Management of Drug-Drug Interaction with Statins

Joseph Saseen, PharmD, BCPS, BCACP, CLS, FNLA
Professor and Vice Chair
Disclosure

• Dr. Joseph Saseen has no disclosures.
Outline

• Overview of drug-drug interaction (DDI)
• Mechanisms of statin DDIs
• American Heart Association recommendations
  – CCB with statin
  – Fibrate with statin
  – Colchicine with statin
  – Warfarin with statin
• Summary and take home messages
Impact of Drug-Drug Interactions (DDI)

- Common causes of adverse effects
- Prevalence rate of 20-40%
- Responsible for ~2.8% of hospital admissions
- Removed or restricted due to DDI
  - Cerivastatin (Baycol) 2001
  - Terfenadine (Seldane®) 1998
  - Mibefradil (Posicor®) 1998
  - Astemizole (Hismanal®) 1999
  - Cisapride (Propulsid®) 2000
Risk Factors and Causes for Variability in DDIs with Statins

Medication Specific
- Dose
- Timing/sequence of administration
- Duration of therapy
- Pharmacokinetic characteristics
- Serum concentrations

Patient Specific
- Gender
- Age
- Genetic polymorphisms
- Diseases affecting drug metabolism (hepatic/renal)
Types of DDIs

• Pharmacokinetic Interactions
  – Absorption (reduced GI absorption)
  – Distribution (protein binding displacement)
  – Metabolism (alterations in the liver)
    • Phase 1: oxidation/reduction/hydrolysis
      – Microsomal enzymes (e.g., CYP450)
    • Phase 2: conjugation
  – Excretion (bile or kidney)

• Pharmacodynamic Interactions
  – Additive effects or antagonistic effects
<table>
<thead>
<tr>
<th></th>
<th>Absorption</th>
<th>Distribution</th>
<th>Metabolism</th>
<th>Excretion</th>
</tr>
</thead>
</table>
|                  | Bio-
 availability (%) | T_{max} (hr) | Protein Binding (%) | Lipophilicity (log P) | Major P450 Hepatic Enzyme | Pro-
drug | Active Metabolite | Renal Excretion (%) | t_{1/2} (hr) |
| Atorvastatin     | 14         | 1-2          | ≥98        | 4.1       | CYP3A4       | No     | Yes          | <2             | 14         |
| Fluvastatin      | 24         | <1           | 98         | 3.24      | CYP2C9 (CYP2C8, CYP3A4 are minor) | No     | No           | 5              | 3          |
| Lovastatin       | <5         | 2-4          | >95        | 4.3       | CYP3A4       | Yes    | Yes          | 10             | 2-3        |
| Pitavastatin     | 43-51      | 1            | 99         | 1.5       | CYP2C9 (CYP2C8 is minor) | No     | No           | 15             | 12         |
| Pravastatin      | 17         | 1-1.5        | 50         | -0.2      | Non-CYP      | No     | No           | 20             | 1.8        |
| Rosuvastatin     | 20         | 3-5          | 88         | -0.3      | CYP2C9       | No     | Minimal      | 10             | 19         |
| Simvastatin      | <5         | 4            | 95         | 4.7       | CYP3A4       | Yes    | Yes          | 13             | 2          |

CYP, cytochrome P; t\_{1/2}, drug half-life; T_{max}, time until maximum serum concentration achieved

_Circulation_. 2016;134:e468–e495.
Metabolizing Enzymes and Transporters Involved in Statin DDIs

- **CYP450 enzymes**: Over 50 types
- **P-glycoprotein (P-gp)**:
  - aka, multidrug resistance-1 (MDR1) or ATP binding cassette sub-family B member 1 (ABCB1)
    - In the GI tract, inhibition results in enhanced drug bioavailability
    - In hepatic and renal tissue, inhibition results in reduced drug elimination
- **Breast cancer resistance protein (BCRP)**
  - Limits systemic and organ exposure of substrates
- **Organic Anion-transporting polyprotein (OATP)**
  - Influx transporters that regulates cellular uptake
Systemic Circulation

Liver

Gut

Statin Acid

Statin Lactone

Glucuronidation
Conjugation

CYP3A4
CYP2C9

OATP 1B1
OATP 1B3

BCRP
MRP2
MRP1 (aka, P-gp or ABCB1)

Portal Blood

Portal Blood

Statin

CYP3A4

MRP1
BCRP

CYP3A4

MRP2

CYP3A4

BCRP

Gut

J Clin Lipidology 2014;8:S30–S46
# Statin Transporters and Enzymes

<table>
<thead>
<tr>
<th>Statin</th>
<th>CYP3A4</th>
<th>CYP2C9</th>
<th>OAT/OATP</th>
<th>MDR1</th>
<th>BCRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>Yes</td>
<td></td>
<td>1B1, 2B1</td>
<td></td>
<td>Yes, intestinal</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>Yes (minimal)</td>
<td>Yes</td>
<td>1B1, 1B3, 2B1</td>
<td></td>
<td>Yes, intestinal</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>Yes</td>
<td></td>
<td>1B1</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>Yes (minor)</td>
<td></td>
<td>1B1, 1B3, 2B1</td>
<td>Yes</td>
<td>Yes, intestinal</td>
</tr>
<tr>
<td>Pravastatin</td>
<td></td>
<td></td>
<td>1B1, 1B3, 2B1</td>
<td></td>
<td>Yes, intestinal</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Yes (minor)</td>
<td></td>
<td>1B1, 1B3, 2B1</td>
<td></td>
<td>Yes, intestinal</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Yes</td>
<td></td>
<td>1B1</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

BCRP, breast cancer–resistant protein; CYP, cytochrome P450; MDR1, multidrug-resistant protein; OAT, organic anion transporters; OATP, organic anion transporting polypeptides
Information about DDIs

• Literature sources
  – Primary (clinical trials, product inserts)
  – Secondary (systematic reviews, Cochrane Database, guidelines/Scientific Statements)
  – Tertiary (textbooks, Micromedex, Drug Facts and comparisons)

Alert Fatigue
A drug-drug interaction (DDI) is a pharmacokinetic or pharmacological influence of 1 medication on another that differs from the known or anticipated effects of each agent alone. A DDI may result in a change in either drug efficacy or drug toxicity for 1 or both of the interacting medications. Pharmacokinetic DDIs result in altered absorption, distribution, metabolism, or excretion of a medication. A pharmacodynamic DDI occurs when 1 medication modifies the pharmacological effect of another in an additive, a synergistic, or an antagonistic fashion.

It is estimated that ≈2.8% of hospital admissions occur as a direct result of DDIs. However, the actual incidence of hospitalization secondary to clinically significant DDIs is likely to be highly underestimated because medication-related issues are more commonly reported as adverse drug reactions. Complex underlying disease states also may make recognizing a DDI more challenging, further contributing to a lower reported incidence. The overall clinical impact of a DDI can range from mild...
Ranking Clinical Significance/Severity of Statin DDIs

- Pharmacokinetic measures used by the FDA
  1. Maximum serum concentration (Cmax):
     - Marker of peak drug exposure
  2. Area Under the Curve (AUC)
     - Reflects total body exposure

<table>
<thead>
<tr>
<th>AUC Change</th>
<th>Minor</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.25 to &lt; 2 Fold</td>
<td>1.25 to &lt; 2 Fold</td>
<td>&gt; 2 to 4.9 Fold</td>
<td>&gt; 5 Fold</td>
</tr>
</tbody>
</table>

Most statin DDI can be quantified using pharmacokinetic measures; however, some cannot

CCB with Statin DDI

• DDI explanations:
  – Amlodipine is a CYP3A4 substrate
  – Diltiazem and verapamil are moderate to weak CYP3A4 inhibitors and substrates of CYP3A4 and P-gp

• DDIs supported by pharmacokinetic studies, clinical trials, and case reports

• FDA labeling identifies statin dose restrictions with combination therapy

## CCB with Statin DDI

### Amlodipine

<table>
<thead>
<tr>
<th>Statin</th>
<th>Magnitude: Statin AUC Change</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td>Minor; 1.8-fold increase</td>
<td>Limit lovastatin or simvastatin to 20 mg daily</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Minor; 1.8-fold increase</td>
<td></td>
</tr>
</tbody>
</table>

### Diltiazem

<table>
<thead>
<tr>
<th>Statin</th>
<th>Magnitude: Statin AUC Change</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>Minor; 1.5 increase</td>
<td>Reasonable</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>Moderate; 3.6-fold increase</td>
<td>Limit lovastatin to 20 mg daily</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Moderate; 4.6-fold increase</td>
<td>Limit simvastatin to 10 mg daily</td>
</tr>
</tbody>
</table>

### Verapamil

<table>
<thead>
<tr>
<th>Statin</th>
<th>Magnitude: Statin AUC Change</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td>Moderate; 3.6-fold increase</td>
<td>Limit lovastatin to 20 mg daily</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Moderate; 2.5-fold increase</td>
<td>Limit simvastatin to 10 mg daily</td>
</tr>
</tbody>
</table>
Gemfibrozil with Statin DDI

- Multiple DDI explanations
  - Pharmacodynamic interaction
  - Gemfibrozil only:
    - Can inhibit glucuronide conjugation
    - Substrate (but not inhibitor) of CYP3A4
    - Potent inhibitor of OAT1B1/3 and OATP2B1

- DDIs documented by pharmacokinetic studies, clinical trials, and case reports
  - Decreased statin metabolism leading to increased concentrations
  - Increased risk of muscle-related toxicity

*Circulation.* 2016;134:e468–e495.
Fenofibrate/Fenofibric Acid with Statin DDI

<table>
<thead>
<tr>
<th>Statin</th>
<th>Magnitude: Statin AUC change</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>Insignificant; 1.0-fold increase</td>
<td>Reasonable</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>Specific data not available; magnitude likely minor</td>
<td>Reasonable</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>Specific data not available; magnitude likely minor</td>
<td>Reasonable</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>Insignificant; 1.2-fold increase</td>
<td>Reasonable</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Insignificant; 1.1-fold increase</td>
<td>Reasonable</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Insignificant; 1.1-fold increase (1.05-fold increase if taken at same time)</td>
<td>Reasonable</td>
</tr>
</tbody>
</table>

Pravastatin not included

- When statin-fibrate combination therapy is indicated, fenofibrate or fenofibric acid is preferred

*Circulation.* 2016;134:e468–e495.
## Gemfibrozil with Statin DDI

<table>
<thead>
<tr>
<th>Statin</th>
<th>Magnitude: Statin AUC Change</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>Minor; 1.4-fold increase</td>
<td>§ May be considered; lower atorvastatin to 10 mg daily (20 mg maximum)</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>Moderate; 2- to 3-fold increase</td>
<td>Avoid</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>Minor; 1.5-fold increase</td>
<td>§ May be considered; lower pitavastatin to 1 mg daily (2 mg maximum)</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>Moderate; 2.0-fold increase</td>
<td>Avoid</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Minor; 1.6- to 1.9-fold increase</td>
<td>§ May be considered; lower rosuvastatin to 5 mg daily (10 mg maximum)</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Moderate; 2- to 3-fold increase</td>
<td>Avoid</td>
</tr>
</tbody>
</table>

Fluvastatin not included

§ Use in combination recommended only when other options have been exhausted!

- Fluvastatin may be used without dose restriction with gemfibrozil, fenofibrate, or fenofibric acid

Colchicine with Statin DDI

• Possible DDI explanations:
  – CYP3A4 competitive inhibition, increasing concentrations of both drugs
  – Colchicine is a substrate for P-gp
  – Pharmacodynamic interaction

• Lack of clinical trials, DDIs from case reports (mostly simvastatin-colchicine)
Colchicine with Statin DDI

<table>
<thead>
<tr>
<th>Statin</th>
<th>Magnitude</th>
<th>Recommendation #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>Variable</td>
<td>May be considered</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>Variable</td>
<td>Reasonable</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>Variable</td>
<td>Reasonable</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>Variable</td>
<td>Reasonable</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>Variable</td>
<td>Reasonable</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Variable</td>
<td>Reasonable</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Variable</td>
<td>May be considered</td>
</tr>
</tbody>
</table>

# Closer monitoring for muscle-related toxicity is recommended when colchicine is used in combination with any statin

- Consider dose reduction with atorvastatin, lovastatin or simvastatin, given potential for CYP3A4 and P-gp mediated interactions

_Circulation_. 2016;134:e468–e495.
Warfarin with Statin DDI

- Most warfarin DDIs result from CYP2C9 inhibition or protein-binding displacement; low likelihood with statins

<table>
<thead>
<tr>
<th>Statin</th>
<th>Magnitude</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvastatin</td>
<td>Variable</td>
<td>Combination is useful</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>Variable</td>
<td>Combination is useful</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Variable</td>
<td>Combination is useful</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Up to 30% change in INR</td>
<td>Combination is useful</td>
</tr>
</tbody>
</table>

Atorvastatin, Pitavastatin, Pravastatin not included

- Monitor INR more closely after statin initiation or dose changes; impact on INR appears lowest for pitavastatin and atorvastatin

DDI between statin and dabigatran?

- **Dabigatran etexilate:**
  - Prodrug with absorption opposed by P-gp
  - Converted to active form by carboxylesterase
- **Simvastatin and lovastatin:**
  - Inhibit both P-gp and carboxylesterase
- **Combined use could increase or decrease effects; product labeling does not mention DDI**

**Observational data:**
- Two population-based case control studies in 45,991 patients taking dabigatran etexilate

- **Simvastatin/lovastatin use:**
  - Ischemic stroke:
    - Adjusted Odds Ratio 1.33 [0.88-2.01]
  - Major hemorrhage:
    - Adjusted Odds Ratio 1.46 [1.17-1.82]

Other Clinically Significant Statin DDIs

• Antiarrhythmic agents (e.g., amiodarone)

• Immunosuppressant drugs for solid organ transplant patients (e.g., cyclosporine)

• Antiretroviral therapy to treat HIV

• Others: ranolazine, conivaptan, ticagrelor

Summary

• Mechanisms of statin DDI are multifaceted
• Many sources of information
• Summary recommendations being the most “interpreted” for clinicians
• Manage **specific** statin DDIs differently:
  – Switch to a safer statin or use statin dose limitations (when appropriate)
  – Avoid/change interacting drug
Take Home Message

Don’t automatically override statin DDI alerts, evaluate each carefully

Avoid statin-gemfibrozil combination use whenever possible
Management of Drug-Drug Interaction with Statins

Joseph Saseen, PharmD, BCPS, BCACP, CLS, FNLA
Professor and Vice Chair