Impact of Lipoprotein(a) As Residual Risk on Long-term Outcomes in Patients After Percutaneous Coronary Intervention

Hirokazu Konishi, MD; Katsumi Miyauchi, MD; Takatoshi Kasai, MD, PhD; Shuta Tsuboi, MD, PhD; Manabu Ogita, MD, PhD; Ryo Naito, MD; Eiryu Sai, MD, PhD; Yoshifumi Fukushima, MD, PhD; Yoshiteru Katoh, MD, Iwao Okai, MD; Hiroshi Tamura, MD; Shinya Okazaki, MD; Hiroyuki Daida, MD

Department of Cardiology, Juntendo University School of Medicine, Tokyo, Japan

Address for correspondence:

Katsumi Miyauchi, MD

Department of Cardiology, Juntendo University School of Medicine

2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8431, Japan

Tel: +81-3-5802-1056; Fax: +81-3-5689-0627

E-mail: ktmmy@med.juntendo.ac.jp

Abstract

Cardiovascular risk remains uncertain in patients with cardiovascular disease (CVD) despite achieving target lipid levels. Serum levels of lipoprotein (a) [Lp(a)] can be risk factors for adverse events. Aim of this study was to determine the role of Lp(a) as a residual risk factor in patients who achieve target lipid levels by the time of treatment by percutaneous coronary intervention (PCI). A total of 3,508 patients were treated by PCI between 1997 and 2011 at our institution. Among them, we analyzed consecutive 569 patients who achieved target lipid levels of low density lipoprotein cholesterol (LDL-C) < 100 mg/dL, high density lipoprotein cholesterol (HDL-C) ≥ 40 mg/dL and triglycerides <150 mg/dL at PCI. Eligible 411 patients were assigned to groups according to Lp(a) levels of ≥ 30 mg/dL [high Lp(a)] (n=119) or < 30 mg/dL [low Lp(a)] (n=292). The primary outcome was a composite of all-cause death and acute coronary syndrome (ACS). The median follow-up period was 4.7 years. Cumulative event-free survival was significantly worse for the group with high Lp(a) than with low Lp(a) group (P = 0.04). Multivariable analysis selected a high Lp(a) level as an independent predictor of primary outcomes (hazard ratio [HR], 1.68; 95% confidence interval [95%CI],1.03-2.70; p=0.04). In conclusion, A high Lp(a) value (≥30 mg/dL) could be associated with a poor prognosis after PCI even for patients who achieved target lipid levels.

Key Words: lipoprotein(a), cardiovascular disease, lipid-lowering, prognosis

Introduction

Lipoprotein (a) [Lp(a)] is a modified form of low density lipoprotein in which the large glycoprotein apolipoprotein(a) is covalently bound to apolipoprotein B by a disulfide bridge [1]. Consequently, elevated high serum levels of Lp(a) are associated with increased risk of major adverse cardiac events in patients with coronary artery disease (CAD) after percutaneous coronary intervention (PCI) [2,3]. However, one significant limitation to these studies is that the clinical relevance of Lp(a) within the context of an optimal lipid profile was not investigated. The importance of the Lp(a) level independently of other lipid parameters and its potential to be a residual risk factor beyond other lipid parameters remains unknown. We therefore investigated the impact of Lp(a) on the long-term outcomes of patients who achieved target lipid profiles at the time of PCI.

Methods

Consecutive Japanese patients who underwent PCI at Juntendo University Hospital (Tokyo, Japan) between January 1997 and October 2011 were considered for this analysis. We enrolled only those who achieved target levels of LDL-C < 100 mg/dL, HDL-C ≥ 40 mg/dL and triglycerides < 150 mg/dL based on guidelines that were current [4 5] at the time of PCI. The exclusion criteria were as follows: 1) missing Lp(a) data 2) kidney dysfunction defined as estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, since Lp(a) plasma levels are obviously increased in such patients due to kidney dysfunction [6] 3) the medications that affect Lp(a) levels (nicotinic acid including niceritrol, tocopherol nicotinate and nicomol).

Baseline data, revascularization procedure-related factors and comorbidities were prospectively collected from each patients. Blood samples were collected during the early morning after an overnight fast. Levels of Lp(a) were measured using latex agglutination immunoassays (Special Reference Laboratories, Hachioji, Japan). The patients were assigned to groups based on serum Lp(a) levels of < 30 or ≥ 30 mg/dL because 90% of healthy Japanese populations have Lp(a) < 30 mg/dL [7], published reports suggest that ≥ 30 mg/dL Lp(a) confers pathological and epidemiological effects [8,9], and this value is the most prevalent cutoff [10,11].

Survival data and information about incident acute coronary syndrome (ACS) were collected by blinded investigators. The primary outcome was a composite of all-cause death and ACS.

The results are expressed as means ± SD or medians (interquartile range) for continuous

variables and as ratios (%) for categorical variables. Baseline data were compared using an unpaired t-test or the Mann-Whitney U-test for continuous variables and the chi squared test or Fisher's exact test for categorical variables. Kaplan-Meier event-free survival curves were compared using the log-rank test. Factors associated with outcomes were determined using univariable Cox regression analysis. Variables with significant or borderline significant associations ($P < 0.10$) with outcomes were then included in multivariable Cox regression analyses. $P < 0.05$ was considered to indicate significance, unless otherwise indicated. All data were analyzed using JMP10.0 MDSU statistical software (SAS Institute, Cary, NC, USA).

Results

Among 3,508 patients who underwent PCI, 569 achieved target levels of all conventional lipid parameters at the time of PCI. Figure 1 shows the remaining 292 and 119 patients with serum Lp(a) < 30 mg/dL [low Lp(a)] and ≥ 30 mg/dL [high Lp(a)] respectively who were finally assessed. TypeB2/C lesions were more likely to be associated with high Lp(a) group compared to low Lp(a) group (Table1). However, no other variables significantly differed between the two groups. Outcome data were fully documented during the follow-up period (median 4.7 years, interquartile range: 1.2 - 6.4). During the follow-up, 53 (12.9%) patients died due to cardiac death (n = 9), carcinoma (n = 10), stroke (n = 3) and other causes (n = 12) in the low Lp(a)

group, and cardiac death (n = 8), carcinoma (n = 3), stroke (n = 1) and other causes (n = 7) in High Lp(a) group. Furthermore 28 (6.8%) patients developed ACS comprising STEMI (n = 6), NSTEMI (n = 2), and UAP (n = 9) in the low Lp(a) group, and STEMI (n = 5), NSTEMI (n = 1) and UAP (n = 5) in high Lp(a) group. Figure 2 shows event-free survival curves. The incidence of all-cause death and/or ACS was significantly higher in the group with high Lp(a) than with low Lp(a). Multivariate Cox proportional hazards regression analysis revealed that Lp(a) and ACS were significant independent predictors of a worse outcome (HR, 1.68; 95%CI, 1.03-2.70; P = 0.04 and HR, 1.82; 95%CI, 1.08-3.07; P = 0.03, respectively) (Table 2).

Discussion

Serum levels of Lp(a) ≥ 30 mg/dL were associated with increased risk of death or ACS recurrence even among patients who had achieved the recommended target levels of all conventional lipid parameters (LDL-C < 100 mg/dL, HDL-C ≥ 40 mg/dL and triglycerides < 150 mg/dL) at the time of PCI. This is notable because one specific dyslipidemic condition was identified as a residual risk factor for increased mortality or CAD recurrence beyond LDL-C and other conventional dyslipidemic conditions including hypertriglyceridemia and low HDL-C. For secondary prevention of CAD, The American Heart Association/American College of Cardiology Foundation guidelines recommend achieving target levels of conventional lipid

parameters: non-HDL-C < 130 mg/dL (if triglycerides ≥ 200 mg/dL) in addition to LDL-C < 100 mg/dL [5], and the Japanese Atherosclerosis Society recommends achieving LDL-C < 100 mg/dL, HDL-C ≥ 40 mg/dL and triglycerides <150 mg/dL [4]. However, many patients with CAD subsequently die or develop recurrent CAD despite achieving these target levels [12,13].

Several previous studies have already indicated relationships between serum Lp(a) ≥ 30 mg/dL and increased risk of CVD in patients with CAD [14,15]. One study found that among 266 patients with acute myocardial infarction, baseline Lp(a) ≥ 30 mg/dL was associated with a 62% increase in cardiac deaths during a three year follow-up [16]. A Japanese group reported that high Lp(a) was an independent risk factor for major adverse cardiac events after acute myocardial infarction [2]. The present study is the first to demonstrate that Lp(a) levels are also clinically important for patients who have achieved target lipid profiles of LDL-C < 100 mg/dL, triglycerides < 150 mg/dL and HDL-C > 40 mg/dL by the time they are treated by PCI.

Follow-up angiography [11] and intravascular ultrasound (IVUS) [17] have uncovered close correlations between Lp(a) and plaque progression, as well as coronary artery calcification determined by computed tomography (CT) [18]. The present study found a higher frequency of more severe type B2/C lesions in the group with high Lp(a) than with low Lp(a). The pathophysiological role of Lp(a) in CAD progression is explained by the atherogenic and inhibitory effects of Lp(a) on fibrinolysis. Accumulating Lp(a) in atherosclerotic plaques

promotes cholesterol accumulation in macrophages that form foam cells [19] as well as the proliferation and migration of smooth muscle cells in atherosclerotic lesions [20]. Because structural similarity with plasminogen, binding to fibrin and exerting anti-fibrinolytic actions, Lp(a) causes thrombosis [21]. These might have contributed to the significantly worse outcomes of the group with high Lp(a) in the present study.

Serum Lp(a) levels are genetically determined; > 90% of the variance in Lp(a) concentrations can be explained by genetics and it cannot be altered by diet or exercise [22]. However, some drugs can modify Lp(a) levels; niacin (nicotinic acid) can decrease Lp(a) levels by 20% - 30% and is the most effective [23]. Whether or not the ability of niacin to lower Lp(a) contributes to a reduction in risk for cardiovascular events remains unclear [24]. Current guideline are still uncertain about Lp(a) since an effect of Lp(a)-reduction drugs remains unclear. However, the present study showed serum levels of Lp(a) could predict worse clinical outcomes for patients with CAD who achieve target lipid levels at the time of PCI. Even though patients with CAD have already reduced risk with respect to conventional lipid parameters, confirming whether Lp(a) values are ≥ 30 or < 30 mg/dL might further help to reduce CVD morbidity and mortality. A recent report describes that some novel drugs might modulate Lp(a) levels. For example, the cholesterol ester transfer protein inhibitor anacetrapib decreased Lp(a) by 38.8% after 76 weeks [25]. Proprotein convertase subtilisin/kexin 9 inhibitor also decreased Lp(a) levels by 10% to 30%

after 12 weeks [26]. Drug therapy that targets Lp(a) reduction might have potential for secondary prevention of CAD beyond other conventional lipid-targeted therapies. Therefore further study are necessary to clarify if a pharmacotherapy, modulating Lp(a) levels, can be useful to reduce cardiovascular events.

The present observational study has some limitations. The study cohort was small and PCI proceeded at a single center. Although we applied multivariable Cox proportional hazards models including several known confounding variables, other unknown confounders might have played more roles.

Acknowledgements: This study was supported in grant-in aid for scientific research from Ministry of Health, Labour and Welfare (23591063). We gratefully acknowledge Ms. Yumi Nozawa and Ms. Ayako Onodera for data collection and management.

Disclosure: The authors have no conflicts of interest to disclose.

References

1. 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.

2. 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.

3. Kardys I, Oemrawsingh RM, Kay IP, Jones GT, McCormick SP, Daemen J, Van Geuns RJ, Boersma E, Van Domburg RT, Serruys PW. Lipoprotein(a), interleukin-10, C-reactive protein, and 8-year outcome after percutaneous coronary intervention. *Clin Cardiol* 2012;35:482-489.

4. Teramoto T, Sasaki J, Ishibashi S, Birou S, Daida H, Dohi S, Egusa G, Hiro T, Hirobe K, Iida M, Kihara S, Kinoshita M, Maruyama C, Ohta T, Okamura T, Yamashita S, Yokode M, Yokote K. Comprehensive risk management for the prevention of cardiovascular disease: executive summary of the Japan Atherosclerosis Society (JAS) guidelines for the diagnosis and prevention of atherosclerotic cardiovascular diseases in Japan -- 2012. *J Atheroscler Thromb* 2013;20:603-615.

5. Smith SC, Jr., Benjamin EJ, Bonow RO, Braun LT, Creager MA, Franklin BA, Gibbons RJ, Grundy SM, Hiratzka LF, Jones DW, Lloyd-Jones DM, Minissian M, Mosca L, Peterson ED, Sacco RL, Spertus J, Stein JH, Taubert KA. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association. *J Am Coll Cardiol* 2011;58:2432-2446.

6. Kronenberg F, Utermann G, Dieplinger H. Lipoprotein(a) in renal disease. *Am J Kidney Dis* 1996;27:1-25.

7. Abe A, Noma A. Studies on apolipoprotein(a) phenotypes. Part 1. Phenotype frequencies in a healthy Japanese population. *Atherosclerosis* 1992;96:1-8.

8. Loscalzo J. Lipoprotein(a). A unique risk factor for atherothrombotic disease. *Arteriosclerosis* 1990;10:672-679.

9. Scanu AM. Lipoprotein(a). A genetic risk factor for premature coronary heart disease. *JAMA* 1992;267:3326-3329.

10. Kamstrup PR, Benn M, Tybjaerg-Hansen A, Nordestgaard BG. Extreme lipoprotein(a) levels and risk of myocardial infarction in the general population: the Copenhagen City Heart Study. *Circulation* 2008;117:176-184.

11. Matsumoto Y, Daida H, Watanabe Y, Sunayama S, Mokuno H, Yokoi H, Yamaguchi H. High level of lipoprotein(a) is a strong predictor for progression of coronary artery disease. *J Atheroscler Thromb* 1998;5:47-53.

12. Barter P, Gotto AM, LaRosa JC, Maroni J, Szarek M, Grundy SM, Kastelein JJ, Bittner V, Fruchart JC. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. *N Engl J Med* 2007;357:1301-1310.

13. Miller M, Cannon CP, Murphy SA, Qin J, Ray KK, Braunwald E. Impact of triglyceride levels beyond low-density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial. *J Am Coll Cardiol* 2008;51:724-730.

14. Danesh J, Collins R, Peto R. Lipoprotein(a) and coronary heart disease. Meta-analysis of prospective studies. *Circulation* 2000;102:1082-1085.

15. Dangas G, Ambrose JA, D'Agate DJ, Shao JH, Chockalingham S, Levine D, Smith DA. Correlation of serum lipoprotein(a) with the angiographic and clinical presentation of coronary artery disease. *The American journal of cardiology* 1999;83:583-585, A587.

16. Stubbs P, Seed M, Lane D, Collinson P, Kendall F, Noble M. Lipoprotein(a) as a risk predictor for cardiac mortality in patients with acute coronary syndromes. *Eur Heart J* 1998;19:1355-1364.

17. Hartmann M, von Birgelen C, Mintz GS, Stoel MG, Eggebrecht H, Wieneke H, Fahy M,

Neumann T, van der Palen J, Louwerenburg HW, Verhorst PM, Erbel R. Relation between lipoprotein(a) and fibrinogen and serial intravascular ultrasound plaque progression in left main coronary arteries. *J Am Coll Cardiol* 2006;48:446-452.

18. Greif M, Arnoldt T, von Ziegler F, Ruemmler J, Becker C, Wakili R, D'Anastasi M, Schenzle J, Leber AW, Becker A. Lipoprotein (a) is independently correlated with coronary artery calcification. *Eur J Intern Med* 2013;24:75-79.

19. Maher VM, Brown BG. Lipoprotein (a) and coronary heart disease. *Curr Opin Lipidol* 1995;6:229-235.

20. Grainger DJ, Kirschenlohr HL, Metcalfe JC, Weissberg PL, Wade DP, Lawn RM. Proliferation of human smooth muscle cells promoted by lipoprotein(a). *Science* 1993;260:1655-1658.

21. Loscalzo J, Weinfeld M, Fless GM, Scanu AM. Lipoprotein(a), fibrin binding, and plasminogen activation. *Arteriosclerosis* 1990;10:240-245.

22. Seed M, Ayres KL, Humphries SE, Miller GJ. Lipoprotein (a) as a predictor of myocardial infarction in middle-aged men. *Am J Med* 2001;110:22-27.

23. Seed M, O'Connor B, Perombelon N, O'Donnell M, Reaveley D, Knight BL. The effect of nicotinic acid and acipimox on lipoprotein(a) concentration and turnover. *Atherosclerosis* 1993;101:61-68.

24. Albers JJ, Slee A, O'Brien KD, Robinson JG, Kashyap ML, Kwiterovich PO, Jr., Xu P, Marcovina SM. Relationship of apolipoproteins A-1 and B, and lipoprotein(a) to cardiovascular outcomes: the AIM-HIGH Trial (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes). *J Am Coll Cardiol* 2013;62:1575-1579.

25. Cannon CP, Shah S, Dansky HM, Davidson M, Brinton EA, Gotto AM, Stepanavage M, Liu SX, Gibbons P, Ashraf TB, Zafarino J, Mitchel Y, Barter P. Safety of anacetrapib in patients with or at high risk for coronary heart disease. *N Engl J Med* 2010;363:2406-2415.

26. McKenney JM, Koren MJ, Kereiakes DJ, Hanotin C, Ferrand AC, Stein EA. Safety and efficacy of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease, SAR236553/REGN727, in patients with primary hypercholesterolemia receiving ongoing stable atorvastatin therapy. *J Am Coll Cardiol* 2012;59:2344-2353.

Figure legends

Figure 1. Study population

Figure 2. 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 = 0.04; Log-rank test).

Figure 1.

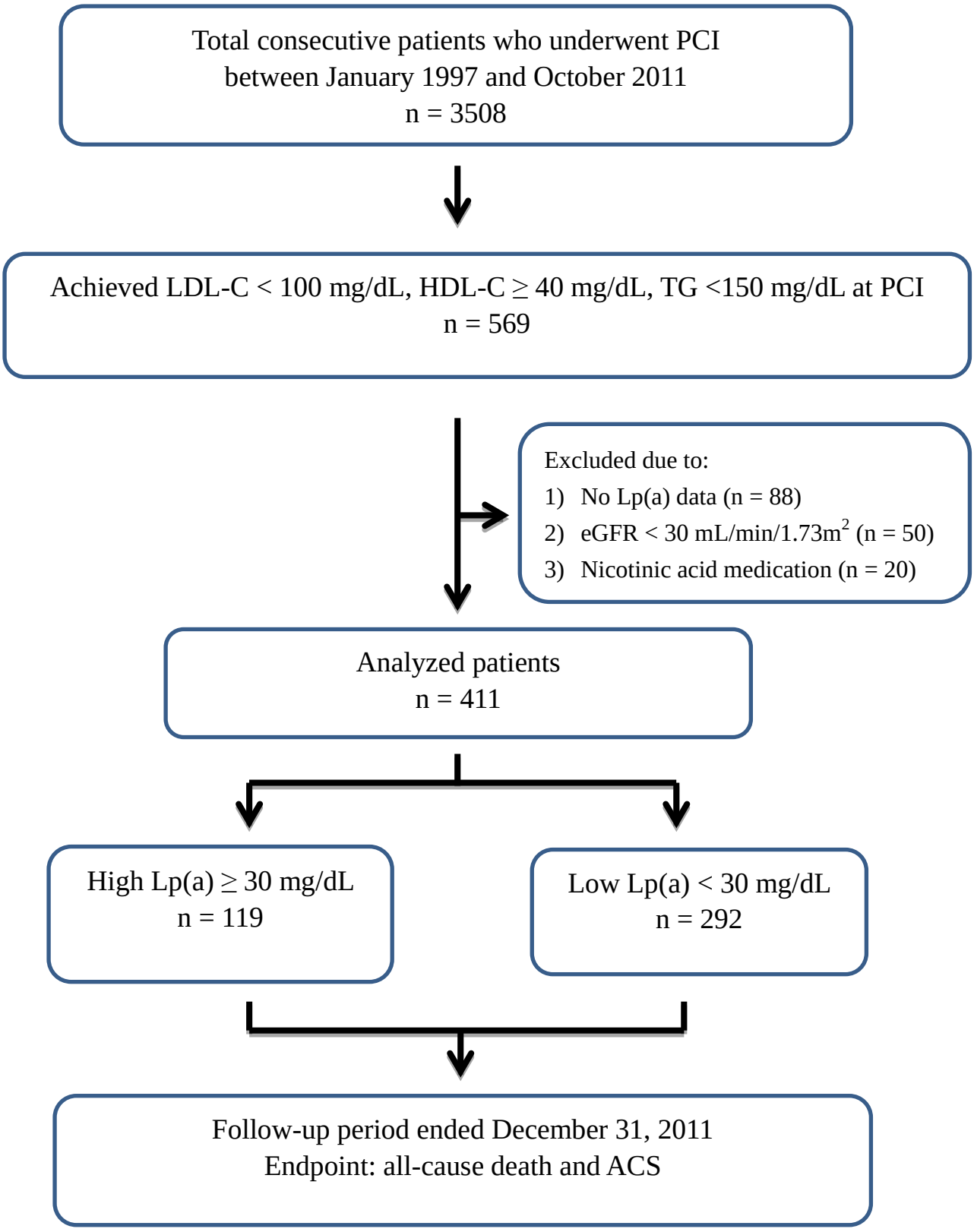
Total consecutive patients who underwent PCI
between January 1997 and October 2011
n = 3508
Achieved LDL-C < 100 mg/dL, HDL-C ≥ 40 mg/dL, TG <150 mg/dL at PCI
n = 569
Excluded due to:
1) No Lp(a) data (n = 88)
2) eGFR < 30 mL/min/1.73m2 (n = 50)
3) Nicotinic acid medication (n = 20)
Analyzed patients
n = 411
High Lp(a) ≥ 30 mg/dL
n = 119
Low Lp(a) < 30 mg/dL
n = 292
Follow-up period ended December 31, 2011
Endpoint: all-cause death and ACS

Figure 2.

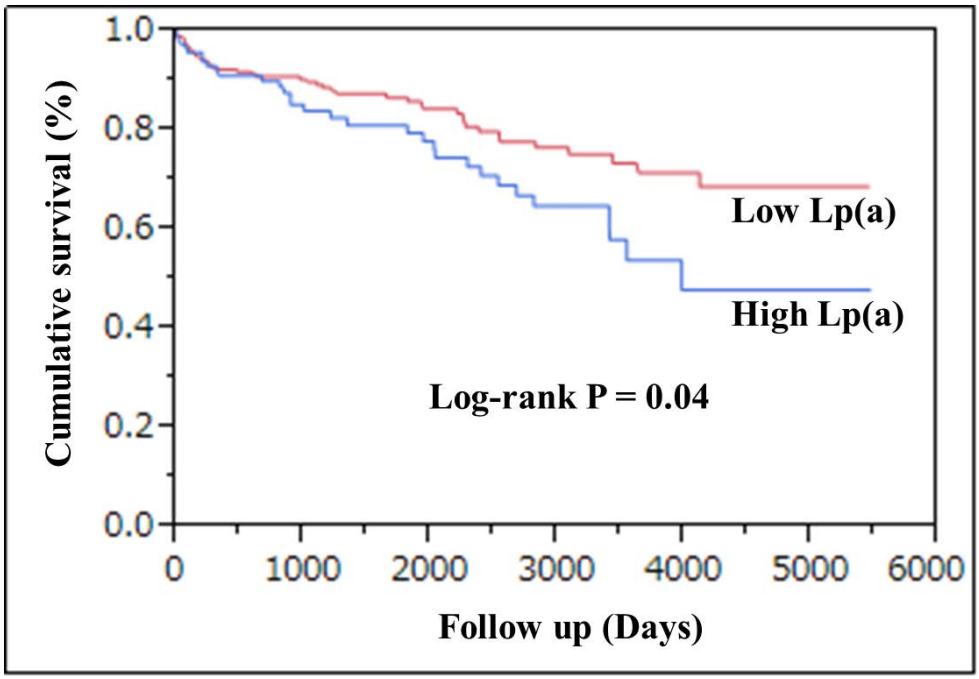
1.0
0.8
0.6
0.4
0.2
0.0
Cumulative survival (%)
Low Lp(a)
High Lp(a)
Log-rank P = 0.04
0
1000
2000
3000
4000
5000
6000
Follow up (Days)

Table 1: Baseline characteristics of the patients.

	Low Lp (a) (n = 292)	High Lp (a) (n = 119)	P
Age (years)	67.8±10.4	67.1±10.7	0.57
Male	237 (81.2%)	93 (78.2%)	0.49
Current smoker	42 (14.4%)	24 (20.2%)	0.15
Hypertension	206 (70.6%)	80 (67.2%)	0.51
Diabetes mellitus	123 (42.1%)	56 (47.1%)	0.36
Body mass index (kg/m^2)	23.5±3.2	23.1±3.4	0.19
Low-density lipoprotein	80.7±13.9mg/dL	82.3±12.4mg/dL	0.28
High-density lipoprotein	52.2±10.5mg/dL	54.2±18.1mg/dL	0.17
Triglycerides	90.1±26.9mg/dL	91.8±28.5mg/dL	0.54
Lipoprotein(a)	13.0 (7.5-20.6) mg/dL	41.1 (36.0-57.0) mg/dL	<0.01
eGFR<60mL/min/$1.73m^2$	70 (23.9%)	35 (29.4%)	0.26
Left ventricular ejection fraction	63.3±11.4%	62.4±11.2%	0.48
Acute coronary syndrome	78 (26.7%)	31 (26.1%)	0.89
Multivessel disease	157 (54.9%)	74 (63.2%)	0.12
Type B2/C lesion	193 (79.4%)	87 (89.7%)	0.02
Left anterior descending lesion	137 (46.9%)	45 (37.8%)	0.09
Use of medication			
Aspirin	273 (93.5%)	110 (92.4%)	0.34
Antiplatelet drug	223 (76.4%)	88 (73.9%)	0.38
β-blocker	124 (42.5%)	51 (42.8%)	0.92
ACE-I/ARB	140 (47.9%)	59 (49.5%)	0.65
Calcium channel blocker	128 (43.8%)	44 (37.0%)	0.21
Statin	170 (58.2%)	76 (63.8%)	0.25
Oral hypoglycemic agents	76 (26.0%)	35 (29.4%)	0.44
Insulin	27 (9.2%)	15 (12.6%)	0.31

ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; eGFR, estimated glomerular filtration rate

Table 2. Cox proportional hazards models for predictors of composite endpoint.

	Univariate			Multivariate		
	HR	95%CI	P	HR	95%CI	P
Age	1.06	1.04-1.08	<0.01	1.06	1.03-1.09	<0.01
Gender (F/M)	1.10	0.64-2.05	0.74			
Hypertension	1.10	0.68-1.74	0.69			
Diabetes mellitus	1.34	0.85-2.09	0.21			
Low-density lipoprotein	0.99	0.97-1.01	0.23			
High-density lipoprotein	1.00	0.98-1.01	0.92			
Triglycerides	1.00	0.99-1.01	0.82			
Lipoprotein(a) (High/Low)	1.61	1.02-2.52	0.04	1.68	1.03-2.70	0.04
Current smoker	1.32	0.71-2.72	0.40			
eGFR<60	1.72	1.07-2.71	0.03	1.34	0.80-2.19	0.25
Acute coronary syndrome	1.77	1.11-2.78	0.02	1.82	1.08-3.07	0.03
Left ventricular ejection fraction	0.98	0.96-0.99	0.02	0.98	0.96-1.01	0.27
Multivessel disease	1.66	1.05-2.67	0.03	1.45	0.88-2.42	0.15
Type B2/C lesion	1.14	0.52-2.27	0.72			
Left anterior descending lesion	1.46	0.82-2.34	0.12			
β-blockers	0.81	0.49-1.28	0.37			
ACE-I/ARB	0.83	0.52-1.32	0.44			
Statins	0.63	0.39-0.99	0.05	0.72	0.43-1.20	0.21

ACE-I, angiotensin-converting enzyme inhibitors; ACS, acute coronary syndrome; ARB, angiotensin-receptor blockers; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio