



# 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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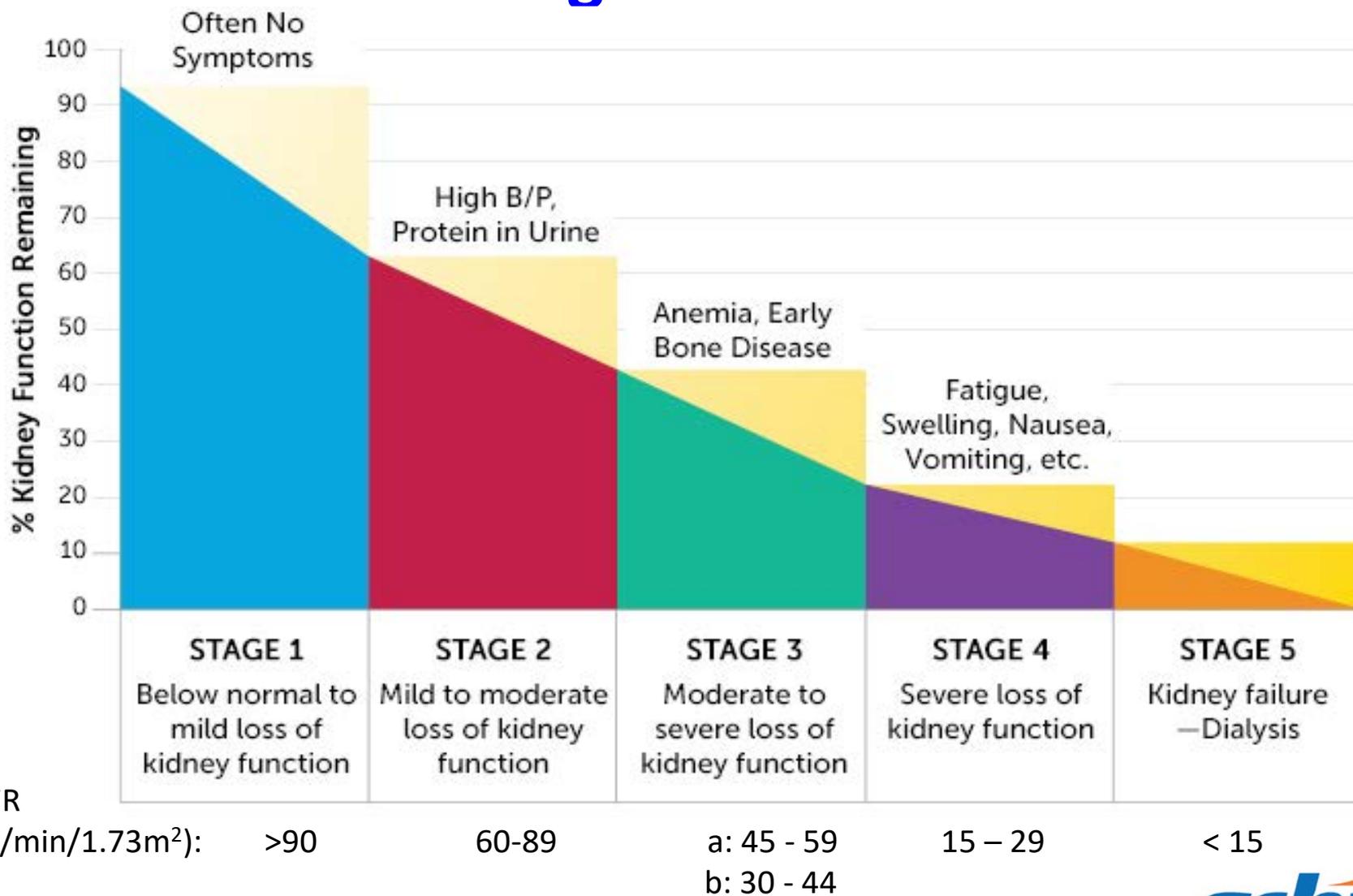
# Objectives

- 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

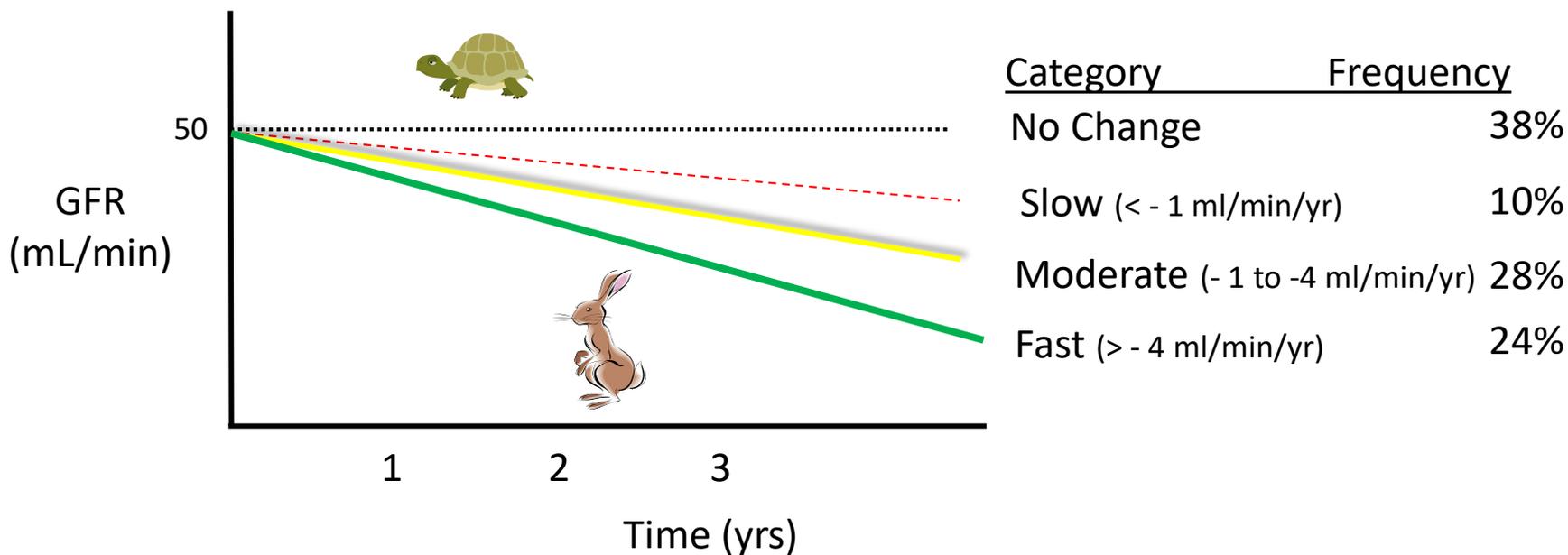


Adapted from the Kidney Disease Outcomes Quality Initiative (KDOQI) Guidelines, from the National Kidney Foundation

<http://www.ultracare-dialysis.com/kidney-disease/chronic/ckd-stages.aspx#sthash.MqLnqAqy.dpuf>

# CKD Progression

- How fast does kidney function decline in CKD?



# Estimating Kidney Function

- Creatinine Clearance (mL/min)
  - Measured (24-hr) CLcr
  - Estimated CLcr: Cockcroft-Gault (CG) Equation (clinical standard); if BMI  $\geq 40$ , use lean body weight<sup>1</sup>
- Estimated GFR (eGFR, mL/min/1.73m<sup>2</sup>)
  - 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/1.73m<sup>2</sup> = mL/min)
- When calculating renal drug dosing - Use CG equation

<sup>1</sup>Park EJ et al, *Ann Pharmacother* 2012;46:317-28

# Proteinuria

- Albumin-to-creatinine ratio (ACR)
- Reduced eGFR and increased ACR are consistent strong risk factors for AKI<sup>1</sup>
- CKD risk prediction models include ACR<sup>2</sup>

1. Am J Kidney Dis. 2015 Oct;66(4):591-601

2. JAMA. 2016 Jan 12;315(2):164-74

# New CKD Staging System (CGA)

Description and eGFR range (mL/min/1.73m <sup>2</sup> )				Persistent Albuminuria Categories, (A) Description and Range		
				Normal to mildly increased	Moderately increased	Severely increased
				<u>1</u> <30 mg/g (<3 mg/mmol)	<u>2</u> 30-300 mg/g (3-30 mg/mmol)	<u>3</u> >300 mg/g (>30 mg/mmol)
GFR Category (G)	1	Normal or high	≥90	1 if CKD	1	2
	2	Mildly decreased	60–89	1 if CKD	1	2
	3a	Mildly to moderately decreased	45–59	1	2	3
	3b	Moderately to severely decreased	30–44	2	3	3
	4	Severely decreased	15–29	3	3	4+
	5	Kidney failure	<15	4+	4+	4+

Key: CKD Progression Risk

- Low Risk
- Moderate Risk
- High Risk
- Very High Risk

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

# em (CGA)

GFR Categories (mL/min/1.73 m <sup>2</sup> ) Stage, Description, and Range		
1	Normal or hi	
2	Mildly decre	
3a	Mildly to mc decreased	
3b	Moderately 1 severely dec	
4	Severely dec	
5	Kidney failur	



Categories, e	Severely increased
>300 mg/g (>30 mg/mmol)	
2	
2	
3	
3	
4+	
4+	

Key: CKD Progression Risk

- Low Risk
- Moderate Risk
- High Risk
- Very High Risk

The numbers in each cell represent the risk of progression to the next GFR category over the next 5 years. Monitoring/year

GFR = glomerular filtration rate

Adapted from *Ann Intern Med*

# Assessment of JZ's kidney function

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

## Lean body weight (LBW, kg)

- Men:  $(9270 * TBW) / (6680 + 216 * BMI)$
  - Women:  $(9270 * TBW) / 8780 + 244 * BMI)$
- In our case, JZ's LBW =  $(9270 * 118) / (6680 + 216(42)) = 69.4$  kg
  - CLcr (mL/min) =  $\frac{(140-46)(69.4)}{(72 * 1.4)} = \underline{64.7}$  mL/min

# Assessment of JZ's kidney function

- eGFR
  - MDRD study equation
    - 65 mL/min/1.73m<sup>2</sup>
    - 84 mL/min
  
- CKD-EPI creatinine equation (2009)
  - 69 mL/min/1.73m<sup>2</sup>
  - 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/1.73m<sup>2</sup>)
- 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

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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

# 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?

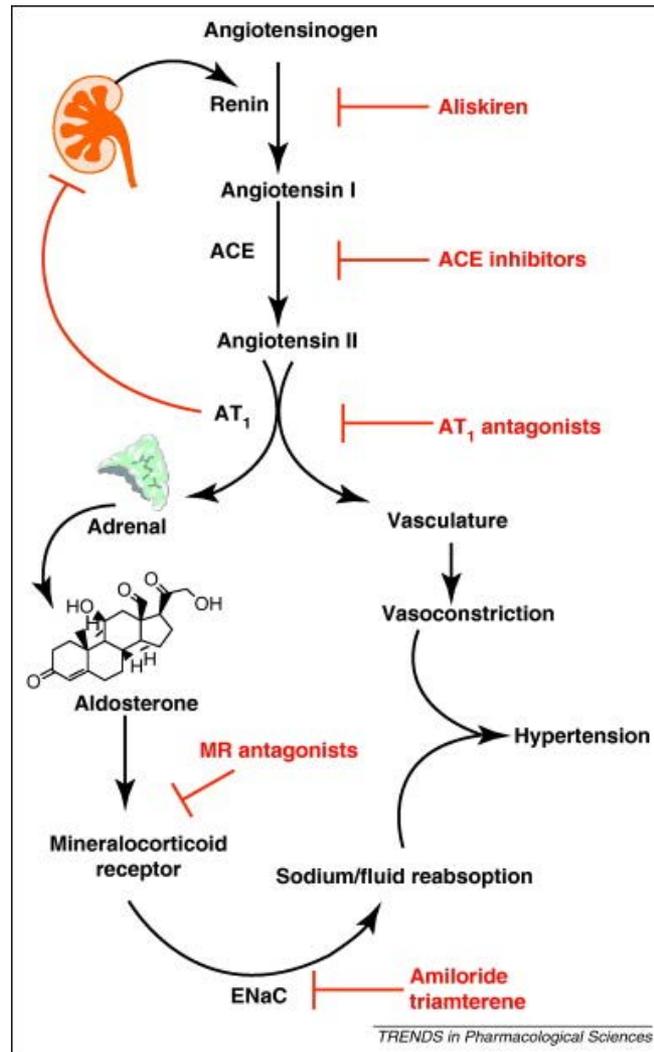
- BP goals of therapy in chronic kidney disease (CKD), non-dialysis (ND)
  - JNC 8 2014
    - Patients 18-70 with eGFR <60 and any age with albuminuria >30mg/g <140/90 mm Hg
  - KDIGO 2012
    - CKD no proteinuria  $\leq$ 140/90 mm Hg
    - CKD + proteinuria  $\leq$ 130/80 mm Hg
      - Subgroup of patients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

Am J Kidney Dis 2013;62:201-13

# 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

*Clin Med* 2015;15:550-57

*Hypertens Res* 2013;36:91-101

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

*Expert Opin Pharmacother* 2010;11:2651-63

# 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

*Clin Med* 2015;15:550-57

*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

# 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)

# 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

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

# 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

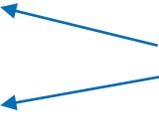
B <140/90 mm Hg

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
- 

# 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

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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 OR.....

# 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**

# Albuminuria

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 !!

# Diabetic Nephropathy Definition

eGFR < 60ml/min/1.73m<sup>2</sup>

OR

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 → 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  
N Engl J Med 2016; 375:323-334

▸

# Prevention

Basics are the most important

- Blood Sugar Control
- Smoking Cessation

Continued smoking exacerbates but cessation ameliorates progression of early type 2 diabetic nephropathy [Am J Med Sci.](#) 2008 Apr;335(4):284-91

# 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

# 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
- N Engl J Med 2016; 375:323-334

# Avoiding Acute Kidney Injury

SGLT-2 Inhibitors / ACE Inhibitors / ARBs

## Risk

Dehydration, CHF, NSAIDs ,

## Prevention

Monitor Serum Creatinine one or two weeks  
after initiation

<http://www.toomanymeds.com/one-minute-genius/pharmacology/ace-inhibitors-and-the-kidney/>

# Prevention

Empagliflozin for patients with Diabetes and CVD

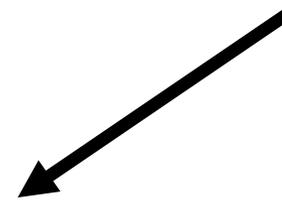
Progression to macroalbuminuria, doubling of the serum creatinine level, initiation of renal-replacement therapy, or death from renal disease

# 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?:

Correct Answer



- 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

# 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.

# 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.

## **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