Managing Dyslipidemia on Dialysis: Is It Different?

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Disclosures

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Objectives

- Review background information on lipids, lipoproteins
- Lipids and pathogenesis of CV disease
- Data on lipids and CV disease/mortality in non-ESRD
- Data on lipids and CV disease/mortality in ESRD
- Personalized/Precision medicine
Background

• Cardiovascular disease is the leading cause of death in the United States and worldwide.

• Even though there was a 31% decline in CVD deaths from 2001 to 2011 in the United States, CVD still accounted for 1 of every 3 deaths in 2011.

• In 2010, the CDC estimated that $444 billion was spent on cardiovascular diseases alone, about $1 of every $6 spent on health care.
Background

- Given the intense focus on smoking cessation and decline in cigarette smoking, dyslipidemia has become the number one modifiable risk factor for CVD.

**INTERHEART: Focus on 9 risk or protective factors**

**Design**
Large international case-control study

**Participants**
12,461 cases; 14,637 controls; 52 countries

**Objective**
To determine association of first MI with:
- Smoking
- Lipids
- Hypertension
- Diabetes
- Obesity
- Diet
- Physical activity
- Alcohol consumption
- Psychosocial factors*

**Follow-up**
4 years, February 1999–March 2003

*eg, stress, depression

Background

• INTERHEART case-control study → dyslipidemia (elevated ApoB/ApoA1 ratio) had the highest mortality odds ratio (3.25),
• followed by smoking (2.87), psychosocial factors (2.67) and history of diabetes (2.37), and hypertension (1.91)
Lipids

- Lipids play an integral role in maintaining the structural integrity of cells

- They are also a major source of energy, steroid hormone production, and bile acid formation

- They are insoluble in plasma and are carried in lipoproteins that transport the lipid
Lipids

- Lipoproteins consist of esterified and nonesterified cholesterol, triglycerides, phospholipids, and proteins.

- Lipoproteins act as vehicles which carry lipids in the blood for delivery to target tissue or disposal.
- **Chylomicrons** - large, ApoB-48

- **Very low density lipoprotein** — Very low density lipoprotein (VLDL) particles carry endogenous triglycerides and to a lesser degree cholesterol. ApoB-100, C-I, C-II, C-III, and E.

- **Intermediate density lipoprotein** — IDL particles carry cholesterol esters and triglycerides. It is associated with apolipoproteins B-100, C-III, and E.

- **Low density lipoprotein** —LDL particles carry cholesterol esters and are associated with apolipoproteins B-100 and C-III.
Reverse transport

- High density lipoprotein: HDL particles carry cholesterol esters and triglycerides back to liver. These particles are associated with apolipoproteins (apo) A-I, A-II, C-I, C-II, C-III, D, and E.
Atherogenesis—mechanisms

• VLDL remnants may enter the vessel wall or be converted to small LDL particles.

• Triglyceride-rich remnant lipoproteins are able to penetrate the arterial wall and may be retained preferentially, thus causing atherosclerosis due to their cholesterol component.

• But mostly, we are talking about HDL and LDL
Atherogenesis - mechanisms

- Circulating LDL that is not taken up by the LDL receptors can enter macrophages through unregulated scavenger receptors.

- Uptake by these receptors requires chemical modification of the LDL particle by enzymatic, nonoxidative alteration such as oxidation, glycosylation or glycoxidation.
Unregulated uptake of LDL via the scavenger pathway leads to excess accumulation of modified LDL within macrophages → foam cells formation → can rupture, releasing oxidized LDL, intracellular enzymes, and oxygen free radicals that can further damage the vessel wall.
HDL As an Atheroprotective Molecule

Apolipoprotein A-I
High Density Lipoprotein

Reverse Cholesterol Transport
Anti-Oxidant Properties
Anti-Inflammatory Properties

Prevention and Reversal of Atherosclerosis

Prevention of Cardiovascular Disease

Main focus- LDL

- Abundance of epidemiologic evidence linking LDL-C levels and CV disease and mortality

- Laboratory evidence elucidating the mechanistic involvement of LDL-C in atherosclerosis
TEN-YEAR MORTALITY FROM CARDIOVASCULAR DISEASE IN RELATION TO CHOLESTEROL LEVEL AMONG MEN WITH AND WITHOUT PREEXISTING CARDIOVASCULAR DISEASE

Juha Pekkanen, M.D., Ph.D., Shai Linn, M.D., Dr.P.H., Gerardo Heiss, M.D., Ph.D., Chirayath M. Suchindran, Ph.D., Arthur Leon, M.D., Basil M. Rifkind, M.D., and Herman A. Tyrold, M.D.

[Graphs showing mortality rates by LDL cholesterol levels and presence of CVD for death from MI and CVD.]
Treatment of LDL

- All patients with high low-density lipoprotein cholesterol (LDL-C) undergo lifestyle modifications such as weight loss in overweight patients, aerobic exercise, and “healthy diet”

- The United Kingdom Lipid Clinics Program study of 2508 subjects found that, with diet alone, 60 percent of subjects had a mean reduction in body weight of 1.8 percent, which was associated with 5 to 7 percent reductions in serum total and LDL-C

- Treatment of LDL→But really, we are talking about statin therapy
THE EFFECT OF PRAVASTATIN ON CORONARY EVENTS AFTER MYOCARDIAL INFARCTION IN PATIENTS WITH AVERAGE CHOLESTEROL LEVELS

FRANK M. SACKS, M.D., MARC A. PFEFFER, M.D., PH.D., LEMUEL A. MOYE, M.D., PH.D., JEAN L. ROULEAU, M.D., JOHN D. RUTHERFORD, M.D., THOMAS G. COLE, PH.D., LISA BROWN, M.P.H., J. WAYNE WARNICA, M.D., J. MALCOLM O. ARNOLD, M.D., CHUAN-CHUAN WUN, PH.D., BARRY R. DAVIS, M.D., PH.D., AND EUGENE BRAUNWALD, M.D., FOR THE CHOLESTEROL AND RECURRENT EVENTS TRIAL INVESTIGATORS*
Secondary prevention-CARE

- 4159 patients (mostly men) with MI were randomized to placebo vs. pravastatin 40 mg per day

- Total cholesterol below 240 mg/dL and LDL-C between 115-174 mg/dL (mean 139)

- Additional medication given to reduce LDL to below 175 mg/dL if needed (cholestyramine)

- Primary end point was fatal or nonfatal MI

Secondary prevention-CARE

Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein


JUPITER

- The JUPITER trial of rosuvastatin 20 mg daily in healthy adult men and women with elevated C-reactive protein levels and LDL-C levels below 130 mg/dL. Study terminated after 1.9 years.

- Found a marked reduction in the primary endpoint of first major cardiovascular (CV) events and for all-cause mortality (HRs 0.56 and 0.80, respectively).

- The absolute benefit for the primary endpoint was 0.59 events per 100 person-years and for all-cause mortality was 0.25 deaths per 100 person-years.
A. **Primary Endpoint**

   - **RR 0.56, 95% CI 0.46-0.69**  
   - **P < 0.000001**

   - Placebo
   - Rosuvastatin

B. **Myocardial Infarction, Stroke, Cardiovascular Death**

   - **RR 0.53, 95% CI 0.40-0.69**  
   - **P < 0.00001**

   - Placebo
   - Rosuvastatin

C. **Revascularization or Hospitalization for Unstable Angina**

   - **RR 0.53, 95% CI 0.40-0.70**  
   - **P < 0.00001**

   - Placebo
   - Rosuvastatin

D. **All Cause Mortality**

   - **RR 0.79, 95% CI 0.65-0.96**  
   - **P = 0.02**

   - Placebo
   - Rosuvastatin
Major Statin Trials

% with CAD event vs. LDL-C (mg/dL)
Chronic Kidney Disease

• Chronic kidney disease (CKD) is associated with a significant increase in the risk for overall and cardiovascular (CV) mortality.

• Approximately 9% of the United States (US) population have CKD, translating into 20 million adults

• Out of this staggering number, more than 400,000 patients have end stage renal disease (ESRD) requiring weekly dialysis
End Stage Renal Disease

- Five year survival for patients with ESRD is about 35%, a mortality rate worse than that associated with many cancers.

- Half of these deaths are attributed to cardiovascular disease

- The prevalence of CKD and ESRD worldwide (especially in countries such as China and India) is increasing and latest projection estimates indicate that China will soon have a higher prevalence of patients with ESRD than United States.

End Stage Renal Disease

- While ESRD is a pro-atherogenic state by itself and the underlying risk factors for ESRD are also major risk factors for atherosclerosis
  - Diabetes is the number one cause of ESRD in the U.S. and soon worldwide
  - Hypertension is the second most common cause of ESRD in U.S.

- Given all the evidence (laboratory and clinical) that we have reviewed so far, statin therapy in the ESRD population should be a given
  - Or is it??
Atorvastatin in Patients with Type 2 Diabetes Mellitus Undergoing Hemodialysis

Christoph Wanner, M.D., Vera Krane, M.D., Winfried März, M.D., Manfred Olschewski, M.Sc., Johannes F.E. Mann, M.D., Günther Ruf, M.D., and Eberhard Ritz, M.D., for the German Diabetes and Dialysis Study Investigators*
ESRD-4D

• Randomized, double-blind, prospective study of 1255 patients with type 2 diabetes mellitus receiving maintenance hemodialysis

• Randomly assigned to receive 20 mg of atorvastatin per day or matching placebo.

• The primary end point was a composite of death from cardiac causes, nonfatal myocardial infarction, and stroke.

• Patients took medication/placebo for two years

• LDL measured directly by gel electrophoresis
Table 1. (Continued.)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo Group (N=636)</th>
<th>Atorvastatin Group (N=619)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid values — mg/dl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>220±42</td>
<td>218±43</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>127±30</td>
<td>125±29</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>36±14</td>
<td>36±13</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>267±168</td>
<td>261±165</td>
</tr>
<tr>
<td>LDL cholesterol levels — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100</td>
<td>120 (18.9)</td>
<td>122 (19.7)</td>
</tr>
<tr>
<td>100–129</td>
<td>241 (37.9)</td>
<td>252 (40.7)</td>
</tr>
<tr>
<td>130–159</td>
<td>186 (29.2)</td>
<td>169 (27.3)</td>
</tr>
<tr>
<td>≥160</td>
<td>89 (14.0)</td>
<td>76 (12.3)</td>
</tr>
<tr>
<td>Antihypertensive medication — %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>47</td>
<td>49</td>
</tr>
<tr>
<td>Angiotensin II–receptor antagonists</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>38</td>
<td>37</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>40</td>
<td>41</td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td>50</td>
<td>54</td>
</tr>
<tr>
<td>Use of erythropoietin — %</td>
<td>81</td>
<td>81</td>
</tr>
<tr>
<td>Dose per wk — IU</td>
<td>6.225</td>
<td>6.202</td>
</tr>
</tbody>
</table>

Figure 2. Median Level of Low-Density Lipoprotein (LDL) Cholesterol from Baseline to the End of the Study.

To convert values for LDL cholesterol to millimoles per liter, multiply by 0.02586.
Figure 3. Estimated Cumulative Incidence of the Composite Primary End Point.
Table 2. Rates of Primary and Secondary End Points.*

<table>
<thead>
<tr>
<th>End Point</th>
<th>Placebo Group (N=636)</th>
<th>Atorvastatin Group (N=619)</th>
<th>RR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiac causes</td>
<td>149 (23)</td>
<td>121 (20)</td>
<td>0.81 (0.64–1.03)</td>
<td>0.08</td>
</tr>
<tr>
<td>Sudden death</td>
<td>83 (13)</td>
<td>77 (12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal myocardial infarction</td>
<td>33 (5)</td>
<td>23 (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death due to congestive heart failure</td>
<td>24 (4)</td>
<td>17 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death after interventions to treat coronary heart disease</td>
<td>4 (0.6)</td>
<td>3 (0.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other death due to coronary heart disease</td>
<td>5 (0.8)</td>
<td>1 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>79 (12)</td>
<td>70 (11)</td>
<td>0.88 (0.64–1.21)</td>
<td>0.42</td>
</tr>
<tr>
<td>Silent</td>
<td>50 (8)</td>
<td>41 (7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsilent</td>
<td>35 (6)</td>
<td>33 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fatal stroke</strong></td>
<td>13 (2)</td>
<td>27 (4)</td>
<td>2.03 (1.05–3.93)</td>
<td>0.04</td>
</tr>
<tr>
<td>Ischemic</td>
<td>7 (1)</td>
<td>18 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>5 (0.8)</td>
<td>3 (0.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (not classified)</td>
<td>1 (0.2)</td>
<td>6 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>32 (5)</td>
<td>33 (5)</td>
<td>1.04 (0.64–1.69)</td>
<td>0.89</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cardiac events combined</td>
<td>246 (39)</td>
<td>205 (33)</td>
<td>0.82 (0.68–0.99)</td>
<td>0.03</td>
</tr>
<tr>
<td>Death from cardiac causes</td>
<td>149 (23)</td>
<td>121 (20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>79 (12)</td>
<td>70 (11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTCA</td>
<td>45 (7)</td>
<td>34 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>30 (5)</td>
<td>24 (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other interventions to treat coronary heart disease</td>
<td>0 (0.2)</td>
<td>1 (0.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Rosuvastatin and Cardiovascular Events in Patients Undergoing Hemodialysis

Bengt C. Fellström, M.D., Ph.D., Alan G. Jardine, M.D., Roland E. Schmieder, M.D., Hallvard Holdaas, M.D., Ph.D., Kym Bannister, M.D., Jaap Beutler, M.D., Ph.D., Dong-Wan Chae, M.D., Ph.D., Alejandro Chevaile, M.D., Stuart M. Cobbe, M.D., Carola Grönhagen-Riska, M.D., Ph.D., José J. De Lima, M.D., Ph.D., Robert Lins, M.D., Ph.D., Gert Mayer, M.D., Alan W. McMahon, M.D., Hans-Henrik Parving, M.D., D.M.Sc., Giuseppe Remuzzi, M.D., Ola Samuelsson, M.D., Ph.D., Sandor Sonkodi, M.D., Ph.D., D. Sci., Gultekin Süleymanlar, M.D., Dimitrios Tsakiris, M.D., Ph.D., Vladimir Tesar, M.D., Ph.D., Vasil Todorov, M.D., Ph.D., Andrzej Wiecek, M.D., Ph.D., Rudolf P. Wüthrich, M.D., Mattis Gottlow, M.Sc., Eva Johnsson, M.D., Ph.D., and Faiez Zannad, M.D., Ph.D., for the AURORA Study Group*
ESRD-AURORA

**AURORA: study design**

**Patients (n~2750)**
- Inclusion criteria:
  - ESRD, on hemodialysis for ≥3 months
  - 50–80 years
- Exclusion criteria:
  - Statin within 6 months
  - Kidney transplant likely within 1 year
  - Creatine kinase >3xULN
  - ALT >3xULN
  - TSH >1.5xULN

**Randomization 1:1**

**Matching placebo (n~1350)**

**Rosuvastatin 10 mg daily (n~1350)**

Month: -14 days
Visit: 1

0 2 3 3 6 4 5 6 6-monthly Final

\(^1\)Study medication was administered until ~620 patients had experienced a major CV event

### Table 1. Baseline Characteristics of the Patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rosuvastatin (N=1389)</th>
<th>Placebo (N=134)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>64.1±8.6</td>
<td>64.3±8.7</td>
<td>0.51</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>538 (38.7)</td>
<td>512 (37.0)</td>
<td>0.35</td>
</tr>
<tr>
<td>Race or ethnic group — no. (%)‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1174 (84.5)</td>
<td>1180 (85.3)</td>
<td>0.60</td>
</tr>
<tr>
<td>Black</td>
<td>50 (3.6)</td>
<td>48 (3.5)</td>
<td>0.92</td>
</tr>
<tr>
<td>Asian</td>
<td>70 (5.0)</td>
<td>69 (5.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hispanic</td>
<td>57 (4.1)</td>
<td>56 (4.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Other</td>
<td>38 (2.7)</td>
<td>31 (2.2)</td>
<td>0.46</td>
</tr>
<tr>
<td>Body-mass index‡</td>
<td>25.4±4.7</td>
<td>25.4±5.1</td>
<td>0.96</td>
</tr>
<tr>
<td>Blood pressure — mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>137.1±24.5</td>
<td>136.8±24.5</td>
<td>0.79</td>
</tr>
<tr>
<td>Diastolic</td>
<td>75.9±12.8</td>
<td>75.6±12.5</td>
<td>0.45</td>
</tr>
<tr>
<td>Current smoker — no. (%)</td>
<td>202 (14.5)</td>
<td>227 (16.4)</td>
<td>0.54</td>
</tr>
<tr>
<td>Cholesterol — mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>176±42</td>
<td>174±43</td>
<td>0.19</td>
</tr>
<tr>
<td>LDL</td>
<td>100±35</td>
<td>99±34</td>
<td>0.34</td>
</tr>
<tr>
<td>HDL</td>
<td>45±15</td>
<td>45±16</td>
<td>0.85</td>
</tr>
<tr>
<td>Triglycerides — mg/dl</td>
<td>157±95</td>
<td>154±97</td>
<td>0.45</td>
</tr>
</tbody>
</table>
ESRD-AURORA

Primary end point: Nonfatal MI, nonfatal stroke, death from CV cause

Figure 2. Kaplan–Meier Curves for the Primary End Point in the Two Study Groups.
The primary end point was the first major cardiovascular event.
ESRD-AURORA

- JUPITER involved patients without hyperlipidemia but with elevated high-sensitivity C-reactive protein levels (≥2.0 mg per liter)

- Rosuvastatin reduced both the high-sensitivity C-reactive protein level (by 37%) and major cardiovascular events (by 44%).

- In contrast, in AURORA, although high-sensitivity C-reactive protein levels were elevated at baseline (by 5.0 mg per liter) and were decreased by rosvastatin, there was no reduction in cardiovascular events.
The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial

ESRD-SHARP

11,792 patients attended screening
- 428 not eligible or refused

11,364 entered run-in phase
- 1,678 not eligible or withdrew

9,686 attended randomisation visit
- 248 not eligible or withdrew

9,438 randomised

4,193 initially assigned simvastatin 20 mg plus ezetimibe 10 mg

1,054 initially assigned simvastatin 20 mg

4,191 initially assigned placebo
- 168 not rerandomised

886 rerandomised after 1 year

Total: 4,650 assigned simvastatin plus ezetimibe

<4 years' follow-up for:
- Mortality, 70 (1.5%)
- Morbidity, 101 (2.2%)

4,650 analysed

Total: 4,620 assigned placebo

<4 years' follow-up for:
- Mortality, 68 (1.5%)
- Morbidity, 103 (2.2%)

4,620 analysed

Lancet 2011; 377: 2181–92
ESRD-SHARP

**Statins – the SHARP study**

- History of chronic kidney disease
  - not on dialysis: elevated creatinine on 2 occasions
    - Men: ≥1.7 mg/dL (150 μmol/L)
    - Women: ≥1.5 mg/dL (130 μmol/L)
  - on dialysis: haemodialysis or peritoneal dialysis
- Age ≥40 years
- No history of myocardial infarction or coronary revascularization
- Uncertainty: LDL-lowering treatment not definitely indicated or contraindicated

*Lancet 2011; 377: 2181-92*
Figure 2: Life-table plot of effects of allocation to simvastatin plus ezetimibe versus placebo on major atherosclerotic events
Numbers remaining at risk of a first major atherosclerotic event at the beginning of each year are shown for both treatment groups.

Lancet 2011; 377: 2181-92
Dyslipidemia of ESRD

- Marked by inflammation, oxidative stress, HDL deficiency and dysfunction

- Nontraditional risk factors

- Not LDL elevation

Association of LDL with Outcomes in ESRD

A

B

Excluded MHD pts with vintage <3 months: Q01-Q11: 13,657 pts, Q12: 5,348 pts

83,250 MHD pts

Excluded 291 pts with missing data

82,959 MHD pts

Identified dialysis clinics where at least 50% of pts had lipid measurements; 215 dialysis clinics are eligible

29,127 MHD pts

Identified patients with available serum lipid value in an eligible calendar quarter

15,859 MHD pts

Are these findings unique?


• Relationships of cholesterol, lipoproteins, and mortality in 1,134 patients with advanced HF of multiple etiologies

• Low total cholesterol was a strong, independent predictor of increased mortality in this cohort (p < 0.00001).

• Patients with higher LDL, HDL, and triglyceride levels had significantly longer survival
Rosuvastatin in Older Patients with Systolic Heart Failure

John Kjekshus, M.D., Ph.D., Eduard Apetrei, M.D., Ph.D., Vivencio Barrios, M.D., Ph.D., Michael Böhm, M.D., Ph.D., John G.F. Cleland, M.D., Jan H. Cornel, M.D., Ph.D., Peter Dunselman, M.D., Ph.D., Cândida Fonseca, M.D., Assen Goudev, M.D., Ph.D., Peer Grande, M.D., Ph.D., Lars Gullestad, M.D., Ph.D., Åke Hjalmarson, M.D., Ph.D., Jaromir Hradec, M.D., Ph.D., András Jánosi, M.D., D.Sc., Gabriel Kamenský, M.D., Ph.D., Michel Komajda, M.D., Jerzy Korewicki, M.D., Ph.D., Timo Kuusi, M.D., Ph.D., François Mach, M.D., Vyacheslav Mareev, M.D., Ph.D., John J.V. McMurray, M.D., Naresh Ranjith, M.D., Maria Schaufelberger, M.D., Ph.D., Johan Vanhaecke, M.D., Ph.D., Dirk J. van Veldhuisen, M.D., Ph.D., Finn Waagstein, M.D., Ph.D., Hans Wedel, Ph.D., and John Wikstrand, M.D., Ph.D., for the CORONA Group*
A  Primary Outcome

B  Death from Any Cause

No. at Risk
Placebo 2497 2315 2156 2003 1851 1431 811
Rosuvastatin 2514 2345 2207 2068 1932 1484 855

No. at Risk
Placebo 2497 2365 2240 2112 1980 1545 881
Rosuvastatin 2514 2379 2260 2139 2018 1566 907

Other conditions

- COPD, AIDS, CHF, cancer

- Advanced age
Chapter 2: Pharmacological cholesterol-lowering treatment in adults

2.1.1: In adults aged ≥ 50 years with eGFR < 60 ml/min/1.73 m² but not treated with chronic dialysis or kidney transplantation (GFR categories G3a-G5), we recommend treatment with a statin or statin/ezetimibe combination. (1A)

2.1.2: In adults aged ≥ 50 years with CKD and eGFR ≥ 60 ml/min/1.73 m² (GFR categories G1-G2) we recommend treatment with a statin. (1B)

2.2: In adults aged 18–49 years with CKD but not treated with chronic dialysis or kidney transplantation, we suggest 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%

2.3.1: In adults with dialysis-dependent CKD, we suggest that statins or statin/ezetimibe combination not be initiated. (2A)

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

2.4: In adult kidney transplant recipients, we suggest treatment with a statin. (2B)
HDL and CVD

• Low level of HDL-C as an independent risk factor for CVD.

• Framingham Heart Study, 44% of coronary events occurred with HDL levels less than 40 mg/dL.

• Patients having HDL levels less than 35 mg/dL had an 8-fold higher incidence of CVD compared with those having HDL levels > 65 mg/dL.

HDL and ESRD

• We have shown through a series of studies that defective HDL-mediated reverse lipid transport and decreased HDL antioxidant/anti-inflammatory function are major contributors to the atherogenic diathesis in the ESRD population.

<table>
<thead>
<tr>
<th>164,789 MHD patients</th>
<th>13,900 patients removed age &lt;18yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>150,889 MHD patients</td>
<td>10,887 removed, restrict to hemodialysis patients</td>
</tr>
<tr>
<td>140,002 MHD patients</td>
<td>2742 patients removed because they were not on dialysis for &gt;90 days</td>
</tr>
<tr>
<td>137,260 MHD patients</td>
<td>104,241 patients removed who had no data on HDL</td>
</tr>
<tr>
<td>33,019 MHD patients</td>
<td></td>
</tr>
</tbody>
</table>
Triglycerides

Association of Serum Triglyceride to HDL Cholesterol Ratio with All-Cause and Cardiovascular Mortality in Incident Hemodialysis Patients


Conclusions Contrary to the general population, elevated TG/HDL-C ratio was associated with better CV and overall survival in patients on hemodialysis. Our findings provide further support that the nature of CV disease and mortality in patients with ESRD is unique and distinct from other patient populations. Hence, it is vital that future studies focus on identifying risk factors unique to patients on MHD and decipher the underlying mechanisms responsible for poor outcomes in patients with ESRD.

Triglycerides

Figure 2. Higher TG/HDL-C ratio was associated with improved survival in incident hemodialysis patients. Time-varying all-cause (A) and cardiovascular (B) mortality hazard ratios (and 95% confidence interval error bars) by serum triglyceride/HDL cholesterol (TG/HDL-C) ratio. Adjustments in case-mix model: age, sex, race/ethnicity, primary insurance, vascular access type, comorbid conditions, alcohol dependence, substance abuse, and single-pool Kt/V; case-mix plus malnutrition-inflammation-cachexia syndrome (MICS) models: case-mix adjusted model plus laboratory parameters, including serum hemoglobin, white blood cell count, albumin, calcium, phosphorus, intact parathyroid hormone, bicarbonate, total iron binding capacity, ferritin, LDL cholesterol, and body mass index; case-mix plus MICS plus statin models: statin therapy on the fully adjusted models. Higher TG/HDL-C ratio was associated with improved survival in incident hemodialysis patients.
Chapter 5: Triglyceride-lowering treatment in adults

5.1: In adults with CKD (including those treated with chronic dialysis or kidney transplantation) and hypertriglyceridemia, we suggest that therapeutic lifestyle changes be advised. (2D)
Treatment

- This will need to be based on each individual patient’s clinical and laboratory characteristics
  - A patient with significant CAD and elevated LDL and TG levels may be different than a patient with no CAD and median LDL level
- There isn’t sufficient data to recommend a target for therapy
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