Lipid Management in the CKD Patient:

A Patient-Centered Approach to Care

Speakers Name and Title
Disclosures

All conflicts of interest have been resolved according to the NJAFP Conflict of Interest Policy
This program has been made possible through an unrestricted educational grant from Merck & Co.
Overview

• Incidence of CKD is increasing
• CVD is very common in patients with CKD and CKD patients often have major lipid abnormalities
• Many clinicians, however, are reluctant to treat CKD patients aggressively

This program will review:
• Staging and epidemiology of CKD
• Epidemiology of CVD in the CKD population
• Characteristics of dyslipidemia found in CKD patients
• Evidence concerning treatment of dyslipidemia
• Results of the SHARP clinical trial

Learning Objectives

At the conclusion of this program the learner should be able to:

1. Review the role of GFR and urine albumin in screening for CKD
2. Discuss risk factors that contribute to CKD
3. Explain the pathophysiology of dyslipidemia in CKD
4. Discuss the importance of LDL reduction in patients with CKD
5. Discuss the pharmacologic and non-pharmacologic options for treating dyslipidemia in patients with CKD
6. Employ a patient-centered approach in treating patients with dyslipidemia in CKD
Pop Quiz

Q: What is the leading cause of death for patients with CKD?

a. Renal failure
b. Cardiovascular disease
c. Infection
d. Cerebrovascular disease
Pop Quiz

Answer: Cardiovascular Disease

Definition of Chronic Kidney Disease

Either present for at least 3 months:

- GFR <60 mL/min/1.73m²
- Evidence of structural kidney damage, e.g. microalbuminuria/proteinuria, polycystic kidney disease, etc.

Epidemiology of Chronic Kidney Disease

Prevalence of CKD is rising:
• 16.8% of US population aged 20 and older (NHANES 2004) up from 14.5% (1988-1994)

Most CKD is stages 1-3
• 97.6% of those with CKD are in stages 1-3, with 2.3% in stages 4-5.

Prevalence rises with age:
• 20 – 39 yrs. = 8.5%
• 40-59 yrs. = 12.6%
• ≥60 yrs. = 39.4%

No significant gender difference

Epidemiology of Chronic Kidney Disease

Modest racial differences:
• White = 16.1%
• Black = 19.9%
• Mexican-American = 18.7%

Prevalence strongly correlated with diabetes, CVD, and hypertension:
• Diabetes: 40.2%
• CVD: 28.2%
• Hypertension: 24.6%

Modest correlation with obesity: 19.8%

Case Study

Mr. Clark: 53-year-old African-American male
PMH: type-2 diabetes, “borderline” hypertension, hypercholesterolemia
No medications
Social history: non-smoker, moderate alcohol, sedentary, sales job with extensive travel
Family history: maternal hypertension, paternal hypertension, DM2 ESRD/HD.
Temperature: 98.1
Pulse: 85
BP: 146/88
BMI: 32
Exam: WNL

What tests would you order?
Case Study

Lab tests ordered (fasting):

• CBC
• BMP
• AST/ALT
• Hgb A1c
• Lipid Profile
• TSH
• Microalbumin
• Baseline EKG
Assessing Kidney Function

- Serum creatinine level alone is an inadequate measure of kidney function/dysfunction

- K/DOQI guidelines recommend:
  - All individuals should be assessed for risk of CKD as part of routine health care
  - GFR should be calculated (either MDRD or CKD-EPI equations)
  - Proteinuria may be assessed with urine dipsticks, but for adults at high risk for CKD, albumin should be measured since this is a more sensitive measure of kidney damage

# Stages of Kidney Disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or elevated GFR (indicated by albuminuria)</td>
<td>≥ 90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mild GFR reduction</td>
<td>60-89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate reduction in GFR</td>
<td>30-59</td>
</tr>
<tr>
<td>4</td>
<td>Severe reduction in GFR</td>
<td>15-29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure (ESRD)</td>
<td>&lt; 15 or dialysis</td>
</tr>
</tbody>
</table>

Risk Factors for Chronic Kidney Disease

• Diabetes
• Hypertension
• Age 60 years or older
• Racial or ethnic minorities
• Exposure to known nephrotoxins
• Low income or education level
• Autoimmune disease
• Systemic infection
• Urinary tract infections
• Nephrolithiasis
• Neoplasia
• Family history of kidney disease
• Recovery from acute kidney injury
• Reduction in kidney mass
• Low birth weight

Lipid Abnormalities Associated with CKD

Dyslipidemia associated with decreased GFR includes:

• Profound dysregulation of lipoprotein metabolism
• Development in early stages of CKD
• ↓ HDL
• ↑ Triglyceride-rich lipoproteins
• Significant atherogenic potential

Lipid Abnormalities Associated with CKD

But in CKD a different cardiovascular pathology also emerges:

- Vascular stiffness
- Vascular calcification
- Structural heart disease
- Sympathetic overactivity

Case Study

Mr. Clark’s lab results come back with the following values:
Cr: 2.0 mg/dL
GFR: 47.9 mL/min/1.73m²
Glu: 257 mg/dL
A1_c: 9.7%
Urine albumin: 123 mg/g
Total cholesterol: 203 mg/dL
LDL: 134 mg/dL
TG: 190 mg/dL
HDL: 31 mg/dL

What is your assessment of Mr. Clark’s medical problems?
Case Study

Mr. Clark’s Medical Problems:
- Stage 3 CKD
- Uncontrolled DM
- Uncontrolled HTN
- Multiple risk factors for CVD

Prescription:
- Therapeutic lifestyle changes
- ACE or ARB for hypertension
- Tx diabetes, avoiding metformin
- Work up etiology of CKD: rule out SLE, HIV, syphilis, hepatitis, multiple myleoma
- After hypertension and diabetes are nominally controlled, initiate statin with target LDL of less than 100
Statins clearly lower the risk of major coronary events in the non-CKD population.

Statins For CKD Lipid Management

Question: Are statins effective for CKD patients and, in particular, patients with more severe (non-atherogenic) CVD?

First attempts to answer involved sub-group analysis and meta-analysis of previous statin trials. Results were difficult to interpret:
• Some evidence for reduction of CV events, regardless of CKD stage, but no reduction in mortality
• Some data suggested benefit of statins only for CKD patients with pre-existing CVD

SHARP trial designed to clarify these data

Methods:

• Randomized, double-blind
• N = 9270 (3023 on dialysis and 6247 not)
• Patients assigned to simvastatin 20 mg plus ezetimibe 10 mg daily versus matching placebo.
• Primary endpoint: non-fatal MI, coronary death, non-hemorrhagic stroke, or any arterial revascularization procedure
SHARP Trial

Results:

SHARP Trial

• No increase in risk of myopathy, liver and biliary disorders, cancer, or non-vascular mortality

• No substantial effect on kidney disease progression

• Similar proportional reductions in all subgroups (including among dialysis and non-dialysis patients)

Guidelines For Lipid Management in CKD Patients

SHARP affirms existing NKF-K/DOQI guidelines for the management of lipids in patients with CKD

1. All adults and teens with CKD should be evaluated for dyslipidemia

2. Assessment should include a complete fasting lipid profile with total cholesterol, LDL, HDL, and triglycerides

Guidelines For Lipid Management in CKD Patients

3. CKD patients with dyslipidemia should be evaluated for remediable, secondary causes
   - Uncontrolled DM
   - Nephrotic-range proteinuria
   - Uncontrolled hypothyroidism

4. Initiate therapeutic lifestyle changes in all patients with lifestyle-related risk factors regardless of lipid levels:
   - Modify diet to reduce cholesterol and saturated fats
   - Increase fiber intake
   - Weight reduction
   - Increase physical activity

Guidelines For Lipid Management in CKD Patients

5. Dyslipidemia treatment varies according to lipid levels

Table 25. The Management of Dyslipidemias in Adults with Chronic Kidney Disease.

<table>
<thead>
<tr>
<th>Dyslipidemia</th>
<th>Goal</th>
<th>Initiate</th>
<th>Increase</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG ≥500 mg/dL</td>
<td>TG &lt;500 mg/dL</td>
<td>TLC</td>
<td>TLC + Fibrate or Niacin</td>
<td>Fibrate or Niacin</td>
</tr>
<tr>
<td>LDL 100-129 mg/dL</td>
<td>LDL &lt;100 mg/dL</td>
<td>TLC</td>
<td>TLC + low dose Statin</td>
<td>Bile acid seq. or Niacin</td>
</tr>
<tr>
<td>LDL ≥130 mg/dL</td>
<td>LDL &lt;100 mg/dL</td>
<td>TLC + low dose Statin</td>
<td>TLC + max. dose Statin</td>
<td>Bile acid seq. or Niacin</td>
</tr>
<tr>
<td>TG ≥200 mg/dL and non-HDL ≥130 mg/dL</td>
<td>Non-HDL &lt;130 mg/dL</td>
<td>TLC + low dose Statin</td>
<td>TLC + max. dose Statin</td>
<td>Fibrate or Niacin</td>
</tr>
</tbody>
</table>
NCEP suggests more intensive statin therapy:

- Treat according to global CVD risk level, not just lipid values
- Achieve at least a 30% to 40% reduction in LDL-C
- May need combination therapy to achieve goals

Statin Dosing

Daily doses of currently-available statins required for a 30% - 40% LDL-C reduction

• 40 mg lovastatin
• 40 mg pravastatin
• 40-80 mg fluvastatin
• 20-40 mg simvastatin
• 10 mg atorvastatin
• 5-10 mg rosuvastatin

Note: dose adjustments for renal function are not required because statins are hepatically metabolized

Clinical Practice Tips Related to Statins

• Statins are relatively safe
• Baseline creatine phosphokinase level
• Re-check lipids 6 – 12 weeks from initiation
• Once target LDL is achieved, test annually
• Be aware of potential polypharmacy hazards
• Consider different statin or “holiday” period for myalgias without CPK elevation
• Side effects vary—don’t give up on statins at first sign of side effects!

Expert Panel Meeting June 6, 2011, Nashville TN.
Other Pharmacotherapeutic Options

Ezetimibe
- Used safely with simvastatin in CKD (SHARP trial)

Fibrates
- Consider for CKD patients if TG levels are persistently above 500 mg/dL

Niacin
- Recent NHLBI trial stopped early because no benefit was seen when added to atorvastatin; small increased risk of ischemic stroke in the high-dose niacin arm

Fish oil
- No trial data showing improved outcomes, but may have other benefits

Expert Panel Meeting June 6, 2011, Nashville TN.
Case Study

Mr. Clark returns in 12 weeks for follow-up tests, which reveal the following:

GFR: 46.2 mL/min/1.73m²
Glu: 195 mg/dL
Urine albumin: 125 mg/g
Total cholesterol: 186 mg/dL
LDL: 119 mg/dL
TG: 185 mg/dL
HDL: 30 mg/dL

How would you proceed?
Case Study

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Upon questioning, Mr. Clark admits he has not been taking the statin regularly because he thinks it is causing muscle soreness and pain—though he also has been trying to exercise more, so the soreness may be unrelated to the statin.
Case Study

Clinical strategy:

• Switch to another statin
• Trial off stain then restart
• Support continuing TLC
Guideline Comparison

The 2 most widely-used guidelines for lipid management differ in some key ways.

<table>
<thead>
<tr>
<th>NKF-K/DOQI Guidelines</th>
<th>Adult Treatment Panel III Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. CKD patients should be considered to be in the highest risk category.</td>
<td>1. CKD patients are not managed differently from other patients.</td>
</tr>
<tr>
<td>2. Evaluation of dyslipidemias should occur at presentation with CKD, after a change status, and annually.</td>
<td>2. Evaluation of dyslipidemias should occur every 5 years.</td>
</tr>
<tr>
<td>3. Drug therapy should be used for LDL 100-129 mg/dL after 3 months of TLC.</td>
<td>3. Drug therapy is considered optional for LDL 100-129 mg/dL.</td>
</tr>
<tr>
<td>4. Initial drug therapy for high LDL should be with a statin.</td>
<td>4. Initial drug therapy for high LDL should be with a statin, bile acid sequestrant, or nicotinic acid.</td>
</tr>
<tr>
<td>5. Recommendations are made for patients &lt;20 years old.</td>
<td>5. No recommendations are made for patients &lt;20 years old.</td>
</tr>
<tr>
<td>6. Fibrates may be used in Stage 5 CKD a) for patients with triglycerides ≥500 mg/dL; and b) for patients with triglycerides ≥200 mg/dL with non-HDL cholesterol ≥130 mg/dL, who do not tolerate statins.</td>
<td>6. Fibrates are contraindicated in Stage 5 CKD.</td>
</tr>
<tr>
<td>7. Gemfibrozil may be the fibrate of choice for treatment of high triglycerides in patients with CKD.</td>
<td>7. No preferences are indicated for which a fibrate should be used to treat hypertriglyceridemia.</td>
</tr>
</tbody>
</table>
Patient-Centered Care

Suggestions for improving patient care:

✓ Ask patients about the non-medical aspects of their lives

✓ Provide culturally-specific educational materials written or produced at an appropriate reading level (typically 7th grade)

✓ Explore patient beliefs about their illnesses and possible treatments

✓ Consider adopting the “medical home” model of health care delivery
Providing culturally competent, patient-centered care

• Physicians can improve their own communication skills and “cultural competence”

• Expert Panel suggestion: physicians bring mindful reflection and creativity to every encounter with a patient

• Clinical care should be patient-centered and tailored to each individual within the context of his or her family and community.
Case Study

Mr. Clark returns in 2 months for $A_1_c$ and other labs with the following results:

- BP: 126/70
- GFR: 46.0 mL/min/1.73m$^2$
- Glu: 182 mg/dL
- $A_1_c$: 7.1%
- Urine albumin: 110 mg/g
- Total cholesterol: 173 mg/dL
- LDL: 104 mg/dL
- TG: 173 mg/dL
- HDL: 34 mg/dL

What is your interpretation?
Case Study

Mr. Clark has made significant progress.
• HTN: controlled
• DM Type 2: markedly improved
• Dyslipidemia: His LDL is nearly at goal, HDL and TG not yet optimal
• Stage 3 CKD: stable

Thoughts/Plans:
• Although TG and HDL are not optimal, neither a fibrate nor niacin is indicated
• TLC and/or titration of statin to achieve LDL goal
• Blood sugar levels are better, but consider additional TLC and/or combination therapy to lower A1c further
• Continue patient-centered approach, supporting TLC with referrals as needed
• Schedule follow-up visit in 3-6 mo.
Conclusions

• Roughly 1 of every 6 US adults has CKD

• Bulk of CKD is in stages 1-3

• Hypertension & diabetes major contributing risk factors

• CV disease accounts for roughly half of CKD mortality

• Family physicians can address this problem

• Assessment must include eGFR and tests for proteinuria—preferably urine albumin
Conclusions

• Focus on lowering LDL with TLC and statin or statin combination therapy

• SHARP demonstrated 17% reduction in CV events in CKD population

• More intense lipid management in CKD patients has the potential to significantly reduce CV morbidity
Discussion