



Impact of Lipoprotein (a) on Long-Term Outcomes in Patients with Coronary Artery Disease Treated with Statin After a First Percutaneous Coronary Intervention

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Aims: Cardiovascular risk persists despite intensive lipid lowering therapy using statins. Serum levels of lipoprotein (a) [Lp(a)] can be a residual cardiovascular risk for adverse events. Aim of the present study was to evaluate the impact of Lp(a) on long-term clinical outcomes in patients treated with statin after percutaneous coronary intervention.

Methods: We prospectively enrolled 3507 consecutive CAD patients who underwent a first percutaneous coronary intervention (PCI) between 1997 and 2011 at our institution. We identified 1768 patients (50.4%) who had treated with statin during PCI. Eligible 1336 patients were stratified to two groups according to Lp(a) levels (median Lp (a) 21.5 mg/dL). The primary outcome was major adverse cardiac events (MACE) including cardiac death and non-fatal acute coronary syndrome.

Results: MACE occurred 144 (10.8%) including 34 (2.5%) cardiac death and 110 (8.7%) non-fatal ACS during median follow-up period of 1920 days. The cumulative rate of MACE was significantly higher in group with high Lp(a) group (log-rank $p=0.0460$). Multivariate Cox regression analysis showed a significant correlation between Lp (a) levels treated as a natural logarithm-transformed continuous variable and increased MACE (adjusted HR for MACE 1.28, 95%CI 1.04-1.58, $p=0.0184$)

Conclusion: Elevated levels of Lp(a) is significantly associated with long-term adverse clinical outcomes among CAD patients who received statin therapy after PCI.

Key words: Lipoprotein (a), Coronary artery disease, Statin, Percutaneous coronary intervention

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Introduction

Cardiovascular disease is the leading cause of mortality and morbidity worldwide. Clinical trials have shown that statins significantly reduce cardiovascular events in patients with coronary artery disease (CAD)^{1, 2)} and statins are the most widely used for individuals with CAD. However, cardiovascular risk

persists despite intensive lipid lowering therapy with statins and has been called residual risk^{3, 4)}. The mechanisms underlying this residual risk are uncertain and identification of these factors is important for more effective tailoring of risk reduction strategies.

A number of additional lipid risk factors have been proposed to be independently associated with cardiovascular disease (CVD). Lipoprotein (a) [Lp(a)] is a low-density lipoprotein like particle with apolipoprotein (apo) B-100, linked by a disulfide bond to apolipoprotein (a)⁵⁾. Lp(a) has enhanced atherogenic and thrombogenic properties and Lp(a) has been identified as an independent, casual risk factor for CVD⁶⁻⁹⁾. Elevated serum Lp(a) are consequently associated with

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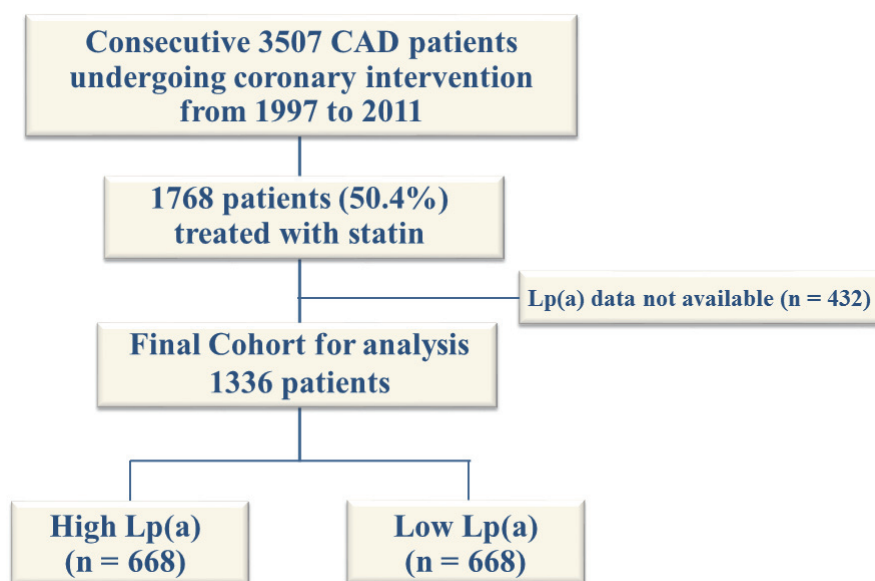


Fig. 1. Study flow chart

an increased adverse clinical events in patients with CAD after coronary intervention^{10, 11}). However, its prognostic utility as a marker of risk in this setting of secondary prevention treated with statin after percutaneous coronary intervention (PCI) is not well established. The association between Lp(a) and cardiovascular events requires ongoing exploration in different population cohorts in order to elucidate its potential role as a marker of clinical risk and target for therapeutic manipulation, especially in such high risk patients. From this perspective, we evaluated the impact of Lp(a) on long-term clinical outcomes in patients with CAD treated with statin after coronary intervention.

Methods

Study Population and Data Collection

We analyzed data from a single-center, observational study of patients who underwent PCI at our institution between January 1997 and December 2011. We included only data from CAD patients with CAD who were treated with statin at the time of PCI. Missing Lp(a) data were excluded from the study. The patients were assigned to two groups based upon Lp(a) values. The cut-offs for Lp(a) were median Lp(a) of 21.5 mg/dL (**Fig. 1**).

Demographic data as well as information about coronary risk factors, medications, revascularization procedure-related factors and comorbidities were prospectively collected and analyzed. Blood samples were collected during the early morning after an overnight

fast and blood pressure (BP) was measured at the time of admission. Patients with BP >140/90 mmHg or under anti-hypertensive medication were considered hypertensive. Diabetes mellitus was defined as either hemoglobin A1c (HbA1c) \geq 6.5% or under medication with insulin or oral hypoglycemic drugs. The estimated HbA1c (%) was calculated as the National Glycohemoglobin Standardization Program (NGSP) equivalent value (%) using the formula $\text{HbA1c (\%)} = 1.02 \times \text{HbA1c (JDS; \%)} + 0.25\%$ ¹²). We defined renal impairment as an estimated glomerular filtration rate (eGFR) of $< 60 \text{ mL/min/1.73 m}^2$, and calculated the eGFR based on the modification of diet in renal disease equation modified with a Japanese coefficient using baseline serum creatinine¹³). Levels of Lp(a) were measured using latex agglutination immunoassays (Special Reference Laboratories, Hachioji, Japan).

Written informed consent was obtained from all patients before undergoing coronary intervention. This study proceeded under the approval of our Institutional Review Board in accordance with the Declaration of Helsinki.

Primary Endpoint

The primary outcomes of this study were cardiac events defined as a composite of cardiac death and non-fatal acute coronary syndrome. Clinical follow-up comprised analyses of office visit charts and responses to questionnaires sent to patients or their families and telephone contact. Mortality data were collected from the medical records of patients who died or who were treated at our institution and details and causes of

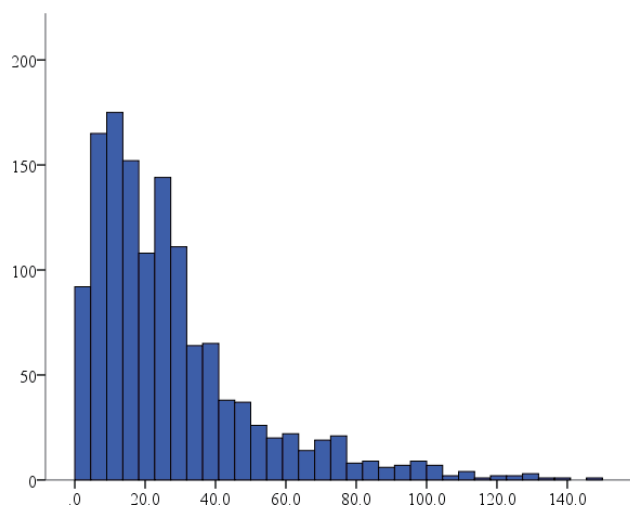


Fig. 2. The distribution of Lp(a) levels

death were obtained from other hospitals where patients had been admitted. Cardiac death was defined as death from CAD, cardiogenic shock and sudden death. We defined acute coronary syndrome (ACS) as unstable angina pectoris (UAP), non-ST segment elevation myocardial infarction (NSTEMI) or STEMI requiring emergency hospital admission for either PCI or coronary artery bypass grafting. Unstable angina was diagnosed as angina at rest or in an accelerating pattern with negative cardiac biomarkers, with or without electrocardiographic (ECG) changes indicative of myocardial ischemia. Myocardial infarction was defined as troponin T positivity.

Statistical Analysis

Quantitative data are expressed as means \pm SD and categorical variables are presented as frequencies. Continuous variables across groups were compared using unpaired *t* test or Mann-Whitney U test for continuous variables and the chi-square test or Fisher's exact probability test for categorical variables. Unadjusted cumulative event rates were estimated using Kaplan-Meier curves and compared between the groups using log-rank test. Hazard ratios and 95% confidence intervals for each variable were calculated using a Cox proportional hazards model. Predictors of cardiovascular events were determined by multivariate Cox regression analysis. Variables with $P < 0.05$ in the univariable model were included in the multivariable analysis as well as age and gender. We also performed multivariable Cox regression analysis that included Lp(a) levels treated as a natural logarithm-transformed continuous variable to determine whether findings differed from the cutoff points. Models were initially adjusted for age and gender (Model 1). Thereafter,

Model 2 was adjusted for lipid parameters including low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglyceride in addition to Model 1. Model 3, adjusted for variables in model 1 plus covariates with $P < 0.05$ in univariable analysis comprised multivessel disease, ACS and diabetes. Values with $P < 0.05$ were considered to indicate statistically significant difference. All data were analyzed using JMP version 10.0 for Windows (SAS Institute, Cary, NC, USA) and SPSS v.18.0 (Chicago, IL, USA).

Results

Among 3507 patients who underwent scheduled PCI during the study period, we analyzed data from 1768 eligible patients with CAD who were treated with statins. **Fig. 1** shows the flow chart of study population. **Fig. 2** shows the distribution of Lp(a) levels. **Table 1** shows the baseline characteristics of patients. The median follow-up period was 1620 (interquartile range, 737 to 2840) days and prognostic data were fully documented during the entire follow-up period. During the follow-up, 144 (10.8 %) cardiac events occurred that included 41 (3.1 %) cardiac deaths, 103 (7.7 %) non-fatal ACS. **Fig. 3** shows the cumulative event free survival curves for all-cause death among the groups. The incidence of cardiovascular events was significantly higher in the group with high Lp(a) than with low Lp(a) (log-rank test, $p = 0.0460$). **Table 2** shows univariate and multivariate Cox hazard regression analyses. Variables with $p < 0.05$ in univariate analysis comprised diabetes, multivessel disease, ACS with Lp(a) values. **Table 3** summarizes the findings of univariate and multivariate Cox hazard regression analyses in which Lp(a) values were treated as natural logarithm-transformed continuous variables. Logarithm-transformed Lp(a) was significantly associated with higher rate of cardiovascular events even after adjustment for other covariates.

Discussion

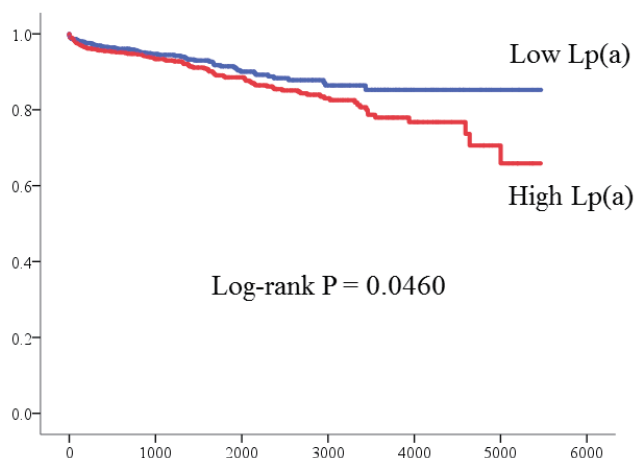
This observational study demonstrated that elevated Lp(a) levels were associated with long-term adverse clinical outcomes in CAD patients treated with statin after PCI. A higher logarithm-transformed Lp(a) value were associated with a greater risk of cardiac events, and the association remained significant even after adjustment for other independent variables. To our knowledge, the present study showed this is the first study to show the clinical impact of Lp(a) levels on long-term clinical outcomes in patients with CAD who underwent PCI and statin therapy.

Lipoprotein (a) has been identified as an inde-

Table 1. Baseline clinical characteristics of the study population

	High Lp(a) Group (n=668)	Low Lp(a) Group (n=668)	P value
Age, years	64.3 ± 10.2	64.7 ± 10.2	0.57
Men, n (%)	523 (78.3)	572 (85.6)	< 0.001
Hypertension, n (%)	474 (71.0)	471 (70.5)	0.86
Diabetes mellitus, n (%)	307 (46.0)	290 (43.4)	0.35
Metabolic syndrome, n (%)	265 (48.3)	317 (51.8)	0.23
Current Smoking, n (%)	172 (25.8)	172 (25.8)	0.98
Family History, n (%)	223 (33.5)	197 (29.6)	0.13
Multivessel Disease,	408 (61.8)	382 (57.6)	0.56
ACS, n (%)	149 (22.3)	173 (25.9)	0.13
Renal impairment, n (%)	180 (26.9)	155 (23.2)	0.11
LVEF, %	61.3 ± 12.9	62.2 ± 11.9	0.38
BMI, kg/m ²	24.4 ± 3.5	24.7 ± 3.3	0.14
SBP, mmHg	132.8 ± 21.9	133.2 ± 21.9	0.82
DBP, mmHg	72.2 ± 13.0	72.8 ± 12.4	0.34
LDL-C, mg/dL	116.6 ± 36.9	105.4 ± 32.9	< 0.001
HDL-C, mg/dL	45.3 ± 14.9	44.7 ± 11.6	0.4
TG, mg/dL	132.4 ± 69.1	146.1 ± 80.0	0.002
FBG, mg/dL	115.8 ± 41.9	118.1 ± 45.1	0.54
eGFR, ml/min/1.73 m ²	73.1 ± 11.1	72.4 ± 17.1	0.43
Medication			
Aspirin, n (%)	635 (95.6)	636 (95.8)	0.89
Ca-channel blockers, n (%)	239 (36.1)	252 (38.0)	0.46
ACE-I/ARBs, n (%)	353 (53.1)	357 (53.2)	0.83
β-Blockers, n (%)	333 (50.2)	353 (53.1)	0.27
Culprit of vessels			
LMT or LAD prox, n(%)	145 (21.7)	151 (22.6)	0.89

ACE inhibitors, angiotensin converting enzyme inhibitors; ACS, acute coronary syndrome; ARBs, angiotensin receptor blockers; BMI, body mass index; DBP, diastolic blood pressure; FBG, fasting blood glucose; eGFR, estimated glomerular filtration rate; high-density lipoprotein cholesterol; LAD, left anterior descending coronary artery; LDL-C, low-density lipoprotein cholesterol; LMT, left main trunk; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; TG, triglyceride

**Fig. 3.** Kaplan-Meier curves for MACE

pendent, casual risk factor for CVD which is continuous in shape without a threshold and does not depend of high levels of LDL-C^{14, 15}. A previous meta-analysis also reported the association between elevated Lp(a) and increased CVD risk using 18 prospective studies of general population¹⁶. Recent mendelian randomization studies reported that genetic polymorphisms associated with elevated Lp(a) level and the risk of CVD suggesting a direct role for Lp(a) in atherothrombotic events^{17, 18}.

Statins significantly reduce cardiovascular events in patients with coronary artery disease (CAD) and are the most widely used for individuals with CAD for secondary prevention^{19, 20}, however residual risk still exist²¹. Previous studies have suggested statin may attenuate the cardiovascular risk associated with Lp(a)²². Although Lp(a) may prove to be a casual risk factor for the development of CVD, its clinical utility

Table 2. Univariate and multivariate Cox hazard model predicting clinical events

	Univariate			Multivariate		
	HR	95% CI	<i>P</i>	HR	95% CI	<i>P</i>
Age	1.01	0.99-1.03	0.22	1.89	0.67-5.43	0.23
Male Sex	0.93	0.63-1.42	0.73	0.99	0.64-1.49	0.97
Diabetes Mellitus	1.45	1.05-2.02	0.026	1.38	0.99-1.92	0.054
Hypertension	1.08	0.76-1.55	0.67			
Current Smoking	0.72	0.48-1.07	0.1			
Renal Impairment	1.09	0.74-1.56	0.66			
BMI	0.98	0.93-1.03	0.44			
SBP	1.005	0.99-1.01	0.2			
DBP	0.99	0.98-1.01	0.35			
Low density lipoprotein cholesterol	1.001	0.99-1.01	0.81			
High density lipoprotein cholesterol	0.99	0.98-1.01	0.31			
Triglycerides	1.001	0.997-1.002	0.48			
Lipoprotein(a) high/low	1.41	1.01-1.98	0.012	1.28	1.04-1.58	0.018
ACE-I•ARB	1.01	0.73-1.41	0.93			
βblocker	0.83	0.60-1.15	0.26			
Ca-channel blocker	1.09	0.77-1.53	0.62			
Multivessel disease	1.74	1.23-2.50	0.002	1.75	1.23-2.53	0.002
LAD proximal or LMT lesion	1.12	0.74-1.64	0.58			
Acute coronary syndrome at presentation	1.54	1.09-2.16	0.015	1.8	1.27-1.63	0.006

HR, hazard ratio; 95%CI, 95% confidential interval.

Table 3. Hazard ratios of Lp(a) levels as a natural logarithm-transformed continuous variable for cardiac events

	HR	95% CI	<i>P</i>
Unadjusted	3.5	1.31-9.62	0.012
Model 1	1.29	1.06-1.59	0.011
Model 2	1.31	1.07-1.61	0.009
Model 3	1.32	1.08-1.63	0.006

Model 1, age and gender adjusted

Model 2, adjusted for variables in model 1 plus lipid parameters including LDL-C, HDL-C and TG.

Model 3, adjusted for variables in model 1 plus variables with $p < 0.05$ in univariable analysis comprised diabetes, multivessel disease and ACS.

ACS, acute coronary syndrome; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; MACE, major adverse cardiac events.

as a prognostic biomarker in secondary prevention remains uncertain. A recent study showed the association between Lp(a) concentration and further CVD events in patients with CAD on statin therapy from LIPID study (Long-Term Intervention with pravastatin in Ischaemic Disease)²³. Another secondary prevention population study using 6708 subjects with CAD from 3 studies including two large statin trial, CARE (Cholesterol and Recurrent Event) and PROVE IT-TIMI 22 (Pravastatin or Atorvastatin

Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction) trials, demonstrated Lp(a) is significantly associated with the risk of CV events in patients with established CAD²⁴. In the present study using Japanese PCI cohort, we evaluated Lp(a) values as a natural logarithm-transformed continuous variable to determine whether findings differed from the cutoff points and we confirmed a higher logarithm-transformed lipoprotein(a) was associated with a greater risk of cardiac events in patients with CAD who underwent PCI and statin therapy which was consistent with the current secondary prevention trials. In a coronary angiographic study among 2769 patients being treated with statins, elevated Lp(a) defined as >30 mg/dL was associated significantly with the severity of coronary atherosclerosis and a greater risk of CVD events, particularly revascularizations⁶. Another recent study evaluated the association between Lp(a) levels and vulnerable plaque phenotype using optical coherence tomography (OCT)²⁵. Mitsuda T et al reported lipoprotein (a) levels predict adverse vascular events in 176 patients with ST-elevated myocardial infarction during 3-year follow-up after primary PCI²⁶. In contrast to these previous studies which included coronary revascularization in the primary endpoint, we focused the primary endpoint on cardiac events defined as cardiac death and non-fatal acute coronary syndrome reflecting more

coronary atherogenic property of Lp(a) with longer follow-up period. Our study showed that patients with CAD who have a high level of Lp(a) may be at an increased risk of subsequent adverse events after PCI and may serve as a potential surrogate marker to predict the future clinical cardiac events after PCI.

Accumulated data suggest that new therapeutic lipid-modifying therapies that reduce Lp(a)²⁷⁾, such as cholesteryl ester transfer protein (CETP) inhibitors²⁸⁾, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors²⁹⁾. In particular, evolocumab is a fully human monoclonal antibody to PCSK9, a protein synthesized and secreted by hepatocyte, which binds to LDL receptor, targeting it for lysosomal degradation. LAPLACE-TIMI 57 (the assessment with proprotein convertase subtilisin kexin type 9 monoclonal antibody inhibition combined with statin therapy-thrombolysis in myocardial infarction 57) trial demonstrated that evolocumab reduced Lp(a) up to 32% among subjects with hypercholesterolemia receiving statin therapy³⁰⁾. A pooled analysis of data from 4 clinical trials showed the inhibition of PCSK9 with evolocumab resulted in significant dose-related reductions in Lp(a)³¹⁾. A further clinical trials would give us some clues for the Lp(a) targeted therapy in addition to statin in patients with CAD.

Several limitations of the present study require consideration. This single-center, observational study included a small sample cohort, and other unknown confounding factors might have affected outcomes regardless of adjustments in the statistical analyses. In addition, relatively few events occurred during the present study, which resulted in the absence of statistically significant differences in outcome measures. Thus, an observational study of a larger cohort is necessary. Furthermore, the choice or dose of statins depended on each physician and we had no information about the patient compliance with prescribed medical therapy during follow-up.

In conclusion, elevated Lp(a) values are significantly associated with long-term mortality in patients CAD treated with statin after PCI and might serve as residual risk.

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