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 (CI: 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+], luse 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 Deaths

Deaths From Congestive Heart Failure, U.S., 1968-2002

Source: Vital Statistics of the United States, NCHS.

Year

Deaths (Thousands)


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

Adapted from The Heart, 8th Ed. Page 1092
CHF - % Hospitalization

Principal Ambulatory Care Sensitive Conditions Resulting in Hospitalization

1991 - 1994

- Kidney infection: 9.28%
- Dehydration: 16.49%
- Diabetes: 11.18%
- Congest. Heart Failure: 16.10%
- Bacterial Pneumonia: 13.90%

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

vicious cycle

heart tissue remodeling (hypertrophy)

cardiomyopathy
	pumping function disrupted

Figure 16.4
Cardiovascular consequences of heart failure.
CHF Therapy Overview

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

**Drug Therapy:**
A. Positive inotropic agents:
   - cardiac glycosides eg. digoxin
   - 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)

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

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

2. Increased Ca**+ concentration initiates the contractile process.

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

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

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.

Increased Ca** concentration initiates the contractile process.

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

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

Figure 15.3 Ion movements during the contraction of cardiac muscle.

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 Glycosides

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>Biovail. %</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 metabolites)
- 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
dizziness
nausea
vomiting
vision disturbances (halo effect, mostly yellow and green)

Therapeutic Index

![Therapeutic Index diagram showing ratios of fatal dose to effective dose for various substances.](image)
**Digoxin Drug Interactions**

Many potential interactions:

- **Hypokalemia** → ↑ CG binding (esp. with diuretics)
- Hyperkalemia → ↓ CG binding (ACEI/ARB, K-sparing)
- Quinidine → displaces CG from plasma 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
- $\uparrow$ cAMP $\rightarrow$ $\uparrow$ 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 $\rightarrow$ asthma
- $\uparrow$ cAMP $\rightarrow$ $\uparrow$ 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

Renin-Angiotensin System

- Angiotensinogen
- Renin
- Angiotensin I
- Angiotensin II
- ACE inhibitors
- ARBs
- BK-R
- Bradykinin
- Enzymatic activity
- Blockade
- NO
- Vasodilation
- Ischemia
- Platelet agg
- Inotrope
- Vasoconstriction
- Cell growth
- Na+/H2O retention
- SNS activation
- Aldosterone
- Antidiuretic hormone
- Vasoconstriction
- Anti proliferation
- Kinins
- NO

- Enzymatic activity
- Blockade

- Output of sympathetic nervous system
- Vasodilation of vascular smooth muscle
- Retention of sodium and water
- Levels of bradykinin
- Decreased blood pressure
Actions of Angiotensin-Converting Enzyme (ACE) Inhibitors/ARBs

- decrease activity of sympathetic NS
- ↓ TPR, CO unchanged, HR unchanged
- no reflex ↑ HR, probably due to resetting (↓) of baroreceptor reflex sensitivity
- ↓ aldosterone production → ↓ Na/water retention
- ↑ bradykinin level (inhibit metabolism, only ACEIs)
- improves intrarenal hemodynamics
- less effective in elderly and Afro-Americans

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

Glossitis

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
  - ↓ peripheral edema
  - ↓ HF symptoms
  - ↓ preload
  - ↓ pulmonary congestion

↓ HF symptoms
Drugs without Positive Inotropic Effects

Diuretics (frontline)
- loop (acute & chronic), thiazide diuretics (chronic)
- potassium-sparing used in combo Rx
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Actions of Vasodilators

<table>
<thead>
<tr>
<th>Ca++ Antagonists</th>
<th>Open K⁺ Channels</th>
<th>Nitric oxide (NO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verapamil</td>
<td>Minoxidil</td>
<td>β-natriuretic peptide</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Diazoxide</td>
<td>Nitroprusside</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Direct Vasodilation</td>
<td>Nitrates</td>
</tr>
</tbody>
</table>

Diagram:
- Serotonin (5-HT) → cAMP → relaxation
- nNOS → NO → cyclic GMP → relaxation
- NO → cGMP → relaxation
- Nitric oxide (NO): nitroglycerin, isosorbide dinitrate, nitroprusside
- beta-type natriuretic peptide (iv., severe CHF) → ↑ cGMP

Diagram:
- Ca²⁺ channels
- Ca²⁺-calmodulin complex
- MLCK* → MLC kinase (MLCK)
- MLC kinase (MLCK) → MLC-Po₂
- MLC-Po₂ → Actin → Contraction
- MLCK* → MLC kinase (MLCK)
- MLC kinase (MLCK) → MLC-Po₂ → Relaxation
- Nitric oxide (NO): nitroglycerin, isosorbide dinitrate, nitroprusside
- beta-type natriuretic peptide (iv., severe CHF) → ↑ cGMP
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:
- reflexory 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

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

**Hydralazine**
- Direct ↓ arterial tone
  - ↓ arterial resistance

Lupus erythematosus

- Chronic inflammatory disease
- Autoimmune disease

Drug induced: Procainamide, Hydralazine, Isoniazid
Beta-Blockers

Metoprolol, Carvedilol, Bisoprolol (EBM)

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

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 $\beta_1$/$\beta_2$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</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>$\alpha$-blocking activity</td>
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<tr>
<td>Labetalol</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td>ISA; $\alpha$-blocking activity</td>
</tr>
<tr>
<td>Nadolol</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td>long acting</td>
</tr>
<tr>
<td>Penbutolol</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td>ISA</td>
</tr>
<tr>
<td>Pindolol</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>ISA; MSA</td>
</tr>
<tr>
<td>Propranolol</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</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></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>primarily used for glaucoma</td>
</tr>
<tr>
<td>$\beta_1$-selective</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td>Acebutolol</td>
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<td>X</td>
<td></td>
<td></td>
<td>ISA</td>
</tr>
<tr>
<td>Atenolol</td>
<td>X</td>
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<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>Betaxolol</td>
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<td>X</td>
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<td></td>
<td>MSA</td>
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<tr>
<td>Bisoprolol</td>
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<td>X</td>
<td></td>
<td>X</td>
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<tr>
<td>Esmolol</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>short acting; operative arrhythmia</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>MSA</td>
</tr>
</tbody>
</table>
MERIT-HF: Use of Metoprolol in CHF

- Metoprolol vs Placebo, USA & 13 other countries
- β₁-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

- US carvedilol study: Carvedilol (n = 696)
  - Placebo (n = 399)
  - Risk reduction = 63%
  - P < 0.001

- CIBIS II: Bisoprolol (n = 1227)
  - Placebo (n = 1133)
  - Risk reduction = 34%
  - P < 0.0001

- MERIT-HF: Metoprolol CR/XL (n = 1996)
  - Placebo (n = 2001)
  - Risk reduction = 34%
  - P = 0.0062

- COPERNICUS: Carvedilol (n = 1156)
  - Placebo (n = 1133)
  - Risk reduction = 35%
  - P = 0.0014
Beta-Adrenoceptor Antagonists

Multiple possible mechanisms of action:

i. CNS effect to decrease sympathetic NS tone

ii. ↓ renin secretion: beta1-receptors mediate renin release

iii. block cardiac beta1-receptors: ↓HR → ↓CO → ↓BP

Beta-Blockers in CHF: 2002 Guideline
**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 (T₁/₂: 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><strong>Class I</strong> (no limitations on activity)</td>
<td>ACE Inhibitor/AT₁ - RB</td>
</tr>
<tr>
<td><strong>Class II</strong> (slight, mild limitation of activity, comfortable at rest)</td>
<td>Digoxin*, Furosemide, ACE Inhibitor/AT₁ - RB, Beta-blocker</td>
</tr>
<tr>
<td><strong>Class III</strong> (marked limitation of activity, only comfortable at rest)</td>
<td>Bi-Ventricle pacing, Bidil, Digoxin*, Furosemide, Thiazide, ACE Inhibitor/AT₁ - RB, Beta-blocker/K+-sparing</td>
</tr>
<tr>
<td><strong>Class IV</strong> (complete rest, confined to bed or chair)</td>
<td>Bi-Ventricle pacing, Bidil, Digoxin*, Furosemide (IV), Thiazide, ACE Inhibitor/AT₁ - Receptor blocker, K+-sparing/Inotropic therapy/Beta-type Natriuretic peptide</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
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

ACC/AHA vs NYHA Classification of HF

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>No equivalent</td>
</tr>
<tr>
<td>B</td>
<td>I (Mild)</td>
</tr>
<tr>
<td>C</td>
<td>II (Mild)</td>
</tr>
<tr>
<td></td>
<td>III (Mod.)</td>
</tr>
<tr>
<td>D</td>
<td>IV (Severe)</td>
</tr>
</tbody>
</table>

AHA/ACC 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></th>
<th>HR</th>
<th>MAP</th>
<th>PCWP</th>
<th>CO</th>
<th>SVR</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nesiritide</td>
<td>○</td>
<td>↓</td>
<td>↓</td>
<td>○</td>
<td>↑</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>○↑</td>
<td>○</td>
<td>↓</td>
<td>○</td>
<td>↓</td>
<td>Arrhythmias, angina, palpitations</td>
</tr>
<tr>
<td>Digoxin</td>
<td>↓</td>
<td>○</td>
<td>↑</td>
<td>○</td>
<td>↓</td>
<td>Arrhythmias, palpitations</td>
</tr>
<tr>
<td>Milrinone</td>
<td>○↑</td>
<td>○</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>Arrhythmias, hypotension</td>
</tr>
<tr>
<td>Dopamine Lo</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>↑</td>
<td>Arrhythmias, hypertension, angina, decreased peripheral perfusion</td>
</tr>
<tr>
<td>Dopamine Hi</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>○↑</td>
<td>○↓</td>
<td>↓</td>
<td>○</td>
<td>○↓</td>
<td>Headache, dizziness, reflex tachycardia, hypotension</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>○↑</td>
<td>○↓</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>Same as nitroglycerin, plus thiocyanate toxicity</td>
</tr>
<tr>
<td>Furosemide</td>
<td>○</td>
<td>○</td>
<td>↓</td>
<td>○</td>
<td>○</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 (Device)</th>
<th>β₁-AR blockade</th>
<th>β₂-AR blockade</th>
<th>α₁-AR blockade</th>
<th>β₂-AR effects</th>
<th>NE lowering</th>
<th>NO release</th>
<th>ISA, human</th>
<th>β₁,Arg/Arg inverse agonism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvedilol</td>
<td>++++</td>
<td>+++</td>
<td>+++</td>
<td>Antagonist</td>
<td>+</td>
<td>0−</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>++++</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0−</td>
<td>0</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>++++</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>?</td>
<td>0</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>++++</td>
<td>+</td>
<td>0</td>
<td>?</td>
<td>?</td>
<td>+++</td>
<td>0</td>
<td>?</td>
</tr>
<tr>
<td>Clonidine</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>++++</td>
<td>?</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>(Carotid sinus Stimulation)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>++++</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>