ORIGINAL RESEARCH

Serum Lipoprotein(a) as Predictive Factor for Early Neurological Deterioration of Acute Ischemic Stroke After Thrombolysis

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Objective: This study aimed to explore the relationship between serum lipoprotein(a) (LP(a)) levels and early neurological deterioration (END) in patients with acute ischemic stroke (AIS) after thrombolysis.

Methods: In total, 236 patients with AIS after thrombolysis were enrolled in this study. Serum LP(a) levels were measured on admission after thrombolysis. END was defined as an increase of at least two points in the NIHSS score within 48 hours after thrombolysis. Binary logistic regression analysis was used to assess the association between serum LP(a) levels and END.

Results: Overall, patients with END had higher LP(a) than those without END (high LP(a): 38.3% vs 22.2%, intermediate LP(a): 40.3% vs 41.8%, low LP(a): 21.3% vs 36.0%, p<0.005). In the multivariate analysis, high LP(a) (defined as LP(a) level≥ 300 mg/L) was an independent risk factor for END post-thrombolysis (OR=3.154, 95% CI=1.067–9.322, p=0.038).

Conclusion: Our findings demonstrated that LP(a) was an independent risk factor for END post-thrombolysis and that LP(a) level≥ 300 mg/L could be associated with END post-thrombolysis in this study population.

Keywords: Lipoprotein(a), early neurological deterioration, acute ischemic stroke, thrombolysis

Introduction

Acute ischemic stroke (AIS) remains a leading cause of disability and mortality globally.[1] Although thrombolysis provides an opportunity to recover cerebral blood flow and perfusion,[2] the outcomes after thrombolysis are not always positive in all patients. Some AIS patients still suffer from early neurological deterioration (END) even after thrombolysis, which could lead to poor clinical outcomes.[3] Besides obvious causes like intracerebral hemorrhage and malignant edema, previous study suggested female sex, hypertension, diabetes, and smoking, were associated with END.[4] In clinical practice, treating END may involve strategies such as plasma volume expansion, induced hypertension and enhanced antithrombotic therapy, though none have been definitively validated to date.[5] Recent research has shown that the use of argatroban and tirofiban could be helpful in the prevention of END in AIS.[5,6] Therefore, it is important to explore the risk factors of END to facilitate early intervention.

The pathophysiological mechanism of END post-thrombolysis remains unclear; some reports suggest that hemodynamic changes due to thrombus extension could be a possible cause.[7] Lipoprotein(a) [LP(a)] is associated with the occurrence, recurrence, and prognosis of AIS.[8,9] Research has suggested that elevated serum LP(a) level are associated with inflammation, atherosclerosis, and thrombus formation,[10] suggesting a possible link between LP(a) and the mechanisms underlying END post-thrombolysis. However, the relationship between LP(a) levels and risk of END post-thrombolysis remains unknown.

By researching this relationship, our study aimed to identify the role of LP(a) as a predictive biomarker for END, offering insights into the pathophysiological mechanisms of END post-thrombolysis, and potential strategies to reduce this risk.

Method

Subjects

This was a single-center observational study. AIS was diagnosed according to criteria set forth by the World Health Organization. Consecutive patients with AIS who were admitted to our hospital with voluntary participation in this study were enrolled between February 2021 to November 2023. The inclusion criteria were as follows: (1) age ≥18 years; (2) thrombolysis treatment (alteplase, 0.9 mg/kg up to a maximum of 90 mg, 10% of the total dosage as a bolus, and the rest for 1 hour); (3) blood samples collected within the first 24 h following the onset of stroke; (4) completed computed tomography (CT) /magnetic resonance imaging (MRI) scans to confirm the diagnosis. The exclusion criteria were as follows: (1) patients without laboratory test data; (2) endovascular interventions; (3) patients with severe chronic diseases or cancer before stroke onset.

Ethics Statement

All subjects provided written informed consent prior to the study, and the protocols were approved by the ethics committee of the Hangzhou Traditional Chinese Medicine Hospital affiliated to Zhejiang Chinese Medical University. All clinical investigations were conducted in accordance with the principles of the Declaration of Helsinki.

Clinical and Laboratory Data Collection

Demographic and clinical data were collected for all enrolled patients, including sex, age, history of smoking, history of drink, hypertension, diabetes mellitus, atrial fibrillation, and previous stroke. Timing data for the thrombolysis procedure were also recorded. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS), and stroke etiology was determined using the modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification. Treatment during hospitalization was followed the guidelines established by the American Heart Association and the American Stroke Association. These data were also registered on the Zhejiang Stroke Medical Quality Control Center Platform, an academic institution that monitors the quality of all reperfusion therapy cases performed at stroke centers in hospitals in Zhejiang Province, China.[11]

END was defined as an at least 2 points increase in the NIHSS score by at least two points within 48 h post-thrombolysis.[6] LP(a) was measured using an immunoturbidimetric method with blood samples drawn after a 12-hour overnight fasting period after thrombolysis at admission.[12] According to previous studies,[13,14] low LP(a) was defined as LP(a)< 100 mg/L, intermediate LP(a) as 300 mg/L >LP(a)≥100 mg/L, and High LP(a) as LP(a)≥ 300 mg/L.

Statistical Analysis

Statistical analyses were performed using the SPSS software version 22 (IBM Corporation). All analyses were blinded to the participants' identification information. Measurement data with a normal distribution were described as mean ± standard deviation, measurement data with a non-normal distribution were described as median and interquartile range, and count data were described as the number of cases and percentages. In univariate analysis for comparison between two groups, independent samples *t*-test was used for measurement variables with normal distribution, non-parametric test was used for measurement data with non-normal distribution, and the chi-square test was used for count data. In the multivariate analysis, binary logistic regression analysis was used with sex, age, and variables with $p<0.2$ in the univariate analysis in the model. Statistical significance was accepted at the 0.05 level (two-tailed).

Results

A total of 236 patients were included; detailed patient enrollment was shown in Figure 1. No participants died during the follow up. There were no statistical differences between the clinical characteristics of included and excluded subjects.

Subject Characteristics

79 (33.5%) patients were female, and the average age was 68.75±14.15 years old. The average level of LP(a) was 277.63 ±287.96 mg/L.47 (19.9%) patients experienced END. A detailed distribution of LP(a) was shown in Figure 2. 78 (33.1%)
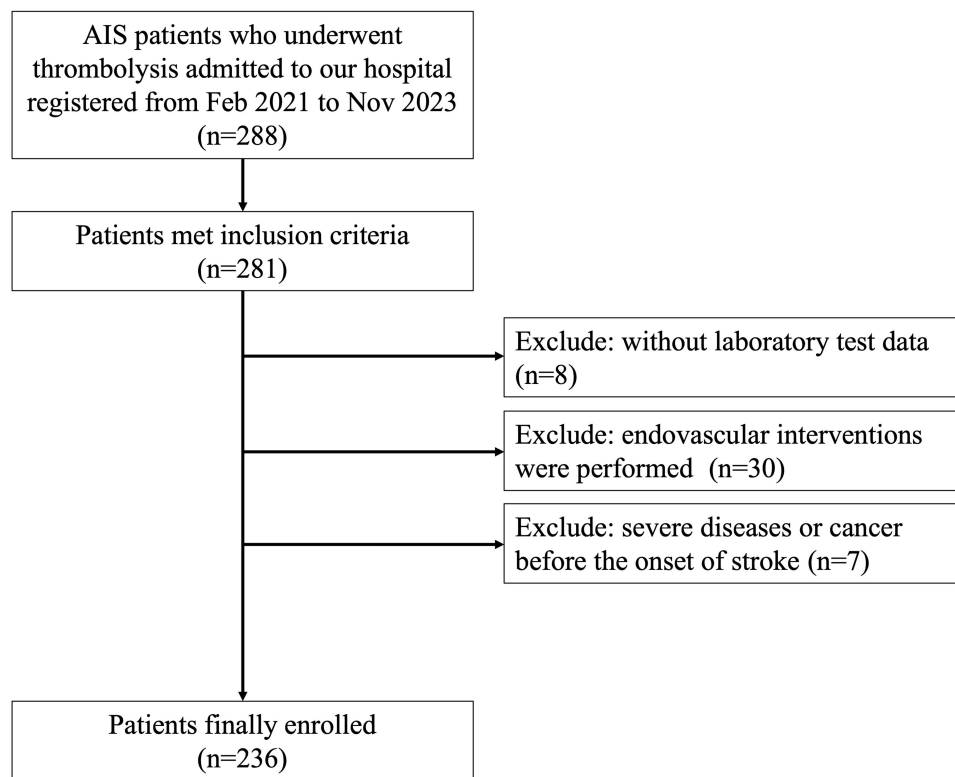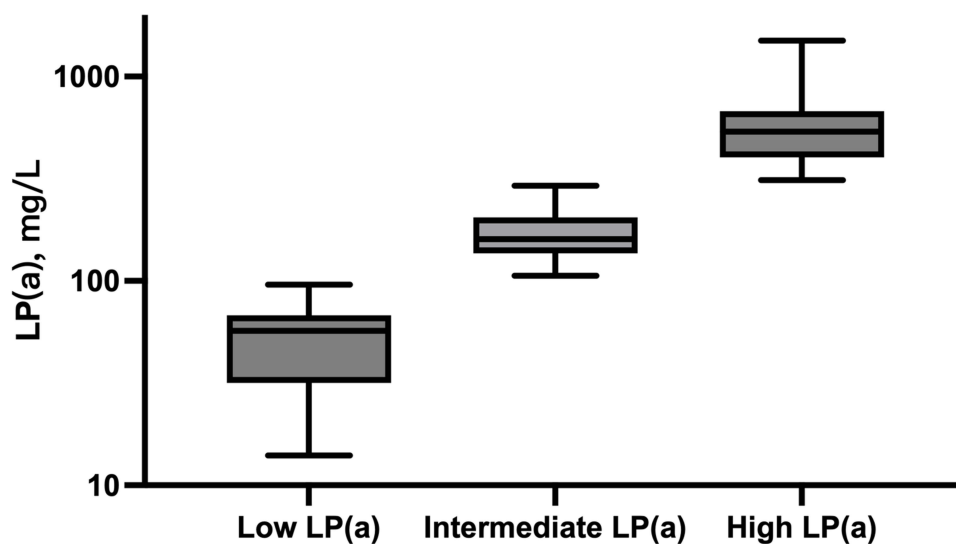
Figure 1 The patient flowchart.

Figure 2 Distributions of LP(a).

were low LP(a) with an average LP(a) level of 52.89±21.87 mg/L, 98 (41.5%) were intermediate LP(a) with an average LP(a) level of 176.87±54.56 mg/L and 60 (25.4%) were high LP(a) with an average LP(a) level of 572.32±301.85 mg/L. Detailed characteristics of the participants according to LP level (a) were presented in Table 1. Except for hypertension (56 (71.8%) vs 76 (77.6%) vs 35 (58.3%), p=0.038), SVO (31 (39.7%) vs 26 (26.5%) vs 12 (20.0%), p=0.032), LDL (2.56±0.87 vs 2.94±0.91 vs 2.91±1.05, p=0.023), and END (10 (12.8%) vs 19 (19.4%) vs 18 (30.0%), p=0.047), there were no statistical differences for other variables between the three groups with different levels of LP(a).

Table 1 Characteristics of Participants According to the Level of LP(a)

	Low (LP(a) <100mg/L, n=78)	Intermediate (300mg/L>LP(a)≥100 mg/L, n=98)	High (LP (a)≥300mg/L, n=60)	P
Sociodemographic Characters				
Age	67.03±14.78	70.79±13.45	67.68±14.25	0.172
Female	25(32.1%)	38(38.8%)	16(26.7%)	0.289
mRS>1	5(6.4%)	4(4.1%)	3(5.0%)	0.814
Vascular Risk Factors				
Hypertension	56(71.8%)	76(77.6%)	35(58.3%)	0.038
Diabetes	27(34.6%)	33(33.7%)	13(21.7%)	0.199
Hyperhomocysteinemia	3(3.8%)	3(3.1%)	0(0.0%)	0.386
Hyperuricemia	4(5.1%)	11(11.2%)	6(10.0%)	0.335
Atrial fibrillation	16(20.5%)	31(31.6%)	17(28.3%)	0.247
Coronary artery disease	12(15.4%)	13(13.3%)	9(15.0%)	0.917
History of smoke	20(25.6%)	28(28.6%)	24(40.0%)	0.166
History of drink	9(11.5%)	23(23.5%)	11(18.3%)	0.126
Previous stroke or TIA	14(17.9%)	14(14.3%)	4(6.7%)	0.139
Stroke Characteristics				
Initial NIHSS score	9(4,14)	10(5,16)	6(3,13.5)	0.448
DNT	57.40±22.26	56.70±30.67	54.58±28.82	0.831
ASPECT score	9(8,10)	9(8,10)	9(7,10)	0.421
Use of Lipid-lowering Medicine before hospitalization	25(32.0%)	32(32.7%)	25(41.6%)	0.540
Statins	14(17.9%)	24(24.5%)	11(18.3%)	0.543
Other	11(14.1%)	8(8.2%)	14(23.3%)	0.159
TOAST				
LAA	18(23.1%)	32(32.7%)	22(36.7%)	0.187
CE	14(17.9%)	31(31.6%)	14(23.3%)	0.115
SVO	31(39.7%)	26(26.5%)	12(20.0%)	0.032
SOE	5(6.4%)	3(3.1%)	4(6.7%)	0.522
SUE	10(12.8%)	6(6.1%)	8(13.3%)	0.216
Laboratory Testing				
Fasting blood sugar	9.82±4.65	9.05±4.68	8.34±2.76	0.388
Systolic blood pressure, mmHg	150.69±21.06	153.56±22.91	146.18±20.51	0.119
Diastolic blood pressure, mmHg	89.27±13.17	84.91±14.57	84.57±12.94	0.062
TC	4.18±1.09	4.58±1.06	4.51±1.38	0.078
TG	1.43±1.03	1.24±0.82	1.30±0.67	0.384
HDL	0.99±0.27	1.06±0.28	1.03±0.30	0.311
LDL	2.56±0.87	2.94±0.91	2.91±1.05	0.023
END	10(12.8%)	19(19.4%)	18(30.0%)	0.047

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; END, Early Neurological Deterioration; mRS, Modified Rankin Scale; DNT, Door-to-Needle Time; ASPECT, Alberta Stroke Program Early CT Score; TOAST, Trial of Org 10172 in Acute Stroke Treatment; LAA, Large Artery Atherosclerosis; CE, Cardioembolism; SVO, Small Vessel Occlusion; SOE, Stroke of Other Determined Etiology; SUE, Stroke of Undetermined Etiology; TC, Total Cholesterol; TG, Triglycerides; HDL, High-Density Lipoprotein; LDL, Low-Density Lipoprotein.

Univariate Comparison Between END Group and No END Group

As shown in Table 2, patients with END had more SUE (10 (21.3%) vs 14 (7.4%), p=0.012) and higher LDL (3.18±1.04 vs 2.72±0.91, p=0.005) than those without END. As shown in Figure 3, significant differences in LP(a) levels were observed between the two groups according to the END. There were no other statistically significant differences between the two groups.

Binary Logistic Regression of Serum Level of LP(a) for END

As Figure 4 shows, after adjusting for age, sex, mRS>1 before onset, history of smoke, SVO, SUE, TC, HDL, LDL, and diastolic blood pressure, High LP(a) (OR=3.154, 95% CI=1.067–9.322, p=0.038) was an independent risk factor for END post-thrombolysis (reference to Low LP(a)).

Table 2 Characteristics of Participants According to END

	No END (n=189)	END (n=47)	p
Sociodemographic Characters			
Age	68.28±14.11	70.66±14.30	0.303
Female	62(32.8%)	17(36.2%)	0.730
mRS>1	7(3.7%)	5(10.6%)	0.066
Vascular Risk Factors			
Hypertension	131(69.3%)	36(76.6%)	0.374
Diabetes	56(29.6%)	17(36.2%)	0.384
Hyperhomocysteinemia	5(2.6%)	1(2.1%)	1.000
Hyperuricemia	15(7.9%)	6(12.8%)	0.388
Atrial fibrillation	51(27.0%)	13(27.7%)	1.000
Coronary artery disease	29(15.3%)	5(10.6%)	0.493
History of smoke	63(33.3%)	9(19.1%)	0.076
History of drink	36(19.0%)	7(14.9%)	0.673
Previous stroke or TIA	25(13.2%)	7(14.9%)	0.812
Use of Lipid-lowering Medicine before hospitalization	66(34.9%)	16(34.0%)	0.538
Statins	39(20.6%)	10(21.3%)	0.589
Other	27(14.3%)	6(12.8%)	0.553
Stroke Characteristics			
Initial NIHSS score	9(4,15)	6(4,13)	0.715
DNT	55.45±28.03	60.19±25.62	0.292
ASPECT score	9(8,10)	9(7,10)	0.572
TOAST			
LAA	55(29.1%)	17(36.2%)	0.378
CE	50(26.5%)	9(19.1%)	0.351
SVO	60(31.7%)	9(19.1%)	0.107
SOE	10(5.3%)	2(4.3%)	1.000
SUE	14(7.4%)	10(21.3%)	0.012
Laboratory Testing			
Fasting blood sugar	8.40±3.92	9.00±5.11	0.381
Systolic blood pressure, mmHg	149.99±21.60	153.74±22.67	0.292
Diastolic blood pressure, mmHg	85.67±13.13	88.66±16.25	0.185
TC	4.33±1.12	4.85±1.27	0.010
TG	1.30±0.86	1.37±0.87	0.646
HDL	1.02±0.29	1.08±0.24	0.191
LDL	2.72±0.91	3.18±1.04	0.005

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; END, Early Neurological Deterioration; mRS, Modified Rankin Scale; DNT, Door-to-Needle Time; ASPECT, Alberta Stroke Program Early CT Score; TOAST, Trial of Org 10172 in Acute Stroke Treatment; LAA, Large Artery Atherosclerosis; CE, Cardioembolism; SVO, Small Vessel Occlusion; SOE, Stroke of Other Determined Etiology; SUE, Stroke of Undetermined Etiology; TC, Total Cholesterol; TG, Triglycerides; HDL, High-Density Lipoprotein; LDL, Low-Density Lipoprotein.

Discussion

The main findings of this study were that the LP(a) level was an independent risk factor for END post-thrombolysis and LP(a) ≥ 300 mg/L was associated with END post-thrombolysis in this study population.

Our findings were consistent with previous study. A previous study demonstrated that serum lipoprotein-associated phospholipase A2 (Lp-PLA2), which binds to lipoproteins in peripheral blood circulation, was associated with END (defined as an increase in the NIHSS score within 10 days after admission) in AIS patients with the TOAST subtype of large arterial atherosclerosis (LAA).[15] Our study further confirmed that LP(a) levels were associated with END post-thrombolysis in patients with AIS within 48 h, which could be helpful for early diagnosis and therapy.
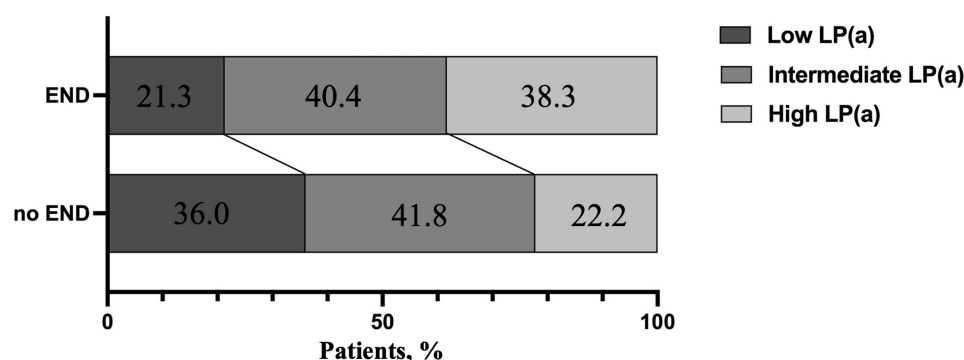
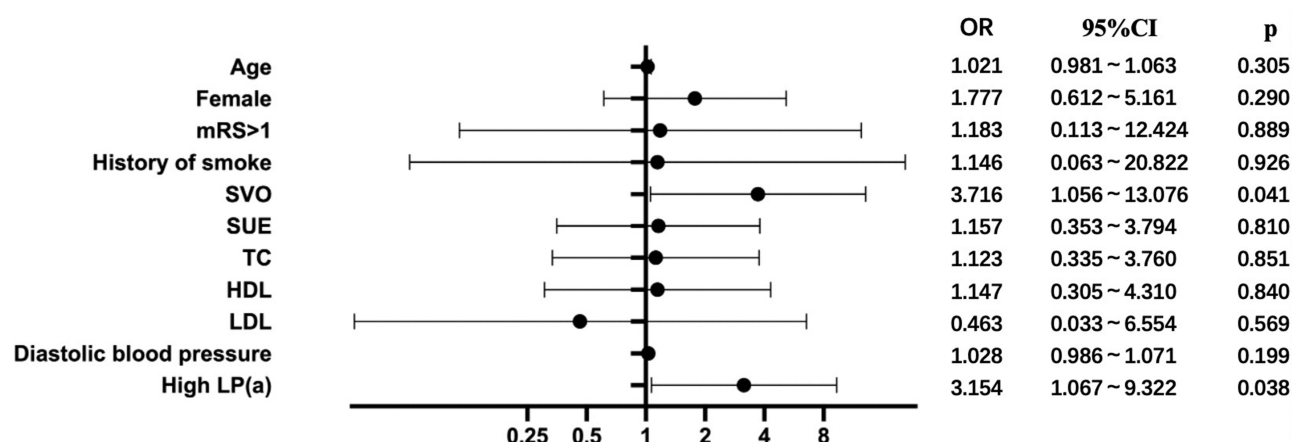**Figure 3** Distributions of LP(a) according to END.

Figure 4 Forest plots of binary logistic regression of serum level of LP(a) for END.

The underlying mechanisms of END post-thrombolysis are multifaceted, including reperfusion injury, secondary collateral dysfunction, and extension of thrombus.[7] This result is biologically reasonable, considering the roles of LP(a) in ischemic stroke. The apo(a) component of LP(a) shares high homology with plasminogen (PLG) and competes with PLG receptors, thereby interfering with the conversion of PLG to plasmin, blocking fibrin clot dissolution, and promoting thrombus formation.[16] What's more, LP(a) regulates fibrinolysis and promotes thrombus formation by competitively inhibiting tissue plasminogen activator (tPA) via competition with plasminogen activator inhibitor 1 (PAI-1) and PLG.[17] Additionally, elevated LP(a) levels can impair platelet function.[18] Furthermore, overexpression of the tissue factor pathway inhibitor (TFPI) weakens thrombus formation,[19] whereas LP(a) can promote thrombus formation by binding to TFPI through its apo(a) component, leading to TFPI inactivation.[20] Therefore, we believe that LP(a) causes END by promoting the progression of arterial thrombus. Moreover, LP(a) promotes inflammation by interacting with inflammatory factors and recruiting inflammatory cells to atherosclerotic plaques, exacerbating atherosclerosis.[21,22] Given the critical role of inflammation and atherosclerosis in ischemic stroke, LP(a) may contribute to END by promoting inflammation and atherosclerosis.

Our study carries substantial clinical significance. Our findings suggest that serum LP(a) level is a predictive factor for END post-thrombolysis in AIS. Reducing serum LP(a) to a certain level may prevent END and the poor short-term functional outcomes of thrombolysis. Besides, our study also provides potential targets for therapeutic intervention to improve the outcomes of patients with AIS patients with END. However, this hypothesis should be validated in future studies.

Our study had several limitations. First, this was a single-center prospective study with a small sample size, and further research with larger cohorts and follow-up is required in the future, especially in extremely elderly population

since the demographics and risk factors are quite different in this age segment.[23] Second, our study did not include laboratory animal experiments to explore the mechanistic pathways underlying the association between apolipoproteins and intracranial pathophysiological changes after thrombosis. Third, no intervention was performed on LP(a) for comparison, which requires further clinical trial. Fourth, due to the exclusion of thrombectomy, some severe cases with large vessel occlusion were not included, which may have led to a bias in the study population. Fifth, our study did not stratify patients based on the cerebral artery territory involved. Since the stroke location could affect prognosis,[24] future studies could benefit from considering the topography of cerebral infarcts to see if the predictive value of LP(a) varies by stroke location.

Conclusion

In summary, our study found that serum LP(a) level was an independent factor for END post-thrombolysis, and it could be reasonable to control the LP(a) level below 300 mg/L to avoid END, offering insights into the pathophysiological mechanisms of END post-thrombolysis, and potential strategies to reduce this risk. Future research could explore interventions targeting LP(a) reduction to assess if this decreases the risk of END. Additionally, studying the interaction of LP(a) with other biomarkers of inflammation and thrombosis in diverse populations could provide further insights into the pathophysiology of END.

Data Sharing Statement

The data presented in this manuscript were acquired for this study. Due to privacy issues, it is not available to the community via an open repository. The datasets generated in this study are available from the corresponding author upon reasonable request. Considerations are made based on a review of the reasons for requesting data and procedures to ensure data privacy.

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Disclosure

The authors report no conflicts of interest in this work.

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