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Real-world association between elevated lipoprotein (a) and cerebrovascular and cardiovascular outcomes: A federated EHR cohort study

Meet P. Kachhadia[1], Piyush Puri[2], Gaurang H. Suhagiya[3], Sarah Meadows[1], Usmaan Topiwala[4], Juber D. Shaikh[5], Marc A. Swerdloff[6], Nirali Borad[7], Gurnoor Gill[1], Jay Patel[8], Samarth Shah[9] & Harshal A. Sanghvi[10,*]

[1]Department of Medicine, Charles E. Schmidt College of Medicine, Florida Atlantic University, Boca Raton, FL, USA; [2]Department of Internal Medicine, Icahn School of Medicine at Mount Sinai, NYC Health + Hospitals/Queens, New York, NY, USA; [3]Department of Cardiology, Jiangsu University, China; [4]Department of Medicine, Smt. NHL Municipal Medical College, Ahmedabad, Gujarat, India; [5]Department of Medicine, Henry Ford Health System, Detroit, MI, USA; [6]Department of Neurology, Marcus Neuroscience Institute, Boca Raton Regional Hospital, Boca Raton, FL, USA; [7]Department of Medicine, Thomas Memorial Hospital, South Charleston, WV, USA; [8]Department of Biomedical Engineering, Florida Atlantic University, Boca Raton, FL, USA; [9]Department of Technology and

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Clinical Trials, Advanced Research LLC, FL, USA; [10]Department of Information Technology and Operations Management, College of Business, Florida Atlantic University, Boca Raton, FL, USA; *Corresponding author

Affiliation URL:
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Author contact:
Meet P. Kachhadia - E-mail: mkachhadia@health.fau.edu
Piyush Puri - E-mail: puri.piyush777@gmail.com
Gaurang H. Suhagiya - E-mail: gaurangsuhagiya1996@gmail.com
Sarah Meadows - E-mail: meadows.sarahb@gmail.com
Usmaan Topiwala - E-mail: usmaantopiwala@gmail.com
Juber D. Shaikh - E-mail: jubershaikh703@yahoo.com
Marc A. Swerdloff - E-mail: mswerdloff@baptisthealth.net
Nirali Borad - E-mail: niraliborad@gmail.com
Gurnoor Gill - E-mail: ggill2023@health.fau.edu
Jay Patel - E-mail: jay16501@gmail.com
Samarth Shah - E-mail: samarthshah341@gmail.com
Harshal A. Sanghvi - E-mail: hsanghvi2020@fau.edu

Abstract:
Elevated lipoprotein(a) (Lp(a)) is a causal cardiovascular risk factor, yet its association with incident ischemic stroke in routine clinical care remains uncertain. Adults in the TriNetX US Collaborative Network with Lp(a) ≥50 mg/dL were compared with those having Lp(a) <50 mg/dL after 1:1 propensity score matching. Among 97,882 matched adults, incident ischemic stroke or transient ischemic attack occurred in 2.45% versus 2.69% (hazard ratio 0.956, 95% CI 0.878–1.041; p=0.299). Alternative-cutoff, dose-response and landmark analyses were uniformly null and only a post-hoc composite adding myocardial infarction reached nominal significance (hazard ratio 1.058, 1.004–1.116). Thus, real-world stroke risk in patients with elevated Lp(a) appears attenuated by testing-indication bias and intensified preventive management.

Keywords: Lipoprotein (a) (Lp(a)), ischemic stroke, cardiovascular outcomes, propensity score matching, dose-response, federated electronic health records

Background:
Lipoprotein (a) (Lp(a)) is a genetically determined, atherogenic lipoprotein composed of apolipoprotein B-100 covalently linked to apolipoprotein(a), with concentrations largely heritable and stable across the lifespan **[1]**. Plasma Lp(a) is minimally responsive to statins and other conventional lipid-lowering therapy **[1]**. Mendelian randomization supports a causal role for Lp(a) in coronary artery disease and calcific aortic valve stenosis **[2]**. A 2026 Mendelian randomization analysis linked each 100 nmol/L increment in genetically predicted Lp(a) to large-artery atherosclerotic stroke (OR 1.23, 95% CI 1.14–1.33) but not to small-vessel stroke (OR 0.98) **[3]**. The 2022 European Atherosclerosis Society consensus statement accordingly recommends Lp(a) measurement for risk stratification and intensified control of modifiable risk factors when concentrations are elevated **[4]**. Patients who undergo Lp(a) testing in routine care therefore differ systematically from the general population, typically presenting after premature or recurrent events, with a strong family history, or with high calculated risk, which introduces testing-indication and treatment-by-indication bias **[5]**. A 2026 clinical cohort reported no difference in stroke subtype distribution across Lp(a) strata, although higher Lp(a) tracked with greater stroke severity **[6]**. Olpasiran, a small interfering RNA and pelacarsen, an antisense oligonucleotide, lower Lp(a) by roughly 80% to 98% and phase 3 cardiovascular outcome trials are ongoing **[7, 8]**. Therefore, it is of interest to describe the real-world association between elevated Lp(a) and incident ischemic stroke across multiple thresholds and concentration strata in a large federated electronic health record network.

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Materials and Methods:

Data source and study design:

We used the TriNetX US Collaborative Network (TriNetX, LLC; Cambridge, MA), a federated health research network providing standardized de-identified electronic health records from 66 to 67 US healthcare organizations **[9, 10]**. Data elements include diagnoses (ICD-10-CM), procedures (CPT and ICD-10-PCS), medications (RxNorm), laboratory values (LOINC) and vital signs. The observation period spanned January 1, 2015, through December 31, 2025. We conducted a retrospective, propensity score-matched cohort study in which patients entered at their first qualifying Lp(a) measurement, reported in accordance with the STROBE statement **[11]**. Because the platform returns only aggregated de-identified data, the study met criteria for non-human-subjects research under 45 CFR 46.104(d) and informed consent was waived.

Cohort definition and eligibility:

The study population comprised adults aged ≥18 years with at least one serum or plasma Lp(a) measurement (LOINC 10835-7; values 0–250 mg/dL) during the observation period. The index date was the first qualifying Lp(a) measurement; patients whose index event preceded the analysis date by more than 20 years were excluded. Two primary exposure cohorts were defined: C-HIGH (Lp(a) ≥50 mg/dL) and C-LOW (Lp(a) <50 mg/dL), using the European Atherosclerosis Society high-risk threshold **[5]**. A pre-specified alternative-cutoff cohort used Lp(a) ≥30 versus <30 mg/dL. Exclusion criteria were prior intracranial hemorrhage (I60–I62), brain neoplasm (C71, D33, D43), necrotizing vasculopathies (M31), demyelinating disease (G36–G37), sickle cell disorders (D57) and antiphospholipid syndrome (D68.61).

Primary outcome:

The primary outcome was incident ischemic stroke/TIA, defined by the first occurrence of ICD-10-CM I63 (cerebral infarction) or G45 (transient cerebral ischemic attack) after the index date. Follow-up began 1 day post-index. Patients with any stroke/TIA diagnosis before the index date were excluded from the primary outcome analysis to ensure incident-event capture. A systematic review of validation studies reported a positive predictive value exceeding 81% for ICD-9 430–438/ICD-10 I60–I69 codes for any cerebrovascular disease but 68% or lower for acute stroke specifically **[12]**.

Propensity score matching:

Propensity scores were estimated by logistic regression using pre-specified covariate blocks: endocrine/metabolic disease (E00–E89); other heart disease (I30–I52); ischemic heart disease (I20–I25); cerebrovascular disease (I60–I69); hypertensive disease (I10–I1A); cardiovascular medications (CV000); nicotine dependence (F17); tobacco use (Z72.0); personal history of nicotine dependence (Z87.891); LDL cholesterol; HbA1c; eGFR (CKD-EPI 2021); and body mass index. Demographic covariates (age, sex, race) were included automatically by the platform. Matching used 1:1 greedy nearest-neighbor matching without replacement, with balance assessed by standardized mean differences (SMD); |SMD| <0.1 was considered acceptable. An SMD of 0.113 was observed for LDL-C and is reported transparently as a limitation.

Statistical analysis:

The primary effect estimate was the hazard ratio (HR) from a Cox proportional hazards model, with Kaplan-Meier curves compared by the log-rank test. The proportional hazards (PH) assumption was tested using weighted Schoenfeld residuals. Crude measures (risk difference, risk ratio, odds ratio) were calculated but interpreted cautiously given differential follow-up time. Pre-specified additional analyses included the ≥30 mg/dL cutoff (A1); a three-stratum dose-response analysis versus the <30 mg/dL reference (A2); a 2-year landmark analysis restricting outcomes to days 730–1,825 (A3); and post-hoc composite endpoints (A4, A5). Quantitative bias analysis used the E-value framework **[13]**. Statistical significance was two-sided at p<0.05; all analyses were performed within the TriNetX platform (Study ID 365036).

Table 1: Baseline characteristics before and after expanded propensity score matching (primary analysis, Lp(a) ≥50 vs <50 mg/dL).

Characteristic	C-HIGH pre-PSM (n=50,080)	C-LOW pre-PSM (n=84,138)	C-HIGH post-PSM (n=48,941)	C-LOW post-PSM (n=48,941)	Post-PSM SMD
Diagnoses					
Endocrine/metabolic (E00–E89)	34,544 (69.0%)	53,884 (66.0%)	34,539 (70.6%)	34,574 (70.6%)	0.002
Cerebrovascular (I60–I69)	7,232 (14.8%)	12,814 (15.7%)	7,231 (14.8%)	7,217 (14.7%)	0.001
Hypertensive (I10–I1A)	20,398 (41.7%)	31,425 (38.5%)	20,394 (41.7%)	20,364 (41.6%)	0.001
Other heart disease (I30–I52)	13,096 (26.8%)	20,270 (24.8%)	13,095 (26.8%)	13,050 (26.7%)	0.002
Ischemic heart disease (I20–I25)	12,593 (25.7%)	17,677 (21.7%)	12,588 (25.7%)	12,558 (25.7%)	0.001
Nicotine dependence (F17)	3,145 (6.4%)	4,787 (5.9%)	3,144 (6.4%)	3,010 (6.2%)	0.011
Tobacco use (Z72.0)	759 (1.6%)	1,194 (1.5%)	759 (1.6%)	664 (1.4%)	0.016
Personal hx nicotine dep (Z87.891)	3,554 (7.3%)	5,692 (7.0%)	3,554 (7.3%)	3,470 (7.1%)	0.007
Cardiovascular medications					
CV medications (CV000)	30,422 (62.2%)	47,246 (57.9%)	30,417 (62.2%)	30,453 (62.2%)	0.002
Laboratory values (mean ± SD)					
LDL cholesterol, mg/dL	113.9 ± 50.0	109.6 ± 47.9	113.9 ± 50.0	108.4 ± 48.1	0.113†
HbA1c, %	6.1 ± 1.4	6.1 ± 1.3	6.1 ± 1.4	6.1 ± 1.3	0.034
eGFR, mL/min/1.73 m²	83.0 ± 23.2	85.3 ± 22.4	83.0 ± 23.2	84.7 ± 22.5	0.075
BMI, kg/m²	28.9 ± 6.5	28.6 ± 6.5	28.9 ± 6.5	28.8 ± 6.5	0.021

C-HIGH = Lp(a) ≥50 mg/dL; C-LOW = Lp(a) <50 mg/dL; PSM = propensity score matching; SMD = standardized mean difference. † SMD >0.10 indicates residual imbalance for LDL cholesterol post-matching; reported transparently as a limitation. All other post-PSM SMDs <0.08.

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Table 2: Incident ischemic stroke/TIA, Lp(a) ≥50 vs <50 mg/dL.

Parameter	C-HIGH (Lp(a) ≥50 mg/dL)	C-LOW (Lp(a) <50 mg/dL)	p-value / statistic
Matched patients (post-PSM)	48,941	48,941	
Patients analyzed for primary outcome[1]	41,311	41,164	
Prior stroke/TIA excluded	7,630	7,777	
Incident stroke/TIA events	1,014	1,107	
Crude risk	2.45%	2.69%	
Mean follow-up, days (SD)	791.1 (674.7)	851.4 (697.5)	
Median follow-up, days	570	657	
KM survival at end of window	95.34%	95.33%	
Cox hazard ratio (95% CI)[2]	0.956 (0.878–1.041)	Reference	p=0.299
Log-rank chi-square (df=1)			1.080; p=0.299
PH proportionality test (χ^2, p)			χ^2=4.322; p=0.038[3]
Risk difference (95% CI)			−0.002 (−0.005, −0.000); p=0.033[4]
Risk ratio (95% CI)			0.913 (0.839–0.993); p=0.033[4]
Odds ratio (95% CI)			0.911 (0.835–0.993)
E-value (point estimate / upper CI)			1.18 / 1.0

[1]After exclusion of patients with prior stroke/TIA. [2]Cox HR is the pre-specified primary estimate. [3]PH assumption violated; log-rank test confirms null finding. [4]Crude proportion-based estimates; biased by differential follow-up time.

Table 3: Dose-response analysis: incident ischemic stroke/TIA by Lp(a) stratum vs <30 mg/dL reference.

Lp(a) tier vs ref (<30 mg/dL)	Matched N (per arm)	Analyzed C-tier / C-LOW	Events C-tier (%)	Events C-LOW (%)	HR (95% CI)	Log-rank p
T1: 50–99 mg/dL	25,027	20,850 / 20,817	504 (2.4%)	583 (2.8%)	0.897 (0.797–1.011)	0.075
T2: 100–149 mg/dL	7,371	5,892 / 5,830	221 (3.8%)	194 (3.3%)	1.164 (0.960–1.412)†	0.122
T3: ≥150 mg/dL	9,529	8,212 / 8,114	182 (2.2%)	215 (2.6%)	0.879 (0.722–1.071)†	0.202

All strata matched separately against C-LOW-30 (<30 mg/dL) using the same expanded PSM specification. Prior stroke/TIA excluded from each analysis. † PH assumption violated at p<0.01; log-rank p-values are the primary inferential test.

Table 4: Comprehensive summary of all primary and sensitivity analyses

Analysis	Matched N (per arm)	Events C-HIGH / C-LOW	Analyzed N C-HIGH / C-LOW	HR (95% CI)	Log-rank p	PH test p
PRIMARY: Lp(a) ≥50 vs <50 mg/dL	48,941	1,014 / 1,107	41,311 / 41,164	0.956 (0.878–1.041)	0.299	0.038*
A1: Lp(a) ≥30 vs <30 mg/dL	60,538	1,243 / 1,379	50,921 / 50,375	0.947 (0.878–1.023)	0.168	0.054
A2-T1: 50–99 vs <30 mg/dL	25,027	504 / 583	20,850 / 20,817	0.897 (0.797–1.011)	0.075	0.073
A2-T2: 100–149 vs <30 mg/dL	7,371	221 / 194	5,892 / 5,830	1.164 (0.960–1.412)	0.122	0.006*
A2-T3: ≥150 vs <30 mg/dL	9,529	182 / 215	8,212 / 8,114	0.879 (0.722–1.071)	0.202	0.004*
A3 Landmark: days 730–1825	48,941	263 / 277	40,560 / 40,334	1.071 (0.905–1.268)	0.427	0.934
A4 Post-hoc composite†	48,947	1,816 / 1,941	37,140 / 37,046	0.979 (0.918–1.044)	0.512	NR
A5 Broader MACE-like composite‡	48,944	2,778 / 2,809	31,494 / 31,705	1.058 (1.004–1.116)*	0.034	0.639

** A5: Cox HR nominally significant (p=0.034) but crude RD −0.000 (p=0.863); discrepancy attributable to differential follow-up time. PH assumption satisfied (p=0.639). † A4: composite of ischemic stroke/TIA + cardiac arrest + HF; nonfatal MI not included. ‡ A5: broader MACE-like composite including MI, angina, precerebral artery events, intracranial hemorrhage, hypertensive heart disease, other circulatory disorders and death; not pre-specified. NR = not reported.*

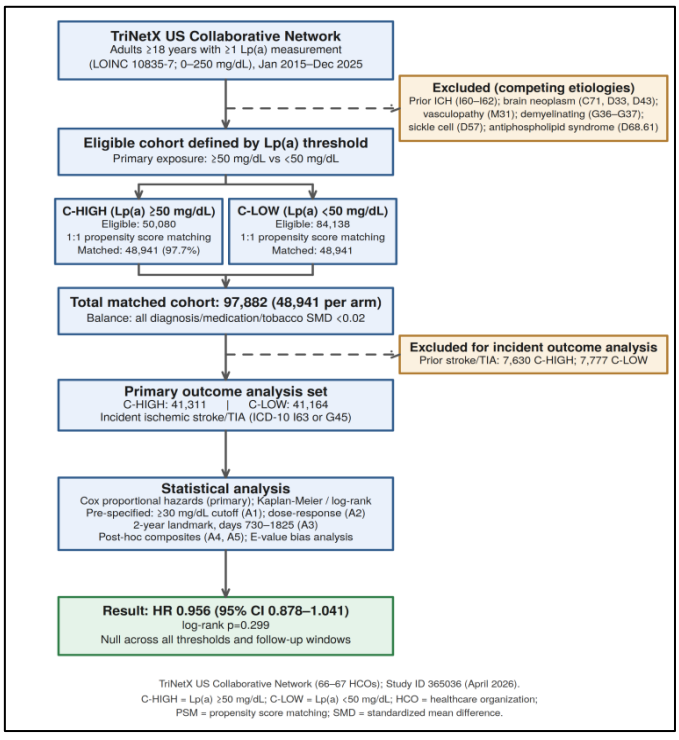

Figure 1: Study cohort attrition flowchart. From the Lp(a)-measured base population in the TriNetX US Collaborative Network (66 to 67 HCOs), successive steps leading to the primary matched cohorts and primary outcome analysis are shown. Primary analysis: C-HIGH 50,080 eligible to 48,941 matched; C-LOW 84,138 eligible to 48,941 matched. Numbers reflect the final analysis run (TriNetX Study ID 365036, April 2026). C-HIGH = Lp(a) ≥50 mg/dL; C-LOW = Lp(a) <50 mg/dL; HCO = healthcare organization; PSM = propensity score matching; SMD = standardized mean difference.

Results and Discussion:

The TriNetX US Collaborative Network contributed 50,080 C-HIGH patients (66 HCOs) and 84,138 C-LOW patients. After 1:1 propensity score matching, each cohort comprised 48,941 matched patients (97,882 total), reflecting 97.7% retention in the C-HIGH arm **(Figure 1)**. Matching achieved close covariate balance across diagnoses, medications and tobacco history (all SMD <0.02), with residual imbalance limited to LDL cholesterol (post-match SMD 0.113) and eGFR (SMD 0.075) **(Table 1)**. Mean follow-up after matching was 791.1 days (SD 674.7; median 570) in C-HIGH and 851.4 days (SD 697.5; median 657) in C-LOW. After excluding patients with prior stroke/TIA (7,630 C-HIGH; 7,777 C-LOW), the incident-event analysis included 41,311 C-HIGH and 41,164 C-LOW patients. Incident ischemic stroke/TIA occurred in 1,014 of 41,311 (2.45%) C-HIGH and 1,107 of 41,164

(2.69%) C-LOW patients **(Table 2)**. The Cox HR was 0.956 (95% CI 0.878–1.041; log-rank χ^2=1.080, df=1, p=0.299). Kaplan-Meier survival at the end of the observation window was 95.34% (C-HIGH) versus 95.33% (C-LOW). A mild PH violation was noted (Schoenfeld χ^2=4.322; p=0.038); the log-rank statistic, which requires no proportionality assumption, independently confirms the null result. The E-value for the point estimate was 1.18. In the pre-specified ≥30 mg/dL analysis (A1), 60,538 patients were retained per arm (121,076 in total) and the Cox HR was 0.947 (95% CI 0.878–1.023; log-rank p=0.168). Concordance of the ≥50 and ≥30 analyses demonstrates threshold independence of the null finding. Across all three Lp(a) strata (A2), no statistically significant increase in ischemic stroke/TIA risk was observed **(Table 3)**. The pattern was non-monotonic (T1 HR 0.897; T2 HR 1.164; T3 HR 0.879), inconsistent with a concentration-dependent atherogenic gradient. Significant PH violations at T2 (p=0.006) and T3 (p=0.004) indicate time-varying hazards; log-rank p-values are the primary inferential tests for these strata. In the 2-year landmark analysis (A3), the Cox HR was 1.071 (95% CI 0.905–1.268; log-rank p=0.427), with no PH violation (p=0.934). These data confirm that the null primary result is not attributable to inadequate early follow-up. In A4 (composite of ischemic stroke/TIA, cardiac arrest and heart failure), events occurred in 4.89% (C-HIGH) versus 5.24% (C-LOW) (Cox HR 0.979, 95% CI 0.918–1.044; log-rank p=0.512). In A5 (broader MACE-like composite additionally incorporating myocardial infarction, angina, cerebral/precerebral artery occlusion, intracranial hemorrhage and circulatory events), events occurred in 8.8% versus 8.9% (Cox HR 1.058, 95% CI 1.004–1.116; p=0.034; PH p=0.639). The crude risk difference was −0.000 (p=0.863), entirely null, reflecting differential follow-up time. **Table 4** presents all primary and sensitivity analyses. Hazard ratios ranged from 0.879 to 1.164; none achieved log-rank significance. In this propensity-matched federated cohort of 97,882 adults across 66 to 67 US healthcare organizations, elevated Lp(a) assessed at two pre-specified thresholds (≥30 and ≥50 mg/dL) and across three concentration strata was not associated with incident ischemic stroke/TIA over follow-up extending to 5 years. The null finding persists in the late follow-up window, which argues against a delayed atherogenic effect emerging over the study period. These findings contrast with Mendelian randomization studies establishing a causal effect of genetically elevated Lp(a) on coronary artery disease and on large-artery atherosclerotic stroke **[2, 3]**. The discrepancy is consistent with several non-exclusive explanations. Testing-indication bias is the most likely dominant mechanism: Lp(a) is measured selectively in patients with premature cardiovascular events, strong family histories or high calculated risk, precisely those who then receive the most aggressive pharmacologic management **[4]**. Baseline medication data are consistent with this but do not prove it. Before matching, cardiovascular medication exposure was already high in both groups and differed only modestly (62.2% C-HIGH versus 57.9% C-LOW); the identical post-match figures (62.2% in each arm) follow directly from matching on medication class and are not independent evidence of equalized treatment. The non-monotonic dose-response pattern deserves comment. At T2 (100–149 mg/dL) the point estimate was numerically elevated (HR 1.164), though non-significant (log-rank p=0.122) with a significant PH violation (p=0.006). At the highest concentrations (T3, ≥150 mg/dL) the HR was paradoxically 0.879, plausibly reflecting particularly aggressive preventive management in patients with extreme elevations, although treatment intensity was not measured directly. These patterns are most parsimoniously explained by heterogeneous treatment-by-indication effects across strata rather than genuine reversal of atherogenic risk. The PH violations across multiple analyses indicate time-varying hazards. The landmark analysis offers a partial solution: restricting to days 730–1,825, where no PH violation was detected (p=0.934), produced an HR of 1.071 (0.905–1.268) consistent with the null. The discrepancy between significant crude risk ratios and the null Cox HR is explained by differential follow-up time. C-LOW patients had approximately 8% longer mean follow-up (851 versus 791 days), providing more observation time to accumulate events. The Cox HR, conditioning on time-at-risk, is the methodologically correct primary estimate. The post-hoc composites add mechanistic resolution. The cerebrovascular finding remains null in A4 (HR 0.979; log-rank p=0.512) and the directional shift in A5, from null toward elevated only when myocardial infarction codes are added, is consistent with the coronary-predominant causal signal noted above. The nominal A5 result must be read against the completely null crude risk difference (−0.000, p=0.863), the differential follow-up artifact identified throughout and the fact that A5 was not pre-specified. ICD-10 codes I63 and G45 also do not discriminate stroke mechanism, so a genetic signal confined to large-artery atherosclerosis would be diluted within an all-cause ischemic stroke endpoint. These observations carry practical implications. A null real-world association does not imply absence of causal risk and these data do not contradict Mendelian randomization or phase 2 trial evidence supporting Lp(a) as a causal cardiovascular risk factor. They should not discourage Lp(a) screening or enrollment in ongoing phase 3 outcome trials (Lp(a)HORIZON, OCEAN(a)-OUTCOMES) **[7, 8]**.

Conclusion:

Elevated Lp(a) was not associated with incident ischemic stroke/TIA among 97,882 propensity-matched adults. This null real-world signal most likely reflects testing-indication bias and intensified preventive treatment rather than absence of causal risk. Quantifying the gap between genetic and observational estimates will aid interpretation of ongoing Lp(a)-lowering outcome trials.

Strengths and limitations:

Key strengths include the large sample size (>97,000 matched patients in the primary analysis, >121,000 in A1), the multi-institutional federated design, expanded matching across 13 co-variate groups incorporating laboratory values, pre-specified dose-response and landmark analyses, E-value bias quantification and paired post-hoc composite endpoints. Limitations are as follows. First, EHR-based Lp(a) measurement introduces testing-indication bias that matching on observed

covariates cannot fully resolve. Second, residual LDL-C imbalance (SMD 0.113) persists after matching, though E-value analysis suggests it cannot materially alter the null conclusion. Third, significant PH violations in the primary analysis and dose-response strata indicate time-varying hazards. Fourth, ICD-based stroke ascertainment is imperfect, with lower positive predictive value for acute stroke specifically than for cerebrovascular disease broadly. Fifth, TriNetX uses administrative date-of-last-fact as the censoring mechanism and the approximately 8% difference in mean follow-up between arms raises the possibility of informative censoring. Sixth, neither post-hoc composite maps directly to the 3-point MACE endpoints used in the Lp(a)HORIZON or OCEAN(a)-OUTCOMES trials and A5 in particular incorporates heterogeneous circulatory codes and death. Seventh, ICD-10 code I63 does not capture stroke etiology, preventing subtype-specific analysis.

Abbreviations:
CI: confidence interval; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CV: cardiovascular; EAS: European Atherosclerosis Society; eGFR: estimated glomerular filtration rate; EHR: electronic health record; HCO: healthcare organization; HR: hazard ratio; ICD-10-CM: International Classification of Diseases, Tenth Revision, Clinical Modification; KM: Kaplan-Meier; LDL-C: low-density lipoprotein cholesterol; LOINC: Logical Observation Identifiers Names and Codes; Lp(a): lipoprotein(a); MACE: major adverse cardiovascular events; MI: myocardial infarction; MR: Mendelian randomization; PH: proportional hazards; PSM: propensity score matching; SMD: standardized mean difference; TIA: transient ischemic attack.

Declarations:
Acknowledgments: None.

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Conflicts of interest: The authors declare no conflicts of interest.

Ethics approval and informed consent:
This study used fully de-identified, aggregate data from the TriNetX US Collaborative Network and met criteria for exemption from Institutional Review Board oversight under the Common Rule (45 CFR 46.104[d]); informed consent was not applicable. The study adhered to the principles of the Declaration of Helsinki.

Use of artificial intelligence:
Large language model tools were used to assist with manuscript organization and formatting. All analytic decisions, data interpretation and final content were reviewed and approved by the authors, who take responsibility for the integrity of the work.

Author contributions:
All authors contributed to study conception and design, data interpretation and critical revision of the manuscript and approved the final version.

Data availability:
Data were accessed through the TriNetX US Collaborative Network (https://trinetx.com). Access requires a data use agreement with TriNetX; patient-level data cannot be shared by the authors.

Authors declare: This work was previously posted as a preprint (DOI: https://doi.org/10.64898/2026.04.30.26352189).

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