Pharmacotherapy of Heart Failure (CHF)  
Inotropics and Other Agents

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Agents used in HT, CHF, Arrhythmia and Angina

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Hyper-tension</th>
<th>HF</th>
<th>Arrhythmia</th>
<th>Angina</th>
<th>Contraindications/Cautions/Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-Blockers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HF (Cl: unstable HF, broncho-spasm, significant bradycardia, depression); Raynaud D. Caution in diabetes, asthma (use β1-)</td>
</tr>
<tr>
<td>Ca++-Channel blockers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HF, constipation, gingival hyperplasia, edema, reflex tachycardia</td>
</tr>
<tr>
<td>ACEI / ARBs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Angioedema, hyperkalemia, cough (acei), tetrogenic, glossitis, taste</td>
</tr>
<tr>
<td>Diuretics (Thiazides)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GFR &gt;30, hypokalemia (CG); ↑Ca++, diabetes (↓glucose tolerance)</td>
</tr>
<tr>
<td>Cardiac glycosides</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Many Rx interactions, [K+], ↓use HF important, low K+→↑toxicity</td>
</tr>
<tr>
<td>Vasodilators</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Flushing, dizziness, headache, nausea, reflex tachycardia</td>
</tr>
<tr>
<td>Na+-Channel blockers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Effects enhanced in depolarized, damaged tissue, Phase 0, ↓CV</td>
</tr>
<tr>
<td>Nitrates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NO/cGMP, tolerance (off periods), flushing, dizziness, headache, reflex tachycardia, many forms</td>
</tr>
</tbody>
</table>
Congestive Heart Failure (CHF)

CO inadequate for body demand of oxygen (demand-supply)

5 million in USA
50% mortality @ 5 year
500,000 new cases each year

CHF - % Hospitalization

Principal Ambulatory Care Sensitive Conditions Resulting in Hospitalization

- Congest. Heart Failure: 16.10%
- Bacterial Pneumonia: 13.90%
- Diabetes: 11.10%
- Dehydration: 10.49%
- Kidney Infection: 9.28%

Adapted from The Heart, 8th Ed. Page 1062
**Congestive Heart Failure (CHF) - Definition**

**Compensated heart failure:**
- resting cardiac function, OK
- excessive stress or exercise, No

**Congestive heart failure (CHF, Decompensated):**
- resting cardiac function inadequate
- venous pooling $\rightarrow$ edema, especially lungs
- shortness of breath, fatigue
- ejection fraction of less than 40%

**Causes**
- coronary artery disease (70%)
- hypertension
- primary cardiomyopathy
- toxic injury by chemicals
- congenital or genetic abnormalities
- drug: adriamycin

**Hemodynamic Changes**

**“Hormonal Storm”**

**BP is well maintained in CHF:**
- $\uparrow$ sympathetic tone (tachycardia)
- $\downarrow$ parasympathetic tone
- activation of renin-angiotensin system
- $\uparrow$ blood volume
- $\uparrow$ vasopressin release

**Consequences:**
- $\downarrow$ force of contraction
- $\downarrow$ CO, $\uparrow$ TPR, $\downarrow$ stroke volume
- $\uparrow$ venous pressure, $\downarrow$ tissue perfusion
- cardiac hypertrophy
- Na$^+$ & water retention
- edema
**CHF Therapy Overview**

**Non-Drug:**
- exercise as tolerated
- salt restriction

**Drug Therapy:**
A. Positive inotropic agents:
   - cardiac glycosides eg. digoxin, digitoxin
   - catecholamines eg. dobutamine
   - phosphodiesterase III inhibitors eg. inamrinone

B. Beta-blockers (caution) eg. metoprolol

C. Diuretics eg. thiazides, loop, K-sparing

D. ACE inhibitors / ARB eg. lisinopril / losartan

E. Vasodilators (non-inotropic) eg. hydralazine,
   beta-type natriuretic peptide (nesiritide)

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**Heart Physiology**

<table>
<thead>
<tr>
<th>mM</th>
<th>Na⁺</th>
<th>K⁺</th>
<th>Ca²⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>Out</td>
<td>140</td>
<td>4</td>
<td>2.5</td>
</tr>
<tr>
<td>In</td>
<td>10</td>
<td>150</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Cardiac Glycosides inhibit Na⁺/K⁺-ATPase
Cardiac Muscle Contraction

Polarized

Voltage-sensitive slow Ca** channel

Na*/Ca** Exchange

Na*/K** ATPase

Ca** entry from outside the cell triggers the release of a much larger quantity of Ca** from the sarcoplasmic reticulum.

Ca** is removed by re-uptake into the sarcoplasmic reticulum and by extrusion from the cell by a Na*/K** exchange.

Sodium balance is restored by Na*/K** ATPase.

increased Ca** concentration initiates the contractile process.

Mycobacterium

Figure 16.3
Ion movements during the contraction of cardiac muscle.

Cardiac Glycosides

Source:
- white and purple foxglove (Digitalis lanata and D. purpurea)
- Mediterranean sea onion (Strophantus gratus) - ouabain
- numerous other plants
- certain toads

History:
- Egyptians (3000 yr ago) - diuretic effect, tones the heart
- 1785, clinical effect of foxglove plant described (Digitalis purpurea)

Foxglove
Fairy Gloves
Dead Men's Bells
Witches' Gloves
Wooly Foxglove
Lion's Mouth
Bloody Fingers
Cardiac Glycosides Chemistry

Steroid nucleus:
- lipophilic
- essential for activity, OH is very reactive (synthesis)

Unsaturated five-membered lactone ring:
- hydrophilic, essential for activity
- opening the ring → loss of activity
- saturation → loss of activity

Series of sugars linked to C 3 of the steroid nucleus
- nonessential, hydrophilic

Digoxin
Kidney
Digitoxin
Liver (-OH, C12)

Mechanism of Action

Cardiac glycosides (CG)
- Inhibition of Na⁺/K⁺ ATPase (Na⁺ pump)
- membrane bound transporter (3 Na⁺ / 2 K⁺)
- found all over the body, α/β-subunits
- 3 mammalian isoforms
- extracytoplasmic binding site for CG
- phosphorylation of cytosol α-subunit → stabilize CG binding
- ↑ [K⁺]EC → dephosphorylates α-subunit → ↓ CG binding
- ↓ [K⁺]EC → phosphorylates α-subunit → ↑ CG intoxication

Inhibition of (Na+, K+-ATPase)
→ ↓ exchange Na⁺ - K⁺ (3:2)
→ ↑ [Na⁺]IC (8 → 9 - 9.5 mM)
→ ↑ Na⁺ - Ca²⁺ exchange (3:1) (depolarized)
→ ↑ [Ca²⁺]IC
→ ↑ SR uptake Ca²⁺ (↑ stores)
→ ↑ contractile force
Cardiac Muscle Contraction

**Therapeutic consequence of Cardiac Glycosides**

Moderate but persistent positive inotropic effect,
↑ sensitivity of the baroreceptor reflex

→ ↑ CO → ↓ sympathetic activity
→ ↓ HR and vascular tone
→ ↓ pre- and afterload to the heart
→ ↓ heart size
→ ↓ oxygen demand

→ ↑ CO → ↑ renal blood flow
→ improved GFR
→ ↓ renin-angiotensin activity level
→ ↑ Na⁺ excretion → ↓ body Na⁺
→ ↓ volume + vascular reactivity
→ ↓ pre- and afterload
Cardiac effects of Cardiac Gycosides

1. Increase in contractile force (inotropic effect)
2. Increase in vagal activity - cardiac slowing (chronotropic effect)
3. Major effects on electrophysiologic parameters
   a. decreased A-V conductivity due to decreased CV and an increase in the refractory period
   b. EKG changes
      1. T wave becomes inverted
      2. ST segment becomes depressed
      3. PR interval becomes prolonged
4. Heart size is decreased due to more complete ventricular emptying

Summary of the Effects of CHF and the Results of Digitalis Administration

<table>
<thead>
<tr>
<th></th>
<th>Heart Failure</th>
<th>Digitalis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial contractility</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>End diastolic and venous pressure</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Renal blood flow</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Blood volume</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Heart rate</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Heart size</td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>
Frank-Starling Curve

Need to bring curve towards normal without an increase in HR

Digitalis Glycosides

<table>
<thead>
<tr>
<th>Agent</th>
<th>Route</th>
<th>Bioavail. %</th>
<th>Bound%</th>
<th>Peak effect</th>
<th>T1/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td>oral, iv</td>
<td>45-85</td>
<td>25</td>
<td>6 hr</td>
<td>35 hr (kidney)</td>
</tr>
<tr>
<td>Digitoxin</td>
<td>oral, iv</td>
<td>&gt;90</td>
<td>90</td>
<td>12 hr</td>
<td>6-7 day (liver)</td>
</tr>
</tbody>
</table>

Digoxin:
- water insoluble
- absorption by gut bacteria (10% resistant *Eubact. lentum*)
- unchanged excretion by kidney (85%), not removed by dialysis
- 15% liver metabolism, can crosses the placenta

Digitoxin:
- good oral absorption
- mainly metabolized by the liver (cardioactive metabolities)
- large interpatient variations (bacterial flora)
- enterohepatic recycling
### Dosage & Toxicity

<table>
<thead>
<tr>
<th></th>
<th>Digoxin</th>
<th>Digitoxin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic [plasma]</td>
<td>0.5 – 2 ng/ml</td>
<td>10 – 25 ng/ml</td>
</tr>
<tr>
<td>Toxic [plasma]</td>
<td>&gt; 2 ng/ml</td>
<td>&gt; 35 ng/ml</td>
</tr>
</tbody>
</table>

Narrow therapeutic window (50%):
- → oscillatory afterdepolarization
- → ventricular tachycardia

**Toxic effects**
- tachycardia
- delirium
- fatigue
- dizziness
- nausea
- vomiting
- vision disturbances (halo effect, mostly yellow and green)

**Digitalis: Van-Gogh’s “Yellow Period”**

Dr. Gachet

1890
Digoxin Drug Interactions

Many potential interactions:

- Hypokalemia → ↑ CG binding (esp. with diuretics)
- Hyperkalemia → ↓ CG binding (ACEI/ARB, K-sparing)
- Quinidine → displaces CG from tissue binding
- Ca++-blockers → enhance effect (eg. verapamil)
- Catecholamines → enhance toxicity
- Amiodarone → ↑ serum [CG] (↓ clearance)
- Cholestyramine → decrease CG absorption
- Thyroid function/disease
  - Hyperthyroidism - decreases digoxin levels
  - Hypothyroidism - increases digoxin levels
- Antibiotics → ↑ bioavailability (eg. erythromycin)
- Altered renal function and many other drugs

Digoxin Treatment of Toxicity

Digoxin increases quality of life but not survival. Patients must be closely monitored for signs of toxicity OR therapeutic failure (loss of effect).

a. discontinue agent (GC), lower dose
b. discontinue K+ depleting diuretics
c. K+ replacement → ↓ arrhythmias (esp. with diuretics)
d. use of antiarrhythmic agent eg. lidocaine, phenytoin
e. antidigoxin antibodies eg. digoxin immune FAB (used for high toxicities ie. suicide)
Catecholamines

Dobutamine (*Dopamine*)
- short-acting, metabolism by COMT, MAO
- acute, emergency treatment iv
- ↑ cAMP → ↑ Ca++ influx
- can induce angina, arrhythmias (discontinue)
- dopamine can activate renal D-receptors

Phosphodiesterase III Inhibitors:
  Inamrinone (was Amrinone), Milrinone
- acute and chronic treatment
- additional benefit → asthma
- ↑ cAMP → ↑ Ca++ influx (as per catecholamines)
- reported to have less inotropic effect
- long-term higher mortality than cardiac glycosides or other treatments

Catecholamines – Mechanism of Action in CHF

[Diagram showing the mechanism of action of catecholamines and phosphodiesterase III inhibitors in the context of CHF.]
Drugs without Positive Inotropic Effects used in CHF

A. Angiotensin converting enzyme (ACE) inhibitors / ARBs
   - side benefit → hypertension
   - decrease load
   - frontline, increasing in use, ↑ survival
   - used in combination with CG
   - hyperkalemia, dry cough (ACEI only), loss of taste (Zn loss), angioedema (<1%, less with ARBs), glossitis (<5%), tetrogenic
   - need to take before or after meals

\[ \text{Angiotensinogen} \rightarrow \text{Angiotensin I} \rightarrow \text{Angiotensin II} \rightarrow \text{Angiotensinat} \]

\[ \text{BK-R} \rightarrow \text{Bradykinin} \]

\[ \uparrow \text{NO} \]

\[ \uparrow \text{Vasodilation} \]

\[ \downarrow \text{Ischemia} \]

\[ \uparrow \text{Platelet agg} \]

\[ \uparrow \text{inotrope} \]

\[ \rightarrow \text{Enzymatic activity} \]

\[ \rightarrow \text{Blockade} \]

\[ \text{Arts} \rightarrow \text{Angiotensinogen} \]

\[ \text{Renin} \rightarrow \text{Angiotensin I} \]

\[ \text{ACE} \rightarrow \text{Angiotensin II} \]

\[ \text{ACE inhibitors (Lisinopril)} \]

\[ \text{ARBs (Losartan)} \]

\[ \uparrow \text{Vasoconstriction} \]

\[ \uparrow \text{Cell growth} \]

\[ \uparrow \text{Na+/H2O retention} \]

\[ \uparrow \text{SNS activation} \]

\[ \uparrow \text{Aldosterone} \]

\[ \uparrow \text{Antidiuretic hormone} \]

\[ \uparrow \text{Kinins} \]

\[ \uparrow \text{NO} \]

\[ \text{Decreased blood pressure} \]
Guidelines to ACE Inhibitor Therapy

• **Contraindications**
  – Pregnancy (C & D)
  – Renal artery stenosis
  – Renal insufficiency (relative)
  – Hyperkalemia
  – Arterial hypotension
  – Cough
  – Angioedema

• **Alternatives**
  – Hydralazine + ISDN ie Afro-Americans

ACEI – Angioedema; Glossitis

• Angioedema (<1%)
• Dry mouth
• Glossitis (<5%)
• Oral ulceration
• Oral bleeding
Drugs without Positive Inotropic Effects

B. Diuretics (frontline)
- loop (acute & chronic), thiazide diuretics (chronic)
- potassium-sparing used in combo Rx
- ↓ plasma volume → ↓ venous return (preload)
- relieve pulmonary congestion & peripheral edema
- K⁺ loss (loop, thiazides): interaction with CG

C. Direct Vasodilators
- not Ca++ antagonists
- dilation of venous vessels → ↓ preload
- dilation of arterioles → ↓ afterload
- hydralazine → direct vasodilation → relaxation
- nitrates (NO): nitroglycerin, isosorbide dinitrate, nitroprusside
- beta-type natriuretic peptide (iv., severe CHF) → ↑ cGMP

Diuretics: Overview

• Loop diuretics (Furosemide)
  - ↓ Na⁺, H₂O reabsorption: ascending loop of Henle
  - hypokalemia, hypomagnesemia, hypocalcemia
  - ototoxicity, most potent

• Thiazides (Hydrochlorothiazide)
  - ↓ Na⁺, H₂O reabsorption: distal tube
  - hypokalemia, hypercalcemia

• K⁺-sparing (Spironolactone)
  - aldosterone antagonism at collecting tube
  - hyperkalemia, least potent, adjunct
  - decreases mortality
Diuretics: Reduction of volume overload

- ↓ plasma volume
  - ↓ afterload
  - ↓ preload
  - ↓ peripheral edema
  - ↓ pulmonary congestion
  - ↓ HF symptoms

Drugs without Positive Inotropic Effects

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### Actions of Vasodilators

**Ca**\(^{2+}\) Antagonists
- Verapamil
- Diltiazem
- Nifedipine

**Open K\(^{+}\) Channels**
- Minoxidil
- Diazoxide

**Nitric oxide (NO)**
- \(\beta\)-natriuretic peptide
- Nitroprusside
- Nitrates

**Direct Vasodilation**
- Hydralazine

### Vasodilators

- **Ca**\(^{2+}\) channel blockers
  - Relax smooth muscle of arterioles → ↓ TPR
  - High clinical value (in combinations and hypertensive emergencies)

**Hydralazine**
- Direct vasodilation
- Dilate arterioles but not veins
  - ↓ TPR → ↓BP → reflex tachycardia

**Adverse effects:**
- Reflectory sympathetic activation
- Headache, nausea, sweating, flushing
- Palpitations, ↑ HR → angina
- Lupus reaction (mainly in slow acetylators)
Bidil: Isosorbide-dinitrate & Hydralazine

- Approved 2005 for HF in Afro-Americans
- 1st race-based drug
- Blacks do not respond well to ACEIs/ARBs and beta-blockers
- Bidil was found to reduce mortality among blacks by 43%

Isosorbide-dinitrate conversion to NO
↓ vascular tone
↑ venous filling
↓ arterial resistance
↓ cardiac load

Hydralazine
direct ↓ arterial tone
↓ arterial resistance
↓ cardiac load
D. Beta-Blockers

Metoprolol, Carvedilol, Bisoprolol
Main action to decrease HR and catecholamine action on the heart

Positive Actions
- ↓myocardial O$_2$ consumption (demand) by ↓HR and ↓force contraction
- ↓BP → ↓afterload, ↓preload (less)

Negative Actions
- remove positive sympathetic activity
- decrease cardiac contractility

MERIT-HF : Use of Metoprolol in CHF

- Metoprolol vs Placebo
- β$_1$-selective, no ISA, LA-action
- USA & 13 European countries
- Left ventricular ejection fraction <0.40 and NYHA class II-IV heart failure
- Stabilized by optimum standard therapy (any combination of diuretics + ACE inhibitor
- 2.4 years, terminated early after 1 year

- Mortality ↓34%
- Hospitalization ↓29%
- Felt better ↑25%
- Prevent 1 death per 27 patients treated per year
Mechanism of Action

- β-Adrenoceptor blockers
  - Activation of adrenoceptors on heart
  - Cardiac output
  - Peripheral resistance
  - Decrease in blood pressure
  - Renin
  - Angiotensin II
  - Aldosterone
  - Sodium, water retention
  - Blood volume
  - CNS sympathetic outflow
  - BP

Beta-Blockers in CHF: 2002 Guideline

Asymptomatic
- History of myocardial infarction or LVEF <40%

Stable heart failure
- START
- Beta-blocker therapy and titration
- Bronchospasm
- Reduce dose
- STOP

Unstable heart failure
- Any of:
  - Current symptoms at rest
  - Evidence of fluid overload
  - Hypotension
  - Declining renal function
  - Recent hospitalization for intravenous therapy

Unstable heart failure
- If remains unstable, beta-blocker therapy not indicated

Persistent gastrointestinal symptoms, headaches, dizziness
- Occasional severe depression
- Persistent (3 to 6 months)
  - Exertional fatigue, lethargy
  - in patients in otherwise stable condition

Reduce dose
- STOP
- Try another beta-blocker
- Reduce dose
E. Beta-type Natriuretic peptide - Nesiritide (Natrecor)

- binds to A-type receptor on vascular smooth muscle cell
- activates cGMP → muscle relaxation and vasodilation
- arterial & venous dilation → ↓ preload & afterload
- dilation of afferent renal arterioles leads to increased GFR and decreased sodium reabsorption, causing a diuresis
- SNS and RAA systems are also suppressed
  - acute decompensated heart failure
  - use - severe (Class IV) CHF
  - iv administration (T_{1/2}: 20 mins, duration: 2 hrs))
  - Main adverse effect - hypotension

Natriuretic peptides: ANP, BNP, CNP

- atrial natriuretic peptide (ANP, 28 aa), brain natriuretic peptide (BNP, 32 aa) and C-type natriuretic peptide (CNP, 22 aa) are peptides released in response to atrial and ventricular volume/pressure expansion.
- ANP and BNP are released from the atria and ventricles, respectively, and both promote vasodilation and natriuresis.
- BNP, in particular, produces selective afferent arteriolar vasodilation and inhibits sodium reabsorption in the proximal convoluted tubule.
- BNP inhibits renin and aldosterone release and, possibly, adrenergic activation as well.
- ANP and BNP are elevated in chronic heart failure.
- BNP, in particular, has potentially important diagnostic, therapeutic, and prognostic implications: Nesiritide, a recombinant BNP
Type-A natriuretic peptide receptor

Binding of atrial natriuretic peptide, brain natriuretic peptide, or nesiritide to ligand binding domain results in ATP binding, and conformational change in the hinge region allows for activation of the guanylyl cyclase domain and biologic effects.

<table>
<thead>
<tr>
<th>Biologic Effect</th>
<th>BNP</th>
<th>ATII</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasoconstriction</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Diuresis</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Natriuresis</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Sympathetic activity</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Parasympathetic activity</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Renin secretion</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Aldosterone secretion</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Myocyte hypertrophy</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>

Pharmacotherapy of Congestive Heart Failure: 2004

<table>
<thead>
<tr>
<th>NYHA</th>
<th>Pharmacotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I (no limitations on activity)</td>
<td>ACE Inhibitor/AT₁ - RB</td>
</tr>
<tr>
<td>Class II (slight, mild limitation of activity, comfortable at rest)</td>
<td>Digoxin*, Furosemide, ACE Inhibitor/AT₁ - RB, Beta-blocker</td>
</tr>
<tr>
<td>Class III (marked limitation of activity, only comfortable at rest)</td>
<td>Bi-Ventricle pacing, Bidil</td>
</tr>
<tr>
<td>Class IV (complete rest, confined to bed or chair)</td>
<td>Bi-Ventricle pacing, Bidil</td>
</tr>
</tbody>
</table>

Recommended Digoxin not be used in females for routine CHF. 8/10/04
Recommended Pharmacotherapy of CHF requires 4 or more agents
Bidil: (isosorbide dinitrate and hydralazine) African Americans very effective
Summary: Pharmacotherapy of Heart Failure

- Improved survival
  - ACE inhibitors/ARBs, β-blockers, K-sparing
- Increased mortality
  - Phosphodiesterase III inhibitors (chronic)
- Neutral on survival
  - Digoxin, Loop diuretics, Thiazides
- Quality of life
  - Digoxin, Loop diuretics, β-blockers
- Reduction of edema
  - Loop diuretics, Thiazides
- Tissue Remodeling
  - ACE inhibitors/ARBs, K-sparing
- Prevention of ischemia
  - β-blockers, Anticoagulant therapy
- Hemodynamic improvement: All agents
  - ACEI, ARBs, Digoxin, Diuretics, β-blockers, K-sparing

ACC/AHA vs NYHA Classification of HF

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A Asymptomatic with no heart damage but have risk factors for heart failure.</td>
<td>No equivalent</td>
</tr>
<tr>
<td>B Asymptomatic but have signs of structural heart damage</td>
<td>I (Mild) No limitation of physical activity. Ordinarity physical activity does not cause undue fatigue, palpitation, or dyspnea.</td>
</tr>
<tr>
<td>C Have symptoms and structural heart damage</td>
<td>II (Mild) Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.</td>
</tr>
<tr>
<td></td>
<td>III (Mod.) Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.</td>
</tr>
<tr>
<td>D Endstage disease with advanced structural heart disease and marked symptoms at rest and require specialized interventions.</td>
<td>IV (Severe) Unable to carry out any physical activity without discomfort. Cardiac insufficiency at rest.</td>
</tr>
</tbody>
</table>

AHA/ACC classification intended to complement rather than replace the NYHA functional classification.