Cardio-Renal Syndrome: Managing risk and treating disease

A heart failure specialist’s perspective and approach

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Disclosures

☐ I have no disclosures pertinent to this lecture

☐ Other (non-promotional) current relationships:
  ☐ Boston Scientific: Steering Committee (MANAGE-HF), consultant/advisor
Objectives

The attendee will:

1. Describe the relationship between venous congestion and renal function, in the setting of CRS
2. State the survival impact of mild to moderate WRF in the setting of diuresis for ADHF
3. List 2 biomarkers indicative of renal tubular injury
4. Describe a reasonable approach to the use of diuretics and RAAS-I in a patient with chronic CRS
5. Identify the primary treatment goal for a patient presenting with volume overload and CRS
Outline

- Incidence of CKD in HF population, and demographics
- CRS definition, pathophysiology, diuretic resistance, biomarkers
- Things learned from pertinent clinical trials
- Treatments: diuretics, RAAS-I
- Practical consideration/tips
- Case study

Abbreviations

ADHF = acute decompensated HF
AKF = acute kidney failure
CKD = chronic kidney disease
Cr = creatinine
CRS = cardiorenal syndrome
EF = ejection fraction
GFR = glomerular filtration rate
HF = heart failure
HFrEF = heart failure reduced EF
HFpEF = heart failure preserved EF
NH = neurohormones
RAAS-I = renin-angiotensin-aldosterone system inhibition
WKF = worsening kidney function
Incidence of renal dysfunction in a “real” heart failure population is high: data from the ADHERE Registry

N=118,465
10,660 (9%) had normal GFR

ADHERE
- >100,000 HF patients
- 1/3 had history of CKD (cr >2.0 mg/dL)
- Mean GFR 55 mL/min per m²

Adams KF et al. AHJ 2005;149:209

Impaired renal function is common in HF patients

ADHERE: Initial Creatinine Level

All Enrolled in the Last 12 Months (01.01.2002-12.31.2002)

45,740/46,599 patients 98.2% with Cr value ADHERE (Data on file Scios, April 2003)
Comorbidities associated with CKD are prevalent in the HF population:


Risk factors for WKF during hospitalization:
- Hx of HF
- Hx of DM
- Cr >1.5 mg/dL
- Uncontrolled HTN

Forman DE et al. JACC 2004;43:61
Krumholz HM et al. AJC 2000;85:1110

Not all CKD is of hemodynamic/CRS cause, as HF patients have numerous co-moribids associated with intrinsic renal disease.
Relationship of GFRc with Mortality in 1,906 Pts. with Chronic Heart Failure

Mortality Risk By Decreasing Quartiles of LVEF and GFRc

What is Cardio-Renal syndrome (CRS)?

- Complex interaction between the heart and the kidneys; includes both HF with reduced ejection fraction (HFrEF) and preserved EF (HFpEF)

- Combined cardiac and renal dysfunction which is progressive and associated with increased morbidity and mortality

- It’s bidirectional, as dysfunction of the heart or the kidneys, can induce further dysfunction of the other organ

- Manifested by reduced GFR (AKI usually defined as an acute increase in serum creatinine ≥ 0.3mg/dl, or reduction in GFR ≥20%)
A patient with HFrEF and cardio-renal syndrome is hospitalized for acute decompensation and fluid overload.

Which plays a more important role in regards to diuresis and renal function?

a. Cardiac output
b. Central venous pressure*
c. They play equal roles
**CRS Type 1**

Acute HF → AKI

- Acute renal injury
  - Acute hypoperfusion reduced oxygen delivery necrosis/apoptosis decreased GFR resistance to ANP/BNP
- Biomarkers
  - KIM-1
  - Cystatin-C
  - N-GAL
  - Creatinine

**CRS Type 2**

Chronic HF/CVD → CKD

- Chronic progressive dz
  - BUN/Cr ratio
  - BUN
  - Cr
  - Cystatin-C
  - Hyponatremia
  - RAP

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**Pathophysiology of cardiorenal syndrome**

- Venous congestion
- Left heart dysfunction
- Ventricular remodeling
- Myocardial toxicity
- Intra-renal hemodynamics & venous flow more affected by volume than cardiac output
- Activation of vasopressin, RAAS, SNS
- Vasoconstriction, sodium and water retention
- Decreased renal perfusion/ischemia
- Vasodilatation, natriuresis
- Intrinsic renal disease

- CVP ↑
- LVEDP ↑
- SVCO ↑
- RAPCKD

- Increased renal vein pressure
- Decreased renal perfusion/ischemia

- Release of natriuretic peptides, bradykinin, prostaglandins

- Other causes: NSAIDs, ACEI, ARBs, contrast

Figure adapted from: Kiernan MS et al. Cardiorenal system. UpToDate 2018
Neurohormonal Actions Influencing Diuretic Action

Glomerulus
Norepinephrine, Endothelin: decrease renal blood flow and GFR

Proximal Tubule
Increases Na reabsorption

Collecting Duct
Aldosterone increases Na reabsorption

Thiazides
Loop, MRAs

Vaso-constrict GFR
Vaso-dilate GFR

NSAIDs NPs PGs
RAAS activation
RAAS inhibition

Slide adapted from (courtesy of) Maria Rosa Costanzo, MD
NHs, Renal Hemodynamics, Sodium & Water Retention in HF

Chronic Decrease in Cardiac Output
Or Decrease in Peripheral Vascular Resistance

Increased Cardiac Filling Pressures

Decrease Fullness of The Arterial Circulation

Water Retention

V2 Receptors Stimulation

Baroreceptor Desensitization
Decreased Renal Perfusion Pressure
Renal Vasoconstriction

Increased SNS Activity
Increased RAAS Activity
Increased Water and Sodium Reabsorption in the Proximal Tubule

Decreased GFR

Increased Sodium and Water Retention

Resistance to Natriuretic Peptides
Failure to Escape From Aldosterone

Reduced Distal Delivery of Sodium

Nonosmotic AVP Release

Slide courtesy of Maria Rosa Costanzo, MD
(Adapted from Schrier RW: J Am Coll Cardiol 2006; 47:1-08)
Diuretic Resistance

- Diuretic response is diminished or lost before the therapeutic goal of relief from fluid congestion has been reached
- Potential contributing factors
  - Under-dosing of diuretic (before reaching “threshold”)
  - Reduced diuretic uptake
  - Excess sodium or fluid intake
  - Increased sodium reabsorption
  - Reduced GFR
  - RAAS activation
  - Sympathetic stimulation, vasopressin

Ellison, DH. Cardiology 2001;96:132-143
HF Patients demonstrate diuretic resistance

**Dose Response Curves for Loop Diuretic**
Patients with HF demonstrate diuretic resistance, with rightward and downward shift.

**Efficacy of dual diuretics: Furosemide plus HCTZ**

**Combined Loop plus Thiazide Diuretic**
Demonstrated to be more effective than higher doses of either drug alone.
(Loop diuretics increase sodium delivery/reabsorption in distal tubule where thiazides are effective.)

Figures from: Ellison, DH. Cardiology 2001;96:132-143
Despite adequate urinary delivery of the loop diuretic, there is progressively smaller natriuresis, due to increased tubular sodium reabsorption outside of the loop.

A: Must give enough diuretic to cross the “threshold” and get a response.
B: There is a “ceiling” effect of the diuretic.
C: Regardless of further increases in diuretic dose, no increase in rate of diuresis.

Concepts from: Ellison, DH. Cardiology 2001;96:132-143
In a patient with decompensated heart failure, mild to moderate worsening of renal function due to diuresis and decongestion, is associated with lower mortality and re-hospitalization.

a. True*
b. False
“The primary finding of this study (ESCAPE) is the lack of statistically significant associations supporting the hypothesis that low CO is an important driver for renal dysfunction in pts with HF.”

Hanberg JS, et al. JACC 201:2199-2208

No significant association between markers of decongestion (diuretic efficacy or change Hgb) and cardiac index (pts w better CI did not diurese more effectively)
Increase CVP associated with impaired renal function, mortality in broad CV population

N=2,557 (Netherlands single center database 1989 – 2006) with RHC and eGFR

As CVP increased from 1 to 6mmHg, eGFR increased. CVP> 6mmHg associated with steep eGFR decrease.

Figure 1: Distribution of CVP and Curvilinear Relationship Between CVP and eGFR in the Study Population

Mean follow up 10.7 years. 29% pts died.

Figure 3: Kaplan-Meier Analysis of Event-Free Survival According to Tertiles of CVP

HR: 1.22 (95% CI: 1.00 to 1.49), p = 0.0466 for CVP 4 to 6 mm Hg; HR: 1.65 (95% CI: 1.35 to 2.01), p < 0.0001 for CVP >6 mm Hg, both compared with CVP 0 to 3. CI = confidence interval; HR = hazard ratio; other abbreviations as in Figure 1.
DOSE:
Diuretic Optimization Strategies Evaluation Trial

□ NHL&B sponsored, DB, prospective trial of 308 subjects

□ Criteria: ADHF, h/o chronic HF (no EF criteria), SBP ≥90mmHg, Cr ≤3.0mg/dL, baseline oral furosemide 80-240mg (or equiv. loop)

□ Randomized to strategy (2x2 factorial design) of IV furosemide intensification
  □ HIGH *(2.5 x baseline oral dose) vs LOW **(1.0 x baseline oral dose)
  □ IV continuous infusion vs IV bolus every 12 hours

□ Treatment period: 72 hours with option to adjust dose at 48 hrs

□ Co-primary endpoints: global assessment of symptoms, and change in serum creatinine from baseline to 72 hours (plus secondary endpoints)

IV furosemide median doses:
*HIGH=260mg/day LOW= 120mg/day

Felker GM et al. NEJM 2011;364(9):797-805
Changes in renal parameters at 72 hours:
- Mean change sCR = 0.04 ± 0.31 mg/dL.
- 18% subjects demonstrated WRF (mean ↑ Cr 0.54 ± 0.27 mg/dL).
- 9.1% demonstrated IRF (mean ↓ 0.43 ± 0.14 mg/dL).

Conclusions:
- At 72 hrs, increase in Cr associated with a lower risk for composite outcome (HR 0.81 per 0.3 mg/dL increase).
- For every 10% worsening in eGFR the risk of adverse outcomes decreased by more than 10%.
- Strong relationship between improved renal function and composite endpoint of death, re-hospitalization, ER visit.
- WRF in the setting of beneficial decongestive intervention may have limited prognostic importance.

Brisco MA et al. JCF 2016;22(10):753-760
In the presence of decongestion, WRF is not associated with worse outcomes.

WRF/congestion
No WRF/congestion
WRF/no congestion
No WRF/No congestion

599 subjects hospitalized ADHF. Serum Cr & signs of congestion measured daily during admission.
- WRF (sCr increase ≥0.3mg/dL) alone is not an independent determinant of outcomes in the absence of persistent congestion.
- WRF has prognostic value when it occurs in pts with persistent congestion on discharge, and is associated with increased risk of death and/or re-hospitalization.

Metra M et al. Circ Heart Fail; 2012;5:54-62
Heart failure patients aggressively diuresed in the ROSE trial, displayed evidence of significant increases in the following renal biomarkers:

a. Cystatin-c*
b. NGAL, KIM-I
c. NAG
d. All of the above
ROSE: renal tubular injury and worsening renal failure

AHF + Renal Dysfunction (eGFR 15 – 60 ml/min/1.73 m²) Enrolled <24 hours after Admission N=360

Open; 1 to 1 randomization

Nesiritide Strategy
N = 177

Dopamine Strategy
N = 183

Double-blind; 2 to 1 randomization

Low Dose*
Nesiritide
(72 hours)
N = 119

Placebo
N = 58

Placebo
N = 61

Renal Dose†
Dopamine
(72 hours)
N = 122

Pooled Placebo (N=119)

All patients received open-label IV loop diuretic, recommended daily dose 2.5 X out-patient oral dose (bid bolus)

End-points: 72 hr urine volume as index of diuresis, and change cystatin C

Conclusion: There were no differences in endpoints between groups
No differences in change in biomarkers of tubular injury

Ahmed T et al. 10:1161/ CIRCULATIONAHA.117.030112
ROSE AHF: cohort of 283 pts

- Aggressively diuresed with high dose loop diuretic (median 560mg IV furosemide equivalent, inducing 8425 ml urine output over 72 hour period)
- Baseline & 72 hr urine tubular injury biomarkers (NGAL, NAG, KIM-1) analyzed for WRF (>20% decreased GFR) against cystatin C

Results:
- No change in levels NAG, KIM-1
- NGAL decreases slightly
- WRF occurred in 21.2% subjects

Conclusion:
Kidney tubular injury does NOT appear to be assoc/w WR function in context of aggressive diuresis for AHF; IS assoc/w improved survival

Ahmed T et al. 10:1161/CIRCULATIONAHA.117.030112
## Biomarkers of kidney function and damage

<table>
<thead>
<tr>
<th>Marker</th>
<th>Renal function (functional marker)</th>
<th>Tubular injury (damage marker)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR</td>
<td>X</td>
<td></td>
<td>Rough estimate number of functioning nephrons (eGFR: Cockroft-Gault, MDRD, CKD-EPI, or measurement of urinary clearance/filtration)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>X</td>
<td></td>
<td>Breakdown of creatinine phosphate in muscle. Byproduct of muscle metabolism. Filtered / removed by glomerulus. Estimate of GFR. Affected by muscle mass</td>
</tr>
<tr>
<td>Cystatin C</td>
<td>X</td>
<td></td>
<td>Protein produced by nucleated cells, filtered by glomerulus, metabolized in tubules. Not affected by muscle mass. Better estimate of GFR than sCr for identification of mild to moderate renal insufficiency</td>
</tr>
<tr>
<td>NGAL</td>
<td>+/-</td>
<td>X</td>
<td>Expressed by neutrophils, epithelial cells in proximal convoluted tubule. Detected in blood and urine at earliest stages of AKI (2-3 days before rise in serum creatinine).</td>
</tr>
<tr>
<td>NAG</td>
<td>X</td>
<td></td>
<td>High molecular weight enzyme in many body tissues which cannot pass into glomerular ultrafiltrate. Sensitive indicator of tubular injury with rising urine levels</td>
</tr>
<tr>
<td>KIM-1</td>
<td>X</td>
<td></td>
<td>Expressed in proximal tubule epithelial cells after toxic or ischemic injury (blood and urine).</td>
</tr>
<tr>
<td>IL-18</td>
<td>X</td>
<td></td>
<td>Pro-inflammatory cytokine. Upregulated with endogenous inflammation, sepsis. Urinary IL-18 is an early marker of AKI.</td>
</tr>
</tbody>
</table>

Cystatin C

- Protein produced by nucleated cells, filtered by glomerulus, metabolized in tubules
- Considered to be a more accurate estimate of GFR than creatinine
- Rate of production more constant and not affected by changes in diet
- Purported to be unaffected by muscle mass, age, sex.
- Particularly useful in situations where serum creatinine may be misleading (low muscle mass, obesity, elderly)
- May have greater value when used in combination with other biomarkers

Figure from Inker, LA, et al. UpToDate 2018
Other Pertinent Clinical Trial Findings

- No clear benefit on outcomes (except perhaps in select populations):
  - Ultrafiltration vs optimizing diuretics (CARRESS-HF, UNLOAD)
  - Renal dose dopamine vs diuretics alone (ROSE)
  - Nesiritide vs diuretics alone (ROSE and others)
  - Vasopressin antagonists (EVEREST)

- Treatment for ADHF is associated with reductions in blood pressure and WRF. However, WRF in this situation is not associated with worse outcomes, as opposed to other causes of WRF (ESCAPE)*

Importance of Adequate Diuresis

Hemodynamic Predictors of Heart Failure Morbidity and Mortality: Fluid or Flow?

LAUREN B. COOPER, MD,1,2 ROBERT J. MENTZ, MD,1,2 SUSANNA R. STEVENS, MS,1 G. MICHAEL FELKER, MD, MHS,1,2 CARLO LOMBARDI, MD,1 MARCO METRA, MD,1 LYNNE W. STEVENSON, MD,1,3 CHRISTOPHER M. O’CONNOR, MD,1,3 CARMELO A. MILANO, MD,1,3 CHETAN B. PATEL, MD,1,2 AND JOSEPH G. ROGERS, MD,1,2

ESCAPE

Early Response of PCW but not CI Predicts Subsequent Mortality in Advanced Heart Failure

Final hemodynamic measurement in 456 advanced HF patients after tailored vasodilator therapy
Fonarow Circulation 1994:90:1-488

Circulation 1994
Are we effectively decongesting patients over the short and long term?

**Relief and Recurrence of Congestion During and After Hospitalization for Acute Heart Failure**

Insights From Diuretic Optimization Strategy Evaluation in Acute Decompensated Heart Failure (DOSE-AHF) and Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARESS-HF)

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**Figure 2.** A, Congestion status at discharge. (B) For patients relieved of congestion at discharge, congestion status at 60-day follow-up.

**Figure 3.** Sixty-day event rates based on discharge orthodema score to represent congestion (P=0.038).
Are we effectively decongesting patients over the short and long term?

**ADHERE: Change in Weight During Hospitalization**

Evidence of Incomplete Relief From Congestion

<table>
<thead>
<tr>
<th>Change in Weight (lbs)</th>
<th>All Enrolled (n=105,388)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-20)</td>
<td>7%</td>
</tr>
<tr>
<td>(-20 to -15)</td>
<td>6%</td>
</tr>
<tr>
<td>(-15 to -10)</td>
<td>13%</td>
</tr>
<tr>
<td>(-10 to -5)</td>
<td>24%</td>
</tr>
<tr>
<td>(-5 to 0)</td>
<td>33%</td>
</tr>
<tr>
<td>(0 to 5)</td>
<td>15%</td>
</tr>
<tr>
<td>(5 to 10)</td>
<td>3%</td>
</tr>
<tr>
<td>(&gt;10)</td>
<td>2%</td>
</tr>
</tbody>
</table>

**Note:** For the chart, n represents the number of patients who have both baseline and discharge weight, and the percentage is calculated based on the total patients in the corresponding population. Patients without baseline or discharge weight are omitted from the histogram calculations. ADHERE: Acute Decompensated National Heart Failure Registry

20% of ADHF patients discharged with weight gain or no change in weight.
Practical approach to treatment

### Strategies for decongesting the patient with ADHF
- IV continuous diuretic infusion vs bolus
- High dose diuretic vs low dose

### Strategies for optimization of therapies for long term benefit
- Give RAAS-I vs withhold RAAS-I during diuresis and or worsening renal function
Audience Response Questions #4

All of the following statements are true regarding treatment strategies with proven effectiveness for patients with decompensated heart failure requiring diuresis except:

a. Continuous infusion of IV furosemide is significantly more effective than intermittent bolus
b. Renal dose dopamine combined with IV diuretics is more effective than diuretics alone
c. Nesiritide combined with IV diuretics is more effective than diuretics alone
d. Both b & c
e. None of the above are true*
## DOSE: Diuretic Optimization Strategies Evaluation Trial

### Bolus vs continuous infusion
- Median total dose (furosemide equivalents) received over course of 72 hours = 592mg bolus group, 480mg continuous infusion (CI)
- Bolus group more likely required dose increase at 48 hours than CI group
- No difference in likelihood to switch to oral diuretics at 48 hours
- No difference in change in serum Cr at 72 hours
- No difference in global assessment of symptoms

### High vs low dose
- Median total dose (furosemide equivalents) received over course of 72 hours = 358mg low dose strategy vs 773 mg high dose strategy (P<0.001)
- High dose patients more likely to switch to oral diuretics at 48 hours
- Low dose patients more likely to require 50% dose increase at 48 hour point than those in high group
- High dose resulted in greater net fluid, wt loss and dyspnea relief. Also met WRF Cr endpoint (23% high vs 14% low dose) but NS difference in mean change in Cr level
- No difference in global assessment

Felker GM et al. NEJM 2011;364(9):797-805
### Table 2. Secondary End Points for Each Treatment Comparison.

<table>
<thead>
<tr>
<th>End Point</th>
<th>Bolus Every 12 Hr (N=156)</th>
<th>Continuous Infusion (N=152)</th>
<th>P Value</th>
<th>Low Dose (N=151)</th>
<th>High Dose (N=157)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC for dyspnea at 72 hr</td>
<td>4456±1468</td>
<td>4699±1573</td>
<td>0.36</td>
<td>4478±1550</td>
<td>4668±1496</td>
<td>0.04</td>
</tr>
<tr>
<td>Freedom from congestion at 72 hr — no./total no. (%)</td>
<td>22/153 (14)</td>
<td>22/144 (15)</td>
<td>0.78</td>
<td>16/143 (11)</td>
<td>28/154 (18)</td>
<td>0.09</td>
</tr>
<tr>
<td>Change in weight at 72 hr — lb</td>
<td>−6.8±7.8</td>
<td>−8.1±10.3</td>
<td>0.20</td>
<td>−6.1±9.5</td>
<td>−8.7±8.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Net fluid loss at 72 hr — ml</td>
<td>4237±3208</td>
<td>4249±3104</td>
<td>0.89</td>
<td>3575±2635</td>
<td>4899±3479</td>
<td>0.001</td>
</tr>
<tr>
<td>Change in NT-proBNP at 72 hr — pg/ml</td>
<td>−1316±4364</td>
<td>−1773±3828</td>
<td>0.44</td>
<td>−1194±4094</td>
<td>−1882±4105</td>
<td>0.06</td>
</tr>
<tr>
<td>Worsening or persistent heart failure — no./total no. (%)</td>
<td>38/154 (25)</td>
<td>34/145 (23)</td>
<td>0.78</td>
<td>38/145 (26)</td>
<td>34/154 (22)</td>
<td>0.40</td>
</tr>
<tr>
<td>Treatment failure — no./total no. (%)†</td>
<td>59/155 (38)</td>
<td>57/147 (39)</td>
<td>0.88</td>
<td>54/147 (37)</td>
<td>62/155 (40)</td>
<td>0.56</td>
</tr>
<tr>
<td>Increase in creatinine of &gt;0.3 mg/dl within 72 hr — no./total no. (%)</td>
<td>27/155 (17)</td>
<td>28/146 (19)</td>
<td>0.64</td>
<td>20/147 (14)</td>
<td>35/154 (23)</td>
<td>0.04</td>
</tr>
<tr>
<td>Length of stay in hospital — days</td>
<td></td>
<td></td>
<td>0.97</td>
<td></td>
<td></td>
<td>0.55</td>
</tr>
<tr>
<td>Median</td>
<td>5</td>
<td>5</td>
<td></td>
<td>6</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>3–9</td>
<td>3–8</td>
<td></td>
<td>4–9</td>
<td>3–8</td>
<td></td>
</tr>
<tr>
<td>Alive and out of hospital — days</td>
<td></td>
<td></td>
<td>0.36</td>
<td></td>
<td></td>
<td>0.42</td>
</tr>
<tr>
<td>Median</td>
<td>51</td>
<td>51</td>
<td></td>
<td>50</td>
<td>52</td>
<td></td>
</tr>
</tbody>
</table>

*Plus–minus values are means ±SD. To convert pounds to kilograms, divide by 2.2. AUC denotes area under the curve, and NT-proBNP N-terminal pro-brain natriuretic peptide.

† Treatment failure was defined as the development of any one of the following during the 72 hours after randomization: increase in serum creatinine level of more than 0.3 mg per deciliter (26.5 μmol per liter), worsening or persistent heart failure, clinical evidence of excessive diuresis requiring intervention (e.g., administration of intravenous fluids), or death.
DOSE: Diuretic Optimization Strategies Evaluation Trial: prespecified secondary endpoint of composite of death, re-hospitalization, or ED visit within 60 days

Figure 3. Kaplan–Meier Curves for the Clinical Composite End Point of Death, Rehospitalization, or Emergency Department Visit.

Kaplan–Meier curves are shown for death, rehospitalization, or emergency department visit during the 60-day follow-up period in the group that received boluses every 12 hours as compared with the group that received a continuous infusion (Panel A) and in the group that received a low dose of the diuretic (equivalent to the patients’ previous oral dose) as compared with the group that received a high dose (2.5 times the previous oral dose) (Panel B).

Felker GM et al. NEJM 2011;364(9):797-805
Subjects who continued on ACE-I in setting of early enalapril related WRF showed survival benefit in patients with HRrEF

(The mechanism of WRF matters....)
Overview of the Effects of Neurohormonal Blockade on Mortality in Patients with HFrEF

*Adapted from clinicaltrialresults.org/Slides/.../Packer%20-PARADIGM-HF*
Treatment options with goal to decongest

**SYSTEMIC CONGESTION**

- **Oral and IV Diuretics**
  - Escalating doses of loop diuretics
  - Multi-diuretic regimen
    - Loop + thiazide (MRAs, carbonic Anhydrase-I)
  - 2X oral dose of loop diuretic given as IV bolus or continuous infusion
  - Escalating doses to reach renal threshold
  - Low sodium diet, fluid restriction
  - Assess volume: dry wt, PE, hemodynamics, device diagnostics, renal parameters, biomarkers

**Diuresis still not achieved?**

- Mod to severe WRF
- Reduced BP
- Signs of low-output

**RHC in appropriate patients**

- Paracentesis in select patients

- Ultra filtration in select patients

- IV Vasodilators

- IV Inotropes for low output

- Mechanical pump assist in appropriate patients with low output
CRS: Key Take Home Points

- Renal dysfunction is common in patients with HF
- Low cardiac output (low forward “flow”) is not the primary issue in CRS
- Venous congestion, elevated CVP and abdominal venous pressure, seem to play more of a key role
- Diuretic induced worsening of renal function (small to moderate increase in serum creatinine) in the setting of decongestion, is acceptable and does not worsen outcomes
- WRF associated with diuresis in ADHF is not renal injury; this is a functional process
- The beneficial effects of treating the ADHF optimally and decongesting the patient, may offset the negative effects on renal function, much like we have seen with RAAS-I
- Decongest and optimize GDMT (RAAS-I) for long term benefits
The beneficial effects of RAAS-I outweighs the mild associated reduction in GFR

Withholding diuretics or RAAS-I to improve renal function does not improve outcomes in an inadequately treated patient with HFrEF (not necessarily so in HFpEF where the benefits of RAAS-I have not been established)

Titrating HF GDMT during periods of ADHF does not negatively impact diuresis or outcomes

Consider those at highest risk for intolerance to RAAS-I:
- Low BP: systolic < 80-90mmHg, MAP <65mmHg (critical level for renal perfusion)
- Creatinine >3mg/dL
- Hx of DM, low serum sodium
- Patients intravascularly depleted
A patient with HFrEF and cardio-renal syndrome is hospitalized for acute decompensation and fluid overload.

Which plays a more important role in regards to diuresis and renal function?

a. Cardiac output  
b. Central venous pressure*  
c. They play equal roles
In a patient with decompensated heart failure, mild to moderate worsening of renal function due to diuresis and decongestion, is associated with lower mortality and re-hospitalization.

a. True*
b. False
Heart failure patients aggressively diuresed in the ROSE trial, displayed evidence of significant increases in the following renal biomarkers:

a. Cystatin-c*
b. NGAL, KIM-I
c. NAG
d. All of the above
All of the following statements are true regarding treatment strategies with proven effectiveness for patients with decompensated heart failure requiring diuresis except:

a. Continuous infusion of IV furosemide is significantly more effective than intermittent bolus
b. Renal dose dopamine combined with IV diuretics is more effective than diuretics alone
c. Nesiritide combined with IV diuretics is more effective than diuretics alone
d. Both b & c
e. None of the above are true*
Case Study 1:
56 y/o AA female, long-standing NICM, biventricular failure, LVEF 25%. No options for advanced therapies

- H/o recurrent admissions with volume overload
- Volume retention initially attributed to gross nonadherence with diet, and sometimes medications
- But in time also demonstrated worsening diuretic resistance
- Maintained on modest beta blocker, high MRA in setting of chronic hypokalemia, but off ace-I for recurrent symptomatic hypotension
- Baseline BUN: 20-30, Cr: 1.1-1.5, SBP 80s-100s
Case Study 1: 56 y/o AA female, long-standing NICM, biventricular failure, LVEF 25%. No options for advanced therapies.

Hospitalized April 2016

- Prior to this admission, responded well to escalating doses of single oral diuretics, then combined diuretics, until becoming diuretic resistant with each progressive regimen
  - Oral furosemide dose escalated → max of 160mg bid
  - Furosemide switched to oral torsemide ≤ 100mg bid
  - Metolazone 2.5mg added prn, then standing intermittent
  - Metolazone → 5mg
  - Concurrent administration of spironolactone 50-100mg daily
  - IV diuretic therapy in office was not offered due to very difficult IV access and difficulty maintaining adequate serum potassium level. PICC not offered due to recurrent infections.
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Site</td>
<td>office</td>
<td>hosp</td>
<td>hosp</td>
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<td>hosp</td>
<td>hosp</td>
<td>hosp</td>
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<td>home</td>
</tr>
<tr>
<td>WT (lbs)</td>
<td>173</td>
<td>187</td>
<td>191</td>
<td><strong>191</strong></td>
<td>177</td>
<td>173</td>
<td>164</td>
<td>?</td>
<td>151</td>
<td>152</td>
<td></td>
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<tr>
<td>BP</td>
<td>97/68</td>
<td>92/46</td>
<td>109/64</td>
<td>112/51</td>
<td>96/50</td>
<td>88/42</td>
<td>93/47</td>
<td>77/45</td>
<td>90/47</td>
<td><strong>88/50</strong></td>
<td></td>
</tr>
<tr>
<td>BUN</td>
<td>n/a</td>
<td>20</td>
<td>21</td>
<td>30</td>
<td>34</td>
<td>37</td>
<td>31</td>
<td>32</td>
<td>34</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Cr</td>
<td>n/a</td>
<td>1.1</td>
<td>1.2</td>
<td>1.4</td>
<td>1.4</td>
<td><strong>1.7</strong></td>
<td>1.2</td>
<td>1.4</td>
<td>1.5</td>
<td><strong>1.5</strong></td>
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<tr>
<td>eGFR</td>
<td>n/a</td>
<td>&gt;60</td>
<td>56</td>
<td>47</td>
<td>47</td>
<td>44</td>
<td>56</td>
<td>47</td>
<td>44</td>
<td>44</td>
<td></td>
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<tr>
<td>Pro bnp</td>
<td>15,432</td>
<td>27,809</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>18,223</td>
<td></td>
</tr>
</tbody>
</table>

**Case Study:** DS dry weight 150-155lbs (4/13/16–4/21/16 hospital admission)

- **Furosemide IV**
  - Failed oral diuretics
  - 160mg q12hr
  - 160mg x1 then 10mg/hr infusion
  - 160mg bolus, 20mg/hr infusion
  - 20mg/hr infusion
  - 20mg/hr infusion
  - 20mg/hr infusion
  - Hold

- **Metolazone mg**
  - 5mg prn
  - 5mg
  - 5mg
  - 5mg
  - 5mg
  - Hold
  - Hold
  - Hold
  - 5mg TIW

- **Oral torsemide**
  - 100mg bid

- **Spironolactone**
  - 100mg
  - 100mg
  - 100mg
  - 100mg
  - 100mg
  - 100mg
  - 100mg
  - 100mg
  - 100mg

- **KCL supp**
  - As needed

- **“Warm and Wet”**

- **Threshold passed:**

- **As needed to keep K ≥4.0**
### Case Study: DS. Re-admission 3 mo. later 7/20/16-7/29/16 (prior discharge wt 152lbs)

<table>
<thead>
<tr>
<th></th>
<th>Office 7/20/16</th>
<th>Admission 7/20/16</th>
<th>Hospital course</th>
<th>Discharged 7/26/16</th>
<th>Post Disch: 07/29/16</th>
<th>Office 08/08/16</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WT (lb)</strong></td>
<td><strong>☆ 168</strong></td>
<td>168</td>
<td>Slow, gradual weight loss</td>
<td>159 (- 9lbs)</td>
<td>163</td>
<td>170</td>
</tr>
<tr>
<td>Dry: 150s</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BP</strong></td>
<td><strong>☆ 70/50</strong></td>
<td>80-100/60</td>
<td>80s – 100s</td>
<td>100/60</td>
<td>104/64</td>
<td>94/60</td>
</tr>
<tr>
<td><strong>BUN</strong></td>
<td>Baseline: 30s</td>
<td>46</td>
<td>Gradual fall</td>
<td>37</td>
<td>--</td>
<td>36</td>
</tr>
<tr>
<td><strong>Cr</strong></td>
<td><strong>☆ 1.5-1.7</strong></td>
<td><strong>2.4</strong></td>
<td>Gradual fall</td>
<td>1.7</td>
<td>--</td>
<td>1.7</td>
</tr>
<tr>
<td><strong>Oral diuretic</strong></td>
<td>Torsemide 100mg bid + Metolazone 5mg 5x/week</td>
<td>XXXXXXXXXX</td>
<td>XXXXXXXXXX</td>
<td>Torsemide 100mg bid</td>
<td>Add: Metolazone 5mg daily</td>
<td></td>
</tr>
<tr>
<td><strong>IV diuretic</strong></td>
<td>Furosemide 160mg bolus, 10mg/hr gtt &gt;&gt;20mg/hr gtt</td>
<td>Continued until 7/28/17</td>
<td></td>
<td>XXXX</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IV</strong></td>
<td></td>
<td></td>
<td>Dobutamine 2.5ug/kg/min added 7/21/16. Weaned off by 7/24/16</td>
<td>XXXX</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Exam</strong></td>
<td>+JVP, HJR, S3, ascites, sacral &amp; peripheral edema</td>
<td>“Cold &amp; Wet”</td>
<td></td>
<td>“Warm &amp; still wet”</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

New baseline for Cr, trading tissue wt for fluid wt, + low output, slower response to treatment.

Diuretic resistant
Case Study 2:
71 y/o M, ischemic CM, EF 20%, NYHA III (stable)

- Pertinent medications: carvedilol 25mg bid, spironolactone 12.5mg daily, torsemide 30mg daily, lisinopril 40mg
- History of borderline hyperkalemia. Tolerates moderate dose MRA, and full ACEI-I. Maintained on diet low in potassium sources.
- History of CKD with baseline creatinine 2.0mg/dL
- Plan to transition from ACE-I (lisinopril) to ARNI (secubitril-valsartan).
- Felt to have mild fluid retention when initially transitioned
Case Study: SR

Lis 40mg d/c
ARNi 49/51 bid started 36 hr later

ARNi 97/103 bid

Torsemide 20mg

**19 April**
BP: 119/70
BUN/Cr: 25/2.1
K: 5.0

<table>
<thead>
<tr>
<th>Date</th>
<th>BUN/CR</th>
<th>Serum K</th>
<th>BP</th>
<th>Torsemide Dose/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 Apr</td>
<td>23/2.0</td>
<td>4.5</td>
<td>128/70</td>
<td>30mg</td>
</tr>
<tr>
<td></td>
<td>25/2.1</td>
<td>5.0</td>
<td>119/71</td>
<td>30mg</td>
</tr>
<tr>
<td></td>
<td>28/2.4</td>
<td>4.8</td>
<td>97/61</td>
<td>↓20mg</td>
</tr>
</tbody>
</table>
Thank you for your attention
Enjoy your meeting!

Marie Galvao, MSN, ANP-C, CHFN
Center for Advanced Cardiac Therapy
Montefiore Medical Center
Bronx, NY
mgalvao@montefiore.org
2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

Figure 2. Treatment of HFrEF Stage C and D

Step 1: Establish Dx of HFrEF; assess volume; initiate GDMT

- HF/EF NYHA class I–IV (Stage C)
  - ACEI or ARB AND GDMT beta blocker, diuretics as needed (COR I)

Step 2: Consider the following patient scenarios

- NYHA class II–IV, provided est. CrCl >30 mL/min & K+ <5.0 mEq/L
  - Aldosterone antagonist (COR I)

- NYHA class II–III HF Adequate BP on ACEI or ARB*: No C/I to ARB or sacubitril
  - Discontinue ACEI or ARB; initiate ARNI* (COR I)

- NYHA class III–IV, in black patients
  - Hydral-Nitrates†† (COR I)

- NYHA class II–III, LVEF ≤35% (caveat: >1 y survival, >40 d post MI)
  - ICD† (COR I)

- NYHA class II–IV, LVEF ≤35%, NSR & GRS ≥150 ms with LBBB pattern
  - CRT or CRT-D†† (COR I)

- NYHA class II–III, NSR, heart rate ≥70 bpm on maximally tolerated dose beta blocker
  - Ivabradine (COR IIa)

Step 3: Implement indicated GDMT. Choices are not mutually exclusive, and no order is inferred

- Palliative care‡ (COR I)
- Transplant‡ (COR I)
- LVAD‡ (COR IIa)
- Investigational studies$