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REVIEW ARTICLE

Statin, cholesterol, and sICH after acute ischemic stroke: systematic review and meta-analysis

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Abstract

Background and purpose Conflicts exist regarding relationship between prior/new statin use, cholesterol, and early poststroke intracranial hemorrhage (ICH) in acute ischemic stroke (AIS) patients. This meta-analysis is aimed at evaluating the safety of prior/new statin use, cholesterol level and risk of ICH in AIS patients.

Methods We searched PubMed and Embase for studies examining relation between statin use, cholesterol level, and early poststroke ICH in AIS. Included studies should report risk of early poststroke symptomatic ICH (sICH) or overall ICH. A random-effects model was used to pool the data.

Results Twenty-five articles involving 26,327 participants were included, among whom 925 had sICH. Prior statin use was not associated with overall ICH (adjusted odds ratio (OR), 1.478; 95% confidence interval (CI), 0.924–2.362; $p = 0.103$) and sICH in patients who received thrombolysis (adjusted OR, 1.567; 95% CI, 0.994–2.471; $p = 0.053$) or overall ICH in patients, most of whom had not received recanalization therapy (crude OR, 1.342; 95% CI, 0.872–2.065; $p = 0.181$). New statin use was associated with decreased sICH after recanalization therapy (crude OR, 0.292; 95% CI, 0.168–0.507; $p < 0.001$).Cholesterol level was not associated with overall ICH.

Conclusion Prior/new statin use and lower cholesterol level are not risk factors for sICH and overall ICH in AIS patients, whether or not the patient has received recanalization therapy. New statin use is likely associated with decreased sICH.

Keywords Stroke · Intracranial hemorrhage · Cholesterol · Statin

Introduction

Early poststroke intracranial hemorrhage (ICH) is a serious complication worsening outcome in acute ischemic stroke (AIS) patients, especially those receiving thrombolysis [1]. Previous meta-analysis associated statin use before or during the acute stage of stroke with better functional outcome and reduced mortality [2], but concerns exist about the potentially increased risk of ICH. In AIS patients, statin pretreatment was an independent predictor of symptomatic ICH (sICH) after intravenous thrombolysis (IVT) [3, 4]. However, these results have not been validated [5, 6].

Adequate cholesterol levels are important for the integrity of small blood vessels and their resistance to rupture [7]. Lower cholesterol levels were associated with increased risk of hemorrhagic transformation in AIS patients [[8–10]]. A meta-analysis found that ICH tended to occur more often in ischemic stroke patients with lower low-density lipoprotein cholesterol (LDL-C) levels [11]. However, these results have not been consistently replicated [12–14, 15].

The relationship between statin, cholesterol, and early ICH in AIS patients is controversial. This study is aimed at evaluating the influence of prior/new statin use and cholesterol levels on the risk of sICH and overall ICH in AIS patients who received recanalization therapy and in those who did not.

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Method

This study was performed according to the guidelines recommended by the "Meta-analysis of Observational Studies in Epidemiology" [16] statements. This study did not require approval by the Institutional Review Board, because the data used was published and publicly available.

Search strategy

PubMed and Embase were searched for studies examining the relation between statin, cholesterol, and early poststroke ICH in AIS patients, published in English from January 1966 to May 2018. PubMed search strategy: ("Intracranial Hemorrhages" [Mesh] or "hemorrhagic stroke" or "hemorrhagic transformation" or hemorrhag* or haemorrhag*) and (stroke [Mesh] or stroke or "brain ischemia" [Mesh] or (brain infarct*) or (cerebral infarct*) or "brain ischemia" or "brain ischaemia" or "cerebral ischemia" or "cerebral ischaemia" or (cerebrovascular accident*) or (cerebrovascular disorder*) or (cerebrovascular disease*) or (brain embol*) or (brain thromb*) or (cerebral embol*) or (cerebral thromb*) or (intracerebral embol*) or (intracerebral thromb*) or (intracranial embol*) or (intracranial thromb*)) and ("Hydroxymethylglutaryl-CoA Reductase Inhibitors" [Mesh] or statin or statin* or pravastatin or lovastatin or atorvastatin or simvastatin or fluvastatin or cerivastatin or rosuvastatin or pitavastatin or lipids [Mesh] or lipid* or Cholesterol[Mesh] or cholesterol or LDL or HDL or TG or TC or triglyceride or "dyslipidemias" [Mesh]). And the Embase search strategy was derived from PubMed search strategy. Two investigators (W. Z. and J. J) examined the titles and abstracts to identify potential eligible articles. More studies were screened in reference lists of retrieved articles and relevant reviews.

Study selection

We included observational (cohort or nested case-control) studies and randomized control trials (RCTs). Studies that reported early poststroke ICH was included. Studies involving cholesterol, effect estimates (risk ratio, hazard ratio, or odds ratio (OR)), and 95% confidential intervals (CIs) for > 2 categories of cholesterol concentrations must be reported for comparing different concentration levels or analyzing the results per 1 mmol/L increment. Excluding criteria were: (1) no ICH data available or ICH occurred > 2 weeks from stroke onset and (2) no full text. Among studies based on the same cohort, the one with most complete data was included.

Data extraction and quality assessment

Two authors (H.W., W.P) independently extracted the following data: author, publication year, study design, nation (continent if multiple countries were involved), sample size, age, sex, exposure, covariates in the adjusted model, event, comparison categories and corresponding relative risk, hazard ratio, or OR with 95% CI, and other risk factors for ICH. Disagreement was resolved by consensus. We did not contact authors of the studies for incomplete or unpublished data. Newcastle-Ottawa Scale (NOS) was used to evaluate methodological quality of studies [17].

Definitions of outcome

Early poststroke sICH defined as any hemorrhage on the follow-up CT/MRI scan with NIHSS score increase ≥ 4 or leading to death within 14 days [18]. Early ICH was defined as ICH occurring within 2 weeks post-AIS onset.

Statistical analysis

Considering variability in sample sizes and ineffectiveness of confounder control in observational studies, a random-effects (DerSimonian-Laird) model was used to pool adjusted ORs. Crude ORs were calculated based on patient numbers. ORs were recorded as OR (95% CI). Heterogeneity was estimated using Cochran's Q test and I^2 value [19]. If heterogeneity existed, subgroup analysis and sensitivity analysis were performed.

Meta-regression was performed to detect the source of heterogeneity, including study design, sample size (< 500, 500–1500, > 1500), proportions of atrial fibrillation (AF), and cardiac embolism (CE) (< 25%, ≥ 25%). Egger's test was used to assess publication bias. All statistical analyses were performed using STATA software (version 13.0; Stata Corporation, College Station, USA). $p < 0.1$ was considered with significant heterogeneity or publication bias [20]. $p < 0.05$ was considered statistically significant.

Results

Search result

Ten thousand ninety-one records (2401 from PubMed) were identified. After excluding duplicates and irrelevant studies, 74 studies remained. After detailed evaluations, 27 studies were included. After search of reference lists of studies, another one study was identified [21] (Fig. 1). However, 3 studies [4, 15, 21] were excluded due to duplicate data from 1 study [5]; as a result, 25 studies were included finally.

Study characteristics

Twenty-five articles were included, comprising 3 prospective cohort studies [22–24], 14 retrospective cohort studies [3, 5, 6,

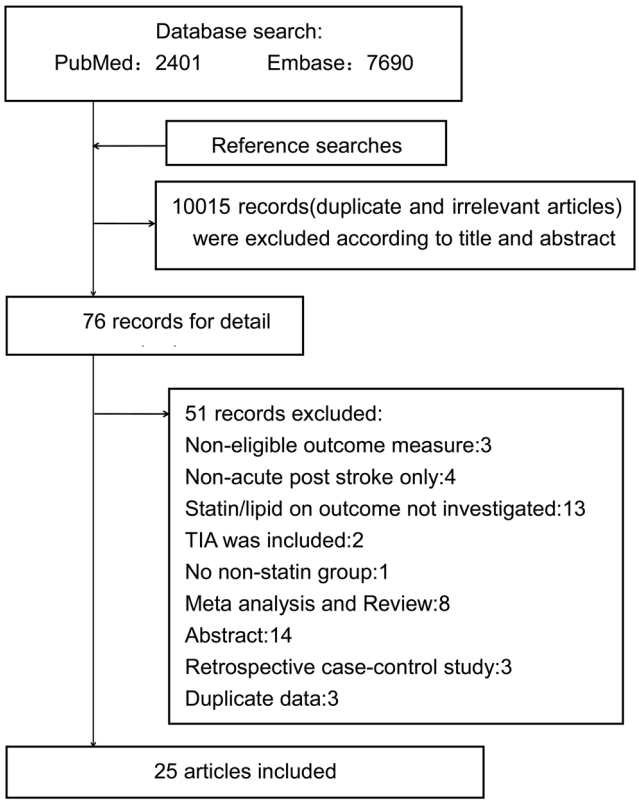

Fig. 1 Flow diagram

9, 10, 14, 25–27, 28–32], 6 nested case-control studies [8, 12, 13, 33–35] and 2 RCTs [36, 37]. Including 5260 statin users and 18,492 non-users as well as 925 sICH events (258 in statin users), 26,327 participants were included. Among these studies, 7 reported relation between cholesterol and ICH [8–10, 12, 13, 14, 25], 7 reported relation between new statin use and ICH [[25, 28, 29, 30, 32, 36, 37], and 16 reported relation between prior statin use and ICH [3,5, 6, 8, 9, 12, 13, 22–24, 26, 27, 31–35]. AIS patients in 21 studies all received recanalization therapy, in 5 studies partly received recanalization therapy [10, 32, 33, 36,37], and in 2 studies received no recanalization therapy [9, 24]. One study [32] reported effect of potent statins on the incidence of sICH (Table 1).

Statin and early poststroke sICH

No association between prior statin use and sICH in patients who underwent recanalization therapy

Twelve observational studies involving 11,828 patients were eligible [3, 5 , 6, 8, 12, 22, 23, 26, 32–35]. Prior statin use was associated with sICH (crude OR, 1.507 (1.235–1.839); $p < 0.0001$) (Fig. 2a). No significant heterogeneity or publication bias was detected ($I^2 = 6.0\%$, $p = 0.387$, Egger's test $p = 0.185$). Combined adjusted results available in 7 studies (Table 2) (all patients received IVT) [5, 6, 12, 26, 32, 34, 35], revealed no association between prior statin use and sICH (adjusted OR 1.567 (0.994–2.471); $p = 0.053$) with no significant publication bias (Egger's test $p = 0.982$) but obvious heterogeneity ($I^2 = 65.2\%$, $p = 0.008$) (Fig. 2b). Meta-regression identified no source of heterogeneity (sample size (< 500 versus 500–1500, $p = 0.419$; < 500 versus > 1500, $p = 0.647$), study design ($p = 0.192$), and AF or CE ($p = 0.192$)). Further sensitivity analysis found no association between prior statin use and sICH after excluding the 3 case-control studies (adjusted OR 1.213 (0.922–1.597); $p = 0.168$) (Fig. 2c), without heterogeneity ($I^2 = 0.0\%$, $p = 0.397$).

New statin use may decrease early poststroke sICH

Three cohort studies [28–30] (2758 participants) reported the influence of new statin use on sICH in patients who received recanalization therapy. New statin treatment was significantly associated with decreased sICH (crude OR, 0.292 (0.168–0.507); $p < 0.001$) without evident heterogeneity ($I^2 = 0\%$, $p = 0.535$) (Fig. 2d).

Two RCTs [36, 37] reported new statin use in AIS patients who partly received IVT (3.11% and 52.9%, respectively), and there was no difference in sICH incidence between statin users and controls.

Cholesterol and early sICH post AIS

Three observational studies [12, 14,15] reported association between cholesterol and sICH in AIS patients who received IVT. We cannot pool the ORs because the authors reported the results in different ways: some reported ORs and 95% CIs between low versus high levels of cholesterol, while others per 1 mmol/L increment of cholesterol concentration.

Levels of total cholesterol (TC), LDL, and high-density lipoprotein (HDL) were not reported as risk factors of sICH after AIS [14], only 1 nested case-control study associated high triglyceride (TG) levels with higher risk of sICH [12]; however, the other 2 cohorts with obviously larger samples failed to replicate this finding [14, 15].

Statins and overall ICH

No association between prior statin use and overall ICH in recanalization patients

Six observational studies [3, 5, 8, 13, 23, 27] involving 4074 patients were eligible. The crude OR was 1.215 (1.032–1.430) ($p = 0.019$) without significant heterogeneity or publication bias ($I^2 = 0.0\%$, $p = 0.584$, Egger's test $p = 0.508$) (Fig. 3a). However, combined adjusted results available in 3 studies [5, 13, 23] (Table 2) showed no significant association (adjusted OR 1.478 (0.924–2.362); $p = 0.103$) with moderate heterogeneity ($I^2 = 51.0\%$, $p = 0.130$).

Table 1 Characteristics of studies included in meta-analysis

Study	Study design	Region	Size	Female	Age	Recanalization	Exposure	ICH	NOS score
Montaner 2016	RCT	Spain	104	48	74 (62.5–82)	Partly	Simvastatin	ICH/sICH	–
Heo 2016	RCT	Korea	289	126	65 ± 12.3	Partly	Rosuvastatin	Overall ICH	–
Paciaroni 2008	Prospective nested case-control	Italy	1125	495	76	Partly	Statin (prior)	Overall ICH	9
Bang 2007	Nested case-control	USA	104	53	70	Combined	Statin (prior) LDL	Overall ICH/sICH	9
D'Amelio 2011	Retrospective cohort	Italy	215	101	No report	No	Statin (prior) TC, LDL	Overall ICH	9
Meier 2009	Prospective cohort	Switzerland	311	134	63	IAT	Statin (prior)	Overall ICH/sICH	9
Scheitz 2016	Retrospective cohort	Europe	8535	3904	69.8	Partly	Statin (prior/new)	sICH	9
Makihara 2011	Nested case control	Japan	489	171	70 ± 11.6	IVT	Statin (prior) LDL	Overall ICH	8
Kim 2009	Retrospective cohort	Korea	377	143	66 ± 1.7	Partly	TC, LDL	Overall ICH	9
Meseguer 2012	Retrospective cohort	France	606	259	68	IVT/IA/both	Statin (prior)	sICH	9
Erdur 2018	Prospective nested case control	Germany	1336	650	No report	IVT	Statin (prior)	sICH	9
Kang 2015	Retrospective cohort	Korea	337	149	69 ± 12.4	IVT/IA/both	Statin (new)	sICH	9
Engelter 2011	Retrospective cohort	Europe	4012	1753	69	IVT	Statin (prior)	Overall ICH/ sICH	9
Cougo-Pinto 2012	Nested case control	Brazil	113	54	63 ± 12.8	IVT	Statin (prior)	sICH	9
Georgiadis 2009	Retrospective cohort	USA	77	39	66 ± 14	Combined	Statin (prior)	Overall ICH	9
Martinez-Ramirez 2011	Retrospective cohort	Spain	182	83	68 ± 11.4	IVT	Statin (prior)	Overall ICH/sICH	9
Nardi 2012	Retrospective cohort	Europe	1847	747	70 (58–78)	IVT	TC, LDL, TG, HDL	sICH	9
Restrepo 2009	Retrospective cohort	Korea	142	69	68 ± 17	IAE, PME	Statin (new) TC,LDL	Overall ICH	7
Tsivgoulis 2015	Retrospective cohort	Europe	1660	681	67 ± 13	IVT	Statin (prior)	sICH	9
Yi 2016	Prospective cohort	China	1124	503	69	No	Statin (prior)	Overall ICH	8
Miedema 2010	Retrospective cohort	Netherlands	476	219	69	IVT	Statin (prior)	sICH	8
Tong 2015	Retrospective cohort	China	367	136	69	IVT	Statin (new)	sICH	9
Zhao 2014	Prospective cohort	China	193	69	65 ± 10.3	IVT	Statin (prior)	sICH	8
Cappellari 2013	Retrospective cohort	Italy	2054	862	66 ± 12.5	IVT	Statin (new)	sICH	8
Uyttenboogaart 2008	Nested case control	Netherlands	252	116	68 ± 15	IVT	Statin (prior) TC, TG	sICH	8

No association between prior statin use and overall ICH in patients who partly received recanalization

Four studies [,9, 24, 32, 33] involving 10,999 patients (24% received recanalization therapy) were eligible. Patients in 2 studies partly received recanalization therapy [, 32, 33]. Prior statin use was not associated with overall ICH (crude OR 1.342 (0.872–2.065); $p = 0.181$) with moderate heterogeneity ($I^2 = 36.1\%$, $p = 0.195$) (Fig. 3b). Sensitivity analysis by excluding the study with largest sample size [32] presented stable result (crude OR 1.011 (0.593–1.724); $p = 0.967$) without evident heterogeneity ($I^2 = 0.0\%$, $p = 0.493$).

New statin use and overall ICH

Only one study [25] revealed no association between new statin use and risk of overall ICH (adjusted OR 1.5 (0.95–4.1)).

Cholesterol and overall ICH

LDL and overall ICH (dose–response analysis) Four observational studies [8, 10, 13, 14] involving 2817 patients reported ICH incidence increase per 1 mmol/L LDL reduction (Table 2). The adjusted OR was 0.950 (0.836–1.078) ($p =$

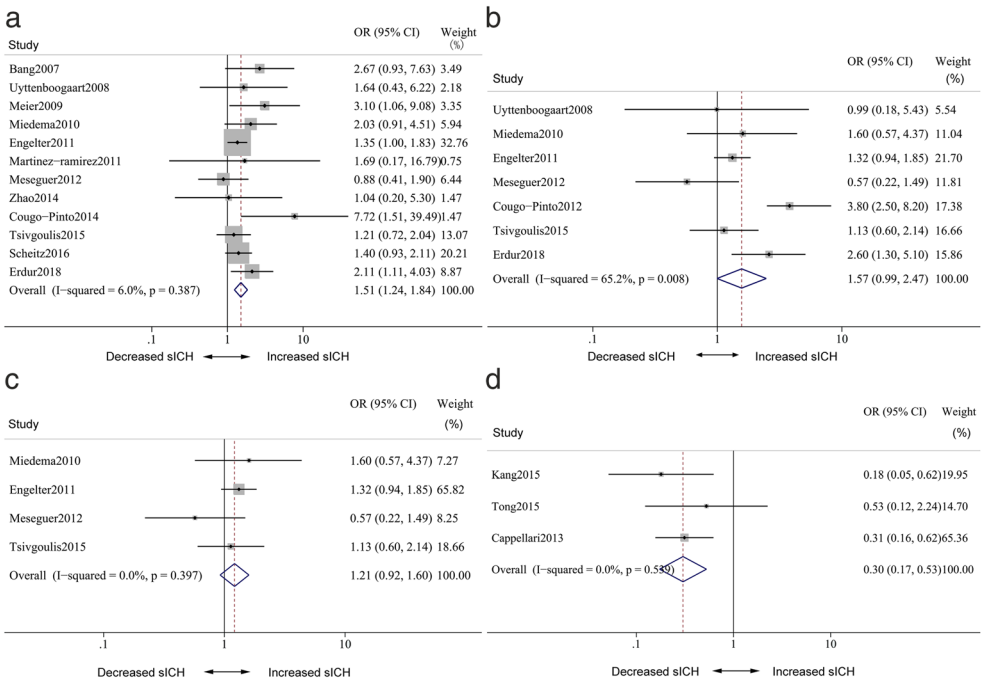

Fig. 2 **a** Crude odds ratio (OR) of prior statin use and sICH in patients who received recanalization. **b** Adjusted OR of prior statin use and sICH in patients who received recanalization. **c** Sensitivity analysis by excluding case-control studies of prior statin and sICH in patients who received recanalization. **d** Crude OR of new statin use and sICH in patients who received recanalization

0.424) with moderate heterogeneity ($I^2 = 35.5\%$; $p = 0.199$) (Fig. 3c).

TC and overall ICH (dose–response analysis) Four observational studies [10, 12–14] involving 2965 patients reported ICH incidence increase per 1 mmol/L TC reduction (Table 2). The adjusted OR was 0.941 (0.810–1.094) ($p = 0.431$) without significant heterogeneity ($I^2 = 0\%$, $p = 0.594$) (Fig. 3d). After excluding 1 study investigating patients who partly received recanalization therapy, the adjusted OR was 0.981 (0.821–1.173) ($p = 0.835$) without heterogeneity ($I^2 = 0\%$, $p = 0.555$).

Discussion

This meta-analysis included 26,327 patients and discussed the overall effect of statins and cholesterol on AIS. Strengths of our analysis include large sample size and performance of sensitivity analysis. Furthermore, the starting time of statin use and whether patients received recanalization therapy were stratified.

We found that (1) prior statin use, LDL, and TC were not associated with risk of sICH and overall ICH after recanalization therapy; (2) new statin use may decrease the risk of sICH after recanalization therapy; (3) prior statin use was not associated with overall ICH in patients who partly (24%) received recanalization therapy; and (4) new statin use, LDL, and TC were not associated with overall ICH.

A meta-analysis reported positive relationship between prior statin use and sICH [38], but it included replicated data. Furthermore, the authors did not perform sensitivity analysis, which may allow bias. We performed sensitivity analysis by excluding case-control studies, which likely contribute to bias due to their smaller number and less strict design.

sICH seems to be a result of multiple factors such as recanalization therapy, time to treatment, stroke severity [1, 33,], and multiple vascular risk factors [5, 39, 40]. These factors were not randomized, which may explain the following findings: (1) The crude OR of prior statin use on sICH were significant, while after adjustment and excluding case-control studies, the significance disappeared. (2) The crude OR of prior statin use on overall ICH were significant in patients who all received IVT, but the increase disappeared in studies where only a small number of patients received IVT, indicating a relationship between IVT and ICH rather than statin use. The evidence was strengthened by post hoc analysis [41] of a large RCT in which vascular risk factors were randomized, showing that lipid-lowering pretreatments (most with statins) decreased the risk of sICH. However, in the lipid-lowering pretreatment group, the time from stroke onset to IVT was shorter and more patients received low-dose IVT. These factors may affect the results of this study.

Data [42] showed that statin treatment starting within 24 h after IVT, but not before stroke, improved outcomes without increasing sICH. Similarly, we found that new statin use decreased the risk of sICH after IVT. It is possible that statin decrease ICH risk by suppressing MMP9, a predictor of ICH which could be elevated by rtPA [22, 43, 44].

Statins can improve cerebral perfusion by opening collaterals [45] and have neuroprotective effects [46]; these may decrease sICH. The difference between prior and new statin

Table 2 Characteristics of studies with adjusted OR for association between statin treatment and outcome

Study	Exposure	Outcome	Covariates in adjusted model
Bang 2007	LDL	Overall ICH	Male, blood glucose, TC, NIHSS, smoking, hypertension
D'Amelio 2011	TC, LDL	Overall ICH	Moderate/severe impairment, early CT signs large infarct size, cardioembolic source
Meier 2009	Statin (prior)	Overall ICH	Age, males, hypertension, current smoking, atrial fibrillation, stroke severity, mean time to thrombolysis, good collaterals
Scheitz 2016	Statin (prior/new)	sICH/good outcome/death	Age, sex, baseline NIHSS, atrial fibrillation, previous stroke, onset to treatment time, prior use of antiplatelets, and thrombolysis
Makihara 2011	Statin (prior) HDL, LDL	Overall ICH/good outcome	Sex, age, diabetes mellitus, atrial fibrillation, prior antithrombotics, blood glucose, onset-to-treatment time, i.v. antihypertensives, occlusion of the internal carotid artery
Kim 2009	TC, LDL	Overall ICH	Gender, age, hypertension, diabetes, serum glucose level, systolic blood pressure, NIHSS score, and thrombolytic treatment
Meseguer 2012	Statin (prior)	sICH/good outcome	Age, sex, treated hypertension, diabetes, admission glucose level, smoking, and antiplatelet therapy
Erdur 2018	Statin (prior)	sICH	Age, diabetes mellitus, antiplatelets, NIHSS, glucose, systolic blood pressure
Engelter 2011	Statin (prior)	Overall ICH/sICH/good outcome	Stroke severity, age, systolic blood pressure, gender, and preexisting antithrombotic treatment
Cougo-Pinto 2012	Statin (prior)	sICH	NIHSS
Nardi 2012	TC, LD, LTG, HDL	sICH/good outcome/death	Age, baseline NIHSS, blood glucose concentration, ongoing statin therapy, TC, LDL-C, HDL-C, and TG
Restrepo 2009	Statin (new)	Overall ICH	Age, SBP, DBP, glucose on admission, NIHSS, DM, atrial fibrillation, TC, LDL, successful recanalization, IVF,IAF, use of Merci, INR, platelet count, antiplatelet therapy, and warfarin use before stroke
Tsivgoulis 2015	Statin (prior)	sICH/good outcome/death	Age, sex, hypertension, DM, atrial fibrillation, congestive heart failure, current smoking, onset-to-treatment time, NIHSS, admission systolic and diastolic blood pressure
Miedema2010	Statin (prior)	sICH/good outcome	Age, NIHSS, glucose concentration, time until treatment, atherothrombotic, early ischemic changes on brain CT scan, hypodensity area > 33% on brain CT scan, hypertension, diabetes, hyperlipidemia ,smoking, previous stroke/transient ischemic attack, history of ischemic heart disease, prior use of antiplatelets, diastolic blood pressure, TC,LDL
Cappellari 2013	Statin (new)	sICH/good outcome/death	Age, time to IVT, NIHSS, hypertension, hypercholesterolemia, atrial fibrillation, antiplatelet, antihypertensive, MCA hyperdensity, TC, LDL
Uyttenboogaart 2008	Statin (prior)TC, TG	sICH	Age, NIHSS, early sign CT scan, treatment beyond 3 h, stroke subtype (lacunar versus non-lacunar), glucose, arterial hypertension, diabetes mellitus and use of antiplatelets, TC, LDL

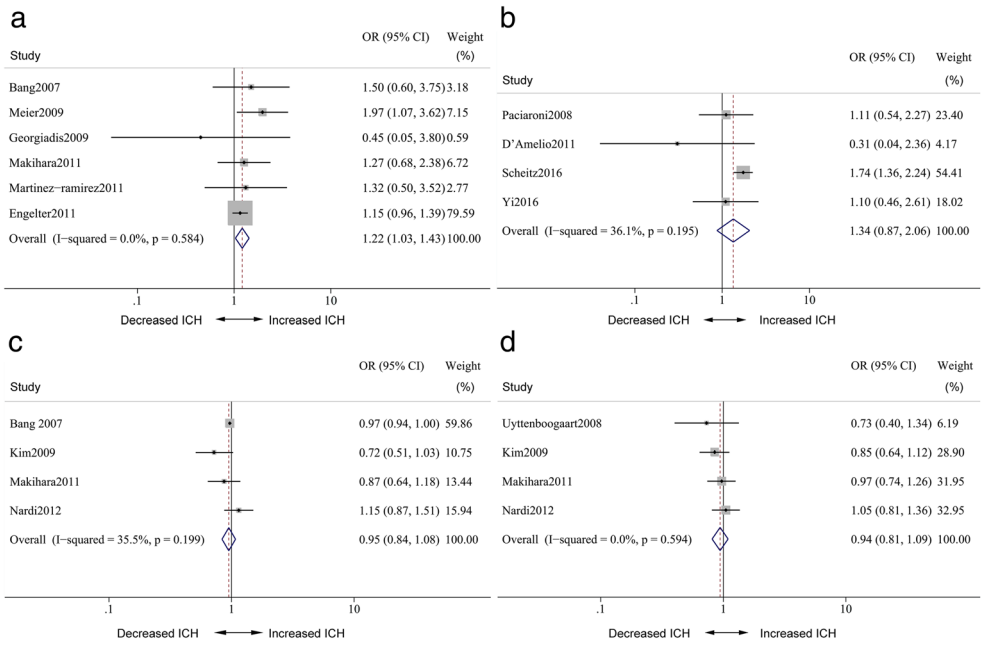

Fig. 3 **a** Crude odds ratio (OR) of prior statin use and overall ICH in patients who received recanalization. **b** Crude OR of prior statin use and overall ICH in patients who partly received recanalization. **c** Adjusted OR of LDL and overall ICH (dose–response analysis). **d** Adjusted OR of TC and overall ICH (dose–response analysis)

use on the outcome of AIS may be due to "saturation effect"; in that case, a tolerance to the beneficial effect of statins develops over time such that their effects are conferred only during the initial few weeks of usage [42]. However, new statin use may not be associated with ICH because such association was not observed in two RCTs. This strengthens the notion that uncontrolled factors can be a source of bias.

This meta-analysis did not associate cholesterol levels with ICH, which is contrary to a previous meta-analysis [47] which found inverse association between cholesterol levels and risk of hemorrhagic stroke. Different from the previous meta-analysis, we focused on cholesterol levels on ICH in AIS; but short follow-up period of exposure to low cholesterol levels in our meta-analysis may underestimate risk of ICH [10]. Additionally, our result is in accordance with a recent meta-analysis that found further lowering LDL-C levels in patients with median LDL-C levels of 1.8 mmol/L or less is not associated with increased risk of hemorrhagic stroke [48].

Our study has several limitations. First, the results were derived from data obtained in observational studies, which can introduce bias; in addition, the number of studies was limited for studies with cholesterol and with patients who partly received recanalization therapy and new statin users. Thus, the results might be insufficient for drawing definite conclusions. Second, we included only studies written in English and might therefore have missed relevant articles in non-English journals. Third, data regarding the duration of and compliance with prior statin treatment and the duration of cholesterol exposure were not available, but these may affect outcome; information on whether statin use was continued or switched after stroke onset was not available. Finally, evidence about dose-related analysis and statin type was not sufficient to draw relevant interpretations.

Conclusion

This meta-analysis showed that statin use (prior or new) and low cholesterol levels are not risk factors of sICH in AIS patients, irrespective of whether the patients received recanalization therapy. However, new statin use is likely associated with a decreased risk of sICH. sICH is likely to be affected by multiple factors, including recanalization therapy, time to treatment, stroke severity, and vascular risk factors other than statin. However, due to the limitations mentioned above, further evidence from large RCTs is needed.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Whiteley WN, Emberson J, Lees KR et al (2016) Risk of intracerebral haemorrhage with alteplase after acute ischaemic stroke: a secondary analysis of an individual patient data meta-analysis. Lancet Neurol 15(9):925–933. https://doi.org/10.1016/S1474-4422(16)30076-X

2. Ní Chróinín D, Asplund K, Åsberg S et al (2013) Statin therapy and outcome after ischemic stroke: systematic review and meta-analysis of observational studies and randomized trials. Stroke 44:448–456. https://doi.org/10.1161/STROKEAHA.112.668277
3. Martinez-Ramirez S, Delgado-Mederos R, Marín R et al (2012) Statin pretreatment may increase the risk of symptomatic intracranial haemorrhage in thrombolysis for ischemic stroke: results from a case-control study and a meta-analysis. J Neurol 259(1):111–118. https://doi.org/10.1007/s00415-011-6137-3
4. Scheitz JF, Seiffge DJ, Tütüncü S et al (2014) Dose-related effects of statins on symptomatic intracerebral hemorrhage and outcome after thrombolysis for ischemic stroke. Stroke 45(2):509–514. https://doi.org/10.1161/STROKEAHA.113.002751
5. Engelter ST, Soinne L, Ringleb P et al (2011) IV thrombolysis and statins. Neurology 77(9):888–895. https://doi.org/10.1212/WNL.0b013e318281cc83
6. Meseguer E, Mazighi M, Lapergue B et al (2012) Outcomes after thrombolysis in AIS according to prior statin use: a registry and review. Neurology 79(17):1817–1823. https://doi.org/10.1212/WNL.0b013e318270400b
7. Thrift A, McNeil J, Donnan G (2002) Reduced frequency of high cholesterol levels among patients with intracerebral haemorrhage. J Clin Neurosci 9:376–380
8. Bang OY, Saver JL, Liebeskind DS et al (2007) Cholesterol level and symptomatic hemorrhagic transformation after ischemic stroke thrombolysis. Neurology 68(10):737–742. https://doi.org/10.1212/01.wnl.0000252799.64165.d5
9. D'Amelio M, Terruso V, Famoso G et al (2011) Cholesterol levels and risk of hemorrhagic transformation after acute ischemic stroke. Cerebrovasc Dis 32(3):234–238. https://doi.org/10.1159/000329315
10. Kim BJ, Lee SH, Ryu WS et al (2009) Low level of low-density lipoprotein cholesterol increases hemorrhagic transformation in large artery atherothrombosis but not in cardioembolism. Stroke 40(5):1627–1632. https://doi.org/10.1161/STROKEAHA.108.539643
11. Nardi K, Leys D, Eusebi P et al (2011) Influence of lipid profiles on the risk of hemorrhagic transformation after ischemic stroke: systematic review. Cerebrovasc Dis Extra 1(1):130–141. https://doi.org/10.1159/000335014
12. Uyttenboogaart M, Koch MW, Koopman K et al (2008) Lipid profile, statin use, and outcome after intravenous thrombolysis for acute ischaemic stroke. J Neurol 255(6):875–880. https://doi.org/10.1007/s00415-008-0797-7
13. Makihara N, Okada Y, Koga M et al (2012) Effect of serum lipid levels on stroke outcome after rt-PA therapy: SAMURAI rt-PA registry. Cerebrovasc Dis 33(3):240–247. https://doi.org/10.1159/000334664
14. Nardi K, Engelter S, Strbian D et al (2012) Lipid Profile in Thrombolysis Study Group. Lipid profiles and outcome in patients treated by intravenous thrombolysis for cerebral ischemia. Neurology 79(11):1101–1108. https://doi.org/10.1212/wnl.0b013e3182608c82
15. Rocco A, Sykora M, Ringleb P, Diedler J (2012) Impact of statin use and lipid profile on symptomatic intracerebral haemorrhage, outcome and mortality after intravenous thrombolysis in acute stroke. Cerebrovasc Dis 33(4):362–368. https://doi.org/10.1159/000335840
16. Stroup DF, Berlin JA, Morton SC et al (2000) Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 283(15):2008–2012
17. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed December 15, 2012.
18. Hacke W, Kaste M, Fieschi C et al (1998) 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 352(9136):1245–1251
19. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327(7414):557–560. https://doi.org/10.1136/bmj.327.7414.557
20. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315:629–634
21. Scheitz JF, Endres M, Heuschmann PU et al (2015) Reduced risk of poststroke pneumonia in thrombolyzed stroke patients with continued statin treatment. Int J Stroke 10(1):61–66. https://doi.org/10.1111/j.1747-4949.2012.00864.x
22. Zhao HD, Zhang YD (2014) The effects of previous statin treatment on plasma matrix metalloproteinase-9 level in Chinese stroke patients undergoing thrombolysis. J Stroke Cerebrovasc Dis 23(10):2788–2793. https://doi.org/10.1016/j.jstrokecerebrovasdis.2014.07.001
23. Meier N, Nedeltchev K, Brekenfeld C et al (2009) Prior statin use, intracranial hemorrhage, and outcome after intra-arterial thrombolysis for acute ischemic stroke. Stroke 40(5):1729–1737. https://doi.org/10.1161/STROKEAHA.108.532473
24. Yi X, Han Z, Wang C, Zhou Q, Lin J (2017) Statin and Aspirin Pretreatment Are Associated with Lower Neurological Deterioration and Platelet Activity in Patients with Acute Ischemic Stroke. J Stroke Cerebrovasc Dis 26(2):352–359. https://doi.org/10.1016/j.jstrokecerebrovasdis.2016.09.030
25. Restrepo L, Bang OY, Ovbiagele B et al (2009) Impact of hyperlipidemia and statins on ischemic stroke outcomes after intra-arterial fibrinolysis and percutaneous mechanical embolectomy. Cerebrovasc Dis 28(4):384–390. https://doi.org/10.1159/000235625
26. Miedema I, Uyttenboogaart M, Koopman K et al (2010) Statin use and functional outcome after tissue plasminogen activator treatment in acute ischaemic stroke. Cerebrovasc Dis 29(3):263–267. https://doi.org/10.1159/000275500
27. Georgiadis AL, Hussein HM, Vazquez G et al (2009) Premorbid use of statins is associated with higher recanalization rates in patients with acute ischemic stroke undergoing endovascular treatment. J Neuroimaging 19(1):19–22. https://doi.org/10.1111/j.1552-6569.2008.00319.x
28. Cappellari M, Bovi P, Moretto G et al (2013) The THRombolysis and Statins (THRaST) study. Neurology 80(7):655–661. https://doi.org/10.1212/WNL.0b013e318281cc83
29. Kang J, Kim N, Park TH et al (2015) Early statin use in ischemic stroke patients treated with recanalization therapy: retrospective observational study. BMC Neurol 15(122). https://doi.org/10.1186/s12883-015-0367-4
30. Tong LS, Hu HT, Zhang S et al (2015) Statin withdrawal beyond acute phase affected outcome of thrombolytic stroke patients: an observational retrospective study. Medicine (Baltimore) 94(17):1–7. https://doi.org/10.1097/MD.0000000000000779
31. Tsivgoulis G, Kadlecová P, Kobayashi A et al (2015) Safety of Statin Pretreatment in Intravenous Thrombolysis for Acute Ischemic Stroke. Stroke 46(9):2681–2684. https://doi.org/10.1161/STROKEAHA.115.010244
32. Scheitz JF, MacIsaac RL, Abdul-Rahim AH et al (2016) Statins and risk of poststroke hemorrhagic complications. Neurology 86(17):1590–1596. https://doi.org/10.1212/WNL.0000000000002606
33. Paciaroni M, Agnelli G, Corea F et al (2008) Early hemorrhagic transformation of brain infarction: rate, predictive factors, and influence on clinical outcome: results of a prospective multicenter study. Stroke 39(8):2249–2256. https://doi.org/10.1161/STROKEAHA.107.510321

34. Cougo-Pinto PT, Santos BL, Dias FA et al (2012) Frequency and predictors of symptomatic intracranial hemorrhage after intravenous thrombolysis for acute ischemic stroke in a Brazilian public hospital. Clinics (Sao Paulo) 67(7):739–743
35. Erdur H, Polymeris A, Grittner U et al (2018) A Score for Risk of Thrombolysis-Associated Hemorrhage Including Pretreatment with Statins. Front Neurol 9(74). https://doi.org/10.3389/fneur.2018.00074
36. Heo JH, Song D, Nam HS et al (2016) Effect and Safety of Rosuvastatin in Acute Ischemic Stroke. Stroke 18(1):87–95. https://doi.org/10.5853/jos.2015.01578
37. Montaner J, Bustamante A, García-Matas S et al (2016) Combination of Thrombolysis and Statins in Acute Stroke Is Safe: Results of the STARS Randomized Trial (Stroke Treatment With Acute Reperfusion and Simvastatin). Stroke 47(11):2870–2873. https://doi.org/10.1161/strokeaha.116.014600
38. Hong KS, Lee JS (2015) Statins in Acute Ischemic Stroke: A Systematic Review. Stroke 17(3):282–301. https://doi.org/10.5853/jos.2015.17.3.282
39. Liu Y, Gong P, Sun H, Zhang S, Zhou J, Zhang Y (2019 Mar) Leukoaraiosis is associated with poor outcomes after successful recanalization for large vessel occlusion stroke. Neurol Sci 40(3):585–591. https://doi.org/10.1007/s10072-018-3698-2
40. Lansberg MG, Albers GW, Wijman CA (2007) Symptomatic intracerebral hemorrhage following thrombolytic therapy for acute ischemic stroke: a review of the risk factors. Cerebrovasc Dis 24(1):1–10. https://doi.org/10.1159/000103110
41. Minhas JS, Wang X, Arima H et al (2018) Lipid-Lowering Pretreatment and Outcome Following Intravenous Thrombolysis for Acute Ischaemic Stroke: A Post Hoc Analysis of the Enhanced Control of Hypertension and Thrombolysis Stroke Study Trial. Cerebrovasc Dis 45(5-6):213–220. https://doi.org/10.1159/000488911
42. Cappellari M, Deluca C, Tinazzi M et al (2011) Does statin in the acute phase of ischemic stroke improve outcome after intravenous thrombolysis? A retrospective study. J Neurol Sci 308(1-2):128–134. https://doi.org/10.1016/j.jns.2011.05.026
43. Wang S, Lee SR, Guo SZ et al (2006) Reduction of tissue plasminogen activator-induced matrix metalloproteinase-9 by simvastatin in astrocytes. Stroke 37:1910–1912. https://doi.org/10.1161/01.str.0000226923.48905.39
44. Montaner J, Molina CA, Monasterio J et al (2003) Matrix metalloproteinase-9 pretreatment level predicts intracranial hemorrhagic complications after thrombolysis in human stroke. Circulation 107:598–603
45. Ovbiagele B, Saver JL, Starkman S et al (2007) Statin enhancement of collateralization in acute stroke. Neurology 68:2129–2131. https://doi.org/10.1212/01.wnl.0000264931.34941.f0
46. Cimino M, Gelosa P, Gianella A et al (2007) Statins: multiple mechanisms of action in the ischemic brain. Neuroscientist. 13(3):208–213. https://doi.org/10.1177/1073858406297121
47. Wang X, Dong Y, Qi X et al (2013) Cholesterol levels and risk of hemorrhagic stroke: a systematic review and meta-analysis. Stroke 44(7):1833–1839. https://doi.org/10.1161/STROKEAHA.113.001326
48. Sabatine MS, Wiviott SD, Im K et al (2018) Efficacy and Safety of Further Lowering of Low-Density Lipoprotein Cholesterol in Patients Starting With Very Low Levels: A Meta-analysis. JAMA Cardiol 3(9):823–828. https://doi.org/10.1001/jamacardio.2018.2258