Antihypertensive Agents

Essential Hypertension

In 90–95% of cases the cause isn't known = ESSENTIAL HYPERTENSION

Symptomatic treatment, i.e. reduce blood pressure. No real cure yet.

Identifiable Causes of Secondary Hypertension

- Sleep apnea
- Drug-induced or related causes
- Chronic kidney disease
- Primary aldosteronism
- Renovascular disease
- Chronic steroid therapy and Cushing's syndrome
- Pheochromocytoma
- Coarctation of the aorta
- Thyroid or parathyroid disease

Prevalence

- High in this country: 50% of adults, 60% of whites, 71% of African Americans, 61% Mexican Americans over the age of 60
- More prevalent in men than in women
- Highest prevalence in elderly African-American females

Complications

- Cardiovascular system
- CNS
- Renal system
- Retinal damage

Target Organ Damage

- Heart
  - Left ventricular hypertrophy
  - Coronary artery disease
  - Myocardial infarcts
  - Heart failure
- Brain
  - Stroke or transient ischemic attacks
- Chronic kidney disease, kidney failure
- Retinopathy

Contributing Factors

- Obesity
- Stress
- Lack of exercise
- Diet (excess dietary salt)
- Alcohol intake
- Cigarette smoking

National Heart Lung Blood Institute National High Blood Pressure Education Program

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7, 2003)

http://www.nhlbi.nih.gov/guidelines/hypertension/index.htm

Why Guidelines for Hypertension?

50 million people with hypertension in USA 10 years ago – 1:4 overall (Currently 31 %), half of people > age 60

Only 1 in 2 on drug treatment to lower BP

Only 1 in 4 age 18-74 controlled to <140/<90 in USA

New BP Goals

- <140/<90 and lower if tolerated
- <130/<80 in diabetics
- <130/<85 in cardiac failure
- <130/<85 in renal failure
- <125/<75 in renal failure with proteinuria>1.0 g/24 hours

Highlights of Current Guidelines

JNC, WHO/ISH, BHS, Canada, and More

- New aggressive treatment strategies based on a patient's medical profile
- Treat to goal and hit the target, not to be satisfied with less

Treatment Overview

- Goals of therapy
- Lifestyle modification
- Pharmacologic treatment
  - Algorithm for treatment of hypertension
- Classification and management of BP for adults
- Follow-up and monitoring

Lifestyle Modifications

- Reduce weight to normal BMI (<25kg/m^2): 5-20 mmHg/10kg loss
- DASH eating plan: 8-14 mmHg
- Dietary sodium reduction: 2-8 mmHg
- Increase physical activity: 4-9 mmHg
- Reduce alcohol consumption: 2- 4 mmHg

DASH Diet

***D**ietary*

***A**pproaches*

to

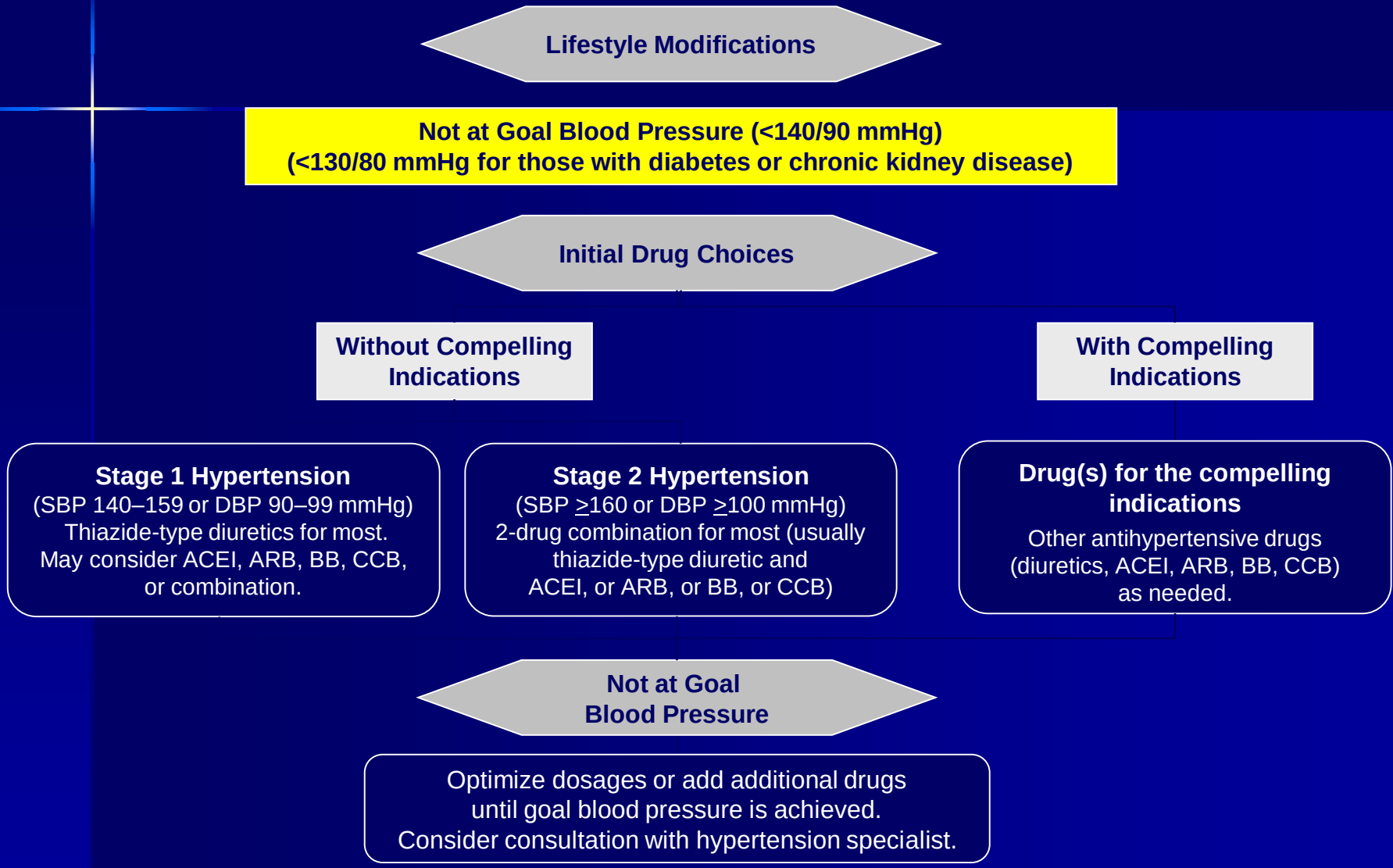
***S**top*

***H**ypertension*

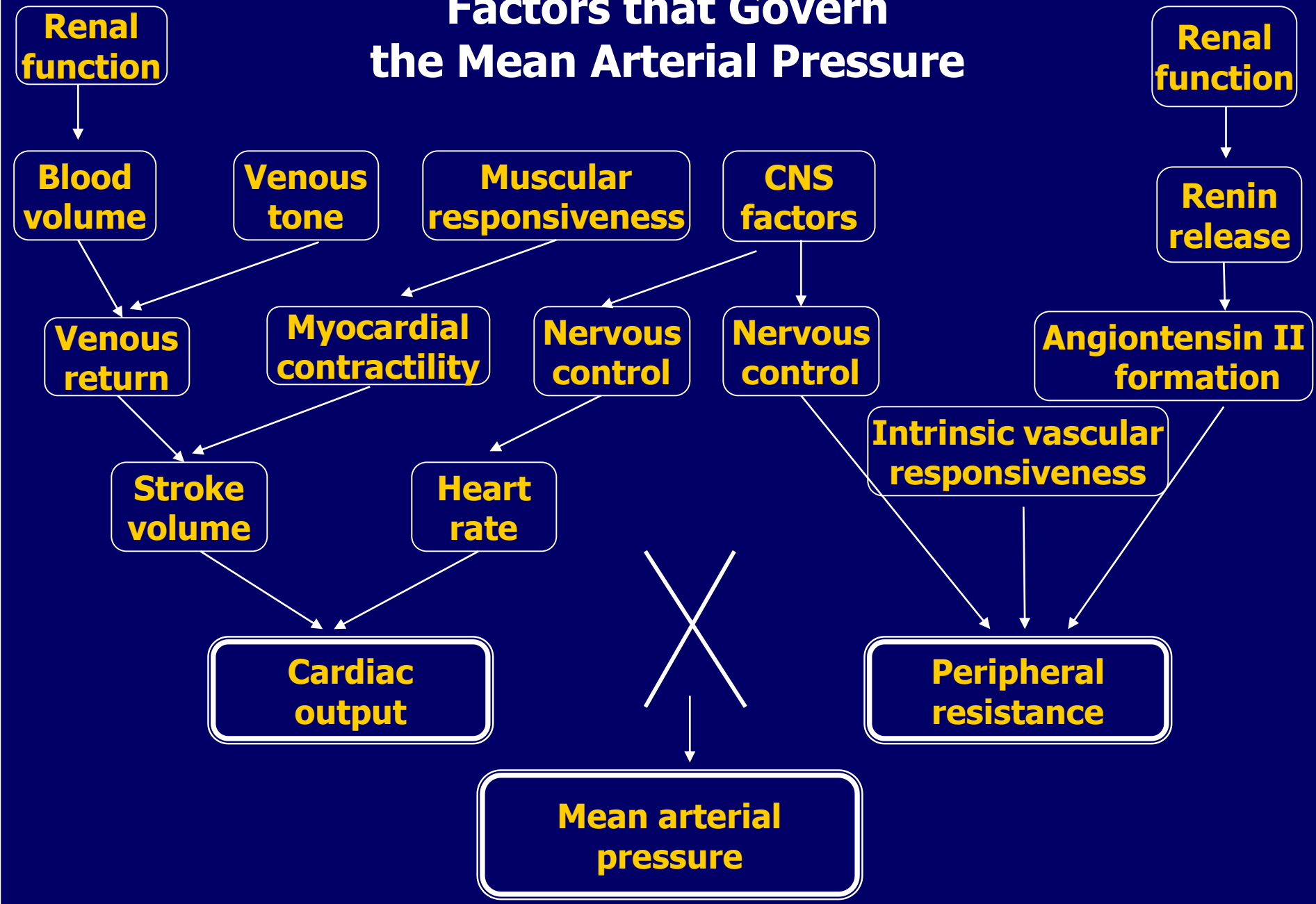
- **Emphasizes: Fruits, vegetables, low fat dairy foods, and reduced sodium intake**
- **Includes whole grains, poultry, fish, nuts**
- **Reduced amounts of red meat, sugar, total and saturated fat, and cholesterol**

Sacks FM et al: NEJM 344;3-10, 2001

Algorithm for Treatment of Hypertension



Factors that Govern the Mean Arterial Pressure



Mean Arterial Pressure

MAP = CO X PVR

CO = HR X SV

SNS

Blood volume
Heart contactility
Venous tone

myogenic tone
vascular responsivenes
nervous control

vasoactive metabolites
endothelial factors
circulating hormones

Antihypertensive Drugs Classification

- Diuretics
- Agents affecting adrenergic function
- Vasodilators
- Agents affecting Renin Angiotensin System (RAS)

Diuretics

Used as initial therapy alone or in combination with drugs from other groups

Adverse effects: renin secretion due to volume and Na depletion

- **Thiazides:** chlorothiazide, hydrochorothiazide
- **Loop Diuretics:** furosemide, bumetanide, ethacrynic acid
- **Potassium sparing diuretics:** spironolactone, triamterene, amiloride

About Diuretics

Antihypertensive and Lipid Lowering
Diuretics have been virtually unsurpassed in preventing the cardiovascular complications of hypertension.

Diuretics enhance the antihypertensive efficacy of multidrug regimens, can be useful in achieving BP control, and are more affordable than other anti-hypertensive agents.

Despite these findings, diuretics remain under-utilized.

Agents that affect adrenergic function

a) Agents that prevent adrenergic transmission (reserpine, guanethedine, guanadrel)

b) Selective alpha-1 adrenergic receptor blockers (prazosin, terazosin, doxazosin)

c) Beta-adrenergic blocking agents (propranolol and others)

d) Agents that act on the CNS (methyldopa, clonidine, guanabenz, guanfacine)

a) Agents that prevent adrenergic transmission: Reserpine (Serpasil)

- **Mechanism:** depletes neurotransmitters (NE, DA, 5HT) in the storage vesicle of the central and peripheral nerve endings
- **Main effects:** depress SNS function centrally and peripherally → decreased HR, contractility and PVR
- **Adverse effects:** depression, insomnia, nightmares, ulcers, diarrhea, abdominal cramping, nasal stuffiness, orthostatic hypotension, dry mouth, impotence
- **Pharmacokinetics:** onset is slow and full effect is seen in weeks
- **Use:** infrequently

a) Agents that prevent adrenergic transmission: **Guanethedine (Ismelin)**

Mechanism: Depletes the nerve ending of NE in the periphery

Main effects: decrease in PVR and decrease in HR $\rightarrow$ decrease in BP

Adverse effects: Orthostatic hypotension, Na^+ and water retention. Other side-effects similar to reserpine except the CNS effects

Pharmacokinetics: Poorly absorbed from the G.I. Onset slow (1-2 weeks). Metabolites excreted in urine

Use: Not used anymore because of severe side effects

a) Agents that prevent adrenergic transmission: Guanadrel (Hylorel)

Mechanism and main effects Similar to guanethidine

Adverse effects are less than gunethidine: less orthostatic hypotension, less diarrhea, less effect on sexual function.

Pharmacokinetics: better absorption, rapid onset, shorter duration of action than guanethidine

b) Selective alpha-1 adrenergic receptor blockers (prazosin-Minipres, terazosin-Hytrin, doxazosin-Cardura)

They favorably influence plasma lipid profile, and do not interfere with glucose metabolism.

Mechanism: block α1 receptors in vasculature

Main effects: decreased PVR → decrease BP

Adverse effects: 1st dose phenomenon, fluid retention, dizziness, headache

Pharmacokinetics: $t_{1/2}$= 4.5, 12, 20, respectively

Use: used in stage 1 and stage 2 HT in combination with a diuretic and a β-blocker

c) Beta-adrenergic blocking agents (see table)

Classification

- **Nonselective (1st generation)**
- **Cardioselective (β-1 selective, 2nd generation)**
- **β–blockers with intrinsic sympathomimetic activity (ISA)**
- **With additional CV actions (3rd generation)**

Proposed mechanisms:

Block cardiac β1 receptors → lower CO

Block renal β1 receptors → lower renin, lower PVR

Decrease SNS output

Non-Selective	β1-Selective (in low dose)	Intrinsic (ISA)
Propranolol	Metoprolol	Pindolol
Timolol (hydrophylic)	*Acebutolol	Acebutolol
*Pindolol	Atenolol (hydrophylic)	Penbutolol
*Penbutolol	Betaxolol	Cartelol
*Cartelol	Bisoprolol	Labetalol (α & β)
*Labetalol (α & β)		
Carvedilol (α & β)		
*Carteolol		
	(Diabetes and Asthma)	*(Reynaud's)*

*has ISA as well

3rd generation

Propranolol (Inderal)

Mechanism:
Block cardiac β1 receptors → lower CO
Block renal β1 receptors → lower renin, lower PVR

Main effects: decrease HR and PVR

Adverse effects: bradycardia, depression, β2 blockade in airways, glucose and lipid metabolism, vasoconstriction in extremities

Pharmacokinetics: GI, 30-50% metabolized in the first-pass in liver. $T_{1/2}$: 3-5 hours, Slow- release propranolol available

Use: used in stage 1 and 2 HT alone or in combinations with a diuretic and/or vasodilator

Drug Interactions: verapamil, diltiazem, digitalis (caution AV Block)

Labetalol (Trandate)

- A combined alpha-1, beta-1, and beta-2 blocker. Beta blocking action is more prominent. It also has some ISA property.
- Can be given i.v. for hypertensive emergencies

d) Agents that act on the CNS

(α–methyldopa-Aldomet, clonidine- Catapres, guanabenz-Wytensin, guanfacine-Tenex)

Favorable effect: lower PRA

Mechanism: α-me-dopa metabolized to α-me-norepinephrine, an α-2 agonist, that suppresses SNS output from the CNS. Others are α-2 agonist themselves.

Main effects: decreases PVR and HR

Adverse effects: sedation, drowsiness, dry mouth, impotence, bradycardia, withdrawal syndrome (rebound HT)) **Pharmacokinetics:** oral or parenteral, transdermal; $T_{1/2}$ = 2, 10, 6, 14-17 h, respectively

Use: stage 1 and 2 HT

Vasodilator Drugs

Common adverse effects: fall in BP → reflex tachycardia, also fall in BP → renin → Na/H_2O retention

a) Calcium entry blockers (nifedipine and others)

b) Potassium channel openers (minoxidil, diazoxide i.v., pinacidil)

c) Direct acting vasodilators (hydralazine, Na-nitroprusside i.v.)

a) Calcium entry blockers

(mechanism: inhibit Ca entry through L-type voltage gated channels)

Phenylalkylamines: verapamil

Benzothiazepines: diltiazem

Dihydropyridines: nifedipine, nicardapine, isradapine, felodopine, amlodipine

Nifedipine (Procardia)

Mech: selective blockade of vascular Ca channels

Main effect: vasodilatation → lower PVR → lower BP

Adverse effects: headache, flushing, nausea, ankle edema, dizziness, reflex tachycardia with short acting version (now have Procardia SR)

(no reflex tachycardia with verapamil and diltiazem)

Use: Hypertension (more effective in African-Americans), angina. Not useful as an antiarrhythmic drug

Verapamil and Diltiazem

Mechanism: Blockade of Ca channels in the vasculature, heart muscle and the AV node

Main effects: same as nifedipine group

Adverse effects: Similar to nifedipine except that they do not cause reflex tahycardia

Drug interactions: Caution for AV block with beta blockers, and digitalis

Use: Hypertension, angina, arrhythmias

b) Potassium channel openers (minoxidil-Loniten, diazoxide i.v.-Hyperstat, pinacidil)

Mechanism: open K-channels of vascular smooth muscle cells → K-efflux → hyperpolarization → vasodilatation

Main effect: vasodilation → lower PVR → lower BP

Adverse effects: reflex tachycardia, Na and fluid retention, (minoxidil: hirsutism-Rogaine. Diazoxide: hyperuricemia, hyperglycemia –used in hypoglycemia)

Use: Diazoxide i.v. in hypertensive emergencies

c) Direct acting vasodilators (**Na-nitroprusside i.v. Nipride**)

Mechanism: metabolite is nitric oxide → cGMP. NO is a rapid acting venous and arteriolar vasodilator

Main effect: vasodilation → lower PVR → lower BP

Adverse Effects: Reflex tachycardia, severe hypotension, possible cyanide poisoning

Pharmacokinetics: rapid acting, i.v. drip, short plasma half-life

Use: Hypertensive emergencies

c) Direct acting vasodilators (**hydralazine-Apresoline**)

Mechanism: Direct vasodilator of arterioles

Main effect: vasodilation → lower PVR → lower BP

Adverse effects: reflex tachycardia, Na retention, hirsutism, lupus–like syndrome

Pharmacokinetics: oral, slow onset

Use: with a beta blocker and a diuretic

Angitensin Converting Enzyme

- Angiotensin I → (ACE) Angiotensin II
- Bradykinin (vasodilator) → (ACE) Inactive peptide

Agents that affect RAS

a) ACE inhibitors

captopril, enalapril, lisinopril

b) Angiotensin II receptor blockers (ARB)

losartan, valsartan, irbesartan

a) ACE inhibitors (captopril-Capoten, enalapril-Vasotec, lisinopril-Privinil, rampiril-Altace)

No adverse effects on plasma lipids, glucose, sexual function. Drug of choice in diabetes-related early stage proteinuria. Contraindicated in pregnancy.

Mechanism: inhibit ACE → low circulating Ang II → decreased PVR

Main effects: decreased PVR → decreased BP

Adverse effects: skin rash, taste, cough, hyperkalemia

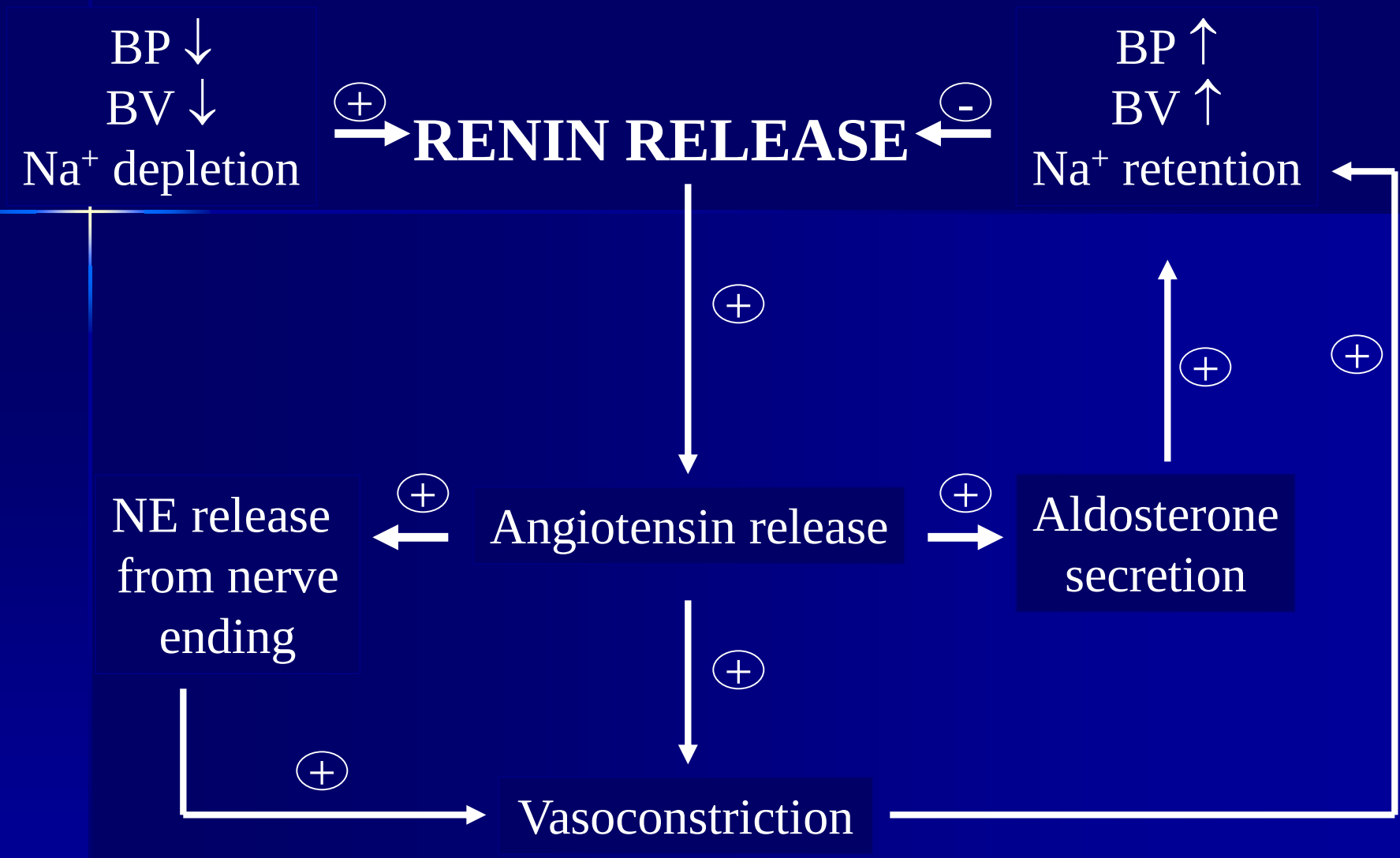
Pharmacokinetics: $T_{1/2}$ = 3, 11, 12, respectively

Use: used in stage 1 and 2 HT; also for congestive heart failure

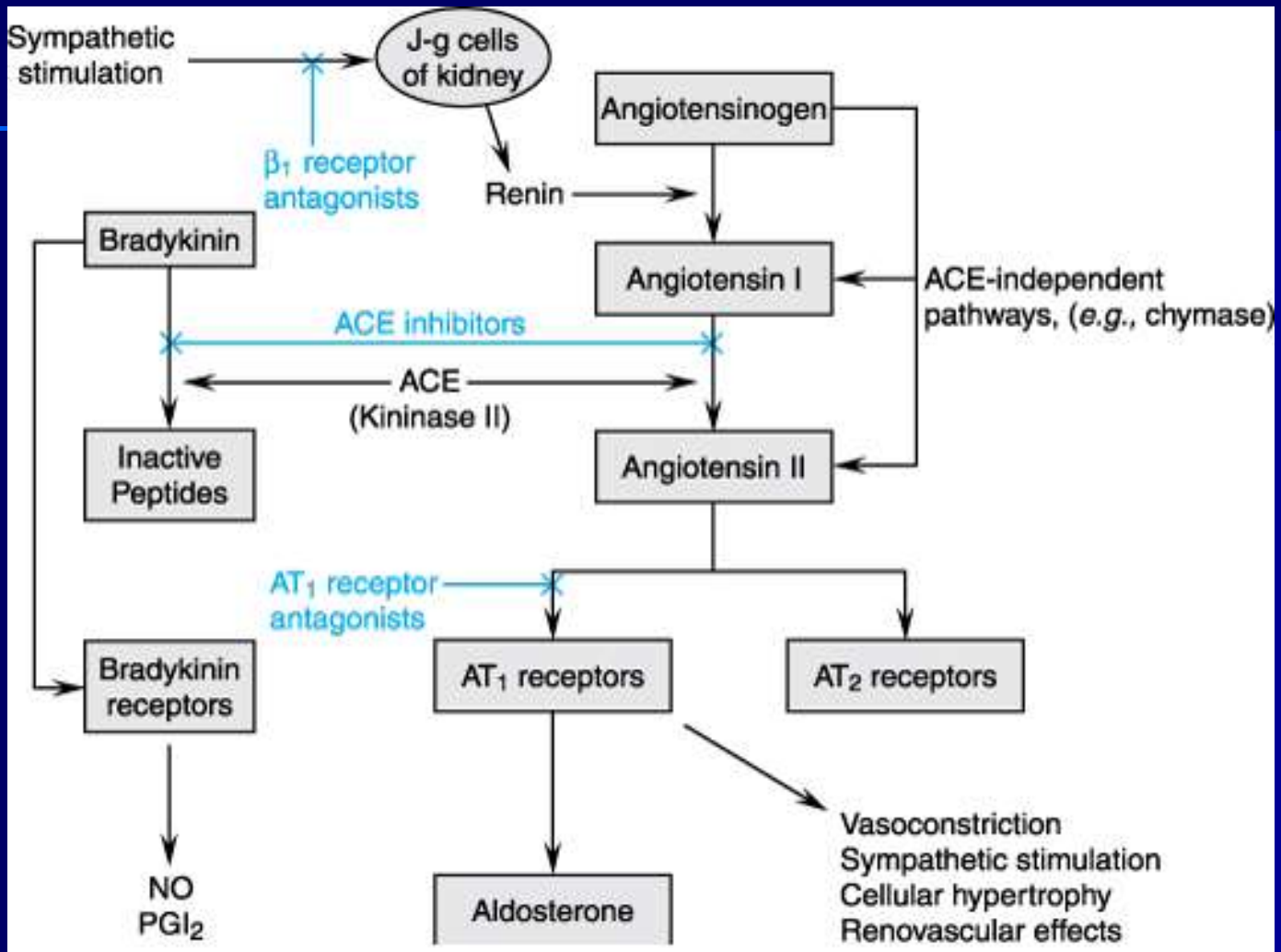
b) Angiotensin II receptor blockers (ARB) (losartan-Coozar, valsartan-Diovan, irbesartan-Avapro)

Mechanism: **selectively** block Ang II AT-1 receptor → decrease PVR → decrease BP

Adverse effects: **No** Cough, very few adverse similar to ACE inhibitors


BP ↓
BV ↓
Na+ depletion
+
RENIN RELEASE
-
BP ↑
BV ↑
Na+ retention
+
+
+
NE release from nerve ending
+
Angiotensin release
+
Aldosterone secretion
+
+
Vasoconstriction

Renin-Angiotensin-Aldosterone System



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