Relation of Serum Lipoprotein(a) Levels to Lipoprotein and Apolipoprotein Profiles and Atherosclerotic Diseases in Japanese Patients with Heterozygous Familial Hypercholesterolemia: Familial Hypercholesterolemia Expert Forum (FAME) Study

Ryo Naito1, Hiroyuki Daida1, Daisaku Masuda2, Mariko Harada-Shiba3, Hidenori Arai4, Hideaki Bujo5, Shun Ishibashi6, Nobuhiko Koga7, Shinichi Oikawa8 and Shizuya Yamashita2, 9 on Behalf of the FAME Study Group

1Department of Cardiovascular Biology and Medicine, Juntendo University, Tokyo, Japan
2Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Osaka, Japan
3Department of Molecular Innovation in Lipidology, National Cerebral and Cardiovascular Center Research Institute, Osaka, Japan
4The National Center for Geriatrics and Gerontology, Aichi, Japan
5Department of Clinical Laboratory and Experimental Research Medicine, Toho University, Sakura Medical Center, Chiba, Japan
6Division of Endocrinology and Metabolism, Department of Medicine, Jichi Medical University, Tochigi, Japan
7Shin Koga Hospital, Kurume City, Fukuoka, Japan
8Director of Diabetes and Lifestyle-related Disease Center, Fukujui Hospital, Japan Anti-Tuberculosis Association (JATA), Tokyo, Japan
9Department of Community Medicine, Osaka University Graduate School of Medicine, Osaka, Japan

Aims: Lipoprotein(a) [Lp(a)] is a plasma lipoprotein consisting of a low-density lipoprotein (LDL)–like particle with apolipoprotein (Apo)(a), attached via a disulfide bond to Apo B100. Previous studies have shown that high Lp(a) levels are associated with an increased risk of cardiovascular disease in patients with familial hypercholesterolemia (FH). To date, limited data are available as to distribution of Lp(a) in FH and associations of Lp(a) with other lipid profiles and cardiovascular disease. Our study aimed to investigate serum Lp(a) levels in relation to other lipid profiles and clinical conditions in the national largest-ever cohort of Japanese FH patients.

Methods: This study is a secondary analysis of the Familial Hypercholesterolemia Expert Forum (FAME) Study that includes a Japanese nationwide cohort of FH patients. In 399 patients under treatment for heterozygous FH who had a baseline measurement of serum Lp(a), the present study examined the distribution of Lp(a) levels and associations of Lp(a) with other lipid profiles and cardiovascular disease. Our study aimed to investigate serum Lp(a) levels in relation to other lipid profiles and clinical conditions in the national largest-ever cohort of Japanese FH patients.

Results: The distribution of Lp(a) was skewed to the right with a median of 20.8 mg/dL, showing a log-normal distribution. Serum Apo B and Apo E levels were positively associated with Lp(a) levels. Age-adjusted mean of Apo B was 8.77 mg/dL higher and that of Apo E was 0.39 mg/dL higher in the highest category (>40 mg/dL) of Lp(a) than in the lowest category (<20 mg/dL). LDL-C levels did not show such an association with Lp(a) levels. A tendency towards a positive relationship between Lp(a) and prevalent CAD was observed in men.

Conclusion: Our study demonstrated a distribution pattern of Lp(a) in Japanese FH patients and positive relationships of Lp(a) with Apo B and Apo E levels.

Key words: Familial hypercholesterolemia, Lipoprotein(a), Lipid-lowering therapy, Atherosclerotic disease

Introduction

Lipoprotein(a) [Lp(a)] is a plasma lipoprotein consisting of a low-density lipoprotein (LDL)–like particle with one additional protein, apolipoprotein(a), attached via a disulfide bond to apolipoprotein B1001.
Lp(a) is a unique lipid profile in terms of its thrombogenic and atherogenic properties. Previous epidemiological and genetic studies have shown that high Lp(a) levels are associated with an increased risk of cardiovascular disease in both the general population and those with FH, independent of LDL cholesterol (LDL-C) levels.\(^1\)\(^-\)\(^8\)

Familial hypercholesterolemia (FH) is a genetic disorder characterized by high serum levels of LDL-C, tendon and skin xanthomas and premature coronary artery disease (CAD).\(^4\)\(^,\)\(^5\) FH is caused by pathogenic mutations in genes of the LDL receptor, apolipoprotein (apo) B-100 and proprotein convertase subtilisin/kexin type 9 (PCSK9), which is involved in the LDL receptor pathway.\(^6\)

Information is limited regarding the distribution of serum Lp(a) and its associations with other lipid parameters and cardiovascular disease in Japanese FH patients. A small Japanese study of 42 patients reported that serum levels of Lp(a) were significantly higher in patients with FH than in those without.\(^7\) Our study aimed to investigate serum Lp(a) levels in relation to other lipid profiles and clinical conditions in the largest cohort of Japanese FH patients studied to date.

**Methods**

This study is a secondary analysis of the Familial Hypercholesterolemia Expert Forum (FAME) Study, which is a multi-center observational study to investigate the clinical features of FH patients and current real-world therapies for FH in Japan.\(^8\) The study was registered with UMIN (UMIN000003211). While patients were largely enrolled during the period between June 2006 and December 2011 and followed up for 4 years, the recruitment was extended until the end of 2012, and the follow-up ended in 3 years for patients enrolled in 2012. A total of 803 patients were enrolled from 52 hospitals and clinics across Japan.

Patients were registered in the FAME study if they met all of the following 4 criteria: 1) they were diagnosed as probable or definite FH assessed by the clinical diagnostic criteria for heterozygous FH defined by the Research Committee of the Japanese Ministry of Health, Labour and Welfare;\(^9\) 2) Patients had serum LDL-C level >100 mg/dL; if patients had been taking ezetimibe, the pretreatment level of LDL-C should be >100 mg/dL; 3) they were outpatients of participating hospitals or clinics; and 4) they gave a written informed consent. Patients were excluded if they had serum triglycerides (TG) of >400 mg/dL; if they were suffering from severe liver dysfunction (acute phase and decompensated cirrhosis); if they had dyslipidemia secondary to hypothyroidism or pancreatitis; if they had uncontrolled diabetes mellitus (HbA1c >9%); if they were pregnant, potentially pregnant or lactating; or if they were inappropriate for enrollment as judged by study physicians.

Details of the diagnostic criteria for heterozygous FH have been described elsewhere.\(^8\) In brief, the scoring was done on the basis of the 5 criterion items: untreated LDL-C level (1, 2, or 4 points), family history of FH (4 or 6 points), xanthoma (6 points), juvenile corneal arcus or premature CAD (4 points), and genetic mutations in the LDL receptor (8 points). Definite and probable FH were diagnosed for a total score of ≥8 points and 6-7 points, respectively. Described below are methodological issues relevant to the present study.

**Study Population**

The study subjects in the current analysis comprised 399 of the 762 heterozygous FH patients aged 15 years or older at baseline.\(^8\) The 399 subjects were under medical treatment for heterozygous FH and had a baseline measurement of serum Lp(a).

**Measurements**

Laboratory measurements including serum Lp(a) were carried out at individual laboratories of the participating institutions. Commercially available immunoassays were used for measurement of Lp(a), the choice of which was at the discretion of each participating institution. In the present report, atherosclerotic disease was defined as CAD, cerebral infarction, and peripheral artery disease. CAD included ischemic heart diseases (I 20.0–I 25.9) of the 10th revision of the International Classification of Diseases), percutaneous coronary intervention, and coronary artery bypass grafting. Family history of CAD was defined as parental and/or sibling CAD.

**Statistical Analysis**

Proportions and means with standard deviation (SD) were calculated for categorical variables and for continuous variables, respectively, as descriptive statistics. The associations of Lp(a) with lipid-related and clinical variables were examined in terms of adjusted mean difference or odds ratio with 95% confidence interval according to Lp(a) categories. Cutoff points of Lp(a) were a priori determined at 20, 30, and 40 mg/dL with reference to the previous studies and guidelines.\(^1\)\(^-\)\(^3\)\(^,\)\(^10\)\(^-\)\(^13\) The adjusted mean difference and odds ratios were estimated by means of multiple regression analysis and logistic regression analysis, respectively. Age and family history of CAD
were found to be potential confounders in a preliminary analysis (see below). Age and family history of CAD (if necessary) were thus included as covariates in the analyses on Lp(a) in relation to lipid and clinical parameters. Those with missing values as to the covariates, family history of CAD excepted, were excluded in the analyses. A category of unknown history was created for the family history of CAD due to the large number of such patients. Serum TG and remnant lipoprotein cholesterol (RLP-C) were transformed to the natural logarithmic scale in the regression analysis because of the skewness to the right side. Lp(a) also showed a log-normal distribution (see below), and changes in Lp(a) from baseline according to the follow-up months were assessed by using the natural log-scale. Anti-logarithmic transformation of mean changes in the log-scale of Lp(a) necessarily leads to percent changes in the original scale of Lp(a). Statistical significance was declared if the two-sided P value was less than 0.05. Statistical analyses and graphical presentation were performed using Stata version 13 (StataCorp, College Station, TX).

**Results**

Baseline characteristics of the study participants are shown separately for males and females in Table 1. Atherosclerotic diseases included CAD (n=99), cerebral infarction (n=11), and peripheral artery disease (n=1). Cholesterol-lowering treatments included statin, ezetimibe, apheresis, and other agents, with 87.4% of the study participants treated on statin-oriented therapy.

The distribution of Lp(a) was highly skewed to the right side (Fig.1A); the median was 20.8 mg/dL, and the first and third quartiles were 11.3 and 38 mg/dL, respectively. The 90th and 95th percentiles were 73.3 mg/dL and 100 mg/dL, respectively. The natural logarithm of Lp(a) showed an almost normal distribution (Fig.1B), with neither substantial skewness (P=0.27) nor kurtosis (P=0.22).

A preliminary analysis showed that age and family history of CAD were significantly related to serum Lp(a) levels, while sex, body mass index, and smoking were unrelated to serum Lp(a) levels (Supplementary Table 1). Therefore, age and family history of CAD were taken into account in the subsequent analyses.

**Lp(a) in Relation to other Lipid Profiles**

Age-adjusted mean differences (95% confidence intervals) of lipid and clinical parameters according to serum Lp(a) categories at baseline are shown in Table 2. Additional adjustment for family history of CAD did not appreciably change the relationships of serum Lp(a) with the other lipid parameters (Supplementary Table 2). While LDL-C did not measurably vary with Lp(a) category, serum Apo B and Apo E levels were positively associated with Lp(a) levels. Apo AI levels were 10 mg/dL lower in the highest category, and high-density lipoprotein (HDL) cholesterol (HDL-C) also showed a similar pattern although the decrease was not statistically significant. TG levels were significantly lower in the highest two categories as compared with the referent category (<20 mg/dL), but the decreases in the two categories were of almost the same magnitude (Fig.2). Neither carotid intima-media thickness nor Achilles tendon thickness showed a notable variation according to Lp(a) categories.

**Lp(a) and Prevalent CAD**

The age-adjusted prevalence odds of CAD and atherosclerotic disease were relatively high in the highest category (40+ mg/dL) of Lp(a), but the elevation did not achieve statistical significance with both sexes combined (Table 3). Further adjustment for family history of CAD attenuated the elevation in odds ratio in the highest category. In the sex-specific analysis (Supplementary Table 3), the prevalence odds of atherosclerotic disease were positively related to Lp(a) levels in males, but not females, although the odds ratios did not progressively increase with increasing levels of Lp(a). The increasing trend was statistically significant in the age-adjusted analysis (P=0.02), but not in the analysis adjusting for age and family history of CAD (P=0.08). A similar pattern was also observed for CAD in males although the trend was not statistically significant in either analysis. However, the interaction between sex and Lp(a) category (ordinary variable) was not statistically significant for either atherosclerotic disease (interaction P=0.11) or CAD (interaction P=0.25) even in the analysis controlling for age alone. It has been suggested that a cutoff of 50 mg/dL be chosen with respect to the risk of CAD

**Changes in Lp(a) during the Follow-Up**

Lp(a) levels tended to be slightly lower at 2–4 years of follow-up as compared with the baseline values (Fig.3).
patients with high Lp(a) values while LDL-C did not show a similar correlation with Lp(a); 3) Lp(a) was not measurably associated with prevalent CAD; and 4) serum Lp(a) levels were slightly lower at 2-4 years of follow-up than at baseline.

Discussion

The main findings of this study are: 1) distribution of Lp(a) was skewed to the right in Japanese FH patients under medical treatment; 2) Apo B and Apo E levels were significantly elevated in

Table 1. Baseline Characteristics of the Study Patients

| Variable                                | N*    | Value   | N*    | Value   | N*    | Value   |
|-----------------------------------------|-------|---------|-------|---------|-------|---------|
| Age (year)                              | 399   | 56.1    | 159   | 53.3    | 240   | 58.1    |
| Heterozygous FH score                   | 399   | 13.8    | 159   | 14.6    | 240   | 13.4    |
| Years from FH diagnosis                 | 388   | 10.3    | 155   | 10.5    | 233   | 10.2    |
| Height (cm)                             | 387   | 160     | 155   | 168     | 232   | 155     |
| Body weight (kg)                        | 393   | 60      | 157   | 69      | 236   | 54      |
| Body mass index (kg/m²)                 | 384   | 23.2    | 155   | 24.4    | 229   | 22.3    |
| LDL cholesterol (mg/dL)                 | 391   | 142     | 154   | 136     | 237   | 146     |
| HDL cholesterol (mg/dL)                 | 399   | 54      | 159   | 47      | 240   | 59      |
| Triglycerides (mg/dL)                   | 399   | 107     | 159   | 112     | 240   | 103     |
| Apolipoprotein AI (mg/dL)               | 352   | 137     | 140   | 126     | 212   | 144     |
| Apolipoprotein B (mg/dL)                | 353   | 110     | 140   | 111     | 213   | 110     |
| Apolipoprotein E (mg/dL)                | 343   | 4.3     | 136   | 4.0     | 207   | 4.5     |
| RLP cholesterol (mg/dL)                 | 312   | 5.3     | 129   | 5.4     | 183   | 5.2     |
| Lp(a) (mg/dL)                           | 399   | 31.6    | 159   | 30.3    | 240   | 32.5    |
| Rf                                       | 149   | 0.34    | 62    | 0.35    | 87    | 0.34    |
| Maximal IMT (mm)                        | 359   | 1.63    | 139   | 1.69    | 220   | 1.59    |
| Mean IMT (mm)                           | 324   | 0.91    | 125   | 0.97    | 199   | 0.87    |
| Achilles tendon thickness (mm)          | 347   | 11.5    | 140   | 12.6    | 207   | 10.9    |
| Smoking                                 | 390   |         | 154   |         | 236   |         |
| Never                                   | 278   | 71.3    | 76    | 49.4    | 202   | 85.6    |
| Past                                    | 82    | 21.0    | 60    | 39.0    | 22    | 9.3     |
| Current                                 | 30    | 7.7     | 18    | 11.7    | 12    | 5.1     |
| Cholesterol-lowering drug               | 399   | 159     | 240   |         |       |         |
| Statin only                             | 131   | 32.8    | 53    | 33.3    | 78    | 32.5    |
| Ezetimibe only                          | 12    | 3.0     | 3     | 1.9     | 9     | 2.5     |
| Statin + ezetimibe only                 | 98    | 24.6    | 43    | 27.0    | 55    | 22.9    |
| Statin + others except ezetimibe        | 58    | 14.5    | 21    | 13.2    | 37    | 15.4    |
| Ezetimibe + others except statin        | 9     | 2.3     | 3     | 1.9     | 6     | 2.5     |
| Statin + ezetimibe + others             | 62    | 15.5    | 28    | 17.6    | 34    | 14.2    |
| Other drugs                             | 12    | 3.0     | 0     | 0.0     | 12    | 5.0     |
| Apheresis only                          | 2     | 0.5     | 2     | 1.3     | 0     | 0.0     |
| Apheresis + drug                        | 10    | 2.5     | 5     | 3.1     | 5     | 2.1     |
| Unknown                                 | 5     | 1.3     | 1     | 0.6     | 4     | 1.7     |

*Numbers of the subjects were not uniform because of missing information.
individuals (12.3–14.1 mg/dL)\textsuperscript{15, 16}. Previous studies reported that serum Lp(a) levels were higher in FH than non-FH subjects\textsuperscript{17, 18} while other reports failed to corroborate such a finding \textsuperscript{19, 20}. To date, it has not been confirmed that LDL-receptor mutations resulting in heterozygous FH affect Lp(a).

It may be of interest whether Lp(a) levels differ

Serum Lp(a) Levels in Japanese FH

The distribution pattern of Lp(a) in our sample was right-skewed, as previously reported in Asian populations and Japanese FH patients\textsuperscript{7, 14}. The median Lp(a) in this study of 20.8 mg/dL seems to be higher than reported in previous studies on Japanese FH patients (12.1 mg/dL) and Japanese healthy individuals (12.3–14.1 mg/dL)\textsuperscript{15, 16}. Previous studies reported that serum Lp(a) levels were higher in FH than non-FH subjects\textsuperscript{7, 18} while other reports failed to corroborate such a finding\textsuperscript{19, 20}. To date, it has not been confirmed that LDL-receptor mutations resulting in heterozygous FH affect Lp(a).

It may be of interest whether Lp(a) levels differ

See Table 2.

### Table 2. Age-adjusted mean differences (95% confidence intervals) of lipid and clinical parameters according to serum Lp(a) categories at baseline\textsuperscript{*}

| Parameter                     | N\textsuperscript{1} | Lp(a) category (mg/dL) | Trend P |
|-------------------------------|-----------------------|------------------------|---------|
|                               | < 20                  | 20–29                  | 30–39   | 40+     |
| LDL cholesterol (mg/dL)       | 391                   | 0.00                   | 5.31    | 1.48    | 5.69    | 0.34    |
| (referent)                    |                       | (−6.45; 17.1)          | (−11.4; 14.4) | (−5.02; 16.4) |
| HDL cholesterol (mg/dL)       | 399                   | 0.00                   | 3.57    | −0.23   | −4.02   | 0.08    |
| (referent)                    |                       | (−0.99; 8.13)          | (−5.28; 4.82) | (−8.20; 0.16) |
| ln (Triglycerides [mg/dL])    | 399                   | 0.00                   | −0.03   | −0.19   | −0.15   | 0.008   |
| (referent)                    |                       | (−0.17; 0.12)          | (−0.35; −0.04) | (−0.28; −0.02) |
| Apolipoprotein AI (mg/dL)     | 352                   | 0.00                   | 2.88    | −5.08   | −9.99   | 0.02    |
| (referent)                    |                       | (−6.33; 12.1)          | (−15.5; 5.32) | (−18.5; −1.49) |
| Apolipoprotein B (mg/dL)      | 353                   | 0.00                   | 2.99    | 3.40    | 8.77    | 0.02    |
| (referent)                    |                       | (−6.33; 11.0)          | (−15.5; 5.32) | (−18.5; −1.49) |
| Apolipoprotein E(mg/dL)       | 343                   | 0.00                   | 0.19    | 0.25    | 0.39    | 0.04    |
| (referent)                    |                       | (−0.22; 0.60)          | (−0.22; 0.72) | (0.01; 0.77) |
| ln (RLPC [mg/dL])             | 312                   | 0.00                   | −0.02   | −0.06   | −0.09   | 0.31    |
| (referent)                    |                       | (−0.22; 0.18)          | (−0.30; 0.18) | (−0.28; 0.09) |
| Rf                            | 149                   | 0.00                   | −0.02   | −0.01   | 0.01    | 0.61    |
| (referent)                    |                       | (−0.04; −0.01)         | (−0.03; 0.02) | (−0.01; 0.02) |
| Maximal IMT (mm)              | 359                   | 0.00                   | 0.10    | −0.08   | 0.12    | 0.39    |
| (referent)                    |                       | (−0.11; 0.31)          | (−0.31; 0.15) | (−0.07; 0.31) |
| Mean IMT (mm)                 | 324                   | 0.00                   | −0.00   | 0.00    | 0.04    | 0.36    |
| (referent)                    |                       | (−0.09; 0.09)          | (−0.10; 0.10) | (−0.04; 0.12) |
| Achilles tendon thickness (mm)| 347                   | 0.00                   | 0.81    | −0.53   | 0.58    | 0.51    |
| (referent)                    |                       | (−0.42; 2.04)          | (−1.91; 0.85) | (−0.52; 1.69) |

*Based on multiple regression analyses including age and indicator variables for Lp(a) category in the model.

Numbers of patients were not uniform due to missing information.
Fig. 2. Age-adjusted mean concentrations of LDL cholesterol (upper left), HDL cholesterol (upper middle), triglycerides (upper right), apolipoprotein B (lower left), apolipoprotein AI (lower middle), and apolipoprotein E (lower right). The values are expressed according to Lp(a) categories at baseline in heterozygous FH patients under medical treatment.

Table 3. Adjusted odds ratios (OR) and 95% confidence intervals (CI) of atherosclerotic disease, coronary artery disease, hypertension, and diabetes mellitus according to serum Lp(a) categories at baseline (N = 399)*

| Disease                        | Lp(a) category (mg/dL) | Trend P |
|-------------------------------|------------------------|---------|
|                               | < 20 | 20–29 | 30–39 | 40+  |
| Atherosclerotic disease       |      |       |       |      |
| No.¹                          | 42/150 | 17/50 | 15/37  | 30/58  |
| OR (95% CI)†                  | 1.00 (referent) | 1.04 (0.53; 2.06) | 1.12 (0.55; 2.31) | 1.47 (0.82; 2.63) |
| OR (95% CI)§                  | 1.00 (referent) | 1.08 (0.54; 2.16) | 1.11 (0.53; 2.30) | 1.30 (0.71; 2.36)  |
| Coronary artery disease       |      |       |       |      |
| No.¹                          | 40/152 | 16/51 | 15/37  | 28/60  |
| OR (95% CI)†                  | 1.00 (referent) | 1.01 (0.51; 2.03) | 1.19 (0.58; 2.47) | 1.40 (0.77; 2.54) |
| OR (95% CI)§                  | 1.00 (referent) | 1.06 (0.52; 2.15) | 1.18 (0.57; 2.48) | 1.22 (0.66; 2.24)  |
| Hypertension                  |      |       |       |      |
| No.¹                          | 53/139 | 18/49 | 19/33  | 31/57  |
| OR (95% CI)†                  | 1.00 (referent) | 0.73 (0.36; 1.47) | 1.05 (0.51; 2.14) | 0.99 (0.54; 1.80) |
| OR (95% CI)§                  | 1.00 (referent) | 0.74 (0.36; 1.51) | 1.04 (0.50; 2.14) | 0.87 (0.47; 1.60)  |
| Diabetes mellitus             |      |       |       |      |
| No.¹                          | 35/157 | 6/61  | 11/41  | 16/72  |
| OR (95% CI)†                  | 1.00 (referent) | 0.32 (0.12; 0.85) | 0.87 (0.39; 1.94) | 0.72 (0.36; 1.43) |
| OR (95% CI)§                  | 1.00 (referent) | 0.32 (0.12; 0.84) | 0.89 (0.40; 1.98) | 0.67 (0.33; 1.36)  |

* Based on multiple logistic regression analyses including age, familial coronary artery disease (if necessary), and indicator variables for Lp(a) categories in the model.
† Number of patients with/without the specified disease.
‡ Adjusted for age.
§ Adjusted for age and familial coronary artery disease.
Theoretically, Lp(a) has a metabolism independent of LDL and Apo B100, although it is basically an LDL with Apo(a) as an extra apoprotein. Since the production of Lp(a) is regulated at the genetic level, Lp(a) concentrations highly significantly correlate with its own production rate, and lifestyle modifications such as diet and physical activity are unlikely to substantively affect the levels.

Lp(a) and CAD

A positive association between serum Lp(a) levels and prevalent CAD was not substantiated in our study subjects under cholesterol-lowering therapy. A significant association between Lp(a) and CAD incidence was not demonstrated in the present study probably because the number of cases was small. It has been documented that Lp(a) was positively related to atherosclerotic disease including CAD, via several mechanisms including the LDL component, increasing endothelial cell permeability, increased expression of adhesion molecule, and antifibrinolytic effects. A recent meta-analysis revealed an odds ratio of 2.57 and a hazard ratio of 1.91 for the risk of cardiovascular disease (CVD) in relation to Lp(a) (high Lp(a) over low Lp(a) with varying cut-off values depending on studies included). In another meta-analysis on the relationship of Lp(a) with CVD in a general population, a relative risk of 1.57 for CAD events was observed for the group with the high Lp(a) level as compared to the low Lp(a) group. The fact that our study subjects were under cholesterol-lowering treatment of undefined duration should be taken into account when interpreting the nonsignificant positive relationship between Lp(a) levels and CAD prevalence in this study.

Sex-specific analyses in our study showed that the association between Lp(a) levels and CAD prevalence and atherosclerotic disease were stronger in men than in women. Another interesting finding was that Apo AI was lowered in those with high Lp(a). A previous study reported positive correlations of Lp(a) with the Apo B100/Apo AI ratio, total cholesterol (TC)/HDL-C ratio, and LDL-C/HDL-C ratio. Lp(a) showed significant negative correlations with HDL-C and Apo AI. Relationships between Lp(a) and other lipid profiles were not consistent among different studies. In a French cross-sectional study, a positive correlation between Lp(a) levels and Apo B100/Apo AI ratio was observed while no correlation was found between Lp(a) and Apo B100. A U.S. population-based study reported that no correlation was found between Lp(a) and Apo B100 whereas they found a correlation between Lp(a) and LDL-C in men. A multicenter study of U.S. diabetic patients also reported no correlation between Apo B100 and Lp(a). Further studies are needed to clarify the relationships of Lp(a) with Apo B, Apo AI, LDL-C, and HDL-C. The observed relationship between Apo E and Lp(a) in this study is in agreement with the previous report which has suggested that Apo E influences Lp(a) production, synthesis, or assembly, although exact mechanisms explaining the relationship remain to be uncovered.

Lp(a) in Relation to other Lipid Profiles

Our study showed that Apo B and Apo E levels were positively associated with Lp(a) levels while LDL-C did not show such an association. Another interesting finding was that Apo AI was lower in those with high Lp(a). A previous study reported positive correlations of Lp(a) with the Apo B100/Apo AI ratio, total cholesterol (TC)/HDL-C ratio, and LDL-C/HDL-C ratio. Lp(a) showed significant negative correlations with HDL-C and Apo AI. Relationships between Lp(a) and other lipid profiles were not consistent among different studies. In a French cross-sectional study, a positive correlation between Lp(a) levels and Apo B100/Apo AI ratio was observed while no correlation was found between Lp(a) and Apo B100. A U.S. population-based study reported that no correlation was found between Lp(a) and Apo B100 whereas they found a correlation between Lp(a) and LDL-C in men. A multicenter study of U.S. diabetic patients also reported no correlation between Apo B100 and Lp(a). Further studies are needed to clarify the relationships of Lp(a) with Apo B, Apo AI, LDL-C, and HDL-C. The observed relationship between Apo E and Lp(a) in this study is in agreement with the previous report which has suggested that Apo E influences Lp(a) production, synthesis, or assembly, although exact mechanisms explaining the relationship remain to be uncovered.

Temporal Change in Follow-Up Lp(a) Levels

Of note, serum levels of Lp(a) were slightly lower in homozygotes and heterozygotes of FH. There were 7 cases of homozygous FH patients in the FAME study, and only four of them had Lp(a) measurements at baseline, with a median of 27.3 mg/dL and a range of 5–128 mg/dL. There was no evidence that the distribution of Lp(a) in homozygous FH differed from that of heterozygous FH (Wilcoxon rank sum test).
at 2–4 years of follow-up although PCSK9 inhibitors that can reduce Lp(a) were not yet used during the study period. To date, evidence of Lp(a)-lowering therapy is scarce prior to the development of PCSK9 inhibitors. Statins able to lower LDL-C by upregulating LDL receptor expression increase LDL-C clearance and potentially lower Lp(a) via a hitchhiking-like process due to the structural similarities between Lp(a) and LDL. However, no clear evidence exists for Lp(a)-lowering effects of statins. Niacin, which can raise HDL-C and lower TG, has been demonstrated to reduce Lp(a) through reduced apo(a) transcription or reduced Apo B secretion via inhibition of TG synthesis. Previous clinical trials have reported a 20% reduction in Lp(a) by niacin. As for Lp(a)-lowering effects of ezetimibe, a meta-analysis of randomized controlled trials reported that ezetimibe monotherapy demonstrated a 7.1% reduction in Lp(a) with statistical significance. Although we do not have information on changes in Lp(a) in relation to individual lipid-lowering agents, statin-oriented medical therapy may contribute to a small reduction in Lp(a) in Japanese FH patients. However, caution should be exercised in interpretation because attrition in the number of patients increased year-by-year during cohort follow-up.

**Limitations**

There were several limitations in the present study. First, the diagnosis of FH was based on the scoring system of the Annual Report of the Research Committee on Primary Hyperlipidemia of the Ministry of Health and Welfare of Japan reported by Harada-Shiba et al. Therefore, there may be differences in FH diagnosis and clinical indices when compared to the guidelines currently in use. Second, the data were collected from facilities throughout Japan, suggesting that variations may exist in the data due to different testing equipment and examiners. Especially, commercially-available immunoassays for measurement of Lp(a) were not harmonized across the participating institutions, which might have affected the results of this study. Despite a Lp(a) standardization working group supported by the WHO and an establishment of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), systematic comparison of six commercial immunological assays for measuring Lp(a) concentrations showed that the results of the different assays as compared to an IFCC reference, varied by 8% to 22%. Unfortunately, we do not have data comparing Lp(a) levels measured by different methods, and are unable to evaluate the size of measurement errors. Third, an association between Lp(a) and CAD cannot be confirmed in this study with a cross-sectional study design. The non-significant association observed in this study may have been due to the small number of study subjects. Fourth, since our study participants were already treated with cholesterol-lowering agents, lipid profiles in the present study should not be taken at face value. Lipid treatment might have potentially affected the association between Lp(a) and CAD. Fifth, the observed temporal changes in Lp(a) might be biased because several cases whose Lp(a) values did not change might have been disproportionally dropped from the analyses through fatal events.

**Conclusion**

The present study demonstrated a distribution pattern of Lp(a) in Japanese FH patients and positive relationships of Lp(a) with serum Apo B and Apo E levels. A tendency towards a positive relationship between Lp(a) and the prevalence of CAD was observed in male FH patients on cholesterol-lowering therapy. Further studies are needed to clarify Lp(a) lowering effects on atherosclerotic disease incidence including CAD in FH patients.

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**Conflict of Interest**

Hidenori Arai has received honoraria from Sanofi, Daiichi-Sankyo Co., Ltd., MSD K.K., Kowa Pharmaceutical Co., Ltd., and Pfizer Co., Ltd. Hideaki Bujo has nothing to disclose. Hiroyuki Daida has received honoraria from Amgen Inc., Daiichi-Sankyo Co., Ltd., Kowa Pharmaceutical Co., Ltd., and MSD K.K., and received clinical research funding from Canon Medical Systems Corporation, Philips Japan, Ltd., Toho Holdings Co., Ltd., Asahi Kasei Corporation, and Inter Reha Co., Ltd. HD has also received scholarship grants from Nippon Boehringer Ingelheim Co., Ltd., Otsuka Pharmaceutical Company, Ltd., Sanofi K.K., MSD K.K., Daiichi-Sankyo Co., Ltd., Pfizer Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Astellas Pharma Inc., Takeda Pharmaceutical Co., Ltd., Teijin Pharma, Ltd., Shionogi & Co., Ltd., Actelion Pharmaceuticals, Ltd.,
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### Supplementary Table 1. Multiple regression analysis on serum Lp(a) levels (natural logarithm) in relation to sex, age, body mass index, smoking habit, and family history of coronary artery disease (CAD) at baseline (n=375)*

| Variable                      | Comparison          | Regression coefficient | Standard error | P-value  | Standardized regression coefficient |
|-------------------------------|---------------------|------------------------|----------------|----------|-------------------------------------|
| Sex                           | Female (referent)   | -0.007                 | 0.112          | 0.95     | -0.004                              |
| Age                           | Male                | 0.110                  | 0.032          | <10^-3   | 0.181                               |
| Body mass index               | Per 10 years        | 0.018                  | 0.014          | 0.20     | -0.068                              |
| Smoking                       | Per kg/m^2          | 0.090                  | 0.131          | 0.49     | 0.039                               |
| Family history of CAD         | Past smoking        | 0.233                  | 0.181          | 0.20     | 0.067                               |
|                               | Current smoking     | 0.263                  | 0.115          | 0.02     | 0.140                               |
|                               | Unknown             | 0.164                  | 0.133          | 0.22     | 0.076                               |

*All the listed variables were included as explanatory variables in the multiple regression analysis. Patients with missing information on body mass index (n=15) and smoking (n=9) were excluded. Patients with information missing on family history of CAD were included in the “unknown” category. Two indicator variables were created for categorical variables of three categories, and regression coefficients for the indicator variables represent differences in Lp(a) levels (natural logarithm) in comparison with the referent category.

### Supplementary Table 2. Adjusted mean differences (95% confidence intervals) of lipid and clinical parameters according to serum Lp(a) categories at baseline*

| Parameter                        | N†              | <20 (n=192) | 20–29 (n=67) | 30–39 (n=52) | 40+ (n=88) | Trend P |
|----------------------------------|-----------------|-------------|--------------|--------------|------------|---------|
| LDL cholesterol (mg/dL)          | 391             | 0.00        | 5.59         | 1.39         | 4.70       | 0.43    |
|                                 | (referent)      | (-6.19; 17.4) | (-11.5; 14.3) | (-6.12; 15.5) |            |         |
| HDL cholesterol (mg/dL)          | 399             | 0.00        | 3.62         | -0.24        | -4.24      | 0.07    |
|                                 | (referent)      | (-0.95; 8.19) | (-5.30; 4.83) | (-8.46; -0.01) |            |         |
| ln (Triglycerides [mg/dL])       | 399             | 0.00        | -0.03        | -0.19        | -0.14      | 0.01    |
|                                 | (referent)      | (-0.17; 0.12) | (-0.35; -0.03) | (-0.28; -0.01) |            |         |
| Apolipoprotein A1 (mg/dL)        | 352             | 0.00        | 2.92         | -4.88        | -9.81      | 0.02    |
|                                 | (referent)      | (-6.31; 12.2) | (-15.3; 5.56) | (-18.5; -1.15) |            |         |
| Apolipoprotein B (mg/dL)         | 353             | 0.00        | 3.19         | 3.54         | 7.92       | 0.04    |
|                                 | (referent)      | (-4.81; 11.2) | (-5.57; 12.6) | (0.36; 15.5)  |            |         |
| Apolipoprotein E(mg/dL)          | 343             | 0.00        | 0.20         | 0.25         | 0.36       | 0.06    |
|                                 | (referent)      | (-0.22; 0.61) | (-0.22; 0.73) | (-0.03; 0.75) |            |         |
| ln (RLPC [mg/dL])                | 312             | 0.00        | -0.01        | -0.04        | -0.09      | 0.33    |
|                                 | (referent)      | (-0.21; 0.19) | (-0.28; 0.20) | (-0.28; 0.09) |            |         |
| Rf                               | 149             | 0.00        | -0.02        | -0.00        | 0.01       | 0.50    |
|                                 | (referent)      | (-0.04; -0.00) | (-0.03; 0.02) | (-0.01; 0.03) |            |         |
| Maximal IMT (mm)                 | 359             | 0.00        | 0.10         | -0.08        | 0.10       | 0.51    |
|                                 | (referent)      | (-0.11; 0.31) | (-0.31; 0.15) | (-0.10; 0.30) |            |         |
| Mean IMT (mm)                    | 324             | 0.00        | 0.00         | 0.00         | 0.03       | 0.47    |
|                                 | (referent)      | (-0.09; 0.09) | (-0.10; 0.10) | (-0.05; 0.11) |            |         |
| Achilles tendon thickness (mm)   | 347             | 0.00        | 0.83         | -0.65        | 0.45       | 0.70    |
|                                 | (referent)      | (-0.39; 2.06) | (-2.03; 0.73) | (-0.66; 1.56) |            |         |

*Based on multiple regression analyses including age, familial coronary artery disease, and indicator variables for Lp(a) category in the model.
†Numbers of patients were not uniform due to missing information.
### Supplementary Table 3.

Sex-specific adjusted odds ratios (OR) and 95% confidence intervals (CI) of prevalent atherosclerotic disease and coronary artery disease according to serum Lp(a) categories at baseline (N = 399)*

| Sex          | Lp(a) category (mg/dL) | Trend P  |
|--------------|-------------------------|----------|
|              | <20                     | 20–29    | 30–39 | 40+ |
| **Atherosclerotic disease** |                       |          |       |     |
| Males        |                         |          |       |     |
| No. †        | 23/62                   | 10/13    | 10/8  | 17/16 |
| OR (95% CI)† | 1.00 (referent)         | 1.84 (0.67; 5.10) | 3.37 (1.09; 10.4) | 2.35 (0.97; 5.65) | 0.02 |
| OR (95% CI)‡ | 1.00 (referent)         | 1.79 (0.60; 5.29) | 2.96 (0.91; 9.61) | 1.93 (0.77; 4.81) | 0.08 |
| Females      |                         |          |       |     |
| No. †        | 19/88                   | 7/37     | 5/29  | 13/42 |
| OR (95% CI)† | 1.00 (referent)         | 0.68 (0.24; 1.92) | 0.52 (0.17; 1.60) | 1.03 (0.44; 2.43) | 0.87 |
| OR (95% CI)‡ | 1.00 (referent)         | 0.76 (0.27; 2.15) | 0.53 (0.17; 1.64) | 0.97 (0.40; 2.31) | 0.75 |
| **Coronary artery disease** |                       |          |       |     |
| Males        |                         |          |       |     |
| No. †        | 22/63                   | 10/13    | 10/8  | 15/18 |
| OR (95% CI)† | 1.00 (referent)         | 1.97 (0.71; 5.50) | 3.63 (1.16; 11.4) | 1.91 (0.79; 4.64) | 0.06 |
| OR (95% CI)‡ | 1.00 (referent)         | 2.00 (0.65; 6.16) | 3.32 (0.99; 11.2) | 1.50 (0.59; 3.80) | 0.21 |
| Females      |                         |          |       |     |
| No. †        | 18/89                   | 6/38     | 5/29  | 13/42 |
| OR (95% CI)† | 1.00 (referent)         | 0.60 (0.20; 1.76) | 0.56 (0.18; 1.73) | 1.11 (0.47; 2.64) | 0.95 |
| OR (95% CI)‡ | 1.00 (referent)         | 0.67 (0.22; 2.00) | 0.56 (0.18; 1.77) | 1.06 (0.44; 2.55) | 0.94 |

*Based on multiple logistic regression analyses including age, familial coronary artery disease (if necessary), and indicator variables for Lp(a) categories in the model.
†Number of patients with/without the specified disease.
‡Adjusted for age.
§Adjusted for age and familial coronary artery disease.