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>Contradictions/Cautions/Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-Blockers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HF (CI: unstable HF, broncho- spasms, significant bradycardia, depression) Raynaud D: Caution in diabetes, asthma (see 12r)</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, hypokalemia, cough (sex), heterotopic, glossitis, taste</td>
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<tr>
<td>Diuretics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GFR &gt;30, hypokalemia (CG), TCa++, diabetes (glucose tolerance)</td>
</tr>
<tr>
<td>Cardiac glycosides</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Many Rx interactions, [K+]: Lose HF important, low K+ = toxicity</td>
</tr>
<tr>
<td>Vasodilators</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Effects enhanced in depleted, damaged tissue, Phase II, I-CV</td>
</tr>
<tr>
<td>Non-Channel blockers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NOx/GMP, tolerance (off periods), flushing, dizziness, headache, reflex tachycardia, many forms</td>
</tr>
<tr>
<td>Nitrites</td>
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</tbody>
</table>

Congestive Heart Failure (CHF)

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

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

CHF - % Hospitalization
Principal Ambulatory Care Sensitive Conditions Resulting in Hospitalization

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 → edema, esp. 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 (doxorubicin)
**Hemodynamic Changes**

"Hormonal Storm"

BP is well maintained in CHF:
- ↑ sympathetic tone (tachycardia)
- ↓ parasympathetic tone
- activation of renin-angiotensin system
- ↑ blood volume
- ↑ vasopressin release

Consequences:
- ↓ force of contraction
- ↓ CO, ↑ TPR, ↓ stroke volume
- ↑ venous pressure, ↓ tissue perfusion
- cardiac hypertrophy
- Na⁺ & water retention
- edema

**Heart failure: “Hormonal Storm”**

Need to break the cycle

activation of sympathetic nerve system and of renin-angiotensin-aldosterone axis

additional neuro-humoral activation promoted

pumping function disrupted

**Heart Physiology**

Cardiac Muscle Contraction

**Cardiac Glycosides**

Source:
- white and purple foxglove (Digitalis lanata and D. purpurea)
- Mediterranean sea onion (Strophantus gratiss) - 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)
**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

**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
- extracellplasmic 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⁺]EC (8 → 9 - 9.5 mM)
  → ↑ Na⁺ - Ca²⁺ exchange (3:1) (depolarized)
  → ↑ SR uptake Ca²⁺ (↑ stores)
  → ↑ contractile force

**Cardiac Muscle Contraction**

Polarized

Voltage-sensitive store Ca²⁺ channel

Na⁺/Ca²⁺ Exchange

Na⁺/K⁺ ATPase

**Therapeutic consequence of Cardiac Gycosides**

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 cross the placenta

Digitoxin:
- good oral absorption
- mainly metabolized by the liver (cardioactive metabolites)
- large interpatient variations (bacterial flora)
- enterohepatic recycling

**Dosage & Toxicity**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Therapeutic [plasma]</th>
<th>Toxic [plasma]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td>0.5 – 2 ng/ml</td>
<td>&gt; 35 ng/ml</td>
</tr>
<tr>
<td>Digitoxin</td>
<td>16 – 25 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)

**Therapeutic Index**

**Digoxin Drug Interactions**

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypokalemia</td>
<td>↑ CG binding (esp. with diuretics)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>↓ CG binding (ACEI/ARB, K-sparing)</td>
</tr>
<tr>
<td>Quinidine</td>
<td>displaces CG from plasma binding</td>
</tr>
<tr>
<td>Ca**-blockers</td>
<td>enhance effect (eg. verapamil)</td>
</tr>
<tr>
<td>Catecholamines</td>
<td>enhance toxicity</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>↑ serum [CG] (↓ clearance)</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>decrease CG absorption</td>
</tr>
<tr>
<td>Thyroid function/disease</td>
<td>decreases digoxin levels</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>increases digoxin levels</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>↑ bioavailability (eg. erythromycin)</td>
</tr>
<tr>
<td>Altered renal function</td>
<td>and many other drugs</td>
</tr>
</tbody>
</table>

**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

Angiotensin converting enzyme (ACE) inhibitors / ARBs

Captopril, Lisinopril, Enalapril, Losartan (ARB)
- side benefit antihypertensive, decrease load
- frontline, cornerstone therapy, increasing in use, ↑ survival
- used in combination with CG, tissue remodeling
- hyperkalemia, dry cough (ACEI only), loss of taste (Zn loss), angioedema (<1%, less with ARBs), glossitis (<5%), tetrogenic

Angiotensinogen
Renin
Angiotensin I
ACE inhibitors
Angiotensin II
AT II
• Vasodilation
• Anti proliferation
• ↑↑ Kinins
•• NONO
•• Vasoconstriction
•• Cell growth
•• Na+/H2O retention
•• SNS activation
•• Aldosterone
•• Antidiuretic hormone

AT I
Vasodilation
•• Inactive Peptides
•• Bradykinin
•• Enzymatic activity
•• Blockade

Guidelines to ACE Inhibitor Therapy

• Contraindications
  - Pregnancy (C & D)
  - Renal artery stenosis
  - Renal insufficiency (relative)
  - Hyperkalemia
  - Arterial hypotension
  - Dry 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

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

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)
  - Inhibit Na-K-2Cl ion cotransporter, ↓ Na⁺, H₂O reabsorption: ascending loop of Henle
  - hypokalemia, hypomagnesemia, hypocalcemia ototoxicity, most potent
- **Thiazides** (Hydrochlorothiazide)
  - Inhibit Na-Cl symporter, ↓ Na⁺, H₂O reabsorption in distal convoluted tube
  - hypokalemia, hypercalcemia, ↑ uric acid → gout, DM-2
- **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

Actions of Vasodilators

- Ca++ Antagonists
  - Verapamil
  - Diltiazem
  - Nifedipine
- Open K⁺ Channels
  - Minoxidil
  - Diazoxide
- Direct Vasodilation
  - Hydralazine
- Nitric oxide (NO)
  - β-natriuretic peptide
  - Nitroprusside
  - Nitrates
Vasodilators
- 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
- Lupus syndrome

Adverse effects:
- Refractory sympathetic activation
- Headache, nausea, sweating, flushing
- Palpitations, ↑ HR → angina
- Lupus reaction (mainly in slow acetylators)

Bidil: Isosorbide-dinitrate (ISDN) & 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%

Bidil: Isosorbide-dinitrate & Hydralazine
- Conversion to NO
- Direct ↓ arterial tone
- ↓ vascular tone
- ↓ arterial resistance
- ↑ venous filling, ↓ arterial resistance
- ↓ cardiac load

Lupus erythematosus
- Chronic inflammatory disease
- Autoimmune disease

Drug induced: Procainamide, Hydralazine, Isoniazid

Beta-Blockers
Metoprool, Carvedilol, Bisoprolol (EBM)
Main action to decrease HR and catecholamine action on the heart

Positive Actions
- ↓ myocardial O₂ consumption (demand) by ↓ HR and ↓ force contraction
- ↓ BP → ↓ afterload, ↓ preload (less)

Negative Actions
- Remove positive sympathetic activity
- Decrease cardiac contractility

Clinical use – Beta-blockers
<table>
<thead>
<tr>
<th>Class/Drug</th>
<th>HT</th>
<th>Angina</th>
<th>Arrh</th>
<th>MI</th>
<th>HF</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-selective β₁/β₂</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Carteolol</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ISA; long acting; also for glaucoma</td>
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<tr>
<td>Carvedilol</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>ISA; α-blocking activity</td>
</tr>
<tr>
<td>Labetalol</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>ISA; α-blocking activity</td>
</tr>
<tr>
<td>Nadolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>Long acting</td>
</tr>
<tr>
<td>Pindolol</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ISA; MSA</td>
</tr>
<tr>
<td>Propranolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>MSA; prototypical beta-blocker</td>
</tr>
<tr>
<td>Sotalol</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Also K-channel blocker</td>
</tr>
<tr>
<td>Timolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>ISA; MSA</td>
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<tr>
<td>β₁-selective</td>
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<tr>
<td>Acebutolol</td>
<td>X</td>
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<td></td>
<td>ISA</td>
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<tr>
<td>Atenolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>ISA</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>ISA</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ISA; MSA</td>
</tr>
<tr>
<td>Esmolol</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Short acting; arrhythmia</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>ISA; short acting; arrhythmia</td>
</tr>
</tbody>
</table>
MERIT-HF: Use of Metoprolol in CHF

- Metoprolol vs Placebo, USA & 13 other countries
- $\beta_1$-selective, no ISA, LA-action
- LVEF <0.40 and NYHA class II-IV heart failure
- Stabilized by optimum standard therapy (diuretics/ACEI)
- 2.4 years, terminated early after 1 year

- Mortality ↓34%
- Risk ↓39%
- Hospitalization ↓29%
- Felt better ↑25%
- Prevent 1 death per 27 patients treated per year

Beta-blockers on survival in chronic heart failure

Beta-Adrenoceptor Antagonists

Multiple possible mechanisms of action:

1. CNS effect to decrease sympathetic NS tone
2. ↓renin secretion: beta1-receptors mediate renin release
3. block cardiac beta1-receptors: ↓HR →↓CO →↓BP

Beta-Blockers in CHF: 2002 Guideline

- 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 (T1/2: 20 mins, duration: 2 hrs))
- Main adverse effect - hypotension

Beta-type Natriuretic peptide - Nesiritide (Natrecor)

- 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 vasodilatation and natriuresis.
- BNP, in particular, produces selective afferent arteriolar vasodilatation 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 neprilysin to lidag binding domain results in ATP binding, and conformational change in the hinge region allows for activation of the guanylyl cyclase domain and biologic effects.

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, Thiazides, 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

Pharmacotherapy of Congestive Heart Failure: 2004

NYHA Pharmacotherapy

<table>
<thead>
<tr>
<th>NYHA Classification</th>
<th>Pharmacotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I (no limitations on activity)</td>
<td>ACE Inhibitor/AT1 - R, Beta-blocker</td>
</tr>
<tr>
<td>Class II (slight, mild limitation of activity, comfortable at rest)</td>
<td>Digoxin*, Furosemide, ACE Inhibitor/AT1 - R, Beta-blocker</td>
</tr>
<tr>
<td>Class III (marked limitation of activity, only comfortable at rest)</td>
<td>Bi-Ventricle pacing, Bi-Blocker, Weight loss, Diuretics</td>
</tr>
<tr>
<td>Class IV (complete rest, confined to bed or chair)</td>
<td>Bi-Ventricle pacing, Bi-Blocker, Beta-blocker, Weight loss, Diuretics</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 (ISDN) and hydralazine) African Americans very effective

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)</td>
</tr>
<tr>
<td>C Have symptoms and structural heart damage</td>
<td>II (Mild)</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)</td>
</tr>
</tbody>
</table>

NYHA (2004) ACC/AHA classification intended to complement rather than replace the NYHA functional classification

Comparative Hemodynamic Effects of Agents Administered in Acute Heart Failure

<table>
<thead>
<tr>
<th>Compound</th>
<th>HR MAP PCWP CO SVR</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nesiritide</td>
<td>0 ↑ ↓ ↑ ↑</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>0/1 ↑ ↑ ↑</td>
<td>Arrhythmias, angina, palpitations</td>
</tr>
<tr>
<td>Digoxin</td>
<td>0 ↓ ↑ ↓ ↑</td>
<td>Arrhythmias, palpitations</td>
</tr>
<tr>
<td>Minimine</td>
<td>0/1 ↓ ↑ ↑</td>
<td>Arrhythmias, hypertension</td>
</tr>
<tr>
<td>Dopamine Lo</td>
<td>0 0 0 0</td>
<td>Arrhythmias, hypertension, angina, decreased peripheral perfusion</td>
</tr>
<tr>
<td>Dopamine Hi</td>
<td>↑ ↑ ↑ ↑ ↑</td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>0/1 ↑ ↑ ↑</td>
<td>Headache, dizziness, reflex tachycardia, hypotension</td>
</tr>
<tr>
<td>Nitropresside</td>
<td>0/1 ↓ ↓ ↓</td>
<td>Same as nitroglycerin, plus thiocyanate toxicity</td>
</tr>
<tr>
<td>Furosemide</td>
<td>0 0 0 0</td>
<td>Hypokalemia, hypocalcemia, hypomagnesemia, orthostatic hypotension</td>
</tr>
</tbody>
</table>

PCWP = pulmonary capillary wedge pressure, SVR = systemic vascular resistance

Anti-adrenergic Agents/treatments with Phase II or III Heart failure Clinical Trial Data

<table>
<thead>
<tr>
<th>Compound</th>
<th>β1-AR blockade</th>
<th>β2-AR blockade</th>
<th>β3-AR blockade</th>
<th>NE blockade</th>
<th>NO release</th>
<th>ISB, human</th>
<th>β1/β2 agonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvedilol</td>
<td>++++</td>
<td>+++</td>
<td>+++</td>
<td>NE</td>
<td>NO</td>
<td>ISB, human</td>
<td>β1/β2 agonist</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>NE</td>
<td>NO</td>
<td>ISB, human</td>
<td>β1/β2 agonist</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>NE</td>
<td>NO</td>
<td>ISB, human</td>
<td>β1/β2 agonist</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>NE</td>
<td>NO</td>
<td>ISB, human</td>
<td>β1/β2 agonist</td>
</tr>
<tr>
<td>Clonidine</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>+</td>
<td>ISB, human</td>
<td>β1/β2 agonist</td>
</tr>
</tbody>
</table>

([Cardioid stress Simulation]) | 0 | 0 | 0 | +++++ | + | ISB, human | β1/β2 agonist |