Important Distinctions in Heart Failure Guidelines: USA and Europe

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Heart failure (HF) is a major public health problem resulting in substantial morbidity, mortality, and healthcare expenditures. Despite available effective treatments, a large number of eligible patients are not receiving optimal care. Even with conventional therapy patients remain at risk for disease progression and adverse outcomes.

American Heart Association. 2017 Heart and Stroke Statistical Update. Dallas, Tex: American Heart Association; 2017
Guidelines and Evidence Based Care for Heart Failure

- Evidence based guidelines are based on rigorous and expert analysis of available data documenting relative benefits and risks of procedures and therapies.

- The ACC/AHA practice guidelines reflect a consensus of expert opinion and are intended to assist healthcare providers in clinical decision making by describing a range of generally acceptable approaches for the diagnosis, management, or prevention of specific diseases or conditions.

- These guidelines are intended to help improve the effectiveness of care, optimize patient outcomes, and favorably affect the overall cost of care by focusing resources on the most effective strategies.

Classification of Recommendations and Levels of Evidence

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

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

Helping Cardiovascular Professionals
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New Guidelines Have Emerged - 2016
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

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Stages, Phenotypes and Treatment of HF

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

- **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

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

- **Goals**
  - Control symptoms
  - Improve HRQOL
  - Prevent hospitalization
  - Prevent mortality

- **Drugs**
  - Diuretics for fluid retention
  - ACEI or ARB
  - Beta blockers
  - Aldosterone antagonists

- **In selected patients**
  - Hydralazine/isosorbide dinitrate
  - ACEI and ARB
  - Digoxin

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

- **Goals**
  - Control symptoms
  - Patient education
  - Prevent hospitalization
  - Prevent mortality
  - Establish patient's end-of-life goals

- **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

- **Goals**
  - Control symptoms
  - Improve HRQOL
  - Reduce hospital readmissions
  - Establish patient's end-of-life goals

- **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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**At Risk for 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

- **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

- **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

- **STAGE D**
  - Refractory symptoms of HF at rest, despite GDMT
  - e.g., Patients with:
    - Marked HF symptoms at rest
    - Recurrent hospitalizations despite GDMT

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**Heart Failure**

- **HFpEF**
- **HFrEF**

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Helping Cardiovascular Professionals
Biomarkers
Hospitalized/Acute
Measurement of BNP or NT-proBNP is useful to support clinical judgment for the diagnosis of acutely decompensated HF, especially in the setting of uncertainty for the diagnosis.

Measurement of BNP or NT-proBNP and/or cardiac troponin is useful for establishing prognosis or disease severity in acutely decompensated HF.
The usefulness of BNP- or NT-proBNP guided therapy for acutely decompensated HF is not well-established.

Measurement of other clinically available tests such as biomarkers of myocardial injury or fibrosis may be considered for additive risk stratification in patients with acutely decompensated HF.
Initial and Serial Evaluation of the HF Patient

Biomarkers
Ambulatory/Outpatient
In ambulatory patients with dyspnea, measurement of BNP or N-terminal pro-B-type natriuretic peptide (NT-proBNP) is useful to support clinical decision making regarding the diagnosis of HF, especially in the setting of clinical uncertainty.

Measurement of BNP or NT-proBNP is useful for establishing prognosis or disease severity in chronic HF.
BNP- or NT-proBNP guided HF therapy can be useful to achieve optimal dosing of GDMT in select clinically euvolemic patients followed in a well-structured HF disease management program.

The usefulness of serial measurement of BNP or NT-proBNP to reduce hospitalization or mortality in patients with HF is not well established.

Measurement of other clinically available tests such as biomarkers of myocardial injury or fibrosis may be considered for additive risk stratification in patients with chronic HF.
Causes for Elevated Natriuretic Peptide Levels

<table>
<thead>
<tr>
<th>Cardiac</th>
<th>Noncardiac</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Heart failure, including RV syndromes</td>
<td>• Advancing age</td>
</tr>
<tr>
<td>• Acute coronary syndrome</td>
<td>• Anemia</td>
</tr>
<tr>
<td>• Heart muscle disease, including LVH</td>
<td>• Renal failure</td>
</tr>
<tr>
<td>• Valvular heart disease</td>
<td>• Pulmonary causes: obstructive sleep apnea, severe pneumonia, pulmonary hypertension</td>
</tr>
<tr>
<td>• Pericardial disease</td>
<td>• Critical illness</td>
</tr>
<tr>
<td>• Atrial fibrillation</td>
<td>• Bacterial sepsis</td>
</tr>
<tr>
<td>• Myocarditis</td>
<td>• Severe burns</td>
</tr>
<tr>
<td>• Cardiac surgery</td>
<td>• Toxic-metabolic insults, including cancer chemotherapy and envenomation</td>
</tr>
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</table>
# Recommendations for Biomarkers in HF

<table>
<thead>
<tr>
<th>Biomarker, Application</th>
<th>Setting</th>
<th>COR</th>
<th>LOE</th>
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<tbody>
<tr>
<td><strong>Natriuretic peptides</strong></td>
<td></td>
<td></td>
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<tr>
<td>Diagnosis or exclusion of HF</td>
<td>Ambulatory, Acute</td>
<td>I</td>
<td>A</td>
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<tr>
<td>Prognosis of HF</td>
<td>Ambulatory, Acute</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Achieve GDMT</td>
<td>Ambulatory</td>
<td>IIa</td>
<td>B</td>
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<tr>
<td>Guidance of acutely decompensated HF therapy</td>
<td>Acute</td>
<td>IIb</td>
<td>C</td>
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<td><strong>Biomarkers of myocardial injury</strong></td>
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<tr>
<td><strong>Biomarkers of myocardial fibrosis</strong></td>
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<td>Ambulatory</td>
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<td>Acute</td>
<td>IIb</td>
<td>A</td>
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</table>
2016 ESC Heart Failure Guidelines

Patient with suspected HF* (non-acute onset)

Assessment of HF probability

1. Clinical history:
   - History of CAD (MI, revascularization)
   - History of arterial hypertension
   - Exposure to cardiotoxic drugs/radiation
   - Use of diuretics
   - Orthopnoea / paroxysmal nocturnal dyspnoea

2. Physical examination:
   - Rales
   - Bilateral ankle oedema
   - Heart murmur
   - Jugular venous dilatation
   - Laterally displaced/broadened apical beat

3. ECG:
   - Any abnormality

≥1 present

Assessment of natriuretic peptides not routinely done in clinical practice

Echocardiography

If HF confirmed (based on all available data); determine aetiology and start appropriate treatment

Natriuretic peptides

- NT-proBNP ≥125 pg/mL
- BNP ≥35 pg/mL

HF unlikely: consider other diagnosis

Normal

All absent
Laboratory tests:
– Natriuretic peptides.
– Upon presentation to the ED or CCU/ICU, a plasma NP level (BNP, NT-proBNP or MR-proANP) should be measured in all patients with acute dyspnoea and suspected AHF to help in the differentiation of AHF from non-cardiac causes of acute dyspnoea. NPs have high sensitivity, and normal levels in patients with suspected AHF makes the diagnosis unlikely (thresholds: BNP, 100 pg/mL, NT-proBNP, 300 pg/mL, MR-proANP, 120 pg/mL).

However, elevated levels of NPs do not automatically confirm the diagnosis of AHF, as they may also be associated with a wide variety of cardiac and non-cardiac causes (Table 12.3). Unexpectedly low levels of NPs can be detected in some patients with decompensated end-stage HF, flash pulmonary oedema or right sided AHF.
For NYHA class II-IV patients. Provided estimated creatinine >30 mL/min and K+ <5.0 mEq/dL.
Medical Therapy for Stage C HFrEF: Magnitude of Benefit Demonstrated in RCTs

<table>
<thead>
<tr>
<th>GDMT</th>
<th>RR Reduction in Mortality</th>
<th>NNT for Mortality Reduction (Standardized to 36 mo)</th>
<th>RR Reduction in HF Hospitalizations</th>
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<tr>
<td>ACE inhibitor or ARB</td>
<td>17%</td>
<td>26</td>
<td>31%</td>
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<tr>
<td>Beta blocker</td>
<td>34%</td>
<td>9</td>
<td>41%</td>
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<tr>
<td>Aldosterone antagonist</td>
<td>30%</td>
<td>6</td>
<td>35%</td>
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<tr>
<td>Hydralazine/nitrate</td>
<td>43%</td>
<td>7</td>
<td>33%</td>
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Effects of Neprilysin Inhibition in Heart Failure

Endogenous vasoactive peptides
(natriuretic peptides, adrenomedullin, bradykinin, substance P, calcitonin gene-related peptide)

Neprilysin inhibition

Neurohormonal activation
Vascular tone
Cardiac fibrosis, hypertrophy
Sodium retention

Inactive metabolites

PARADIGM-HF: Primary Endpoint of CV Death or Heart Failure Hospitalization

Number needed to treat = 21

HR 0.80 (95% CI, 0.73–0.87), p<0.001

Sac/Val = Sacubitril/Valsartan.

# Sac/Val vs. Enalapril on Primary Endpoint and on CV Death by Subgroups

<table>
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<tr>
<th>Subgroup</th>
<th>Sac/Val No.</th>
<th>Enalapril No.</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-Value for Interaction</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-Value for Interaction</th>
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<td><strong>All Patients</strong></td>
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<td>4212</td>
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<td>&lt;65 years</td>
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<td>≥65 years</td>
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<td>&lt;60 mL/min/1.73 m²</td>
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<td>≥60 mL/min/1.73 m²</td>
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<td><strong>Ejection fraction</strong></td>
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<td>≤35%</td>
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<td>&gt;35%</td>
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<td><strong>Prior use of aldosterone antagonist</strong></td>
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<td><strong>Prior hospitalization for heart failure</strong></td>
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</table>

NP Changes with Sacubitril/Valsartan

A. Sacubitril/Valsartan

B. Change in NT-proBNP: Effects of Treatment

C. Change in BNP: Effects of Treatment

- **NP Changes with Sacubitril/Valsartan**

- **Figure A**: Diagram of the Natriuretic Peptide System showing the effects of Sacubitril/Valsartan on Pro-BNP, BNP, NT-proBNP, and other components of the Renin Angiotensin System.

- **Figure B**: Graph showing the change in NT-proBNP levels over time with different treatments.

- **Figure C**: Graph showing the change in BNP levels over time with different treatments.
NP Levels in PARADIGM-HF and Outcomes

Figure 1. Effects on Risk of Primary Endpoint if NT-proBNP Achieved or Did Not Achieve a Value of <1,000 pg/ml 1 Month After Randomization
Risk of primary endpoint after 1 month of randomization in patients with a baseline N-terminal pro–B-type natriuretic peptide.


Journal of the American College of Cardiology, Volume 68, Issue 22, 2016, 2425–2436
Newly Approved Heart Failure Drug

**Ivabradine**

- Acts by inhibiting the If channel, present in the cardiac SA node
- Reduces persistently elevated heart rate
- Approved by FDA in April 2015 for stable HF pts who have a resting HR of at least 70 bpm, and who are also taking the highest tolerable dose of a beta blocker

Ivabradine Inhibition of hyperpolarization-activated cyclic nucleotide–gated (HCN) channels.

Mitchell A. Psotka, and John R. Teerlink Circulation. 2016;133:2066-2075

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SHIFT Study: Design

Inclusion Criteria:
• ≥18 years; symptomatic HF NYHA Class II to IV; ischemic/non-ischemic etiology
• LV systolic dysfunction (EF ≤35%); heart rate ≥70 bpm; sinus rhythm
• Documented hospital admission for worsening HF ≤12 months

Ivabradine 5 mg bid, titrate to 7.5 mg bid on D14, adjust dose to 7.5/5/2.5 mg bid according HR and tolerability

Primary endpoint: CV death or hospitalization for worsening HF

SHIFT Study: Primary Endpoint of CV Death or Hospitalization for Worsening HF


**Graph:**
- **Ivabradine** (n=3241)
- **Placebo** (n=3264)

**Patients with Primary Endpoint (%):**
- Placebo: 937 events (29%)
- Ivabradine: 793 events (24%)

**HR 0.82 (95% CI, 0.75–0.90) p<0.0001
ARR = 5%, NNT = 20**
SHIFT Study: Hospitalization for Worsening HF

Patients with First Hospitalization for Worsening HF (%)

- Placebo: 672 events (21%)
- Ivabradine: 514 events (16%)

HR 0.74 (95% CI, 0.66-0.83)  p<0.0001
NNT = 20

SHIFT Study: Effect of Ivabradine on Outcomes

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Ivabradine (n=3241)</th>
<th>Placebo (n=3264)</th>
<th>HR</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>24%</td>
<td>29%</td>
<td>0.82</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>16%</td>
<td>17%</td>
<td>0.90</td>
<td>0.092</td>
</tr>
<tr>
<td>Death from HF</td>
<td>3%</td>
<td>5%</td>
<td>0.74</td>
<td>0.014</td>
</tr>
<tr>
<td>All-cause hospitalization</td>
<td>38%</td>
<td>42%</td>
<td>0.89</td>
<td>0.003</td>
</tr>
<tr>
<td>Any CV hospitalization</td>
<td>30%</td>
<td>34%</td>
<td>0.85</td>
<td>0.0002</td>
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<tr>
<td>CV death, hospitalization for worsening HF, or hospitalization for non-fatal MI</td>
<td>25%</td>
<td>30%</td>
<td>0.82</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Pharmacologic Treatment for Stage C HFrEF

**Strategies:**
- Cardiac Rehab
- Disease Management
- Process Improvement
- Patient Education
- Frailty Assessment
- Palliative Care
- Genetic Counseling

**Devices:**
- ICD
- CRT/D
- Remote PA monitoring

**HFrEF Stage C NYHA Class I – IV**

**Treatment:**

- For NYHA class II-IV patients. Provided estimated creatinine >30 mL/min and K+ <5.0 mEq/dL.
- For persistently symptomatic African Americans, NYHA class III-IV.
- For NYHA class II-IV patients. Provided estimated creatinine >30 mL/min and K+ <5.0 mEq/dL.

- **Class I, LOE A**
  - ACEI or ARB AND Beta Blocker

- **Class I, LOE C**
  - Loop Diuretics

- **Class I, LOE A**
  - Hydral-Nitrates

- **Class I, LOE A**
  - Aldosterone Antagonist

- Valsartan/Sacubutril, COR I
- Ivabradine, COR IIa
Treatment of HF, 2016 & beyond; an increasingly complex task

- 7 drugs (not counting diuretics, digoxin)
- 3 devices
- 7 strategies
- 17 choices

# of permutations for 17 choices taken six at a time?

8,910,720
### 2016 ACC/AHA/HFSA Heart Failure Guideline Update

#### Pharmacological Treatment for Stage C HFrEF

<table>
<thead>
<tr>
<th>Recommendations for Renin-Angiotensin System Inhibition With ACE Inhibitor or ARB or ARNI</th>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>ACE: A</td>
<td>The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors <em>(Level of Evidence: A)</em> (9-14), OR ARBs <em>(Level of Evidence: A)</em> (15-18), OR ARNI <em>(Level of Evidence: B-R)</em> (19) in conjunction with evidence-based beta blockers (20-22), and aldosterone antagonists in selected patients (23, 24), is recommended for patients with chronic HFrEF to reduce morbidity and mortality.</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>ARB: A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>ARNI: B-R</td>
<td>In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality (19).</td>
</tr>
<tr>
<td></td>
<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 (31, 32).</td>
</tr>
<tr>
<td></td>
<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>

ARNI = angiotensin receptor blocker and neprilysin inhibitor; COR = class of recommendation; LOE = level of evidence.

ESC HFrEF 2016 Guidelines

Patient with symptomatic HFrEF

Therapy with ACE-I and beta-blocker
(Up-titrte to maximum tolerated evidence-based doses)

Still symptomatic and LVEF ≤35%

Add MR antagonist
(up-titrte to maximum tolerated evidence-based dose)

Still symptomatic and LVEF ≤35%

Able to tolerate ACEI (or ARB)≤

Sinus rhythm, QRS duration ≥130 msec

ARNI to replace ACE-I

Evaluate need for CRT^d

Ivabradine

These above treatments may be combined if indicated

Resistant symptoms

Yes

Consider digoxin or H-ISDN or LVAD, or heart transplantation

No

No further action required
Consider reducing diuretic dose

Diuretics to relieve symptoms and signs of congestion

If LVEF <35% despite OMT or a history of symptomatic VT/VF, implant ICD

Angiotensin receptor neprilysin inhibitor

Sacubitril/valsartan is recommended as a replacement for an ACE-I to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE-I, a beta-blocker and an MRA^d
Pharmacological Treatment for Stage C HFrEF

<table>
<thead>
<tr>
<th>Recommendation for Ivabradine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COR</strong></td>
</tr>
<tr>
<td>IIa</td>
</tr>
</tbody>
</table>

COR = class of recommendation; LOE = level of evidence.

**ESC HFrEF 2016 Guidelines**

### If-channel inhibitor

Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF \(\leq 35\%\), in sinus rhythm and a resting heart rate \(\geq 70\) 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).

<table>
<thead>
<tr>
<th></th>
<th>IIa</th>
<th>B</th>
<th>180</th>
</tr>
</thead>
</table>

Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF \(\leq 35\%\), in sinus rhythm and a resting heart rate \(\geq 70\) 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).

<p>|  | IIa | C  | 181 |</p>
<table>
<thead>
<tr>
<th>Patient population</th>
<th>Treatment</th>
<th>Recommendation and LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2013 ACC/AHA guidelines</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| For all patients with HFrEF with volume overload, NYHA class II–IV                 | • Loop diuretics  
• In addition to ACE inhibitor or ARB and β-blocker                            | Class I, LOE C                          |
| For persistently symptomatic African American patients, NYHA class III–IV, to reduce morbidity and mortality | • Hydral-nitrates  
• In addition to ACE inhibitor, or ARB and β-blocker                            | Class I, LOE A                          |
| For patients with NYHA class II–IV with eGFR >30 ml/min/1.73 m² and K⁺ <5.0 mEq/l, to reduce morbidity and mortality | • Mineralocorticoid-receptor antagonists  
• In addition to ACE inhibitor or ARB in conjunction with β-blocker | Class I, LOE A                          |
| **2016 ACC/AHA/HFSA guideline update**                                             |                                                                                               |                                        |
| For patients with chronic HFrEF, to reduce morbidity and mortality                 | • ARNI in conjunction with β-blocker                                                         | Class I, LOE B-R                        |
| For patients with chronic symptomatic HFrEF, NYHA class II–III, who tolerate an ACE inhibitor or ARB | • ARNI to replace an ACE inhibitor or ARB                                                    | Class I, LOE B-R                        |
| For patients with stable chronic HFrEF (LVEF ≤35%), NYHA class II–III, who are in sinus rhythm with a heart rate ≥70 bpm at rest, to reduce heart failure hospitalization | • Ivabradine in addition to ACE inhibitor or ARB and β-blocker | Class IIa, LOE B-R                      |
A new classification of HF?

ESC HF GUIDELINES 2016

Table 3.1
Definition of heart failure with preserved (HFrEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

<table>
<thead>
<tr>
<th>Type of HF</th>
<th>HFrEF</th>
<th>HFmrEF</th>
<th>HFpEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Symptoms ± Signs¹</td>
<td>Symptoms ± Signs¹</td>
<td>Symptoms ± Signs¹</td>
</tr>
<tr>
<td>2</td>
<td>LVEF &lt;40%</td>
<td>LVEF 40–49%</td>
<td>LVEF ≥50%</td>
</tr>
<tr>
<td>3</td>
<td>−</td>
<td>1. Elevated levels of natriuretic peptides²;</td>
<td>1. Elevated levels of natriuretic peptide²;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. At least one additional criterion:</td>
<td>2. At least one additional criterion:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>a. relevant structural heart disease (LVH and/or LAE),</td>
<td>a. relevant structural heart disease (LVH and/or LAE),</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b. diastolic dysfunction (for details see Section 4.3.2.)</td>
<td>b. diastolic dysfunction (for details see Section 4.3.2.)</td>
</tr>
</tbody>
</table>
## ACC/AHA 2013 Definition of Heart Failure

<table>
<thead>
<tr>
<th>Classification</th>
<th>Ejection Fraction</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Heart Failure with Reduced Ejection Fraction (HFrEF)</td>
<td>≤40%</td>
<td>Also referred to as systolic HF. Randomized clinical trials have mainly enrolled patients with HFrEF and it is only in these patients that efficacious therapies have been demonstrated to date.</td>
</tr>
<tr>
<td>II. Heart Failure with Preserved Ejection Fraction (HFpEF)</td>
<td>≥50%</td>
<td>Also referred to as diastolic HF. Several different criteria have been used to further define HFpEF. The diagnosis of HFpEF is challenging because it is largely one of excluding other potential noncardiac causes of symptoms suggestive of HF. To date, efficacious therapies have not been identified.</td>
</tr>
<tr>
<td>a. HFpEF, Borderline</td>
<td>41% to 49%</td>
<td>These patients fall into a borderline or intermediate group. Their characteristics, treatment patterns, and outcomes appear similar to those of patient with HFpEF.</td>
</tr>
<tr>
<td>b. HFpEF, Improved</td>
<td>&gt;40%</td>
<td>It has been recognized that a subset of patients with HFpEF previously had HFrEF. These patients with improvement or recovery in EF may be clinically distinct from those with persistently preserved or reduced EF. Further research is needed to better characterize these patients.</td>
</tr>
</tbody>
</table>
Kaplan-Meier Curves, Adjusted for Age and Sex, Across the 3 Heart Failure Groups

The stratified log-rank $\chi^2$ was 15.0 (P < .001) for difference in mortality between groups. HFpEF indicates heart failure with preserved ejection fraction; HFrecEF, heart failure with recovered ejection fraction; and HFrEF, heart failure with reduced ejection fraction.
2016 ESC and ACC/AHA/HFSA heart failure guideline update — what is new and why is it important?

Mariell Jessup, Thomas H. Marwick, Piotr Ponikowski, Adriaan A. Voors and Clyde W. Yancy

Abstract | Heart failure (HF) is a global epidemic affecting millions of individuals worldwide. Although important progress has been made in the management of HF, this condition remains a common cause of morbidity and death. Since the publication of the previous sets of guidelines for the management of HF, new evidence has emerged that may affect daily practice. An update of the guidelines is therefore necessary, especially since the 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure document, summarizing an update on new pharmacotherapy for HF.
## Evidence-Based HFrEF Therapies

<table>
<thead>
<tr>
<th>Guideline Recommended Therapy</th>
<th>Relative Risk Reduction in Mortality</th>
<th>Number Needed to Treat for Mortality</th>
<th>NNT for Mortality (standardized to 36 months)</th>
<th>Relative Risk Reduction in HF Hospitalizations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI/ARB</td>
<td>17%</td>
<td>22 over 42 months</td>
<td>26</td>
<td>31%</td>
</tr>
<tr>
<td>ARNI</td>
<td>16%</td>
<td>36 over 27 months</td>
<td>27</td>
<td>21%</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>34%</td>
<td>28 over 12 months</td>
<td>9</td>
<td>41%</td>
</tr>
<tr>
<td>Aldosterone Antagonist</td>
<td>30%</td>
<td>9 over 24 months</td>
<td>6</td>
<td>35%</td>
</tr>
<tr>
<td>Hydralazine/Nitrate</td>
<td>43%</td>
<td>25 over 10 months</td>
<td>7</td>
<td>33%</td>
</tr>
<tr>
<td>CRT</td>
<td>36%</td>
<td>12 over 24 months</td>
<td>8</td>
<td>52%</td>
</tr>
<tr>
<td>ICD</td>
<td>23%</td>
<td>14 over 60 months</td>
<td>23</td>
<td>NA</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>26%</td>
</tr>
</tbody>
</table>

## Potential Impact of Optimal Implementation of Evidence-Based HFrEF Therapies on Mortality

<table>
<thead>
<tr>
<th>Guideline Recommended Therapy</th>
<th>HF Patient Population Eligible for Treatment, n*</th>
<th>Current HF Population Eligible and Untreated, n (%)</th>
<th>Potential Lives Saved per Year</th>
<th>Potential Lives Saved per Year (Sensitivity Range*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI/ARB</td>
<td>2,459,644</td>
<td>501,767 (20.4)</td>
<td>6516</td>
<td>(3336-11,260)</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>2,512,560</td>
<td>361,809 (14.4)</td>
<td>12,922</td>
<td>(6616-22,329)</td>
</tr>
<tr>
<td>Aldosterone Antagonist</td>
<td>603,014</td>
<td>385,326 (63.9)</td>
<td>21,407</td>
<td>(10,960-36,991)</td>
</tr>
<tr>
<td>Hydralazine/Nitrate</td>
<td>150,754</td>
<td>139,749 (92.7)</td>
<td>6655</td>
<td>(3407-11,500)</td>
</tr>
<tr>
<td>CRT</td>
<td>326,151</td>
<td>199,604 (61.2)</td>
<td>8317</td>
<td>(4258-14,372)</td>
</tr>
<tr>
<td>ICD</td>
<td>1,725,732</td>
<td>852,512 (49.4)</td>
<td>12,179</td>
<td>(6236-21,045)</td>
</tr>
<tr>
<td>Total</td>
<td>-</td>
<td>-</td>
<td>67,996</td>
<td>(34,813-117,497)</td>
</tr>
<tr>
<td>ARNI (replacing ACEI/ARB)</td>
<td>2,287,296</td>
<td>2,287,296 (100)</td>
<td>28,484</td>
<td>(18,230-41,017)</td>
</tr>
</tbody>
</table>

Potential Mortality Reduction With Implementation of Sacubitril/Valsartan Therapy

Optimal implementation of ARNI therapy was empirically estimated to prevent 28,484 (range, 18,230-41,017) deaths per year.

New Medical Therapies for Reduced Ejection Fraction Heart Failure

• RAAS inhibition remains the cornerstone of therapy for HFrEF

• Upregulating endogenous natriuretic peptide activity in concert with RAAS inhibition represents a now proven superior approach in the treatment of HFrEF; however, not every patient is a candidate for ARNI therapy

• Targeting the Hyperpolarization Channels in the SA node leads to important heart rate slowing now proven to be associated with reduced morbidity

• Risks associated with newer therapies are non-trivial and include hypotension & angioedema (ARNI class) and bradycardia and phosphenes (Ivabradine)

• Treatment algorithms are now much more complex and will require care assessment and well informed shared decision making

• A new phenotype of heart failure with “improved ejection fraction” is emerging with evidence of better outcomes; further study may lead to novel mechanisms capable of altering the natural history of HFrEF

• The potential lives saved via the best application of evidence based therapy measures thousands per year and merits our attention to best practices