are the preferred type of diuretic and are considered a **first-line option** for most patients with hypertension.
- **Loop diuretics** are more potent for inducing diuresis but are **not ideal antihypertensives** unless relief of edema is also needed.
 - Loops are sometimes preferred over thiazides in patients with CKD when estimated GFR is less than 30 mL/min/1.73 m², especially when edema is present.

Cont...

- **Potassium-sparing diuretics** are weak antihypertensives when used alone and provide minimal additive effect when combined with a thiazide or loop diuretic.
 - Their primary use is in combination with another diuretic to **counteract potassium wasting properties**.
- **Aldosterone antagonists** (spironolactone and eplerenone) are also potassium sparing diuretics but are more potent antihypertensives with **a slow onset of action** (up to 6 weeks with spironolactone)

Cont...

- Acutely, diuretics lower BP by causing diuresis.
- The reduction in plasma volume and stroke volume associated with diuresis decreases cardiac output and BP.
- The initial drop in cardiac output causes a compensatory increase in peripheral vascular resistance.

Cont...

- With chronic therapy, extracellular fluid volume and plasma volume return to near pretreatment levels, and peripheral vascular resistance falls below baseline.
- Reduced peripheral vascular resistance is responsible for the long-term hypotensive effects.
- Thiazides also mobilize sodium and water from arteriolar walls, which may contribute to decreased peripheral vascular resistance and lowered BP.

Cont...

- When diuretics are combined with other antihypertensive agents, an additive hypotensive effect is usually observed because of independent mechanisms of action.
- Furthermore, many non-diuretic antihypertensive agents induce sodium and water retention, which is counteracted by concurrent diuretic use

Cont...

Side effects of thiazides include

- hypokalemia, hypomagnesemia, hypercalcemia, hyperuricemia, hyperglycemia, dyslipidemia, and sexual dysfunction.
- **Loop diuretics** have less effect on serum lipids and glucose, but hypokalemia is more pronounced, and hypocalcemia may occur.

Cont...

- Hypokalemia and hypomagnesemia may result in cardiac arrhythmias, especially in patients receiving digoxin, patients with L hypertrophy, and those with ischemic heart disease.
- Low-dose therapy (eg, 25 mg hydrochlorothiazide or 12.5 mg chlorthalidone daily) causes small electrolyte disturbances.

Cont...

- Potassium-sparing diuretics may cause hyperkalemia, especially in patients with CKD or diabetes and in patients receiving concurrent treatment with an ACE inhibitor, ARB, direct renin inhibitor, or potassium supplement.
- Eplerenone has an increased risk for hyperkalemia and is contraindicated in patients with impaired renal function or type 2 diabetes with proteinuria.
- Spironolactone may cause gynecomastia in up to 10% of patients; this effect occurs rarely with eplerenone.

β-Blockers

- β-Blockers are only considered appropriate first-line agents to treat **specific compelling indications** (eg, post-MI and coronary artery disease).
- Their hypotensive mechanism may involve decreased cardiac output through negative chronotropic and inotropic effects on the heart and inhibition of renin release from the kidney.

Cont...

- **Atenolol, betaxolol, bisoprolol, metoprolol, and nebivolol are cardioselective at low doses** and bind more avidly to β_1 -receptors than to β_2 -receptors.
- As a result, they are less likely to provoke bronchospasm and vasoconstriction and may be safer than nonselective β -blockers in patients with asthma, chronic obstructive pulmonary disease (COPD), diabetes, and peripheral arterial disease (PAD).
- Cardioselectivity is a dose-dependent phenomenon, and the effect is lost at higher doses.

Cont...

- **Acebutolol, carteolol, and pindolol possess intrinsic sympathomimetic activity (ISA) or partial β -receptor agonist activity.**
- When sympathetic tone is low, as in resting states, β -receptors are partially stimulated, so resting heart rate, cardiac output, and peripheral blood flow are not reduced when receptors are blocked.
- Theoretically, these drugs may have advantages in patients with HF or sinus bradycardia.

Cont...

- Unfortunately, they do not reduce CV events as well as other β -blockers and may increase risk after MI or in those with high coronary disease risk.
- Thus, agents with ISA are rarely needed.
- Atenolol and nadolol have relatively long half-lives and are excreted renally; the dosage may need to be reduced in patients with renal insufficiency.
- Even though the half-lives of other β -blockers are shorter, once-daily administration still may be effective.

Cont...

- Myocardial side effects include bradycardia, AV conduction abnormalities, and acute HF.
- Blocking β_2 -receptors in arteriolar smooth muscle may cause cold extremities and aggravate PAD or Raynaud phenomenon because of decreased peripheral blood flow.
- Increases in serum lipids and glucose appear to be transient and of little clinical importance.

Cont...

- Abrupt cessation of β -blocker therapy may produce unstable angina, MI, or even death in patients with coronary disease.
- In patients without heart disease, abrupt discontinuation of β -blockers may be associated with tachycardia, sweating, and generalized malaise in addition to increased BP.
- For these reasons, the dose should always be tapered gradually over 1 to 2 weeks before discontinuation.

α 1-Receptor Blockers

- **Prazosin, terazosin, and doxazosin are selective α 1-receptor blockers that inhibit** catecholamine uptake in smooth muscle cells of peripheral vasculature, resulting in vasodilation and BP lowering.
- A first-dose phenomenon characterized by orthostatic hypotension accompanied by transient dizziness or faintness, palpitations, and even syncope may occur within 1 to 3 hours of the first dose or after later dosage increases.
- The patient should take the first dose (and subsequent first increased doses) at bedtime.
- Occasionally, orthostatic hypotension and dizziness persist with chronic administration

Cont...

- Sodium and water retention can occur; these agents are most effective when given with a thiazide to maintain antihypertensive efficacy and minimize edema.
- Because doxazosin (and probably other α 1-receptor blockers) may not be as protective against CV events as other therapies, they should be reserved as alternative agents for unique situations, such as men with benign prostatic hyperplasia.
- If used to lower BP in this situation, they should only be used in combination with first-line antihypertensives.

Direct Renin Inhibitor

- **Aliskiren blocks the RAAS at its point of activation, resulting in reduced plasma renin activity and BP.** BP reductions are comparable to an ACE inhibitor, ARB, or CCB.
- Aliskiren is approved for monotherapy or in combination with other agents.
- It should not be used in combination with an ACE inhibitor or an ARB because of a higher risk of adverse effects without additional reduction in CV events.
- Aliskiren is an alternative therapy because of lack of long-term studies evaluating CV event reduction and its significant cost compared with generic agents that have outcomes data.

Cont...

- Many of the cautions and adverse effects seen with ACE inhibitors and ARBs apply to aliskiren.
- It is contraindicated in pregnancy due to known teratogenic effects.

Central α_2 -Agonists

- **Clonidine, guanabenz, guanfacine, and methyldopa lower BP primarily by stimulating α_2 -adrenergic receptors in the brain, which reduces sympathetic outflow from the vasomotor center and increases vagal tone.**
- Stimulation of presynaptic α_2 - receptors peripherally may contribute to reduced sympathetic tone.
- Consequently, there may be decreases in heart rate, cardiac output, total peripheral resistance, plasma renin activity, and baroreceptor reflexes

Cont...

- Chronic use results in sodium and fluid retention. Other side effects include depression, orthostatic hypotension, dizziness, and anticholinergic effects.
- Abrupt cessation may lead to rebound hypertension, perhaps from a compensatory increase in norepinephrine release that follows discontinuation of presynaptic α -receptor stimulation.

Cont...

- Methyldopa rarely causes hepatitis or hemolytic anemia. A transient elevation in hepatic transaminases occasionally occurs.
- Discontinue therapy if persistent increases in liver function tests occur, because this may herald onset of fulminant, life threatening hepatitis.
- Coombs-positive hemolytic anemia occurs rarely, and 20% of patients exhibit a positive direct Coombs test without anemia.
- For these reasons, methyldopa has limited usefulness except in pregnancy.

Reserpine

- Reserpine depletes norepinephrine from sympathetic nerve endings and blocks transport of norepinephrine into storage granules.
- When the nerve is stimulated, less than the usual amount of norepinephrine is released into the synapse.
- This reduces sympathetic tone, decreasing peripheral vascular resistance and BP.

Cont...

- Reserpine has a long half-life that allows for once-daily dosing, but it may take 2 to 6 weeks before the maximal antihypertensive effect is seen.
- Reserpine can cause significant sodium and fluid retention and therefore should be given with a thiazide.

Cont...

- Reserpine's strong inhibition of sympathetic activity results in parasympathetic activity, which is responsible for side effects of nasal stuffiness, increased gastric acid secretion, diarrhea, and bradycardia.
- Dose-related depression can be minimized by not exceeding 0.25 mg daily.

Direct Arterial Vasodilators

- Hydralazine and minoxidil cause direct arteriolar smooth muscle relaxation.
- Compensatory activation of baroreceptor reflexes results in increased sympathetic outflow from the vasomotor center, increasing heart rate, cardiac output, and renin release.
- Consequently, hypotensive effectiveness of direct vasodilators diminishes over time unless the patient is also taking a sympathetic inhibitor and a diuretic.

Cont...

- Patients taking these drugs for long-term hypertension therapy should first receive both a thiazide and a β -blocker.
- The diuretic minimizes the side effect of sodium and water retention.
- Direct vasodilators can precipitate angina in patients with underlying coronary artery disease unless the baroreceptor reflex mechanism is blocked with a β -blocker.
- Non-dihydropyridine CCBs can be used as an alternative to β -blockers in patients with contraindications to β -blockers.

Cont...

- Hydralazine may cause dose-related, reversible lupus-like syndrome, which is more common in slow acetylators.
- Lupus-like reactions can usually be avoided by using total daily doses less than 200 mg.
- Because of side effects, hydralazine has limited usefulness for chronic hypertension management

Cont...

- Minoxidil is a more potent vasodilator than hydralazine, and compensatory increases in heart rate, cardiac output, renin release, and sodium retention are more dramatic.
- Due to significant water retention, a loop diuretic is often more effective than a thiazide in patients treated with minoxidil.
- Reversible hypertrichosis on the face, arms, back, and chest may be a troublesome.
- Reserve minoxidil for very difficult to control hypertension and for patients requiring hydralazine who experience drug induced lupus.

COMPELLING INDICATIONS

- Six compelling indications represent specific comorbid conditions for which clinical trial data support using specific antihypertensive drug classes to treat both hypertension and the compelling indication

Heart Failure with Reduced Ejection Fraction (HFrEF)

- Standard pharmacotherapy consists of three to four drugs:
 - ACE inhibitor or ARB plus diuretic therapy, followed by addition of an evidence-based β -blocker (ie, bisoprolol, carvedilol, and metoprolol succinate) and possibly an aldosterone receptor antagonist.

Cont...

- Start an ACE inhibitor or ARB in low doses to avoid orthostatic hypotension because of the high renin state in HF.
- Diuretics provide symptomatic relief of edema by inducing diuresis.
- Loop diuretics are often needed, especially in patients with more advanced heart failure.

Cont...

- β -Blocker therapy is appropriate to further modify disease in HFrEF and is a component of standard therapy.
- Because of the risk of exacerbating HF, β -blockers must be started in very low doses and titrated slowly to high doses based on tolerability.
- Bisoprolol, carvedilol, and sustained-release metoprolol succinate are the only β -blockers proven to be beneficial in HFrEF.
- After implementation of a standard three-drug regimen, an aldosterone antagonist (spironolactone and eplerenone) may be considered.

Post-myocardial Infarction

- β -Blockers (without ISA) and ACE inhibitors (or ARBs) are recommended.
- β -Blockers decrease cardiac adrenergic stimulation and reduce risk of subsequent MI or sudden cardiac death.
- ACE inhibitors improve cardiac function and reduce CV events after MI.
- These two drug classes, with β -blockers first, are the drugs of first choice for post-MI patients.

Coronary Artery Disease

- β -Blockers (without ISA) are first-line therapy in chronic stable angina; they reduce BP and decrease myocardial oxygen consumption and demand.
- Long-acting CCBs (the nondihydropyridine CCBs diltiazem and verapamil) may be either alternatives or add-on therapy (dihydropyridines) to β -blockers in chronic stable angina

Cont...

- Once ischemic symptoms are controlled with β -blocker and/or CCB therapy, other antihypertensives (eg, ACE inhibitor or ARB) can be added to provide additional CV risk reduction.
- Thiazide diuretics may be added thereafter to provide additional BP lowering and further reduce CV risk

Cont...

- For acute coronary syndromes, first-line therapy includes a β -blocker and ACE inhibitor (or ARB); the combination lowers BP, controls acute ischemia, and reduces CV risk.

Diabetes Mellitus

- Treat all patients with diabetes and hypertension with an ACE inhibitor or ARB.
- Both classes provide nephro-protection and reduced CV risk.
- CCBs are the most appropriate add-on agents for BP control in patients with diabetes.
- The combination of an ACE inhibitor with a CCB is more effective in reducing CV events than an ACE inhibitor plus a thiazide diuretic.
- A thiazide diuretic is recommended add-on therapy to lower BP and provide additional CV risk reduction

Cont...

- β -Blockers, similar to CCBs, are useful add-on agents for BP control in patients with diabetes.
- They should also be used to treat another compelling indication (eg, post-MI).
- However, they may mask symptoms of hypoglycemia (tremor, tachycardia, and palpitations but not sweating) in tightly controlled patients, delay recovery from hypoglycemia, and produce elevations in BP due to vasoconstriction caused by unopposed β -receptor stimulation during the hypoglycemic recovery phase.
- Despite these potential problems, β -blockers can be used safely in patients with diabetes

Chronic Kidney Disease

- In addition to lowering BP, ACE inhibitors and ARBs reduce intra-glomerular pressure, which may further slow CKD progression.
- Start with low doses and evaluate the serum creatinine soon after starting therapy to minimize the risk of rapid and profound BP drops that could precipitate acute kidney failure.

Recurrent Stroke Prevention

- A thiazide diuretic, either as monotherapy or combined with an ACE inhibitor, is recommended for patients with history of stroke or transient ischemic attack.
- Implement antihypertensive drug therapy only after patients have stabilized after an acute cerebrovascular event.

SPECIAL POPULATIONS

Older People

- Elderly patients may present with either isolated systolic hypertension or elevation in both SBP and DBP.
- CV morbidity and mortality are more closely related to SBP than to DBP in patients 50 years of age and older.
- Diuretics, ACE inhibitors, and ARBs provide significant benefits and can be used safely in the elderly, but smaller-than-usual initial doses must be used for initial therapy.

Children and Adolescents

- Secondary hypertension is more common in children and adolescents than in adults.
- Medical or surgical management of the underlying disorder usually normalizes BP.
- Non-pharmacologic treatment (particularly weight loss in obese children) is the cornerstone of therapy of primary hypertension.
- ACE inhibitors, ARBs, β -blockers, CCBs, and thiazide diuretics are all acceptable drug therapy choices.
- ACE inhibitors, ARBs, and direct renin inhibitors are contraindicated in sexually active girls because of potential teratogenic effects.

Pregnancy

- *Preeclampsia is defined as hypertension (elevated BP $\geq 140/90$ mm Hg on more than 2 occasions at least 4 hours apart after 20 weeks' gestation or $\geq 160/110$ mm Hg confirmed within a short interval) in association with thrombocytopenia, impaired liver function, new development of renal insufficiency, pulmonary edema, or new onset cerebral or visual disturbances.*
- It can lead to life-threatening complications for both mother and fetus.

Cont...

- *Eclampsia, the onset of convulsions in preeclampsia, is a medical emergency.*
- Definitive treatment of preeclampsia is delivery, and this is indicated if pending or frank eclampsia is present.
- Otherwise, management consists of restricting activity, bed rest, and close monitoring.
- Salt restriction or other measures that contract blood volume should be avoided.
- Antihypertensives are used prior to induction of labor if the DBP is greater than 105 mm Hg, with a target DBP of 95 to 105 mm Hg.
- IV hydralazine is most commonly used; IV labetalol is also effective.

Cont...

- *Chronic hypertension is hypertension that predates pregnancy.*
- *Labetalol, nifedipine, or methyldopa is recommended as first-line therapy due to favorable safety profiles.*
- β -Blockers (other than atenolol) and CCBs are also reasonable alternatives.
- ACE inhibitors, ARBs, and the direct renin inhibitor aliskiren are contraindicated in pregnancy.

African Americans

- Hypertension is more common and more severe in African Americans than in those of other races.
- Differences in electrolyte homeostasis, glomerular filtration rate, sodium excretion and transport mechanisms, plasma renin activity, and BP response to plasma volume expansion have been noted.
- African Americans tend to have a low renin pattern of hypertension

Cont...

- CCBs and thiazides are most effective in African Americans.
- Antihypertensive response is significantly increased when either class is combined with a β -blocker, ACE inhibitor, or ARB.
- Appropriate drug therapies should be used for compelling indications, even if the antihypertensive effect may not be as great as with another drug class (eg, a β -blocker is first-line for BP control in post-MI African Americans).

Pulmonary Disease and Peripheral Arterial Disease

- Although β -blockers (especially nonselective agents) have generally been avoided in hypertensive patients with asthma and COPD because of fear of inducing bronchospasm, data suggest that cardioselective β -blockers can be used safely.
- Consequently, cardioselective agents should be used to treat a compelling indication (ie, post-MI, coronary disease, or HF) in patients with reactive airway disease.

Cont...

- PAD is considered a noncoronary form of atherosclerotic vascular disease.
- β -Blockers can theoretically be problematic because of possible decreased peripheral blood flow secondary to unopposed stimulation of α -receptors that results in vasoconstriction.
- This can be mitigated by using a β -blocker with α -blocking properties (eg, carvedilol).
- However, β -blockers are not contraindicated in PAD and have not been shown to adversely affect walking capacity.

HYPERTENSIVE URGENCIES AND EMERGENCIES

- **Hypertensive urgencies are ideally managed by adjusting maintenance therapy, adding a new antihypertensive, and/or increasing the dose of a present medication.**
- **Acute administration of a short-acting oral drug (captopril, clonidine, or labetalol) followed by careful observation for several hours to ensure a gradual BP reduction is an option.**

Cont...

- Oral captopril doses of 25 to 50 mg may be given at 1- to 2-hour intervals. The onset of action is 15 to 30 minutes.
- For treatment of hypertensive rebound after withdrawal of clonidine, 0.2 mg is given initially, followed by 0.2 mg hourly until the DBP falls below 110 mm Hg or a total of 0.7 mg has been administered; a single dose may be sufficient.
- Labetalol can be given in a dose of 200 to 400 mg, followed by additional doses every 2 to 3 hours.

Cont...

- **Hypertensive emergencies require immediate BP reduction to limit new or progressing end-organ damage.**
- The goal is not to lower BP to less than 140/90 mmHg; instead, the initial target is a reduction in mean arterial pressure of up to 25% within minutes to hours.
- If BP is then stable, it can be reduced toward 160/100 to 110 mm Hg within the next 2 to 6 hours.
- Precipitous drops in BP may cause end-organ ischemia or infarction.
- If BP reduction is well tolerated, additional gradual decrease toward the goal BP can be attempted after 24 to 48 hours.

Cont...

- Nitroprusside is the agent of choice for minute-to-minute control in most cases.
- It is usually given as a continuous IV infusion at a rate of 0.25 to 10 mcg/kg/min.
- Onset of hypotensive action is immediate and disappears within 1 to 2 minutes of discontinuation.
- When the infusion must be continued longer than 72 hours, measure serum thiocyanate levels, and discontinue the infusion if the level exceeds 12 mg/dL (~ 2.0 mmol/L).
- The risk of thiocyanate toxicity is increased in patients with impaired kidney function.
- Other adverse effects are nausea, vomiting, muscle twitching, and sweating.

TABLE 10–4

Parenteral Antihypertensive Agents for Hypertensive Emergency

Drug	Dose	Onset (min)	Duration (min)	Adverse Effects
Clevidipine	1–2 mg/h (32 mg/h max)	2–4	5–15	Headache, nausea, tachycardia, hypertriglyceridemia
Enalaprilat	1.25–5 mg IV every 6 h	15–30	360–720	Precipitous fall in BP in high-renin states; variable response
Esmolol hydrochloride	250–500 mcg/kg/min IV bolus, then 50–100 mcg/kg/min IV infusion; may repeat bolus after 5 min or increase infusion to 300 mcg/min	1–2	10–20	Hypotension, nausea, asthma, first-degree heart block, heart failure
Fenoldopam mesylate	0.1–0.3 mcg/kg/min IV infusion	<5	30	Tachycardia, headache, nausea, flushing
Hydralazine hydrochloride	12–20 mg IV 10–50 mg IM	10–20 20–30	60–240 240–360	Tachycardia, flushing, headache, vomiting,

				aggravation of angina
Labetalol hydrochloride	20–80 mg IV bolus every 10 min; 0.5–2 mg/min IV infusion	5–10	180–360	Vomiting, scalp tingling, bronchoconstriction, dizziness, nausea, heart block, orthostatic hypotension
Nicardipine hydrochloride	5–15 mg/h IV	5–10	15–30; may exceed 240	Tachycardia, headache, flushing, local phlebitis
Nitroglycerin	5–100 mcg/min IV infusion	2–5	5–10	Headache, vomiting, methemoglobinemia, tolerance with prolonged use
Sodium nitroprusside	0.25–10 mcg/kg/min IV infusion (requires special delivery system)	Immediate	1–2	Nausea, vomiting, muscle twitching, sweating, thiocyanate and cyanide intoxication

(BP, blood pressure; IM, intramuscular; IV, intravenous.)

EVALUATION OF THERAPEUTIC OUTCOMES

- Evaluate BP response 2 to 4 weeks after initiating or making changes in therapy.
- Once goals BP values are obtained, monitor BP every 3 to 6 months, assuming no signs or symptoms of acute end-organ damage.
- Evaluate more frequently in patients with a history of poor control, non adherence, progressive end-organ damage, or symptoms of adverse drug effects.

Cont...

- Self-measurements of BP or automatic ambulatory BP monitoring can be useful to establish effective 24-hour control.
- These techniques are currently recommended only for select situations such as suspected white coat hypertension.
- Monitor patients for signs and symptoms of progressive hypertension-associated complications.
- Take a careful history for chest pain (or pressure), palpitations, dizziness, dyspnea, orthopnea, headache, sudden change in vision, one-sided weakness, slurred speech, and loss of balance.

Cont...

- Monitor funduscopic changes on eye examination, LV hypertrophy on ECG, proteinuria, and changes in kidney function periodically.
- Monitor for adverse drug effects 2 to 4 weeks after starting a new agent or dose increases, then every 6 to 12 months in stable patients.

Cont...

- For patients taking aldosterone antagonists, assess potassium concentration and kidney function within 3 days and again at 1 week after initiation to detect potential hyperkalemia.
- Assess patient adherence with the regimen regularly.
- Ask patients about changes in their general health perception, energy level, physical functioning, and overall satisfaction with treatment

Cont...

- Thank you!