Chronic Kidney Disease and End-Stage Renal Disease: Prevention, Diagnosis, and Treatment

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**Learning Objectives**

1. Incorporate the major points of the National Kidney Foundation Quality Outcomes Initiative for chronic kidney disease (CKD) into practice.
2. Accurately identify, screen, evaluate and classify patients who are at risk or have the diagnosis of CKD.
3. Reduce the risk for progression of CKD to ESRD by applying appropriate, proven therapeutic interventions early in the disease process.
4. Devise management strategies for anemia, bone disease, malnutrition, and electrolyte abnormalities in the later stages of CKD.

**Audience Engagement System**

1. Step 1
2. Step 2
3. Step 3
Agenda

- Prevalence of CKD
- Definition and Diagnosis of CKD
- Cardiovascular Disease in CKD
- Therapy to reduce CVD and progression in CKD
- Indications for referral to Nephrologist
- Cautions in Patients with CKD

“Chronic Kidney Disease can be as Lethal As Cancer of the Lung”

Katherine Tuttle MD. Chronic Kidney Disease and Diabetes / Risks of Kidney Disease / Future Therapies / Diagnosis, Presentation, and Prevention. Diabetes Insight Volume 05, Issue 20 October 7, 2014

CKD Prevalence

- CKD affects approximately 13.6% of all US adults,
- The prevalence increases with age; among adults aged 60 to 69 years, nearly 25% have either albuminuria or reduction in GFR,
- Among adults older than 70 years, nearly 50%
- Diabetes and Hypertension responsible for 75% of cases

PKD Epidemiology

- 20 million adults have CKD in the United States — 1 in 10 adults— >3X in African Americans—Most have Diabetes
- Most patients with CKD will die of a CV event before they reach end stage renal disease (ESRD).
- Less than 2% progress to ESRD
- Prevalence of Diabetic Kidney Disease is 35%; 17% with albuminuria, 10.8% with impaired Glomerular Filtration Rate <60, 6.9% with both albuminuria and impaired GFR.

Polling Question

Which of the following statements is true about Chronic Kidney Disease (CKD) and End Stage Renal Disease?

A. Most patients with CKD will die from a CV event before they reach end stage renal disease
B. Less than 2% of patients with CKD go on to end stage renal disease
C. Both A and B
D. None of the above are true

Agenda

- Definition and Diagnosis of CKD
Polling Question
Chronic Kidney Disease (CKD) is defined by which of the following?
A. GFR is <60 ml/min for at least 1 month
B. GFR is <60 ml/min for at least 3 months
C. Albuminuria-Spot urine albumin to creatinine ratio is >30 mg/g
D. B and C
E. A and C

Definitions of Acute and Chronic Kidney Disease
Acute Kidney Disease defined as
- Increase in creatinine by 50% within 7 days or
- Increase in creatinine by 0.3 mg/dl within 48 hrs or
- Urine output <0.5 ml/kg/hour for 6 hrs

Chronic Kidney Disease defined as
- eGFR ↓to < 60 ml/min for 3 months and
- Markers of kidney damage like albuminuria-Albumin to Creatinine ratio >30 mg/g

eGFR=estimated Glomerular Filtration Rate—Normal =>60 ml/min

Levey AS. Glomerular Filtration Rate and Albuminuria for Detection and Staging of Acute and Chronic Kidney Disease in Adults. JAMA. 2015;313(9):907-914

What are the Stages of CKD?

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (mL/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney Damage with Normal or ↑↑ GFR</td>
<td>≥ 90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney Damage with Mild ↓ GFR</td>
<td>89-60</td>
</tr>
<tr>
<td>3 A</td>
<td>Mild to Moderate ↓ GFR</td>
<td>59-45</td>
</tr>
<tr>
<td>3 B</td>
<td>Moderate ↓ GFR</td>
<td>44-30</td>
</tr>
<tr>
<td>4</td>
<td>Severe ↓ GFR</td>
<td>25-15</td>
</tr>
<tr>
<td>5</td>
<td>Kidney Failure</td>
<td>&lt;15 or dialysis</td>
</tr>
</tbody>
</table>

Severity increases

Calculating estimated Glomerular Filtration Rate (eGFR)
- Serum Creatinine should not be used as a stand alone source of assessing kidney function
- Serum Creatinine used to calculate eGFR
- Not always sure which equation/formula your lab uses—MDRD, Cockcroft Gault or CKD-EPI

Levey AS. Glomerular Filtration Rate and Albuminuria for Detection and Staging of Acute and Chronic Kidney Disease in Adults. JAMA. 2015;313(9):907-914

CKD-EPI Equation More Accurate than MDRD for GFR at higher levels
- CKD-EPI reclassified 24% of patient from <60 to >60 GFR (older, women, less muscle mass)
- Available at no charge on App Store from National Kidney Foundation—smart phone search “GFR calculator”

Cystatin C for eGFR
- It is generally not affected by extra renal factors such as muscle mass, age, gender, or race
- Cost about $5
- Of significant value if eGFR 59-45 and many will be reclassified to > 60
- Allows for use of more drugs without limitations

Einhorn D, Mende CW. Endocr Pract 2015;21:1301-1302

Agenda
- Cardiovascular Disease in CKD

Risk of CVD, Death and Hospitalization with CKD
Risk of CV events increases with increasing GFR

<table>
<thead>
<tr>
<th>eGFR-STAGE</th>
<th>Risk of events per 100 person Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60</td>
<td>1-2</td>
</tr>
<tr>
<td>45-59</td>
<td>3.65</td>
</tr>
<tr>
<td>30-44</td>
<td>11.29</td>
</tr>
<tr>
<td>15-29</td>
<td>21.8</td>
</tr>
<tr>
<td>&lt;15</td>
<td>36.6</td>
</tr>
</tbody>
</table>


Hospitalization for Cardiovascular Disease increases risk for End Stage Renal Disease (ESRD)
- 1264 patients with chronic kidney disease stages 3 to 5 (glomerular filtration rate <60) followed for 2.5 years
- CV event (myocardial infarction, heart failure, or stroke) associated with a higher risk of subsequent ESRD (hazard ratio, 5.33)
- Intensive secondary preventative strategies may be of particular benefit in these patients because evidence-based therapies, such as statins and antiplatelet drugs, are generally underutilized in patients with CKD

Sud M et al. Risk of End-Stage Renal Disease and Death After Cardiovascular Events in Chronic Kidney Disease. Circulation. 2014;130:458-465
Chronic Kidney Disease Prevalence in Acute Myocardial Infarction (MI)

- CKD (<60 mL·min) prevalence is 30.5% among patients presenting with ST-segment-elevation MI and 42.9% among patients presenting with non-ST-segment-elevation MI.
- The presence of CKD among patients presenting with ACS has been associated with worse outcomes, including higher rates of mortality and bleeding.
- Despite the increased risk for adverse outcomes, CKD patients presenting with ACS are less likely to receive evidence-based therapies.

Despite the increased risk for adverse outcomes, CKD patients presenting with ACS are less likely to receive evidence-based therapies.

Washam JB et al. Pharmacotherapy in Chronic Kidney Disease Patients Presenting With Acute Coronary Syndrome Circulation. 2015;131:000-000. DOI: 10.1161/CIR.0000000000000183.

Annual change in Creatinine and GFR and CV events in Diabetes

- <0.16 mg/dl SCr yearly ↑
- >0.16 mg/dl SCr yearly ↑
- <5 ml eGFR yearly ↑
- >5 ml eGFR yearly ↑


RISK FOR CVD, MORBIDITY AND PROGRESSION TO ESRD BY GFR AND ALBUMINURIA

Colors represent risk of progression, mortality and morbidity:
- Green: Low Risk
- Yellow: Moderate Risk
- Pink: High Risk
- Red: Very High Risk


Why Albumin to Creatinine Ratio (ACR) and not just Albumin?

- Expressing albumin as a ratio to creatinine reduces intra-individual variability.
- Variability reduced from 80% to 52% when expressed as an ACR rather than an albumin concentration.
- Lowest variability for the ACR reported in Early Morning Urine.
- Dipstick not as reliable—24 hour urine collection difficult to do so not as reliable.


Agenda

- Therapy to prevent Cardiovascular Disease and progression of Chronic Kidney Disease.

Polling Question

Which of the following statements is correct about urinary albumin measurement?

A. 24 hour urine measurement is the most reliable
B. Lowest variability for Albumin to Creatinine ratio on a spot urine is specimens obtained late in the day
C. Expressing albumin as a ratio to creatinine reduces intra-individual variability
D. All of the above
E. None of the above

**Assessment and prevention**

- Assessment of eGFR and albuminuria yearly
- Prevention of CVD and CKD progression
  - blood pressure <140/90 mm Hg or <130/80 if albuminuria
  - use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for patients with albuminuria and or hypertension,
  - hemoglobin A1c <7% for patients with diabetes if possible
  - LDL <100 mg/dl
  - Weight reduction

- Reduce risk of CKD progression by prevention of acute kidney injury, cardiovascular disease, anemia as well as mineral and bone disorder.


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**Reducing A1C Reduces Nephropathy Risk in Type 2 Diabetes**

<table>
<thead>
<tr>
<th>A1C reduction (%)*</th>
<th>0.9</th>
<th>0.8</th>
<th>1.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephropathy risk reduction (%)*</td>
<td>30</td>
<td>21</td>
<td>21</td>
</tr>
</tbody>
</table>

**New onset microalbuminuria** ($P$ =0.033)

**New or worsening nephropathy** ($P$ =0.006)

**New microalbuminuria** ($P$ =0.0005)

*Intensive vs standard glucose control.


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**ACE and ARB use and Mortality in CKD**

![ACE and ARB use and Mortality in CKD](image)

Proportion Surviving

Years

No ACE /ARB

ACE /ARB


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**Empagliflozin reduced progression of Kidney disease in T2 Diabetes**

- Empagliflozin (Jardiance) reduced progression or onset of CKD in T2 Diabetes with eGFR ≥30 by 36%
- Doubling of the serum creatinine level occurred 1.5% in the empagliflozin group and 2.6% in the placebo group, a relative risk reduction of 44%
- Empagliflozin reduced ACR in patients with micro & macro albuminuria
- Is this a class effect for all SGLT 2 Inhibitors?


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**Polling Question**

Which of the following statements is correct about use of diabetes drugs in CKD?

A. Stop Metformin when GFR is less than 60
B. The SGLT 2 inhibitor Canaglifozin (Invokana) can be used when GFR <45
C. The DPP4 inhibitor Linagliptin (Trajenta) requires no dose adjustment in CKD
D. None of the above
E. All of the above

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**Use of diabetes drugs in CKD**

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Use in CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazolidinediones (pio, rosiglitazone)</td>
<td>No dose adjustment—but caution with edema</td>
</tr>
<tr>
<td>DPP4 Inhibitors</td>
<td>Reduce dosage for alogliptin, saxagliptin, and sitagliptin if GFR ≤50. Linagliptin no dose adjustment</td>
</tr>
<tr>
<td>GLP 1 RA</td>
<td>Exenatide BID and weekly GFR 30-50 use with caution. Albiglutide, Liraglutide, Dulaglutide no dose adjustment</td>
</tr>
<tr>
<td>SGLT-2 inhibitors</td>
<td>Canagliflozin GFR 45-59 lower dose-Dapaglifozin avoid GFR &lt;60. Empagliflozin avoid use GFR &lt;45</td>
</tr>
<tr>
<td>Metformin</td>
<td>GFR &lt;45 lower dose &lt;30 stop</td>
</tr>
<tr>
<td>Insulin</td>
<td>Lower dose with progressive decrease in GFR</td>
</tr>
</tbody>
</table>

### FDA changes Metformin Guidelines

- **Previous**—stop metformin in men creatinine >1.5 mg/dL and women >1.4 mg/dL. **But as of April 2016**
  - eGFR of >45 no change in dose
  - eGFR of 30-44 lower dose and closely follow eGFR
  - eGFR of <30 stop Metformin

- Discontinue metformin before iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL-
  re-evaluate eGFR 48 hrs after procedure--

Accessed online May 2016 at www.fda.gov/Drugs/DrugSafety/ucm493244.htm

### Hypoglycemia

- Risk of hypoglycemia increases as kidney function becomes impaired.
- Declining kidney function will necessitate changes to some diabetes medications
- Target A1c usually <7 but if GFR <45, comorbidities, limited life expectancy, etc A1C closer to 8 recommended.

### CKD and Obesity

- **Morbidly obese individuals** who lost weight on a 12-week regimen of restricted calories paired with an exercise plan appeared to have significant kidney function improvement,
- The average weight of the participants in the study was 289 lbs at baseline (baseline body mass index 52.67 kg/m²) —
  reduced to an average of 260 lbs at 12 weeks,
- eGFR increased from about 47.41 mL/min to almost 55.17 mL/min, Independent of decrease in BP, A1C and Lipids


### Blood Pressure Control and CKD

- Control of BP more important than exactly which agents are used.
- With proteinuria: diuretic + ACEi or ARB.
- No proteinuria: no clear drug preference- ACEi or ARB ok to use.
- Target blood pressure in non-dialysis CKD:
  - ACR <30 mg/g: 140/90 mm Hg
  - ACR >30 mg/g: 130/80 mm Hg


### National Kidney Foundation Management of Normotensive Patients with and without Albuminuria and Diabetes

- Recommend not using an ACE-I or an ARB for the primary prevention of CKD in normotensive normoalbuminuric patients with diabetes.
- Suggest using an ACE-I or an ARB in normotensive patients with diabetes and albuminuria levels >30 mg/g.
- Hypertension without Albuminuria use any agent to reduce B/P


### Dyslipidemia in CKD

- Large number of patients with CKD are affected by dyslipidemia
- This places them at risk for acute and chronic CVD, recurrent MI, stroke, and CHF
- Poor control of dyslipidemia may accelerate CKD progression
- Reducing LDL-C limits CV mortality, decreases cardio-metabolic risk and may slow the progression of CKD.

Reduction of CVD in CKD with Statins

- The Study of Heart and Renal Protection (SHARP), the largest RCT in people with CKD to date. Results demonstrate that a lipid-lowering strategy which included fixed dose simvastatin and ezetimibe (20/10) resulted in a 17% reduction in atherosclerotic events.
- The cohort enrolled included those with eGFR under 60—age, greater than 40 years or age, including more than 9000 subjects. The lipid-lowering strategy was effective and safe.

Anemia in CKD

- Anemia affects 12% of stage 3a CKD, and 50% of those stage 4 or 5 CKD.
- Normocytic--erythropoietin synthesis by the kidney as well as decreased RBC half-life. Coupled with iron deficiency anemia common.
- Cut points WHO <13 g/dL for men and <12 g/dL for women.
- Treatment of anemia with erythropoietin analogues has become more judicious, initiated at lower Hb levels and with lower Hb targets because of the increased risk of CV events and failure to meaningfully improve quality of life.

Mineral and Bone Disorders (MBD) in CKD

- Complications of CKD-MBD include renal osteodystrophy, tertiary hyperparathyroidism, vascular calcification.
- Measuring serum levels of calcium, phosphate, PTH, at least once in adults with GFR <45 in order to determine baseline values—abnormal consider nephrology consult.
- Bone mineral density testing misleading when eGFR <45.
- Suggest not prescribing bisphosphonate treatment in people with GFR <30 —IV bisphosphonate nephrotoxic.

As GFR decreases serum phosphorus ↑ and serum calcium ↓. Parathyroid hormone increases to return phosphorus and calcium to normal but tradeoff is PTH induced bone disease—Renal Osteodystrophy.

Agenda

- Indications for referral to Nephrologist

Indications for Referral to Nephrologist

- Referral to nephrology improves outcomes and reduces costs. Refer for any of below especially with more than one:
  - Acute kidney injury or abrupt sustained fall in GFR—5 ml/year.
  - Consider if GFR <45 and other morbidities—definite referral when GFR <30.
  - Persistent albuminuria (ACR >300 mg/g) at any stage.
  - Hypertension refractory to treatment with 4 or more antihypertensive agents.
  - Significant Anemia—Phosphorus ↓ Calcium↑ PTH ↑ K.

Agenda

• Cautions in Patients with CKD

Analgesia and CKD

• NSAIDs  Avoid when GFR <30 Ml, Prolonged therapy is not recommended when GFR <60 mL
• Opioids  Reduce dose of renal excreted agents (morphine, hydrocodone, codeine) when GFR <60

Vassalotti JA et al, Practical Approach to Detection and Management of Chronic Kidney Disease for the Primary Care Clinician American Journal of Medicine 2016 129, 153-162

Cautions with other Medications

• Aminoglycosides ↓dose when GFR <60
• Macrolides ↓ dose by 50% when GFR <30
• Fluoroquinolones ↓ dose by 50% when GFR <15
• Tetracycline ↓ dose when GFR <45
• Antifungals avoid amphotericin when GFR <60
• ↓ maintenance dose of fluconazole by 50% when GFR <45


Cautions with other Medications

• ACE and ARB
  – GFR <45 lower dose
  – GFR <30 ↓ dose 50%
  – Access GFR and Potassium 1 week after dose ↑
  – Suspend use before and after radiocontrast, colonoscopy, procedures, sepsis illness when GFR <60

• Statins—use lower dose—myopathy GFR <60
• Proton Pump Inhibitors-like Nexium, Protonix and Aciphex limit use and watch BUN and Creatinine -


Using Radiocontrast Media for CKD

• For patients with GFR <60
  – Avoid of high osmolar agents
  – Use of lowest possible radiocontrast dose
  – Withdrawal of potentially nephrotoxic agents before and after the procedure-NSAIDS, Metformin, NSAIDS etc
  – Adequate hydration before, during, and after the procedure
  – Measurement of GFR 48–96 hours after the procedure

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Practice Recommendations

• Be aggressive in diagnosing and managing CKD to decrease progression and complications (CKD)
• Measure GFR with CKD-EPI Equation—More Accurate than MDRD for GFR
• Blood pressure target 140/90 unless ACR is >30 then 130/80
• Increase use of Statins in CKD—and lower dose to ↓ myopathy
• Treat hyperglycemia to decrease progression of CKD but limit chance of hypoglycemia (insulin and sulfonylureas)
• Be alert for Acute Kidney Failure--
• Be cautious with drug dose, avoid some drugs and IV contrast materials as GFR decreases

Questions

Contact information
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Web Sites
www.diabetesmasterclinician.org
www.diabetesuniversitydmcp.com
www.familymedicinetteams.org

Billing & Coding

When services performed in conjunction with:
Office Visit 992xx *
Nutritional Therapy 97802-97804
*Time-based selection documentation criteria:
• Face-to-face time
• greater than 50% spent counseling/coordinating care

Additional tests to confirm or monitor:
99490 Chronic Care Management-20 minutes monthly
90851- 90870 End-stage renal disease related services for dialysis by age and stage

Associated Session
• Chronic Kidney Disease and End-Stage Renal Disease: PBL
Interested in More CME on this topic?
aafp.org/fmx-internal