Slowing CKD Progression: Are We Making Any Progress?

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Disclosure

- The program chair and presenters for this continuing education activity have reported no relevant financial relationships.
Program Objectives

- Using a set of criteria, evaluate a patient's comprehensive kidney function.

- Given recent controversies and literature, discuss the recommended strategies for slowing the progression of kidney disease in patients with hypertensive nephropathy.

- Discuss key considerations for slowing the progression of kidney disease in patients with diabetic nephropathy.
Comprehensive Assessment of Kidney Function

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Assistant Dean and Director, Office of Research
Ferris State University - College of Pharmacy
Objectives

- Discuss recent trends in evaluating kidney function using estimated creatinine clearance (eCLcr), estimated glomerular filtration rate (eGFR), and urine albumin-to-creatinine ratio (ACR)

- Given a patient case, understand appropriate use of eGFR and creatinine clearance in patient care
Patient Case

- JZ is a 60 year old African American man who presents to the ambulatory care clinic for his 6-month check up.
- His past medical history is significant for hypertension and he is taking HCTZ 12.5 mg/day. He was hospitalized for acute kidney injury (AKI) in the setting of frequent ibuprofen use 6 months ago.
- Other pertinent information:
  - Height: 5’6”
  - Weight: 118 kg (BMI 42)
  - Serum creatinine: 1.4 mg/dL
  - Urine albumin-to-creatinine ratio (ACR): 150 mg/g
  - BP: 140/86
Stages of CKD

<table>
<thead>
<tr>
<th>Stage</th>
<th>% Kidney Function Remaining</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Below normal to mild loss of kidney function</td>
</tr>
<tr>
<td>2</td>
<td>Mild to moderate loss of kidney function</td>
</tr>
<tr>
<td>3</td>
<td>Moderate to severe loss of kidney function</td>
</tr>
<tr>
<td>4</td>
<td>Severe loss of kidney function</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure – Dialysis</td>
</tr>
</tbody>
</table>

eGFR (mL/min/1.73m²):
- >90
- 60-89
- a: 45 - 59
- b: 30 - 44
- 15 – 29
- < 15

Adapted from the Kidney Disease Outcomes Quality Initiative (KDOQI) Guidelines, from the National Kidney Foundation
CKD Progression

- How fast does kidney function decline in CKD?

<table>
<thead>
<tr>
<th>Category</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Change</td>
<td>38%</td>
</tr>
<tr>
<td>Slow (&lt; -1 ml/min/yr)</td>
<td>10%</td>
</tr>
<tr>
<td>Moderate (-1 to -4 ml/min/yr)</td>
<td>28%</td>
</tr>
<tr>
<td>Fast (&gt; -4 ml/min/yr)</td>
<td>24%</td>
</tr>
</tbody>
</table>

Estimating Kidney Function

- Creatinine Clearance (mL/min)
  - Measured (24-hr) CLcr
  - Estimated CLcr: Cockcroft-Gault (CG) Equation (clinical standard); if BMI ≥ 40, use lean body weight

- Estimated GFR (eGFR, mL/min/1.73m²)
  - MDRD (automated in EMR)
  - CKD-EPI (next generation MDRD – moving to EMR?)

- All estimation equations have limitations
- Note: Unit conversions needed for MDRD, CKD-EPI
  - (eGFR * BSA/1.73m² = mL/min)
- When calculating renal drug dosing - Use CG equation

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Proteinuria

- Albumin-to-creatinine ratio (ACR)

- Reduced eGFR and increased ACR are consistent strong risk factors for AKI\(^1\)

- CKD risk prediction models include ACR\(^2\)

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2. JAMA. 2016 Jan 12;315(2):164-74
# New CKD Staging System (CGA)

## Key: CKD Progression Risk
- **Low Risk**
- **Moderate Risk**
- **High Risk**
- **Very High Risk**

### Description and eGFR range (mL/min/1.73m²)

<table>
<thead>
<tr>
<th>GFR Category (G)</th>
<th>Description and eGFR range</th>
<th>Persistent Albuminuria Categories, Description and Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal or high ≥90</td>
<td>1 if CKD, 1 if mildly increased, 2 if markedly increased</td>
</tr>
<tr>
<td>2</td>
<td>Mildly decreased 60–89</td>
<td>1 if CKD, 1 if mildly increased, 2 if markedly increased</td>
</tr>
<tr>
<td>3a</td>
<td>Mildly to moderately decreased 45–59</td>
<td>1 if mildly increased, 2 if markedly increased, 3 if severely increased</td>
</tr>
<tr>
<td>3b</td>
<td>Moderately to severely decreased 30–44</td>
<td>2 if mildly increased, 3 if markedly increased, 3 if severely increased</td>
</tr>
<tr>
<td>4</td>
<td>Severely decreased 15–29</td>
<td>3 if mildly increased, 3 if markedly increased, 4 if severely increased</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure &lt;15</td>
<td>4 if mildly increased, 4 if markedly increased, 4 if severely increased</td>
</tr>
</tbody>
</table>

The numbers in each CGA box are recommendations for the frequency of monitoring/year.

GFR = glomerular filtration rate.

Adapted from *Ann Intern Med.* 2015 Jun 2;162(11):ITC1-16 and KDIGO 2012
New CKD Staging System (CGA)

The numbers in each CGA box are recommendations for the frequency of monitoring/year.

**GFR = glomerular filtration rate.**


### Key: CKD Progression Risk

<table>
<thead>
<tr>
<th>GFR Categories (mL/min/1.73 m²)</th>
<th>Stage, Description, and Range</th>
<th>Low Risk</th>
<th>Moderate Risk</th>
<th>High Risk</th>
<th>Very High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal or high</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>4+</td>
</tr>
<tr>
<td>2</td>
<td>Mildly decreased</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3a</td>
<td>Mildly to moderately decreased</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3b</td>
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<td></td>
<td></td>
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<td>5</td>
<td>Kidney failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GFR = glomerular filtration rate
Assessment of JZ’s kidney function

- Creatinine Clearance (Cockcroft-Gault equation)
  - Since BMI ≥ 40, calculate lean body weight

  **Lean body weight (LBW, kg)**
  - Men: \( \frac{9270 \times TBW}{6680 + 216 \times BMI} \)
  - Women: \( \frac{9270 \times TBW}{8780 + 244 \times BMI} \)

- In our case, JZ’s LBW = \( \frac{9270 \times 118}{6680 + 216 \times 42} \) = 69.4 kg

- \( CLcr \) (mL/min) = \( \frac{(140-46)(69.4)}{(72 \times 1.4)} \) = 64.7 mL/min
Assessment of JZ’s kidney function

- eGFR
  - MDRD study equation
    - 65 mL/min/1.73m²
    - 84 mL/min

- CKD-EPI creatinine equation (2009)
  - 69 mL/min/1.73m²
  - 87 mL/min
JZ’s kidney function is consistent with the following CGA category:

- A G1-A2
- B G2-A1
- C G2-A2
- D G3-A1
JZ’s kidney function is consistent with the following CGA category:

A) G1-A2
B) G2-A1
C) G2-A2 Correct Answer
D) G3-A1
JZ’s CKD Risk level and monitoring plan is:

A. Low risk, monitor yearly
B. Moderate risk, monitor yearly
C. High risk, monitor twice per year
D. Very high risk, monitor three times per year
JZ’s CKD Risk level and monitoring plan is:

- **A** Low risk, monitor yearly
- **B** Moderate risk, monitor yearly  [Correct Answer]
- **C** High risk, monitor twice per year
- **D** Very high risk, monitor three times per year
Key Takeaways

• When monitoring CKD progression, use an eGFR equation (MDRD or CKD-EPI, mL/min/1.73m²)

• When calculating renal drug dose adjustments, use estimated creatinine clearance (mL/min):
  *Use the CG Equation with Actual Body Weight (BMI <40) or Lean Body Weight (if BMI ≥ 40)

• Consider using the CKD Risk Assessment Tool (CGA scoring system) to determine risk for CKD progression
Prevention and Treatment of Hypertensive Nephropathy

Asha L. Tata, PharmD BCPS
Internal Medicine Clinical Pharmacy Specialist
University of Maryland Medical Center
Objectives

- Define blood pressure goals in patients with chronic kidney disease

- Discuss treatment options for the prevention and treatment of hypertensive nephropathy and the role of combination therapy

- Given a patient case, recommend the best antihypertensive based on clinical factors
Patient Case

- JZ is a 60 year old African American man with hypertension, currently taking HCTZ 12.5mg daily, who returns to the ambulatory care clinic for his 1-year check up.

- Other pertinent information:
  - Serum creatinine: 1.7 mg/dL
  - Serum potassium: 4 mEq/L
  - Urine albumin-to-creatinine ratio (ACR): 350 mg/g
  - BP: 150/90 mm Hg
Hypertensive Nephropathy

- Second most common cause of end-stage renal disease (ESRD)

- Accounts for about a third of patients initiated on dialysis annually in the United States

- Associated with significant morbidity and mortality, mostly due to cardiovascular (CV) complications

- Duration and degree of elevated BP affects CV outcomes and rate of chronic kidney disease (CKD) progression

*Expert Opin Pharmacother* 2010;11:2675-86
Albuminuria

- **Microalbuminuria**
  - Albumin excretion of >30 to 299 mg/g
  - Marker of endothelial dysfunction and risk for CV events

- **Macroalbuminuria**
  - Synonymous with proteinuria
  - Albumin excretion of >300 mg/g
  - Associated with higher CV risk
  - Indicates presence of CKD and associated with progression to ESRD

- Reduction in albuminuria decreases CV risk and CKD progression
How Low Do We Go?

- BP goals of therapy in chronic kidney disease (CKD), non-dialysis (ND)
  - JNC 8 2014
    - Patients 18-70 with eGFR <60 and any age with albuminuria >30mg/g <140/90 mm Hg
  - KDIGO 2012
    - CKD no proteinuria ≤140/90 mm Hg
    - CKD + proteinuria ≤130/80 mm Hg
      - Subgroup of patients with macroalbuminuria

- KDOQI commentary
  - "...KDIGO recommendations were generally reasonable but lacking insufficient evidence support and that additional studies are greatly needed"

*JAMA* 2014;311:507-20
*Kidney Int Suppl* 2012;2:337-414
RAAS Is Where It's At
Treatment Options

- Angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB)
- Aldosterone antagonists
- Renin inhibitor
- Diuretics
- Calcium channel blockers
- Beta-blockers
- Restriction of sodium intake
ACEI or ARB

- Standard of care in prevention and treatment of hypertensive nephropathy

- May provide protection against progression of CKD independent of BP

- Generally thought to be equivalent among different drugs between classes

- ARB in general better tolerated than ACEI

Hypertens Res 2013;36:91-101
Expert Opin Pharmacother 2010;11:2675-86
Expert Opin Pharmacother 2010;11:2651-63
Aldosterone Antagonists

Cochrane review

- Evaluate the effect of aldosterone antagonists alone or in combination with ACEI or ARB in adults who have CKD with proteinuria

- Aldosterone antagonists reduced proteinuria and BP in patients who had mild to moderate CKD and were treated with ACEI and/or ARB but resulted in increased hyperkalemia and gynecomastia

- Adding aldosterone antagonists to ACEI and/or ARB on reduction of major CV events or ESRD is unknown

Cochrane Database Syst Rev 2014 Apr 29;(4)
Aldosterone Antagonists

BARACK-D Trial

- Ongoing trial evaluating effects of addition of spironolactone to standard of care management in mild to moderate CKD in reduction of CV events and mortality and decline in renal function

- Unclear role in advanced CKD due to risk of hyperkalemia
Renin Inhibitor: Aliskir-IN or Aliskir-OUT?

AVOID Trial

- Compared losartan + aliskiren vs losartan + placebo on albumin excretion rate in 599 patients with diabetes

- Both groups had similar BPs and aliskiren group had 20% reduction in urinary albumin to creatinine ratios compared to placebo

- Aliskiren may have renoprotective effects that are independent of its BP lowering effect in patients with hypertension, type 2 diabetes, and nephropathy

Renin Inhibitor: Aliskir-IN or Aliskir-OUT?

ALTITUDE Trial

- Compared aliskiren or placebo + ACEI or ARB in reduction of cardiovascular and renal events in 8561 patients with diabetes

- Study terminated early due to lack of reduction in cardiovascular or renal outcomes, as compared with placebo, with an increased number of adverse events

- Need to go beyond surrogate biomarkers and evaluate risk–benefit data from clinical end-point trials

Diuretics

- Primarily used in the management of volume overload

- Help reduce serum potassium concentration

- Loops and thiazides potentiate the antiproteinuric effects of RAAS inhibitors

- Loops preferred over thiazides in more advanced CKD (GFR <30 ml/min)

*Expert Opin Pharmacother 2010;11:2675-86*
*Expert Opin Pharmacother 2010;11:2651-63*
*Hypertens Res 2013;36:91-101*
Calcium Channel Blockers

- Variable effects and may increase proteinuria due to dilation of the afferent arteriole

- Non-dihydropyridines may have greater renoprotective role than dihydropyridines

- Post-hoc analysis of the ACCOMPLISH trial showed that combination of benazepril + amlodipine decreased CKD progression more than benazepril + HCTZ

*Expert Opin Pharmacother* 2010;11:2675-86
*Expert Opin Pharmacother* 2010;11:2651-63
*Lancet* 2010;375:1173-81
*Hypertens Res* 2013;36:91-101
Beta Blockers

- May be beneficial due to decrease in sympathetic nervous system activation

- Carvedilol and labetalol mediate vasodilation through additional $\alpha$-1-adrenergic receptor blockade

- Nebivolol may exert vasodilation through stimulation of nitric oxide

- Carvedilol and nebivolol also have antioxidant effects and may be preferred
Combination RAAS Therapy: Two Isn't Always Better Than One

ONTARGET Trial

- Compared ramipril + telmisartan vs monotherapies on death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure in 25,620 patients with vascular disease or diabetes

- Combination therapy did have a significant benefit in the primary outcome but significantly increased risk of hypotension, syncope, renal dysfunction, and hyperkalemia, with a trend toward an increased risk of renal dysfunction requiring dialysis

Combination RAAS Therapy: Two Isn't Always Better Than One

Meta-analyses

- Dual RAAS inhibition in patients with albuminuria and cardiac risk factors did not decrease progression to ESRD or mortality.

- Dual RAAS inhibition in patients with CKD associated with decrease in albuminuria but higher risk of hypotension, hyperkalemia, and decrease in GFR, without mortality benefit.

- Dual RAAS inhibition resulted in no mortality benefit, regardless of heart failure status, with higher rates of adverse effects.

Nephrol Dial Transplant 2011;26:2827-47
Am J Hypertens 2013;26:424-41
BMJ 2013;346:f360-f360
Patient Case

- JZ is a 60 year old African American man with hypertension, currently taking HCTZ 12.5mg daily, who returns to the ambulatory care clinic for his 1-year check up.

- Other pertinent information:
  - Serum creatinine: 1.7 mg/dL
  - Serum potassium: 4 mEq/L
  - Urine albumin-to-creatinine ratio (ACR): 350 mg/g
  - BP: 150/90 mm Hg
What is JZ’s goal BP?

A. <150/90 mm Hg
B. <140/90 mm Hg
C. <130/80 mm Hg  Correct Answer
D. <120/80 mm Hg
What antihypertensive agent would be best to add to JZ’s current regimen?

A. Lisinopril 10mg daily
B. Losartan 25mg daily
C. Amlodipine 5mg daily
D. Lisinopril 10mg daily + Losartan 25mg daily

Correct Answer: B. Losartan 25mg daily
Key Takeaways

- **BP Goals**
  - CKD no proteinuria <140/90 mm Hg
  - CKD + proteinuria <130/80 mm Hg if macroalbuminuria

- **Preferred treatment options**
  - ACEI or ARB regardless of race or presence of diabetes
  - Diuretics, calcium channel blockers, and beta blockers may play a role as adjunctive therapy to ACEI or ARB

- **Limited role for combination RAAS therapy and should be reserved for selected patients with severe proteinuria who can be closely monitored**
Prevention and Treatment of Diabetic Nephropathy

John Jameson, Pharm.D. FASHP
Professor and Chair of Pharmacy Practice
Ferris State University, College of Pharmacy
Objectives

- The Participants should be able to:
  - Discuss the Importance of Microalbuminuria in Diabetic Nephropathy
  - Recommend an appropriate role of ACEs/ARBs in Diabetic Nephropathy
  - Describe emerging therapies that may be useful in Diabetic Nephropathy
Patient Case

- JZ is a 60 year old African American man with hypertension, currently taking HCTZ 12.5mg daily, who returns to the ambulatory care clinic for his 1-year check up.

- Other pertinent information:
  - Serum creatinine: 1.7 mg/dL
  - Serum potassium: 4 mEq/L
  - Urine albumin-to-creatinine ratio (ACR): 350 mg/g
  - BP: 150/90 mm Hg

New Lab from December 1, 2016  Hgb A1C - 9.0
Diabetic Nephropathy - Epidemiology

- 3% of Type 2’s have nephropathy at diagnosis
- Many more will have microalbuminuria

- 40% of Type 1 and Type 2 will develop Nephropathy

- Risk Factors
  - African American
  - Native American
  - Polynesian / Maori
  - Gene polymorphism of RAA
  - Smoking

- Macro Albuminuria is a risk factor for CVD
Diabetic Nephropathy - Terminology
Albuminuria

- **Microalbuminuria**
  - Albumin / Creatinine ratio of >30 to 299 mg/g
  - Marker of endothelial dysfunction and risk for CV events

  *Moderately Increased Albuminuria*

- **Macroalbuminuria**
  - Synonymous with proteinuria
  - Albumin /Creatinine ratio of >300 mg/g
  - Associated with higher CV risk
  - Indicates presence of CKD and associated with progression to ESRD

  *Could be called Overt Nephropathy*

*Expert Opin Pharmacother* 2010;11:2675-86
Albuminuric

Albumin / Creatinine ratio of >30 to 299 mg/g

- The CRP of renal labs
- Often Present upon Diagnosis of Type 2
- Poor blood sugar control
- **MAY** be a marker for CVD
- Poor predictor of Diabetic Nephropathy !!

*(Pharmacotherapy 2012;32(9):781–783)*
Diabetic Nephropathy Definition

\[
eGFR < 60\text{ml/min/1.73m}^2 \\
\text{OR} \\
\text{Albumin/Creat ratio > 300mg/g}
\]
Pathophysiology

High blood glucose ➔ glomerular hyperfiltration
• Triggers inflammation
• Oxidative damage
• Fibrosis
• Activation of the renin-angiotensin-aldosterone system (RAAS)

Pathophysiology

High blood glucose $\rightarrow$ glomerular hyperfiltration

- Glycosylate Basement Membrane
- Loss of Heparan Sulfate
- Loss of Tubulo-glomerular feedback
The Point?

All Albumin in the urine is NOT created equal

May or May NOT be Diabetic Nephropathy

Discov Med 2010;10:406-15
Prevention

Basics are the most important
• Blood Sugar Control
• Smoking Cessation

Continued smoking exacerbates but cessation ameliorates progression of early type 2 diabetic nephropathy  
Prevention – Hypertension Management

• See Dr. Tata’s Presentation
Prevention

⚠️ Bubble About to be Burst

Remember: Microalbumin is the CRP of the kidney
AND:
Treating Microalbumin with ACE/ARBs= no benefit
UNLESS:
Also Treating Hypertension

(Pharmacotherapy 2012;32(9):781–783)
Prevention

Macroalbuminuria

- Might be some Big Pharma Effect
- ACEs / ARBs slow progression to renal failure
- Use with or without hypertension
- Also benefits cardiovascular outcomes

Prevention

SGLT-2 Inhibitors
Canagliflozin (*Invokana®*)
Dapagliflozin (*Farxig®*)
Empagliflozin (*Jardiance®*)

⚠️  Bad Joke Warning
What Warnings have been issued for SGLT-2 Inhibitors?:

A. Genital Infections
B. Pulmonary Edema
C. Acute Kidney Injury
D. Pancreatitis
What Warnings have been issued for SGLT-2 Inhibitors?:

A. Genital Infections
B. Pulmonary Edema
C. Acute Kidney Injury
D. Pancreatitis

Correct Answers

Avoiding Acute Kidney Injury

SGLT-2 Inhibitors / ACE Inhibitors / ARBs

Risk
Dehydration, CHF, NSAIDs,

Prevention
Monitor Serum Creatinine one or two weeks after initiation

Prevention

Empagliflozin for patients with Diabetes and CVD

Progression to macroalbuminuria, doubling of the serum creatinine level, initiation of renal-replacement therapy, or death from renal disease

Which of the following are important for composite outcomes:

A. That all outcomes have similar severity / importance
B. That there is at least 90% power (non-composite is 80%)
C. That there are no more than 3 items in the composite
D. That there are at least 4 items in the composite
Which of the following are important for composite outcomes?:

A. That all outcomes have similar severity / importance
B. That there is at least 90% power (non-composite is 80%)
C. That there are no more than 3 items in the composite
D. That there are at least 4 items in the composite

Correct Answer
Prevention

Empagliflozin for patients with Diabetes and CVD

Progression to macroalbuminuria, doubling of the serum creatinine level, initiation of renal-replacement therapy, or death from renal disease

NNT was 16 to prevent one composite over 3 years

Possible Mechanism?

$400

Prevention

Uric Acid is Associated With:

- Insulin Resistance
- Cardiovascular Disease
- Inflammation
- Diabetic Nephropathy

There is a big allopurinol study in the works
Watch for it.
JZ is a 60 year old African American man with hypertension, currently taking HCTZ 12.5mg daily, who returns to the ambulatory care clinic for his 1-year check up.

Add Valsartan

Other pertinent information:

**Serum creatinine: 2.0 mg/dL**
- Serum potassium: 4 mEq/L
- Urine albumin-to-creatinine ratio (ACR): 350 mg/g
- BP: 150/90 mm Hg

New Lab from December 1, 2016  Hgb A1C - 9.0
Key Takeaways

- Moderate albuminuria does not necessarily portend Diabetic Nephropathy

- The word Microalbuminuria is no longer cool.

- You do not need to treat microalbuminuria without hypertension
Key Takeaways

First Things First

- Glucose control, Smoking Cessation and HTN management are most important for prevention of Diabetic Nephropathy

- Use ACE/ARB for Albumin/Creat > 300 mg/gm

- SGLT-2 Inhibitors may have a role (stay tuned)

- Uric Acid may be important. Watch for the Study