Antihypertensive Drugs

Munir Gharaibeh, MD, PhD, MHPE
Faculty of Medicine,
The University of Jordan
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Antihypertensive Drugs

What is Hypertension:

A common, incurable, persistent, but usually asymptomatic disease whose treatment provides no obvious benefit.

Introduction

- Thirty percent of people with high blood pressure don’t know they have it.
- Of all people with high blood pressure, 11 percent aren’t on therapy (special diet or drugs), 25 percent are on inadequate therapy, and 34 percent are on adequate therapy.

Average 14 readings: two per session, taken morning and evening for 7 days.

BP variations

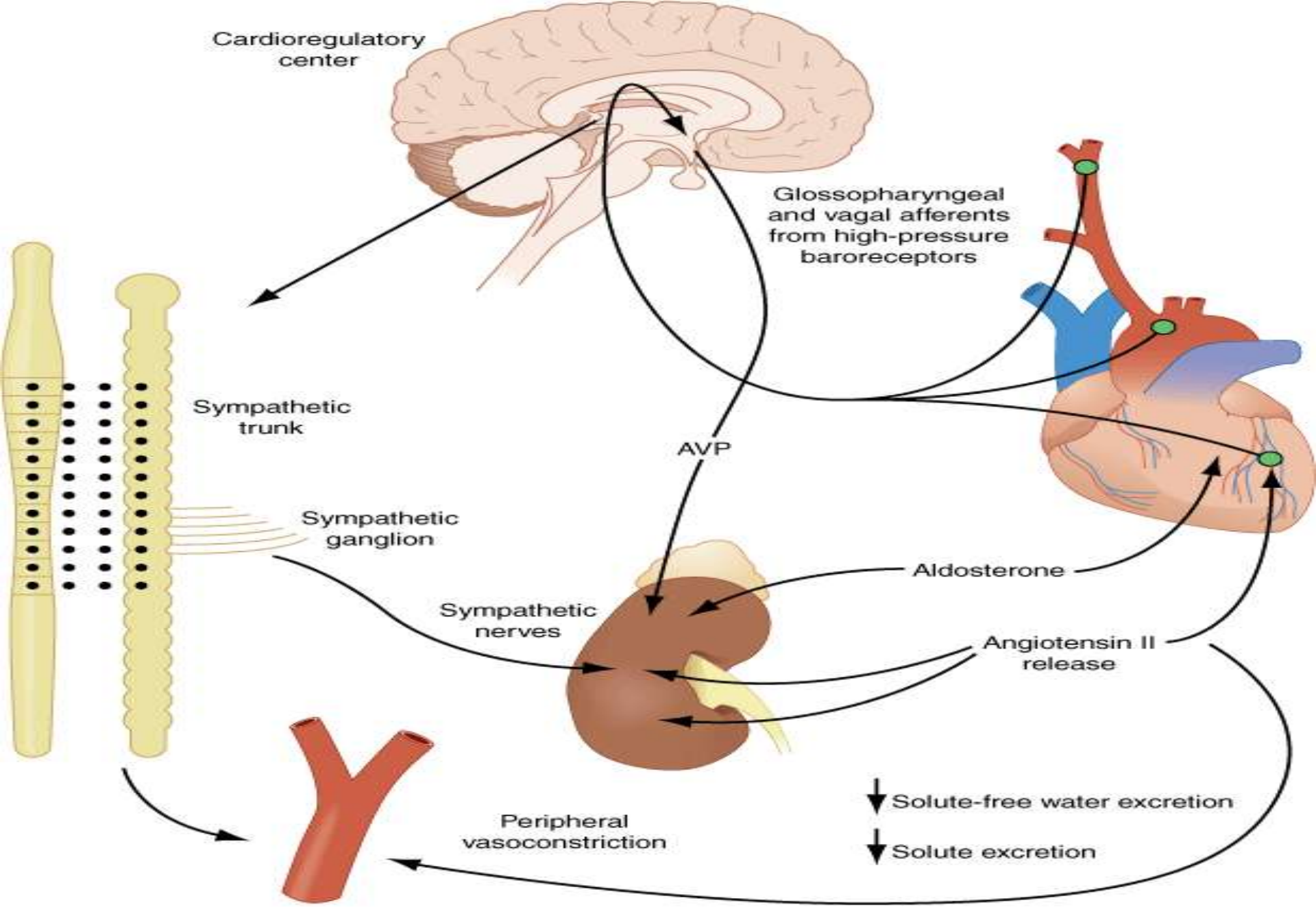
Increased BP variability is associated with increased organ damage and cardiovascular morbidity.

- **"White Coat" or isolated office hypertension.**
- **Masked hypertension.**
- **Morning surge of BP.**
- **During Sleep: "Non dipping' and "extreme dipping".**

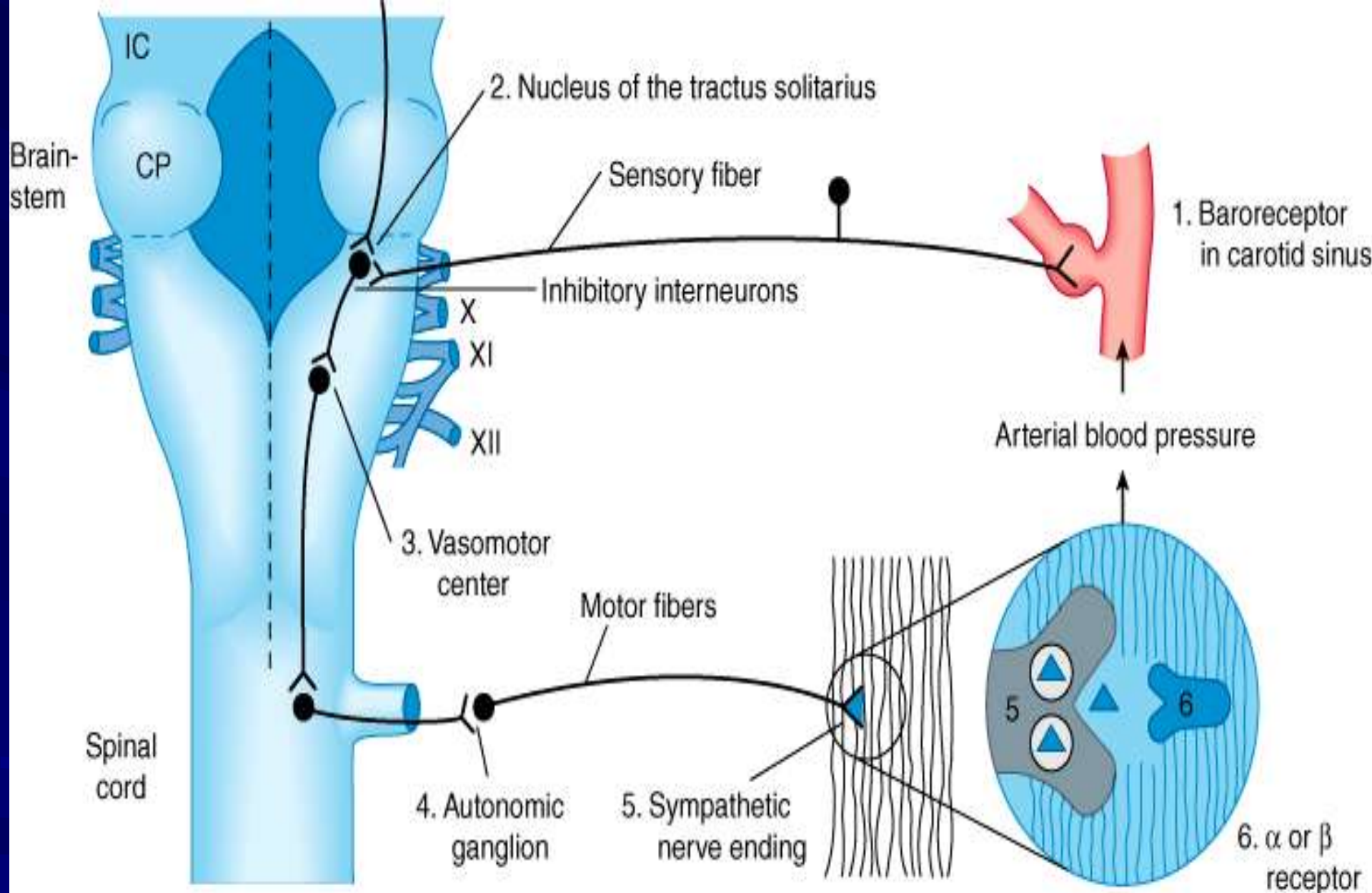
Table 11-1 Classification of Hypertension on the Basis of Blood Pressure.

Systolic/Diastolic Pressure (mm Hg)	Category
< 120/80	Normal
120–135/80–89	Prehypertension
≥ 140/90	Hypertension
140–159/90–99	Stage 1
≥ 160/100	Stage 2

From the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. JAMA 2003;289:2560.



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

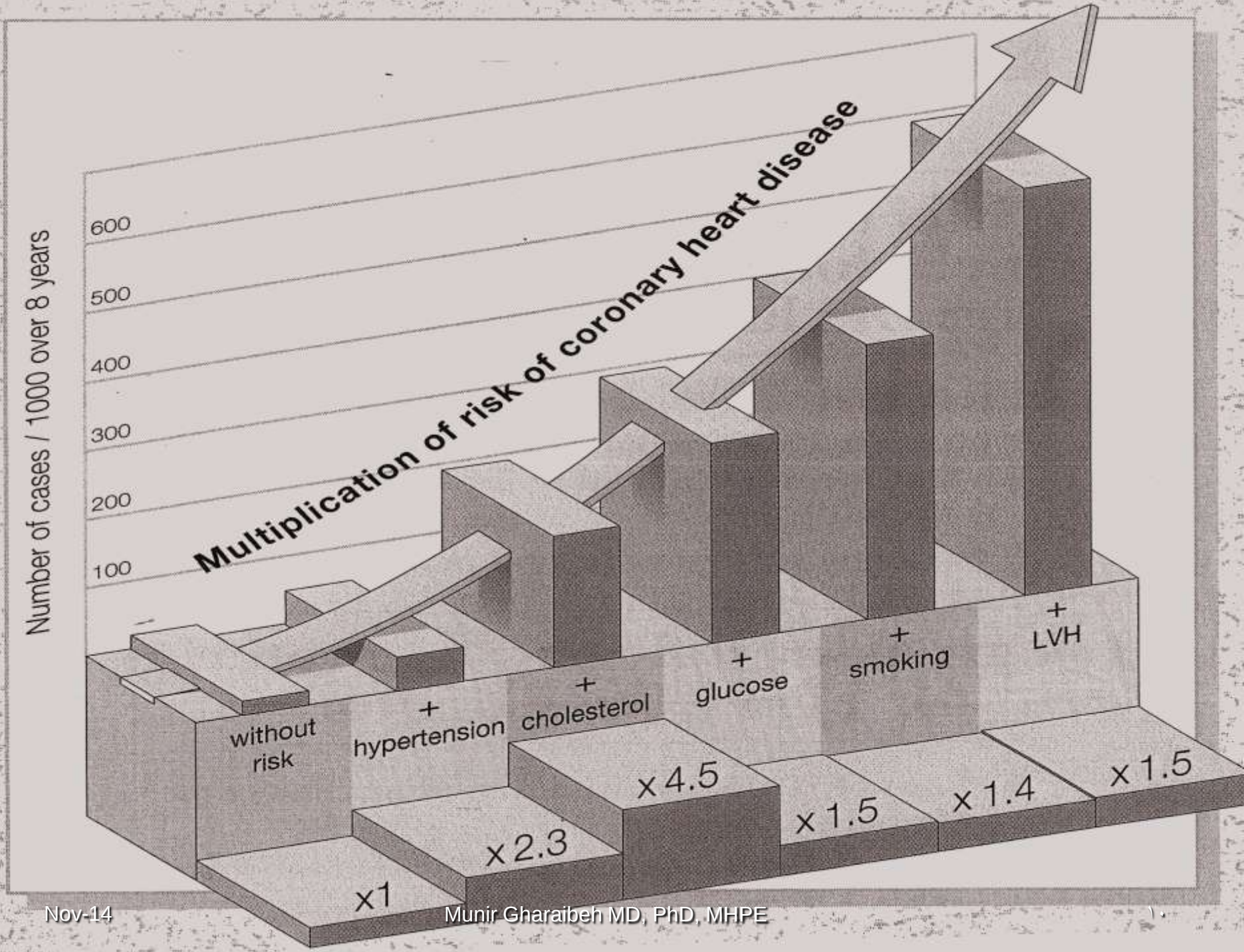


Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology*, 11th Edition: http://www.accessmedicine.com

Benefits of Lowering BP

Antihypertensive therapy has been associated with:

- **35% to 40% mean reduction in stroke incidence.**
- **20% to 25% reduction in myocardial infarction.**
- **More than 50% reduction in HF.**


Multiplication of risk of coronary heart disease
Number of cases / 1000 over 8 years
600
500
400
300
200
100
without risk
+ hypertension
+ cholesterol
+ glucose
+ smoking
+ LVH
x1
x 2.3
x 4.5
x 1.5
x 1.4
x 1.5

Non-pharmacologic Treatment

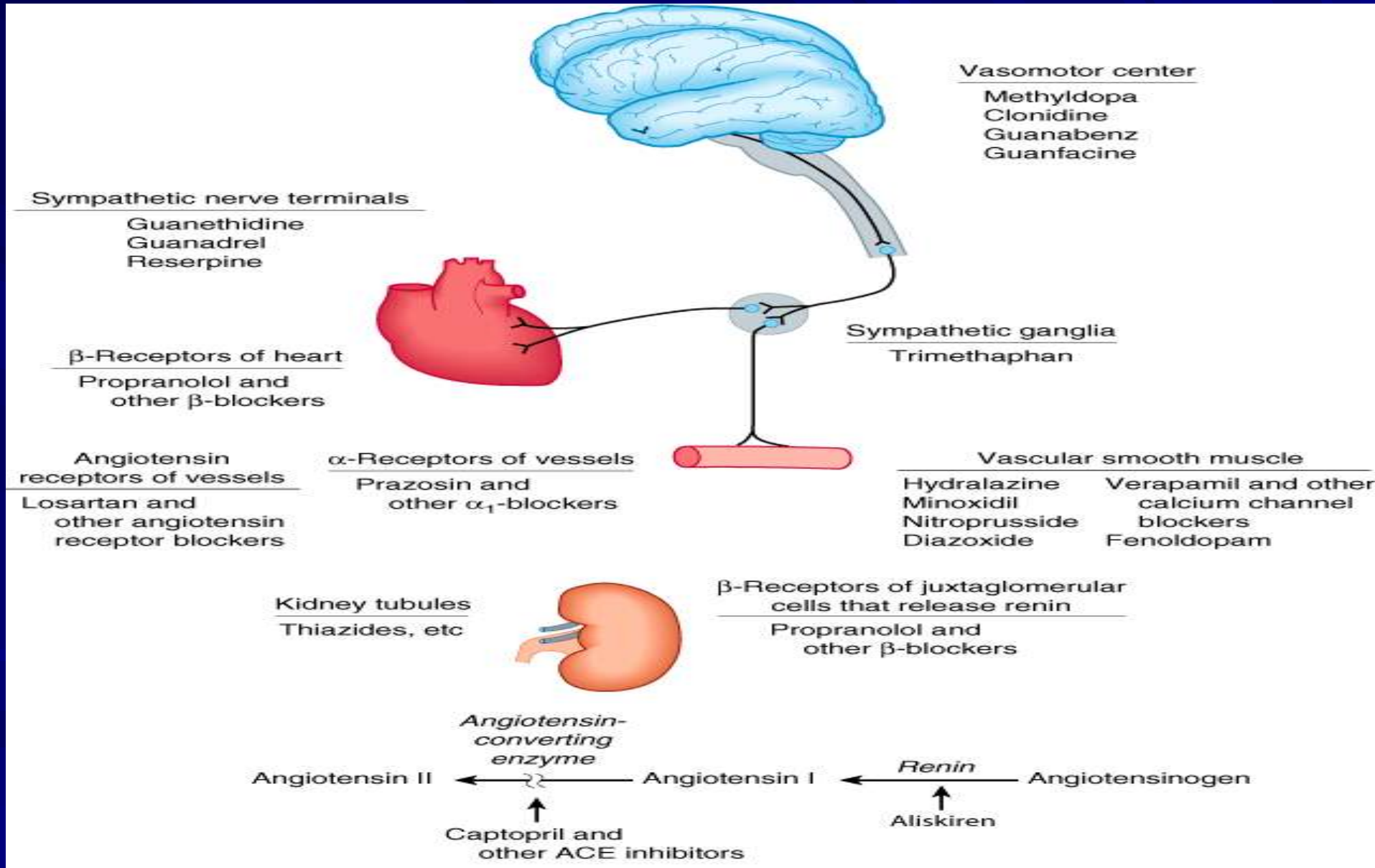
Lifestyle Modifications:

- Weight reduction
- Diet rich in potassium and calcium and sodium reduction.
- Dietary Approaches to Stop Hypertension (DASH) eating plan(1600-mg sodium) has effects similar to single drug therapy.
- Physical activity.

Goals of Therapy

- Maximal protection against cardiovascular consequences with minimal bother to the patient.
- Stroke, coronary, and renal complications increase when BP is vigorously lowered **(Why?)**

Sites of action of antihypertensive drugs.



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Sites of action of antihypertensive drugs.

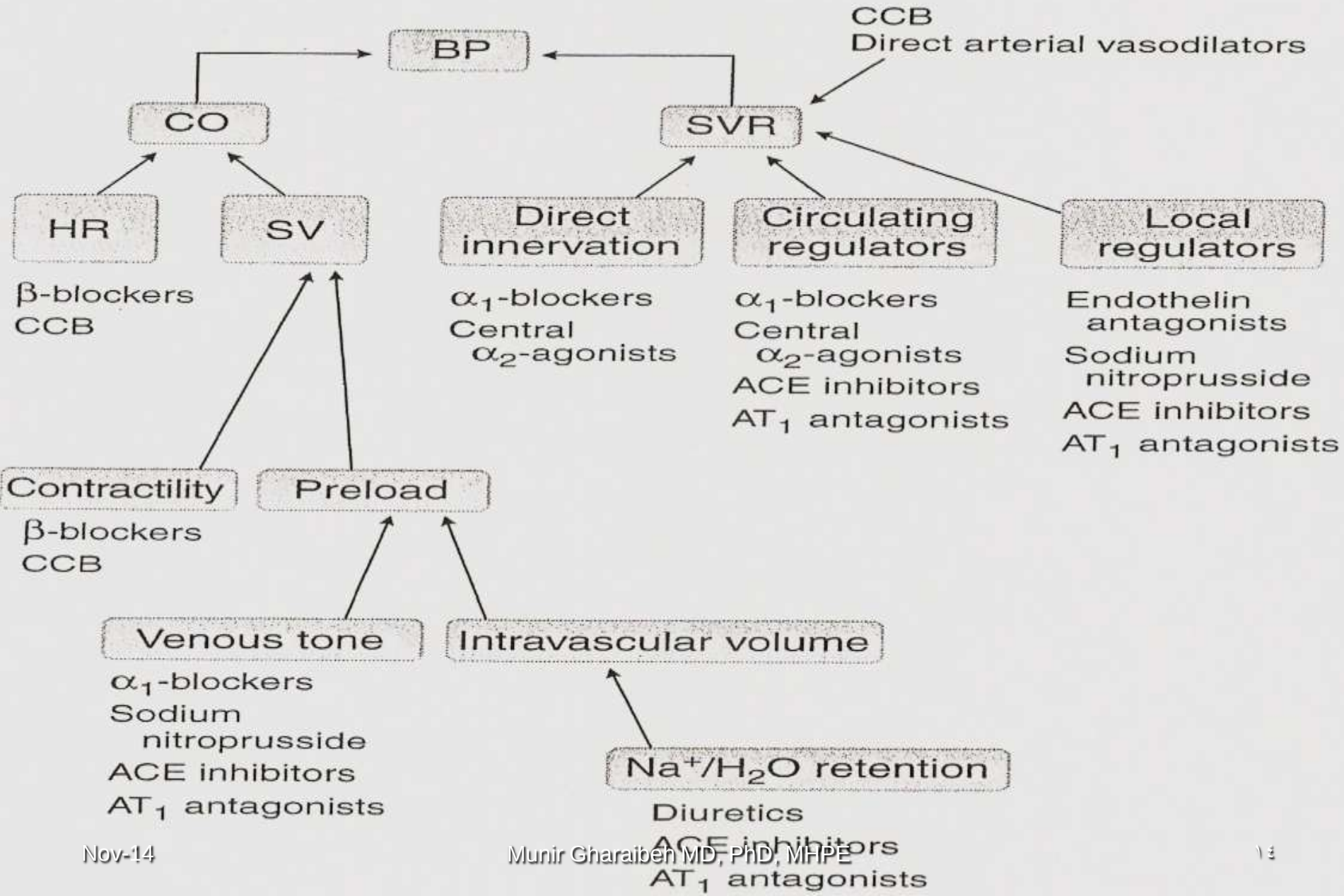


Table 27–5 Classification of Antihypertensive Drugs by Their Primary Site or Mechanism of Action

Diuretics (Chapter 25)

1. **1.** Thiazides and related agents (hydrochlorothiazide, chlorthalidone, chlorothiazide, indapamide, methylclothiazide, metolazone)
2. **2.** Loop diuretics (furosemide, bumetanide, torsemide, ethacrynic acid)
3. **3.** K^+-sparing diuretics (amiloride, triamterene, spironolactone)

Sympatholytic drugs (Chapter 12)

1. β receptor antagonists (metoprolol, atenolol, betaxolol, bisoprolol, carteolol, esmolol, nadolol, nebivolol, penbutolol, pindolol, propranolol, timolol)
2. α receptor antagonists (prazosin, terazosin, doxazosin, phenoxybenzamine, phentolamine)
3. Mixed α-β receptor antagonists (labetalol, carvedilol)
4. Centrally acting adrenergic agents (methyldopa, clonidine, guanabenz, guanfacine)
5. Adrenergic neuron blocking agents (guanadrel, reserpine)

Ca^{2+} channel blockers (verapamil, diltiazem, nisoldipine, felodipine, nicardipine, isradipine, amlodipine, clevidipine, nifedipine[a])

Angiotensin-converting enzyme inhibitors (Chapter 26; captopril, enalapril, lisinopril, quinapril, ramipril, benazepril, fosinopril, moexipril, perindopril, trandolapril)

AngII receptor antagonists (Chapter 26; losartan, candesartan, irbesartan, valsartan, telmisartan, eprosartan, olmesartan)

Direct Renin Inhibitor (*Chapter 26*; aliskiren)

Vasodilators

1. **1.** Arterial (hydralazine, minoxidil, diazoxide, fenoldopam)
2. **2.** Arterial and venous (nitroprusside)

Hemodynamic Effects of Antihypertensive Drugs

	HEART RATE	CARDIAC OUTPUT	TOTAL PERIPHERAL RESISTANCE	PLASMA VOLUME	PLASMA RENIN ACTIVITY
Diuretics	↔	↔	↓	–↓	↑
Sympatholytic agents					
Centrally acting	–↓	–↓	↓	–↑	–↓
Adrenergic neuron blockers	–↓	↓	↓	↑	–↑
α receptor antagonists	–↑	–↑	↓	–↑	↔
β receptor antagonists					
No ISA	↓	↓	–↓	–↑	↓
ISA	↔	↔	↓	–↑	–↓
Arteriolar vasodilators	↑	↑	↓	↑	↑
Ca^{2+} channel blockers	↓ or ↑	↓ or ↑	↓	–↑	–↑
ACE inhibitors	↔	↔	↓	↔	↑
AT_1 receptor antagonists	↔	↔	↓	↔	↑
Renin inhibitor	↔	↔	↓	↔	↓ (but [renin] ↑)

Table 11–2 Pharmacokinetic Characteristics and Dosage of Selected Oral Antihypertensive Drugs.					
Drug	Half-life (h)	Bioavailability (percent)	Suggested Initial Dose	Usual Maintenance Dose Range	Reduction of Dosage Required in Moderate Renal Insufficiency[1]
Amlodipine	35	65	2.5 mg/d	5–10 mg/d	No
Atenolol	6	60	50 mg/d	50–100 mg/d	Yes
Benazepril	0.6[2]	35	5–10 mg/d	20–40 mg/d	Yes
Captopril	2.2	65	50–75 mg/d	75–150 mg/d	Yes
Clonidine	8–12	95	0.2 mg/d	0.2–1.2 mg/d	Yes
Diltiazem	3.5	40	120–140 mg/d	240–360 mg/d	No
Guanethidine	120	3–50	10 mg/d	25–50 mg/d	Possible
Hydralazine	1.5–3	25	40 mg/d	40–200 mg/d	No
Hydrochlorothiazide	12	70	25 mg/d	25–50 mg/d	No
Lisinopril	12	25	10 mg/d	10–80 mg/d	Yes
Losartan	1–2[3]	36	50 mg/d	25–100 mg/d	No
Methyldopa	2	25	1 g/d	1–2 g/d	No
Metoprolol	3–7	40	50–100 mg/d	200–400 mg/d	No
Minoxidil	4	90	5–10 mg/d	40 mg/d	No
Nebivolol	12	Nd[4]	5 mg/d	10–40 mg/d	No
Nifedipine	2	50	30 mg/d	30–60 mg/d	No
Prazosin	3–4	70	3 mg/d	10–30 mg/d	No
Propranolol	3–5	25	80 mg/d	80–480 mg/d	No
Reserpine	24–48	50	0.25 mg/d	0.25 mg/d	No
Verapamil	4–6	22	180 mg/d	240–480 mg/d	No

Diuretics (Saluretics)

- Widely recommended as first-line therapy, especially in the elderly, the obese, and black patients.
- Better at reducing coronary heart disease, HF, stroke, and mortality.
- Inexpensive.
- Combine well with others.
- Lower doses, with sodium restriction, cause fewer metabolic side effects, but retain antihypertensive activity.
- All have same efficacy in lowering BP, although not same diuretic activity.

Diuretics (Saluretics)

- **Early Effects (3-4 days):**
  - Diuresis lowers blood volume and cardiac output.
  - Mainly affects the systolic BP.
- **Late Effects (3-4 weeks):**
  - Decreased Na+ & Cl-, lowers blood vessel contractility. Appear even with low doses.
- **Increase Plasma Renin**
- **Side Effects:**

Diuretics (Saluretics)

- **Thiazide diuretics:**
- **Effective in mild and moderate Ht with normal renal and heart function.**
  - **Hydrochlorthiazide.**
  - **Chlorthalidone: long acting.**
  - **Bendrofluazide.**
  - **Indapamide: vasodilating and lipid neutral. Also induces regression of LVH**

Diuretics (Saluretics)

- **Loop Diuretics:**
- **Needed in severe Ht, in renal insufficiency, and in heart failure or cirrhosis.**
  - **Furosemide: not ideal , short acting.**
  - **Torsemide: free of metabolic side effects.**
- **Potassium- sparing diuretics:**
- **Useful in heart failure.**
  - **Spironolactone:**
  - **Eplerenone.**
  - **Ameloride.**
  - **Triamterene**

VASODILATORS

- Work directly on arterial blood vessels, or veins(organic nitrates and nitroprusside).
- Actions not antagonized by known blockers.
- Reduce peripheral resistance, which will elicit compensatory mechanisms leading to tolerance, resistance or pseudoresistance.
- Usually other drugs are combined with vasodilators to avoid this problem.

Compensatory responses to vasodilators

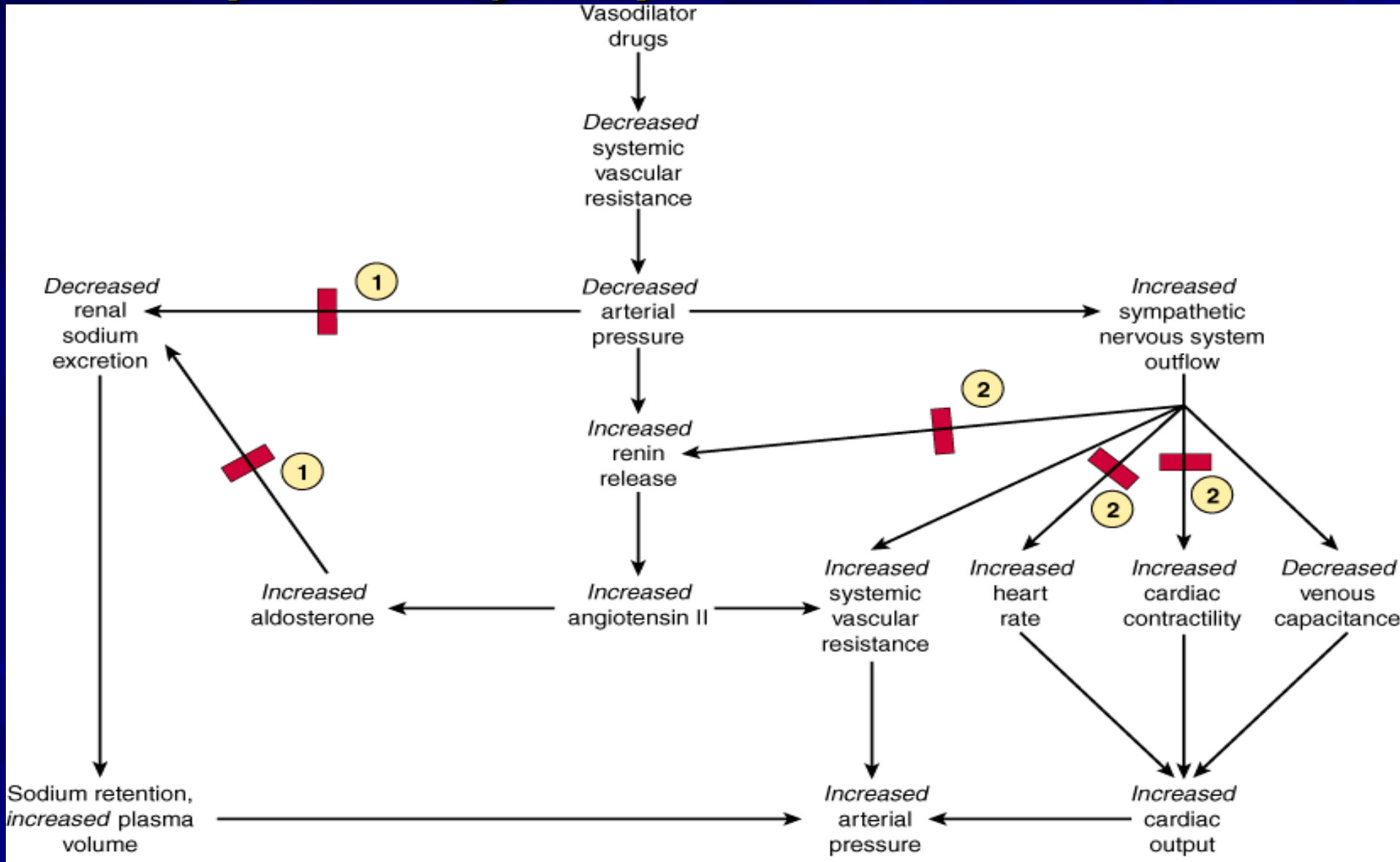


Table 11–3 Mechanisms of Action of Vasodilators.

Mechanism	Examples
Release of nitric oxide from drug or endothelium	Nitroprusside, hydralazine, nitrates,[1] histamine, acetylcholine
Reduction of calcium influx	Verapamil, diltiazem, nifedipine
Hyperpolarization of smooth muscle membrane through opening of potassium channels	Minoxidil, diazoxide
Activation of dopamine receptors	Fenoldopam

VASODILATORS

Hydralazine:

- Oldest vasodilator(1950s), was withdrawn and then came back.
- Arteriolar dilator, works by release of NO.
- Tachyphylaxis (Tolerance or Peusdoresistance).
- Activates baroreceptor reflex.
- Metabolized by acetylation.
- Drug-induced lupus syndrome.
- Other side effects.
- Replaced by CCBs.
- Used in heart failure, combined with isosorbide dinitrate

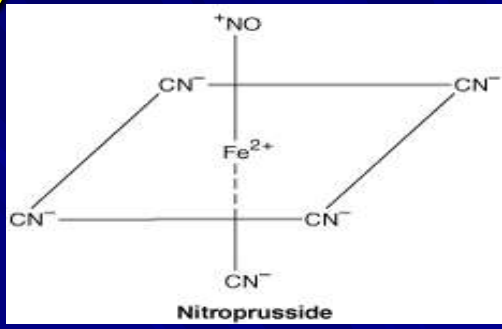
VASODILATORS

Diazoxide:

- Thiazide derivative, but not a diuretic.
- Potent arterial dilator, works by opening potassium channels.
- Causes excessive hypotension.
- Used in emergencies by rapid I.V. bolus injection.
- Rapidly bound to albumin.
- Onset 10-30 seconds.
- Duration 2-4 hours.
- Does not require constant monitoring.

VASODILATORS

Sodium Nitroprusside:

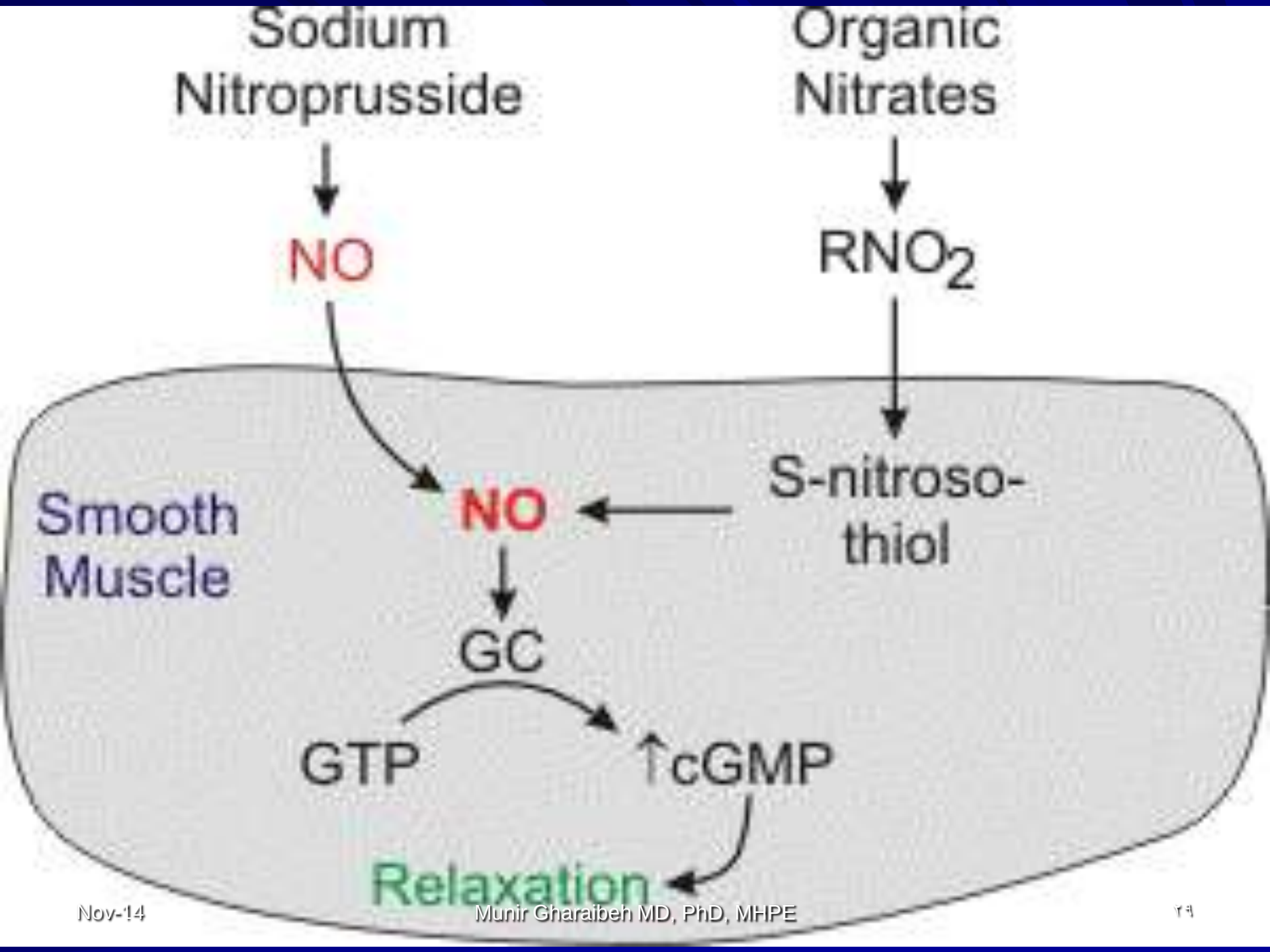


- Cyanide-containing molecule.
- Useful in emergencies, surgery and heart failure.
- Relaxes both arterial and venous smooth muscle, works by release of NO.
- No excessive reflex increase in cardiac output.
- Might increase C.O. if there is failure.

VASODILATORS

Sodium Nitroprusside:

- Short half life.
- Action is immediate, requires constant monitoring in ICU.
- Drug is light sensitive.
- Thiocyanate levels and acid-base balance: weakness, nausea, tinnitus, flushing, lactic acidosis and anoxia.


Sodium Nitroprusside
Organic Nitrates
NO
RNO_2
Smooth Muscle
NO
S-nitroso-thiol
GC
GTP
↑cGMP
Relaxation

VASODILATORS

Minoxidil:

- K+ channel-opener: increases efflux leading to hyperpolarization.
- Prolonged arterial relaxation.
- Superior to hydralazine.
- For severe intractable hypertension, or renal insufficiency, usually in combination with a diuretic and β blocker.
- Hypertrichosis, so useful for baldness.
- Pericarditis.

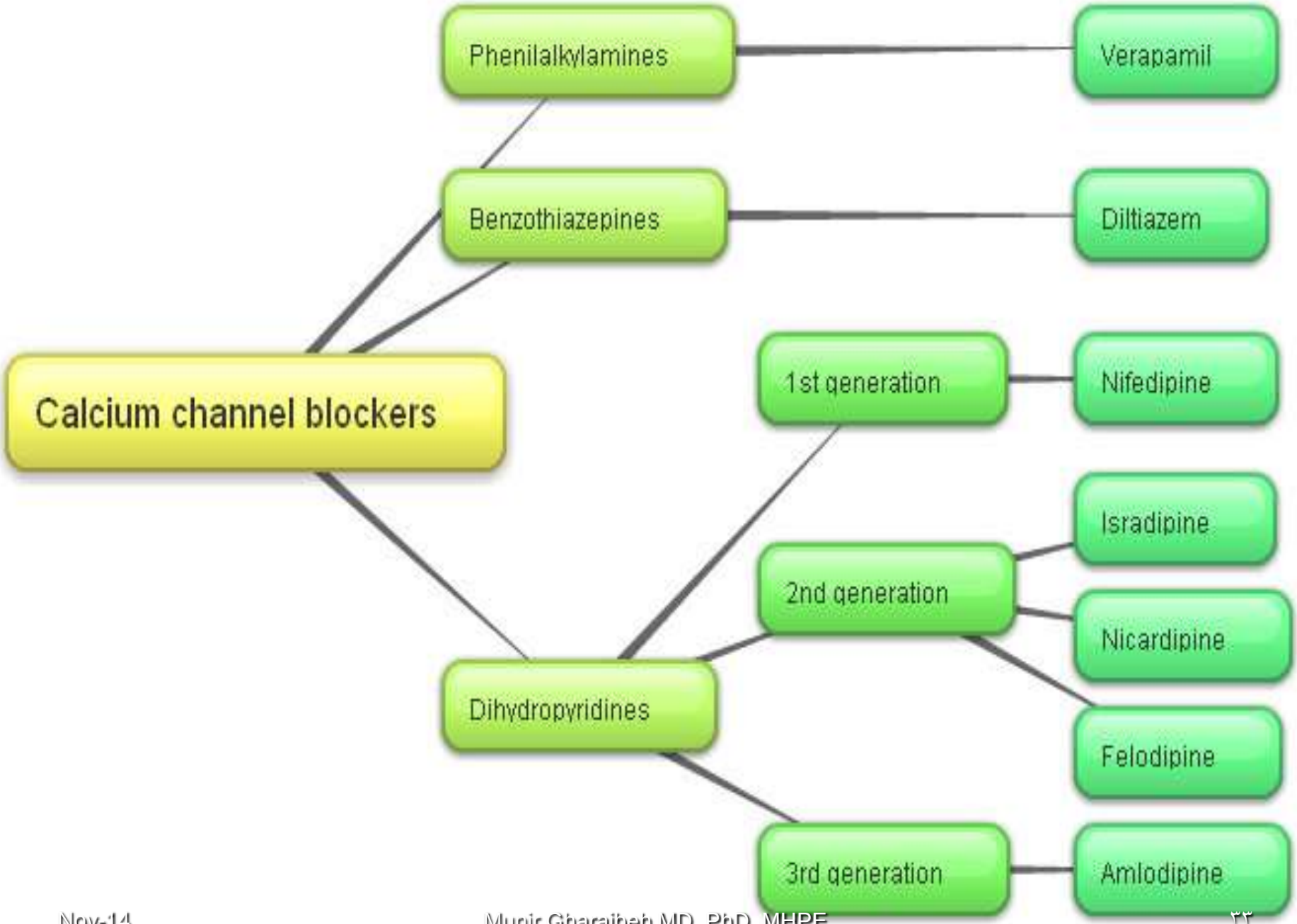
VASODILATORS

Fenoldopam:

- Dopamine D_1 agonist, which results in vasodilation, renal vessel dilation, and natriuresis.
- Rapidly metabolized, short acting.
- Used by continuous infusion in emergencies or postoperatively.

Calcium Channel Blockers

- More effective than others in protection against stroke.
- Primarily act to reduce PVR, aided by at least an initial diuretic effect, especially with the short-acting DHPs.
- Effective in the elderly.
- Equally effective in blacks and nonblacks.
- Cause no metabolic disturbances


Calcium channel blockers
Phenilalkylamines
Verapamil
Benzothiazepines
Diltiazem
Dihydropyridines
1st generation
Nifedipine
2nd generation
Isradipine
Nicardipine
Felodipine
3rd generation
Amlodipine

Calcium Channel Blockers

	PVR	HR	CO
Nifedipine	- - -	+++ (Reflexly)	++
Diltiazem	- -	-	-
Verapamil	- -	- -	--

Angiotensin - Converting Enzyme Inhibitors (ACEI)

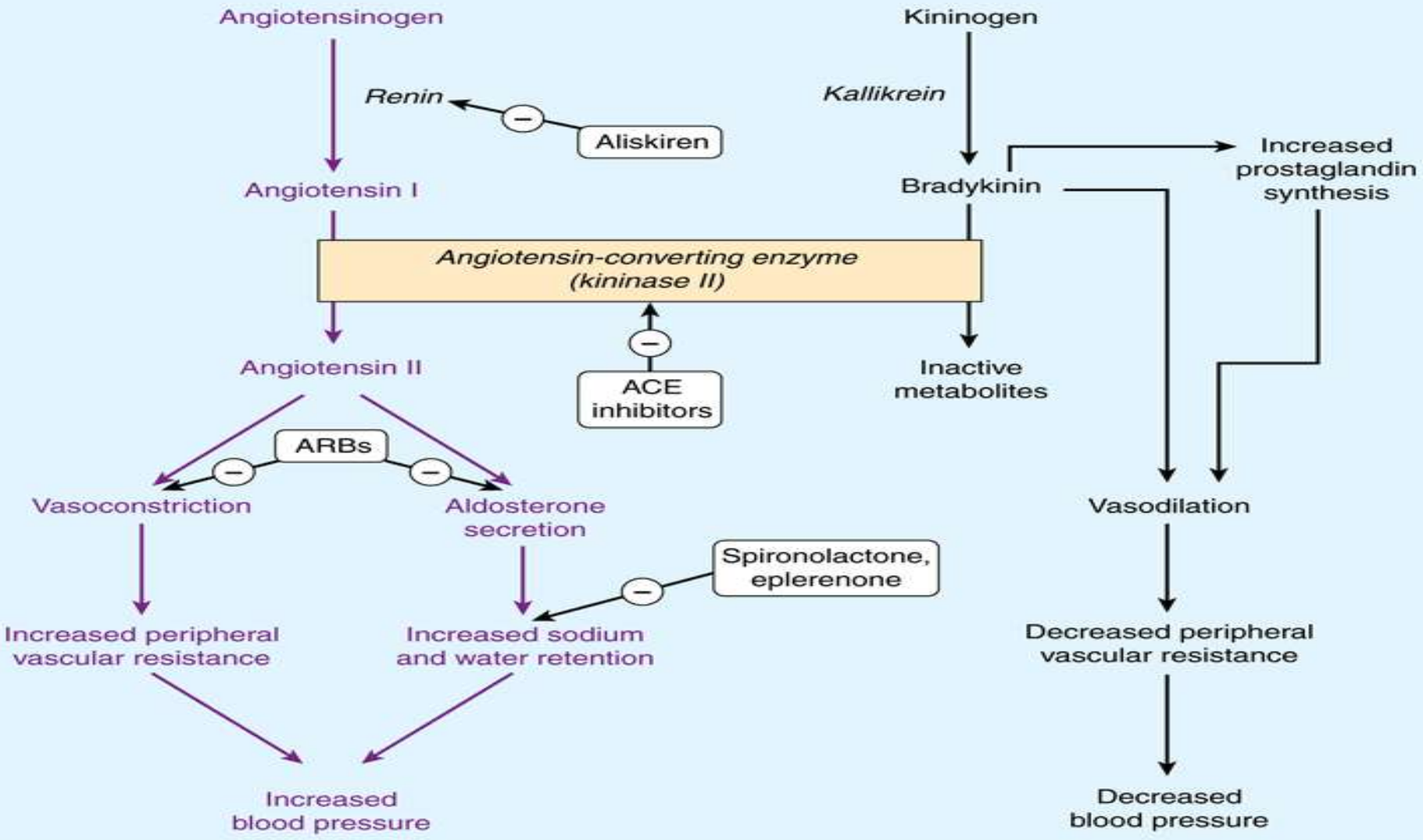
Angiotensin II:

- Potent vasoconstrictor by itself.
- Facilitates release of NE.
- Central actions to increase BP.
- Promotes release of aldosterone.
- Regulates tubular function.
- Regulates intra-renal blood flow.

Angiotensin - Converting Enzyme Inhibitors (ACEI)

- Inhibit ACE in the lungs.
- Also inhibit kinin metabolism.

Sites of action of drugs that interfere with the renin-angiotensin-aldosterone system.



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 12th Edition*
www.accessmedicine.com

Angiotensin - Converting Enzyme Inhibitors (ACEI)

- Captopril ----------Prototype.
- Enalapril
- Quinapril
- Lisinopril.
- Benazepril
- Fosonopril

- *All are similarly effective*
- *Might differ in toxicity*

Angiotensin - Converting Enzyme Inhibitors (ACEI)

Therapeutic Benefits:

- Effective in high-rennin hypertension (20%), HF and Ischemic Heart Disease.
- Do not increase HR.
- Useful in diabetic nephropathy by dilating efferent arterioles thus reducing intraglomerular pressure and consequently protects against progressive glomerulosclerosis.
- No need for a diuretic but can be added.
- Can be combined with CCBs.
- Should not be combined with Beta blockers.
- No metabolic effects.
- * Contraindicated in pregnancy and bilateral renal artery stenosis.

Angiotensin - Converting Enzyme Inhibitors (ACEI)

Side Effects:

Captopril is SH containing drug, so very toxic(bone marrow suppression, disguesia, proteinuria, allergic skin rash, fever)

- Hypotension(*First Dose Phenomena*) especially with renovascular hypertension.
- K+ retention, especially in the presence of renal dysfunction or when combined with K+ sparing diuretics or ARBs.
- Cough(10% of patients).
- Angioedema.

Angiotensin II Receptor Blockers (AT-1)

- Result in more complete inhibition of angiotensin actions (Chymase ?) with no effects on bradykinins.
- May be only indicated when ACEI are intolerable.
- Most expensive, but fastest growing class of antihypertensive drugs.
- Free of side effects, especially cough.
- May be better than ACEI in protection against stroke (activation of AT-2 receptor facilitates collateral vessels and neuronal resistance).

Angiotensin II Receptor Blockers (AT-1)

- Losartan.
- Valsartan.
- Candesartan.
- Irbesartan.
- Telmisartan (***additional peroxisome proliferator- activated receptor-g agonist activity).***
- Eprosartan.

Renin Enzyme Inhibitors

- Aliskiren.

Sympatholytics or Adrenergic Blockers

- Alpha Adrenergic Antagonist
  - Non selective Antagonists
  - α1 -Selective Antagonists.
- Beta Adrenergic Blockers
- Adrenergic Neurone Blockers.
- Ganglionic Blockers

Non selective Alpha Adrenergic Antagonist

- **Phentolamine**
- **Phenoxybenzamine**
  - **Block both α1 and α2 receptors, so cause reflex tachycardia and increased contractility.**
  - **Used only for pheochromocytoma.**

α1 -selective Alpha Adrenergic Antagonists

Prazosin

Terazocin

Doxazosin

- First - Dose Phenomenon.
- All are free of metabolic effects, but can cause drowsiness, diarrhea, postural hypotension, tachycardia, and tolerance due to fluid retention.
- Effective in moderate hypertension as well as benign prostatic hypertrophy.

Beta Adrenergic Blockers

Antihypertensive Mechanisms:

- 1. Decrease HR, SV, and consequently C.O.
- 2. Decrease Rennin Release
- 3. Central Action
- 4. Inhibit NE release

Beta Adrenergic Blockers

Preparations: 30

- Propranolol: Prototype,1957
- Timolol Lipophilic
- Nadolol Long acting
- Pindolol ISA
- Acebutelol ISA
- Esmolol Short half life
- Metoprolol β1 selective
- Atenolol β1 selective.
- Betaxolol β1 selective.
- Bisoprolol β1 selective.

Beta Adrenergic Blockers

Therapeutic Effectiveness:

- Effect not immediate.
- High - rennin hypertension
- Combination or monotherapy
- Hyperkinetic hearts
- Used in other cardiovascular conditions
- Ineffective in blacks
- No postural hypotension

Beta Adrenergic Blockers

Side Effects:

- Bronchospasm , especially with the non selective
- Heart Failure?
- CNS: fatigue, depression, impotence ..etc
- Impair lipid and glucose metabolism
- Masked hypoglycemia !!!
- Claudication
- Withdrawal Syndrome

Vasodilating Beta Adrenergic Blockers

- **Labetalol:**
  - β, α1 (20% of β) antagonist & β2 partial agonist.
  - Useful for pheochromocytoma and emergencies.
- **Carvedilol:**
  - β, α1 (10% of β) antagonist.
- **Esmolol:**
  - β1 selective, rapidly metabolized.
  - Used by continuous IV infusion.
- **Nebivolol**

Adrenergic Neurone Blockers

Guanethidine

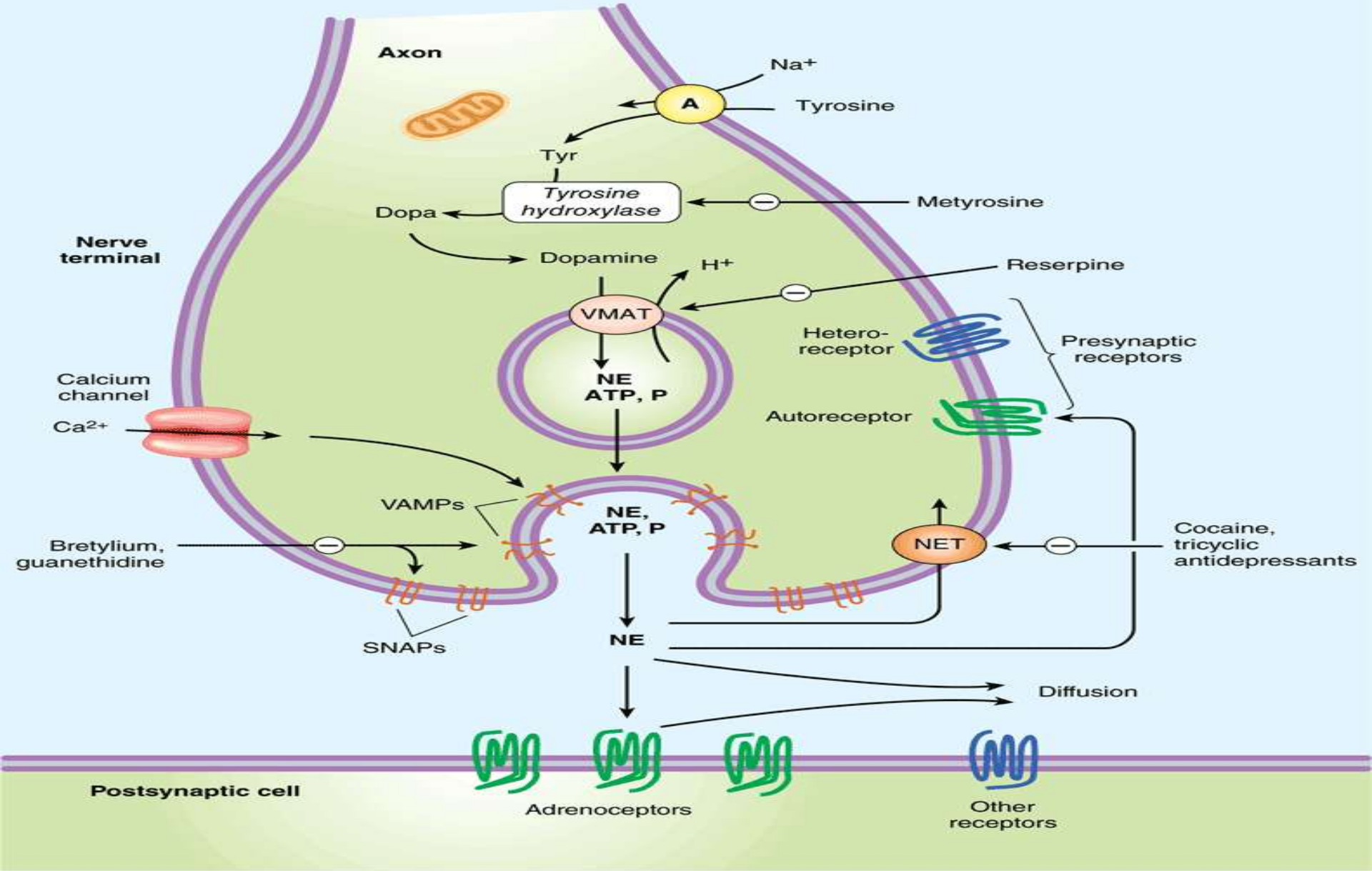
Bethanedine

Debrisoquin

Guanadrel

- Hydrophilic.
- Uptake 1.
- Block NE release.
- Displace NE from vesicles ------- MAO.
- Cause depletion of NE.

Life Cycle of Norepinephrine



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology*, 12th edition
www.accessmedicine.com

Adrenergic Neurone Blockers

Reserpine (Rauwolfia Alkaloids):

- Lipophilic
- Binds to the sympathetic vesicles.
- Prevents DA uptake into vesicles.
- Amines are metabolized by MAO.
- Depletes: NE, 5HT, ACTH, DA.
- Old fashioned, slow onset and offset, very cheap.

Ganglionic Blockers

Trimethaphan

Pentolinium

Mecamylamine

- **Block transmission in both symp & parasypathetic systems.**
- **Act immediately and are very efficacious.**
- **Effect rapidly reversed, so used for short term control of BP, e.g. intraoperatively or emergency.**
- **Many side effects.**

Table 16-2. Predominant Autonomic Tone at Various Neuroeffector Junctions and the Effect Produced by Ganglionic Blockade

Site	Effect of ganglionic blockade
Tissues predominantly under parasympathetic (cholinergic) tone	
Myocardium	
Atrium; S-A node	Tachycardia
Eye	
Iris	Mydriasis
Ciliary muscle	Cycloplegia
GI tract	Decrease in tone and motility; constipation
Urinary bladder	Urinary retention
Salivary gland	Dry mouth
Tissues predominantly under sympathetic (adrenergic) tone	
Myocardium	
Ventricles	Decrease in contractile force
Blood vessels	
Arterioles	Vasodilation; increase in peripheral blood flow; hypotension
Veins	Vasodilation; pooling of blood; decrease in venous return; decrease in cardiac output
Sweat glands*	Decrease in secretion

* Anatomically sympathetic; transmitter is ACh.

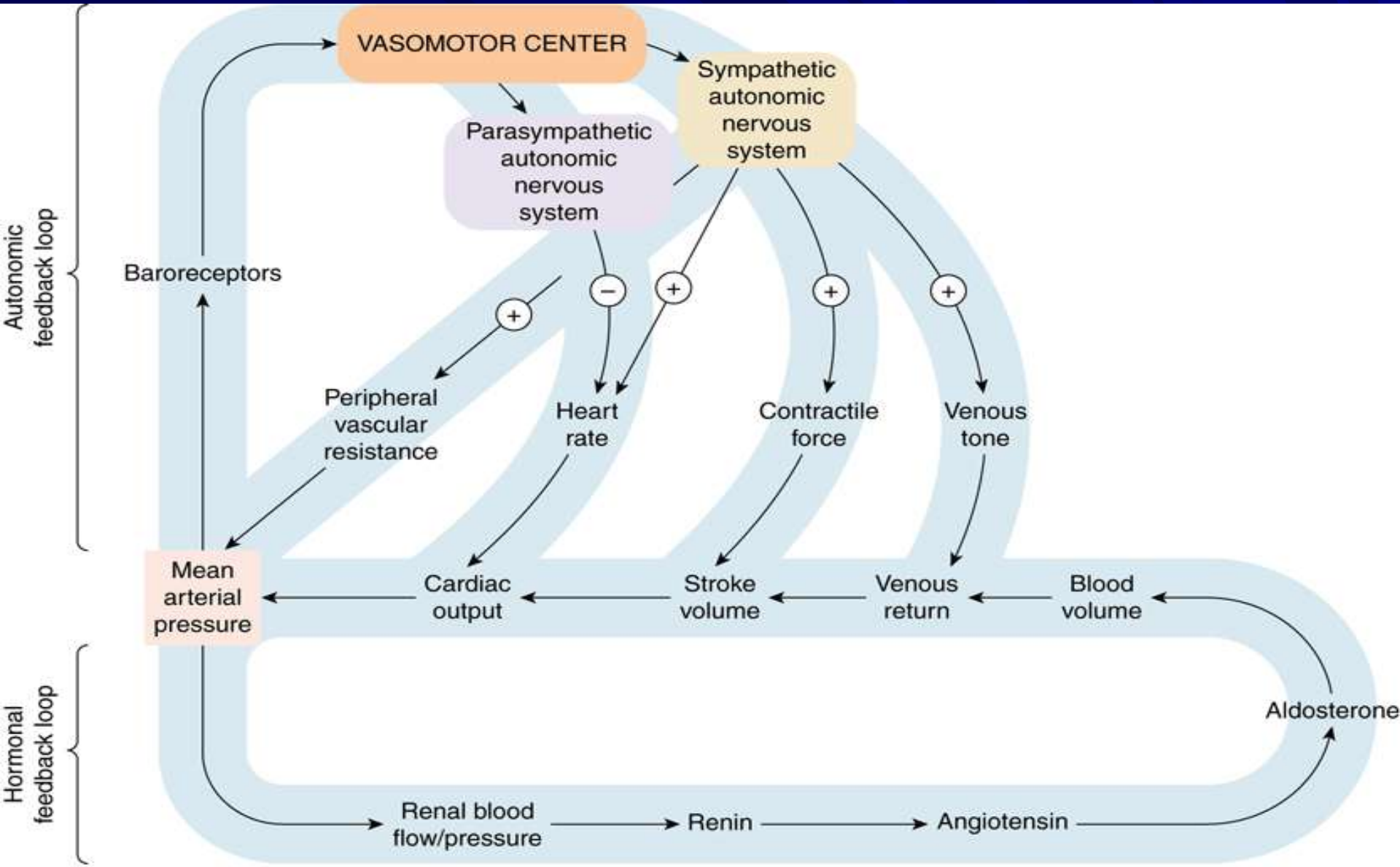
Centrally Acting Antihypertensive Drugs

Vasomotor Center:

- α Receptor activation decreases BP
- β Receptor activation increases BP

- Nucleus Tractus Solitarius
- Nucleus Ambiguus
- Rostral Ventral Medulla

Autonomic and hormonal control of cardiovascular function



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 12th edition*: www.accessmedicine.com

Centrally Acting Antihypertensive Drugs

Common Properties:

- Cross BBB.
- Reduce preganglionic sympathetic activity.
- Orthostasis is unusual, due to preservation of peripheral sympathetic activity.
- CNS side effects.

Centrally Acting Antihypertensive Drugs

1. **Propranolol**
2. **Reserpine.**
3. **α- Methyl Dopa:**

Old drug, thought to work by forming a pseudo transmitter which works peripherally.

Central α agonist.

α MD-------- α MDA -------- α MNE.

Lowers BP but not CO or renal blood flow.

Can cause lactation and positive Coomb's test.

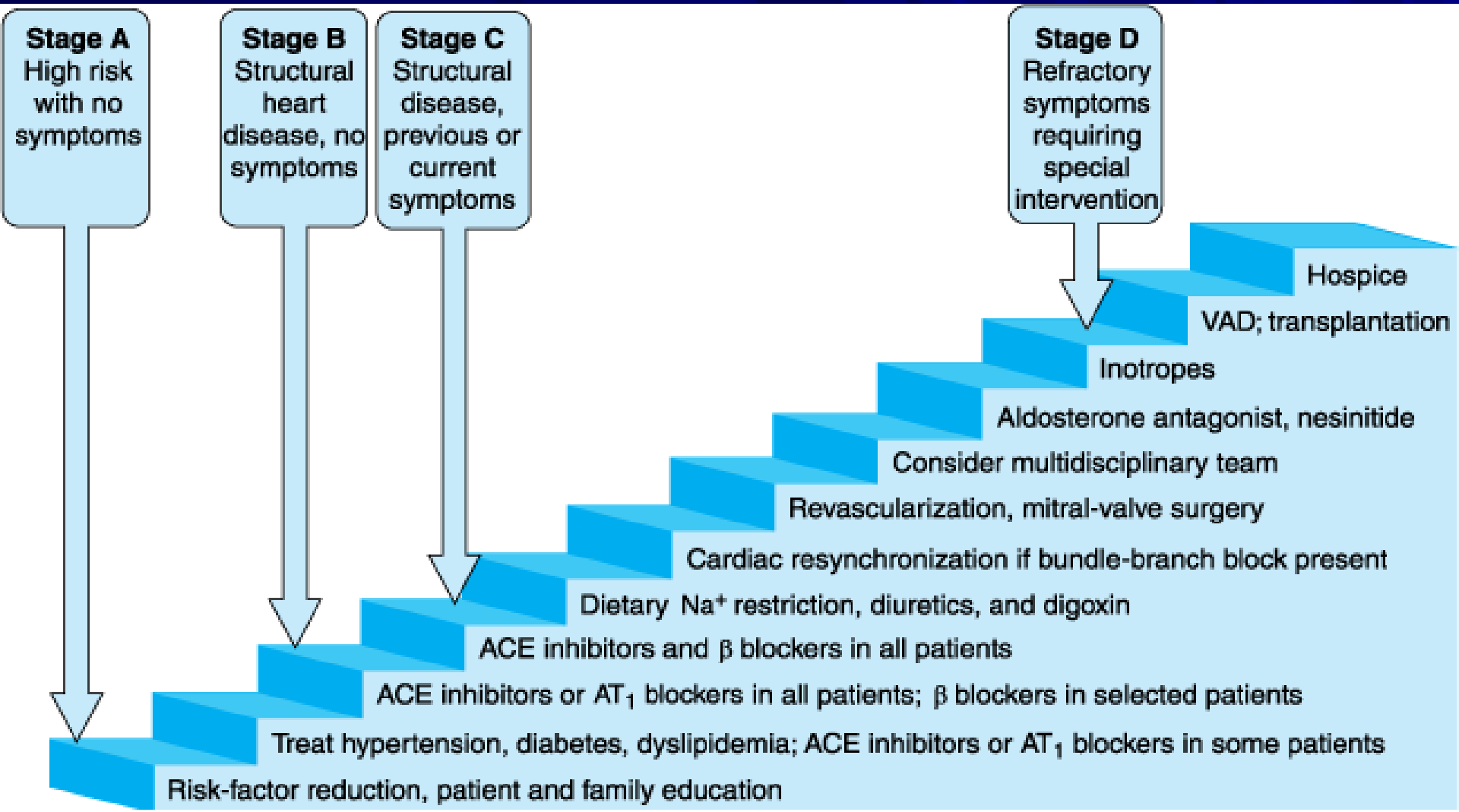
Safe in pregnancy.

Centrally Acting Antihypertensive Drugs

4. Clonidine:

- Imidazoline derivative, tried initially as a nasal decongestant.
- Central α agonist.
- I.V: Biphasic Effect: peripheral then central actions.
- Oral.
- Transdermal Patch(7 days).

Step Therapy of Hypertension



Source: Brunton LL, Lazo JS, Parker KL: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition: http://www.accessmedicine.com

Causes of Resistant Hypertension

- Improper blood pressure measurement, “White Coat Hypertension”.
- Noncompliance.
- Psychological stresses, secondary hypertension, sleep disorders
- Volume overload and pseudotolerance.
- Excess sodium intake
- Volume retention from kidney disease.
- Inadequate diuretic therapy.

Causes of Resistant Hypertension

- Inadequate doses.
- Inappropriate combinations .
- NSAID; cyclooxygenase 2 inhibitors.
- Cocaine, amphetamines, other illicit drugs.
- Sympathomimetics, e.g. decongestants, anorectics

Causes of Resistant Hypertension

- Oral contraceptives
- Adrenal steroids
- Cyclosporine
- Erythropoietin
- Licorice (including some chewing tobacco).
- Excess alcohol intake.

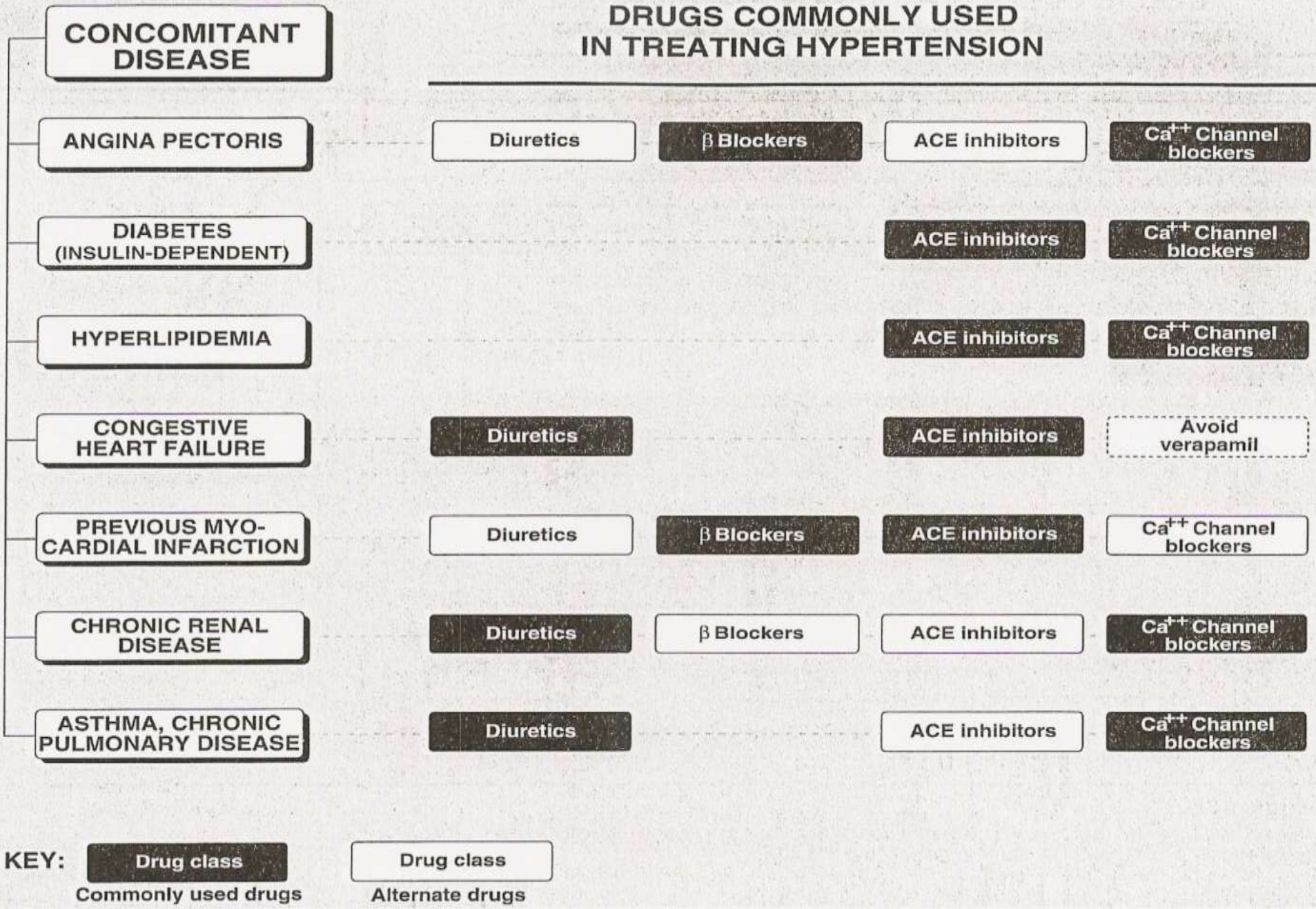


Figure 19.4
Treatment of hypertension in patients with concomitant diseases.