COMPARING THE EFFICACY AND SAFETY OF ATORVASTATIN AND SIMVASTATIN IN ASIANS WITH ELEVATED LOW-DENSITY LIPOPROTEIN-CHOLESTEROL — A MULTINATIONAL, MULTICENTER, DOUBLE-BLIND STUDY

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Background and Purpose: There have been few reports on the efficacy and safety of statins in the Asian population. The study objectives were to compare the efficacy and safety of atorvastatin and simvastatin in Asian people.

Materials and Methods: This was a 16-week, double-blind, double-dummy, randomized, multicenter study involving eight medical centers in six Asian countries or areas. After a 6-week, diet-controlled, placebo lead-in period, 157 patients with low-density lipoprotein cholesterol (LDL-C) of between 160 and 250 mg/dL and serum triglyceride (TG) of less than 400 mg/dL were randomized to receive 10 mg of either atorvastatin (n = 79) or simvastatin (n = 78). After 8 weeks of treatment, all patients had the dose of study medication increased to 20 mg, irrespective of LDL-C concentration. Data obtained by monitoring lipid profiles, adverse events, and laboratory tests during the 16 weeks of study were used to assess the efficacy and safety of both treatments.

Results: After 8 weeks of treatment, LDL-C concentrations were reduced by 42.5% from baseline in patients receiving atorvastatin and 34.8% in those receiving simvastatin ($p = 0.0006$). Patients treated with atorvastatin also had a significantly greater reduction in very-low-density lipoprotein cholesterol (VLDL-C), TG, and total cholesterol (TC) after 8 weeks of treatment. The significantly greater reductions in LDL-C, VLDL-C, TG, and TC from baseline achieved with atorvastatin were still observed after an additional 8 weeks of treatment with 20 mg study medication. Both drugs increased high-density lipoprotein cholesterol (HDL-C) concentrations after 16 weeks of treatment, with no significant difference between the two treatments. After 16 weeks of treatment, 93% of atorvastatin and 85% of simvastatin patients had achieved their National Cholesterol Education Program LDL-C goals. No deaths occurred in the study population and the incidence of treatment-emergent adverse events was the same in the two groups (28%). Only one patient who was treated with simvastatin had a transaminase or creatine phosphokinase concentration that was more than three-fold the upper limit of normal.

Conclusions: Asian people with primary hypercholesterolemia treated with atorvastatin had lower LDL-C, VLDL-C, TG, and TC after 8 weeks and 16 weeks of treatment than those treated with simvastatin. Both drugs demonstrated acceptable safety profiles.

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High plasma low-density lipoprotein cholesterol (LDL-C) concentrations play significant roles in atherosclerotic vascular disease. Reductions in LDL-C are consistently related to reductions in vascular diseases and

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improved outcomes [1]. Statins have revolutionized the treatment of hypercholesterolemia. They are the most commonly prescribed agents for the treatment of hypercholesterolemia because of their high efficacy in reducing LDL-C concentrations and their excellent tolerability and safety [2]. Statins are also modestly effective in raising high-density lipoprotein cholesterol (HDL-C). Triglyceride (TG) lowering is directly proportional to baseline TG concentration and to the LDL-lowering potency of the drug [3, 4].

Atorvastatin has been shown to be effective in lowering LDL-C concentrations by as much as 61% at doses of up to 80 mg [5]. Further studies have indicated that atorvastatin is safe and effective in patients with mixed dyslipidemia, primary hypercholesterolemia, and diabetes mellitus [3, 6–9]. It is well known that genetic and environmental factors contribute not only to the development and progression of diseases but also to their response to medication. Safety data indicate a profile for atorvastatin similar to those of other statins [3, 8, 9]. However, there have been few studies focusing on the Asian population. Asian people in general are known to be not only of smaller average stature but also to have characteristic pharmacokinetics for certain medications [10]. This study evaluated and compared the efficacy and safety of atorvastatin and simvastatin in Asian patients with high LDL-C concentrations.

Materials and Methods

Study design

This was a 16-week, double-blind, double-dummy, randomized, multicenter study. Eight medical centers in six Asian countries or areas (Taiwan, Philippines, Thailand, Singapore, Indonesia, and Hong Kong) enrolled patients in this study. Except at the screening visit, all lipoprotein measurements were completed by a single central laboratory, which was accredited by the College of American Pathologists. The investigator and study sponsor were blinded by the central laboratory with regard to the lipid status of patients randomized to treatment. Local laboratories performed all of the other laboratory tests and the individual study sites provided dietary counseling. Study medications were prepared by the Clinical Pharmaceutical Operations Department of Parke-Davis. Medication was assembled for each patient based on a computer-generated randomization code.

Patients were counseled to follow the National Institutes of Health National Cholesterol Education Program (NCEP) step I diet throughout the study [11]. Participants in the study were outpatients between the ages of 18 and 80 years with elevated LDL-C. Pregnant or breast-feeding women were excluded. Patients also had to meet the following requirements during the baseline phase (diet therapy and placebo run-in period) to be eligible for the double-blind treatment phase: LDL-C concentration greater than 4.2 mmol/L (160 mg/dL) and less than 6.5 mmol/L (250 mg/dL), as calculated by the Friedewald formula [12], and TG concentration less than 4.5 mmol/L (400 mg/dL) at Week –2. If the Week –2 LDL-C was out of range but the average of Week –2 and Week 0 LDL-C was more than 4.2 mmol/L (160 mg/dL) and less than 6.5 mmol/L (250 mg/dL), the patient was included. At the end of the baseline phase, qualifying patients were randomized to receive 10 mg of either atorvastatin or simvastatin (Figure). Randomization was stratified by site, relying on a table of random numbers designed by Boston Biostatistics, Inc. (Framingham, MA, USA). The pill bottles were consecutively numbered so that atorvastatin and simvastatin were randomly interspersed — the next patient received the next pill bottle. After 8 weeks of treatment, all patients had the dose of their study medication increased to 20 mg, irrespective of LDL-C concentration.

Patients were excluded if any of the following conditions were met: hyperlipoproteinemia secondary to uncontrolled primary hypothyroidism, nephrotic syndrome or renal dysfunction, or uncontrolled diabetes mellitus (type II); diabetes mellitus type I; active liver

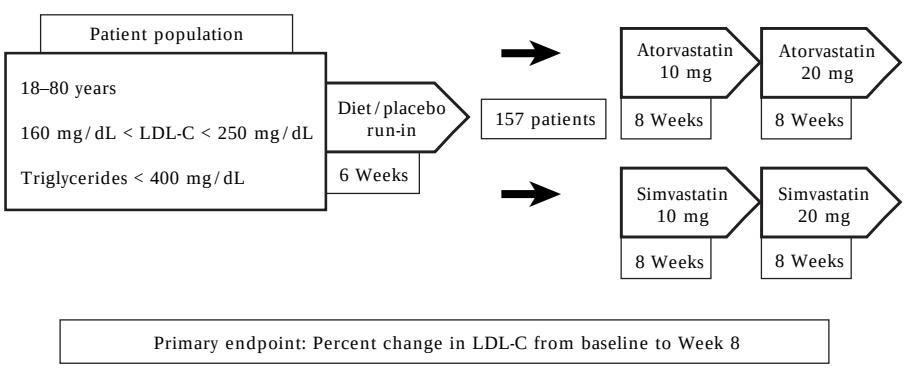

Figure. *ASIA study design. LDL-C = low-density lipoprotein cholesterol.*

disease or hepatic dysfunction; elevated creatine phosphokinase (CPK) concentrations; body mass index greater than 30; uncontrolled hypertension; current or recent history of drug or alcohol abuse; participation in another clinical study concurrently or within the 30 days of screening for entry into this study; known hypersensitivity to reductase inhibitors; use of any lipid-regulating drugs, immunosuppressive agents, drugs known to affect lipid concentration, or drugs associated with rhabdomyolysis in combination with reductase inhibitors; any significant coronary abnormalities as determined by investigators; less than 80% compliance during the baseline placebo phase; or chronic congestive heart failure, dementia, advanced cerebrovascular disease, advanced pulmonary disease, active malignancy (with the exception of treatable skin cancer), or significant abnormalities that the investigator felt might compromise the patient's safety or successful participation in the study.

Efficacy

The primary efficacy endpoint was the percentage change in LDL-C from baseline to the end of Week 8 for the modified intent-to-treat population. The secondary endpoints included nominal change in LDL-C from baseline to Week 8; nominal and percentage change in LDL-C from baseline to Week 16; nominal and percentage change in HDL-C, very-low-density lipoprotein cholesterol (VLDL-C), total cholesterol (TC), and TG concentrations from baseline to Week 8 and Week 16; and percentage of patients achieving their NCEP LDL-C goal at Week 8 and Week 16. All baseline lipid measurements were defined as the mean of those measurements taken at Week –2 and Week 0. If either measurement was missing, the existing value was used. All percentage changes from baseline to endpoints were calculated as the baseline measure subtracted from the time-point measure (Week 8 or Week 16) divided by the baseline measure and multiplied by 100.

Safety

The safety of both treatments was assessed by monitoring adverse events and concentrations of aspartate aminotransaminase (AST), alanine aminotransaminase (ALT), and CPK, and by assessing other laboratory tests, such as hematology and blood chemistry, during the 16 weeks of study treatment. Adverse events were coded and grouped by body system. The AST, ALT, and CPK concentrations were measured at baseline, Week 8, and Week 16. Additional safety assessments were performed as necessary. Patients were withdrawn from the study if AST or ALT concentrations increased to more than three times the upper limit of normal for two consecutive measurements or if the CPK concentration increased to more than 10 times the upper limit of normal for 2 consecutive weeks, or if CPK elevations were associated with muscle pain. All patients who received study medication were evaluated. Adverse events that emerged during the treatment phase or that increased in intensity or frequency from the baseline phase (treatment-emergent signs and symptoms) were summarized by the number and percentage (incidence) of patients with an event for each treatment group.

Data evaluation

Safety analyses were performed on the safety population that consisted of all randomized patients who received at least one dose of study medication and provided any follow-up safety information. Efficacy analyses were performed on a modified intent-to-treat population. The modified intent-to-treat population was a subset of the safety population defined as those patients who had a valid baseline evaluation and any valid post-baseline efficacy information. A valid lipid assessment required that the measurement be made on a 12-hour fasting blood sample.

Statistical methods

Data management activities and statistical analyses were performed by Boston Biostatistics. All statistical analyses were performed using SAS Version 6.12. Comparisons were made between the two treatment groups (atorvastatin *vs* simvastatin). All statistical testing was two-sided and was conducted with a 5% type I error rate with no adjustment for multiplicity of endpoints. Categorical variables are summarized using frequencies and percentages and were compared between treatment groups using Cochran-Mantel Haenszel tests while controlling for country. Continuous variables are summarized using number and mean ± standard deviation and compared between treatment groups using two-way analysis of variance (ANOVA) controlling for country. Within-treatment changes for each lipid parameter from baseline to Week 8 and Week 16 were assessed using paired *t*-tests. Differences in the treatment means at baseline, Week 8, and Week 16 were tested using two-sample *t*-tests. Between-treatment differences in the mean nominal or percentage change from baseline or from Week 8 were assessed using an analysis of covariance (ANCOVA) model adjusting for baseline lipid concentration and country. Treatment interaction effects with baseline lipid concentration or country were evaluated by including the interaction term into the main effects model. The treatment effect was assessed using a Type III sums of squares (SS) F-test. If the treatment-by-country interaction was significant

at the 0.10 level using Type III SS F-tests, exact Wilcoxon rank sum tests were planned to compare treatment groups within each country. Between-treatment differences in the percentage of patients reaching their NCEP goal at Week 8 and Week 16 were assessed using Cochran-Mantel Haenszel tests, stratified by baseline NCEP risk group. The proportions of patients in each treatment group with each adverse event were compared using Fisher's exact test. A *p* value of less than 0.05 was considered statistically significant.

Results

Clinical characteristics

A total of 157 patients with dyslipidemia were randomized into this study. The two treatment groups were comparable with respect to demographic and clinical characteristics at baseline (Table 1). Female patients comprised 56% of the atorvastatin group and 64% of the simvastatin group. The average age was 55 years for the atorvastatin group and 56 years for the simvastatin group and ranged from 31 to 76 years overall. Approximately half of the patients were Chinese. The distribution of Malay, Thai, and Thai-Chinese was similar between treatment groups. Nineteen patients withdrew from the treatment (nine from the atorvastatin group, 10 from the simvastatin group). A total of 138 patients completed the treatment program (70 in the atorvastatin group, 68 in the simvastatin group).

Of the 157 patients randomized into the study, six had no follow-up safety data and there was no confirmation that they had ever taken study medication. The safety population consisted of 76 atorvastatin patients and 75 simvastatin patients. Six patients in the safety population were not evaluated in the modified intent-to-treat population. One patient in the simvastatin group was excluded because there was no valid baseline efficacy data. Three patients in the atorvastatin group and two in the simvastatin group were excluded because there were no follow-up efficacy data. The modified intent-to-treat population consisted of 73 atorvastatin patients and 72 simvastatin patients. Changes in body weight and baseline lipid profile during the 6-week diet and placebo run-in period are summarized in Table 2. The body weight change varied among the whole population, but the absolute levels for each of the five lipid parameters were similar between the two groups ($p = 0.20$).

Efficacy

The percentage and nominal changes in lipid concentrations from baseline to Week 8 and Week 16 are summarized in Table 3 for the modified intent-to-treat population. At Week 8, both treatments produced significant mean percentage decreases from baseline in LDL-C — 42.5% for atorvastatin and 34.8% for simvastatin. Patients treated with atorvastatin, however, had a significantly greater decrease in LDL-C ($p = 0.0006$). No treatment interactions were observed with either country or baseline LDL-C. As was the case at Week 8, a significantly greater percentage reduction in LDL-C was observed at Week 16 in the atorvastatin group compared to the simvastatin group ($p = 0.003$). A significant treatment interaction with baseline LDL-C was demonstrated:

Table 1. Clinical characteristics at baseline of all randomized patients

	Treatment group		*p*-value
	Atorvastatin (79)	Simvastatin (78)	
Age (years)	54.7 ± 10.5 (79)	55.7 ± 11.5 (78)	0.61
BMI (kg/m^2)	23.98 ± 3.15 (78)	23.74 ± 3.17 (77)	0.65
Height (cm)	160.01 ± 9.23 (78)	157.69 ± 8.12 (77)	0.10
Weight (kg)	61.46 ± 10.67 (79)	59.20 ± 9.69 (78)	0.17
Pulse rate (bpm)	74.1 ± 8.4 (79)	73.5 ± 6.2 (78)	0.60
Respiratory rate	16.5 ± 3.3 (79)	16.4 ± 3.0 (77)	0.68
Systolic blood pressure (mmHg)	124.3 ± 15.8 (79)	122.5 ± 17.0 (78)	0.49
Diastolic blood pressure (mmHg)	77.6 ± 8.1 (79)	75.5 ± 8.0 (78)	0.11
NCEP risk group [% (*n*)]			0.30
No CHD			
< 2 risk factors	68% (54)	58% (45)	
≥ 2 risk factors	19% (15)	27% (21)	
With CHD	13% (10)	15% (12)	

Mean ± standard deviation or percentage (numbers of patients analyzed). BMI = body mass index; NCEP = National Cholesterol Education Program; CHD = coronary heart disease.

Table 2. Nominal changes in weight and baseline lipid profile during the basline phase (diet and placebo run-in period) in the modified intent-to-treat population

	Treatment group		*p*-value
	Atorvastatin (73)	Simvastatin (72)	
Weight change (kg)	–0.15 ± 1.22 (72)	–0.41 ± 1.29 (71)	0.20
LDL-C (mg/dL)	184.9 ± 23.4 (73)	188.5 ± 26.6 (72)	0.40
HDL-C (mg/dL)	50.0 ± 14.0 (73)	51.8 ± 12.3 (72)	0.43
VLDL-C (mg/dL)	30.8 ± 10.8 (73)	30.9 ± 13.7 (71)	0.96
TC (mg/dL)	265.7 ± 31.0 (73)	271.0 ± 30.0 (72)	0.30
TG (mg/dL)	153.7 ± 53.6 (73)	154.0 ± 67.9 (72)	0.98

Mean ± standard deviation (numbers of patients analyzed). LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; VLDL-C = very-low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglyceride.

LDL-C percentage change = –5.761% – 0.178% x (baseline LDL-C in mg/dL); $p = 0.02$.

The relative effect of the two treatments differed depending on the baseline LDL-C. Treatment with simvastatin did not result in appreciable LDL-C reduction in a number of patients with baseline LDL-C of less than 200 mg/dL. Because of this, percentage reductions in LDL-C with simvastatin appeared to increase with increasing baseline LDL-C. In contrast, the effect of atorvastatin was more consistent across the range of baseline LDL-C.

At Week 8, there was a statistically significant increase in HDL-C of 9% in the simvastatin group ($p = 0.004$). Although a corresponding positive mean per-

Table 3. Mean percentage and nominal change from baseline of lipid levels in the modified intent-to-treat population

		Atorvastatin	Simvastatin	Treatment difference
LDL-C				
	Δ_{W8} (%)	–42.5 ± 1.6* (71)	–34.8 ± 1.5* (72)	–7.7 ± 1.5†
	Δ_{W16} (%)	–48.1 ± 1.7* (73)	–40.9 ± 1.7* (72)	–7.2 ± 2.3†
	Δ_{W8} (mg/dL)	–79.7 ± 2.9* (71)	–66.4 ± 2.8* (72)	–13.3 ± 3.9†
	Δ_{W16} (mg/dL)	–90.2 ± 3.1* (73)	–78.4 ± 3.1* (72)	–11.8 ± 4.2†
HDL-C				
	Δ_{W8} (%)	+4.6 ± 2.5 (71)	+9.2 ± 2.5* (72)	–4.6 ± 3.4
	Δ_{W16} (%)	+6.1 ± 2.3‡ (73)	+8.7 ± 2.3‡ (72)	–2.6 ± 3.2
	Δ_{W8} (mg/dL)	+1.0 ± 1.4 (71)	+4.1 ± 1.4‡ (72)	–3.1 ± 3.9
	Δ_{W16} (mg/dL)	+2.0 ± 1.1 (73)	+3.4 ± 1.1 (72)	–1.4 ± 1.6
VLDL-C				
	Δ_{W8} (%)	–22.4 ± 3.6* (71)	–10.7 ± 3.6‡ (72)	–11.7 ± 5.0§
	Δ_{W16} (%)	–23.6 ± 3.7* (73)	–10.4 ± 3.7‡ (72)	–13.3 ± 5.0§
	Δ_{W8} (mg/dL)	–7.6 ± 1.3* (71)	–3.3 ± 1.3‡ (72)	–4.3 ± 1.8§
	Δ_{W16} (mg/dL)	–8.2 ± 1.3* (73)	–3.7 ± 1.3‡ (72)	–4.5 ± 1.8§
TC				
	Δ_{W8} (%)	–31.9 ± 1.4* (71)	–23.9 ± 1.4* (72)	–8.1 ± 1.9†
	Δ_{W16} (%)	–35.6 ± 1.4* (73)	–28.6 ± 1.4* (72)	–7.1 ± 1.9†
	Δ_{W8} (mg/dL)	–86.6 ± 3.8* (71)	–65.2 ± 3.8* (72)	–21.4 ± 5.2†
	Δ_{W16} (mg/dL)	–96.6 ± 3.6* (73)	–78.5 ± 3.6* (72)	–18.1 ± 5.0†
TG				
	Δ_{W8} (%)	–22.4 ± 3.8* (71)	–11.3 ± 3.6* (72)	–11.1 ± 5.0§
	Δ_{W16} (%)	–23.5 ± 3.7* (73)	–10.4 ± 3.7‡ (72)	–13.1 ± 5.1§
	Δ_{W8} (mg/dL)	–37.7 ± 6.4* (71)	–17.0 ± 6.4‡ (72)	–20.7 ± 8.8§
	Δ_{W16} (mg/dL)	–40.8 ± 6.4* (73)	–18.4 ± 6.5‡ (72)	–22.4 ± 8.8§

Mean ± standard deviation or percent (numbers of patients analyzed). *$p < 0.01$ compared to baseline; $^{\dagger}p < 0.01$ compared to simvastatin; $^{\ddagger}p < 0.05$ compared to baseline; $^{\S}p < 0.05$ compared to simvastatin. LDL-C = low-density lipoprotein cholesterol; Δ_{W8} (%) = Week 8 percent change; Δ_{W16} (%) = Week 16 percent change; Δ_{W8} (mg/dL) = Week 8 nominal change; Δ_{W16} (mg/dL) = Week 16 nominal change; HDL-C = high-density lipoprotein cholesterol; VLDL-C = very-low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglyceride.

centage change of + 5% was also demonstrated in the atorvastatin group, it was not statistically significant ($p = 0.13$). However, there was no significant difference in percentage change between the two treatment groups ($p = 0.19$). At Week 16, there was a statistically significant increase in HDL-C from baseline in both groups ($p = 0.011$ for simvastatin and $p = 0.015$ for atorvastatin). Again, no difference was demonstrated between the two groups ($p = 0.42$). There were also no statistically significant differences in HDL-C changes observed between the treatment groups in any of the six countries at Week 8. However, the magnitude of the changes appeared to differ among patients from different countries, with the most pronounced increases in HDL-C observed in patients from Indonesia and the Philippines.

Both treatments resulted in a significant percentage decrease in VLDL-C from baseline after 8 weeks. The mean percentage reduction observed with atorvastatin was approximately twice that observed with simvastatin ($p = 0.02$). A significantly greater reduction in VLDL-C was also found in the atorvastatin group after 16 weeks ($p = 0.01$), with most of the reduction having been achieved by Week 8. In patients in all six countries, treatment with either atorvastatin or simvastatin resulted in a significant reduction in VLDL-C at Week 8. This was also true at Week 16, except in patients from Indonesia, where there was a percentage increase in VLDL-C in the simvastatin group.

Eight weeks of treatment with either statin resulted in a significant decrease in TC, with a significantly greater decrease in the atorvastatin group than in the simvastatin group ($p = 0.0001$). This significantly greater decrease in TC was also shown in subjects treated with atorvastatin at Week 16 ($p = 0.0005$). There were significant reductions in TC in both treatment groups of approximately 11% from Week 8 to Week 16 among patients who did not achieve their NCEP goals at Week 8. In patients from five of the six countries or areas — Hong Kong being the exception — the median percentage reduction in TC from baseline to Week 8 was greater in the atorvastatin group than in the simvastatin group. In all six countries, the median percentage reductions in TC were greater in the atorvastatin group at Week 16.

There was a significant mean percentage reduction in TG from baseline to Week 8 in both groups, but patients treated with atorvastatin had a significantly greater reduction compared to those treated with simvastatin ($p = 0.03$), and this difference was maintained at Week 16 ($p = 0.01$). As with the VLDL-C change, most of the TG reduction observed at Week 16 had been achieved by Week 8. In patients from five of the six countries — Singapore being the exception — greater median percentage reductions in TG were observed for the atorvastatin group than for the simvastatin group at both Week 8 and Week 16.

A large proportion of patients in both treatment groups achieved their NCEP goals (Table 4). Overall, 82% of patients treated with atorvastatin and 81% of patients treated with simvastatin had achieved their NCEP goals after 8 weeks of treatment. By Week 16, 93% of patients treated with atorvastatin and 85% of patients treated with simvastatin had reached their NECP goals. There were no significant differences between the two treatment groups at Week 8 and at Week 16. The proportion of patients with coronary heart disease (CHD) achieving their NECP goals at Week 8 was less than 25% for both treatment groups. After another 8 weeks of 20 mg daily dose of the respective statin, the proportion of atorvastatin-treated patients with CHD who achieved their NCEP goals

Table 4. Patients reaching the National Cholesterol Education Program (NCEP) low-density lipoprotein cholesterol (LDL-C) goal at Weeks 8 and 16 in the modified intent-to-treat population

		Treatment group		*p*-value
		Atorvastatin	Simvastatin	
Week 8				
No CHD				
	< 2 risk factors	45/49 (92%)	39/43 (91%)	1.00
	≥ 2 risk factors	11/13 (85%)	17/19 (89%)	1.00
With CHD		2/9 (22%)	2/10 (20%)	1.00
Week 16				
No CHD				
	< 2 risk factors	49/49 (100%)	39/43 (91%)	0.04
	≥ 2 risk factors	11/14 (79%)	18/19 (95%)	0.29
With CHD		8/10 (80%)	4/10 (40%)	0.17

CHD = coronary heart disease.

increased to 80%. In contrast, this proportion increased to only 40% in the simvastatin group. In this study, there were only 20 patients with CHD, less than 15% of the modified intent-to-treat population. This did not provide sufficient power to determine the treatment difference in this group. At Week 16, all patients with fewer than two risk factors in the atorvastatin group had achieved their NECP goals, compared to 91% in the simvastatin group. This difference was statistically significant ($p = 0.04$).

Safety

All treatment-emergent adverse events and associated events are summarized by body system in Table 5, which shows treatment-emergent adverse events that occurred in at least 2% of either treatment group in the safety population. Patients in both treatment groups reported similar incidences of adverse events during the 16 weeks of treatment. There were no deaths during this study. A total of four serious adverse events were reported in four patients. Two patients — one receiving atorvastatin and the other, simvastatin — experienced a myocardial infarction. One patient receiving simvastatin had a cerebrovascular accident and another experienced vertigo. The adverse event in three of these four patients resulted in their withdrawal from the study — the two who had experienced myocardial infarctions and one who had experienced a cerebrovascular accident. Three patients withdrew due to non-serious adverse events. Of the two receiving atorvastatin, one withdrew due to malaise and somnolence, while the other withdrew due to rash. The third patient received simvastatin and reported effort angina, constipation, and drooping eyelids.

There were no statistically significant between-treatment differences in laboratory abnormalities. Table 6 summarizes the shifts from normal at baseline to abnormal at study exit for AST, ALT, and CPK concentrations. In this study, only one simvastatin patient had an AST or CPK concentration that was three-fold or more of the upper limit of normal. No differences were found between the two treatments.

Discussion

The ASIA study is the first clinical trial to compare the efficacy of atorvastatin and simvastatin to lower serum LDL-C and other lipids in Asian people with primary hypercholesterolemia. In this study, patients were similar to the general population requiring treatment to reduce lipid levels. After 8 weeks, both treatments were effective in reducing serum LDL-C. The adjusted mean percentage reduction in atorvastatin patients (–42.5%) was more significant than that in simvastatin patients (–34.8%; $p < 0.01$). Adjusted mean percentage reductions in TC, TG, and VLDL-C were also statistically significantly different between the two groups, with atorvastatin-treated patients showing greater reduc-

Table 5. All and associated treatment-emergent adverse events occurring in at least 2% of the safety population, by body system

Body system / Adverse event	Adverse events		Associated adverse events*	
	Atorvastatin (n = 76)	Simvastatin (n = 75)	Atorvastatin (n = 76)	Simvastatin (n = 75)
Any adverse event	21 (28%)	21 (28%)	7 (9%)	7 (9%)
Body as a whole	8 (11%)	10 (13%)	3 (4%)	3 (4%)
Infection	2 (3%)	5 (7%)	0	0
Malaise	4 (5%)	1 (1%)	3 (4%)	1 (1%)
Chest pain	0 (0%)	3 (4%)	0	0
Cardiovascular	6 (8%)	5 (7%)	1 (1%)	0
Hypertension	4 (5%)	1 (1%)	1 (1%)	0
Digestive	6 (8%)	3 (4%)	4 (5%)	1 (1%)
Constipation	4 (5%)	1 (1%)	4 (5%)	0
Metabolic / nutritional	3 (4%)	0 (0%)	0	0
Nervous	6 (8%)	5 (7%)	3 (4%)	2 (3%)
Dizziness	5 (7%)	2 (3%)	3 (4%)	1 (1%)
Respiratory	1 (1%)	2 (3%)	0	0
Skin and appendages	4 (5%)	3 (4%)	3 (4%)	3 (4%)
Rash	2 (3%)	2 (3%)	2 (3%)	2 (3%)
Special senses	3 (4%)	2 (3%)	0	0

*Events classified by physician as possibly, probably, definitely related, or insufficient information. There were no significant differences between the two treatment groups by Fisher's exact test.

Table 6. Laboratory shifts from normal at baseline to abnormal at study exit in the safety population

		Treatment group		*p*-value
		Atorvastatin (n = 76)	Simvastatin (n = 75)	
AST	< 2 x ULN	3/66 (5%)	3/66 (5%)	1.00
	2–3 x ULN	1/66 (2%)	0/66 (0%)	
	> 3 x ULN	0/66 (0%)	1/66 (2%)	
ALT	< 2 x ULN	7/66 (11%)	9/66 (14%)	0.60
	2–3 x ULN	0/66 (0%)	0/66 (0%)	
	> 3 x ULN	0/66 (0%)	0/66 (0%)	
CPK	< 2 x ULN	5/64 (8%)	4/54 (7%)	0.46
	2–3 x ULN	1/64 (2%)	1/54 (2%)	
	3–5 x ULN	0/64 (0%)	1/54 (2%)	
	> 5 x ULN	0/64 (0%)	0/54 (0%)	

AST = aspartate aminotransaminase; ULN = upper limit of normal; ALT = alanine aminotransaminase; CPK = creatine phosphokinase.

tions in each. Mean percentage reductions in VLDL-C and TG in atorvastatin-treated patients were nearly twice those seen in simvastatin-treated patients.

Patients participating in this study were from six Asian countries. The overall lipid-lowering results and trends observed were similar in the individual countries. No major treatment–country interactions were detected in the analyses. A significant treatment interaction with baseline LDL-C was demonstrated and the relative effect of the two treatments differed depending on baseline LDL-C. After 8 weeks of treatment, 82% of atorvastatin-treated patients and 81% of simvastatin-treated patients achieved their NCEP LDL-C goals. In contrast, in Western countries, only 46% of atorvastatin-treated patients and 27% of simvastatin-treated patients achieved their goals after 16 weeks of 10-mg statin treatment in an Australian population [8], and 59% of patients achieved their goals after 6 weeks of 10-mg simvastatin treatment in a European population [13]. After having their doses increased to 20 mg daily of the respective medications and an additional 8 weeks of treatment, 93% of atorvastatin-treated patients and 85% of simvastatin-treated patients achieved their goals. At Week 16, all atorvastatin-treated patients with fewer than two risk factors achieved their goal compared to 91% of simvastatin-treated patients; this difference was statistically significant (p = 0.04).

The efficacy results for atorvastatin from this study are consistent with those obtained in previous studies [5, 8, 9, 14, 15] using a dose of 10 mg daily. The adjusted mean percentage reduction of 42.5% after 8 weeks compares favorably with the 36% to 41% reductions reported in previous studies. The statistically significant advantage of atorvastatin over simvastatin in reducing LDL-C found in this study was also seen in several previous studies [8, 9]. However, in Dart et al's study, treatment with 10 mg atorvastatin for 16 weeks resulted in mean reductions in LDL-C of 37%, while treatment with the same dose of simvastatin for the same time resulted in 30% reductions in LDL-C [8]. In the CURVES study, treatment with 10 mg atorvastatin for 8 weeks resulted in mean reductions in LDL-C of 38%, while treatment with the same dose of simvastatin for the same time resulted in only 28% reductions in LDL-C [9]. Although they were not tested in the same trial, it seems that the dosage of statins needed to attain NCEP goals or lower lipid levels was smaller in this Asian population to that in Western studies. This phenomenon was more prominent in the simvastatin group, for which treatment with 20 mg reduced LDL-C by 33% in Dart et al's series and 35% in the CURVES study [8, 9]. However, only 10 mg simvastatin resulted in a 34.8% mean percentage reduction in LDL-C in this Asian study. Chinese patients have also been shown to need a much smaller dosage of beta-blockers in previous studies [10, 16, 17], although the underlying mechanism is still unclear. There are several possibilities for the increased sensitivity to statins in Asian populations. People are generally smaller in stature, while dietary habits are very different from those in Western countries. In addition, Asian pharmacokinetics for some drugs might be different from those in the West [17, 18]. Doctors in Asian countries usually treat their patients with a lower starting dose of simvastatin (5–10 mg/day). The results of this study support this clinical experience.

Elevated serum TG concentrations have been recognized as a risk factor for progression of atherosclerosis for many years. Although early attempts to distinguish serum TG as an independent risk factor in univariate analyses were unsuccessful, several recent analyses have confirmed the importance of TG [8]. Serum TG elevations are of particular concern when associated with elevated LDL-C and decreased HDL-C.

Patients with combined dyslipidemia are at greater risk of heart disease than patients with elevated LDL-C alone [19–21]. A greater reduction in TG by atorvastatin than simvastatin has been observed in previous studies in Western countries [8, 9]. In this Asian study, there was a significantly greater two-fold reduction in TG and VLDL-C from baseline to Week 8 in the atorvastatin group. This difference was maintained at Week 16, although most of the reductions in TG and VLDL-C observed at Week 16 had been achieved by Week 8. The increased atherogenic potential of TG and VLDL-C may be due to the increased presence of small, dense, TG-rich lipoproteins found with increased LDL-C, VLDL-C, and TG, and decreased HDL-C. Atorvastatin is particularly effective in correcting each of these lipid parameters in Asian people, even at a starting dose of 10 mg / day. It is also implied that doctors should follow their patients' lipid profile soon after 8 weeks but not as far on as 3 months of statin therapy, because at that point most patients may have gained significant changes in their lipid levels. This approach may help patients to achieve their treatment goal earlier.

Both of the statins were generally well tolerated in this study. No patient, except for one who received simvastatin, experienced clinically significant (> 3 x upper limit of normal) increases in hepatic transaminases or CPK. The incidence of adverse events, both overall (28%) and treatment-emergent (9%), in atorvastatin-treated patients was consistent with previous studies [5, 9] and was similar to that in simvastatin-treated patients. These findings indicate that atorvastatin did not induce more adverse effects, although it was more potent for lipid lowering than simvastatin.

In conclusion, with the use of 10 mg and 20 mg of atorvastatin compared to simvastatin in an Asian population with primary hypercholesterolemia, a clinically and significantly greater reduction in LDL-C, VLDL-C, TG, and TC was achieved with atorvastatin compared to simvastatin. Both drugs increased HDL-C at a dose of 20 mg. Mean percentage lipid reductions following the use of atorvastatin at least corresponded with the results observed in previous studies. The efficacy of both statins seems to be better in Asian people than in Caucasians and the treatment with each of these drugs demonstrated acceptable safety profiles.

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