Outline Presentation

1. Statin Safety
2. Statin Tolerability
3. Statin Adherence
Question: Are Statins Safe?
# Intensity of Statin Therapy

<table>
<thead>
<tr>
<th>High</th>
<th>Moderate</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ LDL-C ≥50%</td>
<td>↓ LDL-C 30 to &lt;50%</td>
<td>↓ LDL-C &lt;30%</td>
</tr>
<tr>
<td><strong>Atorva 40-80 mg</strong></td>
<td><strong>Atorva 10 mg</strong></td>
<td><strong>Simva 10 mg</strong></td>
</tr>
<tr>
<td><strong>Rosuva 20-40 mg</strong></td>
<td><strong>Rosuva 10 mg</strong></td>
<td><strong>Prava 10-20 mg</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Simva 20-40 mg</strong></td>
<td><strong>Lova 20 mg</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Pravas 40 mg</strong></td>
<td><strong>Fluva 20-40 mg</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Lova 40 mg</strong></td>
<td><strong>Pitava 1 mg</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Fluva XL 80 mg</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Fluva 40 mg bid</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Pitava 2-4 mg</strong></td>
<td></td>
</tr>
</tbody>
</table>

Statins in bold were evaluated in randomized controlled trials; those in italics were not.

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, p 34
**Statin Safety in Perspective**

Number needed to treat for 1 year to:

<table>
<thead>
<tr>
<th></th>
<th>Cause a GI Bleed</th>
<th>Cause a Fatal GI Bleed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspirin</strong></td>
<td>248</td>
<td>2066</td>
</tr>
<tr>
<td><strong>Statins</strong></td>
<td>100,000</td>
<td>1,000,000</td>
</tr>
</tbody>
</table>

1Derry S, Loke YK. 2000  
2Thompson PD, et al. 2003
Aspirine and Safety

- Risk for hemorrhagic stroke: 1-2/1000
- Risk for GI bleeding:
  - 60yrs: 1-2/1000
  - 80yrs: 7-8/1000

# Fatal Rhabdomyolysis

<table>
<thead>
<tr>
<th>Statin</th>
<th>Date approved</th>
<th>Fatal cases of rhabdomyolysis</th>
<th>No. of prescriptions</th>
<th>Reporting rate of rhabdomyolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td>8/31/87</td>
<td>19</td>
<td>99 197 000</td>
<td>1 in 5.2 million</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>10/31/91</td>
<td>3</td>
<td>81 364 000</td>
<td>1 in 27.1 million</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>12/23/91</td>
<td>14</td>
<td>116 145 000</td>
<td>1 in 8.3 million</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>12/31/93</td>
<td>0</td>
<td>37 392 000</td>
<td>0</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>12/17/96</td>
<td>6</td>
<td>140 360 000</td>
<td>1 in 23.4 million</td>
</tr>
<tr>
<td>Cerivastatin</td>
<td>6/26/97</td>
<td>31</td>
<td>9 815 000</td>
<td>1 in 316 000</td>
</tr>
</tbody>
</table>

In Summary…The Risk is Small!

There were only 73 reported cases of fatal rhabdomyolysis associated with 484,273,000 prescriptions of statins in the USA.
Muscle Related Side Effects
Effect of Statins on Skeletal Muscle Function

Beth A. Parker, PhD; Jeffrey A. Capizzi, MS; Adam S. Grimaldi, BS; Priscilla M. Clarkson, PhD; Stephanie M. Cole, PhD; Justin Keadle, BS; Stuart Chipkin, MD; Linda S. Pescatello, PhD; Kathleen Simpson, MS; C. Michael White, PharmD; Paul D. Thompson, MD

Background—Many clinicians believe that statins cause muscle pain, but this has not been observed in clinical trials, and the effect of statins on muscle performance has not been carefully studied.

Methods and Results—The Effect of Statins on Skeletal Muscle Function and Performance (STOMP) study assessed symptoms and measured creatine kinase, exercise capacity, and muscle strength before and after atorvastatin 80 mg or placebo was administered for 6 months to 420 healthy, statin-naive subjects. No individual creatine kinase value exceeded 10 times normal, but average creatine kinase increased 20.8±14.1 U/L (P<0.0001) with atorvastatin. There were no significant changes in several measures of muscle strength or exercise capacity with atorvastatin, but more atorvastatin than placebo subjects developed myalgia (19 versus 10; P=0.05). Myalgic subjects on atorvastatin or placebo had decreased muscle strength in 5 of 14 and 4 of 14 variables, respectively (P=0.69).

Conclusions—These results indicate that high-dose atorvastatin for 6 months does not decrease average muscle strength or exercise performance in healthy, previously untreated subjects. Nevertheless, this blinded, controlled trial confirms the undocumented impression that statins increase muscle complaints. Atorvastatin also increased average creatine kinase, suggesting that statins produce mild muscle injury even among asymptomatic subjects. This increase in creatine kinase should prompt studies examining the effects of more prolonged, high-dose statin treatment on muscular performance.


Key Words: atorvastatin ■ exercise test ■ hydroxymethylglutaryl-CoA reductase inhibitors ■ muscle strength ■ myopathy
The Effect of Statins on Skeletal Muscle Function and Performance (STOMP) study

atorvastatin 80 mg VS placebo 6 MONTHS n=420

• exercise capacity  →  No significant changes
• muscle strength →  No significant changes
• Myalgia →  19 vs 10 (p=0.05)
• CK ≥10 x ULN →  none

Myalgic subjects on atorvastatin or placebo had decreased muscle strength in 5 of 14 and 4 of 14 variables, respectively (P=0.69).

Circulation. 2013;127:96-103
The Effect of Statins on Skeletal Muscle Function and Performance (STOMP) study

Circulation. 2013;127:96-103
Discontinuation of Statins in Routine Care Settings
A Cohort Study
Huabing Zhang, MD; Jorge Plutzky, MD; Stephen Skentzos, BA, BS; Fritha Morrison, MPH; Perry Mar, PhD; Maria Shubina, ScD; and Alexander Turchin, MD, MS

Background: Systematic data on discontinuation of statins in routine practice of medicine are limited.

Objective: To investigate the reasons for statin discontinuation and the role of statin-related events (clinical events or symptoms believed to have been caused by statins) in routine care settings.

Design: A retrospective cohort study.

Setting: Practices affiliated with Brigham and Women’s Hospital and Massachusetts General Hospital in Boston.

Patients: Adults who received a statin prescription between 1 January 2000 and 31 December 2008.

Measurements: Information on reasons for statin discontinuations was obtained from a combination of structured electronic medical record entries and analysis of electronic provider notes by validated software.

Results: Statins were discontinued at least temporarily for 57,292 of 107,835 patients. Statin-related events were documented for 18,778 (17.4%) patients. Of these, 11,124 had statins discontinued at least temporarily; 6,579 were rechallenged with a statin over the subsequent 12 months. Most patients who were rechallenged (92.2%) were still taking a statin 12 months after the statin-related event. Among the 2,721 patients who were rechallenged with the same statin to which they had a statin-related event, 1,295 were receiving the same statin 12 months later, and 996 of them were receiving the same or a higher dose.

Limitations: Statin discontinuations and statin-related events were assessed in practices affiliated with 2 academic medical centers. Utilization of secondary data could have led to missing or misinterpreted data. Natural-language-processing tools used to compensate for the low (30%) proportion of reasons for statin discontinuation documented in structured electronic medical record fields are not perfectly accurate.

Conclusion: Statin-related events are commonly reported and often lead to statin discontinuation. However, most patients who are rechallenged can tolerate statins long-term. This suggests that many of the statin-related events may have other causes, are tolerable, or may be specific to individual statins rather than the entire drug class.

Primary Funding Source: National Library of Medicine, Diabetes Action Research and Education Foundation, and Chinese National Key Program of Clinical Science.

For author affiliations, see end of text.
Discontinuation of Statins in Routine Care Settings → 107,835 pts → 57,492 Stopped

- Statin-related events documented: 18,778 (17.4%) patients
- 11,124 had statins discontinued
- 6,579 re-challenged with a statin → 92.2% statin after 12 months
- 2,721 patients re-challenged with the same statin (41%)
- 1,295 the same statin (20%)
- 996 same or a higher dose (15%)
## Musculoskeletal Adverse Events With the 80-mg Dose

<table>
<thead>
<tr>
<th>Reported AE</th>
<th>2006 Safety Analysis</th>
<th>PROVE IT*</th>
<th>IDEAL*</th>
<th>TNT*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Atv 10 (n=7258)</td>
<td>Atv 80 (n=4798)</td>
<td>Prav 40 (n=2063)</td>
<td>Atv 80 (n=2099)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>2.9%</td>
<td>2.7%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Myopathy</td>
<td>0</td>
<td>0.02%†</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Persistent CPK &gt;10 x ULN</td>
<td>0</td>
<td>0.06%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

NR, not reported

*Studies not included in 2006 safety meta-analysis

†Investigator-reported cases: did not meet criteria for definition of myopathy (persistent CPK elevations >10 x ULN with muscle symptoms)

<table>
<thead>
<tr>
<th>Years of follow-up</th>
<th>Simvastatin allocation (per 1000 person-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>80 mg</td>
</tr>
<tr>
<td></td>
<td>20 mg</td>
</tr>
<tr>
<td>0-1</td>
<td>25 (4.2)</td>
</tr>
<tr>
<td>2-7</td>
<td>28 (0.8)</td>
</tr>
<tr>
<td>Total</td>
<td>53</td>
</tr>
</tbody>
</table>

Myopathy: New, unexplained muscle pain or weakness plus CK>10x ULN (7 vs 0 developed rhabdomyolysis)
• No Simvastatin with itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, or nefazodone.
• No simvastatin >10 mg with gemfibrozil, cyclosporine, or danazol
• No simvastatin >20 mg with amiodarone or verapamil
• No simvastatin >40 mg with diltiazem
• Patients of Chinese descent should not receive simvastatin 80 mg with cholesterol-modifying doses of niacin-containing products.
• caution when such patients are treated with simvastatin 40 mg or less in combination with cholesterol-modifying doses of niacin-containing products
Hepatic Safety of Statins
United Network for Organ Sharing (UNOS) Database

- From 1990 – 2002 in the US: 51,741 liver transplants
- three cases of acute liver failure related to statins *
  - 2 → Cerivastatin
  - 1 → Simvastatin

These studies were retrospective analyses, and formal causality assessment of DILI and confirmation that cases were bona-fide cases of DILI from statins were not performed!

Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post-hoc analysis

Vasilis A. Athyros, Konstantinos Tsiamis, Thomas D. Giannikos, Theodora Geia, Panagiota Asopopoulou, Konstantinos Kagiotsis, Efstatios D. Pagoulatos, Efthimios Makris, Antonios Karatzias, Dimitris P. Miliotis, for the GREACE Study Collaborative Group

Summary
Background Long-term statin treatment reduces the frequency of cardiovascular events, but safety and efficacy in patients with abnormal liver tests is unclear. We assessed whether statin therapy is safe and effective for these patients through post-hoc analysis of the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study population.

Methods GREACE was a prospective, intention-to-treat study that randomly assigned by a computer-generated randomisation list 1600 patients with coronary heart disease (aged <75 years, with serum concentrations of LDL cholesterol >1.8 mmol/l and triglycerides >1.5 mmol/l) at the Hippokration University Hospital, Thessaloniki, Greece to receive statin or usual care, which could include statins. The primary outcome of our post-hoc analysis was risk reduction for first recurrent cardiovascular event in patients treated with a statin who had moderately abnormal liver tests (defined as serum alanine aminotransferase or aspartate aminotransferase concentrations of less than three times the upper limit of normal) compared with patients with abnormal liver tests who did not receive a statin. This risk reduction was compared with that for patients treated (or not) with statin and normal liver tests.

Findings Of 457 patients with moderately abnormal liver tests at baseline, which were possibly associated with non-alcoholic fatty liver disease, 227 who were treated with a statin (mainly atorvastatin 24 mg per day) had substantial improvement in liver tests (p<0.001) whereas 210 not treated with a statin had further increases of liver enzyme concentrations. Cardiovascular events occurred in 22 (10%) of 227 patients with abnormal liver tests who received statin (3·3 events per 100 patients-years; 68% relative risk reduction; p<0.001). This cardiovascular disease benefit was greater (p=0·0971) than it was in patients with normal liver tests (9·9 [51%] events in 653 patients receiving a statin [4·0 per 100 patient-years] vs 11·7 [23%] in 510 patients not receiving a statin [7·0 per 100 patient-years]; 39% relative risk reduction; p<0.001). Seven (1·6%) of 580 participants who received a statin discontinued statin treatment because of liver-related adverse events (transaminase concentrations more than three times the upper limit of normal)

Interpretation Statin treatment is safe and can improve liver tests and reduce cardiovascular mortality in patients with mild-to-moderately abnormal liver tests that are potentially attributable to non-alcoholic fatty liver disease.

Funding None.
Enzyme activity during 3-year follow-up in patients with raised liver enzymes

Cardiovascular Events in Patients with Normal and Abnormal LFT’s

68% RRR P<0.0001
22 (10%) of 227 patients

23% RRR p<0.0001
90 (14%) of 653 patients

Event rate /100 patient years

NAFLD at Baseline and Follow up

Risk reduction of moderate to severe hepatic steatosis: 70%!
Use of Atorvastatin or Pravastatin in Patients with NASH

• 5 patients with NASH 20 mg Prava for 6 months\textsuperscript{1}
  - Normalization of liver enzymes in all patients
  - Some improvement in hepatic inflammation and steatosis (liver biopsies)

  7 patients with NASH 20 mg Atorvastatin 21 months (± 2 months)\textsuperscript{2}
  - Well tolerated
  - No increase in liver enzymes
  - Significant improvement of hepatic histology in some patients

# Summary of studies using statin therapy for NAFLD

<table>
<thead>
<tr>
<th>References</th>
<th>N</th>
<th>Study design</th>
<th>Diagnosis</th>
<th>Therapy</th>
<th>Dose</th>
<th>Duration (months)</th>
<th>Aminotransferase improvement</th>
<th>Histological improvement</th>
<th>Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horlander et al. (32)</td>
<td>7</td>
<td>Open label</td>
<td>NASH</td>
<td>Atorvastatin</td>
<td>Varied</td>
<td>12</td>
<td>Improved</td>
<td>Improved IN, S, and F</td>
<td>N/A</td>
</tr>
<tr>
<td>Kiyici et al. (14)</td>
<td>27</td>
<td>Open label</td>
<td>NASH</td>
<td>Atorvastatin</td>
<td>10 mg</td>
<td>6</td>
<td>Improved</td>
<td>N/A</td>
<td>CT improved</td>
</tr>
<tr>
<td>Rallidis et al. (33)</td>
<td>5</td>
<td>Open label</td>
<td>NASH</td>
<td>Pravastatin</td>
<td>20 mg</td>
<td>6</td>
<td>Improved</td>
<td>Improved IN, S, and F, no change in F</td>
<td>N/A</td>
</tr>
<tr>
<td>Halzionios et al. (34)</td>
<td>28</td>
<td>Open label</td>
<td>NAFLD</td>
<td>Atorvastatin</td>
<td>20 mg</td>
<td>6</td>
<td>Improved</td>
<td>N/A</td>
<td>US: improved</td>
</tr>
<tr>
<td>Gomez-Dominguez et al.</td>
<td>22</td>
<td>Open label</td>
<td>NAFLD</td>
<td>Atorvastatin</td>
<td>Varied</td>
<td>12</td>
<td>Improved</td>
<td>N/A</td>
<td>US: no change</td>
</tr>
<tr>
<td>Antonopoulos et al. (36)</td>
<td>23</td>
<td>Open label</td>
<td>NAFLD</td>
<td>Rosuvastatin</td>
<td>10 mg</td>
<td>8</td>
<td>Improved</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

F, fibrosis; CT, computed tomography; IN, inflammation; N / A, not applicable; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steato hepatitis; RCT, randomized control trial; S, steatosis; US, ultrasound.
Statins and Liver Disease

- Decrease the risk of developing hepatocellular carcinoma (HCC)¹
- Improve portal pressure and risk for bleeding liver cirrhosis²
- Double survival in HCC patients³
- Inhibit hepatitis C viral replication and improve treatment response rates⁴,⁵

Statins and Liver Safety

Original Contribution

An assessment by the Statin Liver Safety Task Force: 2014 update

Harold Bays, MD, FNLA*, David E. Cohen, MD, PhD, Naga Chalasani, MBBS,
Stephen A. Harrison, MD, COL, MC

Louisville Metabolic and Atherosclerosis Research Center, 3288 Illinois Avenue, Louisville, KY 40213, USA (Dr Bays);
Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA (Dr Cohen); Indiana University School of Medicine, Indianapolis, IN, USA (Dr Chalasani); and Brooke Army Medical Center, University of Texas Health Center San Antonio, Uniformed Services University of the Health Sciences, San Antonio, TX, USA (Dr Harrison)

KEYWORDS:
Cholesterol;
National Lipid Association;
Lipid;
Liver;
Statin

Abstract: In the 2006 Report of the National Lipid Association’s Statin Safety Task Force, a panel of experts in hepatology published their findings on specific questions related to the liver blood testing during statin therapy. Among their recommendations was that regulatory agencies reconsider the statin-labeling recommendation at that time, which required post-statin liver enzyme testing. Since then, the Food and Drug Administration altered statin labeling such that unless clinically indicated for other reasons, after a pre-statin therapy baseline evaluation, follow-up liver enzyme testing was not uniformly required after statin initiation. This 2014 report provides an update on interim issues relevant to statins and liver safety. Some of the points discussed include the value of baseline liver enzymes before initiating statin therapy, safety of statin use in patients with nonalcoholic fatty liver disease, potential drug interactions between statins and drugs used to treat hepatitis, the use of statins in liver transplant recipients, and the use of statins in patients with autoimmune liver disease. Finally, this panel provides diagnostic and algorithmic approaches when evaluating statin-treated patients who experience elevations in liver enzymes.

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1. Comprehensive List of Causes for Elevated Liver Enzymes

2. Comprehensive approach to patients with elevated liver blood testing (transaminases, 3 times the upper limits of normal)
Renal Safety of Statins
### GREACE Study Design

**Patient Population**
- 1,600 hypercholesterolemic patients with established CHD ([LDL-C >100 mg/dL (>2.59 mmol/L) after 6-week trial on lipid-lowering)
- Patients were randomized to following treatment groups:
  - **Structured Care**
    - (N = 800)
    - Atorvastatin: 10-80 mg/day
    - Mean Atorva Dose: 24 mg/day
    - Goal: LDL-C ≤100 mg/dL
  - **Usual Care**
    - (N = 800)
  - All patients were followed up for a mean period of 3 years

**Primary Endpoints**
- Total mortality
- Coronary mortality
- Non-fatal MI
- Unstable angina
- Congestive heart failure
- PTCA/CABG
- Stroke

**Renal Substudy**
- Post hoc analysis of C-G CCI

GREACE: Atorvastatin vs. Usual Care and No Statins on Renal Function


*Time at which difference became significant (p<0.05) compared with baseline.
# Published Atorvastatin Post-hoc CKD Analyses of Clinical Outcome Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>% CKD</th>
<th>CV Event reduction in CKD</th>
<th>Change in Renal function</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARDS</td>
<td>Diabetes (3.9yrs)</td>
<td>34%</td>
<td>▼48% (HR .52 ) MCVD, p = 0.03</td>
<td>▲0.18 mL/m /1.73/m/y P = 0.01 vs. placebo. Greater improvement in patients with albuminuria</td>
<td>No reduction albuminuria, No increase in CV events in CKD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>▼61% (HR.39) Stroke, p=0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A 10mg vs placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GREACE</td>
<td>Secondary CHD (3yrs)</td>
<td>6%</td>
<td>HR 1.10 - 5%▼ CrCl HR .73 -10%, ▲ CrCl</td>
<td>UCp ▼5.3% CrCl (703) SC A ▲ 12% CrCl (783)</td>
<td>Used CG CrCl</td>
</tr>
<tr>
<td></td>
<td>A  24mg vs. UC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNT</td>
<td>Secondary CHD (5yrs)</td>
<td>32%</td>
<td>▼32% MCVE HR 0.68, p &lt;0.0003</td>
<td>▲ A 10 3.5 mL/m/ 1.73 m2 5.6% ▲ A 80 5.2 mL/m/ 1.73 m2 8.3%</td>
<td>35%▲ of MCVE in CKD</td>
</tr>
<tr>
<td></td>
<td>A 80mg vs. A 10mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALLIANCE</td>
<td>Secondary CHD (4.3yrs)</td>
<td>24%</td>
<td>▼28% CVE (HR, 0.72), p&lt; 0.02</td>
<td>▲A 40 0.8 mL/m/1.73m2 ▼UC -1.36 mL/m/1.73m2</td>
<td>41% ▲of CVE in CKD</td>
</tr>
<tr>
<td></td>
<td>A 40mg vs.UC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDEAL</td>
<td>Secondary CHD (4.8yrs)</td>
<td>26%</td>
<td>No difference in MCE, ▼Any CVE HR 0.84 p=0.021, and ▼33% reduction in stroke HR 0.67, p=0.027</td>
<td>CKD eGFR ▲ A 5.21 ml/min,▲ S 4.30 ml/min p=0.026). non-CKD ▲A 0.35 ml/min, ▼S -1.44 ml/min, P &lt; 0.001</td>
<td>Reduced compliance with A, especially in older patients</td>
</tr>
<tr>
<td></td>
<td>A 80mg vs. S 20mg-40mg</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Statin and the Risk of Renal-Related Serious Adverse Events: Analysis from the IDEAL, TNT, CARDS, ASPEN, SPARCL, and Other Placebo-Controlled Trials

Bangalore S et. Am J Cardiol 2014
PLANET I: Prospective Evaluation of Proteinuria and Renal Function in Diabetic Patients With Progressive Renal Disease

**353 Patients**
- Type 1 or 2 diabetes
- Mild hypercholesterolemia
- Fasting LDL-C ≥90 mg/dL
- Moderate proteinuria
- Receiving ACE inhibitor and/or ARB treatment for >3 months

**PRIMARY END POINT:**
- Change in urinary/creatinine ratio from baseline to Week 52

**KEY SECONDARY END POINTS:**
- Assessment of relationship between renal effects and lipid parameters from baseline to Weeks 26 and 52
- Change in GFR from baseline to Weeks 26 and 52

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de Zeeuw D. European Renal Association — European Dialysis and Transplant Association Congress, Munich, Germany, June 27, 2010.
# PLANET I: Summary of renal adverse events (%)

<table>
<thead>
<tr>
<th></th>
<th>Crestor 10 mg</th>
<th>Crestor 40 mg</th>
<th>Lipitor 80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Cr X 2</td>
<td>0</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>ARF</td>
<td>0</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

de Zeeuw D. European Renal Association — European Dialysis and Transplant Association Congress, Munich, Germany, June 27, 2010.
More than 10% patients taking high dose rosuvastatin experience proteinuria. Prevalence of proteinuria is similar in atorvastatin and placebo.

Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials

13 trials 91 140 participants
DM in 4278 (2226 statins/2052 controls)

- 9% ↑ risk for incident diabetes (95% CI 1.02–1.17)
- ↑risk in older participants
- = baseline body-mass index and change in LDL-cholesterol concentrations

Treatment of 255 (95% CI 150–852) patients with statins for 4 years resulted in one extra case of diabetes.
Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Statin Events</th>
<th>Statin Rate</th>
<th>Placebo or control Events</th>
<th>Placebo or control Rate</th>
<th>OR (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCOT-LLA</td>
<td>7773</td>
<td>154</td>
<td>11.9</td>
<td>134</td>
<td>10.5</td>
<td>1.14 (0.89-1.46)</td>
<td>7.07%</td>
</tr>
<tr>
<td>HPS</td>
<td>14573</td>
<td>335</td>
<td>9.2</td>
<td>293</td>
<td>8.0</td>
<td>1.15 (0.98-1.35)</td>
<td>13.91%</td>
</tr>
<tr>
<td>JUPITER</td>
<td>17802</td>
<td>270</td>
<td>16.0</td>
<td>216</td>
<td>12.8</td>
<td>1.26 (1.04-1.51)</td>
<td>11.32%</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>5974</td>
<td>75</td>
<td>5.2</td>
<td>93</td>
<td>6.5</td>
<td>0.79 (0.58-1.10)</td>
<td>4.24%</td>
</tr>
<tr>
<td>LIPID</td>
<td>6997</td>
<td>126</td>
<td>6.0</td>
<td>138</td>
<td>6.6</td>
<td>0.91 (0.71-1.17)</td>
<td>6.53%</td>
</tr>
<tr>
<td>CORONA</td>
<td>3524</td>
<td>100</td>
<td>20.9</td>
<td>88</td>
<td>18.5</td>
<td>1.14 (0.84-1.55)</td>
<td>4.65%</td>
</tr>
<tr>
<td>PROSPER</td>
<td>5023</td>
<td>165</td>
<td>20.5</td>
<td>127</td>
<td>15.8</td>
<td>1.32 (1.03-1.69)</td>
<td>6.94%</td>
</tr>
<tr>
<td>MEGA</td>
<td>6086</td>
<td>172</td>
<td>10.8</td>
<td>164</td>
<td>10.1</td>
<td>1.07 (0.86-1.35)</td>
<td>8.03%</td>
</tr>
<tr>
<td>AFCAPS/TEXCAPS</td>
<td>6211</td>
<td>72</td>
<td>4.5</td>
<td>74</td>
<td>4.6</td>
<td>0.98 (0.70-1.43)</td>
<td>3.76%</td>
</tr>
<tr>
<td>4S</td>
<td>4242</td>
<td>198</td>
<td>17.3</td>
<td>193</td>
<td>16.8</td>
<td>1.03 (0.84-1.28)</td>
<td>8.88%</td>
</tr>
<tr>
<td>ALLHAT</td>
<td>6087</td>
<td>238</td>
<td>16.4</td>
<td>212</td>
<td>14.4</td>
<td>1.15 (0.95-1.41)</td>
<td>10.23%</td>
</tr>
<tr>
<td>GISSI HF</td>
<td>3378</td>
<td>225</td>
<td>34.8</td>
<td>215</td>
<td>32.1</td>
<td>1.10 (0.89-1.35)</td>
<td>9.50%</td>
</tr>
<tr>
<td>GISSI PRE</td>
<td>3460</td>
<td>96</td>
<td>27.5</td>
<td>105</td>
<td>30.6</td>
<td>0.89 (0.67-1.20)</td>
<td>4.94%</td>
</tr>
</tbody>
</table>

Overall (I²=11.2% [95% CI 0.0-50.2%])

OR (95% CI) = 1.09 (1.02-1.17) 100%

Lancet 2010; 375: 735–42
Meta-analysis Of Clinical Trials Evaluating The Effects Of Statins On Diabetes Risk

**All Studies (n = 6)**

<table>
<thead>
<tr>
<th>Study</th>
<th>No. Statins / Total (%)</th>
<th>No. Placebo / Total (%)</th>
<th>Study Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOSCOPS</td>
<td>57/2999 (1.9)</td>
<td>82/2975 (2.8)</td>
<td>0.69 (0.49, 0.98)</td>
</tr>
<tr>
<td>HPS</td>
<td>335/7291 (4.6)</td>
<td>293/7252 (4.0)</td>
<td>1.14 (0.98, 1.33)</td>
</tr>
<tr>
<td>ASCOT</td>
<td>154/3910 (3.9)</td>
<td>134/3863 (3.5)</td>
<td>1.14 (0.90, 1.43)</td>
</tr>
<tr>
<td>LIPID</td>
<td>172/3970 (4.3)</td>
<td>181/3567 (4.6)</td>
<td>0.95 (0.77, 1.16)</td>
</tr>
<tr>
<td>CORONA</td>
<td>100/1771 (5.6)</td>
<td>88/1763 (5.0)</td>
<td>1.13 (0.86, 1.49)</td>
</tr>
<tr>
<td>JUPITER</td>
<td>270/8901 (3.0)</td>
<td>216/8901 (2.4)</td>
<td>1.25 (1.05, 1.49)</td>
</tr>
<tr>
<td>Combined</td>
<td>1088/28642 (3.8)</td>
<td>994/28751 (3.5)</td>
<td>RR = 1.06 (0.93, 1.22)  p = 0.38</td>
</tr>
</tbody>
</table>

**Excluding WOSCOPS (n = 5)**

<table>
<thead>
<tr>
<th>Study</th>
<th>No. Statins / Total (%)</th>
<th>No. Placebo / Total (%)</th>
<th>Study Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPS</td>
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</tr>
<tr>
<td>LIPID</td>
<td>172/3970 (4.3)</td>
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<td>0.95 (0.77, 1.16)</td>
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<td>CORONA</td>
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<td>JUPITER</td>
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<td>216/8901 (2.4)</td>
<td>1.25 (1.05, 1.49)</td>
</tr>
<tr>
<td>Combined</td>
<td>1031/25843 (4.0)</td>
<td>912/25776 (3.5)</td>
<td>RR = 1.13 (1.03, 1.23)  p = 0.008</td>
</tr>
</tbody>
</table>
Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials

Lancet 2010; 375: 735–42
Risk of New-Onset DM2 According to Number of Risk Factors at Baseline

1. Baseline glucose >5.6 mmol/l (100 mg/dl)
2. Fasting triglycerides >1.7 mmol/l (150 mg/dl)
3. BMI >30 kg/m²
4. History of hypertension

J Am Coll Cardiol 2011;57:1535–45
Major Cardiovascular Events

Event rate was almost the same patients with new onset diabetes compared to patients without diabetes at baseline

HR: 1.02, 95% CI: 0.77 to 1.35
Statin Induced Impairment of Glucose Metabolism

- Inhibition of glucose-induced calcium signaling-dependent insulin secretion
- Decrease Ubiquinone and Mitochondrial transport/ATP production/Reduced Insulin secretion
- Inhibition of the Isoprenylation of GLUT4 transporter
- Beta cell oxidation, oxidative stress and nitric oxide production
- Apoptosis and beta cell destruction from LDL entry

Other Drugs That Affect Glucose

- Atypical antipsychotics
- β-blockers
- Thiazide diuretics
- Protease inhibitors
- Niacin
Statin Effects 9:1 Benefit?

- Of 255 Patients Treated
  +1 case of diabetes

- Of 255 Patients Treated
  -9 cases of CAD/CVA

Lancet 2010; 375: 735–42
An assessment by the Statin Diabetes Safety Task Force: 2014 update

Kevin C. Maki, PhD, FNLA*, Paul M Ridker, MD, MPH, W. Virgil Brown, MD, FNLA, Scott M. Grundy, MD, PhD, FNLA, Naveed Sattar, MD, PhD

Midwest Center for Metabolic & Cardiovascular Research and DePaul University, 6123 North Ashland Avenue, Suite 103, Chicago, IL 60631, USA (Dr. Maki); Brigham and Women’s Hospital and the Harvard Medical School, Boston, MA, USA (Dr. Ridker); Emory University School of Medicine, Atlanta, GA, USA (Dr. Brown); The University of Texas Southwestern Medical Center, Dallas, TX, USA (Dr. Grundy), and University of Glasgow, Glasgow, UK (Dr. Sattar).

KEYWORDS: National Lipid Association; Lipid; Type 2 diabetes mellitus; Statins; Coronary heart disease

Abstract: Statin therapy reduces the risk of myocardial infarction, stroke, and cardiovascular death by 25% to 30% in primary as well as secondary prevention patients. Thus, statins are the pharmacologic therapy of choice for the management of high blood cholesterol levels. Prompted by examination of clinical trial data suggesting a modest, but statistically significant, increase in the incidence of new-onset type 2 diabetes mellitus with statin use, the US Food and Drug Administration in 2012 added a statement to the labels of statin medications indicating that increases in glycated hemoglobin (HbA1c) and fasting glucose levels have been reported with statin use. This labeling change has raised questions among clinicians regarding the relative benefits and risks of statin use, both among patients with diabetes mellitus and among those with diabetes risk factors. This 2014 report from the Diabetes Subpanel of the National Lipid Association Expert Panel on Statin Safety reviews the published evidence relating statin use to the hazard for diabetes mellitus or worsening glycaemia, examines potential mechanisms that may mediate the relationship between statin use and diabetes mellitus risk, and suggests future research efforts. Given the well-established benefits of statin therapy in the primary and secondary prevention of cardiovascular events among those with indications for treatment, no changes to clinical practice are recommended other than the measurement of HbA1c or fasting glucose in those deemed at elevated diabetes risk after initiating statin therapy, and potentially before initiation in selected patients considered to be at elevated risk of developing diabetes. The panel advocates following recommendations from the American Diabetes Association, or other relevant guideline if outside the United States, for screening and diagnosis as well as lifestyle modification or prevention or delay of diabetes mellitus in those with prediabetes or other risk factors. © 2014 National Lipid Association. All rights reserved.
cognitive side effects of statins may occur in rare individuals, the medical evidence supporting a causal effect is weak or nonexistent.
A clinician’s guide to statin drug-drug interactions

Kenneth A. Kellick, PharmD, FNLA*, Michael Bottorff, PharmD, FNLA, Peter P. Toth, MD, PhD, FNLA

Abstract: The statins are widely used worldwide to reduce risk for cardiovascular events in both the primary and secondary prevention settings. Although generally quite safe, the statins can be associated with a variety of serious side adverse effects, including myalgia, myopathy, and changes in plasma enzymes of hepatic origin. Although rare, the most serious of these is rhabdomyolysis. Several drugs can interfere with the metabolism and disposal of the statins, thereby increasing risk for adverse events. It is important that clinicians treating patients with statins be aware of the potential for drug-drug interactions between each statin and specific other drugs and take measures to prevent them. The prediction of potential drug-drug interactions derives from basic pharmacokinetic principles. Certain drug interactions are predicted by measuring the effect of interacting drugs on blood plasma concentrations of the statin. Individual patient variations resulting in part from polymorphisms in the metabolizing enzymes confound some of these predictions. Based on these known effects, a new classification for predicting statin drug interactions is proposed. This report discusses likely prescription and nonprescription interactions as well as potential alternatives for special populations.

KEYWORDS:
Cytochrome; Drug-drug interactions; Glucuronidation; Pharmacogenetics; Pharmacokinetics; Statins
Helping your patients stick to their therapy!
The teacher gave definition n. 1.

WHO defines adherence as “the extent to which a person’s behavior—taking medications, following a diet and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider.”
Barriers to Mediation Adherence

**Patient-related Barriers**
- Complexity of medication regimen
- High out-of-pocket cost
- Concern or risk of side effects
- Receives contradictory information from healthcare providers
- Belief system that is inconsistent with contemporary medicine

**Prescriber-related Barriers**
- Limited time with the patient
- Uncomfortable speaking to patients about adherence
- Lack of incentive to spend additional time counseling on adherence
- Unaware of lower-cost medications

**Pharmacist-related Barriers**
- Difficulties communicating with prescriber
- Limited time to review medication refill histories
- Inability to access refill history across multiple pharmacies
- Limited access to patient’s medical records in the ambulatory setting
Prediction of Adherence

Medication costs
Dosing frequency and timing
Side effects
Elderly patients
Self-efficacy
Characteristics of Patients at HIGH Risk of Non-Adherence

- Not refilling an Rx
- Forgetfulness
- Poor eyesight
- Depression
- Language barrier
- Cultural gaps
- Poor coping skills
- Missing appointments
- Multiple co-morbidities
- Lack of trust in their provider
- No prescription drug coverage
- Inadequate response to therapy or lack of appropriate follow-up
- Does not understand their condition
- Medical condition without symptoms
| S | Simplify the regimen |
|   | - Adjust timing, frequency, and dosage  
|   | - Utilize once-daily medications whenever possible  
|   | - Encourage the use of adherence aids (e.g., pillboxes, cell phone alarms)  
|   | - Consider each patient’s activities of daily living (e.g., swing shift workers) |
| I | Impart knowledge |
|   | - Patient-provider shared decision making  
|   | - Provide clear instructions and expectations for all prescriptions  
|   | - Involve relatives or caregivers when discussing medications  
|   | - Recommend electronic education formats (e.g., video, websites) |
| M | Modify patient beliefs and human behavior |
|   | - Ask patient about their needs and what might help them adhere to therapy  
|   | - Ensure patient understands consequences of non-adherence  
|   | - Addressed perceived barriers of taking the medication  
|   | - Provide rewards for adherence (e.g., praise, coupons, fewer clinic visits) |
| P | Provide communication and trust |
|   | - Practice to improve interviewing skills  
|   | - Embrace active listening and provide emotional support  
|   | - Elicit patient’s input when discussing treatment options  
|   | - Allow adequate time for the interaction and encourage patient to ask questions |
| L | Leave the bias |
|   | - Foster a greater understanding of health literacy and how it affects patients  
|   | - Ensure communication style is patient-centered  
|   | - Take extra time to understand and overcome cultural barriers  
|   | - Tailor education to the patient’s level of understanding |
| E | Evaluating adherence |
|   | - Ask patients simply and directly about adherence  
|   | - Engage patients about adherence at every encounter  
|   | - Measure drug levels or efficacy parameters, when applicable  
|   | - Review medication containers, noting last fill date and remaining medicine |
An assessment by the Statin Intolerance Panel: 2014 update

John R. Guyton, MD, FNLA*, Harold E. Bays, MD, FNLA, Scott M. Grundy, MD, PhD, FNLA, Terry A. Jacobson, MD, FACP, FNLA

Division of Endocrinology, Diabetes, and Metabolism, Duke University Medical Center, 201 Trent Drive, Baker House 281, Durham, NC 27710, USA (Dr. Guyton); Louisville Metabolic and Atherosclerosis Research Center, Louisville KY, USA (Dr. Bays); Center for Human Nutrition, University of Texas Southwestern Medical Center, Dallas, TX, USA (Dr. Grundy); and Office of Health Promotion and Disease Prevention, Department of Medicine, Emory University School of Medicine, Atlanta, GA, USA (Dr. Jacobson)

KEYWORDS:
Drug intolerance; Patient-centered medicine; Statin adverse effects; Statins; Statin safety

Abstract: This article from the National Lipid Association Statin Intolerance Panel provides a framework for understanding statin intolerance and makes general recommendations for health professionals. For specific guidance on adverse events related to muscle, liver, cognition, and glucose metabolism, one should refer to the other reports of the Statin Safety Task Force for those topics. Although statin adverse effects rarely lead to permanent sequelae, symptomatic intolerance frequently hinders cardiovascular risk reduction by statins. We emphasize here the advisory role of the clinician helping each patient to make personal decisions on statin tolerability. We identify a pressing need for further research on statin intolerance and make suggestions for research design.

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Statins

1,000,000 people on statin treatment per year *

Benefits
- Prevent:
  - >3,000 deaths
  - >4,000 nonfatal MIs
  - >10,000 CV events

Risks
- AEs:
  - 40 Rhabdomyolysis leading to:
    - 6 Renal Failures
    - 1 Death

Driving

1,000,000 licensed drivers in U.S. **

Benefits
- Personal
- Efficient
- Affordable
- Reliable
- Fast Transportation

Risks
- Minimized via regulations, incl. drivers licenses, seat belts, car seats, airbags, ABS, public awareness programs, etc.

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Summary of Presentation

1. Statin Safety
2. Statin Tolerability
3. Statin Adherence
Questions?

Lansberg@gmail.com