39th Cardiology Update: Evidence-Based Management

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Heart Failure with Reduced Ejection Fraction

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Potential Conflicts of Interest:

Current Research Grants:

NIH-NHLBI
Novartis
General Electric Medical Imaging
HEART FAILURE DEFINITIONS:

Systolic Dysfunction a.k.a. HFrEF:

- Abnormal systolic properties of LV: abnormal performance, function, contractility.
- LVEF is low: <50-55%
- Diastolic dysfunction may coexist
- Patient may be symptomatic or asymptomatic

Cardiomyopathy Etiologies:

<table>
<thead>
<tr>
<th>INFLAMATORY HEART DISEASE</th>
<th>SECONDARY CARDIOMYOPATHY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral myocarditis</td>
<td>Endocrine</td>
</tr>
<tr>
<td>Idiopathic myocarditis</td>
<td>Rheumatologic</td>
</tr>
<tr>
<td>Giant cell myocarditis</td>
<td>Nutritional</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>Toxic</td>
</tr>
<tr>
<td>Eosinophilic myocarditis (hypersensitivity)</td>
<td>Metabolic</td>
</tr>
<tr>
<td>Infectious</td>
<td>Inherited</td>
</tr>
<tr>
<td>Lyme disease</td>
<td>Neuromuscular disorders</td>
</tr>
<tr>
<td>HIV</td>
<td>X-linked</td>
</tr>
<tr>
<td>Chagas’ disease</td>
<td>Mitochondrial</td>
</tr>
<tr>
<td>Peripartum</td>
<td>Familial dilated cardiomyopathy</td>
</tr>
<tr>
<td></td>
<td>Storage diseases</td>
</tr>
<tr>
<td>EXTRAMYOCARDIAL CARDIOMYOPATHY</td>
<td>Disorders of cardiac energy</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>Neoplastic</td>
</tr>
<tr>
<td>metabolism</td>
<td>Tachycardia-induced</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>Amyloidosis</td>
</tr>
<tr>
<td>cardiomyopathy</td>
<td>Hemochromatosis</td>
</tr>
<tr>
<td>Congenital cardiac anomalies</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
</tr>
</tbody>
</table>
Heart Failure: The Emerging Epidemic:

- HF mortality is increasing despite overall decline in CV deaths, related to
  - Aging population
  - Improved survival of patients with diseases leading to HF
- ~50% of patients die within 5 years after diagnosis
- ~35% with severe HF die within 1 year
- Sudden death accounts for 50% of mortality
- HF is one of the most frequent causes of hospitalization in patients >65 years

Severity of Heart Failure
Modes of Death

MERIT-HF Study Group. LANCET.
Clinical Course of Chronic Heart Failure characterized by acute decompensation
Checklists/Order Sets/EMR Reminders

Risk Factor Therapy:
- Treating known risk factors (hypertension, dyslipidemia, diabetes, obesity, etc.)
- Avoiding behaviors increasing risk (i.e., smoking, excessive alcohol, illicit drug use)
- Periodic evaluation for signs and symptoms of HF
- Ventricular rate control or sinus rhythm restoration
- Noninvasive evaluation of LV function
**Recommendations for Pharmacological Therapy for Management of Stage A-B HFrEF:**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients with a history of MI and reduced EF, ACE inhibitors or ARBs should be used to prevent HF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In patients with MI and reduced EF, evidence-based beta blockers should be used to prevent HF</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>In patients with MI, statins should be used to prevent HF</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Blood pressure should be controlled to prevent symptomatic HF</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>ACE inhibitors should be used in all patients with a reduced EF to prevent HF</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Beta blockers should be used in all patients with a reduced EF to prevent HF</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>An ICD is reasonable in patients with asymptomatic ischemic cardiomyopathy who are at least 40 d post-MI, have an LVEF ≤30%, and on SDMT</td>
<td>Ila</td>
<td>B</td>
</tr>
<tr>
<td>Non-dihydropyridine calcium channel blockers may be harmful in patients with low LVEF</td>
<td>III: Harm</td>
<td>C</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; COR, Class of Recommendation; EF, ejection fraction; guideline-directed medical therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LOE, Level of Evidence; LVEF, ejection fraction; MI, myocardial infarction; and N/A, not available.

2013 ACCF/AHA HF Guidelines

**Optimal Dosing of ACE Inhibitors**

- **General Guideline:**
- Start low and titrate to the target dose used in the clinical trials or the **MAXIMUM TOLERATED DOSE** (ATLAS trial)

  - **Captopril 6.25-12.5 mg ⇒ 50 mg BID-TID (SAVE)**
  - **Enalapril 2.5 mg BID ⇒ 20 mg BID (SOLVD/X)**
  - **Ramipril 2.5 mg BID ⇒ 5 mg BID (AIRE/EX)**
  - **Lisinopril 10 mg OD ⇒ 30-40 mg OD (GISSI 3)**
  - **Trandolapril 1mg ⇒ 4 mg (TRACE)**
β-adrenergic Blocking Agents

- Titrate to target dose
  - Bisoprolol 1.25 - 10 mg OD
  - Carvedilol 3.125 - 25 mg BID
  - Metoprolol 12.5 - 50 to 75 mg /BID
- If unable to tolerate high dose β-blocker, maintain highest tolerated dose
- Continue indefinitely

Recommendations for Pharmacological Therapy for Management of Stage C HFrEF:

2013 ACCF/AHA HF Guidelines
HF and Chronic Diuretics

7,788 Ambulatory HF patients
non-randomized, propensity score


Recommendations for Pharmacological Therapy for Management of Stage C HFrEF:

**Aliskiren**
Aliskiren is recommended in patients with NYHA class II to IV who have LVEF ≤ 39%

**Hydralazine and Isosorbide Dinitrate**
The combination of hydralazine and isosorbide dinitrate is recommended for African Americans with NYHA class III to IV HFrEF on SGMT
A combination of hydralazine and isosorbide dinitrate can be useful in patients with HFrEF who cannot be given ACE inhibitors or ARBs

**Diovan**
Diovan can be beneficial in patients with HFrEF

**Anticoagulation**
- Patients with chronic HFrEF with permanent/persistent/paroxysmal AF and an additional risk factor for cardioembolic stroke should receive chronic anticoagulant therapy
- The selection of an anticoagulant agent should be individualized
- Chronic anticoagulation is reasonable for patients with chronic HFrEF who have permanent/persistent/paroxysmal AF but are without an additional risk factor for cardioembolic stroke
- Anticoagulation is not recommended in patients with chronic HFrEF without AF, a prior thromboembolic event, or a cardioembolic source

2013 ACCF/AHA HF Guidelines
Chronic Heart Failure

Aldosterone Inhibitors

- **Spironolactone**
  - Competitive antagonist of the aldosterone receptor (myocardium, arterial walls, kidney)

ALDOSTERONE

- Retention Na$^+$
- Retention H$_2$O
- Excretion K$^+$
- Excretion Mg$^{2+}$

Edema

Arrhythmias

Collagen deposition

Fibrosis
  - myocardium
  - vessels

Aldosterone Blockade in Systolic Dysfunction

- **RALES**: Randomized Aldactone Evaluation Study. NYHA III-IV patients had 30% mortality reduction over 2 years.
- **Eplerenone**: Selective Aldo blocker w/o androgen/progesterone effects.
- **EPHESUS**: Epleronone post acute MI w/CHF and LVEF< 40%. Mortality decreased 15% after 16 months on optimal Rx.
**Recommendations for Pharmacological Therapy for Management of Stage C HFrEF:**

<table>
<thead>
<tr>
<th>Therapies</th>
<th>2013 ACCF/AHA HF Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldosterone receptor antagonists</td>
<td>I</td>
</tr>
<tr>
<td>Aldosterone receptor antagonists are recommended in patients with NYHA class II–IV who have LVEF ≤ 35%</td>
<td>A</td>
</tr>
<tr>
<td>Aldosterone receptor antagonists are recommended in patients following an acute MI who have LVEF ≤ 40% with symptoms of HF or SM</td>
<td>B</td>
</tr>
<tr>
<td>Inappropriate use of aldosterone receptor antagonists may be harmful</td>
<td>II: Harm</td>
</tr>
<tr>
<td>Hydralazine and isosorbide dinitrate</td>
<td>I</td>
</tr>
<tr>
<td>The combination of hydralazine and isosorbide dinitrate is recommended for African Americans with NYHA class II–IV HF/EF on CDMIT</td>
<td>A</td>
</tr>
<tr>
<td>A combination of hydralazine and isosorbide dinitrate can be useful in patients with HF/EF who cannot be given ACE inhibitors or ARBs</td>
<td>B</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Ia</td>
</tr>
<tr>
<td>Digoxin can be beneficial in patients with HF/EF</td>
<td>B</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>I</td>
</tr>
<tr>
<td>Patients with chronic HF with permanent/persistent/prexysmal AF and an additional risk factor for cardioembolic stroke should receive chronic anticoagulant therapy[a]</td>
<td>A</td>
</tr>
<tr>
<td>The selection of an anticoagulant agent should be individualized</td>
<td>I</td>
</tr>
<tr>
<td>Chronic anticoagulation is reasonable for patients with chronic HF who have permanent/persistent/prexysmal AF but are without an additional risk factor for cardioembolic stroke[b]</td>
<td>C</td>
</tr>
<tr>
<td>Anticoagulation is not recommended in patients with chronic HF/EF without AF, a prior thromboembolic event, or a cardioembolic source</td>
<td>II: No Benefit</td>
</tr>
</tbody>
</table>

*A-HeFT*

-43% reduction in mortality (p=>01)

![Graph showing the reduction in mortality over time for A-HeFT study](image)

### Recommendations for Pharmacological Therapy for Management of Stage C HFrEF:

**Aldosterone receptor antagonists**
- Aldosterone receptor antagonists are recommended in patients with NYHA class II–IV who have LVEF ≤35% (I: Benefit, A)
- Aldosterone receptor antagonists are recommended in patients following an acute MI who have LVEF ≤40% with symptoms of HF or DCM (I: Benefit, B)
- Inappropriate use of aldosterone receptor antagonists may be harmful (II: Harm, B)

**Hydralazine and isosorbide dinitrate**
- The combination of hydralazine and isosorbide dinitrate is recommended for African Americans with NYHA class II–IV HFrEF on CCB/M (I: Benefit, A)
- A combination of hydralazine and isosorbide dinitrate can be useful in patients with HFrEF who cannot be given ACE inhibitors or ARBs (IIa: Benefit, B)

**Digoxin**
- Digoxin can be beneficial in patients with HFrEF (IIa: Benefit, B)

**Anticoagulation**
- Patients with chronic HF with permanent/persistent/paroxysmal AF and an additional risk factor for cardioembolic stroke should receive chronic anticoagulant therapy (I: Benefit, A)
- The selection of an anticoagulant agent should be individualized (I: Benefit, C)
- Chronic anticoagulation is reasonable for patients with chronic HF who have permanent/persistent/paroxysmal AF but are without an additional risk factor for cardioembolic stroke (IIa: Benefit, B)
- Anticoagulation is not recommended in patients with chronic HFrEF without AF, a prior thromboembolic event, or a cardioembolic source (II: No Benefit, B)

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### Recommendations for Pharmacological Therapy for Management of Stage C HFrEF:

**Statins**
- Statins are not beneficial as adjunctive therapy when prescribed solely for HF (II: No Benefit, A)

**Omega-3 fatty acids**
- Omega-3 PUFA supplementation is reasonable to use as adjunctive therapy in HFrEF or HFrEF patients (IIa: Benefit, B)

**Other drugs**
- Nutritional supplements as treatment for HF are not recommended in HFrEF (II: No Benefit, B)
- Hormonal therapies other than to correct deficiencies are not recommended in HFrEF (II: No Benefit, C)
- Drugs known to adversely affect the clinical status of patients with HFrEF are potentially harmful and should be avoided or withdrawn (II: Harm, B)
- Long-term use of an infusion of a positive isotropic drug is not recommended and may be harmful except as palliation (II: Harm, C)
- Calcium channel blockers
- Calcium channel-blocking drugs are not recommended as routine treatment in HFrEF (II: No Benefit, A)

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2013 ACCF/AHA HF Guidelines
Recommendations for Device Therapy for Management of HFrEF:

<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 d post-MI with LVEF ≤35% and NYHA class II or III symptoms on chronic GDMT, who are expected to live &gt;1 yr*</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>CRT is indicated for patients who have LVEF ≤35%, sinus rhythm, and LBBB with a QRS ≥150 ms, and NYHA class II, III, or ambulatory IV symptoms on GDMT</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>ICD therapy is recommended for primary prevention of SCD in selected patients with HFrEF at least 40 d post-MI with LVEF ≤30% and NYHA class I symptoms while receiving GDMT, who are expected to live &gt;1 yr*</td>
<td>I</td>
<td>B</td>
</tr>
</tbody>
</table>

2013 ACCF/AHA HF Guidelines
1. **Uptitrate in small increments** to the recommended target dose or the highest tolerated dose with an appreciation that some patients cannot tolerate the full recommended doses of all medications, particularly patients with low baseline heart rate or blood pressure or with a tendency to postural symptoms.

2. Certain patients (e.g., the elderly, those with chronic kidney disease) may require more frequent visits and laboratory monitoring during dose titration and more gradual dose changes. However, such vulnerable patients may accrue considerable benefits from GDMT. Inability to tolerate optimal doses of GDMT may change after disease-modifying interventions such as CRT.

3. **Monitor vital signs closely** before and during uptitration, including postural changes in blood pressure or heart rate, particularly in patients with orthostatic symptoms, bradycardia, and/or “low” systolic blood pressure (e.g., 80 to 100 mm Hg).

4. **Alternate adjustments of different medication classes** (especially ACE inhibitors/ARBs and beta blockers). Patients with elevated or normal blood pressure and heart rate may tolerate faster incremental increases in dosages.

5. **Monitor renal function and electrolytes** for rising creatinine and hyperkalemia, recognizing that an initial rise in creatinine may be expected and does not necessarily require discontinuation of therapy.

**Strategies for Achieving Optimal GDMT:**
Patients may complain of symptoms of fatigue and weakness with dosage increases; in the absence of instability in vital signs, reassure them that these symptoms are often transient and usually resolve within a few days of changes in therapy.

7. **Discourage sudden spontaneous discontinuation of GDMT medications** by the patient and/or other clinicians without discussion with managing clinicians.

8. **Carefully review doses of other medications** for HF symptom control (eg, diuretics, nitrates) during uptitration.

9. **Consider temporary adjustments in dosages of GDMT** during acute episodes of noncardiac illnesses (eg, respiratory infections, risk of dehydration, etc).

10. **Educate patients, family members, and other clinicians** about the expected benefits of achieving GDMT, including an understanding of the potential benefits of myocardial reverse remodeling, increased survival, and improved functional status and HRQOL.

**Strategies for Achieving Optimal GDMT:**
Neprilysin catalyzes the degradation of B-type natriuretic peptide (BNP) and participates in the breakdown of other vasoactive peptides.

PARADIGM-HF: the largest trial ever in patients with HFrEF (N = 8,442):
- Prospective Comparison an angiotensin receptor-neprilysin inhibitor combined with the ARB valsartan to gold-standard ACE-inhibitor therapy (enalapril) in patients who had HF with a reduced EF.
- Primary endpoint included global mortality and morbidity in heart failure with reduced ejection fraction.
- The combination, known as LCZ696, consists of sacubitril plus valsartan.
- Drugs that have an effect on the renin-angiotensin system (RAS) have only modest effects on survival: about a 15% reduction in CV death for ARBs and 18% for ACE inhibitors.
- Combination therapy can enhance gains. E.g., long-term treatment with enalapril reduces the relative risk of death by 16% whereas adding beta-blockers or mineralocorticoid receptor antagonists results in incremental decreases in risk of death by about 30%.
- Neprilysin degrades several endogenous vasoactive peptides: natriuretic peptides, bradykinin, adrenomedullin, substance P, calcitonin gene-related peptide, and vasoactive intestinal polypeptide.
- Successfully neprilysin would increase the levels of these substances, countering the neurohormonal overactivation that contributes to vasoconstriction, sodium retention, and maladaptive remodeling.
PARADIGM-HF Baseline HF Treatment:

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LCZ696 (N= 4187)</th>
<th>Enalapril (N= 4212)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatments at randomization: no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretic</td>
<td>3363 (80.3)</td>
<td>3375 (80.1)</td>
</tr>
<tr>
<td>Digitalis</td>
<td>1223 (29.2)</td>
<td>1316 (31.2)</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>3899 (93.1)</td>
<td>3912 (92.9)</td>
</tr>
<tr>
<td>Mineralocorticoid antagonist</td>
<td>2271 (54.2)</td>
<td>2400 (57.0)</td>
</tr>
<tr>
<td>Implantable cardioverter–defib.</td>
<td>623 (14.9)</td>
<td>620 (14.7)</td>
</tr>
<tr>
<td>Cardiac resynchronization</td>
<td>292 (7.0)</td>
<td>282 (6.7)</td>
</tr>
</tbody>
</table>

McMurray et al, NEJM 371:993, 2014

Adverse Events during Randomized Treatment:

<table>
<thead>
<tr>
<th>Event</th>
<th>LCZ696 (N = 4187)</th>
<th>Enalapril (N = 4212)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>588 (14.0)</td>
<td>388 (9.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP&lt;90 mm Hg</td>
<td>112 (2.7)</td>
<td>59 (1.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Elevated serum creatinine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2.5 mg/dl</td>
<td>139 (3.3)</td>
<td>188 (4.5)</td>
<td>0.007</td>
</tr>
<tr>
<td>≥3.0 mg/dl</td>
<td>63 (1.5)</td>
<td>83 (2.0)</td>
<td>0.10</td>
</tr>
<tr>
<td>Elevated serum potassium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5.5 mmol/liter</td>
<td>674 (16.1)</td>
<td>727 (17.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>&gt;6.0 mmol/liter</td>
<td>81 (4.3)</td>
<td>238 (5.6)</td>
<td>0.007</td>
</tr>
<tr>
<td>Cough</td>
<td>474 (11.3)</td>
<td>601 (14.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angioedema</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment or use of antihistamines only:</td>
<td>10 (0.2)</td>
<td>5 (0.1)</td>
<td>0.19</td>
</tr>
<tr>
<td>Use of catecholamines or glucocorticoids without hospitalization:</td>
<td>6 (0.1)</td>
<td>4 (0.1)</td>
<td>0.52</td>
</tr>
<tr>
<td>Hospitalization without airway compromise</td>
<td>3 (0.1)</td>
<td>1 (&lt;0.1)</td>
<td>0.31</td>
</tr>
<tr>
<td>Airway compromise</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
</tbody>
</table>

McMurray et al, NEJM 371:993, 2014
PARADIGM-HF Primary Endpoints:

McMurray et al., NEJM 371:993, 2014
Ivabradine

- Specifically binds the Funny channel
  - Reduces the slope for diastolic depolarization
    - Prolongs diastolic duration

- Does not alter...
  - Ventricular repolarization
  - Myocardial contractility
  - Blood pressure

Ivabradine

- 2005-Approved by the European Medicine Agency. **Not** approved in the USA.
- Trade: Procoralan, Coralan (India), Corlentor (Italy)
- 2.5mg, 5mg, 7.5mg. Two times a day

<table>
<thead>
<tr>
<th>Side Effects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphene like events</td>
</tr>
<tr>
<td>Bradycardia (sinus &amp; NOS)</td>
</tr>
<tr>
<td>Ventricular extrasystoles</td>
</tr>
<tr>
<td>Blurred vision</td>
</tr>
</tbody>
</table>

- Teratogenic
  - Pregnancy
  - Breast feeding
SHIFT Trial:

- Randomized, double-blinded, placebo controlled
- 6,500 subjects
  - Male (76%), Caucasian (89%)
  - Class II – IV heart failure, EF<35%, HR>70bpm
  - Admission for heart failure in the previous 2 months
- On optimal medical management
  - 90% on BB, 84% on ACE/ARBs, 60% Aldo antagonists
- Ivabradine vs placebo, followed for 3 years
- Primary endpoint: composite of CV death or hospital admission for heart failure.

Swedberg et al, Lancet 2010

Cardiovascular Mortality:

- Placebo (491 events)
- Ivabradine (449 events)
- HR 0.91 (95% CI 0.80-1.02), p=0.128
Deaths due to Heart Failure:

Placebo (151 events)
Ivabradine (113 events)
HR 0.74 (95% CI 0.58–0.94), p=0.014

Heart Failure Admissions:

Placebo (672 events)
Ivabradine (514 events)
HR 0.74 (95% CI 0.66–0.83), p<0.0001
What Can We Conclude from the SHIFT Trial?

- In patients with all-cause cardiomyopathy (EF<35%), and heart rates > 70bpm,
- While there was no difference total cardiovascular mortality,
- Ivabradine reduces...
  1. Mortality due to Heart Failure
  2. Heart failure admissions

Current Indications from the European Medicines Agency (not approved in the USA):

- It causes pure heart rate reduction.
- It could be used in the following groups
  – Patients who cannot take or tolerate beta-blockers
  – Patients whose disease is not controlled with beta-blockers and whose heart rate is above 60 bpm.