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Plasma lipoprotein(a) predicts major cardiovascular events in patients with chronic kidney disease who undergo percutaneous coronary intervention

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ABSTRACT

Background: Chronic kidney disease (CKD) is associated with increased risk for cardiovascular disease. The predictive power of traditional risk factors for cardiovascular disease is diminished in patients with CKD. The serum level of lipoprotein(a) [Lp(a)] can be a risk factor for adverse events, but the clinical implications of Lp(a) in patients with CKD who have been treated by percutaneous coronary intervention (PCI) remain uncertain. We aimed to determine the role of Lp(a) on long-term outcomes in patients with CKD after PCI.

Methods: We analyzed data from 904 patients with CKD among 3508 patients who underwent a first PCI between 1997 and 2011 at our institution. We divided patients into 2 groups [high (n = 454) or low (n = 450)] according to median levels of Lp(a). The primary outcome was a composite of all-cause death and acute coronary syndrome (ACS).

Results: The baseline characteristics of the groups were similar and the median follow-up period was 4.7 years. Cumulative event-free survival was significantly worse for the group with high, than low Lp(a) (P = 0.01). Multivariable analysis indicated a high Lp(a) level as an independent predictor of primary outcomes (hazard ratio, 1.35; 95% CI, 1.01–1.82; P = 0.04).

Conclusions: A high Lp(a) value is associated with a poor prognosis after PCI for patients with CKD.

1. Introduction

Chronic kidney disease (CKD) is defined as either kidney damage or decreased kidney function with a decreased glomerular filtration rate persisting for over three months [1]. Although some cardiovascular risk factors such as hypertension, diabetes, dyslipidemia, smoking and advanced age are more prevalent among patients with CKD [2], CKD itself is considered an independent risk factor for cardiovascular disease (CVD) even if kidney function is only mildly impaired [1,3]. This might be explained by evidence showing that CKD is associated with endothelial dysfunction and inflammatory activity [4,5]. Cardiovascular disease is the main cause of death among patients with CKD [6], and the risk of mortality due to CVD increases as glomerular filtration rates decline [7]. Therefore, patients with CKD are recognized to be at high risk for cardiovascular morbidity and mortality during both the primary [3,8] and secondary [9,10] prevention of coronary artery disease (CAD). Despite recent advances in the devices, technology and techniques associated with percutaneous coronary intervention (PCI), major cardiovascular events remain major issues for patients with CKD even in the era of drug eluting stents (DES) [11]. Therefore, residual risk factors involved in cardiovascular events should be investigated in patients with CKD to reduce such events.

Lipoprotein(a) [Lp(a)] is a modified low-density lipoprotein in which a disulfide bridge covalently binds the large glycoprotein apolipoprotein (a) to apolipoprotein B [12]. Elevated serum levels of Lp(a) are consequently associated with an increased risk of major adverse cardiac events in patients with CAD after PCI [13,14].

Several studies of the primary prevention of CAD in patients with CKD have associated high serum Lp(a) levels with increased of risk for CVD [15,16], whereas others have found no such correlation [17]. Therefore, whether Lp(a) contributes to increased risk of cardiovascular disease in patients with CKD remains unclear. Furthermore, no evidence has yet associated serum Lp(a) levels with long-term outcomes of secondary CAD prevention in patients with CKD. We therefore investigated the impact of Lp(a) on long-term outcomes of patients with CKD after PCI.

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2. Methods

2.1. Patients

We analyzed data from a single center, observational study of patients who underwent PCI at Juntendo University Hospital (Tokyo, Japan) between January 1997 and October 2011. All patients were Japanese. We enrolled patients with CKD defined as an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 and calculated eGFR based on the modification of diet in renal disease equation modified with a Japanese coefficient using baseline serum creatinine [18]. The exclusion criteria comprised missing Lp(a) data (n = 82) and being on dialysis, since the extent and severity of CAD among patients on hemodialysis are disproportionate to the traditional risk factor profile [19]. The patients were divided into 2 groups [high Lp(a) or low Lp(a)] according to median levels of Lp(a). The internal review board of Juntendo University Hospital approved this study in which all patients provided written, informed consent to participate.

2.2. Data collection

Baseline data including age, gender, body mass index (BMI), blood pressure (BP), total cholesterol, HDL-C, LDL-C, triglycerides, Lp(a), fasting blood glucose (FBG) at the time of PCI, smoking status, family history of CAD, medication use, factors associated with revascularization procedures and comorbidities were prospectively collected and analyzed. Blood samples were collected during the early morning after an overnight fast. Hypertension was defined as systolic blood pressure (BP) ≥140 mmHg, diastolic BP ≥90 mmHg or medication with antihypertensive drugs. Diabetes mellitus was defined as fasting plasma glycemic levels ≥126 mg/dL, medication with oral hypoglycemic drugs or insulin injections. A current smoker was defined as a person who smoked at the time of PCI or who had quit smoking within the year before PCI. Indications for PCI were based on objective evidence of myocardial ischemia (positive stress test), ischemic symptoms, or signs associated with significant angiographic stenosis.

Levels of Lp(a) were measured using latex agglutination immunoassays which is not affected by apo(a) isoform variation (Special Reference Laboratories, Hachioji, Japan).

2.3. Outcome data

The follow-up period ended on December 31, 2011. Survival data and information about incident acute coronary syndrome (ACS) were collected by serial contact with the patients or their families, and assessed from the medical records of patients who had died or of those who were followed up at our hospital. Information about the circumstances and date of death were obtained from the families of patients who died at home, and details of events and the cause of death were supplied by other hospitals or clinics where the patients had been admitted. All data were collected by blinded investigators. We defined ACS as ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI) or unstable angina (UAP). We determined STEMI based on symptoms of ischemia with ST-segment elevation on ECG and increased serum levels of cardiac enzymes (troponin, CK-MB, CK ≥2-fold increase) [20,21] and NSTEMI based on symptoms of ischemia without ST-segment elevation on ECG and increased serum levels of cardiac enzymes. Unstable angina pectoris was determined based on symptoms of ischemia at rest or having a crescendo of symptoms or new-onset symptoms associated with transient ischemic ST-segment shifts and normal serum levels of cardiac enzymes [22]. The primary outcome was a composite of all-cause death and incident ACS.

2.4. Statistical analysis

The results are expressed as means ± SD or medians (interquartile range, IQR) for continuous variables and as ratios (%) for categorical variables. Baseline data were compared using unpaired t-tests or Mann–Whitney U-tests for continuous variables and χ^2 or Fisher's exact tests for categorical variables. Kaplan–Meier event-free survival curves were compared using log-rank test. Factors associated with outcomes were determined using univariable Cox regression analysis including age, gender, BMI, hypertension, diabetes mellitus, LDL-C, HDL-C, triglycerides, high or low Lp(a) levels, current smoker, eGFR, ACS, left ventricular ejection fraction, multivessel disease, type B2/C lesions, left anterior descending lesions, drug eluting stents, β-blockers, angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers and statins as independent variables. Variables with significant or borderline significant associations (P < 0.10) with outcomes were then included in multivariable Cox regression analyses. The assumption of proportional hazards was assessed using a log-minus-log survival graph. P < 0.05 was considered to indicate significance unless otherwise indicated. All data were analyzed using JMP 10.0 MDSU statistical software (SAS Institute, Cary, NC, USA).

3. Results

3.1. Characteristics of patients

We selected 1079 patients with CKD from among 3508 patients who underwent PCI. Patients on dialysis and those who did not have Lp(a) data at the time of PCI were excluded. Table 1 shows the baseline characteristics of the remaining 904 patients. By definition, Lp(a) levels were significantly higher in the group with high, than with low Lp(a). All other characteristics were the similar between the two groups.

Table 1
Baseline characteristics of the patients.

	Low Lp(a) (n = 450)	High Lp(a) (n = 454)	P
Age	70.1 ± 9.2	69.9 ± 9.4	0.76
Male, n (%)	366 (81.3)	358 (78.9)	0.38
BMI	24.2 ± 3.6	24.0 ± 3.3	0.52
Current smoker, n (%)	81 (18.0)	86 (18.9)	0.85
HT, n (%)	347 (77.1)	344 (75.8)	0.65
DM, n (%)	169 (37.6)	199 (43.8)	0.10
LDL-C (mg/dL)	108.4 ± 32.2	112.9 ± 34.2	0.07
HDL-C (mg/dL)	43.6 ± 12.3	43.2 ± 12.6	0.66
TG (mg/dL)	135.3 ± 75.3	128.6 ± 65.7	0.21
Lp(a) (mg/dL)	12.5 ± 5.7	42.0 ± 22.6	<0.01
eGFR (mL/min/1.73 m^2)	46.9 ± 9.8	46.1 ± 10.6	0.35
LVEF (%)	61.1 ± 13.9	61.4 ± 14.5	0.73
ACS, n (%)	109 (24.2)	108 (23.8)	0.88
Multivessel disease, n (%)	255 (56.7)	270 (59.5)	0.35
Type B2/C lesion, n (%)	393 (87.3)	394 (86.8)	0.85
LAD lesion, n (%)	193 (42.9)	193 (42.5)	0.96
Drug eluting stent, n (%)	161 (35.8)	148 (32.6)	0.39
Use of medication			
Aspirin, n (%)	432 (96.0)	432 (95.2)	0.58
Antiplatelet drug, n (%)	359 (79.8)	364 (80.2)	0.45
β-blocker, n (%)	218 (48.4)	207 (45.6)	0.44
ACE-I/ARB, n (%)	238 (52.9)	216 (47.6)	0.12
Calcium channel blocker, n (%)	219 (48.7)	214 (47.1)	0.59
Statin, n (%)	203 (45.1)	221 (48.7)	0.28
Insulin, n (%)	68 (15.1)	81 (17.8)	0.11

ACE-I, angiotensin-converting enzyme inhibitors; ACS, acute coronary syndrome; ARB, angiotensin-receptor blockers; BMI, body mass index; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein; HT, hypertension; LAD, left anterior descending; LDL-C, low-density lipoprotein; Lp(a), Lipoprotein(a); LVEF, left ventricular ejection fraction; OHA, oral hypoglycemic agents; TG, triglycerides.

3.2. Outcome data

Outcome data were fully documented during the follow-up period (median, 4.7 years; IQR, 1.2–6.4). Fig. 1 shows event-free survival curves. The incidence of all-cause death and/or ACS was significantly higher in the group with high, than with low Lp(a) levels. Among the composite endpoint, event rate of cardiac death and ACS were higher in the group with high, than with low Lp(a) levels (Table 2). Univariate analysis identified age, BMI, Lp(a) (high/low), eGFR, ACS, left ventricular ejection fraction (LVEF), multivessel disease, drug eluting stent, β-blockers and statins as significant variables (Table 3). Multivariable

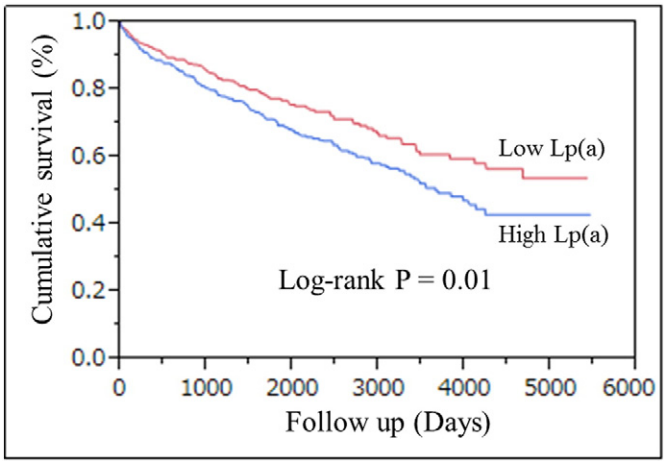

Fig. 1. Kaplan–Meier curve for composite endpoint of all-cause death and ACS. Outcomes are significantly worse for patients with high, than low Lp(a) (P = 0.01; Log-rank test).