Original Article

Elevated Lipoprotein(a) has Incremental Prognostic Value in Type 2 Diabetic Patients with Symptomatic Coronary Artery Disease

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***Aim*: In addition to type 2 diabetes, an elevated Lp(a) level is known to be a surrogate biomarker of cardiovascular disease. However, recent studies have demonstrated that the Lp(a) levels are lower in type 2 diabetic patients than in non-diabetic subjects. Therefore, we sought to evaluate the prognostic value of elevated lipoprotein(a) [Lp(a)] in type 2 diabetic patients with symptomatic coronary artery disease (CAD).**

***Methods*: A total of 1494 diabetic patients with CAD (62.3% men, mean age: 63.5 ± 10.3 years) were enrolled. CAD was diagnosed using invasive coronary angiography, and laboratory values for lipid parameters, including Lp(a), were obtained on the day of coronary angiography. The patients were divided into tertile groups according to the individual Lp(a) level. The baseline characteristics, coronary angiographic findings, duration of follow-up and major adverse cardiovascular events (MACEs) were recorded.**

***Results*: Over a mean follow-up period of 4.4 ± 2.6 years, there were 59 MACEs (35 cardiac deaths and 24 cases of non-fatal myocardial infarction), for an event rate of 3.9%. A survival probability plot according to the Lp(a) tertile revealed that an elevated Lp(a) level was associated with a worse prognosis ($p=0.008$), after adjusting for age, gender, hypertension, hyperlipidemia, smoking and the extent of CAD. Furthermore, the addition of an elevated Lp(a) level to the reference model improved the integrated discrimination improvement (0.0216, $p<0.001$), continuous net reclassification improvement (NRI) (0.5721, $p=0.012$) and NRI (0.1549, $p=0.004$) values.**

***Conclusions*: In terms of the prognosis, elevated Lp(a) is associated with worse outcomes in type 2 diabetic patients with symptomatic CAD. Furthermore, an elevated Lp(a) level has incremental prognostic value in type 2 diabetic patients with symptomatic CAD.**

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Key words: Lipoprotein(a), Diabetes, Coronary artery disease, Prognosis, Adverse cardiac events

Introduction

Patients with type 2 diabetes present with a metabolic profile different from that of the general population and exhibit a risk of cardiovascular events two- to four-fold higher than non-diabetic patients[1, 2]. In addition to type 2 diabetes, an elevated lipoprotein(a) [Lp(a)] level has been recognized to be a cardiovascu-

lar risk factor in the general population[3, 4]. Furthermore, a recent meta-analysis of 36 prospective studies provided support for the probable causal role of an elevated Lp(a) level in the development of cardiovascular disease in the general population[5]. Although a cross-sectional study reported that type 2 diabetic patients with coronary heart disease have higher Lp(a) levels than those without coronary heart disease, it remains unclear whether an elevated Lp(a) level causally affects cardiovascular risks in type 2 diabetic patients[6]. Additionally, a recent study demonstrated that the Lp(a) levels are lower in type 2 diabetic patients than in non-diabetic subjects, further complicating the association between Lp(a) and cardiovascular risks in this group[7]. Therefore, we sought to evaluate the prognostic value of elevated Lp(a) in type 2 diabetic patients with symptomatic coronary artery disease (CAD).

Materials and Methods

Study Design and Patient Selection

A total of 1,494 diabetic patients with symptomatic CAD (62.3% men, mean age: 63.5 ± 10.3 years) were enrolled from 2000 to 2010 at Gangnam Severance Hospital (Seoul, Korea). CAD was diagnosed using invasive coronary angiography, and laboratory values for lipid parameters, including the Lp(a) level, were obtained on the day of coronary angiography, with the analyses performed shortly after sampling. Baseline risk factors, coronary angiographic findings, length of follow-up and major adverse cardiovascular events (MACEs), including cardiac death and non-fatal myocardial infarction (MI), were recorded. Institutional review committee approval and informed consent was obtained.

Definition of Variables

Risk factors were recorded as categorical variables in all patients. Hypertension was defined as a systolic blood pressure of ≥ 140 mmHg and/or diastolic blood pressure of ≥ 90 mmHg or use of antihypertensive agents. Type 2 diabetes was defined as the use of hypoglycemic agents or insulin, a fasting plasma glucose level of ≥ 126 mg/dl, glycosylated hemoglobin (HbA1c) level of ≥ 6.5% or known but untreated hyperglycemia. The homeostasis model assessment insulin resistance index (HOMA-IR) was calculated as follows:

[fasting insulin (μIU/mL) × fasting plasma glucose (mmol/L)] / 22.5

A patient was considered to be a smoker, if he/she currently smoked or had smoked up until one month prior to the baseline coronary angiography examinations. Non-obstructive CAD was defined as < 50% luminal narrowing, whereas obstructive CAD was defined as ≥ 50% luminal narrowing. The extent of obstructive CAD was categorized based on the number of vessels involved (1, 2 or 3).

Measurement of Lipid Parameters, Including Lp(a)

The total cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride and low-density lipoprotein (LDL) cholesterol levels were measured directly with colorimetric and turbidimetric assays using an autoanalyzer (Beckman Coulter AU5800). Hyperlipidemia was defined as a total cholesterol level of ≥ 240 mg/dl, LDL cholesterol level of ≥ 130 mg/dl, HDL cholesterol level of < 40 mg/dl, triglyceride level of ≥ 200 mg/dl and/or the use of lipid-lowering medications. Lp(a) measurement was performed according to the latex agglutination method with an anti-human Lp(a) monoclonal antibody using a commercial kit [Lp(a) Latex Daiichi] obtained from Daiichi Pure Chemicals Co., Ltd. with an autoanalyzer (Hitachi 7600-110) that is not affected by Apo(a) isoform variation. The patients were divided into three groups according to the respective Lp(a) concentration: 1) T1: lower tertile group [Lp(a) median value: 4.7 mg/dl (range: 0-8.5)], 2) T2: middle tertile group [Lp(a) median value: 13.5 mg/dl (range: 8.6-20.7)] and 3) T3: upper tertile group [Lp(a) median value: 38.8 mg/dl (range: 20.8-218.0)].

Endpoint Determination and Follow-Up Data Acquisition

MACE was defined as cardiac death or non-fatal MI. In order to avoid treatment bias, coronary artery revascularization procedures, such as coronary artery bypass graft surgery (CABG) and percutaneous coronary intervention, were not regarded as endpoints[8]. In patients with multiple cardiovascular events, only the first event was considered for the analysis. Cardiac death was defined as death due to acute MI, ventricular arrhythmia, refractory heart failure or cardiogenic shock. The diagnosis of non-fatal MI required the presence of at least two of the three following criteria: characteristic chest pain, elevated cardiac enzymes or electrocardiographic alterations indicative of MI. Patient follow-up data were collected using an elec-

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tronic medical record review and/or standardized telephone interviews.

Statistical Analysis

Continuous data were expressed as the mean ± standard deviation. In cases of skewed data, median values with interquartile ranges were used. All categorical data are presented as a percentage or absolute number. Analyses of variance (ANOVA) and the χ^2 test were used to assess differences between three groups. The Cochran-Mantel-Haenszel test was used to analyze the correlation between the Lp(a) level and extent of CAD. Cumulative event rates as a function of time were estimated according to the Kaplan-Meier method, and survival curves for MACE were compared using the log-rank test. Univariate and multivariate Cox regression analyses were performed to identify associations between the clinical characteristics (age, gender, hypertension, smoking and hyperlipidemia), lipid parameters, Lp(a), extent of CAD and clinical outcomes. Hazard ratios (HRs) were calculated as an estimate of the risk associated with a particular variable with 95% confidence intervals (CIs) based on binomial distributions. In order to evaluate the incremental value of Lp(a) in predicting MACE, two models were constructed: 1) Model I: reference model including age, gender, hypertension, smoking, hyperlipidemia and extent of CAD; and 2) Model II: all of the variables for Model I with the addition of Lp(a). In order to discriminate whether an elevated Lp(a) level has incremental prognostic value for the prediction of MACE, the likelihood ratio, C-statistics, integrated discrimination improvement (IDI) and net reclassification improvement (NRI) were compared between the two models[9, 10]. All analyses were performed using the SPSS version 15.0 (SPSS, Chicago, IL, USA) and SAS version 9.1.3 (SAS, Cary, NC, USA) software programs. A p-value of less than 0.05 was considered to be statistically significant.

Results

Of the total 1,494 patients in the study, 62.3% were men, and the mean age was 63.5 ± 10.3 years. The median Lp(a) level for the overall population was 13.5 mg/dl (interquartile range: 6.7, 26.3), while that for the T1, T2, and T3 groups was 4.7, 13.5 and 38.8 mg/dl, respectively. The baseline, laboratory and angiographic characteristics of the study population according to the Lp(a) tertile groups are summarized in **Table 1**. The patients with elevated Lp(a) levels tended to be older ($p<0.0001$), female ($p=0.004$) and non-smokers ($p=0.002$) (**Table 1**). More patients with an elevated Lp(a) level had acute coronary syndrome as a clinical presentation ($p=0.014$) (**Table 1**), and an elevated Lp(a) level was found to be associated with higher rates of both obstructive CAD ($p<0.0001$) and three-vessel obstructive CAD ($p<0.0001$) at the time of baseline coronary angiography (**Table 1**). Consequently, the rates of coronary revascularization and CABG were higher in the patients with an elevated Lp(a) level (**Table 1**). The total ($p=0.001$) and LDL ($p<0.0001$) cholesterol levels were higher in the group with an elevated Lp(a) level, whereas the triglyceride levels ($p=0.012$) were higher in the group with a normal Lp(a) level (**Table 1**). In contrast, the HOMA-IR as well as the plasma glucose, serum insulin and HbA1c levels showed no significant differences between the three groups (**Table 1**). Meanwhile, the patients with an elevated Lp(a) level had a higher frequency of treatment with cardiac and antidiabetic medications, such as clopidogrel, vasodilators, diuretics and biguanide (**Table 1**), and a Cochran-Mantel-Haenszel trend analysis comparing the Lp(a) tertile and extent of CAD revealed that the Lp(a) concentration displayed trend toward a positive association with the extent of CAD ($p<0.0001$) (**Table 2**).

Over a mean follow-up period of 4.4 ± 2.6 years, there were 59 MACEs (35 cardiac deaths and 24 cases of non-fatal MI), with an event rate of 3.9%. The respective MACE rates for the T1, T2 and T3 groups were 1.8% (9/499), 3.2% (16/497) and 6.8% (34/498), respectively. According to the multivariate Cox proportional survival analysis, age (HR 1.064, 95% CI 1.033-1.095, $p<0.0001$), a male gender (HR 1.889, 95% CI 1.052-3.394, $p=0.033$) and the extent of CAD ($p<0.0001$) were independent risk factors for MACE (**Table 3**). Furthermore, the T3 group demonstrated an almost 3-fold higher risk of MACE compared to the T1 group (HR 2.890, 95% CI 1.373-6.084, $p=0.005$) (**Table 3**). In addition, the survival probability plot according to the Lp(a) tertile revealed that an elevated Lp(a) level is associated with a worse prognosis ($p=0.008$) after adjusting for age, gender, hypertension, hyperlipidemia, smoking and the extent of CAD (**Fig. 1**).

In order to evaluate whether an elevated Lp(a) level has incremental prognostic value for MACE, statistical analyses, including assessments of the likelihood ratio, C-statistics, IDI, continuous NRI and NRI, were performed between model I (reference model consisting of age, gender, hypertension, smoking, hyperlipidemia and extent of CAD) and model II (model I with the addition of Lp(a)) (**Table 4**). The respective likelihood ratios were 730.511 and 741.112 for models I and II, respectively, with a statistically

Table 1. Baseline, laboratory and angiographic characteristics according to the Lp(a) tertile (n=1,494)

	Lp(a) tertiles (mg/dl)			
	T1	T2	T3	*p*-value
Median (range)	4.7 (0-8.5)	13.5 (8.6-20.7)	38.8 (20.8-218.0)	
Number of patients	(n=499)	(n=497)	(n=498)	
Age (years)	62.0±10.7	63.9±9.7	64.7±10.2	<0.0001
Male gender, *n* (%)	336/499 (67.3%)	310/497 (62.4%)	285/498 (57.2%)	0.004
Hypertension, *n* (%)	368/499 (73.7%)	358/497 (72.0%)	377/498 (75.7%)	0.420
Smoking, *n* (%)	195/499 (39.1%)	150/497 (30.2%)	149/498 (29.9%)	0.002
Hyperlipidemia, *n* (%)	307/499 (61.5%)	312/497 (62.8%)	339/498 (68.1%)	0.073
Clinical diagnosis				0.014
Silent IHD, *n* (%)	103/499 (20.6%)	102/497 (20.5%)	106/498 (21.3%)	
Stable angina, *n* (%)	245/499 (49.1%)	219/497 (44.1%)	186/498 (37.3%)	
Unstable angina, *n* (%)	111/499 (22.2%)	130/497 (26.2%)	146/498 (29.3%)	
NSTEMI, *n* (%)	25/499 (5.0%)	30/497 (6.0%)	32/498 (6.4%)	
STEMI, *n* (%)	15/499 (3.0%)	16/497 (3.2%)	28/498 (5.6%)	
Obstructive CAD, *n* (%)	349/499 (69.9%)	389/497 (78.3%)	435/498 (87.3%)	<0.0001
Extent of CAD				<0.0001
Non-obstructive CAD	150/499 (30.1%)	108/497 (21.7%)	63/498 (12.7%)	
1VD, *n* (%)	104/499 (20.8%)	97/497 (19.5%)	94/498 (18.9%)	
2VD, *n* (%)	112/499 (22.4%)	116/497 (23.3%)	124/498 (24.9%)	
3VD, *n* (%)	133/499 (26.7%)	176/497 (35.4%)	217/498 (43.6%)	
Revascularization, *n* (%)	256/499 (51.3%)	297/497 (59.8%)	333/498 (66.9%)	<0.0001
BMS, *n* (%)	59/499 (11.8%)	95/498 (19.1%)	91/498 (18.3%)	
DES, *n* (%)	157/499 (31.5%)	141/497 (28.4%)	169/498 (33.9%)	
CABG, *n* (%)	40/499 (8.0%)	61/497 (12.3%)	73/498 (14.7%)	
Lp(a) (mg/dl)	4.8±2.2	13.9±3.5	50.9±34.3	<0.0001
Total cholesterol (mg/dl)	159.7±36.4	163.3±37.6	168.6±40.5	0.001
Triglycerides (mg/dl)	158.8±112.8	143.8±81.7	143.3±83.3	0.012
LDL cholesterol (mg/dl)	94.7±30.0	97.7±31.1	104.5±34.0	<0.0001
HDL cholesterol (mg/dl)	41.8±11.5	42.1±10.9	41.7±11.4	0.843
HbA1c (%)	7.58±1.42	7.62±1.49	7.68±1.50	0.599
Glucose (mmol/L)	7.28±2.30	7.32±2.73	7.48±2.89	0.446
Insulin (μIU/mL)	11.5±16.0	11.0±10.8	12.1±16.2	0.499
HOMA-IR	3.8±5.6	3.6±3.9	4.3±6.7	0.125
Cardiac medications				
Aspirin	465/499 (93.2%)	465/497 (93.6%)	470/497 (94.6%)	0.648
Clopidogrel	309/499 (61.9%)	333/497 (67.0%)	350/497 (70.4%)	0.017
Oral anticoagulants	32/499 (6.4%)	23/497 (4.6%)	21/497 (4.2%)	0.247
Vasodilator	273/499 (54.7%)	313/497 (63.0%)	334/497 (67.2%)	<0.0001
β -blocker	261/499 (52.3%)	298/497 (60.0%)	280/497 (56.3%)	0.051
ACE inhibitor	152/499 (30.5%)	166/497 (33.4%)	170/497 (34.2%)	0.415
ARB	279/499 (55.9%)	267/497 (53.7%)	285/497 (57.3%)	0.512
CCB	234/499 (46.9%)	231/497 (46.5%)	223/497 (44.9%)	0.795
Diuretics	109/499 (21.8%)	119/497 (23.9%)	142/497 (28.6%)	0.042
α-blocker	23/499 (4.6%)	22/497 (4.4%)	31/497 (6.2%)	0.360
Antidiabetic medications				
α-glucosidase inhibitor	56/499 (11.2%)	69/497 (13.9%)	85/497 (17.1%)	0.028
Biguanide	258/499 (51.7%)	224/497 (45.1%)	198/497 (39.8%)	0.001
Sulfonylurea/Glinide	279/499 (55.9%)	256/497 (51.5%)	270/497 (54.3%)	0.369
Thiazolidinedione	78/499 (15.6%)	77/497 (15.5%)	70/497 (14.1%)	0.752
DPP-4 inhibitor	14/499 (2.8%)	11/497 (2.2%)	4/497 (0.8%)	0.063
Insulin therapy	53/499 (10.6%)	74/497 (14.9%)	75/497 (15.1%)	0.066

The data are expressed as numbers (%) or the mean±standard deviation.

Abbreviations. ACE=angiotensin converting enzyme; ARB=angiotensin Ⅱ receptor blocker; CAD=coronary artery disease; CCB=calcium channel blocker; DPP-4=dipeptidyl peptidase-4; HDL=high-density lipoprotein; HOMA-IR=homeostasis model assessment insulin resistance index; IHD=ischemic heart disease; LDL=low-density lipoprotein; Lp(a)=lipoprotein(a); NSTEMI=non-ST elevation myocardial infarction; STEMI=ST elevation myocardial infarction; T1=lower tertile; T2=middle tertile; T3=upper tertile; VD=vessel disease

Table 2. Trend analysis between the Lp(a) level and extent of CAD

	Lp(a) tertiles			*p*-value
	T1	T2	T3	
Non-obstructive CAD	150/499 (30.1%)	108/497 (21.7%)	63/498 (12.7%)	<0.0001
1VD, *n* (%)	104/499 (20.8%)	97/497 (19.5%)	94/498 (18.9%)	
2VD, *n* (%)	112/499 (22.4%)	116/497 (23.3%)	124/498 (24.9%)	
3VD, *n* (%)	133/499 (26.7%)	176/497 (35.4%)	217/498 (43.6%)	

The data are expressed as numbers (%).
Abbreviations. CAD = coronary artery disease; Lp(a) = lipoprotein(a); T1 = lower tertile; T2 = middle tertile; T3 = upper tertile; VD = vessel disease

Table 3. Univariate and multivariate Cox regression analysis for predicting MACE (non-fatal MI and cardiac death)

	Univariate			Multivariate		
	HR	95%CI	*p*-value	HR	95%CI	*p*-value
Age	1.068	1.038-1.100	<0.0001	1.064	1.033-1.095	<0.0001
Male gender	1.688	0.951-2.998	0.074	1.889	1.052-3.394	0.033
Hypertension	1.324	0.715-2.451	0.372			
Smoking	0.883	0.511-1.525	0.655			
Hyperlipidemia	0.883	0.521-1.497	0.644			
Obstructive CAD	3.322	1.203-9.177	0.021			
Extent of CAD			<0.0001			<0.0001
1VD	0.733	0.164-3.276	0.684	0.534	0.119-2.401	0.413
2VD	1.191	0.336-4.223	0.787	0.847	0.237-3.022	0.798
3VD	6.223	2.237-17.306	<0.0001	3.541	1.246-10.065	0.018
Lp(a)			<0.0001			0.008
T2	1.849	0.817-4.186	0.140	1.542	0.679-3.503	0.300
T3	3.869	1.855-8.067	<0.0001	2.890	1.373-6.084	0.005
Revascularization	0.908	0.537-1.535	0.718			

Abbreviations. CAD = coronary artery disease; CI = confidence interval; HR = hazard ratio; Lp(a) = lipoprotein(a); MACE = major adverse cardiac event; MI = myocardial infarction; T2 = middle tertile; T3 = upper tertile; VD = vessel disease

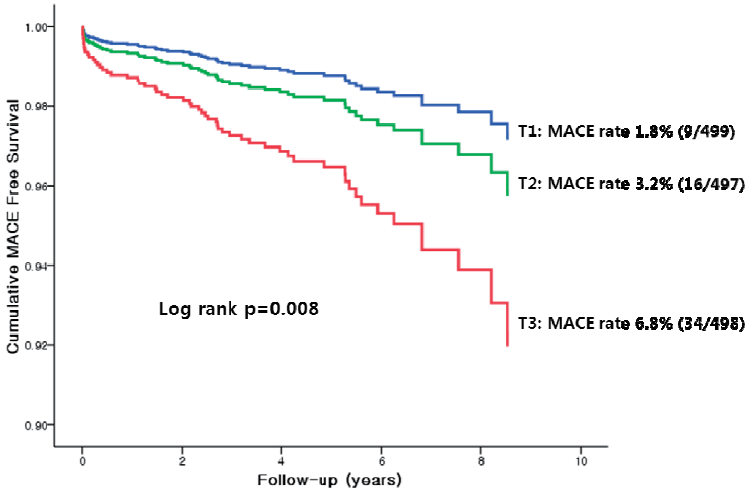

Fig. 1. Survival probability plots according to the Lp(a) tertile after adjusting for age, gender, hypertension, smoking, hyperlipidemia and the extent of CAD

Abbrevviations. Lp(a) = lipoprotein(a); MACE = major adverse cardiac event; T1 = lower tertile; T2 = middle tertile; T3 = upper tertile

Table 4. Incremental prognostic value of Lp(a) for predicting MACE

	Model Ⅰ	Model Ⅱ	Difference	*p*-value
Likelihood ratio	730.531	741.112	10.581	0.005
C-statistics	0.7817 (0.7153-0.8481)	0.7926 (0.7288-0.8564)	0.0108 (−0.0144-0.0362)	0.400
Relative IDI	0.0216 (0.008-0.0409)		-	<0.001
Continuous NRI	0.5721 (0.0867-0.9565)		-	0.012
NRI	0.1549 (0.0241-0.3514)		-	0.004

95% confidence intervals are in parentheses.
Model Ⅰ: age, gender, hypertension, smoking, hyperlipidemia and extent of CAD; Model Ⅱ: Model Ⅰ + Lp(a)
Abbreviations. IDI = integrated discrimination improvement; Lp(a) = lipoprotein(a); MACE = major adverse cardiac event; NRI = net reclassification improvement

significant difference of 10.581 between the two models ($p=0.005$). The respective C-statistics were 0.7817 and 0.7926 for models Ⅰ and Ⅱ, respectively, for a difference of 0.0108 between the two models, without statistical significance ($p=0.400$). However, an elevated Lp(a) level was found to have incremental prognostic value for predicting MACE in terms of the IDI (2.16% improvement, $p<0.001$), continuous NRI (57.21% improvement, $p=0.012$) and NRI (15.49% improvement, $p=0.004$), when comparing the two models (**Table 4**).

Discussion

We evaluated the prognostic value of an elevated Lp(a) level in type 2 diabetic patients with symptomatic CAD. The principal findings in this study are that: 1) the Lp(a) level exhibits a positive correlation with the extent as well as presence of obstructive CAD in type 2 diabetic patients; 2) an elevated Lp(a) level is an independent risk factor for MACE in type 2 diabetic patients with symptomatic CAD; 3) an elevated Lp(a) level is associated with a worse prognosis in type 2 diabetic patients with symptomatic CAD; and 4) an elevated Lp(a) level has incremental prognostic value for MACE in type 2 diabetic patients with symptomatic CAD. Taken together, our findings revealed the value of an elevated Lp(a) level in type 2 diabetic patients with symptomatic CAD.

Patients with type 2 diabetes present with a metabolic profile different from that of the general population and display a cardiovascular risk two- to four-fold higher than non-diabetic individuals[1, 2]. In addition, an elevated Lp(a) level is considered to have a continuous, independent and modest association with the development of cardiovascular diseases in the general population[5]. Both of these cardiovascular risk factors (type 2 diabetes and Lp(a)) are crucial parameters that should be assessed when managing patients at risk for the development of cardiovascular disease. Intriguingly, Mora et al. demonstrated that the Lp(a) level is independently and inversely associated with the risk of type 2 diabetes[7]. As that study consisted of the cohorts from the Women's Health Study and Copenhagen City Heart Study, for a total of 36,398 patients, it is now generally accepted that the Lp(a) levels are lower in type 2 diabetic patients than in non-diabetic patients[11, 12]. However, this finding does not signify that an elevated Lp(a) level is not attributable to cardiovascular disease in type 2 diabetic patients.

Previous studies have reported that the serum insulin level has a negative association with the Lp(a) level[13, 14]. Moreover, another study revealed that the Lp(a) level is inversely related to metabolic syndrome and its components, suggesting that the insulin level and insulin sensitivity are factors disturbing the assessment of Lp(a)[15]. In the current study, biguanides were less frequently used in the elevated Lp(a) group, which may have influenced the insulin sensitivity in type 2 diabetic patients. However, there were no significant statistical differences in the HbA1c, plasma glucose, serum insulin or HOMA-IR levels between the three groups.

Several studies have highlighted the impact of an elevated Lp(a) level in type 2 diabetic patients with or without CAD[16, 17]. One study reported that type 2 diabetic patients with CAD have higher Lp(a) levels than both type 2 diabetic patients without CAD and control subjects (non-diabetic patients without CAD)[16]. Another study reported that type 2 diabetic patients with CAD have lower Lp(a) levels than non-diabetic patients with CAD[17]. However, that study also revealed that type 2 diabetic patients with CAD have higher Lp(a) levels than type 2 diabetic patients without CAD[17]. Cross-sectional studies have previously reported that type 2 diabetic patients with coronary heart disease have higher Lp(a) levels than those without coronary heart disease[6, 18, 19]. In addition, several studies have reported a positive association between an elevated Lp(a) level and CAD among type

2 diabetic patients[16, 20, 21]. In accordance with these studies, our findings demonstrated that an elevated Lp(a) level has a positive correlation with the extent as well as presence of obstructive CAD in type 2 diabetic patients.

The prognostic value of elevated Lp(a) in type 2 diabetic patients remains a subject under dispute. Previous studies in general populations have documented that an elevated Lp(a) level is associated with a worse prognosis[5, 11]. Additionally, subgroup analyses of the type 2 diabetic cohorts in these same studies showed that an elevated Lp(a) level is associated with a worse outcome[5, 11]. Studies of type 2 diabetic patients have also demonstrated that an elevated Lp(a) level is a risk factor for cardiovascular disease[22, 23]. In contrast, several studies have suggested that an elevated Lp(a) has no association with the development of cardiovascular disease in type 2 diabetic patients[24-26]. In the context of these conflicting findings, we evaluated the prognostic value of an elevated Lp(a) level in type 2 diabetic patients with symptomatic CAD. In the current study, we found an elevated Lp(a) level to be associated with a worse outcome in type 2 diabetic patients with symptomatic CAD, even after adjusting for other confounding risk factors. We believe that our data support the clinical value of an elevated Lp(a) level in type 2 diabetic patients.

The inconsistent results regarding the prognostic value of elevated Lp(a) in type 2 diabetic patients may be due to differences in the follow-up period, study cohort size, characteristics of the study cohort (age, gender, ethnicity), duration of type 2 diabetes and Lp(a) assay method, as mentioned by Qi *et al.*[24]. Therefore, a larger cohort-based prospective study is warranted to clarify the prognostic value of an elevated Lp(a) level in type 2 diabetic patients.

Although several of the aforementioned studies have revealed that an elevated Lp(a) level is associated with worse cardiovascular outcomes, none have discriminated the incremental prognostic value of elevated Lp(a) in terms of the prognosis[5, 11, 22, 23]. To our knowledge, this is the first study to demonstrate the incremental prognostic value of an elevated Lp(a) level in type 2 diabetic patients with symptomatic CAD. Our findings suggest that an elevated Lp(a) level may contribute to an increased risk of cardiovascular disease in type 2 diabetic patients and that the Lp(a) level is an important clinical consideration, not only in the general population, but also patients with type 2 diabetes.

There are several limitations associated with the present study. First, this was an observational study. Second, the study was performed at a single center in Korea and consisted only of Korean patients. Since the Lp(a) levels vary according to race and ethnicity, it is uncertain whether our results are equally applicable in general clinical practice.

In conclusion, an elevated Lp(a) level is associated with worse outcomes in type 2 diabetic patients with symptomatic CAD, and an elevated Lp(a) level has incremental prognostic value in this patient population.

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Conflicts of Interest

None.

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