Congestive Heart Failure & Cardiorenal Syndrome: Is there Role for Biomarkers?

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Congestive Heart Failure and Cardio-Renal Syndrome: *Role of Biomarkers*

- Current concepts of CRS are largely based upon biomarker changes (creatinine) during intravascular volume shifts and
Renal Impairment in Acute HF: ADHERE

When admitted for Acute HF:
- 1 out of 5 has rise in creatinine
- 1 out of 10 goes to dialysis
- 1 out of 20 stays on dialysis
- 1 out of 5 dies if BUN >43 mg/dL and SBP <115 mmHg (10% pts)
- 1 out of 5 dies if BUN >43 mg/dL, SBP ≥115 mg Hg, but Cr >2.75 mg/dL (2% pts)

Prevalence of CKD by eGFR (in ml/min/1.73m²)

- 27% ≥90
- 13% 60-89
- 7% 15-29
- 9% <15
- 15% 30-59

65% of ADHF patients presented with eGFR<60 ml/min/1.73m²
Heywood et al, J Card Fail 2007

Fonarow et al, J Card Fail 2003; Fonarow et. al. JAMA 2004
“Worsening Renal Function”

- Serum creatinine $\geq 0.3$ mg/dL:
- In-hospital mortality:
  - Sensitivity of 65%
  - Specificity of 81%
- 2.3 days $\uparrow$ length of stay
- 67% $\uparrow$ risk of death within 6 months after discharge
- 33% $\uparrow$ risk for readmission
- **Risk factors:**
  - Co-morbidities (diabetes)
  - Age
  - CKD (admit Cr $>2.5$ mg/dL)
  - Nephrotoxic drugs

2021 patients in placebo arm of EVEREST trial
53.2% had GFR ≤60 ml/min/1.73m²
13.8% had worsening renal function (WRF) in-hospital
11.9% had WRF post-discharge – more prognostic

Blair et al, *Eur Heart J* 2011
By discharge, 12% of patients had a $\geq 25\%$ decrease in eGFR, and 39% had a $\geq 25\%$ increase in BUN

Klein et. al. *Circ Heart Fail* 2008
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“Cardio-Renal Syndrome” (CRS)

**NHLBI Working Group Definition (2004):** “The extreme of cardio-renal dysregulation whereby therapy to relieve congestive symptoms of heart failure is limited by further decline in renal function”

**ADQI Classification (2009):** Disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other.

**Determinants for CRS:**
- Cardio-renal perfusion
- Renal sodium/water handling
- Mobilization of excess fluid

ADQI Guidelines, Ronco et al, *Eur Heart J* 2009
Complex Interplay in Cardio-Renal Syndrome

Tang & Mullens, *Heart* 2010
Venous Congestion and Renal Function in AHFS

Mullens et al, JACC 2008
Predictors of Improving Renal Function

Predictors:
- ↓ BP / ↓ hypertension
- ↑ Hepatojugular reflux / JVD
- ↓ LVEF / ↑ RV dysfunction
- ↓ eGFR / ↑ BUN
- ↑ β-blocker / spironolactone
- No invasive hemodynamic predictors

Testani et al, AJC 2010; Testani et al, JCF 2011
Decreases in Mean Arterial Pressure rather than Changes in Central Hemodynamics Portend CRS

Dupont et al, Eur J Heart Fail 2013
Benefit of Decongestion & Hemoconcentration Despite Worsening Renal Function

Testani et al, *Circulation* 2010

Testani et al, *J Am Coll Cardiol* 2013
Abdominal Contribution to Cardio-Renal Dysfunction

Verbrugge et al, JACC 2013; Fallick et al, CircHF 2011
Relief of Intra-Abdominal Pressure in CRS

Subgroup presenting with elevated IAP at baseline

![Graph showing changes in INtra-abdominal pressure and serum creatinine](image)

- ↑ sCr
- ↓ sCr

Clinically-Available Biomarkers for Heart Failure

- BNP / NT-proBNP
- Cardiac troponin I or T
- hsCRP
- Soluble ST2
- Myeloperoxidase
- Uric acid
- Renin
- Aldosterone
- Norepinephrine
- Creatinine
- BUN
- Cystatin C
- Sodium (NGAL)
- Galectin-3
- Others:
  - Blood/urine electrolytes
  - Liver function tests
  - Thyroid function tests
  - Complete blood count
  - Iron studies

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- Novel biomarkers are derived from acute kidney injury models that may or may not align with cardio-renal pathophysiology
Baseline and Serial Cystatin C in ADHF: ASCEND-HF

Tang et al, AHA 2011 (abstract)
Lack of Concordance between WRF Defined by Rise in Creatinine versus Rise in Cystatin C

Dupont et al, *Congest Heart Fail* 2013
Increased Interstitial Fibrosis & Inflammation in CRS

Neutrophil gelatinase-associated lipocalin (NGAL)

Cleveland Clinic

GALLIANT

Aghel et al, J Card Fail 2009
Maisel et al, Eur J Heart Fail 2011
Urinary rather than Serum NGAL associated with Diuresis and Natriuresis in Heart Failure

Shrestha et al, *Am J Cardiol* 2012

Schmidt-Ott, *Nephrol Dial Transplant* 2011
NGAL in ADHF: Injury or Insufficiency?

Dupont et al, *Eur J Heart Fail* 2012
Distinct Patterns of AKI Biomarkers in ADHF

Park et al, *Biomarker Insights* 2012
Limited Predictive Value of Novel Urinary AKI Markers in AKI or Persistent Renal Impairment in ADHF

Verbrugge et al, J Card Fail 2013
Current Renal Biomarkers are Non-Specific to Pathogenic Mechanisms or Renal Changes

Mechanisms
- Hemodynamic derangements
- Neurohormonal perturbations
- Oxidative stress and inflammation

Renal Changes
- ↓ Filtration pressure
- Renal injury
- Loss of nephron mass

Biomarkers
- ↑ BUN / creatinine
- ↑ Cystatin C
- ↑ CNP
- AKI Markers (NGAL, KIM1, IL18)
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- Acute biomarker changes may not reliably identify target populations or adverse endpoints
DOSE-HF: Diuretic-induced WRF and Clinical Outcomes

Felker et al, *NEJM* 2011
Changes in Renal Function: DOSE-AHF

Felker et al, *NEJM* 2011; House *CJASN* 2013
Ultrafiltration in CRS: CARRESS-HF

ADHF pts with $\uparrow\text{Cr} > 0.3 \text{ mg/dL}$

Death or HF Rehospitalization

HR = 1.01 (0.62, 1.64)  
$P = 0.9556$

Serum Creatinine

Bart et al, *NEJM* 2012
Weight Loss at 72h in kg
(1° Endpoint)

↑Cr >0.3 mg/dL towards compensation (%)

DUEL vs DOSE:

↓Weight & ↑Creatinine

4/316 (1.4%) in TOR rehospitalized in 60 days
4.2% in TOR required switch to IV

Mareev et al, ESC HF 2011 LBCT
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- Renal biomarkers may provide insights into vulnerable populations for renal-enhancing therapies, but need distinction of therapeutic mechanisms.
Renal Preservation with Serelaxin in ADHF

Metra et al, J Am Coll Cardiol 2013
Benefits for Serelaxin in ADHF: RELAX-AHF

Metra et al, *Eur Heart J* 2013
MEMs-based Pressure Sensor for Monitoring Pulmonary Artery Pressures

- Catheter-based delivery system
- Implanted PA branch diameter 7-15 mm
- Clopidogrel/aspirin combined for 1 month post-implant or previous warfarin
- Daily readings by external device

- Target range (mmHg):
  - PA systolic: 15-35
  - PA diastolic: 8-20
  - PA mean: 10-25
CHAMPION: Primary Results

- 550 NYHA III patients from 63 centers
- Hospitalized for HF ≤12 months
- Excluded eGFR <25 ml/min

Preliminary Findings:
- 30%↓ in HF hospitalizations at 6 months
- 35%↓ in annualized HF hospitalization rates for the entire randomized follow-up
- ↑QoL score with treatment group

Abraham et al, Lancet 2011
Distinct “Breathprint” for Acute HF

Samara et al, J Am Coll Cardiol 2013
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