The Status of Lipid Management in 1,836 Patients with Coronary Artery Disease

: A multicenter survey to evaluate the percentage of Japanese coronary artery disease patients achieving the target low-density lipoprotein cholesterol level specified by the Japan Atherosclerosis Society

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To determine the status of lipid management in patients with coronary artery disease (CAD) in Japan, we assessed CAD patients who had been receiving lipid-lowering therapy for six months in a cross-sectional survey conducted between June 2001 and December 2002. We defined the achievement rate as the percentage of patients who achieved the target LDL-C level (< 100 mg/dl) specified by the Japan Atherosclerosis Society (JAS). A total of 1,836 Japanese CAD patients were enrolled. In total, 549 (29.9%) achieved the target level. The achievement rate among those receiving statin therapy was 41.3%, which was significantly higher than that (23.4%) among the patients not receiving statin ($P < 0.0001$). The rate differed with the type of statin; being 54.7% for atorvastatin, 24.8% for pravastatin, 37.1% for simvastatin, and 27.8% for fluvastatin. A multiple regression analysis revealed that atorvastatin use ($P < 0.001$), and simvastatin use ($P = 0.004$) significantly contributed to the achievement of the target LDL-C level. In conclusion, large proportions of CAD patients are not achieving the JAS target and the success rates are not similar among different statin therapies, suggesting that cardiologists should consider a more aggressive lipid-lowering therapy with the appropriate choice of statins in Japanese CAD patients. *J Atheroscler Thromb*, 2005; 12: 338–342.

Key words: Low-density lipoprotein cholesterol, Guideline, Treatment, Gap

Introduction

Clinical and epidemiological studies have established a link between dyslipidemia and coronary artery disease (CAD) (1–6). Based upon this evidence, the National Cholesterol Education Program (NCEP) issued treatment guidelines that identified low-density lipoprotein cholesterol (LDL-C) as the target for lipid-lowering therapy (7, 8). The guidelines recommend that LDL-C levels should

be less than 100 mg/dl in patients with CAD⁸. Although there is limited evidence on the risks and benefits of lipid management for reduction of the number of CAD events in different populations, NCEP concludes that the evidence for racial differences is not strong enough to justify separate guidelines for Asian populations and that, therefore, no separate algorithm for lipid management should be recommended. In 2002, the Japan Atherosclerosis Society (JAS) presented guidelines based upon evidence for the Japanese population including the J-LIT study (9). The guidelines defined several categories by risk factors for CAD, and LDL-C levels at which diet or drug therapy should be initiated for patients in each category. In the JAS guidelines, the LDL-C target goal in CAD patients (Category C) is less than 100 mg/dl, which

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is the same as that in the NCEP guidelines.

Available data indicate that a significant gap exists between the levels of LDL-C recommended by the NCEP and those achieved in clinical practice in the United States (10–12). However, in Japan, little is known about the extent to which physicians or cardiologists actually follow the JAS guideline. The present survey collected data from Japanese CAD patients to determine the proportion in which JAS LDL-C target levels are achieved when lipid levels are controlled by cardiologists in Japan.

Subjects

A total of 152 cardiologists in 20 facilities (Tokyo Women's Medical University Hospital and 19 university-related hospitals) participated in this cross-sectional survey carried out between June 2001 and December 2002. Patients with CAD including myocardial infarction, angina pectoris, or silent myocardial ischemia, all diagnosed by coronary angiogram, were eligible if they stayed with the same lipid control therapy, which included dietary therapy and/or statin therapy, for 6 months. Patients who were treated with cerivastatin (withdrawn from the market due to its side effect) and whose triglyceride levels were more than 400 mg/dl were ineligible. In total, 1,836 patients were enrolled in this cross-sectional survey.

Methods

Details of the survey

Data on age, sex, weight, height, hyperlipidemia, hypertension, diabetes, smoking status, and family history were collected. Hyperlipidemia was defined as a total cholesterol (TC) level of at least 240 mg/dl. Hypertension was defined as blood pressure of at least 140 mm Hg for systolic pressure or at least 90 mm Hg for diastolic pressure using cuff-size-corrected measurements. Diabetes was defined as either previously diagnosed diabetes or a fasting glucose level of at least 126 mg/dl. Obesity was defined as a body mass index (BMI) of at least 25. BMI was calculated as weight in kilograms divided by the square of height in meters. Family history was defined as the participant's history.

The laboratory data collected included TC, triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C) levels. The LDL-C value was calculated according to the Friedewald equation. All lipid samples were assayed by laboratories that were participants in the certification program of the Cholesterol Reference Method Laboratory Network (CRMLN). Peripheral artery disease was defined as a diagnosis of atherosclerosis obliterans and Buerger's disease. Cerebral vascular disease was defined as a diagnosis of stroke (cerebral infarction, intracerebral hemorrhage, subarachnoid hemorrhage), and transient ischemic attack.

Table 1. Patient background

Variable	Number	(%)
Total	1,836	(100%)
Age, mean $\pm$ SD, y	64.4 $\pm$ 10.3	
Sex		
Male	1,444	(78.6%)
Female	392	(21.4%)
Hyperlipidemia	944	(51.4%)
Hypertension	805	(43.8%)
Diabetes	619	(33.7%)
Smoking		
ex smoker	663	(36.1%)
current smoker	444	(24.2%)
Family history	368	(20.0%)
Obesity	559	(30.4%)
No Statin	1,170	(63.7%)
Statin	666	(36.3%)
Atorvastatin	327	(17.8%)
Pravastatin	214	(11.7%)
Simvastatin	89	(4.8%)
Fluvastatin	36	(2.0%)

Statistical analyses

The primary study parameter was the LDL-C level achievement rate as defined by the JAS guidelines. Patients were classified into a statin therapy group (atorvastatin, pravastatin, simvastatin, and fluvastatin) and a non-statin therapy group.

The analyses were performed with SAS System 8.2 (SAS Institute Inc., Cary, North Carolina, USA). The data were presented as a frequency or mean $\pm$ SD. The difference in proportions was evaluated using the chi-square test. To determine the relationship between the percentage of patients achieving the target lipid level and various risk factors, a logistic regression model was applied. A two-tailed *P*-value of less than 0.05 was considered to indicate statistical significance.

Results

Patient background

The average age of the 1,836 patients, 78.6% of whom were males, was 64.4 years (Table 1). A total of 944 (51.4%) patients had hyperlipidemia. Statins were prescribed in 36.3% of cases. The remaining 1,170 patients (63.7%) had received dietary and exercise therapy, or some drug other than statin. The statin drugs prescribed were as follows; atorvastatin (in 49.1% of cases),

Table 2. Percentage achieving the target LDL-C level

		Achieving target (%)	LDL-C (mg/dl)
Total	(<i>n</i> = 1,836)	549 (29.9%)	115.0 ± 29.9
No Statin	(<i>n</i> = 1,170)	274 (23.4%)	119.3 ± 29.3
Statin	(<i>n</i> = 666)	275 (41.3%)	107.3 ± 29.4
Atorvastatin	(<i>n</i> = 327)	179 (54.7%)	99.9 ± 31.8
Pravastatin	(<i>n</i> = 214)	53 (24.8%)	115.8 ± 24.2
Simvastatin	(<i>n</i> = 89)	33 (37.1%)	109.0 ± 24.1
Fluvastatin	(<i>n</i> = 36)	10 (27.8%)	120.0 ± 29.4

Values are the mean ± SD. LDL-C stands for low density lipoprotein cholesterol the LDL-C level was calculated according to the Friedewald equation.

Table 3. Univariate and multivariate analysis

	Univariate		Multivariate	
	Crude Odds Ratio (95%CI)	<i>P</i> value	Adjusted Odds Ratio* (95%CI)	<i>P</i> value
Age	1.00 (1.00–1.01)	0.508	-	
Male gender	0.85 (0.66–1.09)	0.204	0.76 (0.59–0.99)	0.039
Hypertension	0.83 (0.68–1.02)	0.076	-	
Diabetes	0.86 (0.70–1.06)	0.164	-	
Smoking	1.01 (0.78–1.31)	0.941	-	
Family history	0.83 (0.65–1.06)	0.128	-	
Obesity	0.88 (0.71–1.09)	0.243	-	
Peripheral artery disease	0.88 (0.55–1.42)	0.604	-	
Cerebral vascular disease	1.32 (0.89–1.95)	0.166	-	
Atorvastatin	0.25 (0.20–0.33)	< 0.001	0.25 (0.20–0.32)	< 0.001
Pravastatin	0.93 (0.66–1.30)	0.669	-	
Simvastatin	0.52 (0.33–0.82)	0.004	0.52 (0.33–0.81)	0.004
Fluvastatin	0.80 (0.38–1.68)	0.545	-	

* Adjusted odds ratio was obtained using a multiple logistic regression model with the best subset variable selection method.

pravastatin (32.1%), simvastatin (13.4%), and fluvastatin (5.4%) (Table 1). None of the patients underwent a change of treatment during the study period.

Achieving target LDL-C levels and statin therapy

The overall percentage of patients achieving the target LDL-C level was 29.9% and the mean value was 115.0 ± 29.9 mg/dl for LDL-C (Table 2).

The proportion who achieved the target in the statin and non-statin therapy groups was 41.3% and 23.4%, respectively. Statin therapy was significantly ($P < 0.0001$) more effective at achieving the target LDL-C level than non-statin therapy.

Achievement rates with different statins were also investigated. A significant difference in the rate of achievement was observed among the statins; 54.7% for

atorvastatin, 37.1% for simvastatin, 27.8% for fluvastatin, and 24.8% for pravastatin.

Risk factors and target LDL-C levels

A univariate analysis was used to evaluate the relationship between risk factors and the patients' success at achieving the target levels of LDL-C. Patients with diabetes, a family history, or a smoking habit were no more likely to achieve the target than those without these risk factors (Table 3). Multiple regression analysis indicated that the following variables were significantly related to achieving the target LDL-C level: atorvastatin therapy (odds ratio: 0.25, 95%CI: 0.20–0.32, $P < 0.001$), simvastatin therapy (odds ratio: 0.52, 95%CI: 0.33–0.81, $P = 0.004$), and male gender (odds ratio: 0.76, 95%CI: 0.59–0.99, $P = 0.039$) (Table 3).

Discussion

The JAS guidelines, first issued in 1997 and revised in 2002, defined LDL-C target levels for patients with dyslipidemia to reduce the risk of continued and future CAD. In the 2002 JAS guidelines, the LDL-C target goal is less than 100 mg/dl in patients with CAD (Category C).

This survey demonstrated the present status of lipid control by cardiologists in Japanese CAD patients. The success rate for achieving the target LDL-C level was only 29.9%, indicating that lipid management was not being performed optimally at the time of this survey. This huge treatment gap between the JAS guidelines and clinical practice in Japan is almost the same as that in the United States as demonstrated in the L-TAP survey (12). The gap may be explained by the use of low dosages of drugs, limited drug effectiveness, inappropriate choice of drug, drug tolerability, or poor compliance of patients with recommended treatments.

The efficacy of statin therapy for both the primary and secondary prevention of CAD events has been established by many clinical trials (1–6). Pleiotropic beneficial effects of statins on vascular wall independent of their lipid-lowering action have also been demonstrated by recent basic and clinical investigations (13–18). In the present study, however, only 36.3% of patients received statin therapy. As expected, the success rate was significantly higher for statin therapy (41.3%) than non-statin therapy (23.4%). Furthermore, success rates differed among the statins, ranging from 24.8% for fluvastatin to 54.7% for atorvastatin. Several studies have revealed that atorvastatin was more effective in attaining the LDL-C target goal than four other statins (simvastatin, pravastatin, lovastatin, and fluvastatin) in patients with or without CAD (19–22). Our results were compatible with previous findings in non-Japanese populations. Moreover, new evidence has emerged that intensive therapy with statin, atorvastatin, at approximately 70 mg/dl is associated with better outcomes (23) than moderate therapy.

The JAS guidelines were formulated to reduce the risk of CAD both as primary prevention for patients without evidence of CAD and as secondary prevention in patients with established CAD. The LDL-C target levels specified by the JAS guidelines are achievable. However, the results from this survey clearly demonstrate that current treatment is not adequate to achieve the JAS targets. A more aggressive lipid-lowering therapy with the appropriate choice of statins and/or appropriate dose of statins will be required if the JAS objectives are to be realized.

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