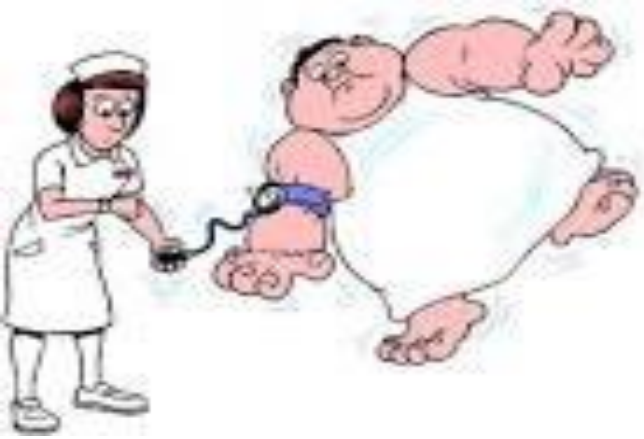
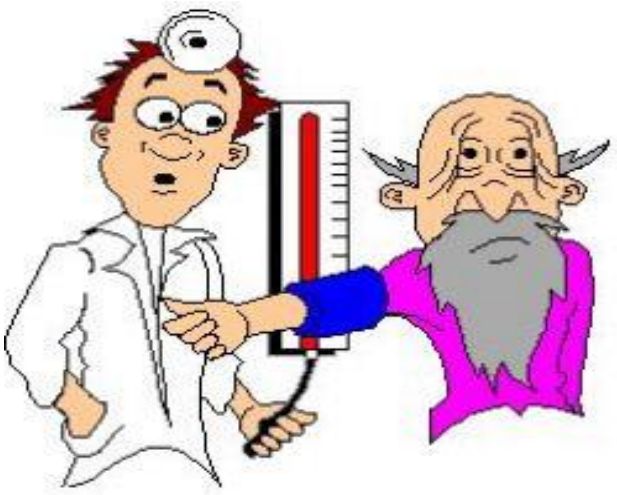



# ANTIHYPERTENSIVES

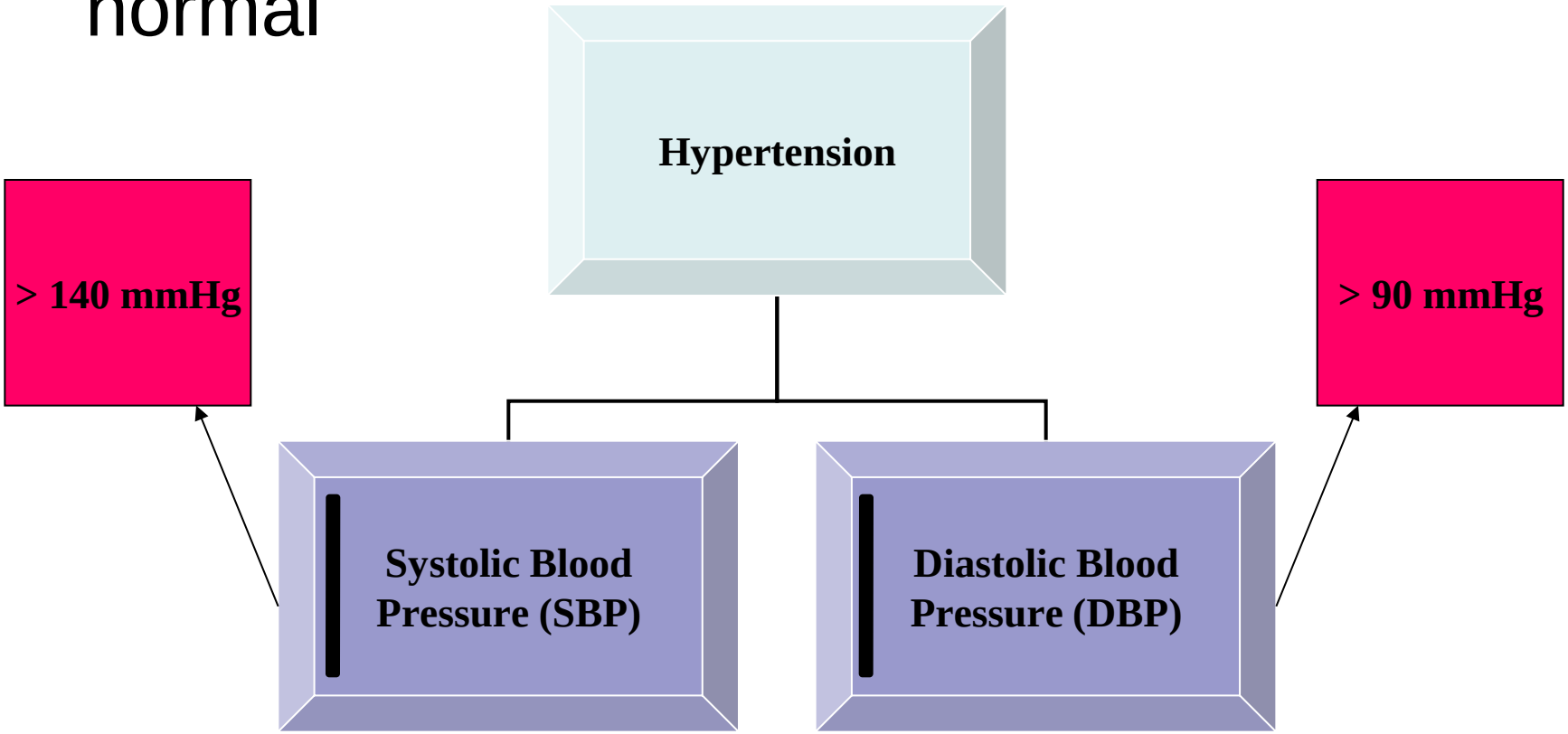
Assoc. Prof. Bilgen Başgut

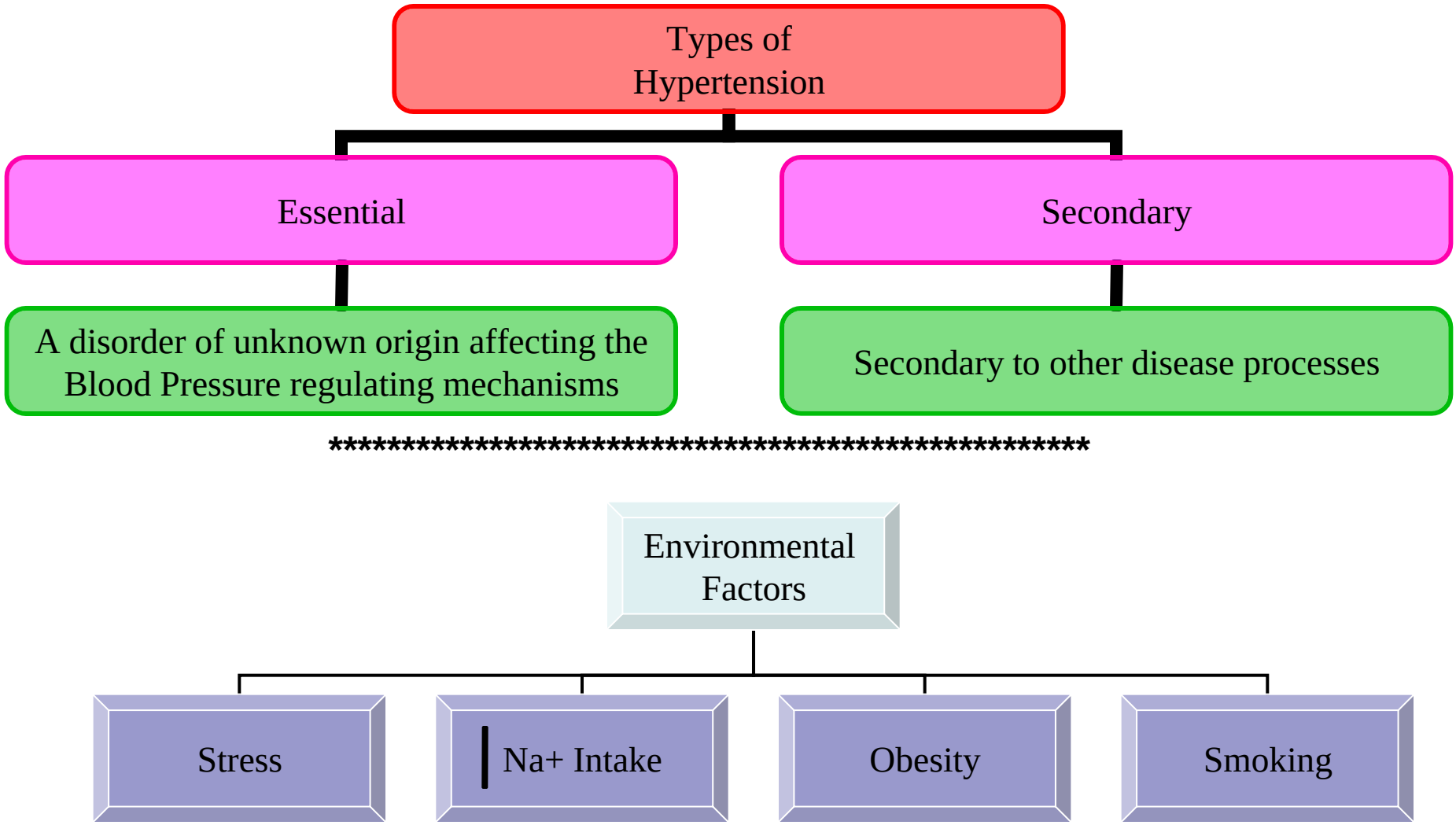




# Hypertension

- Hypertension is a condition in which the blood pressure is persistently higher than normal




Types of Hypertension
Essential
Secondary
A disorder of unknown origin affecting the Blood Pressure regulating mechanisms
Secondary to other disease processes
**********
Environmental Factors
Stress
Na+ Intake
Obesity
Smoking

# Risk Factors

**Major Cardiovascular Risk Factors**

- Hypertension
- Smoking
- Obesity (BMI $\geq$ 30)
- Physical inactivity
- Dyslipidemia
- Diabetes mellitus
- Microalbuminuria or GFR < 60ml/min
- Advanced age
  - Men > 55, women > 65
- Family history of premature CV disease

**Target Organ Disease**

- Heart
  - Left ventricular hypertrophy
  - CAD
    - Angina and/or prior MI
    - Prior coronary revascularization
  - Heart failure
- Brain
  - Stroke or TIA
- Chronic renal insufficiency
- Peripheral arterial disease
- Retinopathy

NHBPEP Coordinating Committee. The JNC 7 Report. *JAMA* 2003;289:2560-72.

# Classification of hypertension (JNC 7)

| Classification | SBP (mmHg) | | DBP (mmHg) |
|---|---|---|---|
| Normal | < 120 | And | < 80 |
| prehypertension | 120~139 | Or | 80~89 |
| stage 1 hypertension | 140~159 | Or | 90~99 |
| stage 2 hypertension | ≧160 | Or | ≧100 |

# Recommended BP goals (ESH/ESC 2007)

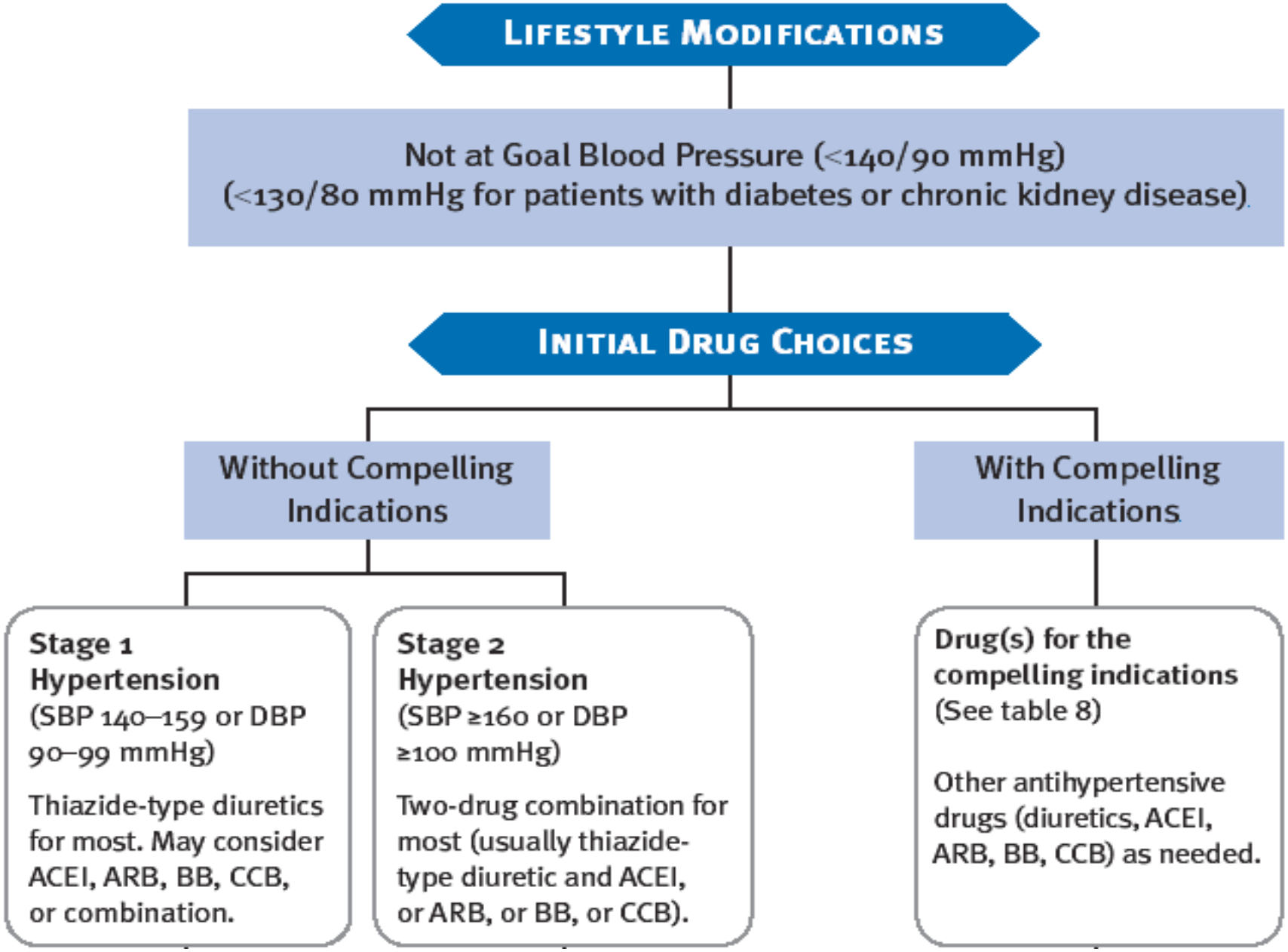
- <140/90 mm Hg in all patients with hypertension
- <130/80 mm Hg in patients with diabetes mellitus and patients with high added risk, with compelling diseases - stroke, myocardial infarction (MI), renal dysfunction or proteinuria

ESH – ESC Guidelines Committee. *J Hypertens* 2007; **25:** 1105–1187

# Treatment of hypertension

- Initial tx. drug- diuretic or B-blocker
- Low dose first, increase dose if necessary
- 2nd med. if needed
- Most respond with diuretic and one other medication (stepped care)

Figure 1. Algorithm for treatment of hypertension




http://www.nhlbi.nih.gov/guidelines/hypertension/express.pdf

# Non-pharmacological management of hypertension

- Lifestyle modification *first*
- No smoking
- Weight control
- Reduce alcohol intake
- Decrease stress
- Sodium control

# Lifestyle modifications to manage hypertension

| Modification | Recommendation | Approximate Systolic BP Reduction, Range |
|---|---|---|
| Weight reduction | Maintain normal body weight (BMI, 18.5-24.9) | 5-20 mm Hg/10-kg weight loss[23,24] |
| Adopt DASH eating plan | Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat | 8-14 mm Hg[25,26] |
| Dietary sodium reduction | Reduce dietary sodium intake to no more than 100 mEq/L (2.4 g sodium or 6 g sodium chloride) | 2-8 mm Hg[25-27] |
| Physical activity | Engage in regular aerobic physical activity such as brisk walking (at least 30 minutes per day, most days of the week) | 4-9 mm Hg[28,29] |
| Moderation of alcohol consumption | Limit consumption to no more than 2 drinks per day (1 oz or 30 mL ethanol [eg, 24 oz beer, 10 oz wine, or 3 oz 80-proof whiskey]) in most men and no more than 1 drink per day in women and lighter-weight persons | 2-4 mm Hg[30] |

# Major factors influencing blood pressure

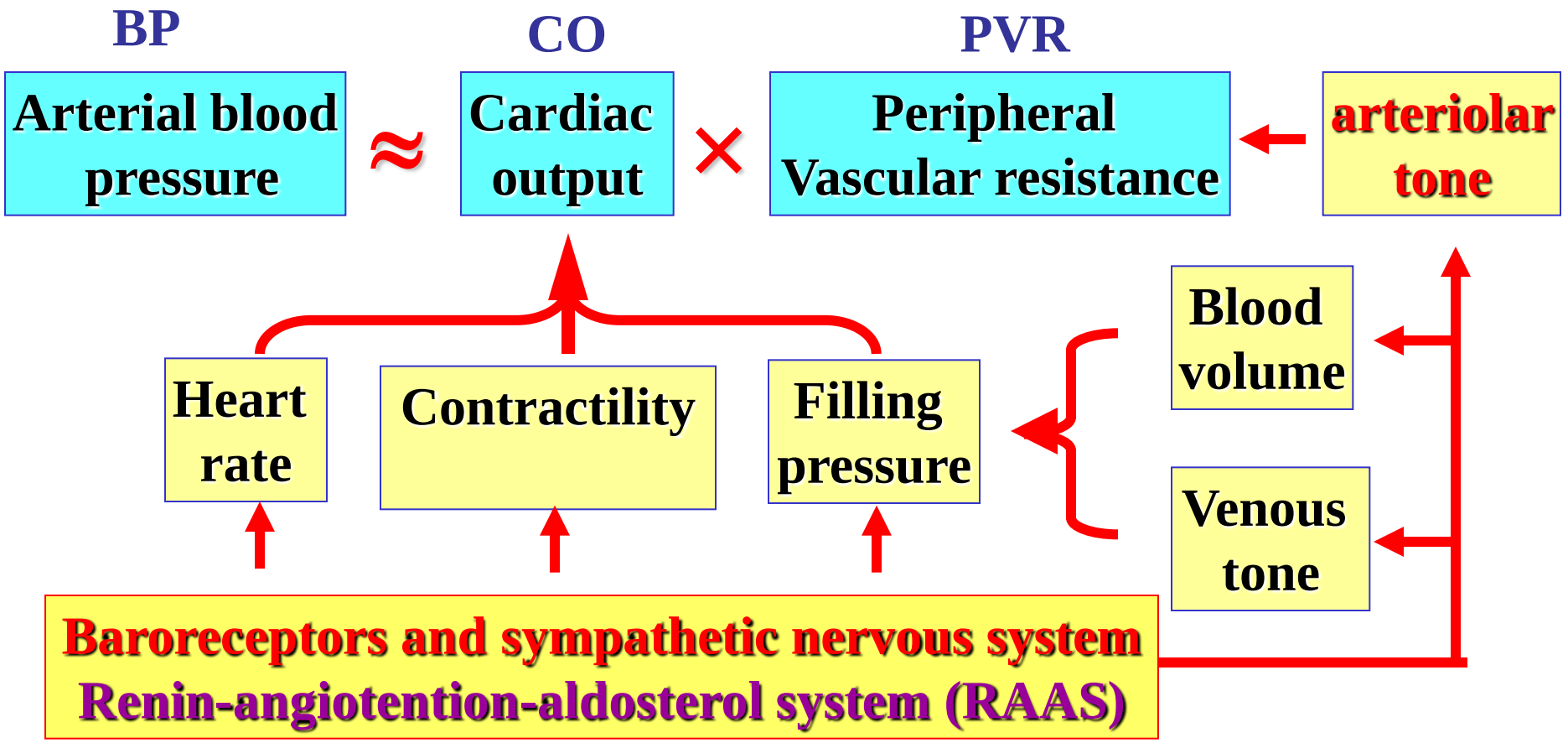
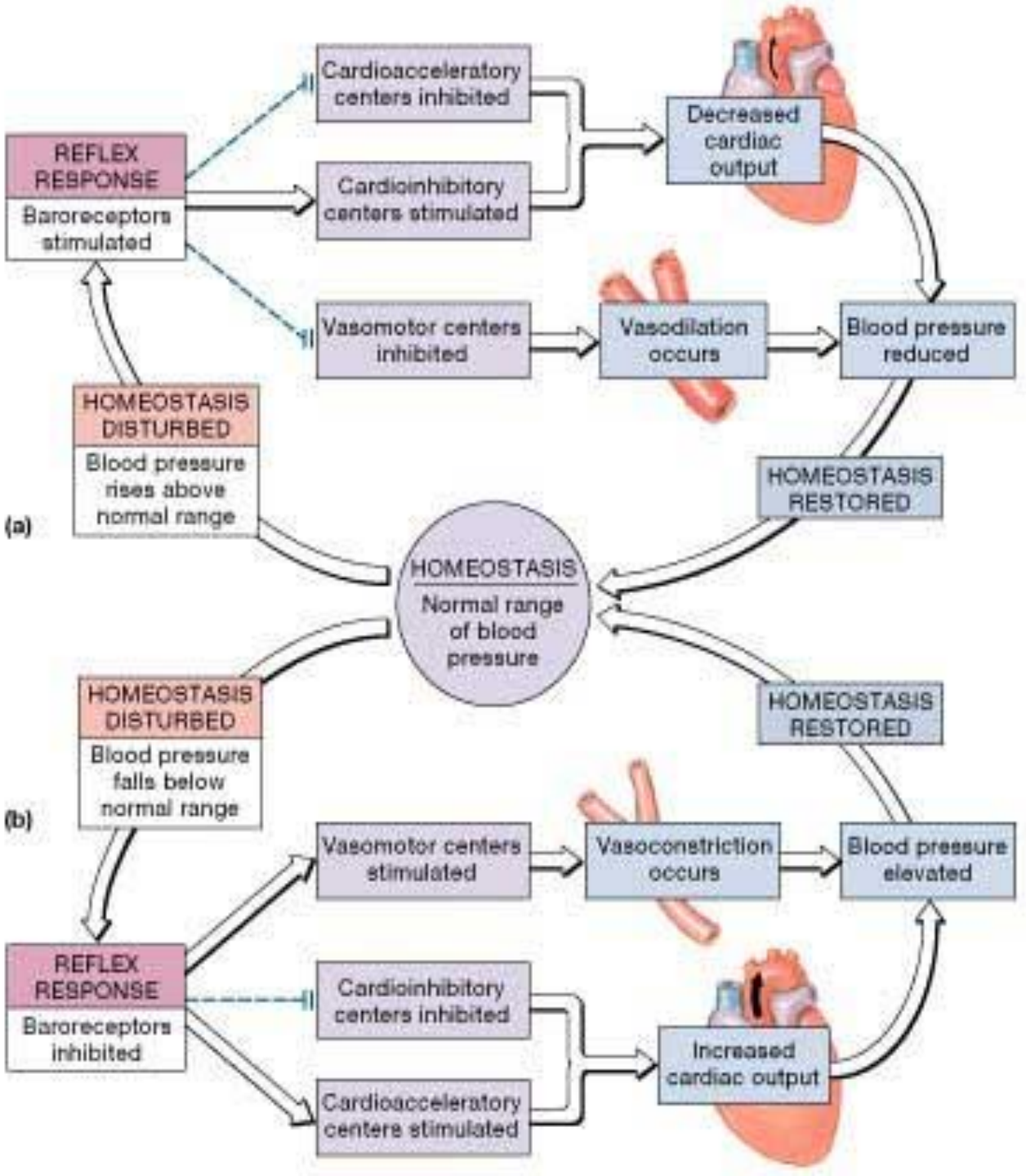


**FIGURE 21-15** The Carotid and Aortic Sinus Baroreceptor Reflexes

# Hypertension & regulation of blood pressure

## A. Baroreceptor reflex mechanism



# Hypertension & regulation of blood pressure

## B. Renin-Angiotensin-Aldosteron (RAAS)

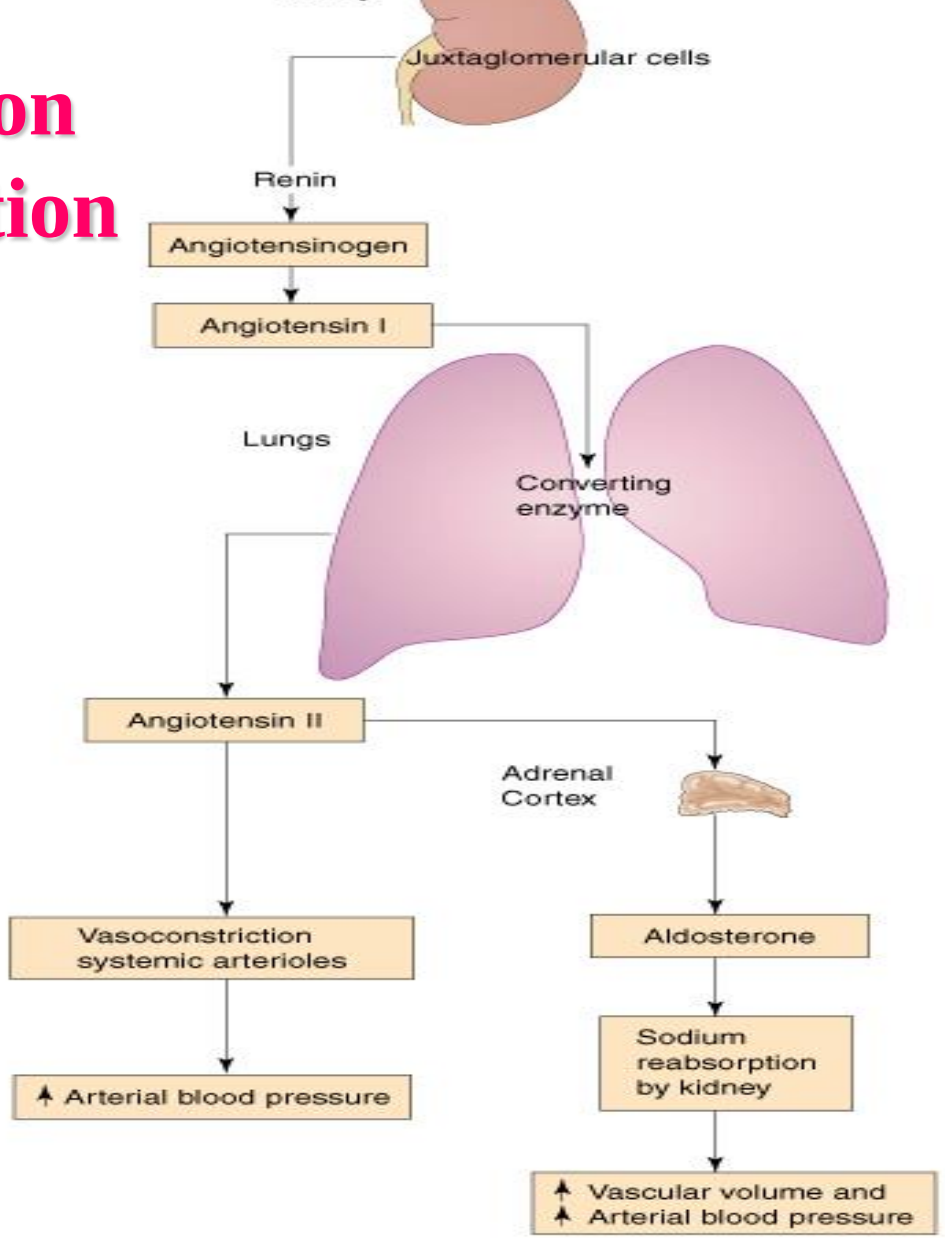



Figure 25-5 Control of blood pressure by the renin-angiotensin-aldosterone system. Renin enzymatically converts the plasma protein angiotensinogen to angiotensin I; angiotensin-converting enzyme in the lung converts angiotensin I to angiotensin II; and angiotensin II produces vasoconstriction and increases salt and water retention through direct action on the kidney and through increased aldosterone secretion by the adrenal cortex.

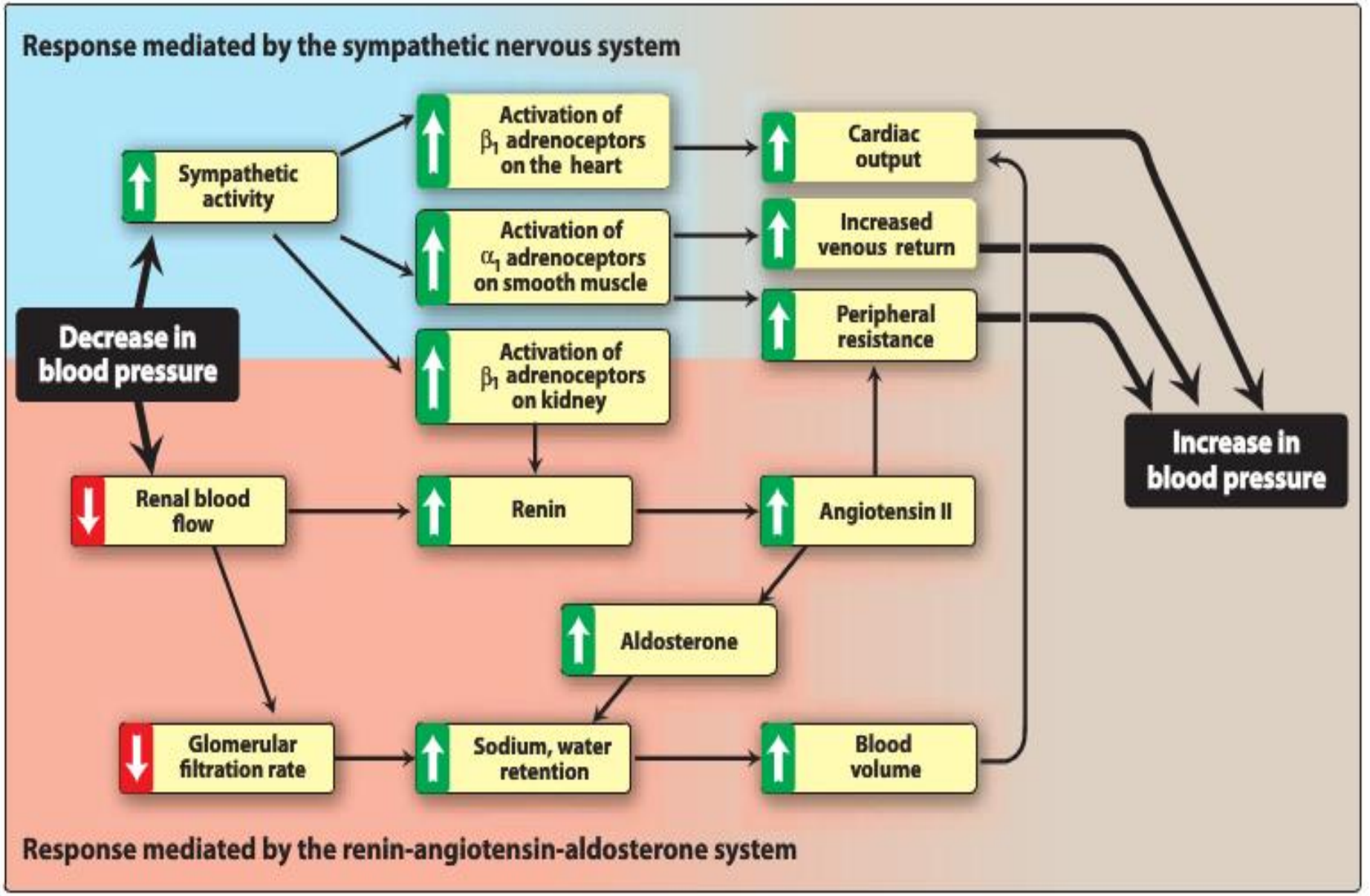
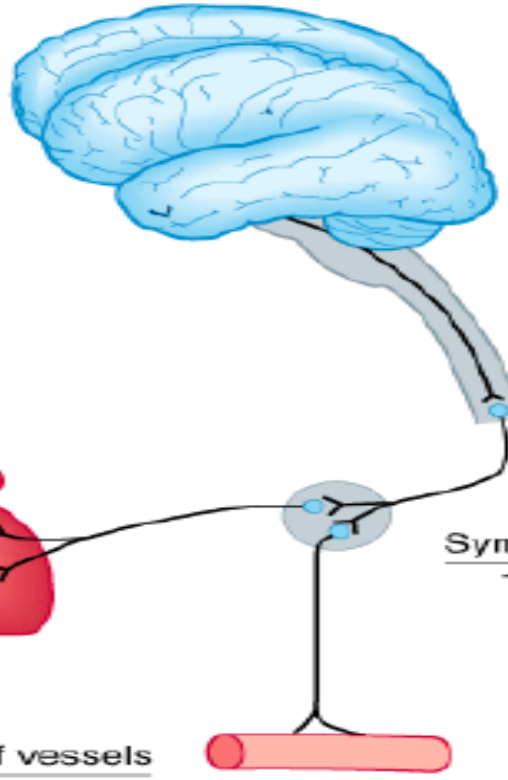



**Figure 19.4**

Response of the autonomic nervous system and the renin-angiotensin-aldosterone system to a decrease in blood pressure.



**Vasomotor center**
Methyldopa
Clonidine
Guanabenz
Guanfacine

**Sympathetic nerve terminals**
Guanethidine
Guanadrel
Reserpine

**Sympathetic ganglia**
Trimethaphan

**β-Receptors of heart**
Propranolol and other β-blockers

**Angiotensin receptors of vessels**
Losartan and other angiotensin receptor blockers

**α-Receptors of vessels**
Prazosin and other $\alpha_1$-blockers

**Vascular smooth muscle**
Hydralazine
Minoxidil
Nitroprusside
Diazoxide
Verapamil and other calcium channel blockers
Fenoldopam

**Kidney tubules**
Thiazides, etc

**β-Receptors of juxtaglomerular cells that release renin**
Propranolol and other β-blockers

Angiotensinogen → (*Renin*) → Angiotensin I → (*Angiotensin-converting enzyme*) → Angiotensin II

Aliskiren

Captopril and other ACE inhibitors

# Antihypertensive Drugs

- Diuretics:
  - Thiazides: Hydrochlorothiazide, chlorthalidone
  - High ceiling: Furosemide
  - K+ sparing: Spironolactone, triamterene and amiloride

MOA: Acts on Kidneys to increase excretion of Na and $H_2O$ – decrease in blood volume – decreased BP

- Angiotensin-converting Enzyme (ACE) inhibitors:
  - Captopril, lisinopril., enalapril, ramipril and fosinopril

MOA: Inhibit synthesis of Angiotensin II – decrease in peripheral resistance and blood volume

- Angiotensin (AT1) blockers:
  - Losartan, candesartan, valsartan and telmisartan

MOA: Blocks binding of Angiotensin II to its receptors

# Antihypertensive Drugs

- Centrally acting:
  - Clonidine, methyldopa

MOA: Act on central $\alpha_{2A}$ receptors to decrease sympathetic outflow – fall in BP

- ß-adrenergic blockers:
  - **Non selective:** Propranolol (others: nadolol, timolol, pindolol, labetolol)
  - **Cardioselective: Metoprolol** (others: atenolol, esmolol, betaxolol)

MOA: Bind to beta adrenergic receptors and blocks the activity

- ß and α – adrenergic blockers:
  - Labetolol and carvedilol
- α – adrenergic blockers:
  - Prazosin, terazosin, doxazosin, phenoxybenzamine and phentolamine

MOA: Blocking of alpha adrenergic receptors in smooth muscles - vasodilatation

# Antihypertensive Drugs –

- Calcium Channel Blockers (CCB):
  - Verapamil, diltiazem, nifedipine, felodipine, amlodipine, nimodipine etc.

MOA: Blocks influx of Ca++ in smooth muscle cells – relaxation of SMCs – decrease BP

- K+ Channel activators:
  - Diazoxide, minoxidil, pinacidil and nicorandil

MOA: Leaking of K+ due to opening – hyper polarization of SMCs – relaxation of SMCs

- Vasodilators:
  - Arteriolar – Hydralazine (also CCBs and K+ channel activators)
  - Arterio-venous: Sodium Nitroprusside

# DIURETICS

- First line drug therapy
- for hypertension

**Thiazide diuretics**

(the most widespread use)

Hydrochlorothiazide

Chlortalidone

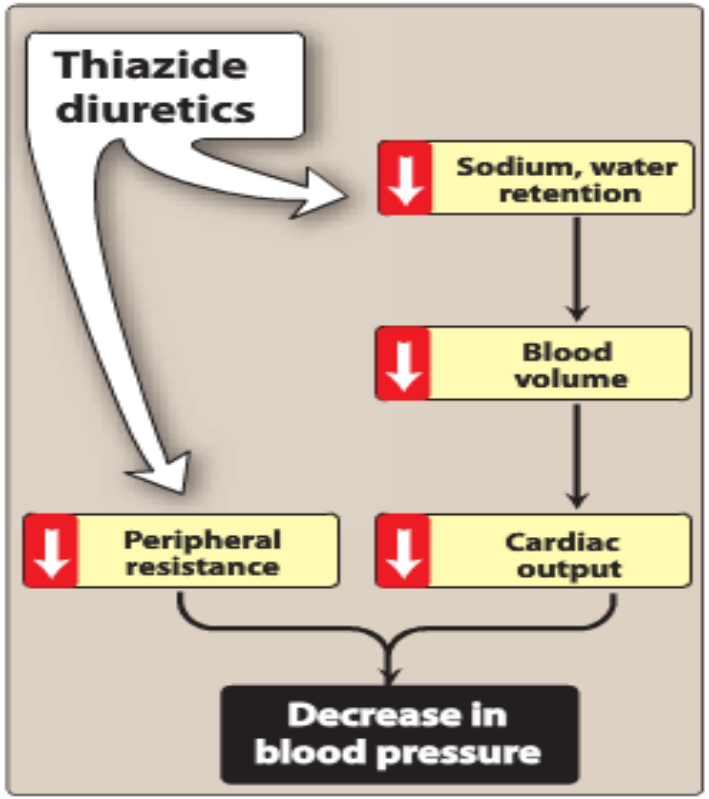



**Figure 19.8**
Actions of thiazide diuretics.

Potassium-sparing diuretics are often used in combination with thiazides to reduce the amount of potassium loss induced by the thiazide diuretics.

- postural hypotension is rarely observed except in elderly during thiazide treatment
- These agents counteract the sodium and water retention observed with other agents used in the treatment of hypertension (for example, hydralazine)
- useful in combination therapy with a variety of other antihypertensive agents, including β-blockers, ACE inhibitors, angiotensin-receptor blockers (ARBs), and potassium-sparing diuretics
- thiazide diuretics are not effective in patients with inad-equate kidney function
- Thiazide diuretics are orally active

# Adverse effects

- Thiazide diuretics induce hypokalemia and hyper-uricemia and hyperglycemia
- Acute gout attacks may be triggered.
- Hypomagnesemia may also occur.
- Serum potassium levels should be monitored closely in patients who are predisposed to cardiac arrhythmias and those who are concurrently being treated with both thiazide diuretics and digoxin.

# Loop diuretics

- furosemide, bumetanide, and torsemide
- They act promptly, even in patients with poor renal function or who have not responded to thiazides or other diuretics.
- Loop diuretics cause decreased renal vascular resistance and increased renal blood flow.
- These agents increase the $Ca^{2+}$ content of urine, whereas thiazide diuretics decrease it.

# Potassium-sparing diuretics

- Amiloride and triamterene
- spironolactone and eplerenone (aldosterone-receptor antagonists)
- These agents inhibit epithelial sodium transport at the late distal and collecting ducts and reduce potassium loss in the urine.

# β-ADRENOCEPTOR–BLOCKING AGENTS

- β-Blockers are currently recommended as first-line drug therapy for hypertension when concomitant disease is present for example, such as supraventricular tachyarrhythmia, previous myocardial infarction, angina pectoris, and chronic heart failure.
- β-Blockers are also used to prevent migraine and cluster headaches

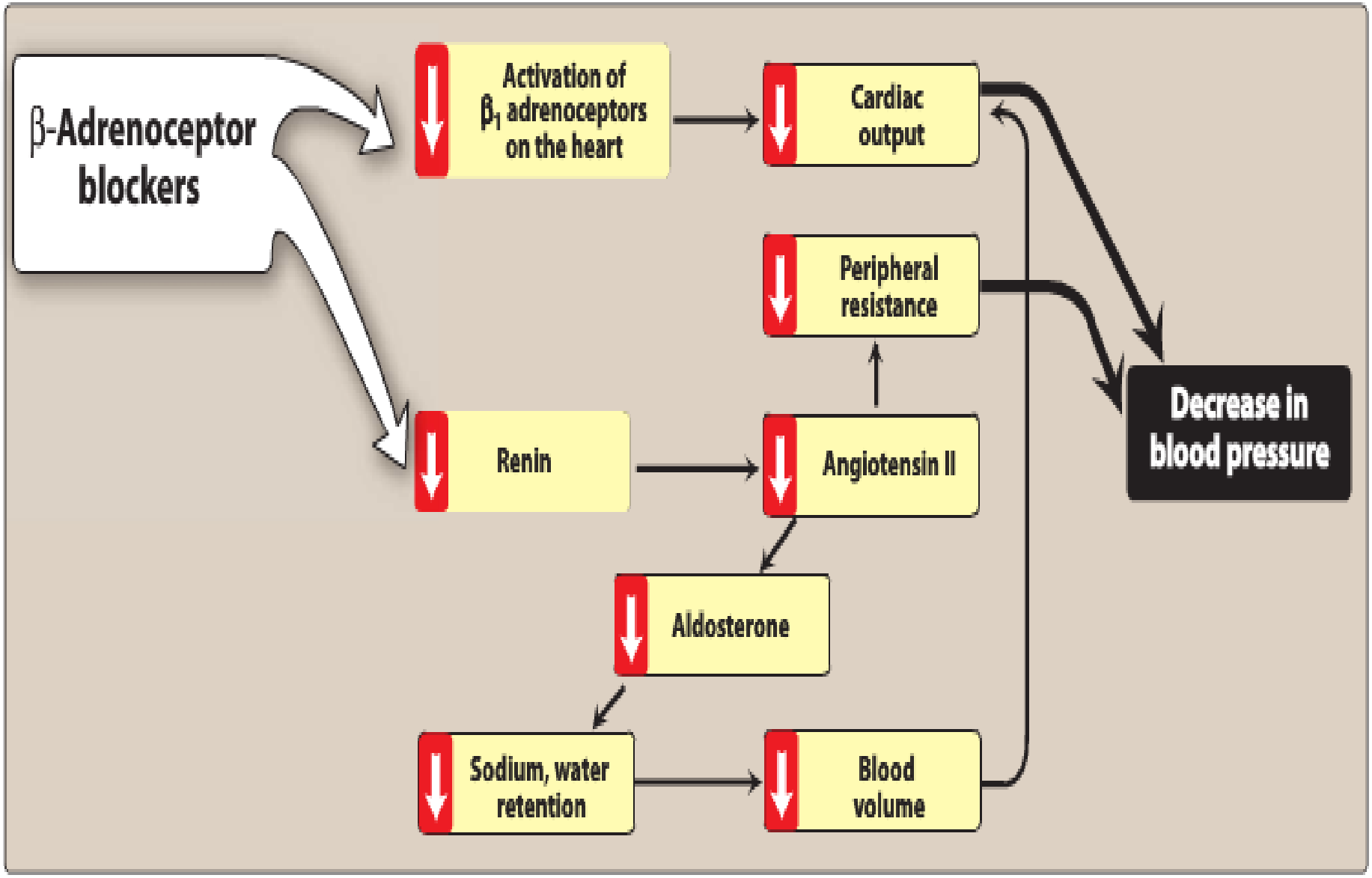



**Figure 19.9**

Actions of β–adrenoceptor blocking agents.

- The prototype β-blocker is propranolol (non-selective).
- Selective blockers of β1 receptors: 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.
- 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 due to their blockade of β2-mediated bronchodilation.
- The β-blockers should be used cautiously in the treatment of patients with acute heart failure or peripheral vascular disease.

- The β-blockers are orally active
- Propranolol undergoes extensive and highly variable frst-pass metabolism.
- The β-blockers may take several weeks to develop their full effects.

## Other adverse effects of beta blockers:

- decreasing high-density lipoprotein cholesterol
- increasing plasma triglycerides
- abrupt withdrawal may induce angina, myocardial infarction, and even sudden death in patients with ischemic heart disease.

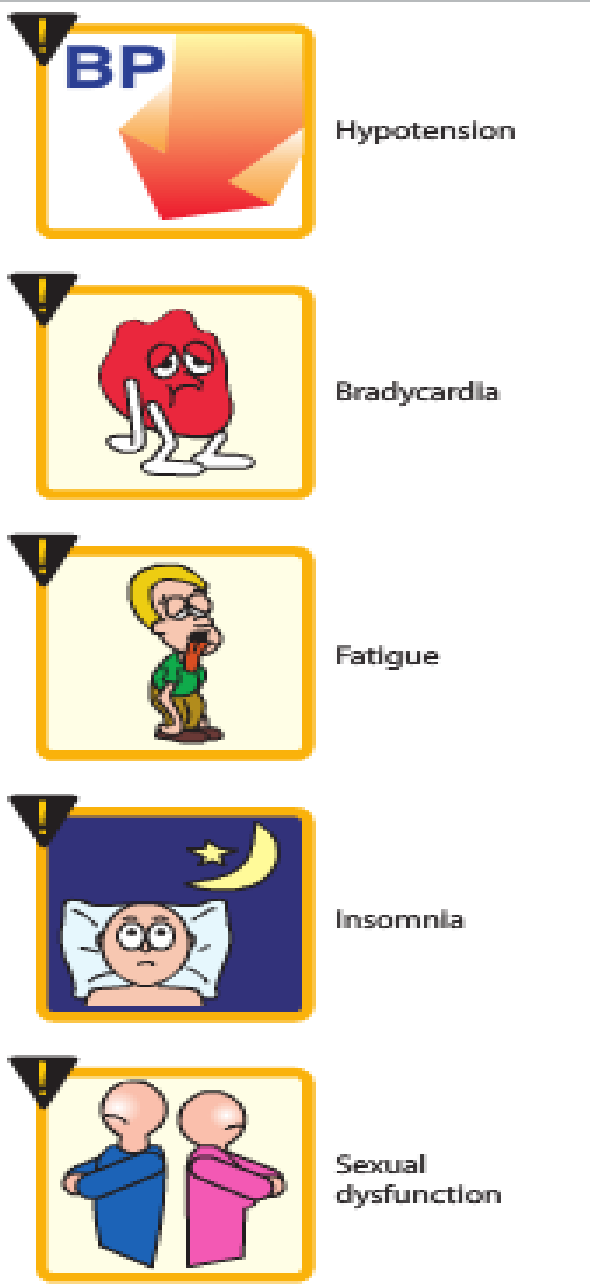
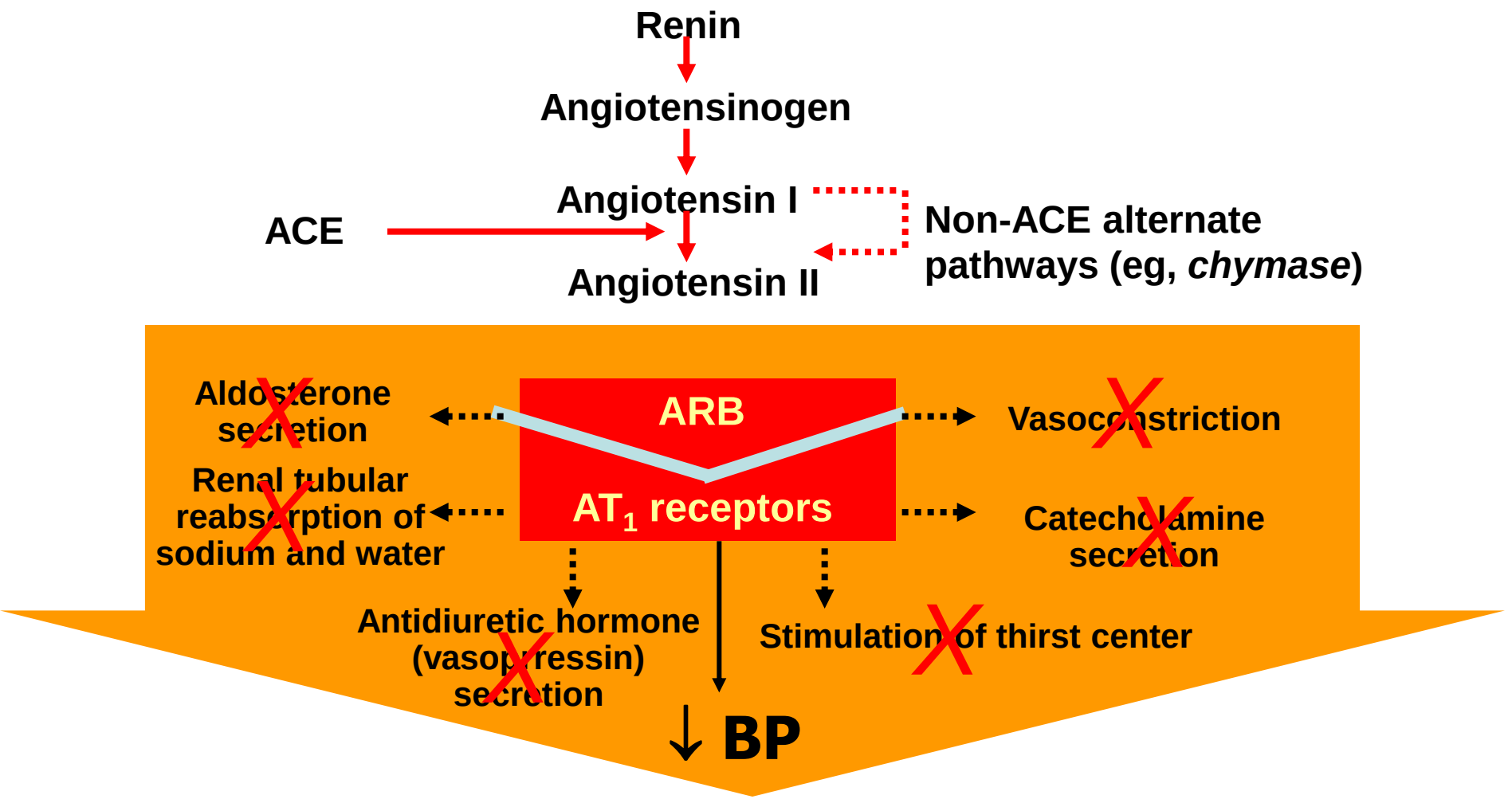



**Figure 19.10**
Some adverse effects of β-blockers.

# ACE INHIBITORS and ARBs



# ACE inhibitors

- These agents are recommended when the preferred first-line agents (diuretics or β-blockers) are contraindicated or ineffective, or if there are compelling reasons to use them such as in diabetes mellitus.
- The ACE inhibitors lower blood pressure by reducing peripheral vascular resistance without reflexively increasing cardiac output, rate, or contractility.

- ACE inhibitors slow the progression of diabetic nephropathy and decrease albuminuria and are, thus, a compelling indication for patients with diabetic nephropathy.
- They are first-line drugs for treating heart failure, to treat hypertensive patients with chronic renal disease, and for patients with increased risk for coronary artery diseas

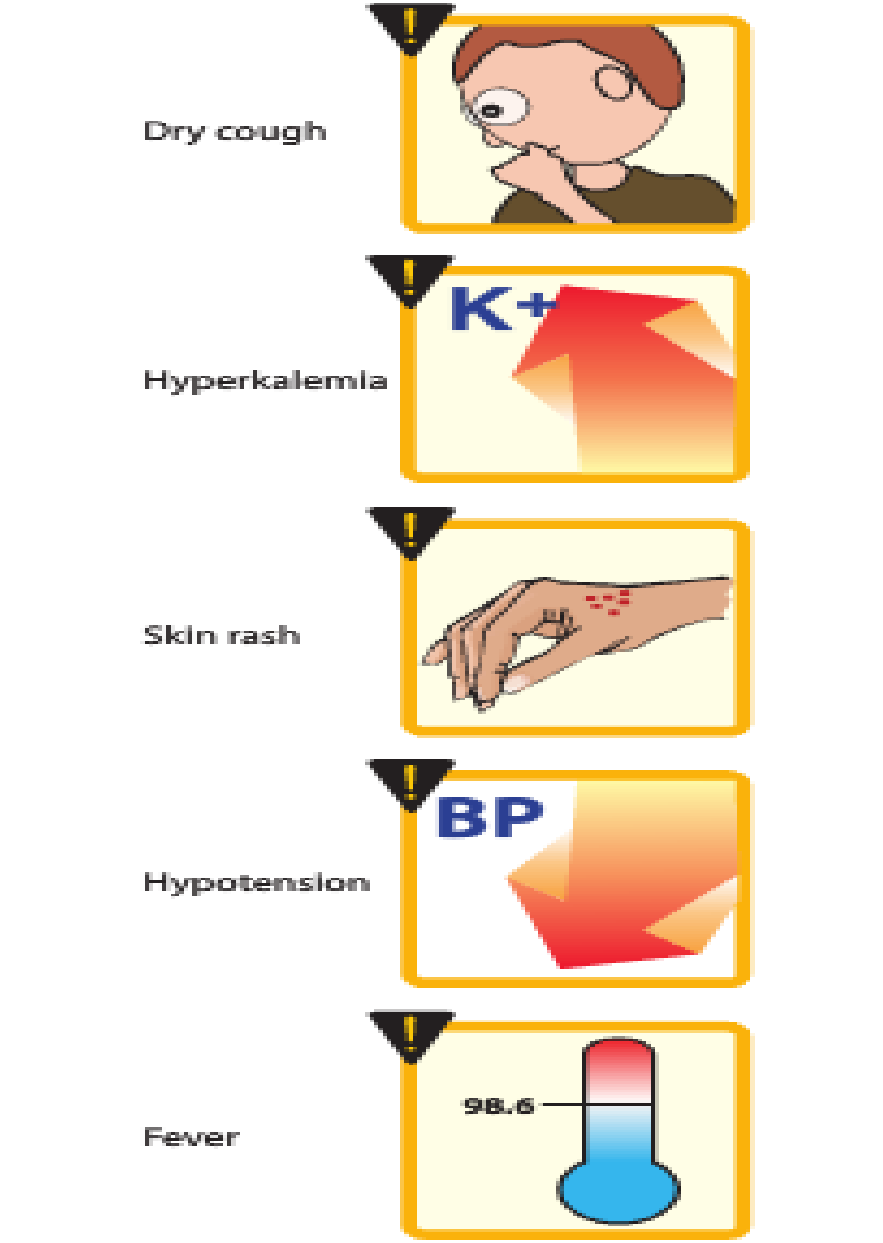



**Figure 19.12**
Some common adverse effects of the angiotensin-converting enzyme inhibitors.

# ARBs

- 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  ACE inhibitors
- ARBs do not increase bradykinin levels.
- ARBs decrease the nephrotoxicity of diabetes, making them an attractive therapy in hyper-tensive diabetics.
- Their adverse effects are similar to ACE inhibitors, although the risks of cough and angioedema are signifcantly decreased. ARBs are also fetotoxic and should not be used by women who are pregnant.

| ACE-INHIBITORS | ANGIOTENSIN II ANTAGONISTS |
| --- | --- |
| Captopril (Capoten®) | Losartan (Cozaar®) |
| Enalapril (Vasotec®) | Valsartan (Diovan®) |
| Benazepril (Lotensin®) | Irbesartan (Avapro®) |
| Lisinopril (Zestril®, Prinivil®) | Telmisartan (Micardis®) |
| Fosinopril (Monopril®) | Candesartan (Atacand®) |
| Quinapril (Accupril®) | Eprosartan (Teveten®) |
| Ramipril (Altace®) | |
| Moexipril (Univasc®) | |
| Trandolapril (Mavik®) | |
| Perindopril (Aceon®) | |

# RENIN INHIBITOR

- Aliskiren
- It directly inhibits renin and, thus, acts earlier in the renin-angiotensin-aldosterone system than do ACE inhibitors or ARBs.
- It lowers blood pressure about as effectively as ARBs, ACE inhibitors, and thiazides.
- Aliskiren can cause diarrhea, especially at higher doses.
- Aliskiren can also cause cough and angioedema but probably less often than ACE inhibitors.
- As with ACE inhibitors and ARBs, aliskiren is contraindicated during pregnancy.

# CALCIUM-CHANNEL BLOCKERS

- Calcium-channel blockers are recommended when the prefferred frst-line agents are contraindicated or ineffective.
- They are effective in treating hypertension in patients with angina or diabetes.

# Classes of calcium-channel blockers

The calcium-channel blockers are divided into three chemical classes, each with different pharmacokinetic properties and clinical indications

1. Diphenylalkylamines: Verapamil has significant effects on both cardiac and vascular smooth muscle cells. It is also used to treat angina, supraventricular tachyarrhythmias, and to prevent migraine and cluster headaches. First-degree atrioventricular block and constipation are dose-dependent common side effects of verapamil.
2. Benzothiazepines: 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.
3. Dihydropyridines: This rapidly expanding class of calcium-channel blockers includes the first-generation nifedipine and five second-generation agents for treating cardiovascular disease: amlodipine, felodipine, isradipine, nicardipine, and nisoldipine. All dihydropyridines have a much greater afinity for vascular calcium channels than for calcium channels in the heart. They are, therefore, particularly attractive in treating hypertension.

- These agents are useful in the treatment of hypertensive patients who also have asthma, diabetes, angina, and/or peripheral vascular disease

**Actions:** 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.

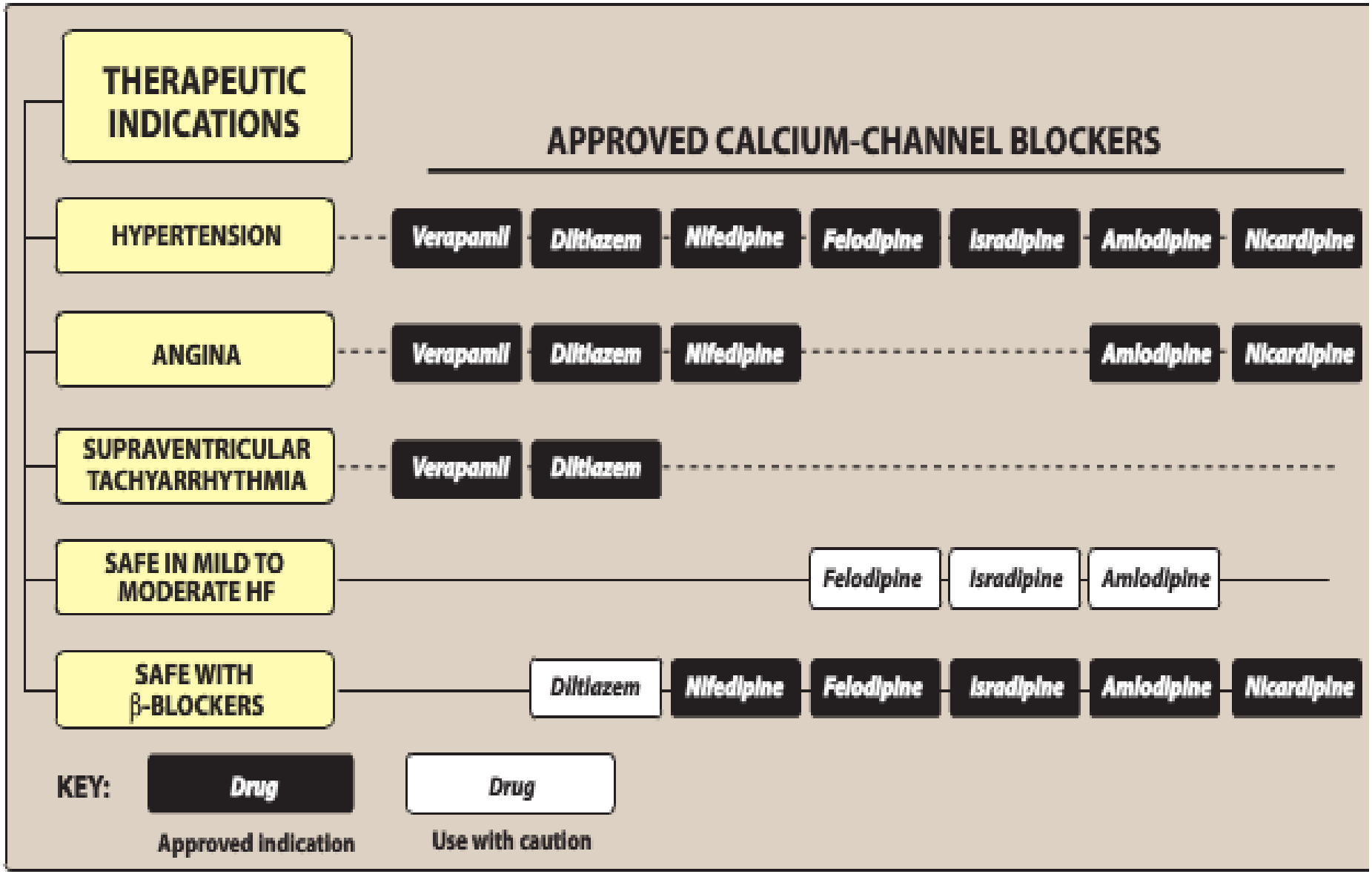


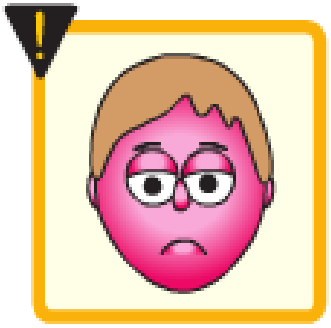

**Figure 19.14**

Some therapeutic applications of calcium-channel blockers. HF = heart failure.

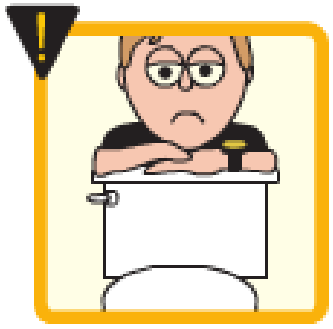
- Most of these agents have short half-lives (3–8 hours) following an oral dose. Sustained-release preparations are available and permit once-daily dosing. Amlodipine has a very long half-live and does not require a sustained-release formulation.

- Adverse effects: Constipation occurs in approximately 10 percent of patients treated with verapamil. Dizziness, headache, and a feeling of fatigue caused by a decrease in blood pressure are more frequent with dihydropyridines

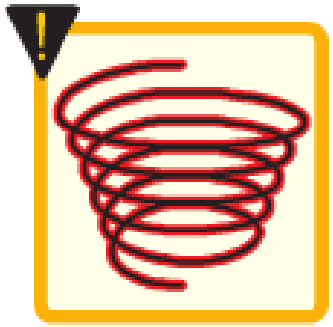
- Verapamil should be avoided in patients with congestive heart failure or with atrioventricular block due to its negative inotropic and dromotropic effects. Nifedipine has caused gingival enlargement.



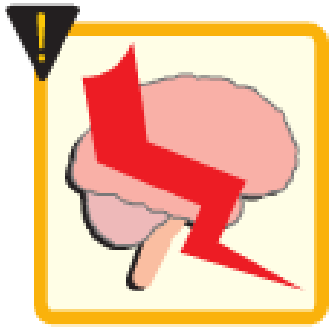
Flushing



Constipation



Dizziness



Headache

Fatigue


Hypotension

**Figure 19.15**
Some common adverse effects of the calcium-channel blockers.

# α-ADRENOCEPTOR–BLOCKING AGENTS

- Prazosin, doxazosin, and terazosin produce a competitive block of α1 adrenoceptors.
- They decrease peripheral vascular resistance and lower arterial blood pressure by causing relaxation of both arterial and venous smooth muscle.
- Postural hypotension may occur in some individuals. α1-Blockers may be used to treat mild to moderate hypertension and are prescribed in combination with propranolol and/or a diuretic for addi-tive effects.
- Reflex tachycardia and first-dose syncope are almost universal adverse effects.
- Concomitant use of a β-blocker may be necessary to blunt the short-term effect of reflex tachycardia.
- Tamsulosin, an α1-blocker with greater selectivity for prostate muscle, has been used in the treatment of benign prostatic hyperplasia

# α-/β-ADRENOCEPTOR–BLOCKING AGENTS

- 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, a selective β1 antagonist, have been shown to reduce morbidity and mortality associated with heart failure.

# CENTRALLY ACTING ADRENERGIC DRUGS

- **Clonidine**

This α2-agonist diminishes the central adrenergic outflow, decreasing the firing rate of the sympathetic nerves and the amount of nor-epinephrine release.

Clonidine does not decrease renal blood flow or glomerular filtration and, therefore, is useful in the treatment of hypertension complicated by renal disease.

- It may cause sodium and water retention, therefore clonidine may be administered in combination with a diuretic.
- Adverse effects: sedation, dry mouth, and constipation.
- Rebound hypertension occurs following abrupt withdrawal of clonidine.
- The drug should, therefore, be withdrawn slowly if the clinician wishes to change agents.

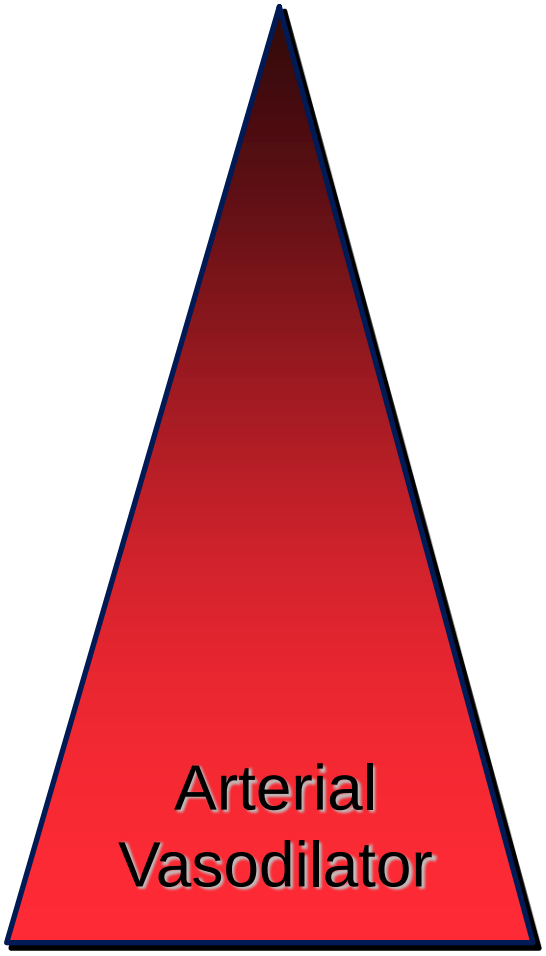
# α-Methyldopa

- This α2-agonist is converted to methylnorepinephrine centrally to diminish adrenergic outflow from the CNS
- This leads to reduced total peripheral resistance and decreased blood pressure.
- Cardiac output is not decreased, and blood flow to vital organs is not diminished. Because blood flow to the kidney is not diminished by its use, α-methyldopa is especially valuable in treating hypertensive patients with renal insufficiency. The most common side effects of α-methyldopa are sedation and drowsiness.
- It has been used in hypertensive pregnant patients.

# VASODILATORS

- They act by producing relaxation of vascular smooth muscle, which decreases resistance and, therefore, blood pressure.
- A significant part of the blood pressure–lowering action of these drugs is due to activa-tion of the potassium channels, increasing potassium eflux and inducing hyperpolarization of the smooth muscle membrane. When the membrane is hyperpolarized, calcium influx is inhibited and the arteriolar smooth muscle relaxes.
- These agents produce reflex stimulation of the heart, resulting in the competing reflexes of increased myocardial contractility, heart rate, and oxygen consumption. These actions may prompt angina pectoris, myocar-dial infarction, or cardiac failure in predisposed individuals.
- Vasodilators also increase plasma renin concentration, resulting in sodium and water reten-tion. These undesirable side effects can be blocked by concomitant use of a diuretic and a β-blocker.

# Classification of Vasodilators




**Venous**

Nitrates

**Mixed**

Calcium Antagonists

$\alpha$-adrenergic Blockers

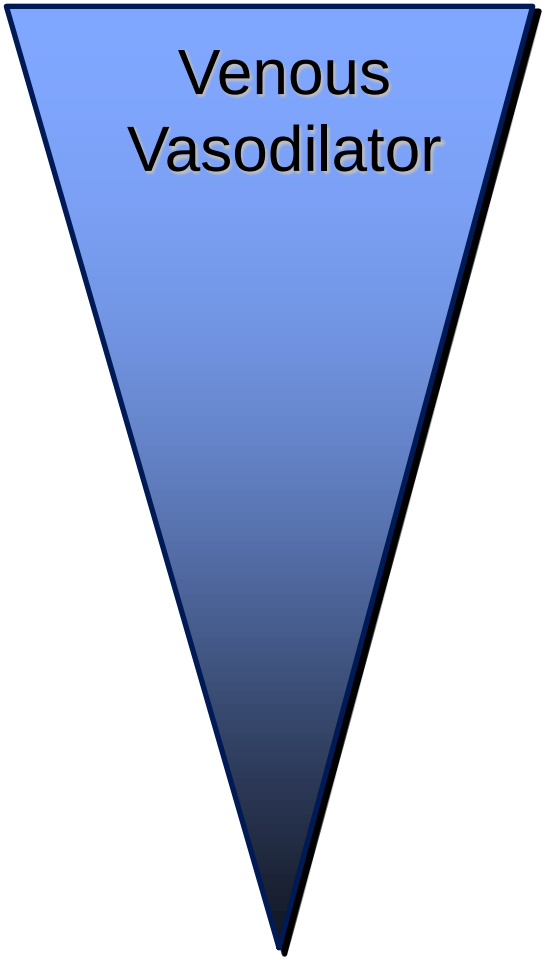
ACEI

Nitroprusside

**Arterial**

Minoxidil

Hydralazine



# Hydralazine

- This drug causes direct vasodilation, acting primarily on arteries and arterioles.
- This results in decreased peripheral resistance, which, in turn, prompts a reflex elevation in heart rate and cardiac output.
- Hydralazine is used to treat moderately severe hypertension. It is almost always administered in combination with a β-blocker, such as propranolol, metoprolol, or atenolol (to balance the reflex tachycardia) and a diuretic (to decrease sodium retention). Together, the three drugs decrease cardiac output, plasma volume, and peripheral vascular resis-tance.
- Hydralazine monotherapy is an accepted method of controlling blood pressure in pregnancy-induced hypertension.
- Adverse effects of hydralazine therapy include headache, tachycardia, nausea, sweating, arrhythmia, and precipitation of angina. A lupus-like syndrome can occur with high dosage, but it is reversible on discontinuation of the drug

# Minoxidil

- This drug causes dilation of resistance vessels (arterioles) but not of capacitance vessels (venules).
- Minoxidil is administered orally for treatment of severe to malignant hypertension that is refractory to other drugs.
- Reflex tachycardia and fluid retention may be severe and require the concomitant use of a loop diuretic and a β-blocker. Minoxidil causes serious sodium and water retention, leading to volume overload, edema, and congestive heart failure. [Note: Minoxidil treat-ment also causes hypertrichosis (the growth of body hair). This drug is used topically to treat male pattern baldness.]

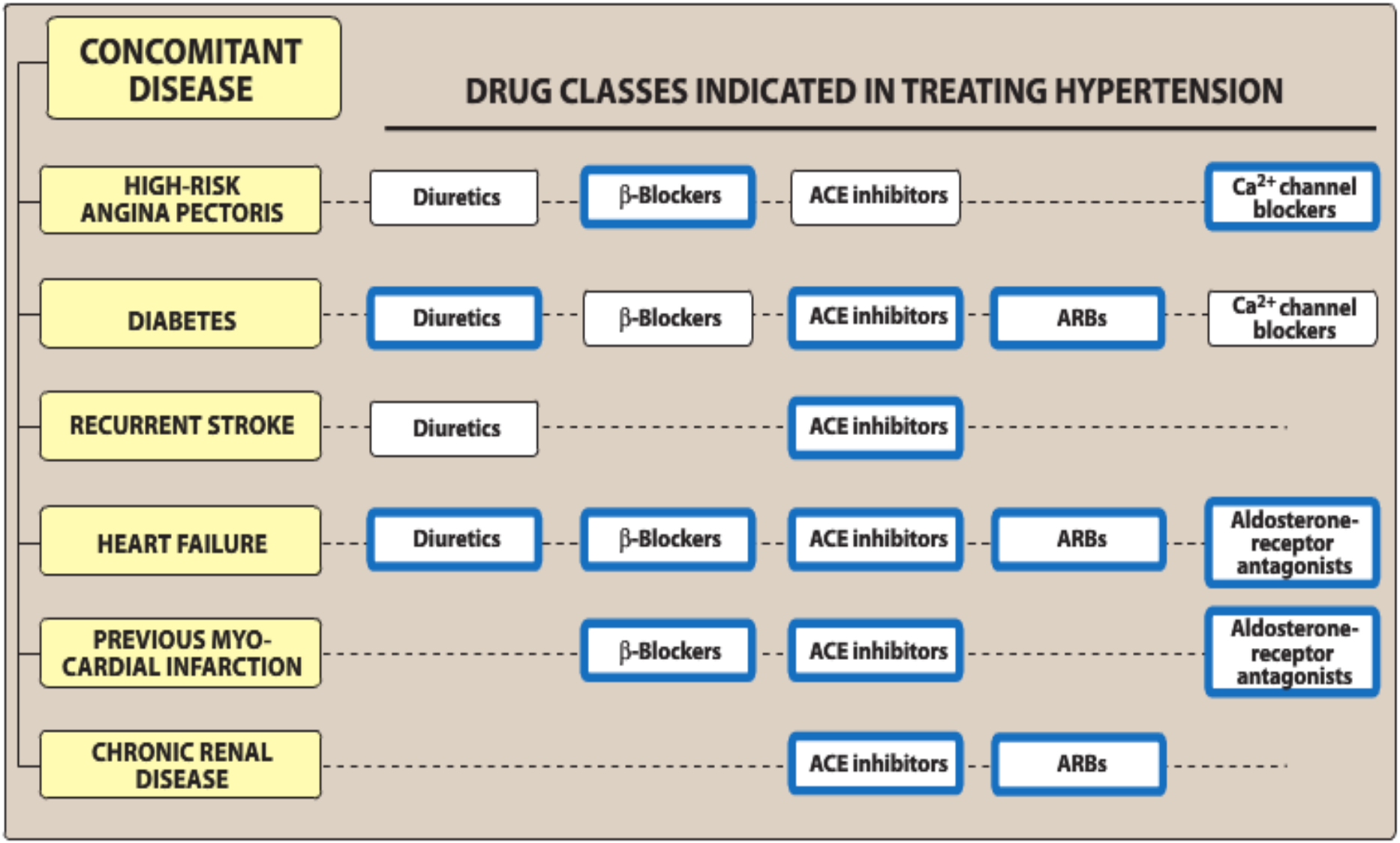



**Figure 19.5**

Treatment of hypertension in patients with concomitant diseases. Drug classes shown in blue boxes provide improvement in outcome (for example diabetes or renal disease) independent of blood pressure. [Note: Angiotensin-receptor blockers (ARBs) are an alternative to angiotensin-converting enzyme (ACE) inhibitors.] ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker.

# Hypertensive Emergencies

- Cerebrovascular accident or head injury with high BP
- Left ventricular failure with pulmonary edema due to hypertension
- Hypertensive encephalopathy
- Angina or MI with raised BP
- Acute renal failure with high BP
- Eclampsia
- Pheochromocytoma, cheese reaction and clonidine withdrawal
- Drugs:
  - Sodium Nitroprusside (20-300 mcg/min) – dose titration and monitoring
  - GTN (5-20 mcg/min) – cardiac surgery, LVF, MI and angina
  - Esmolol (0.5 mg/kg bolus) and 50-200mcg/kg/min - useful in reducing cardiac work
  - Phentolamine – pheochromocytoma, cheese reaction nd clonidine withdrawal (5-10 mg IV)

- Sodium nitroprusside is administered intravenously and causes prompt vasodilation with reflex tachycardia.
- It is capable of reducing blood pressure in all patients regardless of the cause of hyper-tension
- Nitroprusside metabolism results in cyanide ion production. Although cyanide toxicity is rare, it can be effectively treated with an infusion of sodium thiosulfate to produce thiocyanate, which is less toxic and is eliminated by the kidneys.

# Labetalol

- It is both an α- and a β-blocker and is given as an intravenous bolus or infusion in hypertensive emergencies.
- Labetalol does not cause reflex tachycardia.
- Labetalol carries the contraindications of a nonselective β-blocker.

# Fenoldopam

- Fenoldopam is a peripheral dopamine-1 receptor agonist that is given as an intravenous infusion.
- Fenoldopam maintains or increases renal perfusion while lowering blood pressure. Fenoldopam relaxes mainly the renal and mesenteric arterial vessels, with a smaller vasodilating action on coronary and cerebral arteries and on veins (capacitance vessels).
- The diuretic action of fenoldopam is mainly caused by the increase in renal blood fow. Fenoldopam can be safely used in all hypertensive emergencies and may be particularly beneficial in patients with renal insuficiency.
- The drug is contraindicated in patients with glaucoma.

# Special Populations

- **Hypertension in different race:**

  **African Americans (blacks)**

  – Response to diuretics & CCB > response to ACEI, ARB, beta-blockers

  – Angioedema 2 – 4-fold higher

  **Chineese:** are more sensitive to the effects of β-blockers and may require lower doses

- **Elderly (Isolated Systolic HTN)**
  - Same general principles
  - Thiazide or CCB may be better tolerated

- **Pregnancy**
  - Methyldopa, beta-blockers, vasodilators (hydralazine)
  - Avoid ACEI & ARBs

- A 45-year-old man has recently been diagnosed with hypertension and started on monotherapy designed to reduce peripheral resistance and pre-vent Na+ and water retention. He has developed a persistent cough. Which of the following drugs is most likely responsible for this side effect?

A. Losartan.

B. Nifedipine.

C. Prazosin.

D. Propranolol.

E. Enalapril.

- Which one of the following drugs may cause a precipitous fall in blood pressure and fainting on initial administration?

A. Atenolol.

B. Hydrochlorothiazide.

C. Metoprolol.

D. Prazosin.

E. Verapamil.

- Which one of the following antihypertensive drugs can precipitate a hypertensive crisis following abrupt cessation of therapy?

A. Clonidine.

B. Diltiazem.

C. Enalapril.

D. Losartan.

E. Hydrochlorothiazide.

# References

The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure (The JNC7 report). JAMA, 2003, 289(19): 2560-2572.

Basic & Clinical Pharmacology (11th edition), 2009.

Goodman & Gilman's the pharmacological basis of therapeutics (10th), 2002.

Lipincott's Illustrated Reviews, Pharmacology, 5th edition, 2012.