Hypertension

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Hypertension

- Persistent elevation of systolic and /or diastolic B.P. to above 140/90 mmHg in person aged 18 years or older.

Hypertension	Systolic	Diastolic
Grade I (mild)	140-159	90-99
Grade II (moderate)	160-179	100-109
Grade III (sever)	>180	>110
Isolated systolic hypertension	>140	<90

Etiology

- Although hypertension may occur secondary to other disease processes, more than 90% of patients have essential hypertension (hypertension with no identifiable cause).

- A family history of hypertension increases the likelihood that an individual will develop hypertension.

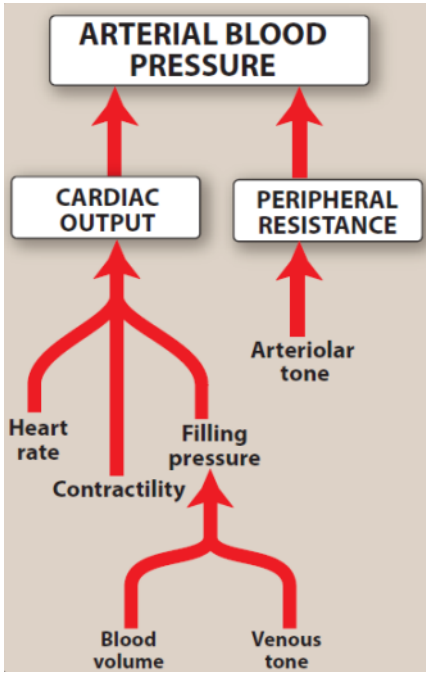
- The prevalence of hypertension increases with age, but decreases with education and income level.

- Persons with diabetes, obesity, or disability status are all more likely to have hypertension than those without.

- In addition, environmental factors, such as a stressful lifestyle, high dietary intake of sodium, and smoking, may further predispose an individual to hypertension.

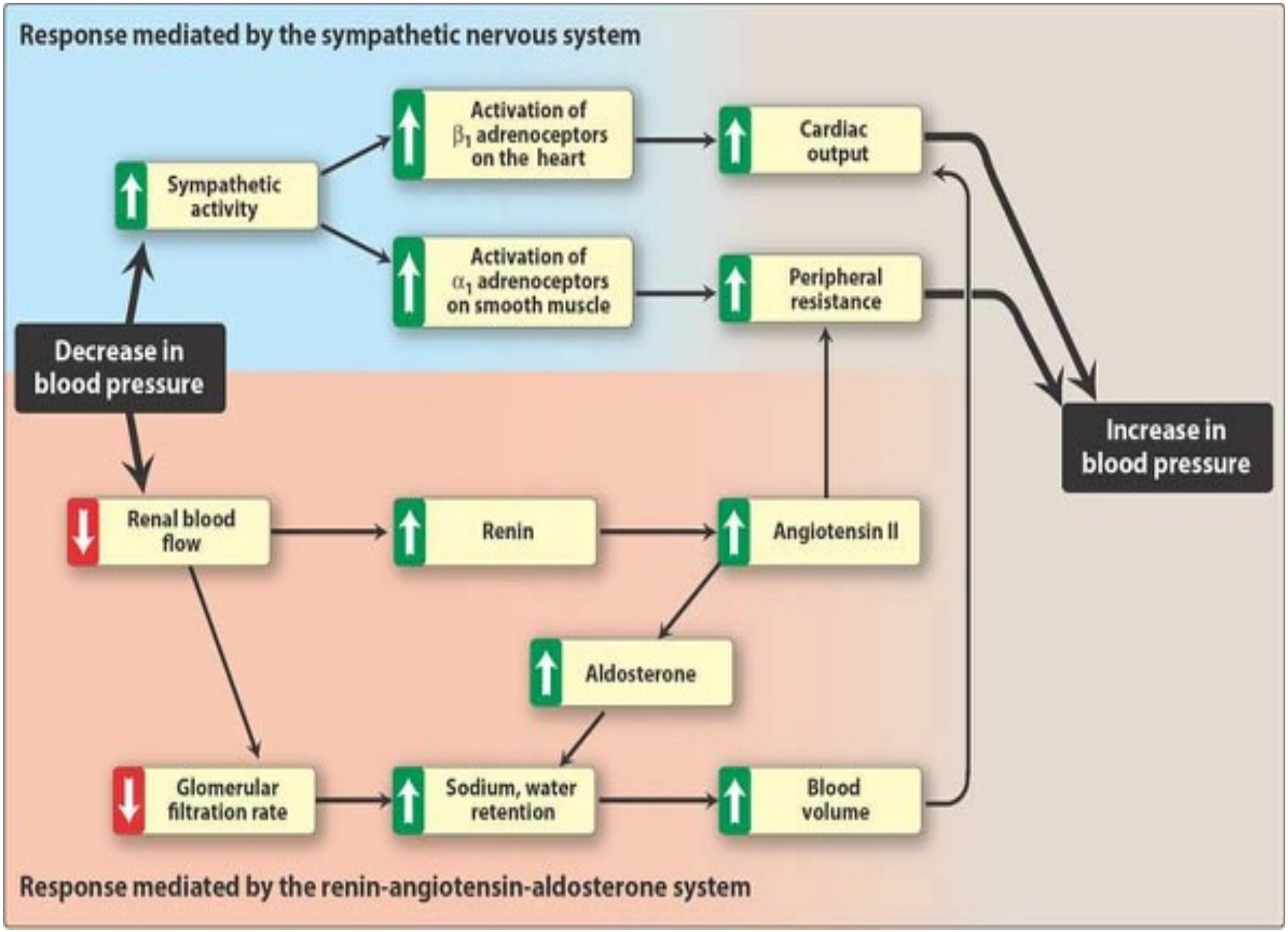
Mechanisms for controlling blood pressure

- Arterial blood pressure is directly proportional to cardiac output and peripheral vascular resistance.
- Cardiac output and peripheral resistance, in turn, are controlled mainly by two overlapping control mechanisms:



A. Baroreceptors and the sympathetic nervous system: Baroreflexes act by changing the activity of the sympathetic nervous system. Therefore, they are responsible for the rapid, moment-to-moment regulation of blood pressure.

B. Renin–angiotensin–aldosterone system

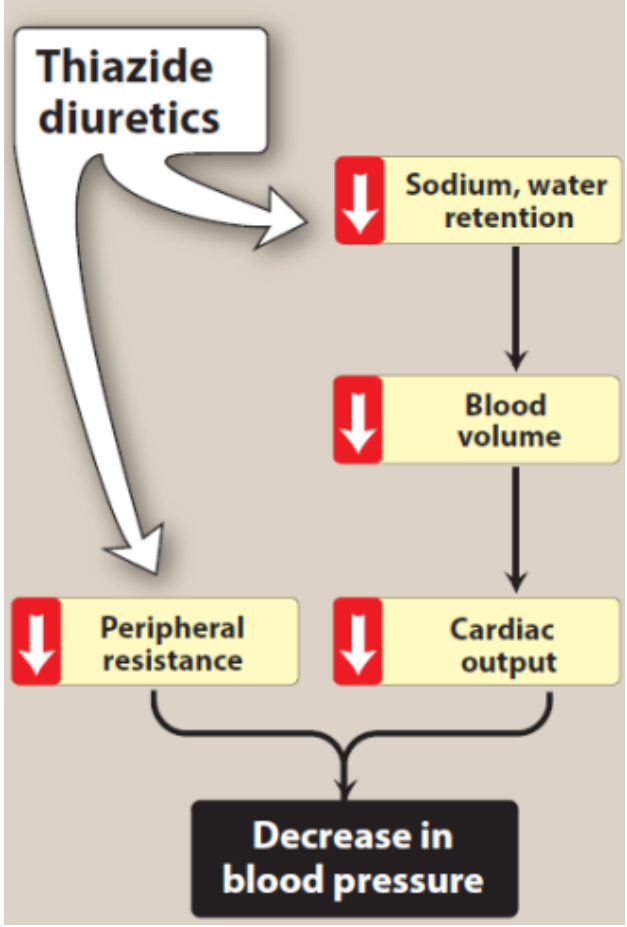

Response mediated by the sympathetic nervous system
Activation of β_1 adrenoceptors on the heart
Cardiac output
Sympathetic activity
Activation of α_1 adrenoceptors on smooth muscle
Peripheral resistance
Decrease in blood pressure
Increase in blood pressure
Renal blood flow
Renin
Angiotensin II
Aldosterone
Glomerular filtration rate
Sodium, water retention
Blood volume
Response mediated by the renin-angiotensin-aldosterone system

1. Diuretics

A. Thiazide diuretics (hydrochlorothiazide, chlorthalidone and metolazone)

- With the exception of metolazone, thiazide diuretics are not effective in patients with inadequate kidney function (estimated glomerular filtration rate less than 30 mL/min/m^2). Loop diuretics may be required in these patients.

- Thiazide diuretics can induce hypokalemia, hyperuricemia and, to a lesser extent, hyperglycemia in some patients.



Loop diuretics

Furosemide, torsemide, bumetanide, and ethacrynic acid

- The loop diuretics act promptly by blocking sodium and chloride reabsorption in the kidneys, even in patients with poor renal function or those who have not responded to thiazide diuretics.

- Loop diuretics cause decreased renal vascular resistance and increased renal blood flow.

- Like thiazides, they can cause hypokalemia. However, unlike thiazides, loop diuretics increase the Ca^{2+} content of urine, whereas thiazide diuretics decrease it.

- These agents are rarely used alone to treat hypertension, but they are commonly used to manage symptoms of heart failure and edema.

Potassium-sparing diuretics

Amiloride and triamterene (inhibitors of epithelial sodium transport at the late distal and collecting ducts)
spironolactone and eplerenone (aldosterone receptor antagonists) reduce potassium loss in the urine

- Aldosterone antagonists have the additional benefit of diminishing the cardiac remodeling that occurs in heart failure.

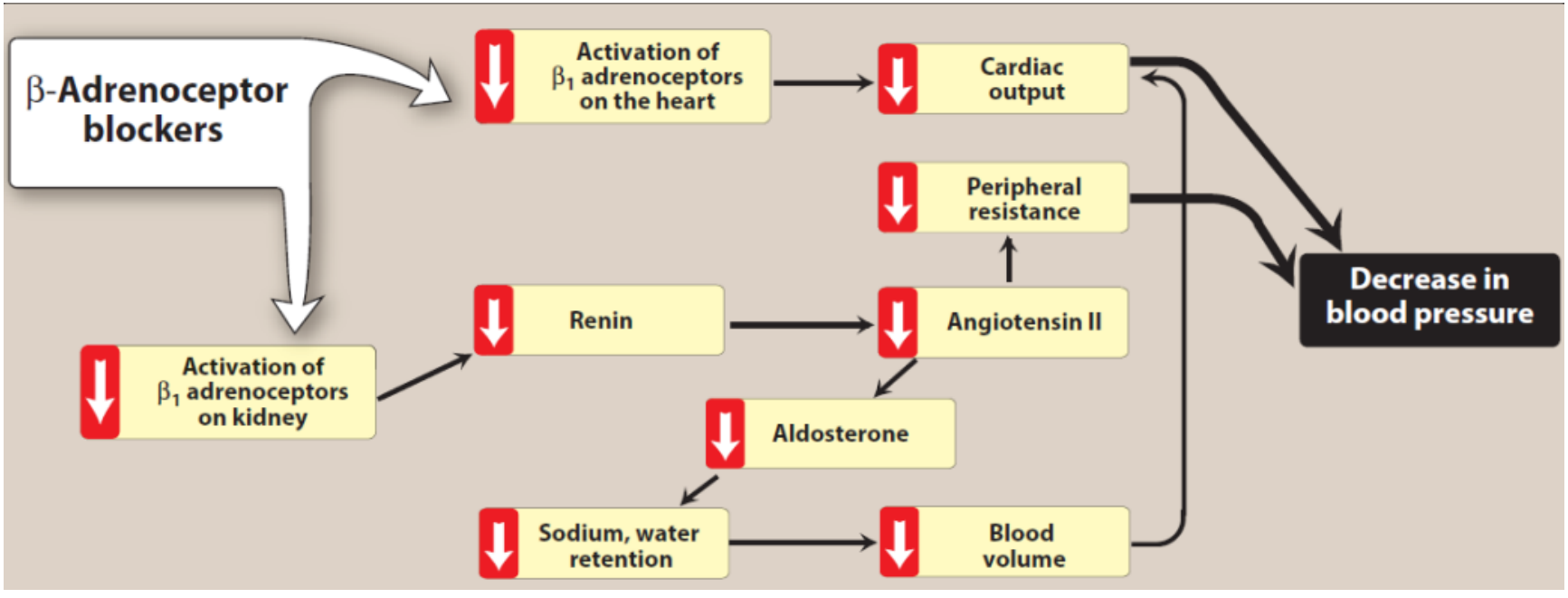
- Potassium-sparing diuretics are sometimes used in combination with loop diuretics and thiazides to reduce the amount of potassium loss induced by these diuretics.

2. β-adrenoceptor–blocking agents

Acebutolol, atenolol, betaxolol, bisoprolol, carvedilol, esmolol, labetalol, metoprolol, nadalol, nebivolol, penbutolol, pindolol, propranolol, timolol

- The β-blockers reduce blood pressure primarily by decreasing cardiac output. They may also decrease sympathetic outflow from the central nervous system (CNS) and inhibit the release of renin from the kidneys, thus decreasing the formation of angiotensin II and the secretion of aldosterone.

- The prototype β-blocker is propranolol, which acts at both β1 and β2 receptors. Selective blockers of β1 receptors, such as metoprolol and atenolol, are among the most commonly prescribed β-blockers.
- Nebivolol is a selective blocker of β1 receptors, which also increases the production of nitric oxide, leading to vasodilation.



2. β-adrenoceptor–blocking agents

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- The selective β-blockers may be administered cautiously to hypertensive patients who also have asthma.
- The nonselective β-blockers, such as propranolol and nadolol, are contraindicated in patients with asthma due to their blockade of β2-mediated bronchodilation.
- β-Blockers should be used cautiously in the treatment of patients with acute heart failure or peripheral vascular disease.

Therapeutic uses:

- The primary therapeutic benefits of β-blockers are seen in hypertensive patients with concomitant heart disease, such as supraventricular tachyarrhythmia, previous myocardial infarction, angina pectoris, and chronic heart failure.

Adverse effects:

- Drug withdrawal: Abrupt withdrawal may induce angina, myocardial infarction, and even sudden death in patients with ischemic heart disease. Therefore, these drugs must be tapered over a few weeks in patients with hypertension and ischemic heart disease.

3. Angiotensin converting enzyme (ACE) inhibitors

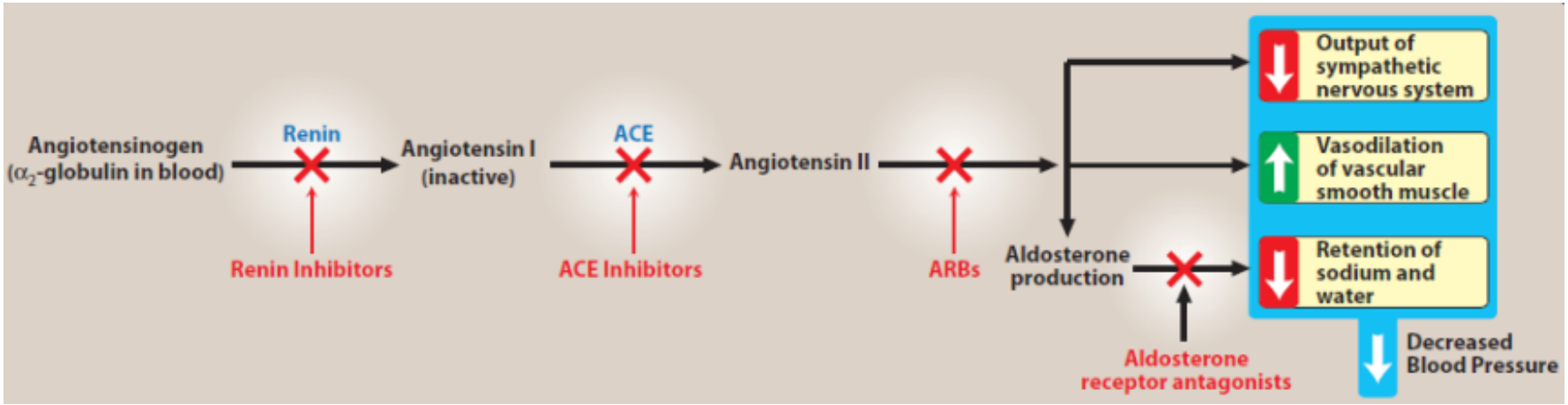
Benazepril, captopril, enalapril, fosinopril , lisinopril, moexipril, quinapril, perindopril, ramipril, trandolapril

- Enalapril and lisinopril are recommended as first-line treatment of hypertension in patients with a variety of compelling indications, including high coronary disease risk or history of diabetes, stroke, heart failure, myocardial infarction, or chronic kidney disease.

- The ACE inhibitors lower blood pressure by reducing peripheral vascular resistance without reflexively increasing cardiac output, heart rate, or contractility.

- **Therapeutic uses**
- ACE inhibitors are first-line drugs for treating heart failure, hypertensive patients with chronic kidney disease, and patients at increased risk of coronary artery disease.

- All of the ACE inhibitors are equally effective in the treatment of hypertension at equivalent doses.
- **Adverse effets:** Dry cough: 10% due to increase in bradykinin.



4. Angiotensin II receptor blockers (ARBs)

Azilsartan medoxomil, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan

- The ARBs are alternatives to the ACE inhibitors.
- These drugs block the AT1 receptors, decreasing the activation of AT1 receptors by angiotensin II.
- Their pharmacologic effects are similar to those of ACE inhibitors in that they produce arteriolar and venous dilation and block aldosterone secretion, thus lowering blood pressure and decreasing salt and water retention.
- ARBs do not increase bradykinin levels. They may be used as first-line agents for the treatment of hypertension, especially in patients with a compelling indication of diabetes, heart failure, or chronic kidney disease.
- Adverse effects are similar to those of ACE inhibitors, although the risks of cough and angioedema are significantly decreased.
- ARBs should not be combined with an ACE inhibitor for the treatment of hypertension due to similar mechanisms and adverse effects.
- These agents are also teratogenic and should not be used by pregnant women.

5. Renin inhibitor

Aliskiren

- Aliskiren directly inhibits renin and, thus, acts earlier in the renin–angiotensin–aldosterone system than ACE inhibitors or ARBs.
- It lowers blood pressure about as effectively as ARBs, ACE inhibitors, and thiazides.
- Aliskiren should not be routinely combined with an ACE inhibitor or ARB.
- Aliskiren can cause diarrhea, especially at higher doses, and can also cause cough and angioedema, but probably less often than ACE inhibitors.
- As with ACE inhibitors and ARBs, aliskiren is contraindicated during pregnancy.

6. Calcium channel blockers (CCBs)

Amlodipine, diltiazem, felodipine, isradipine, nicardipine, nifedipine, nisoldipine, verapamil, clevidipine

- Calcium channel blockers are a recommended treatment option in hypertensive patients with diabetes or angina.
- A. Classes of calcium channel blockers:

1. **Diphenylalkylamines:** **Verapamil** is the least selective of any calcium channel blocker and has significant effects on both cardiac and vascular smooth muscle cells. It is also used to treat angina and supraventricular tachyarrhythmias and to prevent migraine and cluster headaches.

2. **Benzothiazepines:** Like verapamil, **diltiazem** affects both cardiac and vascular smooth muscle cells, but it has a less pronounced negative inotropic effect on the heart compared to that of verapamil. Diltiazem has a favorable side effect profile.

3. **Dihydropyridines:** includes **nifedipine, amlodipine, felodipine, isradipine, nicardipine, and nisoldipine**. These agents differ in pharmacokinetics, approved uses, and drug interactions.

- All dihydropyridines have a much greater affinity for vascular calcium channels than for calcium channels in the heart. They are, therefore, particularly beneficial in treating hypertension.

- The dihydropyridines have the advantage in that they show little interaction with other cardiovascular drugs, such as digoxin or warfarin, which are often used concomitantly with calcium channel blockers.

6. Calcium channel blockers (CCBs)

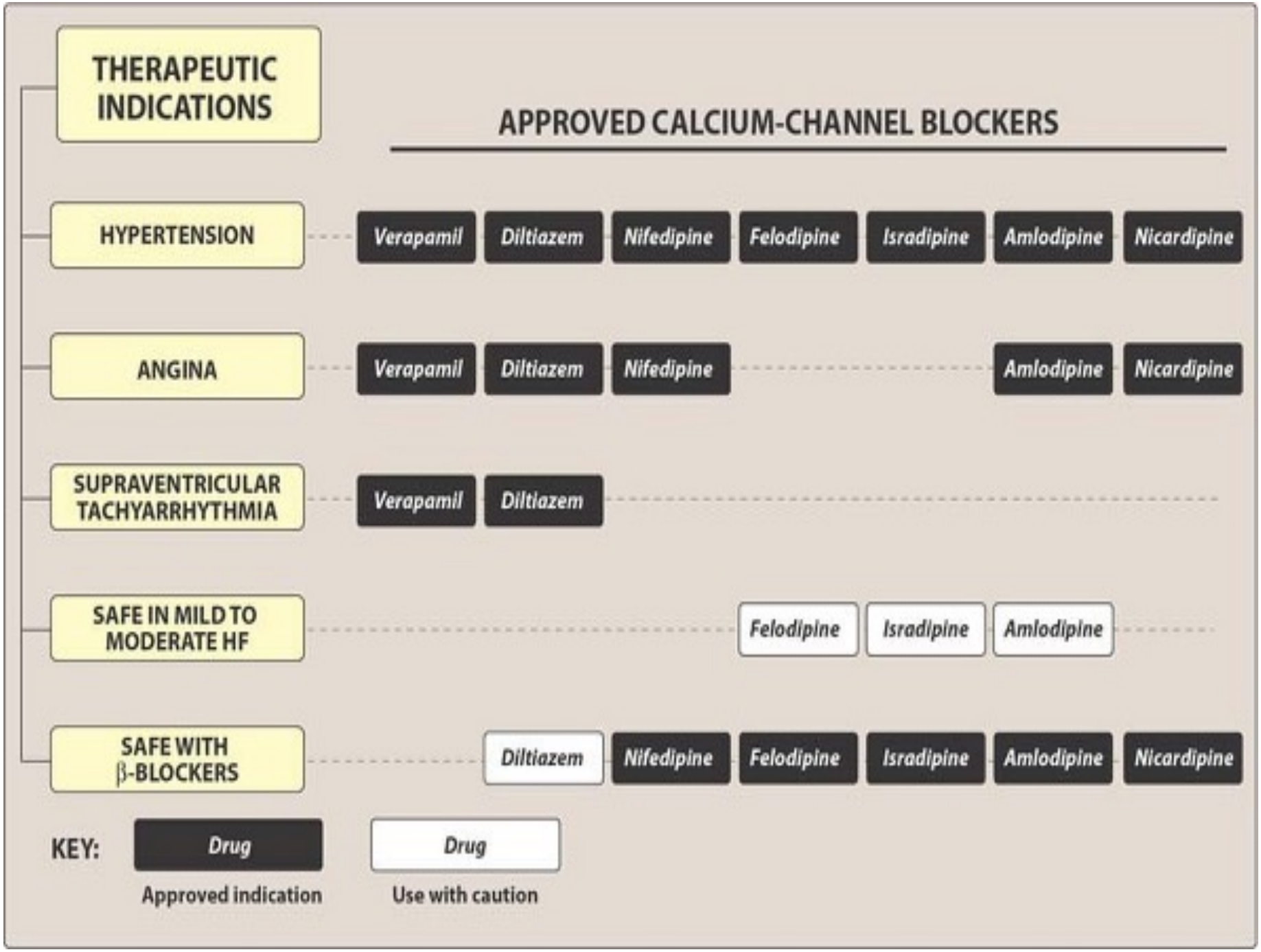
Amlodipine, diltiazem, felodipine, isradipine, nicardipine, Nifedipine, nisoldipine, Verapamil, clevidipine

Action:

- The intracellular concentration of calcium plays an important role in maintaining the tone of smooth muscle and in the contraction of the myocardium. Calcium enters muscle cells through special voltage-sensitive calcium channels. This triggers release of calcium from the sarcoplasmic reticulum and mitochondria, which further increases the cytosolic level of calcium.
- Calcium channel antagonists block the inward movement of calcium by binding to L-type calcium channels in the heart and in smooth muscle of the coronary and peripheral arteriolar vasculature. This causes vascular smooth muscle to relax, dilating mainly arterioles. Calcium channel blockers do not dilate veins.

Therapeutic uses

- In the management of hypertension, CCBs may be used as an initial therapy or as add-on therapy.
- They are useful in the treatment of hypertensive patients who also have asthma, diabetes, and/or peripheral vascular disease, because unlike β-blockers, they do not have the potential to adversely affect these conditions.
- All CCBs are useful in the treatment of angina. In addition, diltiazem and verapamil are used in the treatment of atrial fibrillation.


THERAPEUTIC INDICATIONS
APPROVED CALCIUM-CHANNEL BLOCKERS
HYPERTENSION
Verapamil
Diltiazem
Nifedipine
Felodipine
Isradipine
Amlodipine
Nicardipine
ANGINA
Verapamil
Diltiazem
Nifedipine
Amlodipine
Nicardipine
SUPRAVENTRICULAR TACHYARRHYTHMIA
Verapamil
Diltiazem
SAFE IN MILD TO MODERATE HF
Felodipine
Isradipine
Amlodipine
SAFE WITH β-BLOCKERS
Diltiazem
Nifedipine
Felodipine
Isradipine
Amlodipine
Nicardipine
KEY:
Drug
Approved indication
Drug
Use with caution

7. α-adrenoceptor–blocking agents

Doxazosin, prazosin, terazosin

- They produce a competitive block of α1-adrenoceptors.

- The decrease peripheral vascular resistance and lower arterial blood pressure by causing relaxation of both arterial and venous smooth muscle.

- These drugs cause only minimal changes in cardiac output, renal blood flow, an glomerular filtration rate. Therefore, long-term tachycardia does not occur, but salt and water retention does. Reflex tachycardia and postural hypotension often occur at the onset of treatment and with dose increases, requiring slow titration of the drug in divided doses.

- Due to weaker outcome data and their side effect profile, α-blockers are no longer recommended as initial treatment for hypertension, but may be used for refractory cases.

8. α-/β-adrenoceptor–blocking agents

Labetalol and carvedilol

- Labetalol and carvedilol block α1, β1, and β2 receptors.
- Carvedilol, although an effective antihypertensive, is mainly used in the treatment of heart failure.
- Carvedilol, as well as metoprolol succinate, and bisoprolol have been shown to reduce morbidity and mortality associated with heart failure.
- Labetalol is used in the management of gestational hypertension and hypertensive emergencies.

9. Centrally acting adrenergic drugs

A. Clonidine: acts centrally as an α2 agonist to produce inhibition of sympathetic vasomotor centers, decreasing sympathetic outflow to the periphery. This leads to reduced total peripheral resistance and decreased blood pressure.

- Clonidine is used primarily for the treatment of hypertension that has not responded adequately to treatment with two or more drugs.
- Clonidine does not decrease renal blood flow or glomerular filtration and, therefore, is useful in the treatment of hypertension complicated by renal disease.
- Rebound hypertension occurs following abrupt withdrawal of clonidine. The drug should, therefore, be withdrawn slowly if discontinuation is required.

B. Methyldopa: is an α2 agonist that is converted to methylnorepinephrine centrally to diminish adrenergic outflow from the CNS.

- Its use is limited due to adverse effects and the need for multiple daily doses. It is mainly used for management of hypertension in pregnancy, where it has a record of safety.

10. Vasodilators

Hydralazine and minoxidil

- The direct-acting smooth muscle relaxants are not used as primary drugs to treat hypertension.

- These vasodilators act by producing relaxation of vascular smooth muscle, primarily in arteries and arterioles. This results in decreased peripheral resistance and, therefore, blood pressure.

- Hydralazine is an accepted medication for controlling blood pressure in pregnancy induced hypertension.

- Minoxidil treatment causes hypertrichosis (the growth of body hair). This drug is used topically to treat male pattern baldness.

Hypertensive emergency

- Hypertensive emergency is a rare but life-threatening situation characterized by severe elevations in blood pressure (systolic greater than 180 mm Hg or diastolic greater than 120 mm Hg) with evidence of impending or progressive target organ damage (for example, stroke, myocardial infarction).

- Hypertensive emergencies require timely blood pressure reduction with treatment administered intravenously to prevent or limit target organ damage.

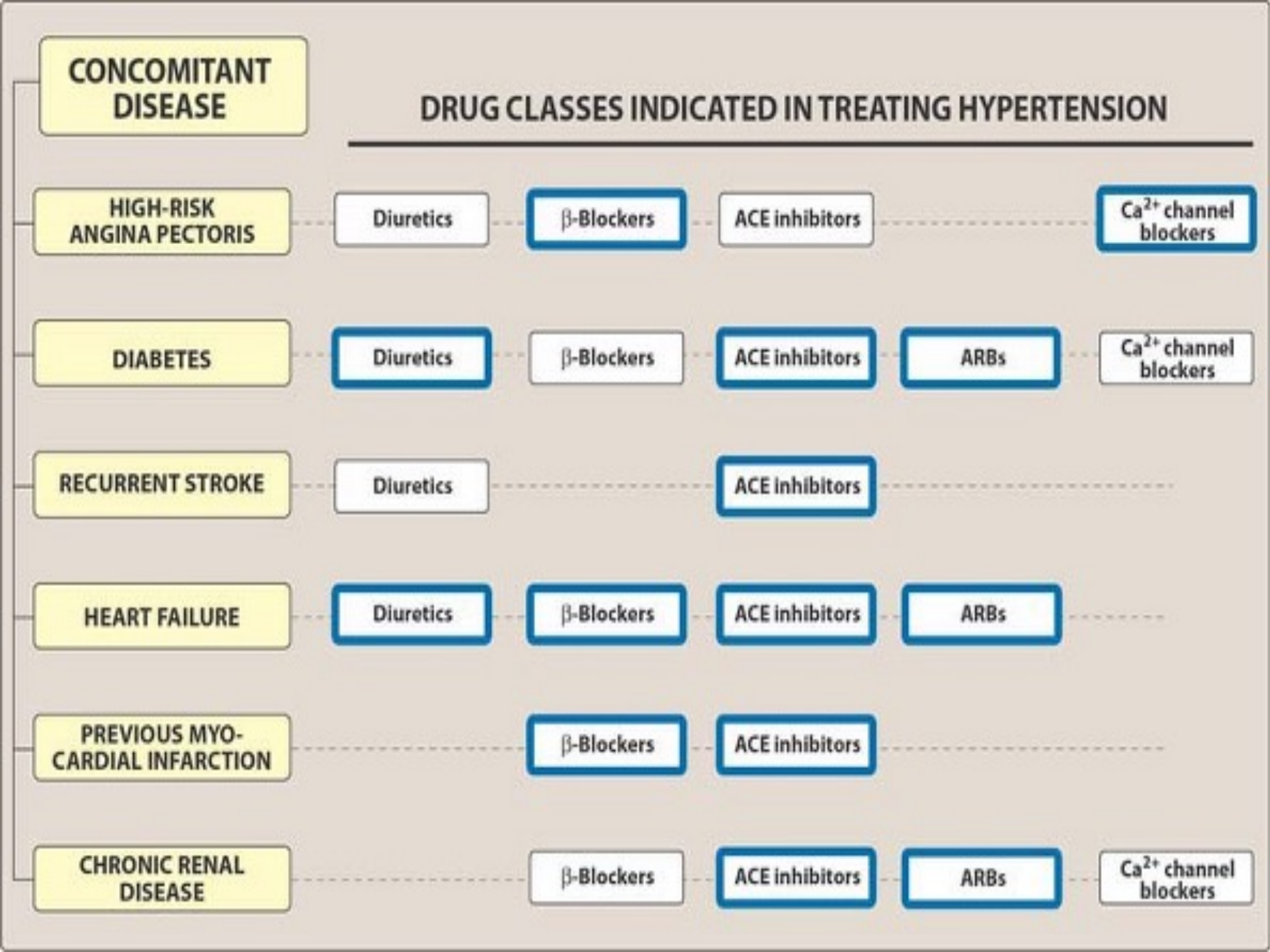
- A variety of medications are used, including calcium channel blockers (nicardipine and clevidipine), nitric oxide vasodilators (nitroprusside and nitroglycerin), adrenergic receptor antagonists (phentolamine, esmolol, and labetalol), the vasodilator hydralazine, and the dopamine agonist fenoldopam.

- Treatment is directed by the type of target organ damage present and/or comorbidities present.

Resistant hypertension

- Resistant hypertension is defined as blood pressure that remains elevated (above goal) despite administration of an optimal three-drug regimen that includes a diuretic.

- The most common causes of resistant hypertension are poor compliance, excessive ethanol intake, concomitant conditions (diabetes, obesity, sleep apnea, hyperaldosteronism, high salt intake, and/or metabolic syndrome), concomitant medications (sympathomimetics, nonsteroidal anti-inflammatory drugs, or antidepressant medications), insufficient dose and/or drugs, and use of drugs with similar mechanisms of action.


CONCOMITANT DISEASE
DRUG CLASSES INDICATED IN TREATING HYPERTENSION
HIGH-RISK ANGINA PECTORIS
Diuretics
β-Blockers
ACE inhibitors
Ca2+ channel blockers
DIABETES
Diuretics
β-Blockers
ACE inhibitors
ARBs
Ca2+ channel blockers
RECURRENT STROKE
Diuretics
ACE inhibitors
HEART FAILURE
Diuretics
β-Blockers
ACE inhibitors
ARBs
PREVIOUS MYO-CARDIAL INFARCTION
β-Blockers
ACE inhibitors
CHRONIC RENAL DISEASE
β-Blockers
ACE inhibitors
ARBs
Ca2+ channel blockers


Thank
you