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Does statin increase the risk of intracerebral hemorrhage in stroke survivors? A meta-analysis and trial sequential analysis

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Abstract

Background: It remains debatable whether statin increases the risk of intracerebral hemorrhage (ICH) in poststroke patients.

Methods: We systematically searched PubMed, EMBASE, and CENTRAL for randomized controlled trials. Trial sequential analysis (TSA) was conducted to assess the reliability and conclusiveness of the available evidence in the meta-analysis. To evaluate the overall effectiveness, the net composite endpoints were derived by totaling ischemic stroke, hemorrhagic stroke, transient ischemic attack (TIA), myocardial infarction, and cardiovascular mortality.

Results: A total of 17 trials with 11,576 subjects with previous ischemic stroke, TIA, or ICH were included, in which statin therapy increased the risk of hemorrhagic stroke (risk ratio [RR], 1.42; 95% confidence interval [CI], 1.07–1.87), but reduced the risk of ischemic stroke (RR, 0.85; 95% CI, 0.75–0.95). For the net composite endpoints, statin therapy was associated with a 17% risk reduction (95% CI, 12–21%; number needed to treat = 6). With a control event rate 2% and RR increase 40%, the TSA suggested a conclusive signal of an increased risk of hemorrhagic stroke in stroke survivors taking statin. However, with the sensitivity analysis by changing assumptions, the conclusions about hemorrhagic stroke risk were less robust.

Conclusions: Statin therapy in poststroke patients increased the risk of hemorrhagic stroke but effectively reduced ischemic stroke risk. Weighing the benefits and potential harms, statin has an overall beneficial effect in patients with previous stroke or TIA. However, more studies are required to investigate the conclusiveness of the increased hemorrhagic stroke risk revealed in our study.

Keywords: cardiovascular events, cerebrovascular disease, meta-analysis, secondary stroke prevention, statin, trial sequential analysis

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Introduction

Statins can reduce cardiovascular events and mortality among patients with coronary heart disease.[1,2] However, in patients with acute or previous history of ischemic stroke and intracerebral hemorrhage (ICH), findings on the use of statins are inconsistent. In a meta-analysis with more than 100,000 patients, statin use in patients with acute stroke was found to be associated with good functional outcomes at 3 months but not at 1 year.[3] A few other meta-analyses also found that statins have no significant benefits in patients with acute stroke in reducing recurrent ischemic stroke or ICH, cardiovascular events, and mortality.[4,5] Some studies found an inverse relationship between low-density lipoprotein cholesterol (LDL-C) and the risk of ICH, and some found a risk of hemorrhagic transformation in patients using statins.[6–11] However, the Stroke Prevention by Aggressive Reduction in Cholesterol Levels

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(SPARCL) study found a significant risk of ICH associated with statin use in poststroke patients.[6] A meta-analysis of four studies in 2008 investigating statin therapy in patients with cerebrovascular diseases suggested that statins reduced risk of overall and ischemic stroke but increased risk of hemorrhagic stroke.[12] However, results of many new studies for stroke survivors were reported after 2008, which provided more information about the effects of statins in poststroke patients.[13–16]

Systematic review and meta-analyses of existing randomized controlled trials (RCTs) can help to summarize the totality of current existing evidence and clarify the conflicting information on the benefits and risks of statin therapy in poststroke patients. However, meta-analysis may result in random errors due to sparse data and repeated significance testing when updating a meta-analysis with new trials. Therefore, trial sequential analysis (TSA) has been developed to reduce the spurious inference from meta-analysis.[17] Consequently, we performed an updated systematic review with meta-analysis and TSA of published RCTs to investigate the effect of statin therapy on stroke recurrence (including ischemic stroke and ICH), major adverse cardiovascular events (MACEs), and cardiovascular mortality, and also to evaluate its overall effectiveness in patients with previous ischemic stroke or ICH.

Methods

The prespecified protocol for this review was registered with the International Prospective Register of Systematic Reviews (PROSPERO), number CRD 42017079212, and the study report adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline (Table S1).[18] All analyses were based on previously published studies, thus no ethical approval and patient consent was required.

Search strategy

We performed the literature search by combining search terms (both free text and medical subject headings thesaurus) for stroke and statins to identify studies that investigated the use of statin in patients with previous stroke. The search was limited to RCTs and human studies, up to March 2018 (Table S2). Databases included were PubMed, CENTRAL, and EMBASE. Reference lists of the retrieved studies, systematic reviews, and meta-analyses were manually searched. Two investigators (RJJT and CPC) independently searched published studies, screened the titles and abstracts, and then identified potential studies according to the prespecified inclusion criteria. Eligibility queries were resolved by discussion. Data from the published reports were used for meta-analyses, and if there were missing data, we contacted the authors to see if the information was available. We also repeated the search to ensure accuracy and completeness.

Inclusion and exclusion criteria

RCTs were included if the patients were 18 years of age or older with a history of ischemic stroke, transient ischemic attack (TIA), or ICH. The intervention group should have received statin therapy, while the control group should have received placebo or standard treatment. The prespecified primary outcome was ischemic or hemorrhagic stroke. Secondary outcomes were myocardial infarction (MI) events, MACEs, cardiovascular mortality, and all-cause mortality.

Studies not using randomization to perform patient allocation or RCTs that did not report the prespecified outcomes of interest were excluded.

Data extraction

The following information were extracted by RJJT and CPC: (a) trial details (first author, year); (b) region of participating centers; (c) treatment duration; (d) number of randomized patients; (e) patient characteristics (e.g. age, sex, comorbidities, and risk factors of cerebrovascular/cardiovascular diseases); (f) baseline LDL-C, high-density lipoprotein cholesterol (HDL-C), total cholesterol, and triglyceride levels; (g) changes in (f); (h) given estimates of each outcome of interest. We extracted the above information into a predesigned form using Microsoft Excel.

Quality assessment

The quality of studies was assessed independently by RJJT and CPC using the Cochrane risk of bias assessment tool. Disagreements were resolved by discussion. Publication bias was detected using funnel plots and Egger's regression asymmetry test.[19] The trim and fill method was further conducted to evaluate the influence resulting from publication bias.[20]

Data and statistical analyses

We used Review Manager software, version 5.3, to analyze our data, create forest and funnel plots, and extract risk-of-bias data. The unadjusted risk ratios (RRs) were derived from the number of patients with each outcome in the statin and control groups. Trials with zero outcomes in both treatment groups were excluded from the analysis, as recommended by the Cochrane Handbook.[21] We pooled the independent outcomes (ischemic stroke, hemorrhagic stroke, TIA, MI, and cardiovascular mortality) as net composite endpoints to reflect the net clinical benefit. Pooled estimates of the outcomes were measured using the DerSimonian and Laird random-effects model, with the Mantel–Haenszel method used to calculate the weighting scheme.[22] Between-study statistical heterogeneity was assessed by calculating the I^2 statistic using Cochran's Q test and was considered substantial when $I^2 \geqslant 25\%$ and the p value was < 0.1.[21,23] A p value cut-off of 0.1 was used because Cochran's Q test was known to be suboptimal in detecting true heterogeneity, especially when the number of included studies was small.[23] We performed prespecified subgroup analyses based on (b) to (g) as mentioned in the section above.

TSA

We conducted the TSA to assess the reliability and conclusiveness of the available evidence in our meta-analysis.[24,25] To address the risk of random errors resulting from sparse data and repetitive statistical testing in a cumulative meta-analysis,[26] TSA combines an estimation of optimum sample size (required information size) for statistical inference with an adjusted threshold (trial sequential monitoring boundaries) for statistical significance.[17,27] We calculated the required information size with heterogeneity adjustment assuming a control event rate of 2% for hemorrhagic stroke in all patients and 1.5% in post-ischemic stroke patients, a relative risk increase (RRI) of 40%, and a diversity of 0%. The control event rate was approximately the median proportion of hemorrhagic stroke in the control group, excluding the zero-event trials, and the estimates of RRI and diversity were derived from the random-effects model. We also carried out sensitivity analyses with several values of lower RRI and higher diversity. All TSA were performed at the level of an overall 5% risk of a two-sided type I error and a power of 80%. A constant continuity correction of 1.0 was applied in trials that had nonevents in either one of the two arms. We used the TSA software (version 0.9.5.10 Beta, available from http://www.ctu.dk/tsa/) for these analyses.

Results

Search results

We identified 3126 titles, then excluded the duplicates and irrelevant records, and retrieved 41 full-text articles for potential eligibility in this review. We further excluded 25 of them after performing a detailed evaluation (Table S3) and identified an additional article. A total of 16 studies (17 trials)[6,13–16,28–39] satisfied the prespecified inclusion/exclusion criteria and were included in the meta-analysis (Figure S1). In this paper, we refer to the Heart Protection Study (HPS)[28,29] as one study and the Japan Statin Treatment Against Recurrent Stroke (J-STARS)[15,16] as two studies. This is because the HPS trial had published two relevant studies, wherein data were extracted for this review and meta-analysis. J-STARS was analyzed as two separate studies as it enrolled two populations of patients and conducted the trials separately. One of the groups was enrolled within 6 months of stroke onset, and another was enrolled 6 months after stroke onset.

Characteristics of the included studies

Characteristics of the included studies are detailed in Table 1. A total of 11,576 patients were included, with 4731 (40.9%) from the SPARCL trial, 3280 (28.3%) from the HPS trial, and 3565 (30.8%) from other trials. Eight studies (n = 5,771, 49.9%) enrolled patients with ischemic stroke, six (n = 1,072, 9.26%) enrolled patients with ICH, and one (SPARCL) enrolled patients with ischemic stroke, ICH, and TIA. A total of 11 studies were conducted in Western countries, while 4 were carried out in Asian countries. The treatment duration ranged from 7 days to 4.9 years. The six studies that enrolled only patients with ICH had a follow-up period of 14–21 days.

Risk of bias in included studies

The quality of the studies was assessed and presented in Figures S2 and S3. Most studies had a low risk of bias in all seven sections indicated in the Cochrane risk of bias assessment tool. Chou

Table 1. Characteristics of selected trials.

Trial	Year of publication	Type of stroke at onset	Region	Statin type	Statin dose (mg/day)	Treatment duration	Randomized patients (A/C)*	Mean age (years)	Male sex (%)	BMI (kg/m^2)	Baseline systolic blood pressure (mmHg)	Between-group LDL-C reduction (%)
FASTER	2007	Ischemic	Canada, USA	Simvastatin	40	90 days	99/95	68.20	48.45	27.25	149.10	–
EUREKA	2016	Ischemic	South Korea	Rosuvastatin	20	14 days	155/ 159	65.00	59.49	23.95	–	45.30
J-STARS	2017	Ischemic	Japan	Pravastatin	10	4.9 years						
Enrolled within 6 months following initial stroke events (J-STARS early)							426/ 417	65.95	68.45	23.70	138.65	–
Enrolled more than 6 months following initial stroke events (J-STARS late)							367/ 368	66.50	69.39	23.50	135.35	–
HPS	2004	Ischemic	UK	Simvastatin	40	4.8 years	1640/ 1640	65.50	74.54	27.60	–	27.30
MISTICS	2008	Ischemic	Spain	Simvastatin	20	90 days	28/28	72.65	51.79	–	153.40	31.60
Muscari	2011	Ischemic	Italy	Atorvastatin	80	7 days	31/31	75.25	32.26	–	–	–
SPARCL	2006	66.7% ischemic, 30.9% TIA, 1.97% ICH	Multinational (93.3% White, 3.0% Black, 0.6% Asian, 3.1% other)	Atorvastatin	80	4.9 years	2365/ 2366	62.75	59.67	27.45	138.65	40.47
STARS	2016	Ischemic	Spain	Simvastatin	40	90 days	50/54	74.25	53.84	–	–	–
Yakusevich	2012	Ischemic	Western Russia	Simvastatin	40	12 months	86/97	65.65	43.72	–	156.40	0.00
Chou	2008	ICH	USA	Simvastatin	80	21 days	19/20	53.00	25.64	–	–	–
Garg	2013	ICH	India	Simvastatin	80	14 days	19/19	49.10	55.26	–	–	–
STASH	2014	ICH	Multinational (92% White, 3% Asian, 2% Black, 3% Hispanic, < 1% other)	Simvastatin	40	21 days	391/ 412	50.00	31.38	–	–	35.7
Tseng	2005	ICH	UK	Pravastatin	40	14 days	40/40	52.90	45.00	–	–	–
Vergouwen	2009	ICH	The Netherlands	Simvastatin	80	15 days	16/16	54.00	37.00	–	161.00	0.00
Wu	2006	ICH	China	Simvastatin	20	21 days	32/48	50.20	27.50	–	–	

*A and C indicate active treatment and control groups, respectively.
BMI, body-mass index; ICH, intracerebral hemorrhage; LDL-C, low-density lipoprotein cholesterol; TIA, transient ischemic attack.

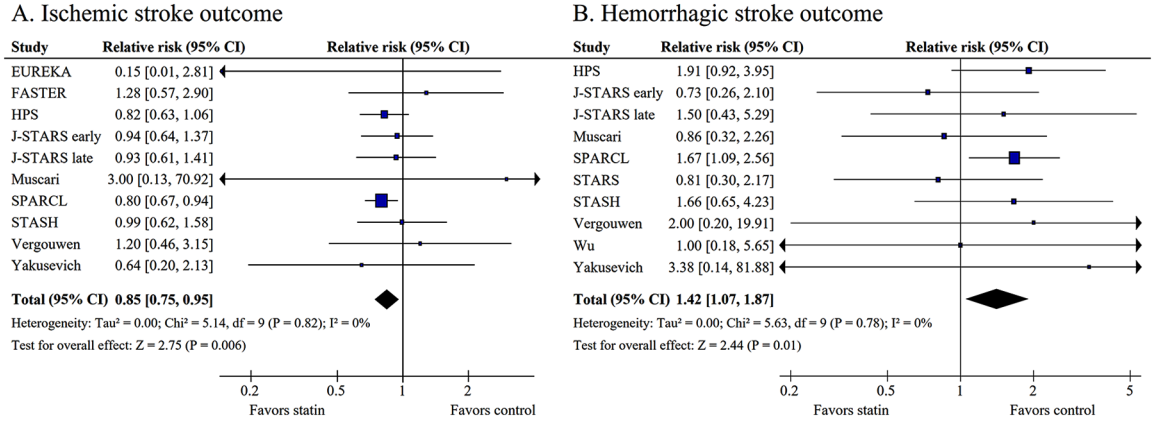

Figure 1. Effects of statin on the risk of ischemic and hemorrhagic stroke in patients with ischemic stroke, transient ischemic attack, or intracerebral hemorrhage. CI, confidence interval; df, degrees of freedom.

and colleagues had many unclear risks because the specified methods such as randomization, allocation concealment, and double-blinding were not mentioned.[34] Yakusevich and colleagues had a high risk of bias because no placebo was used, and the primary outcome was not completely reported.[33] Wu and colleagues did not mention if blinding was performed.[39]

Analysis for publication bias

Publication bias was examined using funnel plots and Egger's test, and none was detected except for cardiovascular mortality ($p < 0.1$, Figure S4). However, the trim and fill analysis showed that its size of effect was not influenced by this potential bias (adjusted pooled RR, 0.83; 95% confidence interval [CI], 0.75–0.92; data not shown).

Primary and secondary outcomes

Statin use in poststroke patients increased the risk of hemorrhagic stroke but reduced the risk of ischemic stroke (Figure 1, Table 2). No heterogeneity was found across the studies for both primary outcomes, and the p values were 0.82 and 0.78, respectively.

We undertook the TSA for the effect of statin use on hemorrhagic stroke in patients with previous stroke at the level of control event rate 2%, RRI 40%, and diversity 0%. The trial sequential significance boundary for harm had been crossed even if the required information size of 11,491 had not been reached, indicating the increased risk of hemorrhagic stroke with statin use was conclusive (Figure 2(a)). The TSA-adjusted 95% CI for a relative risk of 1.42 was 1.04–1.93. The cumulative Z curve still touched this monitoring boundary when assuming a diversity of 20% (TSA-adjusted 95% CI, 1.00–2.01) (Figure 2(b)). However, sensitivity analyses with different assumptions showed that result of increased ICH remained inconclusive, which demands further trials to confirm the signal of increased risk (Figure S5).

For post-ischemic stroke patients, the cumulative Z curve crossed the conventional boundary but did not reach any of the monitoring boundaries, and the calculated optimum sample size was not exceeded (Figure S6). Evidence of a harmful effect was inconclusive (TSA-adjusted 95% CI, 0.93–2.10 under consideration of 1.5% control event rate, 40% RRI, and 0% diversity). For post-ICH patients, a similar inference was made because the cumulative Z curve did not cross both the conventional boundary and the trial sequential monitoring boundary (data not shown).

Statin use in poststroke patients reduced the risk of MI, MACE, and cardiovascular mortality (Table 2). No heterogeneity of treatment effects among studies was found in these outcomes, and the p values for heterogeneity were 0.74, 0.66, and 0.83, respectively.

Statin therapy in patients with previous stroke had a statistically significant net clinical benefit (Table 2). It reduced the risk of the composite endpoints by 17%, and the number needed to

Table 2. Effects of statin on primary and secondary outcomes, stratified by all patients and type of stroke at onset.

Outcome	All patients (both post-ischemic stroke and post-ICH)					Subgroup 1: post-ischemic stroke					Subgroup 2: post-ICH					Interaction between subgroups	
	RR	95% CI	*p* value	No. of patients	No. of studies	RR	95% CI	*p* value	No. of patients	No. of studies	RR	95%CI	*p* value	No. of patients	No. of studies	I^2 (%)	*p* value
Ischemic stroke	0.85	0.75–0.95	0.006	11 177	10	0.83	0.74–0.94	0.004	10 342	8	1.03	0.67–1.57	0.90	835	2	0	0.35
Hemorrhagic stroke	1.42	1.07–1.87	0.01	10 853	10	1.40	1.04–1.89	0.03	9 938	7	1.53	0.70–3.32	0.28	915	3	0	0.84
Myocardial infarction	0.75	0.64–0.87	< 0.001	10 269	8	0.75	0.64–0.88	< 0.001	10 086	6	0.52	0.07–3.86	0.52	183	2	0	0.71
MACE	0.80	0.71–0.91	< 0.001	4 925	2	-[$]											
Cardio-vascular mortality	0.83	0.74–0.92	< 0.001	8 194	3	-[$]											
Net composite endpoints*	0.83	0.79–0.88	< 0.001	11 400	13	0.83	0.78–0.87	< 0.001	10 446	9	1.14	0.80–1.63	0.46	954	4	68.2	0.08
All-cause mortality	1.02	0.89–1.18	0.74	8 089	14	1.05	0.90–1.23	0.53	7 017	8	0.78	0.48–1.28	0.33	1 072	6	19.0	0.27

*Net composite endpoints were derived by totaling ischemic stroke, hemorrhagic stroke, transient ischemic attack, myocardial infarction, and cardiovascular mortality.
[$]No estimate was available in the post-ICH subgroup for MACE and cardiovascular mortality outcome; hence, a subgroup analysis by type of stroke at onset for these two outcomes was not conducted.
CI, confidence interval; ICH, intracerebral hemorrhage; MACE, major adverse cardiovascular event; RR, risk ratio.

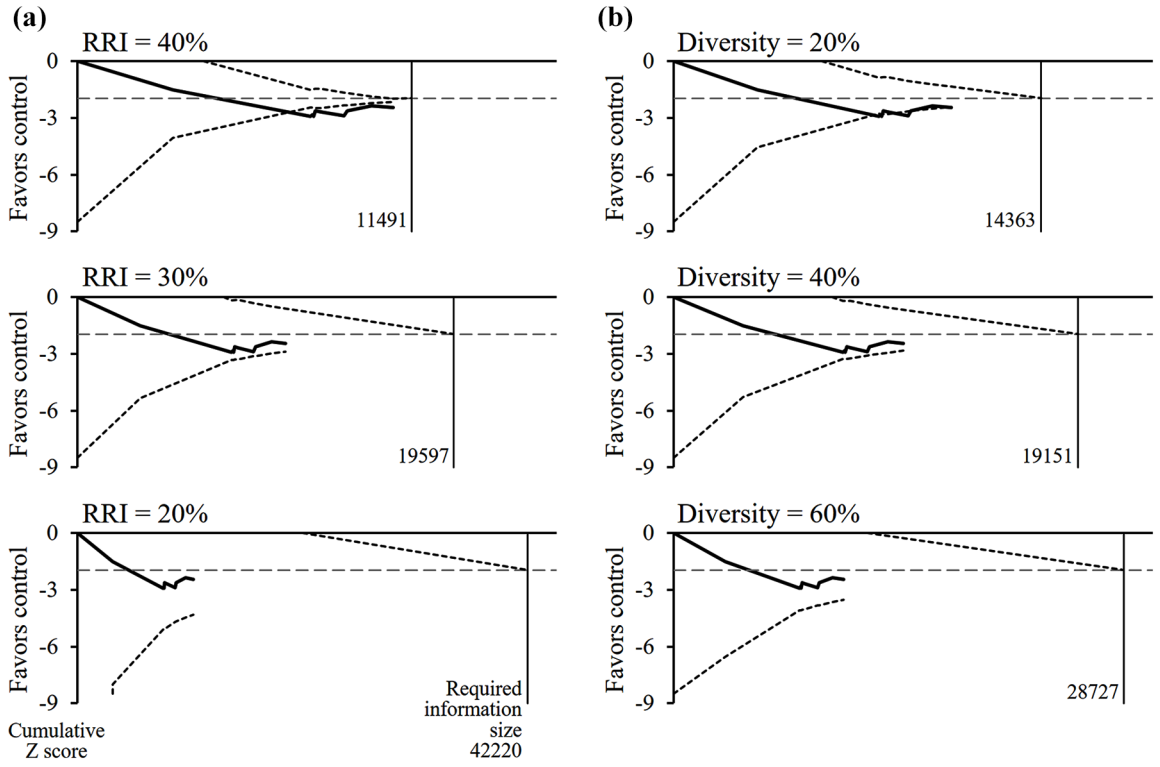

Figure 2. Trial sequential analysis of 10 trials reporting the effects of statin on the risk of hemorrhagic stroke in patients with previous stroke. The required information size was calculated based on α of 0.05 (two sided), β of 0.20, a control event rate of 2%, and other different conditions which assumes (a) a diversity of 0% (model estimated) and ranges of RRIs of 40%, 30%, or 20%, or (b) an RRI of 40% and various degrees of heterogeneity adjustment (diversity of 20%, 40%, or 60%). The cumulative Z curve (bold solid line) was constructed using a random-effects model. The horizontal dashed line at cumulative Z = –1.96 indicates a conventional level of statistical significance. The converged dot line and diverged dot line represent the trial sequential significance boundary and futility boundary, respectively. These monitoring boundaries were constructed based on the O'Brien–Fleming method. RRI, relative risk increase.

treat (NNT) was 6 (pooled RR, 0.83; 95% CI, 0.79–0.88; $p < 0.001$; 11,400 patients). No heterogeneity was found ($p = 0.87$).

Statin use in poststroke did not have a significant effect on all-cause mortality (pooled RR, 1.02; 95% CI, 0.89–1.18; $p = 0.74$; 8089 patients), with no significant heterogeneity ($p = 0.68$).

Subgroup analyses

Statin use was found to increase the risk of hemorrhagic stroke in the Western population but had no significant effect in the Asian population (Figure 3). Risk of hemorrhagic stroke was higher among post-ICH patients than post-ischemic stroke patients. As the mean age of patients increased, the risk of hemorrhagic stroke decreased. However, three out of four studies in the ⩽ 65 years age group recruited only post-ICH patients. However, all p values for interaction were > 0.05.

Our analysis revealed that the risk of hemorrhagic stroke increased as the following factors increased (Figure 3): (a) the percentage of men in the studies; (b) treatment duration of statin use, and components of metabolic syndrome, including (c) the percentage of patients with diabetes mellitus, (d) body-mass index (BMI), and (e) baseline systolic blood pressure (SBP). A larger change in LDL-C and triglyceride reduced the risk of hemorrhagic stroke, but a larger change in total cholesterol increased the risk of hemorrhagic stroke. A higher risk of hemorrhagic stroke was found when the final HDL-C level was lower. Compared with the final HDL-C levels, when the statin group had a lower final HDL-C level than the control group,

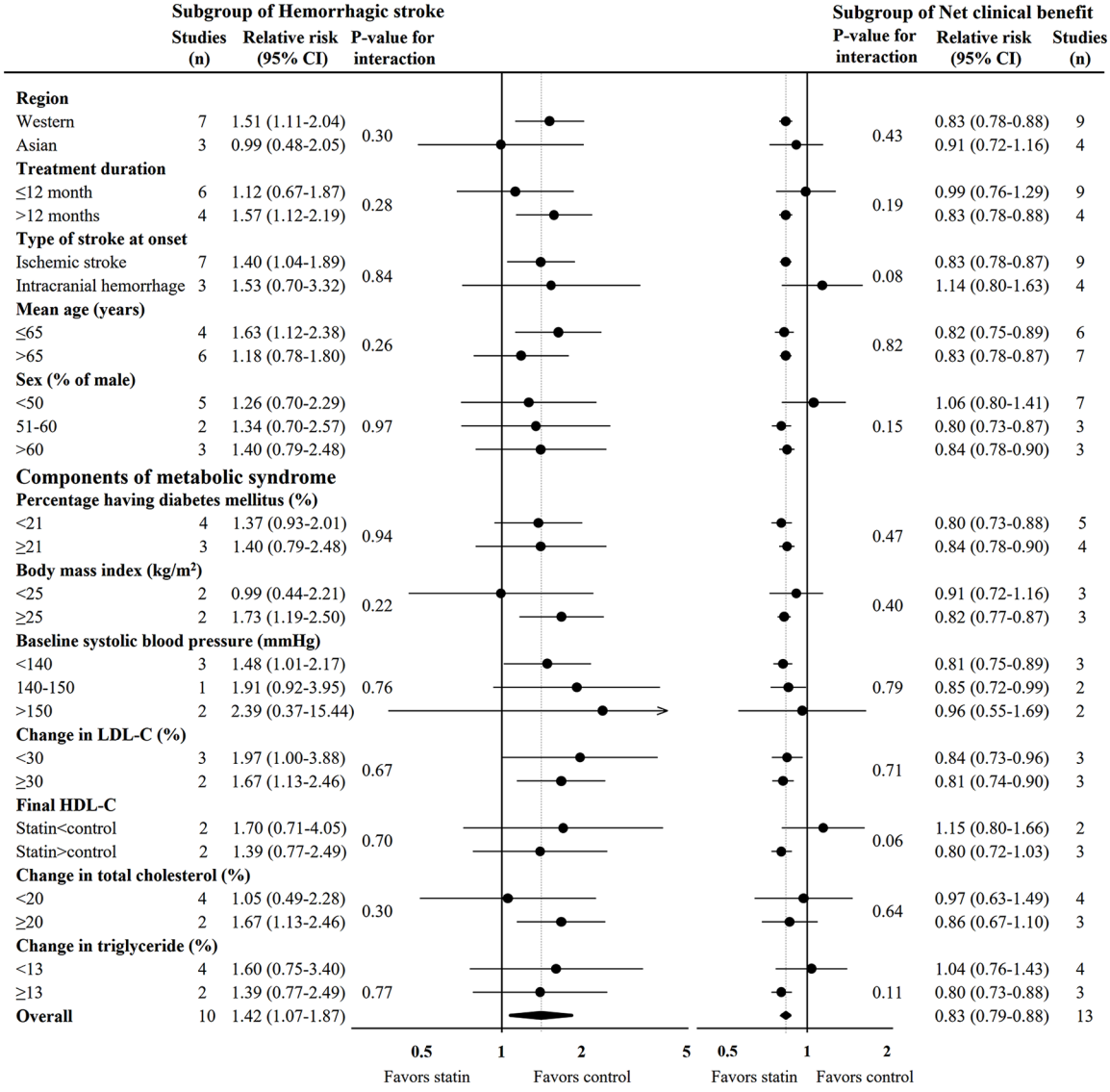

Figure 3. Effects of statin on the risk of hemorrhagic stroke and net clinical benefit in the subgroup of trials. Circles and horizontal lines represent relative risk and 95% CI for each study. The vertical dashed line represents the overall point estimate relative risk according to the horizontal axis. CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

the risk of hemorrhagic stroke was higher than when the statin group had a higher final HDL-C level than the control group.

The subgroup analysis of different statin dosage for hemorrhagic stroke outcome was conducted. Studies were divided into three subgroups (low, moderate, and high intensity) according to the 2013 American College of Cardiology/American Heart Association guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults.[40] RR with 95% CI of low-, moderate-, and high-intensity statin for hemorrhagic stroke outcome were 0.99 (0.44–2.21), 1.51 (0.92–2.46), and 1.51 (1.03–2.22), respectively. The p value for interaction was 0.63. Subgroup analyses relating to study designs (Figure S7) suggested that the trials with better study quality demonstrated a higher risk of hemorrhagic stroke in poststroke patients taking statin. However, all p values for interaction in these subgroups were > 0.05.

Discussion

In this meta-analysis, we included a total of 11,576 patients. We found that statin use had a beneficial effect in reducing ischemic stroke but increased the risk of hemorrhagic stroke in patients who were post ischemic stroke and ICH. For our secondary outcomes, statin use in these patients reduced MI, MACE, and cardiovascular mortality. No significant benefit was found on all-cause mortality. With respect to the net composite endpoints used to reflect the net clinical benefit, statin use can render a risk reduction of 17% in the risk of ischemic or hemorrhagic stroke, TIA, MI, or cardiovascular mortality with an NNT of 6 (pooled RR, 0.83; 95% CI, 0.79–0.88; $p < 0.001$).

Hemorrhagic stroke

In our review, we found that statin use in post-stroke patients increased the risk of hemorrhagic stroke. Our result was consistent with that of a previous meta-analysis which found a trend in increased risk of ICH using statin as a secondary prevention strategy (odds ratio, 1.26; 95% CI, 0.91–1.73).[41] Another meta-analysis by Amarenco and Labreuche that included only the HPS and SPARCL trials also found a significant increased risk of ICH with statin use as secondary prevention (RR, 1.73; 95% CI, 1.19–2.50; $p = 0.004$).[42] However, previous large cohort studies of patients with previous stroke found that ICH was not associated with statin use in these patients.[43,44] Our study was partly in agreement with a systematic review published recently,[45] which included 43 observational and randomized studies and concluded that statin had a nonsignificant trend toward future ICH with statins in patients with previous stroke. To investigate the effects of intervention, benefits or harms, the RCT remains the best study design to avoid allocation bias.[46] Observational studies, with their intrinsic limitations, are prone to the risk of bias resulting from unmeasured confounding factors.[47] In this regard, we decided to include only RCTs in our systematic review.

Whether statins increase the risk of ICH in patients with a previous stroke has long been an arguable topic. To respond to this query, a systematic review with meta-analysis is a better research strategy to synthesize the totality of evidence. However, results from apparently conclusive meta-analyses may be false and the information size required for a reliable and conclusive meta-analysis should be no less rigorous than the sample size of a single, optimally powered RCT.[17] The negative finding may be a result of less than adequate information size, and a positive finding may result from a limited number of events from a few small trials with associated random errors. In our review, only the HPS and SPARCL trials had a sample size greater than 1000 subjects, which indicates that the influence of random errors might be an issue and should be satisfactorily accounted for. In our trial sequential analyses, we demonstrated that the finding of an increased risk of hemorrhagic stroke could be a genuine result with control event rate 2%, RRI 40%, and diversity 0%. However, a series of sensitivity analyses with altered assumptions suggested that the signal of increased hemorrhage stroke was less conclusive (Figures S5 and S6). More studies are required to investigate the conclusiveness of the increased hemorrhagic stroke risk revealed in our study (Figure 1(b)).

In our analysis, we found that components of metabolic syndrome were associated with an increased risk of hemorrhagic stroke in poststroke patients. According to the National Cholesterol Education Program Adult Treatment Panel III, metabolic syndrome was defined by the presence of any three of the five traits: abdominal obesity; hypertriglyceridemia; low HDL-C level; elevated blood pressure; elevated fasting plasma glucose level.[48] Due to the lack of primary data, we conducted a subgroup analysis based on the percentage of patients with diabetes mellitus and BMI as indicators for elevated fasting plasma glucose level and abdominal obesity, respectively. A trend of increased risk of hemorrhagic stroke was found with a higher percentage of diabetes, higher BMI, smaller change in triglyceride level, lower change in final HDL-C level, and higher baseline SBP. Previous studies also suggested similar results that metabolic syndrome increased the risk of cardiovascular diseases[49–51] and stroke.[51] Large prospective cohort studies in China[52,53] and Japan[54] found that it is a significant risk factor of hemorrhagic stroke. Statin therapy in patients with metabolic syndrome and established coronary heart diseases was found to reduce the risk of further cardiovascular events.[55,56] However, a *post hoc* analysis of SPARCL found that statin therapy did not have an effect in reducing recurrent stroke and cardiovascular events in patients with diabetes or

metabolic syndrome.[57] From our meta-analysis, we suggest that statin therapy can still reduce the risk of stroke events in patients with metabolic syndrome and established stroke.

In our analysis, we also found that Western patients had a higher risk of hemorrhagic stroke than Asian patients. This might be explained by the prevalence of metabolic syndrome as an effect modifier, in which a worldwide analysis found that the Western population had a greater prevalence of metabolic syndrome than the Asian population.[58]

In addition, our meta-analysis found that the risk of hemorrhagic stroke was increased in male and post-ICH patients, which was consistent with the *post hoc* analyses of SPARCL on hemorrhagic stroke[59] and systematic review of 24 studies.[60] Our analysis found that as mean age increased, the risk of hemorrhagic stroke decreased. This was not consistent with the *post hoc* analysis of SPARCL.[59] This result could be due to the status of post-ICH being an effect modifier, as we found that post-ICH patients had an increased risk of hemorrhagic stroke and three out of four studies in the $\leqslant$ 65 years age group enrolled only post-ICH patients.

Our study also demonstrated a trend of increased risk of hemorrhagic stroke as treatment duration increased, which might be correlated with the increased risk of hemorrhagic stroke recurrence by time. This is consistent with a few previous studies that were conducted on patients with ICH that found that recurrence of ICH increases with time of follow up.[61,62] A review by Endres and colleagues summarized the studies that investigated statin use and ICH recurrence and concluded that there is no evidence that statin increased risk of ICH recurrence.[63]

Ischemic stroke

The result of our review is consistent with those studies on primary prevention of cardiovascular events using statin.[1,2] Previous studies found that the risk of cerebral ischemia increases when the serum total cholesterol and LDL-C levels increase.[8,64,65] The cholesterol-lowering property of statin could be the mechanism of action in reducing the event of ischemic stroke in poststroke patients. A meta-analysis found a significant association that with every 10% reduction in LDL-C, the risk of all strokes was decreased by 15.6% (95% CI, 6.7–23.6).[66] Nevertheless, a recent cohort study showed that in-hospital mortality rates were lower for patients with acute ICH with higher LDL-C levels[67] in contrast with our meta-analysis indicating a neutral effect of statin use on all-cause mortality (Table 2). It was suggested that the association between higher LDL-C and decreased mortality may be related to a lower likelihood of hematoma expansion due to higher LDL-C.[67] Further studies are necessary to confirm the findings and the corresponding role of statin.

Strength and limitation

We acknowledge some limitations in this analysis. This meta-analysis was not based on individual patient data. Hence, we could not make a conclusion on the association between the risk factors of stroke and the outcome, which was also affected by the limited available data on baseline characteristics of patients' comorbidities in each study. Besides, even though we did put much effort into subgroup analysis, the conclusions about hemorrhagic stroke risk could be substantiated only when adequate adjustment could be made for potential risk factors such as statin dosage, duration of treatment, and presence of unmeasured confounders. As this analysis was performed using a literature search of published RCTs, we might have missed possible unpublished data. We tried to minimize the bias by developing a protocol and adhering to the inclusion and exclusion criteria, data extraction, and data analysis.

Our review is currently the most up to date meta-analysis on statin therapy in patients with a previous ischemic stroke or ICH by including only RCTs in our meta-analysis. This review is also comprehensive, such that we had prespecified subgroup analyses to find an association of relevant characteristics and the risk of stroke recurrence. We also identified a possible gap in the literature on the effect of statin therapy and the increased risk of ICH and proposed the following possible mechanism of (a) metabolic syndrome and (b) treatment duration. By doing so, we hope that this will give a direction for future research and contribute to precision medicine. More importantly, we conducted

TSA to investigate the conclusiveness of the findings obtained from the meta-analysis, which suggests that more trials are required to solve this long-lasting debate.

Conclusion

Despite the increased risk of hemorrhagic stroke with treatment duration and metabolic syndrome, statin therapy in patients with previous stroke could still be recommended, as the net composite endpoints, including ischemic stroke, hemorrhagic stroke, TIA, and MI, are still significantly reduced. Statin should be used with caution in patients with a higher risk of ICH. Further trials might be necessary to identify the potential mechanisms of hemorrhagic stroke occurrence in patients with previous stroke receiving statin therapy.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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Supplemental material

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