FARMAKOTERAPI PADA HIPERTENSI

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2021

Tujuan Instruksional Khusus

Setelah mengikuti perkuliahan / diskusi diharapkan mahasiswa mampu

- Memahami faktor-faktor yang mempengaruhi tekanan darah
- Memahami mekanisme regulasi tekanan darah.
- Memahami *site of action* dan mekanisme kerja obat-obat yang dapat digunakan untuk pengobatan hipertensi.
- Menyebutkan 4 kelompok besar obat antihipertensi
- Menerangkan respon kompensasi dari masing-masing kelompok obat antihipertensi
- menyebutkan 3 mekanisme kerja obat vasodilator dalam menurunkan tekanan darah.
- Menjelaskan perbedaan antara 2 tipe obat antagonis angiotensin.
- Menjelaskan keuntungan penggunaan obat antihipertensi kombinasi.

ACC/AHA 2017:
New Blood Pressure Classification

Blood Pressure Classification SBP* DBP* (mm Hg)
Normal <120 and <80
Elevated 120-129 or <80
Stage 1 hypertension 130-139 or 80-89
Stage 2 hypertension ≥140 or ≥90

*Treatment determined by highest BP category (SBP or DBP).

Adapted from Chobanian AV et al. *JAMA.* 2003;289:2560-2572; NHBPEPCC. 2003. NIH Publication No. 03-5233.

Etiology

- Essential hypertension:
  - > 90% of cases
  - hereditary component
- Secondary hypertension:
  - < 10% of cases
  - common causes: chronic kidney disease, renovascular disease
  - other causes: Rx drugs, street drugs, natural products, food, industrial chemicals

Causes of 2° Hypertension

- Diseases
  - Obesity
  - chronic kidney disease
  - Cushing's syndrome
  - coarctation of the aorta
  - obstructive sleep apnea
  - parathyroid disease
  - pheochromocytoma
  - primary aldosteronism
  - renovascular disease
  - thyroid disease
- Food substances:
  - sodium
  - ethanol
  - licorice

Causes of 2˚ Hypertension

- Prescription drugs:
  - prednisone, fludrocortisone, triamcinolone
  - amphetamines/anorexiants: phendimetrazine, phentermine, sibutramine
  - antivascular endothelin growth factor agents
  - estrogens: usually oral contraceptives
  - calcineurin inhibitors: cyclosporine, tacrolimus
  - decongestants: phenylpropanolamine & analogs
  - erythropoiesis stimulating agents: erythropoietin, darbepoietin

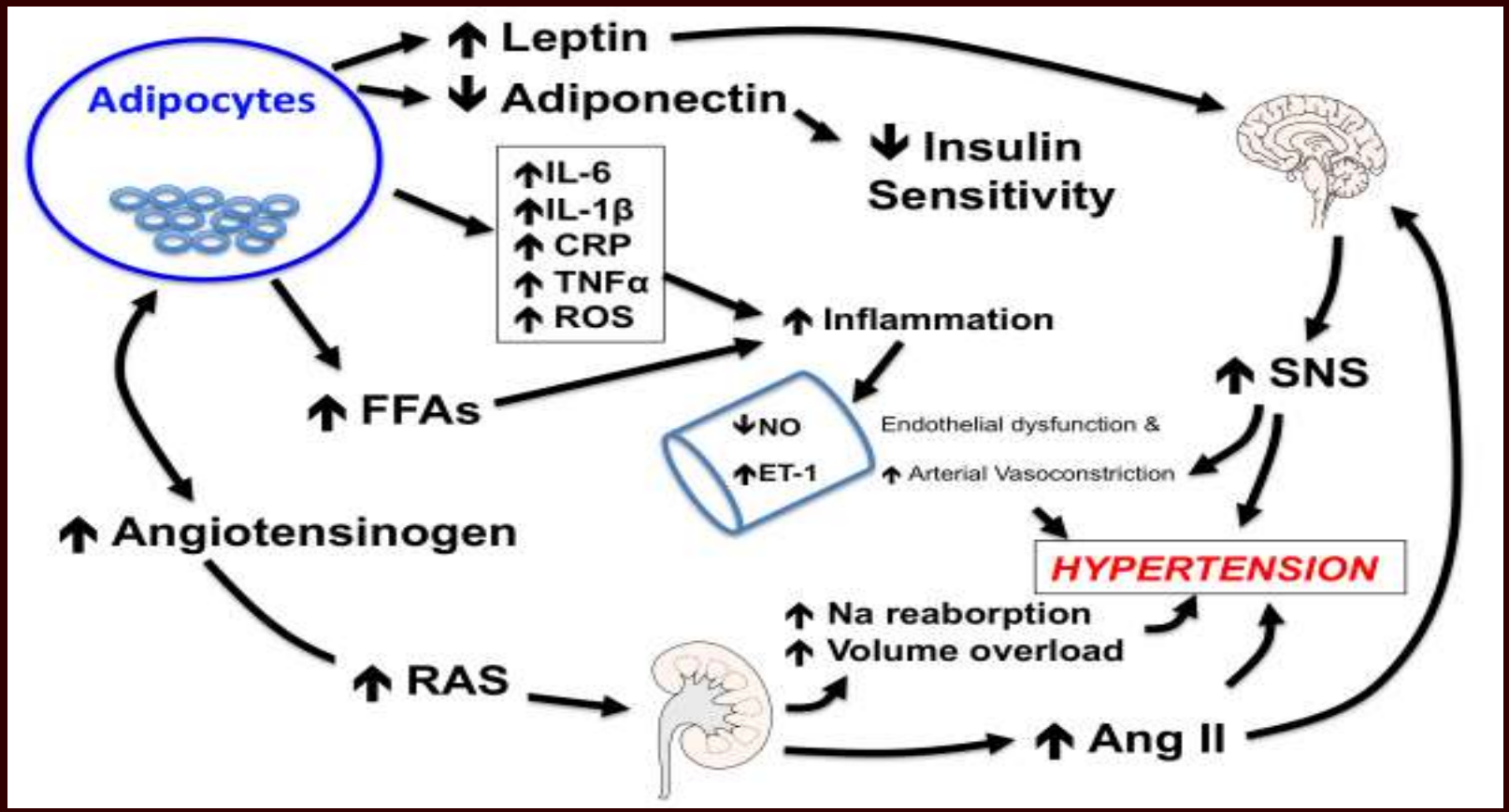
Causes of 2˚ Hypertension

- Prescription drugs:
  - NSAIDs, COX-2 inhibitors
  - venlafaxine
  - bupropion
  - bromocriptine
  - buspirone
  - carbamazepine
  - clozapine
  - ketamine
  - metoclopramide

Causes of 2˚ Hypertension

- Street drugs, other natural products:
  - cocaine
  - cocaine withdrawal
  - ephedra alkaloids (e.g., ma-huang)
  - “herbal ecstasy”
  - phenylpropanolamine analogs
  - nicotine withdrawal
  - anabolic steroids
  - narcotic withdrawal
  - methylphenidate
  - phencyclidine
  - ketamine
  - ergot-containing herbal products
  - St. John's wort

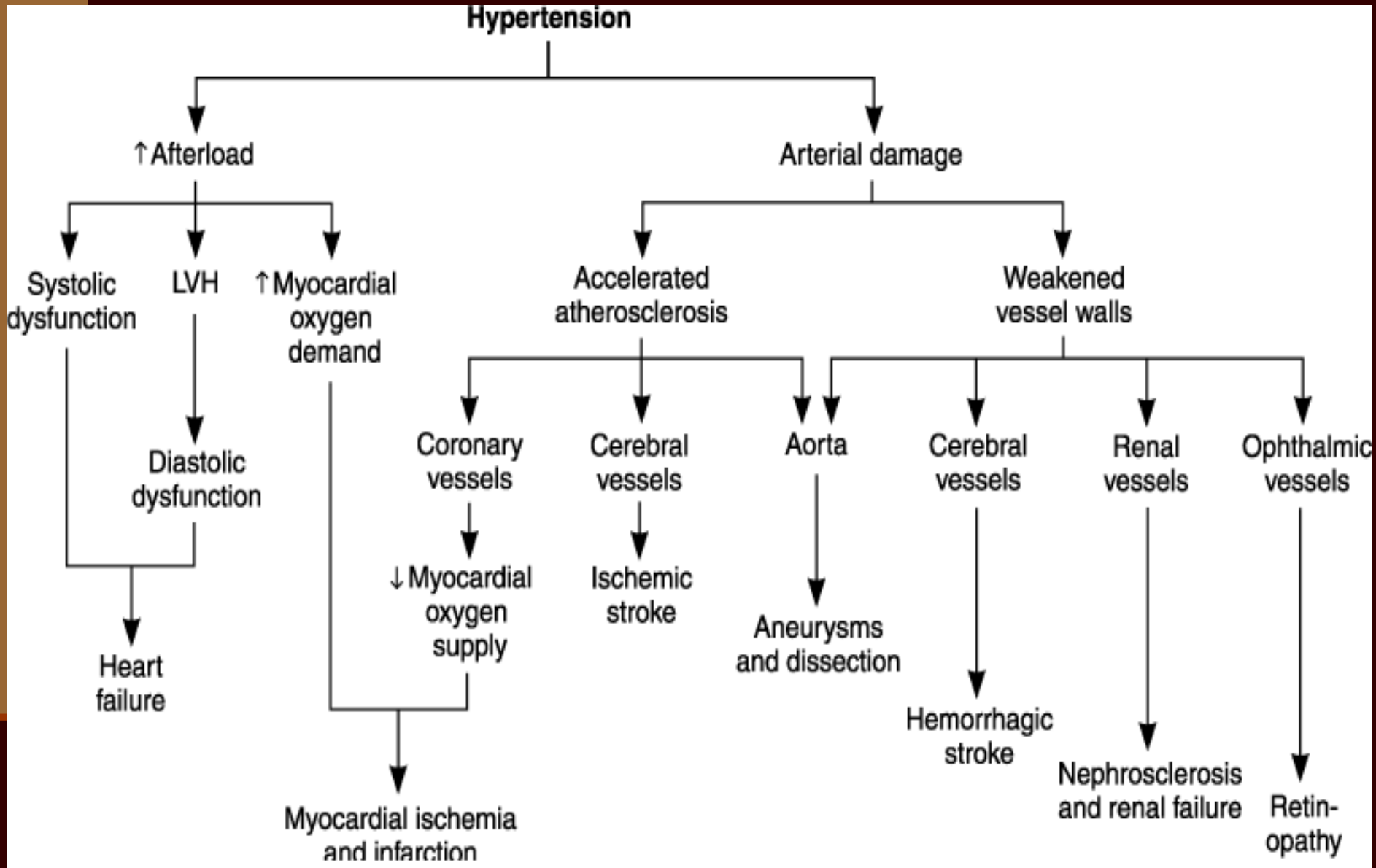
Obesity-induced hypertension



. IL-6: interleukin-6; IL-1β: interleukin-1β; CRP: C-reactive protein; ROS: reactive oxygen species; FFAs: free fatty acids; NO: nitric oxide; ET-1: endothelin-1; RAS: renin-angiotensin system; SNS: sympathetic nervous system (increased tone). Adapted from Kotsis et al (2010).

Mengapa Hipertensi harus diatasi ?

- Morbiditas dan mortalitas meningkat secara progresif seiring dengan makin tingginya TD (MacMahon et al, 1990)
- Mkn tinggi TD, mkn besar resiko terjadinya kerusakan target organ:



Source: McPhee SJ, Ganong WF: *Pathophysiology of Disease: An Introduction to Clinical Medicine*, 5th Edition: http://www.accessmedicine.com

Apa tujuan terapi hipertensi ?

- Menurunkan mortalitas
- Mencegah kerusakan target organ (jantung, otak, ginjal, mata)
- Memperbaiki kualitas hidup (menghilangkan gejala)

Average Percent Reduction

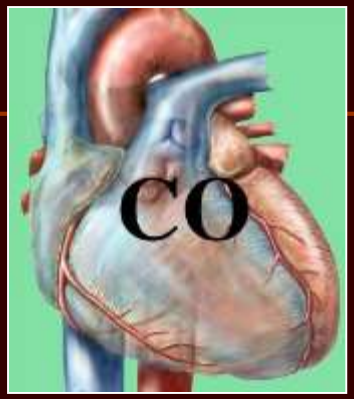
Stoke	**:**	**35% - 40%**
MI	**:**	**20% - 25%**
CHF	**:**	**50%**

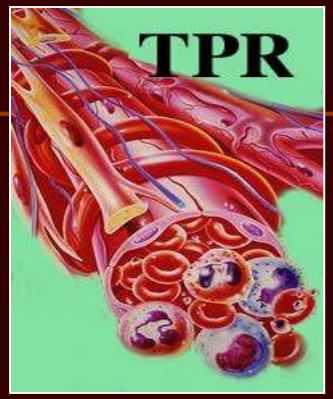
TARGET Tx

- Secara umumTD < 140/90 (tanpa komplikasi)
- TD <130/80 pada hipertensi yang disertai diabetes mellitus atau penyakit ginjal kronik (JNC VII)

Determinants of Arterial Pressure

Mean Arterial Pressure (MAP) = CO X TPR





Blood Volume

Arteriolar Diameter

Stroke Volume

Heart Rate

Contractility

Filling Pressure

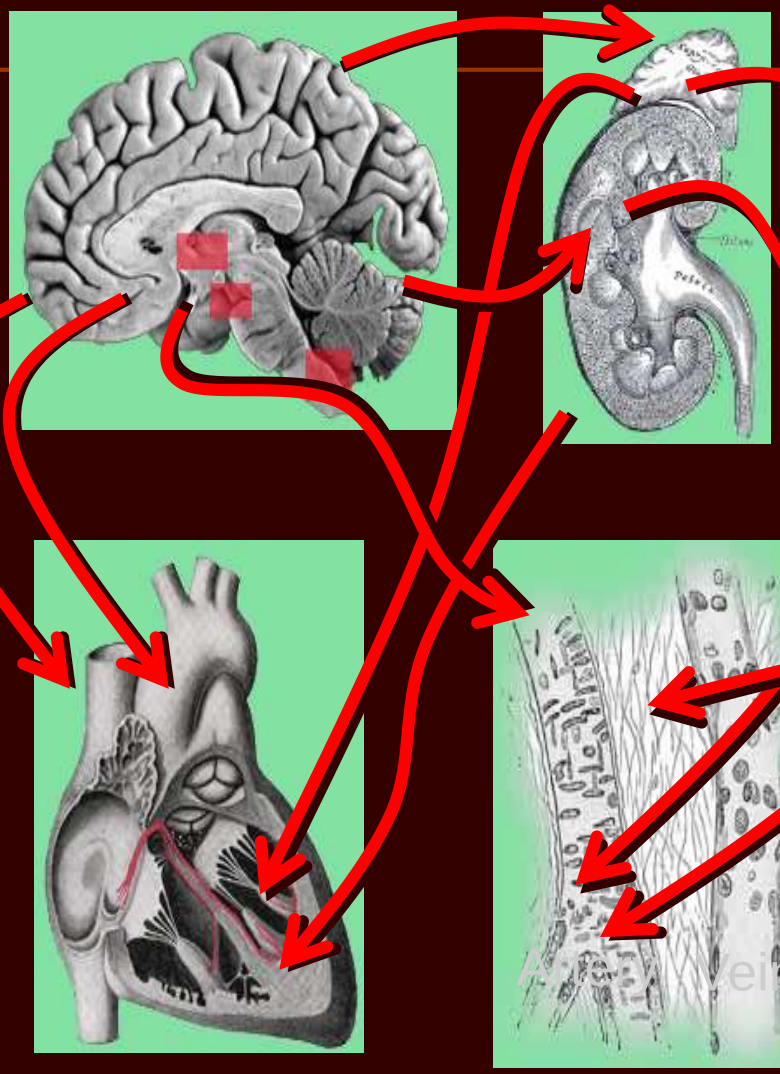
Blood Volume

Venous Tone

CO : Cardiac Output
TPR : Total Peripheral Resistance

Mechanisms Controlling CO and TPR

1. Neural /SSO
   Sympatis
   Parasympatis



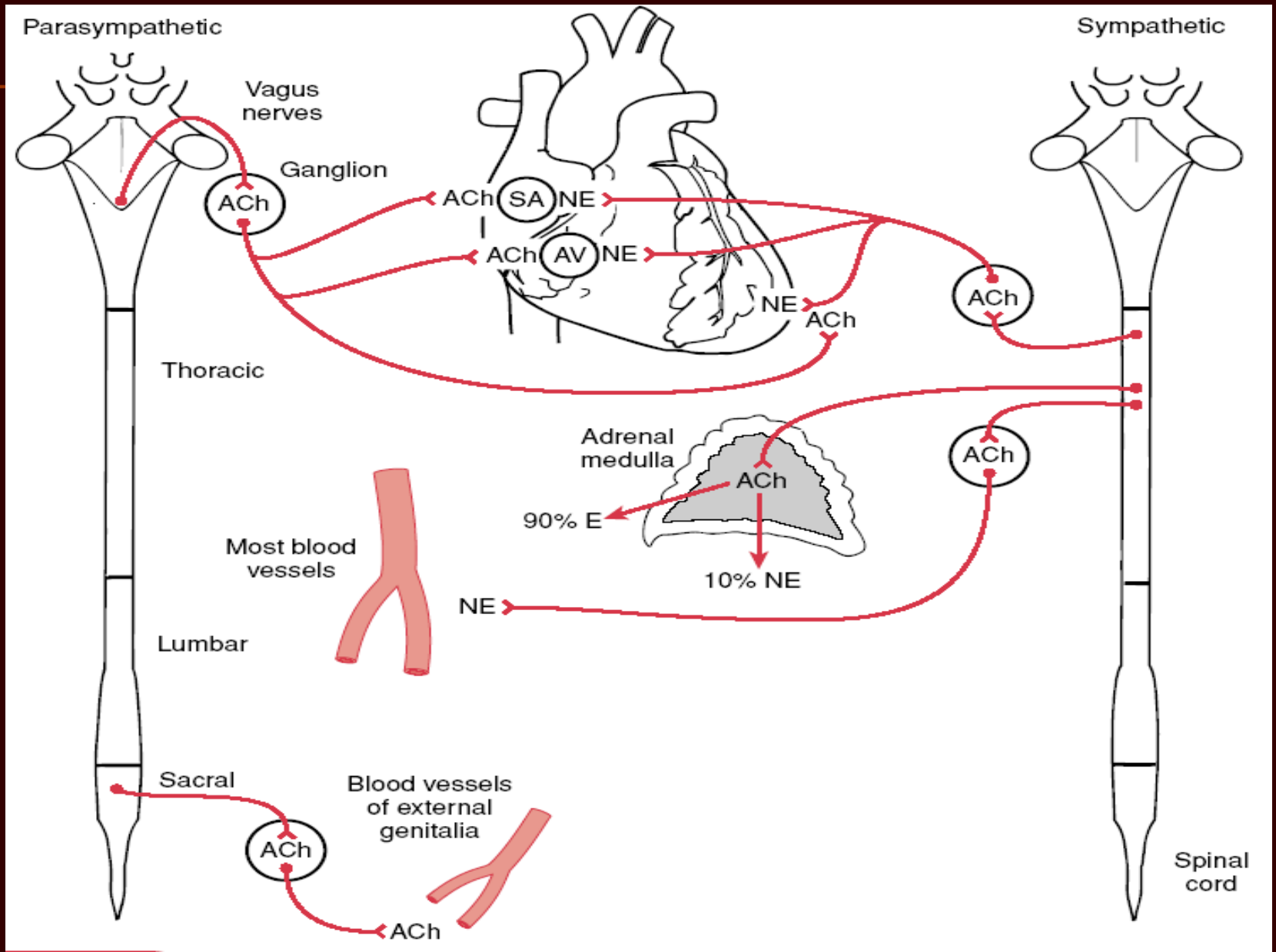
2. Hormonal
   Renal
      Ang II
   Adrenal
      Catecholamines
      Aldosterone

3. Local Factors

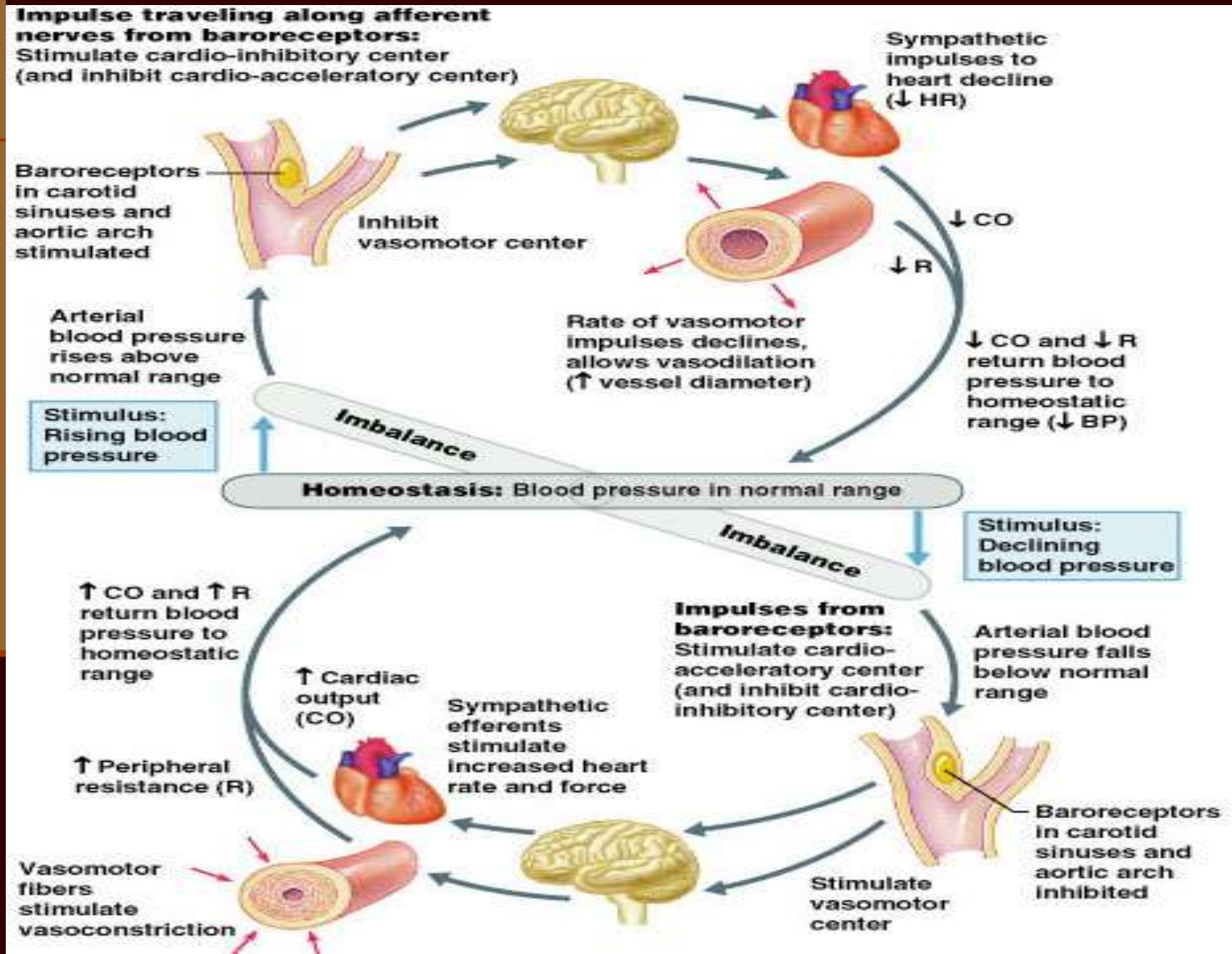
Bagaimana Regulasi Tekanan Darah ?

- **Neural Regulation /Short-term regulation**
  - diperantarai reflek baroreseptor-SSO & kemoreseptor (O_2 & CO_2)
  - mempengaruhi pembuluh darah (diameter) dan jantung (HR dan kontraktilitas)
- **Humoral Regulation / Long-term regulation**
  - mempengaruhi ginjal (Angiotensin II) & Adrenal (Katekolamin dan Aldosteron)
- **Local Regulation**

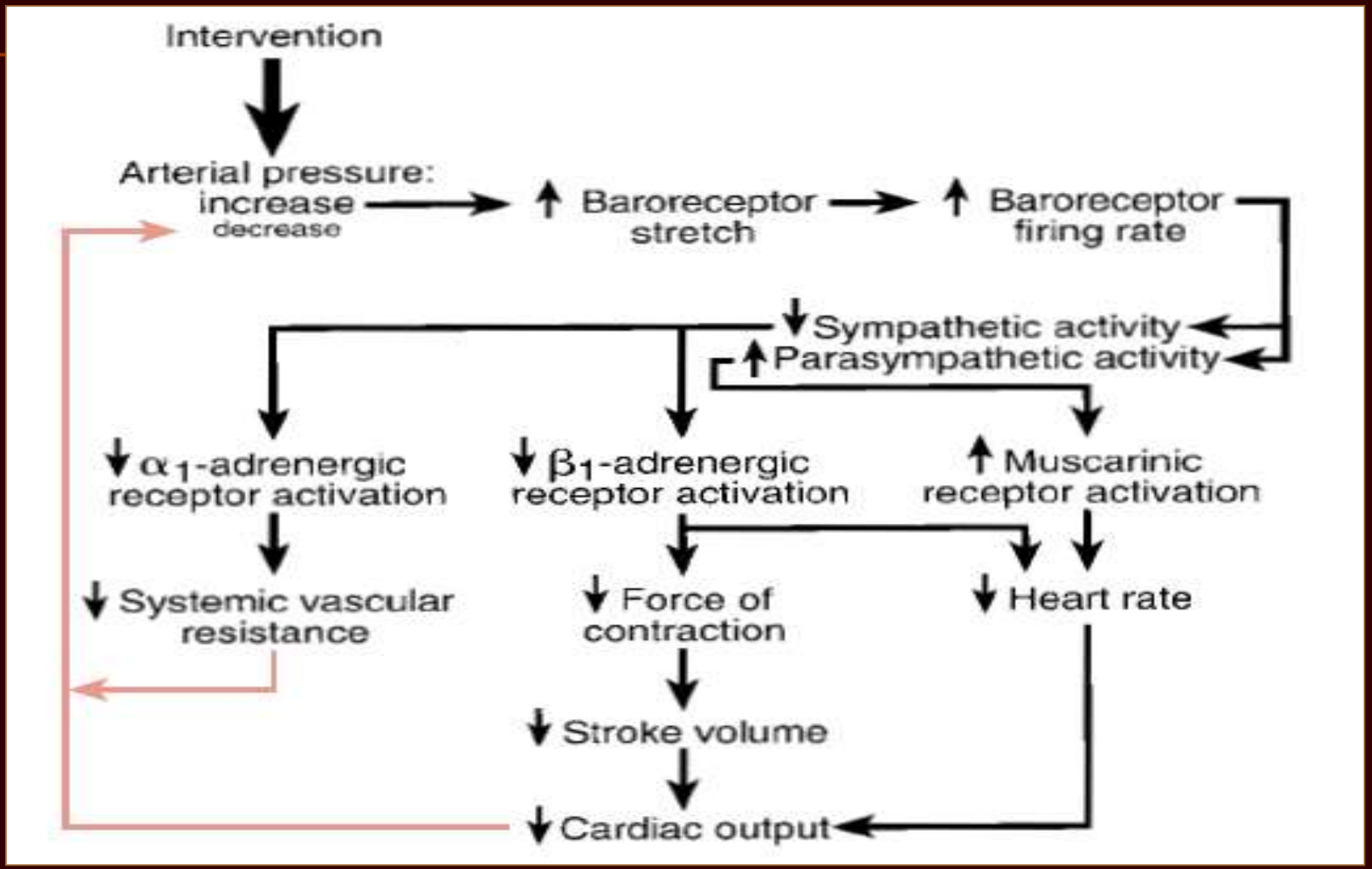
AUTONOMIC NEURAL REGULATION



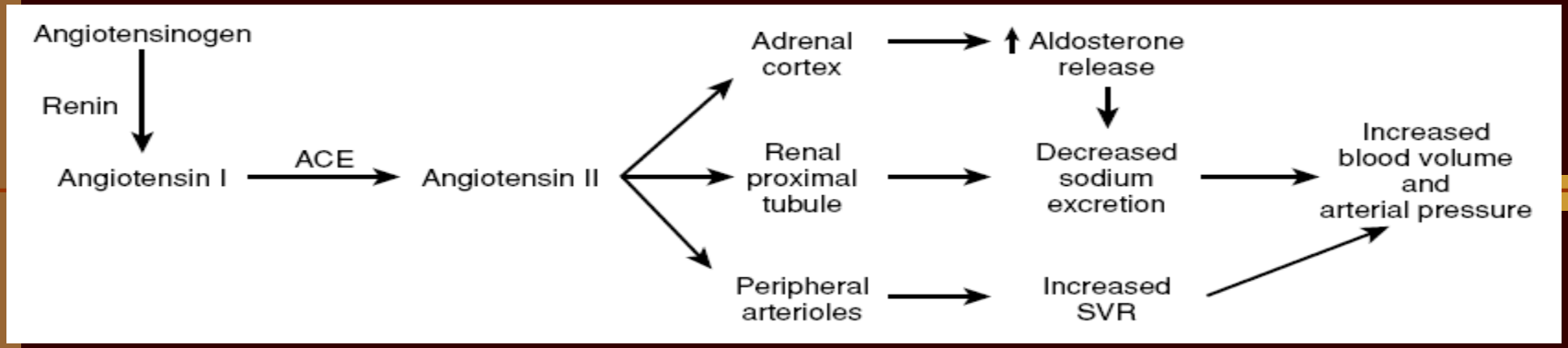
SHORT-TERM MECHANISMS : REFLEKS BARORECEPTOR

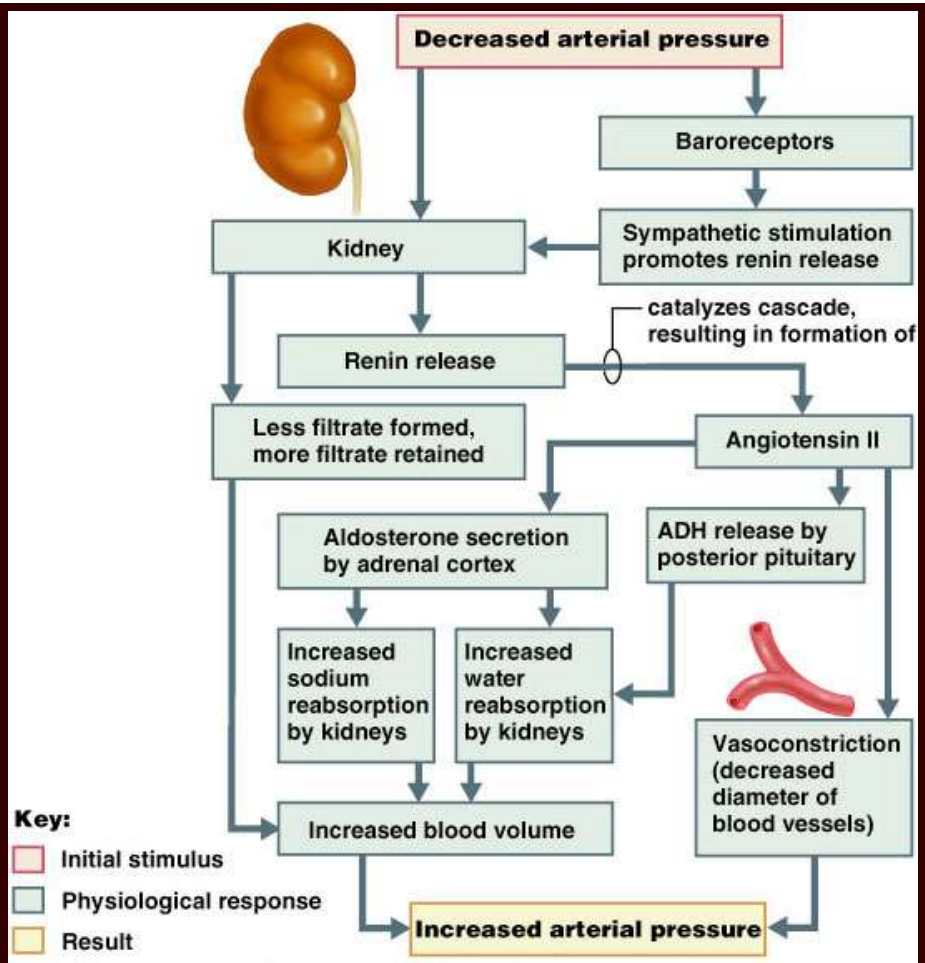


Short-Term Mechanisms : Refleks Baroreceptor



LONG-TERM MECHANISMS / HUMORAL REGULATION





LOCAL REGULATION : AUTOREGULASI

- Substansi kimia lokal
- Mis : NO, potassium and hydrogen ions, ANP, adenosine, lactic acid, histamines, kinins, and prostaglandins

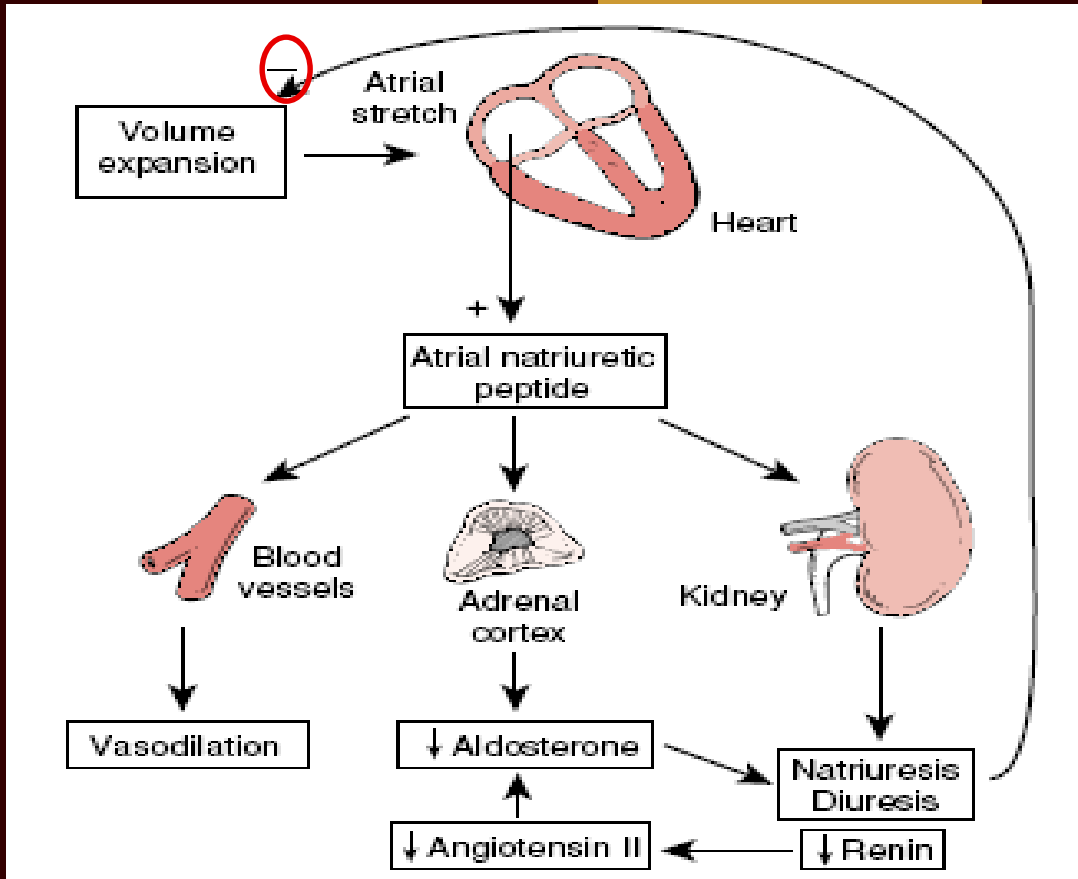


FIGURE 24.10 Atrial natriuretic peptide and its actions. ANP release from the cardiac atria is stimulated by blood volume expansion, which stretches the atria. ANP produces effects that bring blood volume back toward normal, such as increased Na^+ excretion.

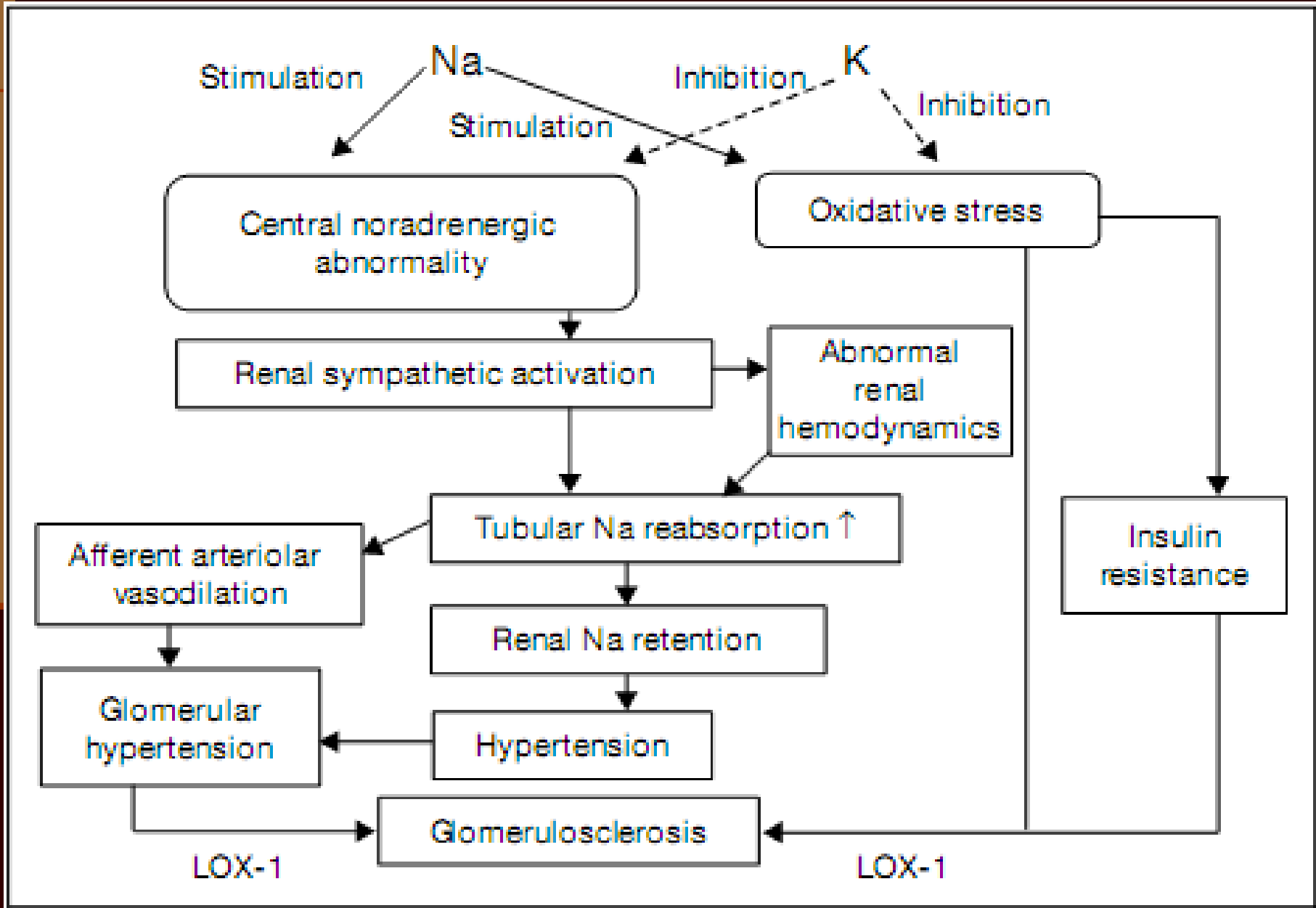
Bagaimana Terapi Hipertensi ?

- **Terapi Non farmakologis** : *Life style modification*

  - stop merokok
  - diet : kurangi makanan berlemak & asupan garam (Na+), tambah suplemen ion K, Ca, Mg
  - menurunkan BB
  - aktivitas fisik / OR
  - relaksasi (kurangi stress)

- **Terapi Farmakologis** : *Obat antihipertensi*

Apa Perlunya Diet Rendah Garam ?



LIFE STYLE MODIFICATIONS

Modification	Recommendation	Systolic Diastolic Chgs
Weight Reduction	BMI 18.5-24.9	5-20mm/10 kg wt loss
Adopt DASH eating	Diet rich in fruits vegetables and low fat with reduced saturated and total fat	8-14 mm Hg
Dietary Sodium	2.4g Na	2-8 mm Hg
Physical Inactivity	Brisk exercise 30" day most days of week	4-9 mm Hg
Moderation of Alcohol intake	2 drinks day max 24 oz beer; 10 oz wine 2 oz 100 proof whiskey	2-4 mm Hg

JAMA. 2003;289:2560-2577.

LIFE STYLE MODIFICATIONS

Modification	Recommendation	Approximate Systolic Reduction (mm Hg)[a]
Weight loss	Maintain normal body weight (body mass index 18.5–24.9 kg/m^2)	5–20 per 10-kg weight loss
DASH-type dietary patterns	Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat	8–14
Reduced salt intake	Reduce daily dietary sodium intake as much as possible, ideally to 65 mmol/day (1.5 g/day sodium, or 3.8 g/day sodium chloride)	2–8
Physical activity	Regular aerobic physical activity (at least 30 min/day, most days of the week)	4–9
Moderation of alcohol intake	Limit consumption to 2 drinks/day in men and 1 drink/day in women and lighter-weight persons	2–4

DASH, Dietary Approaches to Stop Hypertension.

[a] Effects of implementing these modifications are time and dose dependent and could be greater for some patients.

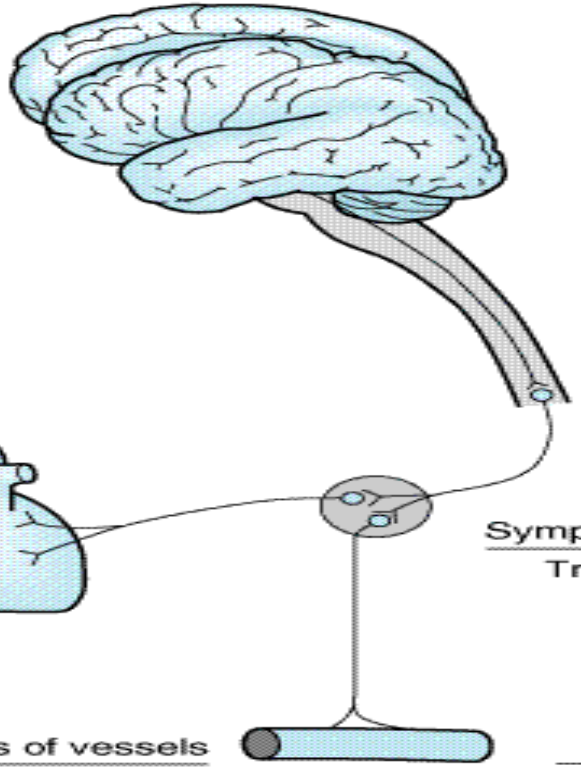
DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: Pharmacotherapy:A Pathophysiologic Approach, 7th Edition: http://www.accesspharmacy.com/

Additional Recommendations

- Diets high in potassium, calcium and magnesium are associated with a lower blood pressure
- JNC VII recommends an adequate dietary intake of these but does not recommend supplementing from an outside source to lower blood pressure
- Omega-3 fatty acids may lower blood pressure
- Caffeine may increase it but tolerance often develops
  - Most studies do not support a relationship between hypertension and caffeine
- Smoking: discontinuation is important
- Exercise: 30 minutes daily recommended

OBAT ANTIHIPERTENSI

Sites of action of the major classes of antihypertensive drugs



Vasomotor center
Methyldopa
Clonidine
Guanabenz
Guanfacine

Sympathetic nerve terminals
Guanethidine
Guanadrel
Reserpine

Sympathetic ganglia
Trimethaphan

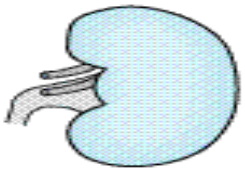
β-Receptors of heart
Propranolol and other β-blockers

Angiotensin receptors of vessels
Losartan and other angiotensin receptor blockers

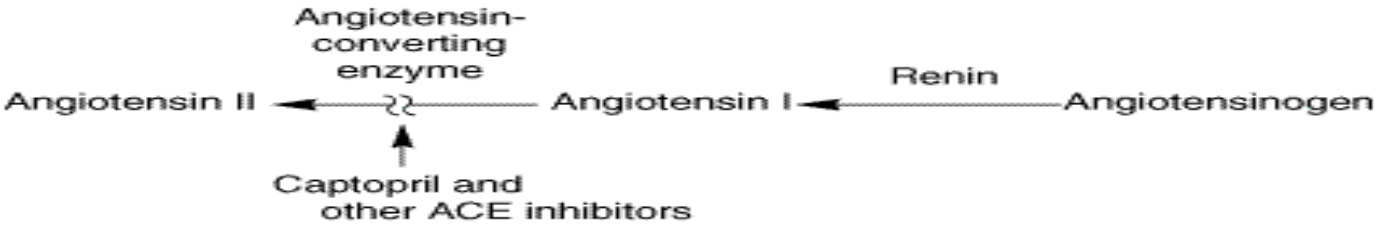
α-Receptors of vessels
Prazosin and other α_1-blockers

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

Kidney tubules
Thiazides, etc



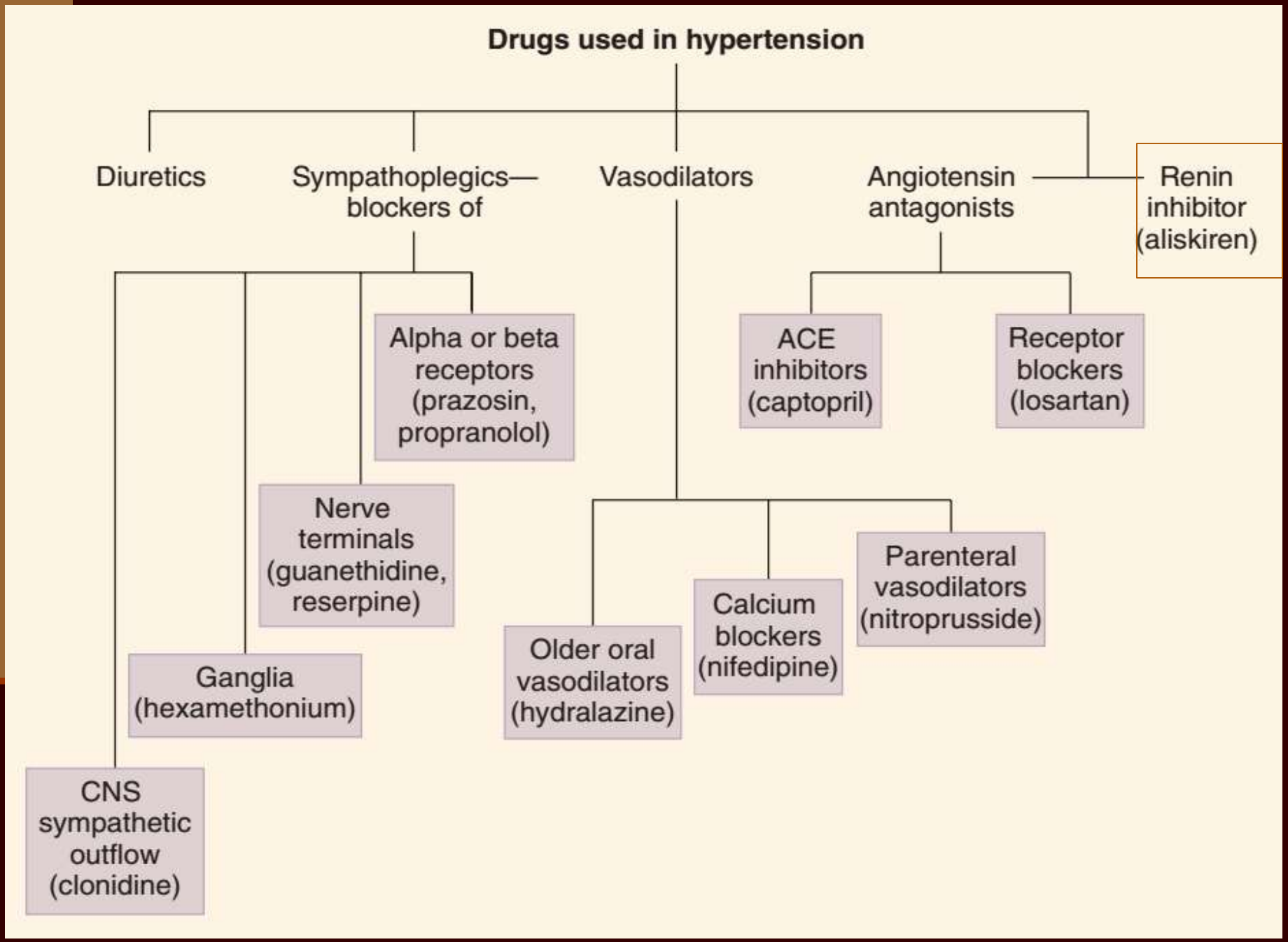
β-Receptors of juxtaglomerular cells that release renin
Propranolol and other β-blockers



PENGGOLONGAN ANTIHT

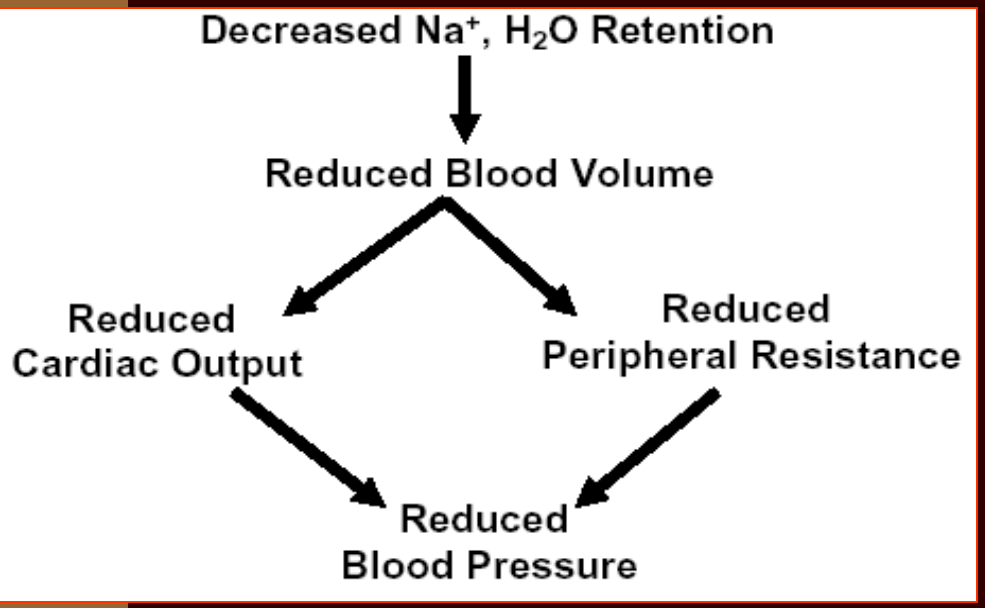
berdasarkan tempat kerjanya

- **Sistem Saraf Simpatis** di :
  - ✓ **Sentral (CNS)** : clonidin, methyldopa
  - ✓ **Ganglion** : heksamethonium, trimethapan
  - ✓ **Ujung saraf** : reserpin, guanethidin
  - ✓ **Reseptor adrenergik** : Prazosin(α1 blocker), Propanolol (β blocker), atenolol (β1 blocker)
- **Ginjal** : Diuretik
- **Otot polos vaskuler** : CCB, Vasodilator
- **RAAS** : ACE inhibitor, ARB, Direct Renin Inhibitor


Drugs used in hypertension
Diuretics
Sympathoplegics—blockers of
Vasodilators
Angiotensin antagonists
Renin inhibitor (aliskiren)
Alpha or beta receptors (prazosin, propranolol)
Nerve terminals (guanethidine, reserpine)
Ganglia (hexamethonium)
CNS sympathetic outflow (clonidine)
Older oral vasodilators (hydralazine)
Calcium blockers (nifedipine)
Parenteral vasodilators (nitroprusside)
ACE inhibitors (captopril)
Receptor blockers (losartan)

DIURETIK

Mekanisme kerja



Initial:
↓ body Na+ → ↓ BV → ↓ CO → ↓BP (↑TPR, reflex)

Chronic:
CO unchanged, ↓ TPR, ↓ NE → ↓ [Ca++]i → ↓ vascular tone

Direct vasodilation effect:
probably by opening K+ channels

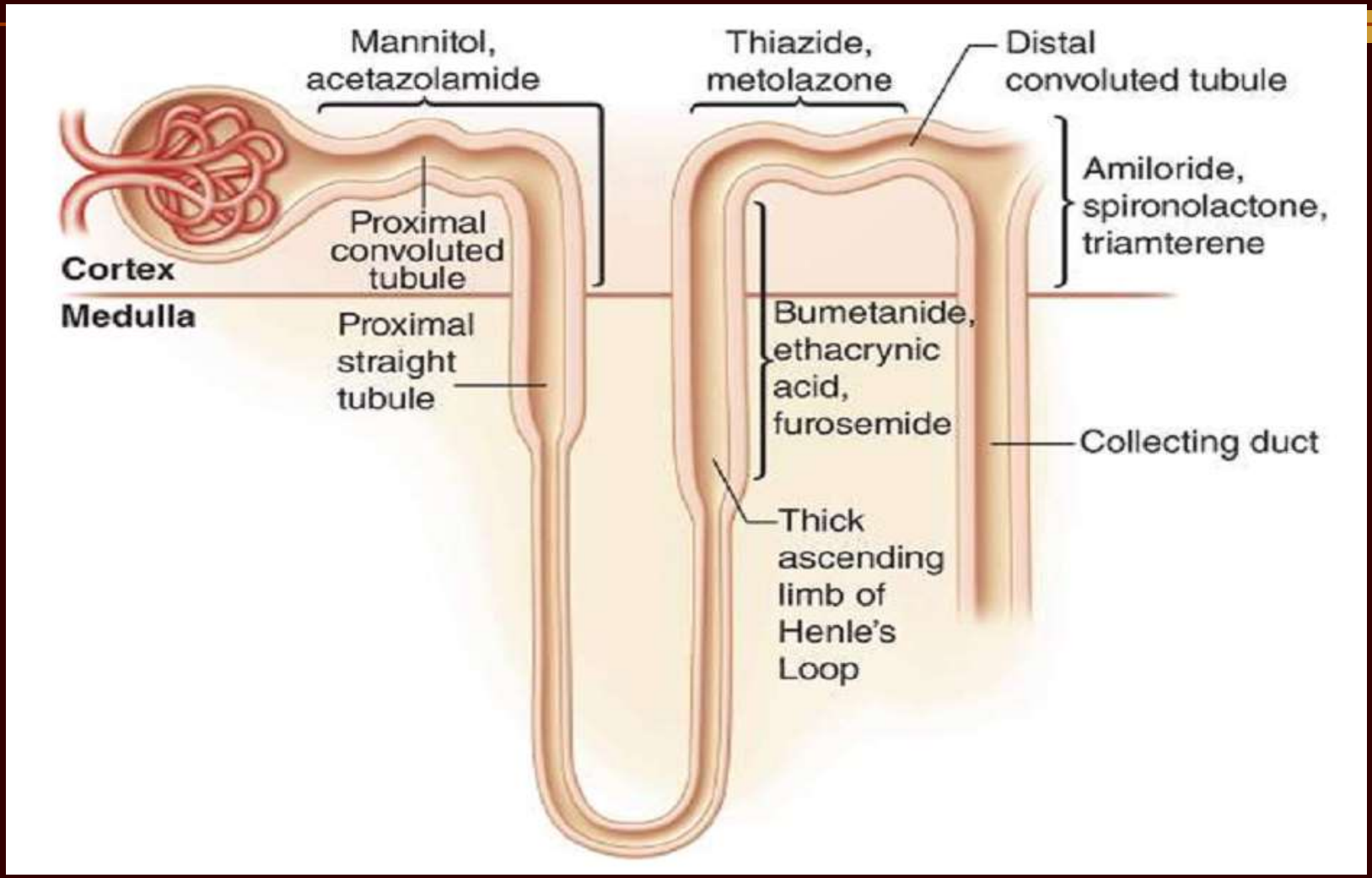
Ada 3 kelas diuretik utk HT

- ✓ Thiazide
  Hidrochlorothiazide (HCT), Chlorothalidone
- ✓ Loop diuretics
  Furosemide, Torsemide, Bumetanide
- ✓ Diuretik Hemat K^+
  Amiloride, Triamterene, Spironolacton

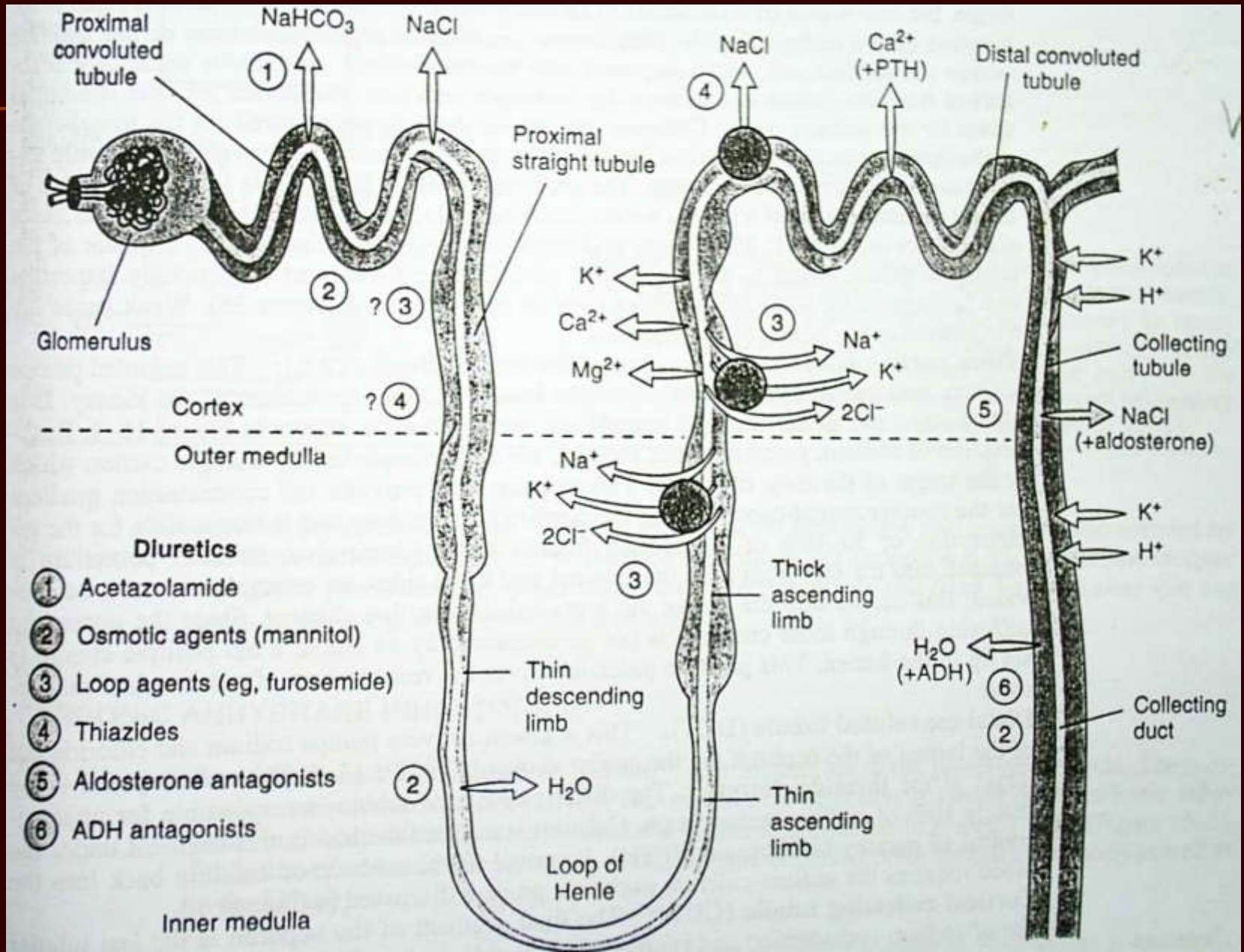
DIURETIK

- Mekanisme kerja :
  - ekskresi Na & H2O ↑
- Efek pd CVS :
  - akut : COP ↓
  - kronik : TPR ↓,COP N
- KI :

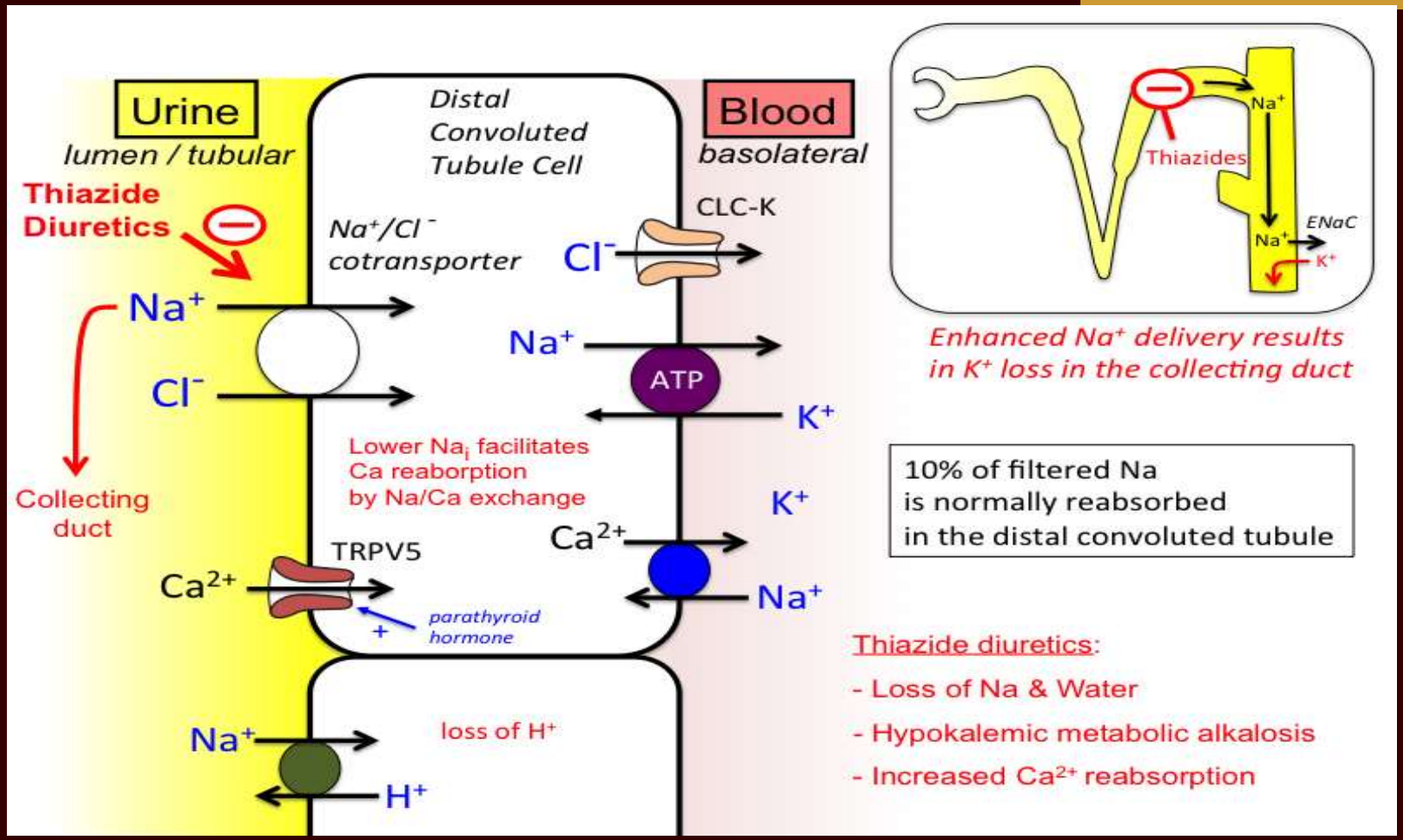
  hypersensitivity, compromised kidney function, Tx cardiac glycosides (K+ effects), hypovolemia,hyponatremia
- ES :
  - dizziness,
  - electrolit imbalance
  - hypokalemia,
  - hyperlipidemia,
  - hyperglycemi(Thiazid)
  - gout


Mannitol, acetazolamide
Thiazide, metolazone
Distal convoluted tubule
Amiloride, spironolactone, triamterene
Proximal convoluted tubule
Cortex
Medulla
Proximal straight tubule
Bumetanide, ethacrynic acid, furosemide
Collecting duct
Thick ascending limb of Henle's Loop

Diuretik


Proximal convoluted tubule
NaHCO3
NaCl
Glomerulus
Proximal straight tubule
Cortex
Outer medulla
Inner medulla
Thin descending limb
Loop of Henle
Thick ascending limb
Thin ascending limb
Distal convoluted tubule
Collecting tubule
Collecting duct
NaCl (+aldosterone)
Ca2+ (+PTH)
H2O (+ADH)
K+
H+
Ca2+
Mg2+
Na+
2Cl−
H2O
Diuretics
1 Acetazolamide
2 Osmotic agents (mannitol)
3 Loop agents (eg, furosemide)
4 Thiazides
5 Aldosterone antagonists
6 ADH antagonists

THIAZIDE

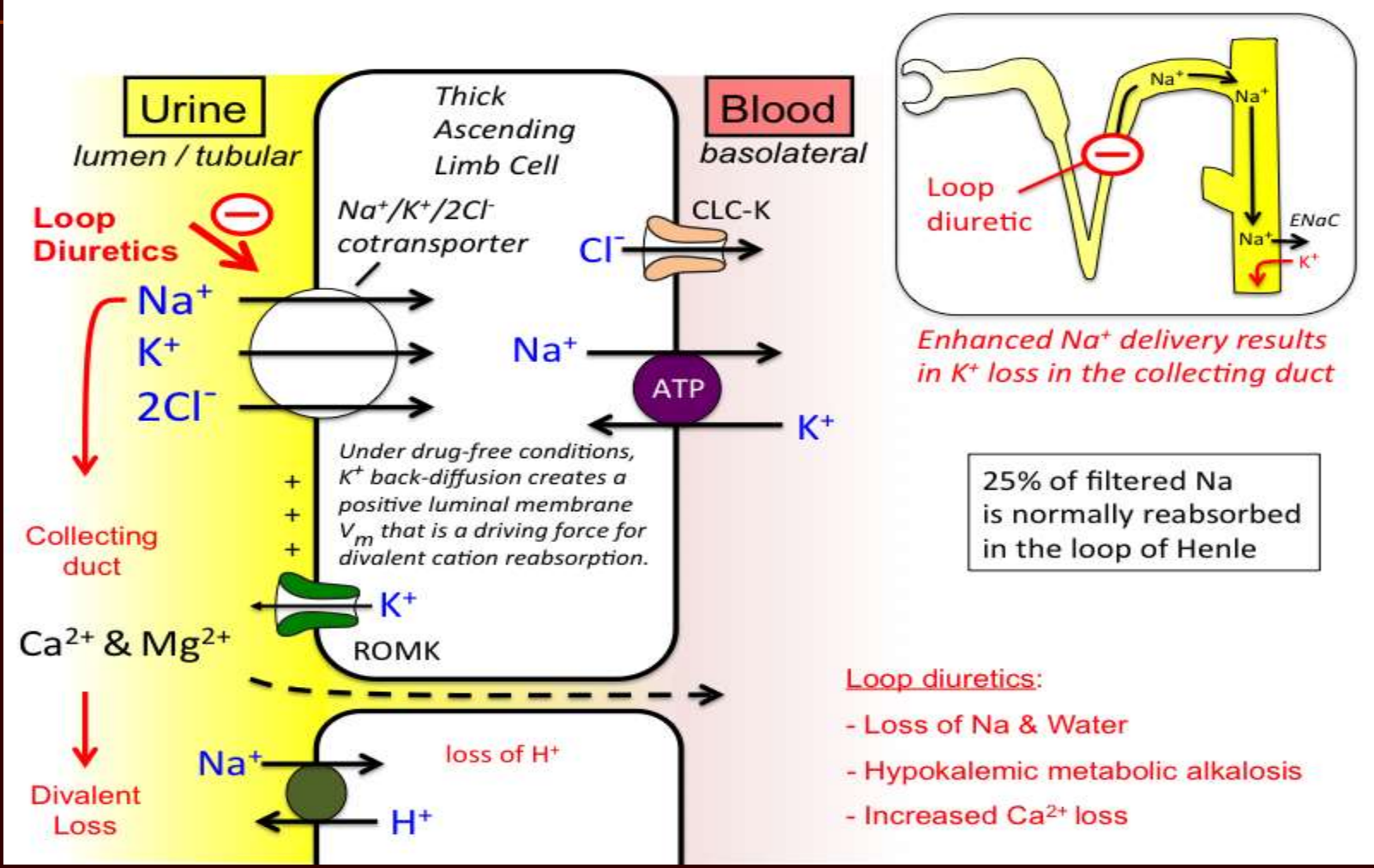

Urine
lumen / tubular
Thiazide Diuretics
Distal Convoluted Tubule Cell
Blood
basolateral
Na+/Cl- cotransporter
CLC-K
Cl-
Na+
Cl-
Na+
ATP
K+
Lower Nai facilitates Ca reaborption by Na/Ca exchange
Collecting duct
K+
Ca2+
TRPV5
Ca2+
Na+
parathyroid hormone
+
Na+
loss of H+
H+
Thiazides
Na+
ENaC
Na+
K+
Enhanced Na+ delivery results in K+ loss in the collecting duct
10% of filtered Na is normally reabsorbed in the distal convoluted tubule
Thiazide diuretics:
- Loss of Na & Water
- Hypokalemic metabolic alkalosis
- Increased Ca2+ reabsorption

THIAZIDE

- FD= inhibit Na/Cl co-transporter
  - depleting the body of Na & reducing blood volume
  - reduce intracellular Ca levels in vascular smooth muscle via Na/Ca exchange → smooth muscle vasodilator
- Side effect =
  - dose-dependent hypokalemia
  - dyslipidemia
  - impaired glucose tolerance
  - increased uric acid levels & can precipitate gout
- KI relatif = gout

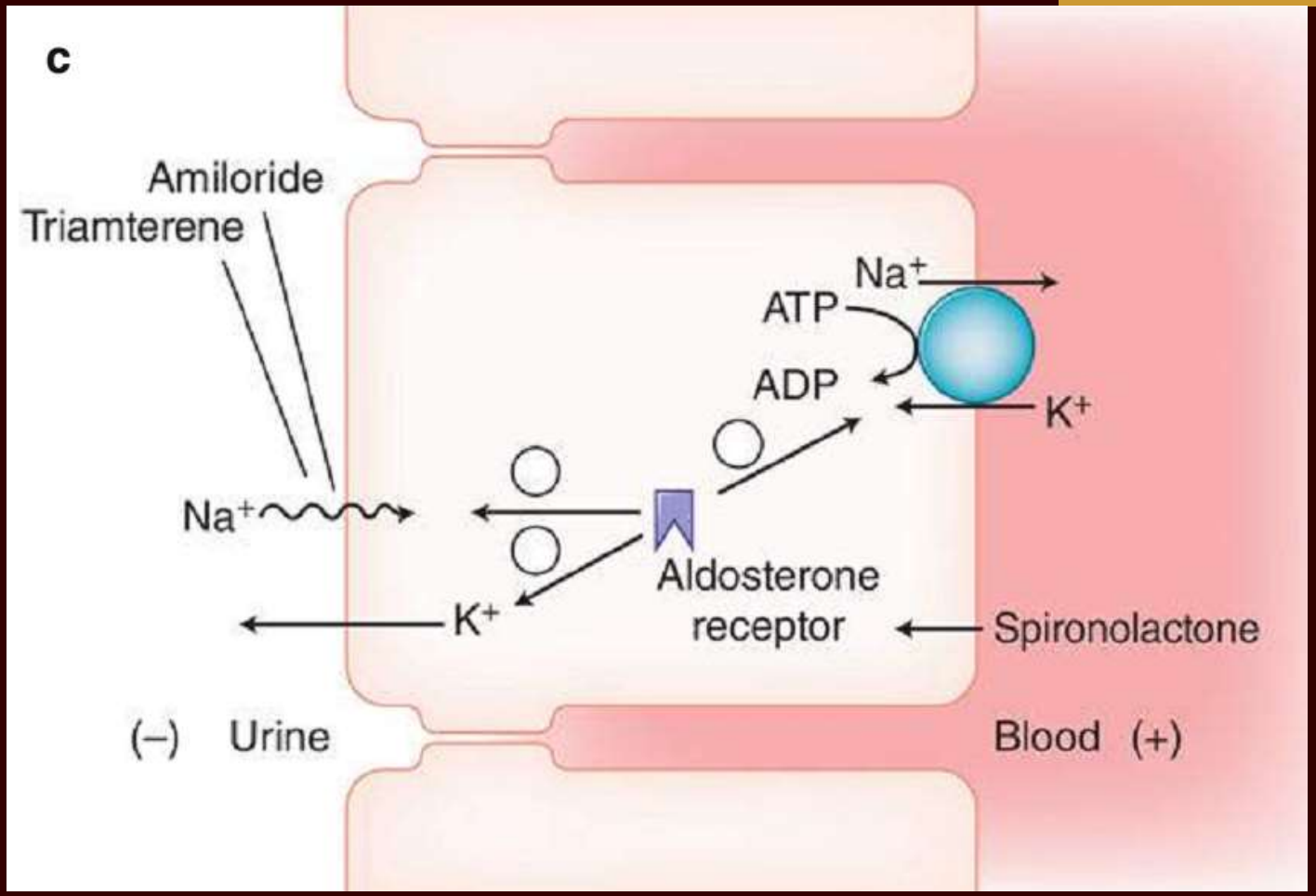
- Indication
  - hypertension. They are especially effective in lowering BP in elderly
  - heart failure (reduce blood volume, venous pressure & preload).
  - kidney stones caused by hypercalciuria
  - nephrogenic diabetes insipidus

LOOP DIURETIC

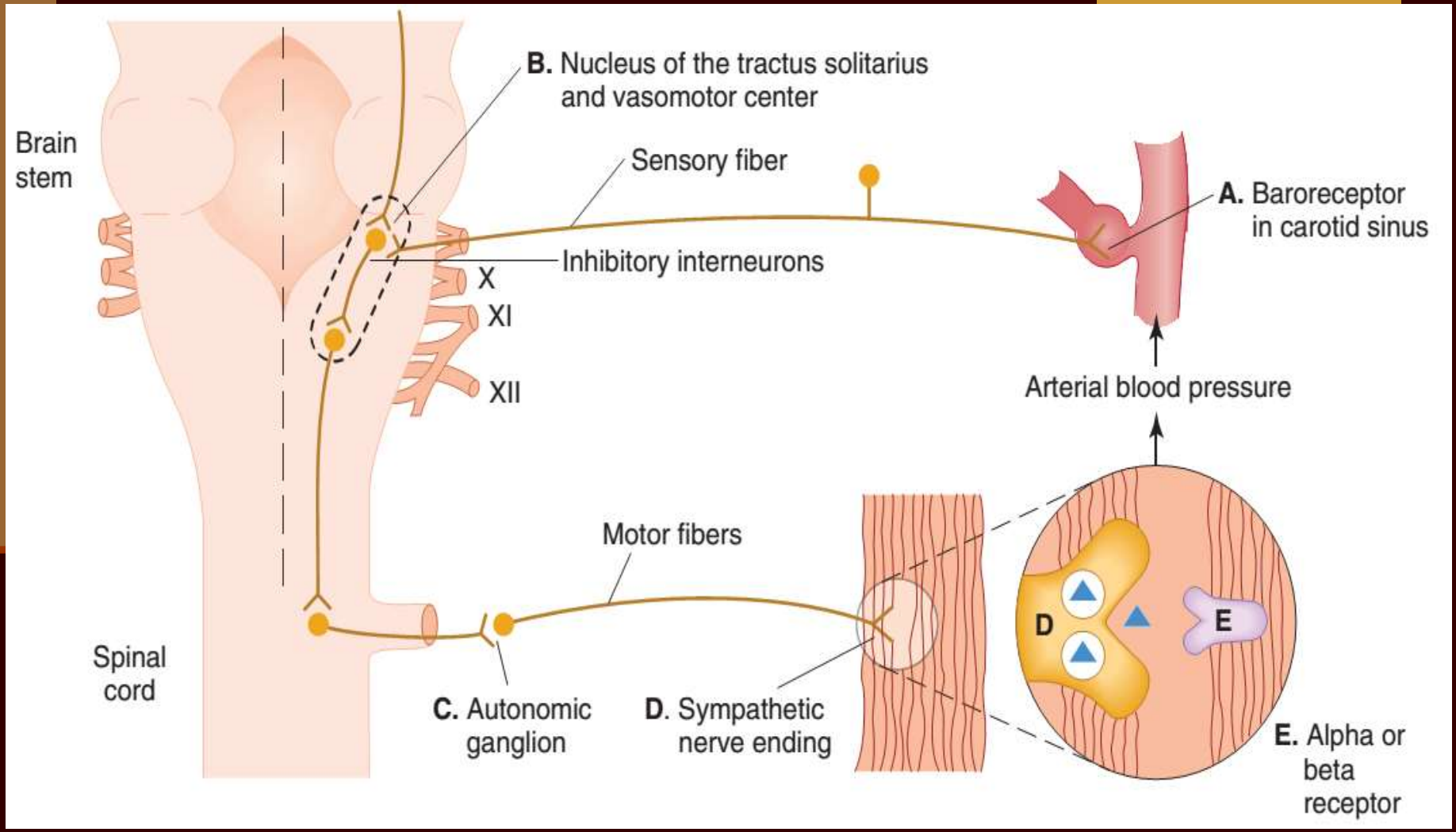


LOOP DIURETIC

- FD= inhibit Na/K/2Cl co-transporter **in the thick ascending limb of the loop of Henle**.
- Indication :
  - **produce *a more potent diuresis* for** Patient with severe edema (**congestive heart failure, cirrhosis of the liver, and renal disease (e.g. GFR <30 ml/min), including the nephrotic syndrome)**
  - **are *less effective in lowering BP than thiazide diuretics***


c
Amiloride
Triamterene
Na+
ATP
ADP
K+
Na+
K+
Aldosterone
receptor
Spironolactone
(–) Urine
Blood (+)

SYMPATHOLITICS AGENTS



BLOK ADRENERGIK DI CNS (CNS AGENTS)

- Site of action : CNS medullary , cardiovasc centers
- Mekanisme kerja :

  - agonis R/ α-2 di CNS : Clonidine, Guanabenz, Guanfacine

    Aktivasi R/α-2 di medulla → NE release dr SSP↓→ peripheral sympathetic activity ↓→ vasc tone ↓→ vasodilation → TPR ↓.

  - membentuk neurotransmiter palsu : Methyldopa

- ES : dry mouth, sedasi, impotence
- KI : mental depression
- NOT 1st line drug,
- Prolong used → retensi Na & air →sering digunakan bersama diuretic
- stop mendadak → rebound SymNS → TD ↑
- Methlydopa : DOC in pregnancy

Mekanisme Kerja Clonidin dan Methyldopa

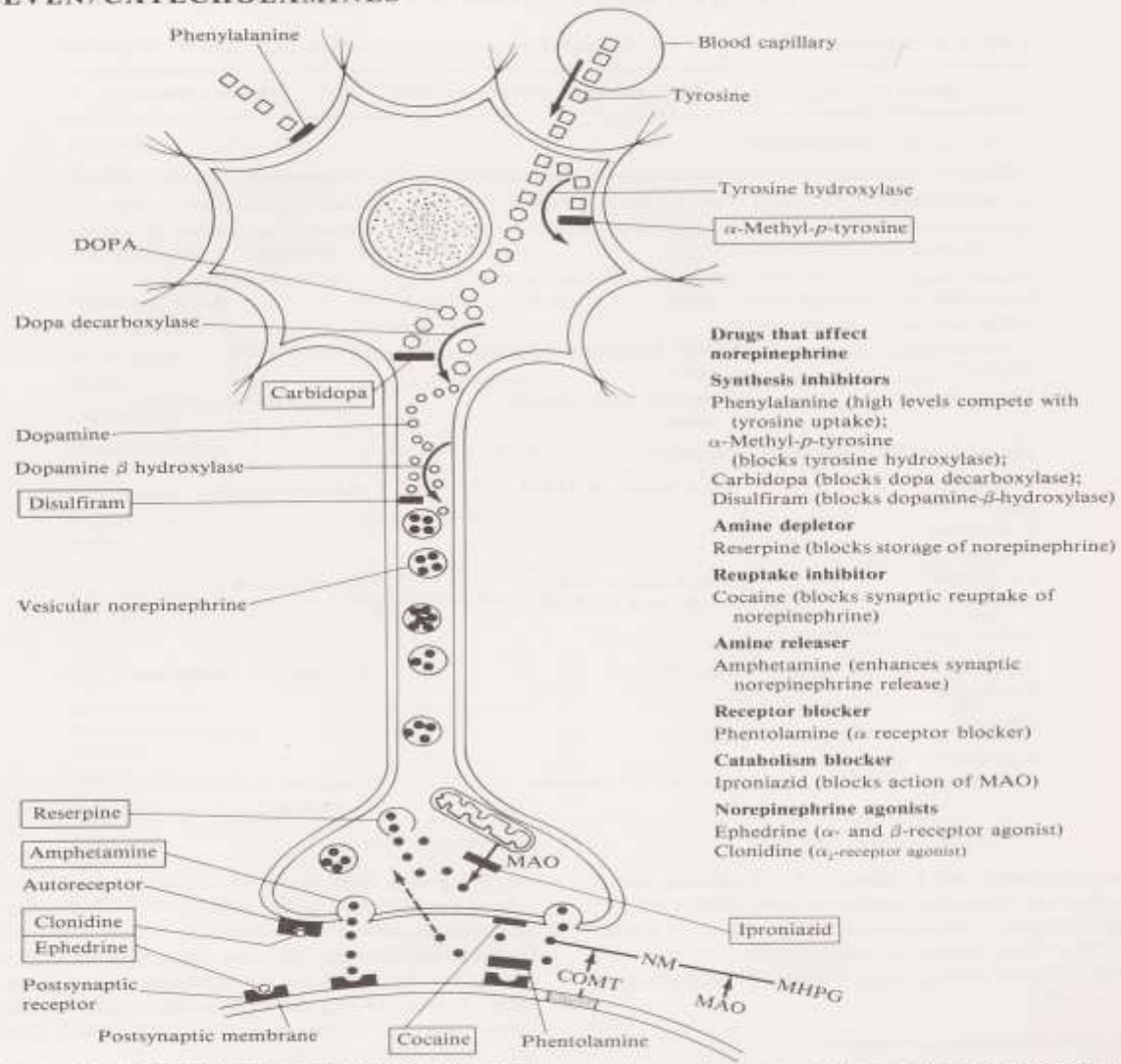


FIGURE 19 NORADRENERGIC SYNAPSES IN THE CNS. NE synthesis, storage, and release is shown in the neuron; and NA receptors are shown on the presynaptic as well as on the postsynaptic membrane. Some noradrenergic drugs are listed on the right, and their sites of action are shown in the figure.

Blok Adrenergik di Ganglion Otonom

- **Contoh** : Hexamethonium
- **Mekanisme kerja :**

  memblok reseptor nikotinik di ganglion

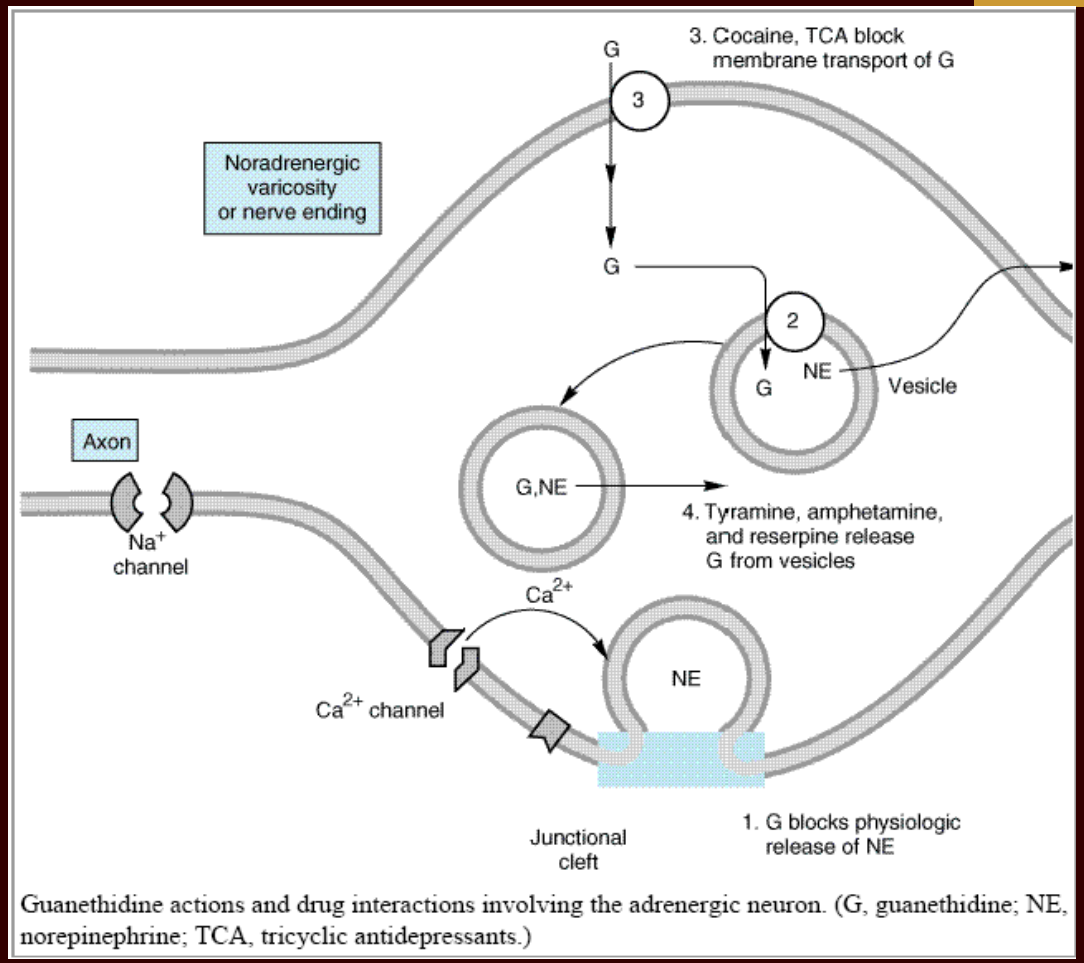
Blok Adrenergik di Ujung Saraf

- Contoh : Reserpin, Guanethidin
- Mekanisme kerja :

  - menghambat transport NE ke vesikel sinap : reserpin

  - mengosongkan dan memblok pelepasan NE dari tempat penyimpanannya : guanethidin

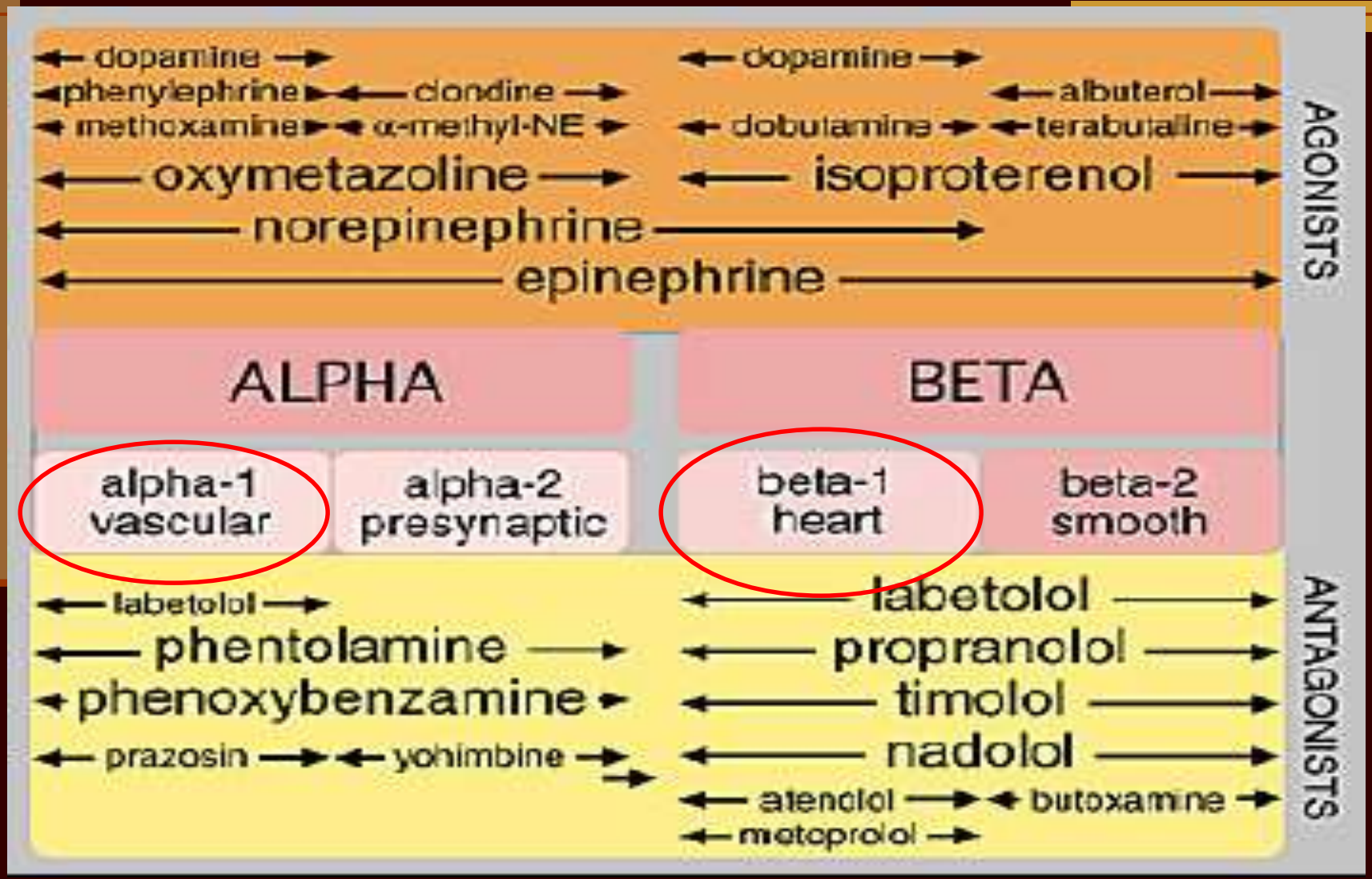
- inhibit uptake of NE into storage vesicle (also DA, 5-HT) → leads to depletion of transmitter stores (peripheral & CNS action)
- ES: sedation, mental depression, Parkinsonism, gastric acid secretion→ ulcer



Guanethidine actions and drug interactions involving the adrenergic neuron. (G, guanethidine; NE, norepinephrine; TCA, tricyclic antidepressants.)

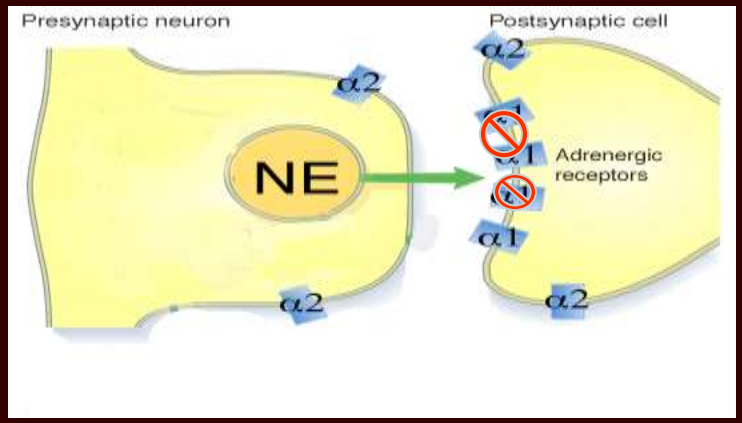
Katzung 9th ed

Blok Adrenergik di Reseptor Adrenergik



BLOK ADRENERGIK DI RESEPTOR - α1

- Contoh : Prazosin, Oxazosin, Terazosin
- Site of action : otot polos vaskuler perifer



- Mekanisme kerja :

  memblok reseptor α-1 → relaksasi otot polos vaskuler→dilatasi vaskuler→resistensi vaskuler ↓.
- Efek pd COP <<</(-)

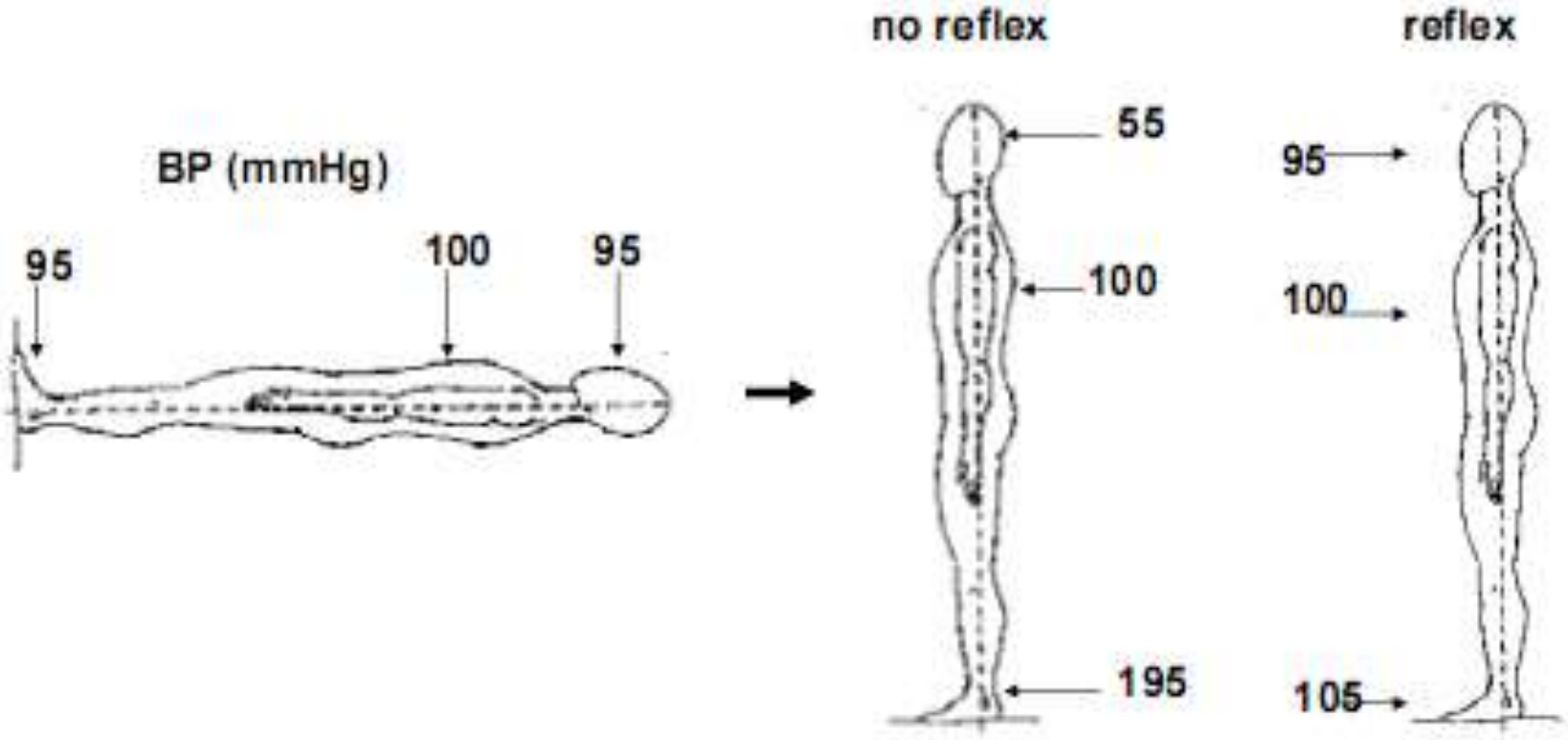
- ES : nausea, postural hipotensi s.d synkope
- KI : hipersensitif
- reflex tachycardia (-);
- Awali dg dosis kecil
- Pilihan utk : pt dg DM, asma dg / tanpa hiperkolesterol, mild-moderate HT
- Sering dikombinsi dg diuretic, β antagonist

Postural (Orthostatic) Hypotension

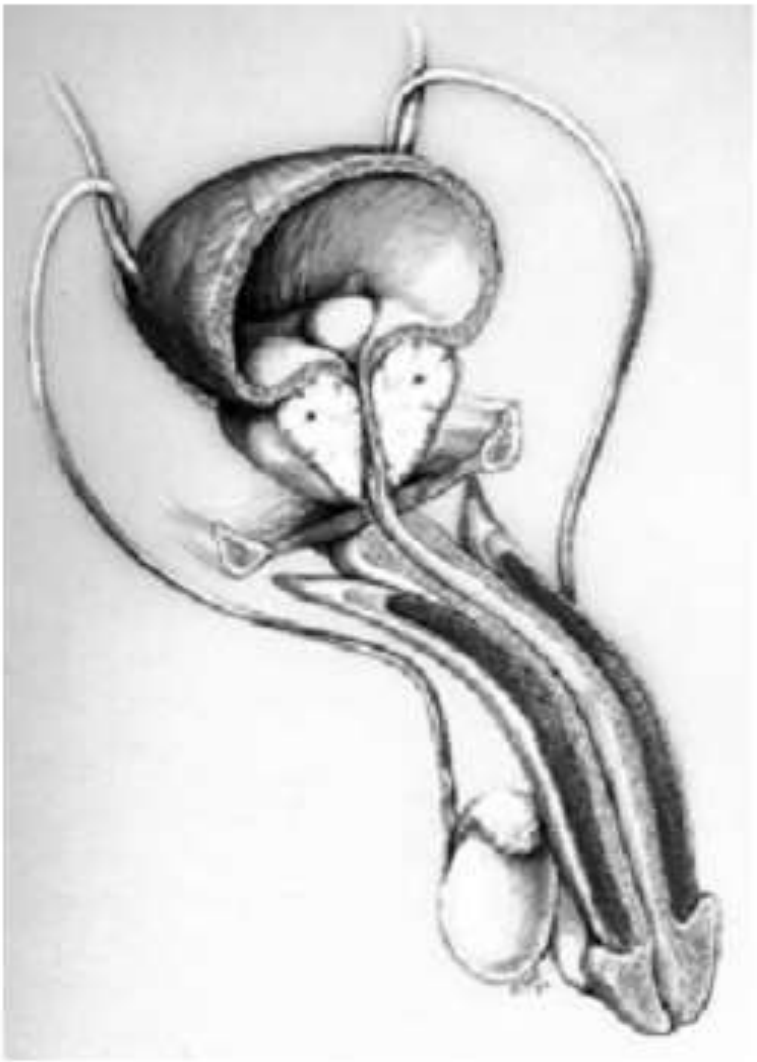
- Venous return falls
- Blood pressure falls

- Sympathetic activity increases
  - Constriction of great veins
  - Constriction of arteries (↑ TPR)
  - Increase in heart rate

reflex mediated



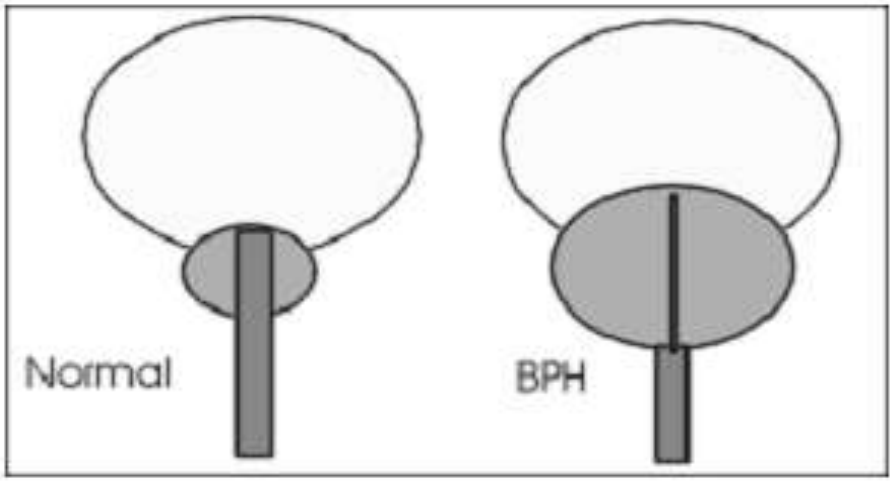
Benign Prostrate Hypertrophy (BPH)



Enlarged prostrate leads to difficulty in urination

Alpha-receptor blocker (ie Prazosin) cause prostrate relaxation

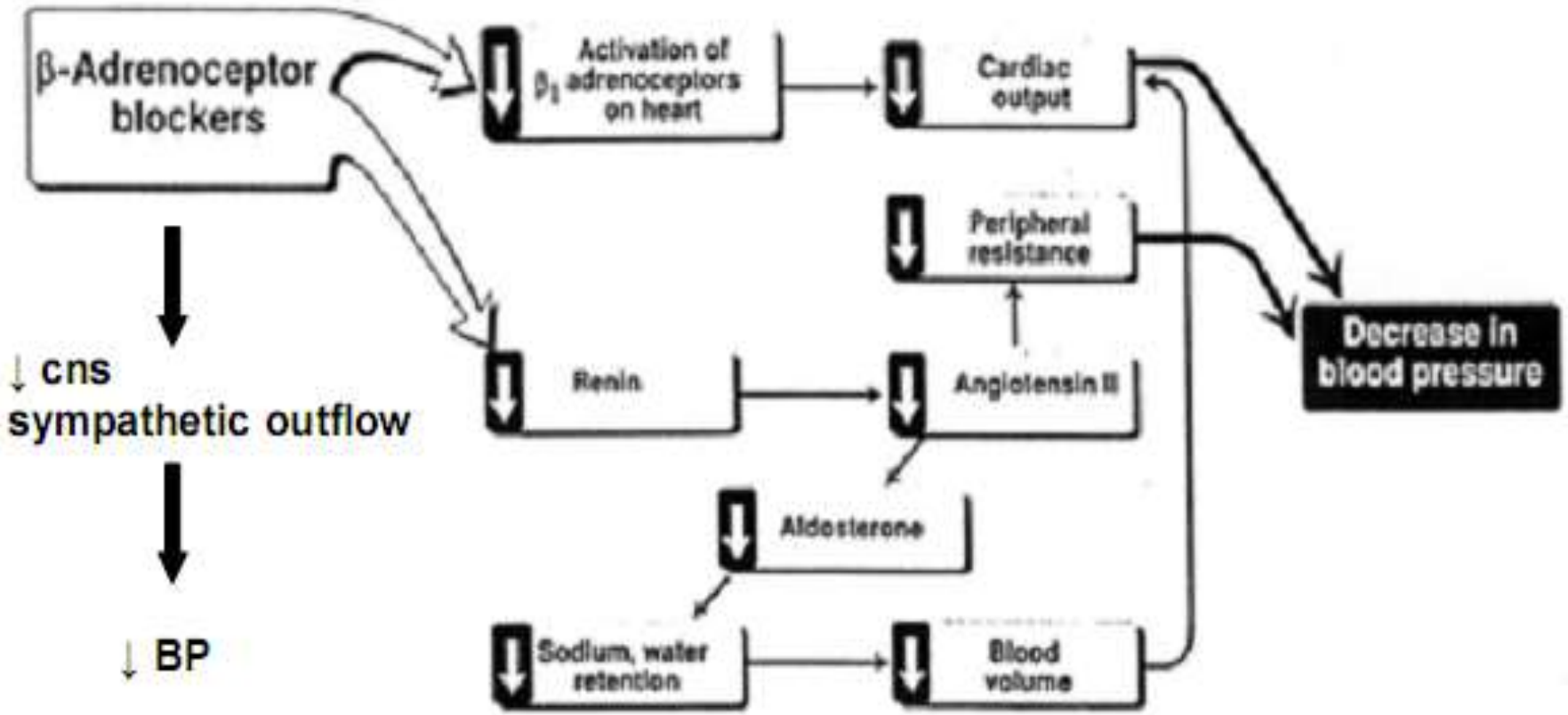
Relaxed prostrate improves urination



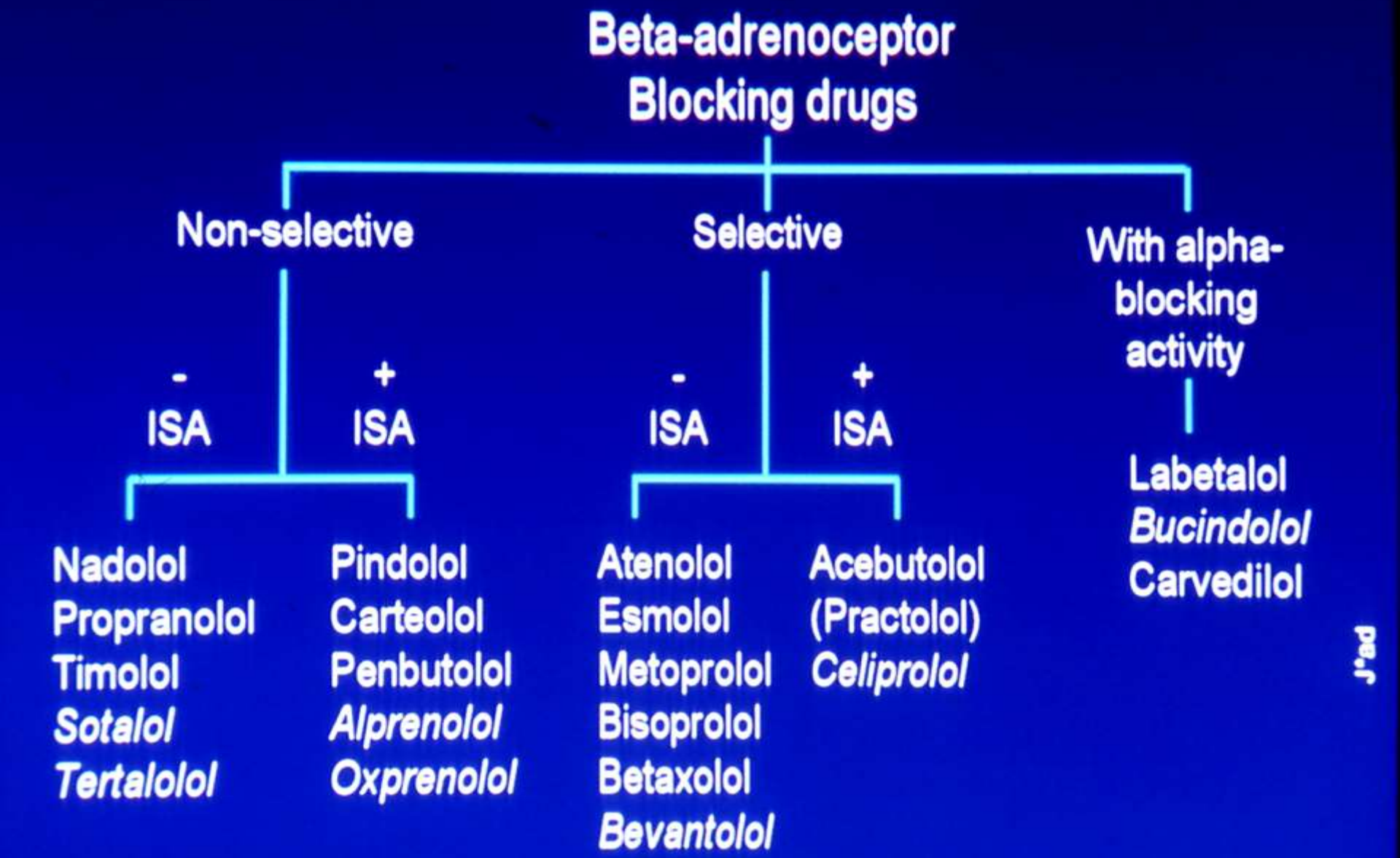
Blok Adrenergik di Reseptor-β

- β–blocker non selektif : Propanolol
  β1–blocker selektif : Atenolol, Metoprolol
- **Mekanisme kerja** :
  - Blok reseptor β1 di jantung →HR dan kontraktilitas jantung ↓ → CO ↓ → TD ↓
  - Blok reseptor β1 di ginjal → release renin ↓
  - Blok reseptor β2 presinap → release NE ↓
  - Blok reseptor β di CNS →aliran simpatis ↓ →tonus vaskuler ↓
- **Efek samping** :
  insomnia, unpleasant dreams (bisa nembus BBB), erectile dysfunction, akral dingin (hambat vasodilatasi β2), TG ↑ dan HDL ↓ (hambat metabolisme lemak di hepar),arritmia, hipoglikemia
- **Kontraindikasi** :
  asthma,bradycardia berat, AV block, severe unstable LV failure, diabetes

Beta-Blockers - Mechanism of Action



Classification of β-adrenoceptor Blockers Based on Cardioselectivity & ISA



Vasodilator

- Calcium Channel Blocker
- Vasodilator Oral : hidralazin, minoksidil
- Vasodilator parenteral
- Agonis R/Dopamin-1

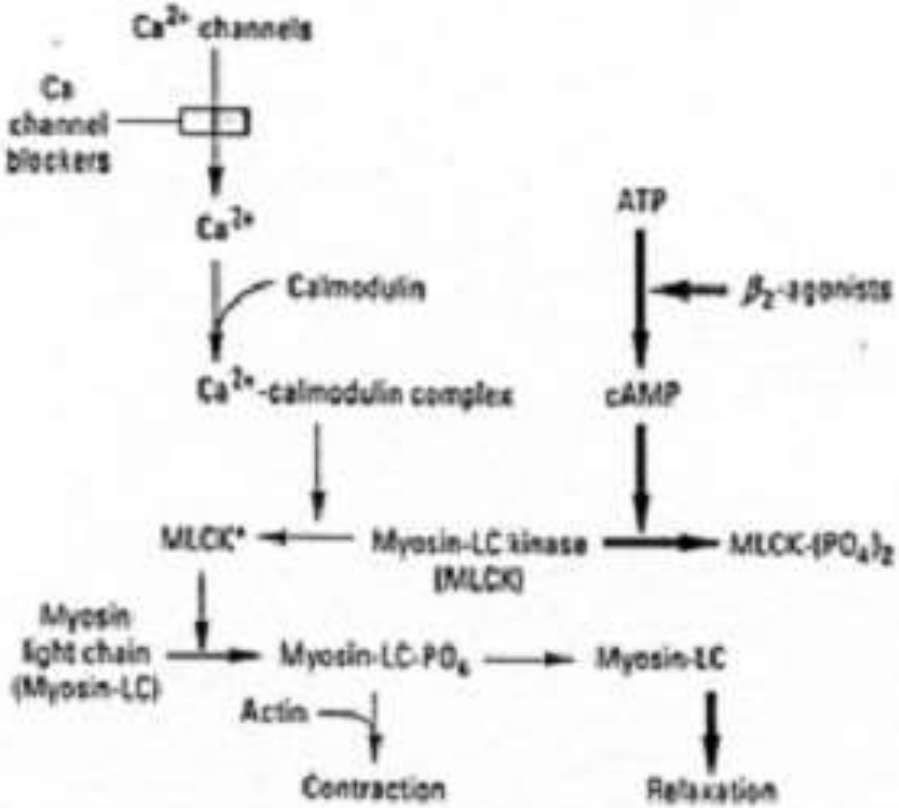
Mechanism of Smooth Muscle Relaxation	Examples
Reduction of calcium influx via L-type channels	Dihydropyridines: vessels > heart Verapamil, diltiazem: heart ≥ vessels
Release of nitric oxide from drug or vascular endothelium	Nitroprusside, hydralazine
Hyperpolarization of vascular smooth muscle through opening of potassium channels	Minoxidil sulfate, diazoxide
Activation of dopamine D_1 receptors	Fenoldopam

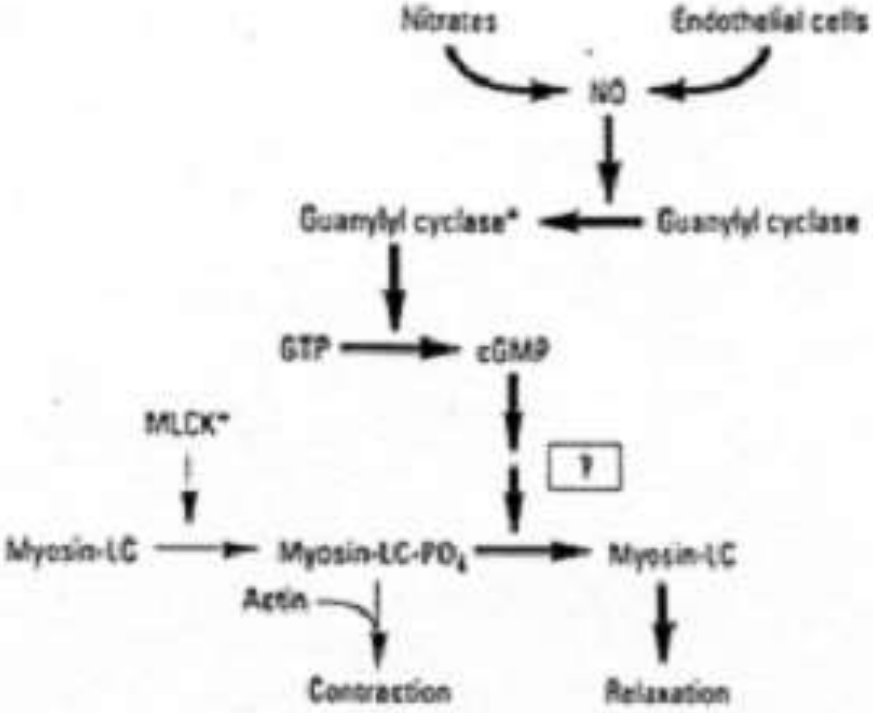
Actions of Vasodilators

Ca^{++} Antagonists
Verapamil
Nifedipine

Open K^+ Channels
Minoxidil
Diazoxide

Nitric Oxide (NO)
Hydralazine
Nitroprusside
Nitrates





Calcium Channel Blocker

- Contoh : Nifedipine, Verapamil, Diltiazem
- **Mekanisme kerja** : memblok kanal Ca type-L → hambat influk Ca ke intrasel →kadar Ca intrasel ↓ → * kontraktilitas sel otot polos vaskular ↓→ vasodilatasi → resistensi perifer ↓

  *pd otot jantung →kontraktilitas, HR ↓

Nifedipine:
- mainly arteriole vasodilation, little direct cardiac effect
- may cause reflex tachycardia, flushing, peripheral edema

Verapamil:
- some cardiac slowing, constipation
- caution in digitalized patients (↑ digoxin levels)

Diltiazem:
- similar to Verapamil / Nifedipine (less)
- both cardiac and vascular actions

VASODILATOR : RELEASE NO

hidralazin (p.o),

- EDRF / Nitric oxide (NO) / cGMPinvolvement
- dilate arterioles but not veins
- TPR↓, BP↓→reflex tachycardia
- ES :

  -reflectory symp activation

  -headache, nausea, sweating, flushing

  -palpitations, HR↑→ angina

  -lupus reaction (mainly in slow acetylators)

nitroprussid (i.v)

- melepaskan NO → stimulasi guanilil siklase → cGMP di otot polos →relaxation of vascular smooth
- dilates arterial (TPR) and venous vessels
- venous return ↓, reflex tachy
- Indikasi : hypertensive emergency, acute CHF
- ES : metab acidosis, arrhythmias, severe hypotensio

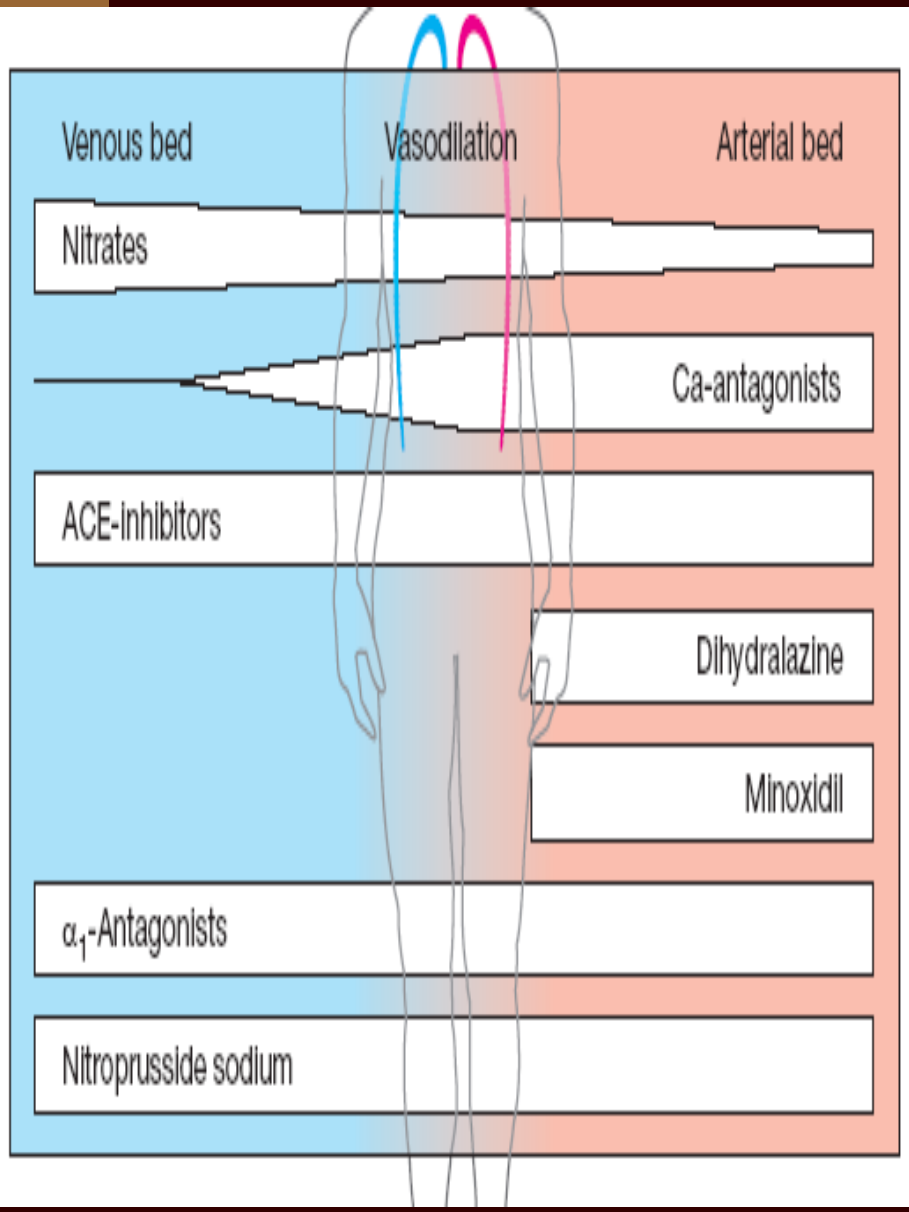
VASODILATOR : OPEN K-CHANNEL

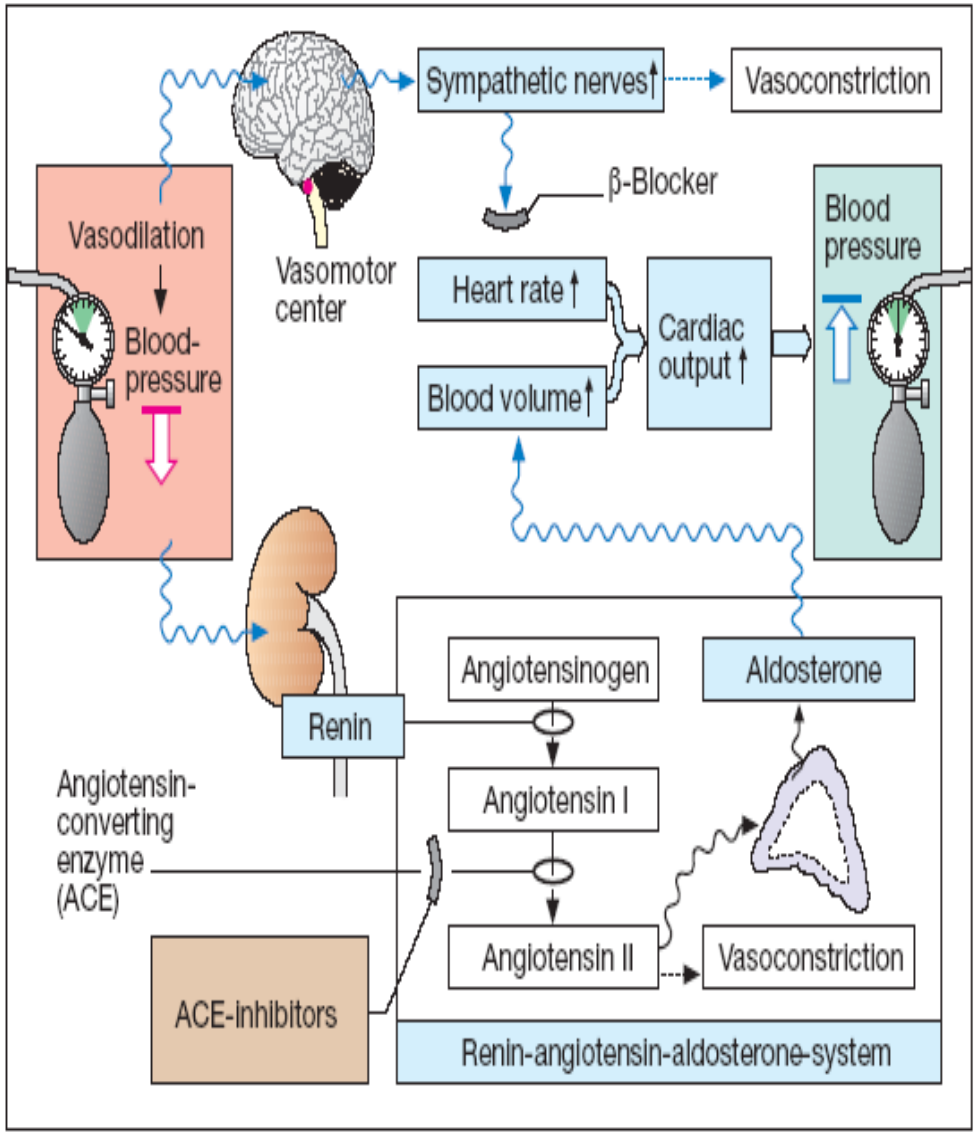
minoksidil (p.o),

- membuka kanal K^+ → hiperpolarisasi , stabilisasi membran saat resting potensial →relaksasi otot polos vask
- dilates arterioles, not veins
- ES : reflex sympathetic stimulation, fluid retention (value in combination therapy), hypertrichosis

diazoksid (i.v)

- dilates arteriolar vessels
- TPR↓→ reflex ↑HR→CO↑
- inhibits insulin release (via opening K beta cell membrane)
- similar structure as thiazidediuretics but no diuretic effect

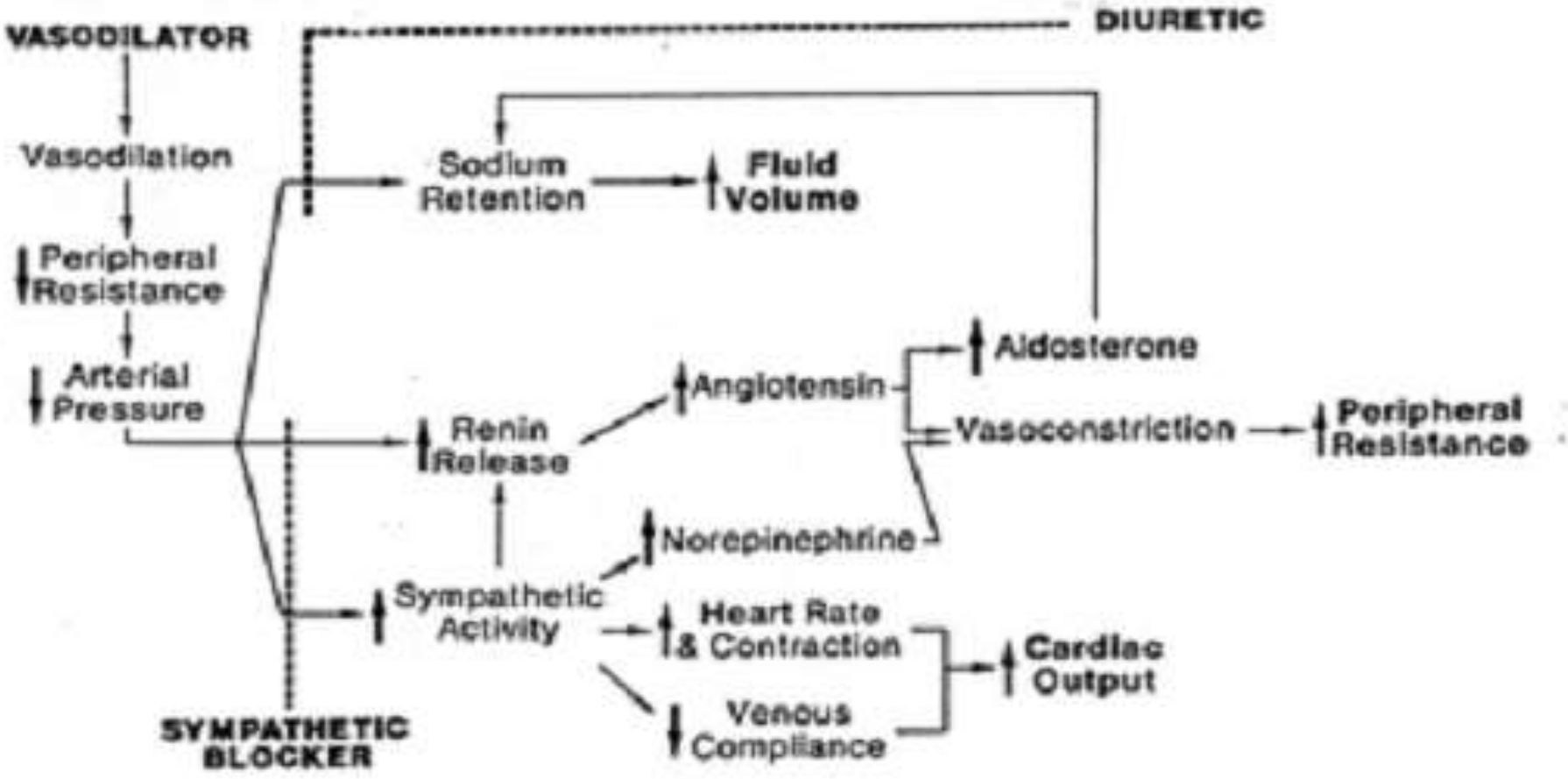




B. Counter-regulatory responses in hypotension due to vasodilators

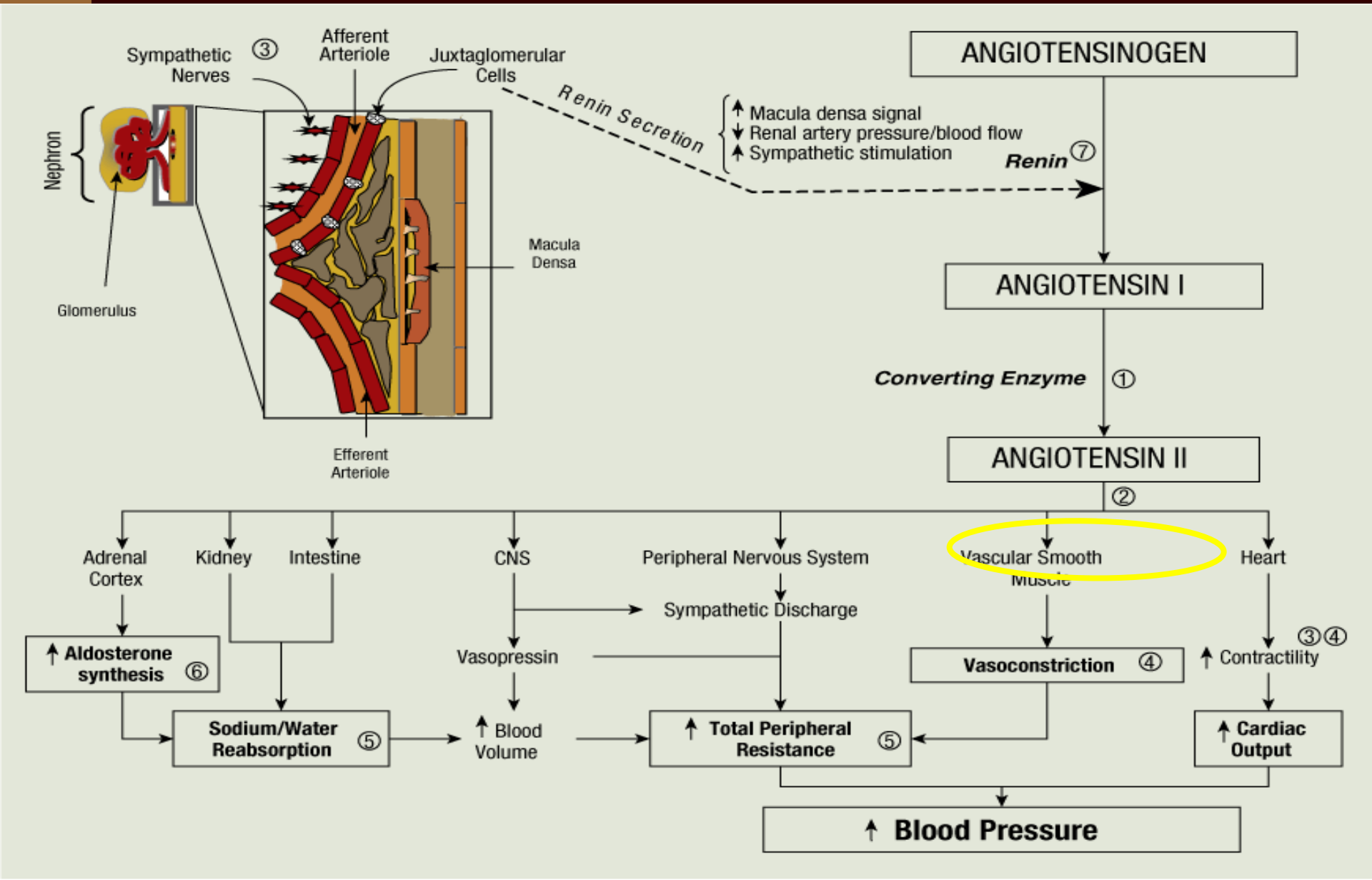
Action of Vasodilators

eg. Calcium blockers, Hydralazine, Minoxidil etc

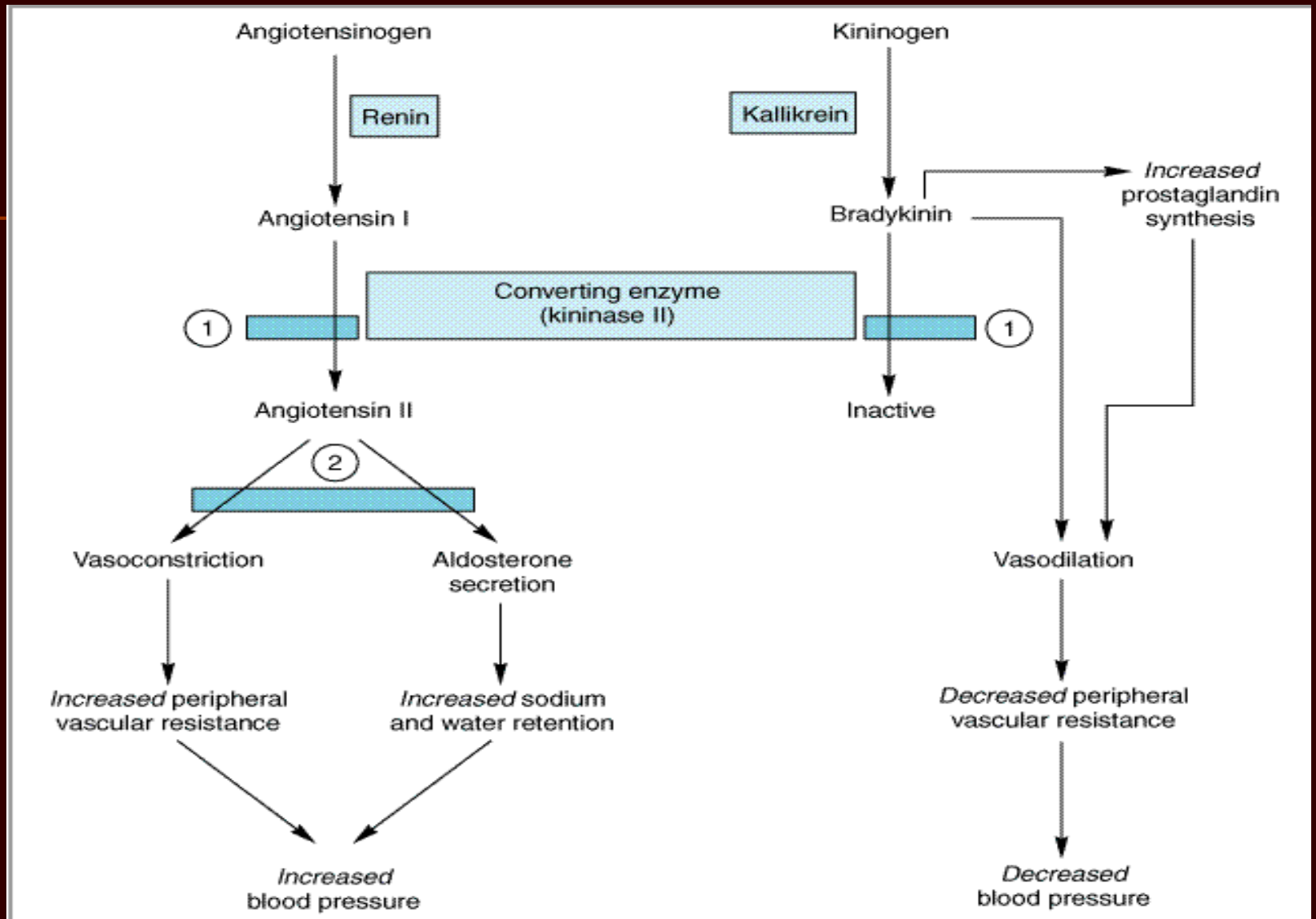


Primary and secondary effects of vasodilator therapy in essential hypertension and the manner by which diuretic and beta-adrenergic blocker therapy can overcome the undesirable secondary effects. (From Koch-Weser J. Vasodilator drugs in the treatment of hypertension. *Arch Intern Med* 1974;133:1017–1027, copyright 1974, American Medical Association.)

SISTEM RENIN-ALDOSTERON ANGIOTENSIN

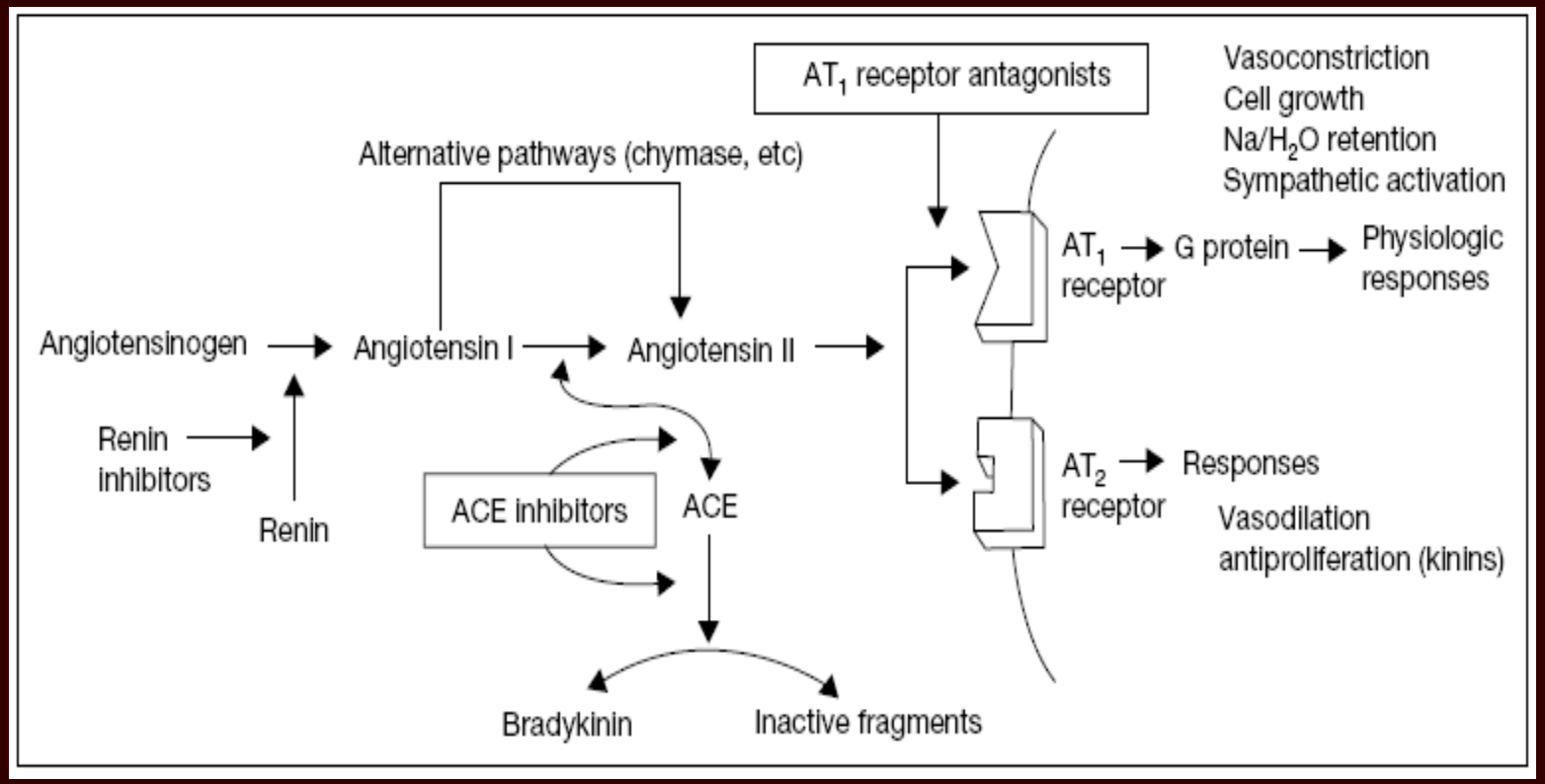


DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A pathophysiologic Approach,* 7th Edition: Http://www.accesspharmacy.com



Sites of action of ACE inhibitors and angiotensin II receptor blockers. ①Site of ACE blockade. ② Site of receptor blockade.

Katzung 9ed



Kidney and Blood Pressure Regulation

ACE Inhibitor

- **Contoh** : Captopril , Enalapril , Ramipril, Lisinopril
- **Mekanisme kerja :**

  hambat Angiotensin Converting Enzyme shg :
  - hambat pembentukan AII → AII merupakan salah satu vasokonstriktor kuat.
  - kadar bradikinin ↑ →menstimulasi release NO dan prostasiklin → vasodilatasi.
- **Keuntungan** : respon kompensasi (-)→ mencegah remodelling jantung dan vaskuler

Angiotensin II Receptor Blocker (ARB)

- **Contoh** : Irbesartan, Losartan , Valsartan, Candesartan
- **Mekanisme kerja** : menduduki R/ AII (AT1).

  AT1 tdpt di otot polos vaskuler, korteks adrenal, ginjal, dan otak. Obat ini tidak mempunyai efek pada metabolisme bradykinin. Menghambat AII lebih kuat dp ACE inhibitors karena ada enzim lain yang juga bisa menghasilkan AII.

ES ACE- INHIBITOR & ARB

- severe hypotension in hypovolemic patients, bilateral renal artery stenosis
- hyperkalemia (↑[K^+])
- dry cough (ACEI), dry mouth, skin rushes, glossitis
- altered sense of taste due to loss of Zinc (10-20%)
- tetrogenic, contraindicated during the second and third trimester of pregnancy
- drug interactions with potassium-sparing diuretics, NSAID

ACE INHIBITOR

↓TPR, CO unchanged, HR unchanged

- no reflex ↑HR, probably due to resetting (↓) of baroreceptor reflex sensitivity
- improves intrarenal hemodynamics (good for diabetes)
- reverse cardiac hypertrophy seen in HT
- less effective with age and in Afro-Americans
- need to take before or after meals

ARB

- competitive inhibitor of AgII at its receptor
- has a weak agonist activity (depends on circulating AgII level)
- diagnostic value (AgII dependency of HT)

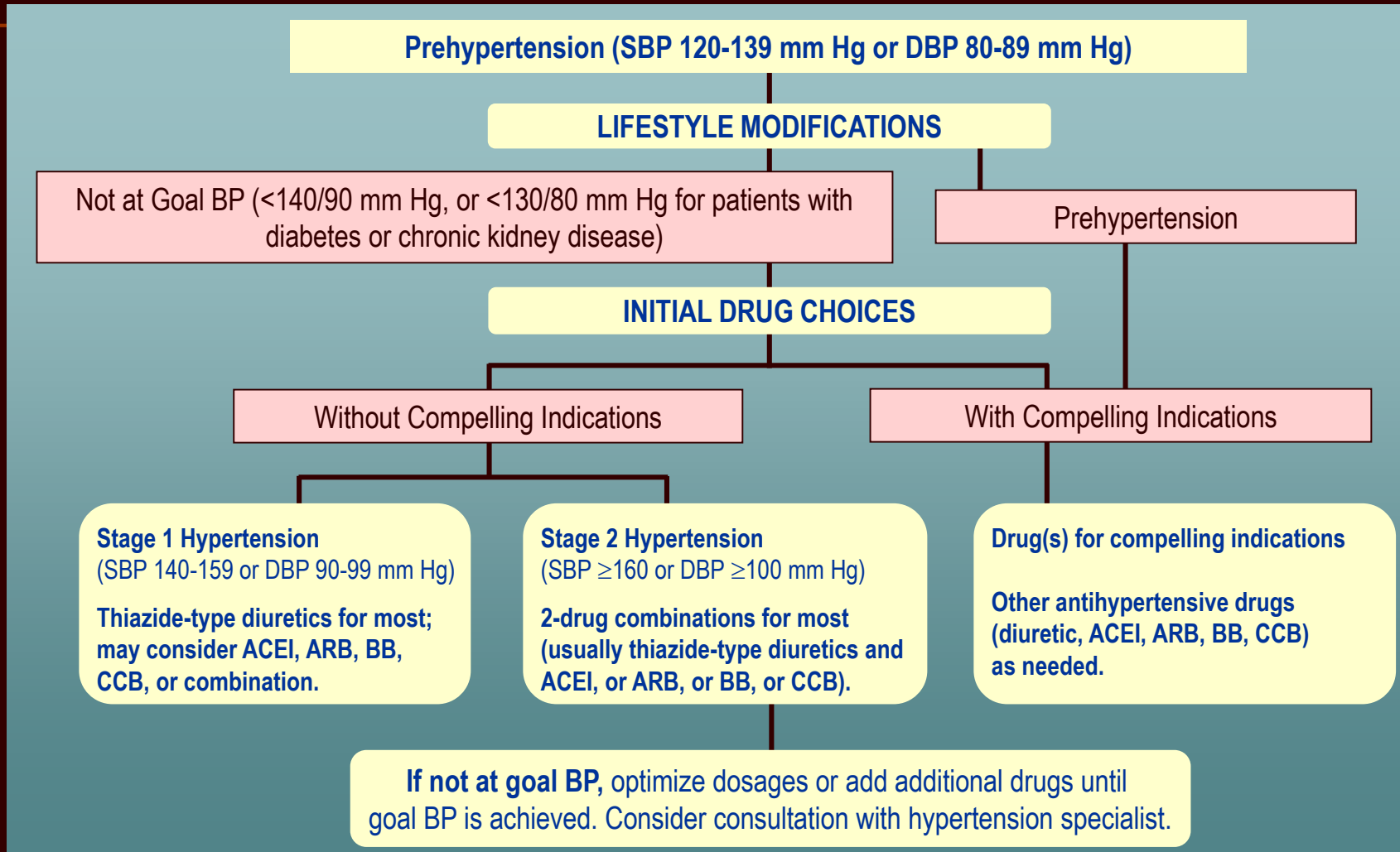
Direct Renin Inhibition Inhibits the Entire Renin System[1-4] Aliskiren

Class	PRA	Ang I	Ang II
ACEI	↑	↑	↓
ARB	↑	↑	↑
Direct Renin Inhibitor (DRI)	↓	↓	↓

Increased peptide levels have not been shown to overcome the blood pressure–lowering effect of these agents.
ACEI, angiotensin-converting enzyme inhibitor; Ang, angiotensin; ARB, angiotensin receptor blocker;
PRA, plasma renin activity.

1. Johnston CI. *Blood Press Suppl*. 2000;1:9(suppl 1):9-13.
2. Widdop RE et al. *Hypertension*. 2002;40:516-520.
3. Fabiani ME et al. *Angiotensin II Receptor Antagonists*. 2001:263-278.
4. Lin C et al. *Am Heart J*. 1996;131:1024-1034.

JNC 7:
Algorithm for Treatment of Hypertension



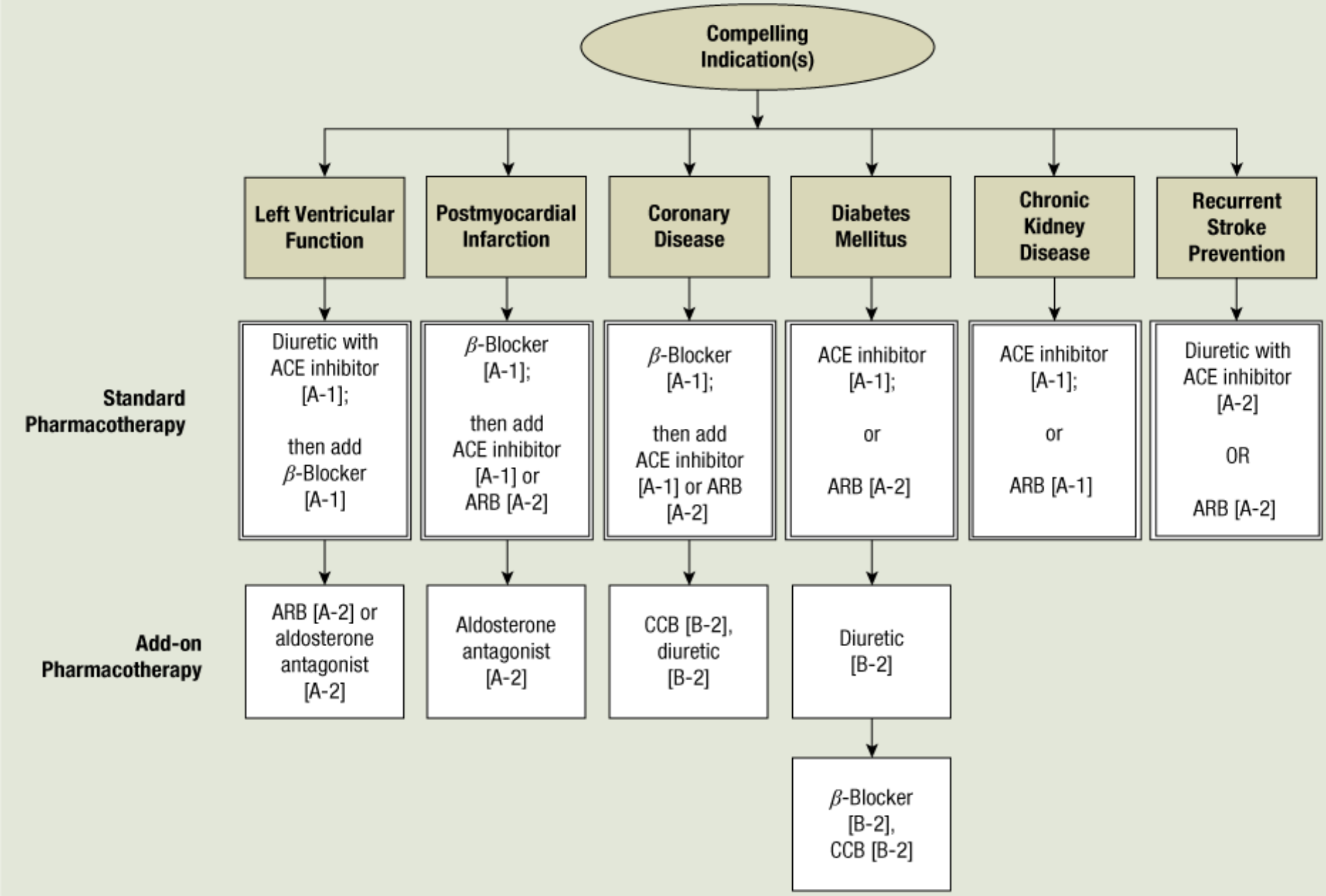
Adapted from NHBPEP CC. 2003. NIH Publication No. 03-5233.

- **Compelling indications:**
  - → Ischemic Heart Disease
  - → Recent ST Segment Elevation-MI or non-ST Segment Elevation-MI
  - → Left Ventricular Systolic Dysfunction
  - → Cerebrovascular Disease
  - → Left Ventricular Hypertrophy
  - → Non Diabetic Chronic Kidney Disease
  - → Renovascular Disease
  - → Smoking

JNC 7: Classification and Management of Blood Pressure for Adults

BP Classification	SBP* (mm Hg)	DBP* (mm Hg)	Lifestyle Modification	Initial Drug Therapy: Without Compelling Indications	Initial Drug Therapy: With Compelling Indications
Normal	<120	and <80	Encourage		
Prehypertension	120–139	or 80–89	Yes	No antihypertensive drug indicated.	Drug(s) for compelling indications.
Stage 1 hypertension	140–159	or 90–99	Yes	Thiazide-type diuretic for most. May consider ACEI, ARB, BB, CCB, or combination.	Drug(s) for compelling indications.
Stage 2 hypertension	≥160	or ≥100	Yes	Two-drug combination for most (usually thiazide-type diuretic and ACEI or ARB or BB or CCB).	Other antihypertensive drugs (diuretic, ACEI, ARB, BB, CCB) as needed.

JNC 7. May 2003. NIH publication 03-5233.



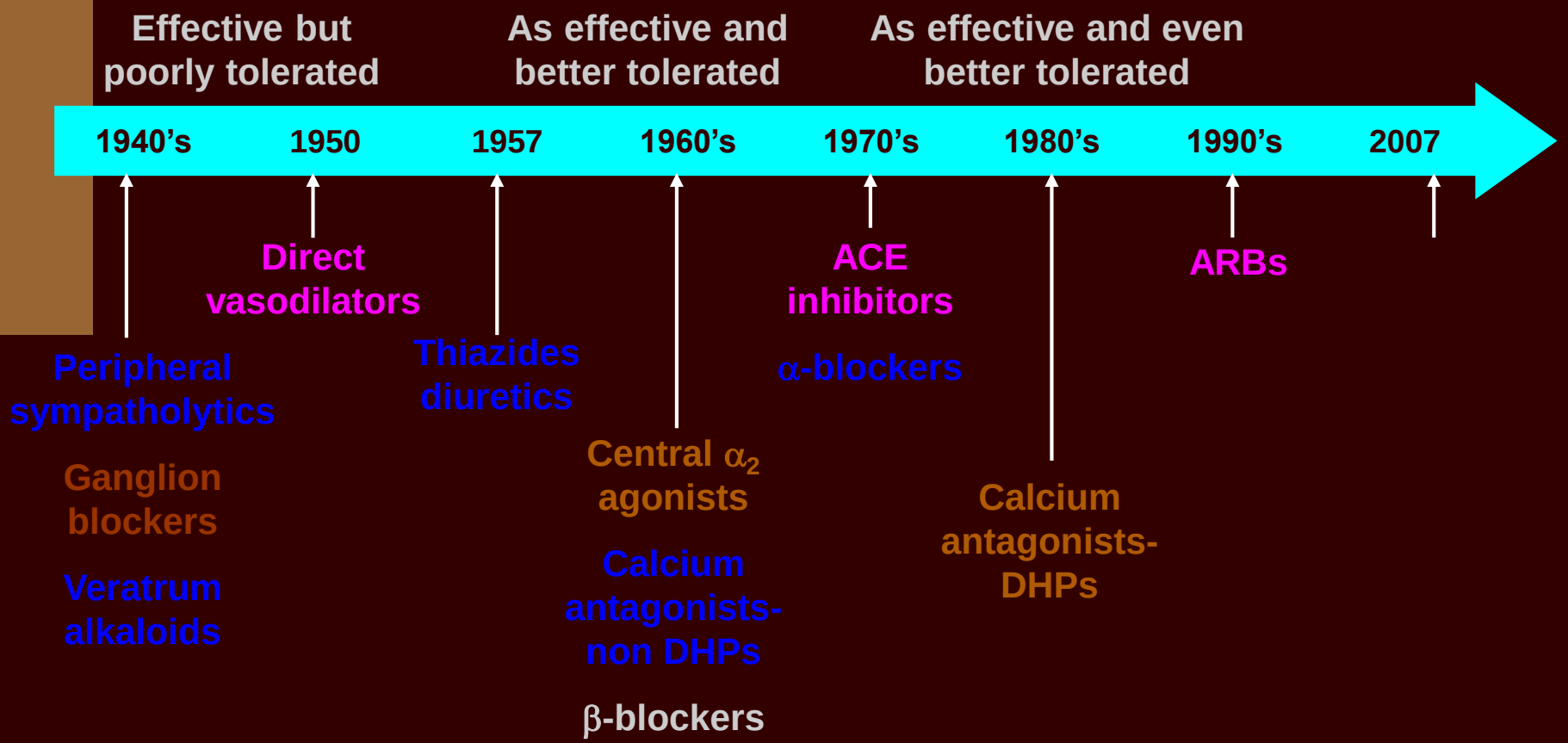
DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A pathophysiologic Approach,* 7th Edition: Http://www.accesspharmacy.com

JNC 7: Compelling Indications for Individual Antihypertensive Drug Classes

Compelling Indication*	Recommended Drugs					
	DIURETIC	BB	ACEI	ARB	CCB	Aldo ANT
Heart failure	●	●	●	●		●
Post-MI		●	●			●
High coronary disease risk	●	●	●		●	
Diabetes	●	●	●	●	●	
Chronic kidney disease			●	●		
Recurrent stroke prevention	●		●			

*Compelling indications for antihypertensive drugs are based on benefits from outcome studies or existing clinical guidelines; the compelling indication is managed parallel with the BP.
ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; Aldo ANT = aldosterone antagonist; BB = beta-blocker; CCB = calcium channel blocker.
Adapted from NHBPEP Coord. 2003. NIH Publication No. 03-5233.

Perkembangan Terapi Antihypertensi



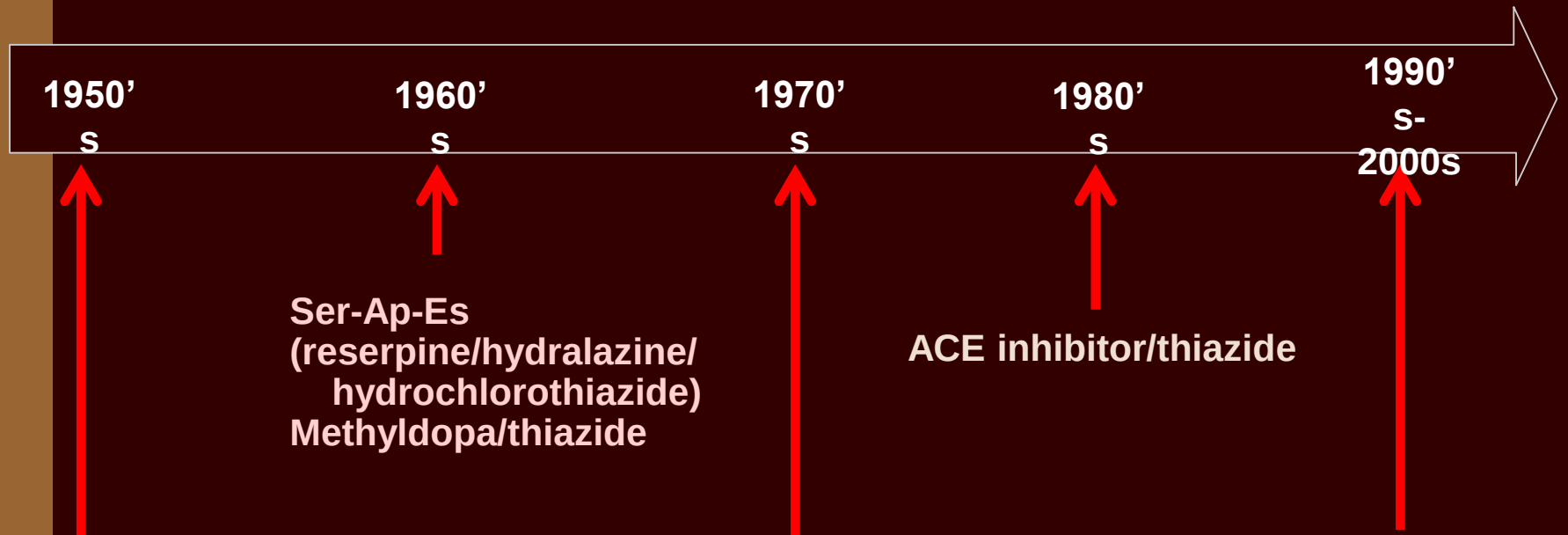
Penggunaan *Dual Combinations*

Kolom 1	Kolom 2
• Thiazide diuretic • Long-acting calcium channel blocker *	• Beta adrenergic blocker • ACE Inhibitor • ARB

Tujuan : meningkatkan efek hipotensif

kombinasikan obat pada kolom 1 dengan obat pd kolom 2

Terapi Antihipertensi Kombinasi



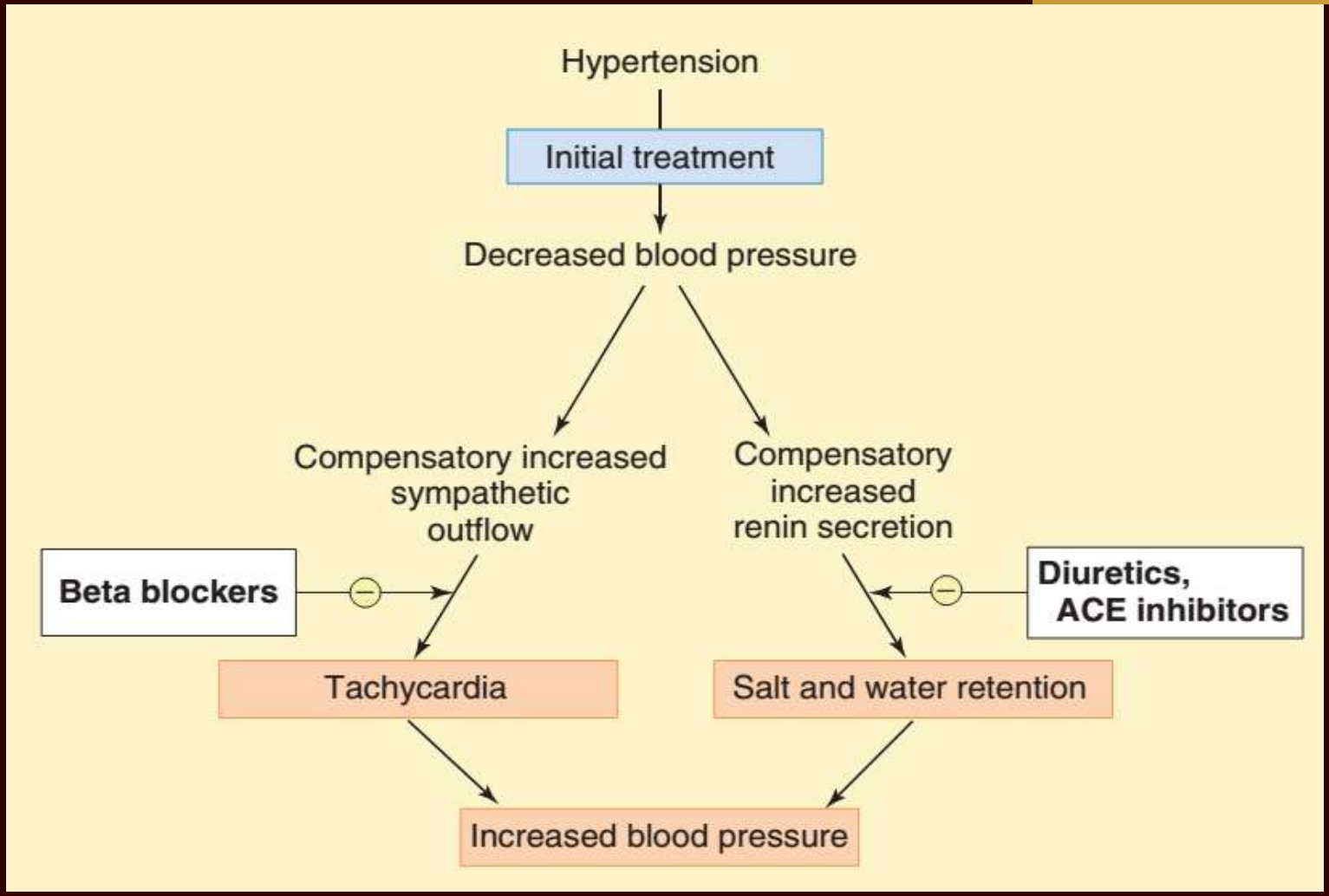
Penyebab Kurangnya Respon terhadap Terapi Hipertensi

- Pseudoresisten : salah diagnosa, pseudohipertensi pada lansia, salah pemeriksaan
- Penderita tidak patuh dalam menjalani terapi (biaya, instruksi tdk jelas, ESO, pemakaian tdk praktis)
- Volume overload (asupan garam berlebih, kerusakan ginjal yg berat, retensi cairan akibat penurunan TD, terapi diuretik tidak adekuat.
- Kondisi tertentu : perokok, obesitas, resistensi insulin, peminum alkohol, serangan cemas/panik
- Obat : dosis terlalu rendah, kombinasi tdk cocok
- Interaksi obat : simpatomimetik, nasal decongestan, apetite suppressan, kokain, kafein, kontrasepsi oral, steroid adrenal,antidepressan, NSAID
- Mekanisme kompensasi

Respon kompensasi thd anti HT

Class and Drug	Compensatory Responses
Diuretics (thiazides, loop agents)	Minimal
Sympathoplegics	
Centrally acting (clonidine, methyldopa)	Salt and water retention
Ganglion blockers (obsolete)	Salt and water retention
Alpha$_1$-selective blockers	Salt and water retention, slight tachycardia
Beta blockers	Minimal
Vasodilators	
Hydralazine	Salt and water retention, moderate tachycardia
Minoxidil	Marked salt and water retention, marked tachycardia
Nifedipine, other calcium channel blockers	Minor salt and water retention
Nitroprusside	Salt and water retention
Fenoldopam	Salt and water retention, tachycardia
Angiotensin-renin antagonists (ACE inhibitors, ARBs, aliskiren)	Minimal

Mekanisme Gagal Terapi Hipertensi akibat Respon Kompensasi



Krisis Hipertensi

- Hipertensi Gawat (Emmergency)
- Hipertensi Darurat (Urgency)

Hipertensi Emergensi

TD Diastolik > 120 mmHg disertai dengan satu atau lebih kondisi akut.

- Pendarahan intra pranial, ombotik CVA atau pendarahan subarakhnoid.
- Hipertensi ensefalopati.
- Aorta diseksi akut.
- Oedema paru akut.
- Eklampsi.
- Feokhromositoma.
- Funduskopi KW III atau IV.
- Insufisiensi ginjal akut.
- Infark miokard akut, angina unstable.
- Sindroma kelebihan Katekholamin yang lain :
  - Sindrome withdrawal obat anti hipertensi.
  - Cedera kepala.
  - Luka bakar.
  - Interaksi obat.

Penatalaksanaan HT Emergensi

- TD harus turun dalam **hitungan menit**, ok ada ancaman kerusakan target organ
- Obat parenteral (i.v):

  - sodium nitroprussid
  - nitrogliserin
  - diltiazem HCl
  - hidralazin

HYPERTENSIVE EMERGENCY

Drug	Dose	Onset (min)	Duration (min)	Adverse Effects	Special Indications
Sodium nitroprusside	0.25–10 mcg/kg/min intravenous infusion (requires special delivery system)	Immediate	1–2	Nausea, vomiting, muscle twitching, sweating, thiocyanate and cyanide intoxication	Most hypertensive emergencies; caution with high intracranial pressure, azotemia, or in chronic kidney disease
Nicardipine hydrochloride	5–15 mg/h intravenous	5–10	15–30; may exceed 240	Tachycardia, headache, flushing, local phlebitis	Most hypertensive emergencies except acute heart failure; caution with coronary ischemia
Clevidipine butyrate	1-2 mg/h intravenous infusion; may double dose every 90 sec initially; maximum: 32 mg/h; typical maintenance dose: 4 to 6 mg/h	2-4	5-15	Headache, syncope, dyspnea, nausea, vomiting	Most hypertensive emergencies except severe aortic stenosis; caution with heart failure
Fenoldopam mesylate	0.1–0.3 mcg/kg/min intravenous infusion	< 5	30	Tachycardia, headache, nausea, flushing	Most hypertensive emergencies; caution with glaucoma

DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: Pharmacotherapy:A Pathophysiologic Approach, 7th Edition: http://www.accesspharmacy.com/

HYPERTENSIVE EMERGENCY

Drug	Dose	Onset (min)	Duration (min)	Adverse Effects	Special Indications
Nitroglycerin	5–100 mcg/min intravenous infusion	2–5	5–10	Headache, vomiting, methemoglobinemia, tolerance with prolonged use	Coronary ischemia
Hydralazine hydrochloride	12–20 mg intravenous 10–50 mg intramuscular	10–20 20–30	60–240 240–360	Tachycardia, flushing, headache vomiting, aggravation of angina	Eclampsia
Labetalol hydrochloride	20–80 mg intravenous bolus every 10 min; 0.5–2.0 mg/min intravenous infusion	5–10	180–360	Vomiting, scalp tingling, bronchoconstriction, dizziness, nausea, heart block, orthostatic hypotension	Most hypertensive emergencies except acute heart failure
Esmolol hydrochloride	250–500 mcg/kg/min intravenous bolus, then 50–100 mcg/kg/min intravenous 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	Aortic dissection; perioperative

DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: Pharmacotherapy:A Pathophysiologic Approach, 7th Edition: http://www.accesspharmacy.com/

Hipertensi Urgensi

- Hipertensi berat dengan TD Diastolik > 120 mmHg, tetapi dengan minimal atau tanpa kerusakan organ sasaran dan tidak dijumpai keadaan pada tabel I.
- KW I atau II pada funduskopi.
- Hipertensi post operasi.
- Hipertensi tak terkontrol / tanpa diobati pada perioperatif.

- Penanganan

  - dalam **hitungan jam**

  - Obat HT diberikan secara per oral, sublingual

Monitoring Antihypertensives

Class	Parameters
Diuretics	blood pressure BUN/serum creatinine serum electrolytes (K+, Mg2+, Na+) uric acid (for thiazides)
β-Blockers	blood pressure heart rate
Aldosterone antagonists ACE inhibitors Angiotensin II receptor blockers Direct Renin inhibitors	blood pressure BUN/serum creatinine serum potassium
Calcium channel blockers	blood pressure heart rate

DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: Pharmacotherapy:A Pathophysiologic Approach, 7th Edition: http://www.accesspharmacy.com/

RESUME

Treatment strategy

Initial step: Nonpharmacological
- sodium intake, weight loss, physical activity, alcohol, stress,
- overview of medication, other risk factors

IF NOT ENOUGH OR INITIALLY HIGHER STAGE OF HT

Drug therapy:
- start with drug therapy (frontline agents, thiazide 1st)
- choose the proper medication for lifestyle
- β-blockers efficacy may decrease as age increases
- β-blockers are less effective in smokers
- blacks respond less to β-blockers and ACE inhibitors
- β-blockers and ACE inhibitors better in ↑ plasma renin
- use long-lasting drugs (↑compliance)

Start with monotherapy:
- if necessary add second, or third agent (from different class)

Good Combotherapy: vasodilator with either β-blocker or diuretic

Subclass	Mechanism of Action	Clinical Applications	Pharmacokinetics	Toxicities, Interactions
Diuretics (see also Chapter 15)				
Hydrochlorothiazide, chlorthalidone	Block Na^+/Cl^- transporter in distal convoluted tubule	Hypertension, mild edema	Oral Duration: 8–12 h	Hypokalemia, hyperglycemia, hyperuricemia, hyperlipidemia
Furosemide	Block $Na^+/K^+/2Cl^-$ transporter in thick ascending limb	Hypertension, heart failure, edema, hypercalcemia	Oral, parenteral Duration: 2–4 h	Hypokalemia, hypovolemia, ototoxicity
Sympathoplegics				
Centrally acting				
Clonidine	Agonist at α_2 receptors • in CNS this results in *decreased* SANS outflow	Hypertension	Oral and transdermal Oral duration: 2–3 days • transdermal 1 wk	Sedation, danger of severe rebound hypertension if suddenly stopped
Methyldopa	Prodrug converted to methylnorepinephrine in CNS, with effects like clonidine	Hypertension	Oral Duration: 12–24 h	Sedation, induces hemolytic antibodies
Ganglion blockers				
Hexamethonium	Obsolete prototype nicotinic acetylcholine (ACh) receptor blocker in ganglia • blocks all ANS transmission	None	Oral, parenteral; no CNS effect	Severe orthostatic hypotension, constipation, blurred vision, sexual dysfunction
Trimethaphan: IV, obsolete short-acting parenteral ganglion blocker for hypertensive emergencies, controlled hypotension				
Mecamylamine: oral ganglion blocker, several hours' duration, enters CNS				

Subclass	Mechanism of Action	Clinical Applications	Pharmacokinetics	Toxicities, Interactions
Postganglionic neuron blockers				
Reserpine	Blocks vesicular pump (VMAT) in adrenergic neurons	Obsolete in hypertension, still used in Huntington's disease	Oral Duration: 5 days	Sedation • severe psychiatric depression (high doses)
Guanadrel: blocks release of norepinephrine, depletes stores; oral, long duration; severe orthostatic hypotension (*guanethidine*, a similar, older drug, was withdrawn in the United States)				
Alpha blockers				
Prazosin	Selective α_1 blocker • reduces peripheral vascular resistance, prostatic smooth muscle tone	Mild hypertension, benign prostatic hyperplasia	Oral Duration: 6–8 h	First dose orthostatic hypotension
Doxazosin, terazosin: similar to prazosin but longer duration of action				
Beta blockers				
Propranolol	Prototype nonselective β blocker • reduces cardiac output • possible secondary reduction in renin release	Hypertension • many other applications (see Chapter 10)	Oral, parenteral Duration: 6–8 h (extended release forms available)	Bronchospasm in asthmatics • excessive cardiac depression, sexual dysfunction, sedation, sleep disturbances
Atenolol, metoprolol, others: like propranolol but β_1-selective; fewer adverse effects				
Labetalol, carvedilol: combined α and β blockade; oral and parenteral				

Subclass	Mechanism of Action	Clinical Applications	Pharmacokinetics	Toxicities, Interactions
Vasodilators, oral				
Calcium channel blockers				
Nifedipine, many other dihydropyridines	Prototype L-type calcium channel blockers • combine moderate vascular effect with weak cardiac effect	Hypertension, angina	Oral Duration: 6–24 h	Constipation; risk of myocardial infarction from prompt-release nifedipine
Verapamil, diltiazem: oral and parenteral; also used in arrhythmias; greater cardiodepressant effects than dihydropyridines; verapamil blocks P-glycoprotein transporter (see Chapter 4)				
Older oral vasodilators				
Hydralazine	Probably causes release of nitric acid (NO) by endothelial cells • causes arteriolar dilation	Hypertension; also used in heart failure in combination with isosorbide dinitrate	Oral Duration: 6–8 h	Tachycardia, salt and water retention, lupus-like syndrome
Minoxidil	Prodrug, sulfate metabolite opens K^+ channels, causes arteriolar smooth muscle hyperpolarization and vasodilation	Severe hypertension • male-pattern baldness	Oral, topical Duration: 6–8 h	Marked tachycardia, salt and water retention • hirsutism

Subclass	Mechanism of Action	Clinical Applications	Pharmacokinetics	Toxicities, Interactions
Vasodilators, parenteral				
Nitroprusside	Releases NO from drug molecule	Hypertensive emergencies • acute cardiac decompensation	Parenteral only Duration: minutes • requires constant infusion	Excessive hypotension; tachycardia, salt and water retention • prolonged infusion may cause thiocyanate and cyanide toxicity
Diazoxide	K^+ channel opener in smooth muscle, secretory cells	Hypertensive emergencies • hypoglycemia due to insulin-secreting tumors	Parenteral for hypertension, oral for insulinoma	Hyperglycemia • edema, excessive hypotension
Fenoldopam	D_1 agonist • causes arteriolar dilation	Hypertensive emergencies	Parenteral only, very short duration	Excessive hypotension; tachycardia, salt and water retention; angina
Renin antagonist				
Aliskiren	Renin inhibitor • reduces angiotensin I synthesis	Hypertension	Oral Duration: 12 h	Angioedema, renal impairment
Angiotensin antagonists				
ACE inhibitors				
Captopril	ACE inhibitor • reduces angiotensin II synthesis	Hypertension, diabetic renal disease, heart failure	Oral Half-life: 2.2 h but large doses provide duration of 12 h	Cough • hyperkalemia • teratogen
Benazepril, enalapril, lisinopril, others: like captopril but longer half-lives				
Angiotensin II receptor blockers (ARBs)				
Losartan	Blocks AT_1 receptors	Hypertension; combination used in heart failure	Oral Duration: 6–8 h	Hyperkalemia • teratogen
Candesartan, irbesartan, others: like losartan				

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