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RESEARCH LETTER

Elevated Homocysteine Intensify the Effect of Lipoprotein(a) on Stroke Recurrence

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Lipoprotein(a) (Lp[a]) is a unique liver-derived lipoprotein with primarily genetically determined concentrations that contributes to cardiovascular disease via multiple mechanisms. Evidence from observational and genetic studies support a causal role of Lp(a) in the acute ischemic stroke (AIS), especially in the atherosclerosis subtype.[1] Plasma total homocysteine (tHcy) is a methionine intermediate metabolite. Despite the controversy, tHcy has been recognized as a risk factor for AIS. Furthermore, tHcy showed great impact on Lp(a) binding to plasmin-modified fibrin and augmented the interaction between Lp(a) and Macrophage-1 antigen integrin, which might intensify the proatherogenic, prothrombotic, and proinflammatory pathway mediated by Lp(a). Several past studies showed that Lp(a) and tHcy had an interaction effect on the occurrence of coronary artery disease and retinal arteriosclerosis, and both are atherosclerosis diseases.[2] Therefore, we aimed to examine the effect of Lp(a) on stroke recurrence within 1 year in patients with AIS or transient ischemic attack (TIA), with and without elevated baseline tHcy.

We derived data from the CNSR-III (Third China National Stroke Registry). The rationale and design of CNSR-III have been previously published. Briefly, CNSR-III is a nationwide, prospective, multicenter registry cohort study. Between August 2015 and March 2018, a total of 11 261 patients with AIS and TIA within 7 days from onset and with biological samples were enrolled from 171 hospitals across the country.[3] The protocol of CNSR-III was approved by the ethics committee of Beijing Tiantan Hospital and participating hospitals; patients provided written informed consent before participation in the study. The data that support the findings of this study are available from the corresponding author on reasonable request.

A total of 10 068 patients with complete baseline Lp(a) and tHcy information were included in our study. The cutoff value of Lp(a) was set as the 80th percentile, and the cutoff value of tHcy was set as 15 μmol/L. Included patients were further categorized to different stroke subtypes according to the trial of ORG 10172 in acute stroke treatment criteria: large artery atherosclerosis (LAA), cardioembolism, small artery occlusion, and other/undetermined determined cause. The interaction between Lp(a) and tHcy was tested. Adjusted hazard ratios (aHRs) and 95% CIs were derived from Cox proportional hazard models using stroke recurrence during the 1-year follow-up. Major covariables were adjusted for age, sex, body mass index, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, National Institutes of Health Stroke Scale, past medical history (smoking, drinking, diabetes, coronary artery disease), and discharge medication (antiplatelets, antihypertensives, lipid-lowering medications).

Of 10 068 included patients, 8054 patients were classified into the ≤80th percentile group and 2014 patients were classified into the >80th percentile group.

Key Words: acute ischemic stroke ■ homocysteine ■ interaction effect ■ lipoprotein(a) ■ stroke recurrence ■ transient ischemic attack

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No significant differences were found between the 2 groups in terms of age, sex, and traditional risk factors of AIS/TIA (P>0.05).

During a 1-year follow-up, there were 999 recurrence events. Compared with patients with Lp(a)≤80th percentile, patients with Lp(a)>80th percentile had a higher risk of stroke recurrence (aHR, 1.20 [95% CI, 1.03–1.40]; P=0.02). We then investigated the interaction between tHcy and Lp(a)-related stroke recurrence (Figure). Patients were further stratified into elevated tHcy (>15 μmol/L) and normal tHcy (≤15 μmol/L). Among the overall patients, the highest risk of stroke recurrence (12.8%) was observed in the patients with both elevated Lp(a) and tHcy (aHR, 1.41 [95% CI, 1.14–1.74]), and an interaction between Lp(a) and tHcy on stroke recurrence was observed (interaction P=0.03). We also found a significant interaction between Lp(a) and tHcy among LAA subtype (interaction P<0.01), in which patients with both elevated Lp(a) and tHcy showed the highest stroke recurrence rate (17.1% in LAA). Patients with small artery occlusion showed a near-significant interaction (interaction P=0.06). There was no interaction between Lp(a) and tHcy among the cardioembolism (interaction P=0.68) and other/undetermined determined cause (interaction P=0.96) subtypes.

Several limitations warrant consideration. The cutoff value of Lp(a) was not uniform around the world. The National Lipid Association recommended Lp(a)>50 mg/dL as a risk-enhancing factor.[4] However, this level corresponds to the 80th percentile in White patients. A recent study including only Chinese patients with myocardial infarction suggested that the 75th percentile of Lp(a) ranged from 18.84 to 41.43 mg/dL.[5] Thus, we chose the 80th percentile but not 50 mg/dL as the cutoff value. The 80th percentile value corresponds to 42.15 mg/dL in our study, which remained consistent with the aforementioned range. Further work will be needed to determine a precise cutoff value of Lp(a) for Chinese patients with AIS/TIA.

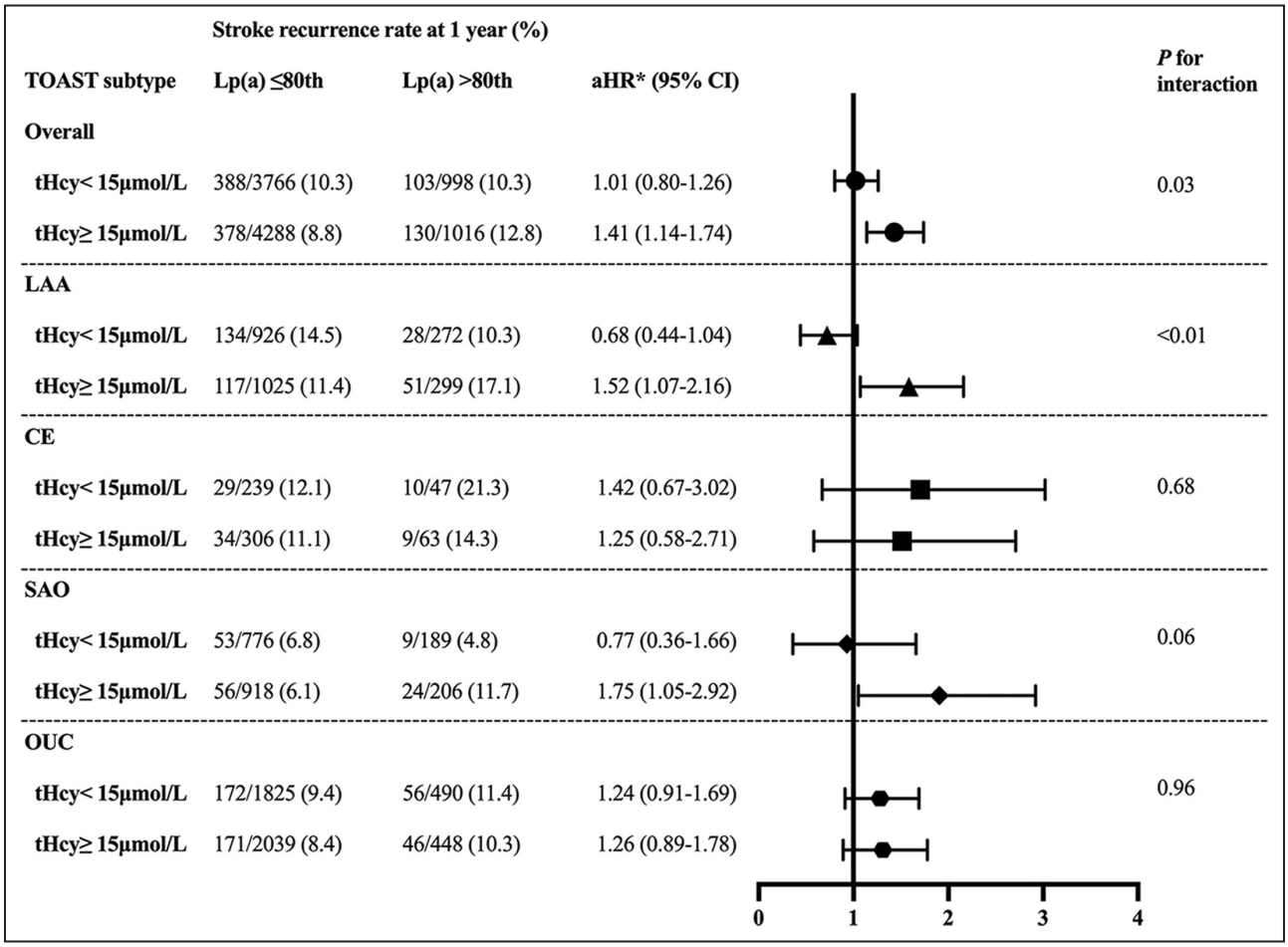

Figure. Interaction effect between Lp(a) and tHcy on stroke recurrence based on different trial of ORG 10172 in acute stroke treatment subtypes.

*Major covariables were adjusted for age; sex; body mass index; low-density lipoprotein cholesterol; high-density lipoprotein cholesterol; National Institutes of Health Stroke Scale; smoking; drinking; diabetes; coronary artery disease; and discharge antiplatelets, antihypertensives, and lipid-lowering medications. aHR indicates adjusted hazard ratio; CE, cardioembolism; LAA, large artery atherosclerosis; Lp(a), lipoprotein(a); OUC; other or undetermined cause; SAO, small artery occlusion; and tHcy, plasma total homocysteine.

The results showed that elevated Lp(a) level is independently associated with 1-year stroke recurrence in patients with AIS/TIA. The interaction between Lp(a) and tHcy on stroke occurrence was observed, especially in the LAA subtype, which indicated that elevated tHcy might intensify Lp(a)-associated stroke recurrence in a secondary prevention setting. Our results suggested that elevated Lp(a) should receive more attention in patients with AIS/TIA with elevated tHcy, especially in the LAA subtype. The results are clinically relevant because tHcy and Lp(a) are 2 modified risk factors (tHcy can be lowered with B vitamins, and RNA interference shows potential in lowering Lp[a]). Further studies should be carried out regarding the intervention of Lp(a) and tHcy in patients with AIS/TIA. The mechanisms involved in Lp(a), tHcy, and stroke recurrence have not been established yet, and therefore our results need to be interpreted with caution.

ARTICLE INFORMATION

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Disclosures

None.

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