HEART FAILURE: Current Concepts, Diagnosis and Management

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Roper St. Francis HealthCare
Coastal Cardiology, PA
Objectives

- Etiology and Diagnosis of Heart Failure
- Pathophysiology of Heart Failure
- Pharmacological Considerations
- Current Guidelines about Treatment of Comorbidities (2017 Focused Update)
- Cardio-Oncology
Facts About Heart Failure

- About 5.7 million U.S. adults have heart failure
- 50% of those patients will die in the next 5 years
- Heart failure costs about $30.7 BILLION EACH YEAR
- About 50% of these patient costs are related to HFpEF
- The prevalence of HFpEF is increasing over that of HFrEF due to aging population with accumulation of risk factors
Definition of Heart Failure

- Heart failure (HF) is a complex clinical syndrome that can result from any structural or functional cardiovascular disorder causing systemic perfusion inadequate to meet the body’s metabolic demands without excessively increasing left ventricular filling pressures.
- It is characterized by symptoms, such as dyspnea and fatigue, and signs, such as fluid retention.
- There are many ways to assess cardiac function. However, there is no diagnostic test for HF, since it is largely a clinical diagnosis that is based upon a careful history and physical examination.
Heart Failure can exist along the ENTIRE SPECTRUM of Ejection Fractions.

Elevated Cardiac Filling Pressures is the issue at heart.
Classification and Types of Heart Failure

- **Based on Ejection Fraction/Ventricle**
  - Ejection Fraction
    - Systolic, diastolic, mid-range (EF 41-49%)
  - High-Output Heart failure
    - Anemia, hyperthyroidism, AV fistula, sepsis, Paget’s
  - Right-sided, left-sided, combined
  - Classes of HF (NYHA 1-4) = symptoms
  - Stages of HF (A-D)
Etiologies of Heart Failure

**VALVULAR DISEASE**
- Stenosis and Regurgitation
- Diastolic and systolic

**VOLUME OVERLOAD**
- Renal failure
- Iatrogenic (e.g. post-operative fluid infusion)

**HIGH OUTPUT STATES**
- Anaemia
- Sepsis
- Thyrotoxicosis
- Paget’s disease
- Arteriovenous fistula

**MYOCARDIAL DISEASE**
- Coronary artery disease
- Hypertension
- Cardiomyopathy

**ENDOCARDIAL DISEASE**
- With/without hypereosinophilia
- Endocardial fibroelastosis

**PERICARDIAL DISEASE**
- Constrictive pericarditis
- Pericardial effusion

**CONGENITAL HEART DISEASE**

**ARRHYTHMIA**
- Tachyarrhythmia
- Atrial
- Ventricular
- Bradyarrhythmia
- Sinus node dysfunction

**CONDUCTION DISORDERS**
- Atrioventricular block
HEART FAILURE WITH PRESERVED EJECTION FRACTION

DIAGNOSIS OF HEART FAILURE

- **Signs and symptoms**
- **Cardiac Biomarkers**
  - BNP/NT-BNP
  - Troponin
- **Evidence of elevated LV filling pressures**
  - Echo/Stress Echo
  - Right heart cath
Signs and Symptoms of Heart Failure

**LEFT SIDED HEART FAILURE**
- Paroxysmal Nocturnal Dyspnea
- Elevated Pulmonary Capillary Wedge Pressure
- Pulmonary Congestion - Cough
  - Crackles
  - Wheezes
  - Blood-Tinged Sputum
  - Tachypnea
- Orthopnea
- Tachycardia
- Exertional Dyspnea
- Fatigue
- Cyanosis
- Restlessness
- Confusion

**RIGHT SIDED HEART FAILURE**
- Fatigue
- Peripheral Venous Pressure
- Ascites
- Enlarged Liver & Spleen
- Distended Jugular Veins
- Anorexia & Complaints of GI Distress
- Weight Gain
- Dependent Edema

(Cor Pulmonale)

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Challenges of the HFrEF Diagnosis

- Echocardiogram: EF may be normal
- NT-proBNP: may be low
- Symptoms: not specific
- Elevated filling pressures: rest/exercise
H2FPEF Scoring

- **H2** Heavy / Hypertensive
- **FP** Atrial Fibrillation
- **PE** Pulmonary Hypertension
- **EF** Elder
- **FF** Filling Pressure

**BMI > 30 kg/m²**
- ≥ 2 antihypertensive medications
  - 2 points for BMI; 1 point for antihypertensive agents

**Paroxysmal or persistent**
- 1 point

**Doppler echocardiographic estimated pulmonary artery systolic pressure > 35 mm Hg**
- 3 points

**Age > 60 years**
- 1 point

**Doppler echocardiographic E/e’ > 9**
- 1 point

**H2FPEF score**

<table>
<thead>
<tr>
<th>Total Points</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
</table>

**Probability of HFpEF**

Pathophysiology of Heart Failure - Neurohormonal Activation

↑ Sympathetic Tone/SNS activation

↑ RAAS Activity

Counterbalanced by:

↑ but weaker Natriuretic peptide system (NPS)

= 

Increased inflammation
Increased Oxidative Stress
Increased cardiac tissue fibrosis

Key: ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide; NP = natriuretic peptide; RAAS = renin–angiotensin–aldosterone system; SNS = sympathetic nervous system

Adapted from Kaira et al. 

June 2016 Br J Cardiol 2016;23(suppl 1):S1–S16 doi:10.5837/bjc.2016.s01
Goal of Management Strategies

- Prevention
- Improve symptoms/hospitalization/complications/quality of life (Morbidity)

AND

- Improve Life Span (Mortality)
Management of Acute SYSTOLIC Heart Failure

Current Treatment of Acute Heart Failure

- **High Preload**
  - Reduce fluid volume
  - Diuretics
    - LASIX

- **High Afterload**
  - Vasodilators
    - Nitroglycerin

- **Poor Contractility**
  - Augment contractility
  - Inotropes
    - reduce afterload
Pharmacological Management of Chronic SYSTOLIC Heart Failure

- **Inhibit Sympathetic Tone**
  - **BETA BLOCKERS**
    - Carvedilol
    - Metoprolol Succinate
    - Bisoprolol
    - Nebivolol

- **Inhibit RAAS Activation**
  - **ACEi**
    - Enalapril et. al
  - **ARB**
    - Candesartan/Valsartan/losartan
  - **MRA**
    - Spironolactone
    - Eplerenone

- **Volume Removal**
  - Furosemide
  - Torsemide
  - Bumetanide
  - Ethacrynic Acid
  - Metolazone/HCTZ

- **Augment Natriuretic Peptide System Activity and Other Mechanisms**
  - **ARNI** (sacubitril-valsartan)
  - **SGLT2 inhibitors** (gliflozins)

- **AFTERLOAD REDUCER**
  - ISDN/Hydralazine (Bidil)
<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Daily Dose(s)</th>
<th>Maximum Dose(s)</th>
<th>Mean Doses Achieved in Clinical Trials</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACE Inhibitors</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>6.25 mg TID</td>
<td>50 mg TID</td>
<td>122.7 mg QD</td>
<td>(158)</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 mg BID</td>
<td>10-20 mg BID</td>
<td>16.6 mg QD</td>
<td>(129)</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>5-10 mg QD</td>
<td>40 mg QD</td>
<td>N/A</td>
<td>–</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5-5 mg QD</td>
<td>20-40 mg QD</td>
<td>32.5-35.0 mg QD</td>
<td>(130)</td>
</tr>
<tr>
<td>Perindopril</td>
<td>2 mg QD</td>
<td>8-16 mg QD</td>
<td>N/A</td>
<td>–</td>
</tr>
<tr>
<td>Quinapril</td>
<td>5 mg BID</td>
<td>20 mg BID</td>
<td>N/A</td>
<td>–</td>
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<tr>
<td>Ramipril</td>
<td>1.25-2.5 mg QD</td>
<td>10 mg QD</td>
<td>N/A</td>
<td>–</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>1 mg QD</td>
<td>4 mg QD</td>
<td>N/A</td>
<td>–</td>
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<tr>
<td><strong>ARBs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>4-8 mg QD</td>
<td>32 mg QD</td>
<td>24 mg QD</td>
<td>(137)</td>
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<tr>
<td>Losartan</td>
<td>25-50 mg QD</td>
<td>50-150 mg QD</td>
<td>129 mg QD</td>
<td>(136)</td>
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<tr>
<td>Valsartan</td>
<td>20-40 mg BID</td>
<td>160 mg BID</td>
<td>254 mg QD</td>
<td>(134)</td>
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<tr>
<td><strong>ARNI</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Sacubitril/valsartan</td>
<td>49/51 mg BID (sacubitril/valsartan) (therapy may be initiated at 24/26 mg BID)</td>
<td>97/103 mg BID (sacubitril/valsartan)</td>
<td>375 mg QD: target dose: 24/26 mg, 49/51 mg OR 57/103 mg BID</td>
<td>(138)</td>
</tr>
<tr>
<td><strong>I1 channel inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ivabradine</td>
<td>5 mg BID</td>
<td>7.5 mg BID</td>
<td>6.4 mg BID (at 28 d) 6.5 mg BID (at 1 y)</td>
<td>(155-157)</td>
</tr>
<tr>
<td><strong>Aldosterone antagonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>12.5-25 mg QD</td>
<td>25 mg QD or BID</td>
<td>26 mg QD</td>
<td>(142)</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>25 mg QD</td>
<td>50 mg QD</td>
<td>42.6 mg QD</td>
<td>(159)</td>
</tr>
<tr>
<td><strong>Beta blockers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>1.25 mg QD</td>
<td>10 mg QD</td>
<td>8.6 mg QD</td>
<td>(160)</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 mg BID</td>
<td>50 mg BID</td>
<td>37 mg QD</td>
<td>(161)</td>
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<tr>
<td>Carvedilol CR</td>
<td>10 mg QD</td>
<td>80 mg QD</td>
<td>N/A</td>
<td>–</td>
</tr>
<tr>
<td>Metoprolol succinate extended release (metoprolol CR/XL)</td>
<td>12.5-25 mg QD</td>
<td>200 mg QD</td>
<td>159 mg QD</td>
<td>(139)</td>
</tr>
<tr>
<td><strong>Isosorbide dinitrate and hydralazine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fixed-dose combination</td>
<td>20 mg isosorbide dinitrate/ 37.5 mg hydralazine TID</td>
<td>40 mg isosorbide dinitrate/ 75 mg hydralazine TID</td>
<td>90 mg isosorbide dinitrate/ ~175 mg hydralazine QD</td>
<td>(162)</td>
</tr>
<tr>
<td>Isosorbide dinitrate and hydralazine</td>
<td>20-30 mg isosorbide dinitrate/ 25-50 mg hydralazine TID or QD</td>
<td>40 mg isosorbide dinitrate TID with 100 mg hydralazine TID</td>
<td>N/A</td>
<td>(163)</td>
</tr>
</tbody>
</table>

Modified (Table 15) from the 2013 HF guideline (9).

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BID, twice daily; CR, controlled release; CR/XL, controlled release/extended release; HF, heart failure; HFpEF, heart failure with reduced ejection fraction; N/A, not applicable; QD, once daily; and TID, 3 times daily.
WHAT ABOUT HFpEF?
HFpEF Therapeutic Strategies

**HFpEF**

**Symptomatic treatment**
- Pulmonary congestion
- Pulmonary hypertension
- Chronotropic incompetence
- Muscle deconditioning

**Phenotype treatment strategies considering associated comorbidities**
- Systemic hypertension
- Overweight/Obesity/Diabetes mellitus
- Renal dysfunction
- Coronary artery disease
- Chronic obstructive pulmonary disease
- Ageing specific conditions

**Device therapies**
- Resynchronization
- Renal denervation
- Intracavitary shunt

**Which place for traditional neurohormonal modulation?**

**Failure of usual recommended drugs in HFpEF:**
- ACE inhibitors (perindopril)
- ARBs (candesartan, irbesartan)
- MRA (spironolactone)
- Beta-blockers (nebivolol)
- 

**Lifestyle management**
- Exercise training
- Patient education

**Future pharmacological approaches of biological pathways involved in the proinflammatory comorbid-related state**

- **Systemic inflammatory axis**
  - Cytokin inhibitors
  - IL-1 antagonists
  - Coleheicne

- **cGMP/protein kinase G signalling**
  - NO donors (nitrites, aitrtes)
  - Activators of endothelial NO-synthase
  - PDE family (PDE-5 and PDE-9) inhibitors
  - Direct sGC stimulators (vericiguat, riociguat)
  - ARB/Nephrilysin inhibitors

- **Extracellular matrix and collagen controlling**
  - Spironolactone
  - Torasemide
  - Matrix metalloproteinase inhibitors

- **Modulation of calcium homeostasis**
  - Ryanodin receptor stabilizers
  - SERCA-2 modulators

- **Modulation of myocardial energy**
  - GLP-1 analogues
  - Sodium-glucose cotransporter-2 inhibitors

- **Other future potential therapies**
  - Cell therapy
  - HDL stimulators
  - MicroRNAs

Heart failure with preserved ejection fraction: A systemic disease linked to multiple comorbidities, targeting new therapeutic options - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Cardiac-and-extracardiac-factors-involved-in-the-pathophysiology-of-heart-failure-with_fig1_326036459
TOPCAT Trial (2014)
Spironolactone vs. Placebo in HFP EF

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

Heart Failure Hospitalizations

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>Placebo</th>
<th>Spiromolactone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spiro</td>
<td>1722</td>
<td>1462</td>
</tr>
<tr>
<td>Placebo</td>
<td>1723</td>
<td>1184</td>
</tr>
<tr>
<td>HR</td>
<td>0.89</td>
<td>0.77 - 1.04</td>
</tr>
<tr>
<td>p</td>
<td>0.138</td>
<td></td>
</tr>
</tbody>
</table>

HR = 0.89 (0.77 - 1.04)
p = 0.138

Placebo

HR = 0.83 (0.69 - 0.98)
p = 0.042
Exploratory (post-hoc): Placebo vs. Spiro by region

US, Canada, Argentina, Brazil
HR=0.82 (0.69-0.98)

Russia, Rep Georgia
HR=1.10 (0.79-1.51)

Interaction p=0.122

Placebo:
280/881 (31.8%)

Placebo:
71/842 (8.4%)
**PARAGON-HF**

**#ESC19**

**Trial Description:** Patients with heart failure with preserved ejection fraction were randomized to sacubitril-valsartan 97/103 mg twice daily versus valsartan 160 mg twice daily.

**RESULTS**
- Primary efficacy endpoint: rate of cardiovascular deaths or hospitalizations for heart failure was 12.8 events per 100 patient-years in the sacubitril-valsartan group vs. 14.6 events per 100 patient-years in the valsartan group (p = NS)
- NYHA class improvement: 15.0% in the sacubitril-valsartan group vs. 12.6% in the valsartan group (p < 0.05)

**CONCLUSIONS**
- Among patients with heart failure with preserved ejection fraction, sacubitril-valsartan was not effective at reducing the incidence of cardiovascular death or hospitalization for heart failure compared with valsartan

**Solomon SD, et al. N Engl J Med 2019;Sep 1:[Epub]**
Heart Failure and Glycemic Control Medications (SGLT-2 Inhibitors)

SGLT-2 INHIBITORS

- Empagliflozin
- Canagliflozin
- Dapagliflozin
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D. for the EMPA-REG OUTCOME Investigators

Figure 1. Cardiovascular Outcomes and Death from Any Cause.

Shown are the cumulative incidence of the primary outcome (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) (Panel A), cumulative incidence of death from cardiovascular causes (Panel B), the Kaplan–Meier estimate for death from any cause (Panel C), and the cumulative incidence of hospitalization for heart failure (Panel D) in the pooled empagliflozin group and the placebo group among patients who received at least one dose of a study drug. Hazard ratios are based on Cox regression analyses.
Canagliflozin and Heart Failure in Type 2 Diabetes Mellitus

Results From the CANVAS Program

Karin Rådholm, Gemma Figtree, Vlado Perkovic, Scott D. Solomon, Kenneth W. Mahaffey, Dick de Zeeuw, Greg Fulcher, Terrance D. Barrett, Wayne Shaw, Mehul Desai, David R. Matthews and Bruce Neal

Originally published: 11 Mar 2018
https://doi.org/10.1161/CIRCULATIONAHA.118.034222 | Circulation. 2018;138:458–468
Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

John J.V. McMurray, M.D., Scott D. Solomon, M.D., Silvio E. Inzucchi, M.D., Lars Køber, M.D., D.M.Sc., Mikhail N. Kosiborod, M.D., Felipe A. Martinez, M.D., Piotr Ponikowski, M.D., Ph.D., Marc S. Sabatine, M.D., M.P.H., Inder S. Anand, M.D., Jan Bělohlávek, M.D., Ph.D., Michael Böhm, M.D., Ph.D., Chern-En Chiang, M.D., Ph.D., et al., for the DAPA-HF Trial Committees and Investigators

Patients with HFrEF (irrespective of diabetes status) were randomized to dapagliflozin 10 mg daily (n = 2,373) versus placebo (n = 2,371).

- Total number of enrollees: 4,744
- Duration of follow-up: 18.2 months
- Mean patient age: 66 years
- Percentage female: 24%
- Percentage with diabetes: 42%

Inclusion criteria:

- Symptomatic heart failure
- Left ventricular ejection fraction (LVEF) ≤40%
- N-terminal pro-B-type natriuretic peptide ≥600 pg/ml (if hospitalized for heart failure within last 12 months ≥400 pg/ml; if atrial fibrillation/flutter ≥900 pg/ml)

Exclusion criteria:

- Estimated glomerular filtration rate <30 ml/min/1.73 m²
- Symptomatic hypotension or systolic blood pressure <95 mm Hg
- Type 1 diabetes mellitus
SGLT2 inhibitor reduces CV death and worsening HF events in HFrEF patients

DAPA-HF trial, in HFrEF patients (EF ≤40%) both with and without T2DM (n=4744)

Outcomes with dapagliflozin 10 mg once daily on top of standard care

**Primary endpoint**
- At 24 months

**All-cause death**
- At 24 months

**KCCQ**
- At 8 months

**Primary endpoint**: worsening of HF events (unplanned HHF or an urgent HF visit requiring intravenous therapy) and CV death

HFrEF: heart failure with reduced ejection fraction; HHF: hospitalization for heart failure; KCCQ: Kansas City Cardiomyopathy Questionnaire

McMurray J et al., ESC 2019
2017 Focused Update on HF Guidelines (Management of Comorbidities)

- Sacubitril-valsartan (Class I indication over ACEi, ARB in HFrEF)
- Ivabradine (Class IIa indication in HFrEF)
- Spironolactone in HFpEF
- Anemia /iron deficiency without anemia
- Hypertension
- Sleep disordered breathing
### Pharmacological Treatment for Stage C HF With Reduced EF

**Renin-Angiotensin System Inhibition With ACE-Inhibitor or ARB or ARNI**

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
<th>Comment/Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>ACE-I: A</td>
<td>The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors (Level of Evidence: A), OR ARBs (Level of Evidence: A), OR ARNI (Level of Evidence: B-R) in conjunction with evidence-based beta blockers, and aldosterone antagonists in selected patients, is recommended for patients with chronic HFrEF to reduce morbidity and mortality.</td>
<td>NEW: New clinical trial data prompted clarification and important updates.</td>
</tr>
</tbody>
</table>
### Pharmacological Treatment for Stage C HF With Reduced EF

**Renin-Angiotensin System Inhibition With ACE-Inhibitor or ARB or ARNI**

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
<th>Comment/Rationale</th>
</tr>
</thead>
<tbody>
<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.</td>
<td><strong>NEW:</strong> New clinical trial data necessitated this recommendation.</td>
</tr>
</tbody>
</table>
# Pharmacological Treatment for Stage C HF With Reduced EF

## Ivabradine

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
<th>Comment/Rationale</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 HF/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>
<td>NEW: New clinical trial data.</td>
</tr>
</tbody>
</table>

*In other parts of the document, the term “GDMT” has been used to denote guideline-directed management and therapy. In this recommendation, however, the term “GDEM” has been used to denote this same concept in order to reflect the original wording of the recommendation that initially appeared in the “2016 ACO/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure”.*
### Pharmacological Treatment for Stage C HF With Preserved EF

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
<th>Comment/Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B</td>
<td>Systolic and diastolic blood pressure should be controlled in patients with HFrEF in accordance with published clinical practice guidelines to prevent morbidity</td>
<td>2013 recommendation remains current.</td>
</tr>
<tr>
<td>I</td>
<td>C</td>
<td>Diuretics should be used for relief of symptoms due to volume overload in patients with HFrEF.</td>
<td>2013 recommendation remains current.</td>
</tr>
<tr>
<td>COR</td>
<td>LOE</td>
<td>Recommendations</td>
<td>Comment/Rationale</td>
</tr>
<tr>
<td>-----</td>
<td>-----</td>
<td>---------------------------------------------------------------------------------</td>
<td>-----------------------------------------</td>
</tr>
<tr>
<td>Ila</td>
<td>C</td>
<td>Coronary revascularization is reasonable in patients with CAD in whom symptoms (angina) or demonstrable myocardial ischemia is judged to be having an adverse effect on symptomatic HFpEF despite GDMT.</td>
<td>2013 recommendation remains current.</td>
</tr>
<tr>
<td>Ila</td>
<td>C</td>
<td>Management of AF according to published clinical practice guidelines in patients with HFpEF is reasonable to improve symptomatic HF.</td>
<td>2013 recommendation remains current.</td>
</tr>
<tr>
<td>Ila</td>
<td>C</td>
<td>The use of beta-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HFpEF.</td>
<td>2013 recommendation remains current.</td>
</tr>
</tbody>
</table>
### Pharmacological Treatment for Stage C HF With Preserved EF

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
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<th>Comment/Rationale</th>
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<tr>
<td>IIb</td>
<td>B-R</td>
<td>In appropriately selected patients with HFpEF (with EF (\geq 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.</td>
<td>NEW: Current recommendation reflects new RCT data.</td>
</tr>
<tr>
<td>IIb</td>
<td>B</td>
<td>The use of ARBs might be considered to decrease hospitalizations for patients with HFpEF.</td>
<td>2013 recommendation remains current.</td>
</tr>
</tbody>
</table>
## Anemia

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
<th>Comment/Rationale</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.</td>
<td><strong>NEW</strong>: New evidence consistent with therapeutic benefit.</td>
</tr>
<tr>
<td>III: No Benefit</td>
<td>B-R</td>
<td>In patients with HF and anemia, erythropoietin-stimulating agents should not be used to improve morbidity and mortality.</td>
<td><strong>NEW</strong>: Current recommendation reflects new evidence demonstrating absence of therapeutic benefit.</td>
</tr>
</tbody>
</table>
Treating Hypertension to Reduce the Incidence of HF

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<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.</td>
<td>NEW: Recommendation reflects new RCT data.</td>
</tr>
</tbody>
</table>
Hypertension

Treating Hypertension in Stage C HFrEF

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</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.</td>
<td>NEW: Recommendation has been adapted from recent clinical trial data but not specifically tested per se in a randomized trial of patients with HF.</td>
</tr>
</tbody>
</table>
Treating Hypertension in Stage C HFpEF

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<tr>
<td>I</td>
<td>C-LD</td>
<td>Patients with HFpEF and persistent hypertension after management of volume overload should be prescribed GDMT titrated to attain systolic blood pressure less than 130 mm Hg.</td>
<td>NEW: New target goal blood pressure based on updated interpretation of recent clinical trial data.</td>
</tr>
</tbody>
</table>
# Sleep Disorders

<table>
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<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>
<td><strong>NEW</strong>: Recommendation reflects clinical necessity to distinguish obstructive versus central sleep apnea.</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>
<td><strong>NEW</strong>: New data demonstrate the limited scope of benefit expected from CPAP for obstructive sleep apnea.</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>
<td><strong>NEW</strong>: New data demonstrate a signal of harm when adaptive servo-ventilation is used for central sleep apnea.</td>
</tr>
</tbody>
</table>
CARDIO-ONCOLOGY

Dr. W. Blount Ellison