Heart Failure 2015: An Update on Therapy

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Objectives

Distinguish why to use new and traditional standard therapies for chronic Heart Failure with reduced Ejection Fraction (HFrEF);
Identify how, when and where to select the most appropriate drugs and devices for HFrEF; and
Design effective therapy for patients with HFrEF.

Disclosures

Mark A. Munger, Pharm.D. "declare(s) no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria."
Risk Factors to Heart Failure in the Cardiovascular Continuum

Adapted with permission from Dzau V, Braunwald E. Am Heart J. 1991;121:1244.

Risk Factors
- Hyperlipidemia
- HTN
- Diabetes
- Insulin Resistance

Atherosclerosis
CAD
LVH
CAD
Myocardial ischemia
Coronary thrombosis
MI
Arrhythmia
Loss of muscle
Neurohormonal activation
Remodeling
Ventricular dilation
Heart Failure
Death
Sudden death

Changing Strategies in Heart Failure

Organ Physiology
- Starling’s Law
- Hemodynamic parameters

Cell Biochemistry
- Excitation-contraction coupling
- Myocardial contractility

Molecular Biology
- Altered gene expression
- Apoptosis

β-adrenergic agonists
Phosphodiesterase inhibitors
Converting enzyme inhibitors
Aldosterone Antagonists
LCZ696
β-adrenergic blockers
Nitrates
Arrestor dilators
Calcium channel blockers

Cardiac glycosides
Diuretics
1940’s
1960’s
1970’s
1980’s
1990’s
2015

“Pathology is the accomplished tragedy: Physiology the basis which our treatment rests”

Edmund Martin 1859-1936
Response to the Low-Output State in Cardiac Failure

Pharmacological Treatment of HFrEF

“Doctors are men who prescribe medicine of which they know little to cure diseases of which they know less in human beings of which they know nothing.”

Voltaire 1674-1778

Symptoms
Population-Attributable Risks for Development of CHF

Population-attributable risk defined as:
\[(100 \times \text{prevalence} \times (\text{hazard ratio} - 1)) / (\text{prevalence} \times (\text{hazard ratio} - 1) + 1)\]

Men
- HTN: 35%
- DM: 6%
- LVH: 4%
- VHD: 7%
- AP: 5%

Women
- HTN: 59%
- DM: 12%
- LVH: 9%
- VHD: 8%
- AP: 5%

Treating Hypertension to Prevent HF

Aggressive blood pressure control:
- Decreases risk of new HF by ~50%.
- 56% in DM2.

Aggressive BP control in patients with prior MI:
- Decreases risk of new HF by ~80%.

Pharmacologic Treatment for Stage C HF/EF

- NYHA Class I, IV: Hospitalized
- NYHA Class II, III: Hospitalized

- NYHA Class I, IV: Inpatient
- NYHA Class II, III: Outpatient
- NYHA Class I, IV: Outpatient
- NYHA Class II, III: Outpatient
Ten Commandants of HFrEF

1. Maintain patient on 2- to 3-g sodium diet. Follow daily weight. Monitor standing blood pressures in the office, as these patients are prone to orthostasis.

2. Determine target/ideal weight, which is not the dry weight. In order to prevent worsening azotemia, some patients will need to have some edema. Achieving target weight should mean no orthopnea or paroxysmal nocturnal dyspnea. Consider home health teaching.

3. Avoid all nonsteroidal anti-inflammatory drugs because they block the effect of ACE inhibitors and diuretics.

4. Use ACE inhibitors in all heart failure patients unless they have an absolute contraindication or intolerance. Use doses proven to improve survival and back off if they are orthostatic. In those patients who cannot take an ACE inhibitor, use an angiotensin receptor blocker (ARB).

5. Use loop diuretics (like furosemide) in most NYHA class II through IV patients in dosages adequate to relieve pulmonary congestive symptoms. Double the dosage (instead of giving twice daily) if there is no response or if the serum creatinine level is > 2.0 mg per dL.

6. For patients who respond poorly to large dosages of loop diuretics, consider adding 5 to 10 mg of metolazone one hour before the dose of furosemide once or twice a week as tolerated.

7. Consider adding 25 mg spironolactone in most class III or IV patients. Do not start if the serum creatinine level is > 2.5 mg per dL (220 µmol per L).

8. Use metoprolol, carvedilol, or bisoprolol in all class II and III heart failure patients unless there is a contraindication. Start with low doses and work up. Do not start if the patient is decompensated (excessively dry or wet).

9. Use digoxin in some symptomatic heart failure patients.

10. Encourage a graded exercise program.
Pharmacological Treatment for Stage C HF\(\text{r}\)EF (cont.)

Routine combined use of an ACE inhibitor, ARB, and aldosterone antagonist is potentially harmful for patients with HF\(\text{r}\)EF.

Use of 1 of the 3 beta blockers proven to reduce mortality (i.e., bisoprolol, carvedilol, and sustained-release metoprolol succinate) is recommended for all patients with current or prior symptoms of HF\(\text{r}\)EF, unless contraindicated, to reduce morbidity and mortality.

Question #1 (Objectives 1/2/3)

ZC is a 64 yo WM who presents to the primary care clinic with increasing shortness of breath. He has a LVEF 27%. BP: 134/82 mmHg. He is started on furosemide 40mg qday for volume control.

What should be the next HF\(\text{r}\)EF therapy for ZC?

A. Metoprolol 12.5mg SR i qday
B. Lisinopril 2.5mg i qday
C. Spironolactone 12.5mg i qday
D. Digoxin 1.25mg i qday

Response to the Low-Output State in Cardiac Failure
ACEi Pharmacology in HFrEF

ACEi/ARBs interfere with formation of AII but also enhance kinin-mediated PG synthesis.

These agents lower afterload (AII), but more importantly lower preload (kinins, PGs, NO). Lowering preload effects lower LVEDP and LV wall stress.

Lowering LV wall stress results in favorable effects on cardiac remodeling and survival.

Question #2 (Objectives 1/2/3)

MN is a 59 yo AAF who presents with increasing fatigue and exercise intolerance. She has no signs/symptoms of fluid overload. LVEF 23%, BP 142/84 mmHg. BP med: HCTZ 12.5mg i qday, H/O: hyperlipidemia (atorvastatin 80mg qday), DM type 2 (metformin 500mg BID, insulin)

What should be the next HFrEF therapy for ZC?

A. Metoprolol 12.5mg SR i qday
B. Lisinopril 2.5mg i qday
C. Spironolactone 12.5mg i qday
D. Carvedilol 3.125mg i qday
β-Adrenergic Blocker Pharmacology in HFrEF

• Metoprolol IR or SR
  • β₁-selective (up to 75 mg)¹
  • Unfavorable effects on lipids (LDL, TG, Tchol), glucose intolerance (↑ gluc)
  • Questionable effect on BP control

• Carvedilol IR or SR
  • β non-selective (at all doses)
  • α₁-blockade
  • Neutral effects on Lipids, glucose intolerance
  • Dual blockade of BP (more effective BP control)

¹ Zebrack JS et al. Pharmacotherapy 2009; 29:980-96

Question #3 (Objective 3)

You are caring for a patient with HFrEF who is receiving Lisinopril 10mg qday and spironolactone 12.5mg qday. Which lab value will be most important to monitor?

A. Sodium
B. Blood urea nitrogen (BUN)
C. Potassium
D. Alkaline phosphatase (ALP)

The Role of Aldosterone in Cardiovascular Disease*
Effects on Potassium Homeostasis

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Placebo</th>
<th>Eplerenone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious Hyperkalemia (K⁺ ≥ 6.0 mEq/L)</td>
<td>0%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Hypokalemia (K⁺ ≤ 3.5 mEq/L)</td>
<td>4.7% Absolute decrease</td>
<td>P &lt; 0.001</td>
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</tbody>
</table>

Question #4 (Objective 2)

Two weeks ago, a 63 year old HFrEF female patient in your clinic had her carvedilol dosage up-titrated to 25 mg qday. Upon evaluation in the outpatient clinic these symptoms are found. Which is the most concern?

A. Complaints of lightheadedness and some pre-syncope.
B. Weight increase of 0.5kg in 2 weeks.
C. Sinus bradycardia, rate 50 as evidenced by the EKG.
D. All of the Above

African-American Heart Failure Trial (A-HeFT)

1050 African-American patients with NYHA FC III or IV heart failure
Standard background therapy
Fixed-dose combination BiDil (ISDN 20 mg + hydralazine 37.5 mg) given 3 times daily or placebo
Trial stopped early due to 43% mortality decrease
Add to standard therapy in AA patients with symptomatic HF and LVSD
Consider adding to non-AA patients who remain symptomatic with standard therapy
Consider in patients intolerant of ACEI and ARBs

NYHA FC = New York Heart Association functional class.
A-HeFT = African-American Heart Failure Trial.
Pharmacological Treatment for Stage C HFrEF (cont.)

Digoxin can be beneficial in patients with HFrEF, unless contraindicated, to decrease hospitalizations for HF.

Patients with chronic HF with permanent/persistent/paroxysmal AF and an additional risk factor for cardioembolic stroke (history of hypertension, diabetes mellitus, previous stroke or transient ischemic attack, or ≥75 years of age) should receive chronic anticoagulant therapy (in the absence of contraindications to anticoagulation).

Anticoagulation is not recommended in patients with chronic HFrEF without AF, a prior thromboembolic event, or a cardioembolic source.

Statins are not beneficial as adjunctive therapy when prescribed solely for the diagnosis of HF in the absence of other indications for their use.

Omega-3 polyunsaturated fatty acid (PUFA) supplementation is reasonable to use as adjunctive therapy in patients with NYHA class II-IV symptoms and HFrEF or HFrEF, unless contraindicated, to reduce mortality and cardiovascular hospitalizations.

Nutritional supplements as treatment for HF are not recommended in patients with current or prior symptoms of HFrEF.

Hormonal therapies other than to correct deficiencies are not beneficial for patients with current or prior symptoms of HFrEF.

Drugs known to adversely affect the clinical status of patients with current or prior symptoms of HFrEF are potentially harmful and should be avoided or withdrawn whenever possible (e.g., most antiarrhythmic drugs, most calcium channel blocking drugs (except amlodipine), NSAIDs, or TZDs).
Severity of Heart Failure

Modes of Death

<table>
<thead>
<tr>
<th>NYHA II</th>
<th>CHF</th>
<th>Other</th>
<th>Sudden Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>64%</td>
<td>24%</td>
<td>12%</td>
<td>12%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NYHA III</th>
<th>CHF</th>
<th>Other</th>
<th>Sudden Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>33%</td>
<td>50%</td>
<td>11%</td>
<td>12%</td>
</tr>
</tbody>
</table>


A Look At Drug Therapy Data...

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>Trial Design</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAST</td>
<td>1498</td>
<td>Encainide, Flecainide / Placebo</td>
<td>Terminated due to excessive death in treatment arm</td>
</tr>
<tr>
<td>CHF-STAT</td>
<td>674</td>
<td>Amiodarone / Placebo</td>
<td>No change in overall mortality</td>
</tr>
<tr>
<td>SWORD</td>
<td>546</td>
<td>d-Sotalol / Placebo</td>
<td>Terminated due to excessive death in treatment arm</td>
</tr>
<tr>
<td>ESVEPM</td>
<td>486</td>
<td>EPS-guided / Holter-guided</td>
<td>Mortality high in both arms</td>
</tr>
<tr>
<td>EMIAT</td>
<td>1200</td>
<td>Amiodarone / Placebo</td>
<td>No change in overall mortality</td>
</tr>
</tbody>
</table>

A Look At ICD Therapy Data...

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>Trial Design</th>
<th>All-cause Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVID</td>
<td>1106</td>
<td>ICD / Best drug Rx</td>
<td>31% all-cause reduction (3 yrs)</td>
</tr>
<tr>
<td>CBIS</td>
<td>659</td>
<td>ICD / Amiodarone</td>
<td>20% all-cause reduction (3 yrs)</td>
</tr>
<tr>
<td>CASBI</td>
<td>200</td>
<td>ICD / Amiodarone or Metoprolol</td>
<td>23% all-cause reduction (3 yrs)</td>
</tr>
<tr>
<td>MADIT</td>
<td>196</td>
<td>ICD / Best drug Rx</td>
<td>54% all-cause reduction (3 yrs)</td>
</tr>
<tr>
<td>MUST**</td>
<td>2022</td>
<td>EP-guided therapy / No treatment</td>
<td>51% all-cause reduction (5 yrs)</td>
</tr>
<tr>
<td>CABG-PCt</td>
<td>900</td>
<td>CABG plus ICD / CABG</td>
<td>No difference in mortality</td>
</tr>
<tr>
<td>MADIT**</td>
<td>1232</td>
<td>ICD and best drug Rx / Best drug Rx</td>
<td>31% all-cause reduction (4 yrs)</td>
</tr>
</tbody>
</table>

Device Therapy for Stage C HF\(\text{r}EF\) (cont.)

ICD therapy is recommended for primary prevention of SCD to reduce total mortality in selected patients at least 40 days post-MI with LVEF less than or equal to 30%, and NYHA class III symptoms while receiving GDMT, who have reasonable expectation of meaningful survival for more than 1 year.

CRT can be useful for patients who have LVEF of 35% or less, sinus rhythm, a non-LBBB pattern with a QRS duration of 150 ms or greater, and NYHA class III/ambulatory class IV symptoms on GDMT.

Stage B (cont.)

To prevent sudden death, placement of an ICD is reasonable in patients with asymptomatic ischemic cardiomyopathy who are at least 40 days post-MI, have an LVEF of 30% or less, are on appropriate medical therapy and have reasonable expectation of survival with a good functional status for more than 1 year.

Harm

Nondihydropyridine calcium channel blockers with negative inotropic effects may be harmful in asymptomatic patients with low LVEF and no symptoms of HF after MI.

CRT-Cardiac Resynchronization

**HOW IT WORKS:**

Standard implanted pacemakers—equipped with two wires (or “leads”)—conduct pacing signals to specific regions of heart (usually at positions A and C). Biventricular pacing devices have added a third lead (at position B) that is designed to conduct signals directly into the left ventricle. Combination of all three lead[s] = synchronized pumping of ventricles, inc. efficiency of each beat and pumping more blood on the whole.
 CRT in Patients with Advanced HF and a Prolonged QRS Interval: COMPANION

Primary End Point: All-Cause Mortality

Risk of all-cause mortality reduced by 19% in group with CRT (HR 0.81; p = .014)
Risk of death or hospitalization from HF reduced by 34% in ICD group and by 40% in ICD-CRT group (p < .001)

Ventricular Assist Devices (VADs)

• Indications for VAD therapy
  • Extension of cardiopulmonary bypass
  • Failure to wean
  • Postcardiotomy cardiogenic shock
  • Bridge to recovery or cardiac transplantation

• Patients with New York Heart Association Classification IV who have failed medical therapy
Stepped Therapy for Heart Failure Disease Severity

Asymptomatic       Symptomatic       Advanced       Refractory

Disease Management Programs

- ACE Inhibitor or Angiotensin II Receptor Blocker if Severe Cough or Angioedema
- May Need to Withdraw As Tolerated
- Exercise Training
- No Added Salt (4 gm Na+) + 2 g Na+
- Consider 2 L fluid restriction

β-Blockers

- Aerobic Activity
- Salt & Fluid Medications
  - Digoxin for Persistent Symptoms
  - Diuretics to Treat Fluid Retention
  - Add Spironolactone if Normal Potassium-Handling
  - If Needed, Use Torsemide, Intermittent Metolazone

Heart Failure Disease Management Programs

- Transplantation, Mechanical Assist Devices
- Hospice
- Reevaluate Diagnosis and Therapy
- To Relieve Persistent Congestion: More Diuresis? Nitrates ± Hydralazine?
- Transplantation/Mechanical Assist Devices

Natriuretic Peptides
Effects on Heart, Vessel and Kidney

- Increased secretion of NPs in response to cardiac stress reduces BP and plasma volume through actions in the brain, adrenal gland, kidney and vasculature, leading to:
  - natriuresis and diuresis
  - vasodilation
  - inhibition of RAAS and sympathetic activity
  - attenuation of cardiac remodeling (LVM) and fibrosis
  - reverse vascular remodeling (arteriolar stiffness)
  - attenuation of renal fibrosis and improved renal hemodynamics
  - enhanced endothelial function - lipid mobilization

Nepriyisin (neutral endopeptidase 24.11; NEP)
Role in Natriuretic Peptide Degradation

- NEP is the major enzyme responsible for degrading the ANP (BNP, CNP)1,2
- NEP catalyzes the degradation of other vasodilatory peptides:
  - natriuretic peptides
  - endothelin1
  - vasopressor peptides
  - ET
  - Ang II
- NEP converts big ET-1 to the active vasodilator peptide ET-1

PARADIGM-HF
Primary endpoint: Death from CV causes or first hospitalization for HF

![Graph showing cumulative probability over days since randomization for Enalapril vs LCZ696]

PARADIGM-HF
Prospectively defined safety events

<table>
<thead>
<tr>
<th>Event</th>
<th>LCZ696 (n=4587)</th>
<th>Enalapril (n=4212)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>588 (14.3)</td>
<td>399 (9.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>112 (2.7)</td>
<td>59 (1.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Elevated serum creatinine</td>
<td>139 (3.5)</td>
<td>116 (2.8)</td>
<td>0.027</td>
</tr>
<tr>
<td>&gt;3.0 mg/dL</td>
<td>83 (1.9)</td>
<td>83 (2.0)</td>
<td>0.50</td>
</tr>
<tr>
<td>Elevated serum potassium</td>
<td>93 (2.1)</td>
<td>72 (1.7)</td>
<td>0.18</td>
</tr>
<tr>
<td>&lt;4.5 mmol/L</td>
<td>181 (4.3)</td>
<td>236 (5.6)</td>
<td>0.007</td>
</tr>
<tr>
<td>Cough</td>
<td>474 (11.3)</td>
<td>851 (14.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>* Fever patients in the LCZ696 group than in the enalapril group stopped their study medication because of an AE (10.7 vs 12.0%, p=0.01)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Question #5 (Objective 3)

You or your mother or father is newly diagnosed with HFrEF. Which of the following treatment is the first pharmacotherapy you want to receive?

A. ACEi or ARB alone  
B. β-adrenergic blocker  
C. Mineralocorticoid Receptor Antagonist (Spironolactone)  
D. Angiotensin Receptor Nephrilysin Inhibitor (LCZ696)