Guidelines for Prevention and Management of Heart Failure

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Disclosures

• No Financial Disclosures
• American Heart Association Heart Failure Workgroup
Objectives

- Articulate the key elements for early detection of heart failure (Stage A) and recommended treatments
- Classify heart failure patients into stages and apply treatments, interventions and processes from the 2013 AHA/ACC/HFSA Heart Failure Guidelines / 2017 focused Update
- List the key pharmacological treatments for HFrEF for heart failure
- List Guideline recommendations for HFpEF
Burden of Heart Failure

• Lifetime risk > 20% for Americans >40 years of age

• 870,000 new cases diagnosed annually

• Prevalence in US: ~ 6.5 million

• 2014: Primary: ≈1.1 million ER visits, 1 million hospitalizations, and 80,000 deaths

• Annual cost of HF care in US ~ 30.7 billion in 2012

Definition of Heart Failure

A clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood

Normal Heart

HF with Reduced Ejection Fraction (HFrEF)

HF with Preserved Ejection Fraction (HFpEF)


## Classification of Heart Failure

<table>
<thead>
<tr>
<th>Classification</th>
<th>EF (%)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF with reduced EF (HFrEF)</td>
<td>≤40</td>
<td>Same as <em>systolic HF</em>. RCTs have mainly enrolled patients with HFrEF.</td>
</tr>
<tr>
<td>HF with preserved EF (HFP EF)</td>
<td>≥50</td>
<td>Same as <em>diastolic HF</em>. Diagnosis of HFP EF is challenging because it largely involves excluding other potential noncardiac causes of symptoms suggestive of HF.</td>
</tr>
<tr>
<td>HFP EF, borderline (or HFM EF)</td>
<td>41 – 49</td>
<td>These patients fall into a borderline or intermediate group.</td>
</tr>
<tr>
<td>HFP EF improved</td>
<td>&gt;40</td>
<td>A subset of patients with HFP EF who previously had HFrEF. Patients with improvement or recovery in EF may be clinically distinct from those with persistently preserved or reduced EF.</td>
</tr>
</tbody>
</table>

### Prevalence of Common Risk Factors for HF/CVD

<table>
<thead>
<tr>
<th>Behavior/Risk Factor</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking, Adults</td>
<td>15.5%</td>
</tr>
<tr>
<td>Obesity, Adults</td>
<td>39.6%</td>
</tr>
<tr>
<td>Obesity, Youth</td>
<td>18.5%</td>
</tr>
<tr>
<td>Low-Density Lipoprotein Cholesterol ≥130 mg/dl, Adults</td>
<td>28.5%</td>
</tr>
<tr>
<td>Hypertension, Adults*</td>
<td>45.6%</td>
</tr>
<tr>
<td>Diabetes Mellitus, Diagnosed</td>
<td>9.8%</td>
</tr>
<tr>
<td>Diabetes Mellitus, Undiagnosed</td>
<td>3.7%</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>14.8%</td>
</tr>
<tr>
<td>Recommended Exercise (2008 guidelines)</td>
<td>22.5%</td>
</tr>
</tbody>
</table>

*Hypertension defined by definition in 2017 ACC/AHA guidelines for hypertension

Olmstead County: Coronary heart disease, hypertension, diabetes, obesity, and smoking are responsible for 52% of incident HF cases

Age-adjusted trends in Hypertension and controlled hypertension in adults ≥ 18 years in the US

% of individuals with HTN increases with age:
33% among those aged 40–59 and 63% among those aged 60 and over

Prevalence of Diabetes and Obesity in the US

Diabetes

- 30.3 million Americans have diabetes (9.4% of the U.S. population)
- 84.1 million have prediabetes

Obesity (BMI ≥30 kg/m²)

- 40% of US adults are obese

Age-adjusted Prevalence

<table>
<thead>
<tr>
<th>Year</th>
<th>No Data</th>
<th>&lt;4.5%</th>
<th>4.5%–6.0%</th>
<th>6.0%–7.4%</th>
<th>7.5%–9.0%</th>
<th>&gt;9.0%</th>
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</thead>
<tbody>
<tr>
<td>1994</td>
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<td>No Data</td>
<td>No Data</td>
<td>No Data</td>
<td>No Data</td>
<td>No Data</td>
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<td>2000</td>
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<td>No Data</td>
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<tr>
<td>2015</td>
<td>No Data</td>
<td>No Data</td>
<td>No Data</td>
<td>No Data</td>
<td>No Data</td>
<td>No Data</td>
</tr>
</tbody>
</table>

http://www.cdc.gov/diabetes/data
HF Severity: ACC/AHA Stages and NYHA Functional Classification

ACCF/AHA Stages

- **Stage A**
  - High risk for developing HF
  - No structural disease of the heart
  - No symptoms of HF

- **Stage B**
  - Structural disease
  - No symptoms of HF

- **Stage C**
  - Structural disease
  - Past or current symptoms of HF

- **Stage D**
  - Refractory HF
  - Requires specialized treatment strategies

NYHA Functional Classification

- **Class I**
  - No limitation of physical activity
  - Ordinary physical activity does not cause symptoms of HF

- **Class II**
  - Slight limitation of physical activity
  - Comfortable at rest
  - Ordinary activity results in symptoms of HF

- **Class III**
  - Marked limitation of physical activity
  - Comfortable at rest
  - Less than ordinary activity results in symptoms of HF

- **Class IV**
  - Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest

Annual Mortality

- 5-10%
- 10-25%
- 25-60%

**Stages of Heart Failure**

**STAGE A**
At high risk for HF but without structural heart disease or symptoms of HF

- e.g., Patients with:
  - HTN
  - Atherosclerotic disease
  - DM
  - Obesity
  - Metabolic syndrome or Patients
  - Using cardiotoxins
  - With family history of cardiomyopathy

**THERAPY**
- Goals
  - Heart healthy lifestyle
  - Prevent vascular, coronary disease
  - Prevent LV structural abnormalities
- Drugs
  - ACEI or ARB in appropriate patients for vascular disease or DM
  - Statins as appropriate

**STAGE B**
Structural heart disease but without signs or symptoms of HF

- e.g., Patients with:
  - Previous MI
  - LV remodeling including LVH and low EF
  - Asymptomatic valvular disease

**THERAPY**
- Goals
  - Prevent HF symptoms
  - Prevent further cardiac remodeling
- Drugs
  - ACEI or ARB as appropriate
  - Beta blockers as appropriate
  - In selected patients
  - ICD
- Treatment
  - Diuresis to relieve symptoms of congestion
  - Follow guideline driven indications for comorbidities, e.g., HTN, AF, CAD, DM
  - Revascularization or valvular surgery as appropriate

**STAGE C**
Structural heart disease with prior or current symptoms of HF

- e.g., Patients with:
  - Known structural heart disease and HF signs and symptoms

**THERAPY**
- Goals
  - Control symptoms
  - Improve HRQOL
  - Prevent hospitalization
  - Prevent mortality
- Drugs for routine use
  - Diuretics for fluid retention
  - ACEI or ARB
  - Beta blockers
  - Aldosterone antagonists
- Drugs for use in selected patients
  - Hydralazine/isosorbide dinitrate
  - ACEI and ARB
  - Digoxin
  - In selected patients
  - CRT
  - ICD
  - Revascularization or valvular surgery as appropriate

**STAGE D**
Refractory HF

- e.g., Patients with:
  - Marked HF symptoms at rest
  - Recurrent hospitalizations despite GDMT

**THERAPY**
- Goals
  - Prevent HF symptoms
  - Prevent further cardiac remodeling
- Drugs
  - ACEI or ARB as appropriate
  - Beta blockers as appropriate
- In selected patients
  - ICD
  - Revascularization or valvular surgery as appropriate

- Options
  - Advanced care measures
  - Heart transplant
  - Chronic inotropes
  - Temporary or permanent MCS
  - Experimental surgery or drugs
  - Palliative care and hospice
  - ICD deactivation

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Majority of the population is in Stage A/B

Individuals aged >45 yrs: 56% in Stage A/B

Older individuals (67-91 yrs: ARIC): 82% with Stage A/B
AHA’s My Life Check- Life’s Simple 7 to stay Heart Healthy

- Blood Sugar
- Cholesterol
- Blood Pressure
- No Smoking
- Healthy Weight
- Exercise
- Healthy Diet

Life’s Simple 7

American Heart Association
My Life Check®
Stage A: 2013

Hypertension and lipid disorders should be controlled in accordance with contemporary guidelines to lower the risk of HF.

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.

+ 2017

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></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>
</tr>
</tbody>
</table>
Risk Reduction of HF in Elderly Hypertensives in RCTs

- Coops & Warrender: -35%
- EWPHE: -53%
- SHEP: -54%
- STOP Hypertension: -51%
- HYVET: -64%
- SPRINT: -38%

Goal SBP: <120 vs. <140 mm Hg
BP Thresholds and Recommendations for Treatment & FU

Normal BP (BP <120/80 mm Hg)
- Promote optimal lifestyle habits
  - Reassess in 1 y (Class Ila)

Elevated BP (BP 120-129/<80 mm Hg)
- Nonpharmacological therapy (Class I)
  - Reassess in 3–6 mo (Class I)

Stage 1 hypertension (BP 130-139/80-89 mm Hg)
- Clinical ASCVD or estimated 10-y CVD risk ≥10%
  - No
    - Nonpharmacological therapy (Class I)
    - Reassess in 3–6 mo (Class I)
  - Yes
    - Nonpharmacological therapy and BP-lowering medication (Class I)
    - Reassess in 1 mo (Class I)

Stage 2 hypertension (BP ≥140/90 mm Hg)
- Nonpharmacological therapy and BP-lowering medication† (Class I)
- Reassess in 1 mo (Class I)
- BP goal met

AHA/ACC Guideline on Hypertension, 2017
*Other biomarkers of injury or fibrosis include soluble ST2 receptor, galectin-3, and high-sensitivity troponin; ADHF, acute decompensated heart failure; BNP, B-type natriuretic peptide; COR, Class of Recommendation; ED, emergency department; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; and pts, patients.

Yancy et al. 2017  ACC/AHA/HFSA
### Biomarkers: Indications for Use in Prevention of HF

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
<th>Comment/Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>For patients at risk of developing HF, natriuretic peptide biomarker–based</td>
<td><strong>NEW</strong>: New data suggest that natriuretic peptide biomarker screening and early</td>
</tr>
<tr>
<td></td>
<td></td>
<td>screening followed by team-based care, including a cardiovascular specialist</td>
<td>intervention may prevent HF.</td>
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<tr>
<td></td>
<td></td>
<td>optimizing GDMT, can be useful to prevent the development of left ventricular</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>dysfunction (systolic or diastolic) or new-onset HF.</td>
<td></td>
</tr>
</tbody>
</table>

Yancy et al. 2017  ACC/AHA/HFSA
STOP-HF (The St Vincent’s Screening to Prevent Heart Failure)

- Large-scale (1374 individuals in Ireland), un-blinded study of patients at risk of HF (HTN, DM, or known vascular disease- stage A HF), but without established left ventricular systolic dysfunction or HF

- Patients randomly assigned to receive intervention based on screening BNP or usual primary care.

- Intervention group participants with BNP levels of >50 pg/mL had an echo and were referred to a cardiologist.
STOP-HF
(St Vincent’s Screening to Prevent Heart Failure)

BNP-based screening reduced the composite endpoint of asymptomatic left ventricular (LV) dysfunction (systolic or diastolic) with or without newly diagnosed HF

Ledwidge M et al. JAMA 2013
Global Cardiovascular Prevention (HF, CHD, Stroke)

Primordial-focus on lifestyle & education

Shared etiologic risk factors for CVD
HTN Diabetes Cholesterol Smoking lifestyle obesity genes others

Global CVD and HF risk estimation using traditional risk factors, biomarkers, imaging

ASCVD (MI stroke): High risk

HF: high Risk

Re-emphasize diet, exercise, healthy lifestyle
More intensive bp control
Weight loss for obese ? Bariatric surgery in select
Consider SGLT2 inhibitor in DM
Statins

Consider cardiology referral for echo

Prevention of Clinical HF in Stage B

(Structural cardiac abnormalities without clinical HF)

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients with a history of MI and reduced EF, ACE inhibitors or ARBs should be used to prevent HF</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>In patients with MI and reduced EF, evidence-based beta blockers should be used to prevent HF</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>In patients with MI, statins should be used to prevent HF</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Blood pressure should be controlled to prevent symptomatic HF</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>ACE inhibitors should be used in all patients with a reduced EF to prevent HF</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Beta blockers should be used in all patients with a reduced EF to prevent HF</td>
<td>I</td>
<td>C</td>
</tr>
</tbody>
</table>

Treat co-existing valvular heart disease and CAD as indicated

Yancy et al. 2017  ACC/AHA/HFSA
Initial Workup of Stage C HF

• Detailed history, including 3 generation family history (Class I)

• Initial laboratory evaluation:
  
  • CBC, urinalysis, CMP (including calcium and magnesium), fasting lipid profile, TSH (Class I)
  • Serial monitoring, when indicated, should include serum electrolytes and renal function (Class I)
  • Screening for hemochromatosis, HIV, amyloidosis, pheochromocytoma and other etiologies as indicated
Workup of Stage C HF

• A 12-lead ECG, CXR should be performed initially on all patients presenting with HF.
• Echocardiogram in all patients with new dx of HF (MUGA in some)
• Noninvasive stress imaging or cardiac cath is reasonable in HF and suspected CAD
• Cardiac MRI is reasonable to assess LV volume, EF, myocardial infiltration, or scar

• Repeat echo usually for a significant change in clinical status or for consideration of changes after therapy or to evaluate for device therapy (Not done for routine follow up)

• Validated multivariable risk scores can be useful to estimate risk of mortality in ambulatory or hospitalized HF patients (Class IIa)
Biomarkers Indications for Use: Stage C

- **ACC/AHA Stage A/B HF**
  - At risk for HF
  - Prevention: BNP or NT-proBNP (COR IIa)

- **ACC/AHA Stage C/D HF**
  - Ambulatory pts with new-onset dyspnea
  - NYHA class II-IV
  - Diagnosis: BNP or NT-proBNP (COR I)
    - Prognosis or added risk stratification: BNP or NT-proBNP (COR I)

- **ACC/AHA Acute/Hospitalized HF**
  - Acute dyspnea to ED
  - Hospitalized for ADHF
  - Other biomarkers of myocardial injury or fibrosis (COR IIb)

Yancy et al. 2017  ACC/AHA/HFSA
Non-Pharmacologic Management of Patients with Stage C HF

- Patients with HF should receive specific education to facilitate HF self-care (talk).

- **Sodium restriction** is reasonable for patients with symptomatic HF to reduce congestive symptoms. *(COR IIa; LOE C)*

  *Controversial.* Due to association between sodium intake and HTN, LVH, and CVD, the AHA recommendation for 1500 mg/d is applicable for stage A&B. Stage C&D: Lack of data. Since usual intake > 4 g/d, suggest < 3 g/d in HF for symptom improvement.

- **Fluid restriction** *(1.5 to 2 L/d)* is reasonable in stage D, especially in patients with hyponatremia, to reduce congestive symptoms. *(COR IIa; LOE C).* *No recommendation for routine use of fluid restriction in all HF patients*.

Yancy et al. 2013, ACC/AHA/HFSA
Exercise and Cardiac Rehabilitation

• Exercise training (or regular physical activity) is recommended as safe and effective for patients with HF who are able to participate to improve functional status.

• Cardiac rehabilitation can be useful in clinically stable patients with HF to improve functional capacity, exercise duration, HRQOL, and mortality.
Guideline Directed Therapy for Stage C & D HF

**Step 1**
Establish Dx of HF/EF; assess volume; initiate GDMT

**HF/EF**
NYHA class I–IV (Stage C)

ACEI or ARB AND GDMT beta blockers; diuretics as needed (COR I)

**Step 2**
Consider the following patient scenarios

- NYHA class II–IV, provided est. CrCl >30 mL/min & K+ <5.0 mEq/L
  - Aldosterone antagonist (COR I)

- NYHA class II–III HF
  - Adequate BP on ACEI or ARB*: No C/I to ARB or sacubitril
  - Discontinue ACEI or ARB; initiate ARNI* (COR I)

- NYHA class III–IV, in black patients
  - Hydralazine†† (COR I)

- NYHA class II–III, LVEF ≤35%; (caveat: >1 y survival, >40 d post MI)
  - ICD† (COR I)

- NYHA class II–IV, LVEF ≤35%, NSR & QRS ≥150 ms with LBBB pattern
  - CRT or CRT-D† (COR I)

- NYHA class II–III, NSR, heart rate ≥70 bpm on maximally tolerated dose beta blocker
  - Ivabradine (COR IIa)

**Step 3**
Implement indicated GDMT. Choices are not mutually exclusive, and no order is inferred

**Step 4**
Reassess symptoms

- Refractory NYHA class III–IV (Stage D)
- Symptoms improved

**Step 5**
Consider additional therapy

- Palliative care‡ (COR I)
- Transplant‡ (COR I)
- LVAD‡ (COR IIa)
- Investigational studies§

Continue GDMT with serial reassessment & optimized dosing/adherence

* Yancy et al. 2017 ACC/AHA/HFSA
## HFrEF: Medications & Devices

<table>
<thead>
<tr>
<th></th>
<th>Symptoms</th>
<th>Prevent Hospitalizations</th>
<th>Increase Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>✓</td>
<td>? ✓</td>
<td>✓</td>
</tr>
<tr>
<td>ACE-I/ARBs</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>ARNI</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Hydralazine/nitrates</td>
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<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Aldosterone Blockers</td>
<td>✓</td>
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<tr>
<td>Ivabradine</td>
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<tr>
<td>Digitalis</td>
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</tr>
<tr>
<td>Biventricular Pacing</td>
<td>✓</td>
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</tr>
<tr>
<td>AICD</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>X</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

*Note: X indicates not recommended.*
### Medical Therapy for Stage C HFrEF: Magnitude of Benefit in RCTs

<table>
<thead>
<tr>
<th>GDMT</th>
<th>RR ↓ Mortality</th>
<th>NNT for ↓ mortality (standardized 36 mo)</th>
<th>RR ↓ HF Hosp.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE Inhibitor or ARB</td>
<td>17%</td>
<td>26</td>
<td>31%</td>
</tr>
<tr>
<td>Beta-Blockers</td>
<td>34%</td>
<td>9</td>
<td>41%</td>
</tr>
<tr>
<td>Aldo-antagonists</td>
<td>30%</td>
<td>6</td>
<td>35%</td>
</tr>
<tr>
<td>HDZ/nitrate</td>
<td>43%</td>
<td>7</td>
<td>33%</td>
</tr>
<tr>
<td>Sacubitril/valsartan (over ACE-I)</td>
<td>16%</td>
<td>21 (over 27 mo)</td>
<td>20%</td>
</tr>
</tbody>
</table>
Medical Therapy

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

Step 2
Consider the following patient scenarios

- NYHA class II–IV, provided est. CrCl > 30 mL/min & K+ < 5.0 mEq/L
  - Aldosterone antagonist (COR I)
- NYHA class II–III HF Adequate BP on ACEI or ARB*; No C/I to ARB or sacubitril
  - Discontinue ACEI or ARB, initiate ARNI* (COR I)
- NYHA class III–IV, in black patients
  - Hydral-Nitrates†‡ (COR I)
- NYHA class II–III, NSR, heart rate ≥ 70 bpm on maximally tolerated dose beta blocker
  - Ivabradine (COR IIa)

Step 3
Implement indicated GDMT. Choices are not mutually exclusive, and no order is inferred

Step 4
Reassess symptoms

Refractory NYHA class III–IV (Stage D)
Symptoms improved

Yancy et al. 2017  ACC/AHA/HFSA
PARADIGM-HF: CV Death or HF Hospitalization

HR = 0.80 (0.73-0.87)
\( P = .0000004 \)
Number needed to treat = 21

PARADIGM-HF: Other Key Endpoints

- Cardiovascular Death: 16.5% (Enalapril), 13.3% (Sacubitril/valsartan) with a 20% reduction
- HF Hospitalization: 15.6% (Enalapril), 12.8% (Sacubitril/valsartan) with a 20% reduction
- Overall Mortality: 17.0% (Enalapril), 19.8% (Sacubitril/valsartan) with a 16% reduction
- HF Death: 4.4% (Enalapril), 3.5% (Sacubitril/valsartan) with a 21% reduction
- Sudden Death: 7.4% (Enalapril), 6.0% (Sacubitril/valsartan) with a 20% reduction

References:
PIONEER-HF: Sacubitril-valsartan initiated in hospitalized HF patients

No increase in adverse effects with sacubitril valsartan; secondary analyses with reduction in HF rehospitalization over 8 weeks
Practical Points for Using Ivabradine in HF

- FDA-approved indication: Reduce risk of HF hospitalization in patients with:
  - stable, symptomatic chronic HFrEF, EF ≤ 35%,
  - SR with resting HR ≥ 70 bpm
  - on maximally tolerated doses of BBs
  - OR have a contraindication to BB

- Do not use in: ADHF or BP <90/50 mmHg, resting HR <60 bpm, pacemaker dependent, atrial fibrillation, severe heart block, severe hepatic impairment

- Interaction with CYP3A4 inhibitors

- Side effects: bradycardia, HTN, AF, and luminous phenomena (phosphenes)
Harmful Drugs in HF (Class III)

- NSAIDs
- Decongestants, e.g., pseudoephedrine
- Thiazolidinediones
- Antiarrhythmics
  - Exceptions: amiodarone, dofetilide (different if ICD in place)
- HFrEF: Diltiazem, Verapamil
  (amlodipine OK if needed for HTN or angina)
Indications for AICD and BiV/CRT Pacing in HFrEF

- NYHA Class II-III, LVEF ≤35%; (caveat: >1 y survival, >40 d post MI) → ICD‡ (COR I)
- NYHA Class II-IV, LVEF ≤35%, NSR & QRS ≥150 ms with LBBB pattern → CRT or CRT-D‡ (COR I)
HF With Preserved EF: Differential Diagnosis

- Fabry
- LAMP2
- PRKAG2

HFpEF

Storage disease

Hypertrophic CMP

Restrictive CMP

Pericardial disease

RV failure

- PAH
- ARVC
- Sarcoidosis
- TR

- Constrictive pericarditis
- Constrictive-effusive disease
- Post-pericardiotomy syndrome

HF signs and symptoms Normal LVEF

- Amyloidosis
- Hemochromatosis
- Endomyocardial fibrosis
- Radiation-induced
- Chemotherapy-induced
- Idiopathic

HFpEF

Trials have not shown significant mortality or morbidity benefit with use of ACEI/ARB specifically in HFpEF
RCT of spiro (15-45 mg) vs. placebo in HFpEF (LVEF >45%) +
- Prior HF hosp.
- BNP > 100 pg/ml

Placebo

Spironolactone

HR = 0.89 (0.77 – 1.04)
p=0.138

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
<th>72</th>
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</thead>
<tbody>
<tr>
<td>Spiro</td>
<td>1722</td>
<td>1502</td>
<td>1168</td>
<td>870</td>
<td>614</td>
<td>330</td>
<td>53</td>
</tr>
<tr>
<td>Placebo</td>
<td>1723</td>
<td>1462</td>
<td>1145</td>
<td>834</td>
<td>581</td>
<td>331</td>
<td>53</td>
</tr>
</tbody>
</table>

Exploratory-Post Hoc: Placebo vs. Spiro by Region

Primary Outcome

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

Placebo: 280/881 (31.8%)
Spiro: 242/886 (27.3%)

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

Interaction p=0.122

Placebo: 71/842 (8.4%)
Spiro: 78/836 (9.3%)
## 2017: Treatment of HFpEF

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Systolic and diastolic blood pressure should be controlled in patients with HFpEF in accordance with published clinical practice guidelines to prevent morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Diuretics should be used for relief of symptoms due to volume overload in patients with HFpEF.</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>C</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IIa</th>
<th>C</th>
<th>The use of beta-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HFpEF.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>IIa</th>
<th>C</th>
<th>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.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>IIa</th>
<th>C</th>
<th>Management of AF according to published clinical practice guidelines in patients with HFpEF is reasonable to improve symptomatic HF.</th>
</tr>
</thead>
</table>

Goal BP < 130/80 mm Hg
## 2017: Treatment of HFpEF

<table>
<thead>
<tr>
<th>Level</th>
<th>Recommendation</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb</td>
<td>B-R</td>
<td>In appropriately selected patients with HFpEF (with EF ≥45%, elevated BNP levels or HF admission within 1 year, estimated glomerular filtration rate &gt;30 mL/min, creatinine &lt;2.5 mg/dL, potassium &lt;5.0 mEq/L), aldosterone receptor antagonists might be considered to decrease hospitalizations.</td>
</tr>
</tbody>
</table>

### Level III: No Benefit

<table>
<thead>
<tr>
<th>Level</th>
<th>Recommendation</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>III: No Benefit</td>
<td>B-R</td>
<td>Routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or QoL in patients with HFpEF is ineffective.</td>
</tr>
<tr>
<td>III: No Benefit</td>
<td>C</td>
<td>Routine use of nutritional supplements is not recommended for patients with HFpEF.</td>
</tr>
</tbody>
</table>
Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction

MULTICENTER, DOUBLE-BLIND, ACTIVE-COMPARATOR TRIAL (PARAGON-HF)

4822 Patients with NYHA class II–IV heart failure and EF ≥45%

Total hospitalizations for heart failure and cardiovascular death

Sacubitril–valsartan 97 mg + 103 mg (twice daily) (N=2419)

Valsartan 160 mg (twice daily) (N=2403)

894 events

1009 events

Rate ratio, 0.87; 95% CI, 0.75–1.01; P=0.06

Patients receiving sacubitril–valsartan more likely to have hypotension and angioedema but less likely to have hyperkalemia
### 2017: Important Comorbidities in HF

#### Anemia

<table>
<thead>
<tr>
<th>Level</th>
<th>Recommendation</th>
<th>Description</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>
</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>
</tr>
<tr>
<td>Level</td>
<td>Code</td>
<td>Recommendation</td>
</tr>
<tr>
<td>-------</td>
<td>------</td>
<td>----------------</td>
</tr>
<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>
• Recognize risk factors (Stage A HF) and structural cardiac abnormalities (Stage B HF); recommend treatments

• Classify heart failure patients into stages and apply treatments, interventions and processes from the 2013 AHA/ACC/HFSA Heart Failure Guidelines / 2017 focused Update

• Review key pharmacological and non pharmacologic treatments for HFrEF and HFpEF
Thank you
Classification of Recommendations and Levels of Evidence (AHA/ACC Guidelines)

<table>
<thead>
<tr>
<th>CLASS (STRENGTH) OF RECOMMENDATION</th>
<th>Benefit &gt;&gt; Risk</th>
<th>LEVEL (QUALITY) OF EVIDENCE‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLASS I (STRONG)</td>
<td></td>
<td>LEVEL A</td>
</tr>
<tr>
<td>Suggested phrases for writing recommendations:</td>
<td>Is recommended</td>
<td>High-quality evidence† from more than 1 RCT</td>
</tr>
<tr>
<td></td>
<td>Is indicated/useful/effective/beneficial</td>
<td>Meta-analyses of high-quality RCTs</td>
</tr>
<tr>
<td></td>
<td>Should be performed/administered/other</td>
<td>One or more RCTs corroborated by high-quality registry studies</td>
</tr>
<tr>
<td>Comparative Effectiveness Phrases‡:</td>
<td>Treatment/strategy A is recommended/indicated in preference to treatment B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treatment A should be chosen over treatment B</td>
<td></td>
</tr>
<tr>
<td>CLASS Ia (MODERATE)</td>
<td>Benefit &gt;&gt; Risk</td>
<td>LEVEL B-R (Randomized)</td>
</tr>
<tr>
<td>Suggested phrases for writing recommendations:</td>
<td>Is reasonable</td>
<td>Moderate-quality evidence† from 1 or more RCTs</td>
</tr>
<tr>
<td></td>
<td>Can be useful/effective/beneficial</td>
<td>Meta-analyses of moderate-quality RCTs</td>
</tr>
<tr>
<td>Comparative Effectiveness Phrases‡:</td>
<td>Treatment/strategy A is probably recommended/indicated in preference to treatment B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>It is reasonable to choose treatment A over treatment B</td>
<td></td>
</tr>
<tr>
<td>CLASS IIb (WEAK)</td>
<td>Benefit ≥ Risk</td>
<td>LEVEL B-NR (Nonrandomized)</td>
</tr>
<tr>
<td>Suggested phrases for writing recommendations:</td>
<td>May/might be reasonable</td>
<td>Moderate-quality evidence† from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies</td>
</tr>
<tr>
<td></td>
<td>May/might be considered</td>
<td>Meta-analyses of such studies</td>
</tr>
<tr>
<td></td>
<td>Usefulness/effectiveness is unknown/unclear/uncertain or not well established</td>
<td>Physical or mechanistic studies in human subjects</td>
</tr>
<tr>
<td>CLASS III: No Benefit (MODERATE)</td>
<td>Benefit = Risk</td>
<td>LEVEL C-LD (Limited Data)</td>
</tr>
<tr>
<td>(Generally, LOE A or B use only)</td>
<td></td>
<td>Randomized or nonrandomized observational or registry studies with limitations of design or execution</td>
</tr>
<tr>
<td>Suggested phrases for writing recommendations:</td>
<td>Is not recommended</td>
<td>Meta-analyses of such studies</td>
</tr>
<tr>
<td></td>
<td>Is not indicated/useful/effective/beneficial</td>
<td>Physiological or mechanistic studies in human subjects</td>
</tr>
<tr>
<td></td>
<td>Should not be performed/administered/other</td>
<td>Consensus of expert opinion based on clinical experience</td>
</tr>
<tr>
<td>CLASS III: Harm (STRONG)</td>
<td>Risk &gt; Benefit</td>
<td>LEVEL C-EO (Expert Opinion)</td>
</tr>
<tr>
<td>Suggested phrases for writing recommendations:</td>
<td>Potentially harmful</td>
<td>A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.</td>
</tr>
<tr>
<td></td>
<td>Causes harm</td>
<td>The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).</td>
</tr>
<tr>
<td></td>
<td>Associated with excess morbidity/mortality</td>
<td>For comparative-effectiveness recommendations (COR I and II; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.</td>
</tr>
<tr>
<td></td>
<td>Should not be performed/administered/other</td>
<td>The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.</td>
</tr>
</tbody>
</table>

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

For comparative-effectiveness recommendations (COR I and II; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.
# Mortality Benefit Using ACEIs in HFrEF

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>HF Severity</th>
<th>Class</th>
<th>Target Dose</th>
<th>Average Dose</th>
<th>Outcomes</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONSENSUS</td>
<td>Enalapril</td>
<td>Chronic HF</td>
<td>IV</td>
<td>20 mg BID</td>
<td>18.4 mg</td>
<td>↓31% mortality</td>
<td>P=0.001</td>
</tr>
<tr>
<td>SOLVD</td>
<td>Enalapril</td>
<td>Chronic HF</td>
<td>I-V</td>
<td>10 mg BID</td>
<td>16.6 mg</td>
<td>↓16% mortality</td>
<td>P=0.0036</td>
</tr>
<tr>
<td>ATLAS</td>
<td>Lisinopril</td>
<td>Chronic HF</td>
<td>II-V</td>
<td>35 mg/d</td>
<td>32.5 - 35 mg</td>
<td>↓12% all-cause mortality and hospitalizations,</td>
<td>P=0.002 (high dose)</td>
</tr>
<tr>
<td>SAVE</td>
<td>Captopril</td>
<td>Post MI LVD</td>
<td>EF ≤ 40%</td>
<td>50 mg TID</td>
<td>NR*</td>
<td>↓19% mortality</td>
<td>P=0.019</td>
</tr>
<tr>
<td>AIRE</td>
<td>Ramipril</td>
<td>Post MI LVD</td>
<td>EF ≤ 40%</td>
<td>5 mg BID</td>
<td>NR</td>
<td>↓27% mortality</td>
<td>P=0.002</td>
</tr>
<tr>
<td>TRACE</td>
<td>Trandolapril</td>
<td>Post MI LVD</td>
<td>EF ≤ 35%</td>
<td>4 mg daily</td>
<td>NR</td>
<td>↓22% mortality</td>
<td>P=0.001</td>
</tr>
</tbody>
</table>
Mortality Benefit Using Beta Blockers in HFrEF

**MERIT HF**
- N=3991
- $P=0.0062$ (adjusted)
- $P=0.00009$ (nominal)
- Mortality: 34%

**CIBIS II**
- N=2647
- $P<0.0001$
- Mortality: 34%

**COPERNICUS**
- N=2289
- $P=0.00013$ (unadjusted)
- $P=0.0014$ (adjusted)
- Mortality: 35%

References:
Mortality Benefit Using Beta Blockers in HFrEF

**MERIT HF**
- N=3991
- Cumulative mortality
  - Placebo
  - ER Metoprolol Succinate
  - P=0.0062 (adjusted)
  - P=0.00009 (nominal)
- Follow-up: (Months)
- Mortality: 34%

**CIBIS II**
- N=2647
- Survival
  - Bisoprolol
  - Placebo
  - P<0.0001
- Time (Days)
- Mortality: 34%

**COPERNICUS**
- N=2289
- Survival
  - Carvedilol
  - Placebo
  - P=0.00013 (unadjusted)
  - P=0.0014 (adjusted)
- Months
- Mortality: 35%