<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>08:00</td>
<td>Registration</td>
</tr>
<tr>
<td>08:25</td>
<td>Welcome and Thank You to Sponsors</td>
</tr>
<tr>
<td>08:30</td>
<td><strong>The new kid on the block – “ ARNI”</strong></td>
</tr>
<tr>
<td>09:15</td>
<td>How do I effectively diurese my patient? Anything new?</td>
</tr>
<tr>
<td>10:00</td>
<td>Tea Break</td>
</tr>
<tr>
<td>10:30</td>
<td>Drugs, devices and procedures to offer the atrial fibrillation patient- new and exciting</td>
</tr>
<tr>
<td>11:15</td>
<td>The NEW ESC Heart Failure Guidelines from Europe</td>
</tr>
<tr>
<td>11:45</td>
<td>Questionnaire</td>
</tr>
<tr>
<td>12:00</td>
<td>Departure</td>
</tr>
</tbody>
</table>
CASE STUDY:

The new kid on the block – “ARNI”
Case - History

- 53 year old male
- Long history of hypertension
- Currently on thiazide diuretic – intermittent adherence
- 20 pack year history of smoking – stopped 3 months ago
- No allergies
- No family history of vascular disease
- History of alcohol abuse
- Now presents with dyspnoea – class III NYHA, orthopnoea and leg swelling of a few weeks duration
• Obese – BMI 35
• BP 163/92 mmHg
• No pallor, both legs oedematous
• Pulses all palpable – low volume, irregular and rapid
• JVP – angle of jaw
• Apex beat displaced lateral to the mid clavicular line
• Pansystolic murmur of mitral regurgitation
• Bilateral lung crepitations
1. Cardiomegaly
2. Increased interstitial markings
3. Upper lobe blood diversion
Case - ECG

- Vent. Rate: 103 bpm
- PR interval: ms
- QRS duration: 78 ms
- QT/QTC: 358/468 ms
- P-R-T axes: /23/29°
- P duration: ms
- RR/PP interval: 580/555 ms

Technician: L. Papenfus
Interpretation:
- Atrial fibrillation with rapid ventricular response
- Abnormal ECG

Heart Failure Society of South Africa
Case - Blood results

- U&E - normal
- TSH - normal
- FBC – Hb. 13.2 g/dL, normal WCC and platelets.
- proBNP – 990 pg/mL
Case - Diagnosis

- Congestive cardiac failure
- LV systolic dysfunction – “HFreF”
- Cause:
  - Hypertension
  - Toxic – ethanol
  - ?genetic component
  - ?ischaemic
CT coronary angiogram

- Calcium score – low
- No evidence of significant coronary stenosis
Case - Management

- Carvedilol 25 mg BD
- Ramipril 5 mg BD
- Spironolactone 25 mg OD
- Furosemide 40 mg BD
- Amlodipine 5 mg OD
- Warfarin 5 mg OD

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting dose (mg)</th>
<th>Target dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACE-Inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 BD</td>
<td>20 BD</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5 OD</td>
<td>20 OD</td>
</tr>
<tr>
<td>Ramipril</td>
<td>2.5 OD</td>
<td>10 OD</td>
</tr>
<tr>
<td><strong>Beta-blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>1.25 OD</td>
<td>10 OD</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 BD</td>
<td>25 BD</td>
</tr>
<tr>
<td><strong>ARBs</strong></td>
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<td></td>
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<tr>
<td>Carbesartan</td>
<td>4 OD</td>
<td>32 OD</td>
</tr>
<tr>
<td>Valsartan</td>
<td>40 BD</td>
<td>160 BD</td>
</tr>
<tr>
<td>Losartan</td>
<td>50 OD</td>
<td>160 OD</td>
</tr>
<tr>
<td><strong>MRAs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eplerenone</td>
<td>25 OD</td>
<td>50 OD</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>25 OD</td>
<td>50 OD</td>
</tr>
<tr>
<td><strong>ARNI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sacubitril/valsartan</td>
<td>49/51 BD</td>
<td>97/103 BD</td>
</tr>
<tr>
<td><strong>If-channel blocker</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ivabradine</td>
<td>5 BD</td>
<td>7.5 BD</td>
</tr>
</tbody>
</table>

Heart Failure Society of South Africa (HFS)
General Measures

* COUNSELLING - SYMPTOMS
  - PROGNOSIS
  - DRUGS

* REST / EXERCISE
* DIET
* ALCOHOL
* PREGNANCY
* DAILY WEIGHT RECORD
6 month follow-up

- Patient improved
- Coping with medication
- Still complaining of shortness of breath on moderate exertion
- Next step?
Patient with symptomatic* HFrEF\( ^b \)

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

Still symptomatic and LVEF ≤35%

Yes

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

Yes

Still symptomatic and LVEF ≤35%

No

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

Sinus rhythm, QRS duration ≥130 msec

Sinus rhythm, HR ≥70 bpm

ARDI 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
Case - Diagnosis

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
          - Able to tolerate ACEI (or ARB)
            - ARNI to replace ACE-I
          - Sinus rhythm, QRS duration ≥130 msec
          - Sinus rhythm, HR ≥70 bpm
            - Evaluate need for CRT
            - 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
What is new in Heart Failure?
Drugs that reduce mortality in HFrEF

Drugs that inhibit the renin-angiotensin system have modest effects on survival.

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

ARNI

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

Neprilysin
Inactive metabolites

↓ Neurohormonal activation
↓ Vascular tone
↓ Cardiac fibrosis, hypertrophy
↓ Sodium retention

Neprilysin inhibition
Neprilysin inhibition must be accompanied by simultaneous RAAS blockade

- Neprilysin metabolizes Ang I and Ang II via several pathways\(^1,2\)
- Inhibition of neprilysin alone is insufficient as it associated with an increase in Ang II levels, counteracting the potential benefits of neprilysin inhibition\(^2\)
- Neprilysin inhibition must be accompanied by simultaneous RAAS blockade (e.g. AT\(_1\) receptor blockade)\(^2\)

---

**Diagram:**
- Angiotensinogen
  - Renin
  - Ang I
    - Neprilysin inhibitor
  - Ang II
    - Neprilysin
    - Neprilysin inhibitor
  - Ang-(1–7)
  - Inactive fragments
  - AT\(_1\) receptor
  - Signaling cascade
    - Biological actions
      - Hypertrophy
      - Fibrosis
      - Vasoconstriction
      - Hypertrophy
      - Na\(^+\)/H\(_2\)O retention
      - Aldosterone release
      - Norepinephrine release
        - ↑ Sympathetic tone

---

ACE=angiotensin-converting enzyme; AT\(_1\)=angiotensin II type 1; Ang=angiotensin; H\(_2\)=water; Na=sodium; RAAS=renin-angiotensin-aldosterone system

Comparison of Omapatrilat and Enalapril in Patients With Chronic Heart Failure

The Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE)

Milton Packer, MD; Robert M. Califf, MD; Marvin A. Konstam, MD; Henry Krum, MBBS, PhD; John J. McMurray, MD; Jean-Lucien Rouleau, MD; Karl Swedberg, MD; for the OVERTURE Study Group*

Ultimately not approved due to increased risk of angioedema and no significant clinical benefit.

Figure 2. Kaplan-Meier analysis of time to death in the omapatrilat or enalapril groups.
Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D.,
for the PARADIGM-HF Investigators and Committees*
How was the trial done?

- 8442 patients
- Class II - IV heart failure
- EF <40%
- LCZ696 vs enalapril 10 mg bd
- Median follow-up 27 months – trial stopped early
- Run in period: all patients stopped the ACE-I or ARB they were on and were then given enalapril for 2 weeks – if they tolerated this they were then given LCZ696 for 4 weeks and if they tolerated this they were then entered into the trial and randomised to either LCZ696 or enalapril
Single-blind run-in period

Enalapril 10 mg bid

LCZ696 100 mg bid

Testing tolerability to target doses of enalapril and LCZ696

2 weeks 1-2 weeks 2-4 weeks

LCZ696 200 mg bid

Enalapril 10 mg bid

On top of standard heart failure therapy (excluding ACEIs and ARBs)

~ 21 to 43 months (event-driven)
Case - Diagnosis

A. Primary End Point

- Hazard ratio, 0.80 (95% CI, 0.73–0.87)
- P<0.001

No. at Risk
- LCZ696: 4187, 3922, 3663, 3018, 2257, 1544, 896, 249
- Enalapril: 4212, 3883, 3579, 2922, 2123, 1488, 853, 236

B. Death from Cardiovascular Causes

- Hazard ratio, 0.80 (95% CI, 0.71–0.89)
- P<0.001

No. at Risk
- LCZ696: 4187, 4056, 3891, 3282, 2478, 1716, 1005, 280
- Enalapril: 4212, 4051, 3860, 3231, 2410, 1726, 994, 279

C. Hospitalization for Heart Failure

- Hazard ratio, 0.79 (95% CI, 0.71–0.89)
- P<0.001

No. at Risk
- LCZ696: 4187, 3922, 3663, 3018, 2257, 1544, 896, 249
- Enalapril: 4212, 3883, 3579, 2922, 2123, 1488, 853, 236

D. Death from Any Cause

- Hazard ratio, 0.84 (95% CI, 0.76–0.93)
- P<0.001

No. at Risk
- LCZ696: 4187, 4056, 3891, 3282, 2478, 1716, 1005, 280
- Enalapril: 4212, 4051, 3860, 3231, 2410, 1726, 994, 279

Switching 1000 patients from an ACE inhibitor/ARB to LCZ696 avoided:

47 primary endpoints
31 cardiovascular deaths
28 patients hospitalized for HF
37 patients hospitalized for any reason
111 admissions for any reason

over a median treatment period of 27 months
## PARADIGM-HF: Adverse Events

<table>
<thead>
<tr>
<th>Proseptively identified adverse events</th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic hypotension</td>
<td>588</td>
<td>388</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum potassium &gt;6 mmol/L</td>
<td>181</td>
<td>236</td>
<td>0.007</td>
</tr>
<tr>
<td>Serum creatinine &gt;220 mmol/L</td>
<td>139</td>
<td>188</td>
<td>0.007</td>
</tr>
<tr>
<td>Cough</td>
<td>474</td>
<td>601</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Discontinuation for adverse event</td>
<td>449</td>
<td>516</td>
<td>0.02</td>
</tr>
<tr>
<td>Discontinuation for hypotension</td>
<td>36</td>
<td>29</td>
<td>NS</td>
</tr>
<tr>
<td>Discontinuation for hyperkalaemia</td>
<td>11</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>Discontinuation for renal impairment</td>
<td>29</td>
<td>59</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Angioedema</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medications, no hospitalisation</td>
<td>16</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>Hospitalised, no airway compromise</td>
<td>3</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Airway compromise</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Should stable patients be switched?
In the PARADIGM-HF trial, CV causes accounted for 81% of all deaths:

- Sudden death, 36%
- Worsening HF, 21%
- Presumed CV death, 10%
- Fatal stroke, 4%
- Fatal MI, 4%
- Presumed sudden death, 3%
- Non-CV death, 15%
- Other CV death, 2%
- Unknown, 4%
- Non-CV death, 15%

45% of CV deaths
26% of CV deaths

ACEI=angiotensin-converting-enzyme inhibitor; ARNI=angiotensin receptor neprilysin inhibitor; CV=cardiovascular; HF=heart failure; MI=myocardial infarction; PARADIGM-HF=Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure

Desai et al. Eur Heart J 2015; DOI: 10.1093/eurheartj/ehv186
• The majority (>80%) of deaths in PARADIGM-HF had a CV cause\(^1\)
• The mortality benefit of LCZ696 is related to the observed reduction in sudden cardiac death and death due to worsening heart failure\(^1\)
• This distribution of cause of death in PARADIGM-HF is comparable to recent HFrEF trials\(^2\)

*Results from death from CV causes as per those reported by McMurray et al. Note that the hazard ratio reported by Desai et al. was HR=0.80 (95%CI: 0.72–0.89); p<0.001

• The drug should be titrated upwards carefully as performed in the trial

• The drug was only evaluated in patients who had stable CCF (chronic)

• The drug was only evaluated in patients who did tolerate enalapril 10 mg 2x/day (in the run-in period) – Is it safe in other scenarios?

• ARNI - depending on lab assay may possibly result in elevated BNP measurements at follow-up due as they prevent the breakdown of BNP

• Watch out for hypotension

• Due to the risk of angioedema with neprilysin inhibition allow for a 3 day period between stopping patients ACE-I and starting ARNI
Specific HF patient subgroups representing a “challenge” for the implementation of LCZ696 in clinical practice

- Low blood pressure
- Hospitalized for AHF
- NYHA IV class / Advanced heart failure
- ACEi-naïve patients
- Intolerance to ACEi or ARB
- Low ACEi dose

- High ACEi dose
- Tolerant to low dose of ARNI
- Renal function worsening on ARNI

1) Currently available in Europe and North America

Available in SA under Section 21

Approval of MCC hopefully 2017
Thank you!