

Drugs Used in Heart Failure

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- Can be reduced or withdrawn.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 severe, 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 purpurea** , **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
<u>Atrial</u> 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 pacemaker 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), Vesaniroline (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

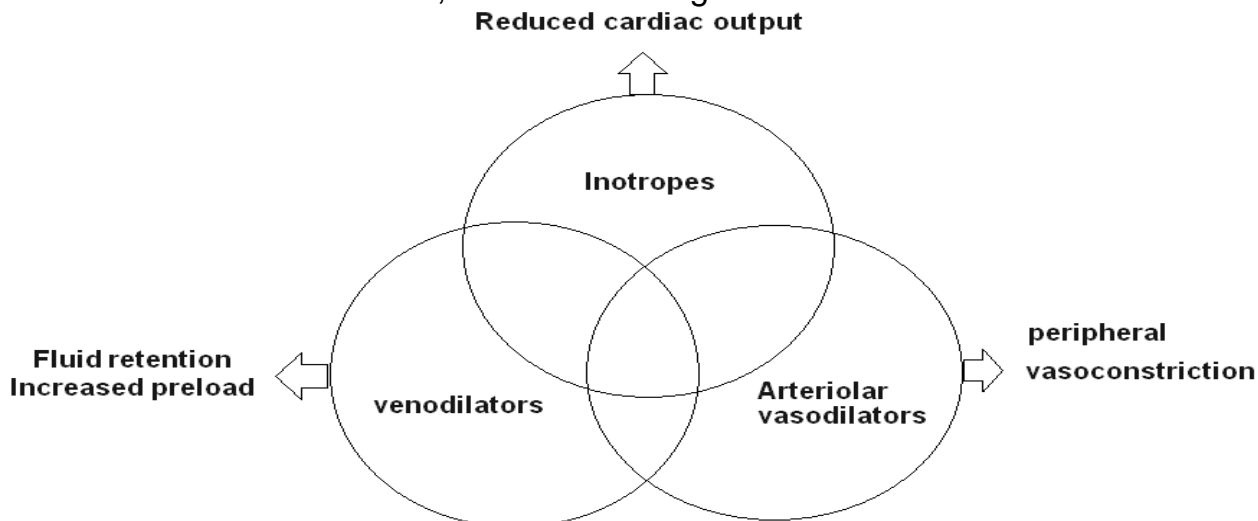
- Affect preload and/or afterload without directly affecting contractility.

- Consequently can decrease myocardial ischemia, enhance coronary blood flow and decrease MVO_2 .

- **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.

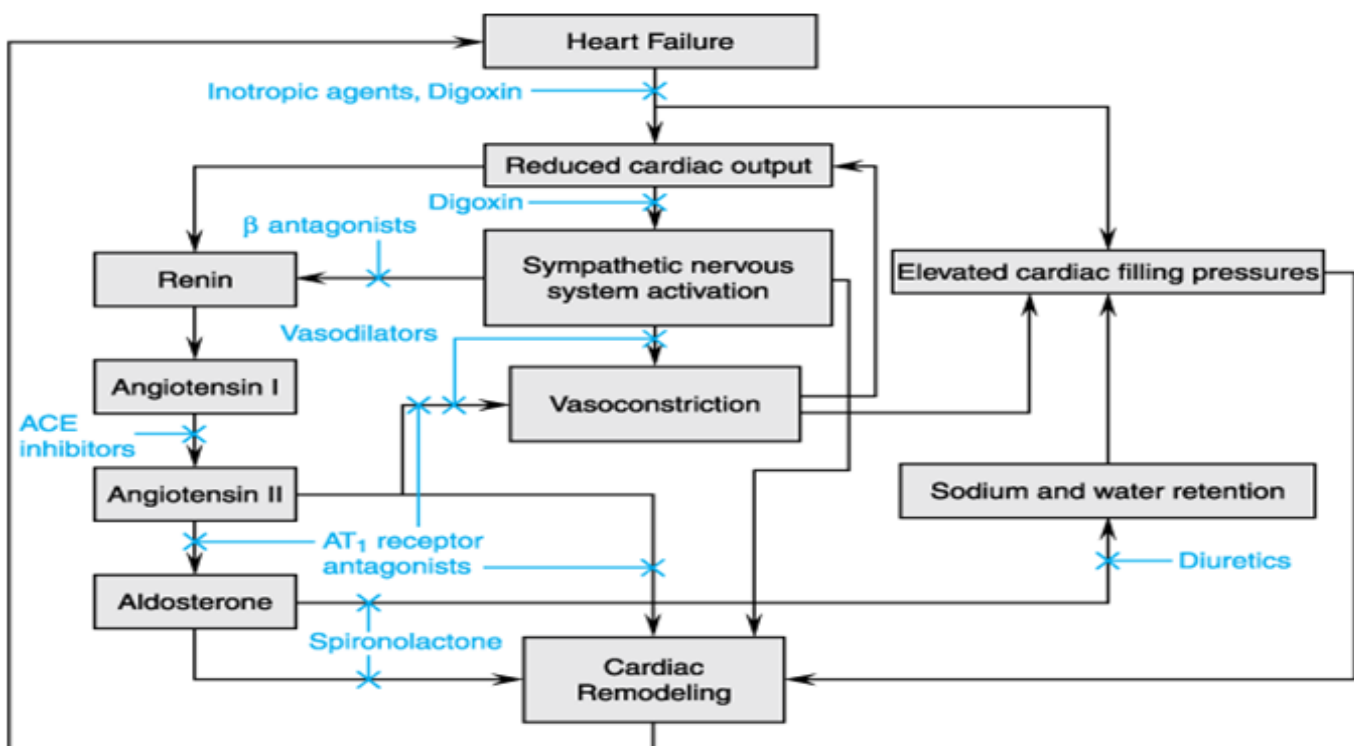


7) (BNP)-Niseritide

- 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