What’s New in the Treatment of Heart Failure
March 28, 2018
Ohio Chapter-ACC

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Disclosures

- Advisory board: Medtronic, Novartis
- Research funding: Corvia, NHLBI, Amgen
Outline

• Definitions
• HF Guideline Updates
• Process of Care
• HFrEF
• HFpEF
• Advanced HF
Outcomes HF; After Hospitalization

HFpEF ≥50%
HFrEF 41-49%
HFrEF ≤40%
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

Developed in Collaboration with the American Academy of Family Physicians, American College of Chest Physicians, and International Society for Heart and Lung Transplantation
<table>
<thead>
<tr>
<th>CLASS (STRENGTH) OF RECOMMENDATION</th>
<th>LEVEL (QUALITY) OF EVIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLASS I: STRONG</strong></td>
<td><strong>LEVEL A</strong></td>
</tr>
<tr>
<td>Benefit &gt;&gt; Risk</td>
<td>- High-quality evidence† from more than 1 RCT</td>
</tr>
<tr>
<td>- Is recommended</td>
<td>- Meta-analyses of high-quality RCTs</td>
</tr>
<tr>
<td>- Is indicated/useful/effective/beneficial</td>
<td>- One or more RCTs corroborated by high-quality registry studies</td>
</tr>
<tr>
<td>- Should be performed/administered/other</td>
<td></td>
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<tr>
<td>- Comparative Effectiveness Phrases:</td>
<td></td>
</tr>
<tr>
<td>- Treatment A is recommended/indicated in preference to treatment B</td>
<td></td>
</tr>
<tr>
<td>- Treatment A should be chosen over treatment B</td>
<td></td>
</tr>
<tr>
<td><strong>CLASS IIa: MODERATE</strong></td>
<td><strong>LEVEL B-R</strong></td>
</tr>
<tr>
<td>Benefit &gt;&gt; Risk</td>
<td>- Moderate-quality evidence† from 1 or more RCTs</td>
</tr>
<tr>
<td>- Is reasonable</td>
<td>- Meta-analyses of moderate-quality RCTs</td>
</tr>
<tr>
<td>- Can be useful/effective/beneficial</td>
<td></td>
</tr>
<tr>
<td>- Comparative Effectiveness Phrases:</td>
<td></td>
</tr>
<tr>
<td>- Treatment A is probably recommended/indicated in preference to treatment B</td>
<td></td>
</tr>
<tr>
<td>- It is reasonable to choose treatment A over treatment B</td>
<td></td>
</tr>
<tr>
<td><strong>CLASS IIb: WEAK</strong></td>
<td><strong>LEVEL B-NR</strong></td>
</tr>
<tr>
<td>Benefit &gt; Risk</td>
<td>- Moderate-quality evidence† from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies</td>
</tr>
<tr>
<td>- May/might be reasonable</td>
<td>- Meta-analyses of such studies</td>
</tr>
<tr>
<td>- May/might be considered</td>
<td></td>
</tr>
<tr>
<td>- Usefulness/effectiveness is unknown/unclear/uncertain or not well established</td>
<td></td>
</tr>
<tr>
<td><strong>CLASS III: NO BENEFIT</strong></td>
<td><strong>LEVEL C-LD</strong></td>
</tr>
<tr>
<td>Benefit = Risk</td>
<td>- Randomized or nonrandomized observational or registry studies with limitations of design or execution</td>
</tr>
<tr>
<td>- Is not recommended</td>
<td>- Meta-analyses of such studies</td>
</tr>
<tr>
<td>- Is not indicated/useful/effective/beneficial</td>
<td></td>
</tr>
<tr>
<td>- Should not be performed/administered/other</td>
<td></td>
</tr>
<tr>
<td><strong>CLASS III: HARM</strong></td>
<td><strong>LEVEL C-ED</strong></td>
</tr>
<tr>
<td>Risk &gt; Benefit</td>
<td>- Physiological or mechanistic studies in human subjects</td>
</tr>
<tr>
<td>- Potentially harmful</td>
<td>- Consensus of expert opinion based on clinical experience</td>
</tr>
<tr>
<td>- Causes harm</td>
<td></td>
</tr>
<tr>
<td>- Associated with excess morbidity/mortality</td>
<td></td>
</tr>
<tr>
<td>- Should not be performed/administered/other</td>
<td></td>
</tr>
</tbody>
</table>

The term *guideline-directed management and therapy* (GDMT) encompasses clinical evaluation, diagnostic testing, and pharmacological and procedural treatments.
2017 HF Update Biomarkers

ARNI Indications

NEW

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>RECOMMENDATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>I</td>
<td>The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors (Level of Evidence: A) (128-133), OR ARBs (Level of Evidence: A) (134-137), OR ARNI (Level of Evidence: B-R) (138) in conjunction with evidence-based beta blockers (9,139,140), and aldosterone antagonists in selected patients (141,142), is recommended for patients with chronic HFrEF to reduce morbidity and mortality.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- ACEi or ARBs or ARNI for HFrEF
- When ARNI not appropriate, continued use of an ACEi is recommended for all classes of HFrEF

**ARNI Indications**

**NEW**

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 (138).

ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor (148,149).

ARNI should not be administered to patients with a history of angioedema.

Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HFrEF (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 (154-157).
2017 Update Treatment of HFrEF Stages C and D

Step 1: Establish Dx of HFrEF; assess volume; initiate GDMT

Step 2: Consider the following patient scenarios:
- NYHA class II-IV, adequate BP on ACEI or ARB. No CI to ARB or sacubitril
- NYHA class II-IV, in black patients
- NYHA class II-III, LVEF ≤35%, (caveat: ≥1 y survival, >40 d post MI)
- NYHA class II-IV, LVEF ≤35%, NSR & QRS ≥150 ms with LBBB pattern
- NYHA class II-III, NSR, heart rate ≥70 bpm on maximally tolerated dose beta blocker

Step 3: Implement indicated GDMT. Choices are not mutually exclusive, and no order is inferred
- Aldosterone antagonist (COR I)
- Discontinue ACEI or ARB, initiate ARNI (COR I)
- Hydral-Nitrates†† (COR I)
- ICD† (COR I)
- CRT or CRT-D† (COR I)
- Ivabradine (COR IIa)

Step 4: Reassess symptoms
- Refractory NYHA class III-IV (Stage D)
- Symptoms improved
- LVAD‡ (COR IIa)
- Investigational studies§

Step 5: Consider additional therapy
- Palliative care‡ (COR IIa)
- Transplant‡ (COR IIa)

Continue GDMT with serial reassessment & optimized dosing/adherence

Recommendations for Stage C HFpEF

NEW

In appropriately selected patients with HFpEF (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).

Use of MRA based upon post hoc analyses and based upon geographic variation in outcomes

Recommendations for Stage C HFP EF

NEW

2013 Recommendations Remain

• BP control target <130 mm Hg
• Diuretics for volume control
• CAD GDMT
• AFIB GDMT
• BP control with ACEi, ARB, BB is reasonable
• Use of nutritional supplements NR

Routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or QoL in patients with HFP EF is ineffective (171,172).
COMORBIDITIES: ANEMIA

NEW

<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 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>
</tbody>
</table>

| III: No Benefit | B-R | In patients with HF and anemia, erythropoietin-stimulating agents should not be used to improve morbidity and mortality (176). |

### STAGE A HYPERTENSION
### STAGE C HF rEF HYPERTENSION

**NEW**

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>RECOMMENDATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-R</td>
<td>In patients at increased risk, stage A HF, the optimal blood pressure in those with hypertension should be less than 130/80 mm Hg (189-193).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>C-EO</td>
<td>Patients with HFrEF and hypertension should be prescribed GDMT titrated to attain systolic blood pressure less than 130 mm Hg (191).</td>
</tr>
</tbody>
</table>
HYPERTENSION SUMMARY

2017 Focused Update

- Class I recommendation (Level of Evidence: B-R) for targeting an optimal blood pressure (BP) of <130/80 mm Hg in those with hypertension and at increased risk (stage A HF).
- Class I recommendation (Level of Evidence: C-EO) for titration of GDMT to attain systolic BP (SBP) <130 mm Hg in patients with HFpEF and hypertension.
- Class I recommendation (Level of Evidence: C-LD) for titration of GDMT to attain SBP <130 mm Hg in patients with HFpEF and persistent hypertension after management of volume overload.

www.acc.org/latest-in-cardiology
## COMORBIDITIES: SLEEP APNEA

### NEW

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>RECOMMENDATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ila</td>
<td>C-LD</td>
<td>In patients with NYHA class II-IV HF and suspicion of sleep-disordered breathing or excessive daytime sleepiness, a formal sleep assessment is reasonable (200,201).</td>
</tr>
</tbody>
</table>

See Online Data Supplement G.

| Iib | B-R   | In patients with cardiovascular disease and obstructive sleep apnea, CPAP may be reasonable to improve sleep quality and daytime sleepiness (204). |

See Online Data Supplement G.

| III: Harm | B-R | In patients with NYHA class II-IV HFrEF and central sleep apnea, adaptive servo-ventilation causes harm (203). |

See Online Data Supplement G.
SLEEP APNEA SUMMARY

2017 Focused Update

• Class IIa recommendation (Level of Evidence: C-LD) for a formal sleep assessment in patients with NYHA class II–IV HF and suspicion of sleep-disordered breathing or excessive daytime sleepiness.
• Class IIb recommendation (Level of Evidence: B-R) for utilization of continuous positive airway pressure in patients with cardiovascular disease and obstructive sleep apnea, to improve sleep quality and daytime sleepiness.
• Class III recommendation: Harm (Level of Evidence: B-R) for use of adaptive servo-ventilation in patients with NYHA class II–IV HFrEF and central sleep apnea, as it causes harm.

Incremental Cost-Effectiveness of Guideline-Directed Medical Therapies for Heart Failure

Gaurav Banka, MD, Paul A. Heidenreich, MD, Gregg C. Fonarow, MD

Los Angeles and Palo Alto, California

Our analysis demonstrates that medical therapies can be pursued in an incremental fashion and may include cost-savings. Greater efforts to ensure optimal cost-effectiveness and may even result in cost-effective and may even result in cost-savings. Greater efforts to ensure optimal cost-effectiveness and benefits for patients with heart failure are warranted. (J Am Coll Cardiol 2013;61:1...
Questions About Guidelines?

• Who reads them?

• Who follows them?

• Do patients have access to GDMT”

• What is gap between guidelines and implementation?
realization that guidelines require effective translation to become reality
“provide practical guidance for transforming guideline recommendations into clinically actionable information”
Ten Pivotal Issues in HFrEF

1. How to initiate, add, or switch therapy to new evidence-based guideline-directed treatments for HFrEF.
2. How to achieve optimal therapy given multiple drugs for HF including augmented clinical assessment that may trigger additional changes in guideline-directed therapy (e.g., imaging data, biomarkers, and filling pressures).
3. When to refer to an HF specialist.
4. How to address challenges of care coordination.
5. How to improve adherence.
6. What is needed in specific patient cohorts: African Americans, the frail, and older adults.
7. How to manage your patients’ cost of care for HF.
8. How to manage the increasing complexity of HF.
9. How to manage common comorbidities.
10. How to integrate palliative care and transition to hospice care.
Consider increasing dose of beta blocker every 2 weeks until maximum tolerated or target dose is achieved.

Monitor heart rate, blood pressure, and for signs of congestion after initiation and during titration.

(i.e. equivalent of 120 mg of furosemide twice daily) consider:

a. changing to a different loop diuretic or
b. adding thiazide diuretic, taken together with loop diuretic

Monitor blood pressure, electrolytes, and renal function after initiation and during titration.
Patient with hypotension

- 32 year old man with new onset HF, DCM, EF 15%
- Lisinopril 5 mg, carvedilol 6.25 mg BID, spironolactone 25 mg daily, furosemide 40 mg daily
- BP 92/70 HR 96

Scenario 2: Symptomatic hypotension.

Hypotensive symptoms may be due to overdiuresis, other vasoactive medication, autonomic dysfunction, or taking multiple medications together. All of these should be addressed prior to deciding to lower doses of evidence-based therapies.

**Action:** After excluding other causes of hypotension, use best-tolerated doses of GDMT, accepting that less data exist for the impact of lower doses in HF management.

Principle 3: Optimal SNS modulation with target doses of beta blocker appears to have the best effect on HFrEF outcomes (cardiovascular mortality, pump failure mortality, and sudden cardiac death).
**Indications for Use of an ARNI**

- HFrEF (EF ≤40%)
- NYHA class II or III HF

**D**

- Hydralazine + isosorbide dinitrate
  - Select initial dose of hydralazine and isosorbide dinitrate, either as individual medications or fixed-dose combination:
    - See Table 1 for dosing information
  - Consider increasing dose of hydralazine and/or isosorbide dinitrate every 2 weeks until maximum tolerated or target dose is achieved
  - Monitor blood pressure after initiation and during titration

**E**

- ARNI
  - Ensure 36 hours off ACEI, adequate blood pressure, and eGFR ≥30 mL/min/1.73 m² before initiating sacubitril/valsartan.
  - Select starting dose:
    - See Tables 1 and 3 for dosing information
  - If patient is taking equivalent of ≤10 mg twice daily of enalapril or equivalent of ≤160 mg daily of valsartan:
    - 24/26 mg twice daily
  - If patient is taking equivalent of >10 mg twice daily of enalapril or equivalent of >160 mg of valsartan:
    - 49/51 mg twice daily
  - In 2–4 weeks, assess tolerability
    - If possible, increase dose stepwise to target of 97/103 mg twice daily
    - Monitor blood pressure, electrolytes, and renal function after initiation and during titration
**Indications for Use of Ivabradine**

- **HFpEF (EF ≤35%)**
- On maximum tolerated doses of beta blocker
- Sinus rhythm with a resting heart rate ≥70 bpm
- NYHA class II or III HF

**Aldosterone Antagonists**

Select initial dose of aldosterone antagonist:
See Table 1 for dosing information

Consider increasing dose of aldosterone antagonist
at least every 2 weeks until maximum tolerated or
target dose is achieved

Monitor electrolytes (especially potassium) and
renal function 2–3 days following initiation, and
then 7 days after initiation/titratration

Then, check monthly for 3 months and every 3 months
afterwards

Clinical status may warrant closer monitoring

**Ivabradine**

Re-assess that beta blockers are adjusted to
maximally tolerated doses and/or target doses
See Table 1 for target beta blocker doses
See Table 2 for indications for ivabradine therapy

Select starting dose of ivabradine:
See Tables 1 and 4 for dosing information

- Age >75 years
  - 2.5 mg twice daily
- Age ≤75 years
  - 5.0 mg twice daily

Re-assess heart rate is at least 2–4 weeks

- Heart rate ≤50 bpm or symptoms of bradycardia
- Heart rate 50–60 bpm
- Heart rate >60 bpm

Reduce dose by 2.5 mg twice daily or
or discontinue if already at 2.5 mg
twice daily

Maintain current dose and monitor
heart rate

Increase by 2.5 mg
twice daily until
reaching maximum
dose of 7.5 mg
twice daily

Monitor heart rate
Remember acronym to assist in decision making for referral to advanced heart failure specialist:

I-NEED-HELP (also see Table 6)

I: IV inotropes
N: NYHA IIIB/IV or persistently elevated natriuretic peptides
E: End-organ dysfunction
E: Ejection fraction ≤35%
D: Defibrillator shocks
H: Hospitalizations >1
E: Edema despite escalating diuretics
L: Low blood pressure, high heart rate
P: Prognostic medication – progressive intolerance or down-titration of GDMT
Emerging Drugs in USA Trials
HFrEF

• Omecamtiv mecarbil inotrope

• Sacubitril/valsartan ARNI

• Vericiguat cGMP promoter
Limitations with current Inhibitors of the Renin-Angiotensin System

Angiotensin

ACE inhibitors
Or angiotensin Receptor blockers

Adverse effects
Heart and vessels

Angiotensin escape

Efficacy

Worsening Renal function

Safety
Biological Antagonism of Neurohormonal Systems

Endogenous compensatory peptides

Bradykinin, natriuretic peptides, adrenomedullin, angiotensin, endothelin, amyloid-β peptide

Inactive metabolites

REDUCE
- Neurohormonal Activation
- Vascular tone
- Cardiac remodeling
- Sodium retention

NEPRILYSIN
PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)

Hazard ratio, 0.80 (95% CI, 0.73–0.87)  
P<0.001

CV death HR .80  
HF hosp HR .79

3.7%age  
20% relative reduction

PARADIGM-HF: Death from any cause (secondary endpoint)

Hazard ratio, 0.84 (95% CI, 0.76–0.93)  
P<0.001

3.2%age  
16% relative reduction

### PARADIGM-HF: Key secondary endpoints

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LCZ 696</th>
<th>Enalapril</th>
<th>HR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in KCCQ</td>
<td>-2.99</td>
<td>-4.63</td>
<td>1.64</td>
<td>0.001</td>
</tr>
<tr>
<td>New Onset AFIB</td>
<td>84(3.1)</td>
<td>83(3.1)</td>
<td>0.97</td>
<td>0.83</td>
</tr>
<tr>
<td>Decline in Renal Function</td>
<td>94(2.2)</td>
<td>108(2.6)</td>
<td>0.86</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Fewer symptoms and physical limitations with sacubitril-valsartan

No increase in AFIB or decline in renal function
## PARADIGM-HF: Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>LCZ696 n=4187</th>
<th>Enalapril n=4214</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>Potassium &gt;5.5 mmol/l</td>
<td>674(16.1)</td>
<td>727(17.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>Potassium &gt;6.0 mmol/l</td>
<td>181(4.3)</td>
<td>236(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>10(0.2)</td>
<td>5(0.1)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

*No treatment or antihistamines only, Steroid treatment or hospitalization p=NS
Sacubitril Valsartan: initiation

- 72 yrs WM 5 year history of HFrEF
  - DCM
  - CRT D
  - Metoprolol succinate 150 mg daily
  - Losartan 50 mg daily
  - Spironolactone 25 mg daily
  - Furosemide 10 mg daily prn
- NYHA Class III
- NT BNP 2200
- GFR 50
- BP 145/80 mm Hg

Options: increase losartan, add amlodipine, substitute ARNI for ARB
Incremental Decrease in Mortality

Effect of ARB vs placebo derived from CHARM-alternative trial
Effect of ACE inhibitor vs placebo derived from SOLVD-Treatment trial
Effect of LCZ696 vs ACE inhibitor derived from PARADIGM-HF trial
Gaps with PARADIGM HF

Limited NYHA IV patients
FDA approval but not included in the guidelines

Perez A et al. JACC HF 2017
INCLUSION

Advanced HFrEF defined as including ALL:

a. LVEF ≤ 35% documented during the preceding 3 months
b. estimated GFR 20-60 mL/min/1.73m2
c. NYHA class IV symptomatology for the majority of the previous month
d. Minimum of 3 months GDMT for HF and/or intolerant to therapy

NCT02816736
Omecamtiv mecarbil: novel inotrope

ATOMIC-HF*
COSMIC-HF

Safety and dose titration

Figure 1: Diagram of Intracellular Signaling Cascades Within Cardiomyocytes Altered by Inotropes

JACC Vol. 63, No. 20, 2014
Teerlink J et al JACC 2016
GALACTIC-HF
A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Assess the Efficacy and Safety of Omecamtiv Mecarbil on Mortality and Morbidity in Subjects With Chronic Heart Failure With Reduced Ejection Fraction

Primary Endpoint:
Measure time to cardiovascular death or first heart failure event

Evaluate the effect of omecamtiv mecarbil as compared with placebo in subjects with chronic heart failure with reduced ejection fraction receiving standard of care therapy

Dose based on plasma levels
Global n=8000

https://clinicaltrials.gov/ct2/show/NCT02929329
Relative deficit of cGMP in heart failure: role of oral soluble guanylate cyclase stimulators?
The primary hypothesis is vericiguat (MK-1242) is superior to placebo in increasing the time to first occurrence of the composite of cardiovascular (CV) death or heart failure (HF) hospitalization in participants with HFrEF

VICTORIA
NCT02861534

• HFrEF inclusion EF <45%
• n=4872
• Event Driven: time to 1st CV death or HF admit
• NYHA II-IV
• Hospitalization and BNP criteria
• Completion 2020

HFpEF

↑ BNP, LAE, LVH, Diastolic/systolic dysfunction
Abnormal hemodynamics
Phenotypes

Hypertensive (majority)

Non-hypertensive (minority)

Valvular
- Mitral stenosis
- Aortic stenosis

Cardiomyopathic
- Hypertrophic
- Restrictive

Extramyocardial
- Pericardial disease

Risk factors/comorbidities
- Advanced age
- Anemia
- Atrial fibrillation
- Chronic obstructive pulmonary disease
- Coronary artery disease
- Diabetes mellitus
- Female gender
- Sleep apnea

Comorbidities and Outcomes

Survival

Hospitalizations

Worse Outcomes Based on Co-Morbidities!

Van Deursen et al. Eur J Heart Fail. 2014 Jan;16(1):103-11
HFpEF JS 74 yo retired RN, LV EF 60%

- BMI 38 BP 165/94 mm HG
- Chronic AFIB post PVI
- CKD GFR 38
- Anemia receives IV iron
- OSA and uses CPAP intermittently
- Syncope and bradycardia; now with DDD pacemaker
- Recurrent hospital admits with weight gain, edema,

- What to do next?
## Negative Trials:

- ACEi
- ARB
- Nitrates
- PDE5 inhibitors
- Beta blockers

**ARB? Candesartan**

**Reduced HF admissions**

### Table – Randomized trials in HFrEF.

<table>
<thead>
<tr>
<th>Study</th>
<th>Region</th>
<th>Number of randomized patients</th>
<th>Ejection fraction cut-off</th>
<th>Primary endpoint</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHARM-preserved</td>
<td>26 countries (Europe, Australia, Asia, Africa, and America)</td>
<td>3025</td>
<td>&gt;40%</td>
<td>CV death or unplanned admission to hospital for the management of worsening chronic HF</td>
<td>Candesartan</td>
<td>Fewer HF admissions</td>
</tr>
<tr>
<td>PEP-CHF</td>
<td>Bulgaria, Czech Republic, Hungary, Ireland, Poland, Russia, Slovakia, and the United Kingdom</td>
<td>850</td>
<td>40-50%</td>
<td>All-cause mortality or unplanned HF-related hospitalization</td>
<td>Perindopril</td>
<td>Fewer HF admissions at 1 year, but differences were not significant for the entire duration of follow-up</td>
</tr>
<tr>
<td>I-PRESERVE</td>
<td>25 countries (Europe, America, Africa, and Australia)</td>
<td>4128</td>
<td>≥45%</td>
<td>Death from any cause or hospitalization for a CV cause</td>
<td>Irbesartan</td>
<td>Neutral</td>
</tr>
<tr>
<td>Kittman et al.</td>
<td>United States</td>
<td>71</td>
<td>≥50%</td>
<td>Exercise capacity or sortic diastensibility</td>
<td>Enalapril</td>
<td>Neutral</td>
</tr>
<tr>
<td>SENORS van Veldhuisen et al. , J Am Coll Cardiol 2009:53:2150-2158</td>
<td>Czech Republic, France, Germany, Hungary, Italy, Netherlands, Romania, Spain, Ukraine, and United Kingdom</td>
<td>2111</td>
<td>≥35% or ≥40% (post-hoc analyses)</td>
<td>All-cause mortality or hospital admissions for a CV cause</td>
<td>Nebivolol</td>
<td>Similar effect of nebivolol between HF patients with impaired ejection fraction and patients with preserved ejection fraction</td>
</tr>
<tr>
<td>ELANDO Conraads et al. , Eur J Heart Fail 2012:14:219-225</td>
<td>Italy, Netherlands, Belgium, Spain, Portugal, Greece, Germany, Austria</td>
<td>116</td>
<td>&gt;45%</td>
<td>6 Minutes walking distance</td>
<td>Nebivolol</td>
<td>Neutral</td>
</tr>
<tr>
<td>J-DHF Yamamoto et al. , Eur J Heart Fail 2013:15: 110-128</td>
<td>Japan</td>
<td>245</td>
<td>&gt;40%</td>
<td>Cardiovascular death or hospitalization</td>
<td>Carvedilol</td>
<td>Neutral</td>
</tr>
<tr>
<td>RAAM-PeP Deswal et al. , Journal of Cardiac Failure 2011:7:634-642</td>
<td>United States</td>
<td>46</td>
<td>≥50%</td>
<td>6 Minutes walking distance</td>
<td>Epesone</td>
<td>Neutral</td>
</tr>
<tr>
<td>Aldo-DHF Edelmann et al. , JAMA 2013:309:781-791</td>
<td>Germany and Austria</td>
<td>422</td>
<td>≥50%</td>
<td>Peak VO2 change in E/e</td>
<td>Spironolactone</td>
<td>– Peak VO2 without a difference between groups</td>
</tr>
<tr>
<td>TOPCAT Pitt et al. , The New England Journal of Medicine 2014:309: 1381-1392</td>
<td>United States, Canada, Brazil, Argentina, Russia, Georgia</td>
<td>3445</td>
<td>&gt;45%</td>
<td>Death from CV causes, aborted cardiac arrest, or hospitalization for HF</td>
<td>Spironolactone</td>
<td>– E/e significantly declined with spironolactone</td>
</tr>
<tr>
<td>DIG Ahmed et al. , Circulation 2006:114:997-403</td>
<td>United States and Canada</td>
<td>988</td>
<td>&gt;45%</td>
<td>HF hospitalization or HF mortality</td>
<td>Digoxin</td>
<td>Neutral</td>
</tr>
<tr>
<td>RELAX Redfield et al. , JAMA 2013:309: 1268-1277</td>
<td>United States and Canada</td>
<td>216</td>
<td>≥50%</td>
<td>Peak VO2</td>
<td>Sildenafil</td>
<td>Neutral</td>
</tr>
</tbody>
</table>

**1° Outcome TOPCAT**
(CV Death, HF Hosp, or Resuscitated Cardiac Arrest)

Spironolactone: HR = 0.89 (0.77 – 1.04)  
*p = 0.138*

Spironolactone: 351/1723 (20.4%)  
Placebo: 320/1722 (18.6%)

Number at risk:
- Spironolactone: 1722, 1502, 1168, 870, 614, 330, 53
- Placebo: 1723, 1462, 1145, 834, 581, 331, 53

TOPCAT Placebo Rates:
Primary Outcome, by region

US, Canada, Argentina, Brazil
Placebo: 280/881 (31.8%)

Russia, Rep Georgia
Placebo: 71/842 (8.4%)

TOPCAT spironolactone for HFpEF ≥45%

Marked regional differences in outcomes

Drug metabolites not present

Trial results obtained in Russia do not reflect the true therapeutic response to spironolactone

Hemodynamic-Guided HF Management

Cardiomems™ HF System

Pulmonary Artery Pressure Sensor

Patient Electronics System

Merlin.net™ PCN

Target location for PA pressure sensor

Progressive Rise in Filling Pressures Leads to Hospitalization

Transition from Chronic Compensated to Acute Decompensated HF

PURPOSE
Evaluate the safety and efficacy of the CardioMEMS™ HF System in reducing HF related hospitalizations in NYHA class III heart failure patients.

Treatment group managed to target PA pressures:
Systolic 15 – 35 mmHg
Diastolic 8 – 20 mmHg
Mean 10 – 25 mmHg

Primary Endpoint: Rate of HF hospitalization

Secondary Endpoints:
- Change in PA pressure at 6 months
- No. of pts admitted to hospital for HF
- Days alive outside of hospital
- QOL (MLHFQ)

Hemodynamic-Guided HF Management

CHAMPION (n=550)


At Risk
Treatment 270
Control 280

HF Hospitalizations, no.

RRR=30%
P<0.001

RRR=39%
P<0.001
HFpEF pts made up 22% of the trial cohort

**PURPOSE**
Evaluate the effect of PA pressure-guided therapy with the CardioMEMS™ HF System in patients with preserved ejection fraction (EF ≥ 40%), a group with no clinically proven therapies.

HF Hospitalization Reduction (18 mo follow-up)

- n=115, p=0.0004

<table>
<thead>
<tr>
<th>Condition</th>
<th>Reduction</th>
<th>HR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFpEF</td>
<td>RRR 46%</td>
<td>0.54</td>
<td>0.38-0.70</td>
</tr>
<tr>
<td>HFrEF</td>
<td>RRR 24%</td>
<td>0.76</td>
<td>0.61-0.91</td>
</tr>
</tbody>
</table>

Angiotensin Receptor Neprilysin Inhibition in Heart Failure With Preserved Ejection Fraction (PARAGON-HF Trial)
Treatment for Heart Failure with preserved ejection fraction

- **valsartan/sacubitril**: PARAGON-HF n=4600 enrolling

- phase III
- EF ≥ 45%, NYHA II–IV, LA enlarged or LV hypertrophy
- Composite: CV death and total HF hospitalizations

NCT01920711

PARAMOUNT HF
*Lancet* Vol 380, No. 9851, p1387–1395
Increased LAP (Left Atrial Pressure)
The Common denominator in HFpEF

VARIOUS TRIGGERS CAN CAUSE SUSCEPTIBILITY TO HFPEF

- Environment / Diet
- Comorbidities
- Genetic

INCREASED LAP

HFpEF

EXERCISE INTOLERANCE

VOLUME OVERLOAD

PULMONARY HYPERTENSION OR HEART FAILURE

Shah SJ. JACC 2013
Inter Atrial Shunt Device (IASD)
Change in PCWP: Baseline to 1 month

**CONTROL**

**IASD**

![Graph showing changes in PCWP (mmHg) from baseline to 1 month for CONTROL and IASD groups.](image-url)
REDUCE-LAP HF I Study Results

A Transcatheter InterAtrial Shunt Device for the Treatment of Heart Failure with Preserved Ejection Fraction (REDUCE LAP-HF I): A Phase 2, Randomized, Sham-Controlled Trial

Ted Feldman, MD; Laura Mauri, MD, MSc; Rami Kahwash, MD; Sheldon Liban, MD; Mark J. Ricciardi, MD; Pim van der Harst, MD, PhD; Martin Penicka, MD, PhD; Peter S. Fiall, MD; David M. Kaye, MD, PhD; Mark C. Petrie, MB, ChB, MRCP; Anupam Basuray, MD; Scott L. Hummel, MD, MS; Rhonda M. Davis, MD; P. Joseph M. Massaro, PhD; Daniel Burkoff, MD, PhD; Sanjiv J. Shah, MD; for the REDUCE LAP-HF I Investigators

The IASD Procedure was successful and safe, no adverse events or death

Treatment group resulted in greater reduction in PCWP during exercise and elevated leg position when compared to sham group

This hemodynamic study demonstrates the beneficial mechanistic effect of the IASD

The IASD could have beneficial clinical effects in patients with HFpEF and HF mid-range EF

REDUCE LAP-HF II pivotal trial is underway (NCT03088033)

Conclusions

- Up to 50% of patients with HF have preserved LVEF (HFpEF)
- Morbidity and mortality in HFpEF and HFrEF as similar
- Comorbidities are frequent both in HFpEF and HFrEF
- There is **no specific proven treatment for HFpEF**
  - Sacubitril valsartan is being evaluated in the PARAGON HF trial
  - Aggressive management of hypertension and all comorbidities should be implemented
- The future identification of successful therapies for HFpEF will require defining specific phenotypes of HFpEF with targeted therapy addressing unique mechanisms
Advanced Heart Failure GUIDELINES

Stage IV Heart Failure

Advanced Therapies
- Ventricular Assist Device
- Heart Transplantation

Standard Medical and Device Therapies
- Beta Blockers, ACE Inhibitors, Spironolactone, ARBs, ICDs, CRT

Palliative Care
- Symptom Management and Psychosocial Support

“The high mortality in both the inotrope groups warrants clinicians to carefully consider all options and priorities for further care.”

Survival at 6 months: 47%  [95% CI, 38% to 56%]
IABP        Impella          TandemHeart          ECMO / ECLS
Impella 2.5    Impella CP        Impella 5.0                   Impella RP*

Percutaneous mechanical support options
V-V                       V-A
* Investigational device
Physiologic Impact of Impella
Impella 5.0L Axillary

- 58 yo CAD, MR, TR, EF 15% pre transplant, IABP
- PA 77/50 (59) PCW 40
  - TPG 19 CO 4 PVR 5
  - +3 TR Mod RV dysfunc
- Impella 5 R axillary art
- POD 2 RA 8 PA 40/24 (30)
  PCW 18 TPG 12 CO 6 PVR 2
- POD 7 HM3 LVAD
Background

- Continuous-flow Left Ventricular Assist Systems (LVAS) improve survival and quality of life in patients with advanced heart failure refractory to medical therapy.¹

The HeartMate II LVAS is a mechanical bearing axial continuous-flow blood pump; An LVAS approved for both Bridge-To-Transplant (BTT) and Destination Therapy (DT) patients

Background

• LVAS, such as the HeartMate II, are associated with significant risk of pump thrombosis requiring pump exchange, limiting long-term durability

• Other major adverse events of concern with LVAS devices include stroke, bleeding and device related infection\(^1\)

HeartMate 3 LVAS

- **Wide** blood-flow passages to reduce shear stress
- **Frictionless** with absence of mechanical bearings
- **Intrinsic Pulse** designed to reduce stasis and avert thrombosis
Heart Mate3 LVAD Pulsatility
Two-Year Outcomes of a Magnetically Levitated Cardiac Pump in Heart Failure


Available now on www.nejm.org
Primary End Point Analysis (ITT)

Survival at 2 years free of disabling stroke (>3 mRS) or reoperation to replace or remove a malfunctioning device

![Graph showing survival rates over time for HeartMate II and HeartMate III, with hazard ratio and P-value for superiority analysis.]

Superiority Analysis
Hazard ratio, 0.46 (95% CI, 0.31-0.69)  
P<0.001 by log-rank test

No. at Risk
HeartMate III 190 161 141 122 111
HeartMate II 176 134 114 90 75

mRS denotes modified Rankin Score; CI, confidence interval
Primary Endpoint Component 1
Overall Survival

Survival similar to heart transplant

HR = 0.71 (95% CI: 0.44 - 1.15)
P = 0.16 by log-rank test
Primary Endpoint Component 2
Freedom from Disabling Stroke

HeartMate II
- 100
- 96.8%
- 94.5%
- 92.8%

HeartMate 3
- 100
- 96.8%
- 93.3%
- 92.5%

HR = 1.25 (95% CI: 0.54 - 2.93)
P = 0.60 by log-rank test

No. at Risk
HeartMate 3: 189, 162, 142, 123, 114
HeartMate II: 172, 139, 121, 97, 84

HR denotes hazard ratio; CI, confidence interval
Primary Endpoint Component 3
Freedom from Reoperation to Replace or Remove Pump

- There was a ten-fold difference in the reoperation rate between HeartMate II and HeartMate 3

- HeartMate 3 reoperations were due to infection (1), electrical fault (1), and outflow-graft twist (1)

- 2/3rd of HeartMate II reoperations were due to “pump thrombosis or severe hemolysis”

No. at Risk
HeartMate 3 189 164 145 126 114
HeartMate II 172 135 114 90 76

HR = 0.10 (95% CI: 0.03 - 0.27)
P < 0.0001 by log-rank test
# Key Adverse Events

## Pump Thrombosis, Neurological Events, Bleeding

<table>
<thead>
<tr>
<th>Event</th>
<th>HeartMate 3 (n=189)</th>
<th>HeartMate II (n=172)</th>
<th>HR (95% CI)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected or confirmed pump thrombosis</td>
<td>2 (1.1) 2</td>
<td>27 (15.7) 33</td>
<td>0.06 (0.01-0.26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resulting in reoperation</td>
<td>0 (0) 0</td>
<td>21 (12.2) 25</td>
<td>NA</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any stroke</td>
<td>19 (10.1) 22</td>
<td>33 (19.2) 43</td>
<td>0.47 (0.27-0.84)</td>
<td>0.02</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>12 (6.3) 14</td>
<td>23 (13.4) 26</td>
<td>0.44 (0.22-0.88)</td>
<td>0.03</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>8 (4.2) 8</td>
<td>16 (9.3) 17</td>
<td>0.42 (0.18-0.98)</td>
<td>0.06</td>
</tr>
<tr>
<td>Other neurologic event*</td>
<td>22 (11.6) 25</td>
<td>15 (8.7) 16</td>
<td>1.27 (0.66-2.45)</td>
<td>0.39</td>
</tr>
<tr>
<td>Bleeding</td>
<td>81 (42.9) 187</td>
<td>90 (52.3) 206</td>
<td>0.71 (0.53-0.96)</td>
<td>0.07</td>
</tr>
<tr>
<td>Bleeding that led to surgery</td>
<td>23 (12.2) 29</td>
<td>30 (17.4) 34</td>
<td>0.66 (0.38-1.13)</td>
<td>0.18</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>51 (27.0) 107</td>
<td>47 (27.3) 100</td>
<td>0.92 (0.62-1.37)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

HR denotes hazard ratio; CI, confidence interval

*P values were calculated with the use of Fisher's exact test. *Includes transient ischemic attacks and neurologic events other than stroke.
Key Adverse Events

Stroke

Stroke Severity

<table>
<thead>
<tr>
<th></th>
<th>HeartMate 3 (N = 189)</th>
<th>HeartMate II (N = 172)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Disabling Stroke (Modified Rankin Score 0-3)</td>
<td>6 (3%)</td>
<td>24 (14%)</td>
</tr>
<tr>
<td>Disabling Stroke (Modified Rankin Score 4-5)</td>
<td>6 (3%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Stroke Related Death (Modified Rankin Score 6)</td>
<td>7 (4%)</td>
<td>6 (3%)</td>
</tr>
</tbody>
</table>

Proportion of Patients with Stroke (%)

- HeartMate 3: 10% (95%CI: 6%-14%) n = 19 (22 events)
- HeartMate II: 19% (95%CI: 13%-25%) n = 33 (43 events)

P = 0.016

Two HeartMate 3 subjects and 9 HeartMate II subjects had >1 stroke. The score for the most severe stroke is shown. 1.6% of HeartMate 3 subjects (n = 3) and 5.2% of HeartMate II subjects (n = 5) had a modified Rankin score of 0 at 60 days post-stroke. CI denotes confidence interval.
Conclusions

- The HeartMate 3 LVAS is **clinically superior** when compared to the HeartMate II axial-flow pump, at 2-years

- These benefits were primarily driven by a **lower reoperation rate** in the HeartMate 3 arm
  - largely due to excess device malfunctions resulting from **pump thrombosis** in the HeartMate II LVAS

- Importantly, we observed a markedly **lower rate of stroke** with the HeartMate 3 LVAS
Thank You

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