

Statins May Increase Intracerebral Hemorrhage Volume

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ABSTRACT: Background: Some studies have suggested an association between hypocholesterolemia and intracerebral hemorrhage (ICH). In the SPARCL trial, statin use increased ICH risk. We tested the hypothesis that use of statins affects the volume of spontaneous ICH and contributes to the progression of ICH volume between baseline and follow-up CT scans. **Methods:** Consecutive cases of spontaneous ICH were reviewed. Secondary causes were excluded. We measured ICH volume on the baseline and follow-up CT scans using the AxBxC/2 method. Multivariate analysis and logistic regression modeling were used. The primary outcome was the ICH volume on the baseline CT scan. Secondary outcomes included volume variation between the baseline and the first follow up CT scans and death. **Results:** Of 303 subjects, 71 were taking a statin at the time of the ICH (23%). Statin users were significantly more likely to be younger, to have co-morbidities and take anticoagulant or anti-platelet medication. They also had a higher baseline ICH volume than non-statin users (median 31.2 [10, 82.1] ml vs 16 [4, 43.8] ml; $p=0.006$). Adjusting for possible confounders, statins remained associated with an increased ICH volume ($p=0.007$). There was a significant mean ICH volume progression between the first and second CT scans in statin users (+10.8 vs +0.9 ml; $p=0.03$; 95% CI: [-1, +22.6] [-2.5, +4.3]). No difference in mortality was seen between the two groups. **Conclusion:** Treatment with HMG-CoA reductase inhibitors may be a risk factor for increased ICH volume in spontaneous brain hemorrhages and could contribute to hemorrhage's volume progression.

RÉSUMÉ: Les statines pourraient augmenter le volume de l'hémorragie intracérébrale. Contexte : Selon certaines études, il existerait une association entre l'hypocholestérolémie et l'hémorragie intracérébrale (HIC). Dans l'essai clinique SPARCL, l'utilisation d'une statine augmentait le risque d'HIC. Nous avons vérifié l'hypothèse selon laquelle l'utilisation de statines influence le volume de l'HIC spontanée et contribue à la progression du volume de l'HIC à la tomodensitométrie cérébrale initiale et de suivi. **Méthodes :** Des cas consécutifs d'HIC spontanée ont été révisés. Les causes secondaires ont été exclues. Nous avons mesuré le volume de l'HIC à la tomodensitométrie initiale et à celle de suivi au moyen de la formule AxBxC/2. L'analyse multivariée et la régression logistique ont été utilisées pour l'analyse des données. L'issue primaire était le volume de l'HIC à la tomodensitométrie initiale. Les issues secondaires étaient la variation du volume entre la tomodensitométrie initiale et la première effectuée au cours du suivi et le décès. **Résultats :** Soixante et onze des 303 sujets prenaient une statine au moment de l'HIC (23%). Les sujets qui prenaient une statine avaient une plus forte probabilité d'être plus jeunes, d'avoir des comorbidités et de prendre des anticoagulants ou des antiplaquetaires. Ils avaient également un volume initial d'HIC plus grand que ceux qui ne prenaient pas de statines (médiane 31,2 [10,82,1] ml versus 16 [4, 43,8] ml ; $p = 0,006$). Après ajustement pour les variables confondantes possibles, les statines demeuraient associées à un volume plus grand d'HIC ($p = 0,007$). Il y avait une progression significative du volume de l'HIC entre la première et la seconde tomodensitométrie chez les sujets qui prenaient une statine (+10,8 versus +0,9 ml ; $p = 0,03$; IC à 95% : -1 à +22,6 et -2,5 à +4,3 respectivement). Nous n'avons pas observé de différence de mortalité entre les deux groupes. **Conclusion :** Le traitement par les inhibiteurs de l'HMG-CoA réductase pourrait constituer un facteur de risque d'un plus grand volume d'HIC dans les hémorragies cérébrales spontanées et pourrait contribuer à la progression du volume de l'hémorragie.

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Several epidemiological studies have demonstrated an association between hypocholesterolemia and the incidence of intracerebral hemorrhage (ICH).¹⁻³ HMG-CoA reductase inhibitors (statin) may theoretically increase the risk of cerebral hemorrhage, given its cholesterol-lowering effect. In addition, statins have been associated with decreased platelet function via direct influence on platelet membrane and inhibition of PAR-1, which is a cell-bound protein that links platelet activation.⁴⁻⁶

An exploratory analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial found that statins overall effect included an increase in the number of treated patients having hemorrhagic stroke (n 55 for active treatment vs n 33 for placebo) with an unadjusted HR 1.68.⁷ The Heart Protection Study (HPS) earlier described this

effect in a subgroup of patients with a history of cerebrovascular disease.⁸ A meta-analysis of four studies including patients with a history of cerebrovascular disease was conducted recently to confirm these data.⁹ The conclusion was that the beneficial effect of statins was partly offset by an increased risk of ICH.

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In contrast, a meta-analysis of previous statin therapy trials—carried out predominately with patients with coronary heart disease—found no relationship between statin treatment and the risk of hemorrhagic stroke.¹⁰

As a result of these observations, controversy remains about HMG-CoA reductase therapy and its association with ICH. Moreover, it is not known whether statins augment the propensity for bleeding and generate larger hematomas. Therefore, we tested the hypothesis that statin use affects the volume of spontaneous ICH and promotes hematoma expansion.

METHODS

Study Subjects

This retrospective observational study was conducted in two affiliated medical centers (Charles-LeMoyné Hospital, Centre Hospitalier, Universitaire de Sherbrooke). All cases \geq 18 years old of spontaneous intracerebral hemorrhage between January 2002 and October 2007 were reviewed. Hematomas were radiologically proven by CT scan. Secondary causes such as arteriovenous malformations, brain trauma, tumor, drugs and aneurysms were excluded. Other exclusion criteria were hemorrhagic infarction, thrombolytic treatment complication of ischemic stroke, and blood dyscrasias.

Measurements

Clinical information—including past medical history, baseline modified Rankin score and medication use—were abstracted from medical records. Patients were defined as anticoagulated if they were taking warfarin, fractionated or low molecular weight heparin. The baseline international normalized ratio (INR) and platelet value upon medical presentation were recorded. Outcomes were adjusted for anticoagulation. Low-density lipoprotein (LDL) cholesterol levels were noted when available.

The Glasgow Coma Scale was noted and a validated modified National Institutes of Health Stroke Scale (mNIHSS) score was estimated from chart review.¹¹

Imaging

The ABC/2 method was used for ICH volume measurement on baseline and follow up CT scans when available.¹² All CT were reviewed by a stroke neurologist (JMB) or a neurology resident (GR). The volume variation between the baseline and the first follow up CT scans was also measured. Twenty five CT scans were reviewed by both JMB and GR to insure the inter-reliability in ICH volume measurement. The location of each intracerebral hemorrhage was categorized as deep or infratentorial (basal ganglia, thalamus, internal capsule, deep periventricular white matter, cerebellum, and brainstem) or lobar (cortex and subcortical white matter). The presence of ventricular extension was also assessed. Patients with craniotomy were excluded from calculations of hematoma variation volume because of potentially confounding bias.

Outcomes

The primary outcome was ICH volume on the baseline CT scan using the ABC/2 method.¹² Secondary outcomes included

volume variation between baseline and first follow up CT scans and death from any causes during hospitalization.

Data Analysis

Patients were dichotomized as using or not using statin. Univariate analyses were used to examine differences between the two groups and to determine whether statin influenced initial and follow up median ICH volume. Fisher Exact and Chi-Square tests were used for nominal variables and Student t-test for continuous normal variables. Lin's concordance correlation coefficient was used for assessment of the inter-rater reliability in ICH volume measurement. Because of the asymmetry of ICH volume's distribution, we expressed our results with medians and the Mann-Whitney non-parametric test was used to compare them. Since ICH volumes do not follow a linear spectrum, a log-transformation was done to make comparisons between groups. For univariate analysis, ICH volumes were also categorized according to the following cut-points: less than 30 cm³, 30 to 60 cm³, and greater than 60 cm³.

A multivariate generalized linear model was constructed to determine whether statin was an independent risk factor for greater ICH volume, after adjusting for age, vascular risk factors (diabetes, hypertension, heart disease), medication use prior to the event (antiplatelet, anticoagulant, and antihypertensive agents) and baseline INR value. P values <0.05 were considered significant.

RESULTS

Five hundred and thirty-nine patients were identified with a diagnosis of nontraumatic ICH (222 from Charles-LeMoyné Hospital and 317 from the CHUS). Ninety-one were excluded based on radiological confirmation of underlying lesions or suspicion of metastases in patients with known primary systemic cancer. Another 98 patients had ischemic stroke with hemorrhagic infarction and nine had blood dyscrasia with severe thrombocytopenia (platelet count less than 50,000). Eight patients were less than 18-years-old. Thirty patients were excluded because of unavailable radiological images for manual volume calculation. Those patients had their CT scan performed in another center prior to their transfer to our hospitals. Baseline characteristics of these patients were similar to the cohort included in our study.

Of 303 consecutive patients who met inclusion criteria for spontaneous ICH, 71 (23%) were taking a statin (atorvastatin 85%, simvastatin 8%, pravastatin 4%, others 3%) at the time of the ICH. Statin users were significantly more likely to be younger, to present comorbidities, and to have used antiplatelet, anticoagulant, or antihypertensive agents prior to the index event (Table 1). The mean INR was not different between the two groups, although the mean INR was lower with anticoagulated statin users than with anticoagulated non-statin users (2.27 ± 1.04 vs. 2.94 ± 2.23 ; $p=0.03$). Low-density lipoprotein levels were lower in HMG-CoA reductase inhibitors but were available in only 20 patients taking a statin and in 47 patients not using a statin. Mean baseline blood pressure was significantly higher in the non-statin group. However, within each group, Pearson correlation coefficient test shown no correlation between blood pressure and hemorrhage volume (statin $p=0.1$, non-statin

Table 1: Baseline characteristics according to presence of statin use

	Statin n=71	Non-statin n=232	<i>p</i>
Age-yr	71.1±10.1	74.9±11.5	0.012
Male sex (%)	39 (55)	126 (54)	0.93
Risk Factors			
diabetes mellitus (%)	22 (31)	41 (18)	0.016
hypertension (%)	61 (86)	166 (72)	0.015
heart diseases(%)	32 (45)	46 (20)	< 0.001
Prior ischemic stroke (%)	17 (24)	45 (19)	0.41
Prior ICH (%)	4 (6)	14 (6)	1
Medication prior to events			
antihypertensive (%)	58 (82)	122 (53)	< 0.001
antiplatelet (%)	54 (76)	89 (38)	< 0.001
Anticoagulant (%)	26 (37)	43 (19)	0.001
Baseline blood pressure			
systolic	151±18	161±25	<0.001
diastolic	77±10	83±14	0.001
INR			
anticoagulated	2.27±1.04	2.94±2.23	0.03
non anticoagulated	1.05±0.2	1.02±0.1	0.89
Platelet (X 10 ⁹ /L)	245±81	252±95	0.59
LDL (mmol/L)	2.47±0.25	2.93±0.37	0.04
NIHSS modified score *	10 [4, 17]	7 [3, 15]	0.17
Glasgow coma scale *	12 [7, 15]	14 [9, 15]	0.23
MRS<2 (%) [†]	49 (69)	151 (65)	0.57
Time to CT scan			
0-6 h (%)	28 (39)	86 (37)	
6-24 h (%)	5 (7)	30 (13)	
>24 h (%)	17 (24)	52 (22)	0.68
Unknown delay (%)	21 (30)	64 (28)	
ICH location			
Left hemisphere (%)	38 (53.5)	104 (44.8)	0.22
Lobar (%)	39 (54.9)	104 (44.8)	
Basal Ganglia (%)	24 (33.8)	100 (43.1)	0.329
Infratentorial (%)	8 (11.3)	28 (12.1)	
Ventricular extension (%)	29 (41)	102 (44)	0.64

ICH indicates intracerebral hemorrhage. MRS indicates modified Rankin Scale.*Continuous variables are showed as mean and mNIHSS and Glasgow coma scale are displayed as median [25th percentile, 75th percentile]. † MRS prior to ICH.

p=0.3). Otherwise, baseline characteristics were similar between groups.

Pre-ICH statin use was associated with a significantly higher median hemorrhage volume (31.2 [10, 82.1] ml vs 16 [4, 43.8] ml in those not taking statin; *p*=0.006) (Table 2). The volumes were expressed in term of medians because of the asymmetric volume distribution in each group. However, mean volumes

were also different (51.5 ± 55.8 ml, compared to 35.2 ± 45.4 ml; *p*=0.027). This difference remained significant (*p*=0.03) when we stratified ICH into volume categories. Volume less than 30ml was present in 49% of statin users vs 66% of non-statin users while 34% and 20% respectively had volume > 60ml. No difference was seen according to the type of statin used. After adjusting for anticoagulant, antiplatelet, antihypertensive medication, INR, platelets, baseline blood pressure, ICH location and other risk factors (age, diabetes, hypertension, ischemic heart disease) in the multivariate analysis, HMG-CoA reductase inhibitors remained associated with an increased baseline ICH volume (*p*=0.007). The other independent variable associated with an increased ICH volume was antiplatelet medication (median ICH volume of 26.3 ml in those taking antiplatelet agents vs 16.4 ml in those not taking antiplatelet agents; *p*=0.025). The inter-rater reliability for ICH volume measurement was excellent for the 25 CT scans reviewed by both JMB and GR (Lin's correlation coefficient 0.98).

The baseline ICH volume was higher in statin users in all "time to CT" subgroups (Table 2) except in the 6-24 hour subgroups for which the number of patients using statin was very small⁵. The median baseline ICH was increased for lobar and infratentorial cases but it did not reach statistical significance for basal ganglia ICH.

A follow-up CT was obtained in 29 (41%) statin patients and in 100 (43%) non-statin patients. Again, the delay between the baseline CT and the first follow up CT scans was not different among groups and two thirds of follow up CT scans were done within 72 hours. The main reasons for the absence of a follow up CT scan were early mortality (50.5%), mild symptoms (19%), futility due to severe baseline disability or comorbidities (8.9%) and unspecified (21.6%). Statin users who did not have a control CT scan had significant higher mean initial ICH volume (71.1±62.6 vs 23.2±25.2; *p*<0.001), a higher mNIHSS score (12.9±7.5 vs 7.96±6.2; *p*=0.001) and a lower Glasgow coma scale (9.7±4.2 vs 12.9±2.9; *p*=0.01) compared to those with a follow up CT scan. Non-statin users without a control CT scan were more likely to have a higher mean initial volume ICH (43.5±54.2 vs 24.3±26.5; *p*<0.001) and to be older (76.9±10.7 vs 72.3±12; *p*=0.002) than non-statin users with follow up brain imaging. Other characteristics between patient with or without a control CT scan were similar.

One patient in the statin group and 13 patients in the non-statin group had craniotomy for hematoma evacuation after the baseline CT scan. Therefore, the median ICH volume on the follow up CT scan and the mean variation of ICH volume between the baseline CT and second CT were calculated for 28 statin users and 87 non-statin users. No difference was observed for the median ICH volume on the follow up CT (13.6 [4.2, 41.8] ml in statin users vs. 12.1 [3.1, 31.5] ml in non statin users; *p*=0.5) (Table 3). When means were compared instead of medians for the follow up CT, a trend toward higher mean ICH volume among statin users was observed (33.6±47.5 ml vs. 21.2±25.2 ml; *p*= 0.076). A significant increase in mean ICH volume progression between baseline and first follow up CT scans was also present in HMG-CoA reductase users compared to others. (+10.8±31.2 ml vs. +0.9±15.9 ml; *p*=0.03; 95% CI: [-1, +22.6] [-2.5, +4.3]).

Table 2: Hemorrhage volume and location on baseline CT-scan

	Statin n=71	Non-Statins n=232	<i>p</i>
Median baseline ICH volume (ml)*	31.2 [10, 82.1]	16 [4, 43.8]	0.006
Median baseline ICH volume (ml) vs time to CT scan			
0-6h	64.3 [15, 105]	21.9 [6, 62]	0.048
6-24h	4.5 [1, 21]	26.2 [7, 56]	0.1
>24 h	16.8 [10, 28]	11.9 [3, 26]	0.3
Unknown delay	43.3 [17, 99]	12.3 [4, 46]	0.009
Median baseline ICH volume (ml) vs ICH location			
Lobar	57.6 [21.4, 107]	28.8 [11.7, 67.3]	0.02
Basal Ganglia	10.0 [2.6, 33.6]	8.3 [1.9, 33.8]	0.973
Infratentorial	33.2 [7.3, 47.8]	9.9 [2.5, 22.2]	0.016

*All ICH volume are displayed as median [25th percentile, 75th percentile].

Finally, the death rate during hospitalization (mean of 16 days) was similar in those exposed and those not exposed to statin (45% vs. 38%; $p=0.31$). This also held true for the percentage of deaths directly related to ICH (88% of deaths in each group; $p=0.9$). Other etiologies of death were related to infection, pulmonary embolism, and ischemic heart disease. Only 16 (23%) statin users and 55 (24%) non-statin users were discharged home after their hospitalization ($p=0.8$).

DISCUSSION

We found a significant increase in the median ICH volume on the baseline CT scan of statin users compared to non-statin users presenting with a spontaneous ICH. This remained significant after adjustments for other medical comorbidities and treatment. This study also showed a significant increased mean ICH volume progression between the first and second CT scans in patients treated with statins. To our knowledge, no research has been conducted to determine the potential effects of statin therapy on initial hematoma volume and on ICH volume expansion between baseline and follow-up CT scans in spontaneous ICH.

Our observations are consistent with the report of a recent clinical trial on high-dose statin therapy.¹³ An exploratory analysis of the SPARCL trial focusing on the 88 patients who experienced ICH while enrolled in the study raised concern about an association between HMG-CoA reductase inhibitors and a significant increase in hemorrhage risk.⁷

One possible explanation relates to statin's cholesterol-lowering effect. In an autopsy supported study, there was evidence that hypocholesterolemia may lead to the rupture of small intraparenchymal cerebral arteries by weakening arterial walls.¹⁴ Other epidemiologic studies also demonstrated that low-

Table 3: Hemorrhage volume and volume variation in patients with follow-up CT scan

	Statin n=28	Non-Statins n=87	<i>p</i>
Median ICH volume ml			
Baseline CT scan	13.8 [3.9, 35.5]	11.3 [3.8, 29.3]	0.7
Follow-up CT scan	13.6 [4.2, 41.8]	12.1 [3.1, 31.5]	0.5
Median ICH volume on follow up CT scan vs delay between CT scans. (% of patient)			
0-6 hours	62 (4)	50.8 [22, 92] (3)	1
6-24 hours	15.8 [11, 93] (14)	5.6 [1, 13] (14)	0.06
24-48 hours	10.7 [3, 19] (32)	7.9 [4, 25] (22)	0.7
48-72 hours	2.3 [0.1, 33] (11)	17.7 [4, 38] (22)	0.2
>72 hours	12.5 [4, 97] (39)	12.3 [4, 30] (39)	0.4
Mean variation ICH volume (ml) between baseline and first follow up CT scans	+10.8±31.2	+0.9±15.9	0.03
95% CI	-1, +22.6	-2.5, +4.3	

Continuous variables displayed as mean \pm SD, or median [25th percentile, 75th percentile]. ICH indicates intracerebral hemorrhage. 95% CI indicates 95% confidence interval.

density lipoprotein (LDL) cholesterol levels were inversely associated with primary ICH risk.¹⁻³ Similarly, Bang et al's retrospective study reported a relationship between recanalization therapy, low cholesterol, and hemorrhagic infarction¹⁵ while low LDL levels were reported by some as associated with hemorrhagic transformation after large artery stroke¹⁶ or increased mortality in ICH.¹⁷ The investigators in the SPARCL trial, however, found no relationship between ICH risk and low-density lipoprotein or total cholesterol levels.¹³ The mechanism by which statin increases ICH risk could also be independent of its lipid-lowering effect and may be related to its pleiotropic and antithrombotic properties. Statin agents have been reported to selectively inhibit platelet G-coupled, α -thrombin protease-activated receptors (PAR-1), which are cell-bound proteins that link platelet activation and thrombin formation.⁵ In addition, statins might directly influence platelet membrane, resulting in decreased function.⁴

Despite increased mean hematoma volume in statin users, we did not detect a difference of mortality between the two groups. Experimental models of ICH in rats showed improvement in neurological outcome after administration of low-dose atorvastatin.¹⁸ The potential benefits of statin therapy for human ICH was also described in a recent study in which it was associated with reduced 30-day mortality, but not improved functional outcome.¹⁹ Conflicting results are otherwise found in the literature. The NASIS study showed a reduction of mortality and neurological disability with statin use²⁰ while FitzMaurice et al failed to reproduce this relationship.²¹ In one of FitzMaurice

et al's analyses, pre-ICH statin use was associated with an interesting but nonsignificant 19% increase in initial hemorrhage volume. HMG-CoA reductase inhibitors were also associated with a higher frequency of ICH after intra-arterial thrombolysis but without any impact on outcome.²² All these observations about mortality are consistent with ours and the SPARCL subgroup analysis, in which no difference was demonstrated in the rate of fatal hemorrhagic strokes with statin agents.⁷

We also showed that the increase in ICH volume among statin users was significant in lobar and infratentorial ICH but not in basal ganglia ICH. Since the number of infratentorial cases was small it is possible that the influence of statins on ICH may be more important in those with underlying amyloid angiopathy than in those with "pure" hypertensive ICH but this deserves further consideration.

Our study has a number of limitations, most of them due to its retrospective nature. First, we had to exclude 30 cases because of unavailable CT data (patients transferred from other centers). It is possible that this may have introduced a bias but this seems very unlikely considering that the baseline characteristics of these patients were similar to cases included in the analysis. Also, LDL, HDL and total cholesterol levels were not systematically assessed upon admission since this was a retrospective study and cholesterol levels are not routinely done in ICH patients. Furthermore, we do not have reliable information about statins dose and duration of therapy prior to the event and it was impossible to analyze the dose response effect of statins on ICH volume and impossible to differentiate if the increase ICH volume was secondary to the statins LDL lowering property or their pleiotropic effects. There were also important confidence interval overlaps between baseline and follow up ICH volume between statin and non-statin users. Because the study was retrospective it is also difficult to draw conclusions regarding the relation between the ICH volume and time to CT. Nevertheless, a trend for higher ICH volume was seen in statin users for all "time to CT" subgroups except for the 6-24 hours subgroups but the number of patients in this group was very small, precluding any reliable conclusions. The significant increase in ICH volume between baseline and follow up CT scans in statin users should also be interpreted with caution because of the relatively small number of follow up CT scans. Furthermore, the increase in ICH volume was only significant when means were compared and not medians, thus probably indicating that a few patients were responsible for the increase in ICH volume. Although baseline characteristics were similar in many regards for patients with and without follow up imaging, those with control CT scan had smaller ICH volumes, lower mNIHSS score, better Glasgow coma scale and were younger. In summary, these patients had a more benign profile than those without a second CT scan. It is possible that we underestimated the effect of statins on ICH volume progression. Selection biases are inherent to retrospective studies. Therefore our findings on ICH volume progression need further confirmation and conclusions would be premature at this point.

CONCLUSIONS

Our results suggest that statin use prior to ICH is associated with higher hematoma volume and may contribute to

hemorrhage volume progression. Statin benefits in reducing the overall risk of ischemic stroke and coronary heart disease is supported by numerous randomized controlled trials and meta-analyses^{9,13} and we would certainly not recommend withdrawing statins in patients at risk of ischemic events but caution is warranted in those with prior ICH.²³ Given the widespread use of HMG-CoA reductase inhibitors and in light of the conflicting results available regarding the effects of statins in ICH, a larger prospective study of how statins pretreatment, upholding, and withdrawal may influence initial ICH volume and variation in hematoma volume is warranted.

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