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Original Research

Impact of lipoprotein(a) on long-term outcomes after percutaneous coronary intervention in patients with reduced low-density lipoprotein cholesterol

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The purpose of this study is to investigate the effect of lipoprotein(a) level on long-range prognosis after Percutaneous Coronary Intervention (PCI) in patients with low-density lipoprotein cholesterol (LDL-C) goal attainment. In this retrospective study, 350 patients in Coronary artery disease (CAD) with LDL-C less than 1.8 mmol/L were enrolled in the Guangdong Institute of Cardiovascular Diseases from January 2011 to December 2013. Follow-up was 1 year after PCI. According to the median value of the study population based on Lp(a), the patients were assigned to the high-level group and low-level group. The clinical data of the 2 groups were collected. We compared the baseline data between the 2 groups and the incidence rate of major cardiovascular events. After statistical analysis, the gender composition, hypertension, diabetes, and age of the patients between the 2 groups were similar, and the distinction was not significant. There was no significant distinction in cardio-vascular death, ischemic stroke, and recurrent myocardial infarction between the 2 groups, but the incidence of revascularization was higher in the high-level group ($P < 0.05$). High Lp(a) level predicts an increased incidence of revascularization of patients in CAD with LDL-C less than 1.8 mmol/L after PCI.

Keywords

Lipoprotein(a); coronary artery disease; intervention

1. Introduction

Coronary artery disease (CAD) is one of the most general causes of death in the world. More than seven million people die per year from CAD, constituting 12.8% of all deaths (Maharjan et al., 2015). Dyslipidemia is a major reason for the development of CAD and low-density lipoprotein cholesterol (LDL-C) is a risk factor that should be well controlled for reducing the incidences of CAD. Previous guidelines recommend patients with CAD reduce LDL-C to < 1.8mmol/L or at least 50% reduction where the baseline LDL-C level is 1.8-3.5 mmol/L (Grundy et al., 2019). However, the new 2019 European guidelines on dyslipidemia suggest that the new therapeutic targets of LDL-C are 1.4mmol/L in patients at very high cardiovascular risk (Mach et al., 2020). There remain substantial residual risks in some patients after lipid-lowering therapy with LDL-C. The residual risks may relate to other risk factors such as low high-density lipoprotein cholesterol (HDL-C) level and high triglyceride (TG) level (Ling et al., 2017). Lipoprotein (a) (LP(a)) is a CAD risk factor that is not routinely screened due to the absence of medical treatment. Studies have shown the close relationship between Lp(a) and CAD incidence (Cao et al., 2017; Hohenstein et al., 2017; Tato et al., 1993). Elevated Lp(a) levels in diabetic patients after percutaneous coronary intervention (PCI) was observed to be increased in major cardiovascular events (Konishi et al., 2016a). Furthermore, Gragnano et al. (2019) confirmed Lp(a) was an independent risk factor for major cardiovascular endpoints in both the overall population and STEMI patients (Gragnano et al., 2019). However, some studies failed to prove the correlation between Lp(a) and the occurrence of recurrent cardiovascular events such as research of the dal-outcomes clinical trial (Schwartz et al., 2018). In patients after PCI with LDL-C <1.8mmol/L, whether elevated Lp(a) contributes to an increase in the annual occurrence rate of major cardiovascular events remains unclear. Therefore, we discussed the effect of Lp(a) on long-range prognosis after PCI in patients with LDL-C goal attainment.

2. Methods

2.1 Data collection

The data analyzed was from a single-center observational study, that included 2892 patients who had undergone PCI according to the outcome of coronary angiography and intravascular ultrasound (IVUS), at Guangdong Cardiovascular Diseases Institute from January 2011 to December 2012. Demographic data (age and gender) and risk factors (smoking, hypertension, diabetes mellitus) were all collected from medical records. The patients had clear indications for coronary angiography and were treated with drug-eluting stent (DES) implantation during hospitalization. We utilized the previous standard of preoperative LDL-C < 1.8 mmol/L in this study because of the limitation of sample size. The exclusion criteria included as below: (1) incomplete medical records, (2) malignant tumors, (3) severe infections and/or anemia,

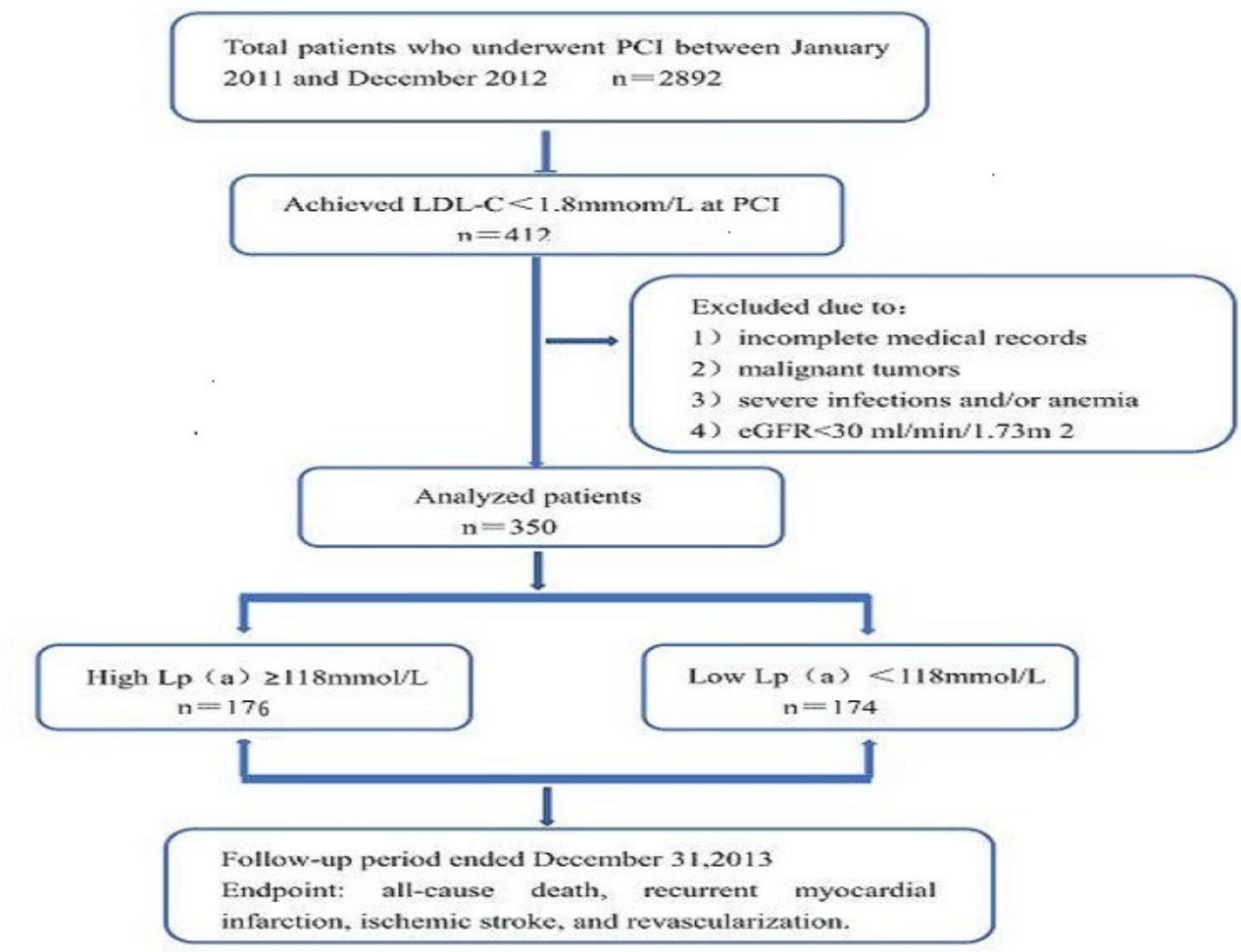

Figure 1. The study flow chart. The inclusion and exclusion criteria, grouping and primary clinical endpoints of the study population were provided. Abbreviation: Lp(a): Lipoprotein(a), PCI: Percutaneous Coronary Intervention, LDL-C: low-density lipoprotein cholesterol, GFR: estimated glomerular filtration rate.

(4) kidney dysfunction defined as estimated glomerular filtration rate <30 ml/min/1.73m^2. 350 patients without taking eicosapentaenoic acid, undergone PCI by radial access were selected, and all of them were ACS. The average age was 63.49 ± 10.85 years, and 281 (80.3%) were male.

Hypertension and diabetes patients were 204 (58.3%) and 103 (29.4%), respectively, while 39.4% of patients were daily smokers. The patients were assigned to the high-level group and low-level group according to the Lp(a) median (118.0 mmol/L). (Fig. 1)

2.2 Coronary angiography results and biochemical indicators

Diagnostic criteria for coronary artery stenosis were performed using the diameter method. Positive when the degree of stenosis is greater than 50% based on the number of vessel stenosis and CAD included 1 vascular lesion, 2 vascular lesions, 3 vascular lesions, and left the main lesion. After an overnight fast, we collected routine blood samples, glycosylated hemoglobin, liver, and kidney function and other biochemical indicators during the early morning. Lp(a) concentration was measured using Enzyme-linked immunosorbent assay (ELISA).

2.3 Primary endpoint

Follow-up was 1 year after PCI. During this period, patients were treated based upon the clinical guidelines and the patient's actual condition such as dual antiplatelet and statin therapy. The primary follow-up clinical endpoints of this study included in-stent restenosis, revascularization, recurrent myocardial infarction, stroke, and cardio-vascular death. In this study, the recurrent myocardial infarction consists of the disease caused by the in-stent restenosis, other parts of the same vessel, or different vessel stenosis. Revascularization means target lesion revascularization (TLR) for the in-stent restenosis or new lesion according to the outcome of coronary angiography and IVUS.

2.4 Statistical analysis

All the data were statistically analyzed by the statistical software SPSS version 21.0. Quantitative data and categorical variables were respectively expressed as Mean ± SD and frequencies. The Kolmogorov-Smirnov test was used to evaluate whether continuous variables were of normal distribution. Continuous variables were compared across groups using the unpaired t-test if the normal distribution was satisfied, and using the non-parametric tests if not. The chi-square test or Fisher's exact probability test

Table 1. Comparison of the Baseline Characteristics among Patients

Variable	Low-Lp(a) (< 118 mmol/L) n = 174	High-Lp(a) (≥ 118 mmol/L) n = 176	P value
Male	144 (82.8%)	138 (78.4%)	0.304
Current smoker*	79 (45.2%)	59 (33.5%)	0.023
Hypertension	100 (57.5%)	104 (59.4%)	0.758
Diabetes mellitus	49 (28.2%)	54 (30.7%)	0.604
Acute myocardial infarction	25 (14.4%)	36 (20.4%)	0.133
Statin	157 (90.2%)	168 (95.5%)	0.059
ACEI/ARB	142 (81.6%)	152 (86.4%)	0.225
BETA	150 (86.2%	151 (85.8%)	0.911
Aspirin	174 (100%)	176 (100%)	-
Clopidogrel	174 (100%)	176 (100%)	-
Left main disease*	21 (12.1%)	36 (20.45%)	0.033
Three vessel lesions	42 (24.1%)	51 (29.0%)	0.305

* the difference was statistically significant.

Abbreviation: ACEI/ARBP: Angiotensin Converting Enzyme Inhibitors/ Angiotensin Receptor Blockers; BETA: beta blocker

Table 2. Comparison of baseline counting data among Patients

Variable	Low-Lp(a) (< 118 mmol/L) n = 174	High-Lp(a) (≥ 118 mmol/L) n = 176	P value
Age (yrs) (mean ± SD)	63.35 ± 10.67	63.63 ± 11.00	0.809
SBP	126.51 ± 17.74	130.03 ± 18.12	0.07
DBP	76.32 ± 11.04	74.50 ± 11.01	0.127
HR	71.88 ± 10.96	72.16 ± 11.73	0.824
creatinine	84.85 ± 21.70	87.32 ± 23.62	0.31
albumin*	36.52 ± 4.71	35.49 ± 4.69	0.045
CHO	3.24 ± 0.87	3.19 ± 0.71	0.573
TG#	(0.17, 1.82)	(0.80, 1.43)	0.063
HDLC	0.92 ± 0.37	0.87 ± 0.25	0.09
LDLC	1.46 ± 0.26	1.48 ± 0.24	0.425
HBA1C	6.50 ± 1.20	6.51 ± 1.47	0.958
LVEF	61.03 ± 11.96	59.69 ± 13.42	0.379

non-normal grouping data,non-parametric test;

* the difference was statistically significant.

Abbreviation: SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HR: heart rate; CHO: cholesterol; TG: triglyceride; HDLC: high-density lipoprotein cholesterol; LDLC: low-density lipoprotein cholesterol: LVEF: left ventricular ejection fraction.

Table 3. Comparison of clinical outcomes between two groups

Variable	Low-Lp(a) (< 118 mmol/L) n = 174	High-Lp(a) (≥ 118 mmol/L) n = 176	P value
Cardio-vascular death	4(2.2%)	6(3.4%)	0.53
Recurrent myocardial infarction	3(1.7%)	6(3.4%)	0.31
Ischemic stroke	2(1.1%)	2(1.1%)	0.99
Revascularization*	12(6.9%)	24(13.3%)	0.031
In-stent restenosis	1(0.6%)	3(1.7%)	0.623

* the difference was statistically significant.

was used for categorical variables. It's considered statistically significant when $P < 0.05$.

The primary clinical endpoints, which were considered statistically significant above, were taken as dependent variables, and univariate logistic regression analysis was used to evaluate the independent variables including Lp(a). It's considered statistically significant when $P < 0.05$. Unconditional multivariate logistic regression analysis (Forward selection) was performed to evaluate multiple significant associated independent variables. Hosmer-Lemeshow statistic test (H-L test) was used to evaluate the goodness-of-fit and a significant p-value corresponded to poor goodness-of-fit. It's considered statistically significant when $P < 0.05$.

3. Results

None of the differences, apart from smoking and left main lesion, were significant between the 2 groups. In the low-level group, the percentage of smokers was higher (45.2% Vs 33.5%, $P = 0.023$) than the high-level group; however, the incidence of the left main lesion was lower (12.1% Vs 20.45%, $P = 0.033$). The incidence of acute myocardial infarction in the high-level group was slightly weaker compared to the low-level group, but the difference was less obvious. (Table 1)

There were minimal differences in age, blood pressure, heart rate, glycated hemoglobin, creatinine, total cholesterol (TC), TG, HDL-C, LDL-C and left ventricular ejection fraction in 2 groups. The albumin was higher in the low-level group ($P < 0.05$). (Table 2)

In general, there was no significant difference in baseline data between study groups. Comparing the cardiovascular endpoint events between 2 groups, the prevalence of revascularization was higher in the high-level group (13.3 Vs 6.9%, $P < 0.05$), while the occurrence rates of recurrent myocardial infarction, ischemic stroke, in-stent restenosis, and cardio-vascular death were not statistically distinction in 2 groups. (Table 3, Fig. 2)

We took revascularization as the dependent variable and used univariate logistic regression analysis. It showed diabetes, SBP, HDL-C, and Lp(a) were statistically significant ($P < 0.05$). The variables above with statistical significance were evaluated by using unconditional multivariate logistic regression analysis. H-L test presented a high value of chi-square ($x^2 = 3.295$) and an insignificant P-value ($P = 0.685$), suggesting better goodness-of-fit. The final results showed that Lp(a) and diabetes were independent risk factors for revascularization ($P < 0.05$). (Table 4)

4. Discussion

CAD is a major cardiovascular event that threatens human health. In China, the number of patients with CAD was 11 million in 2015. The traditional factors that make up the Framingham Risk Score account for most of the increase of CAD risk, including old age, high blood pressure, high LDL-C levels, low HDL-C levels, cigarette smoking, and diabetes et. (Lloyd-Jones et al., 2004). Among those risk factors, LDL-C levels were the

Table 4. Univariate and multivariate p value and ORs of clinical outcomes

Characteristies	TVR group (n = 36)	Non-TVR group (n = 314)	Univariate OR (95%CI)	*P* value	Multivariate OR (95%CI)	P value
Categorical data						
Male	29 (80.6%)	253 (80.6%)	1.331 (0.598-2.961)	0.484	——	——
Current smoker	17 (47.2%)	121 (38.5%)	1.278 (0.648-2.519)	0.479	——	——
Diabetes mellitus$^{1*/2*}$	16 (44.4%)	87 (27.7%)	1.905 (1.168-3.331)	0.038	1.783 (1.053-3.021)	0.044
Statin	36 (100%)	289 (92.0%)	——	0.998	——	——
ACEI/ARB	30 (83.3%)	264 (84.1%)	0.682 (0.295-1.577)	0.368	——	——
BETA	30 (83.3%)	271 (86.3%)	0.567 (0.243-1.322)	0.189	——	——
Aspirin	36 (100%)	314 (100%)	——	——	——	——
Clopidogrel	36 (100%)	314 (100%)	——	——	——	——
Left main disease	6 (16.7%)	51 (16.2%)	0.960 (0.382-2.413)	0.93	——	——
High level of Lp (a)$^{1*/2*}$	24 (66.7%)	152 (48.4%)	2.502 (1.188-4.967)	0.021	2.340 (1.140-4.803)	0.028
Continuous data (mean ± SD)						
Age (yrs)	62.54 ± 9.49	63.61 ± 10.98	0.991 (0.961-1.022)	0.568	——	——
SBP^{1*}	135.68 ± 16.61	126.63 ± 18.16	1.076 (1.032-1.124)	0.042	——	0.083
DBP	73.32 ± 10.06	75.66 ± 11.15	0.980 (0.949-1.012)	0.217	——	——
creatinine	81.46 ± 20.83	86.65 ± 22.87	0.989 (0.973-1.005)	0.183	——	——
albumin	36.00 ± 4.67	36.01 ± 4.74	0.999 (0.928-1.076)	0.987	——	——
CHO	3.01 ± 0.41	3.25 ± 0.83	0.568 (0.305-1.060)	0.075	——	——
TG	1.22 ± 0.71	1.61 ± 2.19	0.835 (0.597-1.167)	0.291	——	——
LDL-C	1.46 ± 0.24	1.47 ± 0.25	0.749 (0.205-2.734)	0.662	——	——
HDL-C1*	0.83 ± 0.21	0.95 ± 0.33	0.380 (0.096-0.992)	0.047	——	0.125
HBA1C	6.45 ± 1.63	6.52 ± 1.31	0.961 (0.720-1.282)	0.787	——	——
LVEF	60.81 ± 12.33	60.30 ± 12.82	1.003 (0.974-1.033)	0.831	——	——

^{1*} the difference was statistically significant in univariate logistic regression,

^{2*} the difference was statistically significant in multivariate logistic regression.

Abbreviation: TVR: Revascularization; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; CHO: cholestrol; TG: triglyceride; HDLC: high-density lipoprotein cholesterol; LDLC: low-density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; ACEI/ARB: Angiotensin Converting Enzyme Inhibitors/Angiotensin Receptor Blockers; BETA: beta blocker

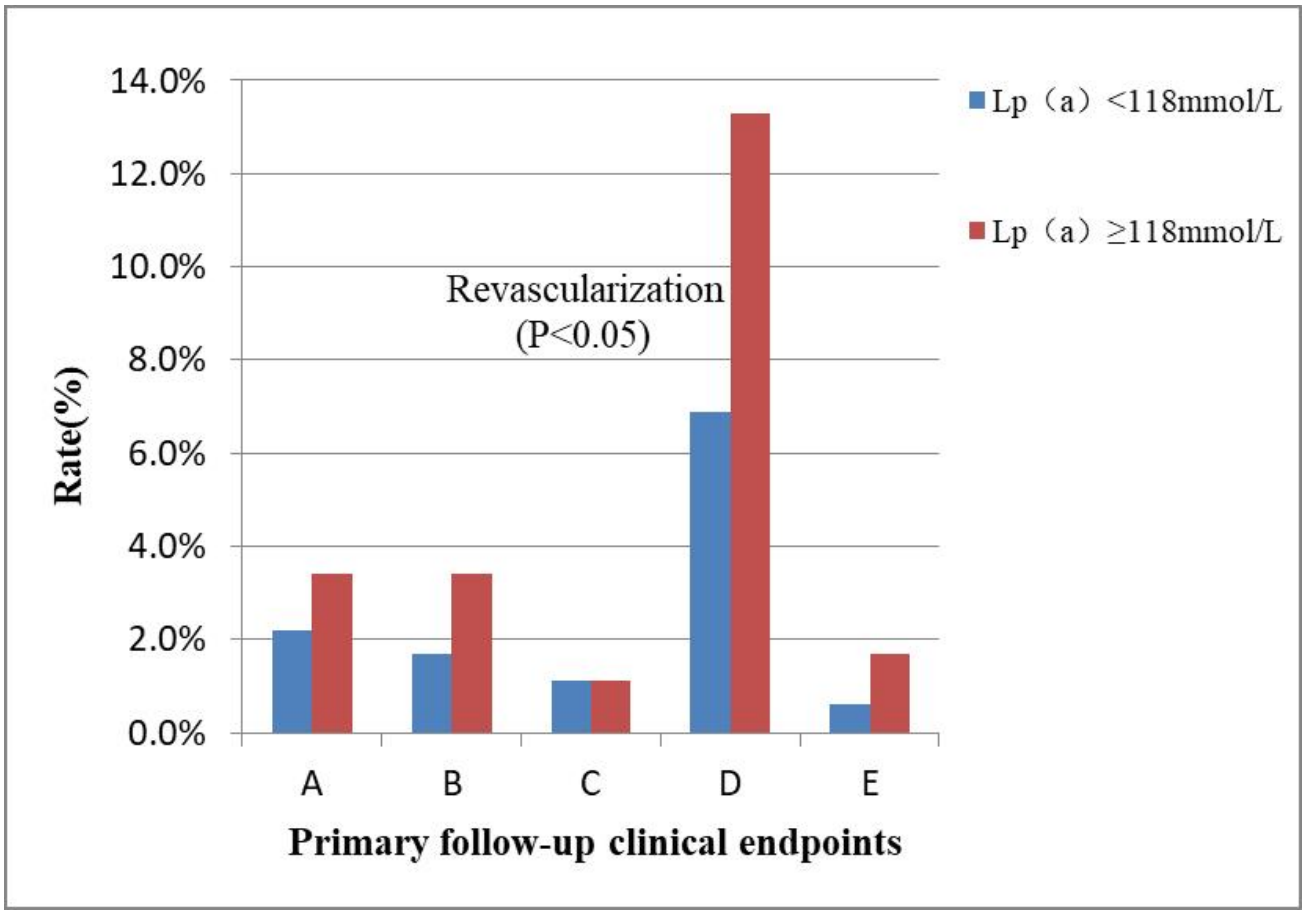

Figure 2. Comparison of primary clinical endpoints between 2 groups. The x-axis represented 5 clinical endpoints, which included cardiovascular death (A), recurrent myocardial infarction (B), ischemic stroke (C), revascularization (D) and in-stent restenosis (E). Patients in each endpoint event were assigned to high-Lp (a) group (≥118mmol/L) and low-Lp (a) group (<118mmol/L), which were shown as "red" and "blue" respectively.

most important and recent guidelines recommend LDL-C as the leading lipid target (Mach et al., 2020). Although patients with CAD after PCI achieved the goal of LDL-C below 1.8mmol / L after lipid-lowering therapy, some of them still had adverse clinical events, such as myocardial infarction, stroke, restenosis after PCI, even cardio-vascular death. It's the residual risk, which some studies have shown may relate to HDL-C and TG levels (Ling et al., 2017). It has also been suggested that increased lipoprotein(a) levels were relevant to risk (Khera et al., 2014).

The structure of Lp(a) consisting of the specific glycoprotein apolipoprotein (APO(a)) and pro-thrombogenic suggests that Lp(a) may have both prothrombotic/antifibrinolytic and atherogenic effect similar to plasminogen and LDL-C. An epidemiological study has shown that the concentration of Lp(a) was relevant to non-HDL-C, TC, apolipoproteinB100, TG. (Park et al., 2015). However, serum Lp(a) levels were not related to age, smoking, BMI, inflammation markers, or statin use (Shai et al., 2005). As we know, oral lipid-lowering medications have a significant effect on reducing the concentration of LDL-C, TC and TG, but show a moderate effect on reducing Lp(a) and only niacin can reduce Lp(a) by ~30% (Tsimikas, 2017). Recently, evidence has indicated that the use of Proprotein convertase subtilisin/kexin type 9(PCSK9) inhibitors can reduce the concentration of Lp(a) with ~30% reduction in Lp(a) levels similar to niacin (Gragnano et al., 2018; Shapiro et al., 2019). In order to study the association between Lp(a) and primary endpoint events, we used LDL-C <1.8mmol/l as one of the screening criteria for the study population. Lp(a) has pro-atherogenic and prothrombotic properties. Its prothrombotic capabilities might relate to the competitive inhibition and process of plasminogen made into the plasmin. Therefore in CAD patients, elevated Lp(a) can cause an imbalance of coagulation and fibrinolytic systems in the body, which further leads to the occurrence of acute myocardial infarction (Hartmann et al., 2006). Recently, studies have indicated that elevated Lp(a) is related to the occurrence rate of acute myocardial infarction (Huang, 2019; Yang et al., 2016). However, our study found that the proportion of myocardial infarction was higher in the high-level group, but the difference was not significant and may be related to the small sample size. Gragnano et al. (2019) observed no cardiovascular death; however, our studies observed cases of cardiovascular death with no difference between the 2 groups. The correlation between Lp(a) and cardio-vascular death is likely to be further explored by expanding the sample size and extending the follow-up time.

In our study, all the patients with left main lesions were treated by a single stent implantation technique. Interestingly, we ob-

served that the occurrence rate of left main lesions was increased in the high-level group (20.45% Vs 12.1%, $P = 0.033$) compared to the lower-level group. Previous research conducted a retrospective analysis of 60 patients with left main lesion by IVUS to assess the relationship between plaque progression and Lp(a). This study showed a positive correlation between both of them (Boullier et al., 2000), and it was consistent with our studies. Early studies have shown that elevated Lp(a) was closely associated with restenosis after PCI (Boullier et al., 2000). Transforming growth factor-b is an inhibitor of the proliferation and the migration dedifferentiation of vascular smooth muscle cells by decreasing the concentration of which, the high Lp(a) level can strengthen the migration of smooth muscle cells. Therefore, Elevated Lp(a) can lead to endothelial dysfunction and restenosis after PCI (Konishi et al., 2016b). On the endpoint of revascularization, our study showed the statistical difference between 2 groups; however, in-stent restenosis cases failed to show statistical significance. Factors such as the limiting control of LDL-C levels reduced the incidence of in-stent restenosis probably, therefore, a study with larger sample size and scale to further discuss the relevance between Lp(a) and in-stent restenosis should be explored.

There are several limitations in this study that we would like to address. Since this was a retrospective single-center study, there may have been selection bias and insufficient sample size. Due to the limitation of sample size, the previous standard (LDL-C $<$ 1.8mmol/L) was still used, which may have been one of the defects in this study. Gragnano et al. (2019) considered Lp(a) was an independent risk factor of the primary endpoint in STEMI patients, but not in stable CAD (SCAD) patients. Our study lacks sample data of SCAD for comparison and verification. Other factors combined may be associated with the outcome, therefore a larger, multicenter, prospective study is needed.

5. Conclusion

Elevated Lp(a) is related to major cardiovascular events, especially in CAD patients after PCI with LDL-C less than 1.8 mmol/L, which suggested that for patients with CAD after PCI, clinicians should not only pay attention to the level of LDL-C but also the level of Lp(a). Whether the reduction of Lp(a) level can reduce restenosis after PCI still needs further experimental confirmation.

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Conflicts of Interest

The authors declare no conflict of interest.

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