Relation Between Serum Lipoprotein (a) and Residual Lesion Stenosis of Coronary Artery After Myocardial Infarction Without Reperfusion Therapy

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SUMMARY

Lipoprotein (a) (Lp(a)) is an independent risk factor for myocardial infarction (MI). It may also inhibit the fibrinolysis system, and Lp (a) affects the natural course of MI and the results of thrombolytic therapy. The purpose of this study was to investigate the influence of Lp (a) on the residual lesion stenosis of the infarction-related arteries (residual stenosis) in acute MI patients in whom reperfusion therapy was not performed.

We studied 129 MI patients not given reperfusion therapy who underwent coronary angiography in the chronic stage. Morning fasting blood was collected and Lp (a), blood sugar, total cholesterol (TC), triglycerides (TG), and hemoglobin A_{1c} (HbA_{1c}) were measured.

Residual stenosis was compared between the low Lp(a) group (< 30 mg/dL) and the high Lp(a) group ($\geq$ 30 mg/dL). It was severe in the high Lp(a) group ($85.0 \pm 24.9\%$ vs $94.5 \pm 15.5\%$, $P = 0.0044$). We also compared residual stenosis and TIMI classification between younger and older, non-DM and DM, non-HT and HT, low-TC (< 220 mg/dL) and high-TC ($\geq$ 220 mg/dL), low-TG (< 150 mg/dL) and high-TG ($\geq$ 150 mg/dL), and low-Lp (a) and high-Lp (a) patients. Only the serum Lp (a) level affected the residual stenosis and TIMI classification ($P < 0.05$). Conclusion: These findings suggest that elevated Lp (a) levels inhibit fibrinolysis. (Jpn Heart J 2004; 45: 397-407)

Key words: Lipoprotein (a), Acute myocardial infarction

LIPOPROTEIN (a) (Lp(a)), discovered by Berg, K.¹⁾ in 1963, is a lipoprotein resembling low density lipoprotein that consists of apolipoprotein (a) (apo(a)) bound to apo B-100 by a disulphide linkage. Lp (a) is thought to be an independent risk factor in atherosclerotic disorders such as myocardial infarction, arteriosclerosis obliterans, and cerebral infarction.²⁻⁵⁾ Plasminogen and apo (a) have structural homology⁶⁾ and apo (a) and Lp (a) competitively affect the action of

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plasminogen, which may result in inhibition of the fibrinolysis system, and this was demonstrated in *in vitro* experiments.^{7,8)}

Based on this background, several studies on the influence of serum Lp (a) levels on the result of thrombolytic therapy for myocardial infarction have been conducted and investigations from the perspective of the coagulation/fibrinolysis system have been performed.⁹⁻¹⁴⁾ However, few studies have investigated the influence of serum Lp (a) levels in the natural course of myocardial infarction in patients in whom thrombolytic therapy was not performed.¹⁵⁾

In this study, we investigated the influence of Lp (a) on the degree of stenosis of the infarction-related artery (degree of residual stenosis) by coronary angiography performed during the chronic stage in patients in whom reperfusion therapy such as thrombolytic therapy could not be conducted during the acute stage.

METHODS

Subjects: Cardiac catheterization was performed in 1,446 patients at the Department of Internal Medicine, Juntendo Urayasu Hospital between 1993 and 1998. Among these patients, 188 patients with myocardial infarction had not received reperfusion therapy such as thrombolytic therapy, percutaneous coronary angioplasty, and aortocoronary bypass surgery. These patients visited our hospital beyond the period for application of reperfusion therapy and were generally treated with nitrates and antiplatelet agents and heparin during the acute stage. From among these patients, 129 patients who underwent coronary angiography between 8 and 180 days after onset and had a clearly discernible infarction-related artery were selected.

Coronary angiography and evaluation method: Coronary angiography was performed using the Sones method, multipurpose catheter method with right brachial artery puncture, or the Judkins method with femoral artery puncture. Before angiography, 0.5-2 mg of isosorbide dinitrate was administered into the coronary artery. Typically, the left anterior 50-degree oblique view and right anterior 30-degree oblique view of bilateral coronary arteries were imaged. Furthermore, to obtain good visualization of the lesion, some images were obtained from other angles, such as cranial and/or caudal angles. Lesion stenosis of infarction-related artery (degree of residual stenosis) was defined according to the AHA classification¹⁶⁾ and antegrade flow was evaluated in the infarction-related artery according to Thrombolysis in Myocardial Infarction criteria (TIMI classification).¹⁷⁾ The number of diseased vessels was presented, with 75% or higher regarded as significant stenosis.

Blood sampling method for serum lipid measurement: Morning fasting blood was collected before coronary angiography, and Lp (a), fasting blood sugar (FBS), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), triglycerides (TG), and hemoglobin A_{1c} (HbA_{1c}) were measured. Serum Lp (a) was measured by enzyme-linked immunosorbent assay (ELISA) in patients at the early stage and by latex agglutination turbidimetry after July 1994 (correlation of measured values between the two methods: $Y = 0.90X - 0.5$, $r = 0.99$). TC, HDL-C, and TC were measured by the enzyme method. For FBS and HbA_{1c}, blood was collected into a tube containing a glycolysis inhibitor (sodium fluoride) and FBS and HbA_{1c} were measured by an electrode method and high performance liquid chromatography, respectively. The mean duration of the period between the onset of myocardial infarction and blood sampling was 58.7 days.

Risk factors for coronary artery disease: Patients with systolic blood pressure of 160 mmHg or higher and/or diastolic blood pressure of 90 mmHg or higher and patients medicated with antihypertensive drugs were classified as hypertensives (HT patients). Similarly, patients with a fasting blood sugar level of 126 mg/dL or higher and patients who were diagnosed with diabetes based on a postprandial blood sugar level of 200 mg/dL or higher were regarded as patients with diabetes mellitus (including patients with or without previous treatment for diabetes) (DM patients). Patients who were habitual smokers were regarded as smokers. Body mass index (BMI: body weight kg/height m²) was used as an index of obesity.

Statistical analysis: For age, BMI, Lp (a), FBS, TC, HDL-C, TG, HbA_{1c}, degree of residual stenosis, TIMI classification, and the number of diseased vessels, the mean $\pm$ standard deviation and median are presented as the representative values. For comparison between two groups, the unpaired *t* test (*t* test) was used for age, BMI, TC, and HDL-C. The Mann-Whitney U test (U test, nonparametric test) was used for FBS, TG, HbA_{1c}, degree of residual stenosis, TIMI classification, and the number of diseased vessels. FBS and HbA_{1c} were analyzed by the U test because the distributions of FBS and HbA_{1c} were not normally distributed among all patients, although the distributions were close to normal distribution among non-DM patients. With regard to gender, the percentage ratio of males was presented. The percentage ratios of HT patients, DM patients, smokers, and patients rated 0-1 in the TIMI classification were also presented and analyzed using a 2×2 contingency table test. For comparison of the degree of residual stenosis among three groups, the Kruskal-Wallis test was used. Stat View 4.5 and DA Stat 1.0 were used for statistical analysis, and a $P < 0.05$ was defined as significant.

RESULTS

The background characteristics of the 129 patients are shown in Table I-1 and Table I-2. Mean age was 59.3 ± 10.2 years old and the ratio of males to all patients was 82.2% (106 males). Patients with hypertension, diabetes mellitus, and smoking habit accounted for 44.9%, 41.9%, and 67.4%, respectively. The infarction-related artery was the left anterior descending branch (LAD) in 74 (57.4%), left circumflex branch (LCX) in 24 (18.6%), and right coronary artery (RCA) in 31 (24.0%).

The patients were divided into two groups, patients with a Lp (a) level lower than 30 mg/dL (low Lp(a) group: 85) and patients with a Lp (a) level of 30 mg/dL or higher (high Lp(a) group: 44). With regard to the background factors, there were no differences between the two groups in age, sex, BMI, FBS, TC, HDL-C, TG, HbA_{1c}, the duration of the period between the onset and angiography, and

Table I-1. Profile of 129 Cases

Age	59.3 ± 10.2	(59.0)
No. of males (%)	106 (82.2%)	
BMI (kg/m ²)	23.3 ± 3.0	(23.1)
Lp (a) (mg/dL)	27.2 ± 25.8	(20.0)
FBS (mg/dL)	121.0 ± 50.9	(102.0)
TC (mg/dL)	194.2 ± 36.1	(194.0)
HDL-C (mg/dL)	41.0 ± 11.7	(39.0)
TG (mg/dL)	139.0 ± 76.5	(116.5)
HbA _{1c} (%)	6.49 ± 1.83	(5.8)
Onset to angiography (days)	32.9 ± 23.5	(25.0)
Onset to blood sampling (days)	58.7 ± 158.3	(13.5)
No. of underlying diseases		
Hypertension (%)	58 (44.9%)	
Diabetes (%)	54 (41.9%)	
Smoking (%)	87 (67.4%)	

() : median

Table I-2. Angiographic Findings of 129 Cases

Infarction-related artery		
No. of cases (%)		
LAD (%)	74 (57.4%)	
LCX (%)	24 (18.6%)	
RCA (%)	31 (24.0%)	
% Residual stenosis	88.2 ± 22.5	(99.0)
TIMI classification	2.0 ± 1.2	(3.0)
Diseased vessels	1.5 ± 0.9	(1.0)

() : median

Table II. Comparison of Low and High Lp (a) Groups

	Lp (a) < 30 mg/dL (n = 85)		Lp (a) ≥ 30 mg/dL (n = 44)		P value
Lp (a) (mg/dL)	Mean ± SD	Median	Mean ± SD	Median	
	13.5 ± 8.0	12.0	53.8 ± 27.6	42.5	----
Age	58.9 ± 9.8	59.0	60.0 ± 11.1	60.0	0.5417
Gender (male (%))	72 (84.7)		34 (77.3)		#0.2957
BMI (kg/m ²)	23.1 ± 2.8	23.0	23.9 ± 3.5	23.1	0.1159
FBS (mg/dL)	120.6 ± 52.7	102.0	121.8 ± 47.9	103.0	0.6870
TC (mg/dL)	193.1 ± 36.4	191.0	196.2 ± 35.7	198.0	0.6530
HDL-C (mg/dL)	40.7 ± 11.9	39.0	41.8 ± 11.6	39.0	0.6147
TG (mg/dL)	147.6 ± 83.7	125.0	121.8 ± 57.1	105.0	0.0530
HbA _{1c} (%)	6.4 ± 1.9	5.7	6.7 ± 1.7	6.5	0.1875
Onset to angiography (days)	31.5 ± 21.2	26.0	35.7 ± 27.5	24.5	0.7167
Onset to blood sampling (days)	63.7 ± 182.5	11.5	49.2 ± 97.9	22.5	0.5838
No. of underlying diseases					
Hypertension (%)	41 (48.2%)		17 (38.6%)		#0.2988
Diabetes (%)	33 (38.8%)		21 (47.7%)		#0.3312
Smoking (%)	60 (70.6%)		27 (61.3%)		#0.2892
Angiographic findings					
Residual stenosis (%)	85.0 ± 24.9	90.0	94.5 ± 15.5	99.0	**0.0044
TIMI classification	2.2 ± 1.2	3.0	1.8 ± 1.3	2.0	0.0606
(No. of TIMI 0 & 1)	19 (22.4%)		16 (36.4%)		#0.0696
Diseased vessels	1.4 ± 0.9	1.0	1.7 ± 0.9	2.0	0.1502

#: 2x2 contingency table analysis;

**: $P < 0.01$.

the presence or absence of hypertension, diabetes, or smoking habit (Table II). The degree of residual stenosis was significantly higher in the high Lp (a) group than in the low Lp (a) group ($94.5 \pm 15.5\%$ vs $85.0 \pm 24.9\%$, $P = 0.0044$). The TIMI classification also tended to be lower in the high Lp (a) group. There was no significant difference in the number of diseased vessels.

Next, we further stratified the patients into subgroups according to gender, presence of DM, TC levels ($TC < 220$ mg/dL or $TC \geq 220$ mg/dL) and compared the coronary angiographic findings between the low and high Lp (a) groups (Table III). There were no significant differences between the low Lp (a) group and high Lp (a) group among female patients, DM patients, or with respect to high TC levels. However, there were significant differences among male patients, non-DM patients, and low TC levels (Table III). When the low and high Lp (a) groups were compared among male non-DM patients with low TC levels, the degree of residual stenosis was $78.9 \pm 31.2\%$ vs $98.4 \pm 3.2\%$ ($P = 0.0012$), TIMI classification was 2.3 ± 1.1 vs 1.3 ± 1.3 ($P = 0.0040$), and the number of diseased vessels was 1.2 ± 0.8 vs 1.8 ± 0.9 ($P = 0.0444$), respectively. Coronary lesions were more severe in the high Lp (a) group (Table III).

Table III. Comparison of Low and High Lp (a) Groups Using Stratification

		Lp (a) < 30 mg/dL		Lp (a) ≥ 30 mg/dL		P value
		Mean ± SD	Median	Mean ± SD	Median	
Male patients			(n = 72)		(n = 34)	
	Residual stenosis (%)	85.5 ± 23.7	90.0	96.8 ± 5.5	99.0	*0.0033
	TIMI classification	2.2 ± 1.2	3.0	1.7 ± 1.3	2.0	*0.0309
	Diseased vessels	1.5 ± 0.9	1.0	1.8 ± 0.9	2.0	0.1269
Female patients			(n = 13)		(n = 10)	
	Residual stenosis (%)	82.4 ± 31.7	90.0	86.6 ± 30.7	99.0	0.5588
	TIMI classification	2.2 ± 1.1	3.0	2.1 ± 1.3	3.0	0.9451
	Diseased vessels	1.3 ± 0.9	1.0	1.3 ± 1.0	2.0	0.7155
Non-DM patients			(n = 52)		(n = 23)	
	Residual stenosis (%)	82.2 ± 28.9	90.0	98.2 ± 3.3	99.0	*0.0014
	TIMI classification	2.2 ± 1.1	3.0	1.6 ± 1.3	2.0	*0.0389
	Diseased vessels	1.3 ± 0.9	1.0	1.7 ± 0.9	2.0	0.1017
DM patients			(n = 33)		(n = 21)	
	Residual stenosis (%)	89.4 ± 16.2	99.0	90.4 ± 21.7	99.0	0.4724
	TIMI classification	2.2 ± 1.2	3.0	2.0 ± 1.3	3.0	0.5579
	Diseased vessels	1.6 ± 0.8	1.5	1.6 ± 1.0	2.0	0.8453
Low-TC patients (TC < 220 mg/dL)			(n = 65)		(n = 35)	
	Residual stenosis (%)	82.4 ± 27.6	90.0	94.5 ± 16.9	99.0	*0.0013
	TIMI classification	2.3 ± 1.1	3.0	1.6 ± 1.3	2.0	*0.0135
	Diseased vessels	1.3 ± 0.8	1.0	1.7 ± 0.9	2.0	0.0610
High-TC patients (TC ≥ 220)			(n = 20)		(n = 9)	
	Residual stenosis (%)	93.4 ± 8.9	99.0	94.4 ± 8.3	99.0	0.9014
	TIMI classification	1.9 ± 1.3	2.0	2.3 ± 1.0	3.0	0.4715
	Diseased vessels	1.9 ± 0.9	2.0	1.8 ± 1.0	2.0	0.7451
Male non-DM, low-TC patients			(n = 34)		(n = 17)	
	Residual stenosis (%)	78.9 ± 31.2	90.0	98.4 ± 3.2	99.0	*0.0012
	TIMI classification	2.3 ± 1.1	3.0	1.3 ± 1.3	1.0	*0.0040
	Diseased vessels	1.2 ± 0.8	1.0	1.8 ± 0.9	1.5	*0.0444

To investigate the correlation between the Lp (a) level and the degree of residual stenosis, the degree of residual stenosis was compared in three groups, low (Lp (a) < 20 mg/dL), intermediate (20 ≤ Lp (a) < 40 mg/dL), and high (40 ≥ mg/dL) Lp (a) groups, among all patients and male non-DM patients with a low TC level (Figure 1). Among male non-DM patients with a low TC level, the degrees of residual stenosis were 76.9 ± 35.5%, 86.4 ± 23.0%, and 98.3 ± 3.4%, in the low, intermediate, and high Lp(a) groups, respectively, showing a significant difference among the three groups ($P = 0.0264$). Significant differences were also observed between the high and intermediate Lp (a) groups, and between the high and low Lp (a) groups. The residual stenosis was more advanced in the order of the low, intermediate, and high Lp (a) groups.

To investigate the effects of other factors on the degree of residual stenosis, the patients were divided into two groups by age (under 60 years or not), presence of DM, presence of HT, smoking status, levels of Lp (a), levels of TC, and levels

Figure 1. Comparison of residual stenosis with low, intermediate, and high Lp (a) levels.

Table IV. Comparison Between Other Factors

		Mean $\pm$ SD	Median	Mean $\pm$ SD	Median	P value
Age	(years)	Younger < 60	(n = 66)	Older $\geq$ 60	(n = 63)	
	Residual stenosis (%)	89.9 $\pm$ 19.0	99.0	86.5 $\pm$ 25.8	99.0	0.8086
	TIMI classification	2.0 $\pm$ 1.2	2.0	2.1 $\pm$ 1.3	3.0	0.3727
	Diseased vessels	1.6 $\pm$ 0.9	1.0	1.5 $\pm$ 0.9	2.0	0.6610
DM		non-DM	(n = 75)	DM	(n = 54)	
	Residual stenosis (%)	87.1 $\pm$ 25.2	99.0	89.8 $\pm$ 18.3	99.0	0.7118
	TIMI classification	2.0 $\pm$ 1.2	3.0	2.1 $\pm$ 1.2	3.0	0.5451
	Diseased vessels	1.5 $\pm$ 0.9	1.0	1.6 $\pm$ 0.9	2.0	0.2587
HT		non-HT	(n = 71)	HT	(n = 58)	
	Residual stenosis (%)	87.4 $\pm$ 25.3	99.0	89.2 $\pm$ 18.8	99.0	0.5835
	TIMI classification	2.1 $\pm$ 1.2	3.0	1.9 $\pm$ 1.3	3.0	0.4896
	Diseased vessels	1.5 $\pm$ 0.8	1.0	1.6 $\pm$ 1.0	2.0	0.6797
Smoker		non-smoker	(n = 42)	smoker	(n = 86)	
	Residual stenosis (%)	90.6 $\pm$ 20.4	99.0	86.9 $\pm$ 23.6	99.0	0.0745
	TIMI classification	1.7 $\pm$ 1.3	2.0	2.2 $\pm$ 1.2	3.0	*0.0118
	Diseased vessels	1.6 $\pm$ 1.0	2.0	1.5 $\pm$ 0.8	1.0	0.4137
TC		low-TC < 220 mg/dL	(n = 100)	high-TC $\geq$ 220 mg/dL	(n = 29)	
	Residual stenosis (%)	86.6 $\pm$ 25.0	99.0	93.7 $\pm$ 8.6	99.0	0.5777
	TIMI classification	2.1 $\pm$ 1.2	3.0	2.0 $\pm$ 1.2	2.5	0.8071
	Diseased vessels	1.4 $\pm$ 0.9	1.0	1.9 $\pm$ 0.9	2.0	*0.0218
TG		low-TG < 150 mg/dL	(n = 86)	high-TG $\geq$ 150 mg/dL	(n = 42)	
	Residual stenosis (%)	89.2 $\pm$ 20.7	99.0	86.1 $\pm$ 26.3	99.0	0.6810
	TIMI classification	2.0 $\pm$ 1.3	3.0	2.2 $\pm$ 1.1	3.0	0.4985
	Diseased vessels	1.5 $\pm$ 0.9	1.0	1.6 $\pm$ 1.0	2.0	0.4137

of TG (TG < 150 or TG $\geq$ 150 mg/dL). The degree of residual stenosis, TIMI classification, and the number of diseased vessels were compared among these groups (Table IV). Between the low and high TC groups, a significant difference was observed only in the number of diseased vessels ($P = 0.0218$). Between the nonsmoking and smoking groups, the TIMI classification was significantly milder in the smoking groups (1.7 ± 1.3 vs 2.2 ± 1.2 , $P = 0.0118$).

DISCUSSION

Lp (a) has been shown to be an independent risk factor for coronary atherosclerosis by many epidemiological and clinical studies. While Lp(a) atherogenically acts as a lipoprotein, it contains apo(a), which has structural homology to plasminogen, and apo(a) may inhibit fibrinolysis, and Lp(a) has been shown to promote thrombus formation *in vitro*. However, this effect has not been clarified *in vivo*.

In many cases of myocardial infarction, ruptured plaque and thrombi occlude the coronary arteries.¹⁸⁻²⁰ Therefore, Lp (a) may affect recanalization of the infarction-related arteries in a natural course, which is often observed. It may also determine the therapeutic result of thrombolytic therapy.

Moliterno, *et al*¹⁵) analyzed 105 patients with myocardial infarction who could not undergo thrombolytic therapy. They performed coronary angiography ≥ 7 days after a first myocardial infarction and categorized the patients as having a patent infarction-related artery or an occluded infarction-related artery, and compared the two groups. The Lp (a) level was significantly higher in the occluded infarction-related artery group.

In this study, we investigated the influence of elevated Lp (a) in coronary angiography findings obtained during the chronic stage in 129 patients who did not receive reperfusion therapy such as thrombolytic therapy, angioplasty, or bypass surgery in the acute stage. The degree of residual stenosis was significantly higher in the group with high Lp (a) levels. This phenomenon was significant in male non-DM patients with low TC levels.

These results suggest that in acute myocardial infarction, elevated Lp (a) levels inhibit fibrinolysis resulting in a high degree of residual stenosis which consists of thrombus enriched plaque. Therefore, this study supports the prior report of Moliterno, *et al* in which Lp (a) may have inhibited the endogenous fibrinolysis.

In contrast, von Hodenberg, *et al*⁹) analyzed 41 patients with acute myocardial infarction who received thrombolytic therapy and found no significant difference in the patency rate of the infarction-related artery between the high and low Lp (a) groups. In another study, the influence of Lp (a) on the results of throm-

bolytic therapy was evaluated by changes in ST segments in electrocardiography and no significant relationship between the improvement of ST segments and Lp (a) levels was observed.¹⁰⁾ Brugemann, *et al*¹¹⁾ also reported that among 58 patients with acute myocardial infarction who received thrombolytic therapy, there was no significant difference in the Lp (a) level between the patients with a patent coronary artery and those with a nonpatent artery. A possible reason for the absence of a relationship between the effect of thrombolytic therapy and serum Lp (a) levels in these reports, is that diabetes mellitus and hypercholesterolemia, which are more potent risk factors, may have masked the influence of Lp (a). Ioka, *et al*¹²⁾ examined the relation between serum Lp (a) levels and the endothelium-dependent vasoresponse to acetylcholine. They excluded patients with hypercholesterolemia and diabetes mellitus, and concluded that high Lp (a) levels might be a strong predictor of endothelial dysfunction in normocholesterolemic and non-DM patients. The weight of Lp (a) as a risk factor for atherosclerosis changes depending on age, sex, and the presence of diabetes.²²⁾ To investigate the influence of elevated Lp (a) on the effect of thrombolytic therapy, it is necessary to stratify the patients by gender, the presence or absence of diabetes, and hyperlipidemia like Ioka, *et al* did in their study.

In a comparison between smokers and nonsmokers, the TIMI classification was milder in the smokers, and a result similar to this finding has been obtained in several studies.²³⁻²⁵⁾ Grines, *et al*²³⁾ investigated the influence of smoking on thrombolytic therapy for myocardial infarction and showed that the degree of stenosis of the infarction-related artery was lower in smokers than nonsmokers during the acute and chronic stages. They considered that since the coagulation system is promoted and thrombotic obliteration accounts for a greater part of the obliteration mechanism in smokers, the degree of residual stenosis after thrombolytic therapy is milder than that in nonsmokers. Similar events may occur in patients who did not receive thrombolytic therapy during the acute stage.

This study revealed that the degree of residual stenosis of coronary arteries after myocardial infarction was more severe in the elevated Lp (a) group. The results suggest that elevated Lp (a) levels may inhibit fibrinolysis in the natural course of myocardial infarction. However, the degree of residual stenosis is determined not only by fibrinolysis but also by the severity of the underlying atherosclerosis. Therefore, the measurement of markers of coagulation and the fibrinolysis system and the estimation of culprit lesions by fiberoptic may be useful for clarifying the role of Lp (a) in myocardial infarction. Lp (a) is different from other risk factors because it may inhibit the fibrinolysis system. From a clinical point of view, residual stenosis is one of the important factors which determines the size of a myocardial infarction. Lp (a) may affect the size and prognosis

of a myocardial infarction. Further investigations including cardiac function and prognosis are also necessary.

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