Advances in Chronic Heart Failure Management

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UCSF Advanced Heart Failure Program
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Disclosures

I have nothing to disclose
Goal statement

To review recently-approved therapies and updates to practice guidelines for chronic heart failure

Overview

- New pharmacologic therapies for heart failure with reduced ejection fraction (HFrEF)
- New pharmacologic options for heart failure with preserved ejection fraction (HFpEF)
- Remote hemodynamic monitoring for heart failure
- Anemia and iron deficiency as a therapeutic target in chronic heart failure
Medical Therapy for HFrEF: 2013 Guidelines

- ACE Inhibitors (Class Ia)
  - ARB as an alternative (Class Ia)
- Beta-blockers (Class Ia)
- Mineralocorticoid receptor antagonists (Class Ia)
- Hydralazine/Isosorbide for African-Americans (Class Ia)
- Other: Diuretics, digoxin, etc

Yancy CW et al, Circulation 2013

Angiotensin-Nephrilysin Inhibition

Vardeny O et al, JACC Heart Failure 2014
PARADIGM-HF

- 8442 patients with class II, III, or IV chronic heart failure
  - EF < 35-40%
  - SBP ≥ 95, GFR ≥ 30, K ≤ 5.4
  - Tolerated enalapril 10 mg daily or equivalent for ≥ 4 weeks
- Randomized to enalapril 20 mg daily vs sacubitril-valsartan 400 mg daily
- Primary outcome was a composite of cardiovascular death or HF hospitalization

2016 Guideline Update

Yancy, CW et al. Circulation 2016

Recommendations for Renin-Angiotensin System Inhibition With ACE Inhibitor or ARB or ARNI

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>ACE: A</td>
<td>The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors (Level of Evidence: A) (9-14), or ARBs (Level of Evidence: A) (15-18), or ARNI (Level of Evidence: B-R) (19) in conjunction with evidence-based beta blockers (20-22), and aldosterone antagonists in selected patients (23, 34), is recommended for patients with chronic HF/EF to reduce morbidity and mortality.</td>
</tr>
<tr>
<td>I</td>
<td>ARNI: B-R</td>
<td>In patients with chronic symptomatic HF/EF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality (19).</td>
</tr>
<tr>
<td>III</td>
<td>Harm</td>
<td>ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor (31, 32).</td>
</tr>
<tr>
<td>III</td>
<td>Harm</td>
<td>ARNI should not be administered to patients with a history of angioedema.</td>
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Sacubitril/Valsartan (Entresto™)

- Starting dose is 49/51 mg BID
  - Start with a reduced dose of 24/26 mg for those not previously taking ACE/ARB, or those on a low dose
  - 36 hour washout period
  - Double the dose after 2-4 weeks to a target dose of 97/103 mg
- The rate of hypotension was slightly higher than with enalapril, but did not lead to higher rates of study drug discontinuation
- $4500/year
Compared to enalapril, sacubitril/valsartan is:

- Associated with **reduced** risk of hyperkalemia when combined with an aldosterone antagonist\(^1\)
- No more likely to cause severe hypotensive events\(^2\)
- More cost-effective\(^3\)

\(^1\)Desai AS et al, JAMA Cardiology 2016
\(^2\)Vardeny O et al, HFSA Scientific Sessions 2016
\(^3\)Gaziano TA et al, JAMA Cardiology 2016

Ivabradine

- Heart rate is an independent predictor of mortality in heart failure
- Ivabradine is an inhibitor of the \(I_f\) current in the SA node
- The SHIFT trial randomized 6558 patients:
  - Symptomatic HF with LVEF \(\leq 35\%\)
  - HR \(\geq 70\) in sinus rhythm
  - HF hospitalization in the past year
  - On background HF therapy including BB if tolerated
- Ivabradine (titrated to a max of 7.5 mg BID) vs placebo

Swedberg K et al, Lancet 2010
Ivabradine: SHIFT Trial

Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HFpEF (LVEF ≤35%) who are receiving GDEM, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest (37-40).

Yancy, CW et al. Circulation 2016

2016 Guideline Update

Recommendation for Ivabradine

<table>
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<tr>
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<th>LOE</th>
<th>Recommendation</th>
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<tr>
<td>IIa</td>
<td>B-R</td>
<td>Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HFpEF (LVEF ≤35%) who are receiving GDEM, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest (37-40).</td>
</tr>
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</table>
**SHIFT Trial: Considerations**

- No patients enrolled from the US
- Only 23% were on target dose beta-blocker
  - Average systolic BP was 122 mmHg at enrollment
  - There was no significant improvement in the primary outcome among patients taking at least 50% target dose beta-blocker at randomization

**Spironolactone for HFpEF**

- Approximately 50% of all patients with heart failure have preserved ejection fraction
- No medical therapy has been proven to improve outcomes for these patients
- Mineralocorticoid receptor antagonists (MRA) improve outcomes in HFrEF and post-MI with LV dysfunction
- Small studies suggested MRAs may improve diastolic function
TOPCAT: Spironolactone for HFpEF

- The TOPCAT trial randomized patients with HFpEF to spironolactone vs placebo
- No significant difference in the primary composite outcome of cardiovascular death, aborted cardiac arrest, or HF hospitalization
- BUT, there were significant differences in the patient populations depending on country

Pitt B, NEJM 2014

TOPCAT: Americas Sub-Analysis

- Patients enrolled from the Americas more likely to have elevated BNP
- Patients enrolled on the basis of elevated BNP or NT-ProBNP did show a reduction in the primary outcome

Pfeffer MA et al, Circulation 2014
2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA
Guideline for the Management of Heart Failure

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America

In appropriately selected patients with HFrEF (with EF ≥45%, elevated BNP levels or HF admission within 1 year, estimated glomerular filtration rate >30 mL/min, creatinine <2.5 mg/dL, potassium <5.0 mEq/L), aldosterone receptor antagonists might be considered to decrease hospitalizations (83, 166, 167).

Yancy, CW et al. Circulation 2017

Remote Hemodynamic Monitoring for HF

CardioMEMS
CHAMPION TRIAL

- NYHA Class III heart failure
- Previous HF hospitalization
- No ejection fraction criteria
- Randomized to a wireless implantable hemodynamic monitoring system vs control
- At least 6 months follow-up
- Primary outcome: re-hospitalization

Abraham WT et al, Lancet 2011

CHAMPION

Risk reduction: 36%
Risk reduction: 29%

Abraham WT et al, Lancet 2011
CardioMEMS

- Inserted via venous catheter, requires selective pulmonary angiogram (10 cc)
- No batteries or leads
- FDA approved May 2014
- Indication:
  - Wirelessly measuring and monitoring PA and HR
  - In patients with functional class III heart failure with at least one hospitalization in the past year
  - Hemodynamic data are used by physicians with the goal of better HF management and to reduce hospitalization

Abraham WT et al, Lancet 2011

Remote PA Pressure Monitoring: NNT Compared to Other HF Therapies

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Trial</th>
<th>Mean Duration of Randomized Follow-Up</th>
<th>Annualized Reduction in HF Hospitalization Rates (%)</th>
<th>NNT per year to Prevent 1 HF Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blocker</td>
<td>COPERNICUS</td>
<td>10 months</td>
<td>33%</td>
<td>7</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>RALES</td>
<td>24 months</td>
<td>36%</td>
<td>7</td>
</tr>
<tr>
<td>CRT</td>
<td>CARE-HF</td>
<td>29 months</td>
<td>52%</td>
<td>7</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>MERIT-HF</td>
<td>12 months</td>
<td>29%</td>
<td>15</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>SOLVD</td>
<td>41 months</td>
<td>30%</td>
<td>15</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>EMPHASIS-HF</td>
<td>21 months</td>
<td>38%</td>
<td>16</td>
</tr>
<tr>
<td>Digoxin</td>
<td>DIG</td>
<td>27 months</td>
<td>24%</td>
<td>17</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>Val-HeFT</td>
<td>23 months</td>
<td>21%</td>
<td>18</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>CHARM</td>
<td>40 months</td>
<td>27%</td>
<td>19</td>
</tr>
<tr>
<td>PA pressure monitoring</td>
<td>CHAMPION</td>
<td>17 months</td>
<td>22%</td>
<td>4</td>
</tr>
</tbody>
</table>
CHAMPION According to LVEF

<table>
<thead>
<tr>
<th>Ejection Fraction</th>
<th>Randomization Group</th>
<th>No. of Heart Failure Hospitalizations</th>
<th>Annualized Rate of Hospitalization for Heart Failure</th>
<th>Incidence Rate Ratio (95% CI; P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;40%</td>
<td>Treatment group (n=62)</td>
<td>29</td>
<td>0.43</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>Control group (n=57)</td>
<td>59</td>
<td>0.86</td>
<td>(0.35–0.70; &lt;0.0001)</td>
</tr>
<tr>
<td>≥50%</td>
<td>Treatment group (n=35)</td>
<td>13</td>
<td>0.41</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td>Control group (n=31)</td>
<td>31</td>
<td>1.39</td>
<td>(0.18–0.48; &lt;0.0001)</td>
</tr>
<tr>
<td>&lt;40%</td>
<td>Treatment group (n=208)</td>
<td>153</td>
<td>0.67</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>Control group (n=222)</td>
<td>220</td>
<td>0.90</td>
<td>(0.63–0.89; 0.0010)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.

Iron Deficiency: A therapeutic Target in HF

- Anemia is common in HF
- Treatment of mild to moderate anemia with Epo agents shows no clear benefit and is associated with increased risk of VTE in HF patients
- Up to 50% of patients with HF have also have iron deficiency
  - Defective absorption
  - Reduced availability of iron recycled in the reticuloendothelial system
Iron Deficiency in Heart Failure

van Veldhuisen, D. J. et al. Nat. Rev. Cardiol 2011

FAIR-HF Trial

- 459 patients with chronic HF and NYHA Class II or III symptoms
- LVEF ≤40% if class II or ≤45% if class III
- Hgb between 9.5 and 13.5 g/dL
- Iron deficiency:
  - Ferritin < 100 μg/L, or:
  - Ferritin 100-299 μg/L if transferrin % sat < 20%
- Randomized to ferric carboxymaltose vs placebo
  - 200 mg weekly until iron stores normal, then q 4 weeks

Anker SD et al, NEJM 2009
CONFIRM-HF

Ponikowski P et al. Eur Heart J 2015
2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America

Yancy, CW et al. Circulation 2017

<table>
<thead>
<tr>
<th>Recommendations for Anemia</th>
<th>Recommendations</th>
<th>Comment/Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IIb</strong></td>
<td>B-R</td>
<td>In patients with NYHA class II and III HF and iron deficiency (ferritin &lt;100 ng/mL or 100 to 300 ng/mL if transferrin saturation is &lt;20%), intravenous iron replacement might be reasonable to improve functional status and QoL. (173, 174)</td>
</tr>
<tr>
<td>See Online Data Supplement D.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Targeting Iron Deficiency in Heart Failure

- No significant difference in adverse events among those receiving IV iron vs placebo
  - No allergic reactions with newer formulations
- The benefits are seen regardless of serum hemoglobin
- High dose oral iron has not shown the same benefit in clinical trials
- FAIR-HF 2, a larger trial of IV iron in HF, is underway

Lewis GD et al, JAMA 2017
Advanced Heart Failure: Know the Signs

- NYHA Class IIIB/IV symptoms
- Worsening renal function
- Systolic BP < 90 mmHg
- Multiple hospitalizations
- Inability to tolerate ACE inhibitors or beta-blockers
  - Need to stop or decrease
- LV ejection fraction < 25%
- High diuretic dose (> 100 mg/day of furosemide)

Left Ventricular Assist Device Therapy
Median survival (years):

All pair-wise comparisons were significant at p < 0.05.

Conclusions
- New therapies continue to improve outcomes for patients with HFrEF
  - Sacubitril/valsartan improves HFrEF outcomes compared to ACEi
  - Ivabradine may be useful in selected HFrEF patients
- Consider aldosterone antagonists for appropriately selected patients with HFpEF
- Remote hemodynamic monitoring reduces heart failure re-hospitalizations in patients at risk
- Patients with chronic HF should be screened for iron deficiency and those who meet criteria should be treated with IV iron
- Prompt referral to a HF center for those with signs of advanced disease
Thank you
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