Comparative Study of Bezafibrate and Pravastatin in Patients With Coronary Artery Disease and High Levels of Remnant Lipoprotein

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Background: Remnant lipoproteinemia is a strong risk factor for cardiovascular (CV) diseases. This study examined which of 2 common lipid-lowering drugs (fibrates and statins) is more effective in patients with remnant lipoproteinemia and if lowering remnant lipoprotein levels can reduce CV risk.

Methods and Results: Remnant lipoprotein levels were measured by an immunoseparation method (remnant-like lipoprotein particles cholesterol: RLP-C) in 274 patients with coronary artery disease and high RLP-C levels (≥ 5.0 mg/dl). They were randomly assigned to receive bezafibrate (200–400 mg/day) or pravastatin (10–20 mg/day), and were prospectively followed-up for 1 year or until the occurrence of CV events. Complete follow-up data were obtained in 180 patients. RLP-C levels at 1 year of treatment were reduced more by bezafibrate than pravastatin (-37% and -25% from baseline, respectively). During follow-up, bezafibrate-treated patients had 3 CV events, compared with 12 events in pravastatin-treated patients ($P < 0.01$). In multivariate logistic regression analysis, a decrease in RLP-C level was significantly associated with a reduction in CV events after adjustment for treatment group and changes in levels of other lipids.

Conclusions: Bezafibrate therapy decreased RLP-C levels to a greater extent than pravastatin and a decrease in RLP-C level may be associated with a reduction in CV events in patients with high RLP-C levels. (*Circ J* 2010; **74**: 1644–1650)

Key Words: Cardiovascular disease; Fibrates; Remnant lipoprotein; Statins

It has been shown that triglyceride (TG)-rich lipoproteins are atherogenic and are a strong risk factor for cardiovascular (CV) disease.^{1–3} We and others have shown that among the TG-rich lipoproteins, remnant lipoproteins, especially from very-low-density-lipoproteins (VLDL), have a strong atherogenic effect.^{1–11} It has been difficult to assay levels of remnant lipoprotein because they have heterogeneous properties. However, a simple and reliable technique for measuring levels of remnant-like lipoprotein particles cholesterol (RLP-C) using an immunoseparation method has been developed.^{6,10,11} It has been shown that this technique can isolate mainly remnants of VLDL from fasting serum, and that high RLP-C levels predict future coronary events in patients with coronary artery disease (CAD).^{6,7} Moreover, it has been shown that high levels of RLP-C are an independent risk factor for CV events in patients with type 2 diabetes mellitus.¹²

We and others have shown that treatment with fibrates, including bezafibrate or gemfibrozil, effectively reduces RLP-C levels,^{8,13,14} and treatment with statins has also resulted in a significant reduction in RLP-C levels.^{14,15} However, those previous studies had small numbers of patients. Previous studies have shown that a reduction in TG-rich lipoproteins may have therapeutic value in subgroup analyses of lipid-lowering trials targeting low-density lipoprotein-cholesterol (LDL-C) or TG.^{16–18} However, no clinical trial has been performed to investigate if lipid reduction targeting primarily remnant lipoproteins could prevent CV events. Thus, the purpose of this study was to determine which of the 2 common lipid-lowering drugs (fibrates and statins) is more effective in patients with high RLP-C levels and if reducing the high RLP-C levels can prevent CV events in these patients.

Received January 31, 2010; revised manuscript received April 1, 2010; accepted April 5, 2010; released online June 22, 2010 Time for primary review: 17 days

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ISSN-1346-9843 doi:10.1253/circj.CJ-10-0079

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Table 1. Comparisons of Baseline Clinical Characteristics of Patients

	Initially enrolled patients		Finally studied patients	
	Bezafibrate (n=137)	Pravastatin (n=137)	Bezafibrate (n=84)	Pravastatin (n=96)
Age (years)	62±9	63±9	62±9	62±9
Male, n (%)	118 (86)	123 (90)	74 (88)	85 (89)
Smoking, n (%)	30 (22)	26 (19)	20 (24)	22 (23)
Diabetes mellitus, n (%)	49 (36)	44 (32)	32 (38)	32 (33)
Hypertension, n (%)	90 (66)	101 (74)	60 (71)	68 (71)
History of stroke, n (%)	8 (6)	8 (6)	3 (4)	6 (6)
History of MI, n (%)	80 (58)	80 (58)	50 (60)	57 (59)
History of PCI/CABG, n (%)	104 (76)	99 (72)	66 (79)	74 (77)
LVEF <40%, n (%)	7 (5)	6 (4)	2 (2)	5 (5)
No. of diseased vessels	1.5±1.0	1.4±1.0	1.2±0.9	1.3±1.0
NYHA classification	1.1±0.3	1.1±0.3	1.1±0.3	1.1±0.3
BMI (kg/m ²)	24.7±2.8	24.8±3.3	24.7±2.7	24.9±3.3
Systolic BP (mmHg)	125±15	129±17	126±15	129±15
Diastolic BP (mmHg)	74±10	75±10	74±10	75±10
HbA _{1c} (%)	5.8 (5.3–6.8)	5.7 (5.4–6.5)	5.7 (5.3–6.6)	5.8 (5.5–6.5)
Fasting glucose (mg/dl)	121±45	117±33	126±51	119±35
Fasting IRI (μU/ml)	7.9 (5.6–12.7)	8.6 (5.8–14.8)	8.5 (5.7–12.6)	8.0 (5.6–11.7)
HOMA-IR	3.0 (1.8–4.1)	3.1 (2.0–4.1)	2.8 (1.6–4.2)	2.8 (1.8–3.9)
Serum creatinine (mg/dl)	0.88±0.19	0.88±0.20	0.88±0.19	0.88±0.20
CRP (mg/dl)	0.06 (0.03–0.14)	0.09 (0.04–0.29)	0.05 (0.03–0.11)	0.10 (0.04–0.24)
Medication use, n (%)				
β-blocker	55 (40)	50 (36)	41 (51)	38 (40)
Calcium antagonist	57 (42)	64 (47)	38 (45)	47 (49)
ACEI or ARB	86 (63)	82 (60)	62 (74)	68 (71)
Aspirin	126 (92)	131 (96)	79 (94)	91 (95)
Thienopyridine	38 (28)	36 (26)	23 (27)	27 (28)
Diuretic	20 (15)	16 (12)	9 (11)	10 (10)
Insulin	3 (2)	10 (7)	2 (2)	7 (7)
Sulfonylurea	28 (20)	11 (8)	7 (8)	4 (4)

Data are expressed as the mean value±SD, the median value (interquartile range), or number (%) of patients. This study initially enrolled 274 patients and finally analyzed 180 patients who completed the study. There was no difference in parameters among the patients groups.

MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; BMI, body mass index; BP, blood pressure; HbA_{1c}, hemoglobin A_{1c}; IRI, immunoreactive insulin levels; HOMA-IR, homeostasis model assessment-insulin resistance; CRP, C-reactive protein; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

Methods

Study Patients

From 2003 December to 2005 March, 274 patients with CAD and high levels of RLP-C (≥5.0 mg/dl) at 17 hospitals (Appendix 1) were enrolled in this study. All patients met the following inclusion criteria: (1) total cholesterol (TC) level in fasting serum ≥180 mg/dl but <260 mg/dl; (2) TG level in fasting serum ≥150 mg/dl but <400 mg/dl; (3) presence of CAD based on angiographic evidence of organic diameter stenosis >50% of at least 1 major coronary artery, but patients were included if they had had a significant stenosis previously, which had been reduced to ≤50% after coronary revascularization; and (4) age 35–75 years. If lipid-lowering drugs were being administered at the time of enrollment, RLP-C, TC, high-density lipoprotein-cholesterol (HDL-C) and TG levels were measured after a wash-out period of more than 4 weeks. The exclusion criteria were: (1) acute coronary syndrome within 10 days prior to enrollment; (2) congestive heart failure (New York Heart Association class III or greater);

(3) history of dialysis or impaired renal function (serum creatinine level ≥1.5 mg/dl); (4) history of adverse reaction to pravastatin or bezafibrate; (5) chronic inflammatory diseases; (6) major injury or surgery within 3 months prior to enrollment; (7) other serious diseases including malignant tumors; and (8) patients judged inappropriate for enrollment by their primary doctor. At enrollment, all included patients were those with stable CAD, no episodes of angina at rest and no changes in the frequency of angina and response to sublingual nitroglycerin. The baseline characteristics of the patients initially enrolled are summarized in Table 1. All patients gave written informed consent for the study before any study-related procedure and received the standard cardiac medications outlined in Table 1. This study was conducted in accordance with the guidelines approved by the ethics committees of Yamanashi University Hospital and each participating hospital and conformed with the principles outlined in the Declaration of Helsinki.

Study Protocol

All enrolled patients were randomly assigned to oral therapy with pravastatin (10–20 mg/day) or bezafibrate (200–400 mg/day). Randomization was carried out centrally by means of a computer-generated sequence. The dosage depended on the primary doctor's judgment in principle. Except for pravastatin and bezafibrate assigned by randomization the following lipid-lowering drugs were not administered during the follow-up period: other statins, other fibrates, probucol, nicotinic acid, and eicosapentaenoic acid. A goal of therapy was LDL-C level <100 mg/dl in principle, according to the Japan Atherosclerosis Society Guidelines for Diagnosis and Treatment of Atherosclerotic Cardiovascular Diseases, 2002.¹⁹ If LDL-C lowering was insufficient, the dosage of the drug was increased to the approved maximum dosage and aggressive dietary therapy was initiated. More than 3 months after randomization, an anion exchange resin was added if the primary doctor judged it to be necessary because of insufficient LDL-C lowering. All patients received standard medical therapy for CAD according to AHA/ACC guidelines, except for the lipid-lowering medications, as shown in [Table 1](#).

Follow-up Study

All patients were followed prospectively every month for 12 months while in the hospital or visiting the outpatient clinic. Patients were instructed to adhere to the AHA Step 1 diet throughout the study. Blood sampling after the recommended 12-h overnight fast was performed before and at 6 and 12 months after enrollment. The blood sample was used for measurement of lipids, C-reactive protein (CRP), glucose and hemoglobin A_{1c} (HbA_{1c}) levels. The primary endpoint was the percent change from baseline in RLP-C levels after 1 year of treatment with either pravastatin or bezafibrate. The secondary endpoint was occurrence of a composite of

the following CV events: cardiac death, nonfatal myocardial infarction, readmission or unplanned coronary revascularization because of recurrent or refractory unstable angina pectoris and ischemic stroke. The interventional cardiologists, independent of this prospective study, decided the need for and timing of revascularization. Follow-up data were collected every 3 months from the patients' primary physicians by the investigators (K.S., Y.K.), who were blinded to the characteristics of the patients at enrollment. All endpoint data were checked strictly for accuracy, consistency, and completeness of follow-up by the other investigators (M.H., T.K.), also without knowledge of the patients' baseline characteristics. Additional information was obtained from the primary physicians as required. The investigators (Y.S., Ki.K., J.O.) were responsible for checking all the data, performing the statistical analyses and security of the data files. Patients were withdrawn from the study for the following reasons: (1) an adverse reaction to the allocated drug; (2) impossible to obtain the patient's information (eg, relocating); (3) the primary physician decided to change the allocated drugs or to withdraw the patient from the trial. The committee (Appendix 1) was responsible for developing the study design and monitoring the implementation of the protocol.

Assays

RLP was isolated by application of the fasting serum sample to an immunoaffinity mixed gel that contained anti-apoA-1 and anti-apoB-100 monoclonal antibodies (Japan Immunoresearch Laboratories, Takasaki, Japan), according to the method described in our previous reports.^{6–9,12} Serum levels of TC, TG, HDL-C, HbA_{1c}, CRP, glucose and insulin were determined as in our previous reports.^{6–9,12} LDL-C levels were calculated according to the Friedewald formula. The homeostasis model assessment of insulin resistance (HOMA-IR) was deter-

Table 2. Changes in the Lipid and Biochemical Parameters During Treatment With Bezafibrate or Pravastatin

	Bezafibrate (n=84)	Pravastatin (n=96)	Repeated ANOVA (P value)		
			Duration	Group	Interaction
RLP-C (mg/dl)					
Baseline	8.9 (6.9–11.9)	8.4 (6.8–11.1)			
6 months	6.1 (4.5–8.2)*	6.8 (4.7–10.7)*,†	<0.01	<0.05	0.03
12 months	5.6 (4.4–7.3)*	6.3 (4.5–9.0)*,†			
Total cholesterol (mg/dl)					
Baseline	213±26	210±28			
6 months	207±28	190±28	<0.01	<0.01	0.01
12 months	201±34	191±31*,†			
LDL-C (mg/dl)					
Baseline	129±26	123±26			
6 months	125±26	106±32*,†	0.01	<0.01	<0.01
12 months	123±29	110±29*,†			
Triglyceride (mg/dl)					
Baseline	191 (163–224)	212 (175–266)			
6 months	115 (85–146)*	155 (118–199)*,†	<0.01	<0.01	<0.01
12 months	109 (92–142)*	149 (120–222)*,†			
HDL-C (mg/dl)					
Baseline	41 (37–48)	41 (35–48)			
6 months	50 (45–60)	44 (37–53)	<0.01	<0.01	<0.01
12 months	51 (45–59)*	46 (38–55)*,†			
Non HDL-C (mg/dl)					
Baseline	170±27	167±28			
6 months	156±28	141±36*,†	<0.01	<0.05	<0.01
12 months	157±31	144±31*,†			
HbA _{1c} (mg/dl)					
Baseline	5.7 (5.3–6.6)	5.8 (5.5–6.5)			
6 months	5.7 (5.3–6.3)	5.8 (5.5–6.5)	0.93	0.43	0.34
12 months	5.8 (5.4–6.6)	5.7 (5.5–6.4)			
CRP (mg/dl)					
Baseline	0.05 (0.03–0.11)	0.10 (0.04–0.24)			
6 months	0.05 (0.03–0.15)	0.09 (0.04–0.18)	0.91	0.68	0.43
12 months	0.07 (0.03–0.18)	0.08 (0.04–0.16)			
Fasting glucose (mg/dl)					
Baseline	126±51	119±35			
6 months	119±39	121±33	0.61	0.59	0.38
12 months	118±34	117±24			
Fasting IRI (μU/ml)					
Baseline	8.5 (5.7–12.6)	8.0 (5.6–11.7)			
6 months	7.8 (4.7–11.6)	8.1 (5.8–10.9)	0.75	0.18	0.06
12 months	8.0 (3.9–10.2)	8.2 (3.9–10.3)			
HOMA-IR					
Baseline	2.8 (1.6–4.2)	2.8 (1.8–3.9)			
6 months	2.5 (1.8–3.1)	2.7 (1.4–4.2)	0.57	0.38	0.06
12 months	2.4 (1.4–3.2)	2.5 (1.4–3.7)			

The data are expressed as the median value (interquartile range) or mean value ± SD. P values are tabulated for duration, group (bezafibrate and pravastatin) effects and interaction by 2-way repeated-measures ANOVA. When the duration effect was significant, differences between time points at each group were compared with Scheffé's test (*P<0.05 vs baseline). When the group effect was significant, differences between groups at each time point were compared with Scheffé's test (†P<0.05 vs respective time points in the bezafibrate group).

RLP-C, remnant-like lipoprotein particle cholesterol; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol. Other abbreviations as in Table 1.

mined by the following formula: fasting serum insulin (in microunits/ml) × fasting serum glucose (in mmol/L)/22.5. The qualitative insulin sensitivity check index (QUICKI) was determined by the following formula: $1/(\log_{10} [\text{fasting serum insulin (in microunits/ml)}] + \log_{10} [\text{fasting serum glucose (in mg/dl)}])$.

Statistical Analysis

Data were expressed as the mean value ± SD or number of patients (percentage). RLP-C, TG, HDL-C, HbA_{1c}, CRP, immunoreactive insulin levels, HOMA-IR and QUICKI were not distributed normally, so these data are expressed as the

median and range (25th and 75th percentiles) and were log-transformed before any statistical analysis was performed. Continuous variables were compared between the 2 groups using Student's unpaired t-test; variables expressed as a frequency were compared using a chi-square test. For comparisons of the lipid and other biochemical levels before and during treatment, 1-way analysis of variance (ANOVA) was used, followed by Scheffé's test for post-hoc comparisons. The lipid and biochemical parameters before and during treatment were compared between 2 groups using 2-way ANOVA for repeated measures followed by post-hoc testing with Scheffé's test. The relationship between changes in lipid levels after treatment and CV events was assessed by logistic regression analysis. Odds ratios (OR) and 95% confidence intervals (CI) are expressed per 1 SD of decrease or increase in average changes in lipid levels from baseline. The Hosmer-Lemeshow goodness-of-fit test was used to assess the logistic model fit. In the multivariate model, interaction analysis between covariates on the outcome was performed using the likelihood test. Statistical significance was defined as $P < 0.05$. Analyses were assessed using Stat View 5.0 for Windows (Tokyo, Japan) and STATA version 10.0 (StataCorp, College Station, Texas).

On the basis of previous reports,^{8,13–15,20,21} we proposed that treatment with bezafibrate and pravastatin would reduce RLP-C levels in patients with higher RLP-C levels by approximately 40% and 10%, respectively. When baseline median value of RLP-C levels was assumed to be approximately 8 mg/dL, on treatment RLP-C levels was approximately 4.8 mg/dL in patients treated with bezafibrate and 7.2 mg/dL in patients treated with pravastatin, respectively. Based on our previous report,¹² a CV event occurred in approximately 10% of CAD patients with a RLP-C level < 5.7 mg/dL and in 30% of those with a RLP-C level ≥ 5.7 mg/dL during 12 months. Thus, we proposed that a CV event may occur in 10% of patients in the bezafibrate treatment group and in 30% in the pravastatin group. A power analysis showed that given this effect size (20%), a probability of type-I error of 0.05 (2-tailed), a power of 0.8, and an expected SD of 30%, the minimum required sample size was 63 patients in each group in order to detect significant difference for frequency of future CV event between the bezafibrate and pravastatin treatment groups.

Results

Study Population

During the follow-up period 94 patients were withdrawn from the study (Figure 1) and of them, 69 were withdrawn because it was the primary physician's judgment to change the allocated drugs. In 2004, just after the start of this study,

the NCEP ATP III guidelines²² announced the importance of intensive reduction of LDL-C levels by use of statins for high-risk patients with CAD. This raised ethical issues regarding prohibition of any statin use in the bezafibrate arm and of the use of a stronger statin than pravastatin in the pravastatin arm of the study. NCEP ATP III resulted in the withdrawal of many patients from the study. Adverse reactions occurred in 6 patients treated with bezafibrate (renal dysfunction in 3, skin eruption in 3) and in 2 patients treated with pravastatin (eosinophilia in 1, myalgia in 1).

In both the patients initially enrolled and those who were finally analyzed, there were no significant differences in lipid profile or frequencies of other coronary risk factors at baseline between patients allocated to treatment with bezafibrate or pravastatin (Table 1). On the basis of relatively high HOMA-IR (Table 1), a majority of the study patients had insulin resistance.

At the end of the follow-up period, mean doses of bezafibrate and pravastatin were 360 ± 81 mg/day and 11 ± 3.0 mg/day, respectively. An anion exchange resin was added during the follow-up period in 2 patients of the pravastatin group and in 3 of the bezafibrate group because of insufficient LDL-C lowering.

Comparison of Lipid-Lowering Effects of Pravastatin and Bezafibrate

A total of 180 patients completed the study protocol. Treatment for 1 year with either bezafibrate or pravastatin significantly reduced RLP-C levels by 37% and 25%, respectively (Table 2). Also, both treatments decreased TG, LDL-C and non-HDL-C and increased HDL-C levels (Table 2). There was a greater decrease in the RLP-C and TG levels in the bezafibrate group than in the pravastatin group (Table 2), but levels of LDL-C and non-HDL-C decreased more in the pravastatin group than in the bezafibrate group. HOMA-IR tended to reduce in the bezafibrate treatment group more than in the pravastatin group, but there was no statistical difference (Table 2). QUICKI tended to increase in the bezafibrate treatment group (0.327 [0.308, 0.355] at baseline, 0.345 [0.324, 0.369] after 1 year treatment) more than in the pravastatin group (0.326 [0.312, 0.349] at baseline, 0.333 [0.315, 0.361] after 1 year's treatment), but there was no statistical difference (duration, $P = 0.35$; group, $P = 0.23$; interaction, $P = 0.06$). A goal of LDL-C level < 100 mg/dL in principle was attained at 1-year follow-up in 22 (26%) patients treated with bezafibrate and 39 (41%) patients treated with pravastatin.

CV Events During Follow-up

CV events occurred in 12 of 96 (12.5%) patients treated with

pravastatin during the 1 year of follow-up (cardiac death in 1, unstable angina pectoris in 11), compared with 3 of 84 (3.6%) patients treated with bezafibrate (cerebral infarction in 1, unstable angina pectoris in 2) ($P < 0.01$ between the 2 groups by χ^2 test). In the multivariate logistic regression analysis, the reduction in RLP-C levels from baseline after 1 year of lipid-lowering therapy was significantly associated with a decrease in CV events after adjustment for treatment group and changes in LDL-C, HDL-C, TG, and non-HDL-C levels (Figure 2). The reduction in RLP-C level by 1 SD (1.1 mg/dl) decreased the risk of future CV events by 45% (Figure 2). There was no significant interaction among the percent changes in the lipid variables on the CV outcomes (P value for interaction > 0.05 in all, by the likelihood test).

Discussion

The present study results showed that both bezafibrate and pravastatin treatment reduced RLP-C levels in patients with high RLP-C levels and that the reduction in RLP-C levels was greater with bezafibrate treatment than with pravastatin treatment. Moreover, there was a significant relationship between the reduction in RLP-C level by lipid-lowering treatment and the risk of CV events. These results indicated that bezafibrate was more effective than pravastatin in reducing RLP-C levels and that a reduction in RLP-C levels may decrease the risk of CV events in patients with high RLP-C levels. However, many enrolled patients dropped out during the follow-up period, which may have biased the interpretation of the data. In particular, the statistical power of analysis for the occurrence of CV events was limited because of the small number of both study patients and CV events. Therefore, the present results are preliminarily and should be confirmed by further comparative studies that have complete follow-up data on a larger number of study patients. However, only a combination statin/fibrate vs statin alone trial may be possible now because of the ethical consideration.

The current method of using immunoaffinity mixed gel for assaying RLP-C levels has been reported as capable of isolating apoE-rich VLDL particles containing apoB-100 together with chylomicron remnants.^{6,10,11,23} Our previous report⁶ has shown that RLP isolated from fasting blood is almost identical to VLDL remnants. Although the precise mechanisms are unclear, it has been shown that fibrates reduce RLP-C levels probably through clearance of VLDL remnants by an increase in lipase activity, in addition to suppressing hepatic production of VLDL.^{24,25} Also, statins have been shown to reduce RLP-C levels mainly through suppression of hepatic production of VLDL and upregulation of hepatic LDL receptors.^{20,24} The greater efficacy of bezafibrate than pravastatin in reducing RLP-C in the present study is in agreement with previous reports^{14,26} that showed fibrates reduced RLP-C or VLDL-C levels more than statins in patients with type 2 diabetes mellitus or type III hyperlipoproteinemia. In contrast, a previous study showed that pravastatin reduced RLP-C levels more than bezafibrate in patients with type 2 diabetes mellitus;²¹ however, the baseline levels of RLP-C and TG in that study were not high, but in the normal range, which may partly explain the differing results compared with those of the present study and other reports.^{14,26} Thus, the effects of lipid-lowering treatment on RLP-C levels seem to be considerably influenced by the baseline lipid profile. In this context, the present report is the first to compare the lipid-lowering efficacy of statin and fibrate treatment on RLP-C levels, targeting patients with high RLP-C levels at baseline.

The present study showed that a reduction in RLP-C levels was significantly associated with a decrease in CV events during the follow-up period, whereas a reduction in LDL-C levels and an increase in HDL-C levels were not associated with a reduction in CV events. The present study primarily recruited patients with high RLP-C levels, and their baseline levels of LDL-C and HDL-C were nearly normal compared with previous large lipid-lowering trials using pravastatin or bezafibrate.^{27,28} Thus, the small number of both study patients and CV events, the short follow-up period, and the nearly normal range of baseline levels of LDL-C and HDL-C may partly explain the lack of a significant association between changes in LDL-C and HDL-C levels and a decrease in CV events during lipid-lowering treatment. In addition, unsatisfactory achievement rate of the LDL-C goal may partly cause the lack of significant association between a reduction in LDL-C levels and CV events in the present study. Our previous studies^{8,12} showed that high RLP-C levels play a pathogenic role in CV complications in patients with metabolic syndrome or type 2 DM. In agreement with those studies,^{8,12} a majority of the present patients had insulin resistance and had a tendency of improvement of insulin resistance after treatment with bezafibrate or pravastatin, although the effect of treatment was not statistically significant. Moreover, it remains unresolved whether the association between a reduction in RLP-C level and the risk of CV events after lipid-lowering treatment was independent of changes in other traditional risk factors. This study was designed as prospective, randomized, open-label, blinded endpoint (PROBE)-type trial and included soft endpoints such as readmission or unplanned coronary revascularization because of recurrent or refractory unstable angina pectoris. These may potentially raise a bias in the interpretation of the present results.

In conclusion, bezafibrate therapy decreased RLP-C levels more effectively than pravastatin, and a decrease in RLP-C levels may be associated with a reduction in CV events in CAD patients with high RLP-C levels. However, the present results should be confirmed by further studies that have complete follow-up data on a larger number of study patients.

Acknowledgments

This study was supported by grants-in-aid for (B)(2)-15390244 and (B)-19390209, Priority Areas (C) "Medical Genome Science 15012222" from the Ministry of Education, Culture, Sports, Science and Technology, Health and Labor Sciences Research Grants for Comprehensive Research on Aging and Health (H15-Choju-012), Tokyo, Japan.

Disclosure

K. Kugiyama has received research funding from Kissei Pharmaceutical Co Ltd, Japan, Daiichi Sankyo Co Ltd, Japan, and Pfizer Inc, Japan, but this is unrelated to the present study.

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Appendix 1

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