Approach to dyslipidemia in Chronic Renal Insufficiency

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Outline

- Does dyslipidemia in renal impairment increase CVD risk?
- Evaluation & monitoring of lipid profile in patients with chronic renal insufficiency
- Dyslipidemia in:
  - Chronic kidney disease (CKD) in adults
  - Dialysis
  - Nephrotic syndrome
  - Kidney transplantation
  - Pediatric population with chronic renal insufficiency
Does dyslipidemia in renal impairment increase CVD risk?

It is well known that dyslipidemia may be the most important risk factor for the development of cardiovascular disease (CVD) in the general population.

On the other hand, the role of dyslipidemia in the pathophysiology of atherosclerotic disease in patients with impaired renal function remains controversial.

Some studies suggested an inverse relationship between serum cholesterol values and mortality in ESRD individuals, a phenomenon also known as “reverse epidemiology”.


Lipid profile in patients with chronic renal insufficiency

<table>
<thead>
<tr>
<th></th>
<th>CKD</th>
<th>Nephrotic syndrome</th>
<th>Hemodialysis</th>
<th>Peritoneal dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>↔</td>
<td>↑↑</td>
<td>↓, ↔</td>
<td>↔, ↑</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>↔</td>
<td>↑↑</td>
<td>↓, ↔</td>
<td>↔, ↑</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>↑</td>
<td>↑↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>↑</td>
<td>↑↑</td>
<td>↑</td>
<td>↑↑</td>
</tr>
</tbody>
</table>

Normal (↔), increased (↑), markedly increased (↑↑), and decreased (↓) plasma levels compared with non-uremic individuals. LDL: low density lipoproteins; HDL: high density lipoproteins; Lp(a): lipoprotein (a); CKD: chronic kidney disease.

Lipid profile evaluation & monitoring

In adults with newly identified CKD (including chronic dialysis or kidney transplantation)

Baseline evaluation with a complete lipid profile. (1C)

In adults with CKD (including those treated with chronic dialysis)

Follow-up measurement is not required for the majority of patients. (Not Graded)


AHA 2013 Four Statin Benefit Groups

ASCVD

LDL-C ≥190 mg/dL

DM 40-75 years & LDL 70-189 mg/dL (without ASCVD)

40 to 75 years, LDL-C 70-189 mg/dL and an estimated 10-year ASCVD risk of ≥7.5% (without ASCVD or diabetes)

What about dyslipidemia in patients with CKD??!!

Pharmacological cholesterol-lowering treatment in adults with CKD

<table>
<thead>
<tr>
<th>In adults aged ≥ 50 years with</th>
<th>In adults aged 18–49 years with CKD</th>
</tr>
</thead>
</table>
| • eGFR < 60 ml/min/1.73 m²  
  • we recommend treatment with a statin or statin/ezetimibe combination. (1A)  
• CKD and eGFR ≥ 60 ml/min/1.73 m²  
  • we recommend treatment with a statin. (1B) | • Statin treatment in people with one or more of the following (2A):  
  • Known coronary disease (myocardial infarction or coronary revascularization)  
  • Diabetes mellitus  
  • Prior ischemic stroke  
  • Estimated 10-year incidence of coronary death or non-fatal myocardial infarction > 10% |

Dyslipidemia management in adults with CKD

KDIGO recommends against “treat-to target” strategy because it has never been proven beneficial in any clinical trial. In addition, higher doses of statins have not been proven to be safe in the setting of CKD.

KDIGO recommends a “fire-and-forget” strategy. Physicians may choose to perform follow-up in patients whom are judged to favorably influence adherence to treatment or other processes of care.


Recommended doses (mg/d) of statins in adults with CKD

<table>
<thead>
<tr>
<th>Statin</th>
<th>eGFR &lt; 60, including patients on dialysis or with a kidney transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td>nd</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>80</td>
</tr>
<tr>
<td><strong>Atorvastatin</strong></td>
<td><strong>20</strong></td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>10</td>
</tr>
<tr>
<td>Simvastatin/Ezetmibe</td>
<td>20/10</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>40</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>40</td>
</tr>
</tbody>
</table>

Rosuvastatin 40 mg daily is not recommended for use in CKD 1-2 non-transplant patients, nd, not done or not studied.

Triglyceride-lowering treatment in adults with CKD

**Fibrates not to be used concomitantly with statins** in patients with CKD due to increased risk of adverse events.

**Fibric acid derivatives** could be considered if serum TG (> 1000 mg/dl). If such therapy is prescribed, fibric acid derivatives must be **dose-adjusted for kidney function**.

- **Fenofibrate**
  - Contraindicated if GFR < 20 ml/min
- **Gemfibrozil**
  - GFR 10 to 50 mL/min: Administer 75% of dose,
  - GFR < 10 mL/min: Administer 50% of dose

**Nicotinic acid** has not been well studied in advanced CKD and **not recommended**, given the risk of toxicity (especially flushing and hyperglycemia).

- www.lexi.com accessed 12/2/2017

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2016 ESC/EAS Guidelines for the Management of Dyslipidemias

**For cardiovascular risk estimation**

- **Categorize kidney disease patient** as high risk or very high risk. (IC)

**Very high risk**

- Severe CKD with GFR < 30 ml/min

**High risk**

- Moderate CKD with GFR 30-60 ml/min

Still what about dyslipidemia in CKD patients on regular dialysis??

Pharmacological cholesterol-lowering treatment in dialysis

In adults with dialysis-dependent CKD:

Statins or statin/ezetimibe combination not to be initiated. (2A)

In patients already receiving statins or statin/ezetimibe combination at the time of dialysis initiation, these agents to be continued. (2C)

The 4D Study (RCT on the Efficacy and Safety of Atorvastatin in Patients with Type 2 Diabetes on Hemodialysis)

The 4D, a multicenter, double blind, randomized trial.

- **Atorvastatin reduced the median LDL-C level by 42%, and placebo by 1.3%.**

Atorvastatin 20 mg

Placebo

1255 HD patients with type 2 diabetes

median follow-up of 4 years

No significant difference in the primary endpoint (a composite of cardiac death, nonfatal MI, and fatal and nonfatal stroke (RR 0.92; 95% CI 0.77–1.10; P = 0.37) or total mortality (RR 0.93; 95% CI 0.79–1.08; P = 0.33).


AURORA Study (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Dialysis: an Assessment of Survival and Cardiovascular Events)

International double-blind randomized trial.

- Mean reduction in LDL-C of 43% in the intervention group.

2776 HD patients

- Rosuvastatin 10mg daily

- Placebo

median follow-up of 3.8 years

Combined primary endpoint of death from cardiovascular causes, nonfatal MI, or nonfatal stroke was not reduced (HR 0.96; 95% CI 0.84–1.11; P = 0.59) nor of all-cause mortality (HR 0.96; 95% CI 0.86- 1.07; P = 0.51).

SHARP (Study of Heart and Renal Protection)

International double-blind randomized trial

- Mean reduction in LDL-C among the treatment group was 32 mg/dl
- 9270 participants ≥ 40 years old with CKD with 3023 HD
- Simvastatin 20mg plus ezetimibe 10 mg daily
- Placebo
- Median follow-up of 4.9 years

Combination treatment did not significantly reduce the risk of the primary outcome of major atherosclerotic events in the subgroup of HD patients (RR 0.90, 95% CI, 0.75-1.08), nor all cause mortality (RR, 1.01, 95% CI, 0.94-1.11)

Dialyzability & doses of lipid lowering agents on regular hemodialysis

<table>
<thead>
<tr>
<th>Non-dialyzable</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>Use with caution; these patients are predisposed to myopathy.</td>
</tr>
<tr>
<td>Fluvastatin (unlikely)</td>
<td>Use with caution, doses &gt;40 mg/day (has not been studied).</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>Use with caution, Initial: 10 mg once daily</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Initial: 5 mg once daily (maximum: 10 mg/day).</td>
</tr>
<tr>
<td>Simvastatin (unlikely)</td>
<td>5–20 mg daily, doses &gt; 10 mg should be used with caution (doses up to 40 mg have been used)</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>Use with caution; may cause hyperchloremic acidosis.</td>
</tr>
<tr>
<td>Colestipol</td>
<td>Dosage adjustment is unlikely because not absorbed from the gastrointestinal tract.</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>Use is contraindicated.</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>Initially 900 mg daily. Monitor carefully</td>
</tr>
<tr>
<td>Ezetimibe (unlikely)</td>
<td>Dose as in normal renal function</td>
</tr>
</tbody>
</table>

Dyslipidemia in Nephrotic syndrome

Before nephrotic syndrome episode

After nephrotic syndrome episode

Cholesterol lowering therapy in nephrotic syndrome

For the initial episode of nephrotic syndrome associated with MCD, statins not be used to treat hyperlipidemia. (2D)

Statins are well tolerated and effective in correcting the lipid profile, although not proven to reduce cardiovascular events in nephrotic syndrome.

It may also be that statin therapy protects from a decline in GFR, although this is not established.

Dyslipidemia in Kidney transplantation

Does dyslipidemia in kidney transplantation increase CVD risk?

Prevalence of dyslipidemia during the first year after transplantation is > 50%, although greatly influenced by the type of immunosuppression used and the presence of other factors, such as proteinuria, acute rejection and graft dysfunction.

In KTRs, there is moderate evidence that dyslipidemias contribute to CVD and that treatment of increased LDL-C with a statin may reduce CVD events.

Effect of immunosuppressive drugs on lipid parameters

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total cholesterol</th>
<th>LDL cholesterol</th>
<th>HDL cholesterol</th>
<th>Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↓</td>
<td>↑↑</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↓</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Everolimus</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↓</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Prednisone</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

Normal (↔), increased (↑), markedly increased (↑↑), and decreased (↓) plasma levels. LDL: low density lipoproteins; HDL: high density lipoproteins.


Screening & goals of therapy

Measure a complete lipid profile in KTRs:

- 2–3 months after transplantation
- after change in treatment
- other conditions known to cause dyslipidemias
- at least annually, thereafter.

Treatment targets:

- **Adults:**
  - LDL <100 mg/dL & non-HDL <130 mg/dL.
- **Adolescents:**
  - LDL <130 mg/dL & non-HDL <160 mg/dL

Pharmacological cholesterol-lowering treatment in Kidney transplant recipients

**KDIGO guidelines for Lipid Management in CKD 2013:**
- In adult kidney transplant recipients, we suggest treatment with a statin. (2B)

**ESC and EAS guidelines for dyslipidemias 2016:**
- In adult kidney transplant recipients treatment with statins may be considered. (IIb- C)

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**Patient Management**

- Concurrent use increases risk for atorvastatin-related toxicities such as **myopathy** and **rhabdomyolysis**.
- Consider changing to a statin that is less sensitive to this interaction (e.g., **pravastatin** or **fluvastatin**) or to an alternative type of LDL-lowering medication.

www.lexi.com last accessed 10/2/2017
Cyclosporine may increase the serum concentration of Fluvastatin or Pravastatin. Severity: Major, Reliability Rating: Good

- Limit Fluvastatin to 20 mg twice daily or Pravastatin to 20 mg/day in patients who are also receiving cyclosporine.
- Monitor for toxic effects (e.g., myalgia, myopathy, rhabdomyolysis).

Dyslipidemia Pediatric population with chronic renal insufficiency
Does dyslipidemia in pediatrics with CKD increase CVD?

Young adults with eGFR < 15 ml/min/1.73m² have at least 10-folds higher risk for CVD mortality compared to the general population.

Few studies demonstrate the association of dyslipidemia with clinical CVD events in adolescents or young adults, especially in the setting of CKD.

Levels of total cholesterol < 170 mg/dL, LDL-C < 110 mg/dL considered acceptable.


Assessment of lipid status in children with CKD

In children with newly identified CKD (including chronic dialysis or kidney transplantation)

- Baseline evaluation with a complete lipid profile. (1C)

In children with CKD (including chronic dialysis or kidney transplantation)

- Annual follow-up measurement of fasting lipid levels. (Not Graded)
- Unlike adults, growth and development in children have potential to influence lipid levels over time. Therefore, the fasting lipid levels be followed in children with CKD to screen for underlying secondary causes of dyslipidemia.

Medications for dyslipidemia in pediatrics

<table>
<thead>
<tr>
<th>Medication</th>
<th>Starting age</th>
<th>General population dose</th>
<th>Renal impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>10 years</td>
<td>10 mg - <strong>20 mg once daily</strong></td>
<td>Use with caution</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>9 years</td>
<td>20-80 mg daily (40mg twice daily)</td>
<td>Use with caution, doses &gt;40 mg/day (has not been studied).</td>
</tr>
<tr>
<td>Pravastatin sodium</td>
<td>8 years</td>
<td>10mg - max. 40mg once daily at night</td>
<td>Use with caution</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>7 years</td>
<td>5 to max. <strong>20 mg once daily</strong></td>
<td>CrCl &lt;30 mL/min: Initial: 5 mg once daily; <strong>maximum: 10 mg/day</strong></td>
</tr>
<tr>
<td>Simvastatin</td>
<td>5 years</td>
<td>10 to max. 40mg at night</td>
<td>eGFR &lt; 30 mL/min : initial 5 mg, doses &gt; 10mg daily used with caution</td>
</tr>
<tr>
<td>Colestyramine</td>
<td>6 years</td>
<td>4g - max. 8 g daily (1-4 doses)</td>
<td>Use with caution in renal impairment; may cause hyperchloremic acidosis.</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>4 years</td>
<td>1 capsule/20 kg body-weight (max. 4 capsules or max. 3 capsules with statin) daily</td>
<td>Reduce dose if eGFR &lt; 60 mL/min; <strong>avoid if eGFR &lt; 20 mL/min</strong></td>
</tr>
</tbody>
</table>


Statins used in pediatric studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Statin dose</th>
<th>Population</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coleman , JE et al. 1996</td>
<td><strong>Simvastatin 5 - 40 mg/day</strong></td>
<td>children, <strong>1.8–16.3 years</strong> of age, who had dyslipidemia 2ry to nephrotic syndrome</td>
<td>There was a significant <strong>reduction in TC &amp; TG</strong> but <strong>two children suffered from transient elevation of CPK</strong></td>
</tr>
<tr>
<td>Sanjad ,SA et al. 1997</td>
<td><strong>Lovastatin maximum of 40 mg / day</strong></td>
<td>children, <strong>8 months to 15 years</strong> of age, with nephrotic syndrome</td>
<td>There was a significant reduction in TC, LDL-C &amp; TG (p&lt;0.004). No change in HDL-C.</td>
</tr>
<tr>
<td>Song, M. et al. 2013</td>
<td><strong>Fluvastatin (5 mg/d if aged &lt;5 years; 10 mg/d if aged ≥5 years)</strong></td>
<td>Pediatric patients (<strong>4–12 years of age</strong>) with minimal change nephropathy</td>
<td>TG, TC, and Upr were significantly decreased (all, P &lt; 0.01)</td>
</tr>
</tbody>
</table>
Take home messages

Role of dyslipidemia in the development of atherosclerotic disease in patients with **impaired renal function** remains controversial & it may have inverse relationship in dialysis patients.

In **KTRs & pediatrics** there is evidence that dyslipidemias contribute to **CVD** and that treatment of increased LDL-C with a **statin** may reduce CVD events.

In patients with **nephrotic syndrome** statins may protect from a decline in **GFR**, but not proven to reduce **CV** events.

Use statins with lower doses than general population and monitor for adverse effects while considering significant drug-drug interactions.

**Safety** and **effectiveness** of lipid lowering therapy in patients with different categories of renal impairment **require more research**.

Thank you!

QUESTIONS?