Case Study 4
KIDNEY DYSFUNCTION AND HEART FAILURE
The heart circulates a continuous supply of oxygenated blood through the body

Kidneys filter blood, extracting waste in form of urine and regulate water and salt levels to control blood pressure

Heart failure is a risk factor for kidney disease

Kidney disease is a risk factor for heart failure
Control of blood pressure is key in management of both kidney failure and heart failure

Diuresis reduces blood pressure and removes excess fluid (kidneys excrete more water and salt), but may worsen kidney function

ACE inhibitors, beta blockers and aldosterone antagonists benefit heart failure, but may have a negative effect on renal function
Chronic kidney disease (CKD) is a major public health problem, affecting 9-13 of general population

Incidence and prevalence of CKD has doubled in last decade

Cardiovascular disease (CVD) is the leading cause of death in patients with CKD
**Definition**: CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health.

**Criteria for CKD (either of the following present for > 3 months)**

A.) Markers of kidney damage (one or more)
- Albuminuria (AER >30 mg/24 hours; ACR >30 mg/g [>3 mg/mmol])
- Urine sediment abnormalities
- Electrolyte and other abnormalities
- Abnormalities detected by histology
- Structural abnormalities detected by imaging
- H/o kidney transplantation

B.) Decreased GFR - GFR <60 ml/min/1.73 m²
# KIDNEY DISEASE

## CKD Classification and Staging

<table>
<thead>
<tr>
<th>Kidney function stage GFR (ml/min/1.73m²)</th>
<th>Description and range</th>
<th>Kidney damage stage Urine albumin/creatinine ratio Description and range</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>Normal or high</td>
<td>≥90</td>
</tr>
<tr>
<td>G2</td>
<td>Mild decrease</td>
<td>60-89</td>
</tr>
<tr>
<td>G3a</td>
<td>Mild to moderate decrease</td>
<td>45-59</td>
</tr>
<tr>
<td>G3b</td>
<td>Moderate to severe decrease</td>
<td>30-44</td>
</tr>
<tr>
<td>G4</td>
<td>Severe decrease</td>
<td>15-29</td>
</tr>
<tr>
<td>G5</td>
<td>Kidney failure</td>
<td>&lt;15</td>
</tr>
</tbody>
</table>

- **Green**: Low risk (LR)
- **Yellow**: Moderate risk (MR)
- **Orange**: High risk (HR)
- **Red**: Very high risk (VHR)
Heart failure (HF) is a serious public health challenge and a leading cause of mortality, with a prevalence of 2-5% in general population, rising sharply in elderly.

50% of patients with HF die within 4 years of diagnosis; 40% of patient admitted to hospital with HF are dead or readmitted within 1 year.

CKD and HF have many shared risk factors.
<table>
<thead>
<tr>
<th>Type of CRS</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 (acute CRS)</td>
<td>Rapid worsening of cardiac function leads to acute kidney injury</td>
</tr>
<tr>
<td>Type 2 (chronic CRS)</td>
<td>Chronic abnormalities in cardiac function lead to progressive chronic kidney disease</td>
</tr>
<tr>
<td>Type 3 (acute renocardiac syndrome)</td>
<td>Acute, primary worsening of kidney function leads to acute cardiac dysfunction</td>
</tr>
<tr>
<td>Type 4 (chronic renocardiac syndrome)</td>
<td>Primary chronic kidney disease contributes to decreased cardiac function, left ventricular hypertrophy, diastolic dysfunction and increase risk of cardiovascular events</td>
</tr>
<tr>
<td>Type 5 (secondary CRS)</td>
<td>Acute or chronic systemic disorders (e.g. diabetes mellitus) cause combined cardiac and renal dysfunction</td>
</tr>
</tbody>
</table>
Table 5  Proposed mechanism in cardiorenal interaction.

<table>
<thead>
<tr>
<th>Common factors for heart and kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional cardiovascular risk factors</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Dyslipidemia</td>
</tr>
<tr>
<td>Other risk factors</td>
</tr>
<tr>
<td>Malnutrition</td>
</tr>
<tr>
<td>Genetic risk factors</td>
</tr>
<tr>
<td>Humorally mediated factors</td>
</tr>
<tr>
<td>Elevated sympathetic nervous system</td>
</tr>
<tr>
<td>Elevated renin-angiotensin system</td>
</tr>
<tr>
<td>Other common factors</td>
</tr>
<tr>
<td>Inflammation</td>
</tr>
<tr>
<td>Endothelial dysfunction</td>
</tr>
<tr>
<td>Immune mediated damage</td>
</tr>
<tr>
<td>Oxidative stress</td>
</tr>
<tr>
<td>Coagulation imbalance</td>
</tr>
<tr>
<td>Treatment related factors</td>
</tr>
<tr>
<td>Undertreatment</td>
</tr>
<tr>
<td>Toxic agents</td>
</tr>
<tr>
<td>Organ-specific factors</td>
</tr>
<tr>
<td>Hemodynamics mediated factors</td>
</tr>
<tr>
<td>Decreased cardiac output (heart)</td>
</tr>
<tr>
<td>Renal hypoperfusion (heart)</td>
</tr>
<tr>
<td>Elevated venous pressure (heart)</td>
</tr>
<tr>
<td>Sodium and water retention (kidney)</td>
</tr>
<tr>
<td>Hypertension (kidney)</td>
</tr>
<tr>
<td>Other specific factors</td>
</tr>
<tr>
<td>Brain natriuretic peptide (heart)</td>
</tr>
<tr>
<td>Anemia (kidney)</td>
</tr>
<tr>
<td>Uremic solute retention (kidney)</td>
</tr>
<tr>
<td>Calcium and phosphate abnormality (kidney)</td>
</tr>
<tr>
<td>Electrolyte, acid-base imbalances (kidney)</td>
</tr>
</tbody>
</table>
CARDIO-RENAL INTERACTION

CVD risk

Increased risk

Damage

↓GFR

Kidney failure

Normal

Cardiovascular disease (CVD) risk

Cardiovascular disease (CVD)

Stage A: At high risk for heart failure (HF)

Stage B: Structural heart disease

Stage C: Prior or current HF

Stage D: Refractory HF

Death

Cardiovascular and renal interaction

Heart Failure Society of South Africa (HFSA)
# CARDIO-RENAL INTERACTION

## Table 4: Prevalence and hazard of chronic kidney disease in patients with chronic heart failure.

<table>
<thead>
<tr>
<th>Ref. no.</th>
<th>Study</th>
<th>Year</th>
<th>No. of pts</th>
<th>NYHA</th>
<th>Age, years</th>
<th>Male, %</th>
<th>EF, %</th>
<th>BP or HTN</th>
<th>DM, %</th>
<th>RAS1, %</th>
<th>eGFR &lt; 60, %</th>
<th>Follow-up</th>
<th>Outcome</th>
<th>Adjusted hazard comparing with pts without CKD for the outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>SOLVD-T</td>
<td>2000</td>
<td>2,161</td>
<td>I–IV</td>
<td>60.7</td>
<td>81.5</td>
<td>24.7</td>
<td>40.4</td>
<td>24.9</td>
<td>50.3</td>
<td>35.7</td>
<td></td>
<td>—</td>
<td>1.41 for eGFR &lt; 60&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>18</td>
<td>PRIME-II</td>
<td>2000</td>
<td>1,906</td>
<td>III–IV</td>
<td>64.7</td>
<td>80.4</td>
<td>26.2</td>
<td>121.6/75.1 mmHg</td>
<td>20.7</td>
<td>91.6</td>
<td>49 (eGFR ≤ 58)</td>
<td>277 days (median)</td>
<td>All-cause mortality</td>
<td>1.91 for eGFR 44–58</td>
</tr>
<tr>
<td>19</td>
<td>DIG</td>
<td>2002</td>
<td>585</td>
<td>II/III: 85%</td>
<td>65</td>
<td>73.9</td>
<td>35</td>
<td>128.3/75.3 mmHg</td>
<td>40.3</td>
<td>88</td>
<td>50 (eGFR ≤ 63.8)</td>
<td>2.6 years (median)</td>
<td>All-cause mortality</td>
<td>2.85 for eGFR &lt;44</td>
</tr>
<tr>
<td>20</td>
<td>McClellan</td>
<td>2002</td>
<td>665</td>
<td>—</td>
<td>75.7</td>
<td>40</td>
<td>38.4</td>
<td>66%</td>
<td>44</td>
<td>54</td>
<td>38&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>—</td>
<td>1.24 at 1-year mortality&lt;sup&gt;b&lt;/sup&gt; for each 10 μmol/l increase in creatinine</td>
</tr>
<tr>
<td>21</td>
<td>UK-HEART</td>
<td>2002</td>
<td>553</td>
<td>II/III: 98%</td>
<td>62.7</td>
<td>76</td>
<td>42</td>
<td>—</td>
<td>0</td>
<td>82</td>
<td>—</td>
<td></td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>22</td>
<td>CHARM</td>
<td>2006</td>
<td>2,680</td>
<td>II–IV</td>
<td>65.3</td>
<td>66.6</td>
<td>38.5</td>
<td>128.2/73.6 mmHg</td>
<td>37.2</td>
<td>45.5</td>
<td>36</td>
<td>34.4 months</td>
<td>CV death + HF hospitalization</td>
<td>1.54 for eGFR 45–59.9</td>
</tr>
<tr>
<td>23</td>
<td>ANCHOR</td>
<td>2006</td>
<td>59,772</td>
<td>—</td>
<td>71.8</td>
<td>54.2</td>
<td>NA</td>
<td>61%</td>
<td>32.4</td>
<td>24</td>
<td>39.2</td>
<td>2.07 years (median)</td>
<td>All-cause mortality + HF hospitalization</td>
<td>1.86 for eGFR &lt;45</td>
</tr>
<tr>
<td>24</td>
<td>CHART</td>
<td>2008</td>
<td>920</td>
<td>II–IV</td>
<td>68.3</td>
<td>65.1</td>
<td>49.3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>39.2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>19.3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>69.1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>42.7</td>
<td>3.45 years</td>
<td>All-cause mortality + HF hospitalization</td>
<td>1.39 for eGFR 30–44</td>
</tr>
<tr>
<td>25</td>
<td>JCARE-CARD</td>
<td>2009</td>
<td>2,013 (mean)</td>
<td>1.8</td>
<td>71.5</td>
<td>58.7</td>
<td>44.8</td>
<td>54.5%</td>
<td>30.7</td>
<td>ACEI: 36.7</td>
<td>70.3</td>
<td>2.4 years</td>
<td>All-cause mortality</td>
<td>1.56 for eGFR &lt;30</td>
</tr>
</tbody>
</table>

EF, ejection fraction; BP, mean blood pressure; HTN, hypertension; DM, diabetes mellitus; RAS1, renin–angiotensin-system inhibitor; eGFR, estimated glomerular filtration rate (ml/min/1.73 m<sup>2</sup>); pts, patients; CKD, chronic kidney disease; HF, heart failure; CV, cardiovascular; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

<sup>a</sup> ml/min.

<sup>b</sup> CKD was defined by serum creatinine of ≥ 1.4 mg/dl for women and ≥ 1.5 mg/dl for men.

<sup>c</sup> Data were retrieved from the previous study that included 1154 patients.
META-ANALYSES OF RENAL IMPAIRMENT IN HF

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Population</th>
<th>Total n</th>
<th>Main results</th>
</tr>
</thead>
</table>
| Smith  | 2006 | Acute and chronic HF | CKD: 80 098, WRF: 12 634 | - CKD present in 63% of patients  
- Baseline CKD associated with mortality: HR 1.56 (1.53–1.60)  
- WRF associated with mortality: HR 1.47 (1.26–1.72) |
| Tonelli | 2006 | CV disease, including chronic HF | Total: 1 371 990, HF: 78 272 | - CKD present in 33% of patients  
- Baseline CKD associated with mortality: HR 1.78 (1.57–2.01) |
| Damman  | 2007 | Acute and chronic HF | HF: 18 634 | - WRF occurred in 25% of patients  
- WRF associated with mortality: OR 1.62 (1.45–1.82)  
- WRF associated with HF hospitalizations: OR 1.30 (1.04–1.62) |
| Clark   | 2014 | Chronic HF patients included in RAAS-inhibitor trials | HF: 20 573 | - WRF occurred in 13 and 9.6% with RAAS inhibitors and placebo, respectively.  
- WRF associated with mortality RR: 1.36 (1.25–1.48), in both treatment groups  
- RAAS inhibition reduced mortality even despite WRF: RR 0.72 (0.62–0.84) |
| Damman  | 2014 | Acute and chronic HF | CKD: 1 076 104, WRF: 49 890 | - CKD present in 32% of patients  
- Baseline CKD associated with mortality: OR 2.34 (2.20–2.50)  
- WRF associated with mortality: OR 1.81 (1.55–2.12)  
- Evidence of publication bias for studies on WRF |
Mr LM, 45 year old man, married father of 3, was a teacher

NYHA functional class I-II baseline, obese

9 month history of progressive decline in effort tolerance, shortness of breath, fatigue, difficulty walking uphill or upstairs. Swelling of the legs, 3 pillow orthopnoea and episodes of paroxysmal nocturnal dyspnoea. Occasional reports of wheeze

Seen at day hospital and diagnosed with asthma: no improvement on MDI and short courses of prednisone
CASE PRESENTATION

Now, sleeps sitting in chair. Difficulty with all ADLs including self care. Has been off work for past three months

On examination: overweight, 3+ pitting oedema, warm peripheries, HR 98 bpm, RR 20 bpm, BP 90/62 mmHg, pallor, JVP 7 cm with prominent CV waves.

Chest: Bibasal crackles, dullness in right base

CVS: Apex displaced to midaxillary line, 6<sup>th</sup> ICS. No heave. Normal S1 and S2, S3 gallop. 3/6 PSM, clinically has MR and TR.

Assessment: Heart failure

?Dilated cardiomyopathy/?Hypertensive heart disease/?Rheumatic heart disease/IHD unlikely
CASE PRESENTATION

Echo:
LVEDD 66 mm, EF 28%, thin LV walls, global hypokinesia of all LV segments, moderate MR and moderate TR, RV pressure 38 mmHg

Bloods:
Hb 8.1 g/dL; MCV 86 fL; WCC 7.1 $10^9$/L; Plt 189 $10^9$/L
Na 129 mmol/L; K 5.8 mmol/L; U 16 mmol/L; Cr 214 $\mu$mol/L
GFR 35 mL/min/1.73m²
What is your approach to management?
RENAL FUNCTION, HF AND MORTALITY RISK
1. Dietary salt restriction and diuretics:

To control fluid overload and symptoms

Effect on morbidity and mortality unknown

Loop diuretics should be first line
2. Managing anaemia in CKD and ESRD:

Anaemia associated with LV hypertrophy and LV dilation

Anaemia should be treated according to guidelines used in CKD population (including IV iron replacement)
3. Hyperphosphataemia, secondary hyperparathyroidism and vitamin D deficiency:

Associated with LV hypertrophy and LV dysfunction

Achieving adequate phosphate, calcium, vitamin D and PTH levels is a good goal in CKD

Symptom benefits

Benefits in preventing or improving HF not proven
4. Beta-blockers:

In CKD and non-CKD patients with HF with reduced systolic function, beta-blockers shown to reduce mortality and hospitalisation rates.

Treatment should be started slow and up-titrated and monitored.

The role of beta-blockers.
5. ACE inhibitors and ARBs:

ACE inhibitors and ARBs have a favourable effect on survival in patients with CKD and HF

Indicated in all patients with mild to moderate CKD (stages 1 to 3)

In patients with advanced CKD, the benefits of ACE inhibitors/ARBs have not been proven

Need to monitor BP, potassium levels and acute kidney injury
6. Aldosterone antagonists

Relatively contraindicated in stages 1 to 3

May rarely be considered for management of HF in patients with renal dysfunction

Only use at low doses

Carefully monitor serum potassium

Absolute contraindication in stages 4 and 5
7. Digoxin

Relatively contraindicated in HF with kidney dysfunction

May be considered in poorly controlled HF with high-ventricular rate atrial fibrillation in presence of optimal dose of RAAS inhibitors and beta-blockers

Use at low doses in kidney disease

Monitor serum levels regularly
8. Cardiac resynchronisation therapy:

Limited evidence

No recommendations can be made about CRT for HF in CKD
9. Renal replacement therapy:

Role of modality of dialysis is unclear, but likely irrelevant.

Adequate ultrafiltration is crucial for controlling volume overload.

Large volume ultrafiltration associated with myocardial stunning.

High-flow arteriovenous fistulae should be avoided: contribute to volume overload, high cardiac output, eccentric LVH and worsening HF.
**Chronic heart failure patient with renal impairment**

**Stable Renal Dysfunction**
- Yes: No additional measures. Check renal function and electrolytes every 6 months*
- No (Worsening Renal Function)
  - **During initiation/titration of RAAS inhibitors**
    - Yes: Increase in serum creatinine < 50% and serum creatinine not > 265 μmol/L (3 mg/dL) / eGFR < 25 mL/min/1.73 m²
      - Yes: Pseudo WRF
        - Accept change and check renal function and electrolytes regularly
      - No: Improvement
        - Pseudo WRF
          - If possible, rechallenge. Consider decreasing dose diuretic
        - Either halve dose or stop drug (if hypotensive, hyperkalemic or extreme increase in creatinine)
  - No: Improvement
    - Pseudo WRF
      - If possible, rechallenge. Consider decreasing dose diuretic
    - True WRF
      - Stop if halved; Stop other renal compromising drugs
      - Refer to nephrologist if renal impairment persists
      - Consider alternative cause (i.e. Renal Artery Stenosis)

**Deterioration in Clinical Status**
- Yes: Pseudo WRF
  - Accept change and check renal function and electrolytes regularly
- No: True WRF
  - Congested kidney
    - Reduce loop diuretic dose when renal function has stabilized. Recheck regularly
  - Hypoperfused and/or Congested kidney
    - Admit Patient for intravenous inotropes/diuretics

**Evidence of hypoperfusion or hypotension**
- Yes: Pseudo WRF
  - Not possible or no improvement
    - Recheck renal function, electrolytes and functional status regularly. Consider rechallenge
  - Improvement
    - True WRF
      - Congested kidney
        - Reduce loop diuretic dose when renal function has stabilized. Recheck regularly
      - Hypoperfused and/or Congested kidney
        - Admit Patient for intravenous inotropes/diuretics
- No: Consider Loop diuretic (optimization) and recheck renal function and electrolytes

**Reduce Diuretics or RAAS inhibitor or antihyperensives if possible**
- Improvement
- No Improvement
- Not possible or no improvement
Acute heart failure patient with renal impairment

**Stable Renal Dysfunction**
- Yes
  - Aggressively dose loop diuretics. Check renal function and electrolytes daily.
- No (Worsening Renal Function)
  - **Favourable Diuretic Response**
    - Yes
      - Possible Pseudo WRF. Re-evaluate congestion and hemodynamic status. If continued volume overload, accept change and check renal function and electrolytes at least daily.
    - No (Diuretic Resistance)
      - **Signs of Hypoperfusion and/or Hypotension**
        - No
          - Increase diuretic intensity
        - Yes
          - Attempt hemodynamic optimization
            - No Improvement
              - No Improvement
                - Improvement
      - Improvement
      - True WRF – Congested kidney
        - Reduce loop diuretic dose when renal function has stabilized and/or patient is euvoletic. Recheck regularly.
      - True WRF – Refractory Hypoperfused and/or Congested kidney
        - Consider invasive monitoring, ICU, Mechanical Support and possible Ultrafiltration or RRT.
      - True WRF – Hypoperfused and/or Congested Kidney
        - Consider invasive monitoring if further clinical or renal deterioration, regularly recheck renal function and electrolytes.
(i) Anemia and CKD-mineral and bone disorder should be treated, using the existing guidelines for the general CKD population.
(ii) Dietary salt restriction, diuretics, and adequate ultrafiltration in dialysis patients are key strategies to control fluid overload and HF symptoms.
(iii) Beta-blockers (bisoprolol, metoprolol, and carvedilol) can reduce mortality and should, therefore, be recommended to all patients, unless contraindicated or not tolerated. Treatment must be started at very low doses and carefully uptitrated and monitored, to avoid worsening HF, bradycardia, and hypotension.
(iv) ACEIs can reduce mortality and should be indicated to all patients with HF and CKD stages 1–3, unless contraindicated or not tolerated. In those with CKD stages 4 and 5, caution is required, considering that the benefits of ACEIs on survival have not been proven and that there is a higher risk of adverse events.
(v) Alternatively, ARBs can be used, particularly in patients who develop cough or angioedema from ACEIs. Dual therapy with ACEIs and ARBs can be considered in resistant cases.
(vi) When using RAAS inhibitors (particularly dual therapy), careful dose titration and clinical monitoring are required to prevent serious side effects, such as hypotension, hyperkalemia, and acute kidney injury.
(vii) In stage 3 CKD patients, aldosterone antagonists may be tried but should be used with great caution and at very low doses, while closely monitoring potassium levels. They should be avoided in patients with CKD stages 4 and 5.
(viii) The addition of digoxin may be considered in selected cases with poorly controlled symptoms of HF or with high-ventricular rate atrial fibrillation, in the presence of optimal-dose therapy with diuretics, RAAS inhibitors, and beta-blockers. Using very low doses and monitoring of serum digoxin concentration are required.
CKD and HR are common. Often coexist and share aetiology and risk factors.

Individuals with CKD have greater risk of CV death.

More than 40% of HF patients have CKD and presence of kidney dysfunction worsens HF; renal dysfunction occurs commonly in all forms of HF.

Updated definition of cardiorenal syndrome.

Pharmacotherapy may be difficult to manage and requires close monitoring.
THE END