International Journal of Stroke
WSO

High-density lipoprotein cholesterol levels and their impact on outcomes in acute ischemic stroke patients treated with mechanical thrombectomy

International Journal of Stroke
1–11

DOI: 10.1177/17474930251374791
journals.sagepub.com/home/wso
Sage

Lucio D'Anna[1,2], Matteo Foschi[3,4], Mariarosaria Valente[5], Simona Sacco[3], Caterina Del Regno[5], Ilaria De Negri[5], Francesco Toraldo[5], Alessandro Mare[5], Massimo Sponza[6], Vladimir Gavrilovic[7], Kyriakos Lobotesis[8], Edoardo Pirera[9], Gian Luigi Gigli[5], Soma Banerjee[1,2] and Giovanni Merlino[5,10]

Abstract

Background: High-density lipoprotein cholesterol (HDL-C) is traditionally considered protective in cardiovascular disease, but its role in acute ischemic stroke (AIS) remains unclear, particularly in patients undergoing mechanical thrombectomy (MT). This study aimed to assess the association between HDL-C levels and clinical outcomes in AIS patients treated with MT for anterior circulation large vessel occlusion (LVO).

Methods: We conducted a multicentre, observational, post hoc analysis of AIS patients treated with MT between January 2016 and March 2023 across three stroke centers. HDL-C levels at admission were categorized, and outcomes included 90-day functional dependence (mRS: 3–6), symptomatic intracranial hemorrhage (sICH), hemorrhagic transformation, and 90-day mortality. We used logistic regression with restricted cubic splines to define an HDL-C threshold associated with increased risk and applied inverse probability weighting (IPW) to adjust for confounding.

Results: Among 2166 patients (median age: 71 years; 52.3% female), HDL-C levels $>$ 1.33 mmol/L were independently associated with a higher risk of poor functional outcome at 90 days (risk ratio (RR): 1.72, 95% confidence interval (CI): 1.55–1.90), increased odds of sICH (RR: 2.3, 95% CI: 1.64–3.12), and higher mRS shift (OR: 2.10, 95% CI: 1.79–2.46). Subgroup analyses revealed significant sex-specific differences, with women at greater risk of adverse outcomes at higher HDL-C levels.

Conclusion: Elevated HDL-C levels ($>$1.33 mmol/L) are associated with worse functional outcomes and increased hemorrhagic complications following MT for anterior circulation AIS.

Keywords
Mechanical thrombectomy, HDL-C, acute ischemic stroke

Received: 9 April 2025; accepted: 4 August 2025

Introduction

High-density lipoprotein cholesterol (HDL-C) has historically been regarded as beneficial in the context of cardiovascular health, primarily due to its role in reverse cholesterol transport and its anti-inflammatory and antioxidant properties.[1,2] Elevated HDL-C levels are commonly associated with a reduced risk of atherosclerosis, myocardial infarction, and other cardiovascular events.[3,4] However, emerging evidence has suggested that in certain clinical scenarios, including acute ischemic stroke (AIS), higher HDL-C levels may not confer the expected protective benefits.[5] Instead, elevated HDL-C has been associated with paradoxical adverse outcomes, such as increased rates of mortality and complications following major cardiovascular or cerebrovascular events.[5–9]

AIS, particularly when caused by large vessel occlusion (LVO), represents a significant global health burden due to its associated high rates of morbidity and mortality.[10] Mechanical thrombectomy (MT) has revolutionized the management of AIS due to LVO, offering improved recanalization rates and better functional outcomes compared to intravenous thrombolysis (IVT) alone.[11] Despite these advances, the identification of reliable predictors of outcomes following MT remains an area of active investigation. While clinical factors such as age, stroke severity, and time to treatment are well-established prognostic markers, the role of biological markers, including lipid profiles, remains less well-defined.

Several studies have explored the role of dyslipidemia in stroke outcomes, primarily focusing on low-density lipoprotein cholesterol (LDL-C) and total cholesterol. Conversely, the role of HDL-C has been less explored and its impact on post-stroke recovery and complications remains uncertain and debated. Indeed, whether very high HDL-C levels might impact the outcome of acute stroke patients undergoing MT remains unknown. Therefore, in our study we investigated the association between levels of HDL-C and clinical outcomes in a large multicentre cohort of AIS patients treated with MT for anterior circulation LVO.

Methods

This is a multicentre observational, investigator-initiated, post hoc analysis from prospective collected data from local registries, that included all acute stroke patients aged 18 years or older consecutively treated with MT for anterior circulation LVO and admitted to three stroke centers: Charing Cross Hospital, Imperial College Healthcare NHS Trust, London (UK); Udine University Hospital, Udine (Italy); S. Maria delle Croci Hospital, AUSL Romagna, Ravenna, (Italy) between 1 January 2016 and 30 March 2023 with local registries available.[12,13] This study was approved by the local institutional review boards. All authors had full access to the data and have read and agreed to the article as written. The study was conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions. Data are available upon reasonable request.

Patient selection

Patients presenting with features of acute stroke were evaluated in the hyperacute setting with appropriate neuroimaging and vascular imaging when indicated: computed tomography (CT) and CT angiography. Patients who fulfilled the relevant indications and without exclusion criteria would undergo acute recanalization therapy. Eligible patients who presented up to 4.5 h of ischemic stroke symptoms onset received IVT. Stroke patients would be considered for MT if they met the following criteria: pre-stroke modified Rankin scale (mRS), 0–2, National Institutes of Health Stroke Scale (NIHSS) score 6 or more and anterior circulation LVO (intracranial occlusion of internal carotid artery (ICA) or occlusion of M1-M2 segments of the middle cerebral artery). Initiation of the MT had to be possible within 6 h after the stroke onset or beyond 6 h only if patients met DAWN or DEFUSE 3 eligibility criteria.[14,15] All patients underwent clinical examination at baseline.

Data collection

Data were collected from prospectively maintained institutional registries by trained clinical researchers at each site using a standardized protocol. Imaging and clinical variables were extracted from electronic medical records and verified by stroke physicians and neuroradiologists involved in patient care. Data on known stroke risk factors were collected from patients' medical records as follows: age, sex, history of hypertension (blood pressure $>$ 140/90 mmHg at least twice before acute stroke or already under treatment with antihypertensive drugs), history of diabetes (a random venous plasma glucose concentration $>$ 11.1 mmol/L or a fasting plasma glucose concentration $>$ 7.0 mmol/L, or HbA1c $>$ 48 mmol/mol or under antidiabetic treatment), frequent alcohol use (more than 14 alcohol units per week),

[1]Department of Stroke and Neuroscience, Charing Cross Hospital, Imperial College London NHS Healthcare Trust, London, UK
[2]Department of Brain Sciences, Imperial College London, London, UK
[3]Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy
[4]Department of Neuroscience, Neurology and Stroke Unit, S. Maria delle Croci Hospital, AUSL Romagna, Ravenna, Italy
[5]Clinical Neurology, Udine University Hospital and DMED, University of Udine, Udine, Italy
[6]Neuroradiology, Udine University Hospital, Udine, Italy
[7]Vascular and Interventional Radiology, Udine University Hospital, Udine, Italy
[8]Neuroradiology, Department of Imaging, Charing Cross Hospital, Imperial College London, NHS Healthcare Trust, London, UK
[9]Internal Medicine and Stroke Care Ward, Department of Promoting Health, Maternal-Infant, Excellence and Internal and Specialized Medicine (ProMISE) "G. D'Alessandro," University of Palermo, Palermo, Italy
[10]Stroke Unit, Udine University Hospital, Udine, Italy

Corresponding author:
Lucio D'Anna, Department of Brain Sciences, Imperial College London, Fulham Palace Rd, London W6 8RF, London, UK.
Email: l.danna@imperial.ac.uk

current cigarette or previous smoking, documentation of atrial fibrillation before the index stroke or detected on admission, history of coronary artery disease, heart failure, previous stroke or transient ischemic attack (TIA). The severity of the index stroke was assessed using the NIHSS score on admission. The mRS was used to assess the patient's initial pre-stroke functional status and at 90 days. The 90-day function assessment was evaluated centrally through a telemedicine consultation or during in-person consultation at the thrombectomy capable center or local primary stroke center. Data on the use of any antiplatelet agents or anticoagulants before admission were recorded. Procedural features were collected and included pre-hospital model of care, use of IVT, onset to groin time, type of anesthesia, first thrombectomy technique used, number of passes and rate of first-pass successful recanalization.

All patients included in the study underwent digital subtraction angiography (DSA) as part of the thrombectomy procedure. The site of LVO was determined through direct review of DSA images and categorized into four predefined anatomical locations: distal ICA, M1 segment, M2 segment, and tandem occlusion. Baseline non-contrast CT scans were used to determine the Alberta Stroke Program Early CT Score (ASPECTS). All imaging parameters were assessed through prospective image review by board-certified neuroradiologists with more than 5 years of experience in acute stroke imaging. In case of uncertainty, consensus was reached through joint evaluation. Blood samples were collected on admission and included white blood count (WBC), C-reactive protein (CRP), glycemia, HbA1c, HDL-C level, total cholesterol and LDL-C.

Study outcomes

The primary outcome was the rates of 90-day unfavorable mRS score (3–6) after index event treated with MT and 90-day mRS score shift. Secondary outcome included rate of successful recanalization assessed by applying the modified thrombolysis in cerebral infarction (mTICI) classification.[16] Safety outcomes included 90-day mortality by all cause; post-procedural hemorrhagic transformation (HT) defined on follow-up CT at 24 h as any of the following: small petechiae along the margins of the infarct (hemorrhagic infarction (HI)-1) or as more confluent petechiae within the infarcted area but without space-occupying effect (HI-2) parenchymal hematoma (PH) was defined as hematoma in $<30\%$ of the infarcted area with some slight space-occupying effect (PH-1) or as dense hematoma in $\geqslant 30\%$ of the infarcted area with substantial space-occupying effect or as any hemorrhagic lesion outside the infarcted area (PH-2) in the case of more than 1 hemorrhagic lesion on brain scan, the worst possible category was assumed, and symptomatic hemorrhage (sICH) as hemorrhage with a decline in neurological status (an increase of more than 4 points in the NIHSS).[17]

Statistical analysis

Relationship between HDL-C level and 90-day unfavorable mRS score. A logistic regression model with restricted cubic splines was employed to assess the continuous relationship between HDL-C and the probability of achieving a 90-day mRS score of 3–6 in the study population. Knots for the splines were positioned at the 10th, 50th, and 90th percentiles of HDL-C. The median HDL-C served as the reference point, with ORs estimated relative to this value. Log ORs were exponentiated to derive ORs, and 95% CIs were calculated using standard errors. The OR curve was examined to determine a clinical cut-off for HDL-C, identifying the value where OR approached 1, suggesting no significant impact on risk. The HDL-C level closest to OR = 1 was selected as a potential cut-off point for stratification.

IPW. To balance patients based on baseline characteristics, we used IPW to create a pseudo-weighted sample between patients with admission HDL-C level above and below the cut-off value determined through Restricted Cubic Spline (RCS) analysis. We first estimated propensity scores using logistic regression, modeling the probability of being in the group with admission HDL-C level above the cut-off based on a pre-specified set of baseline covariates: age, sex, hypertension, diabetes, coronary artery disease, stroke or TIA history, frequent alcohol use, smoking status, known atrial fibrillation, newly discovered atrial fibrillation (AFDAS), heart failure, prior use of antiplatelet, prior use of oral anticoagulants, prior use of statins, prior use of ezetimibe, NIHSS on admission, ASPECTS on admission, site of LVO occlusion, pre-hospital model of care, IVT, onset to groin puncture time, type of anesthesia, first thrombectomy technique used, number of passes and rate of first pass successful. These covariates were chosen to comprehensively control for confounding without relying on data-driven variable selection, which can increase the risk of bias. To address concerns about model complexity relative to sample size, IPW was preferred over multivariable regression adjustment, as this approach reduces the risk of overfitting. Covariate balance was assessed using standardized mean differences (SMDs), with satisfactory results after weighting. From the logistic regression model, we calculated propensity scores for each patient and used these scores to assign inverse probability weights. The covariate balance between groups was evaluated by calculating SMDs. In addition, we examined the distribution of propensity scores to verify overlap between groups, and we applied stabilized weights to mitigate the influence of extreme weights and enhance model stability.

Outcomes analysis in the weighted population. For the primary outcomes, the risk ratio and risk difference with 95% confidence intervals (CIs) were calculated for the 90-day occurrence of unfavorable mRS scores between the two groups

above and below the cut-off value determined through RCS analysis; the shift in 90-day mRS scores was analyzed using an ordinal generalized linear model (GLM), with results presented as odds ratios (ORs) and 95% CIs. A proportional odds model (cumulative logit) was applied, given the ordinal nature of the mRS categories. For secondary outcomes, risk ratios and differences were computed for post-procedural favorable mTICI scores. Safety outcomes, including 90-day mortality, post-procedural HT, and symptomatic intracerebral hemorrhage (sICH), were analyzed using risk differences and risk ratios with 95% CIs. All outcome analyses were conducted in the weighted population.

Subgroup analysis for the primary outcome in the weighted population. Subgroup analysis of the primary outcome (90-day mRS: 3–6) was conducted for predefined categories, including age (≤80 or >80 years), sex, known onset, diabetes, hypertension, heart failure, coronary artery disease, AFDAS, known atrial fibrillation, previous use of statin and ezetimibe, bridging therapy. A GLM model incorporating HDL-C, subgroup variables, and interaction terms was used to assess heterogeneity in HDL-C effects across subgroups, with interaction p values reported.

No formal correction for multiple comparisons was applied to subgroup or secondary analyses, which were considered exploratory and hypothesis-generating. All statistical analyses were performed using R software, version 4.2. Statistical significance was defined as $p < 0.05$.

Results

Overall, our analysis included 2166 patients with AIS undergoing MT due to anterior circulation LVO (median (IQR) age 71 (59–80); 1134 women (47.7%)) (Table 1). The number of excluded patients with reasons is reported in the study flow chart (Supplemental Figure 1). As reported in Supplementary Figure 1, we excluded 121 patients with missing 90-day mRS or TICI scores and 55 patients with missing lipid profile data. Given the low rate of missing data, complete-case analysis was applied, and no imputation was performed.

Relationship between HDL-C and 90-day occurrence of unfavorable mRS

The logistic regression model evaluating the association between admission HDL-C as a continuous variable and the 90-day occurrence of unfavorable mRS revealed that each 1 mmol/L increase in HDL-C was associated with a hazard ratio (HR) of 1.06 (95% CI: 1.01–1.09, $p < 0.001$). The logistic regression model with RCS revealed a non-linear association between HDL-C and 90-day occurrence of unfavorable mRS. We identified an HDL-C cut-off of 1.33 mmol/L as the first point where the OR approximated 1 (Figure 1). A second point was identified at extreme HDL-C values (>1.60 mmol/L), marked by a sharp increase in the risk of the primary outcome. We selected the first point (HDL-C = 1.33 mmol/L) as clinical cut-off for this analysis offering a more reliable threshold for identifying patients transitioning out of high-risk states. We identified 1406 patients (64.9%) with baseline HDL-C < 1.33 mmol/L, while the remaining 760 patients (35.1%) had an HDL-C ⩾ 1.33 mmol/L (Table 1). The baseline characteristics by HDL-C groups for our cohort of patients are shown in Table 1.

IPW

Weighted and unweighted results for baseline characteristics are presented in Table 1. Overall, good balance was obtained for most of the baseline variables which showed a standardized difference (SD) of the propensity scores <0.10. Measures of balance diagnosis indicated that the samples were adequately weighted, with a SD of the propensity scores means between groups of 0.04 (good balance < 0.25), ratio of variances of propensity scores 0.74 (good balance between 0.5 and 2). Graphics of covariates balance distributions confirmed a good overall quality of the weighting (Supplemental Figure 2). After applying IPW, the weighted analytical sample consisted of 2166 patients, including 1406 with HDL-C < 1.33 mmol/L and 760 with HDL-C ⩾ 1.33 mmol/L.

Primary outcome

Patients with HDL-C ⩾ 1.33 mmol/L showed a significant higher rate of 90-day unfavorable outcome (mRS: 3–6) compared to patients with HDL-C < 1.33 mmol/L (risk ratio: 1.72 (95% CI: 1.55–1.90); $p < 0.001$) (risk difference: 22.9 (95 CI: 18.6–27.2); $p < 0.001$) (Table 2). The 90-day mRS shift analysis documented with higher mRS in patients with HDL-C ⩾ 1.33 mmol/L compared to patients with HDL-C < 1.33 mmol/L treated with MT for anterior circulation LVO (OR: 2.10, 95% CI: 1.79–2.46; $p < 0.001$) (Figure 2) (Table 2).

Secondary and safety outcomes

We found no significant differences in successful reperfusion rates (risk ratio: 1.02 (95% CI: 0.99 to 1.05); $p = 0.202$) (risk difference: 1.83 (95 CI: −0.92 to 4.58); $p = 0.229$) (Table 2) between the two groups. We also found no significant differences in the risk of 90-day mortality (risk ratio: 1.84 (95% CI: 0.77 to 4.42); $p = 0.100$) (risk difference: 5.9 (95% CI: −2.4 to 14.1); $p = 0.162$) and risk of HT post MT (risk ratio: 0.90 (95% CI: 0.79 to 1.04); $p = 0.158$) (risk difference: −3 (95% CI: −7 to 1); $p = 0.143$) (Table 2). However, patients with HDL-C ⩾ 1.33 mmol/L showed a significant higher rate symptomatic ICH compared to patients with HDL-C < 1.33

Table 1. Baseline characteristics of HDL-C level <1.33 mmol/L versus ⩾1.33 mmol/L patients.

	Overall population (n = 2166)	HDL-C level < 1.33 mmol/L (n = 1406)	HDL-C level ⩾ 1.33 mmol/L (n = 760)	p value	SMD unweighted*	SMD weighted*
Demographics						
Age, median (IQR), years	71 (59–80)	72 (60–80)	70 (58.8–79)	0.087	0.076	0.003
Sex, Female, No. (%)	1034 (47.7)	687 (48.9)	347 (45.7)	0.168	0.032	0.001
Risk factors						
Hypertension, No. (%)	1256 (58)	808 (57.5)	448 (58.9)	0.535	0.015	0.001
Diabetes, No. (%)	384 (17.7)	240 (17.1)	144 (18.9)	0.302	0.019	0.001
Coronary artery disease, No. (%)	317 (14.6)	207 (14.7)	110 (14.5)	0.926	0.002	0.001
Stroke or TIA history, No. (%)	280 (12.9)	175 (12.4)	105 (13.8)	0.401	0.007	0.001
Frequent alcohol use, No. (%)	199 (9.2)	127 (9)	72 (9.5)	0.794	0.004	0.001
Current/Former smoker, No. (%)	472 (21.8)	299 (21.3)	173 (22.8)	0.453	0.015	0.001
Known atrial fibrillation, No. (%)	578 (26.7)	368 (26.2)	210 (27.6)	0.496	0.015	0.002
AFDAS, No. (%)	417 (19.3)	289 (20.6)	128 (16.8)	**0.042**	0.037	0.002
Heart failure, No. (%)	196 (9)	123 (8.7)	73 (9.6)	0.558	0.009	0.002
Therapy on admission						
Antiplatelet treatment, No. (%)	220 (10.2)	144 (10.2)	76 (10)	0.918	0.002	0.001
Oral anticoagulation, No. (%)	262 (12.1)	163 (11.6)	99 (13)	0.364	0.014	0.001
Statin, No. (%)	673 (31.1)	430 (30.6)	243 (32)	0.536	0.014	0.003
Ezetimibe, No. (%)	681 (31.4)	463 (32.9)	218 (28.7)	**0.047**	0.042	0.002
Acute ischemic stroke characteristics						
NIHSS on admission, median (IQR)	17 (12–21)	17 (12–21)	17 (12–21)	0.857	0.008	0.001
ASPECTS, median (IQR)	8 (6–10)	8 (6–10)	8 (6–10)	0.669	0.019	0.001
Site of distal occlusion, No. (%)				0.760	0.015	0.001
Distal ICA	84 (3.9)	57 (4.1)	27 (3.6)			
M1	1010 (46.6)	639 (45.4)	371 (48.8)			
M2	836 (38.6)	555 (39.5)	281 (36.9)			
Tandem	236 (10.9)	155 (11)	81 (10.4)			
Procedural features						
Pre-hospital model of care, No. (%)				0.818	0.006	0.001
Mothership	673 (31.1)	434 (30.9)	239 (31.4)			
Drip-and-ship	733 (68.9)	972 (69.1)	521 (68.6)			
Intravenous thrombolysis, No. (%)	1318 (60.8)	855 (60.8)	463 (60.9)	0.997	0.001	0.001
Onset to groin time (min), median (IQR)	267 (218-341)	264 (215-336)	275 (224-350)	**0.043**	0.052	0.003

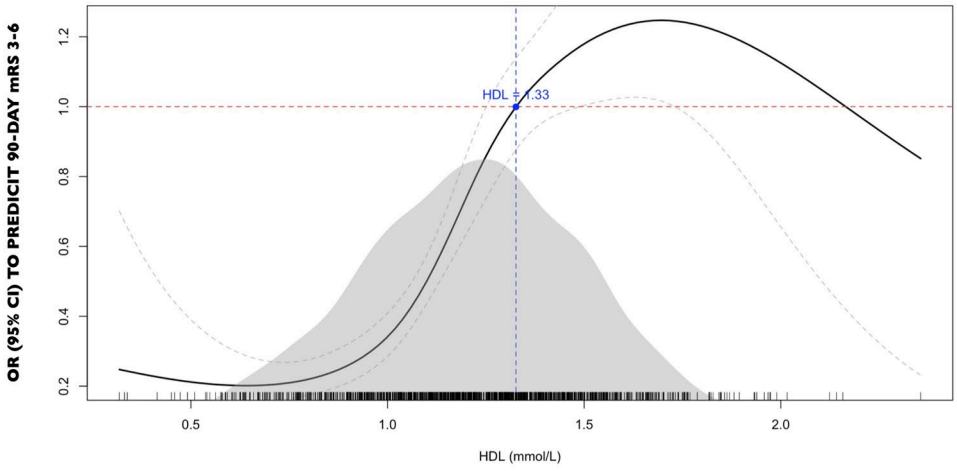
(continued)

Table 1. (continued)

	Overall population (n = 2166)	HDL-C level < 1.33 mmol/L (n = 1406)	HDL-C level ⩾ 1.33 mmol/L (n = 760)	p value	SMD unweighted*	SMD weighted*
Type of anesthesia, No. (%)				0.554	0.012	0.001
General	1696 (78.3)	1095 (77.9)	601 (79.1)			
Local	470 (21.7)	311 (22.1)	159 (20.9)			
First thrombectomy technique used, No. (%)				0.878	0.004	0.001
Stent retriever	1205 (55.6)	780 (55.5)	425 (55.9)			
Aspiration	961 (44.4)	626 (45.5)	335 (44.1)			
Number of passes, median (IQR)	2 (2-2)	2 (2-2)	2 (2-2)	0.099	0.046	0.002
First pass successful, No. (%)	1674 (77.3)	1089 (77.5)	585 (77)	0.841	0.005	0.001

Abbreviations: IQR: interquartile range; NIHSS: National Institute of Health Stroke Scale score; sd: standard deviation; SMD: standardized mean difference. *SMDs > 0.10 in the weighted population are reported in bold, indicating suboptimal weighting (except for baseline mean blood pressure values).

Figure 1. Restricted cubic spline models for risk of 90-day mRS 3–6 in relation HDL-C levels. The odds ratio is represented by the solid line and the 95% confidence interval (CI) by the dotted lines.



mmol/L (risk ratio: 2.3 (95% CI: 1.64 to 3.12); p < 0.001) (risk difference: 5.65 (95 CI: 3.25 to 8.05); p < 0.001) (Table 2).

Subgroup analysis for the primary outcome in the weighted population

We found a significant interaction between level of HDL-C and age group (p for interaction = 0.007), sex (p for interaction = 0.045), presence of heart failure (p for interaction = 0.005) and known atrial fibrillation (p for interaction = 0.032) in predicting 90-day risk of unfavorable outcome (mRS: 3–6). However, HDL-C was associated with the incremental probability of 90-day unfavorable outcome (mRS: 3–6) regardless of presence of diabetes (p for interaction = 0.985), hypertension (p for interaction = 0.687), newly discovered atrial fibrillation (p for interaction = 0.876), previous use of statin (p for interaction = 0.812) or ezetimibe (p for interaction = 0.341), and bridging therapy (p for interaction = 0.608) (Supplemental Table 1 and Figure 3).

Figure 2. Distribution of modified Rankin scale (mRS) scores at 90 days in patients with HDL-C ⩾ 1.33 mmol/L and with HDL-C < 1.33 mmol/L treated with mechanical thrombectomy.

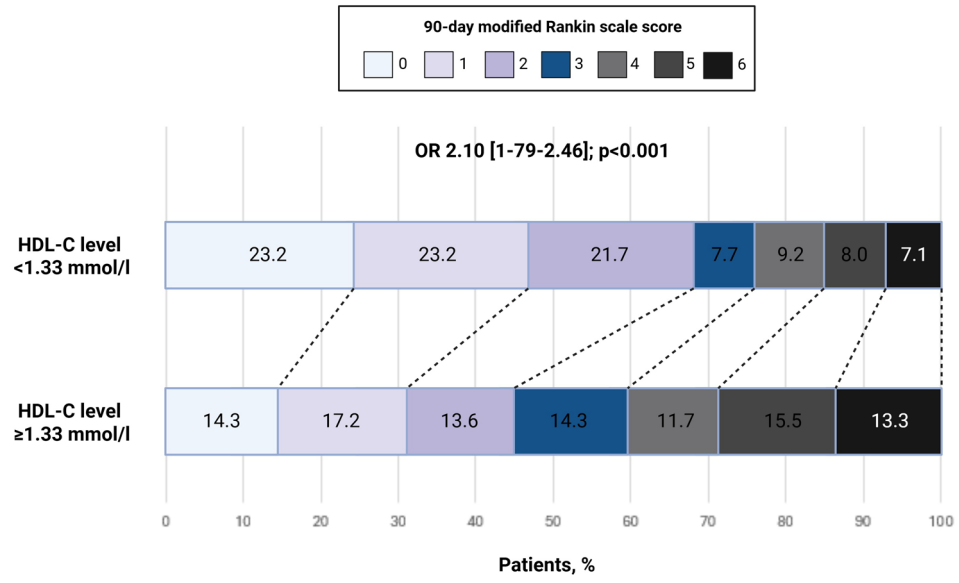


Table 2. Outcome comparisons in the weighted population: HDL-C level <1.33 mmol/L versus ⩾1.33 mmol/L patients.

	Overall population (n = 2166)	HDL-C level < 1.33 mmol/L (n = 1406)	HDL-C level ⩾ 1.33 mmol/L (n = 760)	Statistical metric	Treatment difference (95% CI)	p value
Primary outcomes						
90 day unfavorable mRS score (3–6), n (%)	866 (39.9)	449 (31.9)	417 (54.9)	**Risk ratio**	1.72 [1.55 to 1.90]	**<0.001**
				Risk difference (%)	22.9 [18.6 to 27.2]	**<0.001**
90-day mRS score distribution						
No symptoms (score of 0), n (%)	435 (20.1)	326 (23.2)	109 (14.3)	**Odds ratio**	2.10 [1.79 to 2.46]	**<0.001**
Symptoms without any disability (score of 1), n (%)	457 (21.1)	326 (23.2)	131 (17.2)			
Symptoms with mild disability (score of 2), n (%)	408 (18.8)	305 (21.7)	103 (13.6)			
Symptoms with mild-to-moderate disability (score of 3), n (%)	217 (10)	108 (7.7)	109 (14.3)			
Symptoms with moderate-to-severe disability (score of 4), n (%)	218 (10.1)	129 (9.2)	89 (11.7)			

(continued)

Table 2. (continued)

	Overall population (n = 2166)	HDL-C level < 1.33 mmol/L (n = 1406)	HDL-C level ⩾ 1.33 mmol/L (n = 760)	Statistical metric	Treatment difference (95% CI)	p value
Symptoms with severe disability (score of 5), n (%)	230 (10.6)	112 (8)	118 (15.5)			
Death (score of 6), n (%)	201 (9.3)	100 (7.1)	101 (13.3)			
Secondary outcomes						
Post-procedural favorable TICI score, n (%)	1918 (88.6)	1236 (87.9)	682 (89.7)	**Risk ratio**	1.02 [0.99 to 1.05]	0.202
				Risk difference (%)	1.83 [−0.92 to 4.58]	0.229
Safety outcomes						
90-day death, n (%)	201 (9.3)	100 (7.1)	101 (13.3)	**Risk ratio**	1.84 [0.77 to 4.42]	0.100
				Risk difference (%)	5.9 [−2.4 to 14.1]	0.162
Post-procedural HT, n (%)	655 (30.2)	440 (31.3)	215 (28.3)	**Risk ratio**	0.90 [0.79 to 1.04]	0.158
				Risk difference (%)	−3 [−7 to 1]	0.143
Symptomatic ICH, n (%)	140 (6.5)	63 (4.5)	77 (10.1)	**Risk ratio**	2.3 [1.64 to 3.12]	**<0.001**
				Risk difference (%)	5.65 [3.25 to 8.05]	**<0.001**

Abbreviations: mRS: modified Rankin scale; statistically significant p values (<0.05) are reported in bold.

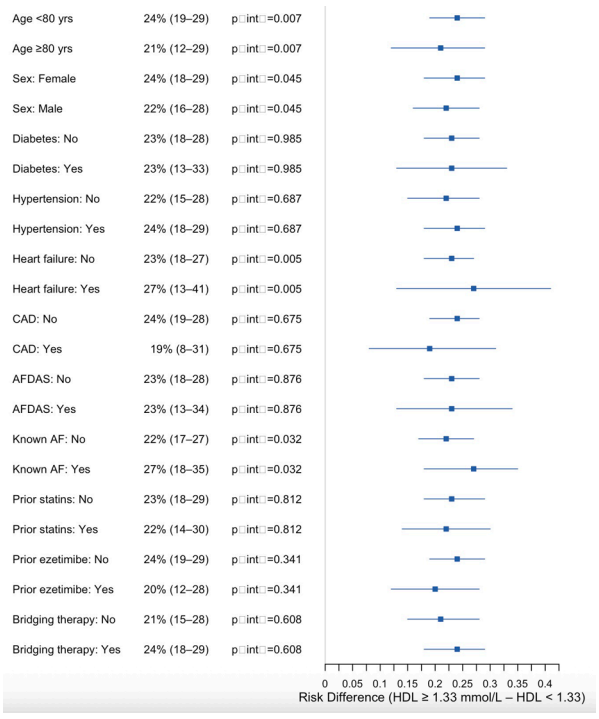
Discussion

Our study provides novel insights into the association between HDL-C levels and clinical outcomes in AIS patients treated with MT for anterior circulation LVO. We observed that higher HDL-C levels were associated with increased risk of 90-day unfavorable functional outcome and symptomatic ICH compared to patients with lower levels of HDL-C treated with MT for anterior circulation LVO. These findings might contribute to redefine the conventional perception of HDL-C as uniformly protective, suggesting a more complex role in cerebrovascular disease.

Interestingly, our findings appear in contrast with those reported by Sedghi et al., who observed that higher HDL-C levels were associated with improved functional outcomes and a lower risk of post-thrombectomy intracranial hemorrhage.[18] However, several methodological distinctions may account for this discrepancy. First, Sedghi et al. conducted a single-center retrospective analysis using propensity score matching (PSM) to balance covariates such as age, sex, ASPECTS, IVT, onset-to-recanalization time, mTICI (and log-transformed mTICI), and HbA1c (including a quadratic term). Although they achieved good balance in the matched cohort, their approach resulted in the exclusion of nearly one-third of eligible patients (reducing the sample from 481 to 320), which may have compromised the generalizability and statistical power of their findings. In contrast, our multicenter study used IPW to retain the entire cohort of 2166 patients while achieving excellent balance across a broader range of clinically relevant variables. These included demographic factors, vascular risk factors, pre-stroke medication use, procedural characteristics, and stroke severity. Furthermore, while Sedghi et al. dichotomized HDL-C using the sample median (~1.06 mmol/L), we employed a logistic regression model with RCS to explore non-linear relationships between HDL-C and outcome. This analysis identified 1.33 mmol/L as the inflection point beyond which the risk of unfavorable outcome increased, and this threshold was used in all subsequent analyses. The use of a biologically plausible, data-driven cut-off may have enhanced the validity of our stratification.

Recent literature suggests that HDL-C may not be universally protective in the context of AIS. Several studies have reported associations between higher HDL-C and increased hemorrhagic risk after reperfusion therapy or poor outcomes in specific populations.[19–22] Ding et al.[20]

Figure 3. Subgroup analysis for the primary outcome in the weighted cohort.



Abbreviations: RD: risk difference; AFDAS: newly discovered atrial fibrillation.

reported that elevated serum HDL-C was associated with a higher risk of lobar cerebral microbleeds in older patients, while Liu et al.[19] identified high HDL-C as a risk factor for HT. It is noteworthy to mention that in the study by Liu et al.[19] 10.02% of the patients had MT alone and 18.31% of the patients was treated with bridging therapy. In contrast to the previous studies, our analysis has focused on patients treated with MT with or without IVT for anterior circulation LVO. Our results align with Li et al.[23] who documented that lower triglyceride to HDL-C ratio could predict post-procedural HT in 155 patients treated with MT. However, this single-center study did not assess the relationship between HDL-C levels and other long-term outcomes, such as 90-day functional independence and mortality.

Although the mechanism by which HDL-C levels are associated with adverse stroke outcomes remains unclear, there are several pathophysiological mechanisms which may explain this phenomenon. HDL-C is an essential structural element that plays an important role in maintaining cell membrane homeostasis and exerts anti-inflammatory and endothelial-protective effects.[24–26] However, excessively high HDL-C levels can lead to HDL dysfunction, causing the lipoprotein to lose its atheroprotective properties and instead acquire pro-inflammatory, pro-oxidative, and prothrombotic characteristics.[27] Dysfunctional HDL has been associated with endothelial dysfunction, increased vascular permeability, and a heightened risk of intracranial hemorrhage—factors particularly relevant in the post-thrombectomy setting.[5] Another possible mechanism involves the interaction between HDL-C and coagulation pathways. While physiological HDL-C levels have antithrombotic properties, abnormally high levels may disrupt the balance between coagulation and fibrinolysis, increasing hemorrhagic risk.[27] This could help explain the significantly higher rates of sICH observed in patients with HDL-C levels exceeding 1.33 mmol/L in our study. Although high HDL levels were associated with worse outcomes in our study, we cannot exclude that this relationship may be influenced by the acute-phase response. HDL is a negative acute-phase reactant and may undergo functional alterations during systemic inflammation, potentially limiting its protective vascular effects. Therefore, its prognostic role in the context of acute stroke may differ from its traditional interpretation in chronic cardiovascular disease. From a clinical perspective, these insights highlight the need for more careful evaluation and monitoring in practice.

Another key finding of our study is that the impact of HDL-C levels on 90-day functional recovery was particularly pronounced in younger patients (<80 years) and those with a history of heart failure. This might suggest that specific subpopulations may be more susceptible to the detrimental effects of high HDL-C levels. The observed decline in functional recovery among these groups may reflect a combination of increased vascular permeability, impaired endothelial function, and heightened susceptibility to hemorrhagic complications, all of which can adversely impact post-stroke rehabilitation and neurological recovery. A notable aspect of our findings is that patients with history of atrial fibrillation who had high HDL-C levels exhibited a significantly increased risk of poor 90-day functional outcome. This might reinforce the hypothesis that HDL-C may exert different effects depending on the underlying stroke etiology. Notably, sex-specific differences were observed, with female experiencing a significantly higher risk of 90-day poor functional outcome and sICH HDL-C levels > 1.33 mmol/L. Our finding is consistent with the study by Ranasinghe et al.[28] Their work demonstrated that elevated HDL-C was paradoxically associated with adverse cardiovascular outcomes in women with symptoms of ischemic heart disease. This suggests that HDL-C may not confer uniform protection and that its role could be influenced by sex-specific biological factors.

Our study has several important strengths. First, it is based on a large, multicentre cohort of AIS patients treated with MT, enhancing the generalizability of the findings. Second, we employed robust statistical methods, including IPW and restricted cubic spline modeling, to minimize

confounding and capture non-linear associations between HDL-C levels and outcomes. Third, the comprehensive dataset allowed for detailed subgroup analyses, revealing clinically relevant interactions, including sex-specific differences, that add to the growing evidence questioning the uniformly protective role of HDL-C. Nonetheless, several limitations should be acknowledged. As a post hoc observational analysis, the possibility of residual confounding cannot be excluded despite adjustment for multiple covariates. HDL-C was measured only once upon admission, and dynamic changes over time were not captured, which may underestimate its temporal effects. Furthermore, functional aspects of HDL-C—such as its antioxidant or anti-inflammatory capacity—were not assessed, limiting insights into mechanistic pathways. The HDL-C threshold of 1.33 mmol/L was identified using a restricted cubic spline model within our dataset and has not been externally validated. While this method allowed us to detect a non-linear association and identify a meaningful inflection point in risk, the data-driven nature of this approach may introduce overfitting or bias. As with other studies in this field—including that of Sedghi et al.,[18] who also adopted a data-derived cut-off of ⩾1.15 mmol/L—the selected threshold should be interpreted as exploratory and hypothesis-generating. Further validation in independent cohorts is warranted to confirm its prognostic utility and generalizability. Another limitation of our study is the lack of comprehensive etiological classification. Due to the high proportion of patients treated via a drip-and-ship model (approximately 70%), the etiological work-up was often completed at the referring hospitals, and patients typically remained at the comprehensive stroke center for only 24–48 h. As a result, detailed information on stroke etiology, such as TOAST classification,[29] was not consistently available. This precluded stratification by stroke mechanism, which may have different biological interactions with lipid parameters. As this was a multicenter study, some degree of inter-site variability in laboratory measurements, imaging interpretations, and clinical data collection cannot be entirely excluded. Although all centers followed national standards and shared stroke management protocols, we acknowledge that local differences in procedures may have introduced unmeasured heterogeneity. Although we adjusted for baseline ASPECTS and NIHSS to account for initial infarct burden, we did not have access to quantitative infarct volume measurements either before or after thrombectomy, which limits the precision in assessing the relationship between HDL levels and infarct extent. This study specifically focuses on the acute phase of ischemic stroke and short-term functional outcomes. Therefore, the findings should not be generalized to long-term stroke management or rehabilitation outcomes beyond the early recovery period.

In conclusion, our study provides evidence that higher HDL-C levels are associated with poorer functional outcomes and increased rates of symptomatic HT following MT. These findings emphasize the importance of a more comprehensive approach to lipid management in stroke patients, considering not only HDL-C levels but also its functional properties. Further research is needed to better understand the underlying mechanisms and explore potential therapeutic strategies to optimize outcomes in this population.

Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: SB is a key opinion leader for RAPIDAI. All other authors have no conflicts of interests.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was partially funded by the Graham-Dixon charity.

Ethical approval

This study has obtained approval from the UK Health Regulator Authority (HRA) (HRA Reference No.: 275260). The study has also received confirmation of capacity and capability from the Imperial College Healthcare NHS Trust.

Informed consent

Informed consent was not a legal requirement as the research was carried out using data collected as part of routine care and any researchers outside the direct care team only had access to anonymized data.

ORCID iDs

Lucio D'Anna https://orcid.org/0000-0002-4349-3322
Matteo Foschi https://orcid.org/0000-0002-0321-7155
Kyriakos Lobotesis https://orcid.org/0000-0001-5093-9751
Edoardo Pirera https://orcid.org/0000-0003-3011-7405

Data availability

Data available upon reasonable request.

Supplemental material

Supplemental material for this article is available online.

References

1. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *J Am Coll Cardiol* 2014; 63. DOI: 10.1016/j.jacc.2013.11.002.
2. Glomset JA. The plasma lecithins:cholesterol acyltransferase reaction. *Journal of Lipid Research*; 9. Epub ahead of print 1968. DOI: 10.1016/s0022-2275(20)43114-1.
3. Dammerman M and Breslow JL. Genetic basis of lipoprotein disorders. *Circulation*; 91. Epub ahead of print 1995. DOI: 10.1161/01.cir.91.2.505.

4. Munshi A, Babu MS, Kaul S, et al. Association of LPL gene variant and LDL, HDL, VLDL cholesterol and triglyceride levels with ischemic stroke and its subtypes. *J Neurol Sci*; 318. Epub ahead of print 2012. DOI: 10.1016/j.jns.2012.04.006.
5. Qie R, Liu L, Zhang D, et al. Dose–response association between high-density lipoprotein cholesterol and stroke: a systematic review and meta-analysis of prospective cohort studies. *Prev Chronic Dis* 2021; 18: 200278.
6. Ko DT, Alter DA, Guo H, et al. High-density lipoprotein cholesterol and cause-specific mortality in individuals without previous cardiovascular conditions: the CANHEART study. *J Am Coll Cardiol*; 68. Epub ahead of print 2016. DOI: 10.1016/j.jacc.2016.08.038.
7. Madsen CM, Varbo A and Nordestgaard BG. Extreme high high-density lipoprotein cholesterol is paradoxically associated with high mortality in men and women: two prospective cohort studies. *Eur Heart J*; 38. Epub ahead of print 2017. DOI: 10.1093/eurheartj/ehx163.
8. Liu C, Dhindsa D, Almuwaqqat Z, et al. Association between high-density lipoprotein cholesterol levels and adverse cardiovascular outcomes in high-risk populations. *JAMA Cardiol* 2022; 7: 672.
9. Ali A, Obaid O, Akhtar N, et al. Association between HDL levels and stroke outcomes in the Arab population. *Sci Rep* 2024; 14: 3071.
10. Li X, Kong X, Yang C, et al. Global, regional, and national burden of ischemic stroke, 1990–2021: an analysis of data from the global burden of disease study 2021. *Eclinicalmedicine* 2024; 75: 102758.
11. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*; 50. Epub ahead of print December 2019. DOI: 10.1161/STR.0000000000000211.
12. D'Anna L, Dolkar T, Vittay O, et al. Comparison of Drip-and-Ship Versus Mothership Delivery Models of Mechanical Thrombectomy Delivery. *Stroke: Vasc Int Neurol*; 3. Epub ahead of print March 2023. DOI: 10.1161/SVIN.122.000690
13. Merlino G, Tereshko Y, Pez S, et al. Hyperdense middle cerebral artery sign predicts favorable outcome in patients undergoing mechanical thrombectomy. *J Thromb Thrombolysis* 2022; 55: 312–321.
14. Albers GW, Marks MP, Kemp S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *New Engl J Med* 2018; 378: 708–718.
15. Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *New Engl J Med* 2018; 378: 11–21.
16. Higashida RT, Furlan AJ, Roberts H, et al. Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke. *Stroke*; 34. Epub ahead of print 2003. DOI: 10.1161/01.str.0000082721.62796.09
17. von Kummer R, Broderick JP, Campbell BCV, et al. The heidelberg bleeding classification. *Stroke* 2015; 46: 2981–2986.
18. Sedghi A, Schreckenbauer S, Kaiser DPO, et al. Association of high-density lipoprotein cholesterol with reduced intracranial haemorrhage and favourable functional outcome after thrombectomy for ischaemic stroke: a propensity-matched analysis. *Neurol Res Pract* 2025; 7: 16.
19. Liu J, Wang Y, Jin Y, et al. Prediction of hemorrhagic transformation after ischemic stroke: development and validation study of a novel multi-biomarker model. *Front Aging Neurosci*; 13. Epub ahead of print 2021. DOI: 10.3389/fnagi.2021.667934
20. Ding J, Sigurdsson S, Garcia M, et al. Risk Factors Associated With Incident Cerebral Microbleeds According to Location in Older People. *JAMA Neurol*; 72. Epub ahead of print 2015. DOI: 10.1001/jamaneurol.2015.0174
21. Ding J, Sigurdsson S, Garcia M, et al. Risk factors associated with incident cerebral microbleeds according to location in older people: The age, gene/environment susceptibility (AGES)-Reykjavik study. *JAMA Neurol*; 72. Epub ahead of print 2015. DOI: 10.1001/jamaneurol.2015.0174
22. Luo Y, Chen J, Yan X-L, et al. Association of non-traditional lipid parameters with hemorrhagic transformation and clinical outcome after thrombolysis in ischemic stroke patients. *Curr Neurovasc Res*; 17. Epub ahead of print 2021. DOI: 10.2174/1567202617999210101223129
23. Li J, Long L, Zhang H, et al. Impact of lipid profiles on parenchymal hemorrhage and early outcome after mechanical thrombectomy. *Ann Clin Transl Neurol*; 10. Epub ahead of print 2023. DOI: 10.1002/acn3.51861.
24. von Eckardstein A, Nordestgaard BG, Remaley AT, et al. High-density lipoprotein revisited: biological functions and clinical relevance. *Eur Heart J* 2023; 44: 1394–1407.
25. Kontush A. HDL-mediated mechanisms of protection in cardiovascular disease. *Cardiovasc Res* 2014; 103: 341–349.
26. Chiesa ST and Charakida M. High-density lipoprotein function and dysfunction in health and disease. *Cardiovasc Drugs Ther* 2019; 33: 207–219.
27. van der Stoep M, Korporaal SJA and Van Eck M. High-density lipoprotein as a modulator of platelet and coagulation responses. *Cardiovasc Res* 2014; 103: 362–371.
28. Ranasinghe S, Cui Y, Muhyieddeen A, et al. Elevated high-density lipoprotein cholesterol and adverse outcomes in women with symptoms of ischemic heart disease. *Am Heart J Plus: Cardiol Res Pract* 2024; 40: 100376.
29. Adams HP, Bendixen BH, Kappelle LJ, et al. 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.