Update on Hyponatremia in HF &
The Complex Interplay Between
Congestion, Kidney Injury and
“Worsening Renal Function”

TIEN M.H. NG, PHARM.D., FHFS, FACC, FCCP, BCPS AQ CARDIOLOGY
ASSOCIATE PROFESSOR OF CLINICAL PHARMACY AND MEDICINE
DIRECTOR, PGY2 RESIDENCY IN CARDIOLOGY
VICE CHAIR, TITUS FAMILY DEPARTMENT OF CLINICAL PHARMACY
SCHOOL OF PHARMACY AND KECK SCHOOL OF MEDICINE
UNIVERSITY OF SOUTHERN CALIFORNIA, LOS ANGELES, CA
Disclosures

- Research funding: Otsuka America Pharmaceuticals
- Consulting: Amgen
Update on Hyponatremia in HF
PREVALENCE IN HOSPITALIZED PATIENTS WITH HF

- Hyponatremia (Na < 135 mEq/L) in patients hospitalized with HF

![Bar chart showing prevalence of hyponatremia in hospitalized patients with HF across different studies: OPTIME CHF, ACTIV, OPTIMIZE-HF, ESCAPE, EVEREST.]

PROGNOSTIC IMPLICATIONS IN HOSPITALIZED PATIENTS WITH HF

*OPTIMIZE-HF registry data; N=48,612.

Arginine Vasopressin

- Hyperosmolarity
- Decreased atrial receptor firing Baroreceptors
- Angiotensin II
- Sympathetic stimulation

Hypothalamus

Posterior Pituitary

Vasopressin

- $V_{1A}$
  - Myocytes (Growth)
  - Remodeling

- $V_{1A}$
  - Blood Vessels (Constriction)
  - Increased Systemic Vascular Resistance

- $V_2$
  - Kidneys (Fluid Reabsorption)
  - Increased Blood Volume

- $V_{1B}$
  - ACTH
# TACTICS and SECRET OF CHF

<table>
<thead>
<tr>
<th>Design</th>
<th>TACTICS-HF</th>
<th>SECRET OF CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R, DB, PCB</td>
<td>R, DB, PCB</td>
</tr>
</tbody>
</table>

| N             | 257                 | 250                 |

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>TACTICS-HF</th>
<th>SECRET OF CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within 24h of presentation</td>
<td></td>
<td>Within 36h of presentation</td>
</tr>
<tr>
<td>Dyspnea (rest or with minimal exertion)</td>
<td></td>
<td>Challenging decongestion:</td>
</tr>
<tr>
<td>BNP &gt; 400, NT-proBNP &gt; 2000 pg/mL</td>
<td></td>
<td>Renal dysfunction (eGFR &lt; 60 mL/min/1.73m2) or</td>
</tr>
<tr>
<td>Orthopnea, peripheral edema, JVD, rales, CXR pulmonary congestion</td>
<td></td>
<td>Na ≤ 134 mEq/L or</td>
</tr>
<tr>
<td>Orthopnea, peripheral edema, JVD, rales, CXR pulmonary congestion</td>
<td></td>
<td>UO ≤ 125 mL/h (furosemide 40mg IV or eq)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intervention</th>
<th>TACTICS-HF</th>
<th>SECRET OF CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furosemide 40mg IV BID +/- Tolvaptan 30mg PO daily</td>
<td></td>
<td>Tolvaptan 30mg PO daily vs Placebo On top of SOC</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Results</th>
<th>TACTICS-HF</th>
<th>SECRET OF CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater wt and fluid loss @ 24 and 48h with tolvaptan</td>
<td></td>
<td>Greater wt loss days 1-3 with tolvaptan</td>
</tr>
<tr>
<td>More WRF at 72h</td>
<td></td>
<td>No difference WRF</td>
</tr>
</tbody>
</table>
% moderate or better improvement in dyspnea (Likert Scale)

*Dyspnea by numerical rating scale better with tolvaptan at 48h, p=0.05
*Potential greater benefit early with tolvaptan in those without JVD or ascites.
AQuaresis Utility for hyponAtremic Acute Heart Failure (AQUA-AHF; NCT02183792)

- N=33, AHF with Na⁺ < 135 mEq/L
- Randomized, open-label, parallel-group

Ng, Grazette, Fong, Yoon, Elkayam HFSA 2018
## AQUA-AHF: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Tolvaptan (N=18)</th>
<th>Furosemide (N=15)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>53±11.7</td>
<td>59±8.9</td>
<td>0.142</td>
</tr>
<tr>
<td>Male, %</td>
<td>11 (61.1)</td>
<td>14 (93.3)</td>
<td>0.046</td>
</tr>
<tr>
<td>LVEF</td>
<td>24±7.2</td>
<td>33±14.3</td>
<td>0.093</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>2 (11.1)</td>
<td>4 (28.6)</td>
<td>0.365</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>9 (50.0)</td>
<td>8 (53.3)</td>
<td>0.849</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>3 (16.7)</td>
<td>3 (21.4)</td>
<td>1.000</td>
</tr>
<tr>
<td>Loop diuretic</td>
<td>15 (83.3)</td>
<td>12 (80.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Home Loop Dose (Furosemide Equivalents)</td>
<td>93±63.5</td>
<td>109±77.5</td>
<td>0.693</td>
</tr>
<tr>
<td>Thiazide diuretic</td>
<td>3 (16.7)</td>
<td>2 (13.3)</td>
<td>1.000</td>
</tr>
</tbody>
</table>
AQUA-AHF: Diuresis Comparison

- Median daily dose throughout study: tolvaptan 30mg and furosemide 120mg
- Metolazone use: tolvaptan (4) and furosemide (1)

Ng, Grazette, Fong, Yoon, Elkayam HFSA 2018
In tolvaptan group:

- ↓ cystatin C
- ↑ serum Na and copeptin
- No differences in NT-proBNP, PRA, uNGAL:Cr
AQUA-AHF: Conclusions

- Diuresis with an oral tolvaptan-based diuretic regimen was similarly effective compared to an intravenous furosemide-based diuretic regimen for acute HF
- Tolvaptan was associated with signals for improved kidney function, but clinical significance needs to be tested in a larger study

Applications?:
- Alternative diuretic for acute HF
- Potential of tolvaptan in short-term outpatient management to reduced need for hospitalizations or TOC
The Complex Interplay Between Congestion, Kidney Injury and “Worsening Renal Function”
Common Scenarios

- GS 55yo patient admitted with complaints of increasing lower extremity and abdominal edema, decreasing exercise tolerance and weight gain for the past 2 weeks.
  - PMHx:
    - HFrEF (LVEF 30%)
    - MI 2010
    - HTN, DM
  - PE:
    - BP 118/79, HR 95, RR 20, \( O_2 \text{sat } 99\% \) 2L/min
    - JVP 15cm, + rales, RRR, +S3, PMI displaced, RV heave, abd distention, 2+LE edema

- HT 68yo patient admitted with complaints in increased DOE, swelling in the feet, and decreased appetite.
  - PMHx:
    - HFpEF (LVEF 55%)
    - HTN
    - AF
    - CKD stage III
  - PE:
    - BP 155/94, HR 86, RR 16, \( O_2 \text{sat } 99\% \) RA
    - JVP 10cm, CTA, irreg/irreg, 2+ LE edema
**Common Scenarios continued…**

- Patients started on furosemide 40mg IV BID

<table>
<thead>
<tr>
<th></th>
<th>GS</th>
<th>HT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Net fluid balance</td>
<td>SCr</td>
</tr>
<tr>
<td>Day 1</td>
<td>-1000</td>
<td>1.22</td>
</tr>
<tr>
<td>Day 2</td>
<td>-1120</td>
<td>1.15</td>
</tr>
<tr>
<td>Day 3</td>
<td>-900</td>
<td>1.19</td>
</tr>
<tr>
<td>Day 4</td>
<td>-840</td>
<td>1.58</td>
</tr>
</tbody>
</table>
- D/C diuretic
- D/C RAAS blocker
- Consider dopamine IV 3 mcg/kg/min
- Renal consult
**WRF and HF Prognosis**

- Meta-analysis, 28 studies (48,890 patients; 11,476 experiencing WRF)
- WRF = ↓eGFR, ↑Scr or cystatin C

<table>
<thead>
<tr>
<th>OR All-Cause Mortality (95% CI)</th>
<th>All definitions of WRF</th>
<th>WRF defined as increase &gt;0.3 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute HF</td>
<td>1.75 (1.47, 2.08)</td>
<td></td>
</tr>
<tr>
<td>Chronic HF</td>
<td>1.95 (1.48, 2.81)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>1.81 (1.55, 2.12)</td>
<td>1.54 (1.29, 1.85)</td>
</tr>
</tbody>
</table>

Damman K. EHJ 2014;35:455-69
CONGESTION (Worsening) KIDNEY FUNCTION

KIDNEY INJURY

HF PROGNOSIS

CONGESTION
WRF (as currently defined) is a flawed metric
Traditional “Worsening Renal Function” in HF

- $\uparrow \text{Scr} \geq 50\% \ (1.5X) \text{ above baseline}$
- $\uparrow \text{Scr} \geq 25\% \text{ above baseline if Scr} > 2 \text{ mg/dL}$
- $\uparrow \text{Scr} \geq 0.3 \text{ mg/dL above baseline}$
- $\downarrow \text{eGFR} \geq 20\% \text{ below baseline}$
## Limitations in Serum Creatinine

<table>
<thead>
<tr>
<th></th>
<th>Caveats</th>
<th>HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breakdown product of skeletal muscle</td>
<td>Affected by age, gender, race, diet</td>
<td>Commonly have altered production (muscle wasting, malnutrition)</td>
</tr>
<tr>
<td>Freely filtered</td>
<td>Also secreted</td>
<td>Overestimates in renal dysfx</td>
</tr>
<tr>
<td>Use of any serum creatinine-based estimate requires that kidney function be at a steady state. (NIDDK)</td>
<td></td>
<td>Dynamic changes in kidney function are common</td>
</tr>
<tr>
<td>Changes in eGFR linked to prognosis</td>
<td>Does not infer mechanisms</td>
<td>Both increases and decreases associated with improved or worse outcomes</td>
</tr>
</tbody>
</table>
Not all “WRF” is reflective of kidney injury
Renal Optimization Strategies Evaluation—Acute Heart Failure (ROSE-AHF)

- WRF defined as ≥20% decrease in eGFR (cystatin C) to 72h

Increases in injury biomarker and WRF were independently associated with improved survival

Congestion is a significant modulator of kidney function and is more important than “WRF”
Type 1 CRS Proposed Pathophysiology

- Arterial Underfilling
- Sympathetic Nervous System (RAAS, Arginine Vasopressin, Endothelin)
- Increased Susceptibility
- Functional (Pre-renal)
- Glomerular-interstitial damage
- AKI
- Decreased Perfusion Pressure
- Ineffective Natriuretic Peptides, Kinin-kallikrein System, Prostaglandins, Endothelial Relaxin Factor
- Increased Venous Pressure
- Parenchymal Damage
- Sclerosis Fibrosis
- Repeated Episodes of AKI, Uremic Milieu
- CKD
- ADHF
- Venous Congestion
- Relative Decrease in Cardiac Output
Congestion and HF

- Most ADHF present with congestion as opposed to hypoperfusion (ADHERE)
- Not all congestion is secondary to overt volume overload:

- Neurohormonal Activation
  - Inflammation and Inflammatory Cytokines
  - Oxidative Stress

- Increased hydrostatic pressure
  - Increased capillary permeability
  - Decreased lymphatic flow

- Decreased venous capacitance
  - Increased intra-abdominal pressure
  - Decreased lymphatic flow

- Decreased LV compliance
  - Increased LVEDP
Sources of Congestion in HF and Effect on the Kidney

<table>
<thead>
<tr>
<th>Source</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart/ Exogenous Fluid Accumulation</strong></td>
<td>Arterial underfilling, Increased CVP, Humoral activation</td>
</tr>
<tr>
<td><strong>Splanchnic</strong></td>
<td>Reduced capacitance, Inflammation, Endotoxemia</td>
</tr>
<tr>
<td><strong>Liver/Portal</strong></td>
<td>Increased intra-abdominal pressure, Altered GUT flora, Decreased abdominal lymph flow</td>
</tr>
<tr>
<td><strong>Pulmonary</strong></td>
<td>Inflammation, endothelial dysfx, oxidative stress, Hypercapnia induced vasodilatation and neurohormonal activation, PVR and RV function, Mechanical ventilation</td>
</tr>
</tbody>
</table>

- Reduced RBF and GFR
- Glomerular vasoconstriction
- Neurohormonal activation
- ↑Na/H2O reabsorption
- ↑Fibrosis
- ↑Apoptosis
Congestion and eGFR

- 2647 patients, LVEF≤35%, NYHA FC III-IV (CIBIS II)

Any signs of congestion and # of signs were both independently associated with lower eGFR at baseline and mortality.

Damman K. EJHF2010:12:974-82.
Congestion and WRF

- 145 patients with ADHF; LVEF<30%
- WRF ≥ 0.3 mg/dL during hospitalization (N=40)

Subclinical changes in volume and kidney function/injury

- 30 patients with chronic HFrEF
- Underwent diuretic withdrawal x 3 days, then diuretic re-institution.

Furosemide stopped

Furosemide 50mg IV

Damman K. JACC2011;57:2233-41.
Congestion is more important than WRF
WRF and Persistent Congestion in AHF

- 599 patients with AHF with daily Scr
- WRF defined as $\uparrow$Scr $\geq 0.3$ mg/dL; $\geq 1$ sign of congestion at discharge

![Graph showing survival rates for different groups: No Cong and no WRF (N=265), WRF but no Cong (N=253), Cong but no WRF (N=31), WRF and Cong (N=45). HR death or HF rehospitalization: 0.99 (0.74,1.31) for WRF but no congestion vs No WRF/Cong.]

Metra M. Circ Heart Fail 2012;5:54-62.
NT-proBNP, WRF, and Prognosis

- 1232 patients with AHF cohort analysis
- WRF ↑Scr >0.3mg/dL + 25%; NT-proBNP >30%

PROTECT post-hoc: WRF with or without residual congestion

- 1537 patients with AHF
- WRF ↑0.3 mg/dL; daily congestion score

Metra M. CircHF 2018;11.
Decongestion does not adversely affect outcomes despite WRF
DOSE Trial

Scr $\uparrow$ or $\downarrow$ >0.3 mg/dL

eGFR $\uparrow$ or $\downarrow$ $\geq$ 20%

Stepped Intensified Diuresis vs Standard Diuretic Therapy (CARRESS vs. ROSE/DOSE)

A. Δ Weight [lbs]

- Greater Diuresis

B. Δ Net Fluid [L]

- Greater Scr Improvement

C. Δ Creatinine [mg/dL]

D. Δ BUN [mg/dL]

Hemoconcentration and clinical signs of greater decongestion were associated with increase in renal tubular injury score.
CARRESS-HF Biomarker Substudy

Ahmad T. HFSA 2018
Caveats and Unanswered Questions

- Classification and interpretation of WRF
  - What does it really mean? True cause and effect?
  - Should it be an endpoint?
- Detection and rating of renal injury
  - Transient vs persistent?
  - Magnitude or threshold that matters clinically?
- Subclinical AKI events
  - Repeated subclinical events predispose to future AKI?
- Assessment of congestion
  - Different phenotypes in different HF pt populations
    - BUN/Cr, BNP, SBP changes, hemoconcentration, physical exam, hemodynamic monitoring

WRF/renal injury really doesn’t matter or matters less than clinical improvements with decongestion? Can mild-moderate or transient injury be acceptable?
Summary

- CRS in HF is multifactorial
  - Congestion plays a major role in modulating kidney function

- WRF does not always correlate with kidney injury biomarkers, and is inconsistently associated with worse outcomes.

- Congestion appears to be a more robust predictor of prognosis
  - Decongestive treatment may be associated with neutral/better patient outcomes despite WRF

- Many questions remain!