The Effect of Lipoprotein(a) on Stroke Recurrence Attenuates at Low LDL-C and Inflammation Levels

Running Title: Lp(a), LDL-C, inflammation and stroke

Jie Xu, MD, PhD [1,2]*; Xiwa Hao, MD, PhD [1,2,4]*; Rui Zhan, PhD [2,3]*; Xue Jiang, PhD [2,3]; Aoming Jin, PhD [1,2]; Jing Xue, PhD [2,3]; Aichun Cheng, MD [1,2]; Jiewen Liu,BS [5]; Jinxi Lin, MD [1,2]; Xia Meng, MD, PhD [1,2]; Hao Li, MD, PhD [1,2]; Lemin Zheng, PhD [2,3]#; Yongjun Wang, MD [1,2]#

* These authors contributed equally to the manuscript

[1] Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.

[2] China National Clinical Research Center for Neurological Diseases, Tiantan Hospital; Advanced Innovation Center for Human Brain Protection, The Capital Medical University, China.

[3] The Institute of Cardiovascular Sciences and Institute of Systems Biomedicine, School of Basic Medical Sciences, Key Laboratory of Molecular Cardiovascular Sciences of Ministry of Education, Health Science Center, Peking University; Key Laboratory of Cardiovascular Molecular Biology and Regulatory Peptides of Ministry of Health, Beijing Key Laboratory of Cardiovascular Receptors Research; Beijing, China.

[4] Department of Neurology, Baotou Central Hospital, Inner Mongolia, China.

[5] McGill University, Montreal, Quebec,Canada.

Corresponding author: Yongjun Wang

Address: No. 119 South 4th Ring West Road, Fengtai District, Beijing 100070, China

Tel: 0086-010-67098350; Fax: 0086-010-67013383

E-mail: yongjunwang@ncrcnd.org.cn

Lemin Zheng

Address: No. 38 Xueyuan Road, Haidian District, Beijing 100871, China

Tel: 0086-010-82805452; Fax: 0086-010-82805452

E-mail: zhengl@bjmu.edu.cn

Total word count:4,723 words

Abstract

BACKGROUND: Lipoprotein(a) [Lp(a)] contributes to cardiovascular disease mainly through proatherogenic and proinflammatory effects. In this study, we aimed to evaluate whether a residual stroke risk of Lp(a) will remain if both LDL-C and inflammatory levels are kept at low levels.

METHODS: The study included 9,899 ischemic stroke (IS) or transient ischemic attack (TIA) patients from the Third China National Stroke Registry (CNSR-III) with measurements of plasma Lp(a). Cut-offs were set at the 50mg/dL for Lp(a) proposed by guidelines. LDL-C was corrected for Lp(a)-derived cholesterol (LDL-Cc) and cut-offs were set at 55 and 70 mg/dL. The threshold values of IL-6 and hsCRP were the median 2.65 ng/L and 2 mg/L. Multivariable-adjusted hazard ratios (HR) were calculated using Cox regression models for each category to investigate associations of Lp(a) with stroke recurrence within 1 year.

RESULTS: Individuals with an Lp(a)≥50mg/dL were at increased stroke recurrence risk compared to those with Lp(a)<50mg/dL among total patients (11.5% vs 9.4%, adjusted HR=1.20 [95%CI=1.02-1.42]). However, the risk associated with elevated Lp(a) was attenuated in patients with LDL-Cc <55 mg/dL (high Lp(a) vs low Lp(a): 8.9% vs 9.0%, adjusted HR=0.92, 95%CI[0.65-1.30]) or IL-6 <2.65 ng/L (9.0% vs 7.8%,adjusted HR=1.14, 95% CI[0.87-1.49]). Notably, in the group with both low LDL-Cc and inflammation levels, the rate of patients with high Lp(a) was not significantly different to the rate in their low Lp(a) counterparts (LDL-Cc <55 mg/dL and IL-6 <2.65 ng/L: 6.2% vs 7.1%, adjusted HR=0.86, 95% CI [0.46-1.62]; LDL-Cc <55 mg/dL and hsCRP <2 mg/L: 7.7% vs 7.6%,adjusted

HR=0.97,95%CI [0.57-1.66]). However,there was no interaction between LDL-Cc,IL-6, hsCRP and Lp(a) levels on stroke recurrence risk.

CONCLUSIONS: Increased Lp(a) was significantly associated with stroke recurrence risk among IS/TIA patients. However, at both low LDL-Cc or IL-6 levels, stroke recurrence risk associated with elevated Lp(a) attenuated in secondary prevention setting.

Keywords: Lipoprotein(a); Stroke Recurrence; LDL-C; Inflammation

Introduction

Lipoprotein(a)[Lp(a)] has been demonstrated to be a genetic, independent, and likely causal risk factor for cardiovascular disease (CVD).[1-4] Lp(a) is an LDL-like particle in which apolipoprotein B is covalently bound by a single disulfide bond to apolipoprotein A, which potentially contributes to CVD through proatherogenic effects of its LDL-like moiety and proinflammatory effects of its oxidized phospholipid content.[5] With the coming era of intensive lipid-lowering (such as PCSK9) and anti-inflammatory (such as Canakinumab and colchicine) therapy in CVD patients, LDL-C and inflammation levels will be reduced to very low levels.[6-8]

Recently, two studies have examined whether CVD risk can be affected by an interaction of Lp(a) and LDL-C, or Lp(a) and inflammation, in the primary and secondary CVD prevention settings. A large cohort study showed that CVD risk associated with elevated Lp(a) levels was attenuated at LDL-C levels below <2.5 mmol/L in a primary prevention setting.[9] Meanwhile, another study found that Lp(a) associated CVD risk was only observed in patients with hsCRP levels >2 mg/L but not in patients with hsCRP levels <2 mg/L.[10] Therefore, we have reason to believe that if both LDL-C and inflammation are controlled to low levels, Lp(a)-associated risks may be reduced. To our knowledge, no studies focused on this question in stroke patients until now. Hence, using the Third China National Stroke Registry (CNSR-III) study, we aimed to investigate whether the risk associated with elevated Lp(a) levels would be attenuated at low LDL-C and inflammation levels in ischemic stroke (IS) or transient ischemic attack (TIA) patients.

Methods

Study design and population

The CNSR-III study consists of 15,166 individuals recruited from patients with IS or TIA in 201 hospitals that cover 22 provinces and four municipalities in China. Of these hospitals, 171 participated in the biomarker study. The participants aged >18 years were enrolled from August 2015 to March 2018. The detailed design and methods of the CNSR-III, which was undertaken in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline recommendations[11], have been previously described.[12] The protocol and data collection methods of CNSR-III were approved by the ethics committee of Beijing Tiantan Hospital and participating hospitals. Written informed consent was obtained from each participant or legally authorized representative.

Baseline data collection

Baseline data on demographics and medical history, such as age, sex, body mass index (BMI, calculated as weight in kilograms divided by height in meters squared, kg/m^2), were collected through face-to-face interviews by trained interviewers (neurologists from participating hospitals). Etiology subtypes were classified according to the TOAST criteria (large-artery atherosclerosis [LAA], cardio-embolism [CE], small-artery occlusion [SAO], other determined cause, or undetermined cause).[13] Other data were extracted from medical records that include medical history (hypertension, diabetes mellitus, coronary heart disease, atrial fibrillation, stroke), systolic blood pressure [SBP] at admission, lab testing at admission (high-density lipoprotein cholesterol [HDL-C], fasting blood glucose [FBG], estimated glomerular filtration rate [eGFR, expressed as the CKD-EPI equation[14]]), and discharge

medications (antiplatelet, anticoagulant, statin, anti-hypertension, and antidiabetics).

Lp(a), Interleukin-6 (IL-6) and hsCRP measurement

EDTA fasting blood samples were collected within 24 hours of admission from 171 study sites. All the blood samples were transported to the center laboratory in Beijing Tiantan Hospital in a maintained cold chain and stored at −80℃ until testing was performed. Lp(a) concentrations were determined by using enzyme-linked immunosorbent assay (ELISA) kits (Mercodia AB, Sweden). Mercodia Lp(a) ELISA is based on the direct sandwich technique in which two monoclonal antibodies are directed against separate antigenic determinants on the Apo(a) molecule. This is a well-validated assay, with good reproducibility (coefficient of variation, 5.52-6.98%), that yields robust results and is generally insensitive to apolipoprotein(a) size heterogeneity. The concentrations of IL-6 were determined by using enzyme-linked immunosorbent assay kits(catalogue number:PHS600C,R&D Systems, Inc, Minneapolis, MN, USA). The concentrations of plasma hsCRP were measured on a Roche Cobas C701 analyzers.

Patient Follow-Up and Outcome Evaluation

Patients were followed up clinically by face-to-face interviews at discharge and 3 months, and the trained research coordinators contacted the patients by phone at 6 months and 1 year. Stroke recurrence events that occurred during follow-up were recorded. The trained research coordinators would contact the participants to ask whether they had stroke-related symptoms during one year follow-up, and whether to be admitted to the hospital for diagnosis and treatment. If the participants had new stroke symptoms but they didn't see the doctor, they were required to complete brain imaging (CT or MR) at their attending hospital for confirmation. Finally, these suspected recurrent cerebrovascular events without

hospitalization were judged by independent endpoint judgement committee.Participants with missing outcome data would be censored at the last follow-up visit time (One-year visit or last visit preceding loss to follow-up). After the completion of baseline investigation, information at discharge were collected for all patients. Thus, all patients in the cohort were followed up and had at least one follow-up visit. The primary outcome was stroke recurrence (time-to-first) within 1 year, including new IS and hemorrhagic stroke.

Statistical analyses

Continuous variables are presented as medians with interquartile ranges and categorical variables as percentages. Baseline characteristics between Lp(a) categories were compared using chi-square statistics for the categorical variables and Kruskal-Wallis test for the continuous variables.

Two Lp(a) categories were established by setting the cut-off at the 50mg/dL proposed by the European Atherosclerosis Society (EAS) and American Heart Association and American College of Cardiology (AHA/ACC).thereby dividing the subjects into groups with Lp(a) levels<50mg/dL and ≥50mg/dL[15, 16]. LDL-C was corrected for Lp(a) derived cholesterol (LDL-Cc),[4, 17] and cut-offs were set at 55 and 70 mg/dL,[18] dividing patients into three distinct groups with LDL-Cc levels <55, 55-70, and ≥70 mg/dL. The median and quartiles were used to create four patients groups for their respective IL-6 levels. The threshold of hsCRP was set as 2 mg/L in reference to the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) study.[6] Percentages of patients with recurrent stroke events within 1-year follow-up were estimated using Kaplan–Meier survival analysis. Association of baseline Lp(a) with stroke recurrence risk within 1 year for each category (LDL-Cc, IL-6, hsCRP level) and

combinations thereof were investigated using Cox proportional-hazards models. Multivariable-adjusted hazard ratios (HR) with corresponding 95% confidence interval (CI) were calculated for overall cohorts (age, sex, BMI, history of stroke, history of coronary heart disease, TOAST subtype, GFR, HDL-C, LDL-Cc, IL-6, and hsCRP) and for each category (age, sex, BMI, history of stroke, history of coronary heart disease, TOAST subtype, GFR, HDL-C). The interaction was assessed among Lp(a) and LDL-Cc/IL-6/hs-CRP on stroke recurrence risk in the entire cohort. Additionally, we performed a sensitivity analysis in the background of statin therapy, which was defined as statin therapy during hospitalization or discharge.A two-sided *P* value of <0.05 was recognized as statistical significance. SAS software, version 9.4 (SAS Institute, Inc, Cary, NC), was used for all statistical analyses.

Results

Study participants and characteristics

A total of 15,166 patients with IS or TIA were enrolled in the CNSR-III study. Blood samples of 12,603 patients were collected from 171 participating study sites for the biomarker sub-study. Of these, 1,1261 blood samples were ultimately transported to the center laboratory. After further excluding patients with missing data of baseline Lp(a), LDL-C, IL-6, and hsCRP levels, 9,899 patients were finally included in the analysis (Supplemental Figure I). For all participants, the mean follow-up time was 326 days and the median follow-up time was one year.

Among the 9,899 patients, the average age was 63 (54-70) years, and 6,756 (68.3%) were male. Within 1 year, a total of 963 (9.73%) patients had a recurrent stroke. The median Lp(a)

was 18.08 (8.85-35.68) mg/dL. Baseline Lp(a) distribution was skewed to the left and the proportion of patients with an Lp(a) level ≥50 mg/dL was 15.44% (Supplemental Figure II). Baseline characteristics of the patients defined by an Lp(a) ≥50mg/dL and <50mg/dL are shown in Table 1. Study participants in the Lp(a) ≥50mg/dL seemed more likely to have a previous history of coronary heart disease; a higher proportion of large-artery atherosclerosis stroke; higher HDL-C, LDL-C, IL-6, and hsCRP levels; but lower LDL-Cc and eGFR levels. .

The effect of Lp(a) on stroke recurrence

As shown in Figure 1, the Kaplan–Meier analysis with the log-rank test showed that subjects with Lp(a) level ≥50mg/dL had a significantly higher cumulative recurrence than those with Lp(a) level <50mg/dL(p=0.0159). After multivariable adjustment, Lp(a) levels ≥50mg/dL remained significantly associated with stroke recurrence risk (adjusted HR=1.20, 95% CI[1.02-1.42]) (Figure 2). The association between Lp(a) and stroke recurrence was analyzed by age stratification. In the patient group aged between 18 and 63, the stroke recurrence risk significantly increased with patients of the Lp(a)≥50mg/dL (11.7% vs 8.3%, adjusted HR=1.30, 95% CI[1.02-1.66]) compared to those with Lp(a) <50mg/dL. This association was not observed in patients over 63 years (11.8% vs 10.5%, adjusted HR=1.12, 95% CI[0.89-1.40])(Supplementary Table I). Additionally, the sensitivity analyse in the background of statin therapy, further demonstrated the recurrence rate was significantly different between the Lp(a)≥50mg/dL and Lp(a) <50mg/dL (11.4% vs 9.4 %,adjusted HR=1.20,95%CI [1.02-1.42]). (Supplementary Table II)

Associations of Lp(a) with stroke recurrence according to LDL-Cc level

A significant association between Lp(a) and stroke recurrence (12.2% vs 9.5%, adjusted

HR=1.30,95%CI[1.05-1.61]) was observed for LDL-Cc levels ≥70 mg/dL. However, for LDL-Cc levels <55 mg/dL, the recurrence rate was not significantly different between the Lp(a) ≥50mg/dL and Lp(a) <50mg/dL groups (8.9% vs 9.0%, adjusted HR=0.92,95%CI [0.65-1.30]).There was no significant interaction between LDL-Cc and Lp(a) levels on stroke recurrence risk in this cohort ($p_{interaction}$=0.19).(Figure 2)

Associations of Lp(a) with stroke recurrence according to IL-6 level

We divided patients into two groups based on the IL-6 median (2.65 ng/L) as the cut-off value. In the patient group characterized by IL-6 ≥2.65 ng/L, stroke recurrence risk significantly increased in patients of the Lp(a) ≥50mg/dL (13.7% vs 11.1%, adjusted HR=1.24, 95% CI[1.00-1.52]) compared to those of the Lp(a) <50mg/dL. This association was not observed in patients with IL-6<2.65 ng/L (9.0% vs 7.8%, adjusted HR=1.14, 95% CI[0.87-1.49]).There was no significant interaction between IL-6 and Lp(a) levels on stroke recurrence risk in this cohort ($p_{interaction}$=0.68).(Figure 2) Then,according to the quartile of IL-6 categories groups, the adjusted HR with corresponding 95%(CI) of the IL-6 quartile category groups were 1.03 (0.70-1.53), 1.29 (0.89-1.86), 1.08 (0.77-1.52), and 1.32 (1.01-1.72) for the first, second, third, and fourth quartiles of the IL-6 groups (Supplementary Table III).

Associations of Lp(a) with stroke recurrence according to hs-CRP level

In the patient group characterized by hs-CRP≥2mg/L, margin statistical significance was found in multivariate adjusted analysis(Lp(a)≥50mg/dL vs Lp(a) <50mg/dL: 13.1% vs 11.1%, adjusted HR=1.18, 95%CI[0.94-1.47]). This association was not observed in patients with hs-CRP<2mg/L (9.9% vs 7.9%, adjusted HR=1.22, 95% CI[0.95-1.56]).There was no significant interaction between hs-CRP and Lp(a) levels on stroke recurrence risk in this

cohort($p_{interaction}$=0.81).(Figure 2)

Associations of Lp(a) with stroke recurrence at different LDL-Cc and IL-6 or hsCRP level

In the patient group with both low LDL-Cc (<55 mg/dL) and hsCRP (<2 mg/L) levels, the event rate of patients with high Lp(a) was not significantly different to that of their counterparts with low Lp(a) levels (7.7% vs 7.6%, adjusted HR=0.97,95%CI [0.57-1.66]). Similarly, in the patient group characterized by both low LDL-Cc (<55 mg/dL) and IL-6 (<2.65 ng/L) levels, patients with high Lp(a) levels appeared to have a lower recurrence rate than those with low Lp(a) levels; however, the difference was not statistically significant (6.2% vs 7.1%,adjusted HR=0.86, 95% CI [0.46-1.62]) (Figure 3).

Discussion

Our study demonstrated that elevated Lp(a) levels were associated with one-year stroke recurrence among IS/TIA patients. However, Lp(a)-associated risk attenuated at low LDL-Cc (<55 mg/dL) and/or low inflammation levels (hsCRP<2 mg/L or IL-6 <2.65 ng/L).

Several prior studies have explored the value of Lp(a) for predicting CVD across different LDL-C levels in a primary or secondary CVD prevention setting.[9, 19-23] The findings of most studies showed that increased Lp(a)-associated CVD risk was maintained independently of LDL-C levels.[24 25] High Lp(a) concentrations increased CVD risk even in individuals with LDL-C < 70 mg/dL.[26] However, two recent studies showed converse findings. In the EPIC-Norfolk and CCHS cohorts, they found that, Lp(a)-associated CVD risk attenuates at LDL-C levels below <2.5 mmol/L in a primary prevention setting.[9] The GeneBank study reported that the association between elevated Lp(a) levels (≥30 mg/dL) and cardiovascular

outcomes became markedly attenuated below an uncorrected LDL-C threshold of <70 mg/dL in patients who underwent coronary angiography.[19] The findings of our research were consistent with above two studies. The difference was that our research background is based on secondary prevention of IS patients.

Vast evidence from clinical studies, in particular the CANTOS and the Low Dose Colchicine for secondary prevention of cardiovascular disease (LoDoCo Trial), has confirmed the causal role of inflammation in the pathogenesis of CVD and related complications.[6, 8, 27] Lp(a) induces monocyte trafficking to the arterial wall and mediates proinflammatory responses through its OxPL content by *in vivo* MR imaging and *ex vivo* analysis of monocytes.[28] Yet, to date, there is few evidence of the residual CVD risk of Lp(a) associated with inflammation. The *post hoc* analysis of the Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition With Evacetrapib in Patients at a High Risk for Vascular Outcomes (ACCELERATE) trial, comprising of 12,092 patients at high risk of CVD (acute coronary syndrome, stroke, peripheral arterial disease, or type 2 diabetes with coronary artery disease), showed that increasing Lp(a) levels during treatment were significantly associated with cardiovascular death, myocardial infarction, and stroke in individuals with hsCRP levels of ≥2 mg/L during treatment but not in those with levels <2 mg/L.[10] In our study, both hsCRP and IL-6 were used as inflammation markers to explore Lp(a)-associated risk modulated by inflammation. And we also found a similiar result, which showed that Lp(a)-associated CVD risk attenuated at low hsCRP and/or IL-6 levels in a stroke secondary prevention setting.

Considering that the combined therapy of intensive lipid-lowering and anti-inflammatory likely to be applied in CVD patients, this study simultaneously analyzed the Lp(a)-associated

CVD risk with LDL-C and inflammation in the same population. Our results showed that , the increased stroke recurrence risk linked to Lp(a) appeared to be gone at both low LDL-C and inflammation levels. This finding indicated that Lp(a)-lowering drugs may specifically benefit patients with high LDL-C and inflammation levels, providing a direction for future Lp(a) interventional RCT studies. We assessed the interaction among Lp(a) and LDL-Cc/IL-6/hs-CRP on stroke recurrence risk in our study.The interaction effect was not statistically exist, which is also consistent with previous literature on primary or secondary prevention of cardiovascular disease.[9, 22, 29] Lp(a) itself has an LDL element and pro-inflammatory effect in terms of pathophysiological mechanisms, hence we investigated the association between Lp(a) and outcome events through LDL-Cc and inflammation stratification.

Our study also has several limitations. First, our primary analysis was based on baseline Lp(a) level rather than dynamic change. Though Lp(a) is genetically determined it is also an acute phase reactant that may be elevated during stress.[30,31,32] Second, although LPA genotypes were not evaluated in this study, Lp(a) levels are predominantly genetically determined and directly measured Lp(a) levels offered a comparable stroke risk prediction to the LPA gene. Third, Lp(a) concentrations are known to vary with ethnicity. This cohort only included Chinese individuals; therefore, our findings might not be readily extrapolated to other populations. Finally, The results of stratification in subgroup analyses should be affected by lack of statistical power due to the small sample size and low event rate, because subgroups were stratified simultaneously by LDL-Cc and IL-6 levels. Hence, these results must be interpreted with caution and need to be verified in a large sample study.

Conclusions

We demonstrate that high Lp(a) levels were associated with increased risk of one-year stroke recurrence in a large IS/TIA cohort population. However, at low LDL-Cc or inflammation levels, Lp(a)-associated stroke recurrence risk appears to be substantially attenuated in secondary prevention setting.

Acknowledgments

The authors thank the participants and staff of the Third China National Stroke Registry (CNSR-III) study.

Source of Funding

This work was supported by grants from the National Key R&D Program of China (2016YFC0901002, 2017YFC1310901, 2018YFC1312903), grants from Beijing Municipal Science & Technology Commission (D171100003017002), National Science and Technology Major Project (2017ZX09304018), grants from the National Natural Science Foundation of China (81701141, 91639108, 81770272, 81970425), and Young Scientist Program [YSP201704].

Conflict of interest

None declared.

References:

1. Burgess S, Ference BA, Staley JR, Freitag DF, Mason AM, Nielsen SF, Willeit P, Young R, Surendran P, Karthikeyan S, et al. Association of LPA variants with risk of coronary disease and the implications for Lipoprotein(a)-Lowering therapies: A mendelian randomization analysis. Jama Cardiol. 2018;3:619-627

2. Nordestgaard BG, Langsted A. Lipoprotein (a) as a cause of cardiovascular disease: Insights from epidemiology, genetics, and biology. J Lipid Res. 2016;57:1953-1975

3. Lamina C, Kronenberg F. Estimation of the required Lipoprotein(a)-Lowering therapeutic effect size for reduction in coronary heart disease outcomes: A mendelian randomization analysis. Jama Cardiol. 2019;4:575-579

4. Bittner VA, Szarek M, Aylward PE, Bhatt DL, Diaz R, Edelberg JM, Fras Z, Goodman SG, Halvorsen S, Hanotin C, et al. Effect of alirocumab on lipoprotein(a) and cardiovascular risk after acute coronary syndrome. J Am Coll Cardiol. 2020;75:133-144

5. Tsimikas S. A test in context: Lipoprotein(a): Diagnosis, prognosis, controversies, and emerging therapies. J Am Coll Cardiol. 2017;69:692-711

6. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD,et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. The New England journal of medicine. 2017;377:1119-1131

7. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. N Engl J Med. 2018;379:2097-2107

8. Nidorf SM, Eikelboom JW, Budgeon CA, Thompson PL. Low-dose colchicine for

secondary prevention of cardiovascular disease. J Am Coll Cardiol. 2013;61:404-410

9. Verbeek R, Hoogeveen RM, Langsted A, Stiekema LCA, Verweij SL, Hovingh GK, Wareham NJ, Khaw K, Boekholdt SM, Nordestgaard BG, et al. Cardiovascular disease risk associated with elevated lipoprotein(a) attenuates at low LDL-C levels in a primary prevention setting. Eur Heart J. 2018;39:2589-2596

10. Puri R, Nissen SE, Arsenault BJ, St JJ, Riesmeyer JS, Ruotolo G, McErlean E, Menon V, Cho L, Wolski K, et al. Effect of C-Reactive protein on Lipoprotein(a)-Associated cardiovascular risk in optimally treated patients with High-Risk vascular disease: A prespecified secondary analysis of the ACCELERATE trial. Jama Cardiol. 2020;5:1136-1143

11.von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.PLoS Med. 2007;16:e296

12. Wang Y, Jing J, Meng X, Pan Y, Wang Y, Zhao X, Lin J, Li W, Jiang Y, Li Z, et al. The Third China National Stroke Registry (CNSR-III) for patients with acute ischaemic stroke or transient ischaemic attack: Design, rationale and baseline patient characteristics. Stroke Vasc Neurol. 2019;4:158-164

13. Adams HJ, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh ER. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993;24:35-41

14. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AR, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150:604-612

15. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;139:e1082-e1143

16. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, Hoes AW, Jennings CS, Landmesser U, Pedersen TR, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. Eur Heart J. 2016;37:2999-3058

17. Viney NJ, Yeang C, Yang X, Xia S, Witztum JL, Tsimikas S. Relationship between "LDL-C", estimated true LDL-C, apolipoprotein B-100, and PCSK9 levels following lipoprotein(a) lowering with an antisense oligonucleotide. J Clin Lipidol. 2018;12:702-710

18. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41:111-188

19. Nicholls SJ, Tang WH, Scoffone H, Brennan DM, Hartiala J, Allayee H, Hazen SL. Lipoprotein(a) levels and long-term cardiovascular risk in the contemporary era of statin therapy. J Lipid Res. 2010;51:3055-3061

20. von Eckardstein A, Schulte H, Cullen P, Assmann G. Lipoprotein(a) further increases the risk of coronary events in men with high global cardiovascular risk. J Am Coll Cardiol. 2001;37:434-439

21. Suk DJ, Rifai N, Buring JE, Ridker PM. Lipoprotein(a), measured with an assay independent of apolipoprotein(a) isoform size, and risk of future cardiovascular events among initially healthy women. JAMA. 2006;296:1363-1370

22. O'Donoghue ML, Morrow DA, Tsimikas S, Sloan S, Ren AF, Hoffman EB, Desai NR, Solomon SD, Domanski M, Arai K, et al. Lipoprotein(a) for risk assessment in patients with established coronary artery disease. J Am Coll Cardiol. 2014;63:520-527

23. Luc G, Bard J, Arveiler D, Ferrieres J, Evans A, Amouyel P, Fruchart J, Ducimetiere P. Lipoprotein (a) as a predictor of coronary heart disease: The PRIME Study. Atherosclerosis. 2002;163:377-384

24. Bittner VA, Szarek M, Aylward PE, Bhatt DL, Diaz R, Edelberg JM, Fras Z, Goodman SG, Halvorsen S, Hanotin C, et al. Effect of alirocumab on lipoprotein(a) and cardiovascular risk after acute coronary syndrome. J Am Coll Cardiol. 2020;75:133-144

25. Hoogeveen RC, Ballantyne CM. Residual cardiovascular risk at low LDL: Remnants, lipoprotein(a), and inflammation. Clin Chem. 2021;67:143-153

26. Zhao Y, Delaney JA, Quek RG, Gardin JM, Hirsch CH, Gandra SR, Wong ND. Cardiovascular disease, mortality risk, and healthcare costs by lipoprotein(a) levels according to low-density lipoprotein cholesterol levels in older high-risk adults. Clin Cardiol. 2016;39:413-420

27. Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, Pinto FJ, Ibrahim R, Gamra H, Kiwan GS, et al. Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. N Engl J Med. 2019;381:2497-2505

28. van der Valk FM, Bekkering S, Kroon J, Yeang C, Van den Bossche J, van Buul JD,

Ravandi A, Nederveen AJ, Verberne HJ, Scipione C, et al Oxidized phospholipids on lipoprotein(a) elicit arterial wall inflammation and an inflammatory monocyte response in humans. Circulation. 2016;134:611-624

29. Afshar M, Pilote L, Dufresne L, Engert JC, Thanassoulis G. Lipoprotein(a) interactions with Low-Density lipoprotein cholesterol and other cardiovascular risk factors in premature acute coronary syndrome (ACS). J Am Heart Assoc. 2016;5:e003012

30.Cegla J, Neely R, France M, Ferns G, Byrne CD, Halcox J, Datta D, Capps N, Shoulders C, Qureshi N, et al. HEART UK consensus statement on Lipoprotein(a): A call to action. Atherosclerosis. 2019;291:62-70

31.S Maeda 1 , A Abe, M Seishima, K Makino, A Noma, M Kawade.Transient changes of serum lipoprotein(a) as an acute phase protein.Atherosclerosis.1989;78:145-150

32.W Y Craig, T B Ledue.Lipoprotein(a) and the acute phase response. Clin Chim Acta.1992;210:231-232

Table 1. Baseline Clinical Characteristics According to Baseline Lp(a) Concentration

Variable	Overall N=9,899	Lp(a) <50 mg/dL N=8,371	Lp(a) ≥50 mg/dL N=1,528	P value
Age, years, median (IQR)	63(54-70)	63(54-70)	63(55-70)	0.42
Male, n (%)	6,756(68.3%)	5,755(68.8%)	1,001(65.5%)	0.01
Current smoker,n (%)	3,108(31.4%)	2,652(31.7%)	456(29.8%)	0.15
BMI, kg/m^2, median (IQR)	24.49(22.60-26.57)	24.49(22.65-26.57)	24.24(22.32-26.41)	0.02

Diseases history,n (%)				
Hypertension	6,229(62.9%)	5,275(63.0%)	954(62.4%)	0.67
Diabetes mellitus	2,360(23.8%)	2,013(24.1%)	347(22.7%)	0.26
Stroke	2,264(22.9%)	1,895(22.6%)	369(24.2%)	0.20
Coronary heart disease	1,063(10.7%)	878(10.5%)	185(12.1%)	0.06
Atrial fibrillation	693(7.0%)	599(7.2%)	94(6.2%)	0.16
Type of stroke, n(%)				0.57
IS	9,231 (93.3%)	7,801 (93.2%)	1,430 (93.6%)	
TIA	668 (6.8%)	570 (6.8%)	98 (6.4)	
TOAST classification, n (%)				0.08
Large-artery atherosclerosis	2,514(25.4%)	2,088(24.9%)	426(27.9%)	
Cardioembolic	627(6.3%)	546(6.5%)	81(5.3%)	
Microangiopathic	2,063(20.8%)	1,753(20.9%)	310(20.3%)	
Other cause	109(1.1%)	90(1.1%)	19(1.2%)	
Unknown cause	4,586(46.3%)	3,894(46.5%)	692(45.3%)	
Discharge medications, n (%)				
Antiplatelet	9,090(92.1%)	7,671(91.9%)	1,419(93.1%)	0.12
Anticoagulant	307(3.1%)	263(3.2%)	44(2.9%)	0.58
Aanti-hypertension	4,898(49.6%)	4,164(49.9%)	734(48.1%)	0.21
Statin	9,159(92.5%)	7,726(92.3%)	1,433(93.8)	0.04
Aantidiabetics	2,396(24.3%)	2,040(24.4%)	356(23.3%)	0.36
eGFR (mL/min/1.73 m^2)	92.95(81.54-101.70)	93.20(82.17-101.92)	91.65(78.50-100.48)	＜0.001

FPG(mmol/L), median (IQR)	5.53(4.90-6.88)	5.52(4.90-6.91)	5.55(4.89-6.70)	0.51
BP at admission, mmHg, median (IQR)	148.50(135.00-164.00)	148.50(135.00-164.50)	148.00(135.00-163.25)	0.62
Lipid profile				
HDL-C(mg/dL), median (IQR)	36.38(30.19-43.34)	35.99(29.80-42.96)	37.15(30.57-44.89)	＜0.001
LDL-C(mg/dL), median (IQR)	89.78(66.95-115.71)	87.46(65.40-113.39)	100.81(76.82-130.81)	＜0.001
LDL-Cc(mg/dL), median (IQR)	81.39(59.17-107.39)	82.17(60.64-107.76)	75.22(49.91-106.05)	＜0.001
Lp(a)(mg/dL), median (IQR)	18.08(8.85-35.68)	14.85(7.62-25.30)	75.63(60.81-103.81)	＜0.001
Inflammatory biomarkers				
IL-6(ng/L), median (IQR)	2.65(1.59-5.06)	2.62(1.57-4.98)	2.80(1.68-5.57)	＜0.001
hs-CRP(mg/dL), median (IQR)	1.77(0.82-4.70)	1.75(0.82-4.53)	1.95(0.85-5.59)	＜0.001

Abbreviations: IQR=interquartile range; SBP=systolic blood pressure; FPG=fasting plasm glucose; LDL-C= low-density lipoprotein cholesterol; LDL-Cc=low-density lipoprotein cholesterol corrected; HDL-C=high-density lipoprotein cholesterol;Lp(a)=Lipoprotein(a); hsCRP=high-sensitive C-reactive protein;eGFR=estimated glomerular filtration rate; BMI=body mass index. BMI is the weight in kilograms divided by the square of the height in meters. TOAST denotes stroke etiology classification criteria according to the Trial of Org 10172 in Acute Stroke Treatment.

Figure legends

Figure 1. Cumulative Incidence Rates of Stroke Recurrence with Elevated Lp(a) Levels During 1-year Follow-up.

Figure 2. Association of Stroke Recurrence with Lp(a) According to the Different Groups of LDL-Cc , IL-6 and Hs-CRP Levels.

Figure 3. Association of Stroke Recurrence with Lp(a) at Different IL-6, hsCRP, and LDL-Cc Levels.