



# Racial Differences in the Cholesterol-Lowering Effect of Statin

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**Statin treatment to reduce low-density lipoprotein cholesterol (LDL-C) is associated with the prevention of cardiovascular events in Western patients. Similar results have been reported in studies conducted in Japan. However, the dose of statins and the degree of LDL-C reduction achieved with statins are different between Asian and Western patients. In addition, there are limited data regarding racial differences in response to statins. In this review, racial differences between Asians and Westerners in response to statins are described.**

**Key words:** Statin, Racial differences, Asian, Westerner

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## Introduction

3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (HMG-CoA reductase inhibitors; statins) were introduced in clinical practice<sup>1,2</sup> in 1976. Large clinical trials proved the efficacy of statins in clinical outcomes. Statins have drastically changed not only the treatment regimen for hypercholesterolemia but also the treatment strategy for preventing cardiovascular disease. Then, nearly 25 million people received statin therapy worldwide<sup>3</sup>. However, there were limited data regarding racial differences in response to statins. In addition, mechanisms regarding racial differences are not sufficiently elucidated. In this review, racial differences between Asians and Westerners in response to statins are described.

## Evidence in Support of Statins

Several large-scale clinical trials have demonstrated the safety and efficacy of statins in reducing cardiovascular events<sup>4-8</sup>. The Cholesterol Treatment Trialists Collaboration conducted a meta-analysis of five randomized trials of statins that compared more intensive (higher dose or more powerful statin) and less intensive (lower dose or less powerful statin) regi-

mens in 39 612 patients with coronary artery disease (CAD). Intensive statin treatment was associated with a greater reduction in major vascular events compared with less intensive therapy and a 1 mmol/L (39 mg/dL) decrease in low density lipoprotein cholesterol (LDL-C) was associated with a reduction in all-cause mortality, cardiac events, and coronary events by 19, 21, and 23%, respectively<sup>9</sup>. All of these data have updated the clinical guidelines of the European Society of Cardiology, the American College of Cardiology/American Heart Association, the Japanese Cardiology Society, and the Japan Atherosclerosis Society<sup>10-13</sup>. However, there is a wide variation in inter-individual or inter-racial differences in response to statins. In particular, Asians and Westerners are reported to have different responses to statin from each other.

## Racial Differences in Response to Statins (Asians and Westerners)

Racial differences in response to statins have been previously reported<sup>14</sup>. In Japanese patients, a lower dose of statins has demonstrated similar relative risk reduction of cardiovascular events to a higher dose of statins in Western patients<sup>15</sup>. In fact, the maximum dose of atorvastatin in clinical practice was 40 mg per day in Japan, while the dose is 80 mg per day in the United States. The maximum dose of available statins in Japanese and Westerners is shown in **Table 1**.

DISCOVERY (the direct statin comparison of LDL-C values: an evaluation of rosuvastatin therapy) programs consisted of a series of trials incorporating

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**Table 1.** Maximum dose of statins in Japan and U.S.

	Rosuvastatin	Pitavastatin	Atorvastatin	Simvastatin	Pravastatin	Fluvastatin
Japan (mg)	20	4	40	20	20	60
U.S. (mg)	40	4	80	80	80	80

14,000 patients from several countries<sup>16</sup>), which investigated the impact of rosuvastatin on cardiovascular risk reduction. Also, clinical outcomes in a number of different populations worldwide and differences in lipid responses to rosuvastatin and atorvastatin between Chinese and Caucasian were examined<sup>17</sup>. This study compared the percentage change in LDL-C in response to rosuvastatin or atorvastatin in patients with type IIa or IIb hypercholesterolemia between Chinese and Caucasian, which was performed using the following studies: DISCOVERY-Hong Kong, DICOVERY-Asia, DICOVERY-Alpha, DICOVERY-Netherlands, DICOVERY-PENTA, DICOVERY-UK, DICOVERY-Triple Country, and other databases. The LDL-C reduction with rosuvastatin (10 mg) in Chinese patients was significantly greater than in Westerners (-52.8% versus -40.9 to -49.7%) while no significant difference was observed in the LDL-C response to atorvastatin (10 mg). A meta-analysis reported that the dose-response relationship between statin dose and LDL-C reduction by rosuvastatin and atorvastatin was similar in Western and Asian populations, whereas a three to four-fold greater dosage of statins was administered to the Western vs the Asian population<sup>18</sup>. In the report, a >40% reduction in LDL-C required atorvastatin 80 mg or rosuvastatin 40 mg in the Western population, whereas the dose of atorvastatin or rosuvastatin required to achieve the same result in Asians was 18.9 mg or 14.1 mg, respectively. Additionally, the required duration of statin administration for lipid-lowering was significantly longer in the Western vs the Asian population. In concrete terms, the duration over which reduction in LDL-C was exhibited by rosuvastatin was 24.0 and 10.3 months in Westerners and Asians, respectively. Similarly, the duration was 22.0 and 7.8 months for reduction in LDL-C by atorvastatin in Westerners and Asians, respectively (Table 2). Yang *et al.* examined the dose-response of rosuvastatin to LDL-C reduction in their meta-analysis including 36 randomized trials. There was no significant difference in the dose-response relationship for LDL-C reduction by rosuvastatin between Westerners and Asians<sup>19</sup>. For atorvastatin, no difference was also observed in pharmacokinetics of the drug between Asians and Caucasians<sup>20</sup>.

A paucity of data regarding the difference in the dose-response relationship between Asians and West-

erners for other statins has been reported. For simvastatin, LDL-C reduction by simvastatin of 5 mg daily was 26.0% in the Japan Lipid Intervention Trial<sup>21</sup>. The magnitude of the reduction was similar to the results of other simvastatin studies using higher doses (20–40 mg daily) conducted in Western countries<sup>22, 23</sup>. For pitavastatin, the pharmacokinetics and dose-response relationship in LDL-C reduction were not different between Japanese and Caucasian in an open-label, single-dose, two-way crossover pharmacokinetic study<sup>24</sup>, resulting in the recommended dose by the regulatory authorities being similar between the two countries. In summary, the differences in response to statins between Asians and Westerners were observed for all statins except for pitavastatin.

### Why the Difference between Asians and Westerners ?

It was speculated that the differences in the LDL-C response to rosuvastatin between Chinese and Caucasian was yielded by the different pharmacokinetics<sup>25</sup>. Pharmacokinetics is the study of the time course of drug absorption, distribution, metabolism, and excretion. In clinical practice, pharmacokinetics is applied to achieve both a safe and effective therapeutic range of drugs in an individual. A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic, and African-American or Afro-Caribbean groups<sup>26</sup>, while other pharmacokinetic studies of rosuvastatin have demonstrated an approximate two-fold elevation in median exposure (maximum plasma concentration and the area under the plasma concentration curve) in Asian populations compared with Westerners<sup>14, 19, 27</sup>. In both populations, rosuvastatin showed dose-dependent reductions in LDL-C<sup>28, 29</sup>. Yang and colleagues also examined racial differences between Asian and Western populations in rosuvastatin pharmacodynamics in which an indirect comparison was performed<sup>19</sup>. Pharmacodynamics assesses the relationship between the drug concentration at the site of action and the resulting effect quantitatively, which includes both therapeutic and adverse effects. The pharmacodynamics was examined by assessing a relationship between the dose of rosuvastatin and LDL-C reduction, which showed no significant difference between Westerners

**Table 2.** Comparison in response to rosuvastatin or atorvastatin between Asian and Westerner

	Rosuvastatin			Atorvastatin		
	Asian (N=304)	Westerner (N=869)	<i>P</i>	Asian (N=366)	Westerner (N=772)	<i>P</i>
LDL-C at baseline	123.1 ± 14.6	124.2 ± 5.1	0.93	124.1 ± 12.7	129.8 ± 14.2	0.61
LDL-C at follow-up	67.2 ± 13.8	61.9 ± 0.9	0.64	72.9 ± 14.2	73.1 ± 4.1	0.97
LDL-C reduction (%)	44.0 ± 4.8	49.9 ± 2.6	0.22	40.7 ± 5.5	43.0 ± 2.1	0.60
Statin dose (mg)	14.1 ± 4.9	40.0 ± 0.0	0.006	18.9 ± 2.9	80.0 ± 0.0	<0.001
Duration (month)	10.3 ± 3.7	24.0 ± 0.0	0.016	7.8 ± 2.2	22.0 ± 2.8	<0.001

and Asians. Based on these data, the differences in response to statins between Westerners and Asians might derive from the pharmacokinetics rather than the pharmacodynamics.

Detailed mechanisms of the differences in response to statins between Asians and Westerners are not fully elucidated. To date, several studies have reported that genetic factors were related to differences in reactions to statin and statin-related side effects, which could potentially explain the racial differences between Asians and Westerners<sup>30, 31</sup>. A genome-wide study in patients treated with simvastatin found a significant association between single-nucleotide polymorphisms (SNPs) located within the *SLCO1B1* gene on chromosome 12 and muscular side effects of statins<sup>32, 33</sup>. *SLCO1B1* encodes an organic anion transporting polypeptide 1B1 (OATP1B1) that is expressed on the basolateral membrane of hepatocytes and can facilitate hepatic uptake of certain clinically relevant drugs such as statins except for fluvastatin. *SLCO1B1* polymorphisms included two SNPs (388A>G, 521T>G) and four haplotypes (*SLCO1B1*\*1a, *SLCO1B1*\*1b, *SLCO1B1*\*5, and *SLCO1B1*\*15). *SLCO1B1*\*1a is a wild type, *SLCO1B1*\*1b has one SNP (388A>G), *SLCO1B1*\*5 has the other SNP and *SLCO1B1*\*15 has both SNPs. The transport activity on hepatic cells was upregulated in people with *SLCO1B1*\*1b, while the activity was downregulated in people with *SLCO1B1*\*5. In people with *SLCO1B1*\*15, the transport activity was significantly decreased. The frequency of the four important haplotypes was different among different races (Table 3)<sup>34</sup>, which could affect racial differences in response to statin.

Major genetic determinants of rosuvastatin pharmacokinetics is the 421C>A polymorphism in the drug efflux transporter ATP-binding cassette G2 gene (*ABCG2*). Subjects with the variant allele have plasma rosuvastatin concentration twice as high as those with the wild-type genotype<sup>35, 36</sup>. LDL-C response to rosuvastatin therapy was also influenced by the genetic variant<sup>29, 37, 38</sup>. The *ABCG2* polymorphism is more

common in East Asians than in Westerners, which might contribute to the difference in pharmacokinetics and lipid response to rosuvastatin between the two ethnic groups<sup>17</sup>.

A large-scale genetic analysis among 148 SNPs within 10 genes participating in cholesterol biosynthesis, cholesterol transport, and statin metabolism was conducted. This analysis assessed lipid reductions in response to pravastatin therapy in 1536 individuals (Caucasian: 88.7%, African-American: 6.5%, Hispanic: 2.9%, Asian: 1.2%, and others: 0.7%) in which two SNPs (SNP 12 and SNP 29) in the gene coding for HMG-CoA reductase were significantly associated with efficacy of pravastatin in LDL-C. In individuals with a minor allele of each SNP, pravastatin reduced total cholesterol by 22% (absolute difference: 9.2 mg/dL) compared with those without the SNPs. LDL-C was also reduced by 19% (absolute difference: 6.4 mg/dL). The association between the SNPs and the lipid-lowering effect of pravastatin was observed after adjusting for the other 33 SNPs evaluated in the HMG-CoA reductase gene as well as for 148 SNPs in 10 genes evaluated in the study. In addition, the association between SNP 29 and the lipid-lowering effect of pravastatin was more profound in Westerners compared with the other ethnic groups<sup>39</sup>. Candidate genes by which statins influence LDL-C reduction are shown in Table 4.

### Genetic Effect on Statin-Induced Adverse Effect

Genetic effects, not only on efficacy but also on adverse effects of statin, have been previously reported. In the study of the effectiveness of additional reductions in cholesterol and homocysteine (SEARCH) and in the Heart Protection Study, rs4363657 C and rs4149056 C alleles in *SLCO1B1* had markedly elevated risks of myopathy<sup>32</sup>, which was also found in the statin response examined by genetic HAP markers (STRENGTH) trial<sup>33</sup>. In the STRENGTH trial, car-

**Table 3.** Differences in activity of drug transporter among four haplotypes, separated by Japanese, European–American, and African–American

	Allele frequency		
	Japanese	European–American	African–American
SLCO1B1*1a	0.33	0.61	0.22
SLCO1B1*1b	0.47	0.25	0.76
SLCO1B1*5	0	0.02	0
SLCO1B1*15	0.17	0.14	0.01

**Table 4.** Candidate gene/SNPs related to response to statin

Gene	Encoded protein	Functional role	Statin	References No.
ABCG2	ATP-binding cassette, subfamily G, member 2	Cholesterol transport across the plasma membrane	Rosuvastatin, Atorvastatin	29, 35-38
SLCO1B1	Organic anion transporter	Hepatic uptake of statin	All statins except for fluvastatin	30, 32-34
LDLR	LDL receptor	Receptor for plasma LDL	Rosuvastatin	30
HMGCR	3-Hydroxy-3-methylglutaryl coenzyme A reductase	Cholesterol synthesis	Pravastatin	39
CYP2D6	Cytochrome P450, subfamily 2D, polypeptide 6	Statin metabolism	Simvastatin	31

riers of 2 alleles and 1 allele of the rs4149056 had a 2.6- and 1.4-fold higher incidence of adverse effects by simvastatin, while the LDL-C-lowering effect of simvastatin was similar between carriers and non-carriers. In the subjects treated with atorvastatin and pravastatin, no statistically significant difference was observed in the incidence of adverse effects between those with at least 1 allele and those without. In the SEARCH trial, participants with rs4363657C and rs4149056 alleles had a 4-fold higher risk of severe myopathy and a 17-fold higher risk when comparing the participants with and without both alleles. For patients treated with pravastatin, no excess risk was observed in carriers of rs4149056. In the Justification for the use of statins in prevention: an intervention trial evaluating rosuvastatin (JUPITER), the effect of rs4363657C and rs4149056C in SLCO1B1 on clinically reported myalgia was assessed<sup>40</sup>. In the rosuvastatin-treated group, the rate of myalgia was 4.1 events per 100 person-years, which was comparable with the rate in the placebo group. Among those on rosuvastatin, there were no differences in the rate of myalgia in subjects with each allele compared with those with neither allele. The hazard ratio for myalgia of the subjects with an rs4363657C or rs4149056C allele compared with those without neither allele was 0.95 (95%

confidence interval (CI) 0.79–1.14) and 0.95 (95% CI 0.79–1.15), respectively. Taken together, these lines of evidence indicate that the effect of the rs4363657C and rs4149056C alleles on the risk of myalgia was different between populations treated with rosuvastatin and simvastatin.

Carriers of this polymorphism would be expected to have reduced hepatic uptake of statins, resulting in higher circulating statin concentrations and an increased risk of myopathy. It is possible that increased circulating statin levels as a result of the SLCO1B1 polymorphism are less toxic to muscle cells for hydrophilic agents, such as rosuvastatin and pravastatin, compared with more hydrophobic statins such as simvastatin.

### Future Perspectives

In this text, the differences in statin response between Asians and Westerners and genetic influences on the differences were described. However, genetic effects on statin response are still controversial<sup>40-43</sup>. In addition, the lipid-lowering effect of statins involved several processes to exhibit lipid-lowering, which include absorption of the drug, transportation to hepatic cells, inhibition of HMG-CoA reductase,



nuclear translocation of SREBP-2, increased synthesis of LDL receptor, and endocytosis of LDL-C by the LDL receptor. Because each process is affected to some extent by different genetic factors, known genetic variants per se could not fully explain inter-individual or inter-racial differences in response to statins. Therefore, future research is needed to clarify which gene polymorphisms are related to the processes that act to exhibit lipid-lowering effects and to what extent the genetic factors affect the response to statins. In addition, we should recognize that not only genetic factors but also non-genetic factors, such as body surface area, dietary style, and adherence to drugs play important roles in different responses to statins between different races.

### Conclusion

Racial differences exist in the response to statins between Asians and Westerners through different pharmacokinetics, which is partially explained by genetic factors. Future research is required to elucidate to some extent the gene factors that are associated with racial differences in statin response.

### COI

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