Heart Failure: Optimal Medical Care

Allen E. Atchley, MD FACC FASE RPVI
Conflicts

• None
Outline

- Epidemiology
- Evaluation
- Medical Therapy (GDMT)
  - HFrEF
- HFpEF
- Non-medical Considerations
- Care coordination
Epidemiology

- 6 million HF patients in U.S.A.
- ≥ 550k new dx annually
- ≥ 1 million inpatient admissions annually
- # 1 inpatient diagnosis age > 65

Impact

• ≈ 50% 5/year mortality
• ≈ 24% 30-day readmission rate
  – Approximately 2/3 in the first 14 days post-D/C

• Cost 1-90 days post-D/C = index admit
• $35+ billion direct health care cost

Initial Evaluation

- History and Physical
- ECG
- CXR
- CBC, CMP, Mg++, TSH, Ferritin
- BNP (NT-proBNP)
- Echocardiogram

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<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with suspected, acute, or new-onset HF should undergo a chest x-ray</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>A 2-dimensional echocardiogram with Doppler should be performed for initial evaluation of HF</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Repeat measurement of EF is useful in patients with HF who have had a significant change in clinical status or received treatment that might affect cardiac function or for consideration of device therapy</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Noninvasive imaging to detect myocardial ischemia and viability is reasonable in HF and CAD</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Viability assessment is reasonable before revascularization in HF patients with CAD</td>
<td>IIa</td>
<td>B281-285</td>
</tr>
<tr>
<td>Radionuclide ventriculography or MRI can be useful to assess LVEF and volume</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>MRI is reasonable when assessing myocardial infiltration or scar</td>
<td>IIa</td>
<td>B286-288</td>
</tr>
<tr>
<td>Routine repeat measurement of LV function assessment should not be performed</td>
<td>III: No Benefit</td>
<td>B289-290</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease; COR, Class of Recommendation; EF, ejection fraction; HF, heart failure; LOE, Level of Evidence; LV, left ventricular; LVEF, left ventricular ejection fraction; and MRI, magnetic resonance imaging.

B-type Natriuretic Peptide

- Valve disease
- HTN
- Atrial fibrillation
- CAD- ACS/MI
- Pulmonary Embolism
- COPD
- OSA
- Cor pulmonale
- Pulmonary HTN
- Sepsis
- ARF/CKD
- Hyperthyroidism
- Etc…

TIME-CHF Trial

BNP vs. symptom guided Rx. n=499, age > 60 with LVEF < 45% + NYHA II-IV
- All cause hospitalization and QoL measures: no difference*
- HF hospitalization improved in BNP arm: HR 0.68, p=0.01

*Age dependent (age 60-75 improved)

Pfisterer M et al. JAMA. 2009 Jan 28;301(4):383-92
HFrEF-GDMT

HFrEF Stage C
NYHA Class I – IV
Treatment:

Class 1, LOE A
ACEI or ARB AND
Beta Blocker

For all volume overload,
NYHA class II-IV patients

Add

Class 1, LOE C
Loop Diuretics

For persistently symptomatic
African Americans,
NYHA class III-IV

Add

Class 1, LOE A
Hydral-Nitrates

For NYHA class II-IV patients:
Provided estimated creatinine
>30 mL/min and K+ <5.0 mEq/dL

Add

Class 1, LOE A
Aldosterone Antagonist

NNT for Mortality

<table>
<thead>
<tr>
<th>GDMT</th>
<th>RR Reduction in Mortality (%)</th>
<th>RR Reduction (Standardized to 36 mo)</th>
<th>RR Reduction in HF Hospitalizations (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor or ARB</td>
<td>17</td>
<td>26</td>
<td>31</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>34</td>
<td>9</td>
<td>41</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>30</td>
<td>6</td>
<td>35</td>
</tr>
<tr>
<td>Hydralazine/nitrate</td>
<td>43</td>
<td>7</td>
<td>33</td>
</tr>
</tbody>
</table>

## HFrEF-GDMT

### ACE inhibitors
- Captopril: 6.25 mg 3 times
- Enalapril: 2.5 mg twice
- Fosinopril: 5 to 10 mg once
- Lisinopril: 2.5 to 5 mg once
- Perindopril: 2 mg once
- Quinapril: 5 mg twice
- Ramipril: 1.25 to 2.5 mg once
- Trandolapril: 1 mg once

### ARBs
- Candesartan: 4 to 8 mg once
- Losartan: 25 to 50 mg once
- Valsartan: 20 to 40 mg twice

### Aldosterone antagonists
- Spironolactone: 12.5 to 25.0 mg once
- Eplerenone: 25 mg once

### Beta blockers
- Bisoprolol: 1.25 mg once
- Carvedilol: 3.125 mg twice
- Carvedilol CR: 10 mg once
- Metoprolol succinate extended release (metoprolol CR/XL): 12.5 to 25.0 mg once

### Hydralazine and isosorbide dinitrate
- Fixed-dose combination (180)
  - Hydralazine: 37.5 mg hydralazine/20 mg isosorbide dinitrate 3 times daily
  - 75 mg hydralazine/40 mg isosorbide dinitrate 3 times daily
- Hydralazine and isosorbide dinitrate (188)
  - Hydralazine: 25 to 50 mg, 3 or 4 times daily and isosorbide dinitrate: 20 to 30 mg 3 or 4 times daily
  - Hydralazine: 300 mg daily in divided doses and isosorbide dinitrate: 120 mg daily in divided doses
Carvedilol

• “β-blocker” ≠ class effect
  – Carvedilol: $\alpha_1\beta_1 + \text{other}$?
  – Metoprolol: $\beta_1$ selective
  – Bisoprolol: $\beta_1$ selective
  – Nebivolol: $\beta_1 + \text{Nitric Oxide “potentiating”}$

• COMET
• GEMINI (Metabolic Effects)
• $\beta$-arrestin
COMET Trial

3,029 patients with Class III-IV heart failure

Carvedilol
25 mg BID (n = 1,511)

Metoprolol tartrate
50 mg BID (n = 1,518)

Primary Endpoints:
1) All-cause mortality
2) All-cause mortality or all-cause hospitalization

HR 0.83
95% CI 0.74-0.93
p=0.0017

HR 0.93
95% CI 0.86-1.10
p=0.1222

**GEMINI Trial**

1235 patients HTN + DM2 (A1c 6.5-8.5%) on ACE-I or ARB

<table>
<thead>
<tr>
<th></th>
<th>Metoprolol</th>
<th>p</th>
<th>Carvedilol</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ HbA1c, % (SD)</td>
<td>0.15 (0.04)</td>
<td>&lt;0.001</td>
<td>0.02 (0.04)</td>
<td>0.65</td>
</tr>
<tr>
<td>Insulin sensitivity (%)</td>
<td>-2.0</td>
<td>0.48</td>
<td>-9.1</td>
<td>0.004</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>+11.1</td>
<td></td>
<td>+6.6%</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Primary Endpoints:
1) Δ A1C %
2) Δ Insulin Sensitivity
3) New microalbuminuria

**GEMINI Trial - Lipid Effects**

<table>
<thead>
<tr>
<th>End point</th>
<th>Carvedilol vs. Metoprolol</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>- 2.9%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>- 9.8%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>non-HDL</td>
<td>-4.03%</td>
<td>&lt; 0.0006</td>
</tr>
<tr>
<td>Statin +/-↑</td>
<td>11%</td>
<td>32%</td>
</tr>
</tbody>
</table>


Similar Metabolic effects seen with Carvedilol vs. Atenolol.

β-arrestin = multifunctional adapter protein
- “desensitizes” G-protein receptor mediated adenylyl cyclase
- promotes ERK arrestin dependent EGFR transactivation
Carvedilol and Alprenolol* - only 2/20 tested
- β-arrestin G-receptor kinase (GRK) phosphorliation

Diuretics

• Loop Diuretics (1C)
  – Lasix 20-40mg daily/BID (max 600mg)
  – Torsemide* 10-20mg daily/BID (max 200mg)
  – Bumetanide* 1-2mg daily/BID (max 10mg)

• Thiazide Diuretics
  – “Sequential nephron blockade” (IIa)
  – Metolazone, HCTZ, and chlorthalidone
  – Renal function and electrolytes!

* Longer t 1/2 and/or ↑ bioavailability

Aldosterone Antagonist
(Efficacy vs. effectiveness)

RALES Trial
N= 1663 with LVEF < 35% NYHA III/IV
Excluded: Creatinine > 2.5 or K+ > 5

EMPHASIS-HF Trial
N=2584 with LVEF < 30% and NYHA II
Excluded GFR < 30 or K+ > 5

Pitt B et al. NEJM. 1999; 341(10): 709-117.
Aldosterone Antagonist (Efficacy vs. effectiveness)

COMPARE-HF
N=5887
Medicare Claims 2005-2010

Side Effects:

Hyperkalemia
Risk of ↑ K⁺ with ("NNH-23")
GFR < 60
DM2
ACE-I or ARB

Gynecomastia

ARNI

- **Neprilysin**
  - Zinc dependent metalloprotease
  - endopeptidase

- **Inactivates peptide hormones**
  - Enkephalin
  - Substance P
  - Bradykinin
  - Natriuretic peptides
PARADIGM-HF

• Valsartan-sacubitril (Entresto)
• N=8442, LVEF < 40% and NYHA II-IV
  – Study 200mg BID vs. Enalapril 10mg BID
• Excluded
  – Hypotension (SBP < 100)
  – GFR < 30
  – K⁺ > 5.2-5.4
  – Angioedema
Figure 2. Kaplan–Meier Curves for Key Study Outcomes, According to Study Group.
Shown are estimates of the probability of the primary composite end point (death from cardiovascular causes or first hospitalization for heart failure) (Panel A), death from cardiovascular causes (Panel B), first hospitalization for heart failure (Panel C), and death from any cause (Panel D).
PARADIGM-HF

• Generalizable?
  – Run-in (10,513 enrolled/8442 randomized)
  – Drug dose(s)
  – Subgroup analysis
    • NYHA 1-2 better vs. NYHA 3-4 no Δ (p 0.03)
  – 7% North American, 5% black, 15% ICD
    • 1043 centers from 47 countries
  – ? Long term cognitive effect (β-amyloid)
  – Cost
Other Rx

- Digoxin (Class IIa)
  - Low dose, 0.125mg daily or every other day
  - Improved symptoms and QoL with reduce HF hospitalization

- CCB (Class III- not routinely recommended)
  - Amlodipine and Felodipine (dihydropyridine)
  - Safe for BP (PRAISE I, PRAISE II, V-HeFT III)

**HFpEF**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic and diastolic blood pressure should be controlled according to published clinical practice guidelines</td>
<td>I</td>
<td>B (28,247)</td>
</tr>
<tr>
<td>Diuretics should be used for relief of symptoms due to volume overload</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Coronary revascularization for patients with CAD in whom angina or demonstrable myocardial ischemia is present despite GDMT</td>
<td>Ila</td>
<td>C</td>
</tr>
<tr>
<td>Management of AF according to published clinical practice guidelines for HFpEF to improve symptomatic HF</td>
<td>Ila</td>
<td>C</td>
</tr>
<tr>
<td>Use of beta-blocking agents, ACE inhibitors, and ARBs for hypertension in HFpEF</td>
<td>Ila</td>
<td>C</td>
</tr>
<tr>
<td>ARBs might be considered to decrease hospitalizations in HFpEF</td>
<td>IIb</td>
<td>B (248)</td>
</tr>
<tr>
<td>Nutritional supplementation is not recommended in HFpEF</td>
<td>II</td>
<td>C</td>
</tr>
</tbody>
</table>

HFpEF

• “Diastolic” HF
  • Documentation, coding, and billing lexicon

• Complex patients
  – Advanced Age
  – Multiple Comorbidities
    • HTN, DM2, CAD, PAD, AFIB, CKD, OSA
    • Volume sensitive
  – Dyspnea is a difficult symptom to quantify
  – Difficult to prove incremental benefit
HFpEF

- Strain → myocardial deformation
  - What is it?
  - How is it measured?

\[
\text{Strain} = \frac{\Delta \text{Length}}{\text{Length}_0}
\]

(-) % change for systolic shortening
Myocardial Strain

546 consecutive pt’s for LVEF assessment

“Conclusions—GLS is a superior predictor of outcome to either EF or WMSI and may become the optimal method for assessment of global left ventricular systolic function.”

Myocardial Strain

Potential Clinical Uses
Stratification - Mortality
HFpEF
AS - asymptomatic
Chemotherapy Toxicity
Ischemia
Dyssynchrony

130 patients at Duke University Medical Center
Severe AS by AVA < 1cm² and LVEF > 50%

Preserved EF ≠ “normal” systolic function

Non-Medical Interventions

• Tobacco cessation
• Na\(^+\) intake < 4grams/day
  – Caution with K\(^+\) “salt substitute”
• Daily weights
  – Call for Δ 2lb/day or 5lb/week
  – CLOSE FOLLOW-UP

• Nutritional supplements- Class III
Non-Medical Interventions

• Sleep Disordered Breathing
  – Affects ≈ 50% of all HF patients
  – Single Center ADHF Admissions 2007-2010
    • 1117 patients
    • 70% with sleep disordered breathing
    • LoS 9.5 days with OSA vs. 7.2 days with no SDB
    • 30 day readmissions CSA vs. no SDB: HR 1.92 (p=0.009)
    • 36 month mortality CSA vs. no SDB: HR 1.71 (p=0.007)

Sow A et al. Sleep disordered breathing is an independent predictor of one month readmission in decompensated heart failure hospitalizations. HFSA 2013 Scientific Meeting; September 23, 2013; Orlando, FL. Abstract 071.
Non-Medical Interventions

- HF rehab and exercise training
- HF-ACTION Trial
  - 2331 stable outpts: exercise training vs. usual care
  - All cause mortality/hospitalization
    - HR 0.91, p=0.09 (adjusted)
  - CV mortality/hospitalization
    - HR 0.85, p=0.03 (adjusted)
  - Improved QoL and 6-minute walk
- Medicare Benefit
  - LVEF < 35%, NYHA II-IV, stable med Rx > 6 weeks

Advanced HF

• Device Therapy
  – ICD: LVEF < 35% on Med Rx +/- revascularization
  – Bi-V pacing: LVEF < 35%, NYHA II-IV, LBBB

• Stage D HF
  – Ventricular Assist Device
  – Cardiac Transplantation
  – Palliative Care
  – Hospice
LVAD

1 year survival for LVAD DT now \(\approx 80-90\%\)

GDMT and Outcomes


- Optimal GDMT, CRT, and ICD
  - > 69,900 additional lives saved annually

- “These data may underscore the importance of performance improvement efforts to translate evidence-based therapy to routine clinical practice so as to reduce contemporary HF mortality.”
Discharge Transition of Care

Early follow-up ≈ better outcomes

12,285 patients with ED HF visit
Risk of death or hospitalization
Familiar MD vs. Unfamiliar MD

<table>
<thead>
<tr>
<th>Variable</th>
<th>1 (≤32.4)</th>
<th>2 (32.4-37.9)</th>
<th>3 (38.3-44.5)</th>
<th>4 (&gt;44.5)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>7081</td>
<td>8662</td>
<td>7812</td>
<td>6581</td>
<td></td>
</tr>
<tr>
<td>Event, 30 d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortalitya</td>
<td>353 (5.0)</td>
<td>417 (4.8)</td>
<td>352 (4.5)</td>
<td>297 (4.5)</td>
<td>.44</td>
</tr>
<tr>
<td>Readmissionb</td>
<td>1658 (23.3)</td>
<td>1787 (20.5)</td>
<td>1606 (20.5)</td>
<td>1377 (20.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mortality or readmissiona</td>
<td>1849 (26.1)</td>
<td>2015 (23.3)</td>
<td>1813 (23.2)</td>
<td>1544 (23.5)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

30,136 Patients
OPTIMIZE-HF and GWTG-HF registries

HR 0.85 (CI 0.78-0.93)

30d: aHR 0.79 (95% CI 0.71-0.89)
60d: aHR 0.86 (95% CI 0.77-0.95)
90d: aHR 0.87 (95% CI 0.80-0.96)

Any 30d f/u after ED visit ↓ risk of death or repeat ED visit at 6mo. vs. no f/u: aHR 0.78 (HR 0.73-0.82)

Hernandez AF et al. JAMA. 2010;303(17):1716-1722.
Quality Improvement

• Coordinated Care
  – Clinically Integrated Network (CIN)
  – EMR

• Close follow-up
  – Health coach, phone calls, home visits

• Practice Quality
  – Guidelines and Registry participation
    • AHA-GWTG, ADHERE and etc.
Quality Improvement

• LVEF
• Etiology
  – Ischemic vs. non-ischemic cardiomyopathy
• NYHA functional class
• Medical therapy
  – Max tolerated med Rx or contraindication
• Education
• Tobacco cessation
Conclusions

• GDMT implementation/adherence is critical
• HFpEF, preserved EF ≠ normal systolic function
• Don’t forget non-medical interventions
• Registries-practice guidelines can improve care
• Coordination of care and close follow-up is key for improved efficiency, cost, and quality

What is Quality? => EXCELLENCE
Thank you.

Questions?
## Memorial HF Program

<table>
<thead>
<tr>
<th>Recommendation or Indication</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance improvement systems in the hospital and early postdischarge outpatient setting to identify HF for GDMT</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Before hospital discharge, at the first postdischarge visit, and in subsequent follow-up visits, the following should be addressed:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. initiation of GDMT if not done or contraindicated;</td>
<td></td>
<td></td>
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<tr>
<td>b. causes of HF, barriers to care, and limitations in support;</td>
<td></td>
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<tr>
<td>c. assessment of volume status and blood pressure with adjustment of HF therapy;</td>
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<td></td>
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<tr>
<td>d. optimization of chronic oral HF therapy;</td>
<td></td>
<td></td>
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<tr>
<td>e. renal function and electrolytes;</td>
<td></td>
<td></td>
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<tr>
<td>f. management of comorbid conditions;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>g. HF education, self-care, emergency plans, and adherence; and</td>
<td></td>
<td></td>
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<tr>
<td>h. palliative or hospice care</td>
<td></td>
<td></td>
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<tr>
<td>Multidisciplinary HF disease-management programs for patients at high risk for hospital readmission are recommended</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>A follow-up visit within 7 to 14 d and/or a telephone follow-up within 3 d of hospital discharge is reasonable</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Use of clinical risk-prediction tools and/or biomarkers to identify higher-risk patients is reasonable</td>
<td>IIa</td>
<td>B</td>
</tr>
</tbody>
</table>
Memorial HF: Quality Improvement

Hospital Admission

ED or RN Assessment: Activate HF Pathway

1° HF/MCC (2°) Dx

- HF RN
  - Admission: Chart Review and Documentation
  - Discharge: 7 day f/u
  - Discharge: HF Education
  - Discharge: Rx Reconciliation
  - Discharge: Discharge Instructions

- TAV Guide
  - Admission: Database Entry
  - Admission: PCP Notification
  - Discharge: Patient Call 24-48°
  - Discharge: PCP Notification
  - Discharge: Database Update
  - Discharge: HF Education
  - Discharge: Rx Reconciliation

Other 1° with HF CC

- HF RN
  - Discharge: (HF RN or RN)
  - Discharge: HF Education
  - Discharge: Rx Reconciliation

- TAV Guide
  - Discharge: PCP Notification
  - Discharge: Database Update
  - Discharge: Patient Call 24-48°
Memorial HF Data

**CHF Readmission Reasons**
- HF Readmit, 39 patients, 36%
- Other Cardiac Related, 20 patients, 19%
- Non Cardiac Related, 48 patients, 45%

**2014 CHF Readmission Reasons**
- HF Readmit, 15 patients, 27%
- Non Cardiac Related, 34 patients, 61%
- Other Cardiac Related, 7 patients, 13%

Historical Radmission Rate ≈ 18-20%
mGLoS ≈ 4 days

2015 Readmission Rate ≈ 9%
mGLoS ≈ 3.7 days
Future Therapies

- **Serelaxin**, recombinant human relaxin-2
- **↑ CO/stroke volume**
  - Non-adrenergic cardiac Ca\(^{++}\) sensitivity (PKC)
  - ↔ \(O_2\) consumption
- **↑ creatinine clearance/renal blood flow**
- **↓ BP/afterload**
  - Potentiates NO synthase
  - Binds endothelin-B receptor
  - Indirect: inhibits ATII and endothelin
RELAX-AHF Trial

- 1161 inpatients with ADHF
- 48° infusion @ 30µg/kg/day

**RESULTS:**
- ↓ dyspnea score
- ↓ diuretic use
- ↓ ICU and inpatient LoS
- ↓ hs-cTnT and NT-pro BNP
- ↔ 60 d readmission + death
- RELAX-AHF 2 Trial pending

HR 0.63, p=0.020
(37% RRR all cause mortality)
