Assessing Statin Therapy: What are Their Differences?

Educational Partner:

Saturday, June 23, 2012

New York, New York
Session 5: Assessing Statin Therapy: What are Their Differences?

Learning Objectives
1. Recognize statin drug interactions and select appropriate therapies that will not carry an increased risk of adverse events.
2. Apply evidence-based clinical study data into practice that demonstrates statins’ ability to modify both LDL-C and HDL-C to optimize drug selection.
3. Evaluate the available safety data concerning statins, proteinuria, hyperglycemia, and dose reduction requirements in patients with kidney failure and apply this knowledge to therapeutic risk/benefit analysis.

Faculty

Amit Khera, MD, MSc, FACC
Associate Professor
Director, Preventive Cardiology Program
Director, Cardiology Fellowship Training Program
University of Texas Southwestern Medical Center
Dallas, Texas

Amit Khera, MD, MSc, FACC, is an associate professor of medicine at the University of Texas, Southwestern Medical School in Dallas, Texas, where he serves as director of the preventive cardiology program and program director for the cardiology fellowship. He is also medical director of cardiac rehabilitation at University Hospital-St. Paul and Parkland Memorial Hospital. His research interests include the primary and secondary prevention of coronary artery disease, focusing on risk assessment and risk factor modification in those with premature and familial disease. Dr Khera received his undergraduate degree in American history from the University of Pennsylvania, with magna cum laude honors. He obtained his medical degree from Baylor College of Medicine, where he served as class president and was inducted into the Alpha Omega Alpha honor medical society. Dr Khera completed an internal medicine residency at Brigham and Women’s Hospital, Harvard Medical School, followed by a cardiology fellowship at the University of Texas, Southwestern Medical Center. He also completed his masters degree in epidemiology at the Harvard School of Public Health.

Carl E. Orringer, MD, FACC, FNLA
Harrington Chair in Preventive Cardiovascular Medicine
University Hospitals Case Medical Center
Associate Professor of Medicine
Case Western Reserve University School of Medicine
Cleveland, Ohio

Carl E. Orringer, MD, FACC, FNLA, is associate professor of medicine at Case Western Reserve University School of Medicine, where he is the Harrington Chair in Preventive Cardiovascular Medicine. He directs the preventive cardiovascular medicine program, the lipid clinic and LDL apheresis program at the Harrington Heart and Vascular Institute at University Hospitals Case Medical Center. Dr Orringer is a fellow of the American College of Cardiology, and of the National Lipid Association, where he has been on the board of directors since 2009 and is currently the secretary. He is a past president and a member of the board of directors of the Midwest Lipid Association. Dr Orringer served as program co-chairman for the Midwest Lipid Association 2011 Annual Scientific Sessions. He has been an editorial reviewer and faculty contributor to the National Lipid Association Self-Assessment Programs and to the Complex Lipid Management Self-Assessment Programs. He served as faculty chair for the 2011 update of National Lipid Association Self-Assessment Programs and is faculty chair for the 2013 revision of this educational program.
Faculty Financial Disclosure Statements
The presenting faculty report the following:
Amit Khera, MD, MSc, FACC, has no financial relationship to disclose.
Carl E. Orringer, MD, FACC, FNLA, has no financial relationship to disclose.

Education Partner Financial Disclosure Statement
The content collaborators at Vindico Medical Education report the following:
Ronald Codario, MD, Medical Director, has no financial relationship to disclose.
Chris Rosenberg, Director of Medical Education, has no financial relationship to disclose.

Suggested Reading List


Drug List

Generic                             | Trade
-----------------------------------|-------
Colesevelam                        | Welchol
Ezetimibe                          | Zetia
Fenofibrate                        | Altara, Lipofen, Lofibra, Tricor
Fenofibric Acid                    | Fibricor, Telspix
Gemfibrocil                        | Lopid
Omega-3 acid ethyl esters          | Lovaza
Niacin - ER                        | Niaspan
Atorvastatin                       | Lipitor
Fluvastatin                        | Lescol
Fluvastatin - XL                   | Lescol XL
Lovastatin                         | Mevacor
Pitavastatin                       | Livalo
Pravastatin                        | Pravachol
Rosuvastatin                       | Crestor
Simvastatin                        | Zocor
Simvastatin - ezetimibe            | Vytorin

Assessing Statin Therapy: What are Their Differences?
Amit Khera, MD, MSc, FACC
Carl E. Orringer, MD

Which of the following statins is not metabolized by cytochrome P-450 3A4 or 2C9?
1. Atorvastatin
2. Rosuvastatin
3. Simvastatin
4. Fluvastatin
5. Pravastatin

Which of the following statements is false?
1. Lower statin doses generally are less likely to cause side effects
2. Gemfibrozil has no effect on pitavastatin levels
3. Gemfibrozil has no effect on fluvastatin levels
4. There were no cases of rhabdomyolysis reported in the FIELD Trial with statin/fenofibrate combinations

When measured by AUC, which of the following statins has the least drug interaction with cyclosporine?
1. Pravastatin
2. Rosuvastatin
3. Atorvastatin
4. Fluvastatin

Statin Drug Interactions and Special Populations
Amit Khera, MD, MSc, FACC
Associate Professor
Director, Preventive Cardiology Program
UT Southwestern Medical Center
Disclosures

• No relevant financial relationships to disclose

Statin Basic Pharmacological Principles

Relationship between drug dose and clinical utility, and adverse drug event (ADE) is governed by 2 concepts:

• PHARMACODYNAMICS
  – The study of biochemical and physiological effects of drugs & their mechanisms of actions
  – Operationally describes “what Rx does to the body”
    – Receptor affinity and dynamics
    – Age/Genetic variations
    – Therapeutic Window

• PHARMACOKINETICS:
  – Operationally describes “what the body does to the drug”
  – Deals with dynamics of:
    – Bioavailability
    – Absorption (cholestyramine)
    – Distribution
    – Biotransformation
    – Elimination

PK Mechanisms of Statin-drug Interactions (SDI)

• METABOLISM: Induction &/or inhibition of:
  – PHASE I ENZYMES (Redox reactions)
    • FMO, MAO
    • Cytochrome P (CYP450 3A4, 2D6, 1A2, 2C9)
  – PHASE II ENZYMES (Conjugation)
    • Sulfation: sulfotransferase (SULT)
    • Acetylation: N-acetyltransferase (NAT)
    • Glutathione conjugation (GST)
    • Methylation: methyltransferases (MT)
    • Glucuronidation: UDP-glucuronosyltransferase (UGT)


Adapted from Goodman & Gilman, McGraw-Hill Pub.

Predominance of CYP450 System in Drug Metabolism

~75% of Drugs Metabolized Involve CYP450

• CYTOCHROME P450 (CYP450)
  – Group of related enzymes belonging to super family of iron-containing heme proteins (hemoproteins) located in the mitochondria/SER in liver, gut, etc.
  – Most catalyze oxidation of lipids, steroid hormones, and xenobiotics (toxin/Rx metabolism/bioactivation)
  – Monooxygenase reaction (inserting one O atom into organic substrate)
    \[ \text{RH} + \text{O}_2 + 2\text{H}^+ + 2\text{e}^- \rightarrow \text{ROH} + \text{H}_2\text{O} \]
  – Reduced P450s/CO absorb light @ wavelengths ~450nm (Soret peak)
  – Many CYP450 isoenzymes


FMO=flavin-containing monooxygenase; MAO=monoamine oxidase; NAT=N-acetyltransferase; UGT=uridine 5’-diphosphate-glucuronosyltransferase.

PK Mechanisms of Statin-drug Interactions (SDI)

Isoforms of CYP450 System Involved in Drug Metabolism

~50% of CYP450 Metabolism Involves 3A4


Predominance of CYP450 System in Drug Metabolism

~75% of Drugs Metabolized Involve CYP450

Isoforms of CYP450 System Involved in Statin Metabolism

Most Statins Use CYP 3A4 or CYP 2C9 Isoforms


Select Inhibitors of CYP450 3A4

**STRONG/MODERATE**
- Protease inhibitors
  - Ritonavir, indinavir, nelfinavir
- Macrolide antibiotics
  - Erythromycin, clarithromycin, azithromycin
- AzoLTE antifungals
  - Ketoconazole, fluconazole, itraconazole
- Chloramphenicol
- CCBs
  - Verapamil, diltiazem
- Antidepressant
  - Nefazodone
- Antiemetic
  - Aprepitant
- Bergamottin
  - Constituent of grapefruit juice

**WEAK/UNSPECIFIED**
- H2 antagonist
  - Cimetidine
- Antiarrhythmic
  - Amiodarone
- CCBs
  - Amlodipine, felodipine
- Cyclosporine
- Analgesic
  - Buprenorphine
- Antibiotics
  - Norfloxacin, ciprofloxacin
- NNRTIs
  - Nevirapine, efavirenz, delavirdine
- PIs
- Antineoplastics
  - Imatinib
- SSRIs
  - Fluoxetine, norfluoxetine, fluvoxamine
- Echinacea, Star Fruit, Milk Thistle

http://medicine.iupui.edu/clinpharm/ddis/table.aspx

Select Inhibitors of CYP450 2C9

**STRONG/MODERATE**
- Uricosuric
  - Benzbromarone
- Antifungal
  - Fluconazole
- Anticonvulsant
  - Valproic acid
- ARBs
  - Losartan, irbesartan
- Antibacterial
  - Sulfaphenazole
- Amentoflavone
  - Component of Ginkgo Biloba & St. John's Wort

**WEAK/UNSPECIFIED**
- H2 antagonist
  - Cimetidine
- Antiarrhythmic
  - Amiodarone
- Antibiotics
  - Chloramphenicol, sulfamethoxazole
- Fluvastatin
- Fenofibrate
- Lovastatin
- Probenzidin
- Sotalol
- Antifungal
  - Voriconazole
- Chemotherapy
  - Thalidomide
- Leukotriene antagonist
  - Zafirlukast
- Flavonoids

http://medicine.iupui.edu/clinpharm/ddis/table.aspx

PK Mechanisms of Statin-Drug Interactions

**METABOLISM**: Induction & inhibition of:
- PHASE I ENZYMES (Redox reactions)
  - CYP450 3A4, 2D6, 1A2, 2C9
  - FMO, MAO
- PHASE II ENZYMES (Conjugation)
  - Sulfation: sulfotransferase (SULT)
  - Acetylation: N-acetyltransferase (NAT)
  - Glutathione conjugation (GST)
  - Methylation: methyltransferases (MT)
  - Glucuronidation: UDP-glucuronosyltransferase (UGT)


Gemfibrozil Increased Cerivastatin Plasma Concentrations

Gemfibrozil competitively competes with statins for UGT 1A1 and 1A3 and is a potent inhibitor of CYP 2C9 and 2C8 and OA1B1.

Statin-fibrate Combination Therapy: Pharmacokinetic Interactions

<table>
<thead>
<tr>
<th>Statin</th>
<th>Effect on Cmax</th>
<th>Effect on AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pravastatin</td>
<td>↑ in cmax</td>
<td>No effect*</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>No effect</td>
<td>Not available</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>↑ in cmax by 112%</td>
<td>No effect*</td>
</tr>
<tr>
<td>Cerivastatin</td>
<td>↑ in cmax by 2-3 fold</td>
<td>No effect*</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>↑ in cmax by 2-fold</td>
<td>No effect*</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>↑ AUC by 2-3 fold</td>
<td>No effect*</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>↑ in cmax by 31%</td>
<td>No effect*</td>
</tr>
</tbody>
</table>

Adapted from: Davidson MH. *Am J Cardiol*. 2002;90(suppl):50K-60K.
* Significant


Competitive Glucuronidation: Gemfibrozil & Fenofibrate vs. Statins

Gemfibrozil

Fenofibrate

Most Statins Utilize UGT 1A1 and 1A3 for Metabolism

Gemfibrozil competitively competes with statins for UGT 1A1 and 1A3 and is a potent inhibitor of CYP 2C9 and 2C8 and OA1B1.
Rhabdomyolysis in Fibrate Combination Therapy With Statins*

- METABOLISM: Induction &/or inhibition of:
  - HEPATIC UPTAKE:
    - Organic anion transporters (OAT)
    - Organic anion transporter polypeptides (OATP)
    - Na-dependent taurocholate cotransporter (NTCP)
  - ELIMINATION:
    - ACTIVE BILIARY SECRETION:
      - MDR1- [P-glycoprotein (Pgp)]
      - Breast cancer resistance protein (BCRCP)
      - Multidrug resistance proteins (MRP)

*Excludes cases involving cerivastatin

Other Mechanisms of Statin-Drug Interactions

- METABOLISM: Induction &/or inhibition of:
  - HEPATIC UPTAKE:
    - Organic anion transporters (OAT)
    - Organic anion transporter polypeptides (OATP)
    - Na-dependent taurocholate cotransporter (NTCP)
  - ELIMINATION:
    - ACTIVE BILIARY SECRETION:
      - MDR1- [P-glycoprotein (Pgp)]
      - Breast cancer resistance protein (BCRCP)
      - Multidrug resistance proteins (MRP)

Selected Drug/Food Interactions Increasing Statin Levels

Selected Statin-Drug Interactions Dosing Adjustments

Maximum recommended doses are FDA approved from package inserts of respective statins.
NO = No recommendation
*Inhibitors of CYP3A4 & CYP2C9 increase the AUC of adjusted agents
**Inhibitors of CYP3A4 increase the AUC of fluvastatin and rosuvastatin by less than 2-fold.

Selected Statin Pk Properties

<table>
<thead>
<tr>
<th>Statin</th>
<th>Bioavailability</th>
<th>Half-life (hr)</th>
<th>Active Metabolites</th>
<th>Food Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td>5%</td>
<td>2-4</td>
<td>YES</td>
<td>50% incr</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>5%</td>
<td>2-3</td>
<td>YES</td>
<td>NS</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>18%</td>
<td>1-3</td>
<td>NO</td>
<td>30% dec</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>6%</td>
<td>4.7</td>
<td>NO</td>
<td>NS</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>12%</td>
<td>16-30</td>
<td>YES</td>
<td>12% dec</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>20%</td>
<td>21</td>
<td>Minor</td>
<td>20% incr</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>51%</td>
<td>13</td>
<td>NO</td>
<td>NS</td>
</tr>
</tbody>
</table>


Hepatic Statin Transport Pathways

Statin Membrane Transporters

- OATP1B1
- OATP1B3
- NTCP
- OATP2B1
- BCRP
- MDR1 (P-gp)
- MRP2

**SNPs in gene SCLO1B1 affect statin plasma levels; Strong inhibitors include: gemfibrozil, rifampicin, cyclosporine, erythromycin, clarithromycin, telithromycin, atazanavir, indinavir, ritonavir, saquinavir
**All statins except rosuvastatin/fluvastatin are substrates;  Inhibitors include: cyclosporine, verapamil, erythromycin, ketoconazole, itraconazole, quinidine, elacridar: Inducers: rifampicin, St. John’s Wort
***SNPs in gene for ABCG2 increase response to rosuvastatin.

Statin Membrane Transporters

- OATP1B1
- OATP1B3
- NTCP
- OATP2B1
- BCRP
- MDR1 (P-gp)
- MRP2

**SNPs in gene SCLO1B1 affect statin plasma levels; Strong inhibitors include: gemfibrozil, rifampicin, cyclosporine, erythromycin, clarithromycin, telithromycin, atazanavir, indinavir, ritonavir, saquinavir
**All statins except rosuvastatin/fluvastatin are substrates;  Inhibitors include: cyclosporine, verapamil, erythromycin, ketoconazole, itraconazole, quinidine, elacridar: Inducers: rifampicin, St. John’s Wort
***SNPs in gene for ABCG2 increase response to rosuvastatin.
Coadministration of Statins with Protease Inhibitors

<table>
<thead>
<tr>
<th>Proteinase Inhibitors</th>
<th>Possible increase in rosuvastatin concentration</th>
<th>Statin dose recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darunavir</td>
<td>Inc. Rosuv. AUC 213% &amp; Cmax by 6-fold</td>
<td>5 mg; use lowest possible dose</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>Inc. Rosuv. AUC 3-fold &amp; Cmax 7-fold</td>
<td>Limit dose to 10 mg</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>Inc. Rosuv. AUC 2-fold &amp; Cmax 5-fold</td>
<td>Limit dose to 10 mg</td>
</tr>
<tr>
<td>Lopinavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tipranavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atazanavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atazanavir + Ritonavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lopinavir + Ritonavir</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusions

- Knowledge of statin metabolism is crucial to minimizing side effects with concomitant therapies
- Lower statin doses generally are less likely to cause side effects
- Remember to track ALL medications, herbs and supplements taken by your patients
- Be aware of recent FDA dosing adjustments in patients on CYP 450-3A4 drugs

Disclosures

No relevant financial relationships to disclose

Statin Intolerance and Side Effects

Amit Khera, MD, MSc, FACC
Associate Professor
Director, Preventive Cardiology Program
UT Southwestern Medical Center

Drug Interactions

Increasing Statin Levels

<table>
<thead>
<tr>
<th>Statin</th>
<th>Fold</th>
<th>CYP3A4 Inhibitors</th>
<th>Other Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
</tbody>
</table>


Statin Safety

- Hepatic toxicity
- Muscle toxicity
- Toxicity more common in the elderly, frail, or those with liver disease or renal insufficiency
- Toxicity may be increased by certain other meds (e.g., gemfibrozil, antifungals, amiodarone, verapamil, macrolide antibiotics, cyclosporine, certain antidepressants) or foods (e.g., grapefruit juice)
Statins and Rhabdomyolysis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Incidence of Rhabdomyolysis per 10,000 patient-years of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>0.54 (0.22-1.12)</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>0 (0-1.11)</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>0.49 (0.06-1.76)</td>
</tr>
<tr>
<td>Cerivastatin</td>
<td>5.34 (1.46-13.68)</td>
</tr>
<tr>
<td>In combination with statins</td>
<td></td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>3.70 (0.76-10.82)</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>0 (0-14.58)</td>
</tr>
</tbody>
</table>


All Statin Clinical Outcome Trials: Effects on Cancer

- Relative risk of cancer per 1.0 mmol/L (40 mg/dL) reduction in LDL-cholesterol

<table>
<thead>
<tr>
<th>Cancer incidence</th>
<th>Comparison</th>
<th>Treatment arm</th>
<th>Control arm</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>More vs less statin 5 trials (n=39,612)</td>
<td>1466</td>
<td>1472</td>
<td>1.02 (0.89-1.18)</td>
</tr>
<tr>
<td></td>
<td>Statin vs Control 21 Trials (n=129,526)</td>
<td>3594</td>
<td>3592</td>
<td>1.00 (0.95-1.04)</td>
</tr>
<tr>
<td></td>
<td>All 26 trials (n=169,138)</td>
<td>5060</td>
<td>5064</td>
<td>1.00 (0.96-1.04)</td>
</tr>
</tbody>
</table>


Statins and the Liver

- LFT elevations > 3 times the ULN occur with all statins
- Incidence at lower doses is < 1% and 2-3% at 80 mg/day doses
- Almost always reversible with removal of therapy
- Liver failure reports are extremely rare, similar in frequency to that of general population, and causality from statins not established


Withdrawal of Statins Because of Elevated Liver Function Tests

- Withdrawal is recommended if LFTs are three times the upper limit of normal
- Physicians often stop statins for mild LFT elevation
- Role of fatty liver

Statin Advisory: Definitions of Muscle Toxicity

- Myopathy — a general term referring to any disease of muscles; myopathies can be acquired or inherited and can occur at birth or later in life
- Myalgia — muscle ache or weakness without creatine kinase (CK) elevation
- Myositis — muscle symptoms with increased CK levels
- Rhabdomyolysis — muscle symptoms with marked CK elevation (>10x the ULN) and creatinine elevation, usually with brown urine and urinary myoglobin


Statin Advisory: Risk Factors for Statin-associated Myopathy

Concomitant meds or consumption of:
- Fibrates
- Nicotinic acid (rarely)
- Cyclosporine
- Azole antifungals — Itraconazole, ketoconazole
- Macrolide antibiotics — Erythromycin, clarithromycin
- HIV protease inhibitors
- Nefazodone (antidepressant)
- Verapamil
- Amiodarone
- Large quantities of grapefruit juice (>1 qt/d)
- Alcohol abuse

Other considerations
- Advanced age (especially >80 y; women more than men)
- Small body frame, frailty
- Multisystem disease (eg, chronic renal insufficiency, especially due to diabetes)
- Multiple medications
- Perioperative periods

Aggravating Factors in Statin Myopathy

- Vitamin D deficiency and statin-induced myalgias
- One study by Ahmed W, et al suggests that many patients improve with Vitamin D supplementation while continuing their statin therapy
- Study not placebo controlled
- Ongoing studies in progress
- Review of the TNT study did not show a difference in myalgia in those with low vitamin D


Coenzyme Q10 and Statin Therapy

- More heat than light – 1 quality review published1
- 8 RCTs and 8 observational studies concluded that statins ↓ circulating CoQ10 levels by 16-54%, BUT……
- 1 RCT and 1 observational study did not, AND……
- Skeletal muscle CoQ10 levels were NOT consistently lowered in 4 human studies
- Minimal, inconclusive evidence regarding the effects of statins on mitochondrial function
- Only 2 small (44, 32 pts) RCTs of CoQ10 to prevent statin-related myalgias: 1 negative2, 1 positive3

2. Young JM, et al. Am J Cardiol. 2007;100:1400-1403

Statin Myopathy (continued)

- Link between hypothyroidism and statin myopathy
- Additive risk has been reported in case reports
- Potential for misdiagnosis with occult hypothyroidism

CoEnzyme Q10 (Ubiquinone)

- Benefit for statin myalgia controversial
- Issue of reduction in coenzyme Q10 levels in patients on statins
- If patient feels better, no need to prescribe
- CoQ10 carried on LDL particles

CoEnzyme Q10

- ↓ circulating CoQ10 levels by 16-54%
- 1 RCT and 1 observational study did not
- Skeletal muscle CoQ10 levels were NOT lowered in 4 human studies
- Only 2 small (44, 32 pts) RCTs of CoQ10 to prevent statin-related myalgias: 1 negative, 1 positive

Treatment Options

- Change to a different statin
- If the patient is high risk, try all statin options
- Lower statin dose or consider twice weekly therapy (e.g., once or twice weekly rosuvastatin)
- Ezetemibe
- Bile acid sequestrants
- Niacin
- Add water soluble fiber and/or plant stanols
- Role of red yeast rice


Statin Fibrate Combination Therapy

- Cerivastatin/gemfibrozil combination had >4000 times the rhabdo rate compared to statin alone
- Other statins with gemfibrozil rates are 1 to 1.5 per thousand pts treated
- Rhabdo rates with statin/fenofibrate combination are much lower with none reported in FIELD
- Rate of rhabdo is 33 times more for statin/gemfibrozil combination compared to statin/fenofibrate combination

Incident Diabetes in Statin Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Events</th>
<th>Events Rate</th>
<th>Weight (%)</th>
<th>95% CI</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCOT-LLA</td>
<td>1373</td>
<td>154</td>
<td>11.9</td>
<td>7773</td>
<td>0.89-1.54</td>
<td>1.14</td>
</tr>
<tr>
<td>HPS</td>
<td>1457</td>
<td>335</td>
<td>9.2</td>
<td>7573</td>
<td>0.98-1.35</td>
<td>1.15</td>
</tr>
<tr>
<td>JUPITER</td>
<td>1780</td>
<td>270</td>
<td>16.0</td>
<td>7773</td>
<td>1.04-1.51</td>
<td>1.26</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>5974</td>
<td>75</td>
<td>5.2</td>
<td>4667</td>
<td>0.58-1.10</td>
<td>0.79</td>
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<tr>
<td>LIPID</td>
<td>6997</td>
<td>126</td>
<td>6.0</td>
<td>7497</td>
<td>0.71-1.71</td>
<td>0.91</td>
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<td>CORONA</td>
<td>3534</td>
<td>100</td>
<td>20.9</td>
<td>3073</td>
<td>0.84-1.55</td>
<td>1.14</td>
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<tr>
<td>CORONA</td>
<td>5023</td>
<td>165</td>
<td>20.5</td>
<td>3923</td>
<td>1.03-1.69</td>
<td>1.32</td>
</tr>
<tr>
<td>CORONA</td>
<td>6086</td>
<td>172</td>
<td>10.8</td>
<td>5536</td>
<td>0.86-1.35</td>
<td>1.07</td>
</tr>
<tr>
<td>AFCAPS/TEXCAPS</td>
<td>6211</td>
<td>72</td>
<td>4.5</td>
<td>5511</td>
<td>0.70-1.38</td>
<td>0.98</td>
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<tr>
<td>4S</td>
<td>4242</td>
<td>198</td>
<td>17.3</td>
<td>3742</td>
<td>0.84-1.28</td>
<td>1.03</td>
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<tr>
<td>ALLHAT-LLT</td>
<td>6087</td>
<td>238</td>
<td>16.4</td>
<td>5587</td>
<td>0.95-1.41</td>
<td>1.15</td>
</tr>
<tr>
<td>GISSI HF</td>
<td>3378</td>
<td>225</td>
<td>34.8</td>
<td>2878</td>
<td>0.89-1.35</td>
<td>1.10</td>
</tr>
<tr>
<td>GISSI PREVENZONE</td>
<td>3460</td>
<td>96</td>
<td>27.5</td>
<td>2960</td>
<td>0.67-1.20</td>
<td>0.89</td>
</tr>
</tbody>
</table>

Overall (P=11.2% [95%CI 0.0-49.2%]) 1.09 (1.02-1.97) 100%

Association Between Incident Diabetes and Baseline Age or BMI in Statin Trials

Conclusions

- Statin toxicity and side effects can be reduced by avoiding concomitant therapy that may increase risk
- Lower statin doses generally are less likely to cause side effects
- Rule out underlying hypothyroidism
- Vitamin D assessment may be considered
- Consider non-statin therapy if necessary

Case Studies

Case 1

61-year-old male with a myocardial infarction 3 years ago, Hepatitis C diagnosed 2 years ago (on no therapy): currently on Simvastatin 40 mg daily, Amlodipine 10 mg od, Lisinopril 10 mg od, Clopidogrel 75 mg od, aspirin 81 mg daily presents with the following data:

- LDL-C: 115 mg/dL
- HDL-C: 26 mg/dL
- Triglycerides: 177 mg/dL
- TC: 176 mg/dL
- Non-HDL-C: 150 mg/dL
- Fasting glucose: 97 mg/dL
- ALT: 94 mg/dL
- AST: 118 mg/dL
- GGT: 229 mg/dL

What is your LDL-C goal for this patient?

1. < 70 mg/dL
2. < 100 mg/dL
3. < 130 mg/dL
4. Unsure

Case 1

What is your LDL-C goal for this patient?

?
### Case 1

**Lipid Profile:**
- LDL-C: 115 mg/dL
- HDL-C: 26 mg/dL
- Triglycerides: 177 mg/dL
- TC: 176 mg/dL
- Non-HDL-C: 150 mg/dL (on simvastatin 40 mg OD)

What lipid lowering therapy would you add/institute?

1. Change simvastatin to rosuvastatin 20 mg od
2. Change simvastatin to atorvastatin 40 mg od
3. Change simvastatin to pitavastatin 4 mg od
4. Add ezetimibe 10 mg od
5. Change simvastatin to fluvastatin XL 80 od

### Case 2

67-year-old hypertensive female with type 2 diabetes for 10 years currently taking:
- Pioglitazone 30 mg daily
- Metformin 1000 mg twice daily
- Sitagliptin 100 mg daily
- Lisinopril/HCTZ 20/12.5 once daily
- Aspirin 325 mg daily

She states that she has developed leg cramps with atorvastatin, simvastatin, rosuvastatin, and lovastatin. She presents with the following data:

- LDL-C: 145 mg/dL
- HDL-C: 32 mg/dL
- Triglycerides: 326 mg/dL
- TC: 242 mg/dL
- Non-HDL-C: 210 mg/dL
- A1C: 7.4%

What lipid lowering therapy would you add/institute?

1. Pitavastatin 2 mg OD
2. Fluvastatin XL 80 mg OD
3. Fenofibrate/Ezetimibe
4. Red Yeast Rice
5. Rosuvastatin 20 mg once weekly
6. Rosuvastatin 20 mg OW plus colesveleam daily

### Case 3

66-year-old white female with a history of hypertension, coronary disease and renal insufficiency. She stopped smoking in 2002. Her current medications are:
- Aspirin 81 mg
- Amlodipine 5 mg od
- Losartan/HCT 50/12.5

**Laboratory Studies:**
- TC: 237 mg/dL
- LDL-C: 156 mg/dL
- HDL-C: 40 mg/dL
- TG: 205 mg/dL
- Non-HDL-C: 197 mg/dL
- HbA1C: 6.2%
- eGFR: 40 mL/min
- Urine microalbumin/creatinine ratio: 55 mg/mmol (elevated)

What is your LDL-C goal for this patient?

1. < 70 mg/dL
2. < 100 mg/dL
3. < 130 mg/dL
4. Unsure

What lipid lowering therapy would you add/institute?

1. Pitavastatin 1 mg OD
2. Fluvastatin XL 80 mg OD
3. Rosuvastatin 10 mg OD
4. Atorvastatin 10 mg OD
5. Simvastatin 40 mg OD
6. Pravastatin 40 mg OD
Statins in CKD

Carl E. Orringer, MD
Harrington Chair in Preventive Cardiovascular Medicine
University Hospitals Case Medical Center Harrington Heart and Vascular Institute
Associate Professor of Medicine
Case Western Reserve University School of Medicine
Cleveland, OH

Disclosures
- No relevant financial relationships to disclose

Association of CKD and CV Events in Community-Based Studies

<table>
<thead>
<tr>
<th>Population</th>
<th>Number of patients</th>
<th>Definition of CKD</th>
<th>CV endpoints</th>
<th>Unadjusted CV hazard ratio (95% CI)</th>
<th>Adjusted CV hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARIC</td>
<td>15,350</td>
<td>eGFR: 15-59 ml/min/1.73m²</td>
<td>Fatal CHD, MI, stroke, and cardiac procedure</td>
<td>2.89 (2.22-3.77)</td>
<td>1.38 (1.08-1.87)</td>
</tr>
<tr>
<td>CHS</td>
<td>4893</td>
<td>eGFR: 15-59 ml/min/1.73m²</td>
<td>Coronary death, MI, PCTA, CABG, angioplasty, CHD, peripheral vascular disease, stroke, and TIA</td>
<td>2.29 (1.93-2.72)</td>
<td>1.31 (1.06-1.62)</td>
</tr>
<tr>
<td>FHS/FOS women</td>
<td>2837</td>
<td>serum creatinine: 136-265 μmol/l</td>
<td>CHD, CHF, and ischemic stroke</td>
<td>1.17 (0.88-1.57)</td>
<td>1.06 (0.79-1.43)</td>
</tr>
<tr>
<td>FHS/FOS women</td>
<td>3386</td>
<td>serum creatinine: 120-265 μmol/l</td>
<td>CHD, CHF, and ischemic stroke</td>
<td>2.19 (1.70-2.83)</td>
<td>1.04 (0.79-1.37)</td>
</tr>
</tbody>
</table>


Cardiovascular Event Rates in 2000 and 2001 (per 100 patient years)

Analysis of CV Outcomes According to the Presence of Chronic Kidney Disease

Chronic kidney disease as a coronary disease equivalent – a comparison with diabetes over a decade

- Veterans with and without diabetes and with and without CKD were prospectively recruited. A competing Cox regression model was used to describe the risk of myocardial infarction in the two groups (CKD and diabetes) over a decade of follow-up

- CKD is associated with a risk of death similar to that of established coronary artery disease and higher than that of diabetes mellitus. CKD is associated with a risk of MI that is at least as much as that from diabetes mellitus. Among veterans, CKD appears to be a coronary disease equivalent

Factors Affecting Serum Creatinine Concentration

How to Interpret GFR

When is Assessment of GFR Important?

ATP III Update 2004: Pharmacologic Treatment

Mechanisms of Dyslipidemia in CKD

Percentage of Lipid Abnormalities by Target Population
Proposed Treatment Algorithm for Lipid Management in Patients With CKD

**Stage 3 to 5**
Moderate-to-severe CKD, stages 3 to 4 (GFR 15-59 ml/min/1.73 m²)

- Elevated LDL-C
  - Atorvastatin, add ezetimibe if not at LDL-C goal
  - Fluvastatin, add ezetimibe if not at LDL-C goal
- Mixed dyslipidemia (not at non-HDL-C goal)
  - Atorvastatin or fluvastatin, ezetimibe
  - Fluvastatin, gemfibrozil 600 mg/day, ezetimibe if not at non-HDL-C goal
  - Statin, omega-3 fatty acids, ezetimibe if not at non-HDL-C goal
- Very high triglycerides (triglyceride 500 mg/dL)
  - Fenofibrate 600 mg/day
  - Omega-3 fatty acids 3-4 g/day
  - Fenofibrate 48 mg/day

Consult product insert or the Physicians’ Desk Reference for safety and risk information.

**SHARP: Main Outcomes**

- **Key outcome**
  - Major atherosclerotic events (coronary death, MI, non-haemorrhagic stroke, or any revascularization)
- **Subsidiary outcomes**
  - Major vascular events (cardiac death, MI, any stroke, or any revascularization)
  - Components of major atherosclerotic events
- **Main renal outcome**
  - End stage renal disease (dialysis or transplant)

**Drug Dose Modification in CKD**

- **Statins:** GFR 15-59 no dose reductions needed with atorvastatin, simvastatin, or pravastatin; fluvastatin not defined
- **Non-statins:** GFR 15-59 no dose modification required for niacin, bile acid sequestrants, ezetimibe, gemfibrozil, omega 3
- 25% dose reduction recommended for fenofibrate
- For gemfibrozil, the NLA recommends a dose of 600 mg/day for GFR 15-59 ml/min/1.73 m² and avoiding use for GFR 15 ml/min/1.73 m²
NKF Summary

Recommendations

• CKD is considered to be the HIGHEST RISK category
• Drug therapy should be used for LDL-C of 100-129 mg/dL after 3 months of TLC
• Initial drug therapy should be with a statin
• Fibrates may be used in Stage 5 CKD for patients with triglycerides ≥500 mg/dL and for patients with triglycerides ≥200 mg/dL who do not tolerate statins
• Gemfibrozil may be the fibrate of choice for treatment of high triglycerides in patients with CKD
• Evaluation of lipids should occur at presentation of CKD, after a change in status, and annually


Nephrology Referral

• eGFR <30ml/min, early referral improves dialysis survival and allows earlier transplantation
• Heavy proteinuria with albumin/creatinine ratio>1000 mg/g
• Resistant hypertension: above target on 3 or more meds
• Recurrent renal calculi
• Refractory Hyperkalemia K>5.5
• Rapid decline in kidney function
• Autoimmune disease
• Onset of kidney disease at young age (<30 years old)


Statin/Fibrate Combination Therapy: Pharmacokinetic Interactions

<table>
<thead>
<tr>
<th>Gemfibrozil</th>
<th>Fenofibrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>↑ in Cmax by 2.7-fold</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>↑ in Cmax by 2.8-fold</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>↑ in Cmax by 1.8-fold</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>↑ in Cmax by 2-fold</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>No effect</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>↑ in Cmax by 2.8-fold</td>
</tr>
<tr>
<td>Cerivastatin</td>
<td>↑ in Cmax by 2.3-fold</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>↑ in Cmax 31%</td>
</tr>
</tbody>
</table>


Statins Dose Adjustments in CKD

<table>
<thead>
<tr>
<th>Statin</th>
<th>GFR (ml/min/1.73m²)</th>
<th>30-60</th>
<th>15–59</th>
<th>&lt;15</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>5–10 mg</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Reduce by 50% in patients with GFR &lt;30 ml/min/1.73m²</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>No</td>
<td>Reduce by 50% in patients with GFR &lt;30 ml/min/1.73m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td>No</td>
<td>Reduce by 50% in patients with GFR &lt;30 ml/min/1.73m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lovastatin</td>
<td>No</td>
<td>Reduce to 50%</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>


Summary

• CKD is associated with an increased risk of CVD and a worse prognosis
• CKD is a CHD risk equivalent state
• CKD is associated with low HDL-C, TG and excessive # atherogenic particles
• Statin therapy reduces CVD except in dialysis patients, where no benefit has been established
• Lipid medication dosage adjustment is often required in patients with CKD

Which of the following statins is not metabolized by cytochrome P-450 3A4 or 2C9?

1. Atorvastatin
2. Rosuvastatin
3. Simvastatin
4. Fluvastatin
5. Pravastatin

Post?
Which of the following statements is false?

- Lower statin doses generally are less likely to cause side effects
- Gemfibrozil has no effect on pitavastatin levels
- Gemfibrozil has no effect on fluvastatin levels
- There were no cases of rhabdomyolysis reported in the FIELD Trial with statin/fenofibrate combinations

When measured by AUC, which of the following statins has the least drug interaction with cyclosporine?

- Pravastatin
- Rosuvastatin
- Atorvastatin
- Fluvastatin