Outline

• Predisposition for cardiorenal syndromes
• Central role for eGFR and albuminuria
• Acute kidney injury
• Pulmonary edema
• Chronic cardiorenal syndromes
• Conclusions
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Obesity and cardiometabolic changes in the cardiovascular system, including diabetes and hypertension, and later in the course of disease, cachexia, biochemical, and hormonal changes due to bone and mineral disorder, proteinuria, uremic solute retention, and anemia, all contribute to the risk for developing cardio-renal syndrome (CRS) type 1. The course of this syndrome can lead to permanent renal failure and need for dialysis or partial renal recovery. EPO = erythropoietin; GFR = glomerular filtration rate.
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FIGURE 88-3 Relative risks of heart and kidney outcomes in cohorts where eGFR and ACR were measured.

Summary of Relative Risks from Categorical Meta-Analysis
(dipstick included [-, ±, +, ≥++])

<table>
<thead>
<tr>
<th></th>
<th>All-Cause Mortality</th>
<th>Cardiovascular Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACR &lt;10</td>
<td>ACR 10-29</td>
</tr>
<tr>
<td>eGFR &gt; 105</td>
<td>1.1</td>
<td>1.5</td>
</tr>
<tr>
<td>eGFR 90-105</td>
<td>Ref</td>
<td>1.4</td>
</tr>
<tr>
<td>eGFR 75-90</td>
<td>1.0</td>
<td>1.3</td>
</tr>
<tr>
<td>eGFR 60-75</td>
<td>1.0</td>
<td>1.4</td>
</tr>
<tr>
<td>eGFR 45-60</td>
<td>1.3</td>
<td>1.7</td>
</tr>
<tr>
<td>eGFR 30-45</td>
<td>1.9</td>
<td>2.3</td>
</tr>
<tr>
<td>eGFR 15-30</td>
<td>5.3</td>
<td>3.6</td>
</tr>
</tbody>
</table>

Figure 1. Relative proportions of albumin-creatinine ratio (ACR) of 30 mg/g or greater, estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m², and both as positive screening tests for chronic kidney disease in the Kidney Early Evaluation Program (KEEP) and National Health and Nutrition Examination Survey (NHANES) 1999-2004. $P < 0.001$ for eGFR and ACR trend. To convert eGFR in mL/min/1.73 m² to mL/s/1.73 m², multiply by 0.01667.
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Proportion of AKI Cases

- Primary Care
- Outpatient Procedures
- Inpatient

Talabani B, Zouwail S, Pyart RD, Meran S, Riley SG, Phillips AO. Epidemiology and outcome of community-acquired acute kidney injury. Nephrology. 2014;19(5):282-287. Department of Biochemistry and Immunology, Cardiff and Vale University Health Board, University Hospital of Wales, Cardiff UK and Department of Medical Biochemistry, School of Medicine, Alexandria University, Egypt.
When an increase in serum Cr is observed in the clinic it is strongly predictive of HF hospitalization, and thus is an opportunity for machine learning, alerts, and intercurrent care.
Among 11,683 qualifying AKI hospitalizations, 2954 patients (25%) were hospitalized with recurrent AKI within 12 months of discharge. Median time to recurrent AKI was 64 days.

Figure 2. Choice of baseline creatinine for index and recurrent AKI. The baseline for an index AKI event was defined using the mean outpatient serum creatinine 7–365 days prior to hospitalization. To account for potential trajectories of recovery, we defined the baseline for recurrent AKI as the nadir of either the most recent inpatient or outpatient serum creatinine or the admission serum creatinine of the subsequent hospitalization in which recurrent AKI occurred.
Blood and Urine Biomarkers of Acute Kidney Injury


Tubular Enzymuria
GGT, AlkPhos, LDH
NAG, α/πGST,
NGAL, IL-18, KIM-1, L-FABP

G1 cell cycle arrest markers
([TIMP-2].[IGFBP7])

Cr, Cystatin-C
Exclude Transient Hemodynamic ↑Cr ↓UO

Anticipate, Prevent, and Manage Complications
Outline

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• **Pulmonary edema**
• Chronic cardiorenal syndromes
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Cardio-Pulmonary-Renal Interactions
A Multidisciplinary Approach

Faeq Husain-Syed, MD,† Peter A. McCullough, MD, MPH,‡‡ Horst-Walter Birk, MD,‡ Matthias Renker, MD,‡ Alessandra Brocca, MSc,∗ Werner Seeger, MD,‡ Claudio Ronco, MD∗

Renal blood flow ↓
Injury/apoptosis
TIMP-2, IGFBP-7, NGAL, L-FABP, KIM-1, α-GST, m-GST, TNF-α, IL-1β, IL-6 ↑
Tubular reabsorption ↓
Urine albumin, urinary cystatin C, NAG ↑

Vascular permeability ↑
Leukocyte trafficking
Injury/apoptosis
ENaC/NKCC1 ↓
Aquaporin 5 ↓
TNF-α, IL-1β, IL-6 ↑

Leukocyte infiltration
Injury/apoptosis
hs-cTnT, BNP, NGAL, TNF-α, IL-1, IL-8, ICAM-1 ↑

Fibrosis/remodeling
BNP, FGF-23, Galectin-3, Soluble ST2, TGF-β1 ↑

Fibrosis/sclerosis
NGAL, KIM-1, Galectin-3, TGF-β1 ↑

CHRONIC
Lungs
Heart
Kidney

ACUTE
Lungs
Heart
Kidney
Diuretic Strategy

Unguided (inpatient bolus/infusion):
No improvement in outcomes
- DOSE HF Trial
- ROSE HF Trial
- Palazzuloli Trial

Guided (clinic, oral):
- ↓Hospitalization/death
- Biomarkers
  - PA pressure
  - 6 Biomarker Trials Felker 2009
  - CHAMPION Trial PA Pressure monitor 2011

Fig. 3 Strategy for loop diuretic therapy optimization looking for renal dysfunction fluid accumulation and hemodynamic status. AKI acute kidney injury
Volume Depletion

- Diuretics
- Ultrafiltration
- Hypotension
- Tachycardia
- Shock
- Organ Hypoperfusion
- Oliguria
- Normal Heart
- Volume Depletion
- Arterial Underfilling

Fluid Balance

- Management Window
- Optimal Status

Volume Overload

- Liberal Intake
- Positive Balance
- At-Risk Kidneys
- Hypertension
- Peripheral Edema
- Impaired Oxygenation
- Organ Congestion
- Normal Kidneys
- Acute Decompensation

Risk of Cardiorenal Syndrome

- Low
- High
- Blood Pressure
- Low
- High

Organ Hypoperfusion
Oliguria

Management Window

Heart

Diseased Heart
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Simultaneous Cardiac and Renal Fibrosis

Galectin-3 and Risk of Incident Heart Failure in Framingham Heart Study

The cumulative incidence of heart failure (HF) increased with higher galectin-3 (Gal-3) quartiles.
Elevated Galectin-3 Precedes the Development of CKD

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Figure 1. Risk for incident CKD and rapid decline in GFR, but not incident albuminuria, increases by galectin-3 quartile. Error bars represent upper 95% CI for the OR estimate. Incident CKD and rapid decline in GFR analyses adjusted for age, sex, diabetes, hypertension, dipstick proteinuria, and baseline eGFR. Incident albuminuria analysis adjusted for age, sex, diabetes, hypertension, body mass index, smoking, HDL cholesterol, and baseline log urinary albumin-to-creatinine ratio.
Galectin-3 in Disease States

General Population: 11.9 ng/ml
Low Risk HF: 12.2 ng/ml
Mod Risk HF: 20.1 ng/ml
High Risk HF: 26.0 ng/ml
High Mortality ESRD: 64.2 ng/ml

De Boer RA, 4D Trial Circ (Abstr) 2011
HF=heart failure, ESRD=end-stage renal disease
de Boer RA, et al., PREVEND Study Eur Heart J 2011;32:807
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- Estimated GFR and albuminuria are cornerstones of CKD identification and prognosis
- Community acquired AKI is common and approaches for detection are needed
- Pulmonary congestion is part of the cardiorenal syndrome and may contribute to chronic lung disease
- There is a very narrow management window on intravascular volume—*guided* diuretic management can benefit
- Best use of novel AKI markers is to differentiate between azotemia “worsened renal function” due to slow plasma refill versus bona fide AKI
- HF biomarkers are an opportunity for HTN and CKD