Original Research

Effect of lipoprotein(a) levels on long-term outcome in octogenarians with coronary artery disease after drug-eluting stent implantation

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Abstract

Background: High levels of lipoprotein(a) [Lp(a)] are linked to adverse cardiovascular events. The significance of Lp(a) for the survival of octogenarians with coronary artery disease (CAD) after drug-eluting stent (DES) insertion is, however, not known. The purpose of the study is to investigated the connection between Lp(a) and outcome in octogenarians with CAD after DES implantation. **Methods**: We retrospectively enrolled a total of 506 consecutive octogenarians with CAD and DES implantation in our institution between January 2015 to August 2018. Two patient groups were established: a low group with plasma Lp(a) lower than 50 mg/dL (n = 408) and a high group with values above 50 mg/dL (n = 98). **Results**: After following up for a median of 31.53 ± 8.22 months, Kaplan-Meier curves indicated that poorer outcome censored for major cardiovascular events (MACE), myocardial infarction (MI), and target vessel revascularization (TVR) in the high group relative to the low group (log-rank test $p = 0.001$, $p = 0.008$, and $p < 0.001$, respectively). High Lp(a) independently predicted MACE (hazard ratio (HR) 1.90; 95% confidence interval (CI) 1.28–2.84; $p = 0.002$), MI (HR 2.74; 95% CI 1.23–6.11; $p = 0.014$), and TVR (HR 3.65; 95% CI 1.99–6.69; $p < 0.001$) after covariate adjustment. **Conclusions**: High Lp(a) was also significantly related to poor long-term outcome in octogenarians with CAD after DES implantation.

Keywords: Lipoprotein(a); Coronary artery disease; Drug-eluting stent; Octogenarian

1. Introduction

As the life expectancy of the general population increases, coronary artery disease is on the rise in elderly patients. Consequently, we can expect to see more octogenarians presenting with acute coronary syndrome, who are in need of percutaneous coronary intervention. Discovered by Kåre Berg in 1963 [1], Lipoprotein(a) [Lp(a)] has long been connected with the probability of developing cardiovascular disease [2–9] and many studies have, in addition, demonstrated an association with poor outcomes, even regardless of the concentration of low-density lipoprotein cholesterol [10–17]. The drugs of lowering Lp(a) were limited. Antisense therapy and proprotein convertase kexin 9 inhibitors can result in significant reductions in Lp(a) levels.

Several recent studies have shown that octogenarian patients with CAD were associated with increased operative complications, long-term major adverse cardiac events compared with those aged <80 years. As the octogenarian population were underrepresented, the investigators in most clinical studies excluded these patients. And the effects of Lp(a) on the survival of octogenarians with coronary artery disease (CAD) after drug-eluting stent (DES) insertion are not known. Therefore, we investigated the connection between Lp(a) and outcome in octogenarians with CAD after DES implantation.

2. Methods

2.1 Study design and participants

This single-center, observational, retrospective cohort study was undertaken at Beijing Anzhen Hospital Affiliated to Capital Medical University. Between January 2015 and August 2018, 506 octogenarian CAD patients with were consecutively enrolled (Fig. 1). All patients had undergone DES implantation in our hospital. Patients lacking data on Lp(a), those currently receiving hemodialysis, and patients with malignant tumors, severe infection, or anemia were excluded, as were patients who could not complete the follow-up. In accordance with the recommendation of 2016 guidelines [18], the participants were allocated to one of two groups: a "low" group levels below50 mg/dL (n = 408) and a "high" group with levels above50 mg/dL (n = 98).

2.2 Data collection

Patient data, including demographics, risk factors for CAD, and medication, were acquired from hospital records. Venous blood was collected after fasting for a minimum of 12 h when patients were admitted to hospital, and the blood was analyzed at the Clinical Chemistry Department of Beijing Anzhen Hospital, Capital Medical University. Percutaneous coronary interventions (PCIs) were performed if pa-

Table 1. Baseline clinical characteristics.

Variable	High Lp(a) (n = 98)	Low Lp(a) (n = 408)	*p*-value
Age	82.60 ± 2.44	81.89 ± 2.16	0.005
Men (n (%))	65 (66.33%)	263 (64.46%)	0.412
Body mass index, kg/m^2	25.50 ± 2.42	25.60 ± 3.19	0.761
Hypertension (n (%))	61 (68.37%)	291 (71.32%)	0.322
DM (n (%))	31 (31.63%)	125 (30.64%)	0.468
Dyslipidemia (n (%))	43 (43.88%)	117 (36.07%)	0.003
LDL-C, mmol/L	3 ± 0.95	2.43 ± 1.06	<0.005
HDL-C, mmol/L	1.05 ± 0.26	1.07 ± 0.28	0.624
Triglyceride, mmol/L	1.86 ± 1.5	1.51 ± 0.83	0.032
Current smoking (n (%))	64 (65.30%)	264 (65.02%)	0.505
CAD family history (n (%))	14 (14.29%)	67 (16.42%)	0.365
Prior PCI	13 (13.27%)	46 (11.27%)	0.345
Prior CABG	8 (8.16%)	29 (7.11%)	0.428
Prior MI (n (%))	18 (13.37%)	55 (13.48%)	0.141
Prior stroke (n (%))	13 (13.27%)	43 (10.54%)	0.271
CKD	40 (40.82%)	150 (36.76%)	0.264
LVEF <50% (%)	10 (10.20%)	25 (10.05%)	0.544
Baseline medications			
Aspirin (n (%))	93 (94.90%)	388 (95.10%)	0.551
Beta-blocker (n (%))	66 (67.35%)	269 (65.93%)	0.445
ACE inhibitor or angiotensin II receptor antagonist (n (%))	56 (57.14%)	226 (55.39%)	0.422
Statin (n (%))	93 (94.90%)	390 (95.59%)	0.470

Mean ± SD; DM, diabetes mellitus; LDL-C, Low-Density Lipoprotein Cholestero; HDL-C, high-density lipoprotein cholesterol; CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; MI, myocardial infarction; CKD, chronic kidney disease; LVEF, left ventricular ejection fraction; ACE, angiotensin converting enzyme.
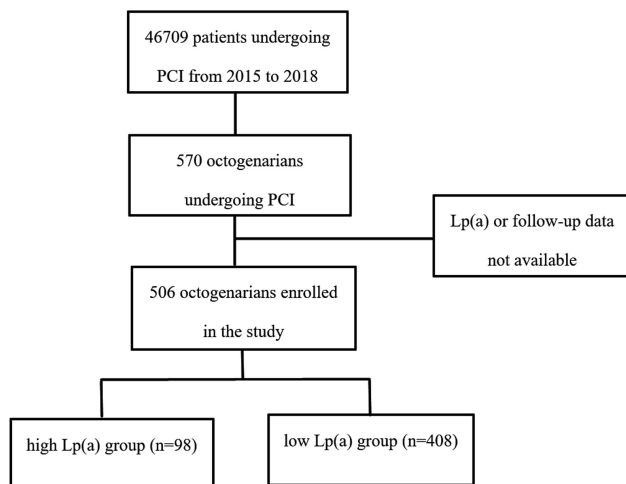

Fig. 1. Study flow chart. 46709 patients undergoing percutaneous coronary intervention (PCI) and 506 octogenarian CAD patients with were consecutively enrolled between January 2015 and August 2018.

tients exhibited myocardial ischemia or its symptoms, or symptoms suggesting angiographic stenosis. Lp(a) was determined by enzyme linked immunosorbent assay (ELISA) (Roche Company, Basel, Switzerland). The process of Lp(a) measurement are described in previous study [19].

2.3 Study endpoint

The primary endpoint was the development of major adverse cardiac events (MACE), classified as all-cause death, myocardial infarction (MI), and the necessity of target vessel revascularization (TVR) conducted either by PCI or coronary artery bypass grafting (CABG). Information on patients who had died at home was given by families, including the cause and date of death, and, in the case of hospitalization, this information was given by the hospital or clinic. All information was checked and verified by independent clinicians.

2.4 Statistical analysis

Continuous variables were expressed as means ± standard deviation (SD) and differences were measured by *t*-tests. Categorical variables were analyzed by χ^2 tests. Unadjusted cumulative event rates were calculated by Kaplan-Meier curves, and compared by the log-rank test. Multivariate analysis of predicting MACE was performed using

the Cox proportional hazards regression. Multivariate Cox regression was utilized to adjust for potential confounders, including age, male sex, hypertension, diabetes mellitus (DM), dyslipidemia, chronic kidney disease (CKD), smoking, CAD family history, left ventricular ejection fraction (LVEF) <50%, previous MI, and previous CABG. Two-sided p-values < 0.05 were considered statistically significant, unless otherwise indicated. All analyses were performed with SPSS version 17.0 (IBM Corp., Chicago, IL, USA).

3. Results

Lp(a) was evaluated both at baseline and follow-up completion in the 506 octogenarian CAD patients who had undergone DES implantation. Of these, 408 (80.63%) had Lp(a) values below 50 mg/dL, while in 98 (19.37%) the values were over 50 mg/dL. The Lp(a) concentration distribution was given in Fig. 2. The baseline features are given in Table 1. The "high" group comprised mostly older patients with a higher incidence of dyslipidemia. However, for both groups of patients, male sex, DM, hypertension, current smoking, CKD, CAD family history, and medication were comparable. In addition, the groups were alike in terms of the use of cardiovascular medication, specifically, aspirin, statins, and angiotensin II receptor blockers.
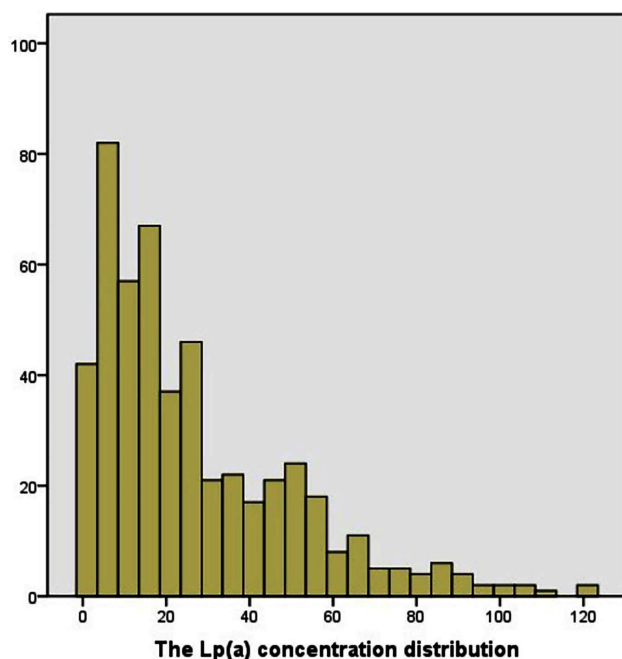

Fig. 2. The Lp(a) concentration distribution. 408 patents (80.63%) had Lp(a) values below 50 mg/dL, while in 98 (19.37%) the values were over 50 mg/dL.

Over the follow-up (median 31.53 ± 8.22 months), 121 patients experienced one or more MACE (Table 2), resulting in all-cause death in 66, MI in 25, and TVR in 45 patients. The overall survival rate censored for MACE

(Fig. 3A), MI (Fig. 3B), and TVR (Fig. 3C) was markedly less in the high group (log-rank tests $p = 0.001$, $p = 0.008$, and $p < 0.001$). The Kaplan-Meier curve (Fig. 3D) confirmed a similar risk for all-cause death in the both group (log-rank test, $p = 0.763$).

Table 2. Numbers of MACEs during follow-up*.

	High Lp(a) (n = 98)	Low Lp(a) (n = 408)	p-value
MACE	35 (35.71%)	86 (21.09%)	0.002
Death (all-cause)	13 (13.27%)	53 (12.99%)	0.527
MI	10 (10.20%)	15 (3.68%)	0.012
TVR	19 (29.39%)	26 (6.37%)	0.000

*n (%); MACE, major adverse cardiovascular events; MI, myocardial infarction; TVR, target vessel revascularization.

The Supplementary Tables showed the results of univariate and multivariate analysis for predicting MACE. Multivariate Cox proportional hazard analysis indicated that after adjustment of potential confounders, including age, male sex, previous MI, current smoking, CKD, previous CABG, previous stroke, LVEF, CAD family history, DM, hypertension, and dyslipidemia, raised Lp(a) was still an independent risk factor for MACE (HR 1.90; 95% CI 1.28–2.84; $p = 0.002$), MI (HR 2.74; 95% CI 1.23–6.11; $p = 0.014$), and TVR (HR 3.65; 95% CI 1.99–6.69; $p < 0.001$) (Table 3).

Table 3. Prognostic value of high Lp(a) *.

	HR	95% CI	p-value
MACE	1.90	1.28–2.84	0.002
Death (all-cause)	0.82	0.43–1.56	0.538
MI	2.74	1.23–6.11	0.014
TVR	3.65	1.99–6.69	0.000

*HR and 95% CI for high Lp(a) were computed using separate models and adjusted for age, male sex, current smoking, dyslipidemia, hypertension, diabetes mellitus, prior history of myocardial infarction, previous coronary artery bypass graft, prior stoke, chronic kidney disease, left ventricular ejection fraction <50%. MACE, major adverse cardiovascular events; MI, myocardial infarction; TVR, target vessel revascularization; HR, hazard ratio; CI, confidence interval.

4. Discussion

This observational investigation of the effect of Lp(a) on CAD prognosis in octogenarians treated with DES insertion found a significantly greater incidence of MACE in individuals with high Lp(a) values and that elevated Lp(a)
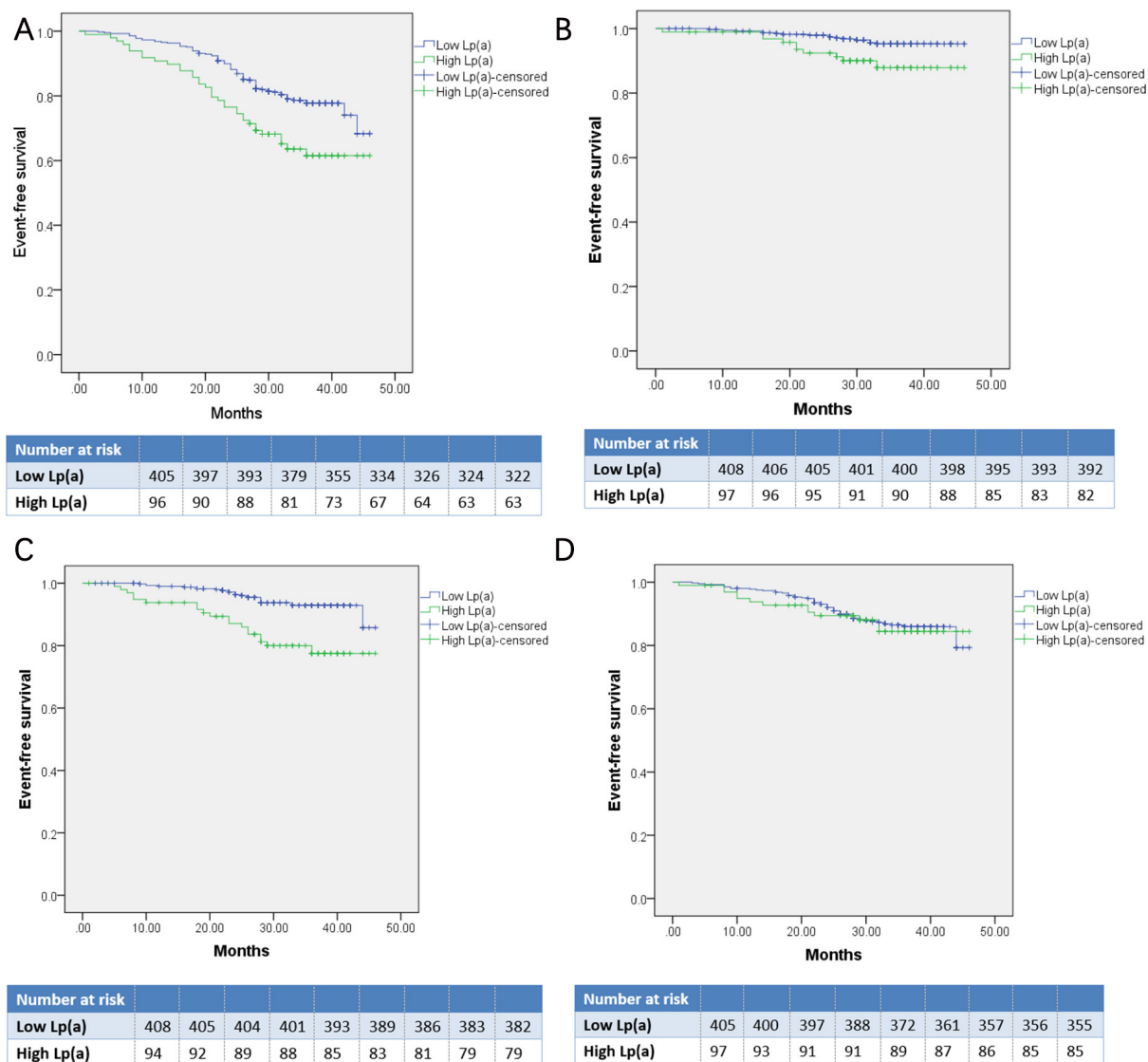
Fig. 3. Kaplan-Meier Survival based on serum levels of Lp(a). Overall survival censored for MACE MACE (A), MI (B), and TVR (C). The overall survival rate was lower in individuals with high Lp(a) (log-rank tests $p = 0.001$, $p = 0.008$, and $p < 0.001$). Overall survival censored for all-cause death (D). The individuals in two group had comparable overall survival rate (log-rank test $p = 0.763$).

was linked to poorer outcomes. This relationship retained significance after the adjustment for a variety of covariates of clinical importance.

Lp(a) is a structurally and functionally oligomeric lipoprotein in which apolipoprotein B and glycosylated apolipoprotein(a) monomers are covalently complexed. The amount of Lp(a) in the body is essentially genetically controlled and is little affected by lifestyle or environmental factors, tending to remain stable throughout life [20,21]. However, there is considerable variation in the concentrations, ranging from below 1 to more than 1000 mg/dL [21]. The exact location of Lp(a) synthesis has not been established [22], nor is its plasma clearance fully understood [22]. Therefore, the exact cause of elevated Lp(a) in humans is uncertain.

To date, numerous studies on Lp(a) epidemiology and genetics, as well as meta-analyses, have observed that high Lp(a) is predictive of CAD [2–7,9]. This relationship does not depend on the levels of blood lipid, nor on other known risk factors. The "Emerging Risk Factors Collaboration" [4] that investigated over 120,000 individuals in a variety of studies reported that the connection between Lp(a) and CAD could be represented by either a curvilinear or log-linear function. A Danish investigation [2] of 40,486 ischemic heart disease-free patients reported a relationship between elevated Lp(a) and MI A study of Lp(a) in people of Chinese Han ethnicity [8], using 3462 cases and 6125 controls, demonstrated significantly increased odds ratios for the association between CAD and Lp(a). In addition, the Lp(a) level appears to influence the severity and morphology of coronary lesions.

There is also accumulating evidence linking raised Lp(a) and MACE in patients with established CAD [10–17,23–28]. A meta-analysis [23] found that individuals with plasma Lp(a) values in the highest quartile were 40% more likely to develop MACE. Konishi *et al.* [11] reported a raised MACE incidence in 569 patients undergoing PCI with high Lp(a), finding that raised Lp(a) was independently linked to both death and acute coronary syndrome recurrence. A clinical trial of 427 CKD patients who had undergone PCI [24] found an independent relationship between raised Lp(a) and increased risk of major adverse coronary and cerebrovascular events and bleeding. Moreover, Sung *et al.* [14] also found raised Lp(a) to be independently linked to the development of MACE as well having prognostic significance for symptomatic patients with TVR. Consistent with these findings, the current investigation demonstrated that elevated Lp(a) values were connected to a greater incidence of MACE, MI, and TVR during follow-up.

However, few previous studies have investigated patients who had undergone DES or elderly patients. In contrast, our study patients were all over the age of 80 and had all received DES implantation. Furthermore, few studies have investigated Chinese patients [16,24,25,29], with most addressing Japanese or Western populations [10,12–14,26–28]. In comparison with young patients, octogenarian people have a higher prevalence of hypertension, diabetes, CKD and more complex coronary lesions, which caused poor prognosis. At present, there are little studies about effect Lp(a) on the outcomes in octogenarian people after coronary DES insertion. The present study suggests that Lp(a) is linked to poorer clinical outcomes and may be a new target for the treatment of CAD.

Numerous nonredundant mechanisms for the part played by Lp(a) in cardiovascular disease have been proposed. One suggestion is that increased cholesterol deposition by Lp(a) in the arterial walls results in increased levels of proinflammatory oxidized LDL [30]. Lp(a) resembles plasminogen in structure and is able to compete with it for receptor binding, resulting in an inhibition of fibrinolysis [31,32]. In addition, Lp(a) has been linked to platelet dysfunction and may thus promote endothelial disorders and chylomicron retention [32].

There are a few limitations to this study. First, this was a single-center, retrospective investigation and involved only Chinese patients, resulting in possible selection bias and restricting the control for confounders despite suitable adjustment. Second, we exclude revascularization for non-culprit vessel and ischemic stroke. As the participants in this study were octogenarians, incomplete revascularization was underwent in most patients. Therefore, we could not distinguish revascularization for non-culprit vessel for the development of the original coronary lesion or the original coronary lesion during the follow-up. And the incidence of ischemic stroke is low. For these reasons, the endpoints of this study endpoints did not include these events. Furthermore, the sample size was relatively small, limiting a comprehensive investigation of the influence of Lp(a) on outcomes. In the future, larger, multicenter, prospective clinical trials or studies should be conducted.

5. Conclusions

In conclusion, it was observed that high Lp(a) values were significantly linked with poor clinical outcome in octogenarian CAD patients after DES implantation. This suggests that the Lp(a) level may be a valuable parameter for assessing risk, and that reducing the level of Lp(a) may improve the outcomes of octogenarians with CAD after DES implantation.

Author contributions

BH, SWY, DMS, YXZ and YJZ designed the research study. BH, SJ, XHX, DAJ and XTM collected the data. BH, DAJ, XTM and XHX performed the research. BH, SWY, DMS, YXZ and YJZ analyzed the data. BH, SJ and XTM drafted the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Beijing Anzhen Hospital, Capital Medical University (approval number: 20210057X).

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Conflict of interest

The authors declare no conflict of interest.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at https://www.imrpress.com/journal/RCM/23/3/10.31083/j.rcm2303079.

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