Antihypertensive Drugs

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What is Hypertension?

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

Why do we treat hypertension?

Benefits of Lowering BP

Antihypertensive therapy has been associated with:

- **40% reduction in stroke incidence.**
- **25% reduction in myocardial infarction.**
- **50% reduction in HF.**

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

BP variations

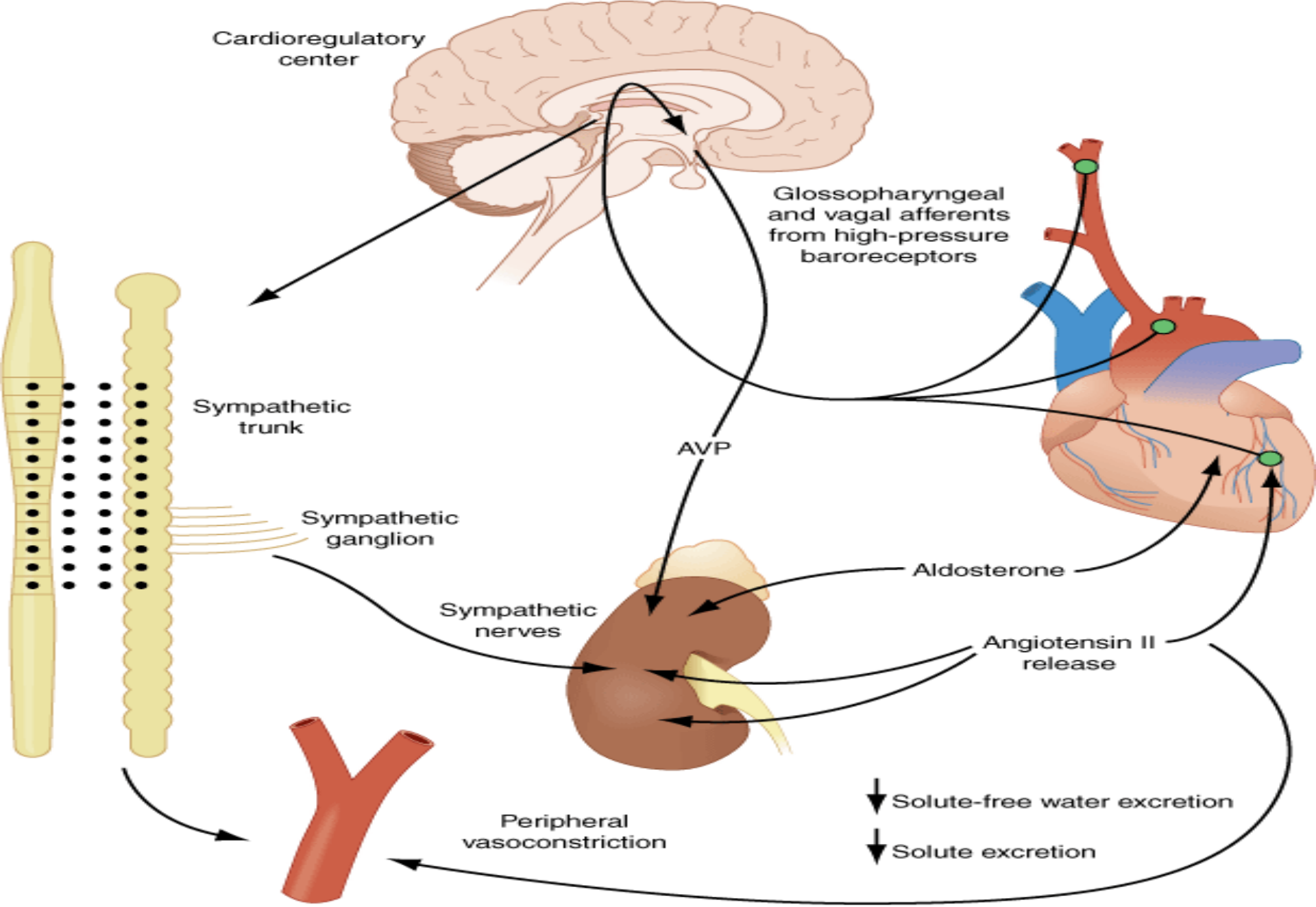
Increased BP variability is associated with increased organ damage and cardiovascular morbidity.

- **"White Coat" or isolated office hypertension.**
- **Masked hypertension, normal at the clinic.**
- **Morning surge of BP.**
- **During Sleep: Two possibilities:**
  - **"Non dipping'**
  - **"Extreme dipping".**

TABLE 11–1 Classification of hypertension on the basis of blood pressure.

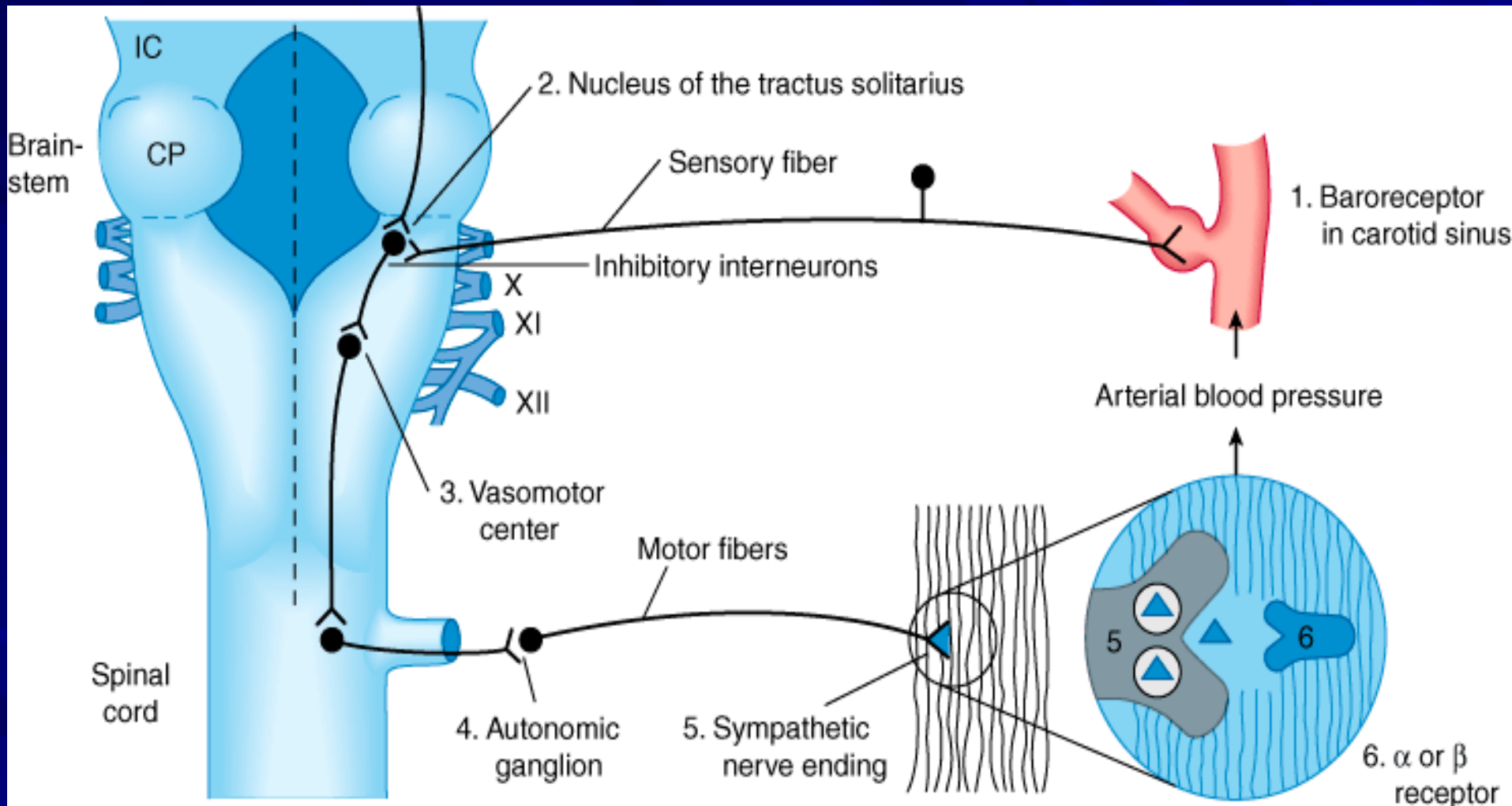
Systolic/Diastolic Pressure (mm Hg)	Category
< 120/80	Normal
120–135/80–89	Prehypertension
≥ 140/90	Hypertension
140–159/90–99	Stage 1
≥ 160/100	Stage 2

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

Neural Control of BP



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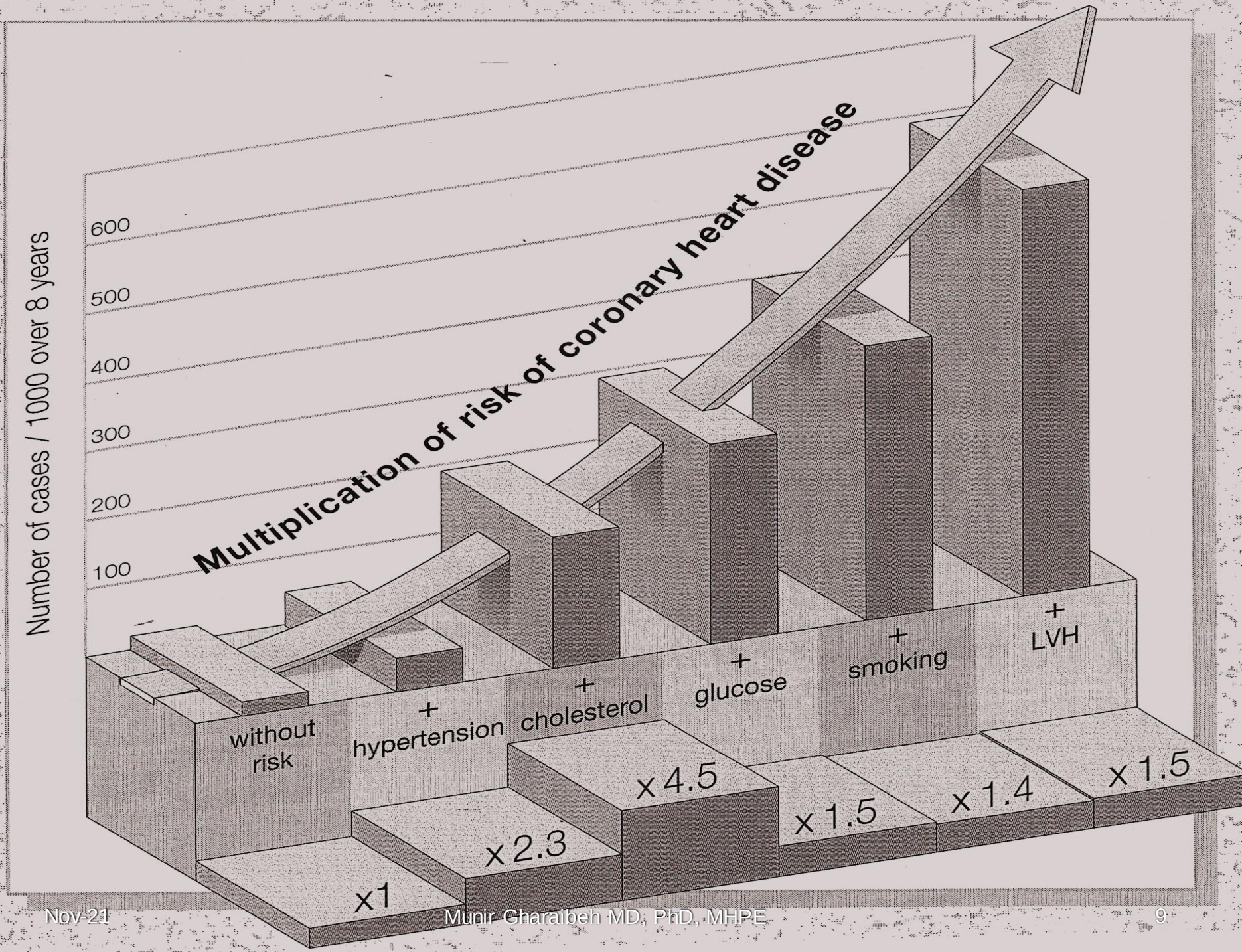

Number of cases / 1000 over 8 years
600
500
400
300
200
100
Multiplication of risk of coronary heart disease
without risk
+ hypertension
+ cholesterol
+ glucose
+ smoking
+ LVH
x1
x 2.3
x 4.5
x 1.5
x 1.4
x 1.5

Introduction

- 30% of patients don't know they have hypertension.
- 11% are not on therapy.
- 25% are on inadequate therapy.
- 34% are on adequate therapy.

Non-pharmacologic Treatment

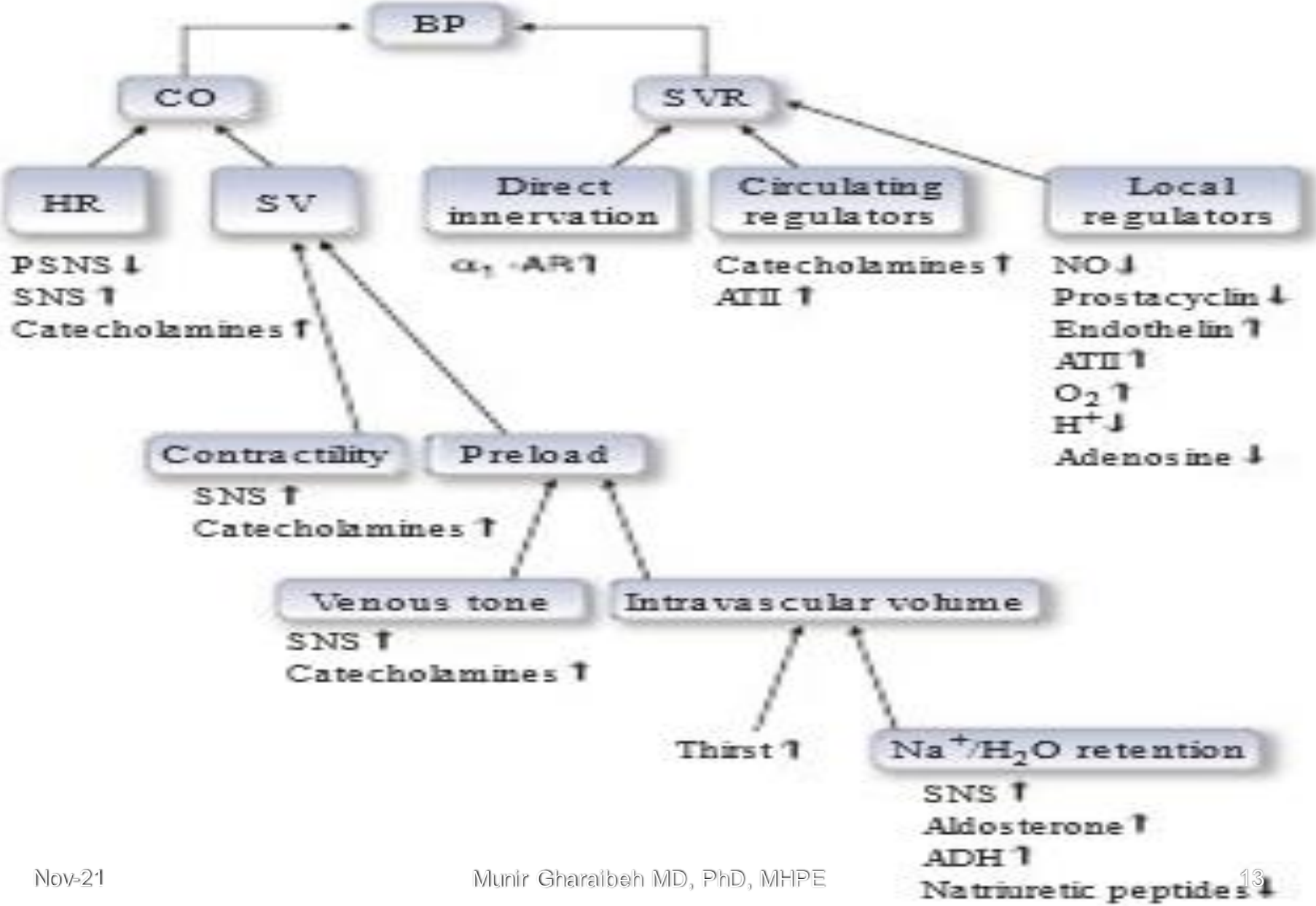
Lifestyle Modifications:

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

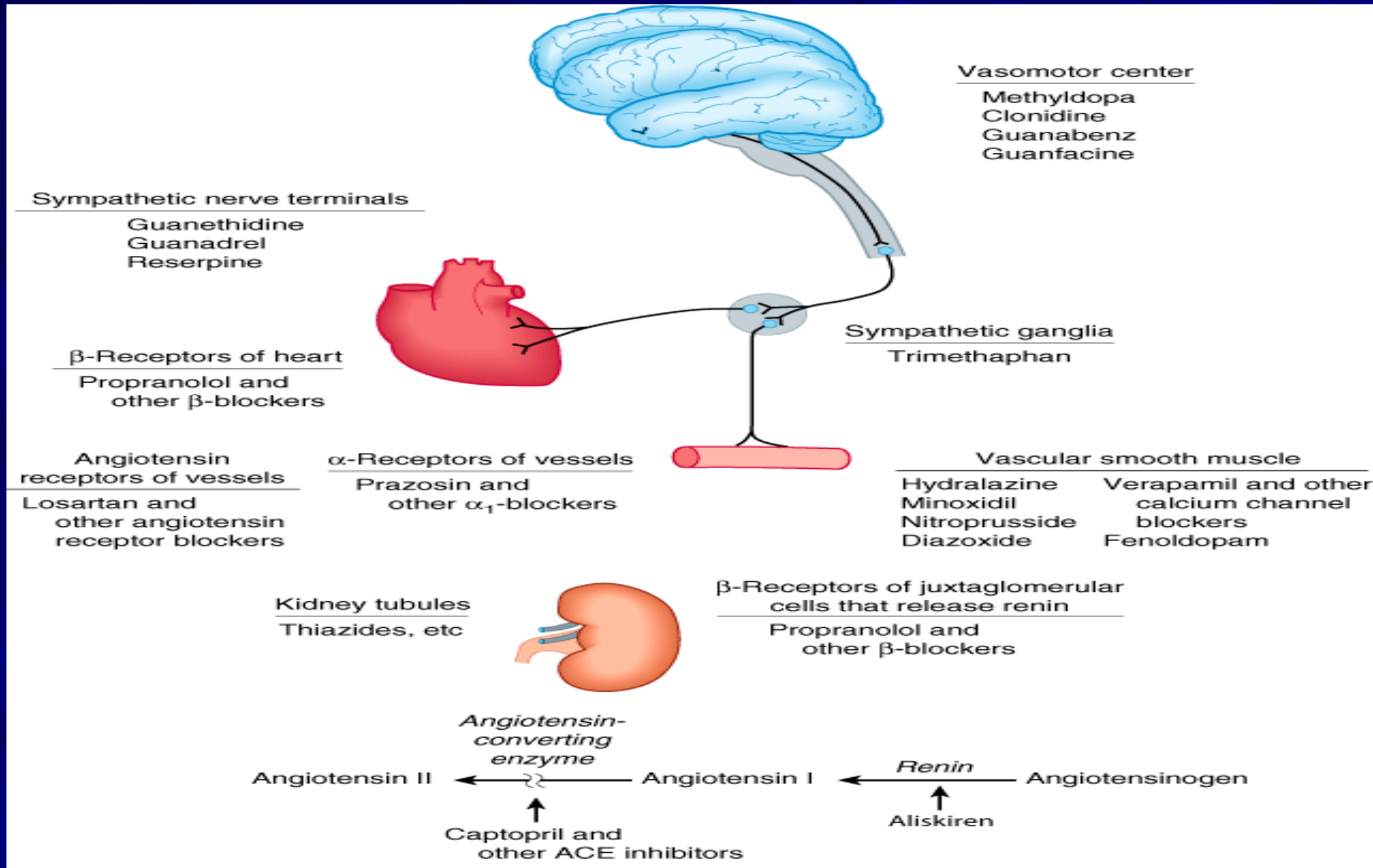
Goals of Therapy

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

Determinants of Blood Pressure



Sites of actions of antihypertensive drugs.



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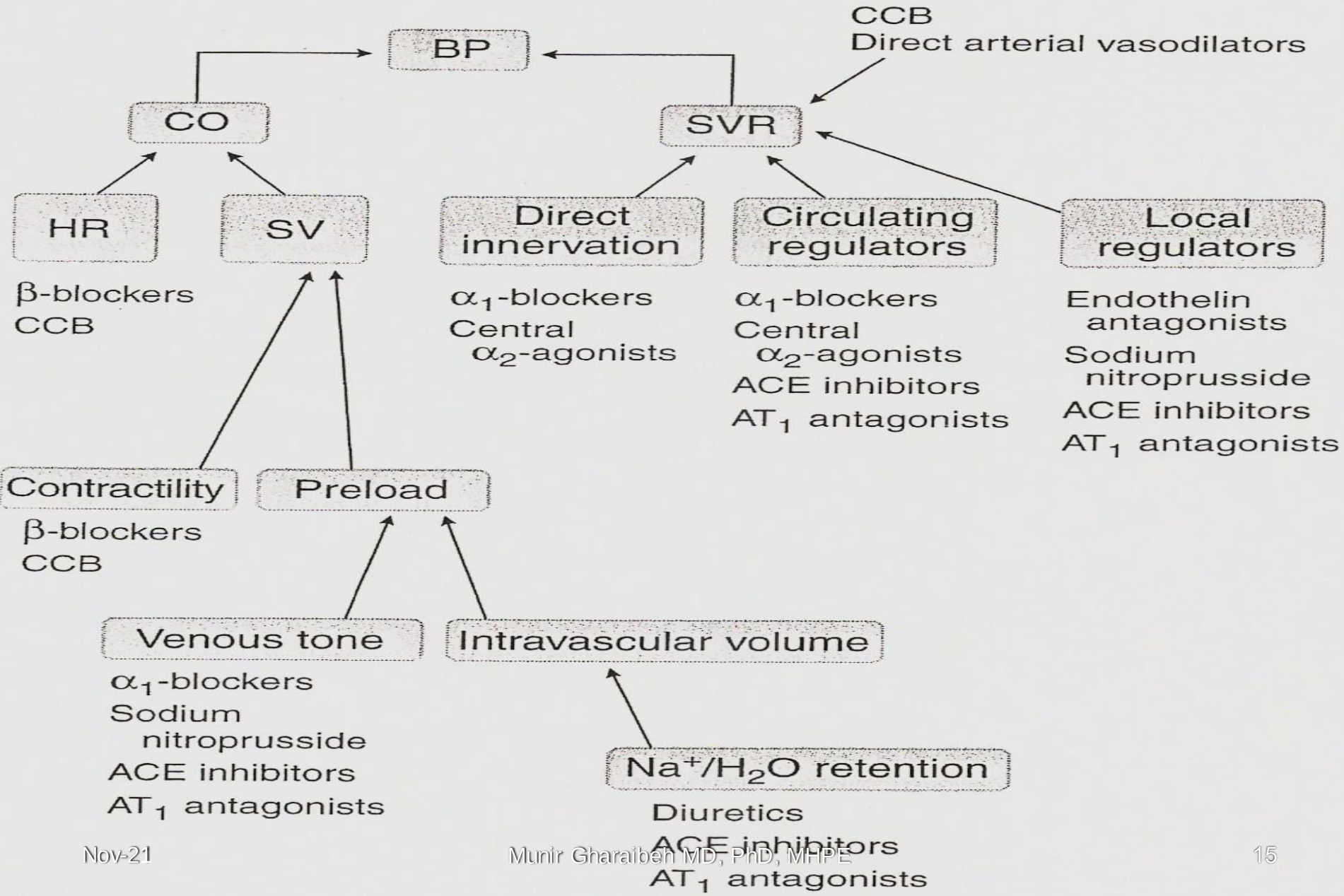


Table 27–5 Classification of Antihypertensive Drugs by Their Primary Site or Mechanism of Action

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- in blood vessels, lowers vessel contractility. Appear even with low doses.
- Increase Plasma Renin
- Side Effects: metabolic side effects(sugar, lipids, uric acid, loss of K+, Na+, Cl-, etc…)

Diuretics (Saluretics)

- **Thiazide diuretics:**
- **Effective in mild and moderate Ht with normal renal and heart function.**
  - **Hydrochlorthiazide.**
  - **Chlorthalidone: long acting.**
  - **Bendrofluazide.**
  - **Indapamide”Natrilex”: 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:**
- **Also useful in heart failure.**
  - **Spironolactone:**
  - **Eplerenone.**
  - **Ameloride.**
  - **Triamterene**

Sympatholytics or Adrenergic Blockers

- Alpha Adrenergic Antagonists
  - 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.**
  - **Blockade of α 2-presynaptic receptors leads to augmented release of NE leading to tachycardia and increased contractility of the heart.**
  - **Used only for pheochromocytoma.**

α1 -selective Alpha Adrenergic Antagonists

Prazosin

Terazocin

Doxazosin

Selective (α 1 > α 2) blockers will lower the BP but will not cause tachycardia.

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 in the vasomotor center.
- 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.
- Useful in 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 nonselective ones.
- Heart Failure in high doses.
- CNS: fatigue, depression, impotence ..etc
- Impair lipid and glucose metabolism
- Mask hypoglycemia !!!
- Claudication, due to α receptor overactivity.
- 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**
  - β1 selective and NO potentiating vasodilatory effect.

Adrenergic Neurone Blockers

Guanethidine

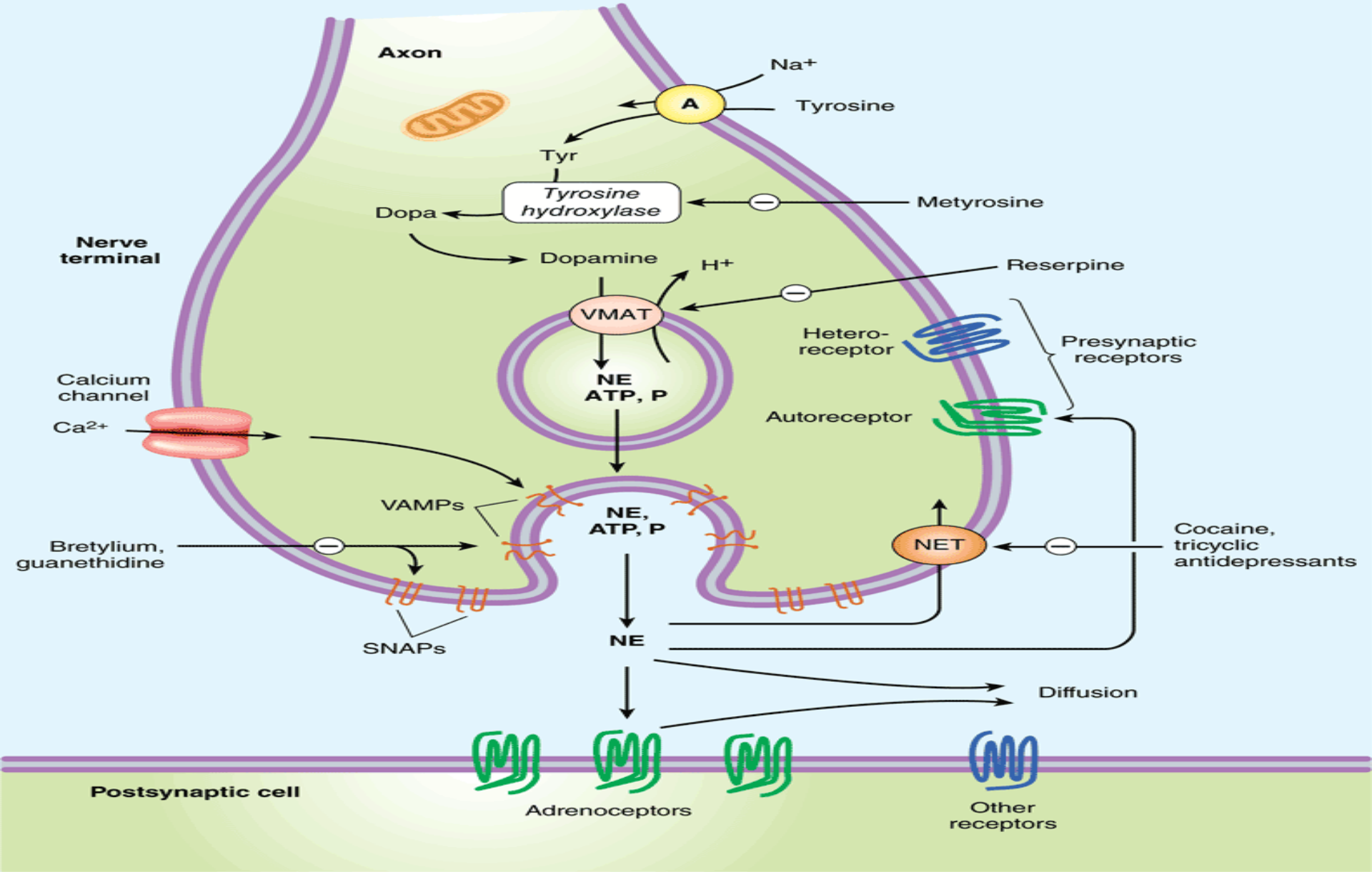
Bethanedine

Debrisoquin

Guanadrel

- **Hydrophilic.**
- **Uptake 1.**
- **Block NE release.**
- **Displace NE from vesicles into the cytoplasm where it will be broken down by MAO .**

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 where it will be metabolized by MAO.
- This will deplete NE.

  Will also deplete DA, 5HT, and ACTH.
- Old fashioned, slow onset and offset, very cheap.
- Can cause depression.

Ganglionic Blockers

Trimethaphan

Pentolinium

Mecamylamine

- **Block transmission in both sympathetic & parasympathetic 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.**

Organ	Predominate System	Results
Cardiovascular System Heart Arterioles Veins	 Parasympathetic Sympathetic Sympathetic	 Tachycardia Vasodilatation Dilation
Eye Iris Ciliary Muscle	 Parasympathetic Parasympathetic	 Mydriasis Cycloplegia
GI Tract	Parasympathetic	Relaxation (constipation)
Urinary Bladder	Parasympathetic	Urinary retention
Salivary Glands	Parasympathetic	Dry Mouth
Sweat Glands	Sympathetic	Anhidrosis