CHRONIC KIDNEY DISEASE
UPDATE: WHAT THE GENERALIST NEEDS TO KNOW

MICHAEL G. SHLIPAK, MD, MPH
CHIEF-GENERAL INTERNAL MEDICINE,
SAN FRANCISCO VA MEDICAL CENTER
PROFESSOR OF MEDICINE, EPIDEMIOLOGY AND
BIOSTATISTICS, UCSF

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Outline
- Definition and Complications
- New CKD Staging 2013
- Screening for CKD
- Treatment of CKD
- Introduction to Cystatin C
- When to refer to nephrologist

Question 1: Which of these patients has CKD?

a) Heart failure patient in ED with creatinine of 2.0
b) Diabetes patient with albumin/creatinine of 100 mg/g, creatinine= 1.0 mg/dL
c) 35 year old African American man with creatinine of 1.5
d) All of the above
DEFINITION & CLASSIFICATION OF CHRONIC KIDNEY DISEASE

KDIGO 2012 Clinical Practice Guideline (CPG) for the Evaluation and Management of Chronic Kidney Disease

INTRODUCTION

Chronic Kidney Disease (CKD):
- Defined in 2002 with original CKD staging
- Replaced earlier terms “chronic renal insufficiency”, “chronic renal failure”, or “high creatinine”
- Previous 5 CKD stages were developed by an expert panel
- Most CKD epidemiology research has been conducted since the 5 stages were defined

DEFINITION AND COMPLICATIONS

Overall CKD definition unchanged

Chronic kidney disease: >3 month duration of either:
- Decreased kidney function (GFR<60)
- Injury/damage to the kidney (e.g. albuminuria, cysts, stones)

Etiology of CKD:
- Common diseases treated by generalists: diabetes, hypertension, cardiovascular disease, heart failure
- Other systemic diseases typically treated by specialists: systemic lupus erythematosus, HIV, urological diseases
- Primary kidney disease: polycystic kidney disease, glomerular disease

Complications of CKD

Kidney failure (end-stage renal disease)
Death

Other chronic disease:
- Atherosclerotic Cardiovascular Disease
- Heart failure
- Osteoporosis/fracture
- Cognitive impairment/dementia
- Frailty

Treatment Complications:
- Medications
- Procedures
Question 2: A 75 yr. old White male with CAD and HF has an eGFR= 25. What is he at most risk for?

a) Death  
b) Dialysis

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**Prognosis by eGFR and Albuminuria**

- Key meta-analysis published in 2010 in Lancet
- Evaluated prognosis by eGFR and albuminuria
- 21 studies, 1.2 million patients

**Predictors:**
- eGFR categories
- Albuminuria (ACR categories)
- Outcome: mortality risk

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**CKD Complications**

Keith et al., Arch Int Med, 2004

- Design: Northwest Kaiser database
- 5 year follow-up
- Death and ESRD outcomes

<table>
<thead>
<tr>
<th>Age</th>
<th>eGFR 30-60 N= 11,278</th>
<th>eGFR 15-30 N= 777</th>
</tr>
</thead>
<tbody>
<tr>
<td>72</td>
<td>20</td>
<td>45</td>
</tr>
<tr>
<td>74</td>
<td>20</td>
<td>45</td>
</tr>
</tbody>
</table>

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**Albuminuria and eGFR grid**


**Table:**

<table>
<thead>
<tr>
<th>Albuminuria Classes (mg/g)</th>
<th>eGFR (mL/min/1.73m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>1.6 1.4 2.0 4.4 1.2</td>
</tr>
<tr>
<td>10-29</td>
<td>1.6 1.3 1.9 3.7 1.6</td>
</tr>
<tr>
<td>20-30</td>
<td>0.6 1.2 1.7 2.6 1.6</td>
</tr>
<tr>
<td>30-44</td>
<td>1.6 1.5 1.8 3.4 2.6</td>
</tr>
<tr>
<td>45-59</td>
<td>1.2 1.5 1.8 3.4 2.0</td>
</tr>
<tr>
<td>60-74</td>
<td>0.6 1.2 1.7 2.6 1.6</td>
</tr>
<tr>
<td>&gt;75</td>
<td>1.6 1.5 1.7 3.4 2.0</td>
</tr>
</tbody>
</table>

**Table Notes:**

- Adjusted hazard ratios for all-cause mortality
- P<0.05

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CKD Prognosis Consortium, Lancet: 2073-81, 2010
Q3: What is the current definition of Stage 3 CKD?

- 1+ proteinuria or ACR > 30
- GFR 30-60
- GFR 45-60
- There’s no such thing

CKD Stages and Prevalence

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>Estimated GFR (mL/min per 1.73 m²)</th>
<th>U.S. Prevalence N (1000s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD Stage 1</td>
<td>90+*</td>
<td>3,200 (1.6)</td>
</tr>
<tr>
<td>CKD Stage 2</td>
<td>60-89*</td>
<td>6,500 (3.2)</td>
</tr>
<tr>
<td>CKD Stage 3</td>
<td>30-59</td>
<td>15,500 (7.7)</td>
</tr>
<tr>
<td>CKD Stage 4</td>
<td>15-29</td>
<td>700 (0.4)</td>
</tr>
<tr>
<td>CKD Stage 5</td>
<td>&lt;15 (or dialysis)</td>
<td>400 (0.2)</td>
</tr>
</tbody>
</table>

*With evidence of kidney damage, e.g. albuminuria
KDOQI Guidelines, AJKD, Feb. 2002

Problems with Old Staging

- Stages 1 and 2 were the same
- Stage 3 (30-60) was too broad; eGFR of 30-45 is very different from 45-60
- Did not address levels of albuminuria; and only used albuminuria for Stages 1 and 2
From Old to New Staging

<table>
<thead>
<tr>
<th>CGA Staging</th>
<th>Estimated GFR (mL/min per 1.73 m²)</th>
<th>U.S. Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD Stage 1</td>
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</table>

Classification of CKD

- It is recommended that CKD be classified by:
  - Cause
  - GFR category
  - Albuminuria category

- This is collectively referred to as “CGA Staging”

- Represents a revision of the previous KDOQI CKD guidelines, which included staging only by level of GFR

Outline

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Screening for CKD

- International CKD guidelines do not address when or how to screen
  - No RCT evidence for or against
  - Relative costs of screening vary by region

- Hypertension, Diabetes, and CVD guidelines all recommend some form of CKD screening.

- The following are my suggestions for primary care:
Who and When to Check Creatinine?

- Begin screening:
  - Age >40 lower-risk populations
  - Age >30 Blacks, Native Americans
- Diagnosis of hypertension, diabetes, cardiovascular disease, heart failure
- Frequency of creatinine monitoring (no evidence)
  - No risk factors: 3-5 years
  - Risk factors: 1-2 years
- Creatinine cost: $0.20

GFR Estimation from Creatinine

- Estimated GFR:
  - Automatic reporting by most labs
  - Equations are rough
  - <60 concerning for kidney disease, but not specific
  - >60 is imprecise, its considered just ">60"
- 3 equations in current use:
  - Cockcroft-Gault (Nephron, 1976)- used by FDA and pharmacies
  - MDRD (Annals, 1999)- used for most automated reporting
  - CKD-EPI (Annals, 2009)- favored by researchers

Question 4: Which of the following is true about creatinine GFR estimates?

- a) More accurate in older populations than middle-aged because prevalence of kidney disease is higher
- b) They have been validated in most ethnic groups
- c) They are more likely to be accurate in healthy persons than in persons with chronic illness
- d) All of the above

Pros and Cons of Estimated GFR

- Pros:
  - Indexes creatinine for demographic characteristics
  - Forces us to think in terms of GFR and kidney function
- Cons:
  - Mostly validated in younger patients with kidney disease
  - Huge assumption that demographic characteristics alone can define muscle mass
  - Only developed in Whites and Blacks
  - Estimated GFR ≠ GFR
Who to Screen with Urine Albumin?

- **Primary prevention screens:**
  - Diabetes: annual
  - Hypertension
  - Elderly

- **CKD Staging:**
  - Urine albumin is now important part of CKD staging
  - Should be measured and documented in all CKD patients
    - Repeat annually in diabetics
    - Every 2-3 years in non-diabetics

How to Measure Urine Albumin

- Often listed as "microalbumin panel"
- Focus on albumin/creatinine ratio (ACR):

<table>
<thead>
<tr>
<th>ACR (mg/g)</th>
<th>OLD</th>
<th>NEW</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30</td>
<td>Normal</td>
<td>Normal or mildly elevated</td>
</tr>
<tr>
<td>30-300</td>
<td>Microalbuminuria</td>
<td>Moderately elevated</td>
</tr>
<tr>
<td>&gt;300</td>
<td>Macroalbuminuria</td>
<td>Severely elevated</td>
</tr>
</tbody>
</table>

- Dipstick: “trace” is abnormal
- If dipstick is abnormal, quantify ACR

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Question 5: Which of the following treatment options will not slow the progression of kidney disease?

- a) ACE/ARB treatments
- b) Blood pressure control
- c) Glucose control
- d) Statins
CKD Treatment

- **Goals:**
  - Prevent progression to ESRD
  - Prevent CKD complications

- **Treatments:**
  - ACE/ARB therapy
  - Blood Pressure Control
  - Glucose Control in Diabetes
  - Statins

ACE/ARB's in Diabetic CKD

- Diabetic CKD- nearly always has albuminuria
- Diabetic CKD- ACE/ARB essential for:
  - Type I or II diabetes
  - Moderate albuminuria (ACR 30-300)
  - Severe albuminuria (ACR > 300)
- ACE/ARB’s do not appear to be helpful to prevent onset of albuminuria

ACE/ARB's in Non-Diabetic CKD

- Meta-analysis-RCTs of CKD patients, comparing ACE vs. other HTN agents (N=1,860)
- Overall RR 0.67 (0.53-0.84) for kidney outcomes
- Subgroup analysis:
  - Benefit limited to group with proteinuria (> 500 mg/g)

ACE/ARB's in CKD Patients without proteinuria?

- **ALLHAT Hypertension Trial** —
  - Subgroup analysis of CKD (eGFR< 60)
  - Compared lisinopril, amlodipine, and chlorthalidone
  - ACE equivalent to thiazides and CCB’s for kidney disease progression (Rahman, Arch Intern Med, 2005)
- Conclusion: For patients with reduced eGFR but normal levels of albuminuria - choice of blood pressure agent probably does not matter
Two Guidelines, Two Opinions

- **The new JNC-8 Guideline:** ACE/ARB should be used in all patients with CKD (eGFR<60)
  - James PA et al. JAMA 2014
- **KDIGO-CKD Hypertension Guideline:** ACE/ARB only necessary if ACR > 30

Advanced CKD – is there a time to stop the ACE?

- RCT: Hou FF et al. NEJM 2006; 354:131-140
- 224 patients with creatinine 3.1-5.0 mg/dL
- Mean eGFR 25; mean urine prot – 1.6g/day
- Benazepril 20 mg daily vs. placebo
- Primary end point: doubling of creatinine, ESRD, death

**Findings:**
- 43% reduction in primary end point
- Effects independent of blood pressure
- Adverse events rare

ACE/ARB Combination?

- Proteinuria reduction from ACE inhibitors and ARBs is similar.
- Combination of ACE/ARB has additional reductions in proteinuria.
- However, ACE/ARB combination carries higher risk of adverse events
- Given added risk of hyper-kalemia and uncertain benefit, I do NOT recommend combination therapy.

Blood Pressure Target Uncertain in CKD

- Meta-analysis in non-diabetic CKD found patients with SBP of 110-130 to have lowest risk of progression (Jafer, Ann Intern Med, 2005).
- Modern RCTs have NOT proven that tighter BP control reduces CKD progression (SPRINT ongoing).
- Guidelines on blood pressure control in CKD:
  - JNC-7 target < 130 (contrast with <140)
  - KDIGO-CKD HTN guideline: <140, though <130 considered optimal.
  - JNC-8 target < 140 (contrast with < 150)
## The Challenge of Blood Pressure Control in CKD

- CKD typically occurs in older patients who have stiff arteries, so SBP < 130 rarely attainable.
- SBP control often requires 3-4 meds at full dose.
- In large health screening study, we found one-third of CKD patients had SBP > 150 ([Peralta CA, Arch Intern Med, 2012](http://dx.doi.org/)).
- DBP may drop to <60 without lowering SBP adequately.

## Glycemic Control in Diabetic CKD

- **Type I Diabetes** - tight glucose control slows kidney disease progression: OR = 0.34 (0.20-0.58)
- **Type II Diabetes** - ADVANCE trial ([NEJM, 2008, 2560-72](http://dx.doi.org/))
  - Tight glucose control (HbA1c 6.5 vs. 7.3): 20% lower risk of “new or worsening nephropathy” (RR 0.80; p=0.006)
  - Low rates: 4.1 vs. 5.2%
- In Type II Diabetes, risks of tight glucose control probably offset kidney benefits in older patients.
- Tailor A1C treatment goal to the individual patient.

## Statins in CKD - beneficial for CVD

- CKD patients have very high CVD Risk
- Statins lower CVD risk in CKD patients:
  - Meta-analysis of 20 early studies (N=18,746 patients) found RR 0.80 (95% CI: 0.70,0.90)
  - SHARP RCT: (N=9,500) simvastatin/ezetimide vs placebo RR = 0.83 (95% CI: 0.74-0.94)
- No effect on CKD progression
- No benefits of statins in patients with ESRD

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Question 6: How familiar are you with cystatin C?

- A. I heard about the test today for the first time
- B. I have heard of the test, but I do not know what it is used for.
- C. I have read an article that involved cystatin C, but I have not measured it in my practice
- D. I have had cystatin C measured on my patients in clinical care.

Cystatin C

- Cystatin C is a blood test of kidney function that is an alternative to creatinine
- Because cystatin C is not related to muscle mass (or age, sex, and race), it has major advantages over creatinine
- Cystatin C is a reliable, standardized, and inexpensive ($4/test) measure that is available for clinical use.

GFR Equations using Cystatin C

- Cystatin C can be used for GFR estimation in the same way that we use creatinine.
- 2 equations published recently in major journals
  1. **CKD-EPI (NEJM July 2012)**
     - eGFRcys, eGFRcys+cr
     - Best GFR by both creatinine + cystatin C
     - Cystatin C has no race bias, so same eGFR formula for Blacks and Whites
  2. **Berlin Study (Ann Intern Med November 2012)**
     - In elderly persons, cystatin C much better than creatinine
     - Best estimate also by creatinine + cystatin C

“Cystatin C versus Creatinine in Determining Risk based on Kidney Function”
Shlipak et al. New England Journal of Medicine, 2013

- Meta-analysis of all available observational studies and clinical trials with creatinine and cystatin C
- 16 studies, 90,000 persons
- Compared associations of eGFRcr, eGFRcys, and eGFRcr-cys with mortality risk
- Determined proportions reclassified by cystatin C in each eGFRcr subgroup and impact on risk associations
eGFR Distributions and CKD Prevalence

**CKD prevalence:**
- 9.7% (eGFRcr)
- 13.7% (eGFRcys)
- 10.0% (eGFRcr-cys)


All-Cause Mortality

12,351 events


Reclassification by eGFRcys and associated risk

**Mortality Associations**

<table>
<thead>
<tr>
<th>eGFRcys (ml/min/1.73m²)</th>
<th>25-29</th>
<th>30-35</th>
<th>36-45</th>
<th>46-59</th>
<th>60-74</th>
<th>75-80</th>
<th>80+</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.88 (0.76, 1.01)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>0.66 (0.57, 0.77)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>0.77 (0.61, 0.98)</td>
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<tr>
<td>0.60 (0.57, 1.36)</td>
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</table>


Guideline Statements Relevant to Cystatin C

**KDIGO 2012 Clinical Practice Guideline (CPG) for the Evaluation and Management of Chronic Kidney Disease**

KDIGO Suggestion #1 (2B)

- **Estimating GFR:**
  1. Use creatinine eGFR
  2. Are you confident that this is accurate?
  3. If not, use either:
     - Cystatin C
     - Direct measure GFR

KDIGO Suggestions #2 (2C)

- **Confirming CKD:**
  Your patient's eGFRcr is 45-60 and is not known to have kidney disease:
  - Measure cystatin C
  - If cystatin C eGFR <60: patient has CKD
  - If cystatin C eGFR >60: patient does NOT have CKD

KDIGO Suggestion #3 (2C)

- **When using cystatin C:**
  - Use eGFR equation
  - Use standardized measure

KDIGO Recommendation (1C)

- For medical dosing of potentially toxic agents, use cystatin C or direct measure GFR
- Potential examples - new anti-coagulants, chemotherapeutics
- Major challenge – FDA has dosing based on creatinine clearance
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Reasons to Consider Referral to Nephrologist

- Combined hematuria and proteinuria
  - Indicates concern for glomerulonephritis
- Estimated GFR < 30
  - Need to start planning for dialysis
- Nephrotic proteinuria
  - Potential for treatable condition
- Mineral metabolism management:
  - High phosphate/high PTH
- Anemia of CKD
  - Hemoglobin target ~10

Thank you!
Any Questions?