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 mmHg, but Cr >2.75 mg/dL (2% pts)

Heywood et al, J Card Fail 2007
Fonarow et al, J Card Fail 2003
Fonarow et al, JAMA 2004
“Worsening Renal Function”

- Serum creatinine $\uparrow \geq 0.3$ 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)
- Nephrototoxic drugs


Serial Renal Indices in ADHF: EVEREST

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

Prognostic Value of Baseline & Change in BUN

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

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

Mulero et al, JACC 2008; Mulero et al, J Card Fail 2008

Testani et al, Circulation 2010  Testani et al, J Am Coll Cardiol 2013
Clinically-Available Biomarkers for Heart Failure

- BNP / NT-proBNP
- Cardiac troponin I or T

Creatinine
BUN
Cystatin C
Sodium (NGAL)

Myeloperoxidase
Uric acid

BNP / NT-proBNP
Cardiac troponin I or T

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Modified from Vaidya et al, Annu Rev Pharmacol Toxicol 2008
Baseline and Serial Cystatin C in ADHF: ASCEND-HF

Lack of Concordance between WRF Defined by Rise in Creatinine versus Rise in Cystatin C

Increased Interstitial Fibrosis & Inflammation in CRS
Neutrophil gelatinase-associated lipocalin (NGAL)

Cleveland Clinic

GALLIAN

Baseline Serum NGAL (ng/mL)

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<th>Yes (n=35)</th>
<th>No (n=65)</th>
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<td>p = 0.001</td>
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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

Verbrugge et al., J Card Fail 2013

limited Predictive Value of Novel Urinary AKI Markers in AKI or Persistent Renal Impairment in ADHF

Current Renal Biomarkers are Non-Specific to Pathogenic Mechanisms or Renal Changes
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DOSE-HF: Diuretic-induced WRF and Clinical Outcomes

High vs. Low = 0.83
95% CI 0.60, 1.16, p = 0.28
Felker et al., NEJM 2011

Changes in Renal Function: DOSE-AHF

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

Bart et al, NEJM 2012

ADHF pts with Cr >0.3 mg/dL

Death or HF Rehospitalization

Mareev et al, ESC HF 2011 LBCT

Weight Loss at 72h in kg

1° Endpoint

DUEL vs DOSE: ↓Weight & ↑Creatinine

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

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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