What is New in Managing Patients with Heart Failure?
Symptom onset: 11:20 3/11/07 VF
Door time: 12:08 3/11/07 QMH
Balloon time: 13:35 3/11/07
Door-to-Balloon Time: 87min

Mechanical Ventilation Shock, IABP

Heart Failure After Acute Myocardial Infarction: “A Lost Battle in the War on Heart Failure”

THIS IS THE BEGINNING OF THE JOURNEY, NOT THE END!
Heart Failure After Acute Myocardial Infarction: “A Lost Battle in the War on Heart Failure”

- 5-year mortality for HF ~50%
- HF death ↑ ~135% (1970-98)
- HF Hospital discharge ↑ ~160% (1979-98)

AHA. 2002 Statistical update

Epidemiology of HF in US

- HF is the final common path of all heart diseases
- In US, 4.9 million living with CHF
- HF incidence ~ 10 per 1000 population >65 years.
- At 40 years, the lifetime risk of developing HF is 1 in 5.

AHA Statistical Update Executive Summary: Heart Disease and Stroke Statistics. 2016 Update
Observational study
Queen Mary Hospital
2005-2012
1,940 patients with new onset HF.
Risk factors
HT: 69.8%
CAD: 29.3%
HFrEF (EF ≤ 40%): 40.2%

Annual incidence of HF (per 1,000 population)

Age (years)

Overall 18-44 45-54 55-64 65-74 75-84 >85

Male
Female

SIU CW. J Cardiac Failure 2016
Compensatory Neuro-hormonal Stimulation

Decreased Cardiac Output

- Sympathetic nervous system
  - Contractility
  - Heart rate

- Renin-angiotensin system
  - Vasoconstriction

- Antidiuretic hormone (vasopressin)
  - Maintaining circulating volume

Anteriolar Venous

- Maintain blood pressure
- Venous return to heart (preload)

Maladaptation

Deterioration

Adaptation

Cardiac output

Stroke volume

Peripheral edema and pulmonary congestion
2012 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure

Diuretics to relieve symptoms/signs of congestion

ACE inhibitor (or ARB if not tolerated)

ADD a beta-blocker

Still NYHA class II–IV?

Yes

No

ADD a MR antagonist

Still NYHA class II–IV?

Yes

LVEF ≤ 35%?

Yes

Sinus rhythm and HR ≥ 70 beats/min?

Yes

ADD ivabradine

No

No

No

Still NYHA class II–IV and LVEF ≤ 35%?

Yes

QRS duration ≥ 120 ms?

Yes

Consider CRT-P/CRT-D

No

Consider ICD

Yes

No

Still NYHA class II–IV?

Yes

No

Consider digoxin and/or H-IsDN if 3rd stage, consider LVAD and/or transplantation

No further specific treatment Continue in disease-management programme
High HF Mortality despite Current HFrEF treatment

1-year Mortality:
- Europe: 16.4%
- Japan: 8.9%
- Korea: 9.2%

SIU CW. J Cardiac Failure 2016
Why is (re-)hospitalization so important?
Cumulative adverse consequence of hospitalizations

Hypothesis: With each hospitalization, there is myocardial and/or renal damage leading to further progression of the disease.

HF-Hospitalization is a Strong predictor for increased mortality

Half patients were dead by 1 year after 3 hospitalizations
In 2014, there were **3,509 acute admissions** (out of total 23,085 admissions, i.e. 15.2%), i.e., **10 HF admissions/day**, and the means **LOS: 4.8 days** in QMH,

- **Estimated total cost in QMH = HKD$72,931,056** (3,509 admission x 4.8 days x HKD$4,330); **Estimated total cost in QMH = HKD$102,103,470 per year**

- Re-hospitalization for HF increases from 56% to 66% over the past decade.
Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF)

LCZ696 400 mg daily  ↔  Enalapril 20 mg daily
What is LCZ696?

What is Neprilysin?
Neurohormonal Stimulation in HF

Decreased Cardiac Output

- Sympathetic nervous system
- Renin-angiotensin system
- Vasopressin

HR Contractility → Vasoconstriction → Circulating volume

Anteriolar → Venous

Maintain blood pressure

Venous return to heart (preload)

Cardiac output

Stroke volume

Natriuretic peptide system:
ANP and BNP from Cardiomyocytes

- NPRs
- NPs
- Vasodilation
- Blood pressure
- Sympathetic tone
- Natriuresis/diuresis
- Vasopressin
- Aldosterone
- Fibrosis
- Hypertrophy

Peripheral edema and pulmonary congestion
Natriuretic Peptides are degraded by the Protease, neprilysin

LCZ696: Angiotensin Receptor Neprilysin Inhibition (ARNI)

LCZ696

VALSARTAN
Angiotensin receptor blocker

SACUBITRIL (AHU377)
Inhibition of Neprilysin

Molar Ratio: 1:1
Neprilysin inhibition must be accompanied by simultaneous RAAS blockade

- Neprilysin metabolizes Ang I and Ang II via several pathways
- Inhibition of neprilysin alone is insufficient as it associated with an increase in Ang II levels, counteracting the potential benefits of neprilysin inhibition
- Neprilysin inhibition must be accompanied by simultaneous RAAS blockade (e.g. AT₁ receptor blockade)
PARADIGM-HF: Inclusion Criteria

• NYHA class II-IV heart failure
• LVEF ≤ 40% → 35%
• BNP ≥ 150 (or NT-proBNP ≥ 600), but one-third lower if hospitalized for heart failure within 12 months
• Any use of ACE inhibitor or ARB, but able to tolerate stable dose equivalent to at least enalapril 10 mg daily for at least 4 weeks
• Guideline-recommended use of beta-blockers and mineralocorticoid receptor antagonists
• Systolic BP ≥ 95 mm Hg, eGFR ≥ 30 ml/min/1.73 m² and serum K ≤ 5.4 mEq/L at randomization
PARADIGM-HF: Key Exclusion Criteria

- History of angioedema
- eGFR <30 mL/min, or a >35% decrease in eGFR between screening and end of enalapril run-in or between screening and randomization
- K⁺ >5.2 mmol/L at screening OR >5.4 mmol/L at the end of the enalapril run-in or end of the LCZ696 run-in
- Requirement for treatment with both ACEI and ARBs
- Symptomatic hypotension, SBP <100 mmHg at screening, OR SBP <95 mmHg at end of enalapril run-in or at randomization
- Current acute decompensated HF
- History of severe pulmonary disease
- ACS, stroke, transient ischemic attack, cardiac, carotid, or other major CV surgery, PCI, or carotid angioplasty within the 3 months prior to screening

PARADIGM-HF: Study Design

- **Single-blind run-in period**
  - **Enalapril**
    - 10 mg BID for 2 weeks
  - **LCZ696**
    - 100 mg BID for 1-2 weeks
    - 200 mg BID for 2-4 weeks

- **Randomization**
  - (1:1 randomization)

- **Double-blind period**
  - **LCZ696 200 mg BID**
  - **Enalapril 10 mg BID**
PARADIGM-HF: Endpoints

Primary endpoint:
• CV death or HF hospitalization

Secondary endpoints:
• All-cause mortality
• Change from baseline in the clinical summary score of the Kansas City Cardiomyopathy Questionnaire at 8 months
• Time to new onset of atrial fibrillation
• Time to first occurrence of a protocol-defined decline in renal function
## PARADIGM-HF: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.8 ± 11.5</td>
<td>63.8 ± 11.3</td>
</tr>
<tr>
<td>Women (%)</td>
<td>21.0%</td>
<td>22.6%</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy (%)</td>
<td>59.9%</td>
<td>60.1%</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>29.6 ± 6.1</td>
<td>29.4 ± 6.3</td>
</tr>
<tr>
<td>NYHA functional class II / III (%)</td>
<td>71.6% / 23.1%</td>
<td>69.4% / 24.9%</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>122 ± 15</td>
<td>121 ± 15</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>72 ± 12</td>
<td>73 ± 12</td>
</tr>
<tr>
<td>N-terminal pro-BNP (pg/ml)</td>
<td>1631 (885-3154)</td>
<td>1594 (886-3305)</td>
</tr>
<tr>
<td>B-type natriuretic peptide (pg/ml)</td>
<td>255 (155-474)</td>
<td>251 (153-465)</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>35%</td>
<td>35%</td>
</tr>
<tr>
<td>Digitalis</td>
<td>29.3%</td>
<td>31.2%</td>
</tr>
<tr>
<td>Beta-adrenergic blockers</td>
<td>93.1%</td>
<td>92.9%</td>
</tr>
<tr>
<td>Mineralocorticoid antagonists</td>
<td>54.2%</td>
<td>57.0%</td>
</tr>
<tr>
<td>ICD and/or CRT</td>
<td>16.5%</td>
<td>16.3%</td>
</tr>
</tbody>
</table>
PARADIGM-HF: CV Mortality / HF Hospitalization (primary endpoint)

**Kaplan-Meier Estimate of Cumulative Rates (%)**

<table>
<thead>
<tr>
<th>Days After Randomization</th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>180</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>360</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>540</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>720</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>900</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1080</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1260</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**HR = 0.80 (0.73-0.87), p = 0.0000002**

**NNT = 21**

**Patients at Risk**

<table>
<thead>
<tr>
<th></th>
<th>LCZ696</th>
<th>Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>4187</td>
<td>4212</td>
<td>3922</td>
</tr>
<tr>
<td>3922</td>
<td>4187</td>
<td>3579</td>
</tr>
<tr>
<td>3663</td>
<td>3922</td>
<td>3018</td>
</tr>
<tr>
<td>3018</td>
<td>3663</td>
<td>2922</td>
</tr>
<tr>
<td>2257</td>
<td>3018</td>
<td>2123</td>
</tr>
<tr>
<td>1544</td>
<td>2257</td>
<td>1488</td>
</tr>
<tr>
<td>896</td>
<td>1544</td>
<td>853</td>
</tr>
<tr>
<td>249</td>
<td>896</td>
<td>236</td>
</tr>
</tbody>
</table>
Kaplan-Meier Estimate of Cumulative Rates (%)

Days After Randomization

Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>LCZ696</th>
<th>Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days</td>
<td>4187</td>
<td>4212</td>
</tr>
<tr>
<td>0</td>
<td>4187</td>
<td>4212</td>
</tr>
<tr>
<td>180</td>
<td>4056</td>
<td>4051</td>
</tr>
<tr>
<td>360</td>
<td>3891</td>
<td>3860</td>
</tr>
<tr>
<td>540</td>
<td>3282</td>
<td>3231</td>
</tr>
<tr>
<td>720</td>
<td>2478</td>
<td>2410</td>
</tr>
<tr>
<td>900</td>
<td>1716</td>
<td>1726</td>
</tr>
<tr>
<td>1080</td>
<td>1005</td>
<td>994</td>
</tr>
<tr>
<td>1260</td>
<td>280</td>
<td>279</td>
</tr>
</tbody>
</table>

HR = 0.80 (0.71-0.89)

P = 0.00004

Number need to treat = 32

PARADIGM-HF: CV Mortality
# PARADIGM-HF: Effect of LCZ696 vs Enalapril on Primary Endpoint and Its Components

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>914 (21.8%)</td>
<td>1117 (26.5%)</td>
<td>0.80 (0.73–0.87)</td>
<td>0.0000002</td>
</tr>
<tr>
<td><strong>Cardiovascular death</strong></td>
<td>558 (13.3%)</td>
<td>693 (16.5%)</td>
<td>0.80 (0.71–0.89)</td>
<td>0.00004</td>
</tr>
<tr>
<td><strong>Hospitalization for heart failure</strong></td>
<td>537 (12.8%)</td>
<td>658 (15.6%)</td>
<td>0.79 (0.71–0.89)</td>
<td>0.00004</td>
</tr>
</tbody>
</table>
PARADIGM-HF: All-Cause Mortality

Kaplan-Meier Estimate of Cumulative Rates (%)

Days After Randomization

Patients at Risk
LCZ696 4187 4056 3891 3282 2478 1716 1005 280
Enalapril 4212 4051 3860 3231 2410 1726 994 279

HR = 0.84 (0.76-0.93)  
P<0.0001

Enalapril  
(n=4212)  
835

LCZ696  
(n=4187)  
711
## PARADIGM-HF: Effect of LCZ696 vs Enalapril on Secondary Endpoints

<table>
<thead>
<tr>
<th></th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>Treatment effect</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KCCQ clinical summary score at 8 months</strong></td>
<td>– 2.99 ± 0.36</td>
<td>– 4.63 ± 0.36</td>
<td>1.64 (0.63, 2.65)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>New onset atrial fibrillation</strong></td>
<td>84/2670 (3.2%)</td>
<td>83/2638 (3.2%)</td>
<td>Hazard ratio 0.97 (0.72, 1.31)</td>
<td>0.84</td>
</tr>
<tr>
<td><strong>Protocol-defined decline in renal function</strong></td>
<td>94/4187 (2.3%)</td>
<td>108/4212 (2.6%)</td>
<td>Hazard ratio 0.86 (0.65, 1.13)</td>
<td>0.28</td>
</tr>
</tbody>
</table>
## Adverse events

<table>
<thead>
<tr>
<th>Event</th>
<th>LCZ696 (N=4187)</th>
<th>Enalapril (N=4212)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>588 (14.0)</td>
<td>388 (9.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptomatic with systolic blood pressure &lt;90 mm Hg</td>
<td>112 (2.7)</td>
<td>59 (1.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Elevated serum creatinine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2.5 mg/dl</td>
<td>139 (3.3)</td>
<td>188 (4.5)</td>
<td>0.007</td>
</tr>
<tr>
<td>≥3.0 mg/dl</td>
<td>63 (1.5)</td>
<td>83 (2.0)</td>
<td>0.10</td>
</tr>
<tr>
<td>Elevated serum potassium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5.5 mmol/liter</td>
<td>674 (16.1)</td>
<td>727 (17.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>&gt;6.0 mmol/liter</td>
<td>181 (4.3)</td>
<td>236 (5.6)</td>
<td>0.007</td>
</tr>
<tr>
<td>Cough</td>
<td>474 (11.3)</td>
<td>601 (14.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angioedema†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment or use of antihistamines only</td>
<td>10 (0.2)</td>
<td>5 (0.1)</td>
<td>0.19</td>
</tr>
<tr>
<td>Use of catecholamines or glucocorticoids without hospitalization</td>
<td>6 (0.1)</td>
<td>4 (0.1)</td>
<td>0.52</td>
</tr>
<tr>
<td>Hospitalization without airway compromise</td>
<td>3 (0.1)</td>
<td>1 (&lt;0.1)</td>
<td>0.31</td>
</tr>
<tr>
<td>Airway compromise</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
</tbody>
</table>
Hospitalizations for Worsening of HF


29% fewer HFrEF patients were hospitalized more than once for HF with LCZ696 than with enalapril (n=170 and n=240, respectively; p=0.001)
Emergency Department Visit for worsening of HF (discharge without hospitalization)

Proportion of patients (%)

<table>
<thead>
<tr>
<th>Number of emergency department visits without hospitalization</th>
<th>LCZ696 (n=4,187)</th>
<th>Enalapril (n=4,212)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2.4%</td>
<td>3.6%</td>
</tr>
<tr>
<td>1</td>
<td>2.6%</td>
<td>3.0%</td>
</tr>
<tr>
<td>2</td>
<td>1.9%</td>
<td>2.2%</td>
</tr>
<tr>
<td>≥3</td>
<td>0.4%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

HR 0.66 (95% CI: 0.52–0.85) p=0.001

Total number of patients visiting the emergency department once and multiple times:
- LCZ696: n=102, n=150
- Enalapril: n=102, n=150

Number of emergency department visits without hospitalization:
- LCZ696: n=102, n=150
- Enalapril: n=102, n=150

P=0.003
PARADIGM-HF: Summary of Findings

In HFrEF, when compared with recommended doses of enalapril:

**LCZ696 was more effective than enalapril in . . .**
- Reducing the risk of CV death and HF hospitalization
- Reducing the risk of CV death by *incremental* 20%
- Reducing the risk of HF hospitalization by *incremental* 21%
- Reducing all-cause mortality by *incremental* 16%
- Incrementally improving symptoms and physical limitations

**LCZ696 was better tolerated than enalapril . . .**
- Less likely to cause cough, hyperkalemia or renal impairment
- Less likely to be discontinued due to an adverse event
- More hypotension, but no increase in discontinuations
- Not more likely to cause serious angioedema
Chronological Development of HF therapy

Captopril

Propranolol

Potential benefit: vasodilation

1960

1970

1980

1990

2000

2005

Recognition of Neurohormonal Maladaptation

CIBIS III

SENIORS

COMET

AIRE, TRACE

SAVE, ISIS-4

COPERNICUS

MERIT-HF

CIBIS II

USCP

CIBIS

MDC

Contraindicated

(-) inotropic effects

1973 Swedberg et al.

1979 Waagstein et al.

Brentano, Eur Heart J 8 (2006): C19-C27
Drugs That Reduce Mortality in Heart Failure With Reduced LVEF

- **Angiotensin receptor blocker**
- **ACE inhibitor**
- **Beta blocker**
- **Mineralocorticoid receptor antagonist**

Based on results of SOLVD-Treatment, CHARM-Alternative, COPERNICUS, MERIT-HF, CIBIS II, RALES and EMPHASIS-HF

Drugs that inhibit the renin-angiotensin system have modest effects on survival.
Incremental All-Cause Mortality Benefits

- **SOLVD-T (1991)**: RRR 23%
  - 15.1
  - Diuretic
  - Digoxin
  - ACEI

- **CIBIS-2 (1999)**: RRR 33%
  - 13.2
  - Diuretic
  - Digoxin
  - ACEI

- **PARADIGM-HF (2013)**: RRR 16%
  - 9
  - Diuretic
  - Digoxin
  - ACEI
  - β-Blocker
  - LCZ696
2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure

Patient with symptomatic HFrEF

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

  - Still symptomatic and LVEF ≤35%
    - No
    - Yes → Add MR antagonist (up-titrate to maximum tolerated evidence-based dose)
      - Yes
        - Still symptomatic and LVEF ≤35%
          - No
          - Yes → Diuretics to relieve symptoms and signs of congestion

  - If LVEF ≤35% despite OMT or a history of symptomatic VT/VF, implant ICD
    - If LVEF ≤35% despite OMT or a history of symptomatic VT/VF, implant ICD
      - ARNI to replace ACE-I
      - Evaluate need for CRT
      - Ivabradine
      - These above treatments may be combined if indicated

- Resistant symptoms
  - Yes → Consider digoxin or H-SDN or LVAD, or heart transplantation
  - No → No further action required Consider reducing diuretic dose
Conclusions

- HF has emerged as a global epidemic of cardiovascular disease

- The advance in pharmacological therapy including ACEI, ARB, MRA, beta-blocker has improved the outcomes of HF.

- Nonetheless, the mortality remains very high ~ 10% per year

- LCZ696, ARNI, has shown in the PARADIGM HF study to be effective in reducing CV mortality, HF hospitalization, and all cause mortality, as well as functional improvement in patients with HFrEF.

- LCZ696 appears to be well tolerated.

- Implementation of GBMT and LCZ696 in clinical practice may improve the overall clinical outcomes of patients with HFrEF.
<table>
<thead>
<tr>
<th>Category</th>
<th>Patients receiving a total daily dose of</th>
<th>Stop ACEi 36 hours before starting ENTRESTO</th>
<th>Start ENTRESTO at the recommended dose of</th>
<th>Double the dose after 2 to 4 weeks, as tolerated by the patient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Angiotensin-converting enzyme inhibitor (ACEi)</strong></td>
<td>&gt;10 mg of enalapril or therapeutically equivalent doses of another ACEi, for example²: • Lisinopril &gt;10 mg • Ramipril &gt;5 mg</td>
<td><strong>Stop ACEi 36 hours before starting ENTRESTO</strong></td>
<td><strong>Start ENTRESTO at the recommended dose of 49/51 mg twice daily</strong></td>
<td><strong>Double the dose after 2 to 4 weeks to 49/51 mg twice daily, as tolerated by the patient</strong></td>
</tr>
<tr>
<td></td>
<td>≤10 mg of enalapril or therapeutically equivalent doses of another ACEi, for example²: • Lisinopril ≤10 mg • Ramipril ≤5 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Angiotensin II receptor blocker (ARB)</strong></td>
<td>&gt;160 mg of valsartan or therapeutically equivalent doses of another ARB, for example²: • Losartan &gt;50 mg • Olmesartan &gt;10 mg</td>
<td><strong>Start ENTRESTO at the recommended dose of 49/51 mg twice daily</strong></td>
<td><strong>Start ENTRESTO at the recommended dose of 24/26 mg twice daily</strong></td>
<td><strong>Double the dose after 2 to 4 weeks to 49/51 mg twice daily, as tolerated by the patient</strong></td>
</tr>
<tr>
<td></td>
<td>≤160 mg of valsartan or therapeutically equivalent doses of another ARB, for example²: • Losartan ≤50 mg • Olmesartan ≤10 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Not on ACEi or ARB</strong></td>
<td>Not currently taking ACEIs or ARBs</td>
<td><strong>Start ENTRESTO at the recommended dose of 24/26 mg twice daily</strong></td>
<td><strong>Start ENTRESTO at the recommended dose of 24/26 mg twice daily</strong></td>
<td><strong>Double the dose after 2 to 4 weeks to 49/51 mg twice daily, as tolerated by the patient</strong></td>
</tr>
</tbody>
</table>