【 ORIGINAL ARTICLE 】

Lipoprotein(a) and the Risk of Chronic Kidney Disease in Hospitalized Japanese Patients

Hayato Tada, Kan Yamagami, Tetsuo Nishikawa, Taiji Yoshida, Ryota Teramoto,
Kenji Sakata, Masayuki Takamura and Masa-aki Kawashiri

Abstract:
Objective Lipoprotein(a), or Lp(a), has been shown to be associated with the development of chronic kidney disease (CKD) in populations of various ethnicities. This study aimed to investigate the association between serum Lp(a) and CKD in Japanese patients.

Methods A total of 6,130 subjects who underwent a serum Lp(a) level assessment for any reason (e.g. any type of surgery requiring prolonged bed rest or risk factors for atherosclerosis, such as hypertension or diabetes) were retrospectively investigated at Kanazawa University Hospital from April 2004 to March 2014. Of these, 1,895 subjects were excluded because of the lack of clinical data. Subjects were assessed for Lp(a), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, hypertension, diabetes, smoking, body mass index (BMI), coronary artery disease (CAD), and CKD (stage ≥3).

Results When the study subjects were divided into quartiles of Lp(a) levels, significant trends were observed with regard to the presence of CKD (p = 2.7×10^{-13}). A multiple regression analysis showed that Lp(a) was significantly associated with CKD [odds ratio (OR), 1.12; 95% confidence interval (CI), 1.08-1.17; p = 1.3×10^{-7}, per 10 mg/dL], independent of other classical risk factors, including age, gender, BMI, hypertension, diabetes, smoking, LDL cholesterol, and triglycerides. Under these conditions, Lp(a) was significantly associated with CAD (OR = 1.11, 95% CI = 1.06-1.16; p = 1.7×10^{-6}, per 10 mg/dL), independent of other risk factors.

Conclusion Serum Lp(a) was associated with CKD, independent of other classical risk factors in a Japanese population.

Key words: Lipoprotein(a), lipoprotein, chronic kidney disease, coronary artery disease

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Introduction

Chronic kidney disease (CKD), which is typically caused by diabetes, high blood pressure, glomerulonephritis, and polycystic kidney disease, is characterized by a gradual loss of the kidney function over a prolonged period (1). The prevalence of CKD is currently estimated to be approximately 10% (1, 2) and is expected to increase with the aging population. CKD has been shown to be associated with high morbidity and mortality (3). CKD progression must be prevented because patients with end-stage kidney disease exhibit extremely high mortality rates and a decreased quality of life, requiring dialysis and/or transplantation that results in a substantial socioeconomic burden (4). Current CKD management guidelines recommend using angiotensin-converting enzyme inhibitors (ACEis) or angiotensin II receptor blockers (ARBs) (5, 6). These medications have been shown to reduce albuminuria and slow CKD progression (7-9). However, further treatment targets are warranted to fully control the development of this condition.

Lipoprotein(a), or Lp(a), is a low-density lipoprotein (LDL)-like particle consisting of an apolipoprotein B100 (Apo B) molecule linked to a very large glycoprotein known as apolipoprotein(a), or apo(a) (10-12). Serum Lp(a) levels have been shown to be associated with CKD in populations

Table 1. Baseline Characteristics of the Study Subjects.

Characteristic	All (n=4,235)	Quartile 1 [0.1 ≤ Lp(a) ≤ 6.6 mg/dL] (n=1,068)	Quartile 2 [6.7 ≤ Lp(a) ≤ 12.1 mg/dL] (n=1,056)	Quartile 3 [12.2 ≤ Lp(a) ≤ 29.7 mg/dL] (n=1,056)	Quartile 4 [29.8 ≤ Lp(a) ≤ 169 mg/dL] (n=1,055)	p value (trends)
Age	59±16	56±16	59±16	61±16	62±15	4.2×10^{-10}
Male (%)	2,270 (53.6)	599 (56.1)	584 (55.3)	543 (51.4)	544 (51.6)	4.8×10^{-4}
BMI (kg/m²)	23.7±4.5	24.1±4.6	23.7±4.4	23.5±4.6	23.4±4.3	8.7×10^{-5}
Hypertension (%)	2,269 (53.6)	536 (50.2)	532 (50.4)	599 (56.7)	602 (57.1)	3.9×10^{-9}
Diabetes (%)	1,464 (34.6)	410 (38.4)	370 (35.0)	335 (31.7)	349 (33.1)	0.16
Smoking (%)	1,830 (43.2)	453 (42.4)	470 (44.5)	451 (42.7)	456 (43.2)	0.18
LDL cholesterol (mg/dL)	115±49	102±41	113±45	121±55	125±53	5.7×10^{-6}
HDL cholesterol (mg/dL)	51±17	52±19	50±16	51±17	51±18	0.51
Triglycerides (mg/dL)	105 [74-156]	105 [72-163]	113 [79-170]	97 [71-141]	103 [75-151]	0.29
CAD (%)	818 (19.3)	165 (15.4)	174 (16.5)	217 (20.5)	262 (24.8)	1.6×10^{-15}
CKD (%)	653 (15.4)	121 (11.3)	129 (12.2)	183 (17.3)	220 (20.9)	2.7×10^{-13}

Lp(a): lipoprotein (a), BMI: body mass index, CAD: coronary artery disease, CKD: chronic kidney disease, HDL: high-density lipoprotein, LDL: low-density lipoprotein

of most ethnicities (13-15) along with coronary artery disease (CAD) (16-18). In addition, a recent Mendelian randomization trial suggested an etiological association between serum Lp(a) levels and CKD (19). Furthermore, Lp(a) appears to be a residual risk factor for cardiovascular disease in the statin era (20). The recent treatment option offered by proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors has been shown to reduce Lp(a) by up to 30%, although the mechanism underlying this effect remains unclear (21).

However, few data exist regarding this issue in the Japanese population. Therefore, this study aimed to investigate the association between serum Lp(a) and CKD in Japanese patients.

Materials and Methods

Study population

A total of 6,130 subjects who underwent serum Lp(a) level assessment were retrospectively investigated at Kanazawa University Hospital from April 2004 to March 2014. Of these, 1,895 subjects were excluded because of the lack of clinical data. Thus, the remaining 4,235 subjects [2,270 men (53.6%), mean age = 59 years, CAD = 818 (19.3%), CKD = 653 (15.4%)] were analyzed. The baseline examination findings were reviewed, including the medical history, physical examination findings, and blood sampling results. Most study subjects were inpatients referred to the hospital, enabling the assessment of fasting blood samples. The characteristics of the study subjects are listed in Table 1.

Ethical considerations

This study was approved by the Ethics Committee of Kanazawa University. All procedures were in accordance with the ethical standards of the institutional and national committees on human experimentation and complied with the 1975 Declaration of Helsinki, as revised in 2008.

Biochemical analyses

Blood samples for biochemical assays were collected after overnight fasting. Serum creatinine levels were measured enzymatically using automated instrumentation. Serum levels of LDL cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol were determined enzymatically using automated instrumentation based on previously described protocols (22). An enzyme-linked immunosorbent assay was used to determine Lp(a) concentrations (23). The same assay was used during the entire study period. The coefficient of variation (CV) for Lp(a) measurement was shown to be < 8% within and between assays (23).

Clinical evaluations

Hypertension was defined as systolic blood pressure of at least 140 mmHg, diastolic blood pressure of at least 90 mmHg, or the use of antihypertensive medication. Diabetes was defined as previously described by the Japan Diabetes Society (24) or the use of diabetes medication. The body mass index (BMI) was defined as the body weight in kilograms divided by the square of the height measured in meters. CKD was defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m², and the eGFR was calculated using the following formulas: eGFR = 194× serum creatinine - 1.094× age - 0.287 (for men) and eGFR = 194× serum creatinine - 1.094× age - 0.287×0.739 (for women) (25). We assessed the subjects' baseline medications, including lipid-lowering, antihypertensive, antidiabetic, and antithrombotic therapies. Covonarry artery disease (CAD) was defined as the presence of angina pectoris, myocardial infarction, or severe stenotic regions in the coronary artery identified either by an angiogram or computed tomography.

Table 2.   The Main Causes of the Referral to Our Hospital.

Tne main cause	Number of samples (%)
Cardiovascular diseases	1,280 (30.2%)
Diabetes	852 (20.1%)
Surgery	576 (13.6%)
Hypertension	345 (8.1%)
Delivery	320 (7.6%)
Stroke (ischemic and hemorrhagic)	224 (5.3%)
Renal failure	107 (2.5%)
Liver diseases	105 (2.5%)
Thrombosis	54 (1.3%)
Others	372 (8.8%)

Cardiovascular diseases include coronary artery disease and heart failure.
"Others" includes inflammatory diseases, malignant diseases, metabolic diseases, and trauma.

Table 3.   Medications at the Baseline.

Medication	Number of samples (%)
Statins	734 (17.3%)
Ezetimibe	143 (3.4%)
Colestimide	21 (0.5%)
Fibrates	56 (1.3%)
Polyunsaturated fatty acids	72 (1.7%)
Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers	571 (13.5%)
Calcium channel blockers	621 (14.7%)
β blockers	314 (7.4%)
Diuretics	213 (5.0%)
Sulfonylurea	367 (8.7%)
Thiazolidine	220 (5.2%)
Biguanide	123 (2.9%)
Dipeptidyl peptidase-4 (DPP-4) inhibitor	145 (3.4%)
Other diabetic drugs	244 (5.8%)
Insulin	149 (3.5%)
Antiplatelet therapy	620 (14.6%)
Anticoagulant therapy	118 (2.8%)

Statistical analyses

Categorical variables were expressed as percentages. Fisher's exact or chi-square test was used as applicable. Continuous variables with normal distribution were shown as the mean ± standard deviation (SD). For values without a normal distribution, the median and interquartile range (IQR) were reported. A multivariate analysis including factors with a p value <0.10 in the univariate analyses was conducted to assess the association of the factors with CAD and CKD. A receiver operating characteristic analysis was performed, and the C-statistic was calculated to estimate the predictive performance of the considered parameters. All statistical analyses were conducted using the R statistical software program. All p values <0.05 were considered statistically significant.

Results

Characteristics of study subjects

The clinical characteristics of the study subjects are shown in Table 1. The median Lp(a) level was 12.1 mg/dL (IQR: 6.6-29.7). When divided into quartiles of Lp(a) levels, significant trends were observed with regard to the age, gender, BMI, hypertension, LDL cholesterol, CAD, and CKD. The main causes of referral to our hospital are shown in Table 2. In addition to subjects with cardiovascular diseases, diabetes, and hypertension, we included many subjects admitted to our hospital due to operation and delivery. Medications for metabolic disorders are shown in Table 3. A total of 949 (22.4%) of the study subjects were taking lipid-lowering agents.

Factors associated with CKD

To clarify the factors associated with CKD, factors potentially associated with atherosclerotic diseases were assessed. A multivariate analysis that included factors with a p values <0.10 in the univariate analyses showed that an older age

[odds ratio (OR) = 1.03, 95% confidence interval (CI) = 1.02-1.04; $p = 3.3\times10^{-4}$], male gender (OR = 1.54, 95% CI = 1.72-1.96; $p = 8.4\times10^{-10}$), hypertension (OR = 5.58, 95% CI = 4.18-7.57; $p <2.0\times10^{-16}$), diabetes (OR = 1.32, 95% CI = 1.09-1.61; p = 0.0053), and high triglyceride (OR = 1.00, 95% CI = 1.00-1.00; p = 0.005) and Lp(a) levels (OR = 1.12, 95% CI = 1.08-1.17; $p = 1.3\times10^{-7}$, per 10 mg/dL) were independently associated with the presence of CKD (Table 4). This trend in Lp(a) was unchanged even after accounting for CAD (OR = 1.10, 95% CI = 1.03-1.24; $p = 2.9\times10^{-6}$, per 10 mg/dL, in model 2).

Factors associated with CAD

To clarify the factors associated with CAD, factors potentially associated with atherosclerotic diseases were assessed. A multivariate analysis that included factors with a p value <0.10 in the univariate analyses showed that an older age (OR = 1.04, 95% CI = 1.03-1.05; $p <2.0\times10^{-16}$), male gender (OR = 1.52, 95% CI = 1.21-1.92; $p = 3.8\times10^{-4}$), hypertension (OR = 3.71, 95% CI = 2.89-4.80; $p <2.0\times10^{-16}$), smoking (OR = 3.32, 95% CI = 2.65-4.18; $p <2.0\times10^{-16}$), and high levels of Lp(a) (OR = 1.11, 95% CI = 1.06-1.16; $p = 1.7\times10^{-6}$, per 10 mg/dL) were independently associated with the presence of CAD (Table 5). This trend in Lp(a) was unchanged even after accounting for CKD (OR = 1.09, 95% CI = 1.04-1.14; $p = 6.8\times10^{-5}$, per 10 mg/dL, in model 2).

Risk discrimination for CKD by Lp(a)

The present study further investigated whether or not the discrimination ability of a model based on traditional risk factors associated with CKD in this study (age, gender, hypertension, diabetes, and triglycerides) differed from that of a model that included Lp(a). The C-statistic for the traditional risk factor model was 0.775 (95% CI = 0.759-0.792),

Table 4.   Factors Associated with CKD.

Characteristics	Model 1		Model 2	
	OR (95% CI)	p value	OR (95% CI)	p value
Age	1.03 (1.02-1.04)	$3.3×10^{-4}$	1.03 (1.02-1.04)	$5.9×10^{-4}$
Male	1.54 (1.22-1.96)	$8.4×10^{-10}$	1.74 (1.22-1.96)	$7.9×10^{-9}$
BMI	0.99 (0.96-1.01)	0.21	0.99 (0.97-1.01)	0.32
Hypertension	5.58 (4.18-7.57)	$<2×10^{-16}$	6.05 (4.04-7.96)	$<2×10^{-16}$
Diabetes	1.32 (1.09-1.61)	0.0053	1.45 (1.11-1.84)	0.0021
Smoking	0.99 (0.79-1.25)	0.95	0.99 (0.81-1.21)	0.89
LDL cholesterol	0.99 (0.99-1.00)	0.15	0.99 (0.99-1.00)	0.21
Triglycerides	1.00 (1.00-1.00)	0.005	1.00 (1.00-1.00)	0.0084
Lp(a) (per *10 mg/dL*)	1.12 (1.08-1.17)	$1.3×10^{-7}$	1.10 (1.03-1.24)	$2.9×10^{-6}$
CAD			1.17 (1.02-1.34)	0.0024

CKD: chronic kidney disease, BMI: body mass index, LDL: low-density lipoprotein, Lp(a): Lipoprotein (a), CAD: coronary artery disease, OR: odds ratio

Table 5.   Factors Associated with CAD.

Characteristics	Model 1		Model 2	
	OR (95% CI)	p value	OR (95% CI)	p value
Age	1.04 (1.03-1.05)	$<2×10^{-16}$	1.04 (1.03-1.05)	$<2×10^{-16}$
Male	1.52 (1.21-1.92)	$3.8×10^{-4}$	1.55 (1.18-1.99)	$1.2×10^{-4}$
BMI	0.99 (0.97-1.01)	0.48	0.99 (0.98-1.01)	0.64
Hypertension	3.71 (2.89-4.80)	$<2×10^{-16}$	4.32 (2.64-4.97)	$<2×10^{-16}$
Diabetes	1.12 (0.93-1.36)	0.22	1.25 (0.75-1.65)	0.55
Smoking	3.32 (2.65-4.18)	$<2×10^{-16}$	3.70 (2.67-4.10)	$<2×10^{-16}$
LDL cholesterol	1.00 (0.99-1.01)	0.78	1.00 (0.99-1.01)	0.82
Triglycerides	1.00 (1.00-1.00)	0.55	1.00 (1.00-1.00)	0.49
Lp(a) (per *10 mg/dL*)	1.11 (1.06-1.16)	$1.7×10^{-6}$	1.09 (1.04-1.14)	$6.8×10^{-5}$
CKD			1.15 (1.00-1.30)	0.008

CAD: coronary artery disease, LDL: low-density lipoprotein, Lp(a): Lipoprotein (a), CKD: chronic kidney disease, OR: odds ratio

which increased to 0.781 (95% CI = 0.764-0.797; Figure, p = 0.00733) after incorporating Lp(a) into the model.

Discussion

In the present study, the association between the Lp(a) levels and CKD in hospitalized Japanese patients was retrospectively investigated. Lp(a) was found to be significantly associated with CKD in this Japanese population, independent of other traditional risk factors, along with CAD.

Lp(a) and development of CKD

Since the discovery of Lp(a) in 1963 (26), studies have reported the association between elevated Lp(a) levels and CKD in populations of different ethnicities (13, 15). The current study provides additional evidence concerning this issue in the Japanese population.

Regarding the etiological association of whether reduced GFR causes an increase in Lp(a) or vice versa, both appear to be true. Concerning the reduced GFR-induced increase in Lp(a), as clarified by Kronenberg et al., Lp(a) levels begin to increase with decreasing GFR, increasing to fourfold

higher in patients with nephrotic-range proteinuria than in healthy controls (27). Concentrations are increased and influenced by the GFR and the amount of proteinuria. This may be due to increased synthesis, similar to that in patients with nephrotic syndrome or those treated by peritoneal dialysis. In patients undergoing hemodialysis, a catabolic block is the reason for this increase (28). Concerning the Lp(a) increase-induced reduction in the GFR, Lp(a) has marked homology with plasminogen, and it has been shown *in vitro* to competitively inhibit the fibrin-dependent activation of plasminogen to plasmin, which plays a crucial role in the catabolism of extracellular matrix proteins, resulting in a reduced GFR (29). Furthermore, a recent Mendelian randomization study showed that reduced Lp(a) levels since birth appear to have a protective effect against the development of CKD (19), suggesting that Lp(a) itself has some etiological role in the development of CKD.

Lp(a) in patients with CKD

In addition to the development of CKD itself, Lp(a) levels have been shown to be associated with adverse events in patients with CKD (30, 31). Accordingly, the assessment of
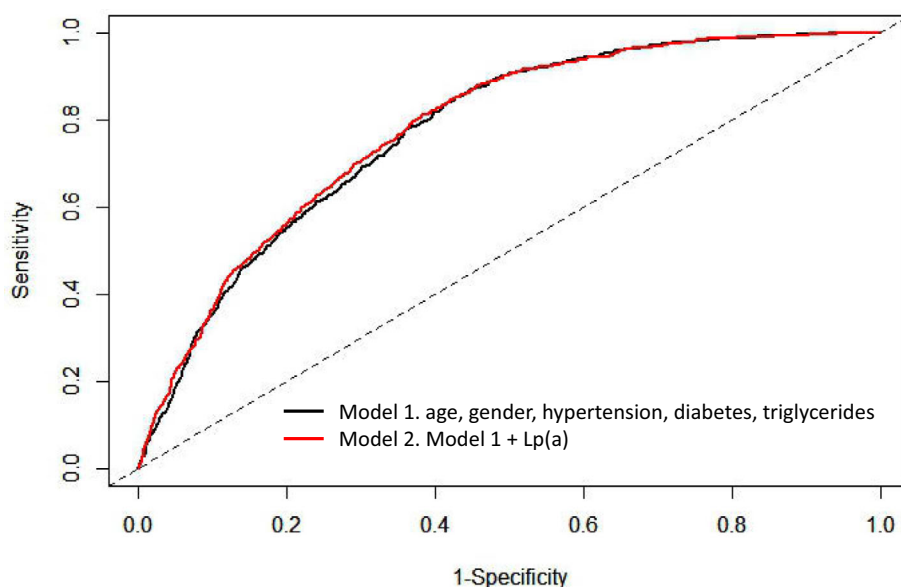
Figure.   Receiver operating characteristic curve. The black line (Model 1) indicates the receiver operating characteristic curve using traditional risk factors. Traditional risk factors were age, gender, hypertension, diabetes, and triglycerides. The red line indicates (Model 2) the receiver operating characteristic curve using the traditional risk factors and Lp (a).

the Lp(a) levels in the routine management of patients with any-stage CKD is recommended.

Study limitations

Several limitations associated with the present study warrant mention. First, this was a retrospective, cross-sectional, observational analysis. Thus, this study cannot show the causal relationship between Lp(a) and CKD directly. Prospective randomized control studies are needed to confirm this issue. However, it investigated one of the largest sample sizes regarding Lp(a) and CKD in a Japanese population, potentially contributing to a better understanding of this issue in populations of different ethnicities. In addition, study findings regarding factors associated with CKD were quite consistent with those in previous studies. Second, the study investigated subjects who had their serum Lp(a) levels measured for any reason, which may have resulted in some bias. In hospitals, most patients who undergo any type of surgery requiring prolonged bed rest and those with any risk factors for systemic atherosclerosis undergo a routine serum Lp(a) level assessment. These factors, along with the large sample size, may have diluted the referred bias. Third, the assay used in this study may have been affected to some extent by the number of Kringle IV domains (32). Therefore, further studies using an assay insensitive to apo(a) isoform size heterogeneity should be performed in a Japanese population. Fourth, we failed to observe a significant association between the LDL-C level and CAD in this study. However, 949 (22.4%) of the study subjects were taking some sort of lipid-lowering agent, which likely affected the association between the LDL-C level and CAD in this cross-sectional study.

In conclusion, serum Lp(a) was associated with the devel-

opment of CKD, independent of other classical risk factors in the Japanese population, which is an association similar to that observed in populations of other ethnicities. Therefore, the assessment of Lp(a) levels is recommended in Japanese patients with a high risk of developing CKD.

Our study was approved by the Institutional Research Review Boards of Kanazawa University. All patients provided their written informed consent before taking part in the study.

The authors state that they have no Conflict of Interest (COI).

References

1. Levey AS, Coresh J. Chronic kidney disease. Lancet **379**: 165-180, 2012.
2. Stevens PE, O'Donoghue DJ, de Lusignan S, et al. Chronic kidney disease management in the United Kingdom: NEOERICA project results. Kidney Int **72**: 92-99, 2007.
3. Herzog CA, Asinger RW, Berger AK, et al. Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int **80**: 572-586, 2011.
4. Kent S, Schlackow I, Lozano-Kühne J, et al. What is the impact of chronic kidney disease stage and cardiovascular disease on the annual cost of hospital care in moderate-to-severe kidney disease?. BMC Nephrol **16**: 65, 2015.
5. Xie X, Liu Y, Perkovic V, et al. Renin-angiotensin system inhibitors and kidney and cardiovascular outcomes in patients with CKD: a bayesian network meta-analysis of randomized clinical trials. Am J Kidney Dis **67**: 728-741, 2016.
6. National Kidney. Foundation. KDOQI clinical practice guideline for diabetes and CKD: 2012 update. Am J Kidney Dis **60**: 850-886, 2012.
7. Jafar TH, Schmid CH, Landa M, et al. Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A

meta-analysis of patient-level data. Ann Intern Med **135**: 73-87, 2001.

8. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med **345**: 851-860, 2001.

9. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med **345**: 861-869, 2001.

10. Marcovina SM, Koschinsky ML. Lipoprotein(a) as a risk factor for coronary artery disease. Am J Cardiol **82**: 57U-66U, 1998.

11. Anuurad E, Boffa MB, Koschinsky ML, Berglund L. Lipoprotein (a): a unique risk factor for cardiovascular disease. Clin Lab Med **26**: 751-772, 2006.

12. Hobbs HH, White AL. Lipoprotein(a): intrigues and insights. Curr Opin Lipidol **10**: 225-236, 1999.

13. Lin J, Reilly MP, Terembula K, Wilson FP. Plasma lipoprotein(a) levels are associated with mild renal impairment in type 2 diabetics independent of albuminuria. PLoS One **9**: e114397, 2014.

14. Kollerits B, Drechsler C, Krane V, et al. Lipoprotein(a) concentrations, apolipoprotein(a) isoforms and clinical endpoints in haemodialysis patients with type 2 diabetes mellitus: results from the 4D Study. Nephrol Dial Transplant **31**: 1901-1908, 2016.

15. Yun JS, Ahn YB, Song KH, et al. Lipoprotein(a) predicts a new onset of chronic kidney disease in people with Type 2 diabetes mellitus. Diabet Med **33**: 639-643, 2016.

16. Jauhiainen M, Koskinen P, Ehnholm C, et al. Lipoprotein(a) and coronary heart disease risk: a nested case-control study of the Helsinki Heart Study participants. Atherosclerosis **89**: 59-67, 1991.

17. Ridker PM, Hennekens CH, Stampfer MJ. A prospective study of lipoprotein(a) and the risk of myocardial infarction. JAMA **270**: 2195-2199, 1993.

18. Erqou S, Kaptoge S, Perry PL, et al.; Emerging Risk Factors Collaboration. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. JAMA **302**: 412-423, 2009.

19. Emdin CA, Khera AV, Natarajan P, et al. Phenotypic characterization of genetically lowered human lipoprotein(a) levels. J Am Coll Cardiol **68**: 2761-2772, 2016.

20. Khera AV, Everett BM, Caulfield MP, et al. Lipoprotein(a) concentrations, rosuvastatin therapy, and residual vascular risk: an analysis from the JUPITER Trial (justification for the use of statins in prevention: an intervention trial evaluating rosuvastatin). Circulation **129**: 635-642, 2014.

21. O'Donoghue ML, Fazio S, Giugliano RP, et al. Lipoprotein(a), PCSK9 inhibition and cardiovascular risk: insights from the FOURIER Trial. Circulation **139**: 1483-1492, 2019.

22. Tada H, Kawashiri MA, Takata M, et al. Infantile cases of sitosterolemia with novel mutations in the ABCG5 gene: extreme hypercholesterolemia is exacerbated by breastfeeding. JIMD Rep **21**: 115-122, 2015.

23. Wu JH, Kao JT, Wen MS, Wu D. Coronary artery disease risk predicted by plasma concentrations of high-density lipoprotein cholesterol, apolipoprotein AI, apolipoprotein B, and lipoprotein(a) in a general Chinese population. Clin Chem **39**: 209-212, 1993.

24. Seino Y, Nanjo K, Tajima N, et al.; Committee of the Japan Diabetes Society on the Diagnostic Criteria of Diabetes Mellitus. Report of the committee on the classification and diagnostic criteria of diabetes mellitus. J Diabetes Investig **1**: 212-228, 2010.

25. Matsuo S, Imai E, Horio M, et al. Collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidey Dis **53**: 982-992, 2009.

26. Berg K. A new serum type system in man-the LP system. Acta Pathol Microbiol Scand **59**: 369-382, 1963.

27. Kronenberg F. Causes and consequences of lipoprotein(a) abnormalities in kidney disease. Clin Exp Nephrol **18**: 234-237, 2014.

28. Ikewaki K. *In vivo* kinetic studies to further understand pathogenesis of abnormal lipoprotein metabolism in chronic kidney disease. Clin Exp Nephrol **18**: 261-264, 2014.

29. Hervio L, Girard-Globa A, Durlach V, Anglés-Cano E. The antifibrinolytic effect of lipoprotein(a) in heterozygous subjects is modulated by the relative concentration of each of the apolipoprotein(a) isoforms and their affinity for fibrin. Eur J Clin Invest **26**: 411-417, 1996.

30. Konishi H, Miyauchi K, Tsuboi S, et al. Plasma lipoprotein(a) predicts major cardiovascular events in patients with chronic kidney disease who undergo percutaneous coronary intervention. Int J Cardiol **205**: 50-53, 2016.

31. Xu N, Tang XF, Yao Y, et al. Association of plasma lipoprotein(a) with long-term adverse events in patients with chronic kidney disease who underwent percutaneous coronary intervention. Am J Cardiol **122**: 2043-2048, 2018.

32. Marcovina SM, Albers JJ, Scanu AM, et al. Use of a reference material proposed by the International Federation of Clinical Chemistry and Laboratory Medicine to evaluate analytical methods for the determination of plasma lipoprotein(a). Clin Chem **46**: 1956-1967, 2000.