Title: **Statins and the risk of intracerebral haemorrhage in stroke patients: Systematic review and meta-analysis**

Study design: Systematic review and meta-analysis

Brief Title: Systematic review of statins in stroke patients

Authors: Oliver J Ziff *NIHR Academic Clinical Fellow*[1,2], Gargi Banerjee *Clinical Research Fellow*[1], Gareth Ambler *Senior lecturer in Medical Statistics*[3] and David J Werring *Professor of Neurology & Consultant Neurologist*[*1,2]

From the [1]Stroke Research Centre, Department of Brain Repair and Rehabilitation, UCL, [2]Institute of Neurology and the National Hospital for Neurology and Neurosurgery, London, UK. [3]Department of Statistical Science, UCL, London, UK.

*Address for correspondence:

Professor David J Werring,

The National Hospital for Neurology and Neurosurgery,

UCL Institute of Neurology,

Queens Square, London

WC1N 3BG, UK

Email: d.werring@ucl.ac.uk   Tel: +44 (0)20 3108 7493

Word count total (text):   3513

References: 73 total (51 in systematic review)

Key Words: Statin; intracerebral hemorrhage; hemorrhagic stroke; mortality; meta-analysis; systematic review.

ABSTRACT

Objective: Whether statins increase the risk of intracerebral hemorrhage (ICH) in patients with a previous stroke remains uncertain. This study addresses the evidence of statin therapy on ICH and other clinical outcomes in patients with previous ischemic stroke (IS) or ICH.

Methods: A systematic literature review and meta-analysis was performed in conformity with the PRISMA guidelines to assess observational and randomised studies comparing statin therapy with control (placebo or no treatment) in patients with a previous ICH or IS. The risk ratios (RR) for the primary outcome (ICH) and secondary outcomes (IS, any-stroke, mortality and function) were pooled using random effects meta-analysis according to stroke subtype.

Results: Forty-three studies, with a combined total of 317,291 patient-years of follow-up were included. In patients with previous ICH, statins had no significant impact on the pooled RR for recurrent ICH (1.04, 95% CI 0.86-1.25; n=23,695), however statins were associated with significant reductions in mortality (0.49, 0.36-0.67; n=89,976) and poor functional outcome (0.71, 0.67-0.75; n=9,113). In patients with previous IS, statins were associated with a non-significant increase in ICH (1.36, 0.96-1.91; n=103,525), but significantly lower risks of recurrent IS (0.74, 0.66-0.83; n=53,162), any-stroke (0.82, 0.67-0.99; n=55,260), mortality (0.68, 0.50-0.92; n=74,648) and poor functional outcome (RR 0.83, 0.76-0.91; n=34,700).

Conclusions: Irrespective of stroke subtype, there were non-significant trends towards future ICH with statins. However, this risk was overshadowed by substantial and significant improvements in mortality and functional outcome amongst statin users.

Registration: PROSPERO: CRD42017079863

Abbreviations

AF	Atrial Fibrillation
CEA	Carotid endartarectomy
CI	Confidence interval
HR	Hazard ratio
ICH	Intracerebral hemorrhage
OR	Odds ratio
RCT	Randomised controlled trial
RoBANS	Risk of Bias Assessment Tool for Nonrandomized Studies
RR	Risk ratio
TIA	Transient ischemic attack

INTRODUCTION

Statin therapy has routinely been used to inhibit cholesterol synthesis and avoid cardiovascular events throughout the last three decades. They are recommended by both American and European guidelines to reduce risk of stroke and cardiovascular events in patients with cerebrovascular disease.[1][2] Despite the demonstrated beneficial effects of statins in preventing first ever stroke, prescriptions remain suboptimal with age, gender, racial and geographic discrepancies.[3] This may partially be explained by concerns around the potential risk of intracerebral hemorrhage (ICH) with statins due to their anti-platelet and anti-coagulant effects, particularly in patients with a previous ICH.[4][5]

In two large randomised trials, Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)[6] and Heart Protection Study (HPS),[7] the benefit in reducing recurrent ischemic stroke was offset in part by an increased risk of hemorrhagic stroke. A risk benefit decision analysis of statin therapy in patients with prior ICH concluded that statin avoidance should be considered following ICH particularly in those with lobar ICH.[8] Conversely, two meta-analyses of randomised trials enrolling patients without prior stroke found no significant association between statins and ICH with significant reductions in all-strokes and all-cause mortality with statin therapy.[9][10] Additionally, statin use after ICH was associated with early neurological improvement at 6 months.[11] There is, therefore, a clear imperative to define the place of statins in the clinical management of patients with a previous stroke at future risk of ICH.

In view of the potential usefulness of statins in patients with a previous stroke, and in an attempt to settle the uncertainty over adverse clinical outcomes, we assessed the efficacy and safety of statins by comprehensively meta-analysing all available observational and experimental studies. We aim to build on the previous meta-analyses by focusing on studies in

which patients had an established ischemic or hemorrhagic stroke. We used meta-regression techniques to evaluate the association of study characteristics with the risk of clinical outcomes.

METHODS

Eligibility criteria & search strategy

All studies comparing clinical outcomes in participants treated with statins and control (placebo or no treatment) were evaluated, regardless of study design. We excluded studies where statins were used for primary prevention or did not provide comparative outcomes. Studies assessing secondary prevention of cerebrovascular disease were included. The definitions of ICH and ischemic stroke used by each individual study were accepted. A systematic review of MEDLINE (1960 to June 2017), EMBASE (1980 to June 2017) and the Cochrane Library (until June 2017 Issue) were performed. The search strategy included keywords and MeSH terms relating to statins and ICH, ischemic stroke, death, and functional outcomes. We manually searched reference lists of relevant studies, investigated registers of on-going trials and included studies after discussion with content experts. The review was conducted according to the PRISMA guidelines and was prospectively registered with the PROSPERO database of systematic reviews (CRD42017079863).[12]

Data collection, synthesis and risk of bias

Two investigators (OJZ and GB) independently extracted and tabulated data in a standardised data extraction form. Discrepancies and missing data were resolved by group discussion, reference to the original publication and additional independent adjudication (DJW). All data were extracted from studies, including crude outcomes and adjusted analyses (multivariate adjustment and propensity-matched), Careful note was made of the analysis method (including risk ratio [RR; preferred], odds ratio [OR] or hazard ratio [HR]) and the population studied. Risk of bias was assessed with the Cochrane Collaboration's Risk of Bias tool for RCTs and the Risk of Bias Assessment Tool for Non-randomized Studies (RoBANS), which address key criteria including selection bias, exposure measurement, blinding and selectivity of reporting.

Assessment of bias risk was performed independently from data extraction, with each study assessed by two authors.

Primary and Secondary Outcomes

The predefined primary outcome was ICH. Secondary outcomes included ischemic stroke, any-stroke, all-cause mortality and poor functional outcome. The definitions used by each individual study were accepted. To investigate whether treatment effects vary between stroke types, analyses were subgrouped by previous ICH and previous ischemic stroke.

Statistical analysis

Baseline demographics in the statin and control groups were compared using meta-analysis and summarised as the OR. Random effects meta-analysis was pre-specified to combine estimates from different studies. Pooled binary event data for statin and control cohorts were compared using a RR with associated 95% confidence intervals (CI) using the method of DerSimonian and Laird. In cases where the OR was described, these were converted to RR (RR = OR / ([1−pRef] + [pRef*OR]), where pRef is the prevalence of the outcome in the reference group). RR and corresponding CI were log-transformed before pooling. HR were included in the systematic review but not meta-analysis due to a scarcity of results presented in this way. Where studies reported several results for the same outcome, we extracted the result based on the longest follow-up duration and most adjustment factors. Sensitivity analyses were performed according to study design (randomised trials and observational cohorts). The degree of heterogeneity between studies was quantitatively assessed using the I^2 statistic (I^2 of $\geq 50\%$ indicates substantial heterogeneity, $\geq 75\%$ suggests considerable heterogeneity). Meta-regression was performed to quantify the heterogeneity, assess the impact of baseline variables and risk of bias on estimates of each outcome, according to stroke subtype. Publication bias was evaluated by inspection of funnel plots and quantitatively assessed using Begg's and

Egger's tests to identify small-study effects. A p-value < 0.05 was considered statistically

significant. Analyses were performed using STATA version 13.1 (StataCorp LP, Texas).

RESULTS

The search strategy identified 51 studies for systematic review, including 1,324,450 patients on statin therapy or control (placebo or no treatment) and 4,098,285 patient-years of follow-up (eFigure 1). Of the 51 studies, 36 were observational,[11 13-46] and 15 were randomised on the basis of statin therapy.[6 7 47-59] Study descriptors are summarised in eTable 1. Forty-three studies were suitable for inclusion in the quantitative meta-analysis comparing statins with control in patients with a previous stroke. Of the 43 studies, 15 provided data on patients with a previous ICH[6 11 17 34-36 38-44 47 48] and 29 reported outcomes in patients with a prior ischemic stroke.[13-15 17-32 45 46 49-56] 84,356 patients were taking statins (47.1%) compared to 94,597 in the control arms (52.8%). The weighted average length of follow-up was 1.77 years with a range of 0.1-7.0.

Differences in key characteristics between statin and control groups are summarised in Table 1 (for full baseline demographics, see eTable 2). Patients receiving statins had more diabetes, hypertension, hyperlipidemia and coronary artery disease than controls and were more often receiving anti-coagulant and anti-platelet drugs.

Meta-analysis was performed for five outcomes: ICH, ischemic stroke, any-stroke, all-cause mortality and functional outcome. A summary of the individual meta-analyses performed is presented in Figure 1 and detailed results are discussed below. The risk of bias in individual studies is presented in eTables 3 and 4. As expected, this was proportional to the robustness of study design, with RCTs having the lowest risk of bias. There was no evidence of small study effects or publication bias in any of the outcomes assessed (all Eggers p>0.1).

Population: Previous intracerebral hemorrhage

Fifteen studies of patients with previous ICH were suitable for meta-analysis (n=50,374; Table 2; Figure 2).[6 11 17 34-36 38-44 47 48]

Table 1: Pooled weighted characteristics

Baseline characteristic	Statin vs. control arm (95% CI)		p-value
Male gender	OR 1.08	(0.98-1.18)	0.11
Diabetes	OR 1.49	(1.31-1.69)	<0.001
AF	OR 1.00	(0.88-1.14)	1.00
Smoker	OR 0.90	(0.73-1.12)	0.34
Hypertension	OR 1.54	(1.25-1.91)	<0.001
Hyperlipidemia	OR 4.32	(2.29-8.13)	<0.001
CAD	OR 2.05	(1.53-2.74)	<0.001
Anti-coagulant	OR 1.71	(1.29-2.26)	<0.001
Anti-platelet	OR 2.36	(1.69-3.30)	<0.001

Meta-analysis of baseline demographics comparing statin-treated patients with control. AF, atrial fibrillation, CAD, coronary artery disease, OR, odds ratio

Table 2: Summary of studies and patients according to cerebrovascular disease subtype

Population	Outcome	Number of Studies	Statin Patients	Control Patients	Total number of patients	Patient-years of follow-up
Systematic Review	-	51	-	-	1,324,450	4,098,285
Meta-analysis	-	43	84,356	94,597	178,953	317,291
Previous intracerebral hemorrhage	Total	15	7,645	42,729	50,374	91,467
	Recurrent ICH	3	3,052	20,643	23,695	62,930
	Ischemic stroke	1	45	48	93	456
	Any stroke	1	45	48	93	456
	All-cause mortality	15	57,189	32,787	89,976	87,954
	Poor functional outcome	7	1,942	7,171	9,113	5,915
Previous ischemic stroke	Total	29	76,711	51,868	128,579	225,824
	ICH	11	64,005	39,520	103,525	210,509
	Recurrent ischemic stroke	3	40,808	12,354	53,162	50,870
	Any stroke	7	41,643	13,617	55,260	59,078
	All-cause mortality	13	51,500	23,148	74,648	43,568
	Poor functional outcome	19	15,858	18,842	34,700	31,907

Outcome: Recurrent intracerebral hemorrhage

One randomised and two observational studies of statins in patients with previous ICH reporting the outcome recurrent ICH were included (n=23,695).[34 44 47] There was no difference in recurrent ICH between patients on statin and control (RR 1.04, 95% CI 0.86-1.25, P=0.70). Two additional studies providing HRs were both concordant with this neutral result.[33 37] Sensitivity analysis of study design demonstrated that although there was no significant difference between the randomised and observational studies, the observational studies had a noteworthy lower pooled relative risk than the randomised SPARCL subgroup (RR 1.02, 95% CI 0.89-1.16 vs. RR 3.73, 95% CI 0.83-17.0; see Figure 1A, eTable5).

Outcome: Ischemic stroke

One sub study of statins in patients with previous ICH (n=93) reported a non-significant increase in incident ischemic stroke (RR 1.60, 95% CI 0.28-9.14).[47]

Outcome: Any stroke

One sub study of statins in patients with previous ICH (n=93) reported a non-significant increase in any-stroke (RR 2.67, 95% CI 0.90-7.90, P=0.08).[47]

Outcome: All-cause mortality

In 15 studies with previous ICH (n=89,976) there was a significant reduction in all-cause mortality with statins versus control (RR 0.49, 95% CI 0.36-0.67, P<0.001) but with significant heterogeneity ($I^2 = 91.7\%$, P<0.001).[6 11 17 34-36 38-41 43 48] Two additional studies reporting HRs were consistent with this finding.[33 42] Sensitivity analysis of study design demonstrated that observational studies had a lower pooled relative risk than the randomised analyses (RR 0.46, 95% CI 0.33-0.63 vs. RR 1.03, 95% CI 0.47-2.49; see eTable5).

We performed an exploratory meta-regression of the impact of differences in key baseline characteristics on all cause mortality between statin and control patients. This analysis demonstrated that the mortality of benefit of statins was diminished when the statin group was composed of a smaller proportion of males than the control cohort (P=0.003; eTable 5). Additionally a greater mortality benefit with statins was associated with a more recent year of publication (P=0.01).

Outcome: Poor functional outcome

Seven studies of patients with previous ICH reported functional outcome (n=9,113), demonstrating a significant reduction in poor functional outcome amongst statin-users compared to control (RR 0.71, 95% 0.67-0.75, P<0.001).[11 17 36 40-43]

Population: Previous ischemic stroke

Twenty-nine studies of patients with previous ischemic stroke were suitable for meta-analysis (n=128,579; Table 2; Figure 3).[13-15 17-32 45 46 49-56]

Outcome: Intracerebral hemorrhage

Eleven studies of statins in patients with prior ischemic stroke reporting ICH were included (n=103,525).[15 18-21 23 26 29 45 51 52] There was a non-significant increase in ICH with statins compared to control (RR 1.36, 95% CI 0.96-1.91; P=0.08) but with substantial heterogeneity ($I^2 = 79.3$; P<0.001). In studies that enrolled only patients with an ischemic stroke undergoing thrombolysis for ischemic stroke there was a non-significant increase in ICH with statins (RR 1.61, 95% CI 0.77-3.34; P=0.20) compared with the remaining 6 studies without thrombolysis (RR 1.21, 95% CI 0.83-1.76; P=0.33).[15 18 19 29 45] Sensitivity analysis of study design demonstrated that observational studies had a lower pooled relative risk than the randomised trials (RR 1.73, 95% CI 1.20-2.49 vs. RR 1.28, 95% CI 0.85-1.93; see eTable5).

An exploratory meta-regression of the effect of study-level bias demonstrated that studies with lower bias reported a greater association of statins with ICH (P=0.017; eFigure 2). This was supported by a sensitivity analysis of study design, where the pooled 2 randomised trials reported a significant increase in ICH (RR 1.73, 95% CI 1.20-2.49; P=0.004), whilst the 9 observational studies reported a neutral association (RR 1.28, 95% CI 0.85-1.93; P=0.23). Meta-regression was used to explore the impact of differences in key baseline characteristics between statin and control patients on ICH. This revealed that studies with a similar incidence of hyperlipidemia in both the statin and control groups were associated with increased ICH with statins (P=0.002). Conversely, studies where patients had a higher incidence of hyperlipidemia in the statin group compared to control were associated with reduced ICH with statins. Additionally studies with larger proportion of males in the statin arm were more likely to report an increase in ICH with statins (P=0.025)

Outcome: Recurrent ischemic stroke

Three studies of patients with previous ischemic stroke (n=53,162) revealed a reduction in recurrent ischemic stroke with statins compared to control (RR 0.74, 95% CI 0.66-0.83; P<0.001).[23][51][52] Two additional studies reporting HRs were both consistent with this outcome.[21][60]

Outcome: Any stroke

Seven studies with previous ischemic stroke were included (n = 55,260).[23][46][49-52][54] There was a borderline significant reduction in any-stroke with statins compared to control (RR 0.82, 95% CI 0.67-0.99; P=0.04) but with significant heterogeneity (I^2 = 72.9; P=0.001).

Outcome: All-cause mortality

In 13 studies pertaining to the prior ischemic stroke cohort (n=74,648), there was a reduction in all-cause mortality with statins compared to control (RR 0.68, 95% CI 0.50-0.92, P=0.01) [13][17][18][23][25][29][30][32][45][46][52][55][56] but with considerable heterogeneity ($I^2 = 86.5$; P<0.001). Two additional analyses reporting HRs both demonstrated significant reductions in mortality.[16][22] Sensitivity analysis of study design demonstrated that although there was a significant reduction in mortality in the pooled observational studies (RR 0.60, 95% CI 0.42 – 0.85) there was no statistical difference in the pooled randomised analyses (RR 1.04, 95% CI 0.87 – 1.24; eTable 5).

Outcome: Poor functional outcome

Twenty-one analyses (n=34,700) in 19 studies of patients with prior ischemic stroke reported functional outcome. Together these demonstrated that statin use was significantly associated with a reduction in poor functional outcome compared to control (RR 0.83, 95% CI 0.76-0.91, P<0.001) albeit with significant heterogeneity ($I^2 = 85.8$; P<0.001).[13][14][17-19][22][24-32][45][52][53][56]

DISCUSSION

In our comprehensive meta-analysis including a combined total of over 300,000 patient-years of follow-up we found that in patients with a previous ICH, statins were not associated with an increased risk of recurrent ICH. In patients with previous ischemic stroke, we found a clear benefit of statins in reducing recurrent ischemic stroke at the expense of a non-significant increase in ICH. Statins were associated with substantial and significant improvements in mortality and functional outcome irrespective of stroke subtype.

Previous intracerebral hemorrhage

Statins exert beneficial cardiovascular pleotropic effects on endothelial dysfunction through normalising vasomotion, increasing bioavailability of nitric oxide and supressing inflammatory responses.[61] However, the anti-platelet and anti-coagulant effects of statins have raised concerns that they may increase the risk of ICH. Statins have also been hypothesised to have potentially harmful consequences in acute ICH where their diverse pharmacological properties may contribute to hematoma expansion.[62] In both the HPS and SPARCL trials, which enrolled patients with a previous stroke, statins were associated with increased ICH compared to placebo.[7 52] Of these two trials, only SPARCL provided a subgroup analysis of patients with a previous hemorrhagic stroke, demonstrating a non-significantly increased risk of recurrent ICH.[47] In contrast, four larger observational cohort studies all demonstrated a neutral effect of statins on recurrent ICH.[33 34 37 44], consistent with our findings.

We found that in ICH survivors statins were associated with improved mortality and functional outcome with no significant effect on recurrent ICH. We were unable to meta-analyse the outcomes ischemic stroke and any stroke-type as the only data available was from the hemorrhagic stroke subgroup population of the SPARCL trial (n=93).[47] These results do not support withholding statins after ICH, but large randomised controlled trials are still needed to consolidate these findings.

Most intracerebral hemorrhages are due to cerebral small vessel disease hypertensive arteriopathy (arteriolosclerosis), which affects deep perforating vessels, and cerebral amyloid angiopathy (CAA), which affects superficial cortical and leptomeningeal vessels. Thus, whilst hypertension is the strongest risk factor for deep ICH, a substantial proportion of lobar ICH are due to CAA. CAA has a high recurrence risk (7·4% per year in a pooled analysis of cohort studies[63]) so has caused the strongest concerns regarding statin use. Observational and randomised data suggest that recurrent ICH can be reduced by anti-hypertensive therapy,[64] however CAA currently lacks any specific preventative therapy. A retrospective analysis found that statins in patients with ICH was associated with microbleeds on MRI, particularly of cortico-subcortical distribution, commonly observed in CAA.[65] Thus, although our findings are reassuring, we were unable to stratify by ICH location or presumed cause, so decisions in ICH survivors require an individualised patient assessment of indication, comorbidity and the goal of statin therapy. Unsurprisingly, amongst stroke physicians the use of statins in patients following ICH remains contentious. American guidelines recommend statins in patients with ICH due to insufficient data to advise restriction (Class IIb; Level C) whilst European guidelines do not address the issue.[1,2] Unfortunately, the only double blinded placebo controlled RCT of statins in patients with ICH (NCT00718328) terminated early due to poor recruitment.

Previous ischemic stroke

In survivors of ischemic stroke, statins were associated with substantial and significant improvements in mortality, functional outcome and ischemic stroke, with a non-significant trend towards increased ICH. Although epidemiological data indicate a modest link between high serum LDL and greater risk of ischemic stroke, they have also pointed towards an association of low LDL and a heightened risk of ICH.[66] By reducing serum cholesterol, statins may reduce the integrity of the vasculature leading to arterial necrosis and microaneurysm formation.[67] A previous meta-analysis of randomised trials of statins for primary and secondary prevention of stroke demonstrated significant reductions in LDL and ischemic

stroke risk in both primary and secondary prevention, but a significant increase in ICH was identified in secondary prevention trials.[68] This finding was largely based on the only dedicated secondary prevention trial of stroke, SPARCL, which identified a significant reduction in recurrent ischemic stroke but with a higher incidence of ICH.[59] Similarly in the HPS trial previous stroke subgroup, there was a 91% increased risk in hemorrhagic stroke with statins.[7] We found that when these trials are combined with observational studies and limited to secondary prevention, this ICH risk persists, albeit non-significantly.

Nevertheless, given the potentially increased risk of ICH with statin treatment, physicians should have caution in recommending statins to individuals with risk factors for ICH. Indeed, we found substantial heterogeneity in treatment effect indicating a "one size fits all" approach to statins may be inappropriate. For example, whilst the effectiveness of statin therapy in patients with previous ischemic stroke due to atherosclerotic disease is clear, in those due to atrial fibrillation (AF) the evidence is less obvious. Indeed stroke patients with AF, who were excluded from SPARCL, often have higher bleeding risks due to concomitant anticoagulation.[52] Another important concomitant therapy to consider is thrombolysis, which further adds to the hemorrhagic transformation risk.[4 5] The results of our sensitivity analysis confirmed that statins increased the risk of ICH in patients with ischemic stroke treated with thrombolysis. Age is another important component of bleeding risk. Unfortunately numerous statin trials excluded frail elders casting doubt on how results might translate to those over 80 years old. Only with careful patient selection can an optimal balance between efficacy and safety be achieved.

If statins are considered in stroke survivors, then further contentious questions arise including: (i) which statin; (ii) what dose; (iii) when to initiate; (iv) and when to withdraw. With regard to agent and dose, the on-going Treat Stroke to Target (TST) trial (NCT01252875) will provide clarity on targeted LDL levels and vascular events amongst survivors of ischemic stroke. Regarding timing, surrogate marker studies indicate a role of statins in the acute phase of ischemic stroke through upregulation of nitric oxide, fibrinolytic and antithrombotic mechanisms, however the major statin trials typically did not enrol patients until ~3 months post stroke.[52 69] The only randomised trial to investigate timing per se demonstrated no

improvement in neurologic function at 90 days with early (<24 hours) versus delayed (7 days) therapy, although included patients had low stroke severity who may not have substantial disease substrate to benefit.[70]

As statins are often not prescribed until clinicians detect presence of cardiovascular disease risk factors, treatment with statins is likely to be influenced by the probability of ICH, creating "confounding by indication." We have demonstrated differences in baseline characteristics between patients in statin and control groups in observational studies and exposed their impact on ICH through meta-regression analysis. These differences may partly explain the conflicting results between randomised and observational studies,[21 45] a problem not exclusive to stroke trials.[71]

Taking all studies into account, despite prescription biases the net effect of statin use appears clearly beneficial for mortality and functional outcome, even though an increased risk of ICH may partly offsets these improvements. Our findings thus suggest that statins should continue to be considered in those with a previous stroke (including ICH) to reduce mortality and improve functional outcome, but caution should be taken in individuals at high risk for ICH (e.g. older anticoagulated patients with poorly controlled hypertension or CAA). In these patients alternative approaches to manage hyperlipidemia should be considered, for instance through upregulation of LDL receptors using the novel PCSK9 inhibitors.[72]

Limitations

Our review is based on published data of independent studies, performed in accordance with explicit, reproducible methodology. While meta-analysis of individual patient data is ideal, it is unrealistic with such large data groupings across a wide number of studies. We recognise a number of drawbacks of our study. Firstly there is a deficiency in sample sizes from both randomized and observational studies to generate adequately powered pooled effect estimates especially in the previous ICH cohort. There was insufficient data to perform meta-analysis of statin dose, statin type or the impact of location of ICH (lobar versus deep). Second, definitions of ICH and ischemic stroke between studies differed with potential for

miscategorisation. Although some studies precisely reported the stroke aetiology, type and severity, many did not. Third, due to expected disparities in study designs and populations, we pre-specified a random-effects model. Indeed, we noted substantial heterogeneity in treatment effect for many of the assessed outcomes. However, most of the heterogeneity was caused by the effect magnitude instead of the effect direction. Finally, although no signal of publication bias was identified, statistical assessments can be misrepresentative particularly with considerable heterogeneity.[73]

Conclusion

In patients with ICH, statins did not increase recurrent ICH. In survivors of ischemic stroke, although statins substantially and significantly reduced recurrent ischemic stroke, there was a non-significant increase in ICH. Nonetheless, statins show clear benefits in reducing mortality and improving functional outcome irrespective of stroke subtype. These results were predominantly based on observational data with insufficient randomised trial data available. Given that observational data is subject to inherent confounding, future randomised trials of statins in patients with cerebrovascular disease (especially ICH survivors) are required to clarify the safety of this therapy on future ICH risk.

Ethics approval:

Not required (based on published data).

Statement:

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd to permit this article (if accepted) to be published in BMJ editions and any other BMJPGL products and sublicences such use and exploit all subsidiary rights, as set out in our licence.

Transparency:

The lead author (the manuscript's guarantor) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

Licence:

The default licence, CC BY NC licence, is required.

Data sharing:

No additional data are available, though details on statistical analysis are available from the corresponding author on request.

Patient involvement:

We have insufficient evidence to comment on whether patients were actively involved in the design or management of the component studies

References

1. Hemphill JC, 3rd, Greenberg SM, Anderson CS, et al. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 2015;46:2032-60.

2. Steiner T, Al-Shahi Salman R, Beer R, et al. European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage. *Int J Stroke* 2014;9:840-55.

3. Albright KC, Howard VJ, Howard G, et al. Age and Sex Disparities in Discharge Statin Prescribing in the Stroke Belt: Evidence From the Reasons for Geographic and Racial Differences in Stroke Study. *J Am Heart Assoc* 2017;6.

4. Hong KS, Lee JS. Statins in Acute Ischemic Stroke: A Systematic Review. *J Stroke* 2015;17:282-301.

5. Cordenier A, De Smedt A, Brouns R, et al. Pre-stroke use of statins on stroke outcome: a meta-analysis of observational studies. *Acta Neurol Belg* 2011;111:261-7.

6. Amarenco P, Benavente O, Goldstein LB, et al. Results of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial by stroke subtypes. *Stroke* 2009;40:1405-9.

7. Heart Protection Study Collaborative G. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7-22.

8. Westover MB, Bianchi MT, Eckman MH, Greenberg SM. Statin use following intracerebral hemorrhage: A decision analysis. *Archives of Neurology* 2011;68

9. McKinney JS, Kostis WJ. Statin therapy and the risk of intracerebral hemorrhage: a meta-analysis of 31 randomized controlled trials. *Stroke* 2012;43:2149-56.

10. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;366:1267-78.

11. Tapia-Perez JH, Rupa R, Zilke R, Gehring S, Voellger B, Schneider T. Continued statin therapy could improve the outcome after spontaneous intracerebral hemorrhage. *Neurosurg Rev* 2013;36:279-87; discussion 87.

12. Ziff OJ, Banerjee G, Ambler A, Werring DJ. The impact of statins on clinical outcomes in patients with a previous stroke: a systematic review and meta-analysis CRD42017079863. *PROSPERO International prospective register of systematic reviews* 2017.

13. Al-Khaled M, Matthis C, Eggers J. Statin treatment in patients with acute ischemic stroke. *Int J Stroke* 2014;9:597-601.

14. Alvarez-Sabin J, Huertas R, Quintana M, et al. Prior statin use may be associated with improved stroke outcome after tissue plasminogen activator. *Stroke* 2007;38:1076-8.

15. Prior statin use, intracranial hemorrhage and outcome after intra-arterial thrombolysis for acute ischemic stroke. 18th European Stroke Conference; 2009; Stockholm, Sweden.

16. Asberg S, Henriksson KM, Farahmand B, et al. Ischemic stroke and secondary prevention in clinical practice: a cohort study of 14,529 patients in the Swedish Stroke Register. *Stroke* 2010;41:1338-42.

17. Biffi A, Devan WJ, Anderson CD, et al. Statin use and outcome after intracerebral hemorrhage: case-control study and meta-analysis. *Neurology* 2011;76:1581-8.

18. Cappellari M, Bovi P, Moretto G, et al. The THRombolysis and STatins (THRaST) study. *Neurology* 2013;80:655-61.

19. Cappellari M, Deluca C, Tinazzi M, et al. Does statin in the acute phase of ischemic stroke improve outcome after intravenous thrombolysis? A retrospective study. *J Neurol Sci* 2011;308:128-34.

20. Chang CH, Lin CH, Caffrey JL, et al. Risk of Intracranial Hemorrhage From Statin Use in Asians: A Nationwide Cohort Study. *Circulation* 2015;131:2070-8.

21. Hackam DG, Austin PC, Huang A, et al. Statins and intracerebral hemorrhage: a retrospective cohort study. *Arch Neurol* 2012;69:39-45.

22. Hjalmarsson C, Bokemark L, Manhem K, Mehlig K, Andersson B. The effect of statins on acute and long-term outcome after ischemic stroke in the elderly. *Am J Geriatr Pharmacother* 2012;10:313-22.

23. Lee M, Saver JL, Wu YL, et al. Utilization of Statins Beyond the Initial Period After Stroke and 1-Year Risk of Recurrent Stroke. *J Am Heart Assoc* 2017;6.

24. Leker RR, Khoury ST, Rafaeli G, et al. Prior use of statins improves outcome in patients with intracerebral hemorrhage: prospective data from the National Acute Stroke Israeli Surveys (NASIS). *Stroke* 2009;40:2581-4.

25. Ni Chroinin D, Callaly EL, Duggan J, et al. Association between acute statin therapy, survival, and improved functional outcome after ischemic stroke: the North Dublin Population Stroke Study. *Stroke* 2011;42:1021-9.

26. Phipps MS, Zeevi N, Staff I, Fortunato G, Kuchel GA, McCullough LD. Stroke severity and outcomes for octogenarians receiving statins. *Arch Gerontol Geriatr* 2013;57:377-82.

27. Restrepo L, Bang OY, Ovbiagele B, et al. Impact of hyperlipidemia and statins on ischemic stroke outcomes after intra-arterial fibrinolysis and percutaneous mechanical embolectomy. *Cerebrovasc Dis* 2009;28:384-90.

28. Scheitz JF, Endres M, Heuschmann PU, Audebert HJ, Nolte CH. Reduced risk of poststroke pneumonia in thrombolyzed stroke patients with continued statin treatment. *Int J Stroke* 2015;10:61-6.

29. Scheitz JF, Seiffge DJ, Tutuncu S, et al. Dose-related effects of statins on symptomatic intracerebral hemorrhage and outcome after thrombolysis for ischemic stroke. *Stroke* 2014;45:509-14.

30. Song B, Wang Y, Zhao X, et al. Association between statin use and short-term outcome based on severity of ischemic stroke: a cohort study. *PLoS One* 2014;9:e84389.

31. Tsai NW, Lee LH, Huang CR, et al. The association of statin therapy and high-sensitivity C-reactive protein level for predicting clinical outcome in acute non-cardioembolic ischemic stroke. *Clin Chim Acta* 2012;413:1861-5.

32. Yeh PS, Lin HJ, Chen PS, et al. Effect of statin treatment on three-month outcomes in patients with stroke-associated infection: a prospective cohort study. *Eur J Neurol* 2012;19:689-95.

33. Statin therapy and the risk of death and recurrent intracerebral hemorrhage. International Journal of Stroke Conference: European Stroke Organisation Annual Conference 2015; Glasgow United Kingdom.

34. Chen PS, Cheng CL, Chang YC, Kao Yang YH, Yeh PS, Li YH. Early statin therapy in patients with acute intracerebral hemorrhage without prior statin use. *Eur J Neurol* 2015;22:773-80.

35. Early statin therapy reduces all-cause mortality in acute hemorrhagic stroke patients without prior statin use. European Society of Cardiology, ESC Congress 2013 2013; Amsterdam Netherlands. European Heart Journal.

36. Dowlatshahi D, Demchuk AM, Fang J, et al. Association of statins and statin discontinuation with poor outcome and survival after intracerebral hemorrhage. *Stroke* 2012;43:1518-23.

37. FitzMaurice E, Wendell L, Snider R, et al. Effect of statins on intracerebral hemorrhage outcome and recurrence. *Stroke* 2008;39:2151-4.

38. Flint AC, Conell C, Rao VA, et al. Effect of statin use during hospitalization for intracerebral hemorrhage on mortality and discharge disposition. *JAMA Neurol* 2014;71:1364-71.

39. Niewada M, Skowronska M, Sarzynska-Dlugosz IM, Kaminski B, Kobayashi A, Czlonkowska A. Pharmacotherapy prior to and in acute haemorrhagic stroke. The use of pharmacotherapy and drugs associated outcomes in real-world practice - findings from the Polish Hospital Stroke Registry. *Neurol Neurochir Pol* 2013;47:517-24.

40. Pan YS, Jing J, Wang YL, et al. Use of statin during hospitalization improves the outcome after intracerebral hemorrhage. *CNS Neurosci Ther* 2014;20:548-55.

41. Siddiqui FM, Langefeld CD, Moomaw CJ, et al. Use of Statins and Outcomes in Intracerebral Hemorrhage Patients. *Stroke* 2017;48:2098-104.

42. Tapia-Perez JH, Zilke R, Schneider T. Match-study of statin therapy in spontaneous intracerebral hemorrhage: is the discontinuation reasonable? *J Neurosurg Sci* 2016;60:301-12.

43. Winkler J, Shoup JP, Czap A, et al. Long-term improvement in outcome after intracerebral hemorrhage in patients treated with statins. *J Stroke Cerebrovasc Dis* 2013;22:e541-5.

44. Schmidt LB, Goertz S, Wohlfahrt J, Melbye M, Munch TN. Recurrent Intracerebral Hemorrhage: Associations with Comorbidities and Medicine with Antithrombotic Effects. *PLoS One* 2016;11:e0166223.

45. Meier N, Nedeltchev K, Brekenfeld C, et al. Prior statin use, intracranial hemorrhage, and outcome after intra-arterial thrombolysis for acute ischemic stroke. *Stroke* 2009;40:1729-37.

46. Milionis HJ, Giannopoulos S, Kosmidou M, et al. Statin therapy after first stroke reduces 10-year stroke recurrence and improves survival. *Neurology* 2009;72:1816-22.

47. Goldstein LB, Amarenco P, Szarek M, et al. Hemorrhagic stroke in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels study. *Neurology* 2008;70:2364-70.

48. Tapia-Perez H, Sanchez-Aguilar M, Torres-Corzo JG, et al. Use of statins for the treatment of spontaneous intracerebral hemorrhage: results of a pilot study. *Cent Eur Neurosurg* 2009;70:15-20.

49. Plehn JF, Davis BR, Sacks FM, et al. Reduction of stroke incidence after myocardial infarction with pravastatin: the Cholesterol and Recurrent Events (CARE) study. The Care Investigators. *Circulation* 1999;99:216-23.

50. White HD, Simes RJ, Anderson NE, et al. Pravastatin therapy and the risk of stroke. *N Engl J Med* 2000;343:317-26.

51. Collins R, Armitage J, Parish S, Sleight P, Peto R, Heart Protection Study Collaborative G. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high-risk conditions. *Lancet* 2004;363:757-67.

52. Amarenco P, Bogousslavsky J, Callahan A, 3rd, et al. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med* 2006;355:549-59.

53. Blanco M, Nombela F, Castellanos M, et al. Statin treatment withdrawal in ischemic stroke: a controlled randomized study. *Neurology* 2007;69:904-10.

54. Kennedy J, Hill MD, Ryckborst KJ, Eliasziw M, Demchuk AM, Buchan AM. Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER): a randomised controlled pilot trial. *Lancet Neurol* 2007;6:961-9.

55. Montaner J, Chacon P, Krupinski J, et al. Simvastatin in the acute phase of ischemic stroke: a safety and efficacy pilot trial. *Eur J Neurol* 2008;15:82-90.

56. Muscari A, Puddu GM, Santoro N, et al. The atorvastatin during ischemic stroke study: a pilot randomized controlled trial. *Clin Neuropharmacol* 2011;34:141-7.

57. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med* 1996;335:1001-9.

58. LIPID. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;339:1349-57.

59. Goldstein LB, Amarenco P, Zivin J, et al. Statin treatment and stroke outcome in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. *Stroke* 2009;40:3526-31.

60. Uchiyama S, Ikeda Y, Urano Y, Horie Y, Yamaguchi T. The Japanese aggrenox (extended-release dipyridamole plus aspirin) stroke prevention versus aspirin programme (JASAP) study: a randomized, double-blind, controlled trial. *Cerebrovasc Dis* 2011;31:601-13.

61. Davignon J. Beneficial cardiovascular pleiotropic effects of statins. *Circulation* 2004;109:III39-43.

62. Ural AU, Yilmaz MI, Avcu F, Yalcin A. Treatment with cerivastatin in primary mixed hyperlipidemia induces changes in platelet aggregation and coagulation system components. *Int J Hematol* 2002;76:279-83.

63. Charidimou A, Imaizumi T, Moulin S, et al. Brain hemorrhage recurrence, small vessel disease type, and cerebral microbleeds: A meta-analysis. *Neurology* 2017;89:820-29.

64. Biffi A, Anderson CD, Battey TW, et al. Association Between Blood Pressure Control and Risk of Recurrent Intracerebral Hemorrhage. *JAMA* 2015;314:904-12.

65. Haussen DC, Henninger N, Kumar S, Selim M. Statin use and microbleeds in patients with spontaneous intracerebral hemorrhage. *Stroke* 2012;43:2677-81.

66. Ebrahim S, Sung J, Song YM, Ferrer RL, Lawlor DA, Davey Smith G. Serum cholesterol, haemorrhagic stroke, ischaemic stroke, and myocardial infarction: Korean national health system prospective cohort study. *BMJ* 2006;333:22.

67. Wang X, Dong Y, Qi X, Huang C, Hou L. Cholesterol levels and risk of hemorrhagic stroke: a systematic review and meta-analysis. *Stroke* 2013;44:1833-9.

68. Amarenco P, Labreuche J. Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. *Lancet Neurol* 2009;8:453-63.

69. Asahi M, Huang Z, Thomas S, et al. Protective effects of statins involving both eNOS and tPA in focal cerebral ischemia. *J Cereb Blood Flow Metab* 2005;25:722-9.

70. LB17 - Randomized Controlled Trial of Early versus Delayed Statin Therapy in Patients With Acute Ischemic Stroke. International Stroke Conference; 2017; Houston, Texas.

71. Ziff OJ, Lane DA, Samra M, et al. Safety and efficacy of digoxin: systematic review and meta-analysis of observational and controlled trial data. *BMJ* 2015;351:h4451.

72. Castilla-Guerra L, Fernandez-Moreno MC, Rico-Corral MA. Cholesterol and stroke: Roll of PCSK9 inhibitors. *Neurologia* 2017; 10.1016/j.nrl.2017.03.009.

73. Terrin N, Schmid CH, Lau J. In an empirical evaluation of the funnel plot, researchers could not visually identify publication bias. *J Clin Epidemiol* 2005;58:894-901.

Figure Legends

Figure 1: Summary of meta-analyses in observational and randomised studies on safety and efficacy of statins in patients with previous stroke

(Total studies). See Figures 2 and 3 for study-level results.

Figure 2: Forest Plot of Studies on Association Between Statins and Clinical Outcomes in patients with previous intracerebral hemorrhage

The diamond represents the pooled difference using a random-effects model. I^2 is the percentage of total variation across studies due to heterogeneity. Eggers test of small-study effects: ICH p = 0.16; all-cause mortality p = 0.88; poor functional outcome p = 0.58. Poor functional outcome was defined as mRS >2 by all studies except Dowlatshahi which defined as mRS >3, Tapia-Perez 2013 and 2016 which defined as NIHSS >15, and Winkler which defined as mBI <15. CT, computed tomography; ICD, international classification of diseases; ICH, intracerebral hemorrhage.

Figure 3. Forest Plot of Studies on Association Between Statins and Clinical Outcomes in patients with previous ischemic stroke

The diamond represents the pooled difference using a random-effects model. I^2 is the percentage of total variation across studies due to heterogeneity. CEA, carotid endartarectomy; TIA, transient ischemic attack; tPA, tissue plasminogen activator. Eggers test of small-study effects: ICH p = 0.78; ischemic stroke p = 0.30; any-stroke p = 0.52; all-cause mortality p = 0.54; poor functional outcome p = 0.69. Poor functional outcome was defined as mRS >2 by all studies except Alvarez-Sabin and Song, which defined as being dependent and Leker as mRS >3.