Original Research Article

EUROPEAN STROKE JOURNAL

European Stroke Journal
2023, Vol. 8(1) 294–300

DOI: 10.1177/23969873221148229
journals.sagepub.com/home/eso
SAGE

Association of cholesterol levels with hemorrhagic transformation and cerebral edema after reperfusion therapies

Irene Escudero-Martínez[1,2], Magnus Thorén[3,4], Marius Matusevicius[3,5], Charith Cooray[3,5], Andrea Zini[6], Christine Roffe[7], Danilo Toni[8], Georgios Tsivgoulis[9], Peter Ringleb[10], Nils Wahlgren[3,5] and Niaz Ahmed[3,5]

Abstract

Background: The association between cholesterol levels and cerebral edema (CED) or hemorrhagic transformation (HT) as an expressions of blood-brain barrier (BBB) dysfunction after ischemic stroke is not well established. The aim of this study is to determine the association of total cholesterol (TC) levels with the incidence of HT and CED after reperfusion therapies.

Methods: We analyzed SITS Thrombolysis and Thrombectomy Registry data from January 2011 to December 2017. We identified patients with data on TC levels at baseline. TC values were categorized in three groups (reference group ⩾200 mg/dl). The two primary outcomes were any parenchymal hemorrhage (PH) and moderate to severe CED on follow up imaging. Secondary outcomes included death and functional independence (mRS 0–2) at 3 months. Multivariable logistic regression analysis adjusted for baseline factors including statin pretreatment was used to assess the association between TC levels and outcomes.

Results: Of 35,314 patients with available information on TC levels at baseline, 3372 (9.5%) presented with TC levels ⩽130 mg/dl, 8203 (23.2%) with TC 130–200 mg/dl and 23,739 (67.3%) with TC ⩾200 mg/dl. In the adjusted analyses, TC level as continuous variable was inversely associated with moderate to severe CED (OR 0.99, 95% CI 0.99–1.00, $p = 0.025$) and as categorical variable lower TC levels were associated with a higher risk of moderate to severe CED (aOR 1.24, 95% CI 1.10–1.40, $p = 0.003$). TC levels were not associated with any PH, functional independence, and mortality at 3 months.

Conclusions: Our findings indicate an independent association between low levels of TC and higher odds of moderate/severe CED. Further studies are needed to confirm these findings.

Keywords

Cholesterol levels, cerebral edema, thrombolysis, reperfusion, recanalization, intracerebral hemorrhage

Date received: 15 September 2022; accepted: 13 December 2022

[1]Department of Neurology, Hospital Universitari i Poltècnic La Fe, Valencia, Spain
[2]Neurovascular Research Laboratory, Instituto de Biomedicina de Sevilla-IBiS, Sevilla, Spain
[3]Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
[4]Department of Neurology, Danderyd Hospital, Stockholm, Sweden
[5]Department of Neurology, Karolinska University Hospital, Stockholm, Sweden
[6]IRCCS Istituto delle Scienze Neurologiche di Bologna, Department of Neurology and Stroke Center, Maggiore Hospital, Bologna, Italy
[7]Stroke Research in Stoke, Faculty of Medicine & Health Sciences, Keele University, Staffordshire, UK
[8]Neurology Department, University La Sapienza Rome, Rome, Italy
[9]Second Department of Neurology, National & Kapodistrian University of Athens, "Attikon" University Hospital, Athens, Greece
[10]Neurology Department, University Hospital Heidelberg, Heidelberg, Germany

Corresponding author:
Irene Escudero-Martínez, Department of Neurology, Hospital Universitari I Politècnic La Fe, Av. Fernando Abril Martorell 126, Valencia 46026, Spain.
Email: imesmar@gmail.com

Introduction

Hemorrhagic transformation (HT) is a complication of acute ischemic stroke (AIS) and more frequent after reperfusion therapy, particularly with intravenous thrombolysis (IVT). HT are mostly asymptomatic but, in some cases, parenchymal hematoma (PH) can cause neurological deterioration or death; in these cases, we refer to it as symptomatic intracerebral hemorrhage (SICH). For this reason, several efforts have been made to predict the risk of SICH by prognostic scores.[1–5] Some predictors for SICH in these score studies have been consistently reported: older age, high systolic blood pressure, glucose level at admission, NIHSS score at baseline or treatment with dual antiplatelet therapy. However, few data are available regarding cholesterol level and the risk of HT. Some studies have reported an association between low LDL cholesterol levels and SICH in AIS patients treated with and without reperfusion therapy.[6–8] Another study in patients with AIS not treated with IVT found that lower total cholesterol (TC) and LDL cholesterol levels were associated with an increased risk of HT, and a systematic review suggested that patients with all types of HT had lower LDL cholesterol levels and patients with SICH had lower TC levels.[9,10] Some studies have also reported as association of low cholesterol levels and spontaneous ICH, so a similar association regarding HT after ischemic stroke could be made, due to similar physiopathological mechanisms.[11] Nevertheless, there is conflicting evidence as some studies did not find an association between low cholesterol levels and HT in AIS patients or in animal models of cerebral ischemia/reperfusion.[12,13]

There are scarce available data regarding the association between cholesterol levels and cerebral edema (CED) in AIS patients. Interestingly, in animal models of cerebral ischemia, high TC levels have been associated with an increased BBB permeability and CED compared to the non-hyperlipidemic model, possibly via mechanisms that have to do with lipid peroxidation and matrix metalloproteinase activation.[14–16]

In view of the former considerations, we sought to determine the association of TC levels at baseline with the incidence of HT and CED after reperfusion therapies.

Methods

Study design and variables

This is a retrospective, observational study based on data from the SITS-International Stroke Thrombolysis and or thrombectomy Registry (ISTR) recorded between January 2011 and December 2017. SITS-ISTR is an internet-based academic driven interactive, prospective register for the monitoring of treatment in acute ischemic stroke. Methods of data collection and management within SITS-ISTR have previously been described.[17–19] All patients had presumed AIS and treated with reperfusion therapy.

We collected data on baseline characteristics and demographics, stroke severity (measured by National Institute of Health Stroke Scale (NIHSS) score), pre-stroke functional status (measured by modified Rankin Scale (mRS) score), risk factors, drug treatment history, admission time, acute intervention, and neuroimaging at baseline and 22–36 h post-acute treatment. SITS-ISTR records history of hyperlipidemia and total cholesterol level within 24 h of stroke onset. The registry does not record levels of LDL and HDL.

Follow-up period for this study was 3 months during which we collected information on functional outcome using the modified Rankin scale (mRS) and death. All assessments of imaging studies, neurological, and functional status were done according to clinical routine at centers participating in the SITS-ISTR.

Patients with unknown or missing information in total cholesterol levels in baseline visit were excluded.

Outcomes and covariates

The primary outcome measures were the proportion of patients with any parenchymal hemorrhage (PH1/PH2 including remote) and the proportion of patients presenting with moderate to severe CED on follow up imaging at 22–36 h according to TC level. To grade the extension of CED we used the SITS-MOST edema scale, which has been used previously.[20,21] We defined mild CED as focal brain swelling up to one-third of the hemisphere (grade 1), moderate CED as focal brain swelling greater than one-third of the hemisphere (grade 2), and severe CED as focal brain swelling with midline shift (grade 3). We specified in advance that the two higher grades of the scale would be put together into a compound outcome (moderate to severe CED).[17,20,21]

Secondary outcome measures included the proportion of patients with symptomatic intracerebral hemorrhage (SICH) according to different definitions (SITS-MOST, ECASS II, and NINDS), the proportion of patients with any CED according to the SITS-MOST definition and the proportion of patients with severe edema on follow up imaging.[17,22,23] Late secondary outcomes were death and mRS score at 3 months. Covariates collected for this study were baseline and demographic characteristics and any acute intervention.

Statistical analysis

Descriptive statistics of the full population, patients with normal TC levels and patients with hypercholesterolemia were performed. In an initial univariate analysis, we compared baseline characteristics and outcomes between patients with normal TC levels and patients with hypercholesterolemia ($\geqslant$200 mg/dl). We calculated mean and standard deviation for continuous variables, median, and interquartile ranges for nonparametric data and percentages for all dichotomous variables. Estimation of proportions was based on reported cases, excluding unknown

Table 1. Baseline and demographic characteristics of patients included (total cholesterol levels information).

	TC levels ⩽130 mg/dl at Baseline	TC levels 130–200 mg/dl at Baseline	TC levels ⩾200 mg/dl at Baseline	*p* Value
	N = 3372 (9.5%)	*N* = 8203 (23.2%)	*N* = 23,739 (67.3%)	
Age (years)	73 (63–80)	72 (62–79)	72 (62–80)	0.042
Gender (female)	1529 (45.3%)	3763 (45.9%)	10,634 (44.8%)	0.229
NIHSS baseline	10 (6–17)	10 (6–16)	10 (6–16)	<0.001
SBP (mm Hg)	152 ± 24	152 ± 24	154 ± 24	<0.001
DBP (mm Hg)	82 ± 14	83 ± 14	84 ± 15	<0.001
Glucose (mg/dl)	133 ± 50	134 ± 51	133 ± 51	0.802
Cholesterol (mg/dl)	115 ± 9	164 ± 20	318 ± 97	<0.001
Weight	75 ± 16	75 ± 16	77 ± 16	<0.001
Hypertension	2400 (71.4%)	5692 (69.7%)	16,150 (68.2%)	<0.001
Diabetes	667 (19.8%)	1586 (19.4%)	4917 (20.4%)	0.023
Hyperlipidemia	1107 (33.2%)	2636 (32.5%)	7364 (31.3%)	0.025
Current smoker	544 (16.5%)	1454 (18.2%)	4027 (17.6%)	0.097
Previous smoker	387 (12.5%)	911 (12.1%)	2739 (12.7%)	0.402
Previous TIA	211 (6.3%)	484 (5.9%)	1558 (6.6%)	0.101
Congestive heart failure	320 (9.5%)	668 (8.2%)	2076 (8.8%)	0.051
Previous AF	725 (21.6%)	1580 (19.4%)	4933 (20.9%)	0.004
Previous disability (previous mRS 2–5)	371 (11.4%)	918 (11.7%)	2975 (13.2%)	<0.001
Antiplatelet treatment	1109 (33.2%)	2465 (30.3%)	7448 (31.6%)	0.006
Anticoagulant treatment	155 (4.9%)	325 (4.3%)	1028 (4.7%)	0.277
Statin at baseline	908 (27.5%)	1947 (24.3%)	7017 (29.9%)	<0.001

or uncertain values from the denominator. TC levels were presented as a continuous variable and categorized in three different groups, low cholesterol levels (⩽130 mg/dl), normal cholesterol levels (130–200 mg/dl), and hypercholesterolemia (⩾200 mg/dl).[24,25] mRS was dichotomized into mRS ⩽ 2 (functional independence) and >2. We used linear Pearson's chi-square test, the unpaired *t* test or ANOVA, non-parametric tests such as Mann–Whitney *U* test or Kruskal Wallis for median comparison between three groups or regression methods, where appropriate.

A significance level of $p < 0.05$ was used through the whole study.

Logistic regression analysis was performed to assess the association between TC levels (as continuous as well as categorical variables) and the outcomes. We selected covariates based on biological relevance and results of univariate tests. The possibility of effect modification, for example, statin therapy modifying the effect of cholesterol on HT, were considered. In the multivariable analyses, we tested the statistical significance hypothesis under the likelihood ratio test. We reported all associations as odds ratios (ORs) with their corresponding 95% Confidence Intervals. All statistical analyses will be conducted using SPSS v.20.

Ethics

Ethical approval or patient consent for participation in the SITS-ISTR differed among participating countries. Ethical approval and patient consent were obtained in countries that required this, while other countries approved the register for conduct as an anonymized audit. The SITS-ISTR registry was approved by the Ethics Committee in Stockholm, Sweden. The SITS Scientific Committee approved the current study proposal and data were obtained from the SITS International Coordination Office, Stockholm (www.sitsinternational.org).

Results

Within the SITS-ISTR, 105,797 patients were recorded between January 2011 and December 2017. Of them, information on TC levels at baseline was available in 35,314 patients (Supplemental Material, study flow chart, Figure 1).

Demographics and baseline characteristics of included patients are presented in Table 1.

Patients with the lowest TC levels were significantly older than those with normal TC levels. Patients with the lowest TC levels presented lower weight.

Regarding NIHSS at baseline and values of SBP and DBP at baseline, almost identical values, there was statistical significance. The percentage of patients with history of hyperlipidemia was similar in the three groups. The percentage of patients taking statins was higher in the highest TC levels group.

Primary outcomes

In the unadjusted analysis, there was no statistically significant difference in TC levels in patients with any PH (267.5

Table 2. Univariate analysis of primary and secondary outcomes.

	TC levels ⩽130 mg/dl at Baseline	TC levels 130–200 mg/dl at Baseline	TC levels ⩾200 mg/dl at Baseline	*p* Value
	N = 3372 (9.5%)	*N* = 8203 (23.2%)	*N* = 23,739 (67.3%)	
Primary outcomes				
Any PH at 24 h	215 (6.8%)	502 (6.5)	1374 (6.1%)	0.238
Moderate and severe CED at 24 h	250 (8.1%)	564 (7.5%)	1321 (6%)	<0.001
Secondary outcomes				
SICH SITS-MOST	38 (1.2%)	88 (1.2%)	258 (1.2%)	0.960
SICH ECASS	126 (4.1%)	290 (3.9%)	751 (3.4%)	0.057
SICH NINDS	192 (6.2%)	447 (5.9%)	1133 (5.1%)	0.004
PH 2 at 24 h	70 (2.1%)	170 (2.1%)	459 (1.9%)	0.675
Any cerebral edema at 24 h	612 (19.7%)	1426 (18.9%)	3177 (14.3%)	<0.001
Severe CED at 24 h	111 (3.6%)	233 (3%)	657 (3%)	0.161
mRS 0–2 at days	1487 (58.5%)	3591 (58.7%)	10,084 (58.4%)	0.974
mRS 0–1 at days	1140 (44.8%)	2778 (45.4%)	7642 (44.5%)	0.446
Death at 90 days	358 (10.6%)	856 (10.4%)	2722 (11.5%)	0.022

vs 279 mg/dl, $p = 0.061$). However, patients who presented CED grade 2 or 3 (moderate or severe) at 24 h had lower TC level at baseline (249 vs 279 mg/dl, $p < 0.001$).

In the initial univariate analysis (Table 2), there were no differences regarding the rates of any PH between the three groups of cholesterol levels. A higher percentage of patients in the group of the lowest TC levels presented CED grade 2 or 3 (moderate or severe, 8.1% vs 7.5% vs 6%, $p < 0.001$).

In multivariable logistic regression analysis, TC level as continuous variable was inversely associated with moderate to severe CED (OR 0.99, 95% CI 0.99–1.00, $p = 0.025$) and as categorical variable lower TC levels were associated with a higher risk of moderate to severe CED (OR 1.24, 95% CI 1.10–1.40, $p = 0.003$). No statistically significant association was detected with TC as continuous and categorical levels with any PH (Table 3).

Secondary outcomes

Table 2 shows the unadjusted results for SICH and CED. Multivariable logistic regression analyses (Table 3) showed that lower TC levels were associated with a higher risk of SICH according to NINDS and ECASS definition, but there was no association of TC levels and SICH according to SITS-MOST definition. Lower TC levels were associated with presence of any CED (OR 1.19, 95% CI 1.03–1.58, $p = 0.016$) and severe CED in control neuroimaging (OR 1.41, 95% CI 1.06–1.88, $p < 0.001$). In the adjusted analysis, there was no statistically significant association with TC levels and functional outcome or death at 90 days.

Discussion

This study of a large cohort of patients with an AIS treated with reperfusion therapies (IVT and/or EVT) shows that TC as a continuous variable was inversely associated with moderate to severe CED but not with PH in the adjusted analysis. We did not find any association between TC levels with functional outcome or mortality rates.

Previous studies have shown an association of low cholesterol levels and an increased risk of SICH.[7,26] We have not found an association of TC levels with SICH defined by SITS-MOST criteria, but patients with lower TC levels had an increased risk of SICH defined using NINDS and ECAS II criteria. These two last definitions are less restrictive and include a higher percentage of patients, which may at least in part, explain these differences. Regarding the risk of primary ICH, results of the INTERSTROKE study have been recently reported and they found that increasing LDL-C values were associated with a reduced risk of ICH.[27]

Regarding CED, we were unable to document any previous studies reporting an association of cholesterol levels with CED.

There is a biological plausibility for an association between low serum cholesterol and hemorrhagic transformation and CED in acute ischemic stroke. Low cholesterol level may reduce the integrity of small vessels, and reduce their resistance to rupture which may lead to HT and also CED by blood brain barrier (BBB) permeability dysfunction in acute ischemic stroke.[9,28]

Regarding hypocholesterolemia, there are less studies than for hypercholesterolemia. Most studies use the TC to define this condition and although there is no consensus about the level below which a clinically significant hypocholesterolemia will ensue, most of the authors use a cut-off value between 120 and 150 mg/dl.[29]

The brain itself contains 25% of total cholesterol, and it is needed for maintaining its complex neuronal circuit. Blood-brain barrier (BBB) is impermeable to circulatory

Table 3. Adjusted OR for outcomes.

		Adjusted OR (95% CI, *p* value)
Primary outcomes		
Any parenchymal hemorrhage on follow up imaging*	First tertile (TC ⩽ 130 mg/dl)	1.16 (0.99–1.34, p = 0.056)
	Second tertile (TC 130–200 mg/dl)	1.25 (1.02–1.53, p = 0.034)
	Third tertile (TC ⩾ 200 mg/dl)	Ref.
Moderate or severe CED on follow up imaging§	First tertile	1.24 (1.10–1.40, p = 0.003)
	Second tertile	1.29 (1.09–1.52, p = 0.001)
	Third tertile	Ref.
	Statins	0.89 (0.79–1.002, p = 0.054)
Secondary outcomes		
SICH NINDS*	First tertile (TC ⩽ 130 mg/dl)	1.18 (1.04–1.33, p = 0.012)
	Second tertile (TC 130–200 mg/dl)	1.17 (0.98–1.39, p = 0.089)
	Third tertile (TC ⩾ 200 mg/dl)	Ref.
SICH ECASS*	First tertile	1.31 (1.07–1.6, p = 0.008)
	Second tertile	1.37 (1.04–1.8, p = 0.023)
	Third tertile	Ref.
SICH SITS-MOST*	First tertile	1.04 (0.80–1.46, p = 0.771)
	Second tertile	0.902 (0.60–1.35, p = 0.617)
	Third tertile	Ref.
Any CED§	First tertile	1.19 (1.03–1.38, p = 0.016)
	Second tertile	1.25 (1.12–1.39, p < 0.001)
	Third tertile	Ref.
Severe CED on follow up imaging§	First tertile	1.41 (1.06–1.88, p = 0.018)
	Second tertile	1.17 (0.94–1.45, p = 0.159)
	Third tertile	Ref.
Secondary late outcomes		
mRS 0–2 at 90 days§	First tertile (TC ⩽ 130 mg/dl)	0.96 (0.87–1.06, p = 0.43)
	Second tertile (TC 130–200 mg/dl)	1.03 (0.9–1.18, p = 0.68)
	Third tertile (TC ⩾ 200 mg/dl)	Ref.
	Statins	1.11 (1.04–1.19, p = 0.003)
Death at 90 days§	First tertile	0.97 (0.85–1.1, p = 0.64)
	Second tertile	0.93 (0.78–1.11, p = 0.44)
	Third tertile	Ref.

Variables in the models
*: age, NIHSS baseline, SBP baseline, glucose baseline, hypertension, diabetes, previous AF, treatment acetylsalicylic acid, treatment statins, IVT and/or EVT, SBP at 24 h.
§: age, NIHSS baseline, SBP baseline, glucose baseline, hypertension, diabetes, previous AF, treatment acetylsalicylic acid, treatment statins, IVT and/or EVT, SBP at 24 h, any PH.

cholesterol. After an AIS, BBB is disrupted due to the sudden hypoxia in the hyperacute stage, and in the acute stage, the neuroinflammatory response aggravates this BBB injury. IVT with rtPA may also increase cerebrovascular permeability by activating latent platelet-derived growth factor-CC (PDGF-CC).[30] All these mechanisms lead to higher BBB permeability, CED, and a consequent risk of ICH.[31] This fact implies that the cholesterol regulation in the brain is not like that of extracerebral cholesterol. So, cholesterol levels outside of the brain should not affect the brain functioning as these two cholesterol pools are different.[32]

For this reason, unlike other peripheral organs, human brain is primarily dependent on de novo cholesterol synthesis rather than peripheral plasma cholesterol.[33]

These above pieces of evidence lead to the hypothesis that the lowering of plasma LDL would not affect the normal brain function.

One explanation for our findings may be an association between low TC levels and critical illness such as stroke. In our study, blood samples for TC levels were obtained within 24 h of stroke onset. There is evidence that TC levels drop at the onset of acute illness and returns to normal during recovery. The mechanisms of this secondary hypocholesterolemia are downregulation of hepatic synthesis, a decreased production of cholesterol precursors and an increased cholesterol catabolism.[29] Furthermore, a history of poor nutritional status in a stroke patient may be associated with lower TC levels, while at the same time, this poor nutritional status can worsen the prognosis of a stroke by

causing larger infarcts, thereby confounding the association between TC and CED.[34,35]

Our study has some limitations. Firstly, the observational design based on retrospective analysis of prospectively collected data. One of the main concerns of observational studies regarding a previous treatment is that the observed effects may be confounded by other unmeasured imbalances. In our study we have used multivariable analysis to reduce imbalances in available clinically important variables. Missing data in general, and particularly on TC information is another limitation of this study. Furthermore, we have information on TC levels, not LDL or non-LDL cholesterol specifically. Moreover, we do not have information on previous nutritional status of patients or other medical conditions related to hypocholesterolemia, such as anemia or cancer, neither on statin type, dose, or duration of the statin treatment. Another limitation is that in some variables, such as NIHSS, SBP, and DBP at baseline, we observed almost identical values between groups. However, due to the large sample size there was statistical significance.

The strengths of our study are that we used an international multicenter registry with a large sample of patients and all data were collected prospectively. This large sample retrospective study might generate new hypothesis for further investigations.

Conclusion

In conclusion, our findings suggest an association of low level of TC and moderate/severe CED and a higher risk of any PH. Further studies are needed to confirm these findings.

Acknowledgement

The authors would like to thank the SITS-Registry Investigators and patients.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Niaz Ahmed is chair of SITS International. Other authors have no disclosures regarding conflict of interest.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The SITS registry is financed directly and indirectly by grants from Karolinska Institutet, Stockholm County Council, the Swedish Heart-Lung Foundation, as well as from an unrestricted sponsorship from Boehringer-Ingelheim. SITS has previously received grants from the European Union Framework 7, the European Union Public Health Authority, and conducted studies supported by EVER Pharma and Ferrer Internacional, as well as in collaboration with Karolinska Institutet, supported by Stryker, Covidien, and Phenox. SITS is currently conducting studies supported by Boehringer-Ingelheim and Biogen. N Ahmed is supported by Stockholm County Council and Swedish Heart-lung Foundation. Irene Escudero-Martínez has received a grant from "Fundación Progreso y Salud, Junta de Andalucía" (grant EF-0437-2018).

Ethical approval

Data collection in this study was done under the umbrella of SITS-MOST II study which was approved by the Stockholm Ethics committee.

Informed consent

Need for ethical approval or patient consent for participation in the SITS-ISTR varied among participating countries. Ethics approval and patient consent were obtained in countries that required this; other countries approved the register for conduct as an anonymized audit.

Guarantor

Access to the anonymized SITS-ISTR data will be available from the corresponding author on reasonable request from qualified researchers contingent on approval by the SITS Scientific Committee.

Contributorship

IEM and NA conceived the study. IEM and MM were involved in data analysis. IEM and NA wrote the first draft of the manuscript. All authors registered patients in the SITS registry, reviewed and edited the manuscript and approved the final version of the manuscript.

ORCID iDs

Irene Escudero-Martínez https://orcid.org/0000-0003-1838-0235
Georgios Tsivgoulis https://orcid.org/0000-0002-0640-3797
Niaz Ahmed https://orcid.org/0000-0001-7970-0146

Supplemental material

Supplemental material for this article is available online.

References

1. Cappellari M, Turcato G, Forlivesi S, et al. STARTING-SICH nomogram to predict symptomatic intracerebral hemorrhage after intravenous thrombolysis for stroke. *Stroke* 2018; 49: 397–404.
2. Mazya M, Egido JA, Ford GA, et al.; SITS Investigators. Predicting the risk of symptomatic intracerebral hemorrhage in ischemic stroke treated with intravenous alteplase: Safe Implementation of Treatments in Stroke (SITS) symptomatic intracerebral hemorrhage risk score. *Stroke* 2012; 43: 1524–1531.
3. Strbian D, Engelter S, Michel P, et al. Symptomatic intracranial hemorrhage after stroke thrombolysis: the SEDAN score. *Ann Neurol* 2012; 71: 634–641.
4. Lou M, Safdar A, Mehdiratta M, et al. The HAT score: a simple grading scale for predicting hemorrhage after thrombolysis. *Neurology* 2008; 71: 1417–1423.

5. Cucchiara B, Tanne D, Levine SR, et al. A risk score to predict intracranial hemorrhage after recombinant tissue plasminogen activator for acute ischemic stroke. *J Stroke Cerebrovasc Dis* 2008; 17: 331–333.
6. Bang OY, Saver JL, Liebeskind DS, et al. Cholesterol level and symptomatic hemorrhagic transformation after ischemic stroke thrombolysis. *Neurology* 2007; 68: 737–742.
7. Lin SF, Chao AC, Hu HH, et al. Low cholesterol levels increase symptomatic intracranial hemorrhage rates after intravenous thrombolysis: a multicenter cohort validation study. *J Atheroscler Thromb* 2019; 26: 513–527.
8. Yang N, Lin M, Wang BG, et al. Low level of low-density lipoprotein cholesterol is related with increased hemorrhagic transformation after acute ischemic cerebral infarction. *Eur Rev Med Pharmacol Sci* 2016; 20: 673–678.
9. D'Amelio M, Terruso V, Famoso G, et al. Cholesterol levels and risk of hemorrhagic transformation after acute ischemic stroke. *Cerebrovasc Dis* 2011; 32: 234–238.
10. Nardi K, Leys D, Eusebi P, et al. Influence of lipid profiles on the risk of hemorrhagic transformation after ischemic stroke: systematic review. *Cerebrovasc Dis Extra* 2011; 1: 130–141.
11. O'Donnell MJ, Xavier D, Liu L, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet* 2010; 376: 112–123.
12. Montaner J. Cholesterol measured before stroke thrombolysis is not associated with tissue plasminogen activator-related hemorrhagic transformation. *Stroke* 2008; 39: e6.
13. Tran-Dinh A, Levoye A, Lambert G, et al. Low levels of low-density lipoprotein-C associated with proprotein convertase subtilisin kexin 9 inhibition do not increase the risk of hemorrhagic transformation. *Stroke* 2014; 45: 3086–3088.
14. ElAli A, Doeppner TR, Zechariah A, et al. Increased blood–brain barrier permeability and brain edema after focal cerebral ischemia induced by hyperlipidemia. *Stroke* 2011; 42: 3238–3244.
15. Menet R, Bernard M and ElAli A. Hyperlipidemia in stroke pathobiology and therapy: insights and perspectives. *Front Physiol* 2018; 9: 488.
16. Deng J, Zhang J, Feng C, et al. Critical role of matrix metalloprotease-9 in chronic high fat diet-induced cerebral vascular remodelling and increase of ischaemic brain injury in mice. *Cardiovasc Res* 2014; 103: 473–484.
17. Wahlgren N, Ahmed N, Dávalos A, et al.; SITS-MOST Investigators. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet* 2007; 369: 275–282.
18. Ahmed N, Mazya M, Nunes AP, et al. Safety and outcomes of thrombectomy in ischemic stroke with vs without intravenous thrombolysis. *Neurology* 2021; 97: e765–e776.
19. Ahmed N, Mazya M, Nunes AP, et al. Safety and outcomes of routine endovascular thrombectomy in large artery occlusion recorded in the SITS register: an observational study. *J Intern Med* 2021; 290: 646–654.
20. Thorén M, Azevedo E, Dawson J, et al. Predictors for cerebral edema in acute ischemic stroke treated with intravenous thrombolysis. *Stroke* 2017; 48: 2464–2471.
21. Thorén M, Dixit A, Escudero-Martínez I, et al. Effect of recanalization on cerebral edema in ischemic stroke treated with thrombolysis and/or endovascular therapy. *Stroke* 2020; 51: 216–223.
22. Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. *Lancet* 1998; 352: 1245–1251.
23. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995; 333: 1581–1587.
24. Glueck CJ, Kelley W, Gupta A, et al. Prospective 10-year evaluation of hypobetalipoproteinemia in a cohort of 772 firefighters and cross-sectional evaluation of hypocholesterolemia in 1,479 men in the National Health and Nutrition Examination Survey I. *Metabolism* 1997; 46: 625–633.
25. Grundy SM, Stone NJ, Bailey AL, et al. AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019; 139: E1082–E1143.
26. Wang X, Dong Y, Qi X, et al. Cholesterol levels and risk of hemorrhagic stroke: a systematic review and meta-analysis. *Stroke* 2013; 44: 1833–1839.
27. O'Donnell MJ, McQueen M, Sniderman A, et al. Association of lipids, lipoproteins, and apolipoproteins with stroke subtypes in an International Case Control Study (INTERSTROKE). *J Stroke* 2022; 24: 224–235.
28. Huff T and Jialal I. Physiology, cholesterol. In: StatPearls [Internet], 2019.
29. Elmehdawi R. Hypolipidemia: a word of caution. *Libyan J Med* 2008; 3: 84–90.
30. Su EJ, Fredriksson L, Geyer M, et al. Activation of PDGF-CC by tissue plasminogen activator impairs blood-brain barrier integrity during ischemic stroke. *Nat Med* 2008; 14: 731–737.
31. Bernardo-Castro S, Sousa JA, Brás A, et al. Pathophysiology of blood–brain barrier permeability throughout the different stages of ischemic stroke and its implication on hemorrhagic transformation and recovery. *Front Neurol* 2020; 11: 1–24.
32. Bandyopadhyay D, Qureshi A, Ghosh S, et al. Safety and efficacy of extremely low LDL-cholesterol levels and its prospects in hyperlipidemia management. *J Lipids* 2018; 2018: 1–8.
33. Orth M and Bellosta S. Cholesterol: its regulation and role in central nervous system disorders. *Cholesterol* 2012; 2012: 292598.
34. Gariballa SE, Parker SG, Taub N, et al. Influence of nutritional status on clinical outcome after acute stroke. *Am J Clin Nutr* 1998; 68: 275–281.
35. Turetsky A, Goddeau RP Jr and Henninger N. Low serum vitamin D is independently associated with larger lesion volumes after ischemic stroke. *J Stroke Cerebrovasc Dis* 2015; 24: 1555–1563.