RISK MANAGEMENT AND CLINICAL ASSESSMENT OF THE PATIENT WITH CKD AND NEPHROTIC SYNDROME

EDGAR V. LERMA, MD, FACP, FNLA
CLINICAL PROFESSOR OF MEDICINE
UNIVERSITY OF ILLINOIS AT CHICAGO/ ADVOCATE CHRIST MEDICAL CENTER
OAK LAWN, ILLINOIS
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ABNORMAL LIPID METABOLISM IS COMMON in patients with kidney disease.

CKD causes a profound dysregulation of lipoprotein metabolism, resulting in MULTIPLE LIPOPROTEIN ABNORMALITIES.
ABNORMAL LIPID METABOLISM IS COMMON in patients with kidney disease

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- Dyslipidemia occurs during the **EARLY STAGES OF CKD**, and **significant changes in apolipoproteins usually PRECEDE** **CHANGES IN LIPID LEVELS**

- The **MAJOR LIPID ABNORMALITIES IN CKD ARE:**
  - ↓ HDL levels
  - ↑ TG-rich lipoproteins
ABNORMAL LIPID METABOLISM IS COMMON in patients with kidney disease

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  - ↓ HDL levels
  - ↑ TG-rich lipoproteins

**MIXED DYSLIPIDEMIA**

**Table 3**

<table>
<thead>
<tr>
<th>Protein</th>
<th>Change</th>
<th>Effect on Plasma Lipids or LP</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoA-I</td>
<td>↓</td>
<td>↓ HDL</td>
</tr>
<tr>
<td>LCAT</td>
<td>↓</td>
<td>↓ HDL-C, HDL-2/ HDL-3</td>
</tr>
<tr>
<td>CETP</td>
<td>↑</td>
<td>↑ HDL-C</td>
</tr>
<tr>
<td>ACAT</td>
<td>↑</td>
<td>↑ VLDL-C, ↓ HDL-C</td>
</tr>
<tr>
<td>LPL</td>
<td>↑</td>
<td>↑ Trig (↑ delipidation of VLDL and CM)</td>
</tr>
<tr>
<td>VLDL receptor</td>
<td>↓</td>
<td>↓ VLDL, Trig</td>
</tr>
<tr>
<td>Hepatic lipase</td>
<td>↓</td>
<td>↓ IDL, CM remnants, HDL-TG, Trig, IDL-TG</td>
</tr>
<tr>
<td>LRP</td>
<td>↓</td>
<td>↓ IDL, CM remnants</td>
</tr>
<tr>
<td>ApoCII/CIII ratio</td>
<td>↓</td>
<td>↑ Trig (↑ LPL activity)</td>
</tr>
<tr>
<td>Pre-β HDL</td>
<td>↑</td>
<td>↑ Trig (↑ LPL activity)</td>
</tr>
</tbody>
</table>

Adapted from Vaziri (4).

- ↓ decreases; ↑ increases; ACAT = acyl-CoA (cholesterol acyl) transferase; Apo = apoprotein; CETP = cholesteryl ester transferase protein; CM = chylomicron; DGAT = acyl-CoA diglycerol acyl transferase; HDL = high-density lipoprotein; HDL-C = high-density lipoprotein cholesterol; HDL-TG = high-density lipoprotein triglyceride; IDL = intermediate-density lipoprotein; LCAT = lecithin cholesterol acyl transferase; LDL-TG = low-density lipoprotein triglyceride; LP = lipoproteins; LPL = lipoprotein lipase; LRP = low-density lipoprotein receptor-related protein; Trig = triglyceride; VLDL = very-low-density lipoprotein; VLDL-C = very-low-density lipoprotein cholesterol; VLDL-TG = very-low-density lipoprotein triglyceride.
ABNORMAL LIPID METABOLISM IS COMMON in patients with kidney disease

- ↓ HDL
  - ↓ ApoA-I
  - ↓ ApoA-II
  - Profound inflammation

Profound inflammation leads to hypoalbuminemia

Albumin serves as a carrier of free cholesterol from the peripheral tissues to HDL
ABNORMAL LIPID METABOLISM IS COMMON in patients with kidney disease

- ↓ HDL
  - ↓ ApoA-I
  - ↓ ApoA-II
  - Profound inflammation leads to hypoalbuminemia
- ↑ TG
  - ↑ ApoC-III

Potent inhibitor of lipoprotein lipase (responsible for degradation of TG-rich particles)
ABNORMAL LIPID METABOLISM IS COMMON in patients with kidney disease

- ↓ HDL
  - ↓ ApoA-I
  - ↓ ApoA-II
  - Profound inflammation leads to hypoalbuminemia

- ↑ TG
  - ↑ ApoC-III

- ↑ Lp (a)

---

ABNORMAL LIPID METABOLISM IS COMMON in patients with kidney disease

- ↓ HDL
  - ↓ ApoA-I
  - ↓ ApoA-II
  - Profound inflammation leads to hypoalbuminemia

- ↑ TG
  - ↑ ApoC-III

- ↑ Lp (a)
↑ Lp (a)

NEPHROTIC SYNDROME
Due to ↑ synthesis

DIALYSIS Patients
Due to ↓ catabolism

The risk is associated with both the CONCENTRATION OF Lp (a) as well as SMALL SIZE

CKD patients having an ACQUIRED ↑ IN Lp (a) have ↑ CV RISK
Managing Dyslipidemia in Chronic Kidney Disease

**Table 1. Lipid Abnormalities by Target Population (Approximate Percentage)**

<table>
<thead>
<tr>
<th>Target Population</th>
<th>Total Cholesterol &gt;240 mg/dl</th>
<th>LDL Cholesterol &gt;130 mg/dl</th>
<th>HDL Cholesterol &lt;35 mg/dl</th>
<th>Triglycerides &gt;200 mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population*</td>
<td>20</td>
<td>40</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>CKD Stages 1 to 4</td>
<td>90</td>
<td>85</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td>With nephrotic syndrome¹</td>
<td>30</td>
<td>10</td>
<td>35</td>
<td>40</td>
</tr>
<tr>
<td>Without nephrotic syndrome¹</td>
<td>20</td>
<td>30</td>
<td>50</td>
<td>45</td>
</tr>
<tr>
<td>CKD Stage 5</td>
<td>20</td>
<td>30</td>
<td>50</td>
<td>45</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>25</td>
<td>45</td>
<td>20</td>
<td>50</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>20</td>
<td>30</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

* Reproduced and modified with permission from Kasikis.²⁰
¹ Data from National Health and Nutrition Examination Survey (NHANES III) and the Framingham Offspring Study.⁵⁴,⁵⁵
² CKD, chronic kidney disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

**SERUM LIPID PROFILE IN KIDNEY DISEASE**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Total Cholesterol</th>
<th>LDL</th>
<th>VLDL</th>
<th>HDL</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrotic Syndrome</td>
<td>↑↑↑</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>↑</td>
<td>↑</td>
<td>↑↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Diabetic Nephropathy</td>
<td>↑</td>
<td>↑</td>
<td>↑↑</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>
MARKED HYPERCHOLESTEROLEMIA IS COMMON in patients with NEPHROTIC SYNDROME

Lipoprotein(a)- and low-density lipoprotein-derived cholesterol in nephrotic syndrome: Impact on lipid-lowering therapy?

FLORIAN KRONENBERG, ARNO LINGENHEIL, KARL LHOTTA, BARBARA RANIER, MARTINA F. KRONENBERG, PAUL KÖNG, JOACHIM THIERRY, MICHAEL KOCH, ARNOLD XAVIER ECKARDSTEIN, and HANS DIEPLINGER

Table 2. Mean (±SD) plasma lipids and lipoprotein(a) [Lp(a)] in patients with nephrotic syndrome and healthy controls

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>N = 254</th>
<th>Nephrotic syndrome</th>
<th>N = 207</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol mg/dL</td>
<td>203 ± 42</td>
<td>302 ± 92*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides mg/dL</td>
<td>136 ± 92</td>
<td>251 ± 174*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol mg/dL</td>
<td>440 ± 126</td>
<td>43.7 ± 16.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total/HDL cholesterol ratio</td>
<td>4.9 ± 1.6</td>
<td>8.0 ± 4.3*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol mg/dL</td>
<td>312 ± 37</td>
<td>208 ± 82*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lp(a) mg/dL</td>
<td>20.0 ± 32.8</td>
<td>60.4 ± 85.4*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± SD [25th percentile, median, 75th percentile]</td>
<td>[20.0, 6.4, 18.5]</td>
<td>[9.6, 29.8, 81.1]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lp(a)-derived LDL cholesterol mg/dL</td>
<td>9.0 ± 14.7</td>
<td>27.2 ± 38.6*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lp(a)-corrected LDL cholesterol mg/dL</td>
<td>123 ± 39</td>
<td>181 ± 82*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: NHE, high-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein(a).

*P < 0.001 by t test for comparison between patients and controls.

Figure 1. The nephrotic syndrome tree is shown. The trunk depicts increasing proteinuria, and the branches represent other components that appear when proteinuria crosses the nephrotic-range threshold.
MARKED HYPERCHOLESTEROLEMIA IS COMMON in patients with NEPHROTIC SYNDROME

- 100 patients with NEPHROTIC SYNDROME
  - TC > 200 mgs/dL (5.2 mmol/L): 87%
  - TC 300 mgs/dL (7.8 mmol/L): 53%
  - TC 400 mgs/dL (10.3 mmol/L): 25%

Fig 1. Cardiovascular risk factors in nephrotic patients: total cholesterol levels.


PATHOGENESIS
ABNORMALITIES OF LIPOPROTEIN METABOLISM IN PATIENTS WITH THE NEPHROTIC SYNDROME

Jorge Joven, M.D., Carlos Villabona, M.D., Elisabet Vilella, Ph.D., Luis Masana, M.D., Rosa Albertí, R.N.P., and Martín Vallés, M.D.

↓ Plasma Oncotic Pressure

↑ Hepatic Apo-B gene transcription

HYPERLIPIDEMIC RESPONSE


Roles of Angiopoietins in Kidney Development and Disease

Adrian S. Woolf,* Luigi Gnudi,* and David A. Long*

*Nephro-Urology Unit, UCL Institute of Child Health, and Cardiovascular Division, Guy's Hospital, King's College London, London, United Kingdom

Carmen Avila-Casado
Toronto General Research Institute (TGRI)
ANGIOPOIETIN-LIKE 4 (Angptl4) has been identified as a biomarker for the development of hyperlipidemia in patients with nephrotic syndrome. These patients will likely respond to treatment with a good prognosis.
Angptl4 has been identified as a biomarker for the development of hyperlipidemia in patients with nephrotic syndrome. These patients will likely respond to treatment with a good prognosis. This new insight challenges the traditional idea (i.e., epiphenomenon or as a result of liver compensation to the protein loss) of how nephrotic syndrome develops and will potentially change the form of treatment.

In nephrotic syndrome, the balance shifts significantly to albumin-bound FFA because of retention of albumin with high FFA content. Angptl4 (secreted from the muscle, heart and adipose tissue) inactivates LPL, conversion of TG to FFA, use of TGs. Hypertriglyceridemia.
NEGATIVE FEEDBACK LOOPS in the link between proteinuria, hypoalbuminemia, and hypertriglyceridemia mediated by Angptl4 and FFA


CLINICAL IMPLICATIONS
LIPID NEPHROTOXICITY

MOORHEAD (1982)
- Proteinuria → Hyperlipoproteinemia → Aggravate Glomerular/Tubulointerstitial Disease

MOORHEAD (2009)
- ↑ LDL ↑ TG ↓ HDL → Progressive loss of kidney function
- ↑ Inflammatory Stress ↑ Oxidative Stress ↑ Endothelial dysfunction → RENAL PATHOPHYSIOLOGY

Hyperlipidemia•Hypercholesterolemia
Abnormal Lipoproteins

- ↑Adiponectin, IL-6, TNF-α
- ∫Resistin, MCP-1, PAI-1, I1RAS

Mesangial Cell Proliferation
Lipoprotein Deposition in Glomerulus

vascular endothelial injury

Increased Mesangial Matrix
Macrophage Infiltration

↑TGF-β, PAI-1, TNF-α, IL-6
↑ROS

Atherosclerosis Hypertension

Glomerulosclerosis
Progressive Renal Disease
Lipoprotein glomerulopathy: Significance of lipoprotein and ultrastructural features

TAKAO SATIO, SHINICHI OKAWA, HIROSHI SATO, TOSHINORI SATO, SASAYOSHI ITO, and JUN SASAKI

Department of Blood Purification, and Second and Third Departments of Internal Medicine, Tohoku University School of Medicine, Sendai, and Second Department of Internal Medicine, Fukushima University School of Medicine, Fukushima, Japan.

NORMAL

LPG (Lipoprotein thrombi)

NORMAL

LPG (Osmiophilic substances in dilated subendothelial space)
NEPHROTIC SYNDROME and CVD

- ↑ Risk of CV Disease

- HYPERLIPIDEMIA

EXCEPTION: Children with MCNS who are responsive to CS therapy because hyperlipidemia is intermittent and of short duration.
NEPHROTIC SYNDROME and CVD

- ↑ Risk of CV Disease

HYPERLIPOIDEMIA

- Strongly associated with severity of hypoalbuminemia, and persistent proteinuria or renal insufficiency

- ↑ Risk of PREMATURE Atherosclerosis
NEPHROTIC SYNDROME and CVD

- ↑ Risk of CV Disease

HYPERLIPIDEMIA

- Strongly associated with severity of hypoalbuminemia, and persistent proteinuria or renal insufficiency
- ↑ Risk of PREMATURE ATHEROSCLEROSIS

The DURATION OF NEPHROTIC HYPERLIPIDEMIA appears to be critical to INITIATING VASCULAR DAMAGE, and patients with UNREMITTING PROTEINURIA AND HYPOALBUMINEMIA ARE THE MOST AT RISK
NEPHROTIC SYNDROME and CVD

- ↑ Risk of CV Disease
  - HYPERLIPIDEMIA
  - ↑ Thrombogenesis

- Endothelial dysfunction
TREATMENT OF DYSLIPIDEMIAS IN KIDNEY DISEASE

<table>
<thead>
<tr>
<th></th>
<th>NEPHROTIC SYNDROME</th>
<th>CHRONIC KIDNEY DISEASE</th>
<th>DIABETIC NEPHROPATHY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DIET</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>STATINS</strong></td>
<td>+++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td><strong>FIBRATES</strong></td>
<td>?</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>NIACIN</strong></td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

- Benefit uncertain with ESRD
- Caution in advanced stages due to drug accumulation and muscle toxicity
- May lower risk of CV events and slow progression of nephropathy
**Table 7**  Dosing Modifications for Lipid-Lowering Drugs in CKD

<table>
<thead>
<tr>
<th>Agent</th>
<th>GFR 60-90 ml/min/1.73 m²</th>
<th>GFR 15-59 ml/min/1.73 m²</th>
<th>GFR &lt;15 ml/min/1.73 m²</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>No</td>
<td>Not defined</td>
<td>Not defined</td>
<td>↓ dose to one-half at GFR &lt; 30 ml/min/1.73 m²</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>↓ to 50%</td>
<td>↓ to 50%</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Start at 10 mg/day for GFR &lt; 30 ml/min/1.73 m²</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>No</td>
<td>5-10 mg</td>
<td>5-10 mg</td>
<td>Start at 5 mg/day for GFR &lt; 30 ml/min/1.73 m²; max dose 10 mg/day</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>No</td>
<td>No</td>
<td>5 mg</td>
<td>Start at 5 mg if GFR &lt;10 ml/min/1.73 m²</td>
</tr>
</tbody>
</table>

**Nonstatins**

<table>
<thead>
<tr>
<th>Agent</th>
<th>GFR 60-90 ml/min/1.73 m²</th>
<th>GFR 15-59 ml/min/1.73 m²</th>
<th>GFR &lt;15 ml/min/1.73 m²</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotinic acid</td>
<td>No</td>
<td>No</td>
<td>↓ to 50%</td>
<td>34% kidney excretion</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Not absorbed</td>
</tr>
<tr>
<td>Colesevelam</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Not absorbed</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>↓ to 50%</td>
<td>↓ to 25%</td>
<td>Avoid</td>
<td>May ↑ serum creatinine</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>NLA recommends a dose of 600 mg/day for GFR 15-50 ml/min/1.73 m² and avoiding use for GFR &lt;15 ml/min/1.73 m²</td>
</tr>
<tr>
<td>Omega-3 FAs</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from the K. Dock clinical assistant. GFR = glomerular filtration rate; NLA = National Lipid Association.

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**Table 5**  Clinical Pharmacokinetics of Statins

<table>
<thead>
<tr>
<th></th>
<th>Rosuva</th>
<th>Atorva</th>
<th>Simva</th>
<th>Lova</th>
<th>Prava</th>
<th>Fluva</th>
</tr>
</thead>
<tbody>
<tr>
<td>T 1/2, h</td>
<td>20.8</td>
<td>15-30</td>
<td>2-3</td>
<td>2.9</td>
<td>1.3-2.8</td>
<td>0.5-2.3</td>
</tr>
<tr>
<td>Urinary excretion, %</td>
<td>10</td>
<td>&lt;2</td>
<td>13</td>
<td>10</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>CYP-3A4 metabolism</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>CYP metabolism</td>
<td>2CY9</td>
<td>3A4</td>
<td>3A4</td>
<td>3A4</td>
<td>sulfation</td>
<td>2CY9</td>
</tr>
</tbody>
</table>

Table 1. Recommended Doses of Statins in Adults With Chronic Kidney Disease*

<table>
<thead>
<tr>
<th>Statin</th>
<th>eGFR G1–G2</th>
<th>eGFR G3a–G5, Including Patients Receiving Dialysis or Who Had a Kidney Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td>Any dose approved for GP</td>
<td>ND</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>Any dose approved for GP</td>
<td>80†</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Any dose approved for GP</td>
<td>20‡</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Any dose approved for GP</td>
<td>10§</td>
</tr>
<tr>
<td>Simvastatin/ezetimibe</td>
<td>Any dose approved for GP</td>
<td>20/10</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>Any dose approved for GP</td>
<td>40</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Any dose approved for GP</td>
<td>40</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>Any dose approved for GP</td>
<td>2</td>
</tr>
</tbody>
</table>

cGFR = estimated glomerular filtration rate; GP = general population; ND = not done.

Statin therapy improves brachial artery endothelial function in nephrotic syndrome

Gursharan K. Dogra, Gerald F. Watts, Susan Herrmann, Mark A.B. Thomas, and Ashley B. Irish

Department of Medicine and Western Australian Heart Research Institute, University of Western Australia, and Department of Nephrology, Royal Perth Hospital, Perth, Western Australia, Australia

![Graph showing post-ischemic flow-mediated dilation (FMD) in nephrotic patients pre-statin, following statin therapy and post-statin. The P-value refers to repeated measures ANOVA; horizontal bars represent mean FMD.](image-url)
NON-LIPID EFFECTS OF STATINS

- PLEIOTROPIC EFFECTS
  - Inhibit proliferation of MESANGIAL CELLS (confer protection of kidney from glomerulosclerosis and any renal injury due to inflammation from hypercholesterolemia)
  - Inhibit proliferation of renal epithelial and smooth muscle cells

- ANTI-INFLAMMATORY
  - ↓ glutathione peroxidase ↓ superoxide dismutase

- IMMUNOMODULATION EFFECT: Inhibit production of TNF-α and eNOS

- NEOVASCULARIZATION
  - ↓ Endothelial fibrinolytic potential
  - Improvement of endothelial vasodilatation
  - ↓ Arterial pressure
  - Inhibition of Osteoclastic activities

- 5 small studies that investigated 4 different lipid-lowering drugs
  - Simvastatin
  - Lovastatin
  - Fluvastatin
  - Gemfibrozil
5 small studies that investigated 4 different lipid-lowering drugs
- Simvastatin
- Lovastatin
- Fluvastatin
- Gemfibrozil

203 participants with NEPHROTIC SYNDROME

There is CURRENTLY NOT ENOUGH HIGH-QUALITY EVIDENCE from published studies to determine if lipid-lowering agents are helpful in managing dyslipidemia in NEPHROTIC SYNDROME

MYOPATHY RISK FACTORS

ENDOGENOUS Risk Factors
- Age > 80 years
- Female
- Asian ethnicity
- Low BMI
- Hx of pre-existing muscle/ joint/ tendon pain
- History of CK elevation
- DM
- Family Hx of myopathy ± statin treatment
- Metabolic muscle disease
- Severe renal disease (eGFR ≤ 30 mL/min)
- Acute/ decompensated hepatic disease
- Hypothyroidism
- Genetic polymorphisms of CYP enzyme

EXOGENOUS Risk Factors
- High statin dose
- ETOH abuse
- Illicit drug use
- Anti-psychotic drug use
- Surgery with severe metabolic demands
- Heavy and/or unaccustomed exercise
- DRUG INTERACTIONS: amiodarone,azole antifungals, cyclosporine, fibrates, macrolide antibiotics, nefazodone, nicotinic acid, protease inhibitors, tacrolimus, verapamil, warfarin, Grapefruit in large quantities

Therapy for Statin Intolerance

Dietary and health behavior measures
- Reduced dietary fat/dietary cholesterol
- Replacing saturated fats with mono- and polyunsaturated fats
- Increased physical activity and weight loss

Statin-based strategies
- For patients who discontinue therapy, rechallenge with the same or lower dose of the same statin or an alternative statin
- Intermittent dosing: reduced frequency or alternate-day dosing

Nonstatin alternatives and adjuncts
- Ezetimibe
- Niacin
- Fibrates
- Bile acid sequestrants
- LDL apheresis

Treatments targeting muscle symptom relief
- Coenzyme Q
- Vitamin D or E

USE OF FIBRATES IN CKD

PROS

CONS
**USE OF FIBRATES IN CKD**

**PROS**
- ↓ Risk of CV events in patients with known Coronary Heart Disease (CHD)

**CONS**

**VA HIGH-DENSITY LIPOPROTEIN INTERVENTION TRIAL (VA-HIT)**

- 1046 men with moderate renal dysfunction (CrCl 30-75 mL/min)
- PRIMARY ENDPOINT: ↓ Risk of Coronary Death and Non-fatal MI (18.2 vs 24.3%, HR 0.73, 95% CI 0.56-0.96)
- NO EFFECT ON TOTAL MORTALITY (HR 1.03)
- Associated with significant decline in renal function
- ↑ Risk of Rhabdomyolysis
USE OF FIBRATES IN CKD

PROS
- ↓ Risk of CV events in patients with known Coronary Heart Disease (CHD)

CONS
- NO EFFECT on total mortality
- May worsen renal function
USE OF FIBRATES IN CKD

PROS
- ↓ Risk of CV events in patients with known Coronary Heart Disease (CHD)

CONS
- NO EFFECT on total mortality
- May worsen renal function
- ↑ Risk of MUSCLE INJURY (particularly those on concurrent STATIN therapy)

USE OF FIBRATES IN CKD

- The potential harm associated with addition of FIBRATES to specifically decrease triglycerides, may outweigh any possible reduction in CV RISK.
CETP INHIBITION

- Cholesterylester Transport Protein (CETP) normally transfers cholesterol from HDL to VLDL or LDL
  - Inhibition of this process leads to
    - ↑ HDL
    - ↓ LDL
    - ↓ Lp (a) ~ 40%

HDL (Healthy persons): Inhibited production of inflammatory cytokines by peripheral monocytes

HDL (Hemodialysis patients): Did not show this anti-inflammatory property; many HDL samples even promoted the production of inflammatory cytokines
**HDL in Children with CKD Promotes Endothelial Dysfunction and an Abnormal Vascular Phenotype**


*Nephrology Unit, Great Ormond Street Hospital for Children, London, United Kingdom; *Vascular Physiology Unit, University College London Institute of Child Health, London, United Kingdom; *Department of Internal Medicine, Nephrology, and Hypertension, Saarland University Medical Centre, Homburg, Saar, Germany; *French Institute of Health and Medical Research Joint Research Unit 1011, European Geriatric Institute for Diabetes, Lille Pasteur Institute, Lille 2 University, Lille, France; Institute of Clinical Chemistry and *Cardiovascular Division, King’s College London, London, United Kingdom

- HDL (Children with CKD) promotes **ENDOTHELIAL DYSFUNCTION** and an abnormal vascular phenotype.

- The null association of HDL-C with CV mortality among participants with an eGFR<60 ml/min per 1.73 m² is consistent with the hypothesis that **HDL particles are rendered dysfunctional in some manner in CKD**.

- However, without data relating HDL composition or function to cardiovascular outcomes, **this hypothesis remains untested**.
The null association of HDL-C with CV mortality among participants with an eGFR<60 ml/min per 1.73 m2 is consistent with the hypothesis that HDL particles are rendered dysfunctional in some manner in CKD.

However, without data relating HDL composition or function to cardiovascular outcomes, this hypothesis remains untested.

HDL IS DYSFUNCTIONAL IN CKD

- 1255 Hemodialysis patients
- 66 yo, BMI ~ 28 mg/m2
- 4 years follow up
  - 49% Death rate
  - 31% CV events
- HDL, ApoA-I, ApoC-III were not related to outcomes
- Inverse association of ApoA-II with mortality
  - HR 0.63%
  - 95% CI: 0.40-0.89
PCSK9 INHIBITION

- ALIROCUMAB and AVOLOCUMAB are fully humanized monoclonal antibodies against PCSK9
  - ↓ LDL by up to 65%
  - Well tolerated in randomized, placebo-controlled, phase II clinical trials up to 1 year in over 3000 hypercholesterolemic patients

Lancet 2012; 380: 995-2006
Circulation 2012; 126: 2408-2417
JAMA 2012; 308: 2497-2506
J Am Coll Cardiol 2012; 59: 2344-2353
Lancet 2012; 380: 29-36
OTHER OPTIONS

- ACAT INHIBITORS
  - CI-976

- ANTITHROMBIN

- L-CARNITINE

- DIETARY CHANGES

- HERBS AND NATURAL COMPOUNDS
  - Macrothelypteris toresiana

- PROBUCOL

- Fosinopril
  - ↓ Serum Cholesterol
  - ↓ Lp (a)
  - ↓ Proteinuria
Fosinopril

- ↓ Serum Cholesterol
- ↓ Lp (a)
- ↓ Proteinuria

The LIPID-LOWERING EFFECT of Fosinopril was preferentially observed in those with reduction of proteinuria thereby suggesting that ATTENUATION OF URINARY PROTEIN LOSS is a mechanism involved in this anti-lipemic action.


Dextran sulfate column (Liposorber, Kaneka)

- LDL-C is adsorbed (due to electrostatic interaction between negatively charged dextran sulfate and positively charged Apo-B on the surface of lipoprotein)
- VLDL is adsorbed
- LDL is adsorbed
- HDL with Apo-A or other plasma components, e.g., albumin are NOT ADSORBED
LDL-A has been **EFFECTIVE IN INDUCING REMISSION IN NEARLY 50% of patients with various diseases, incl., refractory FSGS with a high level of safety.**

Prospective Observational Survey on the Long-Term Effects of LDL-A on Drug-Resistant Nephrotic Syndrome (POLARIS)

- Japanese Society of Kidney and Lipids
- 2013 Japanese Guidelines for Nephrotic Syndrome: LDL-A should be selected as an option for the strategy to treat Refractory NS

SUMMARY

- ABNORMAL LIPID METABOLISM IS COMMON in patients with kidney disease, particularly among THOSE WITH NEPHROTIC SYNDROME, in whom MARKED ELEVATIONS IN PLASMA CHOLESTEROL, TRIGLYCERIDES and LIPOPROTEIN A often occur.
- The hyperlipidemic response is triggered at least in part by the REDUCTION IN PLASMA ONCOTIC PRESSURE which STIMULATES HEPATIC APO-B GENE TRANSCRIPTION.
  - DIMINISHED CATABOLISM also plays a role
  - IMPAIRED METABOLISM (rather than enhanced synthesis) is primarily responsible for NEPHROTIC HYPERTRIGLYCERIDEMIA.
SUMMARY

- SPONTANEOUS or DRUG-INDUCED RESOLUTION OF THE NEPHROTIC SYNDROME REVERSES THE HYPERLIPIDEMIA.
- Patients with NEPHROTIC SYNDROME AND HYPERLIPIDEMIA are at an INCREASED RISK FOR ATHEROSCLEROTIC DISEASE, particularly if CV disease risk factors are present.
- Hyperlipidemia may also ENHANCE THE RATE OF PROGRESSIVE GLOMERULAR INJURY.
- TREATMENT OPTIONS include: DIETARY MODIFICATION, ACE-I or ARBs to reduce proteinuria and possibly OTHER ANTI-HYPERLIPIDEMIC AGENTS.

MN Treatment Algorithm

- Moderate proteinuria ≥4 <8 g/day GFR normal
  - BP ≤125/75 ACEI/ARB, diet Monitor about 6 mo
  - Persistent Proteinuria ≥4 g/day
    - Cytotoxic + steroids or **CNI
      - ACTH
  - **Persistent Proteinuria ≥8 g/day
    - ***CNI
    - **Cytotoxic + steroids
      - ↓ GFR and proteinuria ≥8 g/day

- Heavy proteinuria ≥8 g/day ± ↓ GFR
  - BP ≤125/75 ACEI/ARB, diet Monitor up to 3 mo
  - Persistent Proteinuria ≥8 g/day
    - **Rituximab
    - **Cytotoxic + steroids

*Risk reduction strategies
**Consider drug risks
***See reference 71
The lipid abnormalities induced by the nephrotic syndrome reverse with resolution of the disease.

REFERENCES

GOAL! #ChiVsTBL

SHARP (1st 9:11)
VENNETTE (2nd 10:53)

BLACK HAWKS
CHICAGO

Thank You