Original Article

Superior Benefit of Aggressive Lipid-Lowering Therapy for High-Risk Patients Using Statins: the SUBARU Study

—More Hypercholesterolemic Patients Achieve Japan Atherosclerosis Society LDL-C Goals with Rosuvastatin Therapy than with Atorvastatin Therapy

Masahiko Kurabayashi[1], Tsutomu Yamazaki[2], and the SUBARU Study Group

[1]Department of Medicine and Biological Science, Gunma University Graduate School of Medicine, Maebashi, Japan
[2]Department of Clinical Epidemiology & Systems, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

***Aim*: There have been few comparisons between rosuvastatin and other statins in Japanese patients. This open-label, randomized, parallel-group comparative study was performed to compare the efficacy and safety of rosuvastatin (5 mg) and atorvastatin (10 mg) once daily in Japanese patients with hypercholesterolemia.**

***Methods*: Patients with hypercholesterolemia who had received atorvastatin (10 mg/day) for at least 4 weeks and were in category B3, B4, or C according to the Japan Atherosclerosis Society Guidelines for Diagnosis and Treatment of Atherosclerotic Cardiovascular Diseases 2002 (JAS2002GL) were randomly assigned to rosuvastatin at 5 mg/day (switched treatment) or atorvastatin at 10 mg/day (continued treatment). The primary endpoint was the achievement of JAS2002GL LDL-C goals at 8 weeks.**

***Results*: LDL-C goals were reached by 80.3% of the rosuvastatin group and 67.3% of the atorvastatin group at 8 weeks ($p<0.01$). The percent change of the LDL-C and LDL-C/HDL-C ratio at 8 weeks was significantly greater in the rosuvastatin group than in the atorvastatin group (both $p<0.01$). Furthermore, rosuvastatin improved fasting plasma glucose ($p<0.01$). Both drugs were well tolerated.**

***Conclusion*: Rosuvastatin (5 mg/day) is a useful treatment option for high-risk patients with hypercholesterolemia.**

J Atheroscler Thromb, 2008; 15:314-323.

Key words; Rosuvastatin, Hypercholesterolemia, LDL-C/HDL-C ratio, Atherosclerosis

Introduction

Since the Framingham Heart Study showed that the blood cholesterol level was correlated with the onset of coronary artery diseases[1)], the importance of reducing elevated cholesterol levels to prevent major cardiovascular events has been well established. The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) markedly reduce low-density lipoprotein cholesterol (LDL-C) levels, and it has been shown that such a reduction of LDL-C not only leads to a significant reduction in the mortality rate from coronary artery disease but also reduces the risk of stroke[2-7)]. Statins are now the most widely used treatment for patients with hypercholesterolemia because of achieving a marked reduction of LDL-C.

The Japan Atherosclerosis Society has prepared guidelines (Japan Atherosclerosis Society Guidelines for Diagnosis and Treatment of Atherosclerotic Cardiovascular Diseases 2002: JAS2002GL) that emphasize the need to reduce LDL-C to target levels[8)]. Lowering the serum cholesterol level to reach the goals is the most important objective of treatment that aims

Address for correspondence: Masahiko Kurabayashi, Department of Medicine and Biological Science, Gunma University Graduate School of Medicine, 3-39-22 Showa-machi, Maebashi City, Gunma 371-8511, Japan
E-mail: mkuraba@med.gunma-u.ac.jp
Received: December 25, 2007
Accepted for publication: July 29, 2008

to prevent the progression of atherosclerosis and the onset of coronary artery disease; however, the Japan Lipid Assessment Program (J-LAP) study showed that the achievement of LDL-C goals specified in the JAS2002GL was not satisfactory in spite of including atorvastatin (50.6%, 53.1%, and 29.2% of patients in category B3, B4, and C, respectively)[9].

In Western countries, rosuvastatin has come into widespread clinical use, because it has been reported to exhibit a stronger LDL-C lowering effect and a higher rate of achieving therapeutic goals than atorvastatin[10-13]. Recently, it was reported that regression of coronary atherosclerosis requires a substantial reduction of LDL-C along with an increase of high-density lipoprotein cholesterol (HDL-C) by more than 7.5%, and that LDL-C/HDL-C ≤2.0 was associated with the possible inhibition of plaque progression or even with plaque regression, and a further effect was expected when LDL-C/HDL-C ≤1.5[14]. Although rosuvastatin is expected to be a useful new lipid-lowering drug for high-risk Japanese patients, few reports have compared rosuvastatin with other statins in the Japanese population. In the SUBARU (SUperior Benefit of Aggressive lipid-lowering therapy for high-Risk patients Using statins) study, we compared the achievement of JAS2002GL LDL-C goals and the LDL-C/HDL-C ratio ≤2.0 or ≤1.5, the percent changes of lipids (LDL-C, total cholesterol [TC], HDL-C, triglycerides [TG], and LDL-C/HDL-C ratio), the percent changes of other parameters (high sensitive C-reactive protein [hs-CRP], adiponectin, small dense LDL, and fasting plasma glucose) from baseline to 8 weeks, and safety between rosuvastatin (5 mg/day) and atorvastatin (10 mg/day), which is currently considered to show the most powerful lipid-lowering effect in high-risk patients (category B3, B4, or C) who require active control of their lipid levels.

Subjects and Methods

This open-label, randomized, parallel-group comparative study was performed at 55 institutions between December 2006 and October 2007. The study was performed in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of each institution. Written consent was obtained from all patients before any study-related procedure.

Patients with hypercholesterolemia who had received atorvastatin (10 mg) once daily for at least 4 weeks were enrolled in the present study. They were aged 20 years or more and were classified as being at high risk (JAS2002GL category B3, B4, or C). The

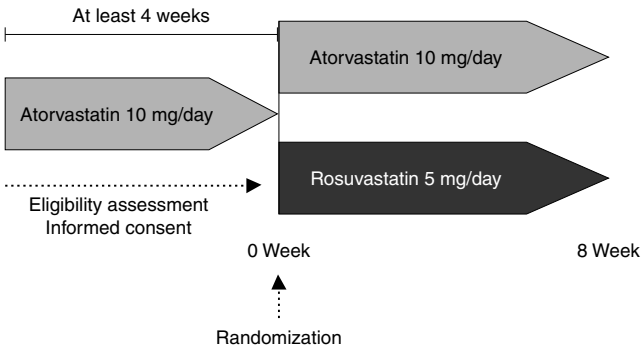

Fig. 1. Study design.

JAS2002GL classifies patients with at least 3 risk factors (or with diabetes) into category B3, patients with at least 4 risk factors (or with cerebral infarction) into category B4, and patients with a history of coronary artery diseases into category C[8]. At the time of enrollment, the baseline characteristics of the patients (gender, birth date, and risk factors for atherosclerotic diseases) were investigated. Eligible patients were randomly assigned to receive either rosuvastatin at 5 mg/day (switched treatment) or atorvastatin at 10 mg/day (continued treatment) using the central registration method, and each treatment was given for 8 weeks (**Fig. 1**). Randomization was performed with stratification for the JAS2002GL category (B3, B4, or C) and achievement of LDL-C goals (yes or no).

The exclusion criteria were patients with severe hypertension, patients with type I diabetes, patients with familial hypercholesterolemia, patients with the occurrence of cerebrovascular disease or myocardial infarction within the last 3 months, patients with active hepatic disease (alanine aminotransferase [ALT] >100 IU/L, aspartate aminotransferase [AST] >100 IU/L, or bilirubin >2.5 mg/dL), patients with renal dysfunction (serum creatinine ≥2.0 mg/dL or creatinine clearance <30 mL/min/1.73 m^2), patients with a serum creatine kinase (CK) >1,000 IU/L, patients with hypothyroidism, pregnant or impregnable women, and women who hoped to be pregnant during the study period. Use of other statins, fibrates, or anion exchange resins was prohibited during the study period.

The primary endpoint was the achievement of JAS2002GL LDL-C goals at 8 weeks, which was 120 mg/dL for category B3 and B4 patients and 100 mg/dL for category C patients[8]. The secondary endpoints were the achievement of JAS2002GL LDL-C goals at 8 weeks in subgroups stratified by baseline characteristics, the percent changes of LDL-C, TC, HDL-C, TG, LDL-C/HDL-C ratio, adiponectin, small dense LDL, hs-CRP, and fasting plasma glucose from baseline to

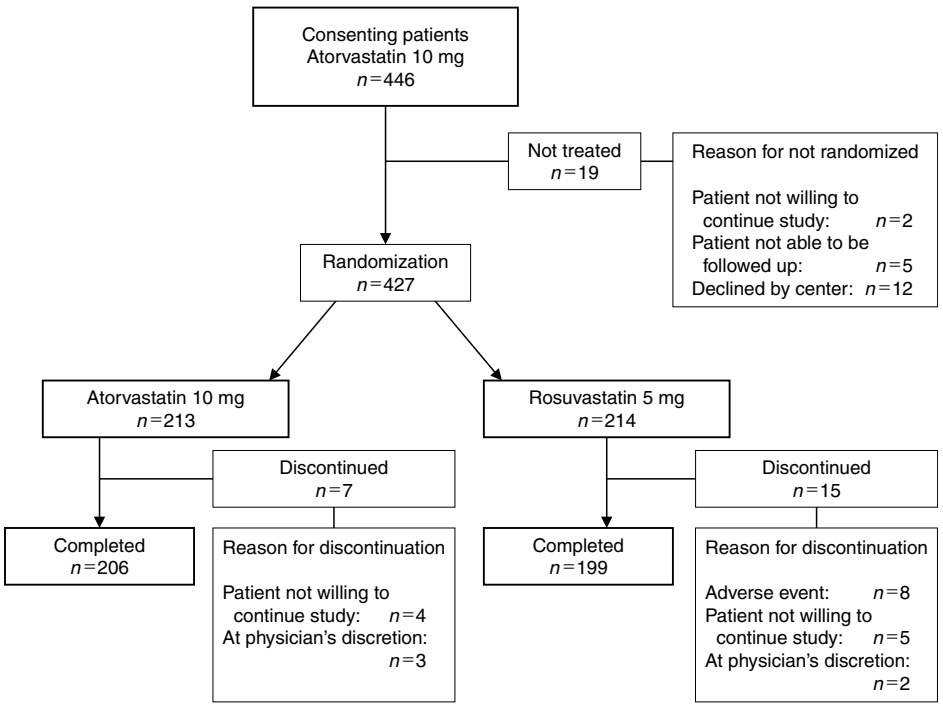

Fig. 2. Disposition of the subjects.

8 weeks, and achievement of the LDL-C/HDL-C ratio ≤2.0 or ≤1.5. To assess safety, the incidence and details of adverse events and laboratory abnormalities were investigated.

Compliance with treatment was assessed at 4 and 8 weeks by interview. Any change of the dosage regimen of concomitant medication was prohibited during the study. Laboratory tests (including biochemistry tests, hematology tests, urinalysis, serum lipids, and other parameters) were performed after an overnight fast at baseline and at 8 weeks. All laboratory tests were performed by SRL Medisearch Inc. (Tokyo, Japan). LDL-C, TC, TG, and fasting plasma glucose were measured by enzymatic methods, HDL-C by the selective inhibition method, hs-CRP by latex-nephelometry, adiponectin by ELISA, and small dense LDL by relative mobility calculated from a densitogram.

Data analysis was performed by Mebix Inc. (Tokyo, Japan), independently of the study group, which was assigned by the chief investigator to act as the central data center. All efficacy analyses were carried out on the full analysis set. Safety was analyzed on the safety population that consisted of patients who had at least one visit after randomization regardless of taking the study drug. The percent changes of each parameter were calculated from the mean ± standard deviation. Differences in the percent changes of each parameter and in the achievement of JAS2002GL LDL-C goals or an LDL-C/HDL-C ratio ≤2.0 or ≤1.5 at 8 weeks were statistically assessed by the *t*-test and Fisher's exact test, respectively. For imbalance of the baseline variables between groups, their influence on the achievement of JAS2002GL goals was explored by variable selection (stepwise method and method of all possible combinations) of logistic regression analysis. All statistical tests were two-sided, with the level of significance being set at $p<0.05$.

Results

The disposition of the study population is summarized in **Fig. 2**. A total of 446 patients were enrolled in the study, while assignment to medication was performed and treatment was started for 427 patients (214 in the rosuvastatin group and 213 in the atorvastatin group). Among them, 199 patients in the rosuvastatin group and 206 patients in the atorvastatin group completed the study.

The baseline characteristics of the patients assigned to each treatment are summarized in **Table 1**. Patients were older in the rosuvastatin than in the atorvastatin group ($p<0.05$), but there were no appreciable differences of other baseline characteristics between the two groups, including gender, smoking, JAS2002GL categories, complications, cardiovascular risk factors, and the achievement of JAS2002GL

Table 1. Characteristics of the patients

		Atorvastatin 10 mg *n* (%) (*n* = 207)	Rosuvastatin 5 mg *n* (%) (*n* = 208)	*p* value
Gender	Male	78 (37.7)	95 (45.7)	$p=0.111$ [1)]
	Female	129 (62.3)	113 (54.3)	
Age	−29	1 (0.5)	0 (0)	$p=0.018$ [2)]
	30−39	0 (0)	1 (0.5)	
	40−49	14 (6.8)	7 (3.4)	
	50−59	52 (25.1)	45 (21.6)	
	60−69	74 (35.7)	65 (31.3)	
	70−79	54 (26.1)	74 (35.6)	
	80−	12 (5.8)	16 (7.7)	
	Average ± SD	64.4 ± 10.3	66.7 ± 9.6	$p=0.020$ [3)]
	Range	27-94	36-87	
Smoking		61 (29.5)	53 (25.5)	$p=0.381$ [1)]
JAS2002GL category	B3	119 (57.5)	120 (57.7)	$p=0.936$ [2)]
	B4	48 (23.2)	49 (23.6)	
	C	40 (19.3)	39 (18.8)	
Complications		199 (96.1)	201 (96.6)	$p=0.800$ [1)]
Cardiovascular risk factors	Hypertension	155 (74.9)	148 (71.2)	$p=0.439$ [1)]
	Diabetes	134 (64.7)	132 (63.5)	$p=0.838$ [1)]
	CAD	40 (19.3)	39 (18.8)	$p=0.901$ [1)]
	Stroke	17 (8.2)	15 (7.2)	$p=0.717$ [1)]
	Low HDL-C	6 (2.9)	11 (5.3)	$p=0.322$ [1)]
	Family history of CAD	64 (30.9)	68 (32.7)	$p=0.752$ [1)]
Achieving JAS2002GL LDL-C goals		146 (70.5)	145 (69.7)	$p=0.915$ [1)]

SD: standard deviation, CAD: coronary artery diseases
1): Fisher's exact test, 2): Wilcoxon rank test, 3): *t*-test

LDL-C goals. Treatment compliance was generally good during this study. Poor compliance (compliance rate below 75%) was only three patients in the rosuvastatin group.

Efficacy

At baseline, JAS2002GL LDL-C goals were achieved in 69.7% and 70.5% of the rosuvastatin and atorvastatin groups, respectively (**Table 1**). JAS2002GL goals were achieved in 80.3% of the rosuvastatin group versus 67.3% of the atorvastatin group after 8 weeks, and the achievement rate of the rosuvastatin group was significantly higher ($p<0.01$) (**Fig. 3**).

The results of stratified analysis of the achievement of LDL-C goals according to cardiovascular risk factors (hypertension, diabetes, coronary artery disease, and stroke) and each patient's category of the JAS2002GL (B3 + B4 or C) are shown in **Fig. 4**. Among patients with hypertension or diabetes, 85.6%

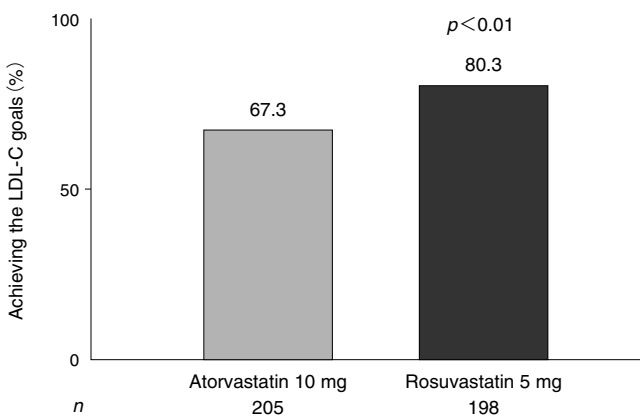

Fig. 3. Achievement of JAS2002GL LDL-C goals at 8 weeks.
LDL-C goal: Category B3 (<120 mg/dL); B4 (<120 mg/dL); C (<100 mg/dL)
Fisher's exact test
P values show differences between the rosuvastatin and atorvastatin groups.

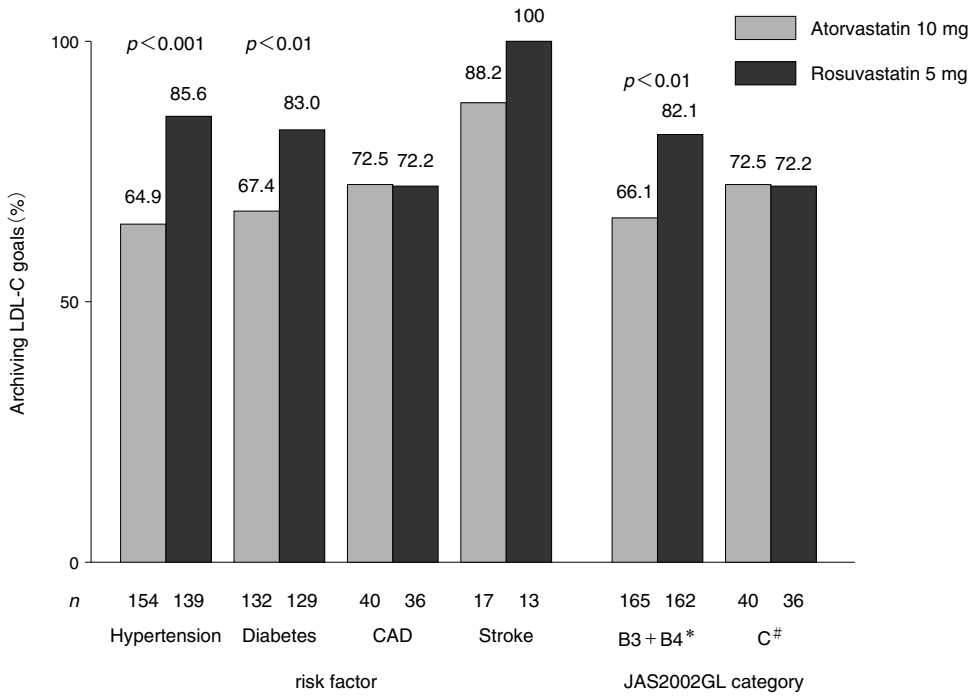

Fig. 4. Stratified analysis of achievement of JAS2002GL LDL-C goals at 8 weeks.

LDL-C goal: Category B3 (< 120 mg/dL); B4 (< 120 mg/dL); C (< 100 mg/dL)
CAD: Coronary artery disease
Fisher's exact test
P values show differences between the rosuvastatin and atorvastatin groups.
*: category Ⅲ (high-risk patients) of primary prevention in JAS GL2007, #: history of CAD of secondary prevention in JAS GL2007

and 83.0% achieved the LDL-C goals in the rosuvastatin group, respectively, while the corresponding rates for the atorvastatin group were 64.9% and 67.4%, respectively. Both rates were significantly higher in the rosuvastatin group ($p < 0.001$ and $p < 0.01$, respectively). Among the patients in category B3 + B4, achievement of LDL-C goals showed a significant difference between the rosuvastatin and atorvastatin groups (82.1% vs. 66.1%, $p < 0.01$).

When the levels of lipids and other parameters at baseline and 8 weeks, as well as their percent changes from baseline to 8 weeks, were investigated, it was found that LDL-C, the LDL-C/HDL-C ratio, and fasting plasma glucose showed significant differences between the rosuvastatin and atorvastatin groups ($p < 0.01$ in favor of rosuvastatin for all parameters) (**Table 2**).

The percent change of LDL-C in patients with hypertension, diabetes, and category B3 + B4 from the rosuvastatin group was, respectively, −6.7%, −7.9%, and −5.9% from baseline to 8 weeks, while the corresponding rates for the atorvastatin group were −0.2%, 0%, and −1.1%. There were significant differences between the two groups (hypertension: $p < 0.01$, diabetes: $p < 0.001$, category B3 + B4: $p < 0.01$) (**Table 3**). The percent change of LDL-C from baseline to 8 weeks stratified by a baseline LDL-C of < 100 mg/dL, 100-120 mg/dL, 120-140 mg/dL, 140-160 mg/dL, and > 160 mg/dL was, respectively, −2.1%, −7.7%, −8.4%, −20.4%, and −21.4% in the rosuvastatin group, while it was, respectively, 3.2%, −3.6%, −2.2%, −7.4%, and −10.0% in the atorvastatin group. There were significant differences between the groups for LDL-C levels of < 100 mg and 140-160 mg ($p < 0.05$ and $p < 0.01$, respectively) (**Table 4**). The percent change of the

LDL-C/HDL-C ratio in patients with hypertension, diabetes and category B3 + B4 in the rosuvastatin group was −5.4%, −6.8% and −4.6%, respectively, while the corresponding rates for the atorvastatin group were 3.1%, 2.7% and 1.3%. There were also significant differences between the groups (hypertension and diabetes: $p < 0.001$, category B3 + B4: $p < 0.01$) (**Table 5**). Achievement of an LDL-C/HDL-C ratio ≤2.0 also showed a significant difference between the rosuvastatin and the atorvastatin groups (70.2% vs. 59.5%,

Table 2. Percent changes of lipids and other parameters from baseline to 8 weeks

	Atorvastatin 10 mg (mean ± SD)			Rosuvastatin 5 mg (mean ± SD)		
	Baseline $n=207$	8 weeks $n=205$	% change from baseline $n=205$	Baseline $n=207$	8 weeks $n=198$	% change from baseline $n=198$
LDL-C (mg/dL)	109.3 ± 30.6	106.7 ± 28.7	− 1.2 ± 14.7	102.9 ± 25.1	95.3 ± 24.2	− 6.0 ± 17.0**
TC (mg/dL)	192.3 ± 34.8	187.4 ± 32.9	− 2.2 ± 10.3	186.1 ± 28.8	178.5 ± 28.5	− 3.3 ± 11.6
HDL-C (mg/dL)	60.1 ± 15.3	58.8 ± 14.6	− 1.7 ± 11.7	60.9 ± 17.6	60.7 ± 17.7	0.1 ± 12.2
TG (mg/dL)	130.9 ± 72.2	129.7 ± 89.5	5.2 ± 43.5	128.5 ± 67.4	136.7 ± 80.4	12.9 ± 48.2
LDL-C/HDL-C ratio	1.94 ± 0.74	1.94 ± 0.75	1.4 ± 16.7	1.84 ± 0.71	1.70 ± 0.64	− 5.0 ± 20.3**
Adiponectin (μg/mL)	12.3 ± 8.3	11.8 ± 7.1	− 2.3 ± 18.5	12.1 ± 7.4	11.3 ± 7.8	− 3.3 ± 20.7
sd-LDL	0.33 ± 0.03	0.35 ± 0.04	4.5 ± 8.6	0.33 ± 0.03	0.35 ± 0.03	4.6 ± 9.0
hs-CRP (mg/L)	1.59 ± 6.31	1.23 ± 3.34	0.13 ± 0.91	0.95 ± 1.47	1.10 ± 2.43	0.14 ± 0.81
Fasting plasma glucose (mg/dL)	119.0 ± 32.7	121.4 ± 35.1	3.3 ± 20.4	124.4 ± 41.4	120.6 ± 38.8	− 2.2 ± 16.2**

SD: standard deviation
P values show differences between the rosuvastatin and atorvastatin groups.
t-test, **: $p<0.01$

Table 3. Percent change of LDL-C from baseline to 8 weeks stratified by risk factors

Risk factor	Atorvastatin 10 mg (mean ± SD)			Rosuvastatin 5 mg (mean ± SD)		
	Baseline (mg/dL)	8 weeks (mg/dL)	% change from baseline	Baseline (mg/dL)	8 weeks (mg/dL)	% change from baseline
Hypertension	109.5 ± 32.4 ($n=155$)	107.6 ± 29.5 ($n=154$)	− 0.2 ± 14.6 ($n=154$)	101.1 ± 23.7 ($n=147$)	92.9 ± 23.1 ($n=139$)	− 6.7 ± 17.7** ($n=139$)
Diabetes	107.4 ± 27.7 ($n=134$)	106.1 ± 26.9 ($n=132$)	0.0 ± 15.7 ($n=132$)	104.8 ± 26.7 ($n=132$)	95.5 ± 24.9 ($n=129$)	− 7.9 ± 16.6*** ($n=129$)
CAD	101.7 ± 28.9 ($n=40$)	98.0 ± 27.5 ($n=40$)	− 1.9 ± 15.9 ($n=40$)	94.4 ± 21.2 ($n=39$)	87.0 ± 23.0 ($n=36$)	− 6.4 ± 18.4 ($n=36$)
Stroke	106.5 ± 26.6 ($n=17$)	96.8 ± 18.9 ($n=17$)	− 7.6 ± 11.4 ($n=17$)	100.3 ± 22.1 ($n=15$)	89.2 ± 16.9 ($n=13$)	− 6.0 ± 19.1 ($n=13$)
B3 + B4	111.2 ± 30.7 ($n=167$)	108.8 ± 28.7 ($n=165$)	− 1.1 ± 14.5 ($n=165$)	104.9 ± 25.6 ($n=168$)	97.1 ± 24.1 ($n=162$)	− 5.9 ± 16.7** ($n=162$)
C	101.7 ± 28.9 ($n=40$)	98.0 ± 27.5 ($n=40$)	− 1.9 ± 15.9 ($n=40$)	94.4 ± 21.2 ($n=39$)	87.0 ± 23.0 ($n=36$)	− 6.4 ± 18.4 ($n=36$)

SD: standard deviation , CAD: coronary artery diseases
P values show differences between the rosuvastatin and atorvastatin groups.
t-test, **: $p<0.01$, ***: $p<0.001$

$p<0.05$) (**Fig. 5**). On the other hand, achievement of an LDL-C/HDL-C ratio ≤1.5 was noted in 42.4% of the rosuvastatin group and 32.7% of the atorvastatin group (**Fig. 5**).

Safety

Safety was analyzed in 415 patients (209 from the rosuvastatin group and 206 from the atorvastatin group). Adverse events were noted in 33 patients from the rosuvastatin group and 31 patients from the atorvastatin group. The incidence of adverse events was 15.8% in the former group and 15.0% in the latter group. All of the adverse events were transient, and none were clinically important.

Adverse events noted in 3 patients or more were increased CK (normal range: 5–97 U/L [male], 32–180 U/L [female]) in 12 patients (5 from the rosuvastatin group and 7 from the atorvastatin group) and upper respiratory tract inflammation in 10 patients (5 from both treatment groups). A serious adverse event occurred in 1 patient from the rosuvastatin group (hospitalization for treatment of a left tibial plateau fracture), but this was considered to be unrelated to the study drug by the investigator. Treatment was dis-

Table 4. Percent change of LDL-C from baseline to 8 weeks by baseline LDL-C

Baseline LDL-C (mg/dL)	Atorvastatin 10 mg (mean ± SD)			Rosuvastatin 5 mg (mean ± SD)		
	Baseline (mg/dL)	8 weeks (mg/dL)	% change from baseline (%)	Baseline (mg/dL)	8 weeks (mg/dL)	% change from baseline (%)
< 100	84.5 ± 11.4 (n = 91)	86.5 ± 14.3 (n = 89)	3.2 ± 14.1 (n = 89)	82.9 ± 10.9 (n = 100)	80.6 ± 17.3 (n = 96)	− 2.1 ± 17.8* (n = 96)
100-120	109.6 ± 5.7 (n = 55)	105.5 ± 16.2 (n = 55)	− 3.6 ± 14.5 (n = 55)	108.7 ± 6.0 (n = 60)	100.7 ± 19.4 (n = 58)	− 7.7 ± 16.2 (n = 58)
120-140	127.7 ± 6.1 (n = 31)	124.6 ± 20.3 (n = 31)	− 2.2 ± 16.8 (n = 31)	128.1 ± 6.1 (n = 31)	117.0 ± 16.6 (n = 30)	− 8.4 ± 13.8 (n = 30)
140-160	149.7 ± 5.8 (n = 13)	138.6 ± 11.4 (n = 13)	− 7.4 ± 6.7 (n = 13)	149.6 ± 6.7 (n = 13)	120.5 ± 19.3 (n = 11)	− 20.4 ± 10.2** (n = 11)
> 160	177.2 ± 26.6 (n = 17)	159.4 ± 31.5 (n = 17)	− 10.0 ± 12.9 (n = 17)	192.0 ± 13.5 (n = 3)	150.0 ± 21.7 (n = 3)	− 21.4 ± 14.7 (n = 3)

SD: standard deviation
P values show differences between the rosuvastatin and atorvastatin groups.
t-test, *: $p < 0.05$, **: $p < 0.01$

Table 5. Percent change of LDL-C/HDL-C ratio from baseline to 8 weeks stratified by risk factors

Risk factor	Atorvastatin 10 mg (mean ± SD)			Rosuvastatin 5 mg (mean ± SD)		
	Baseline	8 weeks	% change from baseline (%)	Baseline	8 weeks	% change from baseline (%)
Hypertension	1.95 ± 0.77 (n = 155)	1.97 ± 0.77 (n = 154)	3.1 ± 16.8 (n = 154)	1.78 ± 0.62 (n = 147)	1.65 ± 0.60 (n = 139)	− 5.4 ± 21.5*** (n = 139)
Diabetes	1.93 ± 0.72 (n = 134)	1.95 ± 0.74 (n = 132)	2.7 ± 17.7 (n = 132)	1.90 ± 0.73 (n = 132)	1.74 ± 0.63 (n = 129)	− 6.8 ± 18.9*** (n = 129)
CAD	1.82 ± 0.77 (n = 40)	1.83 ± 0.83 (n = 40)	1.7 ± 16.1 (n = 40)	1.75 ± 0.56 (n = 39)	1.57 ± 0.51 (n = 36)	− 6.7 ± 21.3 (n = 36)
Stroke	1.94 ± 0.60 (n = 17)	1.82 ± 0.42 (n = 17)	− 3.8 ± 13.4 (n = 17)	1.98 ± 0.64 (n = 15)	1.65 ± 0.56 (n = 13)	− 10.6 ± 24.7 (n = 13)
B3 + B4	1.97 ± 0.74 (n = 167)	1.97 ± 0.73 (n = 165)	1.3 ± 16.9 (n = 165)	1.86 ± 0.74 (n = 168)	1.73 ± 0.66 (n = 162)	− 4.6 ± 20.2** (n = 162)
C	1.82 ± 0.77 (n = 40)	1.83 ± 0.83 (n = 40)	1.7 ± 16.1 (n = 40)	1.75 ± 0.56 (n = 39)	1.57 ± 0.51 (n = 36)	− 6.7 ± 21.3 (n = 36)

SD: standard deviation, CAD: coronary artery diseases
P values show differences between the rosuvastatin and atorvastatin groups.
t-test, **: $p < 0.01$, ***: $p < 0.001$

continued because of adverse events in 8 patients from the rosuvastatin group only.

Thus, there were no major safety problems in eithes treatment group, and rosuvastatin (5 mg/day) and atorvastatin (10 mg/day) were well tolerated by patients with hypercholesterolemia.

Discussion

It is thought that mortality due to atherosclerotic diseases, including cardiovascular and cerebrovascular disease, will increase in Japan in the near future because of rapid enlargement of the elderly population and westernization of the lifestyle, so there has been a growing demand for more effective prevention and treatment of such diseases. Atherosclerosis is induced and aggravated by the accumulation of various risk factors, among which LDL-C is considered to be the most important. therefore, control of LDL-C has been the main treatment objective for atherosclerosis, and lipid-lowering drugs (especially statins) have played an important role in the management of this

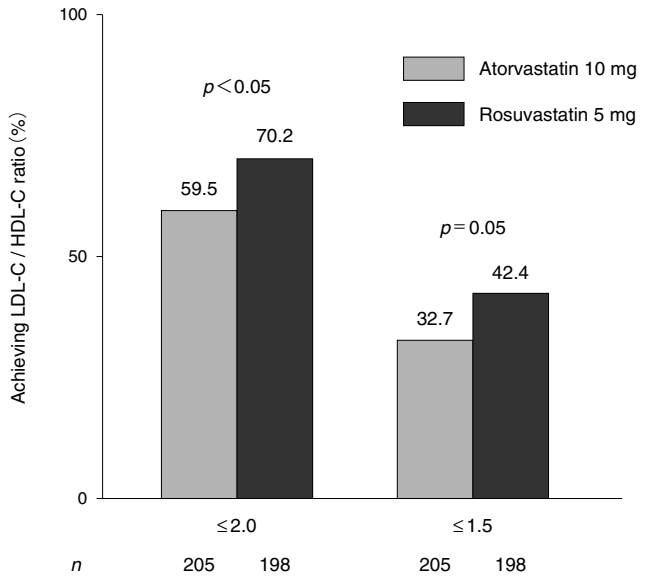

Fig. 5. Achievement of LDL-C/HDL-C ratio ≤2.0 or ≤1.5 at 8 weeks.

Fisher's exact test
P values show differences between the rosuvastatin and atorvastatin groups.

disease.

In the Japan Atherosclerosis Society Guidelines for the Prevention of Atherosclerotic Cardiovascular Diseases (JAS2007GL), which were published in 2007, category B3 and B4 are combined as "primary prevention of high-risk patients" and category C is designated as "secondary prevention patients", but the LDL-C goals are still 120 mg/dL for "primary prevention of high-risk patients" and 100 mg/dL for "secondary prevention patients"[15]. Although LDL-C is the most important target of treatment, control of HDL-C is also considered important according to National Cholesterol Education Program (NCEP) guidelines[16]. Recent studies on the changes of coronary artery plaque after statin therapy have shown that not only the percent reduction of LDL-C but also the change of the LDL-C/HDL-C ratio is related to the percent change of plaque, suggesting that control of this ratio is important for the treatment of plaque and has a direct influence on mortality[14].

In the present study, there was a significant difference of baseline LDL-C levels between the groups, but a significant group-related difference was still detected when the achievement of LDL-C goals was analyzed after adjustment for the difference of baseline LDL-C values ($p=0.035$, logistic regression analysis). Adjustment for baseline characteristics was also performed in the results of stratified analyses and it was confirmed that significant differences were still detected. Since over 70% of the patients had an LDL-C/HDL-C ratio ≤2.0 after treatment with rosuvastatin (5 mg/day), which was more than 10% higher than after treatment with atorvastatin (10 mg/day), rosuvastatin was able to improve both LDL-C and HDL-C. Thus, it seems likely that rosuvastatin would be more useful than atorvastatin for qualitative and quantitative improvement of plaque.

In other Japanese studies, rosuvastatin has been shown to improve TG and HDL-C levels[17-19]. In the present study, however, marked variations between individual patients meant that these parameters were not significantly different in the rosuvastatin group compared with the atorvastatin group. Since no dietary or lifestyle guidelines were specified in the present study, it is possible that parameters which tend to be influenced by these factors showed great variation as a result; therefore, it is necessary to take these points into consideration when designing future studies.

Many large-scale clinical studies of rosuvastatin have been performed around the world, and this series of studies is called the GALAXY Programme[20]. The ultimate objective of the GALAXY Programme is to verify the inhibitory effect of rosuvastatin on the onset of cardiovascular events, and evidence of the effect of this drug on atherosclerotic plaque has already been obtained. The ASTEROID (a study to evaluate the effect of rosuvastatin on intravascular ultrasound-derived coronary atheroma burden) and METEOR (measuring effects on intima media thickness: an evaluation of rosuvastatin) studies from the GALAXY Programme have shown that rosuvastatin reduces coronary artery plaque and slows the progression of carotid plaque[21, 22]. Based largely on the results of the METEOR study, rosuvastatin has become the only statin indicated to slow the progression of atherosclerosis in patients with hypercholesterolemia in the United States of America. Since the LDL-C/HDL-C ratio was also improved by the administration of rosuvastatin (5 mg/day) in the present study, it can be expected that this drug will control atherosclerotic disease or slow its progression in Japanese patients. Recently, the CORONA (controlled rosuvastatin multinational trial in heart failure) study showed an eight per cent reduction in the combined primary endpoint of cardiovascular death, myocardial infarction or stroke in patients with heart failure taking rosuvastatin at 10 mg/day ($p=0.12$). Although this improvement did not reach statistical significance, there were fewer hospitalizations for cardiovascular causes in the rosuvastatin group ($n=2193$) than in the placebo ($n=2564$) ($p<0.001$), and rosuvastatin did not cause safety

problems in patients with systolic heart failure[23].

Safety analysis revealed that both rosuvastatin (5 mg/day) and atorvastatin (10 mg/day) were well tolerated in the present study. It was not rejected, however, that patients with less tolerability to atorvastatin were possibly excluded at screening, as we did not assess adverse reactions to atorvastatin before study entry. In addition, several large-scale epidemiological studies of rosuvastatin have already been reported[24, 25], and it has been confirmed that its safety is similar to that of other statins with respect to the incidence of rhabdomyolysis, myopathy, acute renal failure, or hepatic impairment.

In the present study, rosuvastatin (5 mg/day) exhibited a strong LDL-C lowering effect, as well as a beneficial effect on other lipid parameters (including elevation of HDL-C and reduction of LDL-C/HDL-C ratio) and fasting plasma glucose. Accordingly, rosuvastatin (5 mg/day) seems to be a useful treatment option for high-risk patients with hypercholesterolemia.

Study Organization

Principal Investigator

Masahiko Kurabayashi, Department of Medicine and Biological Science, Gunma University Graduate School of Medicine, Maebashi, Japan.

Steering Committee

Tsutomu Yamazaki, Department of Clinical Epidemiology & Systems, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan.

Acknowledgments

The present study was supported by a grant-in-aid from the Japan Heart Foundation. We gratefully acknowledge the institutions (see Appendix), their investigators and study coordinators, and the patients who participated in this study.

Appendix

We would like to thank the following investigators:

Tetsurou Nakamura, Abe Clinic; Hiroaki Sugihara, Ebina Medical Plaza; Eiri Wada, Fujimi Clinic; Jun Fukuda, Fukuda Medical Cardiological Clinic; Akira Hattori, Hattori Clinic; Tetsuya Hirose, Hirose Hospital; Toshimi Asahi, Hospy Incorporated Medical Institution Urata Clinic; Masamichi Yamada, Idaimae Medical Clinic; Toshihiro Imaki, Imaki Internal Medicine Clinic; Nobuyuki Kashio, Imamura Branch Hospital; Youichi Tatsukawa, Iryouhoujin Keiwakai Oitaoka Byouin; Kazunori Iwasa, Iwasa Clinic; Shinya Tada, Kagawa Rosai Hospital; Hirokazu Kakuda, Kakuda Clinic; Hirotoshi Kamakura, Kamakura Clinic; Masatomo Maekawa, Kanazawa Arimatsu Hospital; Ryoichi Suzuki, Kannaisuzuki Clinic; Tsunenori Kawashima, Kawashima Clinic; Sayuri Hirota, Kichijoji Kokusai Clinic; Shuji Inoue, Kitakonosu Clinic; Masaya Okamoto, Kohashi Internal Medicine Clinic; Youichi Kosaka, Kosaka Clinic; Joji Oshima, Kubojima Clinic; Satoshi Yamada, Kyoai Clinic; Toshimitsu Mashima, Mashima Clinic; Munetoshi Matoba, Matoba Hospital; Tomiyoshi Ikeda, Mayama-Ikeda Clinic; Takashi Kabaya, Minamisenju Hospital; Shigeo Miyazaki, Miyazaki Hospital; Katsura Iguchi, Mominoki Clinic; Hiromasa Nakamizo, Nakamizo Clinic; Kazuo Nemoto, Nemoto Clinic; Masaki Nishikawa, Nishikawa Clinic; Haruki Mori, Ogikubo Gastrointestinal Clinic; Kenji Miyake, Okubo Clinic; Ikkyou Kawa, Ootsuka Kitaguchi Clinic; Toru Orihashi, Orihashi Clinic; Mitsuhiro Teduka, Sakura Chuo Hospital; Akira Sanada, Sanada Clinic; Hideki Yamamoto, Hirohito Takise, Senbon Hospital; Sinichi Itoi, Hitoshi Hujiwara, Noriaki Kanemitu, Sensyunkai Hospital; Tomoyuki Shibuya, Shibuya Clinic; Kazuaki Shiomi, Shiomi Clinic; Yuuhaku Okazaki, Soshigaya Internal Clinic; Minoru Nozaki, Swing Building Nozaki Clinic; Yoshiya Tachibana, Tachibana Clinic; Hidenao Takahashi, Takahashi Clinic; Takato Takamiya, Takamiya Clinic; Yasuo Takeda, Takeda Clinic; Shuya Shimakura, Tsukuba Souai Hospital; Makoto Yaida, Urban Heights Clinic; Hiroshi Yamamoto, Yamamoto Clinic; Minoru Yasuhara, Yasuhara Clinic; Toshimi Yoshida, Yoshida Clinic; Kenji Noma, Yoshimura Internal Medicine; Gaku Ohki, Yuki Hospital.

References

1) Kannel WB, Castelli WP, Gordon T: Cholesterol in the prediction of atherosclerotic disease: New perspectives based on the Framingham study. Ann Intern Med, 1979; 90:85-91
2) Scandinavian Simvastatin Survival Study Group: Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet, 1994; 344:1383-1389
3) Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR, and Braunwald E: The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med, 1996; 335:1001-1009
4) The Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group: Prevention of cardiovascu-

lar events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med, 1998; 339:1349-1357
5) Shepherd J, Cobbe M, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ: Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med, 1995; 333:1301-1307
6) Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Kruyer W, Gotto AM Jr: Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA, 1998; 279:1615-1622
7) Hebert PR, Gaziano JM, Chan KS, Hennekens CH: Cholesterol lowering with statin drugs, risk of stroke, and total mortality: An overview of randomized trials. JAMA, 1997; 278:313-321
8) Japan Atherosclerosis Society: Japan Atherosclerosis Society (JAS) guidelines for diagnosis and treatment of atherosclerotic cardiovascular diseases
9) Teramoto T, Kashiwagi A, and Mabuchi H: Status of lipid-lowering therapy prescribed based on recommendations in the 2002 report of the Japan Atherosclerosis Society guideline for diagnosis and treatment of hyperlipidemia in Japanese adults: a study of the Japan Lipid Assessment Program (J-LAP). Curr Ther Res, 2005; 66:80-95
10) Jones PH, Davidson MH, Stein EA, Bays HE, McKenney JM, Miller E, Cain VA, Blasetto JW; STELLAR Study Group: Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). Am J Cardiol, 2003; 92:152-160
11) Olsson AG, Pears J, McKellar J, Mizan J, and Raza A: Effect of rosuvastatin on low-density lipoprotein cholesterol in patients with hypercholesterolemia. Am J Cardiol, 2001; 88:504-508
12) Schwartz GG, Bolognese MA, Tremblay BP, Caplan R, Hutchinson H, Raza A, Cressman M: Efficacy and safety of rosuvastatin and atorvastatin in patients with hypercholesterolemia and a high risk of coronary heart disease: a randomized, controlled trial. Am Heart J, 2004; 148:e4
13) Schuster H, Barter PJ, Stender S, Cheung RC, Bonnet J, Morrell JM, Watkins C, Kallend D, Raza A: Effects of switching statins on achievement of lipid goals: Measuring Effective Reductions in Cholesterol Using Rosuvastatin Therapy (MERCURY I) study. Am Heart J, 2004; 147:705-713
14) Nicholls SJ, Tuzcu EM, Sipahi I, Grasso AW, Schoenhagen P, Hu T, Wolski K, Crowe T, Desai MY, Hazen SL, Kapadia SR, Nissen SE: Statins, high-density lipoprotein cholesterol, and regression of coronary atherosclerosis. JAMA, 2007; 297:499-508
15) Teramoto T, Sasaki J, Ueshima H, Egusa G, Kinoshita M, Shimamoto K, Daida H, Biro S, Hirobe K, Funahashi T, Yokote K, Yokode M: Executive summary of Japan Atherosclerosis Society (JAS) guideline for diagnosis and prevention of atherosclerotic cardiovascular diseases for Japanese. J Atheroscler Thromb, 2007; 14:45-50
16) Third Report of the NCEP Expert Panel: NIH Publication No. 01-3670 2001. http://hin.nhlbi.nih.gov/ncep_slds/menu.htm
17) Saito Y, Goto Y, Dane A, Strutt K, Raza A: Randomized dose-response study of rosuvastatin in Japanese patients with hypercholesterolemia. J Atheroscler Thromb, 2003; 10:329-336
18) Mabuchi H, Nohara A, Higashikata T, Ueda K, Bujo H, Matsushima T, Ikeda Y, Nii M: Clinical efficacy and safety of rosuvastatin in Japanese patients with heterozygous familial hypercholesterolemia. J Atheroscler Thromb, 2004; 11:152-158
19) Saito Y, Yamada N, Shirai K, Sasaki J, Ebihara Y, Yanase T, Fox JC: Effect of rosuvastatin 5-20mg on triglycerides and other lipid parameters in Japanese patients with hypertriglyceridemia. Atherosclerosis, 2007; 194:505-511
20) Kapur NK: Rosuvastatin: a highly potent statin for the prevention and management of coronary artery disease. Expert Rev Cardiovasc Ther, 2007; 5:161-175
21) Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, Davignon J, Erbel R, Fruchart JC, Tardif JC, Schoenhagen P, Crowe T, Cain V, Wolski K, Goormastic M, Tuzcu EM; ASTEROID Investigators: Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA, 2006; 295:1556-1565
22) Crouse JR 3rd, Raichlen JS, Riley WA, Evans GW, Palmer MK, O'Leary DH, Grobbee DE, Bots ML; METEOR Study Group: Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR trial. JAMA, 2007; 297:1344-1353
23) Kjekshus J, Apetrei E, Barrios V, Böhm M, Cleland JG, Cornel JH, Dunselman P, Fonseca C, Goudev A, Grande P, Gullestad L, Hjalmarson A, Hradec J, Jánosi A, Kamenský G, Komajda M, Korewicki J, Kuusi T, Mach F, Mareev V, McMurray JJ, Ranjith N, Schaufelberger M, Vanhaecke J, van Veldhuisen DJ, Waagstein F, Wedel H, Wikstrand J: Rosuvastatin in older patients with systolic heart failure. N Engl J Med, 2007; 357:2248-2261
24) Goettsch WG, Heintjes EM, Kastelein JJ, Rabelink TJ, Johansson S, Herings RM: Results from a rosuvastatin historical cohort study in more than 45,000 Dutch statin users, a PHARMO study. Pharmacoepidemiol Drug Saf, 2006; 15:435-443
25) McAfee AT, Ming EE, Seeger JD, Quinn SG, Ng EW, Danielson JD, Cutone JA, Fox JC, Walker AM: The comparative safety of rosuvastatin: a retrospective matched cohort study in over 48,000 initiators of statin therapy. Pharmacoepidemiol Drug Saf, 2006; 15:444-453