The Cardiorenal Syndrome and Other Practical Challenges in Congestive Heart Failure

The Cardiorenal Syndrome

John R. Teerlink, M.D., FACC, FAHA, FESC, FRCP(UK)
Professor of Medicine, University of California, San Francisco
Director, Heart Failure Program
San Francisco Veterans Affairs Medical Center,
California, USA
Monterey, CA
17. October, 2014

How Should Physicians View Heart Failure? The Philosophical and Physiological Evolution of Three Conceptual Models of the Disease

- Cardiorenal Model (1940’s on)
  - a derangement of the heart results in changes in intravascular volume and pressure (edema).
- Cardiocirculatory Model (1960’s on)
  - a derangement of the interaction of the heart and the peripheral circulation
- Neurohormonal Disorder Model (1980’s on)
  - neurohormonal activation contributes importantly to the hemodynamic and clinical abnormalities of the disease

The Cardiorenal Syndrome

- Renal Physiology
- Classification of Cardiorenal Syndromes
- Cardiorenal Syndrome Type 2 (CHF)
- Cardiorenal Syndrome Type 1 (AHF)
- Emerging Diagnostics and Therapies
The Cardiorenal Syndrome

- Renal Physiology (BRIEF review!)

Renal Autoregulation

Renal Autoregulation

Tubuloglomerular Feedback

The Cardiorenal Syndrome

- Renal Physiology
- Classification of Cardiorenal Syndromes

Pathophysiology of Cardiorenal Syndrome in Heart Failure

Summary of characteristics of the cardiorenal syndrome
Characteristics of the cardiorenal syndrome
- Reduced RBF and GFR
- Increased venous congestion
- Increased renovascular resistance
- Albuminuria
- Tubular damage
- Worsening renal function
- Diuretic resistance
- Activation of the TGF
- Anemia
- Increased mortality
**Classification of Cardiorenal Syndrome**

**Cardiorenal Syndrome (CRS) General Definition**
A pathophysiological disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ.

**CRS Type 1 (Acute Cardiorenal Syndrome)**
Acute deterioration of cardiac function (e.g., Acutely decompensated congestive heart failure) leading to acute kidney injury.

**CRS Type 2 (Chronic Cardiorenal Syndrome)**
Chronic deterioration in cardiac function due to chronic congestive heart failure causing progressive renal and chronic kidney disease.

**CRS Type 3 (Acute Renocardiorenal Syndrome)**
Acute kidney disease (either acute pyelonephritis or acute interstitial nephritis) occurring in the setting of acute heart failure.

**CRS Type 4 (Chronic Renocardiorenal Syndrome)**
Chronic kidney disease (diabetes nephropathy) contributing to decreased cardiac function, cardiac hypertrophy, heart failure, and/or increased risk of adverse cardiovascular events.

**CRS Type 5 (Secondary Cardiorenal Syndrome)**
Syndrome condition (e.g., cancer) causing both acute cardiac and renal injury and dysfunction.

---

**The Cardiorenal Syndrome**

- Renal Physiology
- Classification of Cardiorenal Syndromes
- Cardiorenal Syndrome Type 2 (CHF)

---

**Pathophysiology of Cardiorenal Syndrome Type 2 in Heart Failure**

**2013 ACC/AHA Heart Failure Guidelines**

**ACE Inhibitors in HF**

- ACE inhibitors are recommended in patients with HFrEF and current or prior symptoms, unless contraindicated, to reduce morbidity and mortality. (IA)
- Absolute contraindications:
  - Life-threatening adverse reactions (i.e., angioedema)
  - Pregnant or plan to become pregnant.
- Use caution if the patient has:
  - Very low systemic blood pressures (<80 mm Hg)
  - Markedly increased serum levels of creatinine (>3 mg/dL)
  - Bilateral renal artery stenosis
  - Serum potassium (>5.0 mEq/L)
Changes in the GFR when the cardiac output and the renal blood flow are reduced


Pathophysiology of Cardiorenal Syndrome in Heart Failure


2013 ACC/AHA Heart Failure Guidelines


EMPHASIS-HF


Mineralocorticoid Receptor Antagonists (MRAs) in HF


- Randomized, double-blind, placebo-controlled, multicenter trial
- Target 3100 pts with NYHA II HF, LVEF ≤ 35%, HF hach in 6 months or elevated BNP/NT-proBNP
- 2737 pts enrolled; stopped for mortality benefit of eplerenone
- Potassium monitored baseline, weeks 1 & 4, then q4 months
- Hyperkalemia: Eplerenone 109 (8.0%) vs. Placebo 50 (3.7%); p = 0.001

- Aldosterone receptor antagonists are recommended in patients with NYHA class II–IV HF and who have LVEF ≤ 35% or less, unless contraindicated, to reduce morbidity and mortality. (NYHA class II HF should have a h/o prior CV hospitalization or elevated plasma natriuretic peptide).
  - Creatinine ≥ 2.5 mg/dl in men or ≥ 2.0 mg/dl in women (eGFR >30 mL/min/1.73 m2)
  - Potassium >5.0 mEq/L.
  - Careful monitoring of potassium, renal function, and diuretics at initiation and closely followed thereafter to minimize risk of hyperkalemia and renal insufficiency. (IA)
- Aldosterone receptor antagonists are recommended to reduce morbidity and mortality following an acute MI in patients who have LVEF ≤ 40% who develop symptoms of HF or who have a history of diabetes mellitus, unless contraindicated (IB).
10/27/2014

2013 ACC/AHA Heart Failure Guidelines


Mechanisms of Diuretic Resistance

Cox ZL, Lenihan DJ. J Cardiac Fail 2014;20:611-622.

Approaches to Diuretic Resistance in Chronic Heart Failure

- Use appropriate doses, adjust for degree of renal insufficiency and fluid status
- Use appropriate dosing intervals (furosemide in AM and later afternoon/early evening)
- Use more potent, bioavailable loop diuretics
- Use combined nephron blockade (loop diuretic + thiazide/thiazide-like diuretic)
- Use MRA as adjunctive therapy
- Actively replete potassium and magnesium

Diuretics in Chronic Heart Failure

Effects of Cardiovascular Drugs in CKD

<table>
<thead>
<tr>
<th>Description</th>
<th>End Point</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvedilol vs placebo in 780 patients with diabetes CM, n=118</td>
<td>Changes in LVEF, SBE, NYHA symptoms</td>
<td>Improvement</td>
</tr>
<tr>
<td>Carvedilol vs placebo in 683 patients with diabetes CM, n=114</td>
<td>All-cause mortality and hospital admissions</td>
<td>Improvement</td>
</tr>
<tr>
<td>Carvedilol vs placebo in 514 patients with diabetes, n=272</td>
<td>All-cause mortality, CV mortality and hospital admissions</td>
<td>Improvement</td>
</tr>
<tr>
<td>Enalapril vs placebo in 780 patients with diabetes, n=118</td>
<td>Composite analysis of final and non-final major CV events</td>
<td>Improvement</td>
</tr>
<tr>
<td>Semaxin vs placebo in CKD stage 2</td>
<td>Changes in LVEF and systolic blood pressure</td>
<td>Improvement</td>
</tr>
<tr>
<td>Innovvent 1 vs placebo in 242 patients, n=173</td>
<td>Frequency of arrhythmic events</td>
<td>Improvement</td>
</tr>
<tr>
<td>Aprotinin vs placebo in 780 patients with diabetes, n=118</td>
<td>CV mortality, non-fatal MI, stroke</td>
<td>No significant improvement</td>
</tr>
<tr>
<td>Aprotinin vs placebo in 683 patients with diabetes, n=114</td>
<td>CV mortality, non-fatal MI, non-fatal stroke</td>
<td>No significant improvement</td>
</tr>
</tbody>
</table>

The Cardiorenal Syndrome
- Renal Physiology
- Classification of Cardiorenal Syndromes
- Cardiorenal Syndrome Type 2 (CHF)
- Cardiorenal Syndrome Type 1 (AHF)

Pathophysiology of AHF

Pathophysiology of Cardiorenal Syndrome Type 1 in Heart Failure

Pathophysiology of Cardiorenal Syndrome in Acute Heart Failure
The Splanchnic Vasculature: Capacitance Function and Cardiac Pre-load

Diuretic Therapy in AHF

2013 ACC/AHA Guidelines for medical therapy of acute heart failure

Diuretics in AHF
• Mechanism of Action:
  – Diuresis (decreased preload)
  – ? Pulmonary vasodilation
• Advantages:
  – Rapid symptomatic improvement
  – Decreases volume overload
• Disadvantages:
  – Increased neurohormonal activation
  – Electrolyte disturbances, arrhythmias
  – Worsen renal function
  – High diuretic doses associated with increased hospitalization and mortality in observational studies

Diuretic Optimization Strategies Evaluation in AHF (DOSE)

DOSE Study Design
DOSE 1st Endpoint PGA VAS AUC


DOSE Outcomes

Death, Hospitalization or ED Visit


DOSE Secondary Endpoints: Low vs. High Intensification


DOSE: Limitations

- DOSE evaluated only patients with chronic heart failure and moderate to high diuretic requirements
- DOSE had limited power to detect differences in clinical events
- DOSE protocol allowed changes in therapy at 48 hours based on clinical response, which may have minimized observed differences between groups
- Clinical trial setting may have influenced results and may limit clinical generalizability

2013 ACC/AHA Guidelines for medical therapy of acute heart failure


Renal Optimization Strategies Evaluation (ROSE)


- Multicenter, double-blind, placebo-controlled
- Hospitalized patients with AHF, eGFR 15-60 mL/min/1.73m²
- Randomized within 24 hours of admit. open, 1:1 to dopamine or nesiritide strategy. Within each strategy, double-blind, 2:1 ratio to active treatment or placebo
- Enrollment occurred Sept 2010 to March 2013 across 26 sites in North America.
- Co-primary end points at 72 hs: 1) Cumulative urine volume 2) Change in serum cystatin C
Renal Optimization Strategies Evaluation (ROSE)


In Dopamine strategy, more pts had study drug stopped or decreased due to hypotension in placebo (Placebo, 10.4% vs. Dopamine 0.9%; p=0.001) and more pts due to tachycardia in dopamine groups (Placebo, 0.9% vs. Dopamine 7.2%; p=0.001).
In Nesiritide strategy, more pts had treatment failure with nesiritide (Placebo, 28% vs. Nesiritide, 40%, p=0.04)

The Dopamine in Acute Decompensated Heart Failure II (DAD-HF II) Trial


- Single-blind, four centers in Greece
- Hospitalized patients with AHF; eGFR >30 mL/min/1.73m²
- 161 pts Randomized 1:1:1 ratio to:
  a) High-dose furosemide
  b) Low dose furosemide + Dopamine
  c) Low dose furosemide
- Enrollment occurred July 2009 to August 2012.
- 1st end point at 60 day and 1 year– post-discharge all-cause mortality (ACM) and recurrent hospitalizations for HF (heid)
- Terminated early due to low conditional probability of benefit, no evidence of other benefit and increased heart rate in Dopamine group

2013 ACC/AHA Guidelines for medical therapy of acute heart failure


Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF)


- Multicenter, active-controlled
- Hospitalized patients with AHF, worsened renal function, and persistent congestion
- 188 patients randomized to a strategy of:
  1) stepped pharmacologic therapy (94 patients) or
  2) ultrafiltration (94 patients).
- 1st end point: bivariate change from baseline in the serum creatinine level and body weight, as assessed 96 hours after random assignment

Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF)


Continuous Ultrafiltration for Congestive Heart Failure (CUORE) Trial


- 2 Italian Heart Failure units, active-controlled
- Hospitalized patients with AHF, NYHA class III-IV, LVEF<40%, 24 kg est wt gain due to peripheral fluid overload within 2 months.
- Exclusion criteria: severe renal insufficiency (serum creatinine >3.0 mg/dL), contraindications to anticoagulation, cardiogenic shock, acute pulmonary edema.
- 56 patients randomized to a strategy of:
  1) control pharmacologic therapy (29 patients) or
  2) ultrafiltration (27 patients).
- 1st end point: incidence of nephrotoxifications for HF
- Clinical trial.gov number: NCT00360918
Continuous Ultrafiltration for Congestive Heart Failure (CUORE) Trial

2013 ACC/AHA Guidelines for medical therapy of acute heart failure

Ultrafiltration and Diuretic Dosing Recommendations

The Cardiorenal Syndrome
- Renal Physiology
- Classification of Cardiorenal Syndromes
- Cardiorenal Syndrome Type 2 (CHF)
- Cardiorenal Syndrome Type 1 (AHF)
- Emerging Diagnostics and Therapies

Cardiorenal Biomarkers
Tan K and Sethi SK. Translational Research 2014;1-13
**Potential Emerging Therapies for Cardiorenal Syndrome in Acute Heart Failure**

* Renal protective/augmenting drugs:

**PROTECT**

- Multicenter, randomized, placebo-controlled trial
- 2033 pts with AHF, persistent dyspnea, impaired renal function (CCr 20-80 ml/min), elevated BNP
- NT-proBNP ongoing intravenous loop-diuretic therapy, and enrolled within 24 hours after admission.
- Randomized 2:1 to rolodylline (30 mg) or placebo for up to 3 days
- 1st endpoint: treatment success, treatment failure, or no change in the patient’s clinical condition (included survival, heart-failure status, and changes in renal function)

Rolofylline group had increased incidence of seizures and stroke risk

---

**Bardoxolone Methyl in CKD with Type 2 Diabetes (BEAM)**

- Phase 2, double-blind, randomized, placebo-controlled trial,
- 227 adults with Type 2 Diabetes, CKD (eGFR 20-45 ml per minute per 1.73 m² of body-surface area)
- Randomized 1:1:1:1 ratio to receive Placebo or Bardoxolone methyl at a target dose of 25, 75, or 150 mg once daily.
- 1° outcome: change from baseline in the eGFR at 24 weeks
- 2° outcome: change at 52 weeks.

**Bardoxolone Methyl in Type 2 Diabetes and Stage 4 Chronic Kidney Disease (BEACON)**

- Multicenter, double-blind, placebo-controlled
- Type 2 diabetes mellitus; Stage 4 chronic kidney disease; eGFR 15-30 ml/min/1.73m²
- Randomized 1:1 to bardoxolone methyl (20 mg) or placebo
- Enrollment from June 2011 through September 2012, including in the United States, European Union, Australia, Canada, Israel, and Mexico
- Primary endpoint: end-stage renal disease (ESRD) or death from cardiovascular causes
- Terminated early

---

**Potential Emerging Therapies for Cardiorenal Syndrome in Acute Heart Failure**

* Renal protective/augmenting drugs
  - Nitroxy donors (CXL-1020; CXL-1427)
  - Corticotropin-releasing factor (CRF) type 2 receptor (CRFR2) selective agonist (Stresscopin; JNJ-39588146)
  - Cardiac myosin activators (Omecamtiv mescabril)

**Omecamtiv Mecabril (OM) is a Novel Selective Cardiac Myosin Activator**

Omecamtiv mescabril increases the entry rate of myosin into the tightly-bound, force-producing state with actin

- "More hands pulling on the rope"
  - Increases duration of systole
  - Increases stroke volume
  - No increase in myocyte calcium
  - No change in dp/dtmax
  - No increase in MVO₂
Omecamtiv mecarbil

- Stable CHF Study: 45 patients (Cleland JGF, et al. Lancet 2011; 378: 676-83.)
- Acute Heart Failure Study: 606 patients (ATOMIC-AHF; Teerlink JR, et al. ESC 2013)
- Chronic Heart Failure Study: ~ 500 patients (COSMIC-HF; Teerlink JR, et al. ESC HF 2014; currently enrolling)

Potential Emerging Therapies for Cardiorenal Syndrome in Acute Heart Failure

- Renal protective/ augmenting drugs
- Safe Cardiac Performance-enhancing drugs
- Other Neurohormonal Agents
  - LCZ696
  - Novel Mineralocorticoid Receptor Antagonists

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure (PARADIGM-HF)

- Multicenter, double-blind, placebo-controlled
- 8442 patients with CHF NYHA Class II-IV, LVEF < 35%, Elevated BNP/NT-proBNP; on stable standard therapy
- After run-in period, randomized to LCZ696 (200 mg bid) or Enalapril 10 mg bid
- 1° outcome: CV death or HF Hosp
- Stopped early after median f/u 27 months due to benefit

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure (PARADIGM-HF)


BAY 94-8862: Non-steroidal MRA

- Current MRAs limited by concerns about renal failure, hyperkalemia, and progestogenic effect (spironolactone)
- BAY 94-8862 has demonstrated superior selectivity compared with spironolactone and improved affinity for the MR compared with eplerenone
- Pre-clinical studies demonstrated more pronounced cardiorenal end-organ protection than the steroidal MRAs
- PEARL-HF Pilot study provided preliminary support for safety and pharmacologic differences

Mineralocorticoid Receptor Antagonist Tolerability Study (ARTS): Part B

- Multicenter, randomized, parallel-group, phase II study
- Double-blind placebo and open-label spironolactone arms
- LVEF ≤40%; moderate CKD (eGFR 30-60 mL/min/1.73 m²)
- Endpoints: change in serum potassium concentration between baseline and days 22 and 29
- On-going DMC review during Part B
  - Potassium
Vasodilators?

Potential Emerging Therapies for Cardiorenal Syndrome in Acute Heart Failure

- Renal protective/augmenting drugs
- Safe Cardiac Performance-enhancing drugs
- Other Neurohormonal Agents
- Agents with Vasodilating Properties
  - Fenoldopam
  - Ularitide
  - Serelaxin

Effects of Fenoldopam in Patients with Acute Kidney Injury after Cardiac Surgery


- Multicenter, double-blind, placebo-controlled
- Pts admitted to ICUs after cardiac surgery with early acute kidney injury (50% increase of serum creatinine level from baseline or oliguria for 6 hours)
- Randomized to fenoldopam or placebo for up to 4 days, starting dose of 0.1 μg/kg/min (range, 0.025-0.3 μg/kg/min)
- Enrollment occurred March 2008 to April 2013 across 19 Italian sites.
- Primary end point: Rate of Renal Replacement Therapy (RRT) administration in the ICU

Effects of Urodilatin (Ularitide):

SIRIUS II


- 221 pts with decompensated chronic heart failure with symptoms at rest, PCWP >18 mmHg and CI<2.5 L/min/m²
- Randomized to placebo or ularitide, 24 hour continuous infusion (7.5, 15, and 30 ng/kg/min)
- Nominally improved PCWP and patient-reported dyspnea

Urodilatin (Ularitide)

- Recently discovered (1988)
- Natriuretic peptide synthesized in the kidneys.
- N-terminal last 4 amino acids only difference from ANP, which are maintained from pro-ANP.
- N-terminal prolongation may be responsible for a higher resistance to endopeptidases with more powerful vasodilating and renal effects.
TRUE-AHF: Trial of Ularitide’s Efficacy and safety in patients with AHF

- ~2,152 patients with unplanned hospitalization or ED visit for ADHF with dyspnea at rest, Radiological evidence of HF on a chest x-ray, BNP > 500 pg/mL or NT-proBNP > 2000 pg/mL, Systolic blood pressure (SBP) ≥ 110 mmHg.
- 1° endpoint: Clinical composite at 48h; all cause mortality; Multiple 2° endpoints

Clinicaltrials.gov NCT01661634 (last updated 24 April, 2014)

Serelaxin in Acute Heart Failure (RELAX-AHF)

- Multicenter, randomized, double-blind
- 1161 pts with AHF, Dyspnea, Congestion on CXR, Elevated BNP/nt-proBNP, SBP >125 mmHg, eGFR 30-75 ml/min 1.73m²
- Randomized within 16 hrs to Serelaxin 30mcg/kg/d vs Placebo
- 1° Endpoints: Dyspnea relief within 24 hrs (Likert) Dyspnea relief over 5 days (VAS AUC)

Relaxin/ Serelaxin

- Insulin-like protein
- Naturally-occurring peptide
- Found in men and women
- Normal hormone of pregnancy
- In humans, contributes to maternal hemodynamic adaptations to pregnancy
- Women “exposed” for 9 months to increased plasma concentrations: 0.8-1.6 ng/ml pregnancy

Worsening Renal Function in RELAX-AHF


Worsening Renal Function in RELAX-AHF

- 15% increase in ALB with serelaxin from baseline through day 5

Fool or Optimist or Optimistic Fool?
Potential Emerging Therapies for Cardiorenal Syndrome in Heart Failure

- Renal protective/augmenting drugs
- Safe Cardiac Performance-enhancing drugs
- Other Neurohormonal Agents
- Agents with Vasodilating Properties

The Cardiorenal Syndrome

- Renal Physiology
- Classification of Cardiorenal Syndromes
- Cardiorenal Syndrome Type 2 (CHF)
- Cardiorenal Syndrome Type 1 (AHF)
- Emerging Diagnostics and Therapies

Cardiorenal Model(+) of Heart Failure


Thank you!

San Francisco Veterans Affairs Medical Center

Fool or Optimist or Optimistic Fool?

San Francisco Veterans Affairs Medical Center

Beta Blockers in HF


- Use of carvedilol, sustained-release metoprolol succinate, or bisoprolol is recommended for all patients with current or prior symptoms of HFrEF, unless contraindicated, to reduce morbidity and mortality. (IA)
Mineralocorticoid Receptor Antagonists (MRAs) in HF