



# Impact of Lipoprotein (a) Levels on Long-Term Outcomes in Patients With Coronary Artery Disease and Left Ventricular Systolic Dysfunction

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**Background:** Serum levels of lipoprotein (a) (Lp(a)) could be a risk factor for adverse events in patients with coronary artery disease (CAD). However, the effect of Lp(a) on long-term outcomes in patients with left ventricular (LV) systolic dysfunction, possibly through the increased likelihood for development of heart failure (HF), remains to be elucidated. This study aimed to determine the prognostic impact of Lp(a) in patients with CAD and LV systolic dysfunction.

**Methods and Results:** A total of 3,508 patients who underwent percutaneous coronary intervention were candidates. We analyzed 369 patients with LV systolic dysfunction (defined as LV ejection fraction <50%). They were assigned to groups according to a median level of Lp(a) (i.e., high Lp(a),  $\geq 21.6$  mg/dL,  $n=185$ ; low Lp(a),  $<21.6$  mg/dL,  $n=184$ ). The primary outcome was a composite of all-cause death and readmission for acute coronary syndrome and/or HF. The median follow-up period was 5.1 years. Cumulative event-free survival was significantly worse for the group with high Lp(a) than for the group with low Lp(a) ( $P=0.005$ ). In the multivariable analysis, a high Lp(a) level was an independent predictor of the primary outcomes (hazard ratio, 1.54; 95% confidence interval, 1.09–2.18;  $P=0.014$ ).

**Conclusions:** A high Lp(a) value could be associated with long-term adverse clinical outcomes among patients with CAD and LV systolic dysfunction.

**Key Words:** Heart failure with reduced ejection fraction; Ischemic cardiomyopathy; Lipoprotein (a)

With the aging of society, the incidence and prevalence of heart failure (HF) continue to rise.<sup>1</sup> In addition, recent advances in treatments of coronary artery disease (CAD) can prolong the patient's life and consequently, increase the likelihood of developing HF.<sup>2–4</sup> In such patients, coexisting left ventricular (LV) systolic dysfunction is a particularly important determinant of clinical outcome, possibly through the increased likelihood of developing HF.<sup>5,6</sup> Similarly, survivors of severe CAD with LV systolic dysfunction have a relatively high incidence of subsequent hospitalization for HF, which is associated with significantly increased mortality.<sup>7,8</sup> A registry of Japanese patients with acute coronary syndrome (ACS) also showed that those with a history of myocardial infarction (MI) have an increased risk of death,<sup>9</sup> suggesting that recurrence of severe CAD, such as ACS, worsens long-

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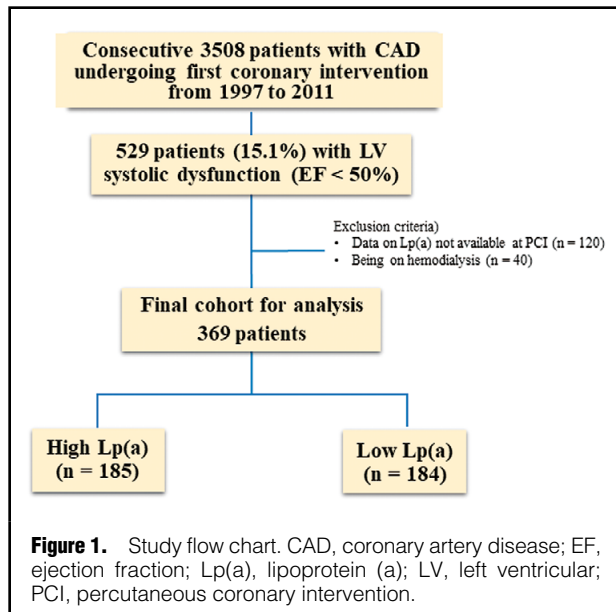
term clinical outcome partially because of the increased likelihood of incident HF in patients with CAD who might have LV systolic dysfunction caused by a previous MI. Therefore, identifying the risk factors for incident ACS and/or incident HF in addition to the all-cause death is important to improve the clinical outcomes of patients with CAD and LV systolic dysfunction.

One such risk factor may be lipoprotein (a) (Lp(a)), which is a low-density lipoprotein (LDL)-like particle with apolipoprotein (apo) B-100, linked by a disulfide bond to apolipoprotein (a).<sup>10</sup> Increased levels of Lp(a) are an independent risk factor for cardiovascular disease;<sup>11,12</sup> more specifically, aortic valve stenosis (AS),<sup>13,14</sup> which is well recognized as a

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major cause of HF. A recent study conducted in a general population showed the relationship between Lp(a) levels and risk of incident HF.<sup>15</sup> In patients with CAD, Lp(a) could be an important risk factor for long-term death and incident ACS independent of other traditional risk factors.<sup>16</sup> Therefore, in patients with CAD and LV systolic dysfunction, higher levels of Lp(a) could be associated with a greater risk of death, incident HF, and ACS (as a predisposing condition for HF). However, no data are available regarding the relationship between Lp(a) levels and clinical outcomes in patients with CAD and LV systolic dysfunction. This study aimed to determine the impact of Lp(a) on long-term outcomes, including all-cause death, incident ACS, and HF, in patients with CAD and LV systolic dysfunction.

## Methods

### Subjects

We used the data from an observational cohort comprising consecutive patients who underwent percutaneous coronary intervention (PCI) at Juntendo University Hospital (Tokyo, Japan) between January 1997 and October 2011. Of them, we analyzed data from patients whose LV ejection fraction (LVEF) was <50% at the time of PCI. Patients with missing Lp(a) data and those on dialysis were excluded, because Lp(a) plasma levels are obviously increased in such patients owing to kidney dysfunction.<sup>17</sup> The patients were divided into 2 groups (high or low Lp(a)) according to a median Lp(a) level of 21.6 mg/dL (**Figure 1**).

Informed consent was given by all patients before undergoing PCI. This study proceeded under the approval of the Juntendo University Hospital review board in accordance with the Declaration of Helsinki.

### Data Collection

Baseline data of the patients' age, sex, body mass index (BMI), blood pressure (BP), smoking status, family history of CAD, blood tests, medication use, and comorbidities were prospectively collected. Blood samples were collected

early in the morning of the PCI after an overnight fast in elective cases, whereas for patients with ACS, blood samples were obtained early in the morning of the next day after an overnight fast within 24 h after an emergency PCI. Hypertension was defined as systolic BP  $\geq 140$  mmHg, diastolic BP  $\geq 90$  mmHg, or medication with antihypertensive drugs. Diabetes mellitus was defined as fasting plasma glycemic levels  $\geq 126$  mg/dL, medication with oral hypoglycemic drugs, or insulin injections. A current smoker was defined as a person who smoked at the time of PCI or who had quit smoking within the year before PCI. The presence of AS was defined as having at least a mild AS on echocardiography at the time of PCI. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) of  $<60$  mL/min/1.73 m<sup>2</sup>, which was calculated based on the Modification of Diet in Renal Disease equation modified with a Japanese coefficient using baseline serum creatinine.<sup>18</sup> Plasma Lp(a) levels were measured using latex agglutination immunoassays (Special Reference Laboratories, Hachioji, Tokyo, Japan).

### Outcomes

The follow-up period ended on 31 December 2011. Survival data and information about hospital admissions were collected by serial contact with the patients or their families and assessed from the medical records of patients who had died or those who were followed up at Juntendo University Hospital. Details of hospital admission and the cause of death were supplied by other hospitals or clinics where the patients had been admitted. All data were collected by blinded investigators.

The primary outcomes of this study were composite events of all-cause death and unplanned readmission for non-fatal ACS or HF. We defined ACS as ST-elevation myocardial infarction (STEMI), non-STEMI, or unstable angina pectoris (UAP). We determined STEMI based on symptoms of ischemia with ST-segment elevation on ECG and increased serum levels of cardiac enzymes (troponin, CK-MB, CK  $\geq 2$ -fold increase),<sup>19,20</sup> and non-STEMI, based on symptoms of ischemia without ST-segment elevation on ECG and increased serum levels of cardiac enzymes. UAP was based on symptoms of ischemia at rest or having a crescendo of symptoms or new-onset symptoms associated with transient ischemic ST-segment shifts and normal serum levels of cardiac enzymes.<sup>21</sup> HF was defined as new-onset or worsening signs and symptoms of HF that required urgent therapy and resulted in hospitalization.<sup>22</sup>

### Statistical Analysis

The results are expressed as mean  $\pm$  SD or medians (interquartile range) for continuous variables and as a ratio (%) for categorical variables. Baseline data were compared using an unpaired t-test or Mann-Whitney U test for continuous variables and the chi-squared test or Fisher's exact test for categorical variables. Kaplan-Meier event-free survival curves were compared using the log-rank test. Factors associated with outcomes were determined using univariable Cox regression analyses with the following variables: age, sex, BMI, family history, diabetes mellitus, hypertension, current smoking status, CKD, LDL-C, high-density lipoprotein cholesterol (HDL-C), triglycerides, use of medications, systolic and diastolic BP, LVEF, multivessel disease, presence of left main trunk lesion, presence of AS, and presentation of ACS in addition to the Lp(a) level (high or low). Variables with a P-value  $<0.1$  in the univariable

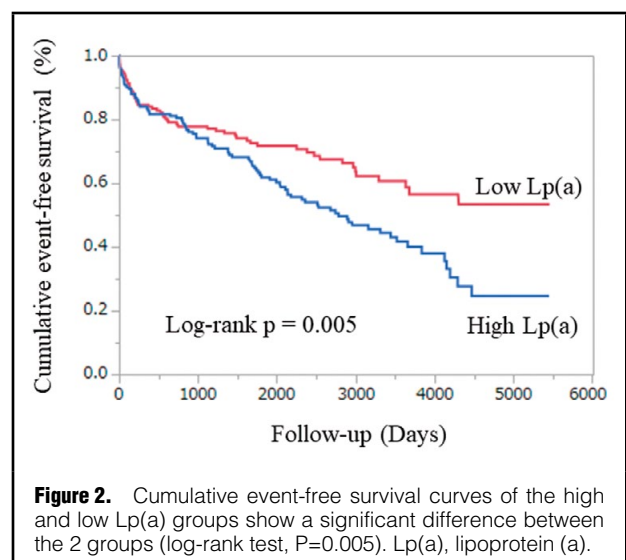
Table 1. Baseline Clinical Characteristics of the Study Population			
	High Lp(a) group (n=185)	Low Lp(a) group (n=184)	P value
Age (years)	65.3±11.5	65.2±12.0	0.969
Men (%)	158 (85.4)	162 (88.0)	0.455
BMI (kg/m <sup>2</sup> )	23.7±3.7	24.3±4.0	0.180
Hypertension, n (%)	118 (63.8)	130 (70.7)	0.160
Diabetes mellitus, n (%)	90 (48.7)	75 (40.8)	0.127
CKD, n (%)	61 (33.9)	55 (30.7)	0.522
Family history of CAD, n (%)	52 (28.1)	47 (25.5)	0.578
Current smoking, n (%)	50 (27.0)	52 (28.3)	0.791
LDL-C, mg/dL	119.5±34.1	108.7±31.8	<0.001
HDL-C, mg/dL	43.3±12.6	42.6±10.5	0.592
Triglycerides, mg/dL	122.3±61.1	125.9±70.4	0.599
Lp(a), mg/dL	43.5±22.2	12.0±5.5	<0.001
Systolic BP, mmHg	130.6±23.4	131.3±23.6	0.758
Diastolic BP, mmHg	72.3±13.9	73.0±14.5	0.608
LVEF, %	39.1±8.2	40.3±7.7	0.167
Aortic valve stenosis, n (%)	9 (4.8)	5 (2.7)	0.277
Multivessel disease, n (%)	115 (62.2)	115 (62.5)	0.946
Presentation of ACS, n (%)	79 (42.7)	85 (46.2)	0.499
LMT lesion, n (%)	3 (1.6)	1 (0.5)	0.306
Medications			
Aspirin, n (%)	165 (90.2)	167 (91.3)	0.451
β-blocker, n (%)	96 (53.0)	87 (48.3)	0.371
Calcium-channel blocker, n (%)	35 (19.2)	38 (20.8)	0.543
ACEI/ARB, n (%)	123 (67.6)	132 (73.3)	0.230
Statins, n (%)	102 (55.7)	93 (51.4)	0.405

ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CKD, chronic kidney disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LMT, left main trunk; Lp(a), lipoprotein(a); LVEF, left ventricular ejection fraction.

able analyses were included in the multivariable Cox regression analysis. The assumption of proportional hazards was assessed using a log-minus-log survival graph. Because Lp(a) levels may differ between patients presenting with and without ACS in association with differences in blood sampling timing, we performed a subgroup analysis regarding the presentation of ACS. The first-order interactions in the multivariable Cox proportional hazard models were examined by entering the interaction terms between the Lp(a) level and the presentation of ACS. We also determined the effect of Lp(a) levels on the clinical events in each subgroup. To determine whether the results differed with the cutoff points, we performed secondary analyses in which Lp(a) levels were treated as a natural logarithm-transformed continuous variable.  $P < 0.05$  was considered to indicate significance, unless otherwise indicated. All data were analyzed using JMP 10.0 MDSU statistical software (SAS Institute, Cary, NC, USA).

## Results

**Figure 1** is a flow chart of the study population. We initially selected 529 patients with LV systolic dysfunction (EF <50%) among 3,508 patients who underwent PCI. Patients on dialysis (n=40) and those with missing Lp(a) data at the time of PCI (n=120) were excluded. Finally, 369 patients were enrolled and assigned to 2 groups according to the



**Figure 2.** Cumulative event-free survival curves of the high and low Lp(a) groups show a significant difference between the 2 groups (log-rank test,  $P = 0.005$ ). Lp(a), lipoprotein (a).

median Lp(a) level of 26.1 mg/dL. **Table 1** shows the baseline characteristics of these 369 patients. By definition, Lp(a) and LDL-C levels were significantly higher in the group with high Lp(a) than in the group with low Lp(a). No significant differences in the presence of AS was found between the 2 groups (9 patients in the high Lp(a) group

vs. 5 patients in the low Lp(a) group). One patient in each group had moderate-to-severe AS. In addition, no significant differences in the other baseline characteristics were found between the groups.

The median follow-up period was 1,878 (interquartile range, 476–3,035) days, and outcome data were fully documented during the entire follow-up period. **Figure 2** shows the cumulative event-free survival curves. The incidence of all-cause death or readmission for ACS or HF was significantly higher in the group of patients with high Lp(a) than in the group of patients with low Lp(a) (log-rank test,  $P=0.005$ ). In total, 151 (40.9%) clinical events were identified during follow-up, including 80 (21.7%) all-cause deaths, 33 (8.9%) readmissions for ACS, and 38 (10.3%) readmissions for HF. (If deaths during rehospitalization for ACS or HF occurred, those events were counted as deaths but not as readmissions for ACS or HF). The numbers and percentages of each event and cause-specific death are shown in **Table 2**. **Table 3** shows the univariate and multivariate Cox hazard regression analyses including variables with  $P<0.1$  in the univariate analysis.

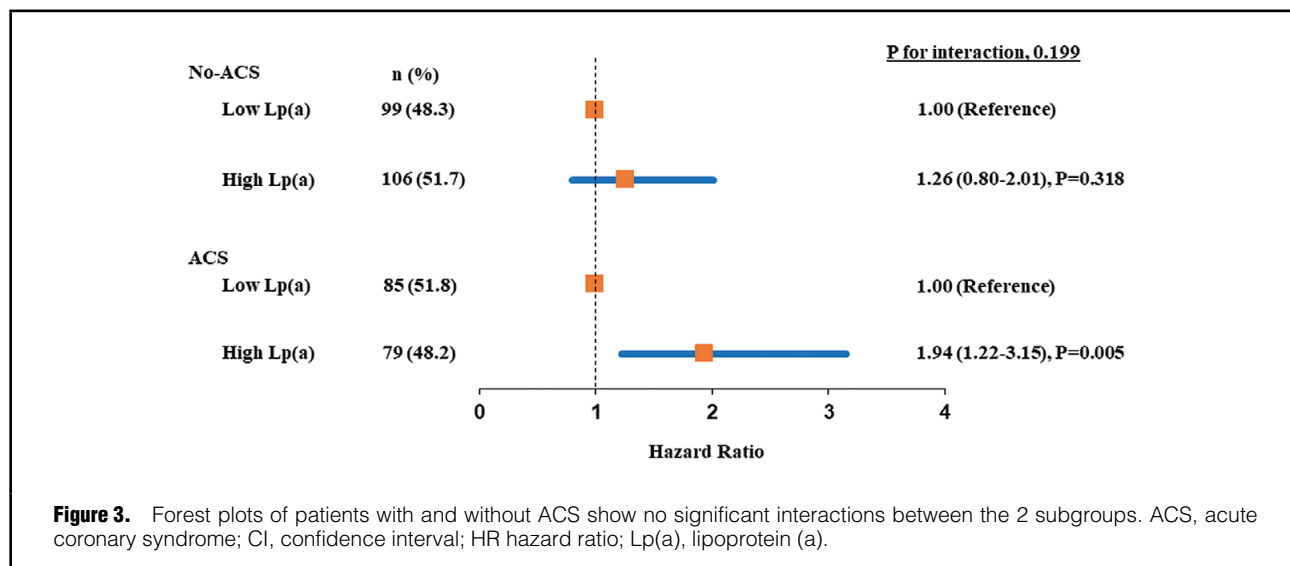
In the subgroup analysis of patients with and without ACS, the prognostic impact of Lp(a) level was similar

	Low Lp(a) group	High Lp(a) group
<b>All-cause death, n (%)</b>	36 (23.8)	44 (29.1)
Cardiac death, n (%)	13 (8.6)	22 (14.6)
HF, n (%)	7 (4.6)	8 (14.6)
Cancer, n (%)	10 (6.6)	6 (4.0)
Stroke, n (%)	2 (1.3)	2 (1.3)
Infection, n (%)	3 (2.0)	6 (4.0)
Others, n (%)	8 (5.3)	8 (5.3)
<b>Readmission for ACS, n (%)</b>	11 (7.3)	22 (14.6)
<b>Readmission for HF, n (%)</b>	12 (8.0)	26 (17.2)

HF, heart failure. Other abbreviations as in Table 1.

	Univariable			Multivariable		
	HR	95% CI	P value	HR	95% CI	P value
Age: 1-year increase	1.05	1.03–1.06	<0.001	1.03	1.01–1.05	<0.001
Men: yes	0.67	0.44–1.05	0.077	0.85	0.54–1.38	0.492
Current smoking: yes	0.70	0.47–1.01	0.058	0.88	0.57–1.32	0.542
CKD: yes	1.62	1.16–2.26	0.005	1.07	0.73–1.56	0.715
Triglycerides: 1 mg/dL increase	1.00	0.99–1.00	0.084	1.00	0.99–1.00	0.889
Statins use: yes	0.70	0.50–0.97	0.033	0.77	0.54–1.09	0.137
Diastolic BP: 1 mmHg increase	0.99	0.97–1.00	0.012	0.99	0.98–1.01	0.325
LVEF: 1% increase	0.97	0.96–0.99	0.007	0.98	0.96–1.00	0.016
Presence of aortic valve stenosis	3.37	1.77–5.84	<0.001	2.68	1.38–4.75	0.005
Lp(a) levels: high	1.59	1.15–2.22	0.005	1.54	1.09–2.18	0.014

CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.



**Figure 3.** Forest plots of patients with and without ACS show no significant interactions between the 2 subgroups. ACS, acute coronary syndrome; CI, confidence interval; HR hazard ratio; Lp(a), lipoprotein (a).

between patients with and without ACS (P for interaction, 0.199; **Figure 3**). Natural log-transformed Lp(a) was also associated with increased risk of clinical events in the univariable analysis (hazard ratio [HR], 1.28; 95% confidence interval [CI], 1.05–1.57;  $P=0.013$ ). In the multivariable Cox proportional hazards regression analysis, high Lp(a) was a significant independent predictor of unfavorable outcomes (HR, 1.54; 95% CI, 1.09–2.18;  $P=0.014$ ) in addition to greater age, lower LVEF, and the presence of AS (**Table 3**). Secondary multivariable analysis in which high/low Lp(a) was substituted by natural log-transformed Lp(a) also showed that natural log-transformed Lp(a) as a significant independent predictor of a worse outcome (HR, 1.26; 95% CI, 1.02–1.57;  $P=0.035$ ).

## Discussion

The current findings are a novel insight into the relationship between Lp(a) levels and clinical outcomes in patients with CAD. First, a high Lp(a) level was associated with a composite of death and readmission for ACS and/or HF in patients with CAD and LV systolic dysfunction. Second, the association remained significant even after adjustment of other potential confounders. Finally, a dose-response relationship was observed between logarithm-transformed Lp(a) and long-term clinical outcome; the risk of clinical events increased with increasing Lp(a) levels. Therefore, in patients with CAD and LV systolic dysfunction, higher levels of Lp(a) were associated with a greater risk of death, incident HF, and ACS as a predisposing condition for HF.

Previous studies have suggested that elevated Lp(a) is an independent causal risk factor for cardiovascular disease.<sup>23–25</sup> Kamstrup et al, in the Copenhagen City Heart Study, showed that high levels of Lp(a) were associated with an increased risk of MI.<sup>26</sup> A meta-analysis of population-based studies and studies involving patients with diabetes, kidney disease, and pre-existing CAD also showed the association between elevated Lp(a), and increased risk of CAD-related deaths and non-fatal MI, both in primary and secondary prevention cohorts.<sup>27</sup> Our group reported that Lp(a) levels can predict cardiovascular events in CAD patients who have diabetes<sup>28</sup> or CKD,<sup>29</sup> or those who are undergoing statin treatment.<sup>30</sup> Taken together, there is a clear association between Lp(a) levels and the morbidity and mortality of CAD in patients, and, among those with comorbidities, in both primary and secondary prevention cohorts.

A recent report from the Copenhagen City Heart Study in conjunction with the Copenhagen General Population Study showed that increased Lp(a) levels were associated with an increased risk of HF in 98,097 normal individuals.<sup>15</sup> That study reported that the association of Lp(a) and incident HF appeared to be partly mediated by MI and AS. The study showed a significant association between Lp(a) and HF even after exclusion of participants with previous diagnoses of MI and AS, suggesting that Lp(a) may increase incident HF through other mechanisms. For instance, high Lp(a) levels may possibly lead to increased arterial stiffness and vascular noncompliance, which will increase afterload and have been associated with an increased risk of HF. In fact, Sorokin et al showed a positive association between Lp(a) and arterial stiffness parameters; that is, increased Lp(a) levels were associated with greater stiffness.<sup>31</sup> This process leads to hypertension, finally resulting in LV hypertrophy or fibrosis, which could cause systolic or diastolic LV dysfunction. In particular, because the failing heart is

sensitive to increased afterload,<sup>32</sup> this mechanism may be more prominent in patients with LV systolic dysfunction. However, very few clinical studies have been conducted to evaluate the relationship between Lp(a) and the incidence of HF in patients with LV systolic dysfunction. In the present study, we evaluated the association between Lp(a) levels and readmission for HF or ACS as a predisposing condition for HF, in addition to all-cause death, some of which may be related to HF in patients with CAD and LV systolic dysfunction. We observed that differences in the specific causes of clinical events between high and low Lp(a) levels were more obvious in terms of readmission for HF (**Table 2**). These findings suggested that the Lp(a) level has an impact on prognosis and could be a useful biomarker for risk stratification in patients with CAD and LV systolic dysfunction. Further studies are warranted to elucidate the mechanism of association between Lp(a) level and the incidence of HF, and to determine whether lowering the Lp(a) level by a specific intervention may improve prognosis in patients with CAD and LV dysfunction.

Serum levels of Lp(a) are genetically determined; >90% of the variance in Lp(a) concentration can be attributed to genetics, and it cannot be altered by diet or exercise.<sup>33</sup> Kamstrup et al also reported an association between high-risk genetic variants in the LPA gene (rs3798220 and rs10455872) and incident HF in the Copenhagen study.<sup>15</sup> Although no specific pharmacotherapy can reduce the Lp(a) level, several drugs, such as fibrates, nicotinic acid, and aspirin, have been reported as effective in reducing Lp(a) levels.<sup>34–36</sup> Furthermore, some new lipid-lowering drugs can reduce Lp(a) levels. Cannon et al reported that anacetrapib decreased Lp(a) levels by 38% after 76 weeks.<sup>37</sup> In the Randomized Evaluation of the Effects of Anacetrapib through Lipid Modification (REVEAL) trial, it was reported that the mean level of Lp(a) was lower by 15 nmol/L in the anacetrapib group than in the placebo group.<sup>38</sup> Another new drug is a proprotein convertase subtilisin/kexin 9 inhibitor, which also decreased Lp(a) levels by 10–30% after 12 weeks.<sup>39</sup> Furthermore, evolocumab reduced Lp(a) levels by 26.9%.<sup>40</sup> If reduction of the Lp(a) level by these drugs could improve long-term outcomes, the causality of the relationship between increased Lp(a) levels and clinical outcome could be proven.

## Study Limitations

First, our study was limited to a single academic center and involved only a Japanese patient population. The association between Lp(a) levels and long-term outcomes in patients with CAD and LV systolic dysfunction needs to be examined in a larger sample size. Second, because the present study was observational in nature, even after the adjusted analysis, other confounders affecting the results cannot be ruled out. Moreover, whether high Lp(a) levels are just a marker of poor long-term outcome or a potential therapeutic target remains unclear. Third, Lp(a) levels have been reported as possibly increased in the acute phase of ACS or after PCI. In our study, even though all blood sampling timing occurred early in the morning after an overnight fast, some sampling data were collected in the acute phase. Therefore, the effects of Lp(a) level on clinical outcomes might differ between patients with and without ACS. However, the differences in the timing of blood sampling between patients with and without ACS might have no effect on clinical outcomes because no significant interaction was observed between the presentation of ACS and



the Lp(a) level/clinical outcome relationship. Fourth, Lp(a) levels are affected by apo (a) phenotype.<sup>41</sup> Therefore, considering this, the results of the present study should be interpreted with caution. Despite these limitations, our study highlighted that high Lp(a) levels are associated with an increased risk of death, incident HF, and incident ACS, which is a predisposing condition for HF, in patients with CAD and LV systolic dysfunction.

## Conclusions

Increased Lp(a) levels were significantly associated with poor long-term clinical outcomes among patients with CAD and LV dysfunction.

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## Role of the Sponsors

These funding sources have no other roles in this study. The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

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