Statin Therapy for Secondary Prevention in Ischemic Stroke Patients with Cerebral Microbleeds

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Abstract:

Background and Objectives:

The association between statin use and the risk of intracranial hemorrhage (ICrH) following ischemic stroke (IS) or transient ischemic attack (TIA) in patients with cerebral microbleeds (CMBs) remains uncertain. This study investigated the risk of recurrent IS and ICrH in patients receiving statins based on the presence of CMBs.

Methods:

We did a pooled analysis of individual-patient data from the Microbleeds International Collaborative Network (MICON), comprising 32 hospital-based prospective studies fulfilling the following criteria: adult patients with IS or TIA, availability of appropriate baseline MRI for CMBs quantification and distribution, registration of statin use after the index stroke, and collection of stroke event data during a follow-up period of ≥3 months. The primary endpoint was the occurrence of recurrent symptomatic stroke (IS or ICrH), while secondary endpoints included IS alone or ICrH alone. We calculated incidence rates and performed Cox regression analyses adjusting for age, sex, hypertension, atrial fibrillation, previous stroke, and use of antiplatelet or anticoagulant drugs, to explore the association between statin use and stroke events during follow-up in patients with CMBs.

Results:

In total, 16,373 patients were included (mean age 70.5 ± 12.8 years; 42.5% female). Among them, 10,812 received statins at discharge, and 4,668 had 1 or more CMBs. The median follow-up duration was 1.34 years (IQR: 0.32-2.44). In patients with CMBs, statin users were compared with non-users. Compared to non-users, statin therapy was

associated with a reduced risk of any stroke (incidence rate [IR] 53 vs 79 per 1,000 patient-years, adjusted hazard ratio [aHR] 0.68 [95% CI 0.56-0.84]), a reduced risk of IS (IR 39 vs 65 per 1,000 patient-years, aHR 0.65 [95% CI 0.51-0.82]), and no association with the risk of ICrH (IR 11 vs 16 per 1,000 patient-years, aHR 0.73 [95% CI 0.46-1.15]). The results in aHR remained consistent when considering anatomical distribution and high burden (≥5) of CMBs.

Conclusions:

These observational data suggest that secondary stroke prevention with statins in patients with IS or TIA and CMBs is associated with a lower risk of any stroke or IS without an increased risk of ICrH.

Classification of Evidence: This study provides Class III evidence that for patients with IS or TIA and CMBs, statins lower the risk of any stroke or IS without increasing the risk of ICrH.

Introduction

Statins are widely used as a secondary prevention measure following ischemic stroke (IS) or transient ischemic attack (TIA) due to their proven ability to lower the risk of recurrent IS or TIA, mainly through their lipid-lowering effects and probably by their pleiotropic properties such as antithrombotic action and facilitation of clot lysis [1-5]. However, findings from studies such as the SPARCL trial (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) and the HPS (Heart Protection Study) have raised concerns that statin use may actually increase the risk of intracerebral hemorrhage (ICH), particularly in patients with a history of IS or ICH [6,7]. However, subsequent observational studies have presented conflicting results, leading to ongoing controversy regarding the risk of ICH in stroke patients who use statins [8]. Prior observational studies have been limited by factors such as small sample sizes, population selection bias, or a lack of a comparable non-user group [8]. Hence, current ICH guidelines emphasize the need for a thorough risk assessment of ischemic cardiovascular and cerebrovascular events versus the risk of recurrent ICH when considering statin use in patients with a history of ICH [9,10].

Cerebral microbleeds (CMBs) are small areas of bleeding presumed to occur from abnormal small blood vessels and are detectable through radiological imaging [10-13]. They are considered to be part of a spectrum of cerebral conditions associated with a tendency to bleed [11-14]. CMBs can be classified based on their location as deep perforator (hypertensive) arteriopathy, lobar (associated with cerebral amyloid angiopathy [CAA]), or mixed regions (associated with both conditions) [11-14]. Considering that CMBs are indicators of advanced conditions prone to hemorrhage, and statins have been linked to an elevated risk of ICH, especially in the elderly population where it is often associated with CAA, there is ongoing uncertainty surrounding the safety of the use of statins in patients with IS or TIA who also have CMBs [15].

There are limited available data on the potential association between statin use and the risk of symptomatic intracranial hemorrhage (ICrH) in patients with recent IS and CMBs. Therefore, we conducted a comprehensive analysis by pooling data from multiple prospective cohort studies within the Microbleeds International Collaborative Network

(MICON). The primary research question was to determine whether using statins in patients with recent IS or TIA and CMBs is associated with a reduction in the risk of IS. Additionally, we investigated whether statin use is linked to an increase in the risk of ICrH.

Methods:

Study Design:

We conducted a pooled analysis using individual-patient data from the MICON. MICON is an international database comprising 38 cohorts and 20,322 participants. These cohorts prospectively enrolled at least 50 patients with IS or TIA and collected data on stroke events over a follow-up period of at least 3 months. Magnetic resonance imaging (MRI) iron-sensitive sequences (gradient echo or susceptibility-weighted imaging) were used, and consensus criteria and validated scales were employed to document the presence, number, and anatomical distribution of CMBs. Additionally, some cohorts examined the presence of cortical superficial siderosis. Detailed information about this database has been previously published [16-17]. For this study, we included only those cohorts that collected data on statin use following the index IS or TIA. In addition, some cohorts collected data regarding the specific type and dosage of statins used, as well as baseline low-density lipoprotein cholesterol (LDL-C) levels. The intensity of the statin therapy was classified into 3 groups (low, moderate or high) according to the 2018 Guidelines on the management of blood cholesterol[2]. The local ethics committees approved the studies conducted at each center and permitted data sharing. All data were anonymized.

Primary Endpoint:

The primary endpoint of this study was a composite measure comprising any symptomatic ICrH confirmed with neuroimaging (intracerebral, subdural, or subarachnoid hemorrhage, excluding traumatic or fibrinolysis-related ICH) or recurrence of symptomatic IS confirmed clinically, with or without neuroimaging, during the follow-up period.

Secondary Endpoints:

The secondary endpoints included any symptomatic IS and any symptomatic ICrH during the follow-up period.

Statistical Analyses:

We compared baseline characteristics between patients using statins and those not using statins in patients with CMBs. For categorical variables, contingency tables with the $\chi 2$ test or Fisher's exact test were used. For quantitative variables with a normal distribution, Student's t-test was employed, while the Mann–Whitney U test was used when a nonparametric test was appropriate. Patients were either censored at the latest available follow-up or the follow-up was concluded when the endpoint event occurred. In cases where multiple events occurred during follow-up, censoring was performed at the occurrence of the first event. We estimated absolute event rates per 1,000 patient-years in patients with CMBs, stratified by statin use at baseline. Event rates were estimated using the Kaplan-Meier method. Cox proportional-hazards regression models were utilized to analyze the primary and secondary endpoints. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated. These models were adjusted for variables based on their availability, biological plausibility, and existing literature on CMBs and outcomes. The adjusted variables included age, sex, presentation with TIA or IS, history of hypertension, previous stroke, atrial fibrillation, and use of antiplatelet or anticoagulant drugs. Furthermore, variables with more than 10% missing data were excluded from the Cox regression models. Interaction terms between statin use at baseline and burden of CMBs were added to the models based on results from the Likelihood Ratio Test for any stroke, symptomatic IS, and symptomatic ICrH. Subanalyses were conducted considering CMBs burden (1, 2-4, ≥5, ≥10) and localization (deep, lobar, mixed). Sensitivity analyses were conducted considering the intensity of statin therapy, baseline LDL-C levels ≤70 mg/dL, and presence of cortical superficial siderosis [2]. LDL-C levels were measured at the beginning of the studies, after the initial stroke. Statistical significance for all analyses was set at 0.05 (2-sided). The statistical analyses were conducted using Stata v.15 (TX)

Data Availability

For purposes of replicating procedures and results, requests for anonymized data not provided in the article because of space limitations will be considered from qualified investigator(s).

Results

From the 38 cohorts of the MICON database, 32 met the inclusion criteria, and 16,373 patients were included (see flow chart in Figure 1). Clinical data and cerebrovascular events for each cohort are provided in Table 1. The mean age was 70.5 ± 12.8 years, and 6,960/16,373 (42.5%) of them were women. Out of the total cohort of 16,373 patients, 10,812 individuals (65% of the population), were documented as having received statin treatment following their initial stroke. Of them, 2,878 patients were treated with high-intensity statin therapy, 3,128 with moderate-intensity statin therapy, 592 with low-intensity statin therapy, while statin details were not available for 4,214 patients. The presence of one or more CMBs was observed in 4,668/16,373 (28.5%) patients. Among patients with CMBs, 2,004 had 1 CMB, 1,642 had 2-4 CMBs, 1,022 had ≥5 CMBs, and 433 had ≥10 CMBs. The anatomical distribution of CMBs in this population was as follows: 2,889 lobar, 3,035 deep, and 1,401 mixed. We followed the patients for a cumulative duration of 35,225 patient-years (median 1.34 years [IQR 0.32-2.44]), and we observed any stroke in 1,161 patients: 848 had symptomatic IS, 151 had symptomatic ICrH (124 ICH, 23 subdural hemorrhage, 3 epidural hemorrhage, 1 subarachnoid hemorrhage [two of these patients had multiple ICrH], and 162 patients had strokes that were not classified as IS or ICrH. eTable 1 presents the baseline characteristics of patients based on whether they received statin treatment following the index IS or TIA. eTable 2 displays the baseline characteristics of patients with and without CMBs.

Comparisons between statins users and non-users in patients with CMBs

Compared to patients with CMBs who received statins at baseline (n=3,150), those with CMBs but not treated with statins (n=1,519) were older, with a mean age of 74.4 years (SD 12.1) compared to 72.0 years (SD 11.4). Additionally, a greater proportion of non-statin-treated patients were women (44.3% vs 40.2%). They also had a higher prevalence of previous IS (22% vs 17.2%), previous ICrH (4.1% vs 2.2%), and were more often using oral anticoagulants at the time of study entry (46.3% vs 39.9%). Moreover, a lower percentage of patients treated with statins had hypertension (74% vs 79.4%) received statin therapy prior to the index stroke (11.1% vs 34.1%), and used antiplatelet agents at study entry (48.9% vs 69.2%) (Table 2).

Primary endpoint:

Compared to patients with CMBs who did not use statins at baseline (Table 3 and Figure 2A), statin users exhibited a reduced risk of any stroke (adjusted hazard ratio [aHR] 0.68 [95% CI 0.56–0.84], p<0.0001). Furthermore, statin users showed a decreased risk of any stroke across various CMBs subgroups, including those with 2-4 CMBs, ≥5 CMBs, mixed CMBs, lobar CMBs, and deep CMBs (Table 3 and eFigures 1,4). Conversely, patients with one CMB and ≥10 CMBs who received statin treatment did not exhibit a significant different risk of stroke events during the follow-up period (Table 3 and eFigure 1). No statistically significant interaction was detected between the burden of CMBs and the use of statins at baseline ($p_{interaction}$=0.522) for any stroke risk.

The incidence rate of any stroke in patients with CMBs who were treated with statins was 53 per 1,000 patient-years, compared to 79 per 1,000 patient-years in those who did not receive statins, resulting in an absolute reduction of 26 events per 1,000 patient-years (95% CI: 11 to 39) (Table 3 and Figure 3). A similar reduction in stroke incidence was also observed in patients with 2-4 CMBs, ≥5 CMBs, mixed CMBs, lobar CMBs, and deep CMBs (Table 3 and Figure 3).

Secondary endpoints:

Ischemic stroke

Compared to patients with CMBs who did not use statins at baseline (Table 3 and Figure 2B), statin users exhibited a reduced risk of IS (aHR 0.65 [0.51-0.82], p<0.0001). In addition, statin users showed a decreased risk of IS across various CMBs groups, including those with 2-4 CMBs, ≥5 CMBs, ≥10CMBs, mixed CMBs, lobar CMBs, and deep CMBs (Table 3 and eFigures 2,5). Conversely, patients with one CMB who received statin treatment did not exhibit a significant different risk of IS events during the follow-up period (Table 3 and eFigure 2). No interaction was detected between the burden of CMBs and the use of statins at baseline ($p_{interaction}$=0.166) for the risk of IS.

The incidence rate of IS in patients with CMBs who were treated with statins was 39 per 1,000 patient-years, compared to 65 per 1,000 patient-years in those who did not receive statins, resulting in an absolute reduction of 26 events per 1,000 patient-years (95% CI: 13 to 39) (Table 3 and Figure 2). This reduction in IS incidence was also observed in patients with 2-4 CMBs, ≥5 CMBs, ≥10 CMBs, mixed CMBs, lobar CMBs, and deep CMBs (Table 3 and Figure 3).

Intracranial Hemorrhage

Compared to patients with CMBs who did not use statins at baseline (Table 3 and Figure 2C), statin users did not show an increase in the risk of ICrH (aHR 0.73 [0.46-1.15], p=0.253). Likewise, statin users did not show a different risk of ICrH during the follow-up period based on the number or anatomical distribution of CMBs (Table 3 and eFigures 3,6). No interaction was detected between the burden of CMBs and the use of statins at baseline ($p_{interaction}$=0.183) for the risk of ICrH.

The incidence rate of ICrH in patients with CMBs who were treated with statins was 11 per 1,000 patient-years, compared to 16 per 1,000 patient-years in those who did not receive statins, resulting in a non-significant reduction of 5 events per 1,000 patient-years (95% CI: -11 to 1). In groups according to the number or anatomical distribution of CMBs, the incidence rate of ICrH did not differ among these groups (Table 3 and Figure 3)

Sensitivity analyses:

Statin intensity

Data regarding the type and dose of statins at baseline were available for 12,159 patients, out of which 3,474 had CMBs. Of them, 2,878 patients were receiving high-intensity statins and 3,128 patients were receiving moderate-intensity statins. Among patients with CMBs, treatment with high or moderate intensity statins was associated with a reduction in the risk of any stroke (aHR: 0.66 [95% CI: 0.65-0.87]) and IS (aHR: 0.61 [95% CI: 0.46-0.82]). The use of statins was not associated with the risk of ICrH (aHR: 0.89 [95% CI: 0. -1.42]).

Low LDL- Cholesterol

Baseline LDL-C levels were reported in 7,074 patients, out of whom 2,289 had CMB. The use of statins in patients with CMBs and baseline LDL-C levels ≤70mg/dl did not show an association with the risk of any stroke (aHR 0.95 [95%CI: 0.68-1.34]), IS (aHR 0.81 [95%CI: 0.53-1.26]) or ICrH (aHR 0.1.22 [95%CI: 0.49-3.03]) during the follow-up period.

Cortical Superficial Siderosis

Cortical superficial siderosis was evaluated in a cohort comprising 11,613 patients. Out of these patients, 3,757 had CMBs, and 215 had cortical superficial siderosis. Among the patients who had both CMBs and cortical superficial siderosis (n=107), 17 stroke events were observed during the follow-up period. These stroke events consisted of 9 IS, 4 ICrH, and 4 strokes that were classified as unclassified. The use of statins did not show a significant association with the risk of any type of stroke (aHR for any stroke: 0.74, 95% CI: 0.47-1.18), IS (aHR: 0.76, 95% CI: 0.10-1.42), or ICrH (aHR: 0.75, 95% CI: 0.38-1.35) in the cohort of patients who had both CMBs and cortical superficial siderosis.

Classification of Evidence

This study provides Class III evidence that for patients with IS or TIA and CMBs, statins lower the risk of any stroke or IS without increasing the risk of ICrH.

Discussion

The findings of this large observational and multinational pooled analysis suggest that using statins in patients who have recently experienced an IS or TIA and have CMBs is associated with a reduction of the risk of symptomatic stroke and any symptomatic IS during follow up. Furthermore, using statins in these patients is not associated with an increased risk of ICrH. These results hold true even when considering factors such as the burden or distribution of CMBs, statin intensity, or baseline LDL-C levels of ≤70 mg/dL.

The use of statins following an IS or TIA is widely supported by the medical and scientific communities [3,18]. However, there are no specific recommendations regarding statin therapy in patients with CMBs and a history of IS or TIA. The 2021 AHA/ASA and 2022 ESO guidelines recommend statin therapy for patients with previous IS or TIA to reduce the risk of stroke recurrence and other major cardiovascular events [3,18]. These recommendations are based on randomized clinical trials (RCTs) such as SPARCL and TST (Treat Stroke to Target) [1, 19]. Furthermore, the 2022 ESO guidelines strengthen these recommendations by conducting a systematic review and meta-analyses of five RCTs involving 10,169 patients, comparing statin therapy versus placebo following TIA or IS. Their findings suggest that statins are expected to reduce 13 cases of stroke per 1,000 patients treated [18]. Consistently, the results of two RCTs [6,18,20], which enrolled patients who initiated statin therapy early after IS or TIA (similar to the cohorts in the present study), also support these findings, demonstrating that statin treatment had 20 fewer events per 1,000 patients-treated compared to no statin treatment. The present study suggests that statin treatment in patients with recent IS or TIA and CMBs has a similar impact in reducing subsequent IS events during follow-up (26 cases of stroke per 1,000 patients-treated) compared to the patients included in the meta-analyses of RCTs [18].

In patients with IS or TIA, ICrH is a significant concern associated with statin therapy. According to the 2022 ESO guidelines, a meta-analysis of three RCTs revealed a significant increase in the rate of ICrH among stroke patients receiving statin therapy compared to those who did not receive statins (odds ratio [OR] 1.55, 95% CI 1.09-2.21). This corresponds to approximately 6 ICrH events per 1,000 patients per year [1,6,18,21]. In contrast, similar to the findings of our study, a meta-analysis of 31 RCTs involving 91,588 patients compared to 91,125 controls did not identify an increased incidence of ICrH during follow-up (OR 1.08; 95% CI 0.88-1.32; $p = 0.47$) [22]. Two primary mechanisms are believed to contribute to the elevated risk ICrH in stroke patients undergoing statin therapy [23]. First, by lowering serum cholesterol levels, statins may compromise the integrity of the blood vessels, resulting in arterial necrosis and the formation of microaneurysms [24]. Second, the pleiotropic effects of statins, particularly their antiplatelet and anticoagulant properties, may also play a role in increasing the risk of ICrH [5,23].

Patients with IS or TIA who have CMBs face a 2.4-fold increased risk of ICrH [16]. Additionally, there is a 20% higher risk of IS recurrence [16]. Irrespective of the burden, distribution, or type of antithrombotic treatment administered, the absolute risk of IS remains significantly greater than that of ICrH [16]. Given the substantial risk of IS recurrence and the presence of multiple vascular risk factors in patients with CMBs, statins hold potential for stroke prevention [12, 16, 25, 26]. Similar to antithrombotic treatment, statins have exhibited promising outcomes in reducing the risk of IS in patients with CMBs.

In our study, we conducted sensitivity analyses to address concerns regarding the risk of ICrH in specific patient groups. These analyses considered the use of moderate or high-intensity statins and patients with baseline LDL-C levels ≤70mg/dl [1, 27]. In the SPARCL trial, which investigated the effects of atorvastatin 80mg/day (currently one of the most commonly used high-intensity statins in stroke patients), a reduction in the risk of stroke was observed in patients with IS or TIA. However, a post-hoc analysis revealed an increase in the incidence of hemorrhagic stroke alongside the overall benefit [1, 7]. The TST trial included 2,860 patients with recent IS or TIA and demonstrated that targeting lower levels of LDL-C (<100 or <70mg/dl) following IS or TIA was a safe approach [19]. In this trial [19], there were 18 cases of ICH in the lower LDL-C target group compared to 13 in the upper target group. Similarly, to the SPARCL trial, ICH events in the TST trial were strongly associated with uncontrolled blood pressure [1,7,28]. Supporting these findings, a Danish population-based cohort study, using propensity score matching and analyzing data from over 55,000 patients with prior IS, indicated that the rate of ICH was approximately halved in statin users compared to non-users [29]. Furthermore, it appears that the extent of LDL-C lowering is not associated to the risk of ICH. This is evident in studies using PCSK9 inhibitors, which aim to reduce LDL-C levels to as low as 30 mg/dL, as they did not demonstrate an increased risk of ICH [30,31]. These findings collectively suggest that statin use, even at high intensities, and aggressive LDL-C lowering strategies, even in patients with CMBs with recent IS, do not significantly increase the risk of ICrH.

Some studies suggested that statin therapy in patients with ICH may be linked to the development of CMBs, particularly CMBs in lobar distribution [32,33]. Lobar CMBs, when combined with certain clinical parameters, are considered markers of possible or probable CAA, which is associated with a high risk of recurrent ICrH [23,34]. Consequently, the use of statins in stroke patients with lobar CMBs may raise safety concerns. However, the results of the present study do not support an association between lobar CMBs and a high risk of ICrH in patients with stroke treated with statins. Furthermore, other studies have not found a correlation between statin therapy and presence of lobar CMBs [35,36]. Patients with a high burden of CMBs (≥10) are infrequent in clinical practice and, individually, they are patients at a high risk of ischemic and cerebral hemorrhagic stroke [16]. Among the subgroups of patients with CMBs that we analyzed, those with ≥10 showed a slight, not statistically significant, trend towards an association with ICrH. Probably, despite studying a large number of patients, our estimates were less precise due to being a subgroup of 420 patients. Future studies are likely needed to validate the safety of statin use in patients with a high burden of CMBs.

In patients who had both cortical superficial siderosis and CMBs, the study did not uncover any significant associations between the use of statins and the risk of any type of stroke, IS or ICrH. It is important to note, however, that there were only a limited number of stroke events observed during the follow-up period. Due to the relatively small number of stroke events, the study might not have had enough statistical power to detect potential associations between statin use and stroke risk in this particular patient group. Further research with a larger number of stroke events and patients may be required to provide more conclusive findings on this matter.

Limitations

This study has several limitations that should be acknowledged. First, due to its observational design, there may be inherent selection bias, and we cannot confirm that all patients were included consecutively. It is important to note that patients with severe strokes may not have been suitable for brain MRI examinations, potentially impacting the generalizability of the findings. Furthermore, many physician decisions, including the choice and dosage of antiplatelet agents, oral anticoagulants, combinations, and statins, or blood pressure control during follow-up, were unmeasured and subject to individual clinical judgment. To mitigate this limitation, some cohorts, such as the HERO or CROMIS-2 studies, employed a pre-determined treatment protocol prior to analyzing the presence, burden, and localization of CMBs on MRI [37, 38]. Moreover, during the follow-up period, certain factors such as changes in therapy, medication adherence, and blood LDL-C were not consistently recorded. This lack of consistent data collection may affect the overall findings and interpretation of the study. It is also possible that some deaths of unknown cause were actually secondary to ICrH, potentially leading to an underestimation of the risk of ICrH. However, it is important to note that this limitation is common in studies and clinical trials evaluating ICrH risk. Neuroimaging assessments were performed by different investigators or across multiple centres within the cohorts, although most utilized validated scales such as the Microbleed Anatomical Rating Scale [39]. Multivariable models were adjusted for potential confounding factors; however, certain candidate variables, such as diabetes, liver disease, tendency to bleed, stroke etiology, or MRI field strength, or type of MRI iron-sensitive sequences (gradient echo or susceptibility-weighted imaging) were not available for all patients, which could introduce residual confounding. Additionally, the study may have limited power to estimate the risk of IS or ICrH in subgroups with small sample sizes or low event rates, such as patients with only one CMB or those with ten or more CMBs. Finally, while we considered the risk of symptomatic cerebrovascular events as a measure of clinical benefit, we did not specifically measure the severity of side effects associated with statin use. This limitation should be taken into account when interpreting the overall clinical implications of the findings.

Indeed, further research is warranted to enhance our understanding of the topic. APOE ε alleles are associated with MRI markers for both hemorrhagic and ischemic cerebrovascular diseases, as well as an increased risk of ICH [40]. Consequently, future investigations involving well-phenotyped patient cohorts are imperative to gain a more comprehensive understanding of the potential role of the APOE gene in individuals with CMBs who are taking statins. Currently, there are two ongoing clinical trials that aim to shed light on different aspects of statin therapy and its impact on hemorrhagic stroke and small vessel disease. (1) The "ICrH Risk of Intensive Statin Therapy in Patients With Acute Ischemic Stroke Combined With CMBs" trial (NCT05589454) focuses on patients with recent non-cardioembolic IS and the presence of CMBs. In this trial, participants will be randomly assigned to receive either atorvastatin 20mg or atorvastatin 80mg. The study will follow them up for up to 36 months to assess the risk of hemorrhagic stroke and observe changes in the degree of CMBs. (2) The "Statins In ICH (SATURN)" trial (NCT03936361) targets patients who were taking statins at the time of ICH. The trial aims to investigate the effects of continuing or discontinuing statin treatment on hemorrhagic and ischemic markers of small vessel disease. Additionally, the study will explore whether the presence and burden of hemorrhagic MRI markers influence the risk of recurrent ICH. These ongoing clinical trials will provide valuable insights into the role of statins in patients with IS, CMBs, and ICH. Their findings will contribute to a more comprehensive understanding of the benefits and potential risks associated with statin therapy in these specific clinical contexts.

In conclusion, this individual large international pooled analysis yields evidence that the use of statins in patients with recent IS or TIA and the presence of CMBs is associated with a decreased rate of overall stroke and IS during follow-up. Importantly, this treatment approach does not pose an increased risk of symptomatic ICrH. Furthermore, the burden and localization of CMBs do not affect the association between statin use and ICrH risk. However, ongoing clinical trials will provide additional evidence on the benefits and risks of statin therapy as secondary prevention in this patient population. These forthcoming results will contribute to further enhancing our understanding of the optimal use of statins in the context of CMBs and stroke prevention.

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We used the STROBE cohort checklist when writing our report[41].

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Appendix: Coinvestigators

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Name	Location	Role	Contribution
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Name	Location	Role	Contribution
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References

1. Amarenco P, Bogousslavsky, J, Callahan, A, et al. Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med. 2006;355:549–559. doi: 10.1056/NEJMoa061894.

2. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019 Jun 18;139(25):e1082-e1143. doi: 10.1161/CIR.0000000000000625.

3. Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline From the American Heart Association/American Stroke Association. Stroke. 2021 Jul;52(7):e364-e467. doi: 10.1161/STR.0000000000000375.

4. Endres M. Statins and stroke. J Cereb Blood Flow Metab. 2005 Sep;25(9):1093-110. doi: 10.1038/sj.jcbfm.9600116.

5. Davignon J. Beneficial cardiovascular pleiotropic effects of statins. Circulation. 2004 Jun 15;109(23 Suppl 1):III39-43. doi: 10.1161/01.CIR.0000131517.20177.5a.

6. Collins R, Armitage J, Parish S, Sleight P, Peto R; Heart Protection Study Collaborative Group. 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; 363:757–767. doi: 10.1016/S0140-6736(04)15690-0.

7. Goldstein LB, Amarenco P, Szarek M, et al. Hemorrhagic stroke in the stroke prevention by aggressive reduction in cholesterol levels study.Neurology. 2008; 70(24 Pt 2):2364–2370. doi: 10.1212/01.wnl.0000296277.63350.77.

8. Ribe AR, Vestergaard CH, Vestergaard M, et al. Statins and Risk of Intracerebral Hemorrhage in Individuals With a History of Stroke. Stroke. 2020 Apr;51(4):1111-1119. doi: 10.1161/STROKEAHA.119.027301.

9. Greenberg SM, Ziai WC, Cordonnier C, et al. 2022 Guideline for the Management of Patients With Spontaneous Intracerebral Hemorrhage: A Guideline From the American Heart Association/American Stroke Association. Stroke. 2022 Jul;53(7):e282-e361. doi: 10.1161/STR.0000000000000407.

10. Steiner T, Salman RA-S, Beer R, et al. European Stroke Organisation (ESO) Guidelines for the Management of Spontaneous Intracerebral Hemorrhage. International Journal of Stroke. 2014;9(7):840-855. doi:10.1111/ijs.12309.

11. Greenberg SM, Vernooij MW, Cordonnier C, et al. Cerebral microbleeds: a guide to detection and interpretation. Lancet Neurol. 2009 Feb;8(2):165-74. doi: 10.1016/S1474-4422(09)70013-4. PMID: 19161908; PMCID: PMC3414436.

12. Vernooij MW, van der Lugt A, Ikram MA, et al. Prevalence and risk factors of cerebral microbleeds: the Rotterdam Scan Study. Neurology. 2008 Apr 1;70(14):1208-14. doi: 10.1212/01.wnl.0000307750.41970.d9.

13. Shoamanesh A, Kwok CS, Benavente O. Cerebral microbleeds: histopathological correlation of neuroimaging. Cerebrovasc Dis 2011;32:528–34. doi: 10.1159/000331466.

14. van Veluw SJ, Biessels GJ, Klijn CJ, Rozemuller AJ. Heterogeneous histopathology of cortical microbleeds in cerebral amyloid angiopathy. Neurology. 2016 Mar 1;86(9):867-71. doi: 10.1212/WNL.0000000000002419.

15. Haussen DC, Henninger N, Kumar S, Selim M. Statin use and microbleeds in patients with spontaneous intracerebral hemorrhage. Stroke. 2012 Oct;43(10):2677-81. doi: 10.1161/STROKEAHA.112.657486.

16. Wilson D, Ambler G, Lee KJ, et al. Cerebral microbleeds and stroke risk after ischaemic stroke or transient ischaemic attack: a pooled analysis of individual patient data from cohort studies. Lancet Neurol. 2019 Jul;18(7):653-665. doi: 10.1016/S1474-4422(19)30197-8.

17. Microbleeds International Collaborative Network. Worldwide collaboration in the Microbleeds International Collaborative Network. Lancet Neurol 2016; 15: 1113–14. doi: 10.1016/S1474-4422(16)30213-7.

18. Dawson J, Béjot Y, Christensen LM, et al. European Stroke Organisation (ESO) guideline on pharmacological interventions for long-term secondary prevention after ischaemic stroke or transient ischaemic attack. Eur Stroke J. 2022 Sep;7(3):I-II. doi: 10.1177/23969873221100032.

19. Amarenco P, Kim JS, Labreuche J, et al. A comparison of two LDL cholesterol targets after ischemic stroke.N Engl J Med. 2020; 382:9. doi: 10.1056/NEJMoa191035521.

20. Amarenco P, Goldstein LB, Szarek M, et al. Effects of intense low-density lipoprotein cholesterol reduction in patients with stroke or transient ischemic attack: the stroke prevention by aggressive reduction in cholesterol levels (SPARCL) trial. *Stroke* 2007; 38: 3198–3204. doi: 10.1161/STROKEAHA.107.493106.

21. Hosomi N, Nagai Y, Kohriyama T, et al. The Japan statin treatment against recurrent stroke (J-STARS): a multicenter, randomized, open-label, parallel-group study. EBioMedicine 2015; 2: 1071–1078. doi: 10.1016/j.ebiom.2015.08.006.

22. McKinney JS, Kostis WJ. Statin therapy and the risk of intracerebral hemorrhage: a meta-analysis of 31 randomized controlled trials. Stroke. 2012 Aug;43(8):2149-56. doi: 10.1161/STROKEAHA.112.655894.

23. Ziff OJ, Banerjee G, Ambler G, Werring DJ. Statins and the risk of intracerebral haemorrhage in patients with stroke: systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2019 Jan;90(1):75-83. doi: 10.1136/jnnp-2018-318483.

24. Wang X, Dong Y, Qi X, et al. Cholesterol levels and risk of hemorrhagic stroke: a systematic review and meta-analysis. Stroke 2013;44:1833–9. doi: 10.1161/STROKEAHA.113.001326.

25.Romero JR, Preis SR, Beiser A, et al. Risk factors, stroke prevention treatments, and prevalence of cerebral microbleeds in the Framingham Heart Study. Stroke. 2014 May;45(5):1492-4. doi: 10.1161/STROKEAHA.114.004130.

26. Zheng H, Yuan Y, Zhang Z, Zhang J. Analysis of Risk Factors for Cerebral Microbleeds and the Relationship between Cerebral Microbleeds and Cognitive Impairment. Brain Sci. 2022 Oct 26;12(11):1445. doi: 10.3390/brainsci12111445.

27. Sturgeon JD, Folsom AR, Longstreth WT Jr, Shahar E, Rosamond WD, Cushman M. Risk factors for intracerebral hemorrhage in a pooled prospective study. Stroke. 2007 Oct;38(10):2718-25. doi: 10.1161/STROKEAHA.107.487090.

28. Amarenco P, Kim JS, Labreuche J, et al. Intracranial hemorrhage in the TST trial. Stroke. 2022; 53:457–462. doi: 10.1161/STROKEAHA.121.035846.

29.Ribe AR, Vestergaard CH, Vestergaard M, et al. Statins and risk of intracerebral hemorrhage in individuals with a history of stroke.Stroke. 2020; 51:1111–1119. doi: 10.1161/STROKEAHA.119.027301.

30.Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease.N Engl J Med. 2017; 376:1713–1722. doi: 10.1056/NEJMoa1615664.

31. Sanz-Cuesta BE, Saver JL. Lipid-Lowering Therapy and Hemorrhagic Stroke Risk: Comparative Meta-Analysis of Statins and PCSK9 Inhibitors. Stroke. 2021 Oct;52(10):3142-3150. doi: 10.1161/STROKEAHA.121.034576.

32. Haussen DC, Henninger N, Kumar S, Selim M. Statin use and microbleeds in patients with spontaneous intracerebral hemorrhage. Stroke. 2012 Oct;43(10):2677-81. doi: 10.1161/STROKEAHA.112.657486.

33. Katsanos AH, Lioutas VA, Charidimou A, et al. Statin treatment and cerebral microbleeds: A systematic review and meta-analysis. J Neurol Sci. 2021 Jan 15;420:117224. doi: 10.1016/j.jns.2020.117224.

34. Charidimou A, Boulouis G, Frosch MP, et al. The Boston criteria version 2.0 for cerebral amyloid angiopathy: a multicentre, retrospective, MRI-neuropathology diagnostic accuracy study. Lancet Neurol. 2022 Aug;21(8):714-725. doi: 10.1016/S1474-4422(22)00208-3.

35. Martí-Fàbregas J, Medrano-Martorell S, Merino E, et al. Statins do not increase Markers of Cerebral Angiopathies in patients with Cardioembolic Stroke. Sci Rep. 2018 Jan 24;8(1):1492. doi: 10.1038/s41598-018-20055-3.

36. Feng X, Tang Q, Cheng C, Xu S. Low serum lipid levels, use of statin and cerebral microbleeds: A systematic review and meta-analysis. J Clin Neurosci. 2021 Dec;94:216-225. doi: 10.1016/j.jocn.2021.10.032.

37. Martí-Fàbregas J, Medrano-Martorell S, Merino E, et al. MRI predicts intracranial hemorrhage in patients who receive long-term oral anticoagulation. Neurology. 2019 May 21;92(21):e2432-e2443. doi: 10.1212/WNL.0000000000007532.

38. Wilson D, Ambler G, Shakeshaft C, et al. Cerebral microbleeds and intracranial haemorrhage risk in patients anticoagulated for atrial fibrillation after acute ischaemic stroke or transient ischaemic attack (CROMIS-2): a multicentre observational cohort study. Lancet Neurol. 2018 Jun;17(6):539-547. doi: 10.1016/S1474-4422(18)30145-5.

39. Gregoire SM, Chaudhary UJ, Brown MM, et al. The Microbleed Anatomical Rating Scale (MARS): reliability of a tool to map brain microbleeds. Neurology 2009;73: 1759–1766. doi: 10.1212/WNL.0b013e3181c34a7d.

40. Schilling S, DeStefano AL, Sachdev PS, et al. APOE genotype and MRI markers of cerebrovascular disease: systematic review and meta-analysis. Neurology. 2013;81:292-300. doi: 10.1212/WNL.0b013e31829bfda4.

41. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

Table 1. Baseline characteristics of each cohort

Cohort	Number of participants	Taking statins, n (%)	Taking oral anticoagulants, n (%)	Taking antiplatelet agents, n (%)	Mean age (SD), years	Women, n (%)	Any CMB, n (%)	Median, Follow-up, years (IQR)	Any composite Stroke event, n (%)	Any IS event, n (%)	Any ICrH event, n (%)
Basel TIA	192	127 (66.1)	33 (17.2)	155 (80.7)	68.6 (12.7)	73 (38)	21 (10.9)	0.24 (0.24-0.24)	26 (13.5)	26 (13.5)	0 (0)
Bern	251	173 (68.9)	73 (29.1)	177 (70.5)	66.5 (13.9)	109 (43.4)	50 (19.9)	0.27 (0.25-0.32)	5 (2)	5 (2)	0 (0)

CASPER	135	108 (80)	18 (13.3)	116 (85.9)	65.6 (10.6)	39 (28.9)	79 (58.5)	1.24 (1.21-1.27)	3 (2.2)	3 (2.2)	0 (0)
CATCH	413	253 (61.3)	67 (16.2)	371 (89.8)	67.1 (14.1)	164 (39.7)	65 (15.7)	0.24 (0.21-0.27)	14 (3.4)	13 (3.1)	1 (0.2)
CROMIS-2	1446	1164 (80.5)	1401 (96.9)	796 (55)	75.8 (10.3)	608 (42)	296 (20.5)	2.13 (1.99-2.71)	69 (4.8)	55 (3.8)	14 (1)
Dublin	245	215 (87.8)	71 (29)	190 (77.6)	67.7 (13.2)	93 (38)	24 (9.8)	0.24 (0.24-0.99)	12 (4.9)	12 (4.9)	0 (0)
FUTURE	19	14 (73.7)	0 (0)	18 (94.7)	43.8 (5.9)	10 (52.6)	1 (5.3)	0.44 (0.35-0.66)	4 (21.1)	4 (21.1)	0 (0)
GRAZ	460	312 (67.8)	78 (17)	372 (80.9)	66.6 (12.6)	179 (38.9)	88 (19.1)	0.51 (0.25-3.38)	65 (14.1)	54 (11.7)	13 (2.8)
HAGAKURE	425	135 (31.8)	157 (36.9)	211 (49.6)	73.3 (12.8)	174 (40.9)	157 (36.9)	2.05 (1.08-2.88)	34 (8.0)	25 (5.9)	9 (2.1)
HERO	934	594 (63.6)	933 (99.9)	78 (8.4-9	77.6 (6.5)	487 (8.4)	247 (26.4)	2.01 (1.97-2.06)	49 (5.2)	32 (3.4)	18 (1.9)
HKU	1003	862 (85.9)	104 (10.4)	881 (87.8-9	69.1 (12.1)	402 (40.1)	450 (44.9)	2.75 (1.63-4.24)	112 (11.2)	92 (9.2)	20 (2.0)
IPAAC	81	28 (34.6)	81 (100)	0 (0)	71.3 (9.0)	40 (49.4)	24 (29.6)	2.02 (1.72-2.17)	8 (9.9)	5 (6.2)	3 (3.7)
Kushiro City General Hospital	784	84 (10.7)	63 (8.0)	620 (79.1)	72.1 (11.4)	330 (42.1)	320 (40.8)	0.09 (0.09-0.2)	139 (17.7)	119 (15.2)	22 (2.8)
Lille	181	138 (76.2)	48 (26.5)	135 (74.6)	63.8 (12.6)	69 (38.1)	24 (13.3)	3.15 (1.14-4.98)	17 (9.4)	17 (9.4)	0 (0)
MGH	660	510 (77.3)	114 (17.3)	457 (69.2)	68.8 (15.4)	289 (43.8)	98 (14.8)	0.24 (0.24-0.24)	4 (0.6)	4 (0.6)	0 (0)
Monash	352	321 (91.2)	349 (99.1)	30 (8.5)	74.9 (10.3)	169 (48)	153 (43.5)	1.45 (0.79-2.47)	14 (4)	9 (2.6)	7 (2)
MSS2	239	194 (81.2)	22 (9.2)	231 (96.7)	66.9 (11.2)	92 (38.1)	39 (16.3)	1.03 (0.98-1.14)	28 (11.7)	28 (11.7)	0 (0)
NNI	184	182 (98.9)	32 (17.4)	151 (82.1)	57.6 (11.4)	57 (31)	50 (27.2)	0.62 (0.23-1.30)	0 (0)	0 (0)	0 (0)
NOACISP	306	226 (73.9)	286 (93.5)	37 (12.1)	78.3 (9.0)	139 (45.4)	87 (28.4)	2.02 (1.30-2.31)	28 (9.2)	19 (6.2)	10 (3.3)

NUS	45	36 (80)	15 (33.3)	31 (68.9)	66.9 (10.0)	13 (28.9)	25 (55.6)	2.89 (1.92-3.34)	6 (13.3)	6 (13.3)	0 (0)
Orken	454	88 (19.4)	454 (100)	6 (1.3)	71.8 (12.1)	233 (51.3)	134 (29.6)	1.57 (0.63-5.00)	11 (2.4)	8 (1.8)	3 (0.7)
Parisk	228	206 (90.4)	0 (0)	221 (96.9)	70.9 (9.0)	67 (29.4)	61 (26.8)	2.15 (2.07-2.24)	10 (4.4)	10 (4.4)	0 (0)
RUNDMC	179	127 (70.9)	19 (10.6)	164 (91.6)	64.6 (8.6)	63 (35.2)	35 (19.6)	5.00 (5.00-5.00)	25 (14)	23 (12.8)	2 (1.1)
Sainte-Anne	385	199 (51.7)	302 (78.4)	0 (0)	79.8 (10.9)	204 (53)	99 (25.7)	1.20 (0.46-2.00)	26 (6.8)	23 (6.0)	5 (1.3)
SAMURAI	1103	271 (24.6)	1039 (94.2)	124 (11.2)	77.5 (10.0)	480 (43.5)	265 (24)	1.97 (0.98-2.04)	82 (7.4)	72 (6.5)	10 (0.9)
SIGNAL	213	74 (34.7)	43 (20.2)	173 (81.2)	72.4 (13.9)	88 (41.3)	94 (44.1)	0.61 (0.55-0.68)	27 (12.7)	26 (12.2)	1 (0.5)
SNUBH	3355	2749 (81.9)	625 (18.6)	3104 (92.5)	66.5 (13.3)	1347 (40.1)	1166 (34.8)	0.97 (0.93-0.99)	172 (5.1)	N/A	N/A
Soo-DOACs	182	137 (75.3)	173 (95.1)	5 (2.7)	73.3 (9.4)	84 (46.2)	68 (37.4)	2.02 (0.47-2.22)	7 (3.8)	6 (3.3)	1 (0.5)
TABASCO	436	205 (47)	33 (7.6)	373 (85.6)	67.0 (9.9)	184 (42.2)	64 (14.7)	5.00 (3.48-5.00	57 (13.1)	57 (13.1)	0 (0)
Veltkamp	621	432 (69.6)	111 (17.9)	491 (79.1)	64.1 (14.1)	228 (36.7)	142 (22.9)	4.23 (3.51-5.00)	29 (4.7)	25 (4)	4 (0.6)
Wurzburg	358	243 (67.9)	122 (34.1)	228 (60.7)	70.6 (13.3)	158 (44.1)	87 (24.3)	0.26 (0.24-0.28)	22 (6.1)	21 (5.9)	1 (0.3)
Yonsei	504	405 (80.4)	487 (96.6)	40 (7.9)	70.3 (10.5)	288 (57.1)	155 (30.8)	2.32 (1.07-3.83)	56 (11.1)	49 (9.7)	7 (1.4)
Total	16373	10812/16373 (66)	7353/16370 (44.9)	9986/16367 (61)	70.5 (12.8)	6960/16365 (42.5)	4668/16335 (28.1)	1·03 (0·33-2·16)	1161/16373 (7.1)	848/13018 (5.2)	151/13018 (0.9)

Table 2. Baseline characteristics of patients with cerebral microbleeds according to whether they received treatment with statins following index ischemic stroke or TIA.

	Statin treatment received after the initial stroke n=3,150	Statins treatment not received after the initial stroke n=1,519	p value
Age mean (SD)	72.0 (11.4)	74.4 (12.1)	<0.001
Sex (women), n (%)	1,268/3150 (40.2)	673/1,519 (44.3)	0.009

Hypertension, n (%)	2,496/3,143 (79.4)	1,123/1,517 (74.0)	<0.001
Previous ischemic stroke, n (%)	589/3,145 (17.2)	335/1,519 (22)	0.009
Previous intracranial hemorrhage, n (%)	68/3,001 (2.2)	61/1,472 (4.1)	<0.001
Diabetes, n (%)	814/3,013 (27)	374/1,472 (25.4)	0.264
Etiology, TOAST (Cardioembolism), n (%)	655/2,070 (31.6)	437/784 (55.7)	0.003
Liver disease (yes), n (%)	62/1,387 (4.4)	39/954 (4.0)	0.680
Bleeding predisposition (yes), n (%)	61/704 (8.6)	56/785 (7.1)	0.289
Anticoagulants prior to index stroke, n (%)	196/1,785 (10.9)	182/1,215 (14.9)	0.001
Antiplatelets prior to index stroke, n (%)	769/1,784 (43.1)	371/1,215 (30.5)	<0.001
Statins prior to index stroke, n (%)	257/753 (34.1)	21/188 (11.1)	<0.001
Ischemic heart disease, n (%)	530/2,941 (18)	183/1,416 (12.9)	<0.001
Stroke (vs TIA) at study entry, n (%)	2,837/3,149 (90)	1,396/1,519 (91.9)	0.047
Anticoagulants after index stroke, n (%)	1,257/3,148 (39.9)	704/1,519 (46.3)	<0.001
Antiplatelet agents after index stroke, n (%)	2,180/3,150 (69.2)	744/1,519 (48.9)	<0.001

Table 3. Rate and risk of events according to the number and anatomical distribution of cerebral microbleeds in statins users and non users from the index stroke.

	Composite any symptomatic ischemic stroke or intracranial hemorrhage				Symptomatic ischemic stroke				Symptomatic intracranial hemorrhage			
Variable, number of patients patients for multivariable model	Rate, per 1,000 patient-years in statins users	Rate, per 1,000 patient-years in no statin users	Absolute rate difference (95% CI)	aHR (95% CI)	Rate, per 1,000 patient-years in statins users	Rate, per 1,000 patient-years in no statin users	Absolute rate difference (95% CI)	aHR (95% CI)	Rate, per 1,000 patient-years in statins users	Rate, per 1,000 patient-years in no statin users	Absolute rate difference (95% CI)	aHR (95% CI)
None CMB (n=11,431)	37	40	-3 (-8 to 3)	0.85 (0.73 - 0.99)	31	35	-4 (-10 to 1)	0.81 (0.67 - 0.96)	4	4	0 (-2 to 1)	1.02 (0.61 - 1.68)
Any CMB (n=4,605)	53	79	-26 (-39 to -11)	0.68 (0.56	39	65	-26 (-39 to -13)	0.65 (0.51	11	16	-5 (-11 to 1)	0.73 (0.46

				- 0.84)				- 0.82)				- 1.15)
Number of CMB												
One (n=1,970)	42	56	-14 (-31 to 3)	0.78 (0.55 - 1.20)	31	47	-16 (-33 to 0)	0.78 (0.46 - 1.05)	7	10	-3 (-11 to 4)	0.84 (0.35 - 1.99)
2-4 (n=1,613)	51	84	-33 (-57 to -8)	0.61 (0.43 - 0.85)	40	70	-30 (-52 to -6)	0.61 (0.41 - 0.90)	8	14	-6 (-16 to 4)	0.66 (0.27 - 1.60)
≥5 (n=1,008)	80	116	-36 (-71 to 0)	0.63 (0.44 - 0.89)	53	92	-39 (-72 to -6)	0.64 (0.41 - 0.98)	27	31	-4 (-24 to 15)	0.78 (0.39 - 1.56)
≥10 (n=420)	132	116	14 (-70 to 101)	0.53 (0.25 - 1.10)	67	91	-24 (-99 to 50)	0.36 (0.14 - 0.92)	32	10	22 (-53 to 58)	1.64 (0.17 - 15.69)
Anatomical distribution of CMB												
Mixed (n=1,384)	66	98	-32 (-60 to -3)	0.68 (0.49 - 0.94)	43	84	-41 (-68 to -14)	0.57 (0.38 - 0.85)	20	18	2 (-11 to 16)	1.11 (0.52 - 2.35)
Deep (n=2,990)	38	42	-4 (-9 to -2)	0.60 (0.47 - 0·76)	39	79	-40 (-58 to -21)	0.55 (0.41 - 0.74)	15	24	-9 (-19 to 2)	0.66 (0.39 - 1.09)
Lobar (n=2,852)	54	77	-23 (-40 to -6)	0.71 (0.55 - 0.91)	39	68	-29 (-45 to -12)	0.64 (0.47 - 0.85)	12	11	0 (-6 to 7)	1.00 (0.53 - 1.88)

aHR, means adjusted Hazard ratio; CMB, cerebral microbleeds.

Multivariable models compared statins users and non-users (reference) and were adjusted for our prespecified coraviates (age, sex, presentation with transient ischemic attack or ischemic stroke, history of hypertension, previous stroke, use of antiplatelet or anticoagulant drugs). Ranges in brackets are 95% confidence interval.

Figure 1. Study Flowchart

Records are publications indexed in Medline or Embase and other studies identified through METACOHORTS, correspondence with other groups, and conference publications. ICH=intracranial hemorrhage. MICON=Microbleeds International Collaborative Network[16].

Figure 2. Kaplan Meier estimates for CMB presence, statin use and outcomes in patients with A) Any Stroke, B) Ischemic Stroke, C) Intracranial Hemorrhage

Figure 3. Rate per 1,000 patient-years, stratified per cerebral microbleeds number or distribution, and statin treatment