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Blood lipid levels and acute ischemic stroke: A meta-analysis

YaPing Huang *MM*, Yun Chen *MM*, Yan Wu *PhD*, Yan Wu *MM*, XinYi Dai *MM*, Juan Feng *MM*, Xia Li *MM*

Department of Neurology, Peking University Shougang Hospital, Beijing, China

Abstract

Objective: This meta-analysis aims to evaluate the association between lipid profiles and the risk of symptomatic intracerebral hemorrhage (sICH) when using thrombolysis to treat acute ischemic stroke (AIS). *Methods:* We included 11 studies from various geographic regions, focusing on patients treated with intravenous thrombolysis. Lipid parameters such as high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol, and triglycerides were examined. *Results:* While no discernible correlation was found between total cholesterol levels and sICH risk, two studies reported significantly lower LDL levels in patients with sICH. Additionally, lower HDL levels and elevated triglycerides correlated with increased sICH risk in specific studies.
Conclusion: These findings highlight the complex role of lipid profiles in stroke management, particularly in the context of thrombolytic therapy. Sensitivity analyses validated the robustness of the findings, suggesting that lipid management strategies should be individualized for AIS patients to balance ischemic and hemorrhagic risks. Future large-scale randomized trials are warranted to validate these findings.

Keywords: Acute ischemic stroke, lipid profiles, thrombolysis, symptomatic intracerebral hemorrhage, meta-analysis

INTRODUCTION

Acute ischemic stroke (AIS) is one of the main causes of morbidity and death globally, making a major contribution to the burden of illness worldwide.[1] It is well established that dyslipidemia, characterized by abnormal levels of blood lipids such as total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol, is essential to the pathogenesis of atherosclerosis and subsequent cardiovascular events, including stroke.[2] Dyslipidemia is one of the main risks for cardiovascular events, and its role in stroke remains a subject of significant research.[3] Studies indicate that abnormal lipid levels, particularly elevated LDL and triglycerides, are associated with poorer outcomes in patients who suffer from strokes.[4] Thus, understanding the relationship between blood lipid levels and the risk of AIS is crucial for developing effective preventive and therapeutic strategies.

Although numerous previous studies have examined the relationship between lipid profiles and stroke risk, the results remain inconsistent and, at times, contradictory.[5,6] The elevated total and LDL cholesterol levels have been reported to be positively correlated with an increased risk of AIS, while others report no significant association.[7-9] On the other hand, there has been inconsistent evidence linking elevated triglyceride and low HDL cholesterol to a higher risk of stroke.[10,11] These disparities may be explained by variations in the population characteristics, research designs, and the differences in lipid measuring techniques. To address these conflicting findings, a comprehensive meta-analysis is warranted. By synthesizing data from multiple studies, a meta-analysis might provide a more accurate approximation of the relationship between various lipid parameters and AIS risk.[12] Such an analysis is critical not only for clarifying the role of blood lipids in stroke pathophysiology but also for guiding clinical practice in lipid management for stroke prevention.

This meta-analysis intends to systematically assess the association between different blood lipid levels and the risk of AIS. Specifically, it will

Address correspondence to: Xia Li, Department of Neurology, Peking University Shougang Hospital, No.9 Jinyuanzhuang Road, Bajiao Street, Shijingshan District, Beijing, 100043 China. Email: xia-li@ldy.edu.rs

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assess the impact of total cholesterol, triglycerides, LDL cholesterol, and HDL cholesterol on AIS incidence. By integrating data from diverse cohorts, this study seeks to elucidate the role of lipid profiles in AIS and contribute to a more nuanced understanding of stroke prevention strategies.

METHODS

Search strategy

The Meta-analysis was carried out in compliance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13] We looked through Embase, PubMed, the Cochrane Library, Web of Science, and Scopus websites from inception to 20th August 2024. Relevant MeSH terms and keywords were combined, including transient ischemic attack (TIA), recombinant tissue plasminogen activator (rt-PA), AIS, intravenous thrombolytic therapy (IVT), National Institutes of Health Stroke Scale (NIHSS), and symptomatic intracerebral hemorrhage (sICH). Time, nation, or language constraints were not further enforced; nonetheless, the term "human only" was limited to participants. To find further relevant publications, we also manually went through each study's reference list.

Selection criteria

Literature inclusion criteria

(1) Study type: Cohort studies, case-control studies, cohort studies, randomized controlled trials (RCTs), and multicenter retrospective studies that provide sufficient data for the analysis. Only studies with full-text availability that report relevant outcomes are included.
(2) Study subjects: Studies involving adult individuals with AIS, who have undergone intravenous thrombolysis or endovascular treatment. Studies that assess the relationship between lipid profiles, such as cholesterol, triglycerides, and other lipid-related factors, and outcomes like symptomatic intracerebral hemorrhage or other clinical outcomes after thrombolysis.
(3) Intervention measures: Research focused on lipid levels, including serum lipid levels, cholesterol, triglycerides, and other related lipid parameters, in the context of their effect on thrombolysis outcomes.
(4) Outcome measures: Studies that report on clinical outcomes such as symptomatic intracerebral hemorrhage, stroke mortality, or overall functional outcomes post-thrombolysis or endovascular treatment.

Literature exclusion criteria

(1) Studies that are not case-control trials; (2) Studies with incomplete and the data cannot be used; (3) Duplicate studies, with preference given to the most recent study; (4) Studies where the evaluation of research efficacy is not significant; (5) Review articles; (6) Clinical case reports.

Quality assessment and data extraction

(1) Bias risk assessment: The Cochrane Handbook for Systematic Reviews of Interventions' "Risk of Bias" tool (version 5.3) was used to assess the risk of bias in the included studies.[14] (2) Literature screening and data extraction: Data extraction, quality evaluation, and literature screening were completed individually by two researchers. To verify correctness, they double-checked the retrieved data. Disagreements were settled by conversation or by seeking advice from a different researcher. NoteExpress literature management software and Excel were applied to data management and extraction. If any data from the included studies were incomplete, the corresponding authors were contacted for additional information. The data extraction focused on the following aspects: (1) Basic details, such as the number of instances, author, and publishing date; (2) Intervention measures, including treatment plan and duration; (3) Outcome indicators.

Sensitivity analysis

In the meta-analysis, sensitivity analyses were carried out to assess the robustness of the pooled effect estimates and to determine if any single study had a disproportionate impact on the total outcomes. This was done by systematically removing each research individually from the analysis and recalculating the pooled WMD and CIs. This method seeks to identify possible sources of heterogeneity, evaluate the result of individual studies on the overall meta-analytic conclusions, and validate the stability of the results. The findings of the sensitivity analyses were plotted for different lipid parameters (e.g., total cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol), displaying how the exclusion of each study affected the pooled estimates. The

consistency in the results across these analyses suggests that no single study substantially altered the pooled effect size, and the meta-analysis findings are robust to the inclusion or exclusion of individual studies.

Statistical analysis

For meta-analysis, RevMan5.3 software was acquired from the Cochrane Collaboration Network. In RevMan5.4, the average and standard deviation of the study group's and the control group's hospitalization times were entered for analysis. The WMD was used as the effect index, and the 95% confidence interval (95%CI) was computed. First, to ascertain if there is heterogeneity among the studies, the $\chi 2$ test is used. The included studies are deemed homogenous if $P>0.05$ and $I2<50\%$, and the updated impact model may be gathered for meta-analysis. The random effect model is used if $P<0.05$, $I2\geq 50\%$, and the combined effect is required to assess the study's homogeneity; descriptive analysis is used instead of meta-analysis if $P<0.05$ and the reason for heterogeneity cannot be identified. To further examine the publishing bias of the contained papers, create an inverted funnel diagram. To determine if a funnel chart is asymmetrical, use Eggers' test. The TrimandFill technique may be used to adjust the impact of a probable publication deviation and fix the funnel graphic whenever the p value of this test is less than 0.1.

RESULTS

Literature search

The outcomes of the process of choosing studies were shown in Figure 1. The first search yielded 3020 items in total, including 368 Medline articles and 2652 Cochrane papers. Fourteen possibly suitable papers with complete texts were chosen after duplicate research were eliminated. Following thorough assessments, 11 papers were chosen for the final meta-analysis. There were no fresh, qualifying research found when the reference lists of these studies were manually searched.

Study characteristics

The meta-analysis included a total of 11 studies

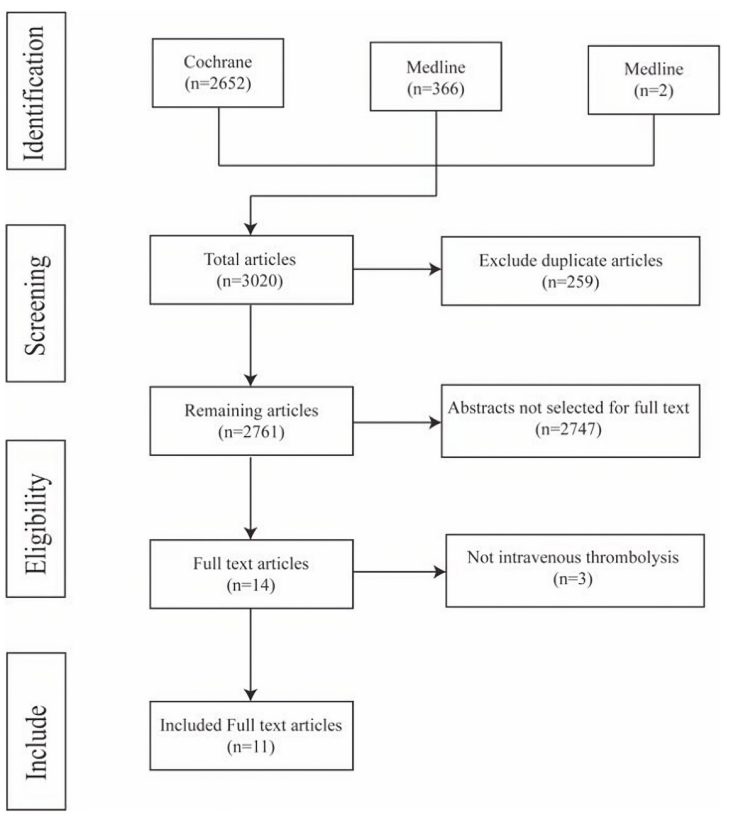

Figure 1. The flow diagram for identifying eligible studies.

carried out across various geographic regions, encompassing both European and Asian populations. The studies primarily focused on individuals with AIS treated with IVT, highlighting the diversity in demographic and clinical characteristics. Participants' ages varied from 60.8 to 82.8 years old on average, reflecting a predominantly elderly cohort. Gender distribution varied across studies, with the proportion of male participants ranging from 51.7% to 82.8%. Sample sizes were heterogeneous, with participant numbers spanning from 60 to 1847, demonstrating variability in study design and power. Most of the included studies reported on the administration of rt-PA, with doses varying between 0.6 and 0.9 mg/kg, while some studies did not specify the rt-PA dose. The NIHSS scores, a measure of stroke severity, were reported in most studies, with sICH being assessed through magnetic resonance imaging (MRI) and/or computed tomography (CT). The time from onset to admission was generally within 4.5 hours, adhering to the recommended therapeutic window for IVT. Several studies provided a clear definition for sICH, employing criteria such as neurological deterioration following rt-PA therapy, as defined by the NINDS/Cochrane protocol, or the SITS-MOST criteria, which consider significant hematoma formation on imaging as a defining feature of sICH. The presence of sICH in the same anatomical region as the ischemic event was inconsistently reported, indicating a potential area for further research. These results can be seen in Table 1.

Collectively, these studies offer a thorough overview of the clinical characteristics and treatment outcomes of AIS patients undergoing IVT, emphasizing the need for standardized definitions and protocols to improve comparability and generalizability of findings in future meta-analyses.

RESULTS

Total cholesterol level

The meta-analysis assessed the effect of various interventions on total cholesterol levels across eight studies, represented by a WMD with corresponding 95% CIs. When comparing the intervention groups to the control groups, the pooled effect size for total cholesterol levels showed a non-significant decrease of -1.27 mg/dL (95% CI: -6.58 to 4.04, p = 0.377), suggesting that there was no statistically meaningful change in total cholesterol levels. The individual studies demonstrated varying effects on total cholesterol levels. Kamal *et al*.[23] reported a positive WMD of 11.30 mg/dL (95% CI: -0.14 to 22.74), suggesting a potential increase in total cholesterol, while Yuan *et al*.[25] observed a decrease of -10.20 mg/dL (95% CI: -22.62 to 2.22). Nardi *et al*.[19] and Lin *et al*.[20] also showed negative WMDs of -3.48 mg/dL (95% CI: -12.86 to 5.91) and -9.00 mg/dL (95% CI: -30.66 to 12.66), respectively, although these results were not statistically significant. The heterogeneity among the included studies was minimal (I^2 = 6.9%, p = 0.377), indicating a low level of variation in the effect sizes across the studies. This suggests that the interventions' effects on total cholesterol were relatively consistent across different populations and settings, with no single study disproportionately influencing the overall outcome.

LDL cholesterol level

The meta-analysis evaluated the effect of various interventions on LDL cholesterol levels across 12 studies, as represented by WMD with corresponding 95%CI. The pooled analysis demonstrated a noteworthy reduction in LDL cholesterol levels (WMD = -3.75 mg/dL, 95% CI: -7.01 to -0.49, p = 0.116), indicating that the interventions collectively contributed to a modest decrease in LDL levels compared to control groups. Individual studies demonstrated variability in the magnitude and direction of the effects on LDL cholesterol levels. For example, Kamal *et al*.[23] reported a considerable increase in LDL levels (WMD = 11.50 mg/dL, 95% CI: 1.01 to 21.99), whereas Lin *et al*.[20] observed a substantial reduction (WMD = -17.00 mg/dL, 95% CI: -32.86 to -1.14). Similarly, Nardi *et al*.[19] and Yuan *et al*.[25] showed decreases of -1.93 mg/dL (95% CI: -8.96 to 5.10) and -5.49 mg/dL (95% CI: -19.09 to 8.11), respectively, although these findings were not statistically significant. The heterogeneity analysis revealed moderate variability among the included studies (I^2 = 35.3%, p = 0.116), recommending that differences in study characteristics or populations might contribute to the observed effect size variations. This level of heterogeneity indicates that while the interventions generally reduce LDL cholesterol, the extent of this effect is not uniform across all studies.

HDL cholesterol level

The meta-analysis investigated the impact of

Table 1: Characteristics of the included studies

Study (Publication Years)	Country (Continents)	Mean age (Years)	Male (%)	Sample size	Types of Participants	rt-PA dose (mg/Kg)	NIHSS	Time from onset to admission	sICH assessed by CT	sICH assessed by MRI	Clear definition for sICH	sICH prove to occur in the same area as the ischemic event
Montaner[15] (2008)	Spain (Europen)	71.9	51.7	60[a]	AIS treated by IVT	NA	All:17(5.93)	< 3h	NA	NA	—	–
Uyttenboogaart[16] (2008)	Netherlands (Europen)	68	54	252[b]	AIS treated by IVT	NA	sICH: 14 (8.89) no sICH: 12 (6.67)	< 4.5h	+	–	+ 1	–
Makihara[17] (2012)	Japan (Asia)	70.8	65	489[c]	AIS treated by IVT	0.6	All:12(6.67)	< 3h	+	+	+ 2	–
Rocco[18] (2012)	Germany (Europen)	73	52.8	1066	AIS treated by IVT	NA	sICH:15(6.67) no sICH: 12(7.41)	NA	+	–	+ 3	–
Nardi [19] (2012)	Multicenter (Europen)	70	56.8	1847[d]	AIS treated by IVT	NA	All:11(7.41)	NA	NA	NA	+ 4	–
Lin[20] (2018)	Taiwan (Asia)	68	56	229	AIS treated by IVT	0.6-0.9	sICH:16(6.67) no sICH: 13(7.41)	< 3h	+	–	+ 5	–
Che[21] (2024)	China (Asia)	63	67.8	590	AIS treated by IVT	NA	sICH:18.33(19.66) no sICH: 18(20.07)	NA	+	+	+ 2	–
Yuan[22] (2020)	China (Asia)	60.8	82.8	151	AIS treated by IVT	0.9	sICH:11(5.77) no sICH: 9.67(3.75)	< 4.5h	+	NA	+ 2	–
Kamal[23] (2020)	American (North America)	71.4	51.5	794	AIS treated by IVT	NA	sICH:14.2(5.4) no sICH: 11.2(6.5)	< 4.5h	NA	NA	+ 1	–
Xue[24] (2022)	China (Asia)	64	65.4	1293	AIS treated by IVT	0.6-09	sICH:14(6.2) no sICH: 7.67(5.94)	< 6h	+	NA	+ 1	–
Yuan[25] (2024)	China (Asia)	67.3	65.6	957	AIS treated by IVT	NA	All:7(6.68)	< 4.5h	+	+	+ 2	–

Note: "+" indicates a fulfilled feature, "–" indicates a non-fulfilled characteristic, and "NA" indicates not available. TIA is for transient ischemic attack; AIS stands for acute ischemic stroke; rt-PA stands for recombinant tissue plasminogen activator; "A" total of 145 individuals were assessed for the correlation between sICH and lipid profile; NIHSS is an acronym for the National Institutes of Health Stroke Scale."b" Among 301 patients, 252 were evaluated for the association between sICH and lipid profile. "c" Among 600 patients, 489 were evaluated for the association between sICH and lipid profile. "1847 patients out of 2485 were assessed for a potential correlation between sICH and lipid profile. "1 "sICH defined as a neurological deterioration within 48 h following rt-PA therapy with hematoma on CT scan."2 "Symptomatic ICH was defined according to the NINDS/ Cochrane protocol as any ICH associated with neurological deterioration corresponding to an increase of >=1 point from the baseline NIHSS score, and according to the SITS-MOST protocol as parenchymal hemorrhage type II combined with an increase of >= 4 points from the baseline NIHSS score."3 "sICH was assessed using the slightly modified European Cooperative Acute Stroke Study (ECASS II) criteria (any haemorrhage with neurological deterioration, as indicated by an NIHSS score 6 4 points higher than the value at baseline, or any haemorrhage leading to death)."4) Use the definitions of sICH provided by NINDS 1 and ECASS 2, since the former is the most widely used and therefore permits cross-study comparisons, while the latter is the one with the best predicted result. "5" sThe development of a hematoma on a noncontrast computed tomography scan of the brain and an increase in the NIHSS score of more than four points within 36 hours of beginning rt-PA treatment were the criteria used to classify ICH as a neurological deterioration.

different interventions on HDL cholesterol levels across seven studies, as presented by WMD with corresponding 95% CI. The overall pooled analysis showed a non-significant reduction in HDL cholesterol levels (WMD = -1.39 mg/dL, 95% CI: -3.99 to 1.21, p = 0.063), indicating that the interventions did not provide a considerable change in HDL levels compared to the control groups. Individual studies exhibited diverse effects on HDL cholesterol levels. Uyttenboogaart *et al*.[16] stated a considerable decrease in HDL cholesterol (WMD = -7.73 mg/dL, 95% CI: -14.50 to -0.96), suggesting a potential adverse effect of the intervention on HDL levels. In contrast, Nardi *et al*.[19] observed a non-significant increase (WMD = 2.72 mg/dL, 95% CI: -1.06 to 6.50). Other studies, such as Makihara *et al*.[17] and Lin *et al*.[20], reported minimal changes with WMDs of 0.78 mg/dL (95% CI: -9.02 to 10.58) and -1.00 mg/dL (95% CI: -10.56 to 8.56), respectively. Moderate heterogeneity was observed among the included studies (I^2 = 49.7%, p = 0.063), indicating variability in the intervention effects across different study populations and methodologies. This level of heterogeneity suggests that the differences in study designs, intervention protocols, and patient characteristics might have influenced the outcomes related to HDL cholesterol levels.

Triglycerides

The meta-analysis examined the result of various interventions on triglyceride levels across eight studies, represented by WMD and 95%CI. The overall pooled analysis indicated a non-significant reduction in triglyceride levels (WMD = -4.55 mg/dL, 95% CI: -9.91 to 0.81, p = 0.068). This suggests that the interventions had a marginal impact on lowering triglycerides compared to control groups. The results from individual studies displayed considerable variability in their impact on triglyceride levels. Uyttenboogaart *et al*.[16] reported a substantial increase in triglycerides (WMD = 62.00 mg/dL, 95% CI: -20.78 to 144.78), though this result was not statistically significant. Conversely, Che *et al*.[21] observed a notable reduction in triglyceride levels (WMD = -83.26 mg/dL, 95% CI: -160.25 to -6.27), suggesting a potentially beneficial effect of the intervention. Similarly, Yuan *et al*.[25] reported a decrease of -22.99 mg/dL (95% CI: -39.16 to -6.82), indicating a significant reduction in triglyceride levels. Other studies, such as Makihara *et al*.[17] and Nardi *et al*.[19], demonstrated minimal changes with WMDs of -0.89 mg/dL (95% CI: -7.84 to 6.06) and -6.20 mg/dL (95% CI: -18.14 to 5.74), respectively, without reaching statistical significance. The heterogeneity among the included studies was moderate (I^2 = 46.8%, p = 0.068), indicating variability in the intervention effects on triglyceride levels. This suggests that differences in study designs, populations, or intervention protocols may have contributed to the observed variation in triglyceride outcomes across studies. These results can be seen in Figure 2.

Association between lipid profiles and risk of sICH following thrombolysis

Table 2 presents a comparison of lipid profiles between individuals with and without sICH following thrombolysis. Among the total cholesterol levels, no notable variations were found between individuals with sICH and those without, as indicated by the p-values greater than 0.05 across all studies (p-values ranging from 0.298 to 0.988).

For LDL cholesterol levels, significant differences were further observed in two studies. The study by Uyttenboogaart *et al*.[16] outlined a significantly lower LDL cholesterol level in patients with sICH compared to those without sICH (116.01 ± 30.94 vs. 119.88 ± 38.67, p = 0.03). Similarly, Yuan *et al*.[22] observed a significantly lower LDL cholesterol level in patients with sICH (93.58 ± 35.58 vs. 114.08 ± 37.12, p = 0.005). These results point to a possible correlation between lower LDL cholesterol levels and the occurrence of sICH.

For HDL cholesterol levels, a significant difference was found in the study by Che *et al*.[21], where individuals with sICH had lower HDL levels compared to those without (49.11 ± 35.96 vs. 58.01 ± 68.83, p = 0.030). Triglyceride levels were considerably higher in individuals with sICH in the study by Uyttenboogaart *et al*.[16] (221.43 ± 150.57 vs. 159.43 ± 97.43, p = 0.02), indicating that elevated triglycerides might be connected to a higher risk of sICH.

Taken together, significant associations between lower LDL cholesterol levels and the occurrence of sICH were found in two studies, while one study identified lower HDL cholesterol and another elevated triglyceride levels as significant factors in individuals with sICH. These findings suggest that certain lipid profile parameters may be associated with the risk of sICH in individuals undergoing thrombolysis for AIS.

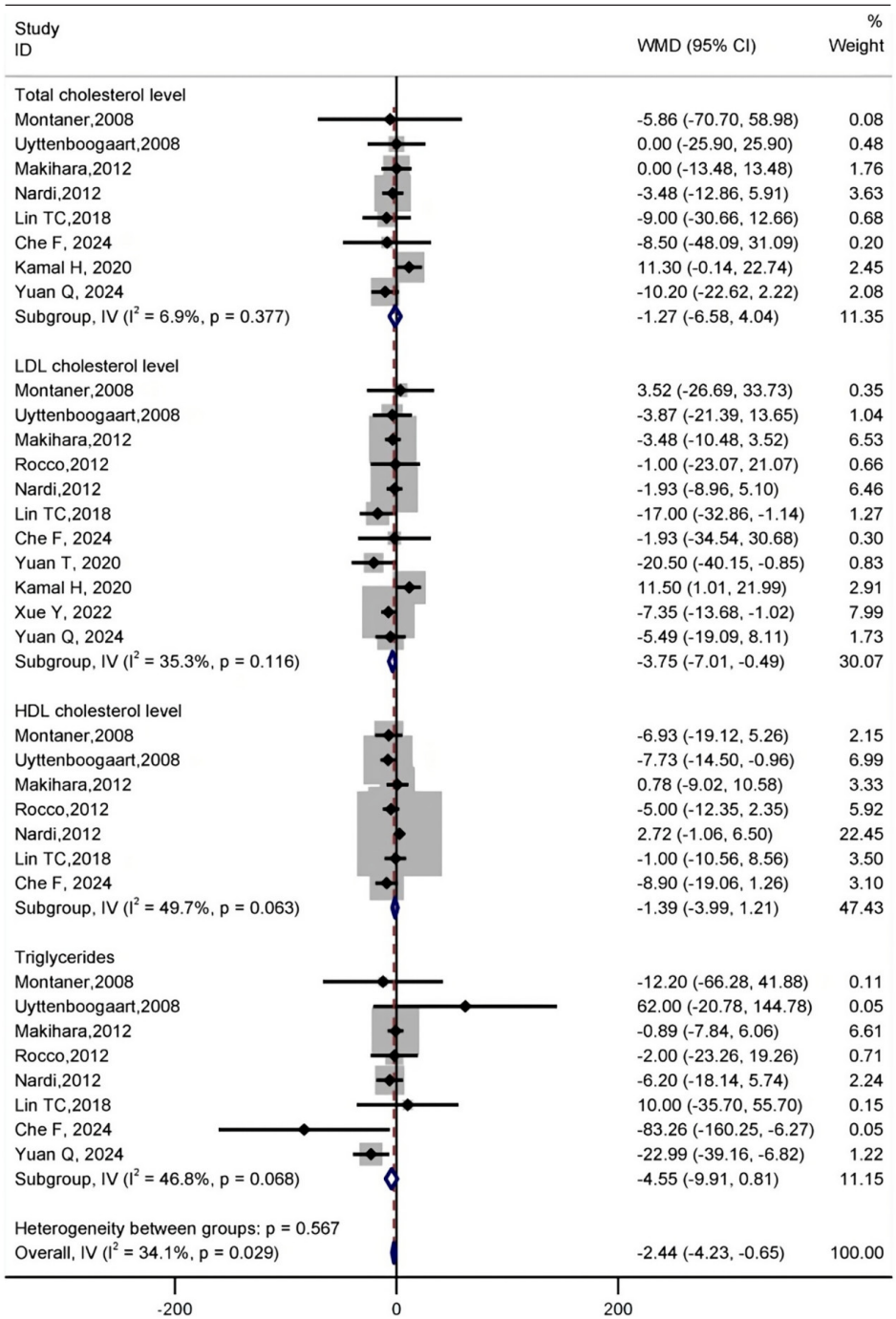

Figure 2. Forest plot of the WMD in lipid levels between patients with and without symptomatic intracerebral hemorrhage following intravenous thrombolysis in AIS. The plot presents the pooled WMD and 95% CIs for total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride levels. Each horizontal line represents a 95% CI, and each gray box's size indicates the study's relative weight inside the meta-analysis. The diamond shapes symbolize the overall effect estimate for each lipid parameter, with the width of the diamond corresponding to the 95% CI. Studies are grouped by lipid subtype, and the overall effect is represented at the bottom of the plot. The I^2 statistic was used to evaluate statistical heterogeneity between research, with the corresponding p-values reported. The analysis demonstrates a statistically significant overall effect for total cholesterol, HDL cholesterol, and LDL cholesterol levels, as indicated by the WMDs crossing the null line (0), while triglyceride levels showed heterogeneity but no significant association. P values and I^2 values for each subgroup and overall are provided to assess heterogeneity. Inverse variance (IV)

Table 2: Comparison of lipid profiles in individuals with and without sICH

	sICH		Absence of sICH		P values
	n	mean (SD)	n	mean (SD)	
Total cholesterol level					
Montaner[15], 2008	5	215.94	55	221.8	0.86
Uyttenboogaart[16], 2008	13	197.22(46.40)	239	197.22(46.40)	0.9
Makihara[17], 2012	93	189.53(63.29)	396	189.53(41.09)	0.988
Nardi[19], 2012	87	174.015(43.69)*	1760	177.49(42.15)*	0.32
Lin[20], 2018	14	176(40)	215	185(41)	0.75
Che[21], 2024	73	180.98(156.61)*	517	189.48(192.96)*	0.373
Kamal[23], 2020	51	174.4(40.1)	743	163.1(43.3)	0.061
Yuan[25], 2024	56	166.86(46.05)*	901	177.06(45.16)*	0.298
LDL cholesterol level					
Montaner[15], 2008	5	139.05	55	135.53	0.82
Uyttenboogaart[16], 2008	13	116.01(30.94)	239	119.88(38.67)	0.03
Makihara[17], 2012	93	110.81(30.16)	396	114.29(34.36)	0.38
Rocco[18], 2012	18	114(47.41)	644	115(35.56)	0.981
Nardi[19], 2012	87	89.33(32.09)	1760	91.26(42.92)	0.601
Lin[20], 2018	14	102(29)	215	119(34)	0.12
Che[21], 2024	73	120.65(128.38)*	517	122.58(162.41)*	0.626
Yuan[22], 2020	14	93.58(35.58)*	137	114.08(37.12)*	0.005
Kamal[23], 2020	51	113.3 (36.9)	743	101.8 (38.2)	0.061
Xue[24], 2022	33	106.34(18.17)*	1260	113.69(22.81)*	0.155
Yuan[25], 2024	56	112(50.75)*	901	117.49(44.18)*	0.23
HDL cholesterol level					
Montaner[15], 2008	5	49.7	55	56.63	0.27
Uyttenboogaart[16], 2008	13	38.67(11.60)	239	46.40(19.34)	0.73
Makihara[17], 2012	93	51.94(45.74)	396	51.16(31.40)	0.824
Rocco[18], 2012	18	39(15.78)	652	44(12.59)	0.081
Nardi[19], 2012	87	58.01(17.4)	1760	55.29(20.11)	0.314
Lin[20], 2018	14	44(18)	215	45(12)	0.843
Che[21], 2024	73	49.11(35.96)*	517	58.01(68.83)*	0.030
Triglycerides					
Montaner[15], 2008	5	135.94	55	148.14	0.66
Uyttenboogaart[16], 2008	13	221.43(150.57)	239	159.43(97.43)	0.02
Makihara[17], 2012	93	118.58(30.09)	396	119.47(33.63)	0.891
Rocco[18], 2012	33	101(61.48)	852	103(51.11)	0.705
Nardi[19], 2012	87	101.86(55.79)§	1760	108.06(48.71)§	0.388
Lin[20], 2018	14	135(85)	215	125(77)	0.76
Che[21], 2024	73	173.59(286.97)§	517	256.85(463.22)§	0.688
Yuan[25], 2024	56	95.59(59.83)§	901	118.58(61)§	0.171

Note: * Multiply by 38.67 to convert to mg/dl; § multiply by 88.57 to convert to mg/dl.

Sensitivity analysis

Sensitivity analyses were performed by methodically removing each included trial from the meta-analysis in order to assess the robustness of the pooled effect estimates. This method evaluates the impact of individual studies on the total outcomes, pinpoints possible sources of heterogeneity, and confirms the consistency of the conclusions. Figure 3A-D illustrate the results of the sensitivity analyses for different outcome measures. For each analysis, the omission of individual studies did not substantially alter the pooled effect size, as evidenced by the narrow confidence intervals (CIs) and minimal shifts in the point estimates. This consistency shows that no one research had a disproportionate impact on the meta-analysis findings, indicating their robustness. Overall, these sensitivity analyses confirm the robustness and reliability of the meta-analysis findings, suggesting that the observed associations are consistent and not unduly affected by the inclusion or exclusion of specific studies. This thorough validation enhances the confidence in the conclusions drawn from this meta-analysis.

DISCUSSION

The meta-analysis presented evaluates the effects of various interventions on lipid profiles, including total cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol, across multiple studies. The findings of this meta-analysis provide some interesting associations in the relationship between lipid profiles and the risk of sICH following thrombolysis for AIS. While total cholesterol levels did not demonstrate a significant association with the occurrence of sICH, both LDL cholesterol and triglyceride levels were found to be associated with an increased risk of sICH in specific studies. These findings offer nuanced perspectives on lipid management in stroke patients, particularly in the context of thrombolytic therapy.

The pooled analysis showed a non-significant reduction in total cholesterol (-1.27 mg/dL, 95% CI: -6.58 to 4.04, p = 0.377). This suggests that, across the studies included, the interventions did not produce a considerably change in total cholesterol levels in contrast with controls. Heterogeneity was low ($I^2 = 6.9\%$). In the context

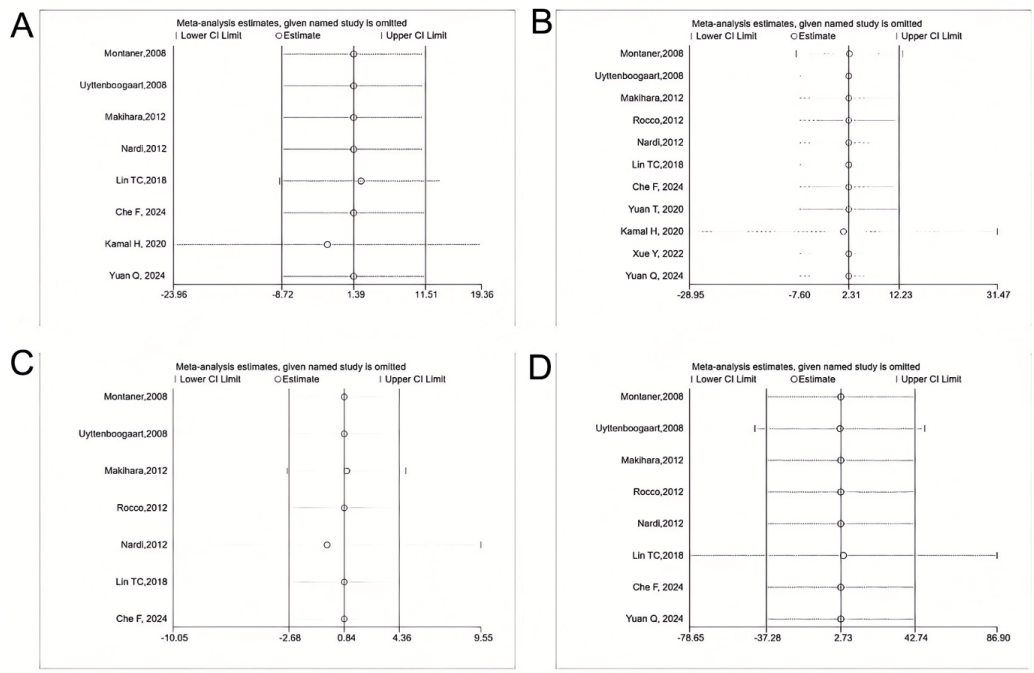

Figure 3. Sensitivity analyses of the meta-analysis investigating how lipid profiles affect the results of intravenous thrombolysis for AIS. Panels A-D depict the results of the "leave-one-out" sensitivity analyses for total cholesterol (A), LDL cholesterol (B), HDL cholesterol (C), and triglycerides (D), respectively. Each point on the plot represents the pooled effect size (WMD) after the exclusion of one study, with the corresponding 95% CI. The minimal changes in the point estimates and narrow CIs across the analyses indicate that the overall results are robust and not influenced by just one research. These analyses confirm the stability of the observed associations between lipid levels and post-thrombolysis outcomes, supporting the reliability of the meta-analytic conclusions.

of AIS and cardiovascular disease management, many existing studies have shown that lipid-lowering interventions, particularly statin therapy, effectively reduce total cholesterol.[26,27] However, the non-significant change here might suggest that the interventions in these studies either did not focus on statins or were less effective in patients with AIS. Moreover, the modest effect might be due to the inclusion of non-pharmacological or less intensive interventions, which contrasts with stronger evidence of statins effectively lowering total cholesterol in secondary stroke prevention.

The pooled analysis showed a considerable reduction in LDL cholesterol levels in individuals who experienced sICH compared to those who did not, with two studies[16,22] identifying lower LDL levels as a significant factor. This suggests that while elevated LDL cholesterol is traditionally associated with atherosclerosis and ischemic stroke risk, lower LDL levels in the context of thrombolysis may predispose patients to hemorrhagic complications. The observed reduction is consistent with findings from studies on statins, which significantly lower LDL cholesterol and reduce stroke recurrence. However, the effect size here is smaller than in studies focused solely on statin interventions, suggesting that the interventions may have included non-statin therapies or were less intensive. These results emphasize the complex interplay between lipid management and hemorrhagic risk, underscoring the need for careful monitoring of LDL levels in stroke patients undergoing thrombolysis.

HDL cholesterol levels were found to be considerably lower in individuals with sICH in one study.[21] HDL is known for its protective role against atherosclerosis through reverse cholesterol transport and anti-inflammatory effects.[28,29] The association between low HDL levels and sICH may suggest that inadequate HDL-mediated protective mechanisms could exacerbate hemorrhagic risks following thrombolysis. However, this association was only identified in one study, warranting further investigation into the potential role of HDL in mitigating hemorrhagic transformation in stroke patients.

Triglyceride levels were also found to be considerably elevated in patients with sICH in the study by Uyttenboogaart *et al*.[16] Hypertriglyceridemia is often linked to metabolic syndrome and a higher risk of heart attacks, strokes, and other cardiovascular events. The observed association between elevated triglycerides and sICH could reflect a broader metabolic dysregulation that increases vulnerability to hemorrhagic complications following thrombolysis. This finding suggests that triglycerides, along with other lipid parameters, should be closely monitored in AIS patients undergoing thrombolysis, particularly those with metabolic syndrome or other risk factors for dyslipidemia. However, like HDL, triglycerides are often secondary targets in lipid-lowering interventions, with most research focused on LDL.[30] Existing study suggest that while statins may reduce triglycerides, the effect is generally modest unless combined with fibrates or omega-3 fatty acids.[31]

Additionally, the findings of this meta-analysis have significant implications for lipid management in AIS patients receiving thrombolytic therapy. While traditional cardiovascular guidelines emphasize the reduction of LDL cholesterol to prevent atherosclerotic events, these findings suggest that overly aggressive LDL lowering in the setting of thrombolysis may increase the risk of hemorrhagic complications. Traditional stroke prevention guidelines emphasize lowering LDL cholesterol, particularly through statin therapy, to reduce the risk of ischemic stroke.[32] However, recent studies suggest that excessively low LDL cholesterol levels may compromise vascular health, potentially increasing the risk of hemorrhagic complications like sICH.[33,34] The findings from Uyttenboogaart *et al*.[16] and Yuan *et al*.[22] are consistent with these emerging concerns, recommending that very low LDL cholesterol could be a risk factor for sICH. The observation that lowers LDL cholesterol levels are associated with sICH is significant, as it points to a potential need for re-evaluating LDL targets in high-risk populations undergoing thrombolytic therapy. While lowering LDL remains crucial for ischemic stroke prevention, these findings suggest that extremely low levels might pose a risk in the context of acute treatments like thrombolysis. Moreover, HDL cholesterol is widely recognized for its protective cardiovascular properties, and reduced risk of ischemia events is often linked to higher levels of HDL. Research also suggests that HDL may help preserve endothelial function and reduce inflammation, which could mitigate the risk of hemorrhagic complications.[35,36] The observed lower HDL cholesterol levels in sICH patients reinforce the idea that HDL may assume a defensive function in preventing hemorrhagic transformation after thrombolysis. These findings align with broader literature, suggesting that enhancing HDL function could be beneficial in stroke management, particularly in reducing the

risk of sICH. Clinicians should weigh the benefits of lipid-lowering therapies against the potential risk of sICH, particularly in patients with already low LDL or HDL levels. Additionally, elevated triglycerides should be considered a potential risk factor for sICH, and strategies to manage hypertriglyceridemia should be incorporated into the broader management of stroke patients.[6]

There are several limitations to this analysis. First, significant heterogeneity was observed in some of the analyses, particularly for HDL cholesterol and triglycerides, suggesting variability in patient populations, study designs, and lipid measurement methodologies. Second, most of the listed research were observational in nature, limiting the ability to establish causality between lipid levels and sICH risk. Future randomized controlled trials analyzing the impacts of lipid-modifying therapies on both ischemic and hemorrhagic outcomes in AIS patients undergoing thrombolysis are warranted to clarify these associations. The meta-analysis supports the idea that while interventions evaluated in these studies do have some beneficial effects on lipid profiles, the results are modest compared to those seen with statins in other studies. Given the role of cholesterol management in preventing recurrent strokes, these findings emphasize the need for robust lipid-lowering strategies, especially targeting LDL cholesterol, which has shown the most consistent and significant reductions across existing research. Future studies may benefit from focusing on more intensive or combination therapies to achieve larger and clinically meaningful reductions in lipid levels for AIS patients.

In conclusion, this meta-analysis highlights the complex relationship between lipid profiles and the risk of sICH following thrombolysis in AIS patients. Lower LDL and HDL cholesterol levels, together with higher triglycerides, were shown to be associated with a heightened risk of sICH in certain investigations. These findings highlight the need for individualized lipid management strategies in stroke individuals, balancing the prevention of ischemic events with the risk of hemorrhagic complications.

DISCLOSURE

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