Advances in the Management of Systolic and Diastolic Heart Failure

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Prevalence of Heart Failure

Life-time Risk of Heart Failure

Relevant Financial Relationship Disclosure Statement

Advances in the Management of Systolic and Diastolic Heart Failure: Liviu Klein, MD, MS

I will discuss off label use and/or investigational use of products.

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Consultant: St. Jude Medical.
Honoraria: None.
Stockholder: None.

Prevalence of Heart Failure

Source: CDC/NCHS and NHLBI.

Life-time Risk of Heart Failure

Temporal Changes in Incidence

Table 1. Temporal Trends in the Age-Adjusted Incidence of Heart Failure

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Men Incidence per 100,000 (95% CI)</td>
<td>360 (323-396)</td>
<td>390 (354-425)</td>
<td>375 (340-409)</td>
<td>363 (351-415)</td>
</tr>
<tr>
<td>Women Incidence per 100,000 (95% CI)</td>
<td>284 (260-307)</td>
<td>292 (270-315)</td>
<td>260 (238-282)</td>
<td>315 (292-338)</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.00</td>
<td>1.07 (0.94-1.22)</td>
<td>1.01 (0.88-1.15)</td>
<td>1.04 (0.92-1.18)</td>
</tr>
</tbody>
</table>

Prevalence by Ejection Fraction


Mortality by Ejection Fraction


Heart Failure Hospitalizations

1.1 mil hospitalizations/ year

### Classification of Heart Failure

<table>
<thead>
<tr>
<th>Stage</th>
<th>Patient Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk for developing heart failure (HF)</td>
<td>Hypertension, CAD, Diabetes mellitus, Family history of cardiomyopathy, Previous MI, LV systolic dysfunction, Asymptomatic valvular disease, Known structural heart disease, Shortness of breath and fatigue, Reduced exercise tolerance, Marked symptoms at rest despite maximal medical therapy (eg, those who are recurrently hospitalized or cannot be safely discharged from the hospital without specialized interventions)</td>
</tr>
<tr>
<td>Asymptomatic HF</td>
<td></td>
</tr>
<tr>
<td>Symptomatic HF</td>
<td></td>
</tr>
<tr>
<td>Refractory end-stage HF</td>
<td></td>
</tr>
</tbody>
</table>


### Management of Heart Failure

- **Establish diagnosis** (labs, ECG, CXR, echo)
- **Determine etiology** (right/ left heart catheterization, cMRI, etc.)
- **Define syndrome** (systolic vs. diastolic)
- **Correct precipitating factors** (NSAIDS, COX2, glitazones, etc.)
- **Evaluate and correct ischemia**
- **Initiate chronic therapy**
  - Non-pharmacologic (exercise, sleep apnea?, etc.)
  - Pharmacologic (ACE-I/ARB, β-Blockers, Aldo blockers, diuretics, etc.)
  - Electrical (ICD, CRT)
  - Surgical (CABG, MVR, LVAD, transplant)
- **Assess response to therapy** (clinical, echo?, CPX, 6MWT, etc.)

### Revascularization in Ischemic SHF

**STICH Trial (1212 pts. NYHA II-III):**

- **LVEF ≤ 0.35** within 3 months of trial entry.
- **CAD suitable for CABG.**
- **MED eligible:**
  - Absence of left main stenosis of ≥ 50%.
  - Absence of CCS III-IV angina (angina markedly limiting ordinary activity).

Revascularization in Ischemic HF


Management of Heart Failure

- Establish diagnosis (labs, ECG, CXR, echo)
- Determine etiology (right/ left heart catheterization, cMRI, etc.)
- Define syndrome (systolic vs. diastolic)
- Correct precipitating factors (NSAIDS, COX2, glitazones, etc.)
- Evaluate and correct ischemia
- Initiate chronic therapy
  - Non-pharmacologic (exercise training)
  - Pharmacologic (ACE-I/ ARB, β-Blockers, Aldo blockers, diuretics, etc.)
  - Electrical (ICD, CRT)
  - Surgical (CABG, MVR, LVAD, transplant)
- Assess response to therapy (clinical, echo?, CPX, 6MWT, etc.)

Exercise Training in Heart Failure

- Structured, group-based, supervised exercise program.
- Goal 3 sessions/ week x 36 sessions in 3 months.
- Exercise initiated at 15-30 min/ session at HR of 60% of HR reserve (Max HR on CPX – resting HR).
- After 6 sessions, duration of exercise increased to 30-35 min, and intensity increased to 70% of HR reserve.
- After 18-36 sessions, exercise continued at home.

**Exercise Training in Heart Failure**

- Exercise is safe:
  - 0.4% in each group died within 3 hours of exercise.
  - No difference in MI, UA, CVA in the two groups.
- Sustained reduction in HF hospitalizations with exercise.
- No difference in mortality with exercise.
- Significant improvement in symptoms:
  - NYHA class decreased in 30% of pts with exercise vs. 25% in usual care.

*Corrigan CM et al. JAMA. 2009; 301: 1439-1450.*

**Management of Heart Failure**

- Establish diagnosis (labs, ECG, CXR, echo)
- Determine etiology (right/ left heart catheterization, cMRI, etc.)
- Define syndrome (systolic vs. diastolic)
- Correct precipitating factors (NSAIDS, COX2, glitazones, etc.)
- Evaluate and correct ischemia (stress test)
- Initiate chronic therapy
  - Non-pharmacologic (exercise, sleep apnea, etc.)
  - Pharmacologic (ACE-I/ ARB, ß-Blockers, Aldo blockers, diuretics)
    - Electrical (ICD, CRT)
    - Surgical (CABG, MVR, LVAD, transplant)
- Assess response to therapy (clinical, echo, CPX, 6MWT, etc.)

**Diuretics in Heart Failure**

- Loop diuretics in pts. with CrCl < 30
- Torsemide ↓ hospitalizations compared to furosemide
- Have to be given bid to avoid rebound Na reabsorbtion
- May use thiazides alone if CrCl > 30
- Use combination (e.g. furosemide + thiazide)
- Metolazone/ chlorthiazide in refractory HF or in pts. with renal failure. Should not be used more than once daily or every other day due to long half life.
- Add spironolactone if Cr < 2 (GFR > 40) and K < 5.


**ACE - I and Survival in Heart Failure**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug (mean dose)</th>
<th>ACEI</th>
<th>Placebo</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic HF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CONSENSUS I</td>
<td>Enalapril (18.4 mg)</td>
<td>39%</td>
<td>54%</td>
<td>0.56 (0.34-0.91)</td>
</tr>
<tr>
<td>SOLVD (T)</td>
<td>Enalapril (11.2 mg)</td>
<td>35%</td>
<td>40%</td>
<td>0.82 (0.70-0.97)</td>
</tr>
<tr>
<td>SOLVD (P)</td>
<td>Enalapril (12.7 mg)</td>
<td>15%</td>
<td>16%</td>
<td>0.92 (0.79-1.08)</td>
</tr>
<tr>
<td>Post-MI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAVE</td>
<td>Captopril (150 mg)*</td>
<td>20%</td>
<td>25%</td>
<td>0.81 (0.68-0.97)</td>
</tr>
<tr>
<td>AIRE</td>
<td>Ramipril (1.25-5 mg)†</td>
<td>17%</td>
<td>23%</td>
<td>0.73 (0.60-0.89)</td>
</tr>
<tr>
<td>TRACE</td>
<td>Trandolapril (1-4 mg)†</td>
<td>35%</td>
<td>42%</td>
<td>0.78 (0.67-0.91)</td>
</tr>
<tr>
<td>SMILE</td>
<td>Zofenopril (7.5-30 mg)†</td>
<td>5%</td>
<td>6.5%</td>
<td>0.75 (0.40-1.11)</td>
</tr>
<tr>
<td>Totals</td>
<td></td>
<td>21%</td>
<td>25%</td>
<td>0.84</td>
</tr>
</tbody>
</table>

ACE Inhibitors in Heart Failure

- Most pts. tolerate ACE - I.
- ACE - I improve symptoms immediately (days).
- Pts. should not be “too dry” (no orthostatic ↓ BP).
- If ↓ BP, check for orthostatic changes. If none, ACE - I OK.
- Low BP and CKD are not CI for ACE - I.
- If BUN/ Cr are raising, adjust the diuretic dose.
- Low BP, low Na, renal dysfunction: low dose, short acting ACE - I, titrate to target dose or the highest dose tolerated.
- Low vs. high dose ACE - I: difference in outcomes.


Low (5 mg) vs. High (35 mg) Dose Lisinopril in Heart Failure

<table>
<thead>
<tr>
<th>Study</th>
<th>Percent Reduction in</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalizations for any reason</td>
<td>Low-Dose</td>
</tr>
<tr>
<td>CIBIS II  (bisoprolol)</td>
<td>4397</td>
</tr>
<tr>
<td>MERIT - HF  (metoprolol XL)</td>
<td>2923</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>1576</td>
</tr>
<tr>
<td>Hospitalization for ischemic events</td>
<td>543</td>
</tr>
</tbody>
</table>


Beta - Blockers in Heart Failure

<table>
<thead>
<tr>
<th>Study</th>
<th>All - cause mortality</th>
<th>All - cause hospitalizations</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIBIS II  (bisoprolol)</td>
<td>↓ 34%</td>
<td>↓ 20%</td>
</tr>
<tr>
<td>MERIT - HF  (metoprolol XL)</td>
<td>↓ 34%</td>
<td>↓ 8.6%</td>
</tr>
<tr>
<td>COPERNICUS  (carvedilol)</td>
<td>↓ 35%</td>
<td>↓ 15%</td>
</tr>
</tbody>
</table>


Beta - Blockers

- Only bisoprolol, carvedilol and metoprolol succinate.
- Start at low doses, increase every 2 weeks to target dose or the highest tolerated dose.
- Intermediate vs. high dose: no difference in outcomes.

Beta - Blockers

- Only bisoprolol, carvedilol and metoprolol succinate.
- Start at low doses, increase every 2 weeks to target dose or the highest tolerated dose.
- Intermediate vs. high dose: no difference in outcomes.
- Do not start in pts. dependent of inotropic support.
- Can start before hospital discharge in pts. not fluid overloaded.
- Do not stop BB in hospitalized pts. who are on chronic BB therapy (may worsen HF).
- BB will take 3-6 months to improve symptoms.
- Low BP and severe HF are not CI for BB.


COMET: Metoprolol vs. Carvedilol

- Metoprolol tartrate 50 mg bid
- Carvedilol 25 mg bid

HR 0.83 (0.74 - 0.93)  
\[ p = 0.0017 \]


Carvedilol: The Cadillac of BB

- “Switches off” beta receptor more than all other beta-blockers.
- Better BP control, insulin sensitivity, peripheral vasodilatation.
- Mitochondrial protection (\( \uparrow \) anti-oxidant moiety)

Carvedilol and Metoprolol Succinate Effects on Blood Pressure


Which Drug First: ACE-I or BB?


Sudden Death: Bisoprolol vs. Enalapril

<table>
<thead>
<tr>
<th>End point</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sudden death</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monotherapy phase (6 mo)</td>
<td>0.50 (0.21-1.16)</td>
<td>0.107</td>
</tr>
<tr>
<td>12 months</td>
<td>0.54 (0.29-1.00)</td>
<td>0.049</td>
</tr>
<tr>
<td>End of study</td>
<td>0.84 (0.51-1.38)</td>
<td>0.487</td>
</tr>
<tr>
<td><strong>All-cause mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monotherapy phase (6 mo)</td>
<td>0.72 (0.42-1.24)</td>
<td>0.24</td>
</tr>
<tr>
<td>12 months</td>
<td>0.69 (0.46-1.02)</td>
<td>0.06</td>
</tr>
<tr>
<td>End of study</td>
<td>0.88 (0.63-1.22)</td>
<td>0.44</td>
</tr>
</tbody>
</table>


Angiotensin Receptor Blockers (ARB)

- Combination ARB + ACE - I + Beta - Blockers is safe.
- No mortality benefit when ARB is added to ACE - I.
- ARB are useful in pts. who are ACE intolerant (candesartan, losartan and valsartan).
- ARB could be added to ACE - I for symptomatic improvement.
- Triple RAAS blockade (ACE - I, ARB, aldosterone blockers) should not be used (Hyper K).

Effect of Candesartan on Mortality and HF Hospitalizations

- All-cause mortality
- Cardiovascular death/HF hospitalizations


Mineralcorticoid (Aldosterone) Receptor Blockers (MRB)

- Effective in preventing hospitalizations in patients with EF < 35% and NYHA class II-IV symptoms.
- Marked mortality benefit when MRB added to ACE-I and BB.
- MRB improve survival and symptoms better than ARB, and should be used in the “combo” with ACE-I and BB.
- Use if Cr < 2 (W) or 2.5 (M) (aka GFR > 40) and K<5.

Spironolactone in NYHA III-IV HF


Eplerenone in HF post-MI

Selected Medications in Systolic HF

- **Statins:**
  - May decrease CVD hospitalizations in ischemic systolic HF patients (CORONA).
  - No effect on CVD outcomes in non-ischemic systolic HF or diastolic HF patients (GISSI-HF).

- **Anticoagulation in SR in systolic HF patients:**
  - Ischemic stroke: 45% ↓ warfarin (INR 2-3) vs. ASA 325 mg (0.7 vs. 1.3 per 100 person years).
  - Offset by increase in bleeding (1.8 vs. 0.9), but not ICH.
  - Individualized decision for treatment (WARCEF).

Selected Medications in Systolic HF

- **Digoxin:**
  - 4th choice if pts. still symptomatic on ACE-I/BB/MRB.
  - Keep serum concentration 0.7 - 0.9 ng/mL (especially women).

- **Hydralazine-nitrates:**
  - Add on therapy in AA pts. still symptomatic on ACE-I/BB.
  - Future research will likely extend this to all GLU 298 GLU in NOS3 (40% of Caucasians have this genotype).

Diastolic Heart Failure

- Control of systolic and diastolic BP.
- Control ventricular rate in pts. with A Fib.
- Diuretics to control pulmonary and peripheral edema.
- Anticoagulation in pts. with A Fib.
- Coronary revascularization in pts. with CAD and ischemia.
- Restoration of sinus rhythm in pts. with A Fib.
- Addition of BB, ACE - I, ARB, or CCB to control HTN.
- ACE - Inhibitors, ARBs, digoxin to minimize HF symptoms?

Management of Heart Failure

- Establish diagnosis (labs, ECG, CXR, echo)
- Determine etiology (right/ left heart catheterization, cMRI, etc.)
- Define syndrome (systolic vs. diastolic)
- Correct precipitating factors (NSAIDS, COX2, glitazones, etc.)
- Evaluate and correct ischemia
- Initiate chronic therapy
  - Non-pharmacologic (exercise, sleep apnea?, etc.)
  - Pharmacologic (ACE-I/ ARB, β-Blockers, Aldo blockers, diuretics, etc.)
  - Electrical (ICD, CRT)
  - Surgical (CABG, MVR, LVAD, transplant)
- Assess response to therapy (clinical, echo?, CPX, 6MWT, etc.)

Mode of Death in Systolic Heart Failure


ICD Clinical Trials in Heart Failure

MADIT II (The Second Multicenter Automatic Defibrillator Implantation Trial).

SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial).

DEFINITE (Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation).

SCD-HeFT Trial: Survival with ICD

2009 Heart Failure Guideline Update

Stage B (class II indications):
- ICD Therapy in ICM, EF < 30%, NYHA class I
- ICD Therapy in NICM, EF < 30%, NYHA class I

Stage C (class I indications):
- ICD Therapy in HF, EF < 35%, NYHA class II-III

---

Dyssynchrony in Heart Failure

LBBB Prevalence
- Increased All-Cause Mortality

<table>
<thead>
<tr>
<th>Preserved EF</th>
<th>Impaired EF</th>
<th>NYHA Class III/IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>8%</td>
<td>24%</td>
<td>38%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>QRS &lt; 120 ms</th>
<th>QRS ≥ 120 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>34%</td>
<td>49%</td>
</tr>
</tbody>
</table>


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CRT Clinical Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th># Pts</th>
<th>NYHA II IV</th>
<th>EF&lt;35%</th>
<th>QRS&gt;150</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUSTIC</td>
<td>131</td>
<td>NYHA III</td>
<td>EF&lt;35%</td>
<td>QRS&gt;150</td>
</tr>
<tr>
<td>MIRACLE</td>
<td>453</td>
<td>NYHA III</td>
<td>EF&lt;35%</td>
<td>QRS&gt;130</td>
</tr>
<tr>
<td>CONTAK CD</td>
<td>490</td>
<td>NYHA III</td>
<td>EF&lt;35%</td>
<td>QRS&gt;120</td>
</tr>
<tr>
<td>COMPANION</td>
<td>1120</td>
<td>NYHA III</td>
<td>EF&lt;35%</td>
<td>QRS&gt;120</td>
</tr>
<tr>
<td>CARE-HF</td>
<td>813</td>
<td>NYHA III</td>
<td>EF&lt;35%</td>
<td>QRS&gt;120</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved 6m walk, pV02, QOL, reduced hospitalizations</td>
</tr>
<tr>
<td>Improved 6m walk, pV02, QOL, reduced hospitalizations</td>
</tr>
<tr>
<td>Composite end-point of all-cause mortality, HF hospitalization or VT/VF therapy not met</td>
</tr>
<tr>
<td>Reduced all-cause mortality and hospitalization</td>
</tr>
<tr>
<td>Reduced all-cause mortality and hospitalization</td>
</tr>
</tbody>
</table>

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CARE-HF: All-cause Mortality or Unplanned CVD Hospitalizations

<table>
<thead>
<tr>
<th>Event-free Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT</td>
</tr>
<tr>
<td>Medical Therapy</td>
</tr>
</tbody>
</table>

HR 0.63 (95% CI 0.51 to 0.77)

P < .0001

Stage C (class I indications):
- CRT in HF, EF < 35%, SR, QRS > 120 ms, NYHA III-IV

Stage C (class II indications):
- CRT in HF, EF < 35%, AF, QRS > 120 ms, NYHA III-IV

Paradigm Shifts: CRT for Prevention
- ICM NYHA I-II or NICM NYHA II (MADIT - CRT).
- ICM or NICM NYHA II-III (RAFT).
- EF ≤ 0.30.
- QRS ≥ 130 ms (MADIT - CRT) or ≥ 120 ms (RAFT).
- Meet AHA/ACC guideline indications for ICD.
- Receiving optimal medical therapy.

2009 Heart Failure Guideline Update

Stage B (class I indications):
- CRT in HF, EF < 30%, SR, EF < 30%, NYHA I-II, QRS > 150 ms, LBBB.

Stage C (class I indications):
- CRT in HF, EF < 35%, SR or AF, QRS > 120 ms, NYHA III-IV.

2013 Heart Failure Guideline Update


Paradigm Shifts: CRT for Prevention

Management of Heart Failure

- Establish diagnosis (labs, ECG, CXR, echo)
- Determine etiology (right/ left heart catheterization, cMRI, etc.)
- Define syndrome (systolic vs. diastolic)
- Correct precipitating factors (NSAIDS, COX2, glitazones, etc.)
- Evaluate and correct ischemia
- Initiate chronic therapy
  - Non-pharmacologic (exercise, sleep apnea?, etc.)
  - Pharmacologic (ACE-I/ ARB, β-Blockers, Aldo blockers, diuretics, etc.)
  - Electrical (ICD, CRT)
  - Surgical (CABG, MVR, LVAD, transplant)
- Assess response to therapy

Risk Stratification in Heart Failure

- NYHA class IIIB - IV (continuous for > 60 days).
- > 2 hospitalizations for heart failure in the past year.
- Inability to tolerate ACE-I and BB.
- Cardiogenic shock or “semi-shock”
  - CI < 2 L/min/m².
  - PCWP > 25 mmHg.
  - Oliguria (< 0.3 mL/ min).
  - Mental status impairment.

Intolerance of ACE-I and Outcomes


Stage D Heart Failure (“End-stage”)


Advanced Heart Failure Profile

- One-year hospitalization: 60% (2/3 > than once).
- One-year mortality 30% (40% heart failure, 20% sudden).


Stage D Heart Failure (“End-stage”)

Class I
- Level A evidence
  - Refer patient to specialist in HF management
- Level B evidence
  - Closely watch for and control fluid retention
  - Refer eligible patients for cardiac transplantation, LVAD

All Class I recommendations for Stages A- C


Adult Heart Transplant (OHT) Survival

![Adult Heart Transplant Survival Graph]


Mechanical Circulatory Support (MCS)

![Mechanical Circulatory Support Images]
CONCLUSIONS

- STAGE A (HTN, CAD or DM):
  - Routine: ACE-I/ARB; selected pts. BB, statin, antiplatelets

- STAGE B (Asymptomatic structural heart disease):
  - Routine: ACE-I/ARB, BB; selected pts. statin, antiplatelets

- STAGE C (Symptomatic HF and low EF):
  - Routine: Exercise, ACE-I/ARB, BB, Aldo blockers, diuretics.
  - Selected pts. CABG, CRT-D, ICD, Hy-ISDN, digoxin, statin, ASA/warfarin.

- STAGE C (Symptomatic HF and preserved EF):
  - Consider ACE-I/ARB, digoxin ?, BB, CCB, Aldo blockers.

- STAGE D (End-stage HF):
  - Referral to advanced HF program for MCS, OHT.

2012 Paradigm for HF Management

- Treat Congestion: Diuretics
- Slow Disease Progression: ACE – I/ARB BB MRB CRT
- Sudden Death: BB MRB ICD
- Treat Residual Symptoms: Digoxin, ARB, Hy-ISDN CRT
- Advanced Disease: LVAD OHT

Heart Failure

The future is here....
Mini VADs as Treatment Platforms

- Smaller less invasive pumps
- No pocket
- No driveline
- Completely Implantable
- Earlier implants in less ill patients