Approach to Heart Failure in 2018: What Do the Recent Guidelines Tell Us?

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Associate Director, CV Research Institute
Baylor College of Medicine, Houston, TX
Outline

- Guidelines for HFrEF
  - New Therapies: ARNI, Ivabradine
  - HTN
  - Anemia
  - Sleep Apnea
- HFrpEF
- HFmEF
- Diabetes
- Biomarkers
HF Guidelines: AHA/ACC/HFSA and ESC

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

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

Clinical Practice Guideline: Focused Update

2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

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Heart Failure

Neprilysin Inhibition and ARNI
NEP is a zinc dependent membrane endopeptidase that cleaves peptides containing up to 40–50 amino acids. It hydrolyzes a variety of substrates, including natriuretic peptides (ANP, BNP, CNP), Bradykinin, Substance P, and Adrenomedullin.
NEP is a zinc dependent membrane endopeptidase. It cleaves peptides containing up to 40–50 amino acids. Examples include:

- Angiotensin II
- Endothelin I
- Neurotensin
- Bradykinin
- Substance P
- Adrenomedullin

Additionally, NEP is involved in the degradation of natriuretic peptides (ANP, BNP, CNP).
NEP is a zinc dependent membrane endopeptidase that cleaves peptides containing up to 40–50 amino acids.
NEP is a zinc dependent membrane endopeptidase that cleaves peptides containing up to 40–50 amino acids.
Balance of NEP Inhibition

Reduced breakdown of ANP, BNP, CNP, Vasodilation, ↓ Fibrosis, ↓ Hypertrophy

Reduced breakdown of angiotensin II, (endothelin I) Vasoconstriction, ↑ Fibrosis, ↑ Hypertrophy

The antihypertensive effects may be offset by an increased activity of the RAAS and sympathetic nervous system and/or by downregulation of ANP receptors.

Neprilysin inhibition alone

- Mixed results due to potentiation of angiotensin

NEP + ACE inhibition

- Potentiation of angioedema

Nep Inh + ARB

- ?
Mechanisms of Action of ARNI

Natriuretic Peptides

Pro-BNP → BNP → NT-proBNP

Angiotensinogen → Angiotensin I → Angiotensin II

AT$_1$ Receptor

Sacubitril

Valsartan

↓ BP, Vasodilation
↓ Fibrosis
↓ Hypertrophy

*NT-proBNP not a neprilysin substrate

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*

- NYHA class II-IV (<1 % NYHA IV)
- LVEF ≤ 40% then ≤35%:
- BNP ≥ 150 (or NT-proBNP ≥ 600)
- β-blockers, MRA,
- **ACEi of ARB ≅ enalapril 10 mg/d ≥4 wks**
- SBP ≥ 95 mm Hg, eGFR ≥ 30, K ≤ 5.4 mEq/L

8442 Patients

LCZ696 (200 mg twice daily) or enalapril (10 mg twice daily)
10,513 patients screened
a single-blind run-in
enalapril (10 mg bid x 2 weeks), if tolerated;

- 10% (n=1102) dropped out
  (hypotension, cough, hyperkalemia, renal dysfunction)

single-blind run-in
period LCZ696 x 4-6 weeks (100 mg bid then escalated to 200mg bid)

- another 10% dropped out (n=977)
  (hypotension, cough, hyperkalemia, renal dysfunction)

if tolerated, then randomized (n=8442)

- 17.8% of LCZ696
- 19.8% of enalapril discontinued
PARADIGM-HF: CV Death or HF Hospitalization (Primary Endpoint)

Kaplan-Meier Estimate of Cumulative Rates (%)

Enalapril (n=4212)

LCZ696 (n=4187)

HR = 0.80 (0.73-0.87)
P = 0.0000002
Number needed to treat = 21

Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>LCZ696</th>
<th>3663</th>
<th>3018</th>
<th>2257</th>
<th>1544</th>
<th>896</th>
<th>249</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enalapril</td>
<td>4212</td>
<td>3579</td>
<td>2922</td>
<td>2123</td>
<td>1488</td>
<td>853</td>
<td>236</td>
</tr>
</tbody>
</table>

PARADIGM-HF: Other Key Endpoints

# PARADIGM-HF: Adverse Events

<table>
<thead>
<tr>
<th>Prospectively identified adverse events</th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic hypotension</td>
<td>588 (14%)</td>
<td>388 (9.2%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Serum potassium &gt; 6.0 mmol/l</td>
<td>181 (4.3%)</td>
<td>236 (5.6%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Serum creatinine ≥ 2.5 mg/dl</td>
<td>139 (3.3%)</td>
<td>188 (4.5%)</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>Discontinuation for adverse event</td>
<td>449</td>
<td>516</td>
<td>0.02</td>
</tr>
<tr>
<td>Discontinuation for hypotension</td>
<td>36</td>
<td>29</td>
<td>NS</td>
</tr>
<tr>
<td>Discontinuation for hyperkalemia</td>
<td>11</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>Discontinuation for renal impairment</td>
<td>29</td>
<td>59</td>
<td>0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Angioedema (adjudicated)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Medications, no hospitalization</td>
<td>16 (0.3%)</td>
<td>9 (0.2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hospitalized; no airway compromise</td>
<td>3 (0.1%)</td>
<td>1 (&lt;0.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Airway compromise</td>
<td>0</td>
<td>0</td>
<td>----</td>
</tr>
</tbody>
</table>

Angioedema in OVERTURE 0.5 %, OCTAVE 0.68 %
<table>
<thead>
<tr>
<th>NAME</th>
<th>TITLE</th>
<th>Primary End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARAGON-HF</td>
<td>Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in HFP EF</td>
<td>CV death and HF hospitalizations</td>
</tr>
<tr>
<td>TITRATION</td>
<td>Safety and Tolerability of Initiating LCZ696 in Heart Failure Patients 200 mg twice daily (bid) over 3 weeks vs 6 weeks</td>
<td>Hypotension, Renal Dysfunction, Hyperkalemia and Angioedema</td>
</tr>
<tr>
<td>PARABLE</td>
<td>ARNI in Asymptomatic Patients With Elevated Natriuretic Peptide and Elevated Left Atrial Volume</td>
<td>impact on LV diastolic function</td>
</tr>
<tr>
<td>PIONEER</td>
<td>comParison Of Sacubitril/valsartaN Versus Enalapril on Effect on ntpRo-bnp in Patients Stabilized From an Acute Heart Failure Episode</td>
<td>Change from baseline in NT-proBNP (hypotension, hyperkalemia, angioedema)</td>
</tr>
<tr>
<td>PARASAIL</td>
<td>Description of Tolerability of LCZ696 (Sacubitril / Valsartan) in Heart Failure With Reduced Ejection Fraction (HFR EF) Treated in Real Life Setting (PARASAIL) in CANADA</td>
<td>% Pts tolerated LCZ696 at the dose of 97.2 mg sacubitril / 102.8 mg valsartan bid at month 6</td>
</tr>
</tbody>
</table>

Source: ClinicalTrials.gov
# 2017 ACC/AHA/HFSA Update: Recommendations for Stage C HFrEF

## 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 <strong>ACE inhibitors (LOE:A)</strong>, <strong>OR ARBs (LOE: A)</strong>, <strong>OR ARNI (Level of Evidence: B-R)</strong> in conjunction with evidence based beta blockers, and aldosterone antagonists in selected patients, is recommended for patients with chronic HFr EF to reduce morbidity and mortality</td>
</tr>
<tr>
<td></td>
<td>ARB: A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ARNI: B-R</td>
<td></td>
</tr>
</tbody>
</table>

2017 ACC/AHA/HFSA Update: Recommendations for Stage C HFrEF

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<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>ACE: A</td>
<td>The use of ACE inhibitors is beneficial for patients with prior or current symptoms of chronic HFr EF to reduce morbidity and mortality</td>
</tr>
<tr>
<td>I</td>
<td>ARB: A</td>
<td>The use of ARBs to reduce morbidity and mortality is recommended in patients with prior or current symptoms of chronic HFr EF who are intolerant to ACE inhibitors because of cough or angioedema</td>
</tr>
<tr>
<td>I</td>
<td>ARNI: B-R</td>
<td>In patients with chronic symptomatic HFr 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</td>
</tr>
<tr>
<td>III: Harm</td>
<td>B-R</td>
<td>ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor</td>
</tr>
<tr>
<td>III: Harm</td>
<td>C-EO</td>
<td>ARNI should not be administered to patients with a history of angioedema</td>
</tr>
</tbody>
</table>

Treatment of HFrEF Stage C and D

† The combination of ISDN/HYD with ARNI has not been robustly tested. BP response should be carefully monitored.


ESC HF Guidelines. Ponikowsky et al EHJ 2016
Heart Failure

Ivabradine
Ivabradine: Specific and Selective Inhibitor of the $I_f$ Ion Channel

$I_f$ ion channel (the funny current) is highly expressed in spontaneously active cardiac regions, such as the sinoatrial node, the AV node, and the Purkinje fibers. The funny current is a mixed Na/K current that activates upon hyperpolarization at voltages in the diastolic range.
SHIFT Study Design

- Patients >18 years old
- NSR and HR ≥70 bpm
- NYHA FC II-IV and stable on meds for ≥4 weeks
- LVEF ≤35%
- On target or maximally tolerated doses of BBs
- Hospitalization for HF in ≤12 mo

14-day run-in

N=6558

Median follow-up duration 22.9 months

N=3268

Ivabradine
5 mg bid x 2 weeks, then 7.5 mg bid

Placebo bid
N=3290

BB, beta-blocker; bpm, beats per minute; HF, heart failure; HR, heart rate; LVEF, left ventricular ejection fraction; meds, medications; mo, months; NSR, normal sinus rhythm; NYHA FC, New York Heart Association functional classification. Swedberg K, et al. Lancet. 2010;376(9744):875-885.
Heart Rate Modulation with Ivabradine - The Systolic HF treatment with the If inhibitor Ivabradine Trial SHIFT Trial

**CV Mortality & HF Hospitalization**

A

- Placebo (937 events)
- Ivabradine (793 events)

HR 0.82 (95% CI 0.75–0.90), p<0.0001

**HF Hospitalization**

B

- Placebo (672 events)
- Ivabradine (514 events)

HR 0.74 (95% CI 0.66–0.83), p<0.0001

NYHA II–IV, EF < 35%, SR rate of ≥70 b.p.m. background therapy β-blocker (90%), and an MRA (60%) Only 26% of patients were on full-dose β-blocker

Heart Rate Modulation with Ivabradine - The Systolic HF treatment with the If inhibitor ivabradine Trial SHIFT Trial

No significant reduction in all cause or CV mortality

CV Mortality

B

All cause mortality

Effect of ivabradine in prespecified subgroups

- **Age**: <65 years, ≥65 years
- **Sex**: Male, Female
- **Beta-blockers**: No, Yes
- **Aetiology of heart failure**: Non-ischaemic, Ischaemic
- **NYHA class**: NYHA class II, NYHA class III or IV
- **Diabetes**: No, Yes
- **Hypertension**: No, Yes
- **Baseline heart rate**: <77 bpm, ≥77 bpm

### Incidence of selected adverse events

<table>
<thead>
<tr>
<th>Patients with an event</th>
<th>Ivabradine N=3232, n (%)</th>
<th>Placebo N=3260, n (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All serious adverse events</td>
<td>1450 (45%)</td>
<td>1553 (48%)</td>
<td>0.025</td>
</tr>
<tr>
<td>All adverse events</td>
<td>2439 (75%)</td>
<td>2423 (74%)</td>
<td>0.303</td>
</tr>
<tr>
<td>Symptomatic bradycardia</td>
<td>150 (5%)</td>
<td>32 (1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Asymptomatic bradycardia</td>
<td>184 (6%)</td>
<td>48 (1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>306 (9%)</td>
<td>251 (8%)</td>
<td>0.012</td>
</tr>
<tr>
<td>Phosphenes</td>
<td>89 (3%)</td>
<td>17 (1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>17 (1%)</td>
<td>7 (&lt;1%)</td>
<td>0.042</td>
</tr>
</tbody>
</table>

**Indications for Use: Ivabradine (FDA)**

- To reduce hospitalization risk for worsening HF in patients with stable, symptomatic chronic HF with LVEF ≤35% in sinus rhythm with resting HR of ≥70 bpm or higher\(^1,2\)
  - **AND** on maximally tolerated doses of beta-blockers
  - **OR** have a contraindication to beta-blocker use

- **Contraindications:**
  - Acute decompensated HF
  - BP <90/50 mm Hg
  - Sick sinus syndrome
  - Sinoatrial or third-degree AV block*\(^*\)

- **Most common (≥1%) adverse events:**
  - Bradycardia, HTN, AF, and temporary vision disturbances

*Unless a functioning demand pacemaker is present.

AF, atrial fibrillation; AV, atrioventricular; BP, blood pressure; HTN, hypertension.

2. US Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products [drug label].
2017 ACC/AHA/HFSA Update: Recommendations for Stage C HFrEF

Recommendations for Ivabradine

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<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 HFr EF (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.</td>
</tr>
</tbody>
</table>

2016 ESC HF Guidelines

<table>
<thead>
<tr>
<th>If-channel inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivabradine should be considered to reduce the risk of HF hospitalization or cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE-I (or ARB), and an MRA (or ARB).</td>
</tr>
<tr>
<td>IIa</td>
</tr>
<tr>
<td>Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm who are unable to tolerate or have contra-indications for a beta-blocker. Patients should also receive an ACE-I (or ARB) and an MRA (or ARB).</td>
</tr>
<tr>
<td>IIa</td>
</tr>
</tbody>
</table>

**2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction**

A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways

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**TABLE 6** Triggers for HF Patient Referral to a Specialist/Program

**TABLE 7** Essential Skills for a Heart Failure Team

**TABLE 8** Infrastructure to Support Team-Based HF Care

**TABLE 10** Interventions to Improve Adherence

**TABLE 11** Ten Considerations to Improve Adherence

**TABLE 12** Specific Patient Cohorts in HF Care

**TABLE 13** Tactics for Managing Costs of HF

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- 2017 ACC Expert Consensus Decision Pathway for Optimization of HF Treatment,
- 2017 ACC/AHA/HFSA Focused Update of HF Guidelines
- 2013 ACCF/AHA Guideline for the Management of Heart Failure.

http://tools.acc.org/TreatHF/#!/content/evaluate
Heart Failure

HF-pEF
<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I</strong></td>
<td>C</td>
<td><strong>Diuretics</strong> should be used for relief of symptoms due to volume overload</td>
</tr>
<tr>
<td><strong>I</strong></td>
<td>B</td>
<td><strong>Systolic and diastolic BP</strong> should be controlled in patients with <strong>HFpEF</strong> in accordance with published clinical practice guidelines to prevent morbidity</td>
</tr>
<tr>
<td><strong>IIa</strong></td>
<td>C</td>
<td><strong>Coronary revascularization</strong> is reasonable in patients with <strong>CAD</strong> in whom symptoms (angina) or demonstrable myocardial ischemia having an adverse effect on symptomatic <strong>HFpEF</strong> despite GDMT.</td>
</tr>
<tr>
<td><strong>IIa</strong></td>
<td>C</td>
<td><strong>Management of AF</strong> according to published clinical practice guidelines in patients with <strong>HFpEF</strong> is reasonable to improve symptomatic <strong>HF</strong>.</td>
</tr>
<tr>
<td><strong>IIa</strong></td>
<td>C</td>
<td>The use of <strong>beta-blocking agents, ACE inhibitors, and ARBs</strong> in patients with <strong>hypertension</strong> is reasonable to control <strong>BP</strong> in patients with <strong>HFpEF</strong>.</td>
</tr>
</tbody>
</table>
Spironolactone for Heart Failure with Preserved Ejection Fraction

TOPCAT

Combined endpoint of death, aborted cardiac death

Hazard ratio, 0.89 (95% CI, 0.77–1.04)
P = 0.14 by log-rank test

Estimated Cumulative Proportion of Patients Hospitalized for Heart Failure

Hazard ratio, 0.83 (95% CI, 0.69–0.99)
P = 0.04 by log-rank test

16 % RR
Pharmacological Treatment for Stage C HF With Preserved EF

<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 or Hfadm/year, eGFR &gt;30 mL/min, creatinine &lt;2.5 mg/dL, K &lt;5.0 mEq/L), aldosterone receptor antagonists might be considered to decrease hospitalizations.</td>
</tr>
</tbody>
</table>

110 patients with HFEF ≥50% randomized to either isosorbide mononitrate or placebo
no beneficial effects on activity levels, QoL, exercise tolerance, or NT-proBNP levels.

PDE-5 inh augments the NO by upregulating cGMP
Randomized 216 patients with HFEF ≥50% on and pVo2 <60% to sildenafil or placebo.
No improvement in O2 consumption or exercise tolerance
<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb</td>
<td>B</td>
<td>The use of ARBs might be considered to decrease hospitalizations for patients with HFpEF.</td>
</tr>
<tr>
<td>III: No Benefit</td>
<td>B-R</td>
<td>Routine use of nitrates or PDE-5 inhibitors to increase activity or QoL in patients with HFpEF is ineffective.</td>
</tr>
</tbody>
</table>
Heart Failure

Mid-Range LVEF
GWTG-HF data linked to Medicare data, ~ 40 k pts,

All 3 groups had similar 5-year mortality (HFrEF 75.3% vs. HFpEF 75.7%; HFbEF 75.7%) CVH and HFH higher in HFrEF and HFbEF compared with those with HFpEF
The Beta-blockers in Heart Failure Collaborative Group (BBmeta-HF) pool individual patient data from 11 major HF RCTs: Australia/New Zealand Heart Failure Study (ANZ), BEST, CAPRICORN, CHRISTMAS, CIBIS I, CIBIS II, COPERNICUS, MDC, MERIT-HF, SENIORS, U.S. Carvedilol HF Program (US-HF)

- to determine efficacy of beta blockers in mid range and preserved EF and also atrial fibrillation patients
- Though guidelines suggest to treat mid-range EF as HF-PEF, in practice most of these patients are treated as HFrEF
- 14262 patients in sinus rhythm, 3050 patients in atrial fibrillation
- Pts with baseline LVEF and ECG showing either sinus rhythm or AF/atrial flutter included
β-blockers improve outcomes for all pts with HF any reduced EF and in SR. Most robust for LVEF<40%, but similar benefit in LVEF 40–49 %
Heart Failure

Hypertension
## Hypertension Management in HF

**ACC, AHA, HFSA HF Guidelines**

<table>
<thead>
<tr>
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<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 BP in those with HTN should be (&lt;130/80) mm Hg.</td>
</tr>
<tr>
<td>I</td>
<td>C-EO</td>
<td>Patients with HFpEF and HTN should be prescribed GDMT titrated to attain (SBP &lt; 130) mm Hg.</td>
</tr>
<tr>
<td>I</td>
<td>C-LD</td>
<td>Patients with HFpEF &amp; persistent HTN after management of volume overload should be prescribed GDMT to attain (SBP&lt;130) mm Hg</td>
</tr>
</tbody>
</table>

### Recommendations for BP Goal for Patients With Hypertension

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td><strong>SBP:</strong> B-R&lt;sup&gt;SR&lt;/sup&gt;</td>
<td>For adults with confirmed hypertension and known CVD or 10-year ASCVD event risk of 10% or higher a BP target of less than 130/80 mm Hg is recommended.</td>
</tr>
<tr>
<td></td>
<td><strong>DBP:</strong> C-EO</td>
<td></td>
</tr>
<tr>
<td>IIb</td>
<td><strong>SBP:</strong> B-NR</td>
<td>For adults with confirmed hypertension, without additional markers of increased CVD risk, a BP target of less than 130/80 mm Hg may be reasonable.</td>
</tr>
<tr>
<td></td>
<td><strong>DBP:</strong> C-EO</td>
<td></td>
</tr>
</tbody>
</table>
BP Thresholds for and Goals of Pharmacological Therapy in Patients With Hypertension According to Clinical Conditions

<table>
<thead>
<tr>
<th>Clinical Condition(s)</th>
<th>BP Threshold, mm Hg</th>
<th>BP Goal, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical CVD or 10-year ASCVD risk ≥10%</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>No clinical CVD and 10-year ASCVD risk &lt;10%</td>
<td>≥140/90</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Older persons (≥65 years of age; noninstitutionalized, ambulatory, community-living adults)</td>
<td>≥130 (SBP)</td>
<td>&lt;130 (SBP)</td>
</tr>
<tr>
<td>Specific comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Chronic kidney disease after renal transplantation</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td><strong>Heart failure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable ischemic heart disease</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Secondary stroke prevention</td>
<td>≥140/90</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Secondary stroke prevention (lacunar)</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
</tbody>
</table>

ASCVD indicates atherosclerotic cardiovascular disease; BP, blood pressure; CVD, cardiovascular disease; and SBP, systolic blood pressure.
Heart Failure

Anemia
# Stages of Iron Deficiency

<table>
<thead>
<tr>
<th></th>
<th>Stage I Prelatent</th>
<th>Stage II Latent</th>
<th>Stage III Anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>BM Iron</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Ferritin</td>
<td>&lt;12 ug/L</td>
<td>&lt;12 ug/L</td>
<td>&lt;12 ug/L</td>
</tr>
<tr>
<td>Hb</td>
<td>Normal</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>MCV</td>
<td>Normal</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
</tr>
</tbody>
</table>
459 patients NYHA II–III, LVEF < 40 %,
iron deficiency (ferritin level <100 μg/L or 100 - 300 μg/L, if the transferrin saturation was <20%), and a Hb 9.5 to 13.5 g/dL.

200 mg of IV ferric carboxy maltose or saline (placebo) for 24 weeks

50% reported being much or moderately improved vs 28% of placebo
Improvements in 6 MWT and QOL with FCM
Death, adverse events, and SAEs similar

Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency†

Piotr Ponikowski1,2*, Dirk J. van Veldhuisen3, Josep Comin-Colet4, Georg Ertl5,6, Thierry Voors1, John Cleland1, J. Philippe Cohn6,8, Robert M.Radovick9 & Norman D. Ezekowicz1,6

▪ 304 patients NYHA II –III, LVEF < 45 %, elevated natriuretic peptides
▪ iron deficiency (ferritin level <100 μg / L or or 100 - 300 μg /L, if the transf saturation <20%).

▪ 200 mg of IV ferric carboxy maltose or
▪ saline (placebo) for 52 weeks

Primary End-Point

FCM prolonged 6MWT distance at 6 mo (difference FCM vs. placebo: 33 ± 11 m, P = 0.002)

Individual patient data from 4 RCTs of FCM vs placebo in patients with systolic HF & iron def

4 Studies 839 pts: FER-CARS-01 FAIR-HF EFFICACY-HF, CONFIRM-HF

**META-ANALYSIS-Anker 2018**

**Effects of ferric carboxymaltose on hospitalisations and mortality rates in iron-deficient heart failure patients: an individual patient data meta-analysis**

Stefan D. Anker\(^1\), Bridget-Anne Kirwan\(^2\), Dirk J. van Veldhuisen\(^4\), Gerasimos Filippatos\(^5\), Josep Comin-Colet\(^6\), Frank Ruschitzka\(^7\),

- **CV Mortality and CV Hospitalizations**

  ![Effectiveness and Safety of Ferric Carboxymaltose](image)

  - **IV iron associated with**
    - ↓ CV mortality & CV hosp (RR: 0.59; p=0.009)
    - ↓ CV mortality & HFH (RR 0.53, p = 0.011)
    - All cause mortality and recurrent CV Hosp (RR 0.6, p = 0.009)
    - No increase in adverse events

  Anker S. BA, at al. Eur J Heart Fail.2018;20:125-133
No efficacy with oral iron in HF in clinical trials

**ORAL IRON**

- Convenient, available and inexpensive, but oral iron is not absorbed well
- Elevated hepcidin prevents iron absorption
- Tolerability and compliance with oral iron is low due to GI side effects

**IRON-OUT HF**

- largest phase 2, double blind RCT
- 225 patients with NYHA class II-IV HF with HFrEF
- Hb 9-15 g/dL (men) or 9-13.5 g/dL (women) and ID (ferritin 15-100 ug/L or 100-299 ug/L with TSAT <20%)
- oral iron polysaccharide 150 mg twice daily or placebo

At 16 weeks, there was no significant difference in
- primary end point: change in peak VO2 from baseline,
- Or secondary endpoints: 6MWD, NT-proBNP levels or KCCQ score
- oral iron increased TSAT, ferritin and hepcidin, and reduced soluble transferrin receptor levels

Possible Explanations for Failure of Oral Iron in HF

- Inadequate repletion of iron stores with oral iron despite large doses
- Higher hepcidin levels associated with less improvement in TSAT and ferritin
- Higher hepcidin levels inhibit duodenal iron absorption

<table>
<thead>
<tr>
<th>STUDY</th>
<th>Total Iron Dose</th>
<th>TSAT increase</th>
<th>Ferritin Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORAL IRON-OUT</td>
<td>33.6 gm</td>
<td>3 %</td>
<td>11 ug/L</td>
</tr>
<tr>
<td>IV FAIR-HF</td>
<td>2 gm</td>
<td>11.3 %</td>
<td>259.5 ug/L</td>
</tr>
</tbody>
</table>
Treatment of Anemia with Darbepoetin Alfa in Systolic Heart Failure

Karl Swedberg, M.D., Ph.D., James B. Young, M.D., Inder S. Anand, M.D., Sunfa Cheng, M.D., Akshay S. Desai, M.D., Rafael Diaz, M.D., Aldo P. Maggioni, M.D., John J. V. McMurray, M.D., Christopher O’Connor, M.D., Marc A. Pfeffer, M.D., Ph.D., Scott D. Solomon, M.D., Yan Sun, M.S., Michal Tendera, M.D.

A Primary Composite Outcome

(death or HF hospitalization)

P=0.87 by stratified log-rank test

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Darbepoetin alfa</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1142</td>
<td>1136</td>
</tr>
<tr>
<td>1</td>
<td>1136</td>
<td>1093</td>
</tr>
<tr>
<td>2</td>
<td>1093</td>
<td>1073</td>
</tr>
<tr>
<td>3</td>
<td>1073</td>
<td>1048</td>
</tr>
<tr>
<td>4</td>
<td>1048</td>
<td>1031</td>
</tr>
<tr>
<td>5</td>
<td>1031</td>
<td>1021</td>
</tr>
</tbody>
</table>

Years since Randomization

### Recommendations

<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%), <strong>IV iron replacement</strong> might be reasonable to improve functional status and QoL.</td>
</tr>
<tr>
<td>III: No Benefit</td>
<td>B-R</td>
<td>In patients with HF and anemia, <strong>erythropoietin-stimulating agents</strong> should not be used to improve morbidity and mortality.</td>
</tr>
</tbody>
</table>

Heart Failure

Sleep Anemia
<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</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.</td>
</tr>
<tr>
<td>IIb</td>
<td>B-R</td>
<td>In patients with cardiovascular disease and obstructive sleep apnea, CPAP may be reasonable to improve sleep quality and daytime sleepiness.</td>
</tr>
<tr>
<td>III: Harm</td>
<td>B-R</td>
<td>In patients with NYHA class II–IV HFrEF and central sleep apnea, adaptive servo-ventilation causes harm.</td>
</tr>
</tbody>
</table>
Heart Failure

Diabetes / Metabolic Syndrome
Other conditions that may lead to or contribute to HF, such as obesity, diabetes mellitus, tobacco use, and known cardiotoxic agents, should be controlled or avoided.

Yancy CW, Jessup M et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure, Circulation; 2013 Oct 15;128
<table>
<thead>
<tr>
<th>Glucose Lowering Agents</th>
<th>Incident HF Risk in High CV risk Patients</th>
<th>Outcomes in Established HF Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfanylurea</td>
<td>Not increased</td>
<td>No large scale RCT</td>
</tr>
<tr>
<td>Insulin</td>
<td>Possibly increased (residual confounding)</td>
<td>No large scale RCT</td>
</tr>
<tr>
<td>Metformin</td>
<td>Not increased</td>
<td>Reduced HFH / all cause mortality in population based retrospective cohorts, No large scale RCT</td>
</tr>
<tr>
<td>DPP4 inh (increase GLP-1)</td>
<td>Increased HF with saxagliptin (SAVOR-TIMI 53), no signal with others (TECOS, EXAMINE Trials)</td>
<td>Not studied</td>
</tr>
<tr>
<td>GLP-1 Agonists</td>
<td>No effect HF, Reduced CVD (LEADER, SUSTAIN trials)</td>
<td>Post ADHF discharge increased trend for HFH+ Mortality with liraglutide (FIGHT- NIH Trial)</td>
</tr>
<tr>
<td>SGLT2i</td>
<td>Reduced HFH, CVD, MACE (EMPA-REG, CANVAS Trials)</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>
Potential Mechanisms of Empagliflozin for Benefit in HF Outcomes

Oxidative stress

Cardio-renal protection

β-hydroxybutyrate as a "superfuel" oxidized by the heart in preference to fatty acids and glucose.

Blood pressure & arterial stiffness

Preload/afterload

Congestion Intravascular Volume

Osmotic diuresis and natriuresis

Neutral effect on sympathetic nervous system

Body weight & visceral adiposity

Uric acid

3-4 mmHg drop in SBP

Improved heart failure outcomes

outcome curves diverged early – hemodynamic effects rather than glucose control effects?

myocardial fuel/energetics hypothesis: ?, increase blood β-hydroxybutyrate a "superfuel" oxidized by the heart in preference to fatty acids and glucose, ? increase mechanical efficiency, prevent pro-hypertrophic transcription pathways.

From Pham D. et al. Trends in Cardiovascular Medicine Aug 4, 2016, Ferrannini et al., 2016; Mudaliar et al., 2016, Tahara et al.,2014, Aubert et al., 2016
Primary and Secondary Prevention of HF with SGLT2i

Stage A: At Risk HF
Stage B: Structural Heart Disease
Stage C: Prevalent HF
Stage D: Advanced HF

✓ ✓ ? ?
Heart Failure

Biomarkers
2017 ACC/AHA/HFSA Update: Biomarkers Indications for Use

For patients at risk of developing HF, natriuretic peptide biomarker–based screening followed by team-based care, including a cardiovascular specialist optimizing GDMT, can be useful to prevent the development of left ventricular dysfunction (systolic or diastolic) or new-onset HF.

**Biomarkers**

### Biomarkers for Diagnosis, Prognosis

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A</td>
<td>In patients presenting with dyspnea, measurement of natriuretic peptide biomarkers is useful to support a diagnosis or exclusion of HF.</td>
</tr>
<tr>
<td>I</td>
<td>A</td>
<td>Measurement of BNP or NT-proBNP is useful for establishing prognosis or disease severity in chronic HF.</td>
</tr>
<tr>
<td>I</td>
<td>A</td>
<td>Measurement of baseline levels of natriuretic peptide biomarkers and/or cardiac troponin on admission to the hospital is useful to establish a prognosis in acutely decompensated HF.</td>
</tr>
<tr>
<td>IIa</td>
<td>B-NR</td>
<td>During a hospitalization for HF, a predischarge natriuretic peptide level can be useful to establish a postdischarge prognosis.</td>
</tr>
<tr>
<td>IIb</td>
<td>B-NR</td>
<td>In patients with chronic HF, measurement of other clinically available tests, such as biomarkers of myocardial injury or fibrosis, may be considered for additive risk stratification.</td>
</tr>
</tbody>
</table>
894 of 1100 enrolled
- HFrEF prior HFH, NT-proBNP >2000 or BNP>400
- Target NT-proBNP < 1000 pg/mL
Change in NT-proBNP

Similar NP levels can be achieved with empirical adjustment in HFrEF medications
ADHF patients with NT-proBNP levels of > 1700

After achieving clinical stability, 405 pts randomized

Treatment to achieve 30% reduction in NT-proBNP

Conventional Treatment

https://doi.org/10.1161/CIRCULATIONAHA.117.029882
December 14, 2017
“Because of the absence of clear and consistent evidence for improvement in mortality and CV outcomes, there are insufficient data to inform specific guideline recommendations related to NP-guided therapy or serial measurements of BNP or NT-proBNP levels for the purpose of reducing hospitalization or deaths”

Individualization

- It is not ONE magical marker (example: rise in creatinine with successful decongestion not associated bad outcomes)
It is the ART of what we do with many markers

Unidirectional Heat Map Analysis of Potential Markers /Biomarkers: Phenomapping

*stretch, fibrosis, injury, cytokines/ proinflammatory neurohormones, cGMP, genetics, metabolomics, miRNA*
It is the ART of what we do with many markers representing multiple pathway targets, in relation to each other and journey of each organism.

Role of AI Technology?
## Heart Failure Stage C Treatment According to Pheno-groups

<table>
<thead>
<tr>
<th>Stage II HFrEF stable</th>
<th>Stage III frequent hosp/congestion</th>
<th>Stage III with LV+RV failure</th>
<th>Stage III HFrEF HTN</th>
<th>Stage II-III HFrEF and DM</th>
<th>Tachycardia/Injury Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximiz e GDMT ACEi, BB, then switch to ARNI</td>
<td>ACEi, BB, MRA, diuretics</td>
<td>ACEi, BB, MRA, diuretics</td>
<td>ACEI/ARB, BB, switch to ARNI, HYD+ISD N for MRA</td>
<td>ACEI/ARB, BB, switch to ARNI, SGLT2i</td>
<td>BB, ACEI</td>
</tr>
</tbody>
</table>
Anticipatory Management in Journey of the Patient-Stage C → Stage D

- Decongestion, maintaining QOL
- Treatment and prevention of precipitating factors
- Guideline driven medical treatment –
- Disease modifying approaches such as CRT
- Consideration for advanced care such as transplant / VAD
- Palliative Care, Decision making strategies, End of Life

HF Hospitalizations
Heart Failure

Stage C/D Treatment Strategies Need to be Individualized for

- Patient’s severity of illness and trajectory
- Responsiveness to therapy
- Goals of care
- Comorbidities and side effect profile
- Tolerability
- Phenogroups
Individualized / Precision Medicine in HF
Treat According to Etiology and Patient Preference

- Patient management should be individualized
- Other organ involvement/comorbidities help further refine targeted therapies
- Specific diagnoses usually warrant specific treatment strategies different than/in addition to GDMT
- Patient Preference, Toxicity and Tolerance Differ
- Further diagnostic strategies should be carried out to define specific etiology
- Guideline directed medical therapy is the foundation / scaffold of HF therapy, but needs to be built on

- scaffold/foundation alone may not be adequate
- each patient will likely need a different approach