Optimising the Efficacy & Safety of Statins

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On-Treatment LDL-C is Closely Related to CVD Events in Statin Trials – Lower is Better

Meta-analysis of Effects of Statins on Any Major Vascular Event* at 1 Year in the Outcome Studies

Statins have diverse chemical structures governing binding affinity and lipophilicity but share the common pharmacophore with resemblance to HMG

Simvastatin and lovastatin are given as lactones and have to be converted to the open acid moiety for enzyme binding

Reappraisal of long term safety of Statins

Safety of statins: an update
Miao Hu, Bernard M.Y. Cheung and Brian Tomlinson

Abstract: Statins are widely used and have been proven to be effective in the prevention of atherosclerotic vascular disease events, primarily by reducing plasma low-density lipoprotein cholesterol concentrations. Although statins are generally well tolerated and present an excellent safety profile, adverse effects from muscle toxicity and liver enzyme abnormalities may occur in some patients. Myopathy and rhabdomyolysis are rare with statin monotherapy at the approved dose ranges, but the risk increases with use of higher doses, interacting drugs and genetic predisposition. Asymptomatic increases in liver transaminases with statin treatment do not seem to be associated with an increased risk of liver disease. Therefore, statin treatment can be safely used in patients with mild to moderately abnormal liver tests that are potentially attributable to nonalcoholic fatty liver disease and can improve liver tests and reduce cardiovascular morbidity in this group of patients. The risks of other unfavorable effects such as the slightly increased risk of new-onset diabetes and potentially increased risk of haemorrhagic stroke are much smaller than the cardiovascular benefits with the use of statins.

Keywords: cardiovascular disease, drug safety, myopathy, rhabdomyolysis, statins

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

Background: Trials of statin therapy have had conflicting findings on the risk of development of diabetes mellitus in patients given statins. We aimed to establish by a meta-analysis of published and unpublished data whether any relation exists between statin use and development of diabetes.

Methods: We searched Medline, Embase, and the Cochrane Central Register of Controlled Trials from 1994 to 2009 for randomised controlled endpoint trials of statins. We included only trials with more than 1000 patients, with identical follow-up in both groups and duration of use of 1 year. We excluded trials with patients with organ transplants or who needed haemodialysis. We used the β statistic to measure heterogeneity between trials and calculated risk estimates for incident diabetes with random-effect meta-analysis.

Findings: We identified 13 statin trials with 91,149 participants, of whom 4278 (2226 assigned statins and 2052 assigned control treatment) developed diabetes during a mean of 4 years. Statin therapy was associated with a 9% increased risk for incident diabetes (odds ratio [OR] 1.09, 95% CI 1.02-1.17), with little heterogeneity (I²=18%) between trials. Meta-regression showed that risk of development of diabetes with statins was highest in trials with older participants, but neither baseline body mass index nor change in LDL-cholesterol concentrations accounted for residual variation in risk. Treatment of 255 (95% CI 150-452) patients with statins for 4 years resulted in one extra case of diabetes.

Interpretation: Statin therapy is associated with a slightly increased risk of development of diabetes, but the risk is low both in absolute terms and when compared with the reduction in coronary events. Clinical practice in patients with moderate or high cardiovascular risk or existing cardiovascular disease should not change.

Statinn N et al., Lancet 2010;375:735-42.
Muscle toxicity

- Muscle toxicity is the most significant and well documented adverse effect with statins.
- Mild symptoms of muscle pain, tenderness and weakness are relatively common, but fortunately, the most severe and potentially fatal condition of rhabdomyolysis is very rare.
- All statins can cause muscle toxicity if given in high enough dosage or if there are drug interactions increasing systemic exposure.
- Several predisposing factors have been identified, including old age, renal/liver dysfunction and hypothyroidism, and some patients have a genetic predisposition which either alters the systemic exposure to the drug or causes susceptibility in the muscles.

Statin safety: Muscle effects - Benefit: Risk

**CK >10 × ULN: Frequency by LDL-C Reduction**

- **Rosuvastatin (5, 10, 20, 40 mg)**
- **Atorvastatin (10, 20, 40, 80 mg)**
- **Simvastatin (40, 80 mg)**
- **Pravastatin (20, 40 mg)**
- **Cerivastatin (0.2, 0.3, 0.4, 0.8 mg)**

### SEARCH: Effects of more vs. less STATIN on MORTALITY

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Simvastatin allocation</th>
<th>Risk ratio &amp; 95% CI</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>80mg (n=6031)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20mg (n=6033)</td>
<td></td>
</tr>
<tr>
<td>CHD</td>
<td>447 (7.4%) 438 (7.3%)</td>
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<tr>
<td>Stroke</td>
<td>57 (0.9%) 67 (1.1%)</td>
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<tr>
<td>Other vascular</td>
<td>53 (0.9%) 56 (0.9%)</td>
<td></td>
</tr>
<tr>
<td>All vascular</td>
<td>557 (9.2%) 561 (9.3%)</td>
<td></td>
</tr>
<tr>
<td>Neoplastic</td>
<td>245 (4.1%) 266 (4.4%)</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>74 (1.2%) 58 (1.0%)</td>
<td></td>
</tr>
<tr>
<td>Other medical</td>
<td>75 (1.2%) 70 (1.2%)</td>
<td></td>
</tr>
<tr>
<td>Non-medical</td>
<td>13 (0.2%) 14 (0.2%)</td>
<td></td>
</tr>
<tr>
<td>All non-vascular</td>
<td>407 (6.7%) 408 (6.8%)</td>
<td></td>
</tr>
<tr>
<td>All causes</td>
<td>964 (16.0%) 969 (16.1%)</td>
<td></td>
</tr>
</tbody>
</table>

Average 0.35 mmol/L greater reduction in LDL-C
6% reduction in major vascular events
Risk ratio 0.94 (95% CI 0.88–1.01; p=0.10).
2 (0.03%) cases of myopathy with 20 mg, 53 (0.9%) with 80 mg.

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**Pharmacokinetics of statins**

- **Lovastatin** (CYP3A4/5)
- **Simvastatin** (CYP3A4)
- **Atorvastatin** (CYP2C8)
- **Cerivastatin** (CYP2C9)
- **Fluvastatin** (CYP2C9)
- **Pitavastatin** (CYP2C9, 2C19 (minor))
- **Pravastatin** (CYP3A4, 2C9, 2C19 (minor))
Hepatic Uptake and Efflux Transporters

**Liver**

- ABCB1/3
- ABCB11
- ABCC2
- ABCG2

**Bile**

- ABCC1/3
- SLC10A1
- SLCO1B1

**Hepatocyte**

- SLC10A1
- OAT2
- OCT1
- ABCC1/3/4

**Portal circulation**

**Systemic circulation**

Myopathy

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**Effect of the SLCO1B1 521 T>C polymorphism on the pharmacokinetics of simvastatin**

**SLCO1B1**

- Open squares — c.521TT genotype (n=16);
- solid squares — c.521TC genotype (n=11);
- solid triangles — c.521CC genotype (n=4).

Simvastatin acid AUC(0-∞)

3.2x in CC vs. TT

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Pharmacogenomics of Statin-Induced Myopathy

Nearly complete LD with rs4149056 (521 T>C) in SLCO1B1

Figure 1. Results of Tests for a Trend in the Association between Myopathy and Each SNP Measured in the Genomewide Association Study.
P values are shown for each SNP measured among 85 participants with myopathy and 90 matched controls who were taking 80 mg of simvastatin daily. Analyses are based on 316,184 of the 318,237 SNPs (99.4%) on the Sentrix HumanHap300-Duo BeadChip (Illumina). A result above the horizontal red line indicates strong evidence of an association ($P<3\times10^{-8}$).


SLCO1B1 Variants and Statin-Induced Myopathy - a Genomewide Study

Estimated cumulative risk of myopathy associated with taking 80 mg of simvastatin daily, according to SLCO1B1 rs4149056 (*5, 521T>C) genotype. 60% of myopathy cases could be attributed to the C variant

FDA guideline on 8 June 2011 on limiting the use of simvastatin 80 mg

**FDA NEWS RELEASE**

For Immediate Release: June 8, 2011

Media Inquiries: Morgan Zoricke, 301-795-0397, morgan.zoricke@fda.hhs.gov

Consumer Inquiries: 888-357-FDA

FDA announces new safety recommendations for high-dose simvastatin

**Increased risk of muscle injury cited**

The U.S. Food and Drug Administration today is announcing safety label changes for the cholesterol-lowering medication simvastatin because the highest approved dose—80 milligram (mg)—has been associated with an elevated risk of muscle injury or myopathy, particularly during the first 12 months of use.

The agency is recommending that simvastatin 80 mg be used only in patients who have been taking this dose for 12 months or more and have not experienced any muscle toxicity. It should not be prescribed to new patients. There are also new contraindications and dose limitations for when simvastatin is taken with certain other medications.

Simvastatin is sold together with diet and exercise to reduce the amount of "bad cholesterol" (low-density lipoprotein cholesterol or LDL-C) in the blood. High levels of LDL-C are linked to a higher risk of heart attack, stroke and cardiovascular death. In 2010, about 2.1 million patients in the United States were prescribed a product containing simvastatin 80 mg.

"The FDA has completed its review of the safety of high-dose simvastatin and is making label changes to reduce the risk of statin-associated muscle injury," said Dr. Richard Coleman, M.D., deputy director of the Division of Metabolism and Endocrinology Products in the FDA's Center for Drug Evaluation and Research. "We want to ensure that patients and health care professionals are aware of the new labeling changes to simvastatin, including the increased risk of myopathy when using the 80 mg dose of simvastatin."

The changes to the label for simvastatin-containing medications are based on the FDA's review of the results of the seven-year Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine clinical trial, other clinical trial data, and analyses of adverse events submitted to the FDA's Adverse Event Reporting System. All showed that patients taking simvastatin 80 mg daily had an increased risk of muscle injury compared to patients taking lower doses of simvastatin or other statin drugs.

Simvastatin is sold under the brand name Zocor and as a single ingredient generic product. It is also sold in combination with ezetimibe as Vytorin and in combination with atorvastatin as Simcor.

The Clinical Pharmacogenomics Implementation Consortium: CPIC

**Guideline for SLCO1B1 and Simvastatin-Induced Myopathy**
Each copy of the 521C variant allele was only associated with -1.28% smaller reductions in LDL-C in response to simvastatin in the Heart Protection Study (>10,000 patients).

No significantly noticeable effect on the lipid-lowering effect of statins.


Pharmacokinetics of statins

Extensive metabolism via CYP
Lovastatin
Simvastatin
Atorvastatin

CYP3A4/5

www.pharmgkb.org
Effect of the CYP3A5*3 polymorphism on the pharmacokinetics of simvastatin

![Graph showing the effect of CYP3A5 polymorphism on simvastatin pharmacokinetics]

**Associations between the genotypes and phenotype of CYP3A and the lipid response to simvastatin in Chinese patients with hypercholesterolemia**

**Aim:** This study examined the associations between the CYP3A4*1G, CYP3A4*22, CYP3A5*2 and PPARA rs4823613 A>G polymorphisms and the phenotypes of CYP3A estimated by the ratio of 6β-hydroxy cortisol:cortisol in urine, and the low-density lipoprotein cholesterol response to simvastatin in Chinese patients with hypercholesterolemia. **Patients & methods:** Lipid profiles were determined off treatment and after 6 weeks of treatment with simvastatin 40 mg in 273 patients. **Results:** There was no significant association between the ratio of 6β-hydroxy cortisol:cortisol and the low-density lipoprotein cholesterol response to simvastatin in the study subjects (r = 0.052; p = 0.455). The genetic polymorphisms examined had no significant association with this measure of CYP3A phenotype or the lipid-lowering responses to simvastatin. **Conclusion:** The results of this study suggest that genetic polymorphisms in CYP3A or other regulatory genes, or the CYP3A activity itself, is unlikely to have a significant effect on the lipid-lowering responses to simvastatin in Chinese patients.

Hu M, Tomlinson B. Pharmacogenomics (2013) 14(1), 25-34

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**Genetic polymorphisms in CYP3A or PPARA had no significant effect on the lipid-lowering responses to simvastatin**

<table>
<thead>
<tr>
<th>Genetic polymorphisms</th>
<th>Genotypes</th>
<th>LDL-C response to simvastatin (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A4*1G</td>
<td><em>1</em>1 (n = 143)</td>
<td>-47.5 ± 11.6</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td></td>
<td><em>1</em>1G (n = 107)</td>
<td>-46.7 ± 10.9</td>
<td></td>
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<tr>
<td></td>
<td><em>1G</em>1G (n = 18)</td>
<td>-47.7 ± 14.8</td>
<td></td>
</tr>
<tr>
<td>CYP3A5*3</td>
<td><em>1</em>1 (n = 18)</td>
<td>-50.2 ± 9.6</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td></td>
<td><em>1</em>3 (n = 107)</td>
<td>-47.2 ± 12.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>3</em>3 (n = 144)</td>
<td>-47.0 ± 11.3</td>
<td></td>
</tr>
<tr>
<td>PPARA rs4823613 A&gt;G</td>
<td>AA (n = 155)</td>
<td>-47.4 ± 11.6</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td></td>
<td>AG (n = 101)</td>
<td>-47.5 ± 11.4</td>
<td></td>
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<tr>
<td></td>
<td>GG (n = 14)</td>
<td>-45.0 ± 11.4</td>
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Hu M, Tomlinson B. Pharmacogenomics (2013) 14(1), 25-34
Ethnic Differences in Statin Disposition

Rosuvastatin Pharmacokinetics: Plasma Levels in East Asians 2x Caucasians

* Not explained by body weight or other phenotypic factors

Lee E et al., Clinical Pharmacology & Therapeutics 2005;78:330-41

Rosuvastatin Dose in Asians

FDA issues rosuvastatin advisory highlighting revised label

March 2, 2005
Wilmington, DE - The Food and Drug Administration (FDA) issued a public-health advisory on rosuvastatin (Crestor®) today that highlights a revised package insert for the cholesterol-lowering medication.

Also, based on a pharmacokinetic study that found elevated drug levels in a population of Asian patients, the "Dosage and Administration" section of the label now advises that the 5-mg dose of rosuvastatin be considered the starting dose in this population.
Ethnic difference in the pharmacokinetics of rosuvastatin

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Ethnic difference in the lipid-lowering response to rosuvastatin

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**The Direct Statin COMparison of LDL-C Values: an Evaluation of Rosuvastatin therapy (DISCOVERY) Program**

*Aim:* The efficacy of rosuvastatin (10mg), atorvastatin (10mg) and other statins for achieving lipid goals

- DISCOVERY-Asia: China, Hong Kong, Malaysia, Korea, Taiwan, and Thailand
- DISCOVERY-Alpha: 93 centres in eastern Europe, Central and South America, and the Middle East
- DISCOVERY Netherlands:
- DISCOVERY UK: UK
- DISCOVERY PENTA: Brazil, Colombia, Mexico, Portugal, and Venezuela.
- DISCOVERY Triple Country: Finland, Iceland, and Ireland
Letter to the Editor

Do the lipid responses to rosuvastatin and atorvastatin differ between Chinese and Caucasians? Comparison of the DISCOVERY-Hong Kong study with other DISCOVERY studies

Miao Hu, Sandra S.H. Lui, Gary T.C. Ko, Brian Tomlinson

*Department of Medicine and Therapeutics, Prince of Wales Hospital, the Chinese University of Hong Kong, Hong Kong SAR
**Hong Kong Institute of Cardiology, the Chinese University of Hong Kong, Hong Kong SAR

Study and patient characteristics at baseline of the various DISCOVERY studies

<table>
<thead>
<tr>
<th>Countries</th>
<th>Randomized population</th>
<th>Randomized groups (ratio)</th>
<th>Non-smokers (%)</th>
<th>Age (years)</th>
<th>Male (%)</th>
<th>BMI (kg/m²)</th>
<th>Diabetes (%)</th>
<th>Non-HDL-C (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hong Kong</td>
<td>126</td>
<td>A10 vs. A10 (2:1)</td>
<td>67/33</td>
<td>58 ± 8.8</td>
<td>51</td>
<td>25</td>
<td>74</td>
<td>A: 4.5 ± 1.0</td>
</tr>
<tr>
<td>Asia, Hong Kong</td>
<td>1506</td>
<td>A10 vs. A10 (2:1)</td>
<td>60/40</td>
<td>58 ± 8.8</td>
<td>51</td>
<td>25</td>
<td>74</td>
<td>A: 4.5 ± 1.0</td>
</tr>
<tr>
<td>Malaysia, Korea</td>
<td>1482</td>
<td>A10 vs. A10 (2:1)</td>
<td>67/33</td>
<td>58 ± 8.8</td>
<td>51</td>
<td>25</td>
<td>74</td>
<td>A: 4.5 ± 1.0</td>
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<td>Thailand, and</td>
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<td>A: 4.5 ± 1.0</td>
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<td>Thailand</td>
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<td></td>
<td></td>
<td></td>
<td>A: 4.5 ± 1.0</td>
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<td>Singapore</td>
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<td></td>
<td></td>
<td></td>
<td>A: 4.5 ± 1.0</td>
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<tr>
<td>Japan</td>
<td>1124</td>
<td>A10 vs. A10 (2:1)</td>
<td>60/40</td>
<td>58 ± 8.8</td>
<td>51</td>
<td>25</td>
<td>74</td>
<td>A: 4.5 ± 1.0</td>
</tr>
<tr>
<td>Brazil, Colombia</td>
<td>1847</td>
<td>A10 vs. A10 (2:1)</td>
<td>60/40</td>
<td>58 ± 8.8</td>
<td>51</td>
<td>25</td>
<td>74</td>
<td>A: 4.5 ± 1.0</td>
</tr>
<tr>
<td>Mexico, Peru,</td>
<td>1024</td>
<td>A10 vs. A10 (2:1)</td>
<td>60/40</td>
<td>58 ± 8.8</td>
<td>51</td>
<td>25</td>
<td>74</td>
<td>A: 4.5 ± 1.0</td>
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<td>and Ireland</td>
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<td>A: 4.5 ± 1.0</td>
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<tr>
<td>UK</td>
<td>1000</td>
<td>A: 87/12</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>A: 4.5 ± 1.0</td>
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<tr>
<td>Holland, Iceland</td>
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<td></td>
<td></td>
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<td></td>
<td>A: 4.5 ± 1.0</td>
</tr>
</tbody>
</table>

A 10 = atorvastatin 10 mg; P 40 = pravastatin 40 mg; R 10 = rosuvastatin 10 mg; S 20 = simvastatin 20 mg; N = naïve; and S = switched.

*P<0.05; **P<0.01; *** P<0.001 for DISCOVERY Hong Kong vs. other studies. NS: non-significant

† VOYAGER is an individual patient data meta-analysis of 32,258 patients treated with statins in 37 studies

The LDL-C response to rosuvastatin 10 mg daily (A) and atorvastatin 10 mg (B) in statin-naive patients in DISCOVERY studies and the VOYAGER database

(A) Rosuvastatin 10 mg daily

(B) Atorvastatin 10 mg daily

*P<0.05; **P<0.01; *** P<0.001 for DISCOVERY Hong Kong vs. other studies. NS: non-significant

ABCG2, the major efflux transporter mediating the intestinal efflux and biliary excretion of rosvustatin

ABCG2, the major efflux transporter mediating the intestinal efflux and biliary excretion of rosvustatin

**Effect of the ABCG2 421 C>A Polymorphism on the Pharmacokinetics of Rosuvastatin in Chinese and Caucasians**

**Chinese**

![Graph showing Rosuvastatin levels over time for Chinese individuals with different genotypes.]


**Caucasians**

![Graph showing Rosuvastatin levels over time for Caucasian individuals with different genotypes.]


**Effect of SLCO1B1, ABCG2, and ABCB1 genotypes on the systemic exposure of various statins**

![Bar chart showing multiples of increase in AUC for different statins in relation to SLCO1B1, ABCG2, and ABCB1 genotypes.]

Adapted from Niemi M. Clin Pharmacol Ther 2010; 87(1): 130-3
ABCG2 Polymorphism Is Associated With the Low-Density Lipoprotein Cholesterol Response to Rosuvastatin


Pharmacogenetic analysis of lipid responses to rosuvastatin in Chinese patients


Lipid changes with statin treatments vary greatly between individuals for reasons which are largely unknown. This study was performed to examine the genetic determinants of lipid responses to rosuvastatin in Chinese patients. A total of 125 polymorphisms in 61 candidate genes from 366 Chinese patients were analyzed for association with the lipid responses to rosuvastatin 10 mg daily. The polymorphisms most highly associated with the low-density lipoprotein cholesterol (LDL-C) response were 421C>A in the ATP-binding cassette G2 gene (P=9.2×10^-8), followed by 16301G>A (I267M) in the flavin-containing monoxygenase 3 gene (P=0.0002), 1421C>G in the lipoprotein lipase gene (P=0.002), and rs4420638 in the apolipoprotein E/C-I/C-I/C-IV/C-II gene cluster (P=0.004). Patients with familial hypercholesterolemia had 2.6% smaller reductions in LDL-C compared with patients without familial hypercholesterolemia. This study identified some genetic determinants of LDL-C response to rosuvastatin in Chinese patients, which need to be replicated in other populations.

Pharmacogenetics and Genomics 2010;20:634–637

Keywords: Chinese, lipid responses, pharmacogenetics, rosuvastatin, single nucleotide polymorphisms

Deutsches Institut für Medizinische Forschung, Institute of Medicinal Chemistry, and University Hospital, Heidelberg, Germany

Correspondence to Prof. Brian Tomlinson, Department of Medicine and Therapeutics, Prince of Wales Hospital, Shatin, Hong Kong SAR

Received 27 April 2010 Accepted 6 July 2010

Hu M et al., Pharmacogenetics and Genomics 2010, 20:634–637
ABCG2 rs1481012 Polymorphism

The intronic rs1481012 A>G polymorphism in ABCG2 is in complete LD with the ABCG2 421C>A (r^2=1)

The allele frequency of the ABCG2 421C>A polymorphism is about 35% in Chinese compared to 14% in Caucasians

Farnesoid X receptor (FXR), a bile-acid-activated nuclear receptor

- FXR is a nuclear receptor and a receptor for bile acids
- Activation of FXR leads to altered expression of many genes responsible for bile acid and lipid and glucose metabolism and transport
- FXR also regulates multiple drug metabolizing enzymes and drug transporters (e.g. SLCO1B1, SLCO1B3, NTCP and some efflux transporters) by binding to FXR response elements and promoting transcription of target genes
Genetic Polymorphisms & Plasma Concentration of Rosuvastatin in Routine Clinical Care
A sensitive method for simultaneous determination of rosuvastatin and N-desmethyl rosuvastatin in human plasma using LC/MS

The lower limit of quantifications of 0.05 and 0.02 mg/L allowed simultaneous determination of plasma rosuvastatin and N-desmethyl rosuvastatin over a period of 24 h in subjects receiving a single oral dose of 10 mg rosuvastatin.

Effects of polymorphisms in ABCG2, SLC10A1, SLC10A1 and CYP2C9/19 on plasma concentrations of rosuvastatin and lipid response in Chinese patients

Aim: This study examined whether the ABCG2 421C>A polymorphism and variants in other genes potentially related to the pharmacokinetics of rosuvastatin influenced the plasma concentration of rosuvastatin in Chinese patients with hypercholesterolemia. Patients & methods: Overnight fasting blood samples were collected from 291 patients who had received a rosuvastatin 10 mg night-time dose for at least 4 weeks. Plasma concentrations of rosuvastatin and N-desmethyl rosuvastatin were quantified using liquid chromatography tandem mass spectrometry. Results: In subjects with the ABCG2 421AA genotype (n = 39), the mean plasma concentrations of rosuvastatin and its metabolite were 63 and 41% greater than the values in those with the 421CA genotype (n = 108) and 120 and 99% greater than in those with the 421CC genotype (n = 129). The plasma concentrations of rosuvastatin were associated (r = −0.194; p = 0.001) with the percentage reduction in low-density lipoprotein cholesterol with rosuvastatin, but the association was not significant after adjusting for the ABCG2 421C>A polymorphism. The SLC10A1 521T>C polymorphism was associated with increased plasma concentrations of rosuvastatin and impaired N-demethylation of rosuvastatin, but had no impact on its lipid-lowering effect. Polymorphisms in CYP2C9, CYP2C19 and SLC10A1 had minimal effects. Conclusion: These findings suggest that the increased plasma concentrations of rosuvastatin in Chinese patients are associated with increased lipid-lowering effects and lower doses of rosuvastatin should be effective in subjects with the ABCG2 421C>A variant.

Original submitted 18 April 2013; Revision submitted 17 June 2013

Effect of the ABCG2 421C>A polymorphism on the plasma concentration of Rosuvastatin in Chinese Patients with hypercholesterolaemia

ABCG2 421C>A polymorphism

![Box plots showing plasma concentrations of rosuvastatin stratified by genotypes of the SLCO1B1 521T>C and ABCG2 421C>A polymorphisms.](image1)


Plasma concentrations of rosuvastatin stratified by genotypes of the SLCO1B1 521T>C and ABCG2 421C>A polymorphisms

![Box plots showing plasma concentrations of rosuvastatin stratified by genotypes of the SLCO1B1 521T>C and ABCG2 421C>A polymorphisms.](image2)

Association between genotypic and phenotypic factors, and the plasma concentrations of rosuvastatin

<table>
<thead>
<tr>
<th>Variables</th>
<th>Model 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta$</td>
</tr>
<tr>
<td>ABCG2 421C&gt;A polymorphism (1 = CC, 2 = CA, 3 = AA)</td>
<td>0.379</td>
</tr>
<tr>
<td>Bodyweight (kg)</td>
<td>-0.238</td>
</tr>
<tr>
<td>Hypertension (0 = no, 1 = yes)</td>
<td>0.192</td>
</tr>
<tr>
<td>SLC01B1 521T&gt;C polymorphism (1 = TT, 2 = TC or CC)</td>
<td>0.123</td>
</tr>
</tbody>
</table>


Genome-wide association studies on the pharmacogenomics of statins

<table>
<thead>
<tr>
<th>Statins</th>
<th>Study population</th>
<th>Reductions in LDL-C or other cardiovascular risk factors$^\dagger$</th>
<th>Myopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>TNT</td>
<td>None, but APOE significant at genome-wide level and PCSK9, HMGCR significant in candidate gene analysis</td>
<td>NA</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>CARDS, ASCOT and PROSPER</td>
<td>APOE and LPA</td>
<td>NA</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>CARE, WOSCOPS and PROSPER/PHASE</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>JUPITER</td>
<td>ABCG2, APOE, LPA (PCSK9 gene-significant); None for changes in CRP$^\dagger$</td>
<td>NA</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>HPS</td>
<td>None, but LPA and APOE significant in candidate gene analysis</td>
<td>NA</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>SEARCH</td>
<td>NA</td>
<td>SLC01B1 $^\dagger$</td>
</tr>
</tbody>
</table>

Summary

- The hepatic uptake transporter SLCO1B1 plays an important role in determining the plasma concentrations and the risk of myopathy of statins.
- The functional SNP 521 T>C in SLCO1B1 significantly increases the pharmacokinetics of statins and increases the risk of myopathy of simvastatin, but it had little effect on the hepatic exposure and lipid-lowering effect of statins.
- The efflux transporter ABCG2 appears to significantly affect the absorption and the biliary excretion of the substrate statins.
- The loss-of-function mutation 421C>A in ABCG2 is the major genetic determinant of the pharmacokinetics and the lipid-lowering effect of rosuvastatin.

Summary

- Pharmacogenomic studies on statins have improved our understanding of how genetic mutations influence drug response.
- Some academic medical centers have already conduct SLCO1B1 genotyping and link this to medical record at the point of prescribing simvastatin.
- Changes in LDL-C may be predictive of clinical outcomes, but it would be more important to examine the impact of genetic polymorphisms on cardiovascular outcomes in statin users.
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Thank You  
For Your Attention!