HMG-CoA Reductase Inhibitors and Renal Function

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Berlin 21-5-08
The Prevalence of CKD in USA

x million

<table>
<thead>
<tr>
<th>Serum creatinine mg/dl</th>
<th>&lt; 1.6</th>
<th>1.6-2.0</th>
<th>&gt;2.0</th>
<th>ESRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>x million</td>
<td>12</td>
<td>10</td>
<td>8</td>
<td>0</td>
</tr>
</tbody>
</table>

- 1.6 >
- 1.6-2.0
- 2.0 <
- ESRD
Relationship Between Estimated GFR (eGFR) and Clinical Outcomes

- **Death from Any Cause**
  - Total Events = 51,424
  - Standardized Event Rate (per 100 Person-Y)

- **Cardiovascular Events**
  - Total Events = 139,011
  - Standardized Event Rate (per 100 Person-Y)

- **Any Hospitalization**
  - Total Events = 554,651
  - Standardized Event Rate (per 100 Person-Y)

Risk Factors for Progressive Kidney Disease

- **Hemodynamic**
  - Hypertension
  - Glomerular hyperfiltration
  - Endothelial dysfunction

- **Non-hemodynamic**
  - RAAS
  - Aldosterone
  - SNS activity
  - Dyslipidemia
  - Hyperglycemia
  - Endothelin
  - Cytokines (TGFβ, HGF, PAI-1, etc.)
  - Oxidative stress
  - Proteinuria
  - Dietary protein intake
  - Calcium and P metabolism
  - Nephron endowment
  - Anemia
  - Ethnicity and gender
  - Tobacco smoking
  - Others
RENAAL: Primary Components

**Doubling of Serum Creatinine**
- Risk Reduction: 25%
- \( p = 0.006 \)

**ESRD**
- Risk Reduction: 28%
- \( p = 0.002 \)

**ESRD or Death**
- Risk Reduction: 20%
- \( p = 0.010 \)

- **P** = placebo
- **L** = losartan

Risk Factors for Progressive Kidney Disease

- **Hemodynamic**
  - Hypertension
  - Glomerular hyperfiltration
  - Endothelial dysfunction

- **Non-hemodynamic**
  - RAAS
  - Aldosterone
  - SNS activity
  - Dyslipidemia
  - Hyperglycemia
  - Endothelin
  - Cytokines (TGFβ, HGF, PAI-1, etc.)
  - Oxidative stress
  - Proteinuria
  - Dietary protein intake
  - Calcium and P metabolism
  - Nephron endowment
  - Anemia
  - Ethnicity and gender
  - Tobacco smoking
  - Others
To what extent do lipid abnormalities contribute to the progression of kidney disease?
Lipid Abnormalities in CKD

- Dyslipidemia is commonly present in patients with CKD, microalbuminuria, proteinuria, and especially those with nephrotic syndrome. It is usually characterized by:
  - Elevated total cholesterol
  - Elevated TG
  - Low HDL$_2$/HDL$_3$
  - Elevated small LDL particles
  - Elevated lipoprotein(a)
Animal Models of Lipid-induced Renal Injury

- Dietary-induced hyperlipidemia
  - Rat, guinea pig, rabbit

- Genetic hyperlipidemia
  - Obese Zucker rat
  - Spontaneously hypertensive obese rat

- Secondary hyperlipidemia
  - Dahl salt-sensitive rat
  - Remnant kidney model

Dyslipidemia and Progression of Kidney Disease

Epidemiological Evidence
The Physicians’ Health Study

- 4483 healthy men provided blood samples in 1982 and 1996
- Outcome measured
  - Elevated creatinine defined as $\geq 1.5 \text{ mg/dL}$
  - Reduced estimated CrCl $\leq 55 \text{ mL/min}$
- After 14 years, 134 (3.0%) had elevated creatinine and 244 (5.4%) had reduced CrCl

The Physicians’ Health Study

Predictors of Risk in the RENAAL Study (End-stage Renal Disease)

**Table: Predictors of Risk**

<table>
<thead>
<tr>
<th>Total cholesterol (mg/dL)</th>
<th>LDL-cholesterol (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;189</td>
<td>&lt;111</td>
</tr>
<tr>
<td>189-220</td>
<td>111-137</td>
</tr>
<tr>
<td>220-260</td>
<td>137-167</td>
</tr>
<tr>
<td>&gt;260</td>
<td>&gt;167</td>
</tr>
</tbody>
</table>

**Hazard ratio**

- LDL-cholesterol:
  - <111: 1.0
  - 111-137: 1.07
  - 137-167: 1.24
  - >167: 1.87

- Total cholesterol:
  - <189: 1.0
  - 189-220: 1.18
  - 220-260: 1.41
  - >260: 1.97

**Significance Levels**

- *P* < 0.05
- †P < 0.001

**References**

Evidence That Statins Inhibit the Progression of Kidney Disease

- **Animal Studies**

- **Human subjects**
  - Patients with hypertension, or dyslipidemia and normal kidney function
  - Patients with CKD: Do statins reduce proteinuria and CKD progression?
Statins Inhibit the Progression of Kidney Disease in the Following Animal Models

- 5/6 nephrectomy in Sprague-Dawley rats
- Obese Zucker rats
- Dahl salt-sensitive rats
- Puromycin aminonucleoside
- Development of polycystic kidney disease in the Han:SPRD rat
- Ischemic renal failure in cholesterol-loaded rats
Treatment of Hyperlipidemia Reduces Glomerular Injury in 5/6 Nephrectomized Rats

Evidence That Statins Inhibit the Progression of Kidney Disease

- **Animal Studies**

- **Human subjects**
  - Patients with hypertension, or dyslipidemia and normal kidney function or Stage 1-3 CKD
  - Patients with CKD: Do statins reduce proteinuria and CKD progression?
Only patients with complete renal data (both baseline and post-baseline creatinine measurements) were included in renal analysis.

Paired serum creatinine samples from baseline and the final study visit were used for MDRD and Cockcroft-Gault estimates of GFR.

TNT Study Design: Analysis of Renal Function

- **Open-label Run-in**
  - **Screening and Wash-out**
  - **Baseline**
  - **Double-blind Period**
    - **n=7965**

<table>
<thead>
<tr>
<th>Screening and Wash-out</th>
<th>Open-label Run-in</th>
<th>Double-blind Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-8 Weeks</td>
<td>8 Weeks</td>
<td>Median Follow-up = 4.9 Years</td>
</tr>
<tr>
<td>Atorvastatin 10 mg</td>
<td></td>
<td>Atorvastatin 10 mg</td>
</tr>
<tr>
<td>LDL-C Target: 100 mg/dL (2.6 mmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=3977</td>
<td></td>
<td>Atorvastatin 80 mg</td>
</tr>
<tr>
<td>LDL-C Target: 75 mg/dL (1.9 mmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=3988</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TNT: Rationale


Content not for presentation. For speakers' reference only.
TNT: Changes in LDL-C by Treatment Group

Mean LDL-C level = 101 mg/dL (2.6 mmol/L)

Mean LDL-C level = 77 mg/dL (2.0 mmol/L)

P<.001


Content not for presentation. For speakers' reference only.
TNT: Primary Efficacy Outcome Measure: Major Cardiovascular Events*

- Atorvastatin 10 mg
- Atorvastatin 80 mg

Mean LDL-C level = 101 mg/dL
Mean LDL-C level = 77 mg/dL

Relative risk reduction 22%

HR = 0.78 (95% CI 0.69, 0.89); P < .001

* CHD death, nonfatal non-procedure-related MI, resuscitated cardiac arrest, fatal or nonfatal stroke.

Both High- and Low-dose Atorvastatin Significantly Improved eGFR

MDRD = Abbreviated Modification of Diet in Renal Disease
All increases from baseline were statistically significant (P<0.0001)

LS mean % change from baseline eGFR

Percent Change From Baseline eGFR in TNT Patients by CKD Status

CKD patients
- Atorvastatin 80 mg
- Atorvastatin 10 mg

Patients with normal eGFR
- Atorvastatin 80 mg
- Atorvastatin 10 mg

Mean changes from baseline with atorvastatin 10 mg and 80 mg at the final visit (LOCF) were +6.6% and +9.8% in CKD patients (P<0.0001), and +5.2% and +7.6% in patients with normal eGFR (P<0.0001)

Time to First Major Cardiovascular Event By Baseline CKD Status Irrespective of Treatment Assignment

**Relative risk increase = 31.9%**
(Absolute risk increase = 2.7%)

HR = 1.35 (95% CI 1.18, 1.54)

*P* < 0.0001

Time to First Major Cardiovascular Event By Treatment

CKD (Stages 3-4)
Relative risk reduction = 32%
(Absolute risk reduction = 4.1%)
HR = 0.68 (95% CI 0.55, 0.84)
P = 0.0003

Normal eGFR
Relative risk reduction = 15%
(Absolute risk reduction = 1.4%)
HR = 0.85 (95% CI 0.72, 1.00)
P = 0.049

SPARCL Renal Sub Analysis

OBJECTIVE

- To investigate the effect of high-dose atorvastatin treatment on renal function in stroke patients with no known CHD
  - Effect stratified by chronic kidney disease (CKD) and glycemic status at baseline
- To determine the risk of primary and secondary cardiovascular end points in patients stratified by CKD status at baseline.
Effect of Atorvastatin on Renal Function by CKD Status

* ANOVA model of treatment, baseline renal function, and treatment–baseline renal function interaction

Without CKD = eGFR ≥60 mL/min/1.73 m²; With CKD = eGFR <60 mL/min/1.73 m²
# Liver and Muscle Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Without CKD</th>
<th>With CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Liver Enzymes, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two consecutive elevations out of time range</td>
<td>20 (1.3)</td>
<td>10 (1.3)</td>
</tr>
<tr>
<td>Placebo (n=1552)</td>
<td>7 (0.5)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Placebo (n=811)</td>
<td>8 (0.5)</td>
<td>1 (0.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Musculoskeletal AEs</strong></th>
<th>Without CKD</th>
<th>With CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhabdomyolysis</td>
<td>2 (0.1)</td>
<td>0</td>
</tr>
<tr>
<td>Myopathy</td>
<td>6 (0.4)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>86 (5.5)</td>
<td>43 (5.4)</td>
</tr>
<tr>
<td>Placebo (n=1552)</td>
<td>4 (0.3)</td>
<td>3 (0.4)</td>
</tr>
<tr>
<td>Placebo (n=811)</td>
<td>88 (5.7)</td>
<td>52 (6.4)</td>
</tr>
</tbody>
</table>

Without CKD = eGFR ≥60 mL/min/1.73 m²; With CKD = eGFR <60 mL/min/1.73 m²
In CKD patients, do statins reduce proteinuria and CKD progression?
Meta-Analysis: The Effect of Statins on Albuminuria

- Randomized, placebo controlled statin trials which included baseline and follow up 24hr urine collection or albumin-to-creatinine ratios
- 15 studies identified, with 1348 patients averaging 24 weeks in duration, published studies were not of high quality
- Statins reduced proteinuria, with greater reductions seen with higher levels of baseline proteinuria
  - <30 mg 2%
  - 30-300 mg -48%
  - >300 mg -47%
- Statins may have a beneficial effect on pathologic proteinuria

Individual and pooled results of 15 randomized, placebo-controlled trials examining the effect of statins on albuminuria or proteinuria, stratified by baseline excretion

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Statin</th>
<th>Sample Size, n</th>
<th>Effect (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Excretion &lt; 30 mg/d</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asselbergs et al., 2004 (18)</td>
<td>Pravastatin</td>
<td>864</td>
<td>12 (–1 to 25)</td>
</tr>
<tr>
<td>Dalla Nora et al., 2003 (20)</td>
<td>Atorvastatin</td>
<td>25</td>
<td>–70 (–171 to 31)</td>
</tr>
<tr>
<td>Fried et al., 2001 (21)</td>
<td>Simvastatin</td>
<td>39</td>
<td>–5 (–90 to 81)</td>
</tr>
<tr>
<td>Subtotal of WMD</td>
<td></td>
<td></td>
<td>2 (–32 to –35)</td>
</tr>
<tr>
<td><strong>Excretion, 30–299 mg/d</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buemi et al., 2000 (19)</td>
<td>Fluvastatin</td>
<td>21</td>
<td>–73 (–136 to –10)</td>
</tr>
<tr>
<td>Lintott et al., 1995 (26)</td>
<td>Fluvastatin</td>
<td>42</td>
<td>–81 (–217 to 55)</td>
</tr>
<tr>
<td>Nakamura et al., 2001 (28)</td>
<td>Cerivastatin</td>
<td>60</td>
<td>–61 (–106 to –16)</td>
</tr>
<tr>
<td>Nielsen et al., 1993 (29)</td>
<td>Simvastatin</td>
<td>18</td>
<td>–44 (–113 to 25)</td>
</tr>
<tr>
<td>Tonolo et al., 1997 (31)</td>
<td>Simvastatin</td>
<td>20</td>
<td>–50 (–93 to –7)</td>
</tr>
<tr>
<td>Zhang et al., 1995 (32)</td>
<td>Pravastatin</td>
<td>20</td>
<td>–8 (–61 to 45)</td>
</tr>
<tr>
<td>Subtotal of WMD</td>
<td></td>
<td></td>
<td>–48 (–71 to –25)</td>
</tr>
<tr>
<td><strong>Excretion ≥ 300 mg/d</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hommel et al., 1992 (22)</td>
<td>Simvastatin</td>
<td>21</td>
<td>–5 (–137 to 128)</td>
</tr>
<tr>
<td>Lam et al., 1995 (23)</td>
<td>Lovastatin</td>
<td>36</td>
<td>–32 (–102 to 38)</td>
</tr>
<tr>
<td>Lee et al., 2002 (25)</td>
<td>Pravastatin</td>
<td>66</td>
<td>–47 (–64 to –29)</td>
</tr>
<tr>
<td>Lee et al., 2005 (24)</td>
<td>Pravastatin</td>
<td>82</td>
<td>–62 (–79 to –45)</td>
</tr>
<tr>
<td>Nakamura et al., 2002 (27)</td>
<td>Cerivastatin</td>
<td>40</td>
<td>–67 (–87 to –48)</td>
</tr>
<tr>
<td>Thomas et al., 1993 (30)</td>
<td>Simvastatin</td>
<td>30</td>
<td>20 (–28 to 67)</td>
</tr>
<tr>
<td>Subtotal of WMD</td>
<td></td>
<td></td>
<td>–47 (–67 to –26)</td>
</tr>
</tbody>
</table>


Annals of Internal Medicine
A Controlled, Prospective Study of the Effects of Atorvastatin on Proteinuria and Progression of Kidney Disease

Bianchi S, Bigazzi R, Caiazza A, Campese VM

Effects of Atorvastatin on Proteinuria and Progression of Kidney Disease

**Objective**

- To assess the effect of atorvastatin on the progression of kidney disease in pts with CKD and proteinuria secondary to idiopathic glomerulopathies

**Population**

- 56 pts with chronic glomerulonephritis (proteinuria >1 g/24 h w/o known etiology)
- Mean age 55.6 yr; mean BMI 27.6
- Baseline BP 144/93 mm Hg (27/56 were hypertensive)
- Baseline lipids:
  - Total-C 320 mg/dL
  - TG 215 mg/dL
  - LCL-C 189 mg/dL
  - HDL-C 36 mg/dL

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Start of 2\textsuperscript{nd} Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of pts (M/F)</td>
<td>56 (38/18)</td>
<td>—</td>
</tr>
<tr>
<td>Age (y)</td>
<td>55.6 ±1</td>
<td>—</td>
</tr>
<tr>
<td>BMI (w/h²)</td>
<td>27.6 ±0.26</td>
<td>—</td>
</tr>
<tr>
<td>Hypertension (yes/no)</td>
<td>27/29</td>
<td>—</td>
</tr>
<tr>
<td>Office SBP (mm Hg)</td>
<td>144.3 ±2.4</td>
<td>133.0 ±1.0</td>
</tr>
<tr>
<td>Office DBP (mm Hg)</td>
<td>93.3 ±1.8</td>
<td>84.8 ±0.8</td>
</tr>
<tr>
<td>CrCl (mL/min)</td>
<td>55.5 ±1.4</td>
<td>50.4 ±1.3</td>
</tr>
<tr>
<td>UPE (g/24 h)</td>
<td>2.7 ±0.1</td>
<td>2.2 ±0.1</td>
</tr>
<tr>
<td>Total-C (mg/dL)</td>
<td>320 ±4.7</td>
<td>310 ±3.3</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>189 ±5</td>
<td>198 ±4.1</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>36.2 ±0.7</td>
<td>36.1 ±0.6</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>3.35 ±0.06</td>
<td>3.30 ±0.06</td>
</tr>
</tbody>
</table>

Effects of Atorvastatin on Proteinuria and Progression of Kidney Disease

N = 56 patients

Optimal Care
- ACEI, ARB, or both
- + meds ↓ BP <140/90 mm Hg
  (BP at 1 yr: 133/84 mm Hg)
- Diet
  - low sodium
  - low protein
  - low cholesterol
  - low fat

Group Demographics
- 19 men, 9 women in each
- Similar BP, BMI, serum lipids, and UPE after 1 yr

Primary efficacy end point:
- Change in UPE
- Change in CrCl

Optimal Care

Optimal Care w/o Atorvastatin (n=28)

Optimal Care with Atorvastatin* (n=28)

1 year

1 year

*Atorvastatin titrated to max of 40 mg to achieve LDL-C < 120 mg/dL or 40% decrease in LDL-C compared to baseline
Effects of Atorvastatin on Proteinuria and Progression of Kidney Disease

The percentage decline in urine protein excretion (UPE) was significantly greater in patients treated with atorvastatin than in those not treated (\(P < 0.01\)).

Effects of Atorvastatin on Proteinuria and Progression of Kidney Disease

-11.1%* -19.5%*

Creatinine Clearance (% change)

Run-in Phase

Study Phase

With atorvastatin
Without atorvastatin

*P < 0.01

The percentage decline in creatinine clearance is significantly greater in patients treated with atorvastatin than in those not treated (P<0.01)

Statins for Improving Renal Outcomes: A Meta-Analysis

- 27 studies with 39,704 individuals identified for eGFR analysis
- Weighted mean differences for eGFR were statistically significant in favor of the statin treated population with a 1.22 mL/min/yr slower fall in GFR

Mechanisms of Lipid Injury

Increased LDL

- Macrophages
  - Cytokines
    - Growth factors
    - Chemoattractants
    - Eicosanoids
    - ROI
  - Foam cells
  - Oxidized LDL
    - Mesangial cell injury
    - Increased matrix production
- Mesangial cell dysfunction
- Altered vasoactive substances
- Endothelial cell dysfunction
  - Altered vascular tone

Glomerulosclerosis

- Increased glomerular pressure
- Mesangial cell proliferation
- Increased matrix production
- Mesangial cell injury
- Foam cells
- Oxidized LDL
Inflammatory Chemokines: Effects of Statins

- Down regulation of:
  - Mesangial production of monocyte chemotactic protein-1 (MCP-1)
  - Monocyte-colony stimulating factor (M-CSF)
  - Vascular cell adhesion molecule (VCAM)
  - Intracellular adhesion molecule-1 (ICAM-1)
  - Platelet-derived growth factors (PDGF)
  - Transcription of the nuclear factor-kB (NF-kB), which plays a major role in mesangial cell inflammatory response

- Inhibition of:
  - Infiltration of monocytes
  - Proliferation of mesangial cells and interstitial fibrosis

TGF-β1 Gene Expression in Subtotal Nephrectomy

Simvastatin-mediated changes in angiotensin II type 1 receptor density

*P<0.05 vs. baseline

Statins exert immunomodulatory and anti-inflammatory effects

Activation of the NADPH Oxidase by Ang II

Ang II → AT1-R → PKC → Nox → p22phox → p47phox

EGF-R
Activation of the NADPH Oxidase by Ang II

Ang II → AT<br>

→ EGF-R

Statins

→ Nox → p22phox

→ p47phox

Rac GDP → Rac GEF

PI-3K

→ PIP₃

Src

→ PLD

→ PKC

→ GDP
Is There Experimental Evidence That Statins Potentiate the Renal Protective Effects of ACE-Inhibitors?
A Combination of Lisinopril and Statin Reduced BP More Than Any Single Drug

• Both PHN animals and control exhibited an increase in SBP at end of the study
• Treatment with an ACEI or a statin alone reduced SBP.
• A combination of the two drugs reduced SBP more than any single drug

A Combination of Lisinopril and Statin Reduced Proteinuria More Than Any Single Drug

- UPE measured at 4 mo (before treatment) and 10 mo after disease induction in PHN rats

A Combination of Lisinopril and Statin Improved Serum Creatinine More Than Any Single Drug

- SCr measured at 4 mo (before treatment) and 10 mo after disease induction in PHN rats

A Combination of Lisinopril and Statin Reduced Kidney Damage More Than Any Single Drug

- Combination of statin and ACEI significantly limited:
  - glomerulosclerosis
  - tubular damage
  - interstitial inflammation

Overall Summary

- Lipid abnormalities contribute not only to increased prevalence of CV disease but also to progressive loss of renal function.
- There is a relationship between degree of hyperlipidemia and progressive renal disease.
- Treatment of hyperlipidemia in patients with nephrotic syndrome and/or renal insufficiency may reduce proteinuria and the rate of progression of kidney disease.
- Aggressive treatment of dyslipidemia in CKD patients potentially reduces the excess CV risk associated with CKD.
Overall Summary

The beneficial effect of statins may be the direct consequence of lipid-lowering, but it also may be due to “pleotropic” effects, such as:

- Regulation of cellular proliferation/apoptosis balance
- Reduction of inflammatory cytokines and oxidative stress
- Involvement in intracellular signaling pathways
- Improvement of endothelial function
Take-Home Message (Opinion-based)

- Lipid-lowering drugs should be used to reduce proteinuria and CKD progression!!
Thank-you for your attention!!