Optimal Pharmacotherapy of the Systolic Heart Failure Patient

Liviu Klein MD, MS
Assistant Professor of Medicine
Associate Director, Mechanical Circulatory Support
and Heart Failure Device Program
University of California San Francisco

Relevant Financial Relationship Disclosure Statement

Optimal Pharmacotherapy of the Systolic Heart Failure Patient: Liviu Klein, MD, MS

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

No conflicts of interest wit the current presentation.
Prevalence of Heart Failure


Heart Failure Hospitalizations

1.1 mil hospitalizations/ year

Classification of Heart Failure

Stage | Patient Description
--- | ---
A | High risk for developing heart failure (HF)
B | Asymptomatic HF
C | Symptomatic HF
D | Refractory end-stage HF

- 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)

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.)
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.):

- LVEF \leq 0.35 within 3 months of trial entry
- CAD suitable for CABG
- MED eligible:
  - Absence of left main stenosis of \geq 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.

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, β-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 reabsorption
- 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 Inhibitors in Heart Failure**

- Prevent and attenuate ventricular remodeling.
- Improve symptoms, clinical status, and exercise capacity as early as 2-4 weeks.
- Improve ejection fraction.
- Decrease hospitalizations.
- Decrease mortality.
- Decrease vascular events (myocardial infarction, stroke).


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

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug (mean dose)</th>
<th>Mortality</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chronic HF</strong></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>
</tr>
<tr>
<td>SOLVD (T)</td>
<td>Enalapril (11.2 mg)</td>
<td>35%</td>
<td>40%</td>
</tr>
<tr>
<td>SOLVD (P)</td>
<td>Enalapril (12.7 mg)</td>
<td>15%</td>
<td>16%</td>
</tr>
<tr>
<td><strong>Post-MI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAVE</td>
<td>Captopril (150 mg)*</td>
<td>20%</td>
<td>25%</td>
</tr>
<tr>
<td>AIRE</td>
<td>Ramipril (1.25-5 mg)†</td>
<td>17%</td>
<td>23%</td>
</tr>
<tr>
<td>TRACE</td>
<td>Trandolapril (1-4 mg)†</td>
<td>35%</td>
<td>42%</td>
</tr>
<tr>
<td>SMILE</td>
<td>Zofenopril (7.5-30 mg)†</td>
<td>5%</td>
<td>6.5%</td>
</tr>
<tr>
<td>Totals</td>
<td></td>
<td>21%</td>
<td>25%</td>
</tr>
</tbody>
</table>

* No mean given; target dose  † No mean given; dose range
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></th>
<th>Low-Dose</th>
<th>High-Dose</th>
<th>Percent Reduction in High-Dose Group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalizations for any reason</td>
<td>4397</td>
<td>3819</td>
<td>13</td>
<td>0.021</td>
</tr>
<tr>
<td>Hospitalizations for cardiovascular reason</td>
<td>2923</td>
<td>2456</td>
<td>16</td>
<td>0.050</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>1576</td>
<td>1189</td>
<td>24</td>
<td>0.002</td>
</tr>
<tr>
<td>Hospitalization for ischemic events</td>
<td>643</td>
<td>432</td>
<td>20</td>
<td>0.085</td>
</tr>
</tbody>
</table>

Beta - Blockers

• Up regulate beta receptors that have been down regulated in heart failure.

• Improve coupling of beta receptors to secondary intracellular messengers, resulting in improved calcium transport and increase contractility over time.

• Increase protein synthesis.

• Inhibit RAAS by inhibiting renin secretion.

• Inhibit endothelin and cytokine release.


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 ¹ (bisoprolol) 2647 pts. NYHA III – IV</td>
<td>↓ 34%</td>
<td>↓ 20%</td>
</tr>
<tr>
<td>MERIT – HF ² (metoprolol XL) 3991 pts. NYHA II - IV</td>
<td>↓ 34%</td>
<td>↓ 8.6%</td>
</tr>
<tr>
<td>COPERNICUS ³ (carvedilol) 2289 pts. NYHA IV</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: 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.


Low (75 mg) vs. High (150 mg) Dose Metoprolol Succinate in Heart Failure

![Bar chart showing deaths per patient years (%)

- Placebo: 10.8%
- Metoprolol CR/XL:
  - Both Groups (n=1806): 6.8%
  - Low-dose (n=604): 8.0%
  - High-dose (n=1202): 6.2%

COMET: Metoprolol vs. Carvedilol


Carvedilol and Metoprolol Succinate Effects on Blood Pressure

Carvedilol: The Cadillac of BB

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


Mineralcorticoid (Aldosterone) Receptor Blockers

• 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 in all HF pts.

• MRB improve survival/symptoms more than ARB, and should be used in the “cocktail” 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 Heart Failure post MI

Eplerenone in NYHA II HF

• Combination ARB + ACE - I + Beta - Blockers is safe.
• No mortality benefit when ARB is added to ACE - I.
• High dose 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).

Angiotensin Receptor Blockers

Effect of Candesartan on Mortality and HF Hospitalizations

**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 synthase (40% of Caucasians have this genotype).
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 (low incidence, ~ 1 per 100 ppy)
  - ↓ warfarin (INR 2-3) vs ASA 325 mg.
  - Offset by increase in bleeding.
  - Individualized decision for treatment.

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.)
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

Intolerance of ACE-I and Outcomes

Risk Stratification in Heart Failure

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 LVADs, heart transplant.
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: LVADs  Heart transplant

UCSF Advanced Heart Failure and Pulmonary Hypertension Program
Tel: 415-353-4145
Iklein@medicine.ucsf.edu