Contemporary Management of Systolic Heart Failure

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Heart Failure Background

<table>
<thead>
<tr>
<th>Population Group</th>
<th>Prevalence</th>
<th>Incidence</th>
<th>Mortality 50% at 5 years</th>
<th>Hospital Discharges</th>
<th>Cost 1 billion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>5,000,000</td>
<td>550,000</td>
<td>1,100,000</td>
<td>$29.6</td>
<td></td>
</tr>
</tbody>
</table>

- Heart failure (HF) is a major public health problem resulting in substantial morbidity and mortality
- 1/3 of pts with HF are hospitalized annually
- Major cost-driver of HF is high incidence of hospitalizations
- Despite treatment advances, large number of eligible patients are not receiving optimal care

Determinants of Cardiac Performance

- Preload
- Afterload
- Heart Rate
- Contractility
  ✓ Force, # of Contractile Units
- Ventricular (diastolic) Compliance

Based on Starling's observation that the mechanical energy released between the resting and contracted state is a function of the resting muscle fiber length in isolated heart tissue.

- In the whole heart, preload is synonymous with end-diastolic volume.
- Practically, preload is estimated by the end-diastolic pressure (the pulmonary capillary wedge pressure).
- Increases in preload, or end-diastolic pressure, are associated with increases in both the extent and velocity of muscle fiber shortening, which combine to produce an increase in stroke volume.
- Failing hearts are less responsive to changes in preload.

The stress or tension distributed in the ventricular wall during ventricular ejection.

- Afterload is not constant during ejection but continually declines as ventricular volume and mid wall radius decrease.
- Inversely related to the velocity and extent of mid wall shortening.
- The sum of forces contributing to ventricular afterload are referred to as impedance, which includes the resistance of small arteries and arterioles, the compliance of the large arteries, the viscosity of blood, and the forces of inertia.
Pathophysiology of Heart Failure

- **Risk Factors**
  - Myocardial injury to the heart (MI, HTN, CMP, Valvular disease)
  - Initial fall in LV performance, ↑ wall stress
  - Activation of RAS and SNS
  - Remodeling and progressive worsening of LV function
  - Morbidity and mortality
  - Arrhythmias
  - Pump failure

- **Hemodynamic alterations**
  - Salt & water retention
  - Remodeling and progressive worsening of LV function

- **Heart Failure symptoms**
  - Dyspnea
  - Edema
  - Fatigue

RAS, renin-angiotensin system; SNS, sympathetic nervous system.

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ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic HF

ACC/AHA Practice Guideline

ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult—Summary Article

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 1995 Guidelines for the Evaluation and Management of Chronic Heart Failure)

Devised in Collaboration With the American Association for Thoracic Surgery

Approved by the ACC/AHA Task Force on Practice Guidelines

Hunt SA et al. J Am Coll Cardiol. 2005

ACE Inhibitors

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AHA/ACC Applying Classification of Recommendations and Level of Evidence

<table>
<thead>
<tr>
<th>Class</th>
<th>Benefit - Risk</th>
<th>Procedure or Treatment</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Benefit &gt;&gt;&gt; Risk</td>
<td>SHOULD be performed or administered</td>
<td>A: Multiple randomized controlled trials</td>
</tr>
<tr>
<td>Class IIa</td>
<td>Benefit &gt;&gt; Risk</td>
<td>MAY BE CONSIDERED</td>
<td>B: Single trial, non-randomized studies</td>
</tr>
<tr>
<td>Class IIb</td>
<td>Benefit ≥ Risk</td>
<td>IT IS REASONABLE to perform procedure or administer treatment</td>
<td>C: Expert opinion</td>
</tr>
<tr>
<td>Class III</td>
<td>Risk ≥ Benefit</td>
<td>No additional studies needed</td>
<td></td>
</tr>
</tbody>
</table>

AHA/ACC Applying Classification of Recommendations and Level of Evidence

Hunt SA et al. J Am Coll Cardiol. 2005

<table>
<thead>
<tr>
<th>Trial</th>
<th>ACEI</th>
<th>Controls</th>
<th>RR  (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic CHF</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>0.62 (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>Post-MI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAVE</td>
<td>20%</td>
<td>25%</td>
<td>0.51 (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>0.76 (0.67–0.81)</td>
</tr>
<tr>
<td>Average</td>
<td>23%</td>
<td>27%</td>
<td></td>
</tr>
</tbody>
</table>

Data shown from individual trials—not direct comparison data.


**ACE Inhibitor Recommendations**

- Recommended for all pts with current or prior symptoms of HF and reduced LVEF, unless contraindicated
  - Indicated in all pts with a recent or remote history of MI regardless of LVEF or presence of HF
  - Should be used in pts with a reduced LVEF and no symptoms of HF, even if they have not experienced an MI

- Can be useful to prevent HF in pts at risk for developing HF with a history of atherosclerotic vascular disease, DM, or HTN with associated risk factors

- Can be beneficial in patients with HTN and LVH and no symptoms of HF

**Beta-Blockers**

- Indicated for all patients with asymptomatic LV dysfunction and for Class I to IV Heart Failure. (Contraindications: hyperkalemia, angioedema, pregnancy)
- Start at low dose and titrate to target doses (example enalapril 10 mg bid, lisinopril 20 qd, ramipril 10 mg qd, benazepril 40 qd)
- Renal insufficiency is not a contraindication but must start at very low dose and very closely monitor
- Monitor serum potassium and renal function. Advise checking chemistry panel 1-2 weeks after first dose.


**Effect of β-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 Dosage (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=0.007)</td>
</tr>
<tr>
<td>CIBIS-II2</td>
<td>bisoprolol</td>
<td>moderate/severe</td>
<td>10 QD</td>
<td>↓34% mortality (P&lt;0.0001)</td>
</tr>
<tr>
<td>MERIT-HF3</td>
<td>metoprolol tartrate</td>
<td>mild/moderate</td>
<td>200 QD</td>
<td>↓34% mortality (P&lt;0.0002)</td>
</tr>
<tr>
<td>COPERNICUS4</td>
<td>carvedilol</td>
<td>severe</td>
<td>25 BID</td>
<td>↓30% mortality (P=0.004)</td>
</tr>
<tr>
<td>CAPRICORN5</td>
<td>carvedilol</td>
<td>Post-MI LVD</td>
<td>25 BID</td>
<td>↓23% mortality (P&lt;0.03)</td>
</tr>
</tbody>
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**COMET: Primary Endpoint of Mortality**

- Risk Reduction ↓17% (P=0.0017)
- Extrapolation from the survival curves suggested that carvedilol extended median survival by 1.4 years as compared with metoprolol tartrate†

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**β-Blockers Differ in Their Long-Term Effects on Mortality in HF**

- Bisoprolol1 Beneficial
- Bucindolol2 No effect
- Carvedilol3-5 Beneficial
- Metoprolol tartrate6 Not well studied
- Metoprolol succinate7 Beneficial
- Nebivolol8 No effect
- Xamoterol9 Harmful


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**Beta-Blocker Recommendations**

- Use of 1 of the 3 beta blockers proven to reduce mortality (i.e., bisoprolol, carvedilol, and sustained release metoprolol succinate) are recommended for all stable pts with current or prior symptoms of HF and reduced LVEF, unless contraindicated
- Indicated in all pts with a recent or remote history of MI regardless of EF or presence of HF
- Indicated in all patients without a history of MI who have a reduced LVEF with no HF symptoms

Beta Blocker Therapy in Heart Failure

- Indicated for all patients with asymptomatic LVD dysfunction and for Class I to IV Heart Failure with LVEF ≤ 0.40
- Contraindications: cardiogenic shock, severe reactive airway disease, 2/3rd degree HB
- Use evidence-based beta blockers in HF: carvedilol, metoprolol succinate, bisoprolol
- Start at very low HF doses and up-titrate to target doses at two week intervals, or highest dose short of target dose that is well tolerated
- Monitor HR and BP


Angiotensin Receptor Blockers

CHARM and Val-HeFT Trials

- Addition of candesartan¹ or valsartan² to ACEI and β-blocker in NYHA functional Class II-III
- 0%-10% lower risk of death (P>.05)
- 13%-15% lower risk of death or hospitalization for HF in both trials (both P<.01)
- Higher risk for hypotension, renal insufficiency, and hyperkalemia with ARB treatment


VALIANT: ACE Inhibitor, Angiotensin Receptor Blocker, or Both in Post-MI LVD

- Addition of candesartan¹ or valsartan² to ACEI and β-blocker in NYHA functional Class II-III
- 0%-10% lower risk of death (P>.05)
- 13%-15% lower risk of death or hospitalization for HF in both trials (both P<.01)
- Higher risk for hypotension, renal insufficiency, and hyperkalemia with ARB treatment

**ARB Recommendations**

- ARBs approved for the treatment of HF are recommended in patients with current or prior symptoms of HF and reduced LVEF who are ACEI-intolerant.
- An ARB should be administered to post-MI patients without HF who are ACEI-intolerant and have a low LVEF.
- Are reasonable to use as alternatives to ACEI as first-line therapy for pts with mild to moderate HF and reduced LVEF, especially for pts already taking ARBs for other indications.
- Can be beneficial in pts with low LVEF and no symptoms of HF who are ACEI-intolerant.
- Addition of an ARB may be considered in persistently symptomatic pts with reduced LVEF who are already being treated with conventional therapy.

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**Aldosterone Antagonists**

- **RALES: Aldosterone Antagonist Reduces All-Cause Mortality in Chronic HF**
  - Spironolactone (25 mg) + standard care (n = 822)
  - Placebo + standard care (n = 841)
  - Probability of Survival (%)
    - 1.00
    - 0.95
    - 0.90
    - 0.85
    - 0.80
    - 0.75
    - 0.70
    - 0.65
    - 0.60
    - 0.55
    - 0.50
  - HR = 0.70 (95% CI, 0.60 to 0.82)
  - P<.001

- **EPHESUS Co-Primary Endpoint: Total Mortality**
  - Eplerenone + standard care (n = 3319)
  - Placebo + standard care (n = 3313)
  - Cumulative Incidence (%)
    - 22
    - 20
    - 18
    - 16
    - 14
    - 12
    - 10
    - 8
    - 6
    - 4
    - 2
    - 0
  - HR = 0.85 (95% CI, 0.75 to 0.96)
  - P = .008

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*Spironolactone (25 mg) + standard care (n = 822)*

*Placebo + standard care (n = 841)*

*Ejection fraction ≤35% Class III or IV symptoms at some point in prior 2 months.*


Aldosterone Antagonist Recommendations

- Recommended in selected pts with moderately severe to severe symptoms of HF and reduced LVEF who can be carefully monitored for preserved renal function and normal potassium concentration.*
- Under circumstances where monitoring for hyperkalemia and renal dysfunction is not anticipated to be feasible, the risks may outweigh the benefits.

*Creatinine <2.5 mg/dL in men or <2.0 mg/dL in woman and K+ <5.0 mEq/L

Underlining represents changes from 2001 guidelines.


Aldosterone Antagonists in Heart Failure

- Indicated for patients with moderately severe and severe HF due to LVD (LVEF < 0.40). Contraindications: hyperkalemia, C Cr > 2.5 in men and > 2.0 in women)
- Spironolactone 12.5 mg POqd starting dose (or 6.25 mg in higher risk patients) or Eplerenone 25 mg qd. Decrease potassium supplementation and loop diuretic dose at time of initiation.
- Critical to very closely monitor serum potassium and renal function. Advise checking chemistry panel at 48 hours, 1 week, and 4 weeks.
- Advance Spironolactone dose at 4 weeks to 25 mg POqd or Eplerenone 50 mg which is the target dose. Avoid higher doses due to risk of hyperkalemia.

Effect of Digoxin on Mortality in Heart Failure: The Digitalis Investigation Group

- All-cause mortality rates: Placebo 35.1%; Digoxin 34.8%

Hunt SA et al. J Am Coll Cardiol. 2005
**Digoxin Recommendations**

+ Digitalis can be beneficial in patients with current or prior symptoms of HF and reduced LVEF to decrease hospitalizations for HF.

Underlining represents changes from 2001 guidelines.


**Special Populations**

- **V-HeFT I: Survival Benefit in Subgroups**

  - **Non-African Americans**
    - Cumulative Mortality
    - Months: 0% 10% 20% 30% 40% 50% 60% 70% 80%
    - Months: 6 18 30 42 54 66
    - Placebo: 42 54 66 61 83 00
    - HYD/ISDN: 518 463 407 359 313 251 13
    - Relative Risk Reduction 47%; P=0.04
    - HYD/ISDN Superior

  - **African Americans**
    - Cumulative Mortality
    - Months: 0% 10% 20% 30% 40% 50% 60% 70% 80%
    - Months: 6 18 30 42 54 66
    - Placebo: 532 466 401 340 285 232 24
    - HYD/ISDN: 518 463 407 359 313 251 13
    - Relative Risk Reduction 47%; P=0.04
    - HYD/ISDN Superior

- **A-HeFT: All-Cause Mortality**

  - Survival (%)
  - Days Since Baseline Visit Date: 0 100 200 300 400 500 600
  - Hazard ratio=.57
  - Fixed-dose Hydralazine / Isosorbide Dinitrate
  - Placebo
  - 43% Decrease in Mortality

Combination Hydralazine-Nitrate Recommendations

- Addition to a standard medical regimen for HF, including ACEIs and β-blockers is reasonable and can be effective in blacks with NYHA functional class III or IV HF. Others may benefit similarly, but this has not yet been tested.

- Addition is reasonable in pts with reduced LVEF who are already taking an ACEI and β-blocker for symptomatic HF and who have persistent symptoms.

- Might be reasonable in pts with current or prior symptoms of HF and reduced LVEF who cannot be given an ACEI or ARB because of drug intolerance, hypotension, or renal insufficiency.

Cardiac Resynchronization Therapy: Weight of Evidence

- > 4,000 patients evaluated in randomized controlled trials
- Consistent improvement in quality of life, functional status, and exercise capacity
- Strong evidence of reverse remodeling
  - ↓ LV volumes and dimensions
  - ↑ LVEF
  - ↓ Mitral regurgitation
- Reduction in HF and all-cause morbidity and mortality

Device Therapy for Heart Failure

- Cardiac resynchronization therapy (CRT)
- Implantable cardioverter-defibrillators (ICD)

CARE-HF: Effect of CRT Without an ICD on All-Cause Mortality

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>0</th>
<th>500</th>
<th>1,000</th>
<th>1,500</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT plus meds</td>
<td>469</td>
<td>376</td>
<td>351</td>
<td>213</td>
</tr>
<tr>
<td>CRT plus ICD</td>
<td>484</td>
<td>365</td>
<td>321</td>
<td>192</td>
</tr>
</tbody>
</table>

HR: 0.64 (95% CI: 0.48-0.85)  
P = 0.0019
CRT Recommendations

Recommended in patients with LVEF less than or equal to 35%, sinus rhythm, NYHA functional class III or ambulatory class IV symptoms despite recommended, optimal medical therapy and who have cardiac dyssynchrony (QRS duration greater than 120 ms) unless contraindicated

Underlining represents changes from 2001 guidelines.


ICD Recommendations*

• Recommended as secondary prevention to prolong survival in pts with current or prior symptoms of HF and reduced LVEF who have a history of cardiac arrest, VF, or hemodynamically unstable VT

• Recommended for primary prevention to reduce total mortality by a reduction in SCD in pts with ischemic heart disease who are at least 40 days post-MI, LVEF less than or equal to 30%, with NYHA functional class II or III symptoms*

• Recommended for primary prevention to reduce total mortality by a reduction in SCD in pts with nonischemic cardiomyopathy, LVEF less than or equal to 30%, with NYHA functional class II or III symptoms*

• Reasonable in pts with ischemic cardiomyopathy who are at least 40 days post-MI, LVEF less than or equal to 30%, with NYHA functional class I symptoms

• Reasonable in pts with LVEF of 30% to 35% of any origin with NYHA functional class II or III symptoms

• Might be considered in pts without HF who have non-ischemic cardiomyopathy and an LVEF less than or equal to 30%, with NYHA functional class I symptoms

*While undergoing chronic optimal medical therapy with reasonable expectation of survival with good functional status >1 year. Underlining represents changes from 2001 guidelines.

Evidence-Based Treatment Across the Continuum of LVD and Heart Failure

EF < 40%

- In selected pts, aldo antagonists, Dig, hydralazine/nitrate

Diuretic

Titrate to optimolemic state

Assessment of volume status

Titrate ACE and β-blocker therapy

EF still < 35%

- ICD

NYHA II-IV or EF < 35% Post-MI NYHA I

NYHA II-IV, EF < 35%, QRS > 120ms

- CRT + D

Summary
Advances in the Treatment of HF

- Increased attention to prevention
- ACEI / β-blocker / aldosterone antagonist combination established as the “triad” of therapy
- Evidence that β-blockers’ effects are not homogeneous
- Downgrade in recommendation for use of digoxin
- Recognition that “special populations” of HF patients may benefit from or require different approaches
- New strategies to improve utilization of evidence-based therapies