Usefulness of Lipoprotein (a) for Predicting Outcomes After Percutaneous Coronary Intervention for Stable Angina Pectoris in Patients on Hemodialysis

Keiichi Hishikari, MD[a,b,*], Hiroyuki Hikita, MD[a], Hiroshi Yoshikawa, MD[a], Fumiyuki Abe, MD[a], Shihoko Tsujihata, MD[a], Naruhiko Ito, MD[a], Yoshinori Kanno, MD[a], Munehiro IIya, MD[a], Tadashi Murai, MD[a], Atsushi Takahashi, MD[a], Taishi Yonetsu, MD[b], and Tetsuo Sasano, MD[b]

Serum lipoprotein (a) level is genetically determined and remains consistent during a person's life. Previous studies have reported that people with high lipoprotein (a) level are at a high risk of cardiac events. We investigated the association between lipoprotein (a) levels and clinical outcomes after percutaneous coronary intervention (PCI) for stable angina pectoris (SAP) in hemodialysis (HD) patients. Serum lipoprotein (a) levels were measured on admission in 410 consecutive HD patients who underwent successful PCI for SAP. Patients were divided into 2 groups: low and high group having lipoprotein (a) level <40 mg/dL (n = 297) and ≧40 mg/dL (n = 113) respectively. After PCI, the incidence of major adverse cardiac event (MACE) including cardiac death, nonfatal myocardial infarction, necessity of a new coronary revascularization procedure (coronary bypass surgery, repeat target lesion PCI, PCI for a new non-target lesion) was analyzed. At a median follow-up of 24 months (12 to 37 months), MACE occurred in 188 patients (45.6%). The rate of MACE rate was significantly higher in the high lipoprotein (a) group than in the low lipoprotein (a) group (59.2% vs 40.7%, long-rank test chi-square = 12.3; p < 0.001). Cox analysis showed that high lipoprotein (a) level (Hazard Ratio, 1.62; 95% Confidence Interval, 1.19 to 2.20; p = 0.002) was an independent predictor for MACE after PCI. In conclusion, high lipoprotein (a) level was associated with a higher incidence of MACE after PCI for SAP in HD patients. **(Am J Cardiol 2020;136:32−37)**

Hemodialysis (HD) patients have a significantly high risk for atherosclerotic cardiovascular disease. This increased risk is only partially explained by the various traditional risk factors associated with HD.[1−3] This has prompted interest in investigating novel cardiovascular risk factors, such as lipoprotein (a) (Lp[a]), which are often elevated in patients on HD.[4] Lp(a) is a cholesterol-rich lipoprotein with structural similarities to LDL[5]; however, it contains apoprotein(a), a glycoprotein with sequence homology to plasminogen.[6] Previous studies showed that Lp(a) plays a causal role in the development of atherosclerosis and is a potentially modifiable risk factor for various vascular diseases.[7−10] However, the association between the serum level of Lp (a) and clinical outcomes after percutaneous coronary intervention (PCI) have not been completely evaluated in HD patients with stable angina pectoris (SAP). This study sought to determine if the preprocedural serum Lp (a) level is a biomarker for clinical outcomes after PCI in HD patients with SAP.

Methods

Data were collected from consecutive HD patients with SAP who underwent PCI and had serum Lp(a) levels measured before the procedure at a single center (Yokosuka Kyosai Hospital, Yokosuka, Japan). From January 2012 to January 2017, a total of 410 consecutive HD patients (mean age 71 years; 315 men) who underwent PCI were enrolled. The institutional Review Board approved the study protocol, and patients provided written informed consent before the intervention. The patients were stratified into 2 groups based on the serum Lp(a) levels: low group <40 mg/dl (n = 297) or high group ≧40 mg/dl (n = 113). The baseline characteristics, lipid profiles, and characteristics of the lesions are presented in Tables 1 and 2.

Laboratory measurements were performed on the day before PCI. The time interval between the last meal and the time the blood sample was drawn was >12 hours in all patients. The plasma levels of total cholesterol, high-density lipoprotein cholesterol, and triglycerides were measured using a standard autoanalyzer in the hospital's clinical laboratory. The low-density lipoprotein (LDL) cholesterol level was calculated based on the Friedewald formula. If the triglyceride level was >400 mg/dl, the LDL cholesterol level was determined using a direct assay. The serum Lp(a) level was measured using a latex agglutination immunoassay (SRL, Yokohama, Japan).

All patients were administered aspirin (100 mg/day) and a thienopyridine (ticlopidine [200 mg/day], clopidogrel

[a]Cardiovascular Center, Yokosuka Kyosai Hospital, Yokosuka, Japan; and [b]Cardiovascular Medicine, Tokyo Medical and Dental University, Tokyo, Japan. Manuscript received June 10, 2020; revised manuscript received and accepted August 28, 2020.

See page 36 for disclosure information.

*Corresponding author: Tel.: +81-46-822-2710; fax: +81-46-825-2103.
E-mail address: hishikari_86@yahoo.co.jp (K. Hishikari).

0002-9149/
https://doi.org/10.1016/j.amjcard.2020.08.049

Table 1
Patient characteristics

Variable	Total (n = 410)	Lipoprotein (a) (mg/dl)		p Value
		(≧40) (n = 113)	(<40) (n = 297)	
Age (years)	70.8±8.8	71.2±9.9	70.6±8.3	0.55
Men	315 (76.8%)	87 (77.0%)	228 (76.8%)	0.54
Hypertension	296 (72.2%)	85 (75.2%)	211 (71.0%)	0.46
Dyslipidemia	151 (36.8%)	52 (46.0%)	99 (33.3%)	0.02
Diabetes mellitus	286 (69.8%)	81 (71.7%)	205 (69.0%)	0.63
HbA1c (%)	6.3±2.0	6.2±1.0	6.3±2.3	0.54
Old myocardial infarction	164 (40.0%)	57 (50.4%)	107 (36.0%)	0.009
LVEF (%)	54.7±12.7	53.0±13.0	55.4±12.5	0.09
BNP (pg/ml)	331 (158-711)	412 (201-768)	299 (140-676)	0.59
CRP (mg/dl)	0.24 (0.09-0.68)	0.22 (0.09-0.75)	0.26 (0.09-0.65)	0.66
Previous PCI	256 (62.4%)	71 (62.8%)	185 (62.2%)	1.00
Previous CABG	40 (9.8%)	12 (10.6%)	28 (9.4%)	0.71
Cerebrovascular disease	55 (13.4%)	15 (13.2%)	40 (13.5%)	1.00
Peripheral artery disease	198 (48.3%)	51 (45.1%)	147 (49.5%)	0.44
Lp(a) (mg/dl)	24 (12-42)	56 (45-85)	19 (10-27)	<0.001
Total cholesterol (mg/dl)	140±36	137±29	142±38	0.21
HDL cholesterol (mg/dl)	43±12	43±11	43±13	0.54
LDL cholesterol (mg/dl)	71±27	68±22	73±30	0.16
Triglyceride (mg/dl)	116±77	111±73	118±78	0.42
Medication at follow-up				
Aspirin	384 (93.7%)	109 (96.5%)	275 (92.6%)	0.18
Ticlopidine or clopidogrel	370 (90.2%)	103 (91.2%)	267 (89.9%)	0.85
DAPT therapy	364 (88.8%)	104 (92.0%)	260 (87.5%)	0.22
Statins	293 (71.5%)	89 (78.8%)	204 (68.7%)	0.05
ACE-I or ARB	167 (40.7%)	42 (37.2%)	125 (42.1%)	0.43
β-blocker	139 (33.9%)	50 (44.2%)	89 (30.0%)	0.007
Calcium antagonist	140 (34.1%)	37 (32.7%)	103 (34.7%)	0.73
Nicolandil	209 (51.0%)	65 (57.5%)	144 (48.5%)	0.12

Abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BNP = brain natriuretic peptide; CRP = C-reactive protein; CABG = coronary artery bypass grafting; DAPT = dual anti-platelet therapy; HbA1c = hemoglobin A1c; HDL = high density lipoprotein; LDL = low density lipoprotein; Lp(a) = lipoprotein (a); LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention.

Continuous data are presented as the means ± standard deviation or median (first, third quartiles); categorical data are given as the counts (percentage).

[75 mg/day], or prasugrel [3.75 mg/day]) at least 24 hours before PCI. Glycoprotein IIb/IIIa receptor inhibitor is not available in Japan and was not used in this study. All patients received an intravenous bolus injection of 10,000 IU heparin and intracoronary nitroglycerin (0.2 mg) before angiography, and an additional bolus of heparin 2000 IU was administered every hour if the procedure lasted >1 hour. PCI procedures were performed using a 6-F or 7-F guiding catheter via the brachial or femoral approach. All procedural and technical details and the choice of devices were at the operators' discretion. The success of the procedure was defined as achievement of <25% residual angiographic stenosis, with thrombolysis in myocardial infarction 3 antegrade flow in the target vessels. Coronary stent implantation was performed with balloon predilation in all patients. The balloon-to-artery ratio for predilation was 0.9 to 1.0 in all patients as per the prespecified PCI protocol, although the type of stent was used was at the operators' discretion. To

Table 2
Lesion characteristics

	Total (n = 410)	Lipoprotein (a) (mg/dl)		p Value
		(≧40) (n = 113)	(<40) (n = 297)	
Culprit coronary artery				
LAD	165 (40.2%)	43 (38.1%)	122 (41.1%)	0.65
LCX	95 (23.2%)	31 (27.4%)	64 (21.5%)	0.24
Right	150 (36.6%)	39 (34.5%)	111 (37.4%)	0.65
Stent use	342 (83.4%)	95 (84.1%)	247 (83.2%)	0.88
Drug eluting stents	337 (82.2%)	93 (82.3%)	244 (82.2%)	1.0
Total stent length (mm)	26.1±16.3	24.8± 14.2	26.6±17.0	0.35
Mean stent diameter (mm)	3.1±0.6	3.1± 0.4	3.1±0.6	0.81

Abbreviations: LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery.

Continuous data are presented as the means ± standard deviation or median (first, third quartiles); categorical data are given as the counts (percentage).

avoid aggressive stent expansion, the stent size was decided using a combination of online quantitative coronary angiography and intravascular ultrasound in all cases. After achieving an angiographic end point, intravascular ultrasound was performed to confirm optimal stent deployment, and an additional PCI procedure was performed for suboptimal results. After the procedure, all patients were prescribed aspirin to be taken for life and prolonged treatment with either ticlopidine, clopidogrel, or prasugrel was recommended for at least 1 year.

Patients were followed up for the occurrence of major adverse cardiac event (MACE) including cardiac death, nonfatal myocardial infarction (MI), necessity of a new coronary revascularization procedure (coronary bypass surgery, repeat target lesion PCI, PCI for a new nontarget lesion). Target lesion revascularization (TLR) was defined as revascularization for a stenosis within the stent or within 5 mm adjacent to the stent. Restenosis during the follow-up was assessed with routine coronary angiography 9 months after PCI and clinical examination 1 month after PCI, and every 3 months thereafter. Cardiac death was defined as any death proceeded by acute mitral regurgitation, decompensated heart failure, ventricular arrhythmia, new acute MI or death preceded by mechanical complications of MI. MI was defined using the third universal definition of MI.[11] Revascularization was defined as repeat revascularization for ischemic symptoms and events by PCI or surgery. Clinical end points were determined by the blinded assessment of hospital records.

Categorical data were expressed as absolute frequencies (percentages) and were compared using the chi-square or Fisher exact test, as appropriate. Continuous variables were expressed as the means ± standard deviations if they were normally distributed and as medians with the interquartile ranges (IQR) if they were not nonparametric; they were compared using the Student t test or the Mann-Whitney U test, respectively. Normality of the data was verified using the Kolmogorov-Smirnov test. The threshold of 40 mg/dl for stratification was selected because it was the cutoff point for progression of coronary artery disease (CAD) and peripheral artery disease in previous studies.[8,12] Primary patency of the PCI and cumulative ratios of MACE after PCI were estimated using the Kaplan-Meier method; the survival curves were compared using the Mantel-Cox test. Univariate Cox regression analysis of clinical variables was used to identify predictors of MACE during the follow-up; outcomes were reported as the hazard ratio with the 95% confidence interval. All variables achieving $p < 0.1$ in the univariate analysis were entered into a multivariate Cox regression model. $p < 0.05$ indicated statistical significance for all analyses. Data were analyzed using IBM SPSS software (version 26.0; IBM Corporation, Armonk, New York).

Results

In all, 410 patients on HD who underwent PCI for SAP were enrolled in this study. All patients received optimal medical therapy whereas they were hospitalized, on discharge from the hospital, and during the follow-up. Table 1 lists the baseline characteristics, laboratory findings, and medication at follow-up of the overall study population. Mean age was 70.8 ± 8.8 years, and 315 (76.8%) were men. There were 296 (72.2%) patients who had a history of hypertension and 286 (69.8%) had diabetes mellitus (DM). The prevalence of dyslipidemia and old myocardial infarction was significantly higher in the high Lp(a) group than in the low Lp(a) group. Age, gender, the prevalence of hypertension and DM were comparable between the 2 groups. There were no significant differences in the past medical histories, hemoglobin A1c levels, brain natriuretic peptide, C-reactive protein, and left ventricular ejection fraction on admission between the 2 groups. No significant differences were observed between the low and high Lp(a) groups in terms of the current medication except the use of β-blocker at follow-up. The median Lp(a) level was 19 mg/dl (IQR 10, 27) in the low Lp(a) group and 56 mg/dl (IQR 45, 85) in the high Lp(a) group. Baseline serum lipid levels were comparable between the 2 groups. No significant differences were observed between the low and high Lp(a) groups with respect to the characteristics of the lesions (Table 2).

All patients completed the follow-up assessments. During a median follow-up of 24 months (IQR 12, 37), the cumulative rate of MACE including cardiac death, nonfatal MI, and necessity of a new coronary revascularization procedure was 45.6% (Table 3). No statistically significant differences were observed in the TLR rates between the low and high Lp(a) groups; however, the revascularization rates for new de novo lesions and the occurrence of nonfatal MI were significantly higher in the high Lp(a) group than in the low Lp(a) group ($p < 0.05$ for both). The cumulative rates of MACE events were about 1.5 times higher in the high Lp (a) group than in the low Lp(a) group.

Kaplan-Meier survival analysis showed that there were no significant differences in the primary patency rates between the high and low Lp(a) groups (Figure 1).

Table 3
Major adverse cardiac events after percutaneous coronary intervention

Variable	Total (n = 410)	Lipoprotein (a) (mg/dl)		p Value
		(≧40) (n = 113)	(<40) (n = 297)	
TLR	55 (13.4%)	12 (10.6%)	43 (14.5%)	0.335
Non-TLR	82 (20.0%)	31 (27.4%)	51 (17.2%)	0.027
Nonfatal MI	20 (4.9%)	11 (9.7%)	9 (3.0%)	0.008
Cardiac death	31 (7.6%)	13 (11.5%)	18 (6.1%)	0.092
Cumulative event	188 (45.6%)	67 (59.2%)	121 (40.7%)	<0.001

Abbreviations: MI = myocardial infarction; TLR = target lesion revascularization.
Data are presented as the counts (percentages).

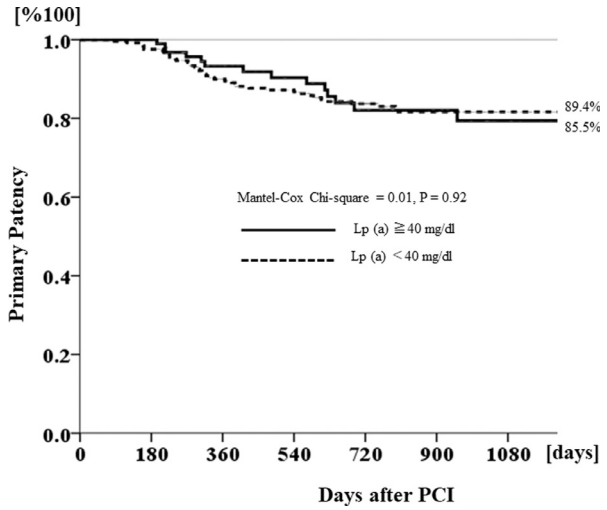

Figure 1. Primary patency rates after percutaneous coronary intervention. There were no significant differences in the primary patency rates between the high and low Lp(a) groups (89.4% vs 85.5%, long-rank test chi-square = 0.01; p = 0.92).

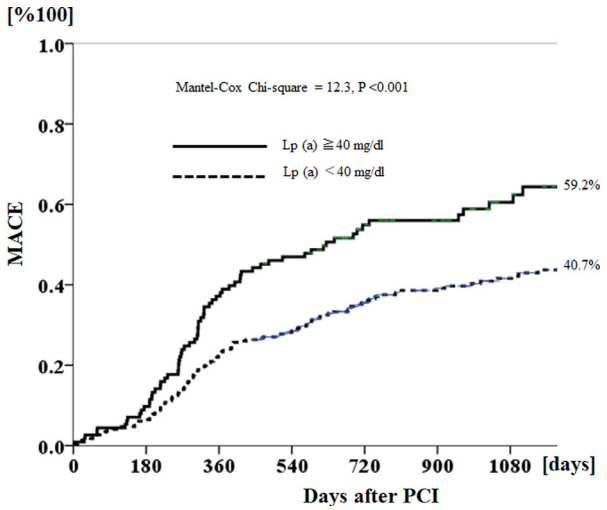

Figure 2. Cumulative risk of major adverse cardiac events after percutaneous coronary intervention. The cumulative rate of MACE events was significantly higher in the high Lp(a) than in the low Lp(a) group (59.2% vs 40.7%, long-rank test chi-square = 12.3; p < 0.001).

However, the cumulative rate of MACE events was significantly higher in the high Lp(a) than in the low Lp(a) group (Figure 2).

Univariate analysis showed that several clinicopathological parameters, including DM, dyslipidemia, old myocardial infarction, left ventricular ejection fraction, brain natriuretic peptide, the use of β-blocker, and serum Lp(a) level, were significantly associated with MACE in patients with HD who underwent PCI for SAP (Table 4). Multivariate regression analysis showed that serum Lp(a) level ≧40 mg/dl (hazard ratio 1.62, 95% confidence interval 1.19 to 2.20, p = 0.002) was a significant independent predictor for MACE after PCI (Table 4).

Discussion

To the best of our knowledge, this is the first study to analyze the association between Lp(a) levels and long-term MACE in patients on HD undergoing PCI for SAP. We confirmed that high serum Lp(a) levels in these patients are associated with an increased risk of MACE after PCI. The main findings of the study are[1] a serum Lp(a) level ≧40 mg/dl was associated with an increased risk of MACE, MI, and the need for revascularization of new de novo lesions;[2] after adjustment for the standard risk factors, serum Lp(a) level ≧40 mg/dl was an independent predictor of MACE in patients on HD undergoing PCI for SAP. Although previous studies reported that higher serum Lp(a) levels were associated with poor clinical outcomes in CAD patients with DM and chronic kidney disease except those on HD after PCI,[13–15] the association between serum Lp(a) levels and clinical outcomes in patients on HD undergoing PCI for SAP is yet unclear.

Lp(a) is a modified form of LDL in which the large glycoprotein apolipoprotein(a) is covalently bound to apolipoprotein B by a disulfide bridge.[16] The serum Lp(a) level is

Table 4
Analysis of factors related to major adverse cardiac events after percutaneous coronary intervention

Variable	Univariate Cox regression			Multivariate Cox regression		
	p Value	HR	95% CI	p Value	HR	95% CI
Age	0.144	0.988	0.972-1.004			
Men	0.285	1.212	0.852-1.726			
Diabetes mellitus	0.016	1.513	1.082-2.117	0.034	1.440	1.027-2.020
Hypertension	0.990	0.998	0.724-1.375			
Dyslipidemia	0.017	1.423	1.066-1.901	0.008	1.502	1.113-2.026
Old myocardial infarction	0.001	1.641	1.231-2.188	0.005	1.559	1.144-2.125
Peripheral artery disease	0.373	0.877	0.658-1.170			
Cerebrovascular disease	0.898	1.027	0.683-1.545			
LVEF (%)	0.011	0.986	0.975-0.997	0.578	0.996	0.984-1.009
BNP (pg/ml)	0.005	1.000	1.000-1.000	0.061	1.000	1.000-1.000
Lp(a) ≧40mg/dl	0.001	1.697	1.258-2.288	0.002	1.619	1.193-2.198
Statin	0.177	1.265	0.899-1.779			
B-blocker	0.046	0.727	0.532-0.994	0.024	0.690	0.500-0.953

Abbreviations: BNP = brain natriuretic peptide; CI = confidence interval; HR = hazard ratio; Lp(a) = lipoprotein (a); LVEF = left ventricular ejection fraction.

increasingly being used as a predictive biomarker in patients with CAD.[17,18] For primary prevention of CAD in patients on HD, several studies found high serum levels of Lp(a) were associated with an increased risk for CAD and cardiovascular diseases.[19, 20] However, there are no reports of Lp(a) about secondary prevention of cardiovascular disease in patients on HD with CAD after PCI. In addition, patients on HD have been shown to have increased Lp(a) levels compared to healthy controls and early stage chronic kidney disease .[21,22]

Lp(a) levels are genetically determined by the variation of the copy number of kringle IV type 2 repeats on the LPA gene and various single nucleotide polymorphisms.[23] The pathophysiological role of Lp(a) in CAD progression has not been fully determined. However, several mechanisms of Lp(a) participation in atherogenesis have been proposed. Lp(a) promotes the expression of a plethora of proinflammatory cytokines and chemokines, and induces the endothelium to switch to an activated state, resulting in the expression of adhesion molecules and inflammatory cell invasion into the arterial wall. The detrimental combination of inflammation and Lp(a) might interfere with the physiologic endothelial repair response, further amplifying the loss of integrity and protective functions of endothelium.[24] Lp(a) potentially constitutes a molecular link between the processes of atherosclerosis and thrombosis that together precipitate events such as MI. In addition, its similarity to plasminogen, might cause thrombosis by inhibition of fibrinolysis.[25] These mechanisms might explain the results of our study.

Higher serum Lp(a) levels might not represent the destabilization of the lesion that is specifically targeted by PCI; however, it might represent all atherosclerotic plaques in patients on HD. The main reason for TLR is the proliferation of smooth muscle cells and fibroatheroma, which is thought to be inhibited by the metallic scaffold of the drug-eluting stent. However, serum Lp(a) promotes smooth muscle cell proliferation and migration in the atherosclerotic lesions by inactivating transforming growth factor-β.[26] Thus, high Lp(a) levels might not be associated with the restenosis that drives TLR but with the progression of new de novo lesions.

We propose that the serum Lp(a) level should be measured in patients on HD who develop SAP; higher levels should prompt further diagnostic action and therapeutic interventions to decrease the Lp(a) levels, thereby improving the clinical outcomes for these patients. However, the treatment of elevated Lp(a) is challenging since there is no ideal treatment for lowering the elevated Lp(a). Recently approved proprotein convertase subtilisin/kexin type 9 inhibitors, which elevate the LDL receptor levels by inhibiting its degradation, have been reported to lower Lp(a) levels by as much as 30%, with the extent of Lp(a) lowering correlating with the LDL reduction.[27,28] Another option could be mipomersen, an apoB inhibitor, which leads to the reduction of Lp(a) about 30%.[29] Another emerging option could be antisense oligonucleotide targeted to apolipoprotein(a).[30] Larger clinical trials of these agents or studies focused on SAP in patients on HD who have high Lp(a) levels are necessary to investigate the effect of Lp(a)-targeted lipid-lowering therapy and the resultant clinical outcomes.

Our findings suggest the serum Lp(a) level predicts secondary vascular events in patients on HD with SAP after PCI. Measurement of serum Lp(a) level could provide useful information for the overall vascular management and might lead to adjunctive therapies after PCI.

Authors contribution

The contribution of each author was as follows

Keiichi Hishikari: Conceptualization, Methodology, Software, Writing - Original Draft. Hiroyuki Hikita: Data curation, Visualization. Hiroshi Yoshikawa: Data curation, Visualization. Fumiyoshi Abe: Data curation, Visualization. Shihoko Tsujihata: Data curation, Visualization. Naruhiko Ito: Visualization, Investigation. Yoshinori Kanno: Visualization, Investigation. Munehiro Iiya: Visualization, Investigation. Tadashi Murai: Visualization, Investigation. Atsushi Takahashi: Supervision. Taishi Yonetsu: Software, Validation. Tetsuo Sasano: Project administration.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

1. Foley RN, Parfrey PS, Sarnac MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998;32:S112–S119.
2. Special Report From the National Kidney Foundation Task Force on Cardiovascular Disease. Controlling the epidemic of cardiovascular disease in chronic renal disease: What do we know? What do we need to know? Where do we go from here? *Am J Kidney Dis* 1998;32:S1–S199.
3. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW. Kidney disease as a risk factor for development of cardiovascular disease: A statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation* 2003;108:2154–2169.
4. Kronenberg F, Konig P, Neyer U, Auinger M, Pribasnig A, Lang U, Reitinger J, Pinter G, Utermann G, Dieplinger H. Multicenter study of lipoprotein(a) and apolipoprotein(a) phenotypesinpatientswithendstagerenaldiseasetreated by hemodialysis or continuous ambulatory peritoneal dialysis. *J Am Soc Nephrol* 1995;6:110–120.
5. Loscalzo J. Lipoprotein(a): A unique risk factor for atherothrombotic disease. *Arteriosclerosis* 1990;10:672–679.
6. Eaton DL, Fless GM, Kohr WJ, McLean JW, Xu Q-T, Miller CG, Lawn RM, Scanu AM. Partial amino acid sequence of apolipoprotein (a) shows that it is homologous to plasminogen. *Proc Natl Acad Sci USA* 1987;84:3224–3228.
7. Murai AT, Miyahara N, Fujimoto M, Matusda M, Kameyama M. Lp (a) lipoprotein as a risk factor for coronary heart disease and cerebral infarction. *Atherosclerosis* 1986;62:249–257.
8. Hishikari K, Hikita H, Nakamura S, Nakagama S, Mizusawa M, Yamamoto T, Doi J, Utsugi Y, Sudo Y, Kimura S, Ashikaga T, Takahashi A, Isobe M. Usefulness of lipoprotein(a) for predicting clinical outcomes after endovascular therapy for aortoiliac atherosclerotic lesions. *J Endovasc Ther* 2017;24:793–799.
9. Armstrong VW, Cremer P, Eberle E, Manke A, Schulze F, Wieland H, Kreuzer H, Siedel D. The association between serum Lp(a) concentrations and angiographically assessed coronary atherosclerosis: dependence on serum LDL levels. *Atherosclerosis* 1986;62:249–257.
10. Walton KW, Hitchens J, Magnani HN, Kahn M. A study of methods of identification and estimation of Lp(a) lipoprotein and of its significance in health, hyperlipidaemia and atherosclerosis. *Atherosclerosis* 1974;20:323–346.
11. Taylor J. Third universal definition of myocardial infarction. *Eur Heart J* 2012;33:2506–2507.

12. Ikenaga H, Ishihara M, Inoue I, Kawagoe T, Shimatani Y, Miura F, Nakama Y, Dai K, Otani T, Ejiri K, Oda N, Nakamura M, Miki T. Usefulness of lipoprotein (a) for predicting progression of non-culprit coronary lesions after acute myocardial infarction. *Circ J* 2011;75:2847–2852.
13. Konishi H, Miyauchi K, Shitara J, Endo H, Wada H, Doi S, Naito R, Tsuboi S, Ogita M, Dohi T, Kasai T, Okazaki S, Isoda K, Suwa S, Daida H. Impact of lipoprotein(a) on long-term outcomes in patients with diabetes mellitus who underwent percutaneous coronary intervention. *Am J Cardiol* 2016;118:1781–1785.
14. Konishi H, Miyauchi K, Tsuboi S, Ogita M, Naito R, Dohi T, Kasai T, Tamura H, Okazaki S, Isoda K, Daida H. Plasma lipoprotein(a) predicts major cardiovascular events in patients with chronic kidney disease who undergo percutaneous coronary intervention. *Int J Cardiol* 2016;205:50–53.
15. Xu N, Tang XF, Yao Y, Zhao XY, Chen J, Gao Z, Qiao SB, Yang YJ, Gao RL, Xu B, Yuan JQ. Association of plasma lipoprotein(a) with long-term adverse events in patients with chronic kidney disease who underwent percutaneous coronary intervention. *Am J Cardiol* 2018;122:2043–2048.
16. Steyrer E, Durovic S, Frank S, Giessauf W, Burger A, Dieplinger H, Zechner R, Kostner GM. The role of lecithin: cholesterol acyltransferase for lipoprotein (a) assembly. Structural integrity of low density lipoproteins is a prerequisite for Lp(a) formation in human plasma. *J Clin Invest* 1994;94:2330–2340.
17. Ikenaga H, Ishihara M, Inoue I, Kawagoe T, Shimatani Y, Miura F, Nakama Y, Dai K, Otani T, Ejiri K, Oda N, Nakamura M, Miki T. Usefulness of lipoprotein (a) for predicting progression of non-culprit coronary lesions after acute myocardial infarction. *Circ J* 2011;75:2847–2852.
18. Nestel PJ, Barnes EH, Tonkin AM, Simes J, Fournier M, White HD, Colquhoun DM, Blankenberg S, Sullivan DR. Plasma lipoprotein(a) concentration predicts coronary and cardiovascular events in patients with stable coronary heart disease. *Atheroscler Thromb Vasc Biol* 2013;33:2902–2908.
19. Cressman MD, Heyka RJ, Paganini EP, O'Neil J, Skibinski CI, Hoff HF. Lipoprotein(a) is an independent risk factor for cardiovascular disease in hemodialysis patients. *Circulation* 1992;86:475–482.
20. Longenecker JC, Klag MJ, Marcovina SM, Liu YM, Jaar BG, Powe NR, Fink NE, Levey AS, Coresh J. High lipoprotein(a) levels and small apolipoprotein(a) size prospectively predict cardiovascular events in dialysis patients. *J Am Soc Nephrol* 2005;16:1794–1802.
21. Parra HJ, Mezdour H, Cachera C, Dracon M, Tacquet A, Fruchart JC. Lp(a) lipoprotein in patients with chronic renal failure treated by hemodialysis. *Clin Chem* 1987;33:721.
22. Aggarwal HK, Jain D, Lathar M, Yadav RK, Sawhney A. Lipoprotein-A and carotid intima media thickness as cardiovascular risk factors in patients of chronic kidney disease. *Ren Fail* 2010;32:647–652.
23. Tsimikas S, Hall JL. Lipoprotein(a) as a potential causal genetic risk factor of cardiovascular disease: a rationale for increased efforts to understand its pathophysiology and develop targeted therapies. *J Am Coll Cardiol* 2012;60:716–721.
24. Pirro M, Bianconi V, Paciullo F, Mannarino MR, Bagaglia F, Sahebkar A. Lipoprotein(a) and inflammation: a dangerous duet leading to endothelial loss of integrity. *Pharmacol Res* 2017;119:178–187.
25. Boffa MB, Koschinsky ML. Lipoprotein (a): truly a direct prothrombotic factor in cardiovascular disease? *J Lipid Res* 2016;57:745–757.
26. Grainger D J, Kirschenlohr H L, Metcalfe J C, Weissberg P L, Wade D P, Lawn R M. Proliferation of human smooth muscle cells promoted by lipoprotein(a). *Science* 1993;260:1655–1658.
27. Reyes-Soffer G, Pavlyha M, Ngai C, Thomas T, Holleran S, Ramakrishnan R, Karmally W, Nandakumar R, Fontanez N, Obunike J, Marcovina SM, Lichtenstein AH, Matthan NR, Matta J, Maroccia M, Becue F, Poitiers F, Swanson B, Cowan L, Sasiela WJ, Surks HK, Ginsberg HN. Effects of PCSK9 inhibition with alirocumab on lipoprotein metabolism in healthy humans. *Circulation* 2017;135:352–362.
28. Watts GF, Chan DC, Somaratne R, Wasserman SM, Scott R, Marcovina SM, Barrett PHR. Controlled study of the effect of proprotein convertase subtilisin-kexin type 9 inhibition with evolocumab on lipoprotein(a) particle kinetics. *Eur Heart J* 2018;39:2577–2585.
29. Nandakumar R, Matveyenko A, Thomas T, Pavlyha M, Ngai C, Holleran S, Ramakrishnan R, Ginsberg HN, Karmally W, Marcovina SM, Reyes-Soffer G. Effects of mipomersen, an apolipoprotein B100 antisense, on lipoprotein (a) metabolism in healthy subjects. *J Lipid Res* 2018;59:2397–2402.
30. Ginsberg HN, Stein EA. Effect of alirocumab, a monoclonal proprotein convertase subtilisin/kexin 9 antibody, on lipoprotein(a) concentrations (a pooled analysis of 150 mg every two weeks dosing from phase 2 trials). *Am J Cardiol* 2014;114:711–715.