Heart Failure (II) Management

R. Zolty
Goal of HF Treatment

“I can’t breathe”

“I can walk 30 minutes without stopping”
Case Study: JB

- 19 year old Caucasian man with known dilated CM and LVEF <20%
- Medications
  - Cozaar 50 mg BID
  - Aldactone 25mg QD
  - Lasix 40 mg QAM, 20mg QPM,
  - Digoxin 0.125 mg QD,
  - Isordil 20 mg TID
  - Hydralazine 25mg TID
- Subj: c/o nausea, vomiting, fatigue, abd pain and distension, no CP/↑ SOB
Case Study: JB

On exam:
- BP 78/-; HR 120 bpm
- JVP ↑↑↑↑, Chest Clear
- Labs: Cardiac enzymes wnl;
- Cr 2.8; K⁺ 5.5
- EKG: Tachycardia; P-R 0.18; LBBB
- CXR: Cardiomegaly; vascular redistribution
- Echocardiogram: EF 10%; Global HK; severe MR and TR
Q To ensure optimal therapy, the most important change would be to

- Increase diuretic dosage
- Decrease ARB/Hydralazine/Isordil
- Admit Patient
- Add a $\beta$-blocker
Q  Next Step:
  • Give patient N/S
  • Give patient IV Lasix
  • Send patient to ER
  • Admit patient to the floor
  • Admit patient to CCU
Goals Of Acute Therapy

• Reduce extracellular fluid volume excess
• Improve hemodynamics
  – Decrease left and right ventricular filling pressures
  – Increase cardiac output
• Maintain systemic perfusion pressure
## Clinical Profiles of HF

### Congestion at Rest

<table>
<thead>
<tr>
<th>Low Perfusion at Rest</th>
<th>NO</th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warm &amp; Dry</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Warm &amp; Wet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold &amp; Dry</td>
<td>L</td>
<td>C</td>
</tr>
<tr>
<td>Cold &amp; Wet</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Possible Evidence of Low Perfusion:
- Narrow pulse pressure
- Sleepy / obtunded
- Low serum sodium
- Cool extremities
- Hypotension with ACE inhibitor
- Renal/hepatic dysfunction

#### Signs/Symptoms of Congestion:
- Orthopnea / PND
- JV Distension
- Hepatomegaly
- Edema
- Rates
- Abd-Jugular Reflex
Algorithm for Acute HF Treatment

Goal of Therapy

- Reduce PCWP (rales, edema)
  - CO low
    - Diuretics
    - Nitroprusside
    - Milrinone
    - Dobutamine+NP

- Improve CO (fatigue, ↑ BUN)
  - PCWP low
    - Fluids

- BP Support (symptomatic)
  - Dopamine (high)
  - Levophed
## Treatment Decisions in HF

<table>
<thead>
<tr>
<th>Warm &amp; Dry</th>
<th>Warm &amp; Wet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimize orally</td>
<td>Diuretics Vasodilators</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cold &amp; Dry</th>
<th>Cold &amp; Wet</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV inotropes</td>
<td>IV inotropes and/or vasodilators</td>
</tr>
</tbody>
</table>
Common Used IV Medication For Acute Heart Failure

- Diuretics
- Nitrates
- Nipride
- Nesiritide
- Dobutamine
- Milrinone
- Dopamine
Case Study: JB

- The patient was admitted to the CCU I/V furosemide 40 mg given; resulted in 0.5 L diuresis
- BP 84/48 HR 110 bpm and patient felt slightly better
Q: To ensure optimal therapy, the most important change would be to

Add Dopamine?

Add Dobutamine?

Add a β-blocker?

I/V NTG or nitroprusside

Other IV inotropic therapy

Hemodynamic evaluation (right heart catheterization)
Heart Failure results in a downward shift of the curve resulting in hypoperfusion (b), pulmonary congestion (c), or both.
Comparative Effects of IV agents
# Medical Therapy for AHF

<table>
<thead>
<tr>
<th>Agent</th>
<th>PCW</th>
<th>CO</th>
<th>HR</th>
<th>SBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrates</td>
<td>↓↓↓↓</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>↓↓</td>
<td>↑↑↑</td>
<td>↓↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>↓</td>
<td>↑↑↑↑</td>
<td>↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Levophed</td>
<td>↑↑</td>
<td>↑</td>
<td>↑↑</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>↑</td>
<td>↑↑</td>
<td>↑↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>↓</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↓</td>
</tr>
<tr>
<td>Dopamine (LD)</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Dopamine (HD)</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Milrinone</td>
<td>↓↓↓↓</td>
<td>↑↑↑↑</td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>
## Mechanism of Action of IV Therapeutic Agents in HF

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sympathomimetic Agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low dose</td>
<td>DA1-stimulation</td>
<td>++ Renal blood flow, vasodilatation, natriuresis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher dose</td>
<td>β1-stimulation</td>
<td>↑ positive inotropy</td>
</tr>
<tr>
<td></td>
<td>α1-stimulation</td>
<td>Peripheral vasoconstriction</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>β1-stimulation</td>
<td>↑pos inotropy, ↑ HR</td>
</tr>
<tr>
<td></td>
<td>β2-stimulation</td>
<td>Peripheral vasodilatation</td>
</tr>
<tr>
<td>Agent</td>
<td>Mechanism</td>
<td>Response</td>
</tr>
<tr>
<td>-------------</td>
<td>-----------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td><strong>Sympathomimetic Agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>β1-stimulation</td>
<td>+↑cyclic AMP, ↑positive inotropy</td>
</tr>
<tr>
<td></td>
<td>α1-stimulation</td>
<td>+++ Peripheral vasoconstriction</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>β1-stimulation</td>
<td>+++ ↑ positive inotropy</td>
</tr>
<tr>
<td></td>
<td>β2-stimulation</td>
<td>+ Peripheral vasodilatation</td>
</tr>
<tr>
<td></td>
<td>α1-stimulation</td>
<td>+++ Peripheral vasoconstriction</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>β1-stimulation</td>
<td>+++ ↑pos inotropy, ↑ HR</td>
</tr>
<tr>
<td></td>
<td>β2-stimulation</td>
<td>+ Peripheral vasodilatation</td>
</tr>
</tbody>
</table>
# Mechanism of Action of IV Therapeutic Agents in HF

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phosphodiesterase Inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milrinone</td>
<td>Phosphodiesterase-III inhibition</td>
<td>++ cyclic AMP, positive inotropy, ↑ peripheral vasodilatation</td>
</tr>
<tr>
<td><strong>Vasodilators</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Nitric oxide donor</td>
<td>++ cellular cGMP, venous and arterial vasodilatation</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>ACE-Inhibitor</td>
<td>++ Venous and arterial vasodilatation</td>
</tr>
<tr>
<td>Enalaprilat</td>
<td></td>
<td>+ natruresis</td>
</tr>
</tbody>
</table>
Current Pharmacologic Approach to Acute Therapy

- Diuretics to reduce ECF volume
  - IV loop diuretics ± metolazone/thiazide
- Intravenous vasodilators to optimize ventricular loading conditions
  - Nitroglycerin (preload + afterload)
  - Nitroprusside (+ afterload)
- Intravenous inotropic agents to improve cardiac performance
  - Sympathomimetic agents
  - Phosphodiesterase inhibitors
Rational Approach to Therapy in Volume Overloaded Patients

Clinical Congestion

- Adequate Perfusion
  - Diuretics
  - plus
  - PO Vasodilators

- Reduced Perfusion
  - Diuretics
  - plus
  - IV Vasodilators/IV Inotropes

- Cardiogenic Shock
  - Diuretics
  - plus
  - IV Inotropes/IV Pressors
Few Principles of Diuretic Use in Management of Acute HF

- Higher doses are required to restore than to maintain optimal volume status
- Doses should be doubled when increased effect is desired
- Addition of metolazone or IV thiazides (Diuril®) frequently resolves apparent “diuretic resistance”.
- Relationship between dose of diuretic and mortality
Intravenous Vasodilators

• After diuretics, IV vasodilators are the most useful medications.
• They reduce filling pressures and symptoms.
• No direct effect on myocardial contractility
• Cardiac output increases
• Decrease mitral regurgitation
• Do not usually increase heart rate or exacerbate arrhythmias
Nitroprusside

- First vasodilator shown to improve cardiac output
- Rapidity of onset and offset
- Half-life of ~ 2 minutes
- Individual response varies markedly
## Hemodynamic Effects of Vasodilators

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>CO</th>
<th>LVEDP</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroglycerin</td>
<td>↔️</td>
<td>↑️</td>
<td>↓️</td>
<td></td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>↔️</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td>↔️</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CO = cardiac output; HR = heart rate; LVEDP = left ventricular filling pressure; SVR = systemic vascular resistance.

• Dobutamine started at 5 mcg/kg/min with no improvement

• Another dose of IV Lasix 80mg was given with no response

• BP was 72/-; periphery was cool; JVD 16 cm; Cr 2.1; HR 120 bpm
Q: The patient is most likely to respond to
- An increase in the dose of Dobutamine
- Addition of or replacement with Milrinone
- Addition of Dopamine?
IV Inotropic Agents

• Phosphodiesterase inhibitors
  – milrinone
  – amrinone

• Sympathomimetics
  – dopamine
  – dobutamine
  – isoproterenol
  – epinephrine
  – norepinephrine
Dobutamine (Inotrope)

- Dobutamine stimulates β- adrenergic receptors (AR) with little effect on α-AR → contractility is increased with peripheral vasodilatation.
- Does not affect dopaminergic receptor.
- Increases cardiac output and decreases filling pressures
- HR is consistently increased, particularly with AFib.
β-Adrenergic Pathway

- β-agonist
- β-receptor

L-type Ca Channel

Gs

AC

ATP

cAMP

PDE III

AMP

SR Ca\(^{2+}\)

PL

SERCA

Protein Kinase A (active)

Protein Kinase A (inactive)

Ca\(^{2+}\)

Ry-sensitive

Ca\(^{2+}\)
# Dobutamine

<table>
<thead>
<tr>
<th>Dose range</th>
<th>Dobu</th>
<th>α₁</th>
<th>β₁</th>
<th>β₂</th>
<th>Heart rate</th>
<th>Cardiac output</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5-20 mcg/kg/min</td>
<td>-</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>↑</td>
<td>↑↑↑</td>
<td>↓</td>
</tr>
</tbody>
</table>
Milrinone (Inotrope/Vasodilator)

- Increases intracellular cyclic adenosine monophosphate (c-AMP) in both heart and vascular muscle cell by blocking its breakdown.
- Increases both contractility and causes marked vasodilatation. (10% of Pts with significant hypotension)
- Less elevation in HR compared to Dobutamine
- Prolonged physiologic half-time of 6 hours.
- When stopped, it persists for several hours within the circulation
β-Adrenergic Pathway

- β-agonist
- β-receptor

L-type Ca Channel

Ca\(^{2+}\)

ATP → cAMP → Protein Kinase A (active)

PDE III

AMP

Protein Kinase A (inactive)

Ca\(^{2+}\)

Ry-sensitive

SR Ca\(^{2+}\)

PL

SERCA

Ca\(^{2+}\)
Hemodynamic Effects of PDE Inhibitors

Cardiac Index (CI) $\uparrow$

SVR/MAP $\downarrow$

PCWP $\downarrow$

HR $\leftrightarrow$

LVEDP $\downarrow$

Ventricular dP/dt $\uparrow$

Distinguishing PDE Inhibitors From Dobutamine

• No dependence on β-receptors
• Vasodilator action
• Relaxation (lusitropic) action
• Minimal effect on heart rate
• Minimal effect on myocardial oxygen consumption

### Selection of an Inotropic Agent

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dobutamine</th>
<th>Milrinone</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP&lt;80</td>
<td>1st choice</td>
<td>Usually in combination with pressor</td>
</tr>
<tr>
<td>Pulmonary HTN</td>
<td>Not a good pulmonary vasodilator</td>
<td>1st choice; lowers PVR</td>
</tr>
<tr>
<td>Myocardial ischemia</td>
<td>More taxing on myocardial O₂ demand</td>
<td>1st choice; least taxing on myocardial O₂ demand</td>
</tr>
</tbody>
</table>

Distinguishing between Nipride and Milrinone
Nesiritide (Natrecor®)

- Recombinant form of BNP
- IV vasodilator
- Like Nipride, increases c-GMP
- Lowers filling pressures
- Causes hypotension
- Also diuretic effect.
- Longer half life than NTG (18 min)
- Controversy if worsens renal function and increases mortality
Case Study: JB (cont’d)

• Dopamine was initiated at 10 mcg/kg/min and BP improved slightly 82/38 HR 130.
• Despite minimal improvement, no urine output and patient became lethargic and unresponsive.
• BP 73/32 HR 150, cyanotic, unresponsive.
• Intubation was performed
• BP 66/31 HR 152 post intubation
• Levophed was initiated at increased dose.
• Right heart catheterization revealed PAP 65/35; PCWP 36; CI 0.9 L/min/m²
Q: The best long term treatment option is likely to be

- IABP
- LVAD
- Cardiac transplantation
- Mitral valvuloplasty and/or LV remodeling surgery
- Medical therapy alone
Dopamine (Inotrope/Vasoconstrictor)

- Dopamine (D) stimulates β-, α- and dopaminergic receptors.
- LD receptor stimulation causes vasodilatation in the renal and peripheral vasculature.
- At ≤ 3 mcg/kg/min: D is predominantly vasodilatory.
- At 3-5 mcg/kg/min: D activates dopaminergic and β-adrenergic receptors and so is also a positive inotrope.
- At ≥ 5 mcg/kg/min: D acts as an arterial and venous constrictor
- For BP support: D dose ≥ 5 mcg/kg/min.
## Dopamine

<table>
<thead>
<tr>
<th>Dose range</th>
<th>Dopa</th>
<th>$\alpha_1$</th>
<th>$\beta_1$</th>
<th>$\beta_2$</th>
<th>Heart rate</th>
<th>Cardiac output</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 mcg/kg/min</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3-5 mcg/kg/min</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5-20 mcg/kg/min</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tbody>
</table>
Distinguish between Dobutamine and Dopamine
## Limitations of IV Agents

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
<th>Limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrates</td>
<td>Nipride</td>
<td>Hypotension</td>
</tr>
<tr>
<td></td>
<td>Nitroglycerin</td>
<td>Tolerance (NTG&gt;NTP)</td>
</tr>
<tr>
<td>Phosphodiesterase Inhibitors</td>
<td>Milrinone</td>
<td>Slow onset of action</td>
</tr>
<tr>
<td>Catecholamines</td>
<td>Dobutamine</td>
<td>Tolerance (β-receptor down regulation)</td>
</tr>
<tr>
<td></td>
<td>Dopamine</td>
<td>Tolerance, Central venous access used</td>
</tr>
</tbody>
</table>
Case Study: JB (cont’d)

- The patient underwent placement of IABP with no improvement of his hemodynamics.
- Underwent placement emergently of LVAD but patient bled profusely during surgery, received numerous blood units and RV failed.
- Patient died the next morning
New Agents (still investigational)

**Levosimendan:**
- Increases Ca sensitivity of Troponin C + has some phosphodiesterase III inhibitor properties. It is a positive inotrope and a vasodilator.
- Improves both systolic and diastolic dysfunction
- REVIVE Study
New Agents (still investigational)

Adenosine $A_1$ Receptor Antagonists

BG9719

• Increases diuresis
If medical therapy fails or inability to wean off IV inotropic drugs

Stabilization → Intervention

Pharmacologic Support

HEMODYNAMIC COMPROMISE

Percutaneous revascularization

Diagnostic and Therapeutic Procedure

Cardiac surgery

LVAD ? Transplantation ?
Left Ventricular Assist Device
If IV medical therapy: successful

- Taper the infusion gradually over 24-48 hours or even more
- Observe patient
Discharge Criteria for Hospitalization with HF

**Clinical Status Goal**
- Achievement of dry weight
- Definition of BP range
- Walking without dyspnea or dizziness

**Stability Goals**
- 24h without changes in oral HF regimen
- ≥48 h off IV inotropic agents, if used
- Fluid balance even on oral diuretics
- Renal Function stable or improving

**Home Plan**
- Clinic appointment within 10 days
- Scheduled call to patient within 3 days
Case Presentation

- 62 year AA old man
- PMH: -DM diag 3 years ago
  - BPH
  - ETOH quit 2/09
  - Tob (60 pyhx) quit 2/09
  - COPD??

- Diagnosed in Feb 09 with CHF
  Echocardiogram
  - LVEDD 6.6cm, LVEDS 5.6
  - Severe global hypokinesis, LVEF 25%
  - Moderate right ventricular hypokinesis
  - Severe MR, mod-severe TR
  - PASP 65mmHg
Case Presentation

- Coronary Angiogram: Clean cors
- LV Angiogram: LVEF 23%, MR3+
- PSH: None
- FMH: unremarkable
- Allergy: NKDA
Case Presentation

SUBJ:
- Chest pressure not related with exertion
- DOE after walking 2 blocks
- can claim 1 flight of stairs
- sleeps on 2-3 pillows
- since on Lasix no PND any more
- some lower extremities edema
- abdominal distension
- No palpitations, dizziness
Case Presentation

- **MEDS:**
  - Cozaar 100 mg QD
  - Metoprolol 50 mg BID
  - Bumex 4 mg BID
  - Proscar 5 mg QD
  - Amlodipine 5mg QD
Case Presentation

PE
- BP 95/60 HR 88, RR 20, Anicteric, Afebrile Acyanotic
- JVP ~ 12cm
- Chest: Clear, no crackles, no rales, no wheezing
- CV: RRR, PMI displaced
- Abd: Soft, 0 tenderness, 0 HSM
- Legs: edema 1+
Case Presentation

LAB

LFTs: Normal
UA: WNL

EKG: Normal Sinus Regular Rhythm, RBBB QRS 150 msec
CXR: Cardiomegaly, no infiltrates
Case Presentation

• Right Beta-Blocker?
• ACE-I vs. ARB?
• Should we put Pts on both ACE-I and ARB?
• Any other vasodilator?
• Is patient a candidate for a device (AICD? BiV Pacer?)
Important Management Questions in Congestive Heart Failure

- What is remodeling?
- Can remodeling be reversed?
- Should ACE inhibitors be prescribed first?
- Does the dose matter?

- Should ACE inhibitor dose be decreased to allow uptitration of beta-blockers?
- Is the specific beta-blocker important?
- Are aldosterone antagonists valuable?
- When should an ARB be added?
MYOCARDIAL REMODELING IN HEART FAILURE

- **EF**
- **no MR**
- **Mild MR**
- **Mod MR**

**Myocyte Damage or Dysfunction**

- **Progressive Myocyte Dysfunction and/or Death**

Cardiac Adrenergic Activation
Renin Angiotensin Activation
Cytokine Activation

Systemic Adrenergic Activation
Systemic Renin Angiotensin Activation
Systemic Cytokine Activation

*Lindenfeld 2000*
Pathophysiology of LV Systolic Dysfunction

Two Main Protagonists

- Renin-Angiotensin System (RAS)
  - Angiotensin II (A II)

- Sympathetic Nervous System (SNS)
  - Norepinephrine (NE)

Hypertrophy, apoptosis, ischemia, arrhythmias, vasoconstriction, remodeling, fibrosis
Pathophysiology of LV Systolic Dysfunction

- Cardiac Injury
- Increased Load
- Activation of RAS and SNS
- Reduced Systemic Perfusion
  - Altered Gene Expression
  - Growth and Remodeling
  - Ischemia and Energy Depletion
    - Apoptosis
    - Necrosis
  - Direct Toxicity
  - Cell Death

## ACE Inhibitors in CHF

<table>
<thead>
<tr>
<th>Trial</th>
<th>Mortality</th>
<th>ACEI</th>
<th>Controls</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chronic CHF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CONSENSUS I</td>
<td></td>
<td>39%</td>
<td>54%</td>
<td>0.56 (0.34–0.91)</td>
</tr>
<tr>
<td>SOLVD (Treatment)</td>
<td></td>
<td>35%</td>
<td>40%</td>
<td>0.82 (0.70–0.97)</td>
</tr>
<tr>
<td>SOLVD (Prevention)</td>
<td></td>
<td>15%</td>
<td>16%</td>
<td>0.92 (0.79–1.08)</td>
</tr>
<tr>
<td><strong>Post MI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAVE</td>
<td></td>
<td>20%</td>
<td>25%</td>
<td>0.81 (0.68–0.97)</td>
</tr>
<tr>
<td>AIRE</td>
<td></td>
<td>17%</td>
<td>23%</td>
<td>0.73 (0.60–0.89)</td>
</tr>
<tr>
<td>TRACE</td>
<td></td>
<td>35%</td>
<td>42%</td>
<td>0.78 (0.67–0.91)</td>
</tr>
<tr>
<td>SMILE</td>
<td></td>
<td>5%</td>
<td>6.5%</td>
<td>0.75 (0.40–1.11)</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td></td>
<td>21%</td>
<td>25%</td>
<td></td>
</tr>
</tbody>
</table>
Trials Examining ACE Inhibitors in HF patients

CONSENSUS Trial

Consensus Study Group, *NEJM* 1987; 316: 1420
Trials Examining ACE Inhibitors in HF patients

SOLVD Treatment Trial

All-Cause Mortality

Events (%)

0 10 20 30 40 50

0 6 12 18 24 30 36 42 48

Months

Placebo
Enalapril

16% Risk Reduction
P = .0036

SOLVD Investigators NEJM 1991: 325:293
Low vs. High Dose ACE Inhibitors: ATLAS

- 3164 pts. f/u for a median of 45.7 months.
- NYHA class II-IV, mostly III (77%).
- LVEF: 23%.
- Lisinopril 2.5-5 mg vs 32.5-35 mg qd.
- 8% reduction in mortality (p = 0.128)
- 12% reduction in death + all-cause hospitalization (p = 0.002).

Packer et al. Circulation 1999;100:2312-2318
ATLAS Assessment of Treatment with Lisinopril And Survival

All death  HF hosp*  Death+hosp*

* p = significant

ACE-I: High-Dose versus Low-Dose

Risk Reduction 8%

$P=0.128$

## Low vs High Dose ACE-I

**ATLAS Trial**

<table>
<thead>
<tr>
<th>Event Description</th>
<th>Low-Dose</th>
<th>High-Dose</th>
<th>Hazard Ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>717 (44.9)</td>
<td>666 (42.5)</td>
<td>0.92 (0.82–1.03)</td>
<td>0.128</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>641 (40.2)</td>
<td>583 (37.2)</td>
<td>0.90 (0.81–1.01)</td>
<td>0.073</td>
</tr>
<tr>
<td>All-cause mortality + hospitalization for any reason</td>
<td>1338 (83.8)</td>
<td>1250 (79.7)</td>
<td>0.88 (0.82–0.96)</td>
<td>0.002</td>
</tr>
<tr>
<td>All-cause mortality + hospitalization for cardiovascular reason</td>
<td>1182 (74.1)</td>
<td>1115 (71.1)</td>
<td>0.92 (0.84–0.99)</td>
<td>0.036</td>
</tr>
<tr>
<td>All-cause mortality + hospitalization for heart failure*</td>
<td>964 (60.4)</td>
<td>864 (55.1)</td>
<td>0.85 (0.78–0.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular mortality + hospitalization for cardiovascular reason</td>
<td>1161 (72.7)</td>
<td>1088 (69.4)</td>
<td>0.91 (0.84–0.99)</td>
<td>0.027</td>
</tr>
<tr>
<td>Fatal and nonfatal myocardial infarction + hospitalization for unstable angina</td>
<td>224 (14.0)</td>
<td>207 (13.2)</td>
<td>0.92 (0.76–1.11)</td>
<td>0.374</td>
</tr>
</tbody>
</table>

Values in parentheses indicate percentage or range. P values determined by log-rank test. Hazard ratios represent 95% CI, except for all-cause mortality, shown as 96.1% CI.

*Analysis not specified in protocol before breaking the blind.

---

*Circulation* 1999; 100: 2312-18.
What is an adequate dose of an ACE inhibitor?

<table>
<thead>
<tr>
<th></th>
<th>Network (enalapril)</th>
<th>Atlas (lisinopril)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.5 bid</td>
<td>5 bid</td>
</tr>
<tr>
<td>n</td>
<td>506</td>
<td>510</td>
</tr>
<tr>
<td>Death</td>
<td>4.2%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Death + HF Hosp</td>
<td>6.8%</td>
<td>6.9%</td>
</tr>
<tr>
<td></td>
<td>5 qd</td>
<td>35 qd</td>
</tr>
<tr>
<td>n</td>
<td>1596</td>
<td>1568</td>
</tr>
<tr>
<td>Death</td>
<td>45%</td>
<td>42%</td>
</tr>
<tr>
<td>Death + HF Hosp</td>
<td>60%</td>
<td>55%</td>
</tr>
</tbody>
</table>

*Cleland, Eur Ht J, 1998, Packer Circ, 1999*
ACE-I or ARB?
ARBS: CHARM-Alternative

CV death or CHF hospitalization

Candesartan

Placebo

HR 0.77 (95% CI 0.67-0.89), p=0.0004
Adjusted HR 0.70, p<0.0001

Number at risk

Candesartan 1013 929 831 434 122
Placebo 1015 887 798 427 126

Granger CB et al. Lancet 2003;362:772-776
ELITE-II: All-Cause Mortality

Probability of Survival

NYHA class II-IV
LVEF < 40%
3152 patients > 60 years

Hazard Ratio (95-7% C.I.) = 1.13 (0.95-1.35)  P = 0.16

Pitt B et al. Lancet 2000;355:1582-87
**VALIANT: All-Cause Mortality**

Valsartan vs. Captopril: HR = 1.00; P = 0.982

Valsartan + Captopril vs. Captopril: HR = 0.98; P = 0.726

Pfeffer MA et al. NEJM 2003;349:1893-1905
## Mortality by ACEI/BB Subgroups (Val-HeFT)

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Favors Valsartan</th>
<th>Favors Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI (no)</td>
<td>366</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEI (yes)</td>
<td>4644</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BB (no)</td>
<td>3260</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BB (yes)</td>
<td>1750</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEI (no), BB (no)</td>
<td>226</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEI (yes), BB (no)</td>
<td>3034</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEI (no), BB (yes)</td>
<td>140</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEI (yes), BB (yes)</td>
<td>1610</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Adapted from Cohn JN, et al. [abstract]. *Circulation*, 2001)
CHARM-Overall: All-cause death

RRR = 9%

Placebo

Candesartan

HR 0.91 (95% CI 0.83-1.00), p=0.055
Adjusted HR 0.90, p=0.032


Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Year 0</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 3.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan</td>
<td>3803</td>
<td>3563</td>
<td>3271</td>
<td>2215</td>
<td>761</td>
</tr>
<tr>
<td>Placebo</td>
<td>3796</td>
<td>3464</td>
<td>3170</td>
<td>2157</td>
<td>743</td>
</tr>
</tbody>
</table>
ACE-I, ARB Rx

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>• Per AHA/ACC Guidelines:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ARB’s only if proven intolerant to ACE-I</td>
</tr>
<tr>
<td>• No evidence of ARB superior to ACE-I</td>
<td></td>
</tr>
</tbody>
</table>
Spironolactone Improves Survival in Advanced Heart Failure (RALES)

p < .001
30% risk reduction

Pitt et al NEJM 1999
Eplerenone: EPHESUS
Relative Risk of Total Mortality

Cumulative Incidence (%)

RR = 0.85 (95% CI, 0.75-0.96)
\(P = 0.008\)

Pitt B. et al. NEJM 348;14:1309-21.
Historical Prospective:

**US Carvedilol Programme**
- Carvedilol
- Placebo
- Risk reduction = 65%
  \[ p < 0.001 \]

**COPERNICUS**
- Carvedilol
- Placebo
- Risk reduction = 35%
  \[ p = 0.00013 \]

**CIBIS-II**
- Bisoprolol
- Placebo
- Risk reduction = 34%
  \[ p < 0.0001 \]

**MERIT-HF**
- Placebo
- Metoprolol CR/XL
- Risk reduction = 34%
  \[ p = 0.0062 \]
## Major Trials of β-Blockade in Heart Failure

<table>
<thead>
<tr>
<th></th>
<th>Patients (n)</th>
<th>Follow-up (yrs)</th>
<th>Target Dosage (mg)</th>
<th>Mean Dosage Achieved (mg/day)</th>
<th>Effects on Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIBIS</td>
<td>641</td>
<td>1.9</td>
<td>bisoprolol 5 mg qd</td>
<td>3.8</td>
<td>All-cause mortality: NS</td>
</tr>
<tr>
<td>CIBIS-II</td>
<td>2647</td>
<td>1.3</td>
<td>bisoprolol 10 mg qd</td>
<td>7.5</td>
<td>All-cause mortality: ↓34% (P&lt;.0001)</td>
</tr>
<tr>
<td>MDC</td>
<td>383</td>
<td>1</td>
<td>metoprolol 50-75 mg bid</td>
<td>108</td>
<td>Death or need for transplant (primary end point): NS</td>
</tr>
<tr>
<td>MERIT-HF†</td>
<td>3991</td>
<td>1</td>
<td>metoprolol CR/XL 200 mg qd</td>
<td>159</td>
<td>All-cause mortality: ↓34% (P=.0062)</td>
</tr>
<tr>
<td>US Carvedilol Trials†</td>
<td>1094</td>
<td>7.5 months</td>
<td>carvedilol 6.25-50 mg bid</td>
<td>45</td>
<td>All-cause mortality*: ↓65% (P=.0001)</td>
</tr>
<tr>
<td>COPERNICUS</td>
<td>2289</td>
<td>10.5 months</td>
<td>carvedilol 25 mg bid</td>
<td>37</td>
<td>All-cause mortality: ↓35% (P=.00013)</td>
</tr>
</tbody>
</table>

*Not a planned end point.
†Carvedilol and metoprolol CR/XL are the only agents with β-blockade approved by the FDA for the treatment of mild to moderate heart failure.
## Beta-Blockers: Recent Trials in HF

<table>
<thead>
<tr>
<th></th>
<th>Annual Placebo Mortality Rate</th>
<th>RRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Carvedilol¹</td>
<td>11.1%</td>
<td>65%</td>
</tr>
<tr>
<td>MERIT-HF²</td>
<td>11.0%</td>
<td>34%</td>
</tr>
<tr>
<td>CIBIS II³</td>
<td>13.2%</td>
<td>34%</td>
</tr>
<tr>
<td>BEST⁴</td>
<td>17%</td>
<td>10%</td>
</tr>
<tr>
<td>COPERNICUS⁵</td>
<td>18.5%</td>
<td>35%</td>
</tr>
</tbody>
</table>

β-blockade — Dose Effect?

β-blockade — Dose Effect?

β-blockade — Dose Effect?

Does it Really Matter?

- Which \( \beta \)-blocker?
COMET Study

3000 patients with stable heart failure, NYHA II-IV, receiving standard treatment including ACE inhibitors

Randomized (no run-in phase)

- (n≈1500) Metoprolol 50 mg bid
- (n≈1500) Carvedilol 25 mg bid

Time to 1020 deaths Estimated to be 4 to 6 years

Screening Titration to maximum tolerated or target dose Assessments every four months during maintenance phase

(start: carvedilol 3.125 mg bid, metoprolol 5 mg bid)
COMET: All-cause Mortality

Hazard ratio 0.83
P = 0.0017

Primary Endpoint: All Cause Mortality

- **Sudden Death**
  - Hazard ratio: 0.81
  - p = 0.0216
  - RR = 19%

- **Circulatory Failure**
  - Hazard ratio: 0.827
  - p = 0.0702
  - RR = 17%

- **Death from stroke**
  - Hazard ratio: 0.332
  - p = 0.0006
  - RR = 67%
Beta-Blockers: How to use them?

- Start low and only in compensated patients
- Carvedilol 3.125 bid (goal 25-50 mg bid) Metoprolol XL 12.5 mg qd (goal 200 mg qd)

  Bisoprolol 1.25 mg qd (goal 10 mg qd) Metoprolol Tartrate 6.25 mg bid, goal 100 mg bid.
- Double the dose every 1 to 2 weeks or as tolerated.
- Increase diuretic dose if dyspnea without hemodynamic compromise
V-HeFT I: ISDN/HDZN

RRR: 36% at 3 years

Placebo: N (cumulative death) 273
I/H: N (cumulative death) 186

Cohn JN et al. NEJM. 1986;314:1547-52
V-HeFT II: Vasodilator–Heart Failure Trial

Racial Differences in Mortality: V-HeFT I

African American

- Placebo (PL) N=79
- Prazosin (PR) N=49
- Hyd-ISO (Hi) N=52

White

- Placebo (PL) N=192
- Prazosin (PR) N=132
- Hyd-ISO (Hi) N=127

J Cardiac Failure 1999; 5(3): 178-87
Racial Differences in Mortality: V-HeFT II

African American

N=106
N=109

White

N=292
N=282

J Cardiac Failure 1999; 5(3): 178-87
African American Heart Failure Trial: A-HeFT

AA, LVEF < 35%, NYHA III-IV
1 prior hospital for HF
Maintained on standard therapy

BiDil: 37.5mg Hydralazine + 20mg ISDN

Primary endpoints:
All cause mortality
Death + 1st Hospitalization + QOL

BiDil 1-2 po TID N=300

6 months

Placebo N=300

A-HeFT: ISDN/HDZN

Days Since Baseline Visit Date

Survival (%)

Hazard ratio=0.57, P=.01

Fixed-dose I/H  | 518  | 463  | 407  | 359  | 313  | 251  | 13  
Placebo       | 532  | 466  | 401  | 340  | 285  | 232  | 24  

Taylor AL et al. NEJM, 2004; 351: 2049-57
# PRAISE 1 & 2: MORTALITY

<table>
<thead>
<tr>
<th></th>
<th>Placebo  (n = 1408)</th>
<th>Amlodipine  (n = 1397)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of deaths</strong></td>
<td>479</td>
<td>466</td>
</tr>
<tr>
<td><strong>% mortality</strong></td>
<td>34.0%</td>
<td>33.4%</td>
</tr>
<tr>
<td><strong>Odds ratio</strong></td>
<td></td>
<td>0.98</td>
</tr>
</tbody>
</table>

Packer M. ACC 49th annual scientific session. March, 2000
The Digitalis Investigation Group (DIG) trial evaluated the effects of digoxin on survival in 6800 patients. The average follow-up was 37 months. Digoxin did not increase or decrease overall mortality.
Digoxin-treated patients had a reduction in the overall rate of hospitalization and also the rate of hospitalization for worsening heart failure.
Digoxin: Level and Survival

Rathore S. et al. JAMA. 2003;289:871-78
The PROMISE of Milrinone

- 1088 pts. With class III or IV heart failure.
- Median duration of f/u was 6.1 months.
- LV EF: 21 %. Digoxin level 1.5 mmol/l.
- Milrinone po vs placebo.
- All-cause mortality was increased by 28 %.
- It increased by 53 % in class IV patients.
- Similar tendencies with vesnarinone, ibopamine and pimobendan.

Packer M et al. NEJM 1991;325:1468-1475
MADIT II Trial

Moss et al. *NEJM* 346 (12): 877,2002
SCD-HeFT: All Cause Mortality


23% RRR for ICD Therapy (p-value 0.007)

<table>
<thead>
<tr>
<th>Hazard Ratio (97.5% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone vs. placebo</td>
<td>1.06 (0.86–1.30)</td>
</tr>
<tr>
<td>ICD therapy vs. placebo</td>
<td>0.77 (0.62–0.96)</td>
</tr>
</tbody>
</table>

Placebo
(244 deaths; 5-yr event rate, 0.361)

Amiodarone
(240 deaths; 5-yr event rate, 0.340)

ICD therapy
(182 deaths; 5-yr event rate, 0.289)
The group that did best was the CRT plus ICD (CRT-D) group, the group that had a device with a defibrillator; there was a 36% reduction in mortality. Interestingly, the group with the CRT pacemaker also had an improvement in mortality, although it did not quite reach statistical significance.
CARE-HF: All-Cause Mortality

HR: 0.64
P<0.002

Cleland JGF et al. for the CARE-HF study investigators. NEJM. 2005;352:1539-49
## Combination therapy in CHF

<table>
<thead>
<tr>
<th></th>
<th>Symptoms</th>
<th>Morbidity</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>High dose ACEI</td>
<td>Same</td>
<td>↓ 10-15%</td>
<td>NS</td>
</tr>
<tr>
<td>Add an ARB</td>
<td>↓</td>
<td>↓ 10-15%</td>
<td>↔</td>
</tr>
<tr>
<td>Add Aldosterone</td>
<td>↓</td>
<td>↓ 8-35%</td>
<td>↓ 15-30%</td>
</tr>
<tr>
<td>Inhibitor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Add β-blockade</td>
<td>↓</td>
<td>↓ 36%</td>
<td>↓ 35%</td>
</tr>
<tr>
<td>AICD</td>
<td>Same</td>
<td></td>
<td>↓ 30%</td>
</tr>
</tbody>
</table>
Case Presentation

- In this Patient:
  - Coreg (to max dose)
  - Lisinopril (at least 5mg QD)
  - Spironolactone (low dose)
  - Hydralazine + Isosorbide ?
  - Digoxin
  - Repeat echocardiogram: if LVEF still <35% → BiV Pacer/AICD
  - V02 exercise test to assess his functional capacity
Heart Failure Therapy Timeline

- **pre-1980s**
  - Non-pharmacologic:
    - Bed rest; inactivity; fluid restriction; digitalis, diuretics
  - Pharmacologic:
    - Digitalis; diuretics; vasodilators; inotropes

- **1980s**
  - Pharmacologic:
    - Digitalis; diuretics; neurohormonal interventions

- **1990s**
  - Device:
    - CRT; ICDs; LVADs; others?

- **2000s**
  - Cellular/Genetic:
    - Gene therapies; cell implantation/regeneration; xenotransplantation
Conclusion

“I can’t breathe”

“I can walk 30 minutes without stopping”
Questions

ILLITERATE?
WRITE FOR FREE HELP.

ILLITERACY FOUNDATION
806 MAIN STREET