Congestive Heart Failure

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CHF: A Growing Burden

- Prevalence: 6 million
- Incidence: 0.8 million/year
- Hospitalizations: 1.3 million/year
- Cost: >$40 billion/year
  - (60% for hospitalizations)

Mortality:
- Class I 20% at 4 years
- Class IV 50% at 1 year
CHF: Epidemiology

• Doubles in prevalence with each decade from age 50-90
  • (from ~1% to ~9%)
• Slight male predominance
• 50-75% of cases associated with CAD and/or HTN
Prevalence of HF Increases With Age

- **Prevalence** increases with age in both males and females.
- The prevalence is significantly higher in older age groups, particularly in the 75+ age category.
- The graph shows a clear trend with age groups 55-64, 65-74, and 75+ having the highest prevalence rates for both males and females.

**Key Observations**:
- **Population (%)** is depicted on the y-axis.
- **Age (yr)** is shown on the x-axis in categories: 20-24, 25-34, 35-44, 45-54, 55-64, 65-74, and 75+.
- Males are represented by orange bars, and females by green bars.
Lifetime Risk for CHD by Age and Sex

Lifetime Risk for CHF by Sex and Age

Men vs. Women

Lloyd-Jones et al. Circulation 2002
Risk Factors for Heart Failure

- CAD
- Hypertension
- Valvular heart disease
- Alcoholism or other cardiotoxins

- Diabetes
- Congenital heart defects
- Other:
  - Age
  - Obesity
  - Smoking
  - Family history
## Risk Factors for CHF

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>HTN</td>
<td>2.07</td>
<td>3.35</td>
</tr>
<tr>
<td>MI</td>
<td>6.34</td>
<td>6.01</td>
</tr>
<tr>
<td>Angina</td>
<td>1.43</td>
<td>1.68</td>
</tr>
<tr>
<td>VHD</td>
<td>2.47</td>
<td>2.13</td>
</tr>
<tr>
<td>LVH</td>
<td>2.19</td>
<td>2.85</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.82</td>
<td>3.73</td>
</tr>
</tbody>
</table>

Levy et al, JAMA 1996
Mild renal insufficiency* and risk of CHF in the elderly

* About 16% of study patients

Chae et al. Am J Cardiol. 2003;92:682-6
The ADHERE® Registry:

Impact of renal dysfunction on survival

Table 8. Mortality According to Renal Function

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic Function</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preserved (n = 26,002)*</td>
</tr>
<tr>
<td>Mortality (Cr &gt; 2 mg/dl vs. Cr ≤ 2 mg/dl)</td>
<td>4.8% vs. 2.3%</td>
</tr>
<tr>
<td>Unadjusted OR (95% CI)</td>
<td>2.12 (1.80–2.49); p &lt; 0.0001</td>
</tr>
<tr>
<td>Adjusted† OR (95% CI)</td>
<td>2.45 (2.07–2.92); p &lt; 0.0001‡</td>
</tr>
</tbody>
</table>
Pulse pressure and risk of CHF in the elderly

Chae et. al. JAMA 1999;281:634-9
Relationship between LA size and new CHF in elderly subjects with normal EF

76% still had normal EF at time of new CHF

Takemoto et.al. Am J Cardiol 2005;96:832-6
Diastolic Heart Failure

- ? ~ 40-50% of CHF
- Marked volume sensitivity

Special importance:

- ischemia
- hypertension
- AF

CO
LVEDP
HCM
LVEDV
LVEDV
Characteristics of Heart Failure Patients Enrolled in the ADHERE® Registry

- N = >150,000
- Average age: 72.5 years
- Women: 52%
- Ischemic etiology (CAD): 60%
- Renal insufficiency (SCr >1.5 mg/dL): 30%
- Preserved LVEF: ≈50%
- AF: 31%
- DM: 44%
## Classification of HF: Comparison Between ACC/AHA HF Stage and NYHA Class

<table>
<thead>
<tr>
<th>ACC/AHA HF Stage&lt;sup&gt;1&lt;/sup&gt;</th>
<th>NYHA Functional Class&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong> At high risk for heart failure but without structural heart disease or symptoms of heart failure (e.g., patients with hypertension or coronary artery disease)</td>
<td>None</td>
</tr>
<tr>
<td><strong>B</strong> Structural heart disease but without symptoms of heart failure</td>
<td>I  Asymptomatic</td>
</tr>
<tr>
<td><strong>C</strong> Structural heart disease with prior or current symptoms of heart failure</td>
<td>II  Symptomatic with moderate exertion III  Symptomatic with minimal exertion</td>
</tr>
<tr>
<td><strong>D</strong> Refractory heart failure requiring specialized interventions</td>
<td>IV  Symptomatic at rest</td>
</tr>
</tbody>
</table>


Neurohumoral Activation

Index Event: MI myocarditis other

LV remodeling cell loss dilation hypertrophy

LV systolic dysfunction

Low circulating volume abnormal baroreflexes

Neurohumoral activation

Vasoconstriction

Na\(^{+}\) and H\(_{2}\)O retention

Reduced organ perfusion

CHF Sxs
HF Therapy

- Treat hypertension and lipids, smoking cessation, exercise, limit alcohol, ACE inhibitors in appropriate populations
- PLUS ACE inhibitors, beta blockers in appropriate populations
- PLUS ACE inhibitors, beta blockers, diuretics, digoxin, aldosterone receptor antagonists, dietary salt restriction
- PLUS inotropes, transplant, ventricular assist device
Diuretics in HF: NYHA II- IV

• Improve symptoms by relieving congestion

• Effect on HF progression, remodeling and mortality not known.
Digitalis in Heart Failure

- Improves symptoms, quality of life
- Improves ejection fraction
- Improves exercise tolerance

- No effect on progression of heart failure
- No effect on remodeling
- No effect on mortality
## Major ACE Inhibitor Trials in Heart Failure

<table>
<thead>
<tr>
<th>Trial</th>
<th>Mortality</th>
<th></th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACEI</td>
<td>Controls</td>
<td></td>
</tr>
<tr>
<td><strong>Chronic HF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consensus I</td>
<td>39%</td>
<td>54%</td>
<td>0.56 (0.34–0.91)</td>
</tr>
<tr>
<td>SOLVD (Treatment)</td>
<td>35%</td>
<td>40%</td>
<td>0.82 (0.70–0.97)</td>
</tr>
<tr>
<td>SOLVD (Prevention)</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>
</tr>
<tr>
<td>SAVE</td>
<td>20%</td>
<td>25%</td>
<td>0.81 (0.68–0.97)</td>
</tr>
<tr>
<td>AIRE</td>
<td>17%</td>
<td>23%</td>
<td>0.73 (0.60–0.89)</td>
</tr>
<tr>
<td>TRACE</td>
<td>35%</td>
<td>42%</td>
<td>0.78 (0.67–0.91)</td>
</tr>
<tr>
<td>SMILE</td>
<td>5%</td>
<td>6.5%</td>
<td>0.75 (0.40–1.11)</td>
</tr>
</tbody>
</table>
## Major Trials of β-Blockade in Chronic Heart Failure

<table>
<thead>
<tr>
<th>Study</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>
<th>NYHA Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIBIS</td>
<td>641</td>
<td>1.9</td>
<td>5 qd</td>
<td>3.8</td>
<td>All-cause mortality: NS</td>
<td>II-III</td>
</tr>
<tr>
<td>CIBIS-II</td>
<td>2647</td>
<td>1.3</td>
<td>10 qd</td>
<td>7.5</td>
<td>All-cause mortality: ↓34% (P&lt;.0001)</td>
<td>II-III</td>
</tr>
<tr>
<td>MDC</td>
<td>383</td>
<td>1</td>
<td>50 to 75 bid</td>
<td>108</td>
<td>Death or need for transplant (primary end point): NS</td>
<td>II-III</td>
</tr>
<tr>
<td>MERIT-HF</td>
<td>3991</td>
<td>1</td>
<td>200 qd</td>
<td>159</td>
<td>All-cause mortality: ↓34% (P=.0062)</td>
<td>II-III</td>
</tr>
<tr>
<td>US Carvedilol</td>
<td>1094</td>
<td>7.5 months</td>
<td>6.25 to 50 bid</td>
<td>45</td>
<td>All-cause mortality†: ↓65% (P=.0001)</td>
<td>II-III</td>
</tr>
<tr>
<td>COPERNICUS</td>
<td>2289</td>
<td>10.5 months</td>
<td>25 bid</td>
<td>37</td>
<td>All-cause mortality: ↓35% (P=.00013)</td>
<td>IIIB</td>
</tr>
</tbody>
</table>
COMET: all-cause mortality

<table>
<thead>
<tr>
<th>Relative</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>risk</td>
<td>0.828</td>
<td>0.0017  **</td>
</tr>
<tr>
<td>0.736, 0.931</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Carvedilol
Metoprolol

17%

COMET: all-cause mortality

Time (years)

Percentage Mortality (%)
β-blockers for CHF in the elderly

- Am J Cardiol. 2005 Apr 1;95(7):896-898

Do elderly systolic heart failure patients benefit from beta blockers to the same extent as the non-elderly?

Meta-analysis of >12,000 patients in large-scale clinical trials.

No statistically significant difference in mortality reduction between elderly and non-elderly.
Randomized ALdactone Evaluation Study (RALES)

30% Risk Reduction
95% CI (18%–40%)
p<0.001

Spironolactone + standard therapy

Standard therapy (ACE inhibitor + loop diuretic ± digoxin)

Neprilysin: degrades natriuretic peptides, bradykinin, and adrenomedullin

Dual-acting ARNI

NEP inhibition

NEP

Metabolites

Natriuretic peptides (ANP, BNP)

F Vasodilatation
F Sodium excretion
F Antihypertrophic effect
F Antifibrotic effect

Angiotensin 1

Vasoconstriction
F Sodium retention
F Pro-hypertrophic effect
F Pro-fibrotic effect

AT1R

Angiotensin 2

Synergistic effect on blood-pressure lowering and reduction of target organ damage

Risk of angio-oedema

Metabolites

Aminopeptidase P

Bradykinin
PARADIGM-HF
– Randomized 8442 HFrEF (EF < 40%) patients (93% on BB)
– Primary outcome: composite of death from cardiovascular causes or hospitalization for heart failure: 21.8% Rx vs. 26.5% placebo (P<0.001)
– Mean follow-up 27 months
– Other outcome individual components:
  • Death from any cause: 17.0% vs. 19.8%, P<0.001
  • Death from cardiovascular causes: 13.3% vs. 16.5%, P<0.001
  • HF hospitalization reduced by 21% (P<0.001)
– Adverse events: more hypotension and nonserious angioedema but less renal impairment, hyperkalemia, and cough


New HF medications 2016
Angiotensin receptor–neprilysin inhibitor

A Primary End Point

B Death from Cardiovascular Causes

C Hospitalization for Heart Failure

D Death from Any Cause

# New HF medications 2016

Angiotensin receptor–neprilysin inhibitor (ARNI) (valsartan/sacubitril)

## Recommendations for Renin-Angiotensin System Inhibition With ACE Inhibitor or ARB or ARNI

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>ACE: A</td>
<td>The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors (<em>Level of Evidence: A</em>)&lt;sup&gt;9–14&lt;/sup&gt; OR ARBs (<em>Level of Evidence: A</em>)&lt;sup&gt;15–18&lt;/sup&gt; OR ARNI (<em>Level of Evidence: B-R</em>)&lt;sup&gt;19&lt;/sup&gt; in conjunction with evidence-based beta blockers,&lt;sup&gt;20–22&lt;/sup&gt; and aldosterone antagonists in selected patients,&lt;sup&gt;23,24&lt;/sup&gt; is recommended for patients with chronic HFrEF to reduce morbidity and mortality.</td>
</tr>
<tr>
<td>I</td>
<td>ARB: A</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>ARNI: B-R</td>
<td></td>
</tr>
</tbody>
</table>

| II  | ARNI: B-R | In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality.<sup>19</sup> |

| III: Harm | B-R | ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor.<sup>31,32</sup> |
| III: Harm | C-EO | ARNI should not be administered to patients with a history of angioedema. |
• ivabradine –
  – randomized, double-blind, placebo-controlled outcomes study with a median duration of 22.9 months (N = 6,505)

Inclusion criteria included stable chronic systolic HF for ≥ 4 weeks, in sinus rhythm, NYHA class II to IV, with a reduced LVEF (≤ 35%), a resting heart rate ≥ 70 bpm, and hospitalization for worsening HF within 12 months.

Exclusion criteria included myocardial infarction within the previous 2 months, ventricular or atrioventricular pacing (≥ 40% of the day), atrial fibrillation or flutter, and symptomatic hypotension.

Primary endpoint: HF hospitalization or CV death (no effect on death), HR 0.82 (18% reduction).

COMPANION: All-Cause Mortality

CRT vs. OPT: RR = 24%, p=0.059 (Adjusted p-value = 0.060)
CRT-D vs. OPT: RR = 36%, p=0.003 (Adjusted p-value = 0.004)

12-month Event Rates
- OPT: 19%
- CRT: 15% (AR=4%)
- CRT-D: 12% (AR=7%)

Days from Randomization

% of Patients Event-Free
0 120 240 360 480 600 720 840 960 1080
100 90 80 70 60 50

OPT
CRT HR 0.76 (CI: 0.58-1.01)
CRT-D HR 0.64 (CI: 0.48-0.86)
CHF: Frequently Overlooked Issues

1. Patient goals
2. Home Environment
3. Compliance
4. Education
5. Screening for:
   1. Depression
   2. Sleep Disorder
   3. Sexual Dysfunction

Readmissions!!!
Treat hypertension and lipids, smoking cessation, exercise, limit alcohol, ACE inhibitors in appropriate populations

PLUS ACE inhibitors, beta blockers in appropriate populations

PLUS ACE inhibitors, beta blockers, diuretics, digoxin, aldosterone receptor antagonists, dietary salt restriction

PLUS inotropes, transplant, ventricular assist device

HF Therapy
ADULT HEART TRANSPLANTATION

Survival by Era


1982-1991 vs. 2002-6/2009: p < 0.0001
1992-2001 vs. 2002-6/2009: p < 0.0001
Long-Term Use of a Left Ventricular Assist Device for End-Stage Heart Failure

## Reasons for Transplant Ineligibility

<table>
<thead>
<tr>
<th>Reason</th>
<th>LVAD (n=68)</th>
<th>OMM (n=61)</th>
<th>( P^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 65 years</td>
<td>47 (69%)</td>
<td>48 (78.6%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Insulin dependent diabetes mellitus with end-organ damage</td>
<td>10 (15%)</td>
<td>7 (11%)</td>
<td>0.79</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>2 (3%)</td>
<td>2 (3%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Significant irreversible comorbidity (e.g., Ca, pulm HTN, Obesity)</td>
<td>20 (29%)</td>
<td>10 (16%)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

* Fisher Exact Test
All cause mortality

Logrank analysis: P=0.001

- VE LVAS (n=68)
- OMM (n=61)
HeartMate® SNAP-VE LVAD
Heartware™ Ventricular Assist System
HeartWare LVAD

Overall Survival

June 2006 – June 2011
Primary Continuous Flow LVADs (+/- RVADs): n = 3405*

Bridge to Transplant Listed, n=1221, deaths=153

Bridge to Candidacy, n=1391, deaths=247

Destination Therapy, n=740, deaths=132

By initial Device Strategy

p < .0001

Event: Death (censored at transplant or explant recovery)

Months after Device Implant

% Survival
## Indications for LVAD Use

<table>
<thead>
<tr>
<th>Indication</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postcardiotomy (Bridge-to-Recovery)</td>
<td>Device intended for short-term support for a condition that is anticipated to be reversible</td>
</tr>
<tr>
<td>Bridge-to-Bridge</td>
<td>Device intended for short-term support (typically inserted in an emergent situation) until a more permanent device can be implanted</td>
</tr>
<tr>
<td>Bridge-to-Transplantation</td>
<td>Device typically intended for short- to intermediate-term support in patients actively listed for transplantation</td>
</tr>
<tr>
<td>Destination Therapy</td>
<td>Device inserted with the intention of long-term support in patients who are not candidates for transplantation</td>
</tr>
</tbody>
</table>
Conclusion

- Elderly patients are at highest risk for CHF
- Numerous risk factors have been identified
- Standard therapies are effective
- Higher order therapies may be considered