Prognostic utility of lipoprotein(a) combined with fibrinogen in patients with stable coronary artery disease: a prospective, large cohort study

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Abstract

Background: Elevated lipoprotein(a) [Lp(a)] and fibrinogen (Fib) are both associated with coronary artery disease (CAD) and the atherogenicity of Lp(a) can be partly due to the potentially antifibrinolytic categories. We hypothesize that patients with higher Lp(a) and Fib may have worse outcomes.

Methods: In this prospective study, we consecutively enrolled 8,417 patients with stable CAD from March 2011 to March 2017. All subjects were divided into 9 groups according to Lp(a) (Lp(a)-Low, Lp(a)-Medium, Lp(a)-High) and Fib levels (Fib-Low, Fib-Medium, Fib-High) and followed up for CVEs, including nonfatal acute myocardial infarction, stroke, and cardiovascular mortality. Caplan-Meier, Cox regression and C-statistic analyses were performed.

Results: During a median of 37.1 months’ follow-up, 395 (4.7%) CVEs occurred. The occurrence of CVEs increased by Lp(a) (3.5% vs. 5.3% vs. 5.6%, p=0.001) and Fib (4.0% vs. 4.4% vs. 6.1%, p<0.001) categories. When further classified into 9 groups by Lp(a) and Fib levels, the CVEs were highest in the 9th (Lp(a)-High and Fib-High) compared with the 1st (Lp(a)-Low and Fib-Low) group (7.2% vs. 3.3%, p<0.001). The highest risk of subsequent CVEs was found in the 9th group (HRadjusted 2.656, 95% CI 1.628-4.333, p<0.001), which was more significant than Lp(a)-High (HRadjusted 1.786, 95% CI 1.315-2.426, p<0.001) or Fib-High (HRadjusted 1.558, 95% CI 1.162-2.089, p=0.003) group. Moreover, adding the combined Lp(a) and Fib increased the C-statistic by 0.013.

Conclusion: Combining Fib and Lp(a) enhance the prognostic value for incident CVEs beyond Lp(a) or Fib alone.

Background

Despite significant advances in the diagnosis and therapy of cardiovascular disease (CVD), patients with established coronary artery disease (CAD) are generally at higher risk of developing recurrent cardiovascular events (CVEs) than the primary prevention individuals [1]. Clinical trials revealed that in the short time window only 20-30% of patients benefit even if traditional risk factors were well managed [2, 3]. As a result, identifying additional modifiable risk factors is necessary to further
improve CVEs prediction in the management of patients with established CAD.

Evidence have established high lipoprotein(a) (Lp[a]) levels are associated with high risk of CVD, observationally and causally from human genetics [4–6]. Multiple studies have indicated that high Lp(a) cause CVD in a primary prevention setting, moreover, Lp(a)-lowering by 50 mg/dL may reduce CVD by 20% in a secondary prevention setting [7]. AS well known, Lp(a) is composed of an LDL-like particle in which apoB is covalently bound by a single disulfide bond to apolipoprotein(a) (apo[a]). Therefore, the pathogenic role of Lp(a) was supposed to be involved in atherosclerosis and thrombosis formation [8]. In fact, the recent study implied that the mortality effect of high lipoprotein(a) is above that explained by its cholesterol content but the number of KIV-2 repeats in the apo(a) [9]. Originally, apo(a) has evolved from the plasminogen gene through duplication and remodeling. Unlike apolipoprotein B, apo(a) does not contain lipid domains or transport lipid, but instead, it potentiates atherothrombosis through additional pathways including proinflammatory, and potentially antifibrinolytic effects by inhibiting plasminogen activation [10]. As one of the important components of fibrinolytic system, plasma fibrinogen (Fib) has been proved to be a pivotal CVD risk factor [11–13]. However, little is known about the inter-relationship of Lp(a) and Fib in the CVEs risk prediction in the secondary prevention setting.

As a consequence, we hypothesize that there is a risk interaction between Lp(a) and Fib, and patients with high Lp(a) and Fib may have worse outcomes. We thereby sought to investigate the association of Lp(a) and Fib in predicting CVEs in patients with stable CAD (SCAD) in the current study.

Methods

Study Population

Our study complied with the Declaration of Helsinki and was approved by the hospital’s ethics review board (Fu Wai Hospital, National Center for Cardiovascular Diseases). Informed written consents were collected from all patients obtained in this study.

From March 2011 to March 2017, a total of 10,042 patients with clinical symptoms such as angina pectoris, or chest distress were recruited in our study. The inclusion criteria were patients with stable and angiography-proven CAD (coronary stenosis ≥50% of at least one coronary artery). The exclusion
criteria were as follows: (1) acute coronary syndrome (ACS); (2) previous myocardial infarction (MI), previous percutaneous coronary artery intervention or bypass grafting; (3) heart failure; (4) other disease status such as severe liver and/or renal insufficiency, thyroid dysfunction, systematic inflammatory disease, and malignant disease. Therefore, 8,417 patients were finally enrolled in the current analysis.

Patients were followed up at 6-months intervals by means of direct interview or telephone. The follow-up was performed by trained nurses or physicians who were blinded to the clinical data. The primary end points were cardiovascular mortality, nonfatal MI, and stroke. Nonfatal MI including ST-segment-elevation MI and non-ST-segment-elevation MI was diagnosed as positive cardiac troponins along with typical chest pain or typical electrocardiogram serial changes. Stroke was confirmed by specialist physicians according to the presence of typical symptoms and imaging.

Diabetes mellitus (DM) was diagnosed by fasting plasma glucose ≥7.0 mmol/L, the 2h plasma glucose of the oral glucose tolerance test ≥11.1 mmol/L, or current use of hypoglycemic drugs or insulin. Hypertension was defined as self-reported, currently taking antihypertensive drugs, or recorded systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg three or more consecutive times. Information regarding other disease, family history, and prior therapy of every patient was collected from self-reported medical history.

**Laboratory Analysis**

Blood samples were obtained from each patient from the cubital vein after at least 12 h of fasting. Concentrations of total cholesterol (TC), triglyceride (TG), low-density lipoprotein-cholesterol (LDL-C), and high-density lipoprotein-cholesterol (HDL-C) were measured using an automatic biochemistry analyzer (7150; Hitachi, Tokyo, Japan) in an enzymatic assay. Lp(a) was determined by immunoturbidimetry method [LASAY Lp(a) auto; SHIMA Laboratories Co., Ltd] with a normal value of <30 mg/dL. An Lp(a) protein validated standard was used to calibrate the examination, and the coefficient of variation value of repetitive measurements was <10%. Concentrations of fibrinogen were measured using a Stago auto
analyzer by the Clauss method with an STA Fibrinogen kit (Diagnostica Stago, Taverny, France).

**Statistical Analysis**

The values were expressed as the mean ± SD or median (25th–75th percentile) for the continuous variables and the number (percentage) for the categorical variables. The Kolmogorov-Smirnov test was used to test the distribution pattern. The differences in clinical characteristics between groups were analyzed using Student t test, Mann-Whitney U test, χ² tests, or Fisher exact test when appropriate. The event-free survival rates among groups were estimated by the Kaplan-Meier method and compared by the log-rank test. Univariate and multivariate Cox regression analyses were performed to calculate the hazard ratios (HRs). A P value of less than 0.05 was considered statistically significant. The statistical analyses were performed with SPSS, version 22.0, software (SPSS, Chicago, IL) and R language, version 3.5.2 (Feather Spray).

**Results**

**Baseline Characteristics**

The baseline characteristics of the study participants were shown in Table 1. Over a median of 37.1 months (25th–75th percentile 22.5–55.4 months) follow-up period, 395 CVEs occurred (160 died, 78 suffered non-fatal MI, and 157 had strokes). Patients suffered CVEs tended to be older (p<0.001), with higher prevalence of hypertension (p=0.005), DM (p<0.001), and stroke (p<0.001). There was no significant difference regarding the baseline lipid profiles (TG, TC, LDL-C, HDL-C, apoA1, apoB, all p>0.05) except Lp(a) levels (p=0.001). Significantly, the concentration of Fib, D-dimer, and hs-CRP were higher in patients with CVEs (all p<0.05). Meanwhile, the rate of statin usage was lower in CVEs compared with patients without events (p=0.005).

**Association of plasma Lp(a) Levels and CVEs**

In the current analysis, the subjects were assigned to 3 groups according to Lp(a) levels (Lp(a)-L: <10mg/dL, Lp(a)-M:10-29.9mg/dL, Lp(a)-H ≥30mg/dL). As shown in Fig. 1, the prevalence of CVEs in the Lp(a)-L, Lp(a)-M, and Lp(a)-H groups was 3.5%, 5.3%, and 5.6%, respectively (p<0.001). Kaplan-
Meier analysis (Fig. 2A) showed that Lp(a)-H subjects had the lowest event-free survival rate among the three groups (p=0.001). As presented in Table 2, univariate Cox regression models showed that Lp(a)-M, and Lp(a)-H group had 1.468-fold and 1.580-fold higher risk of CVEs compared with Lp(a)-L group (Lp(a)-M: HR [95% CI] 1.468 [1.142-1.886], p=0.003; Lp(a)-H: HR[95% CI] 1.580[1.227-2.033], p<0.001). Additional adjustment for other variables in the multivariate Cox regression models did not change the significance of the association (Lp(a)-M: HR[95% CI] 1.564 [1.149-2.129], p=0.005); Lp(a)-H: HR[95% CI] 1.773[1.299-2.419], p<0.001; Table 3).

**Association of plasma Fib Levels and CVEs**

Similarly, patients were divided into 3 groups according to Fib levels (Fib-L:<2.84g/L, Fib-M:2.85-3.42 g/L, Fib-H:≥3.43 g/L). The prevalence of CVEs in the Fib-L, Fib-M, and Fib-H groups was 4.0%, 4.4%, and 6.1%, respectively (p<0.001). The event-free survival rate was lowest in the Fib-H group (p<0.001, Fig. 2B). Compared to Fib-L group, the Fib-H group had 1.613-fold higher risk of CVEs (HR [95% CI] 1.613 [1.282-2.074], p<0.001) even after adjusting for potential confoundings (HR [95% CI] 1.547 [1.151-2.079], p<0.001).

**Inter-relationship of Lp(a), Fib Levels and CVEs**

To evaluate an interaction between plasma Lp(a) and Fib levels on the risk of CVEs, the subjects were assigned to 9 groups according to Lp(a) and Fib levels (G1(Lp(a)-L+Fib-L, G2(Lp(a)-L+Fib-M, G3(Lp(a)-L+Fib-H, G4(Lp(a)-M+Fib-L, G5(Lp(a)-M+Fib-M, G6(Lp(a)-M+Fib-H, G7(Lp(a)-H+Fib-L, G8(Lp(a)-H+Fib-M, G9(Lp(a)-H+Fib-H).

The occurrence of CVEs in the 9 groups was 3.3%, 3.5%, 4.0%, 4.1%, 4.9%, 7.0%, 4.8%, 5.4%, and 7.2%, respectively (p<0.001, Figure 1). Hazard ratios were calculated for each group using the G1 (group 1, Lp(a)-L and Fib-L) as a reference (Table 2). After adjusting for potential confoundings, the 6th group (Lp(a)-M and Fib-H) and 9th group (Lp(a)-H and Fib-H) had 2.383-fold and 2.621-fold higher risk of CVEs (HR [95% CI] 2.383 [1.445-3.930], p=0.001; 2.621 [1.590-4.322], p<0.001, respectively, Table 3).
In the original model, the C-statistic values were 0.633 (95% CI 0.603-0.664) with traditional risk factors, (Table 4). Addition of Lp(a) categories to the original model induced slightly improvement in C-statistic (ΔC-statistic 0.010 [-0.001-0.023], p= 0.088) but did not reach statistical significance. When added Fib categories to the original model did not improve the C-statistic (ΔC-statistic 0.003 [-0.005-0.012], p= 0.443). Nonetheless, the combined Lp(a) and Fib categories resulted in a significant improvement in C-statistic (ΔC-statistic 0.013 [0.002–0.027], p=0.033).

Discussion
In this prospective, large-cohort study, we investigated the association of plasma Lp(a) and Fib on the prediction of CVEs in angiography-proven stable CAD patients. Our data clearly found that both Lp(a) and Fib were independent predictors of CVEs in patients with stable CAD. More interestingly, the study firstly indicated that the combined Lp(a) and Fib categories enhanced the predicting values by incrementally increasing risk of CVEs in this population. The adjusted HR for CVEs was 2.621-fold and 2.383-fold higher among stable CAD patients in the Fib-H with Lp(a)-H or Lp(a)-M group, respectively. Finally, adding Lp(a) and Fib to the Cox model increased the C-statistic by 0.013 beyond that achieved with any single biomarker. These findings suggested that the combination of Lp(a), a complex marker of cholesterol and anti-fibrinolysis, and Fib, a marker of coagulation state, could enhance the predictive value, which would help the future risk stratification of stable CAD patients.

It is uncertain whether plasma Lp(a) levels are associated with CVEs in patients with stable CAD although several studies have suggested an association of elevated Lp(a) concentrations with the risk of CVD including the primary prevention population, familial hypercholesterolemia, statin-treated patients, and so forth. Concerning the secondary prevention setting, especially in patients with stable CAD, the results were controversial due to unknown causes. The Copenhagen City Heart Study showed that for patients with Lp(a) concentrations between 30 and 76 mg/dL, 77 and 117 mg/dL, and above 117 mg/dL, the risk of MI increased by a 1.6-fold, 1.9-fold, and 2.6-fold compared with those below 5 mg/dL in the primary prevention setting [4]. Data in patients with FH showed that the high cardiovascular risk in these patients is further increased by their unusual Lp(a) concentrations, which tend to be 2–3-fold higher than in the general population [14]. Of note, in the secondary prevention
setting for patients with established CAD, inconsistent data were observed [15, 16]. Among 569 patients having undergone PCI and LDL-C levels were well-controlled (< 100 mg/dL), those with higher Lp(a) levels had significantly higher risk of MACEs compared to patients with lower Lp(a) levels, while elevated Lp(a) values were an independent predictor of mortality and recurrence of ACS [17]. Recently, our data proved that elevated Lp(a) levels were significantly associated with the risk of MACEs in patients with CAD combined with DM or pre-DM [18]. However, for patients with recent ACS who are treated with statins, Lp(a) concentration was not associated with MACEs [19]. Based on this situation, we consecutively enrolled 8,417 patients who had angiography-proven stable CAD and followed up for a median of 37.1 months. The data clearly showed that high Lp(a) (≥30 mg/dL) was resulted in 1.773-fold CVEs risk compared with low Lp(a) levels (< 10 mg/dL).

Next, previous including our studies supported the notion that Fib, a coagulation factor, is also a marker for risk of CVD [20, 21]. In this study, we re-examined the role of Fib in prediction of CVEs, and finally proved that high Fib was related to 1.613-fold higher risk of CVEs compared with the low Fib level. Till now, Lp(a) is thought to mediate clinical events by 3 main mechanisms, pro-atherogenic effects via its LDL-C moiety [3, 22], pro-inflammatory effects via its content of oxidized phospholipids [23] and anti-fibrinolytic effects via its apolipoprotein(a) component [24]. Lp(a) has high homology (75–99%) to plasminogen but lacks protease activity, and therefore has been hypothesized to inhibit fibrinolysis and mediate prothrombotic potential. Therefore, we hypnotized that there might be an enhanced impact of Lp(a) and Fib due to their pathophysiological action and previous evidence. A previous study indicated that high Fib associated with high Lp(a) levels significantly increased the risk of CAD [25], the study was designed for the primary prevention and was restricted by the male population. Hence, in this secondary prevention population, we divided our patients into 9 subgroups and found that the Fib-H with Lp(a)-H or Lp(a)-M group had 2.621-fold and 2.383-fold higher risk of CVEs, and the combination of Lp(a) and Fib categories improved the predictive value for CVEs beyond any biomarker alone.

Nevertheless, our study had several limitations. First of all, this is a study among Chinese population with stable CAD in the statin era, and whether the data applied to other populations need to be
testified. Secondly, the Lp(a) and Fib concentrations were only measured at baseline, and the
alterations of these biomarkers may also be clinically significant during the follow-up period. Finally,
as this was an observational study, further investigations are needed to clarify the underlying
mechanism of the associations.

Conclusions

In conclusion, according to the functional similarity of Lp(a) and Fib in pro-atherogenic and anti-
fibrinolytic effects, we examined the potential role of combining Lp(a) with Fib for predicting CVE in
8,417 patients with stable CAD and follow up a average of 37.1 months. Data firstly suggested that
Lp(a) plus Fib could significantly enhanced predicting value for cardiovascular outcome in patients
with stable CAD compared to that of Lp(a) or Fib alone.

Abbreviations
CVD, cardiovascular disease
CAD, coronary artery disease
CVEs, cardiovascular events
Lp[a], lipoprotein(a)
Apo(a), apolipoprotein(a)
Fib, fibrinogen
ACS, acute coronary syndrome
MI, myocardial infarction
TC, total cholesterol
TG, triglyceride
LDL-C, low-density lipoprotein-cholesterol
HDL-C, high-density lipoprotein-cholesterol

Declarations
Ethics approval and consent to participate: Our study was approved by the hospital’s ethics
review board (Fu Wai Hospital, National Center for Cardiovascular Diseases). All patients provided
informed written consents in this study.

**Consent for publication:** All the authors and participants have approved the manuscript for publication.

**Availability of data and materials:** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Competing interests:** The authors declare that they had no conflicts of interests to disclosure.

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**Authors’ contributions:** Y. Z. completed the project, analyzed data, and wrote the manuscript. J.-L.J., Y.X.-C., and H.-W.Z. contributed to data collection. Q.H. and Y.-F.L. contributed to the collections of data. Y.-L.G., N.-Q.W., C.-G.Z. and Y. G. contributed to recruitment of patients, clinical diagnosis of disease, and data collection. H.-H.L., R.-X. X., C.-J. C., G. L., Q.D., and J. S. contributed to the collections of clinical data and procedure of laboratory examination. J.-J.L. designed the study, interpreted data, and contributed to critically revising the manuscript.

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Tables

Table 1 Baseline characteristics of study patients
| Clinical characteristics | Total n=8417 | Events n=395 | No events n=8022 | p value |
|--------------------------|-------------|-------------|------------------|--------|
| Age, years               | 57.4±10.8   | 61.9±10.2   | 57.2±10.8        | <0.001 |
| Male sex, (%)            | 6032(71.7)  | 306(71.5)   | 5726(71.7)       | 0.956  |
| BMI (kg/m²)              | 25.9±4.6    | 25.5±3.3    | 25.9±4.6         | 0.099  |
| Hypertension, (%)        | 62          | 68.4        | 61.6             | 0.005  |
| Dyslipidemia, (%)        | 74.8        | 72.8        | 74.9             | 0.331  |
| Diabetes Mellitus, (%)   | 27.5        | 36.3        | 27               | <0.001 |
| Family history of CAD, (%) | 13.6       | 14.3        | 13.5             | 0.097  |
| Current smoker, (%)      | 54.4        | 52.7        | 54.5             | 0.484  |
| Laboratory findings      |             |             |                  |        |
| TC (mmol/L)              | 4.16±1.17   | 4.17±1.25   | 4.15±1.17        | 0.711  |
| LDL-C (mmol/L)           | 2.53±1.01   | 2.53±1.10   | 2.53±1.01        | 0.990  |
| HDL-C (mmol/L)           | 1.06±0.29   | 1.05±0.29   | 1.06±0.29        | 0.923  |
| TG (mmol/L)              | 1.50(1.10-2.10) | 1.48(1.05-2.09) | 1.50(1.10-2.10) | 0.446  |
| Lipoprotein(a) (mg/dL)   | 15.18(6.74-36.79) | 18.83(8.86-43.49) | 15.01(6.66-36.39) | 0.001  |
| apoA1 (g/L)              | 1.33±0.29   | 1.34±0.30   | 1.33±0.29        | 0.306  |
| apoB (g/L)               | 0.92±0.30   | 0.92±0.30   | 0.92±0.30        | 0.974  |
| Fibrinogen (g/L)         | 3.24±0.79   | 3.32±0.81   | 3.23±0.78        | 0.012  |
| D-dimer (ug/mL)          | 0.42±0.62   | 0.53±0.64   | 0.42±0.62        | <0.001 |
| Medications at admission |             |             |                  |        |
| Statins, (%)             | 75.5        | 68.6        | 75.8             | 0.005  |
| Aspirin, (%)             | 83.5        | 81.3        | 83.6             | 0.345  |
| ACEI, (%)                | 12.5        | 15          | 12.4             | 0.237  |
| ARB, (%)                 | 12.8        | 10.5        | 12.9             | 0.330  |
| β-blockers, (%)          | 48.2        | 50.8        | 48               | 0.402  |
| CCB, (%)                 | 19.2        | 20.3        | 19.1             | 0.623  |

Data are expressed as mean ± SD or median (25th–75th percentile) unless otherwise indicated.

ACEIs, ACE inhibitors; ARBs, angiotensin receptor blockers; CCB, calcium channel blocker.
Table 2 Association of fibrinogen and Lp(a) categories with clinical outcomes

| Risk Factor          | Tertile/Range | KM rates(%) | Hazard Ratio | (95% CI)       | p value |
|----------------------|---------------|-------------|--------------|----------------|---------|
| Lp(a) categories     |               |             |              |                | <0.001  |
| Total (mg/dL)        |               | 3.5         | Reference    |                |         |
| Lp(a)-L (<10)        |               | 5.3         | 1.468        | 1.142-1.886    | 0.003   |
| Lp(a)-M (10-29.9)    |               | 5.6         | 1.580        | 1.227-2.033    | <0.001  |
| Fibrinogen categories|               |             |              |                | <0.001  |
| Total (g/L)          |               | 4.0         | Reference    |                |         |
| Fib-L(<2.84)         |               | 4.4         | 1.123        | 0.867-1.455    | 0.380   |
| Fib-M(2.85-3.42)     |               | 6.1         | 1.631        | 1.282-2.074    | <0.001  |
| Combined categories  |               | 3.3         | Reference    |                | <0.001  |
| G1(Lp(a)-L+Fib-L)    |               | 3.5         | 0.697-1.707  | 0.704          |         |
| G2(Lp(a)-L+Fib-M)    |               | 4.0         | 0.771-1.977  | 0.381          |         |
| G3(Lp(a)-L+Fib-H)    |               | 4.1         | 0.741-1.828  | 0.509          |         |
| G4(Lp(a)-M+Fib-L)    |               | 4.9         | 1.406        | 0.914-2.162    | 0.121   |
| G5(Lp(a)-M+Fib-M)    |               | 7.0         | 2.135        | 1.446-3.152    | <0.001  |
| G6(Lp(a)-H+Fib-L)    |               | 4.8         | 1.348        | 0.849-2.140    | 0.206   |
| G7(Lp(a)-H+Fib-M)    |               | 5.4         | 1.578        | 1.026-2.426    | 0.038   |
| G8(Lp(a)-H+Fib-H)    |               | 7.2         | 2.215        | 1.506-3.257    | <0.001  |

Data are expressed as HR (95%CI). L, low; M, medium, H, high.
Table 3 Adjusted association of fibrinogen and Lp(a) categories with clinical outcomes
| Risk Factor       | Tertile/Range         | KM rates(%) | Hazard Ratio | (95% CI)    | p value |
|-------------------|-----------------------|-------------|--------------|-------------|---------|
| Lp(a) categories  | Total                 |             |              |             | 0.001   |
|                   | Lp(a)-L (<10)         | 3.5         | Reference    |             |         |
|                   | Lp(a)-M (10-29.9)     | 5.3         | 1.531        | 1.128-2.079 | 0.006   |
|                   | Lp(a)-H (≥30)         | 5.6         | 1.786        | 1.315-2.426 | <0.001  |
| Fibrinogen        | Total                 |             |              |             | 0.002   |
| categories        |                       |             |              |             |         |
|                   | Fib-L(<2.84)          | 4.0         | Reference    |             |         |
|                   | Fib-M(2.85-3.42)      | 4.4         | 1.001        | 0.726-1.379 | 0.996   |
|                   | Fib-H(≥3.43)          | 6.1         | 1.558        | 1.162-2.089 | 0.003   |
| Combined          | Total                 |             |              |             | 0.002   |
| categories        |                       |             |              |             |         |
|                   | G1(Lp(a)-L+Fib-L)     | 3.3         | Reference    |             |         |
|                   | G2(Lp(a)-L+Fib-M)     | 3.5         | 1.203        | 0.687-2.107 | 0.518   |
|                   | G3(Lp(a)-L+Fib-H)     | 4.0         | 1.476        | 0.831-2.619 | 0.184   |
|                   | G4(Lp(a)-M+Fib-L)     | 4.1         | 1.482        | 0.846-2.596 | 0.169   |
|                   | G5(Lp(a)-M+Fib-M)     | 4.9         | 1.511        | 0.866-2.636 | 0.146   |
|                   | G6(Lp(a)-M+Fib-H)     | 7.0         | 2.307        | 1.409-3.777 | 0.001   |
|                   | G7(Lp(a)-H+Fib-L)     | 4.8         | 1.912        | 1.085-3.369 | 0.025   |
|                   | G8(Lp(a)-H+Fib-M)     | 5.4         | 1.707        | 0.984-2.962 | 0.057   |
|                   | G9(Lp(a)-H+Fib-H)     | 7.2         | 2.656        | 1.628-4.333 | <0.001  |

Data are expressed as HR (95%CI). L, low; M, medium, H, high. Covariates used for adjustment are age, sex, BMI, diabetes mellitus, hypertension, dyslipidemia, family history of CAD, active smoking, D-dimer, and statin treatment.
Table 4 C-statistic of Lp(a) and Fib categories for predicting CVEs

| Models                                   | C-statistic (95% CI)     | ΔC-statistic (95% CI) | p value |
|------------------------------------------|--------------------------|-----------------------|---------|
| Original model                           | 0.633(0.603-0.664)       | -                     | -       |
| Original model + Lp(a) categories        | 0.643(0.612-0.674)       | 0.010(-0.001-0.023)   | 0.088   |
| Original model + Fib categories          | 0.637(0.606-0.668)       | 0.003(-0.005-0.012)   | 0.443   |
| Original model + combined categories     | 0.647(0.616-0.678)       | 0.013(0.002-0.027)    | 0.033   |

Original model included traditional risk factors as age, sex, BMI, diabetes mellitus, hypertension, dyslipidemia, family history of CAD, active smoking
Figure 1

The KM rates of CVEs in Fib, Lp(a), and combined groups.
Figure 2
The event-free survival rate in Fib, Lp(a), and combined groups.