Antihypertensive Drugs (Slide#1)

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- Oldest vasodilator was withdrawn and then came back , Arteriolar dilator: works by release of NO.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 α1 and α2 receptors, so cause reflex tachycardia and increased contractility.
- Used only for pheochromocytoma.

B) α1 -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

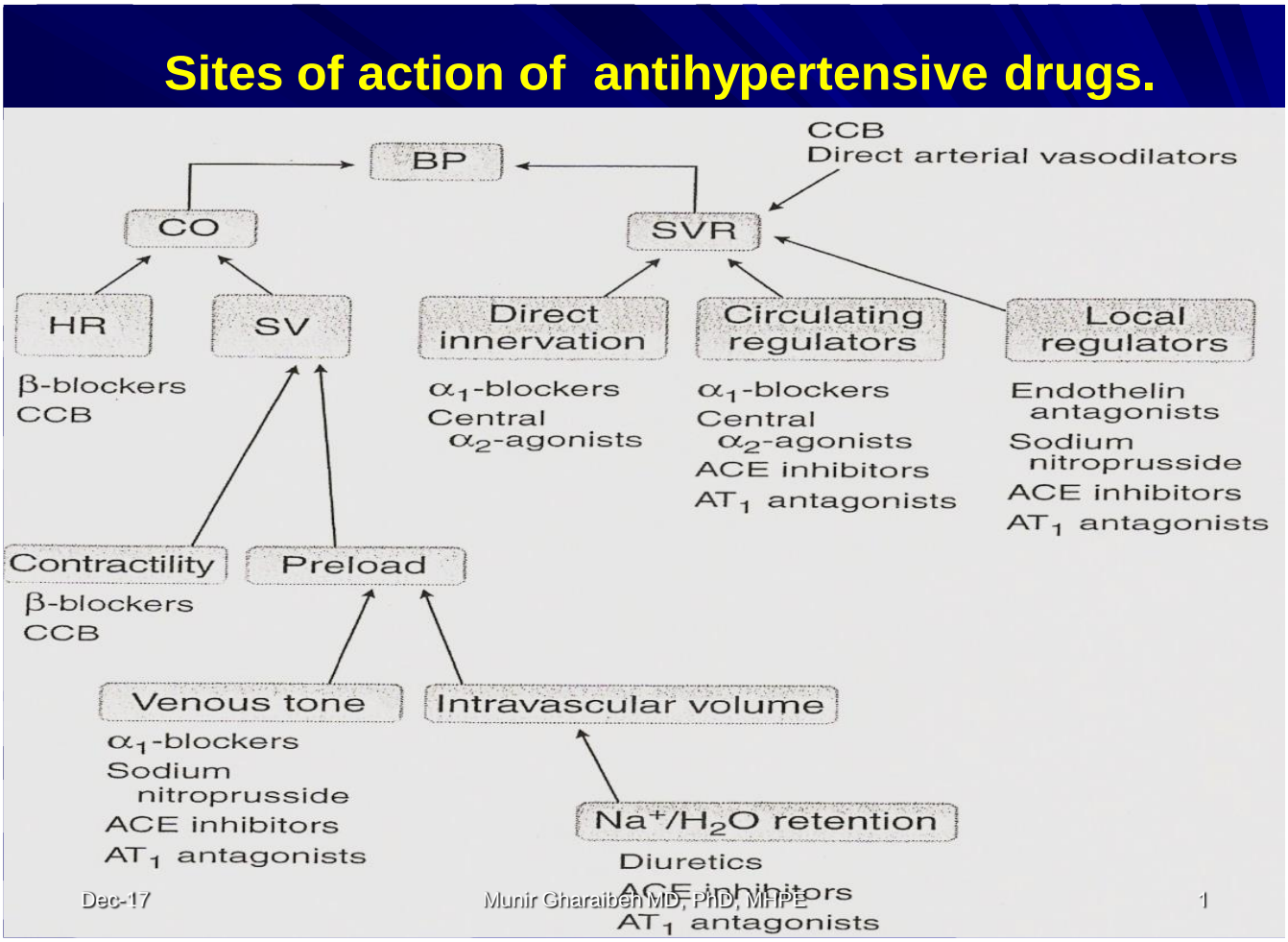
c. α- Methyl Dopa: thought to work by forming a pseudo transmitter which works peripherally , Central α agonist.

- 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] ↑)

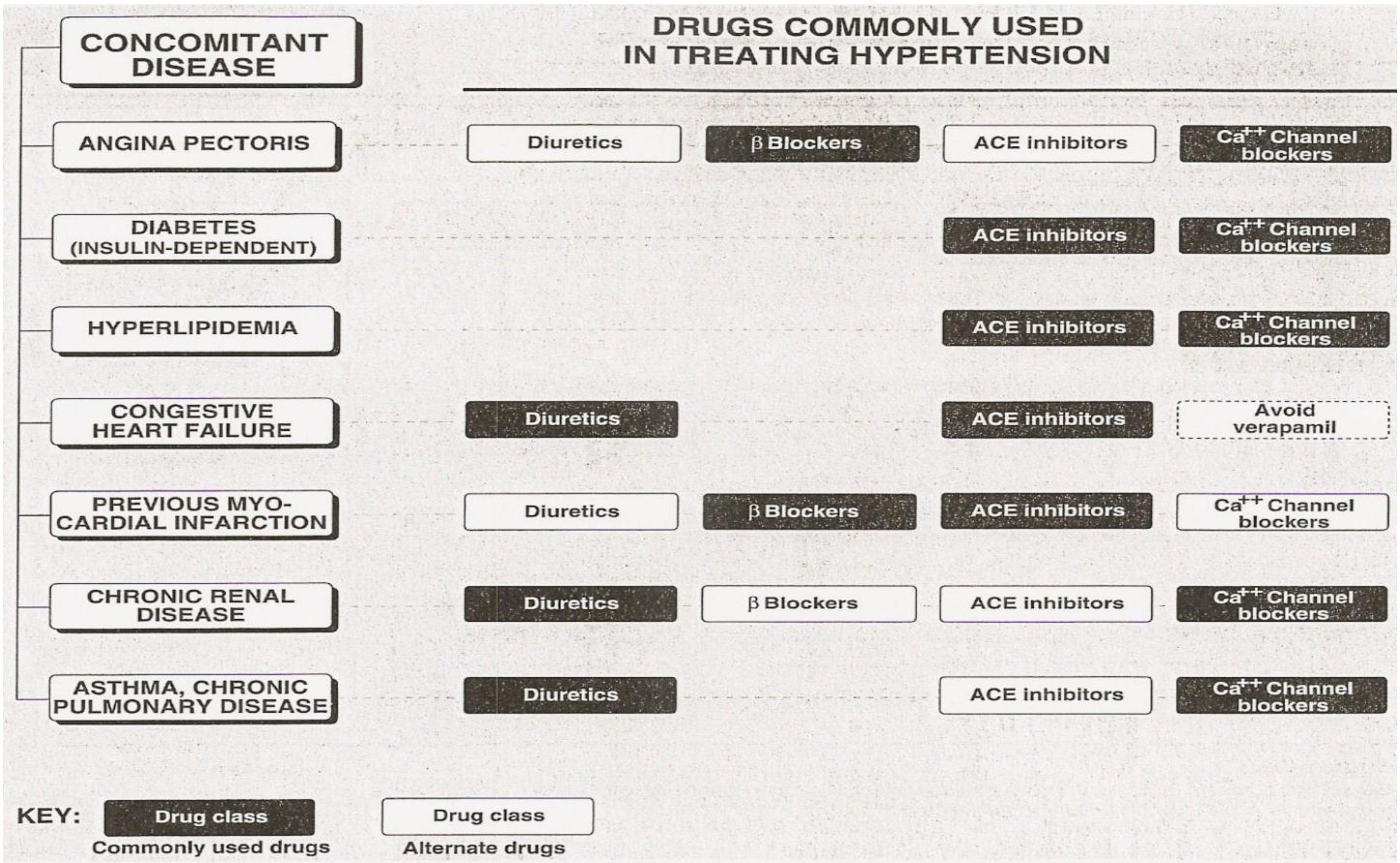


Figure 19.4
Treatment of hypertension in patients with concomitant diseases.

Drugs Used in Heart Failure(Slide#2)

Classification and treatment of chronic heart failure.

ACC/AHA Stage[1]	NYHA Class[2]	Description	Management
A	Prefailure	No symptoms but risk factors present[3]	Treat obesity, hypertension, diabetes, hyperlipidemia, etc
B	I	Symptoms with severe exercise	ACEI/ARB, β blocker, diuretic
C	II/III	Symptoms with marked (class II) or mild (class III) exercise	Add aldosterone antagonist, digoxin; CRT, hydralazine/ nitrate[4]
D	IV	Severe symptoms at rest	Transplant, LVAD

1) Diuretics

- Only for congestive symptoms.
- May be used in combination with digitalis or others.
- Can be reduced or withdrawn.

2) Angiotensin Converting Enzyme Inhibitors (ACEI)

(**Captopril , Enalapril , Lisinopril , Quinapril , Fosinopril**)

- Drugs of choice, No tolerance, Retard progression of HF, Decrease arrhythmias.
- Blockade of ACE, Reduce angiotensin II levels, Increase bradykinin.
- Proved to decrease mortality, but only when the highest tolerated doses are used.

*** Toxicity of ACEI:** Hypotension(First dose phenomenon), Renal Impairment(Proteinurea),K+ retention ,Cough.

3) Angiotensin (AT1) Receptor Blockers (ARBs)

Losartan, Candesartan , Valsartan , Irbesartan(Approvel) , Telmisartan(Micardis)

- Not superior to ACEIs, but may be **useful for patients who can not tolerate ACEIs because of cough.**

4) Beta Blockers

- Negative inotropic effects , Not useful in refractory HF.
- β-Blockers may be beneficial through resensitization of the down-regulated receptor, thus improving myocardial contractility.
- Should be started with low doses and gradually increased.
- Contraindicated in sever, refractory, unstable cases.

5) Positive Inotropic Agents

- These drugs increase force of contraction by increasing intracellular cardiac Ca^{++} concentration.

A) Cyclic AMP Independent Agents:

a) Digitalis Glycosides (**Digitalis purpura , Digitalis lanata , Strophanthus**)

- inhibits Na/KATPase.

*** Actions:** Positive Inotropic Effect,Vascular Muscle Contraction, Vagal Stimulation, Effects on Electrical Properties of Cardiac Tissues.

Effects of Digoxin on the Electrical Properties of Cardiac Tissues.

Tissue or Variable	Effects at Therapeutic Doses(vagal Stimulation)	Effects at Toxic Doses
Sinus node	↓ Rate	↓Rate
Atrial muscle	↓ Refractory period	↓Refractory period, arrhythmias
Atrioventricular node	↓ Conduction velocity, ↑ refractory period	↓ Refractory period, arrhythmias
Purkinje system, ventricular muscle	Slight ↓ refractory period	Extrasystoles, tachycardia, fibrillation
Electrocardiogram	↑ PR interval, QT interval	Tachycardia, fibrillation, arrest at extremely high dosage

* **Digitalis Toxicity :**

- **G.I.T**.(Anorexia, nausea, intestinal cramping, diarrhea)
- **Visual** (Xanthopsia, abnormalities in color vision)
- **Neurologic** (Malaise, confusion, depression, vertigo)
- **Cardiac** (bradycardia, Palpitations, syncope, arrhythmias, AV node block, ventricular tachycardia).
- **Interactions**: Pharmacological and toxic effects are greater in hypokalemic patients , **K^+-depleting diuretics are a major contributing factor to digoxin toxicity.**

*** Treatment of Toxicity:** Reduce or stop the drug , Cardiac pacemeker for heart block , Digitalis antibodies(Digoxin Immune Fab), When the plasma K^+ conc is high, antiarrhythmic drugs, such as lidocaine, phenytoin, procainamide, or propranolol, can be used.

*** Therapeutic Benefits**: only useful in CCHF with supraventricular arrhythmia .

b) Pimobendan : sensitizes myocytes to Ca^{++}, inhibits phosphodiesterase

B) Cyclic AMP Dependant Agents:

a) β-adrenergic Agonists

- All increase myocardial oxygen consumption, so not helpful for chronic use, may be used (IV) for short term or in acute heart failure.

NE: Was used in cardiogenic shock, but caused severe vasospasm and gangrene

Ep: Still used in cardiac arrest, by intracardiac injection.

Dopamine: Widely used in cardiogenic shock.

- **Low doses**: stimulate DA_1 receptors leading to renal vasodilation and improved renal function.
- **Intermediate doses**: work on β_1 receptors leading to positive inotropic actions.
- **High doses**: stimulate α receptors leading to vasoconstriction and elevation of blood pressure, can cause arrhythmias and ischemic changes.

Dobutamine : Selective β_1 agonist, used intermittently (IV) in CCHF. Produces mild vasodilation , Has more inotropic than chronotropic actions.

b) Phosphodiesterase Inhibitors

Inamrinone (PDE-3), Milrinone (PDE-3), Vesanirone (PDE-3), Sildenafil (PDE-5)

- PDE inhibition leads to accumulation of cAMP and cGMP leading to positive inotropic activity and peripheral vasodilation.

*** Toxicity**: arrhythmias, and thrombocytopenia.

- Short acting, so reserved for **parenteral therapy of acute heart failure.**

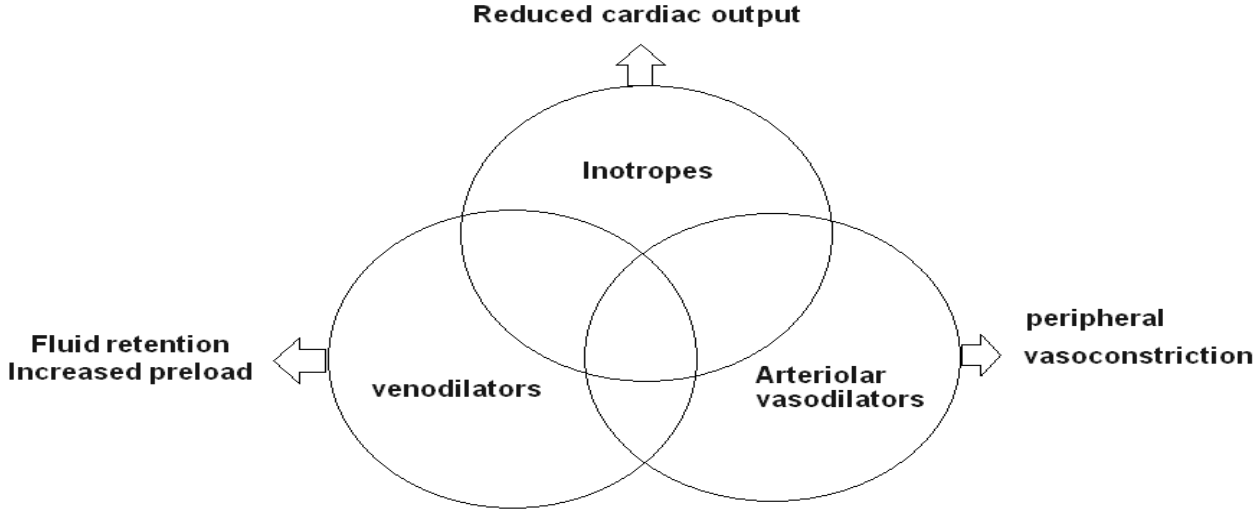
6) Vasodilators

- Affect preload and/or afterload without directly affecting contractility.
- Consequently can decrease myocardial ischemia, enhance coronary blood flow and decrease MVO2.

- Can be used in acute heart failure and for short periods in CCHF.

- Hydralazine-Isosorbide dinitrate combination was found to decrease mortality, maybe by reducing remodeling of the heart.

- Can be combined with ACEI, diuretics and digitalis.

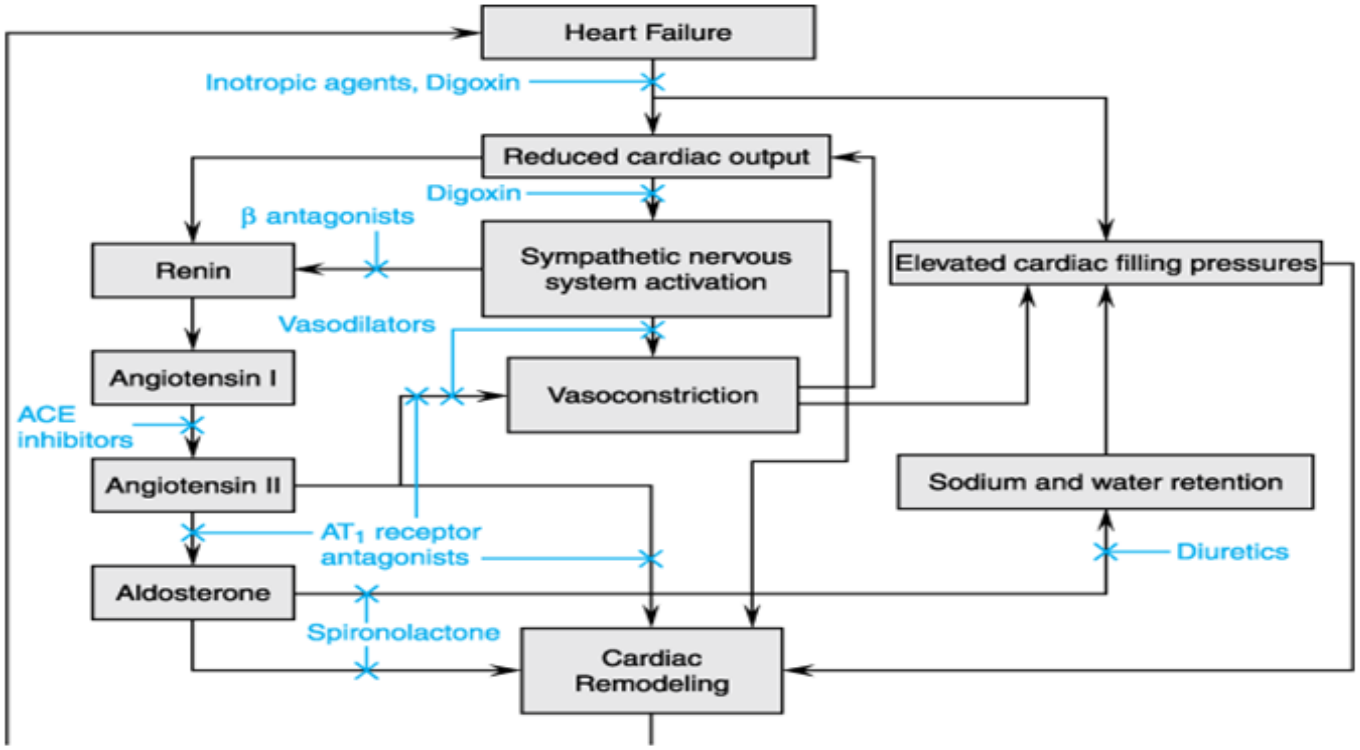


7) **(BNP)-Niseritide**

- Brain (B-type) natriuretic peptide (BNP) is secreted constitutively by ventricular myocytes in response to stretch.
- BNP binds to receptors in the vasculature, kidney, and other organs, producing potent vasodilation with rapid onset and offset of action by increasing levels of cGMP.
- Niseritide is a recombinant human BNP approved for treatment of acute decompensated CHF.
- Reduces systemic and pulmonary vascular resistances, causing an indirect increase in cardiac output and diuresis.
- Effective in HF because of reduction in preload and afterload.
- Hypotension is the main side effect.

Drug groups used in heart failure.

Chronic heart failure	Acute heart failure
Diuretics	Diuretics
Aldosterone receptor antagonists	Vasodilators
Angiotensin-converting enzyme inhibitors	Beta agonists
Angiotensin receptor blockers	Bipyridines
Beta blockers	Natriuretic peptide
Cardiac glycosides	
Vasodilators	



Steps in the Prevention and Treatment of Chronic Heart Failure.

ACC/AHA Stage	Step	Intervention
A, B	1	Control hypertension, hyperlipidemia, glucose metabolism (diabetes), obesity
C	2	Reduce workload of the heart (limit activity, put on temporary bed rest)
	3	Restrict sodium intake, give diuretics
	4	Restrict water (rarely required)
C, D	5	Give angiotensin-converting enzyme inhibitor or angiotensin receptor blocker
	6	Give digitalis if systolic dysfunction with third heart sound or atrial fibrillation is present
	7	Give beta blockers to patients with stable class II–IV heart failure
	8	Give aldosterone antagonist
	9	Give vasodilators
D	10	Cardiac resynchronization if wide QRS interval is present in normal sinus rhythm

Drug Treatment of Ischemic Heart Disease (Slide#3)

1) Nitroglycerine (GTN)

- Nonspecific smooth muscle relaxant, action is due to release of NO, leading to activation of guanylyl cyclase.
- Can be administered by various routes, Fast onset of action(1-3minutes, Peaks at 10 minutes), Short duration (15-30minutes).
-Reductase enzyme, in liver, breaks down the drug.
- Causes general vasodilation:

a) **Arteriolar dilation**: short lived (5-10 min) , Decreases systemic blood pressure (afterload), but causes reflex tachycardia and increased contractility.

b) **Venous dilation**: more intense, even with low doses, lasts for 30 minutes. Decreases venous return (preload) and decreases MVO2.

***Side Effects:**

- Headache, Hypotension , tachycardia, Increased intraocular and intracranial pressures.
- Methemoglobinemia, Tolerance: only for the arteriolar effects.
- Withdrawal: in workers in ammunition industry.

Drug	Duration of Action
Short-acting:	
Nitroglycerin, sublingual	10–30 minutes
Isosorbide dinitrate, sublingual	10–60 minutes
Amyl nitrite, inhalant	3–5 minutes
Long-acting:	
Nitroglycerin, oral sustained-action	6–8 hours
Nitroglycerin, 2% ointment, transdermal	3–6 hours
Nitroglycerin, slow-release, buccal	3–6 hours
Nitroglycerin, slow-release patch, transdermal	8–10 hours

2) Beta Adrenergic Blockers

- Prevent actions of catecholamines, so more effective during exertion.
- Do not dilate coronary arteries, might constrict them, do not increase collateral blood flow.
- Cause subjective and objective improvement: decreased number of anginal episodes, nitroglycerine consumption, enhanced exercise tolerance, and improved ECG.

3) Calcium Channel Blockers

- Particularly beneficial in vasospasm, can affect platelets aggregation.
- May be dangerous in the presence of heart failure and in patients susceptible to hypotension.

- L-type calcium channel can be blocked by Verapamil , T-type calcium channel can be blocked by flunarizine and mibefradil.

Drug	Oral Bioavailability (%)	Half-Life (hours)	Indication
Dihydropyridines			
Nimodipine	13	1–2	Subarachnoid hemorrhage
Nicardipine	35	2–4	Angina, hypertension
Nifedipine	45–70	4	Angina, hypertension, Raynaud's phenomenon
Nitrendipine	10–30	5–12	Investigational
Nisoldipine	< 10	6–12	Hypertension
Isradipine	15–25	8	Hypertension
Felodipine	15–20	11–16	Hypertension, Raynaud's phenomenon
Amlodipine	65–90	30–50	Angina, hypertension
Miscellaneous			
Diltiazem	40–65	3–4	Angina, hypertension, Raynaud's phenomenon
Verapamil	20–35	6	Angina, hypertension, arrhythmias, migraine

***Side Effects:** Hypotension, Headache, dizziness, Flushing, Peripheral edema.

Effects of Nitrates Alone and with Beta Blockers or Calcium Channel Blockers in Angina Pectoris.			
	Nitrates Alone	**Beta Blockers or Calcium Channel Blockers**	**Combined Nitrates with Beta Blockers or Calcium Channel Blockers**
Heart rate	***Reflex↑ increase***	**Decrease**	**Decrease**
Arterial pressure	**Decrease**	**Decrease**	**Decrease**
End-diastolic volume	**Decrease**	**Increase**	**Non or decrease**
Contractility	***Reflex↑ increase***	**Decrease**	**Non**
Ejection time	**Decrease**	**Increase**	**Non**

4) Dipyridamole

- Inhibits the uptake of adenosine and inhibits adenosine deaminase enzyme.
- good coronary dilator, increases the blood flow to the normal area i.e. “Coronary Steal Phenomenon”.
-Still used as an antiplatelet drug but not better than aspirin.

5) Others

ACEI, Anticoagulants and/or Thrombolytic Therapy, Cholesterol Lowering Agents, Angioplasty ,Surgery.

6) Newer Antianginal Drugs

Metabolic modulators: **Ranolazine.**
Direct bradycardic agents: **Ivabradine.**
Potassium channel activators: **Nicorandil.**
Rho-kinase inhibitors: **Fasudil.**
Sulfonylureas: **Glibenclamide.**
Thiazolidinediones.
Vasopeptidase inhibitors.
Nitric oxide donors: L- arginine.
Capsaicin.
Amiloride.

Antiarrhythmic Drugs (slide#4)

*** Causes of some Arrhythmias :**

1) **Torsade de Pointes** : Familial long QT interval, Drug - Induced (drugs which prolong action potential duration), 300 different mutations in at least 8 ion channel genes.
****Treatment**: K+, Drugs that decrease triggered upstrokes (β Blockers or Mg++),Drugs that decrease action potential duration (Pacemaker or isoproterenol).
2) **Short QT Syndrome**: gain function mutations in three potassium channel genes(**KCNH2, KCNQ1,** and **KCNJ2).**
3) **Chatecholaminergic Polymorphic Ventricular Tachycardia (CPVT):** mutations in **sarcoplasmic proteins** that control calcium. - Casuse stress or emotion-induced syncope.
4) **Sick Sinus Syndrome**: mutations in **HCN4** and **SCN5A**
5) **Brugada Syndrome**: loss function mutations in **SCN5A**
6) **Familial Atrial Fibrillation**: gain fucntion mutation in the potassium channel gene, **KCNQ1**.

* **Arrhythmias non-pharmacologic Therapy**: Surgery, Radiofrequency Catheter Ablation, Implantable Cardioverter- Defibrillator (ICD) and Gene therapy.

Antiarrhythmic Drugs

A)Vaughan Williams classification

1) Class IA Drugs

a) Quinidine: Antipyretic, Anti-malarial , Inhibits α and muscarinic receptors , Slows upstroke, conduction, and prolongs action potential and QRS duration.
Uses: restricted to patients with normal hearts(no failure, no ischemia), but have atrial or ventricular arrhythmias , acute severe malaria.
Side Effects: cinchonism, angioedema, diarrhea, thrombocytopenia, excessive prolongation of QT interval, slowed conduction and sudden death, increase **Digoxin** levels , increase **Warfarin** effects.
b) Procainamide: for lupus erythematosus
Acetylated Procainamide ➔ NAPA (Antiarrhythmic Drugs Class III) action.
c) Disopyramide(Na+ blocker): More anticholinergic effects but less diarrhea than quinidine.

2) Class IB Drugs

a) Lidocaine(Na+ blocker):

- Acts selectively in ischemic tissue to promote conduction & block reentry.
- More effective with K+. - Not effective in atrial arrhythmias (used in ventricular arrhythmias)

***Side Effects**: Least cardiotoxic of the class, except for hypotension with high doses due to depression of the myocardium.

***Oral analogs**:

i) Tocainide: side effects➔ CNS, GI and blood dyscrasia,

ii) Mexiletine: side effects➔CNS

b) Phenytoin:

Uses: Digitalis induced arrhythmias,Epilepsy, Arrhythmias after congenital heart surgery, Congenital prolonged QT interval.

3) Classy IC Drugs

a) Flecainide(Na + and K+ blocker):

- Effective in supra-ventricular tachycardia with normal hearts.

***Side Effects**: Ventricular arrhythmias, CNS, and sudden death.

b)Propafenone

-Used for supra-ventricular arrhythmias.

* **Side effects**: metallic taste, constipation, and arrhythmias.

4) Classy II Drugs (β blockers)

a) Propranolol:

-Very effective, well tolerated, and documented to reduce mortality after acute myocardial infarction by reducing arrhythmias , membrane stabilization effect.

b) Esmolol (β1 selective)

- Short acting, used in intraoperative and acute arrhythmias , no membrane stabilization effect.

c) Acebutolol (β1 selective)

- Short acting, used in intraoperative and acute arrhythmias, membrane stabilization effect.

5) Class III Drugs

a) Amiodarone: given IV (Loading dose 10gm) and orally, slow kinetics (t½ 25-110 days), metabolized by **CYP3A4 enzymes**.

- Toxicity: mainly extracardiac and dose related.

-Side effects: Lung fibrosis , GI and liver, corneal deposits, photodermatitis and discoloration of the skin, increase **Digoxin** levels.

b) Sotalol:

-Used for atrial and ventricular arrhythmias.

*Sides effects: Bradycardia, Heart failure, Prolongation of QT.

c) Bretylium Tosylate:

- Originally an antihypertensive, but tolerance develops.
- Rarely used except in the prevention of ventricular fibrillation after failure of cardiversion and lidocaine.

***Side effects**: Hypotension, Parotid swelling.

d) Ibutilide

e) Dofetilide

6) Class IV Drugs (Ca++ Channel Blockers)

Verapamil and **Diltiazem**

- Used for Paroxysmal Supraventricular Tachycardia.

*Side effects: Can cause severe AV block in diseased hearts , increase **Digoxin** levels , Constipation, gastric discomfort, vertigo, headache, nervousness, pruritis.

B) Miscellaneous Drugs

1) Digoxin:

- Used in atrial arrhythmias , Vagotonic Effects, increases AV refractory period

2) Magnesium:

- Effective IV in refractory digitalis- induced ventricular arrhythmias only in hypomagnesemic patients.
- Effective in Torsade de Pointes patients even if serum Mg++ is normal.

3) Potassium salts:

- For digitalis-induced arrhythmias with hypokalemia
- Depress ectopic pacemakers and slow conduction.

4) Adenosine:

- Effective in supraventricular tachycardia, replaced verapamil.
- Less effective in the presence of adenosine receptor blockers, e.g. theophylline and caffeine.

***Side effects**: transient flushing (20%), chest tightness, AV block, headache, hypotension, nausea, and paresthesia , decreases phase 4 depolarization in SA node. decreases AV conduction, No effect on ventricles.

Table 17.1 **The mechanism of action, the electrophysiological actions and clinical uses of selected antidysrhythmic drugs**

		Example	Mechanism of action	Electrophysiological actions	Clinical use
Vaughan Williams classification	Class Ia	Disopyramide	Na^+ channel block	Reduced rate of depolarisation of action potential, increased ERP, decreased AV conduction	Ventricular fibrillation, especially associated with myocardial infarction
	Class Ib	Lidocaine			
	Class II	Propranolol, atenolol	β-Adrenoceptor antagonism	Slowed pacemaker activity, increased AV refractory period	Dysrhythmia prevention in myocardial infarction; paroxysmal atrial fibrillation due to sympathetic activity
	Class III	Amiodarone, sotalol	K^+ channel block	Increased action potential duration and increased ERP	Atrial fibrillation; ventricular fibrillation
	Class IV	Verapamil	Ca^{2+} channel block	Decreased APD, slowed AV conduction	Supraventricular tachycardias; atrial fibrillation
Not classified by system		Adenosine	K^+ channel activation	Slowed pacemaker activity, slowed AV conduction	Given i.v. for supraventricular tachycardias
		Digoxin	K^+ channel activation (vagal action)	Slowed AV conduction (block)	Atrial fibrillation
		Magnesium chloride	? Ca^{2+} channel block		Ventricular fibrillation; digoxin toxicity

Antihyperlipidemic Drugs (Slide#5)

1) Niacin (1H half-life)

- Nicotinic Acid or Vitamin B3, functions only after conversion to NAD or NADP+ Nicotinamide.
- Has hypolipidemic effects only in large doses.
- Increases plasminogen activator, Reduces fibrinogen levels, Affects all lipid parameters: Decreases LDL-C production(20-30%), Lowers triglycerides (35-45%), Best agent to increase HDL-C(35-40%).

***MOA**:

-inhibits the lipolysis of triglycerides by inhibiting adipocyte adenylyl cyclase, inhibit a rate –limiting enzyme of triglyceride synthesis, diacylglycerol acetyltransferase 2 , Inhibits intracellular lipase in adipose tissues.

- Reduction of triglyceride synthesis reduces hepatic VLDL and consequently LDL.

*** Toxicity: acanthosis nigricans** (black hyperpigmentation of the skin) , Elevations in transaminases and possible hepatotoxicity, Insulin resistance and hyperglycemia, Hyperuricemia and gout, Cardiac arrhythmias, Amblyopia, blurring of vision.

- Harmless cutaneous vasodilation and sensation of warmth, can be prevented by NSAIDS.

2) Fibrates or Fibric Acid Derivatives or "PPARs Activators"
(Clofibrate, Gemfobrozil, Fenofibrate, Bezafibrate)

- Drugs of choice in severe hypertriglyceridemia.

*** MOA:**

- Activate PPAR- α (Peroxisome Proliferator Activated Receptor- α) which:
stimulates fatty acid oxidation, increases LPL synthesis, and reduces expression of apo C-III, and increases apoA-I and apoA-II expression.
- Increase lipolysis of lipoprotein triglyceride via LPL, Decrease levels of VLDL and LDL, Moderately increase HDL, have anticoagulant and fibrinolytic activities.

***Toxicity:**

- Rashes, urticaria, hair loss, headache, GIT symptoms, impotence, anemia, myalgia, fatigue, myopathy and rhabdomyolysis.
- Elevated transaminases or alkaline phosphatase .
- Interacts with statins, levels of both drugs will increase, Risk of cholesterol gallstones.
- Used with caution in renal failure.

3) Bile Acid –Binding Resins

(Colestipol, Chlestyramine, Colesevelam)

- The safest drugs

***MOA:**

- These are large polymeric anionic- exchange resins, insoluble in water, which bind the negatively charged bile acids in the intestinal lumen and prevent their reabsorption leading to depletion of bile acid pool and increased hepatic synthesis.
- This leads to increased LDL clearance and lowers LDL-C levels, may increase triglyceride levels.

*** Indications:**

- Lower LDL as much as 25%, but will cause GI side effects. -Relieve pruritus in cholestasis.

***Toxicity:**

- Gritty sensation, Constipation and bloating, Heartburn, Malabsorption of Vitamin K, Gall stones
-Impaired absorption of many drugs(digitalis, propranolol, thiazides, warfarin, folic acid, statins, aspirin….etc).

4) Competitive Inhibitors of HMG-CoA Reductase "Statins"

(Mevastatin , Simvastatin , Lovastatin , Pravastatin , Fluvastatin , Atorvastatin, Rosuvastatin).

-Most commonly prescribed drugs worldwide, Most effective in lowering LDL.

***MOA:**

-Competitively inhibit the early rate- limiting enzyme in de novo synthesis of cholesterol (3- hydroxy-3methylglutaryl coenzyme A reductase). This results in increased expression of the LDL receptor gene.
-Higher doses can reduce triglyceride levels caused by elevated VLDL levels.
-Some (**simvastatin** and **rosuvastatin**) can raise HDL-C levels.
-Decrease oxidative stress and vascular inflammation by enhancing NO production, Reduce platelet aggregation.

***Toxicity:**

- Toxicity is dose-related, associated with advanced age, hepatic or renal dysfunction, small body size, associated diseases, hypothyroidism and concomitant drugs.
-Elevation of transaminases, intermittent and not associated with strong evidence of liver failure, elevation of creatine kinase (CK) activity.
-Rhabdomyolysis, causing myoglobinuria and renal injury and failure or even death. It is extremely rare (less than one in 10,000 people).
- Lupus-like disorder and peripheral neuropathy.

***Pharmacogenetics of Statins:** metabolized by the CYP enzyme system, which is a subject to individual genetic differences. These differences will be exhibited for their: Therapeutic Response and Side Effects.

5) Inhibitors of Sterol Absorption (Ezetimibe)

- Action is complementary to statins(60% reuction in LDL-C)

***MOA:**

-Inhibitor of NPC1L1, a specific transport process in jejunal brush border.

-Reduces cholesterol delivery to the liver by the chylomicron remnants.

-Reduces cholesterol absorption and reabsorption by 54%, precipitating a compensatory increase in cholesterol synthesis.

***Side effects:** allergic reactions, reversible impairment of liver function tests and myopathy

6) Inhibitors of Cholesteryl Ester Transfer Protein

(Torcetrapib: withdrawn **, Anacetrapib, Dalcetrapib)**

-Can increase HDL levels by 45-106% in humans.

***MOA**:

- Inhibits CETP which is a plasma glycoprotein synthesized by the liver that mediates the transfer of cholesteryl esters from HDL to triglyceriderich lipoproteins and LDL in exchange for a molecule of triglyceride.