Antihypertensive Drugs

I) Diuretics (Saluretics)

- **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.
- **Early Effects (3-4 days):** 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:** metabolic side effects.

A) Thiazide diuretics:

(**Hydrochlorthiazide** ,**Chlorthalidone**: long acting ,**Bendrofluazide** , **Indapamide**: vasodilating and lipid neutral, regression of LVH)
- Effective in mild and moderate Ht with normal renal and heart function.

B) Loop Diuretics(Furosemide: not ideal, short acting , Torsemide: free of metabolic side effects)

- Needed in severe Ht, in renal insufficiency, and in heart failure or cirrhosis.

C) Potassium- sparing diuretics(Spironolactone, Eplerenone , Ameloride ,Triamterene):

- Useful in heart failure.

II) VASODILATORS

- Work directly on arterial blood vessels or veins , 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.

1) Hydralazine:

- Oldest vasodilator was withdrawn and then came back , Arteriolar dilator: works by release of NO.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. - Used in heart failure, combined with **isosorbide dinitrate**

2) 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.

3) Sodium Nitroprusside:

-Cyanide-containing molecule, Relaxes both arterial and venous smooth muscle: works by release of NO.

- 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.
- Useful in emergencies, surgery and heart failure.

4) 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.

***Side effcts:** Hypertrichosis so useful for baldness ,Pericarditis.

5) Fenoldopam:

- Dopamine D1 agonist, which results in vasodilation, renal vessel dilation, and natriuresis.
- Rapidly metabolized, short acting. **-Used by continuous infusion in emergencies or postoperatively.**

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

III) Calcium Channel Blockers

- 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
- **More effective than others in protection against stroke.**

Calcium Channel Blockers

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

IV) Angiotensin - Converting Enzyme Inhibitors(ACEI)

(Captopril , Enalapril , Quinapril , Lisinopril, Benazepril , Fosonopril)

- Inhibit ACE in the lungs , inhibit kinin metabolism.

*** Therapeutic Benefits:**

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

***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 , Angioedema.

V) Angiotensin II Receptor Blockers (AT-1)

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

- May be only indicated when ACEI are intolerable, Most expensive, but fastest growing class of antihypertensive drugs.
- May be better than ACEI in protection against stroke, Free of side effects, especially cough.
- Result in more complete inhibition of angiotensin actions (**Chymase**) with no effects on bradykinins.
- Long-term treatment with ACE inhibitors is often associated with so-called "*angiotensin escape,*" characterized by the return of plasma angiotensin II concentration to pretreatment levels.

VI) Renin Enzyme Inhibitors (Aliskiren)

- Other better studied medications are typically recommended due to concerns of higher side effects and less evidence of benefit.

VII)Sympatholytics or Adrenergic Blockers

1) Alpha Adrenergic Antagonists

A)Non selective Antagonists(Phentolamine ,Phenoxybenzamine)

- Block both $\alpha 1$ and $\alpha 2$ receptors, so cause reflex tachycardia and increased contractility.
- Used only for pheochromocytoma.

B) $\alpha 1$ -Selective Antagonists(Prazosin, Terazocin ,Doxazosin)

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

- First - Dose Phenomenon. **- Effective in moderate hypertension as well as benign prostatic hypertrophy.**

2) Beta Adrenergic Blockers

Propranolol (Prototype)**, Timolol** (Lipophilic)**, Nadolol** (Long acting)**, Pindolol and Acebutelol** (ISA)**,Esmolol** (Short HL), **Metoprolol, Atenolol, Betaxolol, Bisoprolol** (β1 selective).

***Antihypertensive Mechanisms**: Decrease HR, SV, and consequently C.O , Decrease Rennin Release, Central Action in the vasomotor center, Inhibit NE release.

*** Therapeutic Effectiveness:** Useful in high - rennin hypertension ,Combination or monotherapy ,Hyperkinetic hearts, Used in other cardiovascular conditions, Ineffective in blacks ,No postural hypotension .

*** Side Effects:** Bronchospasm (especially with the non selective),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 nitric oxide-potentiating vasodilatory effect.

3) Adrenergic Neurone Blockers.

(Guanethidine ,Bethanedine ,Debrisoquin ,Guanadrel)

- Hydrophilic , Block NE release(Cause depletion of NE)

Reserpine (Rauwolfia Alkaloids):

-Lipophilic , Depletes: NE, 5HT, ACTH, DA.

- Old fashioned, slow onset and offset, very cheap.

4) 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.**

5) Centrally Acting Antihypertensive Drugs

*** Vasomotor Center**: α Receptor activation decreases BP ,β Receptor activation increases BP

*** Common Properties:** Cross BBB, Reduce preganglionic sympathetic activity, Orthostasis is unusual, due to preservation of peripheral sympathetic activity, CNS side effects.

a. Propranolol

b. Reserpine

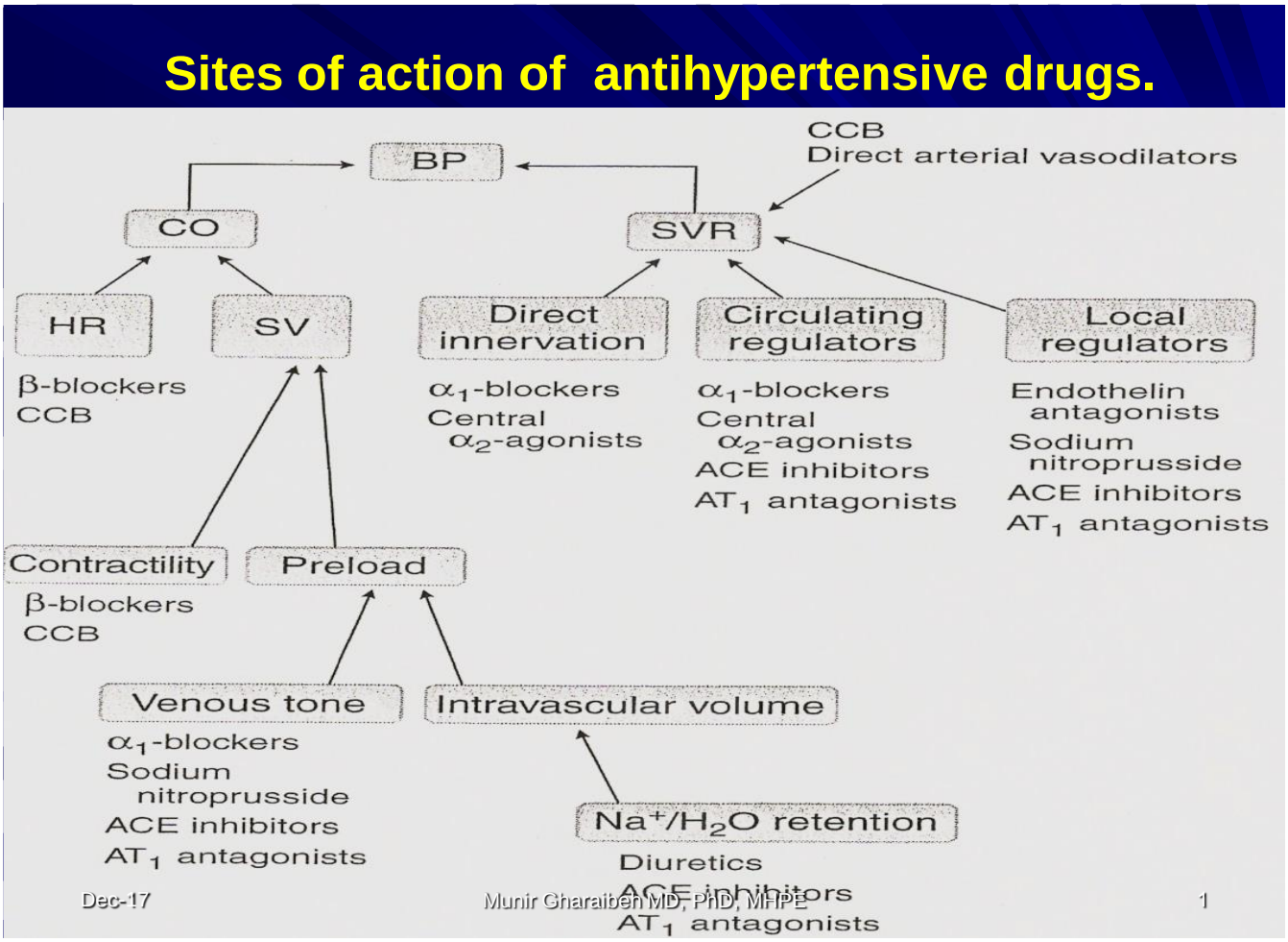
c. α- Methyl Dopa: thought to work by forming a pseudo transmitter which works peripherally , Central α agonist.

- Lowers BP but not CO or renal blood flow , Can cause lactation and positive Coomb's test ,Safe in pregnancy.

d. Clonidine(Central α agonist):

- Imidazoline derivative, tried initially as a nasal decongestant.

- I.V: Biphasic Effect: peripheral then central actions , Oral , Transdermal Patch(7 days).



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 $[renin]^{-2}$↑)

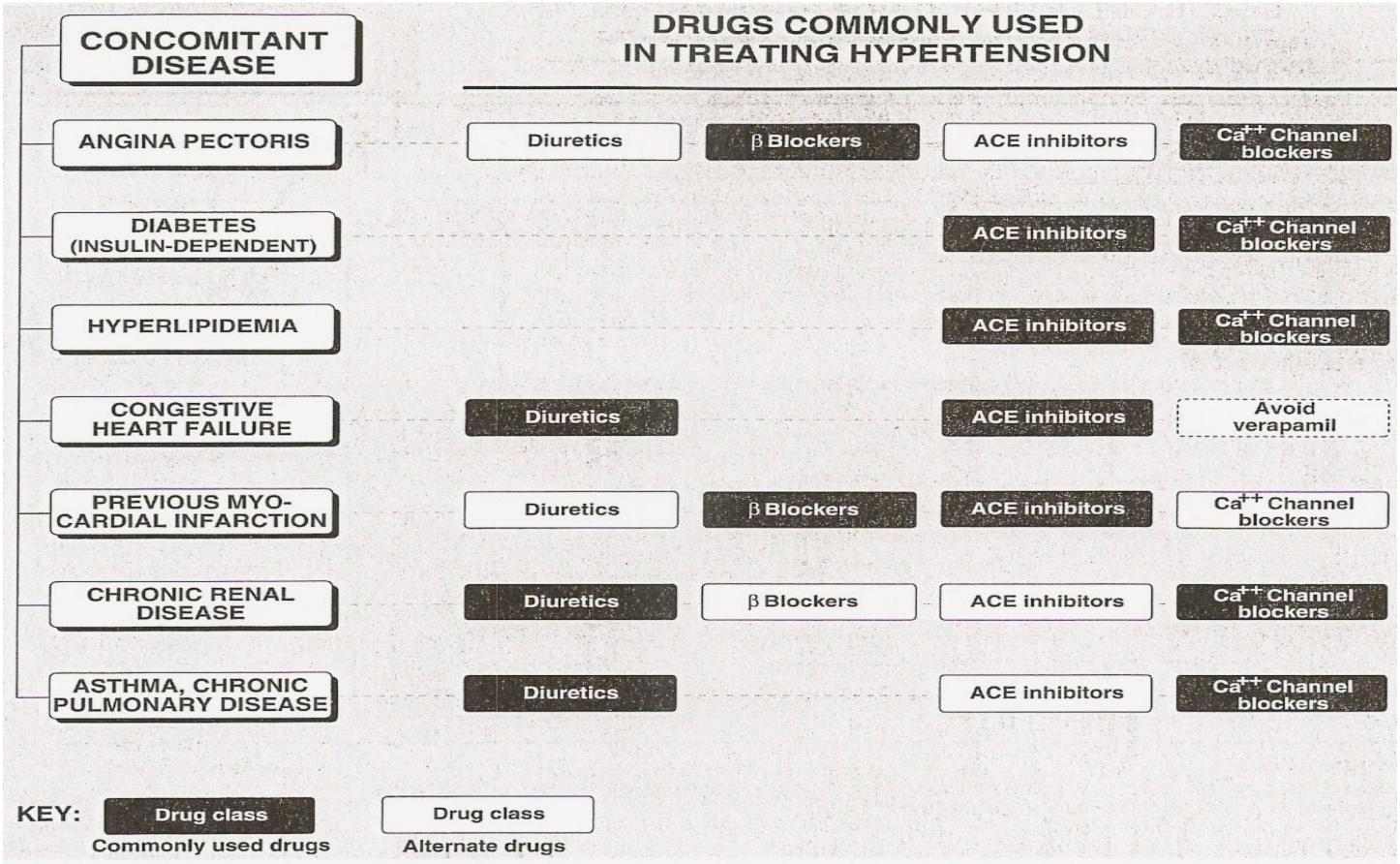


Figure 19.4
Treatment of hypertension in patients with concomitant diseases.