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-</th>
<th>HT</th>
<th>Arthyr-</th>
<th>Angina</th>
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<td>Beta-Blockers</td>
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<td>Ca++-Channel blockers</td>
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<td>ACEI / ARBs</td>
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<td>Diuretics (Thiazides)</td>
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<td>Cardiac glycosides</td>
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<td>Nitrates</td>
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<td>Na+-Channel blockers</td>
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<td>Vasodilators</td>
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<td>Non-Channel blockers</td>
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Contraindications/Cautions/Notes:

HF (Co: unstable HF, bronchoospasm, significant bradycardia, depression): Raynaud D. Caution in diabetes, asthma (see pt)

HF, constipation, gingival hyperplasia, edema, reflex tachycardia

Angioedema, hyperkalemia, cough (aee), tetrogic, glossitis, taste

GFR >30, hyperkalemia (CG), Tc+++, diabetes (glucose tolerance)

Many Rx interactions, [K+], Low HF important, low K+-hyperosmotic

Flushing, dizziness, headache, nausea, reflex tachycardia

Effects enhanced in depolarized, damaged tissue, Phase 0, I-CV

NOS/GMP, tolerance (off periods), flushing, dizziness, headache, reflex tachycardia, many forms

...
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, 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

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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

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

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

Cardiac Glycosides

Source:
- white and purple foxglove (Digitalis lanata and D. purpurea)
- Mediterranean sea onion (Strophantus gratissimo) - 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 Muscle Contraction

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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)

Figure 10-4. Structure of digoxin, a typical cardiac glycoside.

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⁺]ᵢC → dephosphorylates α-subunit → ↓ CG binding
- ↓ [K⁺]ᵢC → phosphorylates α-subunit → ↑ CG intoxication

Inhibition of (Na⁺, K⁺-ATPase)
- ↓ exchange Na⁺ - K⁺ (3:2)
- ↑ [Na⁺]ᵢC (6 → 9 - 9.5 mM)
- ↑ Na⁺ - Ca⁺⁺ exchange (3:1) (depolarized)
- ↑ [Ca⁺⁺]ᵢC
- ↑ SR uptake Ca⁺⁺ (↑ stores)
- ↑ contractile force

Cardiac Muscle Contraction

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>
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<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 metabolites)
- large interpatient variations (bacterial flora)
- enterohepatic recycling

Dosage & Toxicity

<table>
<thead>
<tr>
<th></th>
<th>Digoxin</th>
<th>Digitoxin</th>
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</thead>
<tbody>
<tr>
<td>Therapeutic [plasma]</td>
<td>0.5–2 ng/ml</td>
<td>15 – 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”

Digitalis Van-Gogh’s “Yellow Period”
Dr. Gachet

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)

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

Drugs without Positive Inotropic Effects used in CHF

**A. Angiotensin converting enzyme (ACE) inhibitors / ARBs**
- Captopril, Lisinopril, Enalapril, Losartan (ARB)
  - 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

**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

**Catecholamines – Mechanism of Action in CHF**

**Renin-Angiotensin System**

**ACEI – Angioedema; Glossitis**

- Angioedema (<1%)
- Dry mouth
- Glossitis (<5%)
- Oral ulceration
- Oral bleeding

**Angiotensigen**

**Renin**

**Angiotensinogen**

**ACE inhibitors**

**ACE**

**Angiotensin I**

**AT I**

- Vasodilation
- Decreased blood pressure

**AT II**

- Vasodilatation
- Anti proliferation
- ↓ Renin

**Angiotensin II**

**Inactive Peptides**

**Vasodilation**

**↓ Ischemia**

**↓ Platelet agg**

**↑↑ inotrope**

**↑↑ Kinins**

**↑↑ NONO**

**Vasoconstriction**

**Cell growth**

**Na+/H2O retention**

**SNS activation**

**Aldosterone**

**Antidiuretic hormone**

**Enzymatic activity**

**Blockade**

**Bradykinin**

**Inactive Peptides**

**↑↑ Vasodilation**

**↓↓ Ischemia**

**↓↓ Platelet agg**

**⊕⊕ inotrope**
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: Reduction of volume overload

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

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

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

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%

Bidil: Isosorbide-dinitrate & Hydralazine

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

Hydralazine
- direct ↓ arterial tone

D. Beta-Blockers

Metoprolol, Carvedilol, Bisoprolol
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

MERIT-HF : Use of Metoprolol in CHF

- Metoprolol vs Placebo
- β₁-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

- CNS sympathetic outflow ↓
- BP ↓
- Decrease in blood pressure
- arterioles
- arterioles
- venules
- blood volume

Beta-Blockers in CHF: 2002 Guideline

- Asymptomatic history of myocardial infarction or LVEF < 40%
- Stable heart failure
- Unstable heart failure
- Persistent general-intestinal symptoms, headache, edema
- Persistent oligo-anuria
- Uncontrolled hypertension
- Hemodynamic instability
- If remains unstable, beta-blocker therapy not indicated
- Uncontrolled heart failure
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 (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.

Pharmacotherapy of Congestive Heart Failure: 2004

NYHA Pharmacotherapy
Class I (no limitations on activity) ACE Inhibitor AT1 - RB
Class II (slight, mild limitation of activity, comfortable at rest) Digoxin*, Furosemide, ACE Inhibitor AT1 - RB, Beta-blocker
Class III (marked limitation of activity, only comfortable at rest) Bi-Ventricle pacing Bidil
Class IV (complete rest, confined to bed or chair) Digoxin*, Furosemide, Thiazide, ACE Inhibitor AT1 - RB, Beta-blocker, K+-sparring

Bidil: (isosorbide dinitrate and hydralazine) African Americans very effective

Recommended Digoxin not be used in females for routine CHF. 8/10/04
Recommended Pharmacotherapy of CHF requires 4 or more agents

- ACE Inhibitor/AT1 - RB
- Beta-blocker

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

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<tbody>
<tr>
<td>A</td>
<td>Asymptomatic with no heart damage but have risk factors for heart failure.</td>
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<tr>
<td>B</td>
<td>Asymptomatic but have signs of structural heart damage</td>
</tr>
<tr>
<td>C</td>
<td>Have symptoms and structural heart damage</td>
</tr>
<tr>
<td>D</td>
<td>Endstage disease with advanced structural heart disease and marked symptoms at rest and require specialized interventions</td>
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IV (Severe) | Unable to carry out any physical activity without discomfort. Cardiac insufficiency at rest.

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