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Safety and Efficacy of Statins in Asians

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Abstract

Asian patients frequently have heightened responses to therapeutic drugs. As a consequence, the recommended drug doses are often lower in Asian countries than in Western countries. This practice extends to the use of cardiovascular drugs, including statins for the treatment of dyslipidemia. Pharmacokinetic investigations have noted higher plasma levels of statins in Asians compared with Caucasians, although postmarketing data for all statins have not identified any particular safety issues, even when statins are given at equivalent doses. The potential mechanisms of heightened response to statins in Asians are related to genetically based differences in the metabolism of statins at the level of hepatic enzymes and drug transporters. Studies indicate that lower statin doses achieve lipid improvements in Asian patients comparable with those observed with higher doses in Caucasians. In conclusion, prescribing lower starting doses of statins in Asians appears warranted while research on this subject continues.

Asian populations that were once relatively unburdened by cardiovascular disease (CVD) are now feeling its impact. In China, CVD mortality has doubled in the past 20 years, and CVD prevalence in Japan is expected to escalate because of marked increases in cardiovascular risk factors, chiefly dyslipidemia. [1,2] Recent studies have confirmed that the prevalence of the metabolic syndrome in Asians is comparable with that in Western populations.[3–5] During the past 3 decades in the United States, enormous progress has been made in the battle against CVD, largely because of the use of statins, which continue to show remarkable benefit primarily through their lipid-lowering activity but also through their broad range of pleiotropic effects. Numerous large-scale clinical trials have consistently demonstrated statin efficacy and safety in a variety of populations. However, few clinical trials have examined the effects of statins in various ethnic and racial groups. None of the landmark statin clinical trials differentiated their patient populations on the basis of Asian ethnicity. To date, most studies assessing the efficacy and safety of statin therapy in Asians have been carried out in Asia.

This review focuses primarily on differences in drug response between Westerners (European Americans) and East Asians, specifically Chinese, Japanese, and Koreans. An appreciation of these differences will be clinically relevant for physicians treating patients of East Asian ancestry.

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Implications of Genetic Variability

Although most clinicians are aware that patients of Asian descent may respond differently from patients of European descent to a variety of therapeutic agents for CVD, the emerging field of pharmacogenetics is showing that differences in pharmacokinetic and pharmacodynamic effects are more prevalent than previously realized. These differences appear to exist even after adjustment for other confounding factors, such as differences in age, co-morbid conditions, or socioeconomic status. Although the smaller body sizes of many Asians relative to Westerners is frequently cited as a cause for the differences in drug response,[3,6–8] body size appears to have little or no bearing on statin efficacy in Asians.[7,9] In a recent pharmacokinetic study, body weight accounted for <10% of the differences between Asian and white patients in plasma exposure (area under the plasma concentration-time curve and maximum plasma concentration) to rosuvastatin.[10]

Variants in gene structure, or polymorphisms, can influence a drug's pharmacokinetic or pharmacodynamic properties. Polymorphisms may occur in genes involved in drug metabolism, drug targets, and/or the disease pathway itself. Polymorphisms in drug metabolism genes, for example, may lead to either poor or extensive metabolizing of the drug in question. Poor metabolizers may experience increased time to drug clearance, leading to increased exposure to active drug and thus to potential adverse effects. Polymorphisms of drug targets affect receptors that determine the response to particular medications, and a blunted receptor effect may result in decreased binding of a drug and hence reduced efficacy. Finally, polymorphisms that influence disease pathogenesis may also affect drug response.

Genetic variability in drug metabolism

Of the pharmacokinetic phases (absorption, distribution, metabolism, and excretion), metabolism is most subject to interpatient and interethnic variability, although interethnic differences can exist in all phases.[11] Human oxidative enzymes associated with drug metabolism belong mainly to the cytochrome P450 (CYP450) families, and CYP450-dependent metabolism is 1 area in which ethnic variants have been best characterized.[11] Differences between East Asians and Caucasians are particularly noteworthy in the activity of CYP450 2D6 and the CYP450 2C subfamily, in which functionally significant polymorphisms are common.[11,12] Polymorphic variants in the genes affecting these enzymes may reduce or eliminate them or enhance them, resulting in varying rates of metabolic clearance. For CYP450 2D6, for example, approximately 1% of East Asians have the poor metabolizer phenotype, compared with >7% of Caucasians. [11,12] However, the CYP450 2C19 slow metabolizer phenotype is present in approximately 16% of Asians and in only about 3% of Caucasians.[12]

CYP450 3A4 metabolism is particularly important because 3A4 is the predominant CYP450 isoform; approximately 50% of commonly prescribed drugs are metabolized through this pathway.[11,13] Although differences in the allelic frequencies of CYP450 3A between Asians and whites have been noted, related differences in drug metabolism have not been observed consistently.[11,14] However, a recent study of simvastatin therapy in dyslipidemic Chinese patients found that CYP450 3A4*4 was associated with a functional decrease in the enzyme's activity, resulting in significantly greater reductions in total cholesterol and triglycerides, but not for low-density lipoprotein (LDL) cholesterol.[15] Among the statins, lovastatin, simvastatin, and atorvastatin are metabolized primarily by CYP450 3A4, whereas fluvastatin is metabolized through CYP450 2C9, as is rosuvastatin to a minor extent. Pravastatin is not metabolized through the CYP450 system.

Another determinant of drug disposition is the trans-membrane protein P-glycoprotein, a drug efflux pump that is believed to decrease the bioavailability of many drugs and also affect drug distribution in the body.[16–18] P-glycoprotein shares a substrate overlap with the CYP450 3A4

subfamily,[19] and drugs that undergo efflux by P-glycoprotein and metabolism via CYP450 3A4 are most likely to show ethnic differences in bioavailability.[20,21] Lovastatin, simvastatin, and atorvastatin alter P-glycoprotein transporter activity, whereas pravastatin and rosuvastatin do not.[22,23]

Organic anion transporting polypeptides (OATPs) have also been shown to play a role in the uptake of statins in the liver. Numerous genetic polymorphisms have been identified in the OATP-C gene and found to vary within and across ethnic groups.[24] For example, in healthy Japanese subjects, values for the total and nonrenal clearance of a single 10-mg dose of pravastatin were significantly smaller ($p < 0.05$) in subjects with a specific OATP-C variant, OATP-C*15.[24] Pravastatin and rosuvastatin (and likely atorvastatin, lovastatin, and simvastatin) are transported by OATP-C (OATP1B1) and may be associated with delayed hepatocellular uptake.[25–27]

Effects of Statin Therapy in Asians

Typically, Asians achieve similar benefits as Westerners at lower statin doses (Table 1[6,9,28–39] and Table 2[40–48]). In a comparison of atorvastatin and simvastatin in dyslipidemic patients at 6 Asian centers, just 10 mg of simvastatin and 10 mg of atorvastatin over 8 weeks resulted in average LDL cholesterol reductions of 35% and 43%, respectively, and >80% of patients achieved their United States National Cholesterol Education Program LDL cholesterol goals.[6] In hypercholesterolemic Japanese patients, rosuvastatin doses ranging from 1 to 40 mg achieved LDL cholesterol reductions of 36% to 66% over 6 weeks.[30] In the large-scale Japanese Lipid Intervention Trial (J-LIT), an open-label study of simvastatin at an initial 5-mg dose in 51,321 hypercholesterolemic Japanese patients, the 5-mg dose, which lowered LDL cholesterol by 29% over 6 years, was deemed as effective as the 20-mg dose used in Western countries.[8] A small subgroup (1.4%) labeled “hyper-responders” had a reduction in total cholesterol of >40% during 6 years of low-dose treatment.[8]

Recently, the Management of Elevated Cholesterol in the Primary Prevention of Adult Japanese (MEGA) study, the first trial to assess clinical outcomes of statin therapy in an Asian population, reported a significant 33% reduction (95% confidence interval 9% to 51%, $p = 0.01$) in the risk for coronary heart disease with low-dose (10 to 20 mg) pravastatin plus diet versus diet alone in (7,800 Japanese hypercholesterolemic patients with no CVD.[42] In MEGA, a relatively modest 18% reduction in LDL cholesterol produced risk reductions similar to those observed with higher statin doses in Western trials.[49,50] Further analyses of the data presented in this abstract are needed.

Nevertheless, some studies have shown that the upward dose titration of statins is associated with additional benefit in Asian subjects. The titration of rosuvastatin from 10 to 20 mg in Japanese patients with heterozygous familial hypercholesterolemia brought additional, significant improvements in all lipid parameters.[35] The successful use of standard and even high doses of statins was also reported in the Simvastatin Treats Asians to Target (STATT) study in patients with CVD from 5 Asian countries. In STATT, simvastatin was titrated to achieve the National Cholesterol Education Program Adult Treatment Panel II goal for LDL cholesterol of ≤100 mg/dl. Overall, 72% of patients reached this goal at some time during the 14-week study at a dose of 20 mg; however, with titrations of up to 80 mg, the cumulative percentage getting to goal was 94%. All doses were well tolerated.[36]

Statin Safety in Asian Populations

Most side effects of statins are dose related, so concerns about elevated risks are appropriate in patients who may have increased sensitivity to statins. However, evidence to date shows no increased rates of adverse events in Asian patients taking either lower or higher doses of statins.

6,7,9,29–32,35,45,51 Moreover, elderly Japanese patients,[51] including those with diabetes mellitus,[44] have safely taken low-dose statins (up to 10 mg) for long periods of time.

The largest database on statin safety in Asians, with >51,000 hypercholesteromic patients, is J-LIT, in which the overall rate of side effects with low-dose statin therapy was 3.3% over 6 years. The rate of muscle disorders (0.86% overall) increased slightly with larger reductions in total cholesterol. There were 4 cases of myopathy but no cases of rhabdomyolysis (defined as creatine kinase ≥10,000 IU/L with muscle symptoms). The most frequent side effects were liver disorders (0.97% incidence), none of which were considered serious.[8] In the 7,832 Japanese patients in the MEGA trial, there were no differences in the rates of myopathy or liver enzyme abnormalities between those treated with diet alone or with diet plus pravastatin 10 to 20 mg.[42]

Lee et al[10] recently reported population differences in response to rosuvastatin in subjects of European and Asian ancestry living in Singapore. The approximately twofold greater plasma exposure to rosuvastatin observed in Asian subjects ($p < 0.0001$) did not appear to be the result of body weight or environmental factors. The mechanisms for this effect are not fully explained; SLCO1B1 (the gene for OATP1B1) genotypes did not account for the observed pharmacokinetic differences between Asian and Caucasian subjects. The investigators raised the possibility that other genetic influences or environmental factors could account for the increased plasma exposure. There was no increase in any safety or tolerability issue in the Asian subjects.

Appropriateness of Low-Dose Statin Therapy in Asians

The proved efficacy of statins in reducing risk for CVD in Asians, along with their proved safety in Asian populations, amply justifies their use in Asians and subjects of Asian descent. Nonetheless, the United States Food and Drug Administration recently advised the initiation of rosuvastatin at 5 mg/day in Asian patients, noting the relevance in these patients of potentially increased systemic exposure to the drug.[52] In Japan, none of the statins is approved at the highest doses approved in the United States (Table 3).[53] As research on statin metabolism in Asians and other ethnicities continues, it may be advisable, therefore, to initiate therapy with the older as well as the newer statins at low doses in Asian and Asian-American patients. Even if pharmacokinetics were not altered, a potential pharmacodynamic sensitivity could justify a cautious approach.

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Table 1

Clinical trials of statin therapy in Asian patients: lipid-lowering efficacy

Trial	No.	Locale	Statin (Dose, mg)	Mean % LDL	p Value
Randomized					
ASIA[6]	157	Multiple*	Atorvastatin (10–20)	48%	0.003
			Simvastatin (10–20)	41%	
Chan et al[28]	76	China	Simvastatin (10)	33%	—
J-CLAS[29]	121	Japan	Atorvastatin (5–20)	36%–50%	<0.001
Saito et al[30]	112	Japan	Rosuvastatin (1–40)	36%–66%	<0.0001
Wang et al[31]	54	Taiwan	Atorvastatin (10)	42%	<0.001
Yamamoto et al[32]	60	Japan	Rosuvastatin (1–4)	30–42%	0.001
Open label					
GOALLS[9,33]	198	Multiple†	Simvastatin (20, 40, 80)	41%	—
Itoh et al[34]	201	Japan	Simvastatin (5)	28%	<0.001
Mabuchi et al[35]	37	Japan	Rosuvastatin (10–40)	49%–57%	<0.0001
STATT[36]	133	Multiple‡	Simvastatin (20, 40, 80)	45%	<0.001
Teramoto et al[37]	212	Japan	Fluvastatin (20, 30, 40)	29%	<0.001
Tomlinson et al[38]	31	Hong Kong	Fluvastatin (20, 40)	26%	<0.01
Yoshida et al[39]	22	Japan	Simvastatin (20)	40%	<0.001

*Taiwan, Philippines, Thailand, Singapore, Indonesia, and Hong Kong.

†Argentina, Brazil, Colombia, Costa Rica, Denmark, El Salvador, Finland, Hungary, Mexico, Norway, Peru, Philippines, Singapore, South Africa, United Kingdom, United States of America, and Venezuela.

‡China, Hong Kong, Korea, Taiwan, and Thailand.

ASIA = Atorvastatin and Simvastatin in Asia; GOALLS = Getting to Appropriate LDL-C Levels With Simvastatin; J-CLAS = Japan Cholesterol Lowering Atorvastatin Study; STATT = Simvastatin Treats Asians to Target.

Table 2

Clinical trials of statin therapy in Asian patients: outcomes studies

Trial	No.	Locale	Statin (Dose, mg)	Findings	p Value
Randomized					
KLIS[40,41]*	5,640	Japan	Pravastatin (10–20)	14% ↓ in CHD events†	0.23
MEGA[42]	7,832	Japan	Pravastatin (10–20) + diet	33% ↓ in CHD incidence	0.01
PATE[43,44]	665	Japan	Pravastatin (5 vs 10–20)	42 vs 29 CV events	0.046
Open label					
CLIP[45]	2,529	Japan	Pravastatin (10–20)	2.33 vs 5.16 cardiac events‡§	
Holicos-PAT[46]	2,232	Japan	Pravastatin (10–20)	26% ↓ risk of CHD events vs diet	
J-LIT[47] //	47,294	Japan	Simvastatin (5–10)	0.91 CHD events‡	
J-LIT[48] ¶	5,127	Japan	Simvastatin (5–10)	4.45 CHD events‡	

*Randomization was unsuccessful because some participating physicians did not randomly assign drug regimens.

†Versus conventional treatment.

‡Per 1,000 person-years.

§Statin-continued versus statin-discontinued groups.

//Primary prevention.

¶Secondary prevention.

CHD = coronary heart disease; CLIP = Chiba Lipid Intervention Program; CV = cardiovascular; Holicos-PAT = Hokuriku Lipid Coronary Heart Disease Study-Pravastatin Atherosclerosis Trial; J-LIT = Japan Lipid Intervention Trial; KLIS = Kyushu Lipid Intervention Study; MEGA = Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; PATE = Pravastatin Anti-Atherosclerosis Trial in the Elderly.

Table 3

Recommended dose ranges for selected statins

Statin	Dose Range (mg/day)	
	Japan	United States
Atorvastatin	10–40	10–80
Fluvastatin	20–60	20–80
Pravastatin	10–20	10–80
Rosuvastatin	2.5–20	5–40
Simvastatin	5–20	5–80

Adapted with permission from data in Saito et al[53] and statin package inserts.