Preventing Angiographic Progression of Coronary Atherosclerosis with Pravastatin

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We conducted a prospective study to investigate the relationship between the decrease of serum lipid levels during pravastatin therapy and changes of coronary angiography parameters in Japanese patients with coronary atherosclerosis. The patients were predominantly male, aged between 18 and 75 years (mean: 58 years), had at least 25% stenosis of one or more major coronary arteries, and had a serum total cholesterol (TC) level ≥ 200 mg/dl (5.18 mM/l). Treatment with pravastatin (10 mg/day) was continued for 3 years. Coronary angiography was performed before and 3 years after the start of pravastatin therapy to assess the relationship between the mean segment diameter (MSD), the minimal lumen diameter (MLD), and the annual changes of percent stenosis and TC levels. Of 265 patients who were initially registered, 129 were followed for an average of 35 months. Consequently, second angiograms were only obtained in 68 patients for various reasons, so this group was used for analysis. During pravastatin therapy, the TC level significantly decreased from 239 mg/dl (6.19 mM/l) to 210 mg/dl (5.44 mM/l) (a 12% reduction; $p < 0.001$). In addition, HDL-cholesterol increased by 5% ($p = 0.007$), but the triglyceride level did not show a significant change. Both MSD and MLD were significantly improved on follow-up angiography, increasing from 2.67 mm to 2.76 mm and from 2.09 mm to 2.13 mm, respectively. However, no change of percent stenosis was observed. The mean TC level during treatment did not show any significant correlation with the changes of angiography parameters. However, a significant correlation was observed between the percent reduction of TC and the annual change of MSD ($r = -0.272$, $p = 0.027$). A similar relationship was also found between the change of MLD and the percent reduction of TC ($r = -0.260$, $p = 0.035$). In conclusion, the percent decrease of serum cholesterol may be a better indicator of clinical efficacy than the absolute cholesterol level during pravastatin therapy. *J Atheroscler Thromb*, 2003; 10: 25-31.

Key words: Pravastatin, Quantitative coronary angiography, Percent reduction of serum cholesterol, Prospective study

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Introduction

Coronary artery disease is one of the leading causes of death in Western countries. Although the incidence of coronary artery disease is still much lower in Japan than in the West, the Japanese population is undergoing rapid

social and environmental changes, including westernization of the diet, which have led to a marked increase of hyperlipidemia and diabetes mellitus (1,2). The prevalence of coronary artery disease in Japan has also shown a rapid increase, which has created a medical and social need for an effective strategy to prevent the development and progression of atherosclerosis (3). The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors are the most common drug class used for the treatment of hyper-cholesterolemia. Many clinical trials have shown that reducing the serum cholesterol level with HMG-CoA reductase inhibitor therapy can slow the angiographic progression of coronary atherosclerosis and reduce the clinical manifestations in both primary and secondary prevention populations (4-11). However, only limited data exist to show similar benefits in Japanese subjects (12,13). Therefore, we investigated the effect of pravastatin on angiographic progression in Japanese subjects with coronary atherosclerosis by performing a prospective study.

Materials and Methods

Subjects

This was a 3-year, multicenter, open-label uncontrolled study that investigated the association between angiographic progression and the total cholesterol level during lipid-lowering therapy with pravastatin. The 21 institutions participating in this multicenter study are listed in Appendix 1. For the enrollment of patients, the following criteria were used. Patients aged from 18 to 75 years were eligible if they had more than 25% narrowing of least one major coronary artery detected by coronary angiography. A serum total cholesterol level of more than 200 mg/dl (5.18 mM/l) was also required. Patients with normal coronary angiograms, total occlusion of two major vessels, > 50% narrowing of the left main coronary artery, diffuse lesions for which the % stenosis was difficult to assess, and candidates for coronary artery bypass surgery were excluded. Cholesterol-lowering therapy was performed with pravastatin (10 mg/day), which was administered for 3 years.

Subjects were enrolled between May 1990 and December 1993, and were followed up until June 1997.

Monitoring of subjects

In each patient, the symptoms and the levels of total cholesterol, high density lipoprotein (HDL)-cholesterol, and triglycerides (TG) were assessed at the baseline, one month after enrollment, and every 3 months thereafter. The low density lipoprotein (LDL)-cholesterol level was calculated by Friedewald's formula (14). Follow-up was performed at each participating institution. Repeat coronary angiography was performed at 3 years after the initial angiogram. If the patient developed unstable angina

or other symptoms that needed earlier angiographic assessment, the angiogram obtained at that time was used for endpoint analysis.

Quantitative Coronary Angiography

Paired coronary angiograms were assessed together at a quantitative coronary angiography laboratory. Interpretation was performed by an experienced cardiologist and two technicians who were blinded to the total cholesterol levels, the order of the films, and the identity of each patient. The Cardiovascular Measurement System (CMS-MEDIS Medical Imaging System) was used to measure coronary segments and lesions, with the coronary tree being divided into 15 segments according to the American Heart Association classification (15). Baseline and follow-up angiograms for each patient were viewed simultaneously side-by-side and matching segments and obstructions on both angiograms were carefully selected using identical projections. For each segment, the mean segment diameter (MSD) and the minimal lumen diameter (MLD) were analyzed by two technicians (16).

The inter-observer and intra-observer variabilities were evaluated in advance using 44 segments from eight patients who were not enrolled in this study. Each segment was examined twice after a one-month interval by two observers, and three measurements were obtained at both examinations.

Study Endpoints

The angiographic end-point of this study was the association between the mean total cholesterol level and the annual change of the average MSD, MLD, or % stenosis. Associations between the changes of total cholesterol and these angiographic variables were also assessed.

The annual mean total cholesterol level was estimated from the area under the curve (AUC) during the trial period. The change of total cholesterol was calculated as follows: $\{(\text{mean total cholesterol level} - \text{baseline level}) / \text{baseline level}\} \times 100$. To calculate the average MSD, MLD, or % stenosis per patient, all the MSD, MLD, or % stenosis values were summed and then divided by the number of segments assessed.

Statistics

The inter-observer and intra-observer variabilities were evaluated using a nested design based on a variance component model. The effect of treatment on lipid levels and on the quantitative angiography data was assessed with the paired *t*-test.

To investigate the association between the mean cholesterol level and the changes of angiographic variables, linear regression analysis was performed with and without adjustment for the following covariates: age, gender, the presence/absence of hypertension or diabetes mellitus, body mass index, HDL cholesterol level, and smok-

ing status. The baseline data for all covariates was used.

A two-tailed p value less than 0.05 was considered to indicate significance.

Participating institutions and study organization

The participating institutions, the organization of this study, and the roles and membership of each committee are described in Appendices 1 and 2.

Results

Baseline Characteristics

A total of 265 patients were initially registered, of whom, 136 were excluded for failing to meet all the enrollment criteria, and the other 129 patients were followed. Of these 129 patients, 61 patients did not complete the study because repeat angiograms were not obtained, so the final analysis was performed on the remaining 68 patients. The major reasons for non-completion were the use of prohibited drugs, not attending hospital, and changing hospital (Fig. 1).

The baseline characteristics of the subjects are presented in Table 1. The average age was 58 years and 75% were male. Thirty-four percent of the patients were smokers, 44% had hypertension, and about one third had diabetes. The mean follow-up period was 35 months.

Effect of pravastatin on lipid levels

The effect of pravastatin therapy on lipid levels is shown in Table 2. The total cholesterol level significantly decreased by 12% from 239 mg/dl (6.19 mM/l) to 210 mg/dl

(5.44 mM/l) ($p < 0.001$), while the HDL-cholesterol level increased by 5% ($p = 0.007$). In contrast, the TG level did not change significantly ($p = 0.198$). The LDL-cholesterol level was reduced by 19% from 162 mg/dl (4.20 mM/l) to 132 mg/dl (3.42 mM/l), which was also a significant change ($p < 0.001$).

Inter-observer and intra-observer variabilities of quantitative coronary angiography

Table 3 shows the estimates of the inter-observer and intra-observer variabilities, as well as the measurement error, for quantitative coronary angiography.

The inter-observer variability was very small (0.007 for the MSD, <0.001 for the MLD, <0.001 for % diameter stenosis, and 0.036 for the length), and the total measurement errors made by the observers were 0.075, 0.087, 3.115, and 0.817, respectively.

Quantitative Coronary Angiography

The results of quantitative coronary angiography are shown on a per segment basis in Table 4. The MSD increased significantly from 2.67 mm at the baseline to 2.76 mm at follow-up ($p < 0.001$). MLD also increased significantly improved from 2.09 mm to 2.13 mm ($p = 0.024$). However, the % diameter stenosis showed no change ($p = 0.575$).

Fig. 1. Distribution of the patients

Table 1. Baseline characteristics of the patients

n	68
Age (yrs)	58 ± 8
Gender (M/F)	51/17
BMI	23.9 ± 2.5
Smoking (%)	23 (34)
Hypertension (%)	30 (44)
Diabetes mellitus (%)	19 (28)
Myocardial infarction (%)	35 (51)
Mean observation period (months)	35 ± 16

Figures in parentheses are percentages.

BMI: body mass index.

Table 2. Effect of pravastatin on serum lipid levels

	Baseline	After Treatment	Change	p value
Total cholesterol (mg/dl)	239 ± 35	210 ± 30	-12%	<0.001
HDL-cholesterol (mg/dl)	44 ± 13	47 ± 11	+ 5%	0.007
Triglycerides (mg/dl)	172 ± 74	164 ± 67	- 5%	0.198
LDL-cholesterol (mg/dl)	162 ± 34	132 ± 31	-19%	<0.001

p values were obtained by the paired t -test.

HDL: high-density lipoprotein; LDL: low-density lipoprotein.

Relationship between lipid levels and angiographic changes

No significant correlation was observed between the mean total cholesterol level during the follow-up period and the annual angiographic changes by either simple or multiple linear regression analysis (Fig.2).

On the other hand, significant inverse correlation was observed between the change of total cholesterol and the annual change of MSD ($r = -0.272$, $p = 0.027$).

Similar results were obtained for the relationship between the changes of MLD and total cholesterol ($r = -0.260$, $p = 0.035$), but no significant correlation was observed between the changes of % stenosis and total cholesterol (Fig.3).

Multiple linear regression analysis revealed a similar significant relationship between the change of total cholesterol and the change of MSD or MLD, but there were no significant relationships with the change of % stenosis.

When we conducted similar analyses for LDL cholesterol and HDL cholesterol, a significant inverse correlation was observed between the change of LDL cholesterol and the annual change of MSD ($r = -0.249$, $p = 0.049$). However, no significant correlation was observed between the change of HDL cholesterol and the change of angiographic variables.

With regard to other risk factors, such as diabetes mellitus, hypertension and smoking, no significant correlation was found between these risk factors and angiographic variables.

Discussion

The present prospective, uncontrolled study investigated the association between the angiographic progression of coronary artery disease (determined by quantitative coronary angiography) and the total cholesterol level or the % reduction of total cholesterol level by pravastatin therapy. We observed a significant positive correlation between the % reduction of total cholesterol and the change of MSD or MLD after adjustment for other risk factors, although there was no significant correlation between the absolute cholesterol level during treatment and these angiographic variables.

The Familial Atherosclerosis Treatment Study (FATS) (4), one of the earliest clinical trials using coronary angiography, indicated that intensive lipid lowering therapy using either lovastatin and cholestipol or niacin and cholestipol could reduce angiographic progression and increase regression in 146 men with high apolipoprotein B levels. Since then, several angiographic trials have investigated the effect on coronary atherosclerosis of lowering LDL cholesterol by combined therapy with statins and other drugs or statin monotherapy (5-11). Among these clinical trials, the Monitored Atherosclerosis Regression Study (MARS)(7), the Canadian Coronary Atherosclerosis Intervention Trial (CCAIT)(8), the Multicentre Anti-Atheroma Study (MAAS)(9), the Pravastatin Limitation of Atherosclerosis in the Coronary Arteries Study (PLAC-I)(10), and the Regression Growth Evaluation Statin Study (RE-

Table 3. Restricted maximum likelihood estimates of three variables based on variance component models

	σ_{inter}	σ_{intra}	σ_{error}	$\sigma_{\text{total}} = \sqrt{\sigma_{\text{inter}}^2 + \sigma_{\text{intra}}^2 + \sigma_{\text{error}}^2}$
Mean segment diameter	0.007	0.073	0.013	0.075
Minimal lumen diameter	<0.001	0.069	0.053	0.087
Stenosis	<0.001	2.320	2.080	3.115
Length	0.036	0.761	0.230	0.817

σ_{inter} , σ_{intra} , and σ_{error} indicates the root of inter-individual variance, the root of intra-individual variance, and the root of measurement error variance, respectively. σ_{total} is an estimate of the total measurement errors.

Table 4. Results of Quantitative Coronary Angiography (405 segments)

	Initial	Follow-up	p value
Mean segment diameter (mm)	2.67 ± 0.81	2.76 ± 0.84	<0.001
Minimal lumen diameter (mm)	2.09 ± 0.80	2.13 ± 0.81	0.024
Stenosis (%)	21.4 ± 14.6	21.7 ± 14.5	0.575

p values were obtained by the paired t-test.

Fig. 2. Relationship between the mean total cholesterol level during treatment and angiographic changes. There was no significant correlation between total cholesterol and the annual change of MSD.

GRESS)(11) used statin monotherapy as the lipid-lowering therapy. All of these trials showed the efficacy of statins against the angiographic progression of coronary atherosclerosis. These previous findings support the view that the beneficial effect of pravastatin played an important role in the regression of coronary atherosclerosis in this study.

In FATS (4), an association between the % reduction of Apo B and angiographic changes was observed, indicating that the % reduction of lipid levels was one of the major determinants of the efficacy of cholesterol-lowering therapy with statins. Thompson *et al.* (17) performed a meta-analysis, which showed that the % reduction of lipid levels was closely related to the change of % diameter

Fig. 3. Relationship between the % reduction of cholesterol during treatment and angiographic changes. A significant correlation between the % reduction of total cholesterol and the annual change of MSD was observed. There was a similar correlation between the changes of MLD and the % reduction of total cholesterol.

stenosis. They also found a poor correlation between the LDL-cholesterol level during treatment and angiographic variables, as well as a significant inverse correlation between the baseline total cholesterol level and angiographic changes. This observation was consistent with the results of this study. It might be expected that the benefit of lipid-lowering therapy would be greater in higher-risk patients. Among large clinical event prevention trials, those assessing higher-risk patients, such as the Scandinavian Simvastatin Survival Study (4S)(18), have shown a greater benefit for the prevention of clinical events than trials on lower-risk subjects such as the Cholesterol And Recurrent Event (CARE) trial (19).

In this study, there was no significant correlation between

the absolute total cholesterol level and angiographic variables. It is questionable whether the absolute level of total cholesterol is a suitable index when treating patients with a wide range of baseline levels, like the population of this study. In fact, our results suggest that the % reduction of cholesterol may be a better index of clinical benefit than the absolute cholesterol level during treatment, but further investigations are needed to confirm this.

Limitations of this study

This was an uncontrolled and open-label trial that assessed the relationship between the absolute mean total cholesterol level or the % reduction of cholesterol and angiographic changes during pravastatin treatment. Because of the study design, we could not specify the effect of pravastatin itself. Instead, we investigated the influence of cholesterol reduction on angiographic variables.

Another limitation was the small sample size, which meant that we could not perform detailed subgroup analyses and event analyses. A clinical trial on a larger scale should be performed in Japan in the future.

Appendix 1

Participating institutions

Anjo Kosei Hospital; Kitano Hospital The Medical Research Institute; Nagasaki Kouseikai Hospital; Jichi Medical School; Juntendo University School of Medicine; Department of Cardiology, Teikyo University School of Medicine; Tokyo Medical And Dental University; Department of Cardiovascular Medicine, University of Tokyo; Department of Geriatric Medicine, University of Tokyo; Kasai Cardiology & Neurosurgery Hospital; Kanbara Municipal Hospital; International Medical Center of Japan; The Social Health Insurance Medical Center; Toho University Ohashi Hospital School of Medicine; Fukui Medical University; Matsudo City Hospital; Yokohama Rosai Hospital; Juntendo University Urayasu Hospital; Toranomon Hospital; National Defense Medical College; Yamada Red Cross Hospital.

Appendix 2

Study Organization

Study organization was established by the Executive Committee, Trial Statisticians, Case/Event Evaluation Committee, Angiography Committee, Study Coordinating Center.

Role and Member of Committee

1. Executive Committee:

Organization and conduction of the study

Members; Hiroshi Yamaguchi, Chairman (Juntendo University); Yasuyoshi Ouchi (University of Tokyo); Nobuhiro Yamada (University of Tsukuba); Hiroyuki Daida (Juntendo University School of Medicine); Hisashi Yokoi (YOKOI CLINIC for Internal Medicine & Pediatrics); Kouji Mokuno

(Juntendo University School of Medicine); Yasushi Saito (Chiba University)

2. Trial Statisticians:

Preparation of programs for registration, randomization and analysis of Data

Members; Shusuke Kurashina (Ami Care Center); Shigeto Suzuki (Tokyo Metropolitan Research Laboratory of Public Health); Toshiro Tango (National Institute of Public Health)

3. Case/Event Evaluation Committee:

Evaluation of eligibility of the subjects and event

Members; Yasuyoshi Ouchi (University of Tokyo); Hiroyuki Daida (Juntendo University School of Medicine); Hisashi Yokoi (YOKOI CLINIC for Internal Medicine & Pediatrics); Kouji Mokuno (Juntendo University School of Medicine); Katsuto Ui (Toho University Ohashi Hospital School of Medicine); Toshio Nishide (Higasi Mathudo Municipal Hospital); Toshiro Tango (National Institute of Public Health).

4. Angiography Committee:

Evaluation of the study from the ethical and scientific standpoints

Members: Yasuyoshi Ouchi (University of Tokyo); Masahiro Akishita (Kyorin University School of Medicine); Masato Egashira (University of Tokyo); Hiroyuki Daida (Juntendo University School of Medicine); Hisashi Yokoi (YOKOI CLINIC for Internal Medicine & Pediatrics); Kouji Mokuno (Juntendo University School of Medicine); Ken Kurata (Juntendo University School of Medicine); Shin-ichiro Yamagami (Juntendo University School of Medicine); Takashi Iwase (Toranomon Hospital); Takaaki Isshiki (Teikyo University School of Medicine); Katsuhito Ui (Toho University Ohashi Hospital School of Medicine); Toshio Nishide (Higasi Mathudo Municipal Hospital); Toshiro Tango (National Institute of Public Health).

5. Study Coordinating Center:

Member: Yasuyoshi Ouchi (University of Tokyo)

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