Kidney Disease and Heart Failure: Where Medication Efficacy and Safety Collide

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Conflict of Interest Disclosures

• Nothing to disclose
Learning Objectives

• Explain nuances of treatment of heart failure in patients with CKD
1. Which of the following is NOT a reason for diuretic resistance in patients with AHF and CKD:
   • a. Low salt diet
   • b. High urinary protein
   • c. Patient non-adherence
   • d. Braking phenomenon: distal tubule cells hypertrophy over time and become sodium avid.

2. When may NSAIDs be appropriate in patients with AHF and CKD?
   • a. Anytime
   • b. Never
   • c. If the patient rates pain greater than 6 on a scale of 1-10.
   • d. The patient has some at home.
HFrEF vs. HFpEF

- **HFrEF**
  - Clinical diagnosis of HF and LVEF ≤ 40%

- **HFpEF**
  - Clinical signs or symptoms of HF;
  - Evidence of preserved or normal LVEF; and
  - Evidence of abnormal LV diastolic dysfunction that can be determined by Doppler echocardiography or cardiac catheterization
ACC/AHA HF Stages

**Stage A**
High risk

Address Risk Factors

**Stage B**
Cardiac structural changes but no symptoms of HF

NYHA FC I
- ACEIs
- β-Blockers
- MRAs if post-MI

**Stage C**
Current or previous symptoms of HF

NYHA FC I–IV
- ACEIs/ARBs
- β-Blockers
- MRAs
- Diuretics
- Digoxin
- Other: Devices – ICD & CRT

**Stage D**
Severe and/or resistant HF symptoms

NYHA FC IV
Specialized interventions
- VADs
- Heart Tx

- ACEIs: class effect
- β-Blockers: carvedilol, metoprolol succinate, bisoprolol
- ARBs: candesartan, valsartan preferred, losartan acceptable
## Cardiorenal Syndromes

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Acute worsening of heart function leading to kidney injury and/or dysfunction</td>
</tr>
<tr>
<td>Type 2</td>
<td>Chronic abnormalities in heart function leading to kidney injury or dysfunction</td>
</tr>
<tr>
<td>Type 3</td>
<td>Acute worsening of kidney function leading to heart injury and/or dysfunction</td>
</tr>
<tr>
<td>Type 4</td>
<td>Chronic kidney disease leading to heart injury, disease and/or dysfunction</td>
</tr>
<tr>
<td>Type 5</td>
<td>Systemic conditions leading to simultaneous injury and/or dysfunction of heart and kidney</td>
</tr>
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</table>

Treatment of HF in Patients with CKD

What is the same?
What is different?
# Treatment of HFrEF

<table>
<thead>
<tr>
<th>Medication Indicated</th>
<th>No CKD</th>
<th>CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Blockers</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Yes?</td>
<td>Yes?</td>
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</table>

...But there are nuances to be considered.
β-Blockers

• SR metoprolol, carvedilol, bisoprolol indicated for HF in general population

• No prospective studies in CKD non-dialysis
Differential Effects of Carvedilol and Metoprolol on Kidney Function in HF

• 40 patients with NYHA class II–III HF with various degrees of kidney dysfunction
• Initiation of carvedilol (n=23) or metoprolol (n=17)
• Divided into two groups (high, low eGFR)
• Results
  – In high eGFR but not low eGFR group, eGFR was significantly reduced.
  – eGFR was significantly reduced in metoprolol group, but not in carvedilol group.
• Limitations: Small, retrospective, Japanese-only study

Carvedilol in Dialysis Patients

• 114 patients with dilated cardiomyopathy randomized to carvedilol or placebo (in addition to standard therapies)

• Patients followed for 2 years

• Results: Carvedilol vs. placebo
  – Deaths: 51.7% vs. 73.2% (p<0.01)
  – CV Deaths: 29.3% vs. 67.9% (p<0.0001)
  – Hospitalizations: 34.5% vs. 58.9% (p<0.005)

• Limitations: Small, open-label, unblinded, end points above were secondary outcomes

Cice G. JACC 2003;41:1438-44
**β-Blocker Dialyzability and Implications**

- Highly dialyzable: *Acebutolol, atenolol, metoprolol, nadolol*
- Low dialyzability: *Bisoprolol, propranolol, carvedilol*

- **Study (n=6599)**
  - HD patients initiated on highly dialyzable vs. low dialyzable β-blockers (studied drugs in red above)
  - Retrospective, propensity score matched

- **Results**
  - High-dialyzability β-blockers associated with higher risk of death in 180 days after initiation
  - Limitation: Retrospective, patients not matched for indication for β-blocker, carvedilol not studied

ACEIs or ARBs

- No prospective studies specifically of HF and CKD non-dialysis patients
- One study of dialysis patients (n=332)
  - DB, placebo-controlled, multicenter trial, 3-yr follow-up
  - LVEF < 40%, dilated cardiomyopathy
  - Telmisartan vs. placebo in addition to ACEI treatment
- Results
  - Significant reduction in all-cause & CV mortality and HF hospitalization (HR 0.51, 0.42, and 0.38, respectively, p<0.0001)

Cice G. JACC 2010;56:1701-8
Clinical Tidbits for CKD patients with HFrEF (ACEI and Beta-blockers)

• ACEI first, start with low dose, titrate to low target dose (e.g. lisinopril 20 mg) if tolerated
  – Indications: HF and reduced CKD progression (particularly in patients with albuminuria)

• Add Beta-blocker at LOW dose; titrate to target or maximum-tolerated dose

• Go back and continue to titrate ACEI to target dose (e.g. lisinopril 40 mg) as tolerated
Mineralocorticoid Receptor Antagonist (MRA) in Patients with CKD and HF

• General population: MRAs **recommended** in patients with NYHA class II-IV with LVEF ≤ 35%, unless CI’ed (A recommendation)

• RALES and EPHESUS trials excluded patients with sCr > 2.5 mg/dL.

• Blocking aldosterone with MRAs in CKD considered dangerous
  – Risk of hyperkalemia

• Several small studies have evaluated MRA use in CKD and dialysis patients.
Spironolactone in Patients with HF and CKD

• DB, randomized study of spironolactone 25 mg once daily vs. placebo in CKD stage 2 and 3 (eGFR ≥30) with HF and mean ambulatory daytime BP: < 130/85 mm Hg on ACEI or ARBs (n=112)

• Dose reduced if hyperkalemia developed

• Results
  – ↓ LVM, PWV, & aortic distensibility in Spiro group (SS)
  – K⁺ 4.3 ± 0.3 vs. 4.4 ± 0.8 mEq/L placebo vs. Spiro

• Limitations
  – No patients with eGFR < 30 mL/min/1.73m²
  – ACEI/ARBs were not maximized in all patients

Edwards NC. JACC 2009;54:505-12
# Spironolactone Safety in HD Pts w/HF

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Treatment</th>
<th>Mean K+ Results</th>
</tr>
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<tbody>
<tr>
<td>Hussain 2003</td>
<td>n=15; P, single cohort; duration: 28 days; 40% on ACEI/ARB, HF-NR</td>
<td>25 mg/day</td>
<td>4.6±0.6 at baseline and 4.9±0.6 at study completion (NS)</td>
</tr>
<tr>
<td>Saudan 2003</td>
<td>n=35; P, NR, NB; duration: 4 wk; 54% on ACEI/ARB, HF-NR</td>
<td>Control vs. Spiro 12.5 mg 3x/wk x 2 wk; then 25 mg 3x/wk x 2 wk</td>
<td>Control 4.9±0.7, Spiro 4.9±0.3, p=NR</td>
</tr>
<tr>
<td>Michea 2004</td>
<td>n=9; P, single cohort; duration: 4 wk; 0% on ACEI/ARB, HF-NR</td>
<td>Spiro 50 mg 3x/wk for 2 wk; then placebo x 2 wk</td>
<td>Placebo 4.7±0.1, Spiro 4.6±0.2 (NS)</td>
</tr>
<tr>
<td>Gross 2005</td>
<td>n=8; P, R, DB, PC, crossover; duration: 4 wks; 0% ACEI/ARB, HF-NR</td>
<td>Placebo vs. Spiro 50 mg 2x/day</td>
<td>Placebo 4.7±0.5, Spiro 5.0±0.8 (p≥0.05)</td>
</tr>
<tr>
<td>Taheri 2009</td>
<td>n=16; R, DB, PC; duration 6 mo; 100% ACEI/ARB, 100% HF</td>
<td>Placebo vs. Spiro 25 mg 3x/wk</td>
<td>Baseline: Placebo, 4.7 Spiro 3.9 (p=0.001) End: placebo 4.7, Spiro 4.9 (p=NR)</td>
</tr>
<tr>
<td>Matsu-moto 2009</td>
<td>n=61, P, single cohort; duration 8 mo; 58% ACEI/ARB, HF-NR</td>
<td>Baseline x 2 mo, followed by 6 mo Spiro 25 mg/day</td>
<td>Baseline: 5.0 Spiro period: 5.2 (p&lt;0.05)</td>
</tr>
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*Chua D. Clin Cardiol 2010;33:604-8.*
Using MRAs in Patients with HF and CKD

• Optimize ACEI or ARB and β-blockers first
• Consider in CKD stage 2 and 3 (eGFR > 30 mL/min/1.73m²) or stage 5 on HD.
• Not recommended if K+ > 5.0 mg/dL
• Monitor K⁺ closely, check K+ within 1-2 weeks of initiation and after each dose titration
## Treatment of HFpEF

About 50% of patients with CKD and HF have preserved EF.

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<td>β-Blockers</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>No</td>
<td>No* but...</td>
</tr>
<tr>
<td>MRA</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Digoxin</td>
<td>No</td>
<td>No</td>
</tr>
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*KDIGO CPGs recommend (suggest) ACEI or ARB in patients with CKD with HTN and severely (moderately) increased albuminuria to reduce risk of progression of CKD.

Case

• L.B. 60-y/o black man

• Clinic visit for increasing SOB when walking short distances, ankle edema, 2 pillow orthopnea

• PMH
  – HFpEF dx 2 years ago, NYHA stage 2
  – CKD stage 3b
  – Chronic hyponatremia
  – Type 2 DM
  – HTN

• Medications
  – Metoprolol tartrate 50 mg twice daily x 2 yr
  – Lisinopril 5 mg daily x 1 yr
  – HCTZ 25 mg per day
  – Metformin 500 mg twice daily

• Labs
  – Na: 133 eEq/L, K+: 4.1 mEq/L
  – sCr: 2.2 mg/dL (2.0 mg/dL 6 mos ago)
  – eGFR: 36 mL/min/1.73m²
  – A1c – 6.9% (similar to 1 year ago)

• PE
  – BP: 112/85 mmHg, P: 65 bpm
  – Increased JVP
  – Rales
  – 2+ pitting ankle edema
  – Cool extremities

What medication changes should be considered today?
What medication change(s) should be considered today?

1. Increase metoprolol dose
2. Titrate down metoprolol dose
3. Increase lisinopril dose
4. Stop lisinopril
5. Change HCTZ to loop diuretic
6. 1 and 3
7. 2, 4 and 5
8. 2 and 5
Common Medication-Related Problems in HF Patients with CKD and Clinical Pearls
ACEI and ARBs Plus Diuretics
Normal Perfusion Pressure in Glomerulus

Reprinted with permission from the Massachusetts Medical Society.
Decreased Perfusion Pressure Occurring with HF or Diuretics & Physiologic Compensation

Decreased Perfusion Pressure in HF or with Diuretics in Presence of ACEI/ARB

Reprinted with permission from the Massachusetts Medical Society.
ACEI and ARBs in HF and CKD

Problems

• Lower use in CKD patients than in general population with HF
• Not considered or discontinued inadvertently in HFpEF patients
• Doses not maximized
• Stopped when sCr rises & not restarted at lower dose

Solutions

• Every patient with CKD and HFrEF or HFpEF should be evaluated for ACEI/ARB use
• Don’t start RAS therapy if K⁺ > 5.5 mEq/L or bilateral RAS
• Start low; go slow: titrate every 2–4 weeks
• Check K⁺ and sCr within 1–2 weeks of initiation and with each dose increase
• Reduce dose if sCr increases >30% from initiation

St. Peter, et al. Results from study in progress.
Key Concepts for Loop Diuretics in CKD and HF

• Accumulating organic acids compete for secretion of loops into kidney tubule
  – Higher doses needed in CKD
• Oral bioavailability is not the same among loops
  – Bumetanide and torsemide: \( F \approx 1.0 \)
  – Furosemide: \( F 0.6–0.7 \)
• Ceiling dose in CKD
  – 200 mg of furosemide, 10 mg of bumetanide, 100 mg of torsemide (per dose)
• Twice daily dosing; give 2\(^{nd}\) dose in early afternoon
Diuretic Resistance in CKD

• Common

• Reasons
  – Diuretic dose too low for kidney function
  – Not taking diuretics
  – Too much salt in diet
  – Albuminuria
    • albumin binds loop diuretics → inactive
  – Braking phenomenon
    • distal tubule cells hypertrophy over time and become sodium avid
    • Can use combination of loop plus thiazide
Case LB 6 months later...

- L.B. 60-y/o black man

- Clinic visit for “not being able to pee” and increasing ankle edema and some SOB when climbing stairs.

- PMH
  - HFpEF dx 2.5 years ago, NYHA stage 2, stable at clinic visit 1 week ago
  - CKD stage 3b, stable at clinic visit 1 week ago
  - Chronic hyponatremia
  - Type 2 DM
  - HTN

- Medications
  - Lisinopril 40 mg daily (increased from 20 mg daily 1 week ago)
  - Furosemide 40 mg twice daily x 4 mo
  - Metformin 500 mg twice daily

- Labs
  - Na: 131 mEq/L, K+: 4.8 mEq/L
  - sCr: 3.0 mg/dL (2.0 mg/dL 1 week ago)
  - eGFR: 25 mL/min/1.73m²
  - A1c – 6.9%

- PE
  - BP: 115/85 mmHg, P: 95 bpm
  - Wt up 7 kg since clinic visit 1 week ago
  - Increased JVP
  - Rales
  - 2+ pitting ankle edema

What medication changes should be considered today?
What medication change(s) should be considered today?

1. Decrease lisinopril dose back to 20 mg
2. Stop lisinopril temporarily until sCr lowers
3. Increase furosemide dose to 80 twice daily
4. Add HCTZ 25 mg daily
5. 1 and 3
6. 2 and 4
NSAIDs
Normal Perfusion Pressure in Glomerulus

Reprinted with permission from the Massachusetts Medical Society.
Decreased Perfusion Pressure Occurring with HF or Diuretics & Physiologic Compensation

Reprinted with permission from the Massachusetts Medical Society.
Decreased Perfusion Pressure in HF or with Diuretics in Presence of NSAIDs

No NSAIDs!

Digoxin Use in CKD

• Vd reduced, half-life longer
• MRPs in patients with AHF admission and digoxin use
  – CKD (n=32) and no CKD (n=25)
  – ~50% of patients on digoxin had level checked during timeframes just before, during, or after AHF admission.
  – Of those checked, 68%, 57%, and 45% had ≥ 1 concentration out of therapeutic range,* respectively.
  – CKD vs. non-CKD more likely to have out-of-range values (86% vs. 38%); of those, most were above range

*0.5–0.9 ng/mL for CHF, 0.5–2.0 ng/mL for Afib

Conclusions: HF in Patients with CKD

• Use non-dialyzable β-blockers (carvedilol or bisoprolol) in HD patients.

• Consider ACEI and ARBs in ALL HF pts with CKD.
  – Indicated for HFrEF and for reducing risk of CKD progression in HFpEF
  – Start low, go slow, but work towards target dose
  – Discontinue temporarily if sCr rises (1.5 x baseline; presumed within 1 week—AKI; or ≥ 30% from baseline with chronic use)

• No NSAIDs except for low-dose (75–81 mg) ASA
1. Which of the following is NOT a reason for diuretic resistance in patients with AHF and CKD:
   - a. *Low salt diet*
   - b. High urinary protein
   - c. Patient non-adherence
   - d. Braking phenomenon: distal tubule cells hypertrophy over time and become sodium avid.

   **A. Rationale:** Low salt diet will improve efficacy of diuretic

2. When may NSAIDs be appropriate in patients with AHF and CKD?
   - a. Anytime
   - b. *Never*
   - c. If the patient rates pain greater than 6 on a scale of 1-10.
   - d. The patient has some at home.

   **B. Rationale:** NSAIDS are always to be avoided due to potential risks of sodium retention, fluid overload, acute kidney injury, and hyperkalemia.
Questions and Answers
Additional Resources

• National Kidney Foundation: KDOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease

• American Family Physician: Drug-Induced Nephrotoxicity
http://www.aafp.org/afp/2008/0915/p743.html

• National Kidney Foundation: NEW GUIDELINES RECOMMEND ANTIHYPERTENSIVE THERAPY TO REDUCE CARDIOVASCULAR DISEASE RISK FOR KIDNEY PATIENTS

• Study of Heart and Renal Protection (SHARP)