Drugs Used in Heart Failure

Drug	MOA / Effects	Uses	Side Effects	Notes
Diuretics	✵**Blocks Na+ Reabsorption** -Do not increase the CO, and maybe even decreases CO when used in high doses, since they decrease blood volume which decreases venous return	-Only indicated for HF with congestive symptoms (don't affect heart itself) - They may not work in treating HF in many cases (**Diuretic Resistance in Heart Failure**)	-Causes metabolic side effects; hypokalemia (low K+ can increase the toxicity of drugs like digoxin) -Decrease in BP	-Given IV → rapid relief of symptoms -Cheap drugs, can be reduced or withdrawn easily -Causes of **Diuretic Resistance in Heart Failure:** ▫Noncompliance with medical regimen; excess dietary Na+ intake ▫Decreased renal perfusion and GFR ▫Selective reduction in glomerular perfusion pressure following initiation (or dose increase) of ACEI therapy ▫Nonsteroidal anti-inflammatory drugs ▫Primary renal pathology ▫Reduced or impaired diuretic absorption due to gut wall edema and reduced splanchnic blood flow
Angiotensin Converting Enzyme Inhibitors (ACEI)	✵**Blockade of ACE** -**Reduce** angiotensin II levels -**Increase** bradykinin levels -**Inhibit** SNS, leading to decreased NE release and upregulation of ß1 -**Balanced** (indirect) vasodilators → reduction of afterload & preload -**Decrease** aldosterone causing decreased fluid retention, **decreased** K+ loss → **reduced** arrhythmias -**Reduce** myocyte & fibroblast growth factors causing reduced cardiac remodeling	-**Drugs of choice** in treatment of HF -Retard the progression of HF -Decrease arrhythmias -Proved to decrease mortality, but only when the **highest tolerated doses are used** ***No tolerance**	▫Toxicity: -Hypotension (first dose phenomenon) -Renal Impairment (proteinuria) -K+ retention -Cough (occurs in 10% of patients)	-Preparations include: Captopril, Enalapril, Lisinopril, Quinapril, Fosinopril -They all have same efficacy, but differ in potency -Might differ in toxicity
Angiotensin II Receptor Blockers (AT-1)	✵**Blocks Angiotensin II receptors** -Result in more complete inhibition of angiotensin II actions with no effects on bradykinins	-May be only indicated when ACEIs are intolerable	-Free of side effects, especially cough	-Most expensive, but fastest growing class of antihypertensive drugs -Examples include: Losartan, Valsartan, Candesartan, Irbesartan, Eprosartan, Telmisartan (also increases PPR"-γ activity)

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Beta Blockers	✵**Blocks Beta Receptors** -Slow heart rate → decrease O2 consumption → enhanced efficiency. → lessen the frequency of ischemic events and arrhythmias that can complicate HF -Suggested mechanisms also include reduced remodeling of the heart muscle -**Most important effect:** re-sensitization of the down-regulated beta receptors → improving myocardial contractility	- Their use is limited for **early stages** of HF	- **Contraindicated** in sever, refractory, unstable cases	-Should be started with low doses and gradually increased. To cope with the already down-regulated receptors -Metoprolol, carvedilol, bucindolol, and bisoprolol **have reduced mortality** in patients (compared to propranolol) -On the long run beta blockers are **more effective**
Positive Inotropic Agents: cAMP Independent				
General View	✵**Increases intracellular cardiac Ca^{+2} concentration** -Improve cardiac function -Increase force of contraction			-There are two types: 1. cAMP **Independent**: Digitalis & Pimobendan 2. cAMP **Dependent** Agents: as beta-adrenergic Agonists, Phosphodiesterase Inhibitors
Pimobendan	✵**Sensitizes myocytes to Ca^{+2}** ✵**Inhibits PDE**			-Can also be included as a cAMP dependent agent (Inhibits PDE)
Digitalis Glycosides: **▫Digoxin** **▫Ouabain** **▫Digitoxin**	✵**Inhibits Na/K ATPase** **-Main action:** increasing Heart Contractility **-**Vascular Muscle Contraction **▫In HF patients**: increase CO & decrease PVR **▫In healthy people:** decreases CO & Increases PVR -Effects on Electrical Properties of Cardiac Tissues (direct & indirect) **▫Indirect: Vagal stimulation** → atria & SA node **▫Direct**: at high toxic doses ****Increased PR is diagnostic of digitalis therapy**	-Was a widely used drug in the treatment of HF - Nowadays, use is **restricted only to CCHF** with **supraventricular arrhythmias** ▫Might decrease morbidity and improve quality of life ▫Withdrawal might be hazardous ▫Does not improve mortality	**-GIT:** 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** *Toxic effects are **greater in hypokalemic patients (**K^+ depleting diuretics are a major **contributing** factor to toxicity)	-Egyptians got it from Squill(العنصل) -Chinese →Toad skin -William Withering → Foxglove (we extracted the active ingredient *glycoside* from it) -Species of foxglove: Digitalis purpura, Digitalis lanata, Strophanthus ▫Different cardiac glycosides: -Have different oral absorption → ouabain has to be given I.V. -Different protein binding ability (digitoxin has 97%) → drug-drug interactions

Drugs Used in Heart Failure

Drug	MOA / Effects	Uses	Side Effects	Notes
Digitalis Glycosides (Cont.)			***Treatment of toxicity:** -Reduce or stop the drug -Cardiac pacemaker for heart block. Digitalis antibodies (Digoxin Immune Fab) -Arrhythmias may be converted to normal sinus rhythm by **K+** when the plasma K+ concentration is **low** or within the normal range -When plasma K+ conc is **high**, we can use **antiarrhythmic drugs**, such as lidocaine, phenytoin, procainamide, or propranolol	-Different half-life & different excretion route (digitoxin is eliminated in the intestines while digoxin in the kidneys → incase of renal failure we use **digitoxin**) ***Have to be monitored regularly** ***cAMP independent**
Positive Inotropic Agents: cAMP Dependent				
Phospho-diesterase Inhibitors	**-** PDE inhibition leads to **accumulation of cAMP and cGMP** leading to **positive inotropic** activity and **peripheral vasodilation**	-Reserved for parenteral therapy of acute heart failure -Sildenafil (Viagra) treats erectile dysfunction	- Toxic: arrhythmias, and thrombocytopenia	-Short acting **-Preparations:** Inamrinone (PDE-3), Milrinone (PDE-3) Vesanirone (PDE-3), Sildenafil (PDE-5)
Dopamine	✵**Low doses:** stimulate DA1 receptors leading to renal vasodilation and improved renal function ✵**Intermediate doses:** work on β1 receptors leading to positive inotropic actions. ✵**High doses**: stimulate α receptors leading to vasoconstriction & ↑BP	- Widely used in cardiogenic shock	-High doses can cause arrhythmias and ischemic changes	**-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
Dobutamine	✵**Selective β1-adrenergic Agonist** **-** Produces mild vasodilation **-** Has more inotropic than chronotropic actions	-Used intermittently (IV) in CCHF		
Nor-epinephrine	✵**β-adrenergic Agonists**	-Was used in cardiogenic shock	-Caused severe vasospasm and gangrene	
Epinephrine	✵**β-adrenergic Agonists**	- Still used in cardiac arrest, by intracardiac injection (works better in young people with better functioning hearts)		

Drugs Used in Heart Failure

Drug	MOA / Effects	Uses	Side Effects	Notes
Vasodilators				
Vasodilators (General View)	✵**Arterial and venous vasodilation** -Affect preload and/or afterload without directly affecting contractility -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 documented to decrease mortality, maybe by reducing remodeling of the heart		-Can be combined with ACEI, diuretics and digitalis
Venous Dilators: ▫**Nitroglycerin** ▫**Isosorbide Dinitrate**	-Cause pooling of blood in veins which will reduce the burden on the right heart → causing decrease in left ventricular end diastolic volume LVEDV and decrease in MVO2	-Decreases the congestive symptoms of heart failure		-Unlike healthy people, decreasing the venous return in HF patient**s will not affect the CO**, because it decreases the congestive symptoms of heart failure
Arterial Dilators: ▫**Hydralazine** ▫**Minoxidil**	-Don't affect the LVEDV, but they will reduce PVR and thus increasing the cardiac output CO, reducing the stress on the left heart and improving organs' blood perfusion			
Mixed Action Drugs	-Will produce the two effects together reducing LVEDV, MVO2 and increasing CO			-Examples include: Nitroprusside, Captopril, Enalapril
BNP – Niseritide & Sacubitril				
BNP - Niseritide	✵**Increases levels of cGMP** -Released under atrial and ventricular stress leading to vasodilation & natriuresis -Reduces systemic and pulmonary vascular resistances → indirect increase in CO and diuresis	-Approved for treatment of acute decompensated CHF -Effective in HF and pulmonary hypertension because of reduction in preload and afterload	-Hypotension is the main side effect	-Brain natriuretic peptide (BNP) is secreted constitutively by ventricular myocytes in response to stretch -Niseritide is a recombinant human form **-BNP is cleaved by Neprilysin**
Sacubitril	✵**Neprilysin inhibitor** -↑BNP -↑Angiotensin II	-Used in combination with valsartan (an ARB) to reduce the risk of cardiovascular events in patients with chronic heart failure		- Neprilysin breaks down BNP, angiotensin I and II, endothelin-1 and peptide amyloid betaprotein.

✵**This summary includes the pharmacological treatment mentioned in sheets 6 and 7. First 6 pages of sheet 6 aren't included.**

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