Guideline Directed Medical Therapy in Heart Failure with Reduced Ejection Fraction: The Old and the New

Esther Shao, MD PhD
Maine Chapter ACP Meeting
September 23, 2018
Objectives:

Review the Stages of CHF

Follow a case presentation while progressively discussing the components of Guideline Directed Medical Therapy

Diuretics
Ace-Inhibitors / ARB
Beta Blockers
Aldosterone Antagonists
Entresto
Device Therapies

Briefly discuss when to refer to a Heart Failure Cardiologist

Highlight the current activities of MMC’s Heart Failure Clinic and LVAD Program

What’s new/coming in heart failure?
Case Presentation

30 y/o M transferred with respiratory failure from outside hospital

- History of HFrEF
  - Diagnosis April 2014 at OSH
  - Echocardiogram showed depressed LVEF of 10%
  - At that time, heavy alcohol use
    - Deemed alcoholic cardiomyopathy
    - Discharged on lisinopril 2.5, carvedilol 12.5 BID, furosemide 40 BID
    - Rehospitalized multiple times over the next 8 months locally
    - Quit alcohol on his own after diagnosis and went through DTs without any assistance at home
More History

• Transferred to MMC December 31, 2014
  ◦ SOB, LE edema
  ◦ B/L Pleural effusions, AoCKD, lactic acidosis
  ◦ Echocardiogram
    ▪ EF 10%
    ▪ Severe MR
    ▪ Moderate-Severe TR
• Asked by ICU team for heart transplant/LVAD evaluation.
Case Presentation

Initial exam

- BP 82/62, HR 92, O2 sat 94%
- JVD to the angle of the jaw at 30 degrees
- NR, RR, +S3. Visible LV heave. 3/6 holoSM at apex radiating to axilla
- Lungs clear
- Pulsatile liver
- 3+ pitting edema bilaterally with cool extremities

Labs

- Cr 0.93, LFTs normal, BNP 1348
Current Hospitalization
What do we do?

HFrEF (biventricular), hospitalized, hypotensive, severe MR

- Options
  - Medical Therapy
  - VAD
  - Transplant
  - Mitral valve replacement
ACC/AHA STAGES AND CLASSES OF HEART FAILURE

**Stage A**
- High risk for developing CHF
- No structural disorder of heart

**Stage B**
- Structural disorder of heart
- Never developed symptoms of CHF

**Stage C**
- Past or current symptoms of CHF
- Symptoms associated with underlying heart disease

**Stage D**
- End-stage disease
- Requires specialized treatment strategies

**NYHA:**

**Class I**
- No limitation of physical activity

**Class II**
- Slight limitation of physical activity
- Comfortable at rest

**Class III**
- Marked limitation of physical activity
- Comfortable at rest

**Class IV**
- Inability to carry on any physical activity without discomfort
- Symptoms present even at rest

**Class IIIa**
- No dyspnea at rest

**Class IIIb**
- Recent dyspnea at rest
Objectives:

Review the Stages of CHF and Evaluation of Systolic CHF

Follow a case presentation while progressively discussing the components of Guideline Directed Medical Therapy

- Diuretics
- Ace-Inhibitors / ARB
- Beta Blockers
- Aldosterone Antagonists
- Entresto
- Device Therapies

Briefly discuss when to refer to a Heart Failure Cardiologist

What’s new/coming in heart failure?

Highlight the current activities of the LVAD Program
Diuretic Guidelines

Class I LOE C:

- Diuretics are recommended in patients with HFrEF who have evidence of fluid retention, unless contraindicated, to improve symptoms.

How much diuretic?
Normal plasma volume results in 100% survival with almost no rehospitalizations

FIGURE 3. Kaplan-Meier plot of proportion of patients with hypervolemia surviving without urgent transplantation over time (dashed line) and in patients with normovolemia or hypovolemia (solid line).
Update: CARRESS-HF Study--Changes from Baseline in Serum Creatinine and Body Weight at Various Time Points, According to Treatment Group

188 patients randomized to either ultrafiltration or high dose diuretic qtt

Acute decompensated HF (both sys and diast)

Worsened renal function (>0.3 mg/dL)

Outcomes—changes in weight and Cr

Ultrafiltration: 200 ml/hr

Diuretics: titrate to UO 3-5L/day. Maximum dose of 600 mg furosemide/day allowed.
Update: CARRESS-HF Study--Changes from Baseline in Serum Creatinine and Body Weight at Various Time Points, According to Treatment Group.

Patient’s treatment regimen:
Furosemide 80 mg IV q12h

ACEI or ARB?
ACE-I guidelines

Class I, LOE A

- The use of ACE inhibitors is beneficial for patients with prior or current symptoms of chronic HFrEF to reduce morbidity and mortality

Mean trial doses of common ACE-I

- Captopril (122.7 mg/d)
- Enalapril (16.6 mg/d)
- Lisinopril (32-35 mg/d)
SOLVD Trial

![Graph showing mortality rates over time for Placebo and Enalapril groups.]

- Placebo: 1284, 1159, 1085, 1005, 939, 819, 669, 487, 299
- Enalapril: 1285, 1195, 1127, 1069, 1010, 891, 697, 526, 333

P = 0.0036

Angiotensin Receptor Blocker Guidelines

Class I, LOE A

- The use of ARBs to reduce morbidity and mortality is recommended in patients with prior or current symptoms of chronic HFrEF who are intolerant to ACE inhibitors because of cough or angioedema

2016 ACC/AHA updated guidelines

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.
Angiotensin Receptor Blocker Trials

- **ELITE-II 2000**
  - All CM, LVEF <40%, NYHA Class II-IV

- **CHARM-Alternative 2003**
  - Candesartan improved mortality in patients who were intolerant of ACE-I
ELITE-II Study: captopril vs losartan

All-cause mortality or hospital admission

Event-free probability

Follow-up (days)

p=0.18
What is Entresto (sacubitril/valsartan)?

Endogenous peptides upregulated in HF:

- Natriuretic peptides (vasodilate and promote diuresis)
- Angiotensin II
- Bradykinin

Neprilysin is an enzyme produced mostly in the kidney that degrades these peptides

Sucubitril is a neprilysin inhibitor

- Therefore levels of A-, B-, & C-NPs, Angiotensin II, and bradykinin should go up

Initially tried to administer sucubitril by itself which failed to lower BP

Then tried to pair with ACEI which caused angioedema (thought due to increased bradykinin levels from ACEI also causing increased bradykinin levels)

Entresto (sucubitril/valsartan) is 1:1 molar ratio of the two drugs in one pill with goal of inhibiting angiotensin II activity, not generate more bradykinin, and promote circulating levels of the natriuretic peptides
PARADIGM Trial--Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

8000 patients randomized to either enalapril versus ARB+Neprilysin (single blind)

LVEF<35%

Hospitalized for HF within past 12 months

Elevated BNP

On a beta-blocker for at least 4 weeks

Exclusion: SBP<95 at randomization, GFR<30, high baseline K, side effects to ARB/ACEI.

Primary outcome: composite of death or hospitalization for HF

Kaplan–Meier Curves for Key Study Outcomes, According to Study Group.


- Death from any cause: enalapril 19.8% vs LCZ696 17% p<0.001
- Death from CV cause: enalapril 16.5% vs LCZ696 13.3% p<0.001
- Readmissions: enalapril 15.6% vs LCZ696 12.8% p<0.001
Patient’s treatment regimen:
Furosemide 80 mg IV q12h
Lisinopril 2.5 mg once daily

Hydralazine and nitrates?
Hydralazine and Nitrates

Class I LOE A

- The combination of hydralazine and isosorbide dinitrate is recommended to reduce morbidity and mortality for patients self-described as African Americans with NYHA class III–IV HFrEF receiving optimal therapy with ACE inhibitors and beta blockers

Class IIa LOE B:

- A combination of hydralazine and isosorbide dinitrate can be useful to reduce morbidity or mortality in patients with current or prior symptomatic HFrEF who cannot be given an ACE inhibitor or ARB because of drug intolerance, hypotension, or renal insufficiency
VHEFT-II

**Trial design:** Patients with evidence of cardiac dysfunction and decreased exercise tolerance were randomized to enalapril (goal 20 mg daily) (n = 2,511) vs. hydralazine/ISDN (goal 300 mg/160 mg daily divided QID) (n = 2,499). Mean follow-up was 2.5 years.

**Results**
- Similar overall mortality for enalapril and hydral/ISDN (32.8 vs 38.2%, p=0.08)
- Two year mortality lower in enalapril group (18 vs 25%, p=0.016)
- Lower mortality in enalapril group driven mainly by reduction in sudden death.
- EF increased in both groups, but significantly greater in hydral/ISDN group.

**Conclusions**
Enalapril improved mortality more than hydralazine/isosorbide dinitrate in this study and had significant impact on exercise and LVEF.

Hydralazine and Isordil: A-HEFT TRIAL

![Graph showing overall survival over days since baseline visit for placebo and isosorbide dinitrate plus hydralazine groups.](image)
Figure 4
Change in Mean SBP in Baseline SBP Quartiles and in Baseline SBP ≤100 mm Hg

[Graph showing changes in mean systolic blood pressure (SBP) over months for different baseline SBP quartiles.]

Patient’s treatment regimen:
Furosemide 100 mg IV q12h
Lisinopril 2.5 mg daily

Beta blockers?
BB guidelines

Class I, LOE A

- Use of 1 of the 3 beta blockers recommended for all patients with current or prior symptoms of HF with reduced LVEF:
  
  Carvedilol (CAPRICORN, COPERNICUS)
  
  25 mg bid (74% at goal)

  Bisoprolol (CIBIS-II)
  
  10 mg daily (43% at goal)

  Metoprolol succinate (MERIT-HF)
  
  200 mg daily (mean dose 159 mg)
COPERNICUS Study

% Event-Free Survival

Months After Randomization

Carvedilol

Placebo

Circulation. 2002 Oct 22;106(17):2194-9
Guidelines and reviews lack the historical details

Table 1. Demonstrated benefits of guideline-recommended HF therapies

<table>
<thead>
<tr>
<th>Guideline-recommended therapy</th>
<th>Relative risk reductions in pivotal randomized clinical trial(s) (%)</th>
<th>Number needed to treat for mortality (m)</th>
<th>Number needed to treat for mortality (standardized to 12 m)</th>
<th>Relative risk reduction in meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI/ARB⁴-⁶</td>
<td>17</td>
<td>22 over 42</td>
<td>77</td>
<td>20%</td>
</tr>
<tr>
<td>β-Blocker⁷-¹⁰</td>
<td>34</td>
<td>28 over 12</td>
<td>28</td>
<td>31%</td>
</tr>
<tr>
<td>Aldosterone antagonist¹¹-¹³</td>
<td>30</td>
<td>9 over 24</td>
<td>18</td>
<td>25%</td>
</tr>
<tr>
<td>Hydralazine/nitrate¹⁴</td>
<td>43</td>
<td>25 over 10</td>
<td>21</td>
<td>NA</td>
</tr>
<tr>
<td>CRT¹⁹-²²</td>
<td>36</td>
<td>12 over 24</td>
<td>24</td>
<td>29%/22%</td>
</tr>
<tr>
<td>ICD¹⁵-¹⁸</td>
<td>23</td>
<td>14 over 60</td>
<td>70</td>
<td>26%</td>
</tr>
</tbody>
</table>

NA, Not available.

Order in which HF GDMT was studied

Effect of Adding Medications/Devices

Survival vs Years

- + ICD 2002-2005
- + Aldo Blocker 1999
- + β Blocker 2001
- +ACEI 1990’s
- Baseline
ACE-inhibitors used widely in β-blocker trials

### Table 1. Pretreatment Characteristics of the Patients.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Randomized Patients</th>
<th>Patients with Recent or Recurrent Decompensation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N=1133)</td>
<td>Carvedilol (N=1156)</td>
</tr>
<tr>
<td></td>
<td>Placebo (N=316)</td>
<td>Carvedilol (N=308)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>63.4±11.5</td>
<td>63.2±11.4</td>
</tr>
<tr>
<td></td>
<td>62.6±11.5</td>
<td>64.9±11.1</td>
</tr>
<tr>
<td>Male sex (% of patients)</td>
<td>80</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>81</td>
<td>79</td>
</tr>
<tr>
<td>Ischemic cause of heart failure (% of patients)</td>
<td>67</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>66</td>
<td>69</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>19.8±4.0</td>
<td>19.9±4.0</td>
</tr>
<tr>
<td></td>
<td>16.1±4.8</td>
<td>16.3±4.7</td>
</tr>
<tr>
<td>Hospitalization for heart failure within previous year (% of patients)</td>
<td>65</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>74</td>
<td>72</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>123±19</td>
<td>123±19</td>
</tr>
<tr>
<td></td>
<td>119±18</td>
<td>118±19</td>
</tr>
<tr>
<td>Diastolic</td>
<td>76±11</td>
<td>76±11</td>
</tr>
<tr>
<td></td>
<td>75±11</td>
<td>74±11</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>83±13</td>
<td>83±12</td>
</tr>
<tr>
<td></td>
<td>83±13</td>
<td>84±12</td>
</tr>
<tr>
<td>Serum sodium (mmol/liter)</td>
<td>137±3</td>
<td>137±3</td>
</tr>
<tr>
<td></td>
<td>137±3</td>
<td>137±3</td>
</tr>
<tr>
<td>Serum creatinine (μmol/liter)</td>
<td>154±56</td>
<td>154±57</td>
</tr>
<tr>
<td></td>
<td>140±42</td>
<td>139±41</td>
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<tr>
<td>Concomitant medications (% of patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digitalis</td>
<td>65</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>72</td>
<td>76</td>
</tr>
<tr>
<td>Diuretics</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>ACE inhibitor or angiotensin II antago-</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>nist (mg/d)</td>
<td></td>
<td>96</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>26</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>22</td>
</tr>
</tbody>
</table>

*All continuous data are expressed as means ±SD. ACE denotes angiotensin-converting enzyme. To convert the values for creatinine to milligrams per deciliter, divide by 88.4.

ACE-inhibitors used widely in β-blocker trials

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Metoprolol CR/XL group (n=1990)</th>
<th>Placebo group (n=2001)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male/female</td>
<td>1353 (77%)/451 (23%)</td>
<td>1354 (78%)/447 (22%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>678 (33%)</td>
<td>682 (34%)</td>
</tr>
<tr>
<td>60-69</td>
<td>700 (35%)</td>
<td>702 (35%)</td>
</tr>
<tr>
<td>&gt;70</td>
<td>628 (32%)</td>
<td>617 (31%)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>63.9 (9.8)</td>
<td>63.7 (9.7)</td>
</tr>
<tr>
<td>Ethnic origin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1870 (94%)</td>
<td>1886 (94%)</td>
</tr>
<tr>
<td>Black</td>
<td>107 (6%)</td>
<td>101 (5%)</td>
</tr>
<tr>
<td>Other</td>
<td>13 (1%)</td>
<td>14 (1%)</td>
</tr>
<tr>
<td>Current daily smoker</td>
<td>282 (14%)</td>
<td>207 (10%)</td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic</td>
<td>1294 (65%)</td>
<td>1312 (66%)</td>
</tr>
<tr>
<td>Non-ischaemic</td>
<td>696 (35%)</td>
<td>688 (34%)</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>811 (41%)</td>
<td>825 (41%)</td>
</tr>
<tr>
<td>III</td>
<td>1120 (56%)</td>
<td>1100 (55%)</td>
</tr>
<tr>
<td>IV</td>
<td>60 (3.4%)</td>
<td>76 (3.8%)</td>
</tr>
<tr>
<td>Previous myocardial infarction (years)*</td>
<td>950 (48%)</td>
<td>974 (49%)</td>
</tr>
<tr>
<td>Time since last myocardial infarction (years)*</td>
<td>151 (8%)</td>
<td>139 (7%)</td>
</tr>
<tr>
<td>&lt;1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-5</td>
<td>341 (17%)</td>
<td>336 (18%)</td>
</tr>
<tr>
<td>&gt;5</td>
<td>457 (23%)</td>
<td>469 (23%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>324 (16%)</td>
<td>341 (17%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>671 (44%)</td>
<td>876 (44%)</td>
</tr>
<tr>
<td>Diastolic pulse</td>
<td>439 (23%)</td>
<td>486 (24%)</td>
</tr>
<tr>
<td>Mean (SD) measurements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>0.28 (0.07)</td>
<td>0.28 (0.07)</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>82.4 (10.1)</td>
<td>82.7 (10.3)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>130.0 (17.0)</td>
<td>129.9 (17.3)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>78.4 (9.2)</td>
<td>78.1 (9.1)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80.5 (15.3)</td>
<td>80.7 (15.9)</td>
</tr>
<tr>
<td>Drug therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>1652 (81%)</td>
<td>1602 (80%)</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>1773 (89%)</td>
<td>1708 (89%)</td>
</tr>
<tr>
<td>Angiotensin II blocker</td>
<td>155 (7%)</td>
<td>129 (6%)</td>
</tr>
<tr>
<td>ACE inhibitor or angiotensin II blocker</td>
<td>1897 (95%)</td>
<td>1922 (96%)</td>
</tr>
</tbody>
</table>

**ACE-inhibitors used widely in β-blocker trials**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo (n=1320)</th>
<th>Bisoprolol (n=1327)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (range) age (years)</td>
<td>61 (22–80)</td>
<td>61 (26–80)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>1062 (80%)/258 (20%)</td>
<td>1070 (81%)/257 (19%)</td>
</tr>
<tr>
<td><strong>NYHA class</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>1096 (83%)</td>
<td>1106 (83%)</td>
</tr>
<tr>
<td>IV</td>
<td>224 (17%)</td>
<td>221 (17%)</td>
</tr>
<tr>
<td><strong>Heart failure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Documented ischaemic heart</td>
<td>654 (50%)</td>
<td>662 (50%)</td>
</tr>
<tr>
<td>disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary dilated cardiomyopathy</td>
<td>157 (12%)</td>
<td>160 (12%)</td>
</tr>
<tr>
<td>Others*</td>
<td>509 (40%)</td>
<td>505 (38%)</td>
</tr>
<tr>
<td>Duration of heart failure</td>
<td>2.31/3.60</td>
<td>2.25/3.49</td>
</tr>
<tr>
<td>Median/mean</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) systolic blood pressure</td>
<td>130.2 (19.5)</td>
<td>129.2 (19.2)</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) diastolic blood pressure</td>
<td>80.0 (10.9)</td>
<td>79.4 (11.2)</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) heart rate (beats/min)</td>
<td>81.0 (15.5)</td>
<td>79.9 (14.5)</td>
</tr>
<tr>
<td>Mean (SD) left-ventricular</td>
<td>27.6 (5.5)</td>
<td>27.5 (6.0)</td>
</tr>
<tr>
<td>ejection fraction (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) left-ventricular end-diastolic diameter (cm)</td>
<td>6.7 (0.9)</td>
<td>6.7 (0.9)</td>
</tr>
<tr>
<td>Mean (SD) left-ventricular end-systolic diameter (cm)</td>
<td>5.7 (0.9)</td>
<td>5.7 (1.0)</td>
</tr>
<tr>
<td>Mean (SD) left-ventricular fractional shortening</td>
<td>15.5 (5.7)</td>
<td>15.5 (5.7)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>264 (20%)</td>
<td>257 (20%)</td>
</tr>
<tr>
<td><strong>Concomitant medications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretic</td>
<td>1310 (99%)</td>
<td>1309 (98%)</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>1274 (96%)</td>
<td>1273 (96%)</td>
</tr>
</tbody>
</table>

Titrate every 2 weeks if tolerated

Figure 2: Beta-blocker dosage changes in acutely decompensated heart failure
Patient’s treatment regimen:
Furosemide 80 mg IV q12h
Lisinopril 2.5 mg once daily
Carvedilol 6.25 mg BID

Mineralocorticoid receptor antagonists?
MRA Guidelines

Class I LOE A:

- Aldosterone receptor antagonists (or mineralocorticoid receptor antagonists) are recommended in patients with NYHA class II–IV HF (II if elevated BNP or CV hospitalization) and who have LVEF of 35% or less.
  - eGFR > 30 mL/min/1.73 m2
  - K < 5.0 mEq/L

Spironolactone

- Initial dose 12.5 mg daily
- Uptitrate to 25 mg daily or BID after 4 weeks

Eplerenone

- Initial dose 25 mg daily
- Uptitrate to 50 mg daily after 4 weeks
Spironolactone/Eplerenone

Trial results:

- **RALES 1999** (Spironolactone, all CM, NYHA class III/IV, LVEF <35%)

RALES followed by:

- **EPHESUS 2003** (Eplerenone, ICM, NYHA class I-IV, LVEF <40%)
- **EMPHASIS-HF 2011** (Eplerenone, NYHA class II, EF <35%)
RALES Study

ACE-inhibitors used widely in RALES trial

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo Group (N=841)</th>
<th>Spironolactone Group (N=822)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>65±12</td>
<td>65±12</td>
</tr>
<tr>
<td>White race — %</td>
<td>86</td>
<td>87</td>
</tr>
<tr>
<td>Sex — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>614 (73)</td>
<td>603 (73)</td>
</tr>
<tr>
<td>Female</td>
<td>227 (27)</td>
<td>219 (27)</td>
</tr>
<tr>
<td>Blood pressure — mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>122±20</td>
<td>123±21</td>
</tr>
<tr>
<td>Diastolic</td>
<td>75±11</td>
<td>75±12</td>
</tr>
<tr>
<td>Heart rate — beats/min</td>
<td>81±15</td>
<td>81±14</td>
</tr>
<tr>
<td>New York Heart Association class — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>3 (0.4)</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td>III</td>
<td>581 (69)</td>
<td>592 (72)</td>
</tr>
<tr>
<td>IV</td>
<td>257 (31)</td>
<td>226 (27)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction — %</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25.2±6.8</td>
<td>25.6±6.7</td>
</tr>
<tr>
<td>Cause of heart failure — no. (%)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>453 (54)</td>
<td>454 (55)</td>
</tr>
<tr>
<td>Nonischemic</td>
<td>386 (46)</td>
<td>368 (45)</td>
</tr>
<tr>
<td>Medications — %</td>
<td></td>
<td></td>
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<tr>
<td>Loop diuretics</td>
<td>106</td>
<td>106</td>
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<tr>
<td>ACE inhibitors</td>
<td>94</td>
<td>95</td>
</tr>
<tr>
<td>Digital</td>
<td>72</td>
<td>73</td>
</tr>
<tr>
<td>Aspirin</td>
<td>37</td>
<td>36</td>
</tr>
<tr>
<td>Potassium supplements</td>
<td>27</td>
<td>29</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>10</td>
<td>11</td>
</tr>
</tbody>
</table>

Patient’s treatment regimen:
Furosemide 80 mg IV q12h
Carvedilol 6.25 mg BID (reduced)
Lisinopril 2.5 mg once daily
Spironolactone 12.5 mg daily

Digoxin ?
Digoxin - Class IIa indication to decrease hospitalizations

Figure 1 Kaplan-Meier plots for cumulative risk of death due to all causes by SDC.

Figure 3 Kaplan-Meier plots for cumulative risk of hospitalization due to worsening HF by SDC.
Regimen Comparison

Admission
- Lisinopril 2.5 daily
- Carvedilol 12.5 BID
- Furosemide 40 BID

BP 82/62

Discharge
- Lisinopril 5 BID
- Carvedilol 6.25 BID
- Spironolactone 25 daily
- Digoxin 0.125 daily
- Furosemide 80 daily

BP 94/68

Follow-up
- Lisinopril 5 BID
- Carvedilol 12.5 BID
- Spironolactone 25 daily
- Digoxin 0.125 daily
- Furosemide 80 daily

BP 80/64
## Device Therapy for Stage C HFrEF (cont.)

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD therapy is recommended for primary prevention of SCD in selected patients with HFrEF at least 40 days post-MI with LVEF ≤35%, and NYHA class II or III symptoms on chronic GDMT, who are expected to live ≥1 year*</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>CRT is indicated for patients who have LVEF ≤35%, sinus rhythm, LBBB with a QRS ≥150 ms</td>
<td>I</td>
<td>A (NYHA class III/IV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B (NYHA class II)</td>
</tr>
<tr>
<td>ICD therapy is recommended for primary prevention of SCD in selected patients with HFrEF at least 40 days post-MI with LVEF ≤30%, and NYHA class I symptoms while receiving GDMT, who are expected to live ≥1 year*</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>CRT can be useful for patients who have LVEF ≤35%, sinus rhythm, a non-LBBB pattern with a QRS ≥150 ms, and NYHA class III/ambulatory class IV symptoms on GDMT.</td>
<td>IIa</td>
<td>A</td>
</tr>
<tr>
<td>CRT can be useful for patients who have LVEF ≤35%, sinus rhythm, LBBB with a QRS 120 to 149 ms, and NYHA class II, III or ambulatory IV symptoms on GDMT</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>CRT can be useful in patients with AF and LVEF ≤35% on GDMT if a) the patient requires ventricular pacing or otherwise meets CRT criteria and b) AV nodal ablation or rate control allows near 100% ventricular pacing with CRT</td>
<td>IIa</td>
<td>B</td>
</tr>
</tbody>
</table>

*Helping Cardiovascular Professionals
# Regimen Comparison

## Admission
- BP 82/62
- Lisinopril 2.5 daily
- Carvedilol 12.5 BID
- Furosemide 40 BID

## Discharge
- BP 94/68
- Lisinopril 5 BID
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- Spironolactone 25 daily
- Digoxin 0.125 daily
- Furosemide 80 daily

## Follow-up
- BP 80/64
- Lisinopril 5 BID
- Carvedilol 12.5 BID
- Spironolactone 25 daily
- Digoxin 0.125 daily
- Furosemide 80 daily

**NO DEVICE (QRS narrow, <90 days med Rx, poor 1 year survival)**
Back to our patient

CPST results on med Rx are terrible
Implanted with LVAD
Relapsed after LVAD and began smoking
10 months later, LVEF improved to 60%
Explanted 12/2/15
Last follow up August 2018, LVEF still 45%, back to work full time
Objectives:

Review the Stages of CHF and Evaluation of Systolic CHF

Follow a case presentation while longitudinally discussing the components of Guideline Directed Medical Therapy

- Diuretics
- Ace-Inhibitors / ARB
- Beta Blockers
- Aldosterone Antagonists
- Entresto
- Device Therapies

Briefly discuss when to refer to a Heart Failure Cardiologist

Highlight the current activities of MMC’s Heart Failure Clinic and LVAD Program

What’s new/coming in heart failure?
Referral to Heart Failure Cardiology

New Onset Heart Failure

Chronic Heart Failure with High Risk Features

≥ 2 hospitalizations / ER visits in 12 months
Persistent NYHA III or IV symptoms
Systolic BP < 90 mmHg
Worsening renal insufficiency
Inability to tolerate previous doses of GDMT
High dose loop diuretics
RHC with PA Saturation < 60%, Cardiac Index < 2.5 L/min/m²
Consideration of Device Therapy or Inotropes
New or worsening atrial or ventricular arrhythmias

Consideration of Advanced Therapies such as LVAD or Cardiac Transplantation

Assessment of Etiology of Heart Failure
Objectives:

Review the Stages of CHF and Evaluation of Systolic CHF

Follow a case presentation while longitudinally discussing the components of Guideline Directed Medical Therapy

- Diuretics
- Ace-Inhibitors / ARB
- Beta Blockers
- Aldosterone Antagonists
- Entresto
- Device Therapies

Briefly discuss when to refer to a Heart Failure Cardiologist

**Highlight the current activities of the Heart Failure and LVAD Program**

What’s new/coming in heart failure?
Maine Medical Center Heart Failure Clinics

Scarborough

- CHF Clinic
- Cardiopulmonary Exercise Test
- PET Imaging

Portland - Maine Medical Center

- VAD Clinic
- Transplant Clinic
- Cardiac MRI
MMC Heart Failure Outreach Clinics

North Conway - Memorial

Augusta – Maine General

Lewiston – St. Mary’s

Lincoln Health Miles
European Heartmate 3 (CE mark) Trial

**Figure 7** Functional Capacity

Change in the New York Heart Association classification from baseline through 6-month follow-up shows marked improvement in functional capacity.

**Figure 8** 6-Min Walk Test

Compared with baseline, patients had improved walk distances at 1, 3, and 6 months.

Netuka et al. JACC 2015; 66:2579-89
Objectives:

Review the Stages of CHF and Evaluation of Systolic CHF

Follow a case presentation while longitudinally discussing the components of Guideline Directed Medical Therapy

- Diuretics
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- Beta Blockers
- Aldosterone Antagonists
- Entresto
- Device Therapies

Briefly discuss when to refer to a Heart Failure Cardiologist

Highlight the current activities of the Heart Failure and LVAD Program

What’s new/coming in heart failure?
CardioMEMS *Champion* HF Monitoring System

Pressure Sensor on Catheter-based Delivery System

Home Electronics

PA Monitoring Database

Proprietary database for secure storage of patient data
Champion Trial

>18 yo, NYHA class III HF, hospitalized at least once in past 12 months

Primary Efficacy Endpoint:

• Rate of HF hospitalizations up to 6 months

Primary safety endpoints:

• Freedom from device related complication at 6 months
• Freedom from pressure sensor failure at 6 months
Champion Trial Results

A

Control group (254 hospital admissions for heart failure)
Treatment group (158 hospital admissions for heart failure)

Hazard ratio 0.63
(95% CI 0.52–0.77); p=0.0001

B

Control group (138 patients with event)
Treatment group (107 patients with event)

Hazard ratio 0.73
(95% CI 0.57–0.94); p=0.0146

Lancet Feb 2011
Questions about the study:

Was it the “guidelines for treatment” that made the difference?

Was the control group a fair comparison group?
  • Did the two study groups start off on equal footing?
  • Why were the “guidelines for treatment” not used also with the control group?
Trajectories of LVEF

Ref: Lupon et al. JACC August 2018.
Trajectories of LVEF

Ref: Lupon et al. JACC August 2018.
PARAGON-HF

4600 subjects (July 2014-March 2019)

- Valsartan 80 mg b.i.d. for 1-2 weeks
- LCZ696 100 mg b.i.d. for 2-4 weeks
- Randomization into the Double Blind period (up to 57 months). Target doses LCZ969 200 mg po BID and Valsartan 160 mg po BID

Primary endpoint: Cumulative number of primary composite events of cardiovascular (CV) death and total (first and recurrent) HF hospitalizations.
Jardiance (empagliflozin)

A. Primary Outcome

- **Hazard ratio**: 0.86 (95% CI: 0.74–0.99)
- **P-value**: 0.04 for superiority

B. Death from Cardiovascular Causes

- **Hazard ratio**: 0.62 (95% CI: 0.49–0.77)
- **P-value**: <0.001

C. Death from Any Cause

- **Hazard ratio**: 0.68 (95% CI: 0.57–0.82)
- **P-value**: <0.001

D. Hospitalization for Heart Failure

- **Hazard ratio**: 0.65 (95% CI: 0.50–0.85)
- **P-value**: <0.002

---

Co-APT Study—results negative
Mitochondrial Anti-Oxidants

• Mitochondrial dysfunction and disarray seen in myocardial cells
• Inability to react to oxidative stress resulting in increased ROS
• Drug called MitoQ touted as a potent mitochondrial antioxidant being studied in heart failure