AAFP Chapter Lecture Series:
Chronic Kidney Disease/Cardiovascular Disease

Presented By
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The AAFP would like to thank Todd Thames, MD, FAAFP for creating the content for this series.
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Please select the most appropriate answer to each of the following questions by filling in the bubble next to the corresponding answer. Please be sure to fill in the bubble of you response completely.

### Pre-Assessment Questions:

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### Post-Assessment Questions:

**NOTE:** The orders of the questions and answers have been scrambled and are not in the same order as the pre-assessment questions.

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Please rate your agreement to the following statements. Please be sure to fill in the bubble of you response completely.

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<th>Agree</th>
<th>Neutral</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
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<td>Overall, I would rate Pat Keith Patteson, MD, as excellent.</td>
<td>5</td>
<td>4</td>
<td>3</td>
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<td>The content presented in this session covered the stated learning objectives.</td>
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Please provide any additional comments related to the faculty/session.

_________________________________________________________________

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Based on the content of this activity, my next step will be to:

① Pursue additional education/reading
① Discuss content with colleagues to obtain a consensus about a practice change
① Continue current practice
① Implement a change in practice from what I have learned in this session
Learning Objectives

- Refine evaluation skills to more effectively screen for the presence of chronic kidney disease.
- Construct an appropriate treatment plan for a patient with chronic kidney disease that also considers the potential for cardiovascular disease, including tailoring the treatment regimen for the individual, follow-up monitoring, and making an appropriate referral.
- Address the impact of patient misconceptions of their risk for cardiovascular disease, medication non-compliance, and negative lifestyle factors; recognize these as barriers to appropriate care of chronic kidney disease patients; and devise an action plan to correct these issues.

Martin

- 61-year-old African American male
- History of hypertension since age 35
- New Diagnosis: Type 2 Diabetes Mellitus
- At Risk for CKD?
- If so, what does that mean we should do?
- Does this alter our management choices?

Chronic Kidney Disease

Definition

Kidney damage, as defined by pathologic abnormalities or markers of damage in blood or urine tests or imaging studies, for 3 or more months

OR

Glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m² for 3 or more months

From National Kidney Foundation published in Am J Kidney Dis. 2002; (2 Supp 1)
Johnson CA, et al. Am Fam Physician. 70(3); 869-876

Stages of CKD

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (ml/min/1.73 m²)</th>
<th>ICD-9 Code</th>
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<tr>
<td>0</td>
<td>Risk factors with no kidney damage and normal or ↑↑↑↑ GFR</td>
<td>≥ 90</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>Kidney damage and normal or ↑↑↑↑ GFR</td>
<td>≥ 90</td>
<td>585.1</td>
</tr>
<tr>
<td>2</td>
<td>Kidney Damage and Mild ↓↓↓↓ GFR</td>
<td>60-89</td>
<td>585.2</td>
</tr>
<tr>
<td>3</td>
<td>Moderate ↓↓↓↓ GFR</td>
<td>30-59</td>
<td>585.3</td>
</tr>
<tr>
<td>4</td>
<td>Severe ↓↓↓↓ GFR</td>
<td>15-29</td>
<td>585.4</td>
</tr>
<tr>
<td>5</td>
<td>Kidney Failure &lt;15 (or dialysis)</td>
<td>585.5 no dialysis 585.6 dialysis</td>
<td></td>
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Snapshot of CKD in the US

Primary Management of CKD

The Role of Family Medicine in Helping Martin

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Screening for CKD
Who is at Risk?

Clinical Factors
- Diabetes
- HTN
- Autoimmune disease
- Recurrent urinary tract infection (UTI)
- Urinary stones (recurrent)
- Outlet obstruction
- Family history of CKD
- History of severe acute kidney injury (AKI)
- Any reduction in kidney mass

Sociodemographic Factors
- Older age
- Ethnic minority status
  - Black
  - Hispanic
  - American Indian
  - Pacific Islander
- Lower income

Screening for CKD
The Role of Primary Care/Family Medicine

- NKF Guidelines Recommend:
  - Screening all patients with: Diabetes, Hypertension, Family History of CKD, Age >60, Ethnic Minorities, History of Severe AKI
  - Frequency Recommendations: Annually
  - At a Minimum:
    - Assessment for Proteinuria
    - Calculation of Glomerular Filtration Rate (GFR)

Screening for CKD
K/DOQI Recommendations

- Assessment of Proteinuria (KDOQI Part 5)
  - Albumin to Creatinine Ratio (spot)—"Microalbumin"
    - 24-hour urine collection
    - Timed collection (4-hour or overnight)
    - Urinalysis reagent test strips ("UA dip")
- GFR Estimation (KDOQI Part 4)
  - Modification of Diet in Renal Disease (MDRD) equation
  - CKD-EPI Equation
  - 24-hour creatinine clearance

Screening: What About Martin?

- Screen Him Annually due to HTN, and now DM.
- Obtain Spot UA for Albumin to Creatinine Ratio
- Determine GFR using established formula (MDRD, CKD-EPI)

Spot Proteinuria Measurements

<table>
<thead>
<tr>
<th>Albuminuria Level</th>
<th>Urinary AER (mg/24-hour)</th>
<th>Urinary AER (mg/min) (4-hour timed)</th>
<th>Spot Urine Albumin-Creatinine Ratio (mg/g)</th>
</tr>
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<tbody>
<tr>
<td>Normal</td>
<td>&lt;30</td>
<td>&lt;20</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>30 to 300</td>
<td>20 to 200</td>
<td>30 to 300</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>&gt;300</td>
<td>&gt;200</td>
<td>&gt;300</td>
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AER: albumin excretion rate.
Nephropathy: Mechanism of Sclerosis

Ad libitum protein intake  Chronic reduction in renal mass  Diabetes with long-standing hyperglycemia

Chronic Renal Vasodilatation

HTN

\( Q_a \)

\( hP \)

Mesangial cell injury  Albuminuria

Glomerular Hypertubulation

Glomerular Sclerosis

Adaptive Mechanism to Increase GFR in CKD

Glomerulus

\( \Delta P \)

Blood flow

Oncotic pressure

Hydraulic pressure

Basal membrane: Increase porosity and changes in charge selectivity

Afferent Arteriole

Dilation

- Nitric oxide, prostaglandins

- Increased perfusion pressure (HTN)

Efferent Arteriole:

Constriction

(angiotensin II*)

Hydraulic pressure

Bowman space

Blood flow

Screening: What About Martin?

• Screen Him Annually due to HTN, and now DM.
• Obtain Spot UA for Albumin-to-Creatinine Ratio
  – RESULT: 250 mg/g

Albuminuria / Proteinuria

Albuminuria Reflects:

- Endothelial dysfunction (*the endotheliomoter*)
- Glomerular pressures
  • “Nephrologic Hb A1c”

• 50% of patients with microalbuminuria at presentation have established morphologic changes in the kidney.
• 25% to 50% not associated with retinopathy.
• Cardiovascular mortality increased with albuminuria.

Albuminuria Correlates Linearly With Cardiovascular Risk

Diabetic Nephropathy

Histological Findings: Martin's Kidneys

Graphic 1: Normal Glomerular Architecture

Graphic 2: Diffuse and Nodular Sclerosis
Estimating GFR

- 24-hour urine collection for creatinine clearance
  - Often overestimates GFR due to filtration and secretion of creatinine
- Cockcroft-Gault equation
  - Good estimate, but can overestimate by up to 16%
- The MDRD formula
  - Uses serum creatinine, age, sex, and race for abbreviated
  - Plus BUN, albumin, body surface area (BSA) for extended

GFR (mL/min/1.73 m²) = 175 x (Scr -1.154) x (Age) -0.203 x (0.742 if female) x (1.212 if Black)


Screening: What About Martin?

- Screen Him Annually due to HTN, and now DM
- Determine GFR using established formula (MDRD, CKD-EPI)
  - RESULT:
    - Serum Creatinine = 1.37 mg/dL
    - GFR = 64 mL/min/1.73m² (CKD-Epi)

Staging CKD Based on GFR

- Stage 1:
  - Markers of Renal damage; GFR greater than 90 mL/min/1.73 m²
- Stage 2: GFR 60 to 89 mL/min/1.73 m² ★
  - Stage 2: Expect mild complications
- Stage 3: GFR 30 to 59 mL/min/1.73 m²
  - Stage 3: Expect moderate complications
- Stage 4: GFR 15 to 29 mL/min/1.73 m²
  - Stage 4: Expect severe complications, increased CV Disease
- Stage 5: ESRD, GFR less than 15 mL/min/1.73 m²
  - Stage 5: Uremia, end-organ cardiovascular disease

Gap Analysis
How are we doing…?

Probability of Testing for Microalbumin 2008-2009 (Medicare Claims Data)

- All Patients: 10%
- Diabetes: 33%
- Hypertension (Without Diabetes): 5%
- Patients With DM + HTN: 38%

Source: US Renal Data System, 2011

Chronic Kidney Disease: Management Overview

- BP control
  - Prioritize ACE inhibitors or Angiotensin-II Receptor Blockers (ARBs)
  - Additional medications and evidence for use
- Cardiovascular risk modification
  - 3-Hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors
    - Direct renal-protective effect?
- Glycemic control
- Dietary modifications (salt, protein, phosphates)
- Anticipate and Assess Potential Complications
  - Anemia, Bone Disease, Electrolyte Disturbances
- Co-Management With Nephrology

Hypertension and Kidney Disease
Principles of Treatment

- CKD is both a cause and consequence of HTN.
- HTN and proteinuria are independent variables that predict long-term decline
- Reduction of BP reduces cardiovascular and renal risk
- Reduction of proteinuria (albuminuria) lowers both cardiovascular and CKD progression risk.
Hypertension Treatment: Angiotensin Modulators (ACE Inhibitor, ARB)

- Treatment with ACE-I or ARB is more effective at reducing decline in renal function
  - Decrease de novo albumin excretion
  - Decrease progression to macroalbuminuria
  - Delayed progression of declining GFR
- Mechanism in addition to BP reduction
  - Decrease intraglomerular pressure
  - Reduce membrane permeability
  - Restore loss of anionic charge selectivity

Hypertension Treatment
Who Should Be on ACE Inhibitors and ARBs?

- Patients with Type 1 Diabetes with microalbuminuria
- Patients with Type 2 Diabetes and HTN or microalbuminuria
- Normotensive (BP less than 130/80 mm Hg) patients with type 2 diabetes? Maybe…
  - UKPDS, ABCD trial, Bergamo Nephrologic Diabetes Complications Trial (BENEDICT)
  - But…Evidence remains limited in normotensive patients.

- Stable Average BP: 139/85
- Meds:
  - Amlodipine 10 mg QD
  - HCTZ 25 mg QD
  - Metoprolol 25 mg BID
- What Do We Change Now?
  - Goal BP <130/80 (CKD as well as DM)
  - Add ACE-I or ARB
    - Creatinine before ACE-I = 1.37 mg/dL
    - Creatinine 4 weeks later = 1.55 mg/dL. Now what?

Serum Creatinine With ACE-I or ARB (Remember the Physiology)
Angiotensin Agents in CKD

• Strive toward maintaining ACE inhibitor/ARB therapy
  – Increasing serum creatinine
    • A serum creatinine increase of up to 30% is acceptable.
    • Greater than 30% increase or continued increase on further monitoring should prompt caution.
  – Hyperkalemia
    • Institute low-potassium diet (written instructions).
    • Institute loop diuretic.
    • **Avoid nonsteroidal anti-inflammatory drugs (NSAIDs), salt substitutes, potassium supplements, etc.
    • Consider low-dose sodium polystyrene sulfonate (Kayexalate) (5 g with meals 2 to 3 times/week)—how brave are you? If needed, this should be done in co-management with Nephrology.

Hypertension Treatment Beyond Angiotensin

• ACE-Inhibitor or ARB first-line
• Thiazide Diuretics (good evidence)
• GFR below 30—need loop diuretic
• Calcium Channel Blockers
  • Nondihydropyridine (good evidence)
  • Dihydropyridine (good evidence with an ACE-I)
• Beta Blockers (especially with CAD and/or CHF)
• Peripheral Dilators
• The rest…the kitchen sink?

Renin-Angiotensin System Blockade

• “Direct Renin Inhibitors” (Aliskiren)
  – Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE) Trial—stopped early due to adverse effects.
    • HeartWire, December 2011
• ACE inhibitor and ARB combinations?
  – Initial hope for Improved renal outcomes, but…
  – ONTARGET: Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial

Management: Glycemic Control

Does Glycemic Control affect diabetic nephropathy?

Glycemic Control

• Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial
  – In glycemic control arm, primary improvement was reduced nephropathy (microvascular outcome).
  – BP arm demonstrated reductions in all cardiovascular morbidity and nephropathy.
• Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial
  – Decreased microvascular outcomes but increased cardiovascular deaths in intensive control group
• “Role of Intensive Glucose Control in Development of Renal End Points in Type 2 Diabetes Mellitus: Systematic Review and Meta-analysis”: Coca, et al., Archives of Internal Medicine, May 2012
Martin’s Glycemic Control

- Target Hb A1c is 7% (fasting glucose 90-150)
- Glipizide and gliclazide (Gliclazide not available in the US) are generally preferred sulfonylureas (short-acting preferred to long)
  - Renal dosing needed for most sulfonylureas and insulin
- Repaglinide (“glinides”) does not require renal dosing
- Metformin can be used in stable Stage 1/2/3 CKD

CKD Predicts Cardiovascular Disease

- Smoking Cessation
- Lipid Management
  - LDL goal <100 with consideration of <70
- Blood Pressure Management
  - Goal BP <130/80
- Aspirin 81 mg daily
- Exercise
- Weight Loss

Statin Therapy in Cardiovascular Risk Modification

- Most studies show reduced CV events with statin therapy in Stage 2 and Stage 3 CKD
  - Treating to New Targets (TNT) study
  - Baseline GFR = 65 mL/min/1.73 m² (Stage 2)
- Statin therapy improved renal function over 60 months.
  - Both groups with improvement, but higher dose greater than lower dose
- Study of Heart and Renal Protection (SHARP)
  - Simvastatin + Ezetimibe
  - Improved CVD outcomes in CKD and ESRD (GFR = 26)
  - Improved Renal Outcomes as well in CKD
  - Lancet 2011

Dietary Modification

- Salt restriction to <2.5 g/day
  - Better BP control, less fluid retention
- Protein intake of 0.8 g/kg/day
  - Average American diet contains greater than 1.7 g/kg/day (estimate).
  - Adherence to restriction is difficult
  - Some danger of wasting syndrome in stage 4/5
- Get nutritionist involved!!
Martin’s CV Risk:
10-year CAD Risk: 21-25%

- Nonsmoker (yes!)
- Cholesterol 220 mg/dL
- LDL = 125 mg/dL / HDL 49 mg/dL
  - Recommend LDL GOAL <100, option <70
  - Discuss/Strongly Consider Statin Therapy
- ECASA 81 mg every day
- 4-5 times per week exercise program
- Strive for BMI <30, goal 20-25
- DASH Diet plan
  - Sodium less than 2.5 g/day
  - Optimize dietary Omega-3-FA

Complications

- **Anemia**
  - Results from decreased erythropoietin, decreased erythrocyte half-life, iron deficiency
  - Goal to maintain Hb 10-12 g/dL
  - Goals: Transferrin Sat 20%-50%, Ferritin 100-800 ng

- **Electrolyte Disturbance**
  - Hyperkalemia
  - Non-Anion Gap Acidosis
    - Oral Sodium Bicarbonate
    - Hyperphosphatemia (goal in CKD=2.7-4.6 mg/dL)

Complications

- **Bone Disease/Altered Mineral Metabolism**
  - Monitor markers
    - Calcium
    - Phosphorous
    - Intact PTH (iPTH): 70-110

- **Vitamin D Deficiency**

Nephrology Referral

- Consider referral for co-management:
  - Progression of CKD (GFR <30 mL/min/1.73 m²)
  - Rapid deterioration in renal function
  - Unexplained proteinuria >1,000 to 1,500 g/24 hours
  - Unable to control HTN
- Evidence demonstrates that referral and co-management improves morbidity and decreases mortality.
- Facilitates early and more stable vascular access.

Summary

- Identify patients at risk … screen them!
- Be aggressive with BP control.
- Be comfortable with ACE inhibitor and ARB use.
- Emphasize good glycemic control in DM
- Be aggressive with cardiovascular risk modification.
- Anticipate the complications
- Be ready to refer…but do so at the right time.
- Be a teacher; be an advocate.
- Go forth and conquer!
References


References