Usefulness of Lipoprotein (a) for Predicting Progression of Non-Culprit Coronary Lesions After Acute Myocardial Infarction

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Background: The serum lipoprotein (a) [Lp(a)] level is genetically determined and remains consistent during a person's life. Previous cohort studies have reported that subjects with a high Lp(a) level are at high risk of cardiac events.

Methods and Results: This study consisted of 410 patients who underwent primary percutaneous coronary intervention within 24 h of the onset of acute myocardial infarction (AMI). Lp(a) was measured 1 week after AMI and patients were divided into 2 groups based: high Lp(a) group (>40 mg/dl, $n=95$) and low Lp(a) group (≤ 40 mg/dl, $n=315$). A major adverse cardiac event (MACE) was defined as cardiac death, myocardial infarction and/or revascularization for new lesions. The incidence of MACE during 5 years was significantly higher in the high Lp(a) group than in the low Lp(a) group (34.7% vs. 16.5%, $P<0.001$). This difference was primarily driven by a higher incidence of new lesions requiring revascularization in the high Lp(a) group (31.6% vs. 15.2%, $P<0.001$). Multivariate analysis showed that Lp(a) was an independent predictor for MACE (odds ratio [OR] 1.64, 95% confidence interval [CI] 1.31–2.06, $P<0.001$) and revascularization of a new lesion (OR 1.61, 95%CI 1.32–2.13, $P<0.001$).

Conclusions: Lp(a) levels could predict the progression of the non-culprit coronary lesions after AMI. (*Circ J* 2011; **75**: 2847–2852)

Key Words: Acute myocardial infarction; Lipoprotein (a); Prognosis; Revascularization

Lipoprotein (a) [Lp(a)] consists of a low-density lipoprotein (LDL) particle with its apolipoprotein B-100 component linked by a disulfide bridge to apolipoprotein (a). The serum Lp(a) level is genetically determined, remains consistent within an individual over several years and is unaltered by diet or exercise.¹ Lp(a) has structural similarity to plasminogen, causing competition with plasminogen activators of humans.^{2–4} Experimental studies have reported that Lp(a) enters the arterial intima and promotes thrombosis, inflammation, and foam cell formation.^{5,6} Several clinical studies have demonstrated that elevated levels of serum Lp(a) are associated with the progression of coronary artery disease and an increased risk of cardiovascular events, independent of other conventional risk factors.^{2,4,7} However, there are few data on the prognostic utility of Lp(a) in patients with acute myocardial infarction (AMI) who undergo primary percutaneous coronary intervention (PCI). This study was undertaken to assess whether the Lp(a) level could predict cardiac events after primary PCI for AMI.

Methods

From September 1999 to April 2007 at Hiroshima City Hospital, 894 patients with AMI underwent primary PCI within 24 h of the onset of chest pain. Among these patients, this study investigated 410 in whom Lp(a) was measured 1 week after AMI. AMI was diagnosed by chest pain consistent with ongoing myocardial ischemia persisting longer than 30 min with concomitant ECG changes. Serum creatine kinase (CK) was measured every 3 h and the peak CK value had to be more than twice the normal upper limit. Emergency coronary angiography and primary PCI was performed as previously reported.⁷ Selective coronary angiography was performed in multiple projections before the initiation of reperfusion therapy. Immediately after diagnostic angiography, primary PCI was performed with conventional balloon angioplasty or stent.

One week after AMI, a blood sample was obtained after overnight fasting. Levels of Lp(a), apolipoprotein A1, apolipoprotein B, apolipoprotein E, remnant-like particles cholesterol,

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Figure 1. Histogram of lipoprotein (a) [Lp(a)] value.

Table 1. Baseline Characteristics			
	Low Lp(a) (n=315)	High Lp(a) (n=95)	P value
Age (years)	63±12	64±11	0.32
Male	259 (82%)	79 (83%)	0.83
Hypertension	147 (46%)	43 (45%)	0.80
Diabetes mellitus	70 (22%)	22 (23%)	0.85
Current smoker	166 (53%)	51 (54%)	0.87
Time to angiography (h)	4.3±4.6	4.5±4.3	0.64
Killip class 3–4	29 (9.2%)	7 (7.3%)	0.57
Initial TIMI 0–1 flow	239 (76%)	70 (74%)	0.67
Collateral circulation	135 (45%)	36 (39%)	0.34
Anterior MI	148 (47%)	48 (51%)	0.54
MVD	94 (30%)	29 (31%)	0.90
Final TIMI 3	293 (93%)	90 (94%)	0.61
eGFR <60 ml·min ⁻¹ ·1.73 m ⁻²	111 (35%)	36 (38%)	0.66
Medications at discharge			
Statins	106 (34%)	32 (34%)	0.99
ACEI/ARB	191 (61%)	60 (63%)	0.76
β-blocker	100 (32%)	29 (31%)	0.81

Lp(a), lipoprotein (a); TIMI, Thrombolysis In Myocardial Infarction; eGFR, estimated glomerular filtration rate; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; MI, myocardial infarction; MVD, multi-vessel disease.

Table 2. Serum Lipid and Lp(a) Levels			
	Low Lp(a) (n=315)	High Lp(a) (n=95)	P value
Lp(a) (mg/dl)	18.5±1.0	67.2±1.8	<0.001
Total cholesterol (mg/dl)	190.2±2.1	196.5±3.7	0.14
Triglycerides (mg/dl)	138.0±3.8	142.0±6.9	0.61
HDL-cholesterol (mg/dl)	39.2±0.7	38.2±1.2	0.45
LDL-cholesterol (mg/dl)	123.4±1.9	129.9±3.3	0.09
LDL/HDL-cholesterol ratio	3.41±0.07	3.69±0.14	0.08
Apolipoprotein A1 (mg/dl)	108.1±3.1	103.9±5.6	0.51
Apolipoprotein B (mg/dl)	104.5±1.4	116.3±2.5	<0.001
Apolipoprotein E (mg/dl)	4.3±0.1	4.4±0.1	0.24
apoB/apoA1 ratio	1.02±0.02	1.15±0.03	<0.001
RLP-cholesterol (mg/dl)	5.0±0.2	5.1±0.3	0.89

Lp(a), lipoprotein (a); HDL, high-density lipoprotein; LDL, low-density lipoprotein; apoB/apoA1, apolipoprotein B/apolipoprotein A1; RLP, remnant-like lipoprotein particle.

total cholesterol, LDL-cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, glucose, insulin, hemoglobin A_{1c} and creatinine were measured. Serum Lp(a) was measured by turbidimetric immunoassay system (BML, Tokyo, Japan). The estimated glomerular filtration rate was calculated using the Japanese equation for estimating glomerular filtration rate from serum creatinine, and chronic kidney disease (CKD) was considered to be present if it was $<60 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$. Multivessel disease (MVD) was defined as $\geq 75\%$ stenosis in 1 or more vessels remote from the infarcted artery. Informed consent was given by each patient and the study was approved by the ethical committee at Hiroshima City Hospital.

Patients were classified into 2 groups based on Lp(a) level: high Lp(a) group ($>40 \text{ mg/dl}$; $n=95$) and low Lp(a) group ($\leq 40 \text{ mg/dl}$; $n=315$). Because a serum Lp(a) level of 40 mg/dl was the 75th percentile of this population and 40 mg/dl was the normal upper limit in this assay, we defined patients with a serum Lp(a) level $>40 \text{ mg/dl}$ as the high Lp(a) group. Clinical follow-up was obtained up to 5 years. Follow-up angiography was encouraged at 6 and 12 months after primary PCI or earlier when clinically indicated. A major adverse cardiac event (MACE) was defined as cardiac death, MI and/or revascular-

Table 3. Cofactors of MACE After Hospital Discharge in Patients With High or Low Lp(a)

	Low Lp(a)	High Lp(a)	P value
Cardiac death	5 (1.6%)	5 (5.3%)	0.06
MI	7 (2.2%)	5 (5.3%)	0.14
Non-TLR	48 (15.2%)	30 (31.6%)	<0.001

MACE, major adverse cardiac event; non-TLR, non-target lesion revascularization (revascularization for new lesions). Other abbreviations see in Table 1.

ization for new lesions. Revascularization for new lesions was defined as revascularization for $>75\%$ stenosis for non-target lesion that progressed more than 1 grade according to the classification of the American Heart Association. Cardiac death was defined as death from pump failure, sudden cardiac death or death because of arrhythmia. We also assessed the incidence of target lesion revascularization (TLR), but did not include it in MACE.

Table 4. Independent Predictors for MACE After Hospital Discharge

	χ^2	OR (95%CI)	P value
High Lp(a)	16.96	1.64 (1.31–2.06)	<0.001
MVD	22.76	1.75 (1.39–2.19)	<0.001
CKD	7.98	1.51 (1.13–2.02)	0.005
Age (years)	0.12	1.01 (0.98–1.03)	0.73
Male	0.51	0.90 (0.66–1.19)	0.47
Hypertension	1.38	1.14 (0.91–1.43)	0.24
Diabetes mellitus	<0.01	1.01 (0.77–1.30)	0.93
Current smoker	0.18	0.98 (0.75–1.20)	0.67
Prior MI	1.26	0.81 (0.53–1.16)	0.26
Killip class >1	1.33	1.22 (0.86–1.66)	0.25
Time to angiography (h)	2.15	1.04 (0.99–1.11)	0.14
Anterior MI	2.43	1.19 (0.96–1.50)	0.12
Initial TIMI 0–1 flow	1.45	0.86 (0.68–1.10)	0.23
Final TIMI 3	0.33	1.16 (0.73–2.12)	0.57

OR, odds ratio; CI, confidence interval; CKD, chronic kidney disease. Other abbreviations see in Tables 1,3.

Table 5. Independent Predictors for Revascularization of New Lesions

	χ^2	OR (95%CI)	P value
High Lp(a)	16.57	1.61 (1.32–2.13)	<0.001
MVD	23.81	1.81 (1.43–2.30)	<0.001
CKD	8.02	1.54 (1.14–2.09)	0.005
Age (years)	1.00	1.01 (0.98–1.04)	0.32
Male	0.26	0.92 (0.67–1.24)	0.61
Hypertension	1.86	1.18 (0.93–1.49)	0.17
Diabetes mellitus	0.18	1.06 (0.80–1.37)	0.67
Current smoker	0.20	0.95 (0.73–1.21)	0.65
Prior MI	0.82	0.84 (0.55–1.21)	0.36
Killip class >1	1.18	1.22 (0.85–1.67)	0.28
Time to angiography (h)	2.00	1.04 (0.98–1.11)	0.16
Anterior MI	0.65	1.10 (0.87–1.39)	0.42
Initial TIMI 0–1 flow	0.71	0.89 (0.69–1.17)	0.40
Final TIMI 3	0.08	1.08 (0.67–1.98)	0.78

Abbreviations see in Tables 1,4.

Figure 3. Number of variables and revascularization for new lesions.

Statistical Analysis

We used standard statistical methods. We tested the significance of difference with χ^2 test for categorical variables. Student's t-test was used for continuous variables. Event-free survival curves up to 5 years after AMI were constructed with the Kaplan-Meier method and were compared with the log-rank test. Cox proportional hazard regression was used to identify independent predictors of mortality, adjusting baseline clinical and angiographic variables. We used the JMP statistical package (version 5.0.1 J) for all statistical tests. A significance level of 0.05 was used and 2-tailed tests were applied.

Results

The mean value of Lp(a) was 29.7 ± 26.9 mg/dl, ranging from 1.0 to 190 mg/dl (Figure 1). Baseline clinical and angiographic characteristics of the study patients are shown in Table 1. There was no significant difference in baseline variables between the high and low Lp(a) groups.

Table 2 shows the laboratory data for the 2 groups. Patients with high Lp(a) had a significantly higher apolipoprotein B level and apolipoprotein B/apolipoprotein A1 ratio than patients with low Lp(a).

Figure 2a shows the 5-year cumulative incidence of MACE, which was significantly higher in patients with high Lp(a) than in those with low Lp(a) (34.7% vs. 16.5%, $P < 0.001$). The incidence of each constituent factor of MACE at 5 years is shown in Table 3. The difference in MACE was primarily driven by a higher incidence of revascularization for new lesion (Figure 2b). Cardiac death, MI and revascularization for new lesions tended to be more frequent in patients with high Lp(a), but the differences did not reach statistical significance. There was no significant difference in the incidence of TLR (12.7% vs. 20.0%, $P = 0.10$).

Multivariate analysis showed that Lp(a) was an independent predictor for MACE (odds ratio [OR] 1.64, 95% confidence interval [CI] 1.31–2.06, $P < 0.001$, Table 4) and revascularization for new lesions (OR 1.61, 95%CI 1.32–2.13, $P < 0.001$,

Table 5). Other factors associated with 5-year revascularization for new lesion were MVD and CKD. If the utility of combining these 3 factors (high Lp(a), MVD and CKD), to predict revascularization for new lesions during the 5 years after AMI was assessed, there was a stepwise increase in revascularization for new lesions as the number of factors increased (Figure 3).

Discussion

This study showed that high Lp(a) is an independent predictor of MACE after AMI in patients treated with primary PCI. It was primarily driven by the more frequent need of revascularization for new lesions in patients with high Lp(a). There are some mechanisms underlying the development of atherosclerosis. The pathophysiologic role of Lp(a) in atherosclerotic disease progression is explained by the accumulation of Lp(a) in the vessel wall and its ability to promote cholesterol accumulation in macrophages forming foam cells and subsequent fatty streaks^{3,4} and to promote smooth muscle cell proliferation and migration in atherosclerotic lesions by inactivating transforming growth factor- β .⁵ In contrast, the Lp(a) level was not associated with TLR. Since the introduction of coronary stents, the initial results of primary PCI have dramatically improved.^{8,9} The main cause of TLR is the growth of smooth muscle cells and fibroatheroma, which is thought to be strongly inhibited by the metallic scaffold of the stent.¹⁰ However, this mechanism of TLR is different from that of non-TLR, so Lp(a) level was not associated with TLR. In addition, the procedure of primary PCI affects TLR. The use of drug-eluting stent (DES) further reduces TLR. Recently, the ACC/AHA guidelines updated their recommendations that it is reasonable to use DES as an alternative to bare metal stents for primary PCI in AMI patients. Despite the reduction in the MACE rate, however, DES does not improve survival.¹¹ It has been reported that, for the patients who survived AMI, long-term outcomes are determined mostly by events attributable to disease progression unrelated to the target lesion treated. Early risk stratification to predict disease progression of non-culprit lesions is, thus, important to improve the outcomes of patients with AMI.

Previous studies have investigated the relation of Lp(a) to cardiovascular events.^{12,13} Recently, the Emerging Risk Factors Collaboration reported a meta-analysis of 126,634 participants in 36 prospective studies,¹⁴ which showed that Lp(a) concentration was independently associated with the risk of coronary heart disease and stroke, but was unrelated to the aggregate of nonvascular mortality. The Lp(a) concentration was more consistent within individuals over several years than were levels of cholesterol, blood pressure, or other conventional risk factors.^{15,16} In the current study, we measured Lp(a) 1 week after AMI, and showed that a high Lp(a) concentration was associated with a higher incidence of revascularization for new lesions after AMI. The association was independent of conventional risk factors. Multivariate analysis showed that Lp(a), CKD and MVD, among the conventional risk factors, were independent predictors for MACE and revascularization for new lesions. Lp(a) is a biomarker that is genetically determined and consistent within individuals. On the other hand, CKD is frequently associated with progressive decline in the glomerular filtration rate, which leads to endstage renal disease and cardiovascular disease. CKD might enhance the activation of both the sympathetic nervous system and the renin-angiotensin-aldosterone system.¹⁷ So, CKD is a marker that reflects increased levels of inflammatory and arterial sclerosis. In turn, MVD reflects atherosclerosis that is already present. Lp(a),

CKD and MVD represent different markers of the development of new lesions, and the combination of Lp(a) with MVD and CKD was more useful for early risk stratification in patients with AMI who underwent primary PCI than each factor alone.

Prevention of atherothrombotic events of non-culprit lesions is important to reduce MACE after AMI in patients treated with primary PCI. Several studies have reported that the use of statins with a lower target LDL-cholesterol level slows atherosclerosis progression or reduces coronary plaque volume.^{18–20} However, in this study, statins were prescribed in only one-third of the patients. Aggressive risk management may improve the outcomes of AMI patients with high Lp(a) concentrations. Although apolipoprotein-B100 is a component of Lp(a), contradictory findings have been reported about the effect of statins on the Lp(a) concentration. Importantly, available data are consistent with the existence of a causal relationship between high Lp(a) level and cardiac events, and increase the priority for investigating Lp(a) as a potential therapeutic target. Niacin can reduce the serum Lp(a) level.^{21,22} Recently, the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies (ARBITE 6-HALTS) trial reported that niacin, when added to simvastatin for patients with low HDL level, decreased the carotid intima-media thickness.²³ However, the Lp(a) concentration was not measured and the increased HDL level may be attributable to the benefits obtained by niacin. Further studies are advocated to investigate better therapeutic options for patients with AMI and high Lp(a).

Study Limitations

This study suffers from the limitations of all retrospective studies. Small sample size is another limitation. In this study, 1 week after AMI, the samples were obtained because almost all patients were discharge within 10 days after AMI. However, it was been reported that most lipoprotein values decrease between 7 and 10 days after the onset of AMI.²⁴ By contrast, Slunga et al, in a study of 32 AMI patients, found no clear evidence of Lp(a) elevation in the acute phase.²⁵ Other reports suggest that the Lp(a) concentration reaches a peak on the 5th day and then returns to the initial value within 1 week.²⁶ Further investigations are necessary to determine the transient increase in serum Lp(a) concentration after AMI.

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