2013 Joint Conference of Drug Safety Research Centres

In affiliation with the Pacific Rim Association for Clinical Pharmacogenetics (PRACP)

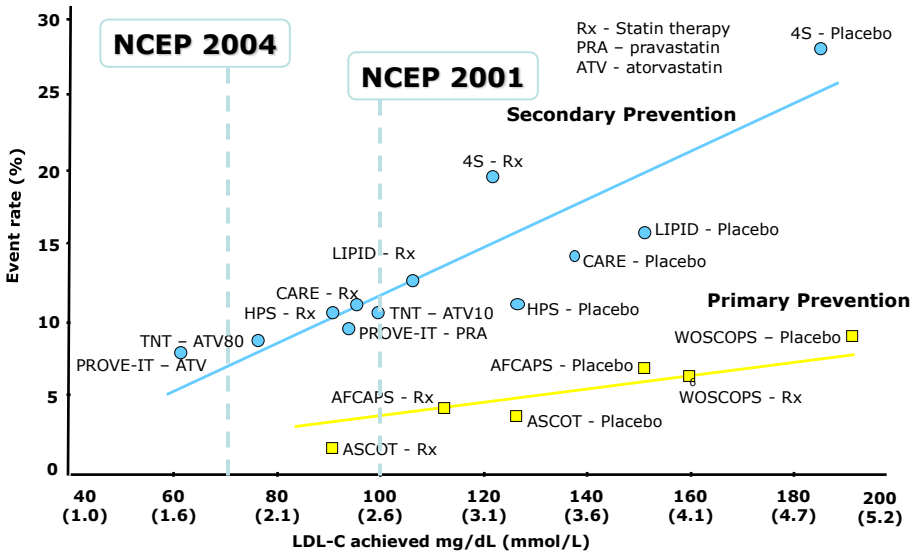
16 October 2013

Optimising the Efficacy & Safety of Statins

Teresa M Hu

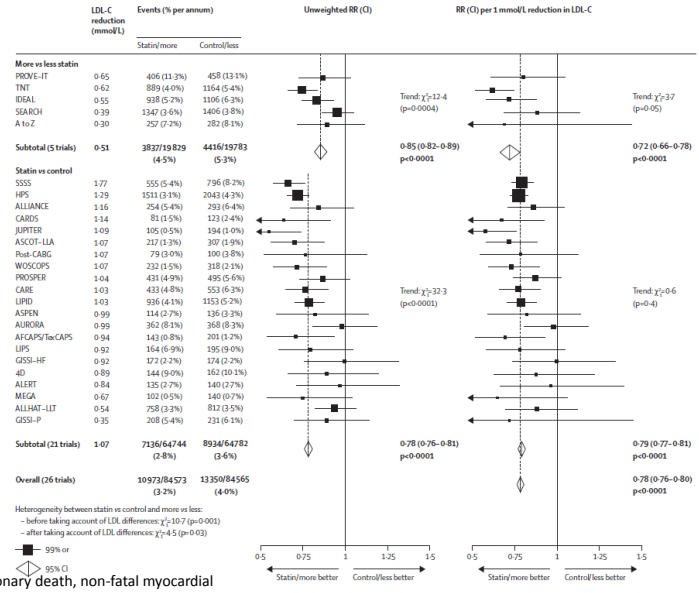
Division of Clinical Pharmacology
Department of Medicine & Therapeutics
The Chinese University of Hong Kong

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



Adapted from Rosensen RS. *Exp Opin Emerg Drugs* 2004;9(2):269-279. LaRosa JC *et al. N Engl J Med* 2005;352:1425-1435

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

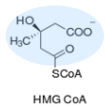


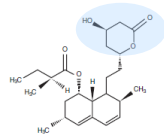
*Defined as coronary death, non-fatal myocardial infarction, coronary revascularisation, or stroke

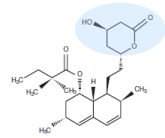
Baigent C et al., Lancet 2010;376:1670-81

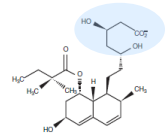
Chemical Structures of the Statins

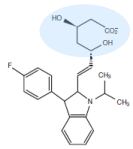
Statins have diverse chemical structures governing binding affinity and lipophilicity but share the common pharmacophore with resemblance to HMG

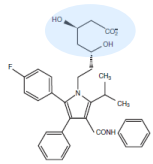


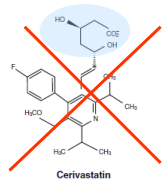




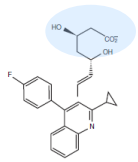


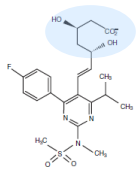






Simvastatin and lovastatin are given as lactones and have to be converted to the open acid moiety for enzyme binding





Adapted from Hu M, et al. Current Pharmacogenomics & Personalized Medicine 2009;7:1-26.

Reappraisal of long term safety of Statins

Therapeutic Advances in Drug Safety *Review*

Safety of statins: an update

Ther Adv Drug Saf
(2012) 3(3) 133–144
DOI: 10.1177/2042098612439884

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

Naveed Sattar, David Preiss, Heather M Murray, Paul Welsh, Brendan M Buckley, Anton J M de Craen, Sreenivasa Rao Kondapally Seshasai, John J McMurray, Dilys J Freeman, J Wouter Jukema, Peter W Macfarlane, Chris J Packard, David J Stott, Rudi G Westendorp, James Shepherd, Barry R Davis, Sara L Pressel, Roberto Marchioli, Rosa Maria Marfisi, Aldo P Maggioni, Luigi Tavazzi, Gianni Tognoni, John Kjekshus, Terje R Pedersen, Thomas J Cook, Antonio M Gotto, Michael B Clearfield, John R Downs, Haruo Nakamura, Yasuo Ohashi, Kyoichi Mizuno, Kausik K Ray, Ian Ford

Summary

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 more than 1 year. We excluded trials of patients with organ transplants or who needed haemodialysis. We used the I^2 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 91 140 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 (I^2=11%) 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 150–852) 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.

Lancet 2010; 375: 735–42
Published Online
February 17, 2010
DOI:10.1016/S0140-6736(09)61965-6
See **Comment** page 700

British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, UK (Prof N Sattar PhD, D Preiss MRCP, P Welsh PhD, Prof J J McMurray MD); **Robertson Centre for Biostatistics, University of Glasgow, Glasgow, UK** (H M Murray MSc, Prof I Ford PhD); **Department of Pharmacology and Therapeutics, Cork University Hospital, Cork, Ireland** (Prof B M Buckley FRCPI); **Department of Gerontology and Geriatrics, Leiden University Medical Centre, Leiden, Netherlands**

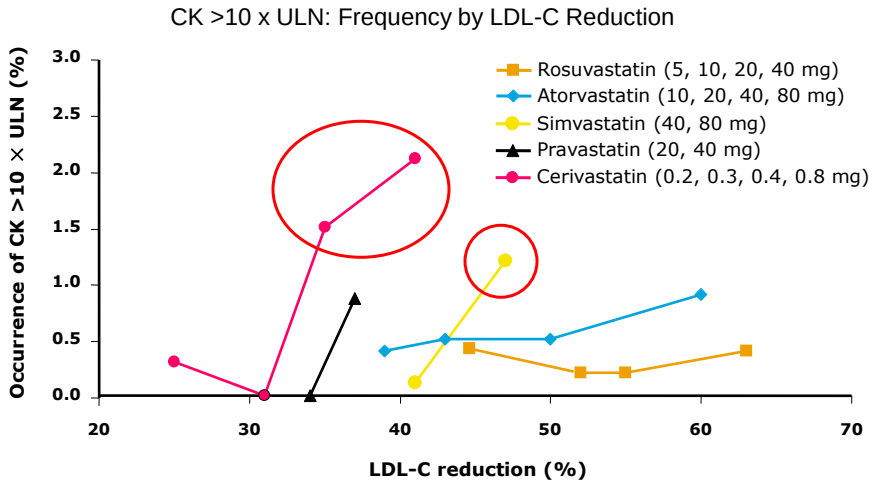
Stattar N, et al., Lancet 2010;375:735-42.

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

Hu M, Cheung BMY, Tomlinson B. Ther Adv Drug Saf 2012;3(3): 133-144

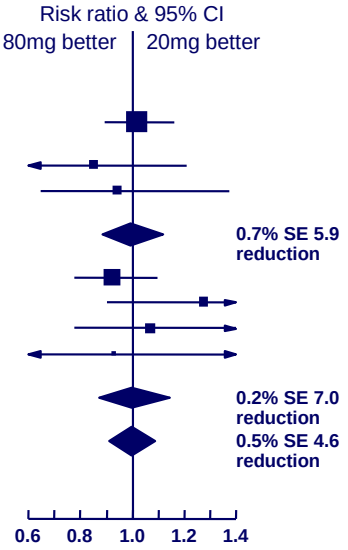
Statin safety: Muscle effects - Benefit: Risk



Brewer H *Am J Cardiol* 2003;92(Suppl):23K–29K
Davidson M *Exp Opin Drug Saf* 2004;3 (6):547-557

SEARCH: Effects of more vs. less STATIN on MORTALITY

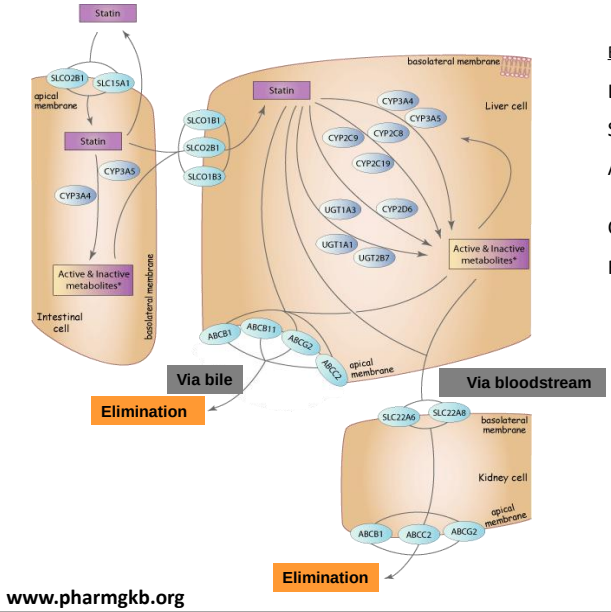
Cause of death	Simvastatin allocation 80mg (n=6031)		20mg (n=6033)	
CHD	447	(7.4%)	438	(7.3%)
Stroke	57	(0.9%)	67	(1.1%)
Other vascular	53	(0.9%)	56	(0.9%)
All vascular	**557**	**(9.2%)**	**561**	**(9.3%)**
Neoplastic	245	(4.1%)	266	(4.4%)
Respiratory	74	(1.2%)	58	(1.0%)
Other medical	75	(1.2%)	70	(1.2%)
Non-medical	13	(0.2%)	14	(0.2%)
All non-vascular	**407**	**(6.7%)**	**408**	**(6.8%)**
All causes	**964**	**(16.0%)**	**969**	**(16.1%)**



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

Search Collaborative Group, Lancet. 2010;376:1658-69.

Pharmacokinetics of statins



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Extensive metabolism via CYP

- Lovastatin
- Simvastatin
- Atorvastatin

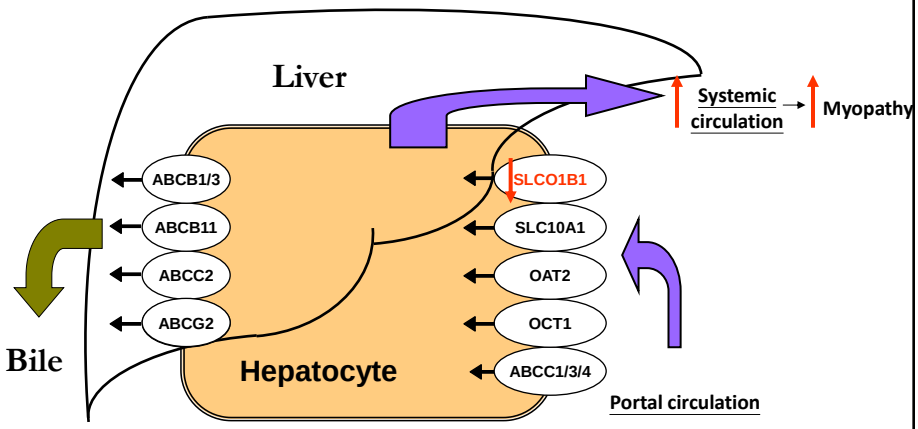
→ CYP3A4/5

- Cerivastatin → CYP2C8
- Fluvastatin → CYP2C9

Little metabolism via CYP

- Pravastatin → CYP3A4
- Rosuvastatin → CYP2C9, 2C19 (minor)
- Pitavastatin → CYP2C9, 2C8 (minor)

Hepatic Uptake and Efflux Transporters

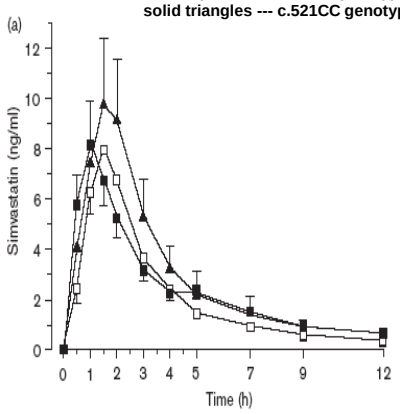


Hu M, et al. (2009) Current Pharmacogenomics & Personalized Medicine 7:1-26

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

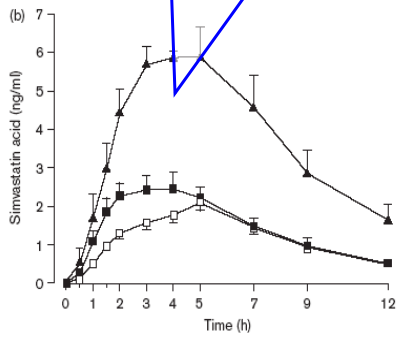
SLCO1B1

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



Simvastatin

Simvastatin acid AUC(0-∞)
↑3.2x in CC vs. TT



Simvastatin acid

Pasanen MK, et al., Pharmacogenetics and Genomics 2006, 16:873–879

Pharmacogenomics of Statin-Induced Myopathy

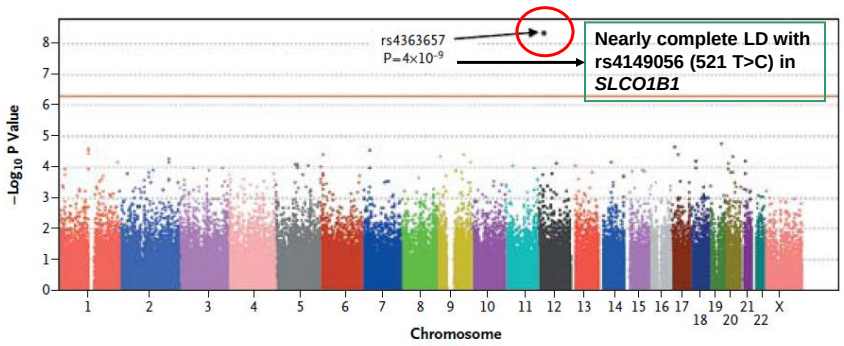
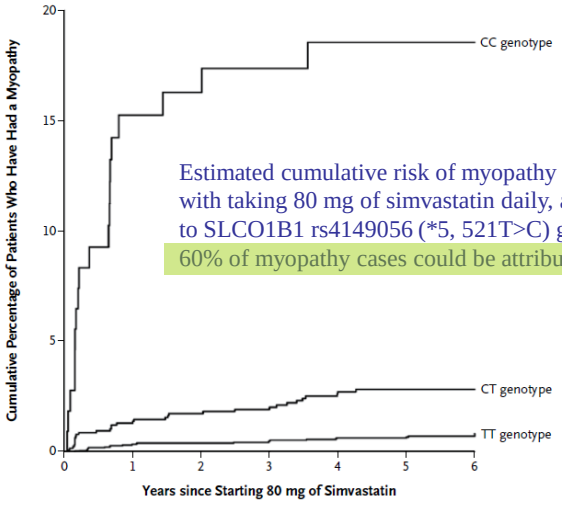


Figure 1. Results of Tests for a Trend in the Association between Myopathy and Each SNP Measured in the Genome-wide Association Study.

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 ($P<5\times10^{-7}$).

The SEARCH Collaborative Group. N Engl J Med 2008; 359: 789-99.

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

The SEARCH Collaborative Group. N Engl J Med 2008; 359: 789-99.

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

U.S. Food and Drug Administration

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News & Events

FDA NEWS RELEASE

For Immediate Release: June 8, 2011
Media Inquiries: Morgan Liscinsky, 301-796-0397, morgan.liscinsky@fda.hhs.gov
Consumer Inquiries: 888-INFO-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.

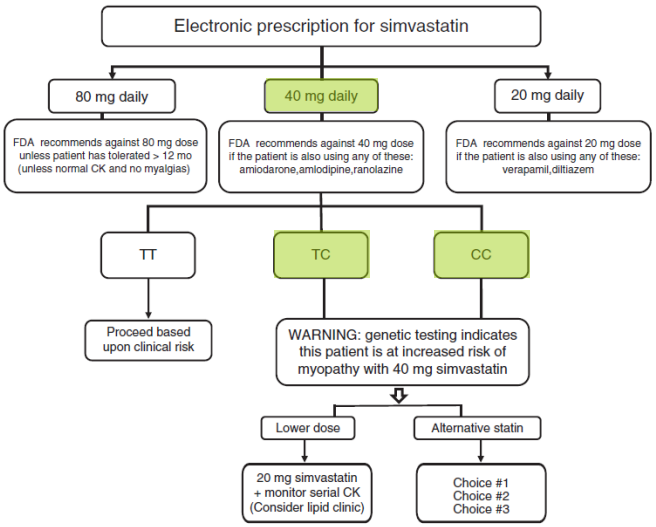
Simvastatin is used together with diet and exercise to reduce the amount of "bad cholesterol" (low-density lipoprotein cholesterol or LDL-C) in the blood. High levels of LDL-C are linked to a higher risk of heart attack, stroke and cardiovascular death. In 2010, about 2.1 million patients in the United 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 Eric Colman, 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. The risk of muscle injury is highest during the first year of treatment with the 80 mg dose of simvastatin, is often the result of interactions with certain other medicines, and is frequently associated with a genetic predisposition for simvastatin-related muscle injury.

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 niacin as Simcor.

The Clinical Pharmacogenomics Implementation Consortium: CPIC Guideline for *SLCO1B1* and Simvastatin-Induced Myopathy



Wilke RA et al., Clinical Pharmacology & Therapeutics 2012;92:112-117

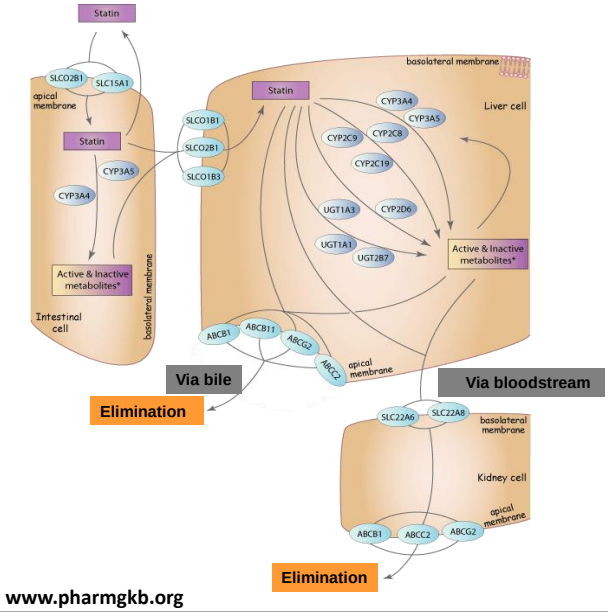
Effect of SLCO1B1 521T>C polymorphism on the lipid-lowering effect of statins

- 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

The SEARCH Collaborative Group. N Engl J Med 2008; 359: 789-99.

Hu M, Tomlinson B. *Pharmacogenomics*. 2013 Jun;14(8):981-95.

Pharmacokinetics of statins



Extensive metabolism via CYP

Lovastatin
Simvastatin
Atorvastatin
→ CYP3A4/5

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Clinical Pharmacology & Therapeutics

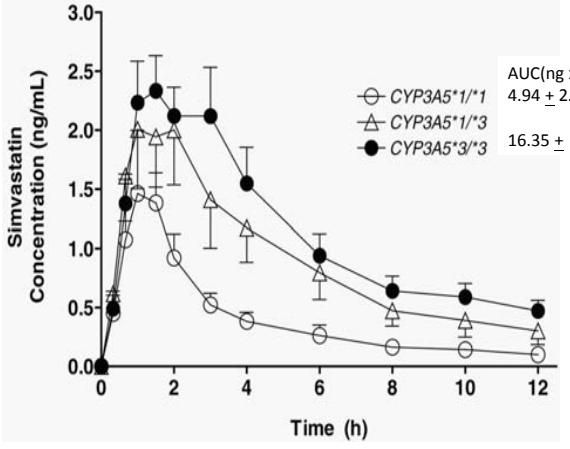
PPARA: A Novel Genetic Determinant of CYP3A4 *In Vitro* and *In Vivo*

Kathrin Klein[1], Maria Thomas[1], Stefan Winter[1], Andreas K. Nussler[2], Mikko Niemi[3], Matthias Schwab[1,4] and Ulrich M. Zanger[1]

Interindividual variability in cytochrome P450 3A4 (CYP3A4) is believed to be largely heritable; however, predictive genetic factors have remained scarce. Using a candidate-gene approach in a human liver bank, we identified single-nucleotide polymorphisms (SNPs) in the Ah-receptor nuclear translocator (*ARNT*), glucocorticoid receptor (GR), progesterone receptor membrane component 2 (*PGRMC2*), and peroxisome proliferator–activated receptor-α (*PPARA*) that are associated with CYP3A4 phenotype. Validation in atorvastatin-treated volunteers confirmed a decrease in atorvastatin-2-hydroxylation in carriers of *PPARA* SNP rs4253728. Homozygous carriers expressed significantly less PPAR-α protein in the liver. Moreover, shRNA-mediated *PPARA* gene knockdown in primary human hepatocytes decreased expression levels of the PPAR-α target ACOX1 and of CYP3A4 by more than 50%. In conclusion, this study identified novel genetic determinants of CYP3A4 that, together with nongenetic factors, explained 52, 55, and 33% of hepatic CYP3A4 mRNA, protein, and atorvastatin-2-hydroxylase activity, respectively. These findings have implications for variability in response to drug substrates of CYP3A4.

Clinical Pharmacology & Therapeutics (2012); **91** 6, 1044–1052

Effect of the CYP3A5 *3 polymorphism on the pharmacokinetics of simvastatin



AUC(ng x h/mL)
4.94 ± 2.25
16.35 ± 6.37 ↑3.3x

Kim KA et al. J Clin Pharmacol 2007; 47: 87-93.

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*3* and *PPARA* rs4823613 A>G polymorphisms and the phenotypes of CYP3A estimated by the ratio of 6β-hydroxycortisol: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-hydroxycortisol: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

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

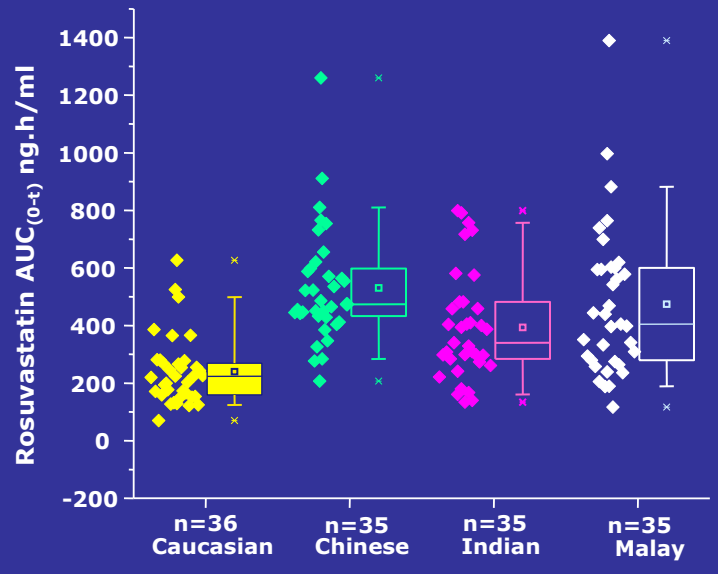
Genetic polymorphisms	Genotypes	LDL-C response to simvastatin (%)	
*CYP3A4*1G*	**1*1* (n = 143)	-47.5 ± 11.6	
	**1*1G* (n = 107)	-46.7 ± 10.9	*P*>0.05
	**1G*1G* (n = 18)	-47.7 ± 14.8	
*CYP3A5*3*	**1*1* (n = 18)	-50.2 ± 9.6	
	**1*3* (n = 107)	-47.2 ± 12.1	*P*>0.05
	**3*3* (n = 144)	-47.0 ± 11.3	
PPARA rs4823613 A>G	AA (n = 155)	-47.4 ± 11.6	
	AG (n = 101)	-47.5 ± 11.4	*P*>0.05
	GG (n = 14)	-45.0 ± 11.4	

↓ CYP3A enzyme activity → ↓ Downstream activity metabolites of simvastatin

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

?

Ethnic difference in the lipid-lowering response to rosuvastatin

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

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International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

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 [a] , Sandra S.H. Lui [a] , Gary T.C. Ko [b] , Brian Tomlinson [a,*]

[a] Department of Medicine and Therapeutics, Prince of Wales Hospital, the Chinese University of Hong Kong, Hong Kong SAR
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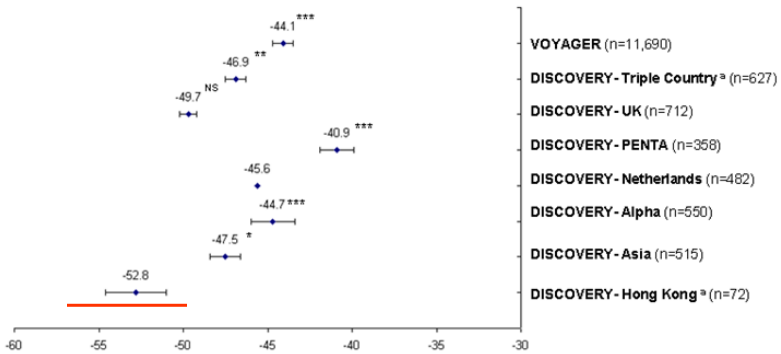
Study and patient characteristics at baseline of the various DISCOVERY studies.

	Hong Kong	Asia	Alpha	Netherlands	PENTA	UK	Triple country
Countries	Hong Kong	China, Hong Kong, Malaysia, Korea, Taiwan, and Thailand	93 countries in eastern Europe, Central and South America, and the Middle East	Netherlands	Brazil, Colombia, Mexico, Portugal, and Venezuela	UK	Finland, Iceland, and Ireland
Randomized population	126	1482	1506	1215	1124	1847	1024
Randomized groups (ratio)	R 10 vs. A 10 (2:1)	R 10 vs. A 10 (2:1)	R 10 vs. A 10 (2:1)	R 10 vs. A 10 vs. S 20 vs. P 40 (3:1:1:1)	R 10 vs. A 10 (1:1)	R 10 vs. A 10 vs. S 20 (2:2:1)	R 10 vs. A 10 (2:1)
Naïve/switched (%)	88/12	67/33	60/40	77/22	69/13	100/0	R: 87/13; A: 86/14
Age (years)	R: 57 ± 11.2; A: 61 ± 9.6	R: 60 ± 10.3; A: 61 ± 10.2	58 ± 10.8	R: 61 ± 9.7; A: 62 ± 9.9	59 ± 11.2	67 ± 8.7	61 ± 10.4
Male (%)	52	51	48	59	41	63	56
CHD (%)	25	55	44	27	37	41	28
Diabetes (%)	74	45	35	26	19	17	27
Baseline LDL-C in all study subjects (mmol/L)	R: 4.4 ± 0.7; A: 4.5 ± 1.0	R: 4.1 ± 0.8; A: 4.2 ± 0.8	R: 4.6 (N); 4.1 (S) A: 4.6 (N); 4.1 (S)	R: 4.5 ± 0.8; A: 4.4 ± 0.7	4.4 ± 1.0	4.5 ± 0.7	R: 4.5 ± 0.8; A: 4.4 ± 0.8

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.

Hu M,…,Tomlinson B Int J Cardiology 2013 May 1 doi: 10.1016/j.ijcard.2013.04.091.

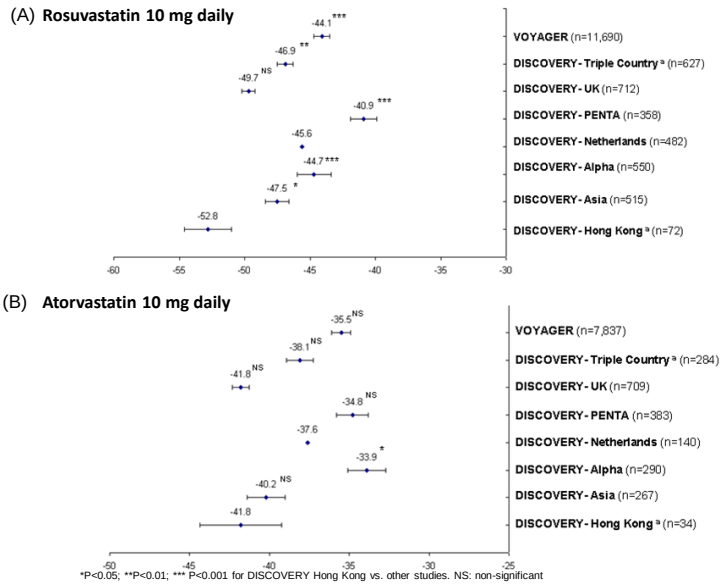
The LDL-C response to rosuvatatin 10 mg daily in statin-naïve patients in DISCOVERY studies and the VOYAGER database†



*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

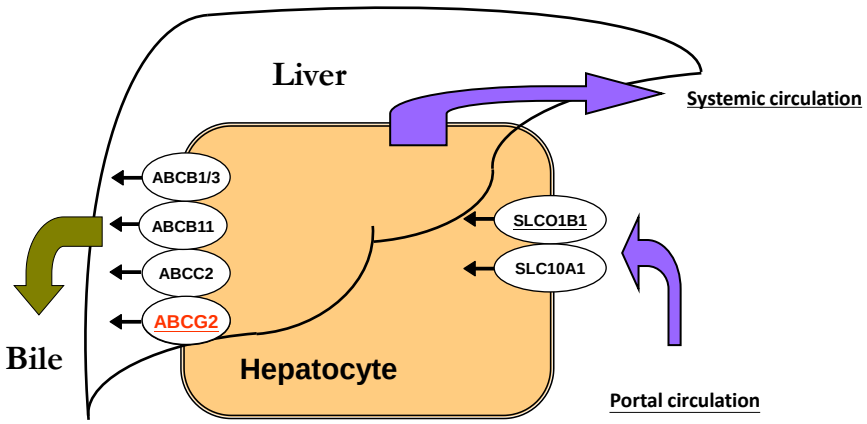
Hu M,…,Tomlinson B Int J Cardiology 2013 May 1 doi: 10.1016/j.ijcard.2013.04.091.

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



Hu M,…,Tomlinson B Int J Cardiology 2013 May 1 doi: 10.1016/j.ijcard.2013.04.091.

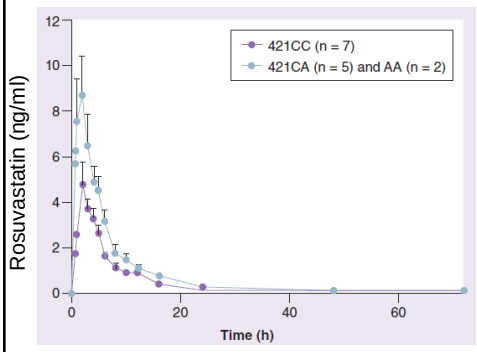
ABCG2, the major efflux transporter mediating the intestinal efflux and biliary excretion of rosuvastatin



Hu M, et al. (2009) Current Pharmacogenomics & Personalized Medicine 7:1-26

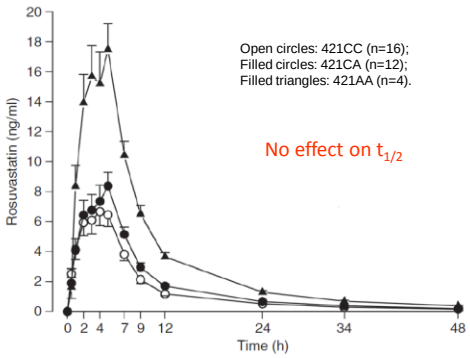
Effect of the *ABCG2* 421 C>A Polymorphism on the Pharmacokinetics of Rosuvastatin in Chinese and Caucasians

Chinese



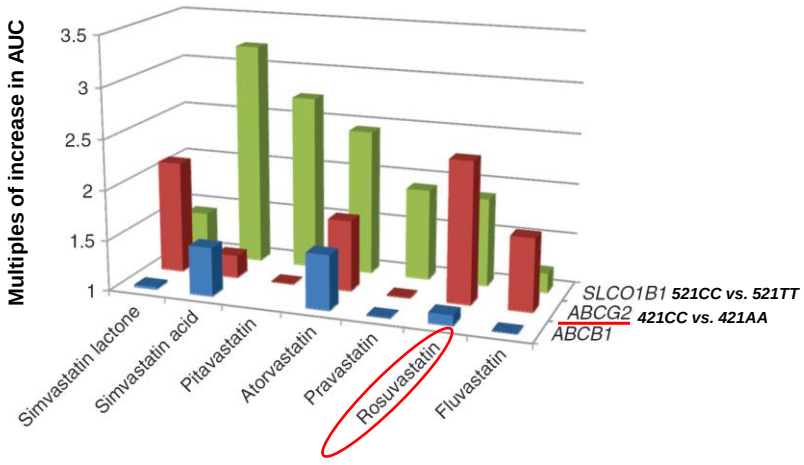
Zhang A et al., Clin Chim Acta 2006; 373: 99-103.

Caucasians



Keskitalo JE, et al. Clin Pharmacol Ther 2009; 86:197-203.

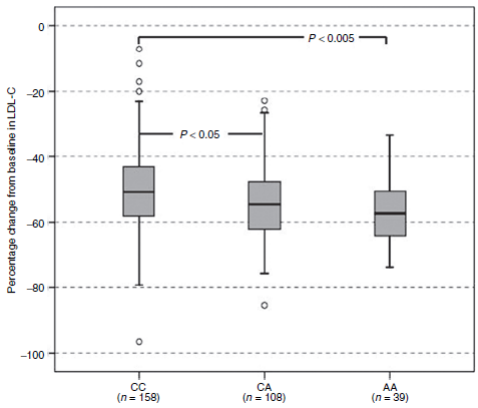
Effect of SLCO1B1, ABCG2, and ABCB1 genotypes on the systemic exposure of various statins



Adapted from Nieml M. Clin Pharmacol Ther 2010; 87(1): 130-3

Clinical Pharmacology & Therapeutics

ABCG2 Polymorphism Is Associated With the Low-Density Lipoprotein Cholesterol Response to Rosuvastatin



ABCG2 421C>A

Tomlinson B, Hu M, Lee VWY et al., Clin Pharmacol Ther 2010;87: 558-62.

Pharmacogenetics and Genomics

Pharmacogenetic analysis of lipid responses to rosuvastatin in Chinese patients

Miao Hu[a], Sandra S.H. Lui[a], Valiant W.L. Mak[a], Tanya T.W. Chu[a], Vivian W.Y. Lee[c], Emily W.M. Poon[a], Teresa K.C. Tsui[b], Gary T.C. Ko[a,d], Larry Baum[c], Lai-Shan Tam[a], Edmund K. Li[a] and Brian Tomlinson[a]

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 386 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 ($P = 9.2 \times 10^{-7}$), followed by 18281G>A (V257M) in the flavin-containing monooxygenase 3 gene ($P = 0.0002$), 1421C>G in the lipoprotein lipase gene ($P = 0.002$), and rs4420638 in the apolipoprotein E/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* 20:634–637 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Pharmacogenetics and Genomics 2010, 20:634–637

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

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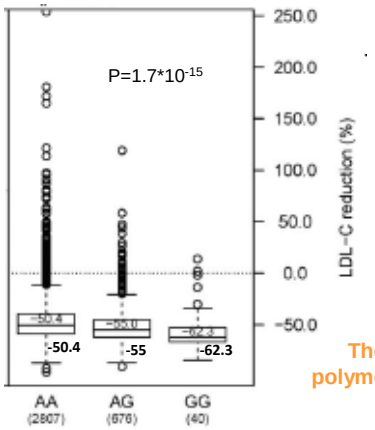
Received 27 April 2010 Accepted 6 July 2010

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

Genetic Determinants of Statin-Induced Low-Density Lipoprotein Cholesterol Reduction in JUPITER Trial

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

Horizontal line and boxes indicate the median and interquartile range of percentage reduction in LDL-C. Values beyond 1.5 times the interquartile range are indicated with circles

Chasman DI et al *Circ Cardiovasc Genet*. 2012;5:257-64

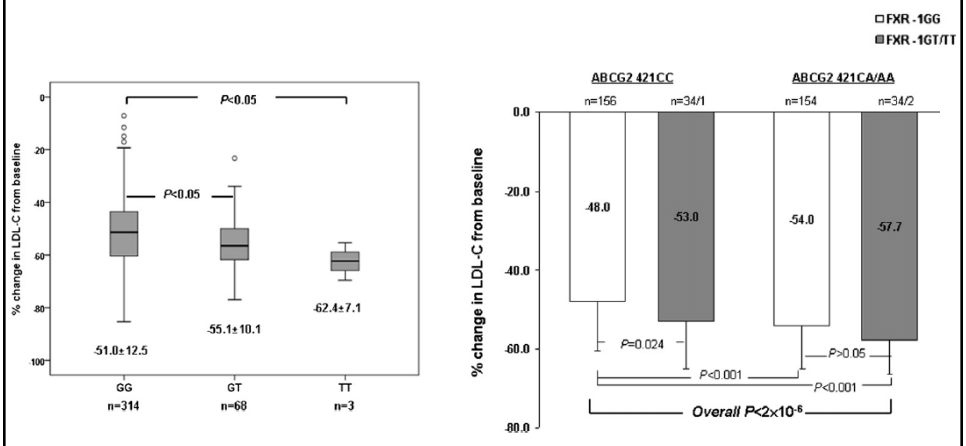
Farnesoid X receptor (FXR), a bile-acid-activated nuclear receptor

- 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

JOURNAL OF LIPID RESEARCH

The farnesoid X receptor -1G>T polymorphism influences the lipid response to rosuvastatin

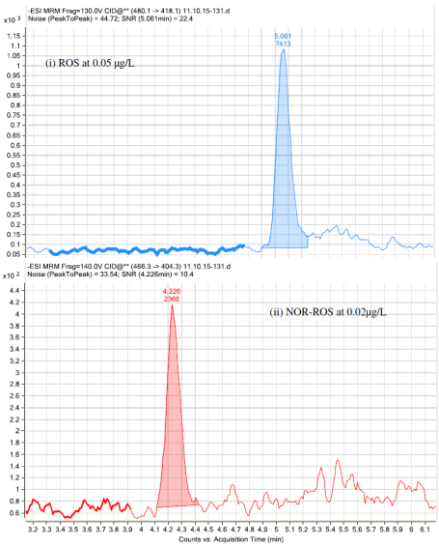
Journal of LIPID RESEARCH



Hu, M....Tomlinson B, *J Lipid Res* 2012; 53: 1384–9

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 10mg rosuvastatin.

Lee HK, Ho CS, Hu M, Tomlinson B, Wong CK. 2013 May 30. doi: 10.1002/bmc.2944. Biomedical Chromatography

RESEARCH ARTICLE

Effects of polymorphisms in *ABCG2*, *SLCO1B1*, *SLC10A1* and *CYP2C9/19* on plasma concentrations of rosuvastatin and lipid response in Chinese patients

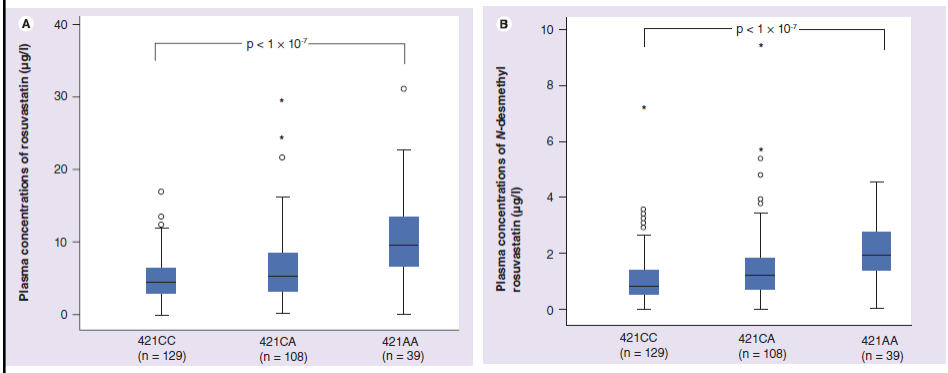
Aim: This study examined whether the *ABCG2* 421C>A polymorphism and variants in other genes potentially related to the pharmacokinetics of rosuvastatin influenced the plasma concentration of rosuvastatin in Chinese patients with hypercholesterolemia. **Patients & methods:** Overnight fasting blood samples 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 *SLCO1B1* 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

Lee HK, Hu M,….Tomlinson B. *Pharmacogenomics* 2013; 14(11): 1283–94

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

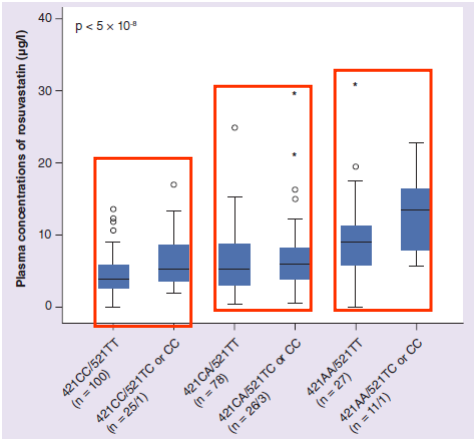
ABCG2 421C>A polymorphism



Lee HK, Hu M,….Tomlinson B. *Pharmacogenomics* 2013; 14(11): 1283–94

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

SLCO1B1 521T>C and *ABCG2* 421C>A



Lee HK, Hu M,….Tomlinson B. *Pharmacogenomics* 2013; 14(11): 1283–94

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

Variables	Model 1		
	β	*p-value*	R^2
ABCG2 421C>A polymorphism (1 = CC, 2 = CA, 3 = AA)	0.379	$<1 \times 10^{-10}$	0.145
Bodyweight (kg)	-0.238	$<1 \times 10^{-4}$	0.043
Hypertension (0 = no, 1 = yes)	0.192	<0.001	0.039
SLCO1B1 521T>C polymorphism (1 = TT, 2 = TC or CC)	0.123	0.024	0.015

Lee HK, Hu M,….Tomlinson B. *Pharmacogenomics* 2013; 14(11): 1283–94

Genome-wide association studies on the pharmacogenomics of statins

Statins	Study population	Reductions in LDL-C or other cardiovascular risk factors†	Myopathy
Atorvastatin	TNT	None, but *APOE* significant at genome-wide level and *PCSK9*, *HMGCR* significant in candidate gene analysis	NA
Atorvastatin	CARDS, ASCOT and PROSPER	*APOE* and *LPA*	NA
Pravastatin	CARE, WOSCOPS and PROSPER/PHASE	NA	NA
Rosuvastatin	JUPITER	*ABCG2*, *APOE*, *LPA* (*PCSK9* gene-significant);	NA
		None for changes in CRP†	NA
		ABCG2 and *LPA* for changes in Lp-PLA_2, but no association after adjustment for LDL-C changes†	NA
Simvastatin	HPS	None, but *LPA* and *APOE* signficant in candidate gene analysis	NA
Simvastatin	SEARCH	NA	*SLCO1B1*

Hu M, Tomlinson B. *Pharmacogenomics*. 2013 Jun;14(8):981-95.

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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Mr. Michael Lee Dr. CS Ho Prof. CK Wong	Department of Chemical Pathology, CUHK

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Thank You
For Your Attention!