Advances in the Treatment of Heart Failure: Medical Therapy and Beyond

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Today’s Objectives

• Discuss advances in the pharmacologic therapy for:
  • Heart failure with reduced ejection fraction (HFrEF)
  • Heart failure with preserved ejection fraction (HFpEF)

• Describe the potential benefits of implantable hemodynamic monitoring in patients with heart failure and identify patients who may benefit from this technology.

• Understand the role of percutaneous mitral valve therapy in the treatment of patients with heart failure.
Advances in pharmacologic therapy for HFrEF

- ARNI
- Ivabradine
- SGLT-2 Inhibitors
Angiotensin Receptor Neprilysin Inhibitor (ARNi)

Menendez JT. Cardiac Failure Review 2016;2:40-46
Sacubitril Valsartan- PARADIGM HF

- EF < 40% → < 35%
- Class II or higher
- Elevated BNP/HF hospitalization
- Run in period
- Excluded: SBP < 100 mmHg → < 95 mmHg, GFR < 30, elevated KCL, angioedema
- Primary end point: Death from CV cause or hospitalization for HF
• Acute decompensated HF
• EF < 40%
• Elevated BNP
• 24 hours to 10 days after presentation
• SBP > 100 mmHg
• No IV vasodilators or inotropes x 24 hours

Exploratory Clinical Outcome: Re-hospitalization for Heart Failure

Sacubitril Valsartan: n = 35 (8.0%)
Enalapril: n = 61 (13.8%)
HR 0.56 (0.37, 0.84)

Key Safety Outcomes: No difference

Worsening renal function
Hyperkalemia
Symptomatic hypotension
Angioedema

Sacubitril Valsartan- Practical Tips

More to come....
Make the change!
Ivabradine

Ivabradine selectively inhibits the I_f current in the sinus node.

Ivabradine reduces the slow diastolic depolarization phase.

Sinus node
The pacemaker of the heart
Ivabradine- SHIFT

- EF < 35%, HF hospitalization
- Sinus rhythm > 70 bpm
- Class II or higher
- Few Class IV patients
- 25% of patients on optimal beta blocker
- Primary end point: Death from CV cause or HF hospitalization

Swedberg K. Lancet. 2010; 376: 875-85
Ivabradine- Practical Tips

**Avoid:**
- Recent MI
- Pacing more than 40% of the day
- Atrial arrhythmias
- Non-dihydropyridine calcium channel blockers
- Class I antiarrhythmic
- Strong cP450 34A inhibitors
SGLT-2 Inhibitors—Impact on Heart Failure Outcomes

7,020 patients with diabetes at high cardiovascular risk randomized to empagliflozin (10 or 25 mg/day) or placebo for a median of 3.1 years (EMPA-REG OUTCOME Trial)

Heart Failure Hospitalization:

Empagliflozin: n = 126 (2.7%)
Placebo: n = 95 (4.1%)
HR 0.65 (0.55-0.79)

SGLT-2 Inhibitors—Impact on Heart Failure Outcomes

17,160 patients with diabetes at high cardiovascular risk randomized to dapagliflozin (10 mg daily) or placebo for a median of 4.2 years (DECLARE-TIMI 58)

Heart Failure Hospitalization and CV death:

Dapagliflozin: n = 417 (4.9%)
Placebo: n = 496 (5.8%)
HR 0.83 (0.73-0.95)

SGLT-2 Inhibitors—HFrEF

4,744 patients with heart failure (NYHA II-IV, EF < 40%) with elevated BNP/HF hospitalization randomized to dapagliflozin (10 mg daily) or placebo for a median of 18.2 months (DAPA HF). ~ 45% with DM.

CV death, HF hospitalization, urgent visit for IV diuresis:

Dapagliflozin: n = 386 (16.3%)
Placebo: n = 502 (21.2%)
HR 0.74 (0.65-0.85)

SGLT-2 Inhibitor - Practical Tips

- Diuretic adjustment
- Blood pressure
- Lipids
- Fungal infections
- UTI’s
- DM medications
Advances in pharmacologic therapy for HFpEF

- MRA
- ANRI?
- SGLT-2 Inhibitors?
# 2013 Heart Failure Guidelines

<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</td>
<td>I</td>
<td>B (27,91)</td>
</tr>
<tr>
<td>published clinical practice guidelines</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Diuretics should be used for relief of symptoms due to volume overload.</td>
<td>Ila</td>
<td>C</td>
</tr>
<tr>
<td>Coronary revascularization for patients with CAD in whom angina or</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>demonstrable myocardial ischemia is present despite GDMT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Management of AF according to published clinical practice guidelines</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>for HFP EF to improve symptomatic HF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of beta-blocking agents, ACE inhibitors, and ARBs for hypertension in HFP EF</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>ARBs might be considered to decrease hospitalizations in HFP EF</td>
<td>IIIb</td>
<td>B (589)</td>
</tr>
<tr>
<td>Nutritional supplementation is not recommended in HFP EF</td>
<td></td>
<td>C</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARBs, angiotensin-receptor blockers; CAD, coronary artery disease; COR, Class of Recommendation; GDMT, guideline-directed medical therapy; HF, heart failure; HFP EF, heart failure with preserved ejection fraction; LOE, and Level of Evidence.

Yancy CW et al. *J Am Coll Cardiol* 2013;62:e147-e239
## Recommendations for Stage C HFpEF (Continued)

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb</td>
<td>B-R</td>
<td>In appropriately selected patients with HFpEF (with EF ≥45%, elevated BNP levels or HF admission within 1 year, estimated glomerular filtration rate &gt;30 mL/min, creatinine &lt;2.5 mg/dL, potassium &lt;5.0 mEq/L), aldosterone receptor antagonists might be considered to decrease hospitalizations.⁸³,¹⁶⁶,¹⁶⁷</td>
</tr>
<tr>
<td>III: No Benefit</td>
<td>B-R</td>
<td>Routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or QoL in patients with HFpEF is ineffective.¹⁷¹,¹⁷²</td>
</tr>
</tbody>
</table>

See Online Data Supplement C.
Mineralocorticoid Receptor Antagonist (MRA)

Regional analysis of 1,767 patients from the Americas (as compared to 1678 from Russia and Georgia) enrolled in the TOPCAT trial which randomized patients with symptomatic heart failure with a LVEF ≥45% to spironolactone or placebo for a mean of 3.3 years. 

CV death, aborted cardiac arrest or HF hospitalization:
Americas
Spironolactone: n = 242 (27.3%)
Placebo: n = 280 (31.8%)
HR 0.82 (0.69-0.98)
Aldosterone Receptor Antagonists

Caution vs avoid:
Cr > 2 in men
Cr > 2.5 in women

Frequent KCL monitoring:
More than HFrEF?
Sacubitril-Valsalartan in HFpEF

**Paramount Trial**
- Sacubitril-Valsalartan vs Valsartan
- Sacubitril-Valsalartan resulted in a greater reduction in NT-proBNP at 12 weeks

**Paragon Trial**
- Sacubitril-Valsalartan vs Valsartan
- Randomized with Run-in Period
- Composite endpoint of CV death and total HF hospitalizations
- Primary end point not met
- Women? Mid-range EF?

Solomon SD et al. *Lancet* 2012;380:1387-1395
Solomon SD et al. *JACC Heart Fail* 2017;5:471-482
SGLT2 Inhibitors and HFpEF
## Ongoing SGLT-2 Inhibitor HFpEF Studies

### Table 4: Ongoing Trials of SGLT-2 Inhibitors in Patients With HFpEF and DM

<table>
<thead>
<tr>
<th>Trial</th>
<th>Therapy</th>
<th>Population</th>
<th>Primary Outcome</th>
<th>Expected Enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPEROR-PRESERVED (NCT03057951)</td>
<td>Empagliflozin</td>
<td>EF &gt;40%, ± type 2 DM, Elevated NT-proBNP</td>
<td>Time to CV death or hospitalization for HF from baseline to 38 months</td>
<td>4,126</td>
</tr>
<tr>
<td>EMBRACE-HF (NCT03030222)</td>
<td>Empagliflozin</td>
<td>EF &gt;40% or &lt;40% Type 2 DM, PA diastolic pressure ≥12 mm Hg</td>
<td>Change in PA diastolic pressure from baseline to 8 to 12 weeks</td>
<td>60</td>
</tr>
<tr>
<td>ERADICATE-HF (NCT03416270)</td>
<td>Ertugliflozin</td>
<td>EF &gt;20% (HFpEF and HFrEF) and DM, Elevated BNP</td>
<td>Proximal tubule sodium reabsorption at 1 and 12 weeks</td>
<td>36</td>
</tr>
<tr>
<td>PRESERVED-HF (NCT03030235)</td>
<td>Dapagliflozin</td>
<td>EF ≥45%, Type 2 DM, Elevated NP</td>
<td>Change from baseline in NT-proBNP at 6 and 12 weeks</td>
<td>320</td>
</tr>
</tbody>
</table>

BNP = brain natriuretic peptide; EMBRACE-HF = Empagliflozin Impact on Hemodynamics in Patients With Heart Failure; EMPEROR-PRESERVED = Empagliflozin Outcome Trial in Patients With Chronic Heart Failure with Preserved Ejection Fraction; ERADICATE-HF = Ertugliflozin in Diabetes With Preserved or Reduced Ejection Fraction Mechanistic Evaluation in Heart Failure; HF = heart failure; PA = pulmonary artery; PRESERVED-HF = Dapagliflozin in PRESERVED Ejection Fraction Heart Failure; SGLT-2 = sodium glucose cotransporter-2; other abbreviations as in Table 1.
Implantable Hemodynamic Monitoring in Heart Failure
Pressure Guided Heart Failure Therapy

CENTRAL ILLUSTRATION The Concept of Pressure-Guided Heart Failure Therapy

Heart Failure Hospitalization

-21 -14 -7 0 Days
Pre-Symptomatic Hemodynamic Changes
("Hemodynamic Congestion")
Symptoms
("Clinical Congestion")

Averted Heart Failure Hospitalization

-21 -14 -7 0 Days
Pre-Symptomatic
Medical Intervention

Implantable Hemodynamic Monitoring for HFrEF

Subgroup of 456 patients with a LV EF <40% enrolled in the CHAMPION trial which randomized patients with chronic heart failure (regardless of EF) and hospitalization to wireless implantable hemodynamic monitoring or control.

Givertz et al. JACC. 2017;15: 1875-1886
Implantable Hemodynamic Monitoring for HFP EF

Subgroup of 119 patients with a LV EF >40% enrolled in the CHAMPION trial which randomized patients with chronic heart failure (regardless of EF) and hospitalization to wireless implantable hemodynamic monitoring or control.

HF Hospitalization at 6 months:
Monitoring: 12.9%
Control: 22.8%
HR: 0.54 (0.38-0.70)

HF Hospitalization, study duration:
Monitoring: 29.9%
Control: 38.6%
HR: 0.50 (0.35-0.70)
Real World Experience

Desai AS. JACC. 2017; 69: 2657-2365
Implantable Hemodynamic Monitoring - Considerations

- HFpEF > HFrEF
- Rural Location
- Hospitalized
- Hard Exam
- Co-Morbidities
- HF partner
Percutaneous Mitral Valve Therapy in Functional Mitral Regurgitation
Functional Mitral Regurgitation in Heart Failure

Lavall D. ESC HF. 2018; 5: 552-561
Functional Mitral Regurgitation in HFrEF

Lavall D. ESC HF. 2018; 5: 552-561
Mitral Clip

Photo from ACC.org
COAPT

614 patients with heart failure and severe secondary mitral regurgitation who remained symptomatic after use of maximal doses of GDMT randomized to transcatheter mitral valve repair and medical therapy or medical therapy alone.

Heart Failure Hospitalization within 24 months:

Mitral clip: 35.8%
Control: 67.9%
HR 0.53 (0.40-0.70)

COAPT patients were on maximally tolerated GDMT; HF consultation (MITRA-HF negative trial)
Can I titrate? Why Not?
Better therapy?
Advanced HF referral?
advanced care planning?
Rehab? Co-morbid?
Cardio-Mems? Clip?
CRT? ICD?

HFrEF
Every Patient
Every Visit
Is it HFpEF?

Better therapy?

Co-morbid?

Weight loss? Exercise?

Cardio-Mems?

Advanced care planning?

HCM Amyloid?

HFpEF Every Patient Every Visit
Key Takeaways

ARNI’s and SGLT-2 inhibitors are changing treatment paradigms for HF.

An implantable hemodynamic monitor is a helpful tool for preventing symptoms and HF hospitalizations in some patients with HF.

Transcatheter mitral valve therapies may be appropriate for some patients with functional mitral regurgitation and refractory symptoms.

Despite recent advances, heart failure remains a challenging disease with poor prognosis.
Thank you