RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2024, Volume 58, no. 3, pages: 316–322
DOI: 10.5603//pjnns.98343
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ISSN: 0028-3843, e-ISSN: 1897-4260

# Lipoprotein (a) concentration as a risk factor for ischaemic stroke and its subtypes

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## ABSTRACT

**Aim of the study.** To investigate the relationship between serum lipoprotein (a) [Lp(a)] concentration and the risk of ischaemic stroke (IS) and its subtypes.

**Clinical rationale for the study.** Lp(a) plays a role in atherogenic, pro-thrombotic, and antifibrinolytic processes. Elevated plasma Lp(a) is a strong independent risk factor for the development and progression of atherosclerotic disease. The association between lipoproteins and IS is more complex than that reported for cardiovascular diseases, with inconsistent and contradictory results from epidemiological studies.

**Material and methods.** 231 patients with acute IS (defined as cases) and 163 age- and sex-matched control subjects were included in this prospective case-control study. Demographic and clinical variables (i.e. age, sex, smoking, presence of chronic diseases and concomitant medication) and laboratory data (i.e. concentrations of total cholesterol, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, triglycerides, Lp(a), apolipoprotein A1, apolipoprotein B) were recorded.

**Results.** The mean age and the percentage of men did not significantly differ between groups. Compared to controls, there was a significantly higher percentage of cases reported with concomitant diseases: diabetes mellitus, myocardial infarction, ischaemic heart disease, peripheral arterial disease, and atrial fibrillation. The study showed a significantly higher serum Lp(a) concentration in cases than in control subjects (81.81 nmol/L [c.32.7 mg/dL] *vs.* 59.75 nmol/L [c.23.9 mg/dL]; p = 0.036) and found an association between Lp(a) levels stratified by quartiles and the risk for ischaemic stroke (Q1 [Lp(a) < 13 nmol/L] *vs.* Q4 [Lp(a) > 117 nmol/L]: OR 2.23; 95% CI 1.23-4.03; p = 0.008). A subgroup analysis based on the TOAST classification of IS also showed a significant association between Lp(a) value of more than 75 nmol/L (30 mg/dL) and the risk of large-artery atherosclerosis stroke compared to the controls (OR 2.4; 95% CI 1.39-3.93; p = 0.001), as well as a statistically non-significant association with other subtypes of IS. The influence of Lp(a) remained significant even after adjusting for established risk factors for IS (OR 1.99; 95% CI 1.05-3.76; p = 0.04; respectively for the large-artery atherosclerotic subtype: OR 2.54; 95% CI 1.39-4.67; p = 0.003).

**Conclusion.** We found that Lp(a) is an independent risk factor for ischaemic stroke, and for the large-artery atherosclerotic subtype of ischaemic stroke.

**Keywords:** ischaemic stroke, subtypes, lipoprotein (a), risk factor

(*Neurol Neurochir Pol 2024; 58 (3): 316–322*)

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Received: 28.11.2023 Accepted: 18.03.2024 Early publication date: 20.05.2024

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## Introduction

Stroke is a major public health problem, the second leading cause of death, and the third leading cause of years of life lost due to disability, worldwide [1]. 80% of strokes are ischaemic strokes (IS) and 20% are haemorrhagic strokes (HS). Globally, the total number of IS-related deaths in 2019 was 3.29 million, accounting for 17% of all cardiovascular disease-related deaths, which is why the prevention of IS is so important [2–4].

Despite significant advances in the identification and control of conventional risk factors for IS, including smoking, hypertension, diabetes, atrial fibrillation and dyslipidemia, there is no obvious cause in 25% of all IS cases [5]. For this reason, it is necessary to identify other potential modifiable risk factors for stroke.

Lipoprotein (a) [Lp(a)] is formed from a low-density lipoprotein (LDL)-like particle and the glycoprotein apolipoprotein(a) [apo(a)] linked to apolipoprotein B in LDL by a single disulfide bond [6]. Serum concentrations of Lp(a) range from 0.2 nmol/L (0.1 mg/dL) to more than 750 nmol/L (300 mg/dL), and appear to be regulated by synthesis rather than catabolism [7]. Lp(a) levels are largely (up to 90%) genetically determined, remain stable throughout life, and are notably unaffected by diet, physical activity, or medication (statins included). Guidelines recommend measuring Lp(a) levels at least once in a lifetime as part of an initial lipid profile [8]. It is estimated that 1.5 billion people have Lp(a) > 125 nmol/L (> 50 mg/dL) [9]. Lp(a) plays a role in atherogenic, pro-thrombotic, and antifibrinolytic processes, inflammatory reactions, binding of oxidised phospholipids, and vascular remodelling [10, 11]. It has been shown that Lp(a) is 10 times more atherogenic than LDL-cholesterol [12]. Observational, genetic, and Mendelian randomisation studies support the role of elevated plasma Lp(a) as a strong independent risk factor for the development and progression of atherosclerotic disease. A causal relationship between elevated Lp(a) and an increased risk of coronary stenosis, myocardial infarction and reocclusion of aorto-coronary bypass vein grafts has been demonstrated [13–16]. The association between lipids and lipoproteins and IS is more complex than that reported for acute myocardial infarction, with inconsistent and contradictory results findings from epidemiological studies [17].

## Clinical rationale for the study

The significance of the association of lipids and lipoproteins with stroke is less than that reported for cardiovascular diseases [18, 19], and appears to differ by stroke subtype [20]. These differences may have clinically relevant implications for defining prevention strategies according to the IS subtype. Therefore, our study aimed to explore the relationship of Lp(a) with IS and its subtypes.

## Material and methods

This was a prospective case-control study investigating the association between serum Lp(a) concentration and the risk of IS and its subtypes. Between September 2019 and September 2023, we prospectively enrolled to the study 231 patients with IS (defined as cases) and 163 control subjects.

Cases were adults of Caucasian origin with acute IS admitted to a tertiary teaching hospital. Stroke was diagnosed using the World Health Organisation clinical criteria for stroke [21]. Neuroimaging (CT or MRI) was completed in all cases. Stroke aetiology was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria as either large-artery atherosclerosis (LAA), small-vessel occlusion, cardioembolism, or undetermined stroke [22]. Patients with transient ischaemic attack or haemorrhagic stroke, or a history of malignant tumor, or chronic liver or renal disease, or systemic autoimmune disease, were excluded.

The age- and sex-matched controls were patients admitted to hospital for non-vascular diseases (i.e. osteoarthrosis of hip or knee joint), with no history of ischaemic or haemorrhagic stroke, malignant tumor, chronic liver or renal disease, or systemic autoimmune disease.

The study was approved by the local institutional review board (no. 2019/EK/10052). Written informed consent was obtained from all study participants. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Demographic and clinical variables (i.e. age, sex, smoking, presence of chronic diseases and concomitant medication) and laboratory data were taken from the discharge reports and the hospital's electronic database.

Blood samples were taken after 12-hour overnight fasting. Concentrations of total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), LDL-cholesterol (LDL-C), triglycerides (TG), lipoprotein (a) [Lp(a)], apolipoprotein A1 (apoA1), and apolipoprotein B (apoB) were measured in the local laboratory on the day of blood sampling. The cut-off values for lipid profile parameters were established according to local laboratory reference standards and determined as follows: Lp(a) > 75 nmol/L, TC > 5.2 mmol/L, LDL-C > 3.0 mmol/L, HDL-C < 1.2 mmol/L, TG > 1.7 mmol/L, apoA1 < 2.02 g/L, apoB > 1.4 g/L.

### Statistical methods

To determine an adequate sample size for the study, we performed a power analysis using G*Power software. A minimum total sample size requirement of 127 subjects was calculated based on a study power of 95%, a significance level of 0.05, with 20 predictors and effect size of 0.28.

Student's t-test was used for statistical analysis of continuous variables. If the files had an abnormal distribution, the Mann-Whitney test was used for the analysis. Frequency data was judged using the chi-squared test. Data for comparison between multiple groups was tested using one-way ANOVA if the data was normally distributed and the Kruskal-Wallis test

**Table 1.** Baseline characteristics of cases and controls after age and sex matching

| Variable | Cases (n = 231) | Controls (n = 163) | P-value |
|---|---|---|---|
| Age (years) | 68.1 (± 10.1; 32-90) | 66.1 (± 10.3; 40–89) | 0.09 |
| Male gender (%) | 54 | 46 | 0.13 |
| DM (%) | 30.5 | 14.1 | **< 0.001** |
| AH (%) | 38.5 | 47.2 | 0.09 |
| MI (%) | 11.3 | 1.3 | **< 0.001** |
| IHD (%) | 40.8 | 8.6 | **< 0.001** |
| PAD (%) | 14.1 | 4.9 | **0.003** |
| AF (%) | 24.4 | 1.3 | **< 0.001** |
| Smokers (%) | 30 | 14 | **< 0.001** |
| Lp(a) (nmol/L) | 81.81 (± 84.35; 0.82–353) | 59.75 (± 70.82; 0.7–240) | **0.036** |
| TC (mmol/L) | 4.81 (± 1.31; 2.08–8.65) | 5.07 (± 1.54; 1.3–9.06) | 0.08 |
| LDL-C (mmol/L) | 3.1 (± 1.01; 1.15–8.65) | 3.36 (± 1.24; 0.92–7.62) | 0.08 |
| HDL-C (mmol/L) | 1.07 (± 0.31; 0.3–2.21) | 1.34 (± 0.36; 0.61–2.79) | **< 0.001** |
| TG (mmol/L) | 1.69 (± 1.1; 0.44–8.04) | 1.71 (± 1.08; 0.53–8.7) | 0.32 |
| ApoA1 (g/L) | 1.07 (± 2.5; 0.36–1.82) | 1.26 (± 0.29; 0.69–2.19) | **< 0.001** |
| ApoB (g/L) | 0.91 (± 0.26; 0.24–1.95) | 1.07 (± 0.93; 0.4–12.09) | **0.048** |

Values are expressed as means, with a standard deviation in parentheses and minimal and maximal values. N — number; DM — diabetes mellitus; AH — arterial hypertension; MI — myocardial infarction; IHD — ischaemic heart disease; PAD — peripheral arterial disease; AF — atrial fibrillation; Lp(a) — lipoprotein (a); TC — total cholesterol; LDL-C — low-density lipoprotein cholesterol; HDL-C — high-density lipoprotein cholesterol; TG — triglycerides; ApoA1 — apolipoprotein A1; ApoB — apolipoprotein B

if it was not normally distributed. Categorical variables were presented as means with standard deviation (±).

To evaluate the impact of Lp(a) on IS, the Lp(a) concentrations were divided into quartiles: Q1 (< 12 nmol/L), Q2 (12––30 nmol/L), Q3 (30.1-117 nmol/L), and Q4 (> 117 nmol/L). The results of univariate logistic analysis were reported as odds ratios (ORs) for IS, with a 95% confidence interval (95%CI) and a corresponding significance level (p) as compared to the group of subjects in the lowest quartile.

Multivariate logistic regression models were used to assess the relationships between ischaemic stroke and variables: age over 55, male sex, smoking, diabetes mellitus [DM], arterial hypertension [AH], ischaemic heart disease [IHD], myocardial infarction [MI], atrial fibrillation [AF], peripheral arterial disease [PAD], concentration of TC > 5.2 mmol/L, HDL-C < 1.2 mmol/L, LDL-C > 3.0 mmol/L, TG > 1.7 mmol/L, Lp(a) > 75 nmo/l [> 30 mg/dL], current treatment with insulin, oral antidiabetic drugs, statins, acetylsalicylic acid, and novel oral anticoagulants. The results of multivariate logistic regression analysis were reported as ORs for IS, with a 95%CI and a corresponding significance level (p).

The level of statistical significance was set at $p < 0.05$ for all tests. SigmaPlot version 12.5 (Systat Software Inc., San Jose, CA, USA) was used for statistical analyses.

## Results

Table 1 sets out the demographic characteristics of cases and controls. The mean age and the percentage of men were not significantly different between groups. Compared to controls, there was a significantly higher percentage of cases reported with concomitant diseases: diabetes (30.5% *vs.* 14.1%; $p < 0.001$), myocardial infarction (11.3% *vs.* 1.3%; $p < 0.001$), ischaemic heart disease (40.8% *vs.* 8.6%; $p < 0.001$), peripheral arterial disease (14.1% *vs.* 4.9%; $p = 0.003$), and atrial fibrillation (24.4% *vs.* 1.3%; $p < 0.001$). Smoking was significantly more common in cases than in controls (30% *vs.* 14%; $p < 0.001$).

**Table 2.** Odds ratios (95% confidence intervals) for ischaemic stroke and Lp(a) concentration

| Group | OR (95% CI) | P-value |
|---|---|---|
| Quartile 1 | Reference | |
| Quartile 2 | 1.29 (0.73–2.9) | 0.88 |
| Quartile 3 | 1.24 (0.69–2.19) | 0.73 |
| Quartile 4 | 2.23 (1.23–4.03) | **0.008** |

Unadjusted model; 25th, 50th and 75th percentile cut-off points for corresponding Lp(a) were 12, 30 and 117 nmol/L, respectively

The mean concentration of Lp(a) in cases was 81.81 nmol/L (SD ± 10.1), which was significantly higher than that in controls (59.75 nmol/L; SD ± 70.82; $p = 0.036$). HDL-C, apoA1, and apoB levels were significantly lower in cases than in controls. Total cholesterol, LDL-C, and TG levels were not different from controls.

Analysis of the association of IS with the distribution in quartiles of Lp(a) concentration revealed that Lp(a) concentration was significantly associated with IS in the highest quartile (Tab. 2). Compared to the lowest quartile, the adjusted odds ratio for IS in subjects with Lp(a) concentrations greater than 117 nmol/L was 2.23 (95% CI 1.23–4.03; $p = 0.008$).

As expected, most variables traditionally linked to IS were independently associated with the outcome in the multivariate logistic regression model adjusted for all assessed risk factors: age (OR 4.66; 95% CI 2.04–10.64; p < 0.001), HDL-C levels (OR 3.95; 95% CI 2.05–7.61; p < 0.001), smoking (OR 4.79; 95% CI 2.17–10.58; p < 0'001), arterial hypertension (OR 14.29; 95% CI 3.84–53.15; p < 0.001), atrial fibrillation (OR 16.43; 95% CI 2.88–93.74; p = 0.002) and the use of acetylsalicylic acid (OR 4.38; 95% CI 1.95–9.83; p < 0.001). We also confirmed that concentrations of Lp(a) greater than 75 nmol/L were associated with a significant risk of IS (OR 1.99; 95% CI 1.05–3.76; p = 0.04). Antihypertensive treatment was associated with a significantly reduced risk for IS (OR 0.10; 95% CI 0.03–0.41; p = 0.001). Total cholesterol and LDL-C were not associated with IS (Tab. 3).

Depending on to the cause of IS, Lp(a) concentration was significantly higher in the large vessel atherosclerosis group (97.91 nmol/L; ± 93.21; p < 0.05) than in the controls (59.75 nmol/L; ± 70.82) and other IS groups (small-artery occlusion: 65.98 nmol/L; ± 75.5; cardioembolic: 72.43 nmol/L; ± 73.54; undetermined: 63.1 nmol/L; ± 81.34). The adjusted odds ratio for the subtypes of IS was significantly higher in subjects with Lp(a) concentrations greater than 75 nmol/L only in the large-artery atherosclerosis group (OR 2.34; 95% CI 1.39–3.93; p = 0.001). The odds ratio for small-artery occlusion stroke was 1.31 (95% CI 0.64–2.7; p = 0.46), for cardioembolic stroke 1.48 (95% CI 0.77–2.86; p = 0.24), and for undetermined strokes 1.02 (95% CI 0.4–2.58; p = 0.97).

Multivariate logistic regression analyses adjusted for classical risk factors for subtypes of IS based on TOAST classification are shown in Table 4. In the small vessel group, only one significant risk factor was revealed: arterial hypertension (OR 3.68; 95% CI 1.21–11.17; p = 0.02). The cardioembolic subtype of IS was associated only with atrial fibrillation (OR 408; 95% CI 75.01–2,227.01; p < 0.001). No statistically significant ischaemic stroke risk factor was found in the group of patients with undetermined stroke. The group of large vessel atherosclerotic stroke subtype was associated with several independent risk factors: age (OR 7.60; 95% CI 2.53–22.81; p < 0.001), low HDL-C concentration (OR 2.90; 95% CI 1.44–5.85; p = 0.003), Lp(a) concentration greater than 75 nmol/L (OR 2.54; 95% CI 1.39–4.67; p = 0.003), smoking (OR 3.54; 95% CI 1.76–7.10; p < 0.001), myocardial infarction (OR 3.68; 95% CI 1.11–12.25; p = 0.03), use of acetylsalicylic acid (OR 3.63; 95% CI 1.75–7.53; p < 0.001), and the use of new oral anticoagulants (OR 5.85; 95% CI 1.02–33.68; p = 0.048).

**Table 3.** Multivariate logistic regression for risk factors and ischaemic stroke

| Variable | OR | 95% CI | P-value |
|---|---|---|---|
| Age > 55 | 4.66 | 2.04–10.64 | **< 0.001** |
| Male gender | 1.03 | 0.57–1.88 | 0.92 |
| TC > 5.2 | 1.81 | 0.69–4.77 | 0.23 |
| LDL-C > 3,0 | 0.70 | 0.27–1.8 | 0.46 |
| HDL-C < 1.2 | 3.95 | 2.05–7.61 | **< 0.001** |
| TG > 1.7 | 0.74 | 0.37–1.46 | 0.38 |
| Lp(a) > 75 | 1.99 | 1.5–3.76 | **0.04** |
| Smoking | 4.79 | 2.17–10.58 | **< 0.001** |
| DM | 3.29 | 0.89–12.08 | 0.07 |
| AH | 14.29 | 3.84–53.15 | **< 0.001** |
| MI | 3.52 | 0.57–21.55 | 0.17 |
| IHD | 1.98 | 0.88–4.44 | 0.10 |
| PAD | 0.41 | 0.14–1.23 | 0.11 |
| AF | 16.43 | 2.88–93.74 | **0.002** |
| Insulin | 0.86 | 0.23–3.27 | 0.83 |
| OAD | 0.32 | 0.08–1.25 | 0.10 |
| Statins | 1.37 | 0.61–3.07 | 0.44 |
| ASA | 4.38 | 1.95–9.83 | **< 0.001** |
| NOAC | 7.86 | 0.29–216.18 | 0.22 |
| AntiHT | 0.10 | 0.03–0.41 | **0.001** |

OR — odds ratio; CI — confidential interval; p — level of statistical significance; TC — total cholesterol; LDL-C — low-density lipoprotein cholesterol; HDL-C — high-density lipoprotein cholesterol; TG — triglycerides; Lp(a) — lipoprotein (a); DM — diabetes mellitus; IHD — ischaemic heart disease; PAD — peripheral arterial disease; AF — atrial fibrillation; OAD — oral antidiabetics; ASA — acetylsalicylic acid; NOAC — novel oral anticoagulants; antiHT — antihypertensive medication. Model adjusted for all risk factors

## Discussion

This case-control study showed a significantly higher serum Lp(a) concentration in cases than in control subjects (81.81 nmol/L [c.32.7 mg/dL] *vs.* 59.75 nmol/L [c.23.9 mg/dL]; p = 0.036) and found an association between Lp(a) levels stratified by quartiles and the risk for ischaemic stroke (Q1 [Lp(a) < 13 nmol/L] *vs.* Q4 [Lp(a) > 117 nmol/L]: OR 2.23; 95% CI 1.23–4.03; p = 0.008). A subgroup analysis based on the TOAST classification also showed a significant association between Lp(a) value of more than 75 nmol/L (30 mg/dL) and the risk of large-artery atherosclerosis stroke compared to the controls (OR 2.4; 95% CI 1.39–3.93; p = 0.001), as well as a statistically non-significant association with other subtypes of IS. The influence of Lp(a) remained significant even after adjusting for established risk factors for IS (OR 1.99; 95% CI 1.05–3.76; p = 0.04; respectively for LAA subtype: OR 2.54; 95% CI 1.39–4.67; p = 0.003).

Two previously published meta-analyses confirmed that elevated Lp(a) is an independent risk factor for IS, however, the risk for IS subtypes based on the TOAST classification needs further investigation [23, 24]. The most recent meta-analysis by Kumar et al. [25] included 41 case-control and prospective studies that examined the association between Lp(a) and the risk of IS and HS compared to control subjects, while 13 studies examined the risk of IS subtypes based on the TOAST classification.

This meta-analysis found that elevated Lp(a) concentrations are significantly associated with the risk of IS in Asian as well as Caucasian populations, and with the risk of the large-artery atherosclerosis subtype compared to the control subjects. Kumar et al. recommended further studies with

**Table 4.** Multivariate logistic regression for risk factors and ischaemic stroke subtype groups according to TOAST classification

| Variable | LAA | | SAO | | CE | | Undetermined | |
|---|---|---|---|---|---|---|---|---|
| | OR (95% CI) | P-value | OR (95% CI) | P-value | OR (95% CI) | P-value | OR (95% CI) | P-value |
| Age > 55 | 7.6 (2.53–22.81) | **< 0.001** | 2.23 (0.88–5.64) | 0.09 | 1.49 (0.22–9.94) | 0.68 | 1.24 (0.45–3.4) | 0.67 |
| Male | 1.04 (0.57–1.92) | 0.89 | 1.5 (0.81–2.79) | 0.20 | 1.51 (0.43–5.29) | 0.52 | 1.28 (0.57–2.89) | 0.55 |
| TC > 5.2 | 2.61 (0.95–7.16) | 0.06 | 0.95 (0.37–2.45) | 0.92 | 0.87 (0.12–6.26) | 0.89 | 1.77 (0.44–7.08) | 0.42 |
| LDL-C > 3.0 | 0.23 (0.09–0.61) | **0.003** | 1.48 (0.6–3.63) | 0.40 | 4.5 (0.61–33.11) | 0.14 | 0.96 (0.26–3.61) | 0.95 |
| HDL-C < 1.2 | 2.9 (1.44–5.85) | **0.003** | 1.47 (0.73–2.98) | 0.29 | 1.31 (0.29–5.88) | 0.72 | 1.74 (0.69–4.39) | 0.25 |
| TG > 1.7 | 1.35 (0.66–2.78) | 0.42 | 0.66 (0.32–1.38) | 0.27 | 0.86 (0.18–4.19) | 0.85 | 0.46 (0.17–1.22) | 0.12 |
| Lp(a) > 75 | 2.54 (1.39–4.67) | **0.003** | 0.77 (0.41–1.47) | 0.43 | 0.91 (0.26–3.18) | 0.88 | 0.76 (0.33–1.77) | 0.52 |
| Smoking | 3.54 (1.76–7.10) | **< 0.001** | 1.27 (0.63–2.57) | 0.51 | 0.4 (0.08–1.98) | 0.26 | 1.56 (0.65–3.75) | 0.33 |
| DM | 1.65 (0.57–4.78) | 0.36 | 1.48 (0.47–4.61) | 0.50 | 0.61 (0.06–6.12) | 0.67 | 2.64 (0.56–12.55) | 0.22 |
| AH | 2.24 (0.77–6.50) | 0.14 | 3.68 (1.21–11.17) | **0.02** | 0.54 (0.05–5.51) | 0.6 | 3.17 (0.9–11.14) | 0.07 |
| MI | 3.68 (1.11–12.25) | **0.03** | 0.12 (0.01–1.02) | 0.05 | 1.08 (0.14–8.53) | 0.94 | 0.54 (0.06–5.32) | 0.60 |
| IHD | 1.18 (0.58–2.4) | 0.65 | 1.45 (0.69–3.02) | 0.33 | 1.13 (0.26–4.95) | 0.87 | 0.74 (0.24–2.24) | 0.59 |
| PAD | 1.97 (0.75–5.17) | 0.17 | 0.39 (0.12–1.32) | 0.13 | 0.25 (0.03–1.99) | 0.19 | 0.12 (0.01–1.23) | 0.07 |
| AF | 0.04 (0.01–0.18) | **< 0.001** | 0.51 (0.16–1.56) | 0.24 | 408.7 (75–2227) | **< 0.001** | 0.37 (0.03–4.21) | 0.42 |
| Insulin | 0.64 (0.2–2.05) | 0.45 | 1.73 (0.49–6.12) | 0.40 | 0.45 (0.01–17.07) | 0.67 | 0.17 (0.02–1.3) | 0.09 |
| OAD | 0.98 (0.32–3.03) | 0.97 | 0.4 (0.12–1.43) | 0.16 | 1.88 (0.14–25.03) | 0.63 | 1.72 (0.6–4.93) | 0.31 |
| Statins | 0.53 (0.25–1.15) | 0.11 | 1.88 (0.87–4.07) | 0.11 | 2.61 (0.53–12.94) | 0.24 | 0.31 (0.1–1.02) | 0.06 |
| ASA | 3.63 (1.75–7.53) | **< 0.001** | 1.07 (0.51–2.25) | 0.86 | 1.1 (0.25–4.93) | 0.9 | 1.39 (0.1–18.66) | 0.80 |
| NOAC | 5.85 (1.02–33.68) | **0.048** | 0.24 (0.02–2.48) | 0.23 | 2.79 (0.43–18.25) | 0.28 | 0.51 (0.15–1.74) | 0.28 |
| AntiHT | 0.53 (0.18–1.59) | 0.26 | 0.39 (0.13–1.14 | 0.08 | 1.41 (0.15–13.10) | 0.76 | 1.24 (0.45–3.4) | 0.67 |

OR — odds ratio; CI — confidential interval; p — level of statistical significance; TC — total cholesterol ; LDL-C — low-density lipoprotein cholesterol; HDL-C — high-density lipoprotein cholesterol; TG — triglycerides; Lp(a ) — lipoprotein (a); DM — diabetes mellitus; IHD — ischaemic heart disease; PAD — peripheral arterial disease; AF — atrial fibrillation; OAD — oral antidiabetics; ASA — acetylsalicylic acid; NOAC — novel oral anticoagulants; antiHT — antihypertensive medication; LAA — large-artery atherosclerosis; SAO — small-artery occlusion; CE — cardioembolic. Model adjusted for all risk fact

defined clinical characteristics of subjects and healthy controls for a better understanding of the relationship between Lp(a) and stroke and its subtypes.

This is consistent with the findings of our study. Lp(a) levels and stroke risk were higher in patients with large-artery atherosclerosis than in other aetiological categories of IS or in control subjects.

There are many possible explanations for our results. On the one hand, it could indicate that Lp(a) seems to accelerate atherogenesis [26]. On the other hand, total cholesterol and LDL-cholesterol were not significantly elevated in IS patients. Therefore, it appears that the mechanisms of the association of Lp(a) with IS in the present study are not only dependent on atherosclerosis. Lp(a) may directly contribute to arterial thrombosis, and has an antifibrinolytic effect. Due to the similarity between apo(a) and plasminogen, Lp(a) can bind to fibrin, but does not have the proteolytic activity of plasminogen and thus attenuates plasminogen activation and fibrinolysis [27, 28]. In addition, Lp(a) can promote thrombus formation by increasing platelet aggregation [29–31] and inactivating the tissue factor pathway inhibitor, which is a major regulator of the tissue factor mediated coagulation pathway [32].

While it is clear that important mechanistic questions, as well as the role of Lp(a) isoform size, remain unresolved, the literature consistently demonstrates that Lp(a)/apo(a) can inhibit fibrinolysis as well as plasminogen activation in the context of fibrin clots or on the vascular cell surface [33].

Some of the classic vascular risk factors such as age, smoking, hypertension, atrial fibrillation, and low HDL-cholesterol levels were associated with ischaemic stroke in the present study. Age, LDL-C, HDL-C, smoking, and atrial fibrillation were associated with large-artery atherosclerosis, while hypertension was associated with small-artery occlusion IS, and atrial fibrillation with the cardioembolic subtype. The undetermined subtype of IS was not associated with any significant risk factor. Diabetes, total cholesterol, and triglycerides are important modifiable risk factors for ischaemic stroke [34–36]. We found an increased risk for IS (OR 3.29) but with borderline significance (p = 0.07). We did not find a statistically significant association with IS and its subtypes for cholesterol or triglycerides. Previous studies have also shown that vascular risk factors differ between the aetiological subtypes of ischaemic stroke [37–40]. This is probably explained by the heterogeneity of the causes of IS.

There have been various cut-off serum Lp(a) values in published studies. Therefore, it is difficult to define which serum Lp(a) value represents the risk threshold for IS [41–43]. The newest clinical guidelines advocate the use of risk thresholds with 'grey' zones (e.g. 30–50 mg/dL or 75–125 nmol/L) to either rule in (≥ 50 mg/dL; 125 nmol/L) or rule out (< 30 mg/dL; 75 nmol/L) cardiovascular risk [9].

Our univariate analysis revealed a significant association of IS with cut-off value of 117 nmol/L (c.46.8 mg/dL) for serum Lp(a) concentration. In a multivariate logistic regression analysis adjusting for traditional risk factors, Lp(a) levels greater than 75 nmol/L (30 mg/dL) were significantly associated with IS.

Our study has several limitations. There is the general limitation of any case-control study, including selection bias, as patients were included in a tertiary centre. Therefore, multicentre studies are needed to confirm the results of the present study. The sample size was relatively small.

The strength of this study was the multivariate analysis in which several traditional risk factors for ischaemic stroke and its subtypes were considered.

## Conclusions

In a case-control study, we found that Lp(a) was an independent risk factor for ischaemic stroke, and the large-artery atherosclerotic subtype of ischaemic stroke.

This finding adds further data to the common risk factors for ischaemic stroke, and may be beneficial in the development of effective and targeted prevention of ischaemic stroke. The measurement of Lp(a) should be routinely included as part of an initial lipid profile to identify subjects at a high risk of stroke.

**Funding:** *This study was supported by the Scientific Grant Agency of the Ministry of Education, Science, Research and Sports of the Slovak Republic : VEGA no. 1/0686/24 and KEGA no. 011UPJŠ-4/2023.*

**Conflict of interests:** *None declared.*

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