The ‘Stable’ Heart Failure... And Beyond

Pardeep S Jhund
Senior Clinical Lecturer and Honorary Consultant Cardiologist
BHF Glasgow Cardiovascular Research Centre
Queen Elizabeth University Hospital
Glasgow

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Disclosures

• Speakers Fees – Novartis
• Advisory Board – Novartis, Vifor Pharma, Boehringer Ingelheim, Cytokinetics
• Research Funding – Boehringer Ingelheim
• Other – Director GCTP Ltd

The ESC guidelines


CRT=cardiac resynchronization therapy; H-ISDN=hydralazine and isosorbide dinitrate; HR=heart rate; ICD=implantable cardioverter defibrillator; LVAD=left ventricular assist device; MR=mineralocorticoid receptor; OMT=optimal medical therapy; VT/VF=ventricular tachycardia/ventricular fibrillation

ACC/AHA/HFSA 2017 heart failure guidelines update

Why don’t we do this?
**The ESC guidelines**

ACEI + BB ✓

MRA ✓

ARNi X

CRT/ICD X

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**EMPHASIS-HF**

Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure

2737 patients, ≥55 years, NYHA class II, with CV hospitalization within 6 months (or elevated BNP/NT pro BNP) and LVEF ≤0.30 (or ≤0.35 if QRS duration >130msec) followed for a median of 21 months

ACEI + BB

MRA

ARNi

CRT/ICD

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**PARADIGM-HF: Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Enalapril (n=4212)</th>
<th>Sacubitril/valsartan (n=4187)</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>28.6 ± 6.1</td>
<td>28.4 ± 6.3</td>
</tr>
<tr>
<td>NYHA functional class II/III (%)</td>
<td>71.6% / 23.1%</td>
<td>66.6% / 24.0%</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 (955-3151)</td>
<td>1034 (683-3200)</td>
</tr>
<tr>
<td>B-type natriuretic peptide (pg/mL)</td>
<td>253 (135-476)</td>
<td>251 (153-460)</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>35%</td>
<td>35%</td>
</tr>
<tr>
<td>Digitalis</td>
<td>39.3%</td>
<td>31.2%</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>93.1%</td>
<td>92.9%</td>
</tr>
<tr>
<td>Mineralocorticoid antagonists</td>
<td>94.2%</td>
<td>97.9%</td>
</tr>
<tr>
<td>CRT</td>
<td>2.0%</td>
<td>0.7%</td>
</tr>
<tr>
<td>ICD</td>
<td>10%</td>
<td></td>
</tr>
</tbody>
</table>

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**PARADIGM-HF: Primary outcome**

Cardiovascular death or heart failure hospitalization

Cumulative Proportion of Patients with Primary End Point (%)

Days after Randomization

HR: 0.80 (0.73, 0.87) p = 0.0000004

Even in well treated patients outcomes were improved

So why don’t we act on this?

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**What does “stable” mean?**

adjective: **stable**

(of a patient or their medical condition) not deteriorating in health after an injury or operation.

"he is now in a stable condition in hospital"
What does “stable” mean?
Are patients with HFREF ever “stable”?

Does “stable” mean remaining in the same clinical state (not deteriorating)?

The natural history of HF

Other manifestations of worsening/instability

Enalapril group in PARADIGM-HF
ACE inhibitor 100%, beta-blocker 93%, MRA 57%, digitalis 31%

Outpatient treatment* (%)  ED visits (%)

Proposition of patients

Enalapril group in PARADIGM-HF
ACE inhibitor 100%, beta-blocker 93%, MRA 57%, digitalis 31%

Cumulative rate of adverse outcomes over time

Enalapril group in PARADIGM-HF
ACE inhibitor 100%, beta-blocker 93%, MRA 57%, digitalis 31%
Primary composite endpoint: CV death or HF hospitalization
Expanded composite: CV death, hospitalization, ED visit or intensification of therapy*

Benefit of sacubitril/valsartan on multiple manifestations of progression/worsening

The natural history of HF

Recurrent HF hospitalizations

Summary: The myth of clinical “stability” in heart failure

- Patients with mild symptoms are not stable and progress rapidly, even on optimal treatment. Over 11% patients per year in the control (enalapril) group in PARADIGM-HF exhibited some manifestation of worsening

Does “stable” mean low risk?

<table>
<thead>
<tr>
<th></th>
<th>LCZ696</th>
<th>Enalapril</th>
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<tr>
<td>Age (years)</td>
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<td>131±16</td>
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<td>72±12</td>
<td>73±12</td>
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<td>1631 (885-3154)</td>
<td>1594 (886-3305)</td>
</tr>
<tr>
<td>B-type natriuretic peptide (pg/ml)</td>
<td>200 (139-474)</td>
<td>215 (135-505)</td>
</tr>
<tr>
<td>History of diabetes</td>
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<td>92.9%</td>
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<td>Mineralocorticid antagonists</td>
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<td>57.0%</td>
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<tr>
<td>CRT</td>
<td>7.0%</td>
<td>6.7%</td>
</tr>
<tr>
<td>ICD</td>
<td>15%</td>
<td>15%</td>
</tr>
</tbody>
</table>

Mild symptoms

NYHA class II: Mild symptoms

MAGGIC risk score

1. Age
2. Sex
3. Diabetes
4. COPD
5. BMI
6. Smoker
7. NYHA class
8. Diagnosis ≤18 months
9. Creatinine
10. SBP
11. LVEF
12. ACEI/ARB
13. Beta-blocker

MAGGIC Risk Score in PARADIGM-HF

Benefit of LCZ696 across MAGGIC risk score quintiles
Benefit of LCZ696 across MAGGIC risk score quintiles

All-cause mortality

Does “stable” mean the patient feels well?

Kansas City Cardiomyopathy Questionnaire (KCCQ)

23 items covering 5 domains


KCCQ: Significance of a 5-point change

• A 5-point change in KCCQ overall score corresponds to:
  – 112 metre change in 6-minute walking distance and
  – 2.50 ml/kg/min change in peak VO₂ in HF-REF patients

• A 5-point decrease in KCCQ overall score corresponds to a deterioration in the patient’s condition

PARADIGM-HF: Percent of patients with at least 5 Points deterioration in KCCQ clinical summary score

PARADIGM-HF: Percent of patients with at least 5 Points deterioration in KCCQ clinical summary score

Summary: The myth of clinical “stability” in heart failure

• Patients with mild symptoms are not stable and progress rapidly, even on optimal treatment. Over 11% patients per year in the control (enalapril) group in PARADIGM-HF exhibited some manifestation of worsening

• An even higher proportion experience a deterioration in symptoms/QoL
“Stable” means patients are not likely to die?

The two major modes of death in HF

Sudden death

Death due to worsening HF

Effect of sacubitril/valsartan on the two major modes of death in HF

Summary: The myth of clinical “stability” in heart failure

- Patients with mild symptoms are not stable and progress rapidly, even on optimal treatment. Over 11% patients per year in the control (enalapril) group in PARADIGM-HF exhibited some manifestation of worsening
- An even higher proportion experience a deterioration in symptoms/QoL
- In a third (33%) of patients, the first manifestation of progression/worsening is cardiovascular death (mainly sudden death) – which is preventable

“Stable” suggests you have time
**PARADIGM-HF: Make a difference quickly**

![Graph showing cumulative proportion of patients hospitalised](image)

**“Only for outpatients – what about the “unstable” patient?”**

**PIONEER-HF: Sacubitril/valsartan in the hospitalized HF patient**

- **Hypothesis:** Initiation of sacubitril-valsartan therapy is safe and effective among patients who are hospitalized for acute decompensated HF
- **Population:** 881 patients; hospitalised HF; EF ≤40%; BNP ≥400 pg/ml or NT-proBNP ≥1600 pg/ml – 52% ACEI/ARB naïve
- **Intervention:** Sacubitril/valsartan vs enalapril
- **Primary endpoint:** Change in NT-proBNP

**PIONEER-HF: Sacubitril/valsartan in the hospitalized HF patient**

![Graph showing changes in N-terminal prohormone brain natriuretic peptide (NT-proBNP) levels](image)

**PIONEER-HF: Sacubitril/valsartan in the hospitalized HF patient**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Sacubitril/valsartan</th>
<th>Enalapril</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worsening renal function</td>
<td>60(14%)</td>
<td>65(15%)</td>
<td>0.93(0.67-1.28)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>51(12%)</td>
<td>41(9%)</td>
<td>1.25(0.84-1.84)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>66(15%)</td>
<td>56(13%)</td>
<td>1.18(0.85-1.64)</td>
</tr>
<tr>
<td>Composite</td>
<td>249(57%)</td>
<td>264(60%)</td>
<td>0.93(0.78-1.10)</td>
</tr>
<tr>
<td>Death</td>
<td>10(2%)</td>
<td>15(3%)</td>
<td>0.66(0.30-1.48)</td>
</tr>
<tr>
<td>HF hospitalization</td>
<td>35(8%)</td>
<td>61(14%)</td>
<td>0.56(0.37-0.84)</td>
</tr>
<tr>
<td>LVAD implant</td>
<td>1(0.2%)</td>
<td>1(0.2%)</td>
<td>0.99(0.06-15.97)</td>
</tr>
<tr>
<td>Listed for heart transplant</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Unplanned outpatient visit</td>
<td>2(0.5%)</td>
<td>2(0.5%)</td>
<td>1.00(0.14-7.07)</td>
</tr>
</tbody>
</table>

**TRANSITION**

- **Hypothesis:** Initiation of sacubitril/valsartan pre-discharge is safe in patients who are hospitalized for acute decompensated HF
- **Population:** 1002 patients; hospitalised HF; EF ≤40% – 24% ACEI/ARB naïve
- **Intervention:** Sacubitril/valsartan pre or post discharge
- **Primary endpoint:** Proportion achieving target dose
TRANSITION: Safety

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pre-discharge</th>
<th>Post-discharge</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperkalaemia</td>
<td>55 (11.1)</td>
<td>56 (11.3)</td>
<td>0.9201</td>
</tr>
<tr>
<td>Hypotension</td>
<td>61 (12.3)</td>
<td>45 (9.1)</td>
<td>0.1229</td>
</tr>
<tr>
<td>Worsening heart failure</td>
<td>34 (6.8)</td>
<td>42 (8.5)</td>
<td>0.3426</td>
</tr>
<tr>
<td>Dizziness</td>
<td>28 (5.6)</td>
<td>21 (4.2)</td>
<td>0.3795</td>
</tr>
<tr>
<td>Peripheral oedema</td>
<td>17 (3.4)</td>
<td>24 (4.8)</td>
<td>0.2696</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>25 (5.0)</td>
<td>15 (3.0)</td>
<td>0.1455</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>12 (2.4)</td>
<td>23 (4.6)</td>
<td>0.0604</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>20 (4.0)</td>
<td>15 (3.0)</td>
<td>0.4918</td>
</tr>
<tr>
<td>Hyperkalaemia</td>
<td>55 (11.1)</td>
<td>56 (11.3)</td>
<td>0.9201</td>
</tr>
</tbody>
</table>

"My patients are not suitable candidates"
Patients with HFREF are not “stable”
- They change clinical state and risk state frequently
- They are not low risk
- They will experience a deterioration in their symptoms
- They are at a substantial risk of dying suddenly
- We have evidence for the safe use of the drug in hospital and treatment naïve patients
- Most patients are eligible for evidence based therapies it is up to us to provide them!

Summary: The myth of clinical “stability” in heart failure