ΣΥΝΟΣΗΡΟΤΗΤΕΣ ΣΤΗΝ ΚΑΡΔΙΑΚΗ ΑΝΕΠΑΡΚΕΙΑ

ΝΕΦΡΙΚΗ ΔΥΣΛΕΙΤΟΥΡΓΙΑ

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DEFINITIONS-ESC Guidelines 2016

- **Kidney dysfunction**: Chronic Kidney Disease (CKD), Acute Kidney Injury (AKI), Cardiorenal Syndrome (CRS), Prostatic Obstruction.

- **CKD**: eGFR < 60 ml/min/1.73m² and/or albuminuria

- **WRF (Worsening Renal Function)**: Further deterioration in RF, indicate an increase in sCreatinine, usually by >26.5mmol/L (0.3mg/dL) and/or a 25% increase or a 20% drop in GFR
Cardiorenal Syndromes - Types

General Definition:

*Pathophysiologic disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ induces acute or chronic dysfunction in the other*

CRS Type I (Acute Cardiorenal Syndrome)

*Abrupt worsening of cardiac function leading to acute kidney injury*

CRS Type II (Chronic Cardiorenal Syndrome)

*Chronic abnormalities in cardiac function causing progressive and permanent chronic kidney disease*

CRS Type III (Acute Renocardiac Syndrome)

*Abrupt worsening of renal function causing acute cardiac disorders*

CRS Type IV (Chronic Renocardiac Syndrome)

*Chronic kidney disease contributing to decreased cardiac function, cardiac hypertrophy and/or increased risk of adverse cardiovascular events*

CRS Type V (Secondary Cardiorenal Syndrome)

*Systemic condition (e.g. diabetes mellitus, sepsis) causing both cardiac and renal dysfunction*
Prevalence of Renal Dysfunction

# Epidemiology: Renal Dysfunction and HF

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (mL/min/1.73m²)</th>
<th>General Population</th>
<th>HFREF</th>
<th>HFPEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or ↑ GFR</td>
<td>≥ 90</td>
<td>64.3</td>
<td>8.2</td>
<td>8.2</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mild ↓ GFR</td>
<td>60 – 89</td>
<td>31.2</td>
<td>37.2</td>
<td>34.9</td>
</tr>
<tr>
<td>3</td>
<td>Moderate ↓ GFR</td>
<td>30 – 59</td>
<td>4.3</td>
<td>45.5</td>
<td>46.1</td>
</tr>
<tr>
<td>4</td>
<td>Severe ↓ GFR</td>
<td>15 – 29</td>
<td>0.2</td>
<td>7.8</td>
<td>8.1</td>
</tr>
<tr>
<td>5</td>
<td>Kidney Failure</td>
<td>&lt; 15 (or dialysis)</td>
<td>0.2</td>
<td>1.3</td>
<td>2.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Albuminuria</th>
<th>UACR (mg/g creatinine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normoalbuminuria</td>
<td>&lt; 17 / &lt; 25*</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>17-250 / 25-355*</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>&gt; 250 / &gt;355*</td>
</tr>
</tbody>
</table>

Data from GISSI-HF and CHARM
Prognostic value of Renal Dysfunction in HF

Forest plot of combined all-cause mortality for CKD vs. no CKD (57 studies, 1,076,104 patients)

Acute heart failure
2.39 [2.25, 2.54]

Chronic heart failure
2.26 [2.08, 2.47]

Total
2.34 [2.20, 2.50]

Damman K et al. Eur Heart J 2013
Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis.

Dammann K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL.

- 57 Studies on HF patients and mortality risk with chronic kidney disease (CKD) and worsening renal function (WRF).

- The prevalence of CKD was 32% and WRF 23%.

- Moderate renal impairment (HR 1.59), severe renal impairment (HR 2.17) and WRF (HR 1.95) were all independent predictors of mortality.

- Baseline CKD, history of HTN and DM, age, and diuretic use were significant predictors for the occurrence of WRF.
Pathophysiology Multifactorial

Systemic factors
- Diabetes
- Obesity
- Metabolic syndrome
- Hypertension
- Amyloidosis

Sympathetic neurohormonal activation
- Inflammation
- Endothelial dysfunction
- Fibrosis
- Oxidative stress

Heart failure

Organ damage Dysfunction

Renal insufficiency
Untoward effects of heart failure on renal function

Modified from Metra et al. Eur Heart J 2012;33:2135-2142
Relative Importance CI/CVP and WRF

Increase in Intraabdominal Pressure, Increases Serum Creatinine

Mullens et al., JACC, 2008
Forest plot of combined all-cause mortality for WRF vs. no WRF (28 studies, 49,890 patients)

Acute heart failure
1.75 [1.47, 2.08]

Chronic heart failure
1.96 [1.48, 2.61]

Total
1.81 [1.55, 2.12]

Survival in Patients Subdivided on the basis of Volume Status and WRF

Metra M et al Circ Heart Fail 2012
Aggressive Decongestion, WRF and Survival

Testani et al Circulation 2010
Haemoconcentration, WRF and Mortality in AHF
Most clinical trials excluded patients with eGFR <30 ml/min/1.73m²
The Diuretic Optimization Strategies Evaluation Study (DOSE)

A Bolus vs. Continuous Infusion

- AUC with bolus infusions, 4236±1440
- AUC with continuous infusion, 4373±1494
- P=0.47

B Low-Dose vs. High-Dose Strategy

- AUC with low-dose strategy, 4171±1436
- AUC with high-dose strategy, 4430±1401
- P=0.06

LVEF 35% / 75% rehospit / Creat 1.5 mg/dl / 130 mg furosemide / >90% CVP+orthopnea

Felker M et al. NEJM 2011; 364:797-805
Worsening renal function during renin–angiotensin–aldosterone system inhibitor initiation and long-term outcomes in patients with left ventricular systolic dysfunction

Hannah Clark¹, Henry Krum¹,², and Ingrid Hopper¹,²*
Reduction in all-cause mortality associated with the use of RAAS-I was significantly greater in the presence of WRF than in the no WRF group.
RAAS Inhibition and WRF in HF Patients

Renin–Angiotensin System Inhibition, Worsening Renal Function, and Outcome in Heart Failure Patients With Reduced and Preserved Ejection Fraction

A Meta-Analysis of Published Study Data

Iris E. Beldhuis, BSc; Koen W. Streng, MD; Jozine M. Ter Maaten, MD, PhD; Adriaan A. Voors, MD, PhD; Peter van der Meer, MD, PhD; Patrick Rossignol, MD, PhD; John J.V. McMurray, MD; Kevin Damman, MD, PhD

Circ Heart Fail 2017
RAAS inhibition causes WRF in both HFrEF and HFP EF.

Risk or WRF in HFrEF but not in HFP EF is lower than the net clinical benefit due to RAAS inhibition.

Figure 3. Funnel plot of included studies in primary analysis. HFP EF indicates heart failure with preserved ejection fraction; HFr EF, heart failure with reduced ejection fraction; RAASi, renin-angiotensin aldosterone system inhibition; and RR, relative risk.
Practice Guidelines on RAAS-I Treatment in HF

- An increase in creatinine up to 50% above baseline OR 3mg/dL / eGFR <25ml/min whichever is the smaller is acceptable.

- An increase in potassium to < 5.5mmol/L is acceptable.

- More severe changes: halve dose ACE-I.

- If K >5.5mmol/L OR creat>100% or to 3.5mg/dL eGFR<20ml/min . stop ACE-I.

Ponikowski et al Eur J Heart Fail 2016
### ROSE trial; Dopamine vs placebo

<table>
<thead>
<tr>
<th>Dopamine strategy</th>
<th>Placebo (n = 119)</th>
<th>Dopamine (n = 122)</th>
<th>Treatment Difference</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative urine volume from randomization to 72 h, mL</td>
<td>8296 (7762 to 8830)</td>
<td>8524 (7917 to 9131)</td>
<td>229 (−714 to 1171)</td>
<td>.59</td>
</tr>
</tbody>
</table>

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### DAD-HF II trial; Dopamine vs placebo

<table>
<thead>
<tr>
<th>Time after initiation of treatment</th>
<th>High-dose furosemide</th>
<th>Low-dose furosemide plus dopamine</th>
<th>Low-dose furosemide</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 h</td>
<td>735 (338–1108)</td>
<td>900 (428–1370)</td>
<td>750 (400–1420)</td>
<td>0.362</td>
</tr>
<tr>
<td>4 h</td>
<td>1190 (585–1720)</td>
<td>1330 (763–1873)</td>
<td>1175 (743–1925)</td>
<td>0.525</td>
</tr>
<tr>
<td>6 h</td>
<td>1390 (858–2263)</td>
<td>1620 (1048–2483)</td>
<td>1680 (1186–2465)</td>
<td>0.522</td>
</tr>
<tr>
<td>8 h</td>
<td>1845 (1088–2640)</td>
<td>1950 (1440–2950)</td>
<td>1990 (1438–3000)</td>
<td>0.700</td>
</tr>
<tr>
<td>24 h</td>
<td>2900 (2100–4640)</td>
<td>3515 (2500–4460)</td>
<td>3500 (2510–4485)</td>
<td>0.686</td>
</tr>
</tbody>
</table>
## Recommendations regarding renal replacement therapy in patients with acute heart failure

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Level&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Ref&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrafiltration may be considered for patients with refractory congestion, who failed to respond to diuretic-based strategies.</td>
<td>IIIb</td>
<td>B</td>
<td>578–580</td>
</tr>
<tr>
<td>Renal replacement therapy should be considered in patients with refractory volume overload and acute kidney injury.</td>
<td>IIa</td>
<td>C</td>
<td></td>
</tr>
</tbody>
</table>

*European Heart Journal*

doi:10.1093/eurheartj/ehw128
ARNI and GFR in pts with HF and Diabetes

Figure 2: Change in eGFR in patients with and those without diabetes based on treatment assignment. Error bars are 95% CIs. eGFR=estimated glomerular filtration rate.

Packer M et al Lancet Diab Endocr 2018
Find the “sweet spot” of euvolemia before discharge.
CONCLUSIONS

- Renal Dysfunction is highly prevalent and has a bad prognosis in Heart Failure patients.
- HF patients with Worsening Renal Function have not always a bad outcome (true WRF or pseudo-WRF?)
- We need a better understanding of the pathophysiology of the cardiorenal dysfunction-interactions to target new therapies (e.g. fibrotic biotargets, monitoring markers of congestion and kidney function etc)