Heart Failure
A Growing Epidemic

- 4.7 million symptomatic patients, estimated 10 million in 2037
- Incidence: About 550,000 new cases/year
- More deaths from heart failure than from all forms of cancer combined
  - 53,000 deaths a year
- Prevalence is 1% between the ages of 50 and 59, progressively increasing to >10% over age 80
- ~ $30 billion/year (5% to 7% of total health care cost)

American Heart Association. 2001 Heart and Stroke Statistical Update.
Classification Systems

- NYHA based on exercise capacity (functional system)
  - Class I
  - Class II
  - Class III
  - Class IV

- ACC/AHA staging of heart failure (progression)
  - Stage A
  - Stage B
  - Stage C
  - Stage D

New Approach to the Classification of Heart Failure

<table>
<thead>
<tr>
<th>Stage</th>
<th>Patient Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High risk for developing heart failure (HF)</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td>CAD</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>Family history of cardiomyopathy</td>
</tr>
<tr>
<td>B</td>
<td>Asymptomatic HF</td>
</tr>
<tr>
<td></td>
<td>Previous MI</td>
</tr>
<tr>
<td></td>
<td>LV systolic dysfunction, LVH</td>
</tr>
<tr>
<td></td>
<td>Asymptomatic valvular disease</td>
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<tr>
<td>C</td>
<td>Symptomatic HF</td>
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<tr>
<td></td>
<td>Known structural heart disease</td>
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<tr>
<td></td>
<td>Shortness of breath and fatigue</td>
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<tr>
<td></td>
<td>Reduced exercise tolerance</td>
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<tr>
<td>D</td>
<td>Refractory end-stage HF</td>
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<tr>
<td></td>
<td>Marked symptoms at rest despite maximal medical therapy (eg, those who are recurrently hospitalized)</td>
</tr>
</tbody>
</table>

Classification of HF

- Which side of heart is affected
  - Left (more common)
  - Right (right-sided MI, pulmonary HTN)

- Which heart function is affected
  - Systolic (↓ contraction and EF, dilated LV)
  - Diastolic (↓ relaxation,)
    - Failure of LV filling
    - Contractile function and EF usually normal

2006 HF Treatment Algorithm by Stage

Stage A → Stage B → Stage C → Stage D

**Stage A**
- Angina
  - nitrate
  - amiodipine
  - PCI
  - CABG
- AF
  - warfarin
  - rate control
  - cardioversion
- treat HTN
- smoking cessation
- treat lipid disorders
- exercise
- treat diabetes

**Stage B**
- stage A, B
- ACE-inhibitors
- beta-blockers
- diuretics
- stage A, B, and C
- IV inotropes
- MCS (bridge to Tx)
- heart transplantation

**Stage C**
- spironolactone
- digitalis
- bivent pacing +/- ICD
- ARBs
- IV inotropes
- MCS (permanent)
- hospice care

Antiendothelin agents, anticytokines, oral inotropes, cardiac support devices, cell and gene Rx
• 32 y/o AA male presents with progressive DOE over the past 3 weeks - unable to walk one flight of stairs without resting. He also complains of severe weight gain over this time period (>15 lbs), feeling bloated, and unable to sleep because he feels like he stops breathing.

• PE: HR 110s, BP 115/75
• JVD to jaw, pitting edema

What to do with Mr. Jones?

• What studies do you want to order?
• What medication first?
  – ACE-I vs. beta blocker
  – Which ACE-I? Which beta blocker?
• Can I start a beta blocker with bad CHF?
• When to start diuretics?
ACE-inhibitors

• First-line treatment
• Beneficial across all functional classes of HF
• Reduce risk of developing HF in at-risk patients (ALVD, previous MI, > 55 y.o. with vascular disease or DM)
• Start low, titrate to target (doses shown effective in clinical trials)

ACE Inhibitors in Heart Failure: From Asymptomatic LVD to Severe HF

SOLVD Prevention (Asymptomatic LVD)
- 20% death or HF hosp.
- 29% death or new HF

SOLVD Treatment (Chronic Heart Failure)
- 16% mortality

CONSENSUS (Severe Heart Failure)
- 40% mortality at 6 mos.
- 31% mortality at 1 year
- 27% mortality at end of study

• No difference in incidence of sudden cardiac death


Heart Failure Society of America
Beta blockers

- Historically contraindicated, but strong evidence now refutes that
- Standard therapy in HF
- Class effect – most studies with carvedilol and metoprolol
- Start when euvoeleic and stable
- Start low and titrate to max tolerated

Effect of Beta Blockade on Outcome in Patients With HF and Post-MI LVD

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>HF Severity</th>
<th>Target Dose (mg)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Carvedilol¹</td>
<td>carvedilol</td>
<td>mild/moderate</td>
<td>6.25-25 BID</td>
<td>↓ 48% disease progression (p=.007)</td>
</tr>
<tr>
<td>CIBIS-II²</td>
<td>bisoprolol</td>
<td>moderate/severe</td>
<td>10 QD</td>
<td>↓ 34% mortality (p &lt;.0001)</td>
</tr>
<tr>
<td>MERIT-HF³</td>
<td>metoprolol succinate</td>
<td>mild/moderate</td>
<td>200 QD</td>
<td>↓ 34% mortality (p = .0062)</td>
</tr>
<tr>
<td>COPERNICUS⁴</td>
<td>carvedilol</td>
<td>severe</td>
<td>25 BID</td>
<td>↓ 35% mortality (p = .0014)</td>
</tr>
<tr>
<td>CAPRICORN⁵</td>
<td>carvedilol</td>
<td>post-MI LVD</td>
<td>25 BID</td>
<td>↓ 23% mortality (p = .031)</td>
</tr>
</tbody>
</table>

### Pharmacologic Therapy: Beta Blocker Overview*

<table>
<thead>
<tr>
<th>General considerations</th>
<th>Initiate at low doses</th>
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<tbody>
<tr>
<td></td>
<td>Up-titrate gradually, generally no sooner than at 2 week intervals</td>
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<tr>
<td></td>
<td>Use target doses shown to be effective in clinical trials</td>
</tr>
<tr>
<td></td>
<td>Aim to achieve target dose in 8-12 weeks</td>
</tr>
<tr>
<td></td>
<td>Maintain at maximum tolerated dose</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>If symptoms worsen or other side effects appear</th>
<th>Adjust dose of diuretic or concomitant vasoactive med.</th>
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<tr>
<td></td>
<td>Continue titration to target after symptoms return to baseline</td>
</tr>
</tbody>
</table>

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<tr>
<th>If up-titration continues to be difficult</th>
<th>Prolong titration interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reduce target dose</td>
</tr>
<tr>
<td></td>
<td>Consider referral to a HF specialist</td>
</tr>
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**Implications of CARMEN**

- First trial comparing BB monotherapy to ACEI monotherapy
  - Beta blockers by themselves good enough
  - Good alternative in ACE-I intolerant patients
  - Combination therapy is likely best
- Consensus supports ACE-I first, if tolerant

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*Consult language of specific recommendations

Back to Mr. Jones…

- Echocardiogram
  - EF 10-20%, global hypokinesis
  - Idiopathic dilated cardiomyopathy
- Carvedilol 3.125mg bid
- Lisinopril 5mg daily
- Lasix 40mg IV BID due to his LE edema

- Mr. Jones now has a dry cough and is uncomfortable
- Now what?

HFSA 2006 Practice Guideline (7.10)
Pharmacologic Therapy:
Angiotensin Receptor Blockers

**ARBs are recommended** for routine administration to symptomatic and asymptomatic patients with an LVEF ≤ 40% who are intolerant to ACE inhibitors for reasons other than hyperkalemia or renal insufficiency.

*Strength of Evidence = A*
CHARM-Alternative

Primary outcome of CV death or CHF hospitalization

Placebo

Candesartan

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

Number at risk
Candesartan 1,013 929 831 434 122
Placebo 1,015 887 798 427 126


ACE/ARB combination

- What if Mr. Jones tolerated the ACE Inhibitor, would it be helpful or harmful add an ARB to his medications?

- BP 100/80 HR 72 Cr 1.1 K+ 4.1
Poor Mr. Jones...

- Titrated up meds
  - Carvedilol 6.25 mg bid
  - Lisinopril 20 mg daily
  - Lasix 80 mg bid
- Still NYHA class III, tired of your continued failure to make him better
- Now what?
HFSA 2006 Practice Guideline (7.14-7.15)
Pharmacologic Therapy:
Aldosterone Antagonists

An aldosterone antagonist is recommended for patients on standard therapy, including diuretics, who have:

- NYHA class IV HF (or class III, previously class IV) due to LV systolic dysfunction (LVEF ≤ 35%)

One should be considered in patients post-MI with clinical HF or diabetes and an LVEF < 40% who are on standard therapy, including an ACE inhibitor or an ARB.

Strength of Evidence = A


Hail to thee, polypharmacy…

So, Mr. Jones is now taking:

- Coreg 6.25mg bid
- Lisinopril 20mg daily
- Spironolactone 25mg qd
- Lasix 80mg bid
- His BP and HR still stable but had to D/C spironolactone due to severe increase K+
- He is still NYHA Class III
- Any other medications we can add?
HFSA 2006 Practice Guideline (7.19)
Pharmacologic Therapy: Hydralazine and Oral Nitrates

A combination of hydralazine and isosorbide dinitrate is recommended as part of standard therapy, in addition to beta-blockers and ACE-inhibitors, for African Americans with LV systolic dysfunction:

- NYHA III or IV HF *Strength of Evidence = A*
- NYHA II HF *Strength of Evidence = B*

A-HeFT All-Cause Mortality

43% Decrease in Mortality

P = 0.01

How did Mr. Jones do?

- Mr. Jones was discharged last week in NYHA class II heart failure, but comes back to the ED after gaining 10 lbs with an increase in fatigue and SOB – he’s having trouble walking up one flight of stairs again.
- BP 95/52 HR 58 Cr 1.5 K+ 3.9
- What happened?
- Which meds should we hold?
- Should we change anything else?

Diet and nutrition in HF

- Sodium restriction (2-3g/day) in all patients with clinical HF
- Fluid intake < 2 liters in patients with fluid retention and hyponatremia
- Consider daily MVI supplementation
- Caloric assessment / supplementation in patients with advanced HF/cachexia
HFSA 2006 Practice Guideline (7.24)
Pharmacologic Therapy: Diuretics

- Restoration of normal volume status may require multiple adjustments.
- Once a diuretic effect is achieved with short-acting loop diuretics, increase frequency to 2-3 times a day if necessary, rather than increasing a single dose. **Strength of Evidence = B**
- Oral torsemide **may be considered** in patients exhibiting poor absorption of oral medication or erratic diuretic effect. **Strength of Evidence = C**
- IV administration of diuretics may be necessary. **Strength of Evidence = A**
- Diuretic refractoriness may represent patient noncompliance, a direct effect of diuretic use on the kidney, or progression of underlying dysfunction.


Digoxin

- Limited role in HF
- Does not improve mortality in mild to moderate HF
- Can reduce hospitalization in poorly controlled patients
- Narrow therapeutic window (0.125-0.250 mg daily)
- Watch for digoxin toxicity
HFSA 2006 Practice Guideline

**Digoxin**

*Recommendation 7.29*

Digoxin *should be considered* for patients with LV systolic dysfunction (LVEF < 40) who have signs or symptoms of HF while receiving standard therapy, including ACE inhibitors and beta blockers:

- NYHA class II-III *Strength of Evidence = A*
- NYHA class IV *Strength of Evidence = B*

Mr. Jones redux

- You started IV lasix 80mg TID and Mr. Jones is not responding – urine output < 1L a day
- Symptoms worsen to NYHA Class IV
- JVD to earlobes, bilateral rales
- Vital signs 95/50  HR 103
- Cr still 1.5  K+ stable
- Any suggestions?
• NATRECOR® (nesiritide) has the same 32 amino acid sequence as the endogenous peptide\(^1\)

• Human BNP increases intracellular cGMP, which serves as second messenger to dilate veins and arteries\(^1\)

• Systemic Hemodynamic Effects\(^1,2,3\)
  – preload and afterload reduction
  – increased cardiac index
  – no significant increase in heart rate

References: 1. NATRECOR® Full Prescribing Information.
2. Golino WE et al. JAMA. 2005;293:246
Acute Decompensated Heart Failure: Nesiritide and Mortality

• No short-term therapy for ADHF has been proven to improve short- or long-term mortality rates.
• Nesiritide is the only approved ADHF therapy which has been shown in large, randomized trials to provide both significant symptomatic and hemodynamic improvement when added to standard care.
• Nesiritide has not been studied in a trial powered to evaluate an effect on mortality.
• Follow dosing instructions and patient exclusion criteria carefully

Other last-ditch options

• Cardiac resynchronization therapy (CRT)
• Biventricular pacing
• ICD placement