Heart Science Amplified
Improving Guideline-Directed Heart Failure Care: New Considerations in HF incl.- ACC/AHA/HFSA Heart Failure Guidelines

Tuesday October 18, 2016
1:00pm – 2:00pm Central

Presenter: Clyde W. Yancy, MD, MSc

Amgen Cardiovascular proudly sponsors Heart Science Amplified: An Online Speaker Series and Get With The Guidelines™-Heart Failure.
Transitions of Care
Presented by Dr. Nancy Albert, PhD, CCNS, CHFN, CCRN, NE-BC

Register: https://engage.vevent.com/rt/ahaevents~110816

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Heart.org/quality
Clyde W. Yancy, MD, MSc

Professor of Medicine,
Professor, Medical Social Science
Chief, Cardiology
Associate Director, Bluhm CV Institute
& Vice-Dean, Diversity & Inclusion
Northwestern University, FSM
& Deputy Editor, JAMA Cardiology
Get With The Guidelines
Webinar: New Considerations in HF incl.- ACC/AHA/HFSA Heart Failure Guidelines

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Northwestern University, FSM
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Deputy Editor, JAMA Cardiology

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DISCLOSURES

• Consultant/speaker/honoraria: none

• JAMA Cardiology, Deputy Editor; Journal of the American College of Cardiology - senior associate editor (HF); American Journal of Cardiology - associate editor, supplements; American Heart Journal, Circulation; Circulation-Heart Failure - editorial boards

• Guideline writing committees: Chair, ACC/AHA, chronic HF; member, atrial fibrillation; hypertrophic cardiomyopathy; syncope guideline committees. Chair, Performance Measures, Sudden Cardiac Death

• Federal appointments: FDA: Immediate Past Chair, Cardiovascular Device Panel; ad hoc consultant; NIH – Scientific Management and Review Board; AHRQ- adhoc consultant; NHLBI- consultant; PCORI- former methodology committee member; IOM- writing group member

• Volunteer Appointments: American Heart Association- President, American Heart Association, 2009-2010; American College of Cardiology, Founder-CREDO
Agenda

• New Epidemiology of Heart Failure
• New Prevention Strategies
• New Treatment Paradigms
Temporal Trends in Heart Failure Incidence Rates Overall and by Reduced or Preserved Ejection Fraction Among Women and Men in Olmsted County, Minnesota, 2000 to 2010

Yearly rates (smoothed using 3-year moving average) per 100,000 persons have been standardized by the direct method to the age distribution of the US population in 2010. HFpEF indicates heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.
Agenda

• New Epidemiology of Heart Failure
• New Prevention Strategies
• New Treatment Paradigms
Stages, Phenotypes and Treatment of HF

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

- Patients with:
  - HTN
  - Atherosclerotic disease
  - DM
  - Obesity
  - Metabolic syndrome

**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

- 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
- Revascularization or valvular surgery as appropriate

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

- Patients with:
  - Known structural heart disease and
  - HF signs and symptoms

**THERAPY**
- Goals: Control symptoms
  - Patient education
  - 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

- Patients with:
  - Marked HF symptoms at rest
  - Recurrent hospitalizations despite GDMT

**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

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

**Heart Failure**

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

**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

**At Risk for Heart Failure**

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

- Development of symptoms of HF
- Refractory 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

- 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

Options:
- Advanced care measures
- Heart transplant
- Chronic inotropes
- Temporary or permanent MCS
- Experimental surgery or drugs
- Palliative care and hospice
- ICD deactivation
Prevalence and prognostic significance of HF Stages

Survival (years)

Ammar et al. *Circulation* 2007; 115:1563
STAGE A HF: Hypertension as a Risk Factor for HF in African Americans

Blood Pressure Lowering Treatment Based on CV Risk: A Meta-analysis of Individual Patient Data

<table>
<thead>
<tr>
<th>5-year risk of stroke</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4.0%</td>
<td>0.75 (0.62 to 0.91)</td>
</tr>
<tr>
<td>4.0%-5.4%</td>
<td>0.83 (0.69 to 0.99)</td>
</tr>
<tr>
<td>5.4%-7.2%</td>
<td>0.84 (0.70 to 1.00)</td>
</tr>
<tr>
<td>&gt;7.2%</td>
<td>0.84 (0.71 to 1.00)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5-year risk of CHD</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5%</td>
<td>0.85 (0.70 to 1.04)</td>
</tr>
<tr>
<td>5%-7%</td>
<td>0.94 (0.78 to 1.15)</td>
</tr>
<tr>
<td>7%-11%</td>
<td>0.85 (0.70 to 1.02)</td>
</tr>
<tr>
<td>&gt;11%</td>
<td>0.87 (0.72 to 1.04)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5-year risk of heart failure</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2.6%</td>
<td>0.91 (0.70 to 1.18)</td>
</tr>
<tr>
<td>2.6%-4.5%</td>
<td>0.93 (0.71 to 1.21)</td>
</tr>
<tr>
<td>4.5%-7.0%</td>
<td>0.87 (0.67 to 1.12)</td>
</tr>
<tr>
<td>&gt;7.0%</td>
<td>0.72 (0.55 to 0.93)</td>
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<table>
<thead>
<tr>
<th>5-year risk of cardiovascular death</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5%</td>
<td>0.83 (0.72 to 1.06)</td>
</tr>
<tr>
<td>5%-8%</td>
<td>0.83 (0.72 to 1.05)</td>
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<tr>
<td>8%-13%</td>
<td>0.87 (0.72 to 1.04)</td>
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<tr>
<td>&gt;13%</td>
<td>0.93 (0.78 to 1.10)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5-year risk of death</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6%</td>
<td>0.93 (0.81 to 1.07)</td>
</tr>
<tr>
<td>6%-10%</td>
<td>0.92 (0.80 to 1.06)</td>
</tr>
<tr>
<td>10%-16%</td>
<td>0.92 (0.80 to 1.05)</td>
</tr>
<tr>
<td>&gt;16%</td>
<td>0.97 (0.85 to 1.08)</td>
</tr>
</tbody>
</table>

Favours active treatment
Favours control
SPRINT Hypertension Trial

• Study Type: Interventional Study
Design: Allocation: Randomized
Endpoint Classification: Efficacy Study
Intervention Model: Parallel Assignment
Masking: Single Blind (Outcomes Assessor)
Official Title: Systolic Blood Pressure Intervention Trial

Primary Outcome Measures: First occurrence of a myocardial infarction (MI), acute coronary syndrome (ACS), stroke, heart failure (HF), or CVD death [Time Frame: 6 years] [Designated as safety issue: No]

Secondary Outcome Measures: All-cause mortality; Development of end stage renal disease (ESRD), Dementia, Decline in cognitive function, Small vessel cerebral ischemic disease

• Estimated Enrollment: 9250 Study Start Date: October 2010 Estimated Study Completion Date: December 2018 Estimated Primary Completion Date: October 2018 (Final data collection date for primary outcome measure)
Increased CV risk as defined by SPRINT:

- clinical or subclinical cardiovascular disease other than stroke;
- chronic kidney disease, excluding polycystic kidney disease, with an estimated glomerular filtration rate (eGFR) of 20 to less than 60 ml per minute per 1.73 m² of body-surface area, calculated with the use of the four-variable Modification of Diet in Renal Disease equation;
- a 10-year risk of cardiovascular disease of 15% or greater on the basis of the Framingham risk score;
- or an age of 75 years or older
Systolic Blood Pressure in the Two Treatment Groups over the Course of the Trial.

No. with Data

<table>
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<tr>
<th></th>
<th>Years</th>
<th>Standard treatment</th>
<th>Intensive treatment</th>
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<tr>
<td>0</td>
<td>4683</td>
<td>4345</td>
<td>4222</td>
</tr>
<tr>
<td>1</td>
<td>4092</td>
<td>3997</td>
<td>4091</td>
</tr>
<tr>
<td>2</td>
<td>3904</td>
<td>3115</td>
<td>3204</td>
</tr>
<tr>
<td>3</td>
<td>1974</td>
<td>1000</td>
<td>2035</td>
</tr>
<tr>
<td>4</td>
<td>1048</td>
<td>274</td>
<td>286</td>
</tr>
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Mean No. of Medications

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<tr>
<th></th>
<th></th>
<th>Standard treatment</th>
<th>Intensive treatment</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>1.9</td>
<td>1.8</td>
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<td>2</td>
<td>1.8</td>
<td>1.8</td>
<td>2.7</td>
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<tr>
<td>3</td>
<td>1.8</td>
<td>1.8</td>
<td>2.8</td>
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<tr>
<td>4</td>
<td>1.8</td>
<td>1.8</td>
<td>2.8</td>
</tr>
<tr>
<td>5</td>
<td>1.8</td>
<td>1.8</td>
<td>2.8</td>
</tr>
</tbody>
</table>

Primary Outcome and Death from Any Cause.

A Primary Outcome

No. at Risk
Standard treatment 4683 4437 4228 2829 721
Intensive treatment 4678 4436 4256 2900 779

B Death from Any Cause

No. at Risk
Standard treatment 4683 4528 4383 2998 789
Intensive treatment 4678 4516 4390 3016 807

Primary and Secondary Outcomes and Renal Outcomes.

**Table 2. Primary and Secondary Outcomes and Renal Outcomes.**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intensive Treatment</th>
<th>Standard Treatment</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients (%)</td>
<td>% per year</td>
<td>no. of patients (%)</td>
<td>% per year</td>
</tr>
<tr>
<td>All participants [N = 4678]</td>
<td></td>
<td></td>
<td>[N = 4683]</td>
<td></td>
</tr>
<tr>
<td>Primary outcome‡</td>
<td>243 (5.2)</td>
<td>1.65</td>
<td>319 (6.8)</td>
<td>2.19</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>97 (2.1)</td>
<td>0.65</td>
<td>116 (2.5)</td>
<td>0.78</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>40 (0.9)</td>
<td>0.27</td>
<td>40 (0.9)</td>
<td>0.27</td>
</tr>
<tr>
<td>Stroke</td>
<td>62 (1.3)</td>
<td>0.41</td>
<td>70 (1.5)</td>
<td>0.47</td>
</tr>
<tr>
<td>Heart failure</td>
<td>62 (1.3)</td>
<td>0.41</td>
<td>100 (2.1)</td>
<td>0.67</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>37 (0.8)</td>
<td>0.25</td>
<td>65 (1.4)</td>
<td>0.43</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>155 (3.3)</td>
<td>1.03</td>
<td>210 (4.5)</td>
<td>1.40</td>
</tr>
<tr>
<td>Primary outcome or death</td>
<td>332 (7.1)</td>
<td>2.25</td>
<td>423 (9.0)</td>
<td>2.90</td>
</tr>
<tr>
<td>Participants with CKD at baseline [N = 1330]</td>
<td></td>
<td></td>
<td>[N = 1316]</td>
<td></td>
</tr>
<tr>
<td>Composite renal outcome‡‡</td>
<td>14 (1.1)</td>
<td>0.33</td>
<td>15 (1.1)</td>
<td>0.36</td>
</tr>
<tr>
<td>≥50% reduction in estimated GFR§§</td>
<td>10 (0.8)</td>
<td>0.23</td>
<td>11 (0.8)</td>
<td>0.26</td>
</tr>
<tr>
<td>Long-term dialysis</td>
<td>6 (0.5)</td>
<td>0.14</td>
<td>10 (0.8)</td>
<td>0.24</td>
</tr>
<tr>
<td>Kidney transplantation</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incident albuminuria¶¶</td>
<td>49/526 (9.3)</td>
<td>3.02</td>
<td>59/500 (11.8)</td>
<td>3.90</td>
</tr>
<tr>
<td>Participants without CKD at baseline [N = 3332]</td>
<td></td>
<td></td>
<td>[N = 3345]</td>
<td></td>
</tr>
<tr>
<td>≥30% reduction in estimated GFR to &lt;60 ml/ min/1.73 m²§§</td>
<td>127 (3.8)</td>
<td>1.21</td>
<td>37 (1.1)</td>
<td>0.35</td>
</tr>
<tr>
<td>Incident albuminuria¶¶</td>
<td>110/1769 (6.2)</td>
<td>2.00</td>
<td>135/1831 (7.4)</td>
<td>2.41</td>
</tr>
</tbody>
</table>

* CI denotes confidence interval, and CKD chronic kidney disease.
† The primary outcome was the first occurrence of myocardial infarction, acute coronary syndrome, stroke, heart failure, or death from cardiovascular causes.
‡ The composite renal outcome for participants with CKD at baseline was the first occurrence of a reduction in the estimated GFR of 50% or more, long-term dialysis, or kidney transplantation.
§ Reductions in the estimated GFR were confirmed by a second laboratory test at least 90 days later.
¶ Incident albuminuria was defined as a doubling of the ratio of urinary albumin (in milligrams) to creatinine (in grams) from less than 10 at baseline to greater than 10 during follow-up. The denominators for number of patients represent those without albuminuria at baseline.
|| No long-term dialysis or kidney transplantation was reported among participants without CKD at baseline.

09/11/2015; Announcement of premature termination of SPRINT for benefit

• “...treating high-risk hypertensive adults 50 years of age and older to a target of 120 mm Hg significantly reduced cardiovascular events by 30% and reduced all-cause mortality by nearly 25% when compared with patients treated to a target of 140 mm Hg...”
Kaplan-Meier Analysis of Major Adverse Cardiovascular Events in the Full Study Sample and in Participants With BNP ≥50 pg/mL

BNP indicates brain-type natriuretic peptide. Major adverse cardiovascular events included arrhythmia, transient ischemic attack, stroke, myocardial infarction, peripheral or pulmonary thrombosis/embolus, or heart failure. In the full sample, 51 (7.3%) of 697 patients were admitted for major adverse cardiovascular events in the intervention group and 71 (10.5%) of 677 were admitted in the control group. In participants with BNP ≥50 pg/mL, 35 (13.3%) of 263 were admitted for major adverse cardiovascular events in the intervention group and 45 (19.1%) of 235 were admitted in the control group.
Agenda

• New Epidemiology of Heart Failure
• New Prevention Strategies
• New Treatment Paradigms
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

Add

Class I, LOE C
Loop Diuretics

Class I, LOE A
Hydral-Nitrates

Class I, LOE A
Aldosterone Antagonist

<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>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor or ARB</td>
<td>17%</td>
<td>26</td>
<td>31%</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>34%</td>
<td>9</td>
<td>41%</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>30%</td>
<td>6</td>
<td>35%</td>
</tr>
<tr>
<td>Hydralazine/nitrate</td>
<td>43%</td>
<td>7</td>
<td>33%</td>
</tr>
</tbody>
</table>

Mechanism of Action of LCZ696

Figure 1

**Single-blind Active Run-in Period**

- Enalapril run-in
  - Visit 2A
  - Enalapril 5 mg bid (optional)
  - 1-2w

**Double-blind Treatment Period**

- LCZ696 run-in
  - LCZ696 100 mg bid
  - LCZ696 200 mg bid

- LCZ696 200 mg bid

- Enalapril 10 mg bid

**Visit 1**

- Time: 1w

**Visit 2**

- Time: 2w

**Visit 3**

- Time: 1-2w

**Visit 4**

- Time: 2-4w

**Visit 5**

- Time: up to end of study

**Visit 6**

- Time: 8w

**Visit 7**

- Time: 4m

**Visit 8**

- Time: 8m

**Visit 9**

- Visit every 4m

**PARADIGM-HF study schema.**
PARADIGM-HF
(Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure trial)

Death from CV causes
20% risk reduction

HF hospitalization
21% risk reduction

HR: 0.80 (0.73, 0.87) p = 0.0000004

McMurray, Packer et al  NEJM 2014
Kaplan–Meier Curve for the Time to First Hospitalization for Heart Failure During First 30 Days After Randomization, According to Study Group

Hazard ratio 0.60 (0.38-0.94)  
P = 0.027

Packer M et al. Circulation. 2015;131:54-61
Pharmacologic Treatment for Stage C HFrEF- 2016

Strategies:
- Disease Management
- Genetic Counseling
- Frailty Assessments
- Palliative Care

Co-morbidities
- Anemia
- Sleep disordered breathing
- Hypertension
- Atrial Fibrillation

Devices
- Remote PA monitoring
- Wearable Vests

Quality Improvement
- Process Improvement
- Patient Education

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:
- Valsartan/Sacubutril
- Ivabradine

For NYHA class II-IV patients:
- Provided estimated creatinine >30 mL/min and K+ <5.0 mEq/dL

- ACEI or ARB AND Beta Blocker

Class I, LOE A

Class I, LOE A

Class I, LOE A

Loop Diuretics

Hydral-Nitrates

Aldosterone Antagonist

Add

Add

Add
New Guidelines Have Emerged- 2016

Yancy, CW, et al.
Heart Failure Focused Update on Pharmacological Therapy

2016 ACC/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

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 International Society for Heart and Lung Transplantation

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Northwestern Medicine
Yancy, CW, et al.
Heart Failure Focused Update on Pharmacological Therapy

Table 1. Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care* (Updated August 2015)

<table>
<thead>
<tr>
<th>CLASS (STRENGTH) OF RECOMMENDATION</th>
<th>LEVEL (QUALITY) OF EVIDENCE‡</th>
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<tbody>
<tr>
<td><strong>CLASS I (STRONG)</strong></td>
<td>Benefit &gt;&gt;&gt; Risk</td>
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<tr>
<td>Suggested phrases for writing recommendations:</td>
<td>High-quality evidence‡ from more than 1 RCT</td>
</tr>
<tr>
<td>Is recommended</td>
<td>Meta-analyses of high-quality RCTs</td>
</tr>
<tr>
<td>Is indicated/useful/effective/beneficial</td>
<td>One or more RCTs corroborated by high-quality registry studies</td>
</tr>
<tr>
<td>Should be performed/administered/other</td>
<td></td>
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<tr>
<td>Comparative-Effectiveness Phrases‡:</td>
<td></td>
</tr>
<tr>
<td>Treatment/strategy A is recommended/indicated in preference to treatment B</td>
<td></td>
</tr>
<tr>
<td>Treatment A should be chosen over treatment B</td>
<td></td>
</tr>
</tbody>
</table>

| CLASS IIa (MODERATE) | Benefit >> Risk | **LEVEL B-R** (Randomized) |
| Suggested phrases for writing recommendations: | Moderate-quality evidence‡ from 1 or more RCTs |
| Is reasonable | Meta-analyses of moderate-quality RCTs |
| Can be useful/effective/beneficial | |
| Comparative-Effectiveness Phrases‡: | |
| Treatment/strategy A is probably recommended/indicated in preference to treatment B | |
| It is reasonable to choose treatment A over treatment B | |

| CLASS IIb (WEAK) | Benefit > Risk | **LEVEL B-NR** (Nonrandomized) |
| Suggested phrases for writing recommendations: | Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies |
| May/might be reasonable | Meta-analyses of such studies |
| May/might be considered | |
| Usefulness/effectiveness is unknown/unclear/uncertain or not well established | |

| CLASS III: No Benefit (MODERATE) | Benefit = Risk | **LEVEL C-LD** (Limited Data) |
| Suggested phrases for writing recommendations: | Randomized or nonrandomized observational or registry studies with limitations of design or execution |
| Is not recommended | Meta-analyses of such studies |
| Is not indicated/useful/effective/beneficial | Physiological or mechanistic studies in human subjects |
| Should not be performed/administered/other | |

| CLASS III: Harm (STRONG) | Risk > Benefit | **LEVEL C-EO** (Expert Opinion) |
| Suggested phrases for writing recommendations: | Consensus of expert opinion based on clinical experience |
| Potentially harmful | | |
| Causes harm | | |
| Associated with excess morbidity/mortality | | |
| Should not be performed/administered/other | | |

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 IIa, 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.
RAAS inhibition- 2016

7.3.2. Pharmacological Treatment for Stage C HF With Reduced Ejection Fraction: Recommendations

7.3.2.10. Renin-Angiotensin System Inhibition With Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker or ARNI: Recommendations

See the Online Data Supplement (http://jaccjacc.acc.org/Clinical Document/2016 Heart Failure Focused Update Data Supplement New Therapy Only S5.pdf) for evidence supporting these recommendations.

<table>
<thead>
<tr>
<th>Recommendations for Renin-Angiotensin System Inhibition With ACE Inhibitor or ARB or ARNI</th>
</tr>
</thead>
<tbody>
<tr>
<td>COR</td>
</tr>
<tr>
<td>-----</td>
</tr>
<tr>
<td>I</td>
</tr>
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<td></td>
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</tbody>
</table>
## RAASi in Heart Failure and Post-MI LV Dysfunction

<table>
<thead>
<tr>
<th></th>
<th>Post-MI Low EF</th>
<th>Mild-Mod CHF Low EF</th>
<th>CHF Severe HF</th>
<th>CHF Preserved EF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACEi</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>AIRE SAVE</td>
<td>SOLVD</td>
<td>CONSENSUS</td>
<td>PEP-CHF (perindopril)</td>
</tr>
<tr>
<td><strong>MRA</strong></td>
<td>EPHESUS&lt;sup&gt;1&lt;/sup&gt; (eplerenone)</td>
<td>EMPHASIS&lt;sup&gt;1&lt;/sup&gt; (eplerenone)</td>
<td>RALES&lt;sup&gt;1&lt;/sup&gt; (spironolactone)</td>
<td>TOPCAT&lt;sup&gt;2&lt;/sup&gt; (spironolactone)</td>
</tr>
<tr>
<td><strong>ARB</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>OPTIMAAL VALIANT</td>
<td>ELITE-II HEALL VAL-HeFT CHARM</td>
<td></td>
<td>CHARM-Preserved I-PRESERVE</td>
</tr>
<tr>
<td><strong>ARNI</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td>PARADIGM-HF (LCZ-696)</td>
</tr>
</tbody>
</table>

RAASi=renin-angiotensin-aldosterone inhibitor; MI=myocardial infarction; EF: ejection fraction; CHF=chronic heart failure; ACEi=angiotensin-converting enzyme inhibitor; MRA=mineralocorticoid receptor antagonist; ARB=angiotensin II receptor blocker; ARNI=angiotensin receptor-neprilysin inhibitor.

The use of ACE inhibitors is beneficial for patients with prior or current symptoms of chronic HFrEF to reduce morbidity and mortality (9-14, 25).

ACE inhibitors have been shown in large RCTs to reduce morbidity and mortality in patients with HFrEF with mild, moderate, or severe symptoms of HF, with or without coronary artery disease (9-14). Data suggest that there are no differences among available ACE inhibitors in their effects on symptoms or survival (25). ACE inhibitors should be started at low doses and titrated upward to doses shown to reduce the risk of cardiovascular events in clinical trials. ACE inhibitors can produce angioedema and should be given with caution to patients with low systemic blood pressures, renal insufficiency, or elevated serum potassium (>5.0 mEq/L). Angioedema occurs in <1% of patients who take an ACE inhibitor, but it occurs more frequently in blacks and women (26). Patients should not be given ACE inhibitors if they are pregnant or plan to become pregnant. ACE inhibitors also inhibit kininase and increase levels of bradykinin, which can induce cough in up to 20% of patients but also may contribute to beneficial vasodilation. If maximal doses are not tolerated, intermediate doses should be tried; abrupt withdrawal of ACE inhibition can lead to clinical deterioration and should be avoided.

Although the use of an ARNI in lieu of an ACE inhibitor for HFrEF has been found to be superior, for those patients for whom ARNI is not appropriate, continued use of an ACE inhibitor for all classes of HFrEF remains strongly advised.

The use of ARBs to reduce morbidity and mortality is recommended in patients with prior or current symptoms of chronic HFrEF who are intolerant to ACE inhibitors because of cough or angioedema (15-18, 27, 28).
<table>
<thead>
<tr>
<th>I</th>
<th>ARNI: B-R</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>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).</strong></td>
<td></td>
</tr>
</tbody>
</table>

Benefits of ACE inhibitors with regard to decreasing HF progression, hospitalizations, and mortality rate have been shown consistently for patients across the clinical spectrum, from asymptomatic to severely symptomatic HF. Similar benefits have been shown for ARBs in populations with mild-to-moderate HF who are unable to tolerate ACE inhibitors. In patients with mild-to-moderate HF (characterized by either 1) mildly elevated natriuretic peptide levels, BNP [B-type natriuretic peptide] ≥150 pg/mL or NT-proBNP [N-terminal pro-B-type natriuretic peptide] ≥600 pg/mL; or 2) BNP ≥100 pg/mL or NT-proBNP ≥400 pg/mL with a prior hospitalization in the preceding 12 months) who were able to tolerate both a target dose of enalapril (10 mg twice daily) and then subsequently an ARNI (valsartan/sacubitril; 200 mg twice daily, with the ARB component equivalent to valsartan 160 mg), hospitalizations and mortality were significantly decreased with the valsartan/sacubitril compound compared with enalapril. The target dose of the ACE inhibitor was consistent with that known to improve outcomes in previous landmark clinical trials (10).

See Online Data Supplements 1 and 18.
<table>
<thead>
<tr>
<th>III: Harm</th>
<th>B-R</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ARNI</strong> should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor (31, 32).</td>
<td></td>
</tr>
</tbody>
</table>

See Online Data Supplement 3.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral neprilysin inhibitors, used in combination with ACE inhibitors can lead to angioedema and concomitant use is contraindicated and should be avoided. A medication that represented both a neprilysin inhibitor and an ACE inhibitor,</td>
<td></td>
</tr>
</tbody>
</table>
7.3.2.11. Ivabradine: Recommendation

See the Online Data Supplement

**Recommendation for Ivabradine**

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</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 HFrEF (LVEF ≤35%) who are receiving GDEM, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest (37-40).</td>
</tr>
</tbody>
</table>

Ivabradine is a new therapeutic agent that selectively inhibits the If current in the sinoatrial node, providing heart rate reduction. One RCT demonstrated the efficacy of ivabradine in reducing the composite endpoint of cardiovascular death or HF hospitalization (38). The benefit of ivabradine was driven by a reduction in HF hospitalization. The study included patients with HFrEF (NYHA class II-IV, albeit with only a modest representation of NYHA class IV HF) and left ventricular ejection fraction (LVEF) ≤35%, in sinus rhythm with a resting heart rate of ≥70 beats per minute. Patients enrolled included a small number with paroxysmal atrial fibrillation (<40% of the time) but otherwise in
### SUMMARY OF ACC/AHA/HFSA 2016 HF Guidelines: Focused Update

**Table 1 | Pharmacological treatment recommendations for patients with stage C HFrEF**

<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>
<tr>
<td>For all patients with HFrEF with volume overload, NYHA class II–IV</td>
<td>• Loop diuretics</td>
<td>Class I, LOE C</td>
</tr>
<tr>
<td></td>
<td>• In addition to ACE inhibitor or ARB and β-blocker</td>
<td></td>
</tr>
<tr>
<td>For persistently symptomatic African American patients, NYHA class III–IV, to reduce morbidity and mortality</td>
<td>• Hydral-nitrates</td>
<td>Class I, LOE A</td>
</tr>
<tr>
<td></td>
<td>• In addition to ACE inhibitor, or ARB and β-blocker</td>
<td></td>
</tr>
<tr>
<td>For patients with NYHA class II–IV with eGFR &gt;30 ml/min/1.73m² and K⁺ &lt;5.0 mEq/l, to reduce morbidity and mortality</td>
<td>• Mineralocorticoid-receptor antagonists</td>
<td>Class I, LOE A</td>
</tr>
<tr>
<td></td>
<td>• In addition to ACE inhibitor or ARB in conjunction with β-blocker</td>
<td></td>
</tr>
<tr>
<td><strong>2016 ACC/AHA/HFSA guideline update</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For patients with chronic HFrEF, to reduce morbidity and mortality</td>
<td>• ARNI in conjunction with β-blocker</td>
<td>Class I, LOE B–R</td>
</tr>
<tr>
<td>For patients with chronic symptomatic HFrEF, NYHA class II–III, who tolerate an ACE inhibitor or ARB</td>
<td>• ARNI to replace an ACE inhibitor or ARB</td>
<td>Class I, LOE B–R</td>
</tr>
<tr>
<td>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</td>
<td>• Ivabradine in addition to ACE inhibitor or ARB and β-blocker</td>
<td>Class IIa, LOE B–R</td>
</tr>
</tbody>
</table>
Evidence-based medical therapy.

Heart Failure with Reduced Ejection Fraction
NYHA Class I-IV patients

Sacubitril-Valsartan or ACEI or ARB
AND
Beta Blocker

For all volume overloaded
NYHA Class II-IV patients

For NYHA class II-IV patients
provided estimated creatinine
 clearance \( \geq 30 \text{ mL/min} \)
and \( K^+ \leq 5.0 \text{ mEq/dL} \)

Loop ± Thiazide Diuretic

Mineralocorticoid Receptor
Antagonist

For persistently
symptomatic
NYHA class III-IV
Blacks (African Descent)

Hydralazine-Nitrates

Contraindications
- Acute Heart Failure
- Blood Pressure Under
90/50 mmHg
- Sick Sinus Syndrome
- Sinoatrial Block
- 3rd Degree AV Block
  (without a pacemaker)
- Pacemaker Dependence
- Atrial Fibrillation
- Severe Hepatic Disease

For persistently
symptomatic NYHA class II-
IV patients with LVEF \( \leq 35\% \)
AND heart rate \( \geq 70 \text{ bpm} \)
in sinus rhythm AND either
intolerant to or on
maximally-tolerated doses
of beta blocker

Ivabradine

Contraindications
- Pregnancy (Fetal Toxicity)
- Strong CYP3A4 Inhibitors
  (Azoles, Macrolides, PIs)

Not Recommended
- Moderate CYP3A4
  Inhibitors
  (Diltiazem, Verapamil,
  Grapefruit Juice)
- 2nd Degree AV Block

Monitor for Adverse Events
- Atrial Fibrillation (Requires ivabradine discontinuation due to lack of efficacy)
- Bradycardia (May require discontinuation or dose adjustment for symptoms)
- Phosphenes (May require discontinuation depending on patient preference)
PATIENT WITH SUSPECTED HF* (non-acute onset)

ASSESSMENT OF HF PROBABILITY

1. Clinical history:
   - History of CAD (Mi, revascularization)
   - History of arterial hypertension
   - Exposition to cardiotoxic drug/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

All absent

HF unlikely; consider other diagnosis

Normal

No

Yes
ESC HFrEF Treatment Algorithm

Patient with symptomatic \(^a\) HFrEF \(^b\)

Therapy with ACE-I \(^a\) and beta-blocker
(Up-titrative to maximum tolerated evidence-based doses)

If LVEF \(\leq 35\%\) despite OMT

Diuretics to relieve symptoms and signs of congestion

or a history of symptomatic VT/VF, implant ICD

Still symptomatic and LVEF \(\leq 35\%\)

Add MR antagonist \(^a\)
(up-titrative to maximum tolerated evidence-based dose)

Still symptomatic and LVEF \(\leq 35\%\)

Able to tolerate ACEI (or ARB) \(^a\)

Sinus rhythm, QRS duration \(\geq 130\) msec

Sinus rhythm, \(HR \geq 70\) bpm

ARNI to replace ACE-I

Evaluate need for CRT \(^d\)

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
A new classification?

ESC HF GUIDELINES 2016

<table>
<thead>
<tr>
<th>Type of HF</th>
<th>HFrEF</th>
<th>HFmrEF</th>
<th>HFP EF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Symptoms ± Signs$\textsuperscript{a}$</td>
<td>Symptoms ± Signs$\textsuperscript{a}$</td>
<td>Symptoms ± Signs$\textsuperscript{a}$</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 peptides$\textsuperscript{b}$; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).</td>
<td>1. Elevated levels of natriuretic 2. At least one additional criterion a. relevant structural heart di</td>
</tr>
</tbody>
</table>
# Definition of Heart Failure

<table>
<thead>
<tr>
<th>Classification</th>
<th>Ejection Fraction</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I. Heart Failure with Reduced Ejection Fraction (HFrEF)</strong></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><strong>II. Heart Failure with Preserved Ejection Fraction (HFrEF)</strong></td>
<td>≥50%</td>
<td>Also referred to as diastolic HF. Several different criteria have been used to further define HFrEF. The diagnosis of HFrEF 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. HFrEF, 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 HFrEF.</td>
</tr>
<tr>
<td>b. HFrEF, Improved</td>
<td>&gt;40%</td>
<td>It has been recognized that a subset of patients with HFrEF 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. HFP EF 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 accumulated. The Joint Task Force on the Practice of Cardiovascular Medicine of the European Society of Cardiology (ESC) and the American Heart Association (AHA) have independently updated their guidelines. Today no one disputes that, by applying evidence-based discoveries, HF has become a treatable disease.

The Task Force on the 2016 ESC HF guidelines, which we had the privilege to co-chair, decided to complete a full document that, in its final form, is the result of extensive interactions between the Task Force, the review team, and the ESC Committee for Practice Guidelines. In parallel, on the other side of the Atlantic, a distinguished group of US colleagues has issued entirely independently the 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure document, summarizing an update on new pharmacotherapy for HF. We see these two documents as presenting similar
### Table. Demonstrated Benefits of Evidence-Based Therapies for Patients With Heart Failure and Reduced Ejection Fraction

<table>
<thead>
<tr>
<th>Evidence-Based Therapy</th>
<th>Relative Risk Reduction in All-Cause Mortality in Pivotal Randomized Clinical Trial(s), %</th>
<th>NNT to Prevent All-Cause Mortality Over Time</th>
<th>NNT for All-Cause Mortality&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI/ARB</td>
<td>17</td>
<td>22 over 42 mo</td>
<td>77</td>
</tr>
<tr>
<td>ARNI&lt;sup&gt;b&lt;/sup&gt;</td>
<td>16</td>
<td>36 over 27 mo</td>
<td>80</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>34</td>
<td>28 over 12 mo</td>
<td>28</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>30</td>
<td>9 over 24 mo</td>
<td>18</td>
</tr>
<tr>
<td>Hydralazine/nitrate</td>
<td>43</td>
<td>25 over 10 mo</td>
<td>21</td>
</tr>
<tr>
<td>CRT</td>
<td>36</td>
<td>12 over 24 mo</td>
<td>24</td>
</tr>
<tr>
<td>ICD</td>
<td>23</td>
<td>14 over 60 mo</td>
<td>70</td>
</tr>
</tbody>
</table>

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator. NNT, number needed to treat.

<sup>a</sup> Standardized to 12 months.

<sup>b</sup> Benefit of ARNI therapy incremental to that achieved with ACEI therapy. For the other medications shown, the benefits are based on comparisons to placebo control.
THANK YOU

More Questions about Get With The Guidelines?

Visit heart.org/QualityHF to find your local Get With The Guidelines representative.

Liz Olson, CVA
Program Manager, Get With The Guidelines® - Resuscitation & Heart Failure
Liz.Olson@heart.org  Phone 214-706-1528
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