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Baseline and on-statin treatment lipoprotein(a) levels for predicting cardiovascular events in patients with familial hypercholesterolemia

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HIGHLIGHTS

- A total of 393 patients with HeFH were prospectively treated with standard lipid-lowering therapy and followed up for 36.5 ± 21.6 months.
- Baseline and on-treatment Lp(a) levels were positively associated with incident CVEs independently of established cardiovascular risk factors.
- Adding Lp(a) to the Cox prediction model increased the C-statistic, net reclassification improvement and integrated discrimination.
- The measurement of Lp(a) levels in FH patients might clinically help further risk stratification..

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ABSTRACT

Background and aims: Lipoprotein(a) [Lp(a)] has been considered as a causal risk factor for cardiovascular disease (CVD) in the general population and levels vary in different ethnicities. However, no systemic analysis is currently available regarding the relation of plasma Lp(a) levels to cardiovascular events (CVEs) in Chinese patients with heterozygous familial hypercholesterolemia (HeFH).

Methods: Three hundred and ninety-three patients with HeFH undergoing Lp(a) measurement at baseline were consecutively enrolled and followed prospectively for an average of 36.5 months. Lp(a) levels were determined using an immunoturbidimetry assay. Cox regression analysis with adjusted hazard ratios (HRs) and Kaplan-Meier analysis were used to evaluate the prognostic value of Lp(a) on CVEs.

Results: Thirty-five events occurred during follow-up. Lp(a) was significantly higher in patients with CVEs (53.3 mg/dL *versus* 31.7 mg/dL, $p < 0.001$). In Kaplan-Meier analysis, patients with upper tertile of Lp(a) had a significant lower event-free survival ($p = 0.004$). After adjusting for confounding risk factors, per log unit increase in baseline Lp(a) was independently associated with CVEs [HR: 2.03(1.28–3.21), $p = 0.002$]. HRs remained unchanged after accounting for hard endpoints and did not vary too much in several relevant subgroups. Adding Lp(a) to the Cox model led to a significant improvement in C-statistic, net reclassification and integrated discrimination. Moreover, HR for upper *versus* lower tertile of change in Lp(a) was 2.68 (1.11–6.48) for CVEs after one year.

Conclusions: Both baseline and on-statin treatment Lp(a) levels were associated with an increased risk of CVEs in patients with HeFH, suggesting that Lp(a) measurement might clinically help further risk stratification of FH patients.

1. Introduction

Familial hypercholesterolemia (FH) is a genetic metabolic disorder characterized by premature cardiovascular disease (CVD) and incident cardiovascular events (CVEs) [1,2]. Although high low-density lipoprotein cholesterol (LDL-C) concentration has been considered as a main driver of CVD in FH, elevated lipoprotein (a) [Lp(a)] has recently received increasing interest concerning its contribution to CVD in FH patients [3]. Interestingly, previous studies, including our data, showed that plasma Lp(a) was significantly higher in FH patients, with a prevalence of 25%–30% [4,5]. Moreover, heterogeneous FH (HeFH) patients with elevated Lp(a) had significantly higher incident premature

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CVD compared to those with normal Lp(a) levels [6,7].

Although previous studies suggested a predictive value of plasma Lp (a) level in the prevalence of CVD, its role in the prognosis of patients with FH remains undetermined. An early retrospective study published in 2005 including 388 FH patients, who satisfied the Dutch Lipid Clinic Network (DLCN) criteria for possible, probable and definite diagnosis, reported a positive association between Lp(a) and CVD outcomes [8]. However, the statistical power of this study was limited by the retrospective design and high proportion of the non-FH population. To establish a model for predicting CVEs in Spanish FH patients, the recent SAFEHEART study showed that Lp(a) was one independent predictor for incident CVEs besides traditional risk factors. Of note, this study did not fully evaluate Lp(a) in FH patients, such as the impact of Lp(a) levels on CVEs after lipid-lowering treatment [9]. In addition, Lp(a) concentration is much lower in the Chinese population than the Caucasian population and the distribution of *LPA* gene polymorphism varies across ethnicities [10]. Unfortunately, no relevant data in regard to the association between Lp(a) and CVEs in Chinese FH patients is currently available [1,5,11]. What is more, the clinical outcomes of FH patients are reported to be heterogeneous [12]. Although FH patients received intensive lipid-lowering therapy, a considerable number of patients still had high risk of CVEs, implying the existence of residual risks [13]. Thereby, the role of Lp(a) in future cardiovascular outcomes in FH patients receiving standard statin therapy should be clarified in different ethnic populations.

Accordingly, the aim of the present study was to assess the association of baseline and on-statin treatment plasma Lp(a) concentrations with future CVEs in Chinese HeFH patients receiving standard lipid-lowering therapy from a sizable and long-term prospective cohort.

2. Materials and methods

2.1. Study design and study population

A total of 69,837 participants with angina-like chest pain and/or positive treadmill exercise test or clinically suspected CVD from Fuwai Hospital were consecutively enrolled between January 2011 and November 2018. Among them, FH patients were selected for this study. Clinical FH diagnosis was established by means of the DLCN criteria and only patients with DLCN score > 6 (definite and probable) were included [14]. During the diagnosis, if the untreated lipid profiles were unavailable, we had the untreated LDL-C levels adjusted by a correction factor depending on the type and potency of lipid-lowering medications [15]. All patients were screened for mutations in 3 FH-related genes: *LDLR*, *APOB* and *PCSK9* as previously described [14]. Patients were excluded from the study if they had a history of severe chronic cardiac failure, severe liver and/or renal insufficiency, thyroid dysfunction or malignant disease. Patients aged < 18 years or diagnosed as homozygote FH were also excluded. All HeFH patients received standard statin therapy, which was defined as rosuvastatin dose 20 mg plus ezetimibe 10 mg per day, the maximal doses approved by the Chinese Food and Drug Administration. During the follow-up period, 5 patients (1.2%) were lost follow-up. Finally, a total of 393 HeFH patients were included in the current study. A flowchart illustrating study inclusion and exclusion according to our study purpose is shown in Supplemental Fig. 1.

The present study complied with the Declaration of Helsinki and was approved by the hospital's ethical review board (Fuwai Hospital & National Center for Cardiovascular Diseases, Beijing, China). Informed written consents were obtained from all participants.

2.2. Definition of CVEs

All FH patients were followed up every half year by clinic revisit or by phone by trained nurses or doctors blind to the clinical data, until death occurred or up to the last day of the follow-up period. CVEs were defined as fatal and nonfatal myocardial infarction (MI), fatal and nonfatal stroke, post-discharge coronary revascularization and cardiac death. The endpoint of MI was confirmed when medical records showed symptoms of ischemia, electrocardiogram changes, and increases in cardiac enzyme concentrations. Stroke was diagnosed as new-onset neurological symptoms lasting more than 24 h with diagnostic computed tomography or magnetic resonance imaging. Coronary revascularization was defined as percutaneous coronary intervention or coronary artery bypass grafting due to angina pectoris or equivalent symptoms refractory to medical treatment and/or positive myocardial stress testing. Diagnosis of cardiac death was done on the basis of death primarily caused by acute MI, congestive heart failure, malignant arrhythmia and other structural or functional cardiac diseases. Hard endpoints were defined as MI, stroke and cardiac death. All CVEs were independently adjudicated by two investigators blind to patients' characteristics.

2.3. Clinical and biochemical examination

Clinical data of each participant were collected by experienced physicians and nurses. Demographic variables, medical history, family history and lifestyle information were assessed as described previously [5]. Weight (kilograms) and height (meters) were measured using a standard physician's scale and a stadiometer, and body mass index (BMI) was calculated. Hypertension was defined as repeated blood pressure measurements ≥140/90 mmHg for at least three times in different environments or use of anti-hypertensive medications. Diabetes was defined as a fasting serum glucose level ≥7.0 mmol/L, glycated hemoglobin > 6.5%, random glucose ≥11.1 mmol/L and/or use of hypoglycaemic drugs or insulin.

Blood samples were obtained from each patient from the cubital vein after at least 12-h fasting at baseline and follow-up. The concentrations of total cholesterol (TC), triglyceride (TG), LDL-C and high-density lipoprotein cholesterol (HDL-C) were measured using an automatic biochemistry analyzer (Hitachi 7150, Japan), whereas the concentration of Lp(a) was measured by an immunoturbidimetry method according to the manufacturer's guide as previously described [5,16]. The concentration of high-sensitivity C-reactive protein (hsCRP) was measured by immunoturbidimetry (Beckmann Assay360, Bera, California). Other related biochemical and hematological indicators were measured according to standard tests.

2.4. Statistical analysis

The values were expressed as the mean ± standard deviation (SD) or median (interquartile range) for the continuous variables and the number (percentage) for the categorical variables. Differences in variables were compared with Student' s *t*-test, analysis of variance (ANOVA), non-parametric test, Chi-square test or Fisher's exact test if applicable. Spearman correlation coefficients were calculated to evaluate the correlation between Lp(a) and other biomarkers. A Kaplan-Meier (KM) estimate with the log-rank test was performed to determine the overall CVE-free survival time according to Lp(a) levels. To estimate the association between Lp(a) and CVEs, Cox regression models with hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using univariate and multivariate analyses for total patients and various subgroups. Skewed variables were log transformed to achieve approximately symmetrical distributions. To increase statistical power, tertiles of Lp(a) concentration were also formed. We additionally performed a *post-hoc* sensitivity analysis of the potential influence of other individual predictors on the relation of Lp(a) to events, which was forced into multivariate models together with Lp(a). The predictive value of Lp(a) on the occurrence of CVEs was analyzed by receiver-operating characteristic curves (ROC). To assess whether adding plasma Lp(a) levels to established cardiovascular risk factors is associated with improvement in prediction of future CVEs, we calculated measures of

Table 1
Clinical and laboratory characteristics of FH patients.

Variables	Total	Event (+)	Event (−)	*p* value
Number of subjects	393	35	358	
Demographics				
Age, years	48.68 ± 12.96	50.34 ± 13.40	48.52 ± 12.92	0.427
Male, n (%)	238 (60.6)	21 (60.0)	217 (60.6)	0.943
Clinical variables				
BMI, kg/(m^2)	21.85 ± 9.50	23.69 ± 8.21	21.66 ± 9.61	0.229
CVD, n (%)	294 (74.8)	30 (85.7)	264 (73.7)	0.119
Family history of CVD, n (%)	165 (42.0)	13 (37.1)	152 (42.5)	0.399
Tendon xanthoma, n (%)	47 (12.0)	3 (8.6)	44 (12.3)	0.511
Cardiovascular risk factors				
Hypertension, n (%)	170 (43.3)	20 (57.1)	150 (41.9)	0.820
Diabetes, n (%)	67 (17.0)	9 (25.7)	58 (16.2)	0.226
Active smoker, n (%)	151 (38.4)	14 (40.0)	137 (38.3)	0.885
Alcohol drinker, n (%)	83 (21.1)	7 (20.0)	76 (21.2)	0.865
Laboratory parameters				
TG, mmol/L	1.60 (1.20–2.14)	1.94 (1.37–2.83)	1.58 (1.18–2.09)	0.066
TC, mmol/L	9.04 ± 2.20	9.78 ± 3.12	8.97 ± 2.09	0.195
HDL-C, mmol/L	1.02 ± 0.43	1.08 ± 0.33	1.13 ± 0.44	0.481
LDL-C, mmol/L	7.27 ± 1.56	7.62 ± 1.84	7.23 ± 1.53	0.164
ApoA, g/L	1.31 ± 0.35	1.32 ± 0.43	1.31 ± 0.34	0.861
ApoB, g/L	1.45 ± 0.48	1.49 ± 0.60	1.45 ± 0.47	0.679
Lp(a), mg/dL	33.5 (14.8–67.2)	53.3 (28.6–76.3)	31.7 (14.2–66.1)	0.014
Lp(a) year score, g·yr/L	16.2 (6.6–32.3)	24.8 (13.8–40.0)	15.6 (6.3–31.3)	0.007
FFA, mmol/L	0.43 (0.31–0.57)	0.43 (0.29–0.57)	0.43 (0.31–0.57)	0.145
Glucose, mmol/L	5.43 ± 1.85	5.79 ± 2.40	5.39 ± 1.79	0.345
HbA1C, %	5.78 ± 1.78	5.71 ± 2.45	5.78 ± 1.71	0.869
HsCRP, mg/L	1.57 (0.73–3.29)	1.88 (1.24–6.78)	1.5 (0.71–3.20)	0.035
Fibrinogen, g/L	3.07 ± 1.02	3.20 ± 1.17	3.06 ± 1.01	0.458
D-Dimer, mg/L	0.29 (0.21–0.40)	0.34 (0.17–0.47)	0.29 (0.21–0.39)	0.522
On-treatment LDL-C, mmol/L	3.18 ± 1.32	3.31 ± 1.50	3.17 ± 1.31	0.732
On-treatment TG, mmol/L	1.53 (1.25–1.87)	1.59 (1.31–2.03)	1.46 (1.17–1.86)	0.086
Prior drug treatment				
Statin, n (%)	298 (75.8)	31 (88.6)	267 (74.6)	0.650
Ezetimibe, n (%)	94 (23.9)	8 (22.9)	86 (24.0)	0.877

Data are presented as mean ± SD, median (interquartile range) and number (%).
FH, familial hypercholesterolemia; BMI, body mass index; CVD, cardiovascular disease; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoA, apolipoprotein A; ApoB, apolipoprotein B; Lp(a), lipoprotein(a); hsCRP, high sensitivity C-reactive protein; FFA: free fatty acid; HbA1c, glycosylated hemoglobin.

discrimination for censored time-to-event data: Harrell's C-statistic, the continuous net-reclassification-improvement (NRI) and integrated discrimination improvement (IDI) [17,18]. The prognostic value of the changes in Lp(a) levels between baseline and year one on CVEs was assessed on a tertile distribution of change in Lp(a) using Cox regression model. Patients who reached endpoint prior to 1 year were excluded from the Landmark model. The criterion for statistical significance level was set as $p < 0.05$. Analyses were conducted using IBM SPSS Statistics version 23.0 (IBM SPSS Statistics, IBM Corporation, Armonk, New York) and R (http://www.r-project.org/) statistical packages.

3. Results

3.1. Baseline characteristics

Baseline demographics and clinical characteristics of patients in event group (n = 35) and non-event group (n = 358) are presented in Table 1. The mean age of participants was 48.68 ± 12.96 years old, of whom 60.6% were male. There was no significant difference between the two groups in the history of CVD, smoking or alcohol drinker. No difference was found in hypertension or diabetes. The mean concentration of TG, TC and LDL-C tended to be higher in the event group, but the difference was not significant. Compared to patients without events, HeFH participants with CVEs had significantly higher plasma Lp (a) concentration [53.3 (28.6–76.3) *vs.* 31.7 (14.2–66.1) mg/dL, $p = 0.014$] and higher Lp(a) year score [24.8 (13.8–40.0) *vs.* 15.6 (6.3–31.3), $p = 0.007$].

3.2. CV risk factors according to tertiles of Lp(a)

The distribution of clinical parameters according to Lp(a) tertiles is summarized in Supplemental Table 1. In Lp(a) tertile 1, 64.1% HeFH patients were male and a similar proportion was observed in tertile 2 (56.5%) and 3 (58.0%). When stratified by baseline Lp(a) levels, there was no statistically significant difference regarding age, BMI, family history of CVD, smoking or alcohol drinker. Furthermore, there was no relationship between hypertension, diabetes or baseline statin use and baseline Lp(a) levels. Besides, highest baseline LDL-C levels were observed in Lp(a) tertile 2. Spearman correlation coefficient between Lp (a) and other biomarkers is shown in Supplemental Table 2. Plasma Lp (a) levels were found to be weakly and positively correlated with TG (r = 0.128) and history of CVD before enrollment (r = 0.140). Likewise, weak positive correlations were also observed for fibrinogen (r = 0.114) and D-Dimer (r = 0.103).

3.3. CVEs during follow-up

During the follow-up period, a total of 35 CVEs were observed, representing 29.3 events per 1000 person-years (95%CI: 20.3–41.4). Among 35 HeFH patients with CVEs, 4 (11.4%) had MI, 7 (20.0%) developed stroke, 13 (37.1%) underwent post-discharge revascularization and 11 (31.4%) died from CVEs. At the end of follow-up, 5 (1.3%) patients modified or stopped receiving standard statin therapy (2 because of poor adherence to treatment and 3 because of statin intolerance).

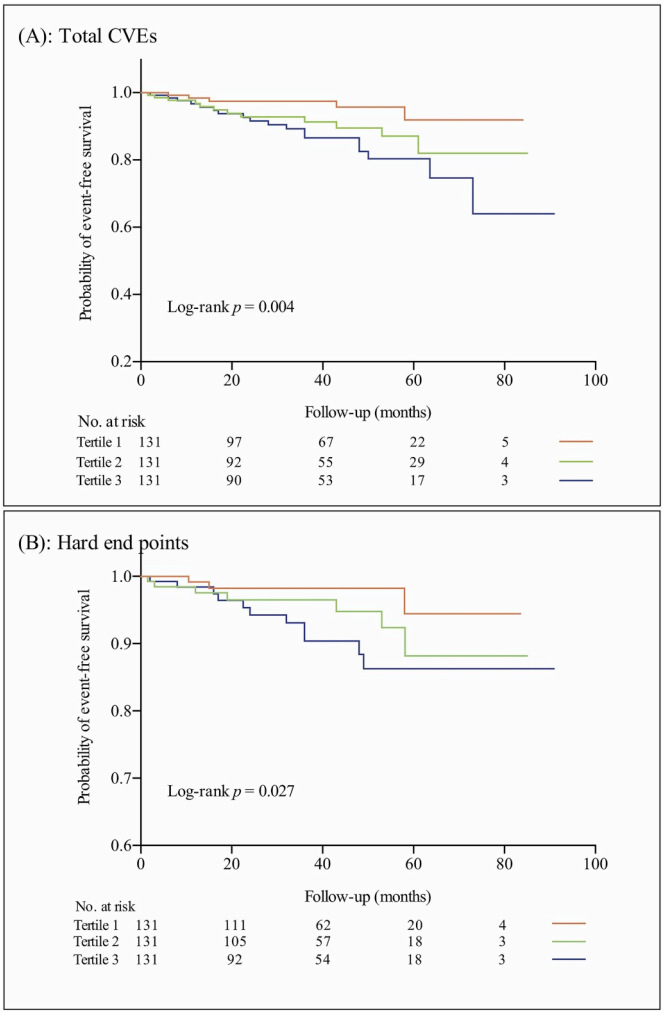

Fig. 1. Kaplan-Meier curves of the cumulative event-free survival analyses according to Lp(a) tertiles at baseline.
The log-rank test was used to compare event-free survival among Lp(a) tertiles. (A) Total cardiovascular events; (B) hard end points. CVE: cardiovascular event; Lp(a), lipoprotein(a).

3.4. Predictive role of baseline Lp(a) on CVEs

KM curves showing the probability of CVE-free survival during the follow-up period according to baseline Lp(a) tertile are presented in Fig. 1. Patients with the highest levels of Lp(a) had the lowest total event-free survival rates (log-rank $p = 0.004$). The association between baseline Lp(a) and CVEs remained significant after restricting the analysis to hard endpoints (log-rank $p = 0.027$). As shown in Table 2, univariate Cox regression revealed a significant association between plasma Lp(a) per log unit increase at baseline and incident CVEs (HR:1.77, 95% CI:1.18–2.66, $p = 0.006$). Moreover, incident CVEs were also positively associated with hsCRP (HR: 1.11, 95% CI: 1.02–1.20, $p = 0.034$). Multivariate Cox regression analysis showed a significant correlation between Lp(a) levels treated as a natural logarithm-transformed continuous variable and increased CVEs (HR: 2.03, 95% CI: 1.28–3.21, $p = 0.002$). When upper *vs.* lower Lp(a) tertiles were compared by Cox regression analysis, there was a significant increase of the hazards to incident clinical events both in univariable model (HR: 3.91, 95% CI:1.45–8.53; $p = 0.007$) and multivariate model (HR: 6.96, 95% CI: 2.24–9.32; $p = 0.001$, Supplemental Table 3). Findings were broadly similar for hard endpoints when Lp(a) was analyzed as a continuous variable [log-Lp(a) HR:1.79, 95% CI: 1.02–3.16, $p = 0.031$] and categorical variable (tertile 3 *vs.* tertile 1 HR: 4.09, 95% CI: 1.49–6.79, Supplemental Table 4). In the *post-hoc* sensitivity analysis, the results remained essentially unchanged when TG, LDL-C, fibrinogen, D-Dimer and prior CVD were separately added to the model (Supplemental Table 5). We also performed subgroup analyses stratified by gender, age, hypertension status, current smoking status, baseline with CVD and TG levels (Supplemental Table 6). For all subgroups, baseline Lp(a) was associated with an increased risk of CVEs.

As shown in Supplemental Table 7 and Fig. 2, baseline Lp(a) combined with CV risk factors provided a stronger estimate value compared with CV risk factors via ROC analyses (AUC: 0.079, 95%CI: 0.014–0.144). The C-statistic of a model that included the CV risk factors was 0.719 (95%CI: 0.628–0.811). Adding Lp(a) to the risk prediction model increased the C-statistic to 0.796 (95%CI:0.751–0.841, $p = 0.001$) with ΔC-statistic of 0.077 (95%CI: 0.039–0.115, $p = 0.001$). Furthermore, the addition of Lp(a) level to the model also resulted in a significant increase in NRI (24.2%, 95%CI: 1.4%–43.6%, $p = 0.041$) and IDI (5.4%, 95%CI: 2.2%–12.8%, $p = 0.037$).

3.5. On-treatment Lp(a) levels and CVEs

The change in Lp(a) levels between baseline to one year was of significant prognostic value in the Landmark model for future CVEs (Table 3). Comparing the highest [Lp(a) increased by ≥ 2.00 mg/dL] *vs.* the lowest [Lp(a) decreased by ≥ 2.19 mg/dL] tertile of changes in Lp (a), crude HR was 2.67 (95%CI:1.12–6.35, $p = 0.025$), similar to HR adjusted for various cardiovascular risk factors (HR:2.68, 95%CI: 1.11–6.48, $p = 0.029$).

4. Discussion

Exploring the potential predicting factors for CVEs in patients with high cardiovascular risk and clinical heterogeneity, such as in FH, will be of great importance. In this sizable prospective study, we found that baseline Lp(a) was significantly and positively associated with incident CVEs independent of several established cardiovascular risk factors. C-statistic, NRI and IDI confirmed the value of Lp(a) as a predictive factor for CVEs in the HeFH population. Moreover, changes in Lp(a) levels between baseline to year one showed significant association for future risk of CVEs, which might suggest the importance of monitoring plasma Lp(a) levels in patients receiving standard statin therapy. Therefore, our study provided additional information and supported the recommendation by a series of International Societies and working groups that all patients with clinical FH should be screened for raised Lp(a) concentrations [11,19].

The ethnic heterogeneity in plasma Lp(a) concentration is considerable: the median value in the Chinese Han ethnic population and Caucasian population is 7.4 and 18 mg/dL, respectively; the cut-off value of cardiovascular risk was recommended as 30 mg/dL in the Chinese population and 50 mg/dL in the Caucasian population [10,11]. Of note, the median Lp(a) concentration of FH patients in our study was 33 mg/dL, but it was almost 40 mg/dL in previous studies enrolling the Caucasian population [8,9]. Moreover, the association between *LPA* gene variants and CAD risk varies in different ethnic populations. Among these polymorphisms, rs10455872 were correlated with elevated Lp(a) levels in Caucasians but rs9364559 has played a role in the pathogenesis of CAD in the Chinese Han population [20,21]. In view of the above situation and the fact that direct evidence regarding the association of Lp (a) with CVEs in Chinese FH patients is lacking, we performed this prospective study to fill in the potential gap.

Lp(a) is a well-recognized risk factor for CVD in the general population [4,5,22], but its role as a predictor for CVD in FH remains controversial. Ferrieres et al. [23] reported a non-significant association between high Lp(a) and CVD risk in French-Canadian patients with HeFH, which was confirmed by two European cohort studies [24,25].

Table 2
Univariate and multivariate Cox proportional hazards regression analyses of cardiovascular events.

	Univariate COX analysis			Multivariate COX analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age	1.001	0.973–1.029	0.969			
Male	1.079	0.549–2.123	0.825			
CVD	1.589	0.614–4.115	0.340			
Tendon xanthoma	1.527	0.459–5.081	0.491			
Hypertension	0.727	0.371–1.426	0.353			
Diabetes	1.340	0.628–2.862	0.449			
Active smoker	0.923	0.469–1.816	0.817			
TG	1.117	0.999–1.248	0.052	1.186	1.053–1.336	0.025
TC	1.171	1.032–1.329	0.025			
HDL-C	0.622	0.211–1.832	0.389			
LDL-C	1.235	0.994–1.534	0.056			
FFA	0.419	0.08–2.207	0.305			
Glucose	1.107	0.942–1.302	0.217			
HsCRP	1.106	1.021–1.200	0.034			
Fibrinogen	1.045	0.728–1.501	0.811			
D-Dimer	1.112	0.857–1.444	0.424			
Statin	1.944	0.683–5.529	0.213			
Log-Lp(a)	1.769	1.179–2.655	0.006	2.029	1.284–3.205	0.002

HR: Hazard Ratio; CI: confidence interval; FH, familial hypercholesterolemia; BMI, body mass index; CVD, cardiovascular disease; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FFA: free fatty acid; hsCRP, high sensitivity C-reactive protein; Lp(a), lipoprotein(a).

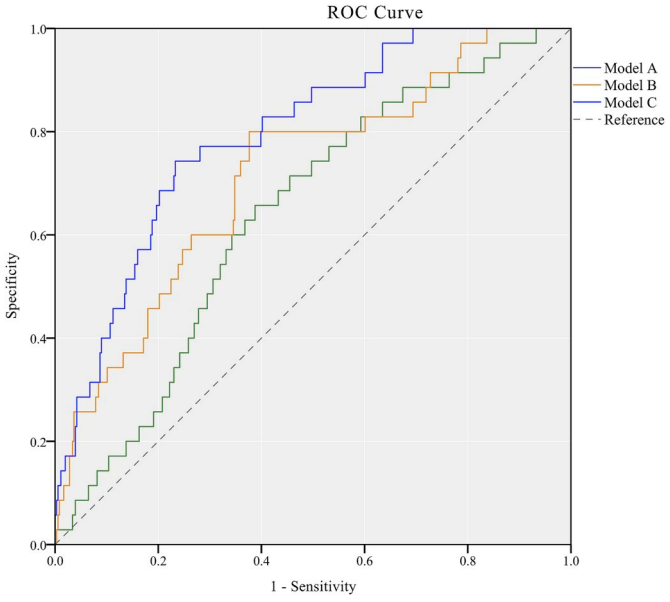

Fig. 2. Receiver operating characteristic (ROC) curve analyses to predict cardiovascular events.
Model A: Log-Lp(a); Model B: cardiovascular risk factors including age, gender, smoking, history of cardiovascular disease before enrollment, baseline statin use, diabetes, triglyceride, total cholesterol and low-density lipoprotein cholesterol. Model C: Model B and Log-Lp(a). Lp(a), lipoprotein(a).

However, data from recent studies supported the notion that elevated Lp(a) was an independent risk factor for CVD in FH. Results from cross-sectional studies have shown an association of elevated Lp(a) concentrations with CVD in FH patients [5,26]. A large retrospective analysis enrolling 1698 HeFH patients demonstrated that Lp(a) was an independent predictor for CVD [6]. Although the reasons for differences are not fully understood, discrepancies among the studies might be due to differences in the ethnic background, FH diagnostic criteria and sample size.

Although previous studies have explored the association between Lp(a) levels and the presence and severity of CVD in FH patients, its relationship to future CVEs is not well defined. Holmes et al. [8] enrolled 388 FH patients into a retrospective study in 2005 and indicated a positive association between Lp(a) and CVD outcomes. Notably, about 20% of participants were possible FH patients and the CVD endpoints excluded cardiac death but included peripheral arterial bypass, repair of abdominal aortic aneurysm and carotid endarterectomy. In another prospective cohort study of 184 FH patients, Langsted et al. [3] showed that HeFH patients with an elevated concentration of Lp(a) exceeding 50 mg/dL had 1.66-time higher risk for MI. However, in this small sample size study, the endpoint included non-fatal MI alone and they pooled participants with possible, probable and definite FH (DLCN score > 3) as clinical FH to obtain statistical power, even though not all of these participants had clinical FH. Besides, to develop a risk prediction equation for incident CVEs in Spanish FH patients, the SAFEHEART study included baseline Lp(a) and other risk factors [9]. In this equation, Lp(a) > 50 mg/dL was used as cut-off value for predicting CVEs, which might not be appropriate for the Chinese population. Notably, this study did not evaluate Lp(a) in FH patients, such as the impact of Lp(a) levels on CVE after statin treatment. Based on that, our study is strengthened by the fact that the HeFH population enrolled was diagnosed with strict clinical diagnostic criteria. In addition, we also performed relatively comprehensive and objective endpoints to increase the reliability of results.

A particularly interesting result of our study was that both baseline and on-statin treatment Lp(a) predicted CVEs, suggesting that Lp(a) still contributes to future CV risk in HeFH patients receiving guideline recommended lipid-lowering therapy. It was noted that compared to patients with unchanged Lp(a) levels, patients with raised Lp(a) concentrations were at a significantly higher risk of CVEs. Our results were consistent with previous studies that the risk of cardiovascular outcomes occurring was greater when Lp(a) levels increased after statin therapy in the general population [27,28]. Additionally, a large meta-analysis with patient-level data encompassing 29,069 patients demonstrated that elevated Lp(a) levels during follow-up were associated with increased CVEs risk in the setting of statin therapy when LDL-C was well controlled, suggesting Lp(a) might be an important residual risk factor [29]. However, similar to the SAFEHEART registry study [9], average on-treatment LDL-C levels of our HeFH participants failed to achieve recommended values (< 1.8 mmol/L) despite applying intensive lipid-lowering treatment. As demonstrated in previous studies [30], the inability to reach target LDL-C might be attributed to the limitation of the statin strategy itself. PCSK9 inhibitors, currently the

Table 3
Change in plasma Lp(a) concentration during 1 year and prediction of CVEs.

	Tertile 1	Tertile 2	Tertile 3
Change in Lp(a) concentration, mg/dL	≤-2.19	−2.19 to +2.00	≥ +2.00
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Crude Model	1 (Reference)	1.10 (0.41–2.95)	2.67 (1.12–6.35)
p value		0.855	0.025
Adjusted for age and sex	1 (Reference)	1.10 (0.41–2.96)	2.69 (1.12–6.43)
p value		0.849	0.021
Full adjusted model[a]	1 (Reference)	1.12 (0.41–3.11)	2.68 (1.11–6.48)
p value		0.822	0.029

Lp(a), lipoprotein(a); CVEs: cardiovascular events.
[a] Adjusted for age, sex, history of cardiovascular disease, diabetes, smoking, tendon xanthoma, triglyceride, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol.

most intensive lipid-lowering therapy [31], may verify the residual CV risk of Lp(a) when HeFH patients achieve target LDL-C levels. Nevertheless, our study provided additional evidence that despite untargeted on-statin treatment LDL-C levels, a rising on-statin treatment Lp(a) level was still associated with CVEs, supporting the concept that long-term elevation in Lp(a) may be causally associated with future cardiovascular outcomes and Lp(a) may be a target for incident CVEs.

When interpreting the results of this study, several limitations need to be considered. Firstly, the total number in this study might be limited. Despite the relatively small sample size, the results are significant and robust. Another limitation is that untreated LDL-C levels were estimated for patients taking statins or ezetimibe before admission. The approach performed in this study was also used in previous studies with high quality [32,33]. Furthermore, despite adjustments for potential confounders in multivariate analysis, we cannot exclude other possible residual biases. Nevertheless, we showed significant associations in Lp (a) (baseline and change) between future CVEs, and the results from a prospective study in a Chinese cohort are worth noting.

In conclusion, the current study found a significant association between baseline Lp(a) concentration and future CVEs in patients with HeFH. We also highlighted the prognostic value of increased Lp(a) concentration at one year after standard lipid-lowering therapy for CVEs. These novel findings may have an important implication, implying that the measurement of Lp(a) levels in FH patients could help identify those with higher risk, even receiving intensive lipid-lowering therapy. Moreover, clinical research designed to reduce Lp(a) may be justified and novel Lp(a)-lowering therapies are warranted in the future.

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Author contributions

CYX completed the project, analyzed the data, and wrote the manuscript. LJJ designed the study, interpreted the data, and contributed to critically revising the article. JJL, GYL, SD and LHH contributed to data collection and genetic analysis. WNQ, XRX and ZCG contributed to recruitment of patients. LG, DQ and SJ contributed to the collections of clinical data and procedure of laboratory examination. All authors have approved the final article.

Declaration of competing interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2019.10.010.

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