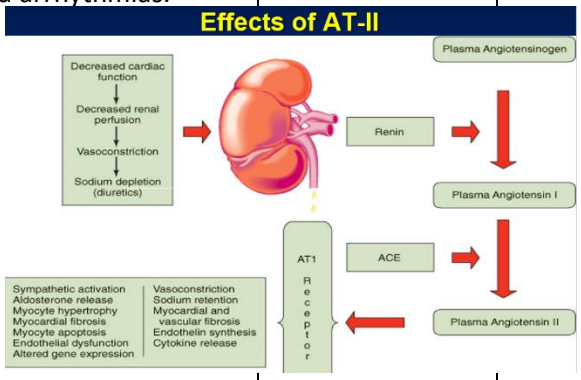
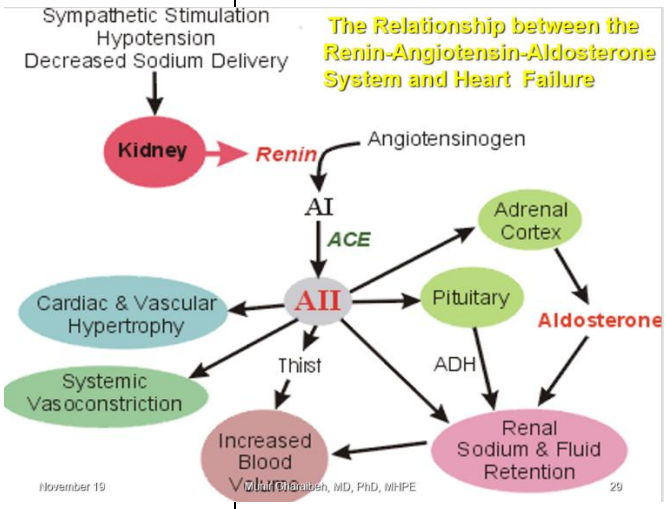
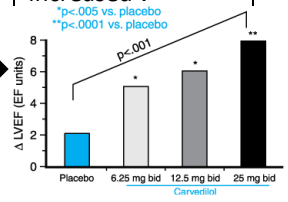
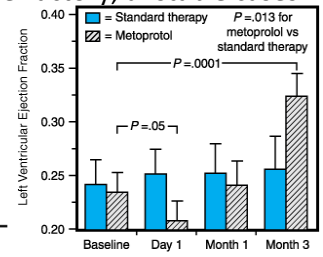
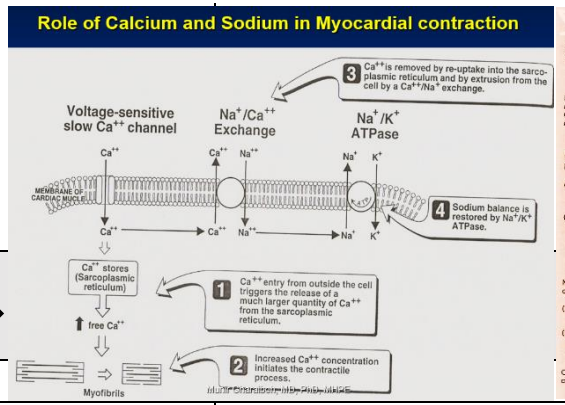
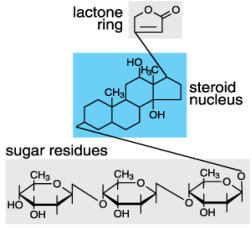
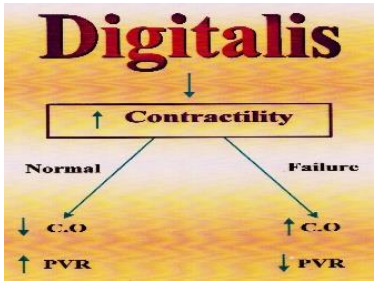
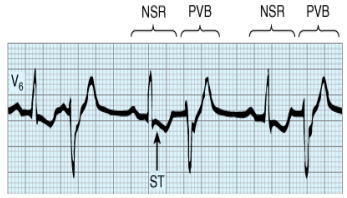
Drug	Mechanism /Action	Uses	Side effects	Notes
Diuretics	Only for congestive symptoms: Don't increase CO (May decrease CO) Causes: K+ loss, Decreased BP, etc...	-Can be used alone initially (IV) -Maybe used in combination with digitalis or others -Can be reduced or withdrawn		<u>Causes of Diuretic Resistance in Heart Failure:</u> -Noncompliance with medical regimen; excess dietary Na+ intake -Decreased renal perfusion and glomerular filtration rate -Selective reduction in glomerular perfusion pressure following initiation (or dose increase) of ACE inhibitor 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" **Captopril** **Enalapril** **Lisinopril** **Quinapril** **Fosinopril** All are similarly effective Might differ in toxicity	<u>Pharmacological Actions:</u> -Blockade of ACE -Reduce angiotensin II levels. -Increase bradykinin. -Inhibit SNS, leading to decreased NE release and upregulation of ?1 receptors. -Balanced vasodilators causing reduction of both afterload and preload -Reduce myocyte & fibroblast growth factors causing reduced cardiac remodeling. -Decrease aldosterone causing decreased fluid retention, decreased K+ loss, and consequently reduced arrhythmias. <u>Cardiorenal Effects of ACE Inhibitors:</u> -Vasodilation (arterial & venous): a. reduce arterial & venous pressure. b. reduce ventricular afterload and preload. -Decrease blood volume: a. natriuretic. b. diuretic. -Depress sympathetic activity. -Inhibit cardiac and vascular hypertrophy.	-Nowadays drugs of choice.	Toxicity: -Hypotension (First dose phenomenon) -Renal Impairment (Proteinuria) -K+ retention -Cough	<u>Therapeutic Values of ACEI:</u> -Nowadays drugs of choice. -No tolerance. -Retard progression of HF. -Decrease arrhythmias. -Proved to decrease mortality, but only when the highest tolerated doses are used.
Angiotensin (AT1) Receptor Blockers "ARBs" **Losartan.**		Not superior to ACEIs, but may be useful for patients who cannot tolerate		





Candesartan. Valsartan. Irbesartan (Approvel). Telmisartan (Micardis).		ACEIs because of cough.		
Beta Blockers	-Traditionally, they have negative inotropic effects. -However, nowadays there is overwhelming evidence to support the use of β-blockers in CHF. -Not useful in refractory HF. -Mechanism involved remains unclear . -Part of their beneficial effects may derive from slowing of heart rate, decreased cardiac work and consequently decreased myocardial O2 consumption and enhanced efficiency . -This would lessen the frequency of ischemic events and arrhythmias. -Suggested mechanisms also include reduced remodeling of the heart muscle. -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. 	-Recent studies with metoprolol, carvedilol, bicindolol, and bisiprolol showed a reduction in mortality in patients treated with these drugs. -This does not mean that other older agents are not effective .
Positive Inotropic Agents	-Logically will improve cardiac function. -These drugs increase force of contraction by increasing intracellular cardiac Ca++ concentration.			
1. Cyclic AMP Independent Agents:				
A.Digitalis Glycosides **Digitalis purpura Digitalis lanata Strophanthus**	Inhibition of Na+/K+ ATPase Actions : -Positive Inotropic Effect -Vascular Muscle Contraction -Vagal Stimulation -Effects on Electrical Properties of Cardiac Tissues.   	-Was widely used in the treatment of heart failure. -Nowadays, use is restricted only to CCHF with supraventricular arrhythmia . a. Might decrease morbidity and improve quality of life.	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.	History: -Egyptians: Squill(العنصل)) -Chinese: Toad skin -William Withering: Foxglove 1785 *<u>Interactions</u> -Pharmacological and toxic effects are greater in hypokalemic patients. -K+-depleting diuretics are a major contributing factor to digoxin toxicity.

		b. Withdrawal might be hazardous. c. Does not improve mortality	*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+ conc. is low or within the normal range. -When the plasma K+ conc is high, antiarrhythmic drugs, such as lidocaine, phenytoin, procainamide, or propranolol, can be used.	
B.Pimobendan	sensitizes myocytes to Ca++, also inhibits PDE.			
2.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 .	severe vasospasm and gangrene	
Epi		Still used in cardiac arrest, by intracardiac injection.		
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 and elevation of blood pressure.	Widely used in cardiogenic shock.	Can cause arrhythmias and ischemic changes.	
Dobutamine	Selective β1 agonist, used intermittently (IV) in CCHF. Produces mild vasodilation. -Has more inotropic than chronotropic actions.	used intermittently (IV) in CCHF		

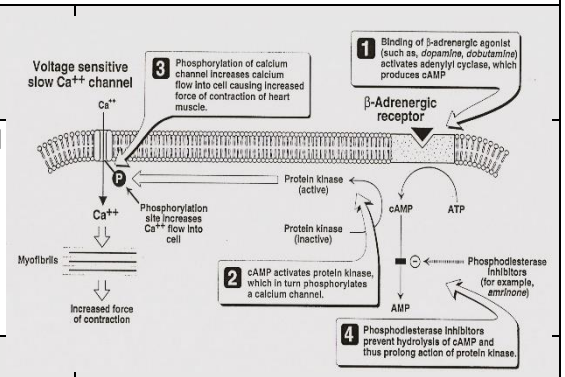
Basic Data of Three Cardiac Glycosides

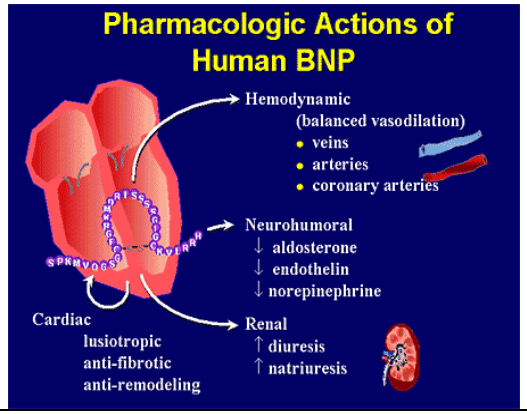
	Digitoxin	Digoxin	Ouabain
GI absorption	100%	70 –85%	0
Polarity	Least	Somewhat	Highest
Protein binding	97%	< 30%	5 – 10%
Half-life	4 – 7 days	1.5-1.6 days	21 hr
Excretion route	Stool and kidneys; as hepatic metabolites*	Kidneys; largely unchanged	Kidneys; largely unchanged
Enterohepatic recycling	27%	6.8%	Unknown
Optimum serum levels	20-35 ng/ml	0.5-2.5 ng/ml	Unknown
V_d	0.6 L/kg	5-10 L/kg	Unknown

* About 8% of digitoxin is metabolized and excreted as digoxin in the urine. Digitoxin seems to be largely recycled to complete its metabolic degradation.

TABLE 13-2 Effects of digoxin on electrical properties of cardiac tissues.

Tissue or Variable	Effects at Therapeutic Dosage	Effects at Toxic Dosage
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



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.	Short acting, so reserved for parenteral therapy of acute heart failure.	Toxic: arrhythmias, and thrombocytopenia.	
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.		*Interactions: -Hydralazine-Isosorbide dinitrate combination was documented to decrease mortality, maybe by reducing remodeling of the heart. -Can be combined with ACEI, diuretics and digitalis.
Brain natriuretic peptide (BNP) **Niseritide (recombinant)**	-BNP binding increase levels of cGMP. -BNP is released under atrial and ventricular stress leading to vasodilation, natriuresis and diuresis. -Reduces systemic and pulmonary vascular resistances, causing an indirect increase in cardiac output and diuresis . 	-Effective in HF and pulmonary hypertension because of reduction in preload and afterload. -Niseritide is a recombinant human BNP approved for treatment of acute decompensated CHF.	Hypotension is the main side effect.	-BNP is secreted constitutively by ventricular myocytes in response to stretch. -Neprilysin cleaves BNP and ANP.
Sacubitril	- Neprilysin inhibitor breaks down angiotensin I and II, endothelin-1 and peptide amyloid beta-protein. -Inhibition of neprilysin therefore leads to reduced breakdown and increased concentration of endogenous natriuretic peptides in addition to increased levels of vasoconstricting hormones such as angiotensin II.	Used in combination with valsartan to reduce the risk of cardiovascular events in patients with chronic heart failure.		It's Neprilysin inhibitor

Saba Alfayoumi

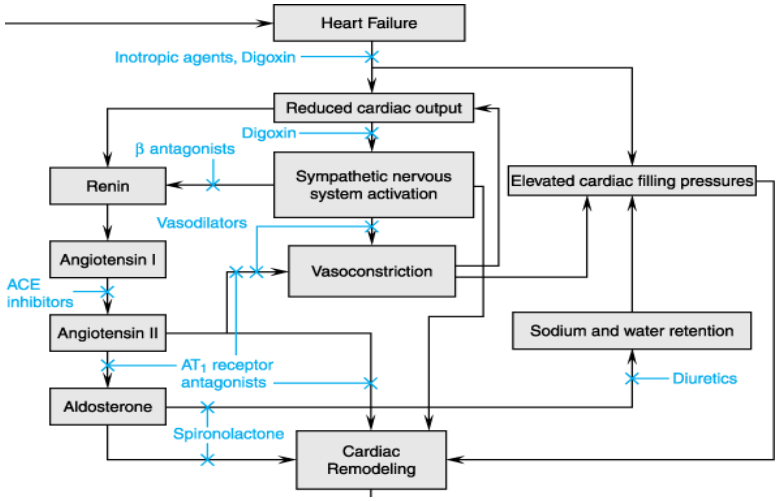
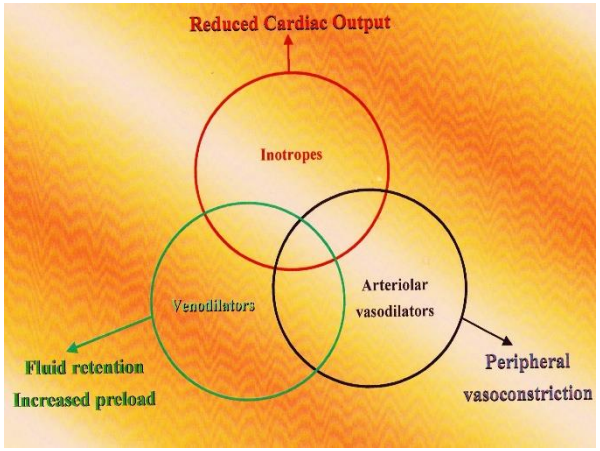


TABLE 13–1 Drug groups used in heart failure.

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	



ACE Inhibitors

Potential Roles of Aldosterone in the Pathophysiology of Heart Failure

MECHANISM	PATHOPHYSIOLOGICAL EFFECT
Increased Na^+ and water retention	Edema, elevated cardiac filling pressures
K^+ and Mg^{2+} loss	Arrhythmogenesis and risk of sudden cardiac death
Reduced myocardial norepinephrine uptake	Potentiation of norepinephrine effects: myocardial remodeling and arrhythmogenesis
Reduced baroreceptor sensitivity	Reduced parasympathetic activity and risk of sudden cardiac death
Myocardial fibrosis, fibroblast proliferation	Remodeling and ventricular dysfunction
Alterations in Na^+ channel expression	Increased excitability and contractility of cardiac myocytes

Vasodilators

Vasodilator Drugs Used to Treat Heart Failure

DRUG CLASS	EXAMPLES	MECHANISM OF VASODILATING ACTION	PRELOAD REDUCTION	AFTERLOAD REDUCTION
Organic nitrates	Nitroglycerin, isosorbide dinitrate	NO-mediated vasodilation	+++	+
Nitric oxide donors	Nitroprusside	NO-mediated vasodilation	+++	+++
Angiotensin-converting enzyme inhibitors	Captopril, enalapril, lisinopril	Inhibition of Ang II generation, decreased bradykinin degradation	++	++
Angiotensin receptor blockers	Losartan, candesartan	Blockade of AT_1 receptors	++	++
Phosphodiesterase inhibitors	Milrinone, inamrinone	Inhibition of cyclic AMP degradation	++	++
Direct-acting K^+-channel agonist	Hydralazine	Unknown	+	+++
	Minoxidil	Hyperpolarization of vascular smooth muscle cells	+	+++
$_1$ Adrenergic antagonists	Doxazosin, prazosin	Selective $_1$ adrenergic receptor blockade	+++	++
Nonselective adrenergic antagonists	Phentolamine	Nonselective adrenergic receptor blockade	+++	+++
Vasodilating adrenergic antagonists	Carvedilol, labetalol	Selective $_1$ adrenergic receptor blockade	++	++
Ca^{2+} channel blockers	Amlodipine, nifedipine, felodipine	Inhibition of L-type Ca^{2+} channels	+	+++
adrenergic agonists	Isoproterenol	Stimulation of vascular $_2$ adrenergic receptors	+	++