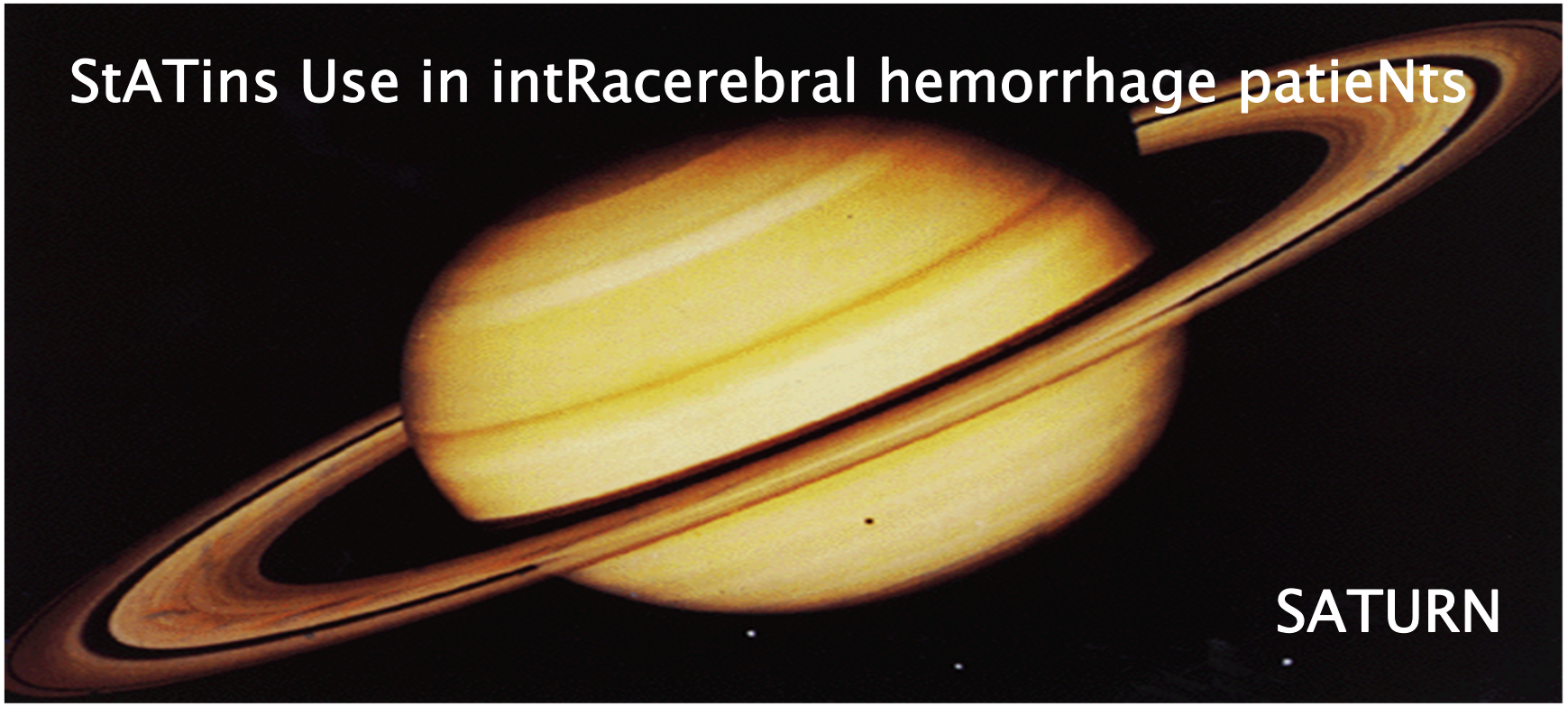
StATins Use in intRacerebral hemorrhage patieNts



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BACKGROUND

- While the benefits of statins for reducing major adverse cerebro- and cardio-vascular events (MACCE) in patients with ischemic stroke are well established, their benefits in patients at high risk for ICH are less clear.

- There is clinical equipoise as to whether statins should be continued or discontinued in patients with lobar ICH, who have a high risk for ICH recurrence and about the clinical circumstances under which statins should be avoided.

Continued Statin Treatment After Acute Intracranial Hemorrhage

Fighting Fire With Fire

Carlos A. Molina, MD, PhD; Magdy H. Selim, MD, PhD

Statin therapy has clearly demonstrated a beneficial effect in reducing the risk of first ever and recurrent ischemic stroke in patients with coronary artery and cerebrovascular diseases. However, the overall benefit of statins in patients with previous stroke appears to be partially offset by an increased risk of intracranial hemorrhage (ICH). Post hoc analyses of 2 large randomized trials, Heart Protection Society and Stroke Prevention by Aggressive Reduction in Cholesterol Levels, suggest that patients with previous stroke may be at increased risk of hemorrhagic stroke independently of cholesterol levels.[1] Like dynamite, statins help fighting fires (ischemic strokes), but with an added risk of potential collateral damages (ICH). Thus, avoidance of statin initiation or continuation after ICH has been recommended by several experts. In contrast, recent observational cohort studies and 1 meta-analysis found no evidence of increased risk of ICH in patients treated with statins after an ischemic stroke. Therefore, it is a matter of controversy whether continuation or initiation of statins in acute ICH patients with history of ischemic stroke is beneficial or harmful in terms of ICH growth, stroke (ischemic and hemorrhagic) recurrence and clinical outcome.

Dr Goldstein, as a senior and experienced fireman, defends a conservative evidence-based position. He considers that statins should not be started or continued during the initial hospitalization in patients with an ICH because there is no evidence of benefit when given early after ICH and at least reasonable concern for collateral damages. In contrast, the brave young firefighters, Drs Bustamante and Montaner, strongly believe in the countless beneficial pleiotropic effects of statins and consider that statin therapy not only is a wet gunpowder with regard to ICH risk but also might even improve ICH outcome. They argue that statin therapy should not be discontinued after ICH, given its neuroprotective properties and potential deleterious effects of statin withdrawal.

Decision on starting/continuation or avoidance/discontinuation of statins in patients with ICH depends, among other factors, on the strength of the evidence available. Although arguments supporting statin discontinuation after ICH are based on few randomized controlled trials, those against statin withholding are mainly based on observational, cohort, and retrospective studies. Although encouraging and hypothesis-generating, observational and retrospective studies are subject to a variety of bias and confounders. On the contrary, however, translation of Heart Protection Society and Stroke Prevention by Aggressive Reduction in Cholesterol Level data into clinical practice is challenging because, as Dr Goldstein points out, available analyses of the impact of statins in patients with ICH are based on small numbers of patients, and almost entirely on post hoc exploratory and secondary analyses.

The mechanism by which statins might amplify ICH risk remains unclear. In addition to their well-known lipid-lowering effects, statins may have antithrombotic properties by inhibiting platelet aggregation and enhancing fibrinolysis.

Secondary analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Level trial showed an additive effect of statins on ICH risk, especially in older patients, with prior stroke and ICH as qualifying event. Unfortunately, because of small numbers, this study did not evaluate the impact of location of ICH index on the recurrence rate. Location of ICH may represent a marker of underlying pathophysiology with different recurrent risk. Lobar ICH in older patients suggests cerebral amyloid angiopathy, whereas hypertensive vascular disease is primarily responsible for deep ICH. The risk of recurrent deep ICH can be reduced by appropriate antihypertensive therapy, whereas cerebral amyloid angiopathy currently lacks an established preventive treatment, leading to an increased risk of ICH recurrence. A mathematical decision analysis[2] showed that for lobar ICH in particular, statin therapy is predicted to raise the baseline annual probability of recurrence up to 22%, offsetting the cardiovascular benefits for both primary and secondary cardiovascular prevention. A recent retrospective study found that statin use in patients with ICH was independently associated with microbleeds on gradient echo T2*-weighted MRI, particularly of cortico-subcortical distribution, suggesting that cortico-subcortical

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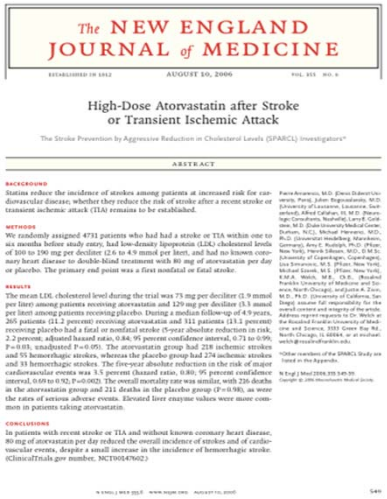


The NEW ENGLAND JOURNAL of MEDICINE

AUGUST 10, 2006

High-Dose Atorvastatin after Stroke or Transient Ischemic Attack

The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators*

ABSTRACT

BACKGROUND

Statins reduce the incidence of strokes among patients at increased risk for cardiovascular disease, whether they reduce the risk of stroke after a recent stroke or transient ischemic attack (TIA) remains to be established.

METHODS

We randomly assigned 4731 patients who had had a stroke or TIA within one to six months before study entry, had low-density lipoprotein (LDL) cholesterol levels of 100 to 190 mg per deciliter (2.6 to 4.9 mmol per liter), and had no known coronary heart disease to double-blind treatment with 80 mg of atorvastatin per day or placebo. The primary end point was a first nonfatal or fatal stroke.

RESULTS

The mean LDL cholesterol level during the trial was 73 mg per deciliter (1.9 mmol per liter) among patients receiving atorvastatin and 129 mg per deciliter (3.3 mmol per liter) among patients receiving placebo. During a median follow-up of 4.9 years, 265 patients (11.2 percent) receiving atorvastatin and 311 patients (13.1 percent) receiving placebo had a fatal or nonfatal stroke (5-year absolute reduction in risk, 2.2 percent; adjusted hazard ratio, 0.84; 95 percent confidence interval, 0.71 to 0.99; P=0.03; unadjusted P=0.05). The atorvastatin group had 218 ischemic strokes and 55 hemorrhagic strokes, whereas the placebo group had 274 ischemic strokes and 33 hemorrhagic strokes. The five-year absolute reduction in the risk of major cardiovascular events was 3.5 percent (hazard ratio, 0.80; 95 percent confidence interval, 0.69 to 0.92; P=0.002). The overall mortality rate was similar, with 216 deaths in the atorvastatin group and 211 deaths in the placebo group (P=0.98), as were the rates of serious adverse events. Elevated liver enzyme values were more common in patients taking atorvastatin.

CONCLUSIONS

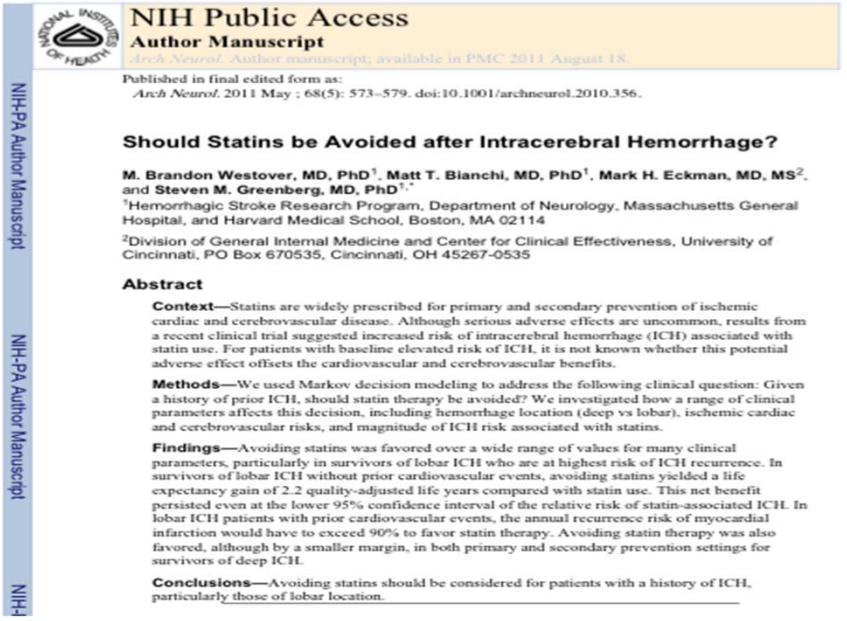
In patients with recent stroke or TIA and without known coronary heart disease, 80 mg of atorvastatin per day reduced the overall incidence of strokes and of cardiovascular events, despite a small increase in the incidence of hemorrhagic stroke. (ClinicalTrials.gov number, NCT00147602.)

Neurology. 2008;70:2364–2370
Vasc Health Risk Mgmt. 2010;6:229-236

- Overall incidence of ICH was 1.8%, BUT
  - ICH was significantly higher in the atorvastatin group vs. the placebo group (2.3% vs. 1.4%)
  - Relative risk of ICH on statin = 1.68 (95% CI: 1.09-2.59), compared with placebo
  - The risk for ICH was independent of the effects of statin therapy on cholesterol levels
- Statins treatment, increasing age, male sex, and having ICH as the qualifying stroke to be enrolled in the study were associated with increased risk for ICH
- 93 out of 4,731 (2%) of subjects enrolled in SPARCL had ICH as the index event (45 received atorvastatin and 48 placebo). These patients did not seem to benefit from atorvastatin

	Atorvastain	Placebo
Stroke/TIA	24%	15%
MACE	23%	12%
Vascular death	16%	10%

- Statin use in survivors of lobar ICH increases the rate of ICH recurrence from 14% to 22% per year (relative risk increase of 1.57)
- This small increase in ICH risk was sufficient to offset any potential benefits for both primary and secondary cardiovascular prevention over a wide range of stipulated event rates
- In sensitivity analyses, avoiding statins remained the preferred option over a wide range of values for statins-associated relative risk for ICH, including the lower limit of the 95% CI of the relative risk for ICH reported in SPARCL, and stipulated MACCE rates



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Should Statins be Avoided after Intracerebral Hemorrhage?

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Abstract

Context—Statins are widely prescribed for primary and secondary prevention of ischemic cardiac and cerebrovascular disease. Although serious adverse effects are uncommon, results from a recent clinical trial suggested increased risk of intracerebral hemorrhage (ICH) associated with statin use. For patients with baseline elevated risk of ICH, it is not known whether this potential adverse effect offsets the cardiovascular and cerebrovascular benefits.

Methods—We used Markov decision modeling to address the following clinical question: Given a history of prior ICH, should statin therapy be avoided? We investigated how a range of clinical parameters affects this decision, including hemorrhage location (deep vs lobar), ischemic cardiac and cerebrovascular risks, and magnitude of ICH risk associated with statins.

Findings—Avoiding statins was favored over a wide range of values for many clinical parameters, particularly in survivors of lobar ICH who are at highest risk of ICH recurrence. In survivors of lobar ICH without prior cardiovascular events, avoiding statins yielded a life expectancy gain of 2.2 quality-adjusted life years compared with statin use. This net benefit persisted even at the lower 95% confidence interval of the relative risk of statin-associated ICH. In lobar ICH patients with prior cardiovascular events, the annual recurrence risk of myocardial infarction would have to exceed 90% to favor statin therapy. Avoiding statin therapy was also favored, although by a smaller margin, in both primary and secondary prevention settings for survivors of deep ICH.

Conclusions—Avoiding statins should be considered for patients with a history of ICH, particularly those of lobar location.

Statin Use and Microbleeds in Patients With Spontaneous Intracerebral Hemorrhage

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Background and Purpose—Statins have been associated with increased risk of intracerebral hemorrhage (ICH), particularly in elderly patients with previous ICH. Recurrent ICH in the elderly is often related to cerebral amyloid angiopathy. Therefore, we investigated whether statin use is associated with increased prevalence and severity of microbleeds (MB), particularly cortico-subcortical microbleeds (csMB), which are frequently observed in cerebral amyloid angiopathy.

Methods—We studied 163 consecutive patients with spontaneous ICH who underwent magnetic resonance imaging within 30 days of presentation. We retrieved clinical information and analyzed magnetic resonance imaging for the presence, location, and number of MB, which were divided into csMB or other (other MB). We performed group comparisons stratified by statin use and by the presence vs absence of any MB (csMB and/or other MB) or csMB alone.

Results—Sixty-four percent had lobar ICH. Overall, 53% had microbleeds and 39% had csMB. Statin users were older, had significantly lower cholesterol and low-density lipoprotein levels, and higher prevalence of hypertension, diabetes, dyslipidemia, and antiplatelet use. The prevalence and number of other MB were similar in statin-treated and statin-untreated individuals. However, more statin-treated patients had csMB (57% vs 33%; $P=0.007$), with almost twice as many lesions (4.6±11.3 vs 2.4±8.0; $P=0.007$) compared with untreated patients. Age and statin use were independently associated with both the presence and increased number of MB (odds ratio [OR], 1.03; 95% confidence interval [CI], 1.00–1.05; $P=0.01$ and OR, 2.72; 95% CI. 1.02–7.22; $P=0.04$, respectively) and csMB (OR, 1.03; 95% CI, 1.00–1.06; $P=0.01$ and OR, 4.15; 95% CI, 1.54–11.20; $P<0.01$) in multivariate analyses.

Conclusions—Statin use in patients with ICH is independently associated with MB, especially csMB. Future studies are needed to confirm our findings and to investigate whether csMB can serve as a surrogate marker for ICH risk in statin-treated patients. **(*Stroke*. 2012;43:2677-2681.)**

Key Words: ■ amyloid angiopathy ■ brain imaging ■ hemosiderin ■ intracerebral hemorrhage ■ intracranial hemorrhage ■ microbleed ■ statins

Table 4. Multivariate Logistic Regression Analysis for Presence of Cortico-Subcortical Microbleed

Variable	OR	95% CI	*P*
Age	1.03	1.00–1.06	0.012*
Male	0.66	0.33–1.31	0.240
Hypertension	0.91	0.42–1.94	0.812
Diabetes	0.42	0.15–1.14	0.090
Dyslipidemia	0.72	0.29–1.75	0.471
Coronary artery disease	0.97	0.35–2.69	0.965
Antiplatelet use	0.75	0.33–1.69	0.496
Statin use	4.15	1.54–11.20	0.005*

CI indicates confidence interval; OR, odds ratio.

Risk Factors, Stroke Prevention Treatments, and Prevalence of Cerebral Microbleeds in the Framingham Heart Study

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Background and Purpose—Cerebral microbleeds (CMBs) are associated with increased risk of stroke and poor cognition. Vascular risk factors and medications used for stroke prevention may increase the risk of CMB. We examined the prevalence of CMB and the association of these risk factors with CMB, postulating that risk factors for cerebral amyloid angiopathy would be associated with lobar CMB and markers of hypertensive vasculopathy with deep CMB.

Methods—We include 1965 Framingham Original and Offspring participants (age, 66.5±11.0 years; 54% women) and evaluated the age- and sex-specific prevalence of CMB. We related various vascular and genetic (apolipoprotein E [*APOE*]) risk factors and medication use to the presence of CMB overall and stratified by brain location (deep, lobar, or mixed).

Results—CMBs were observed in 8.8% of participants, being mostly lobar (63%). CMB prevalence increased with age ($P<0.0001$) and was higher in men ($P<0.001$). Hypertension increased risk of any CMB, and in deep and mixed locations ($P<0.05$), and low total cholesterol and *APOE* ε4 increased risk of lobar CMB ($P<0.05$). Statin use increased risk of lobar and mixed location CMB ($P<0.05$). The latter association was not affected by adjustment for cholesterol levels or concomitant medication use.

Conclusions—We observed the expected association of hypertension with deep CMB and low cholesterol and *APOE* ε4 with lobar CMB. In addition, statin use was independently associated with CMB risk. This potential adverse effect of statin use needs to be examined in other cohorts. (***Stroke*. 2014;45:1492-1494.**)

Table 2. Logistic Regression Models for the Association Among Vascular Risk Factors, Medication Use, and Prevalent CMB

	All CMB (n=173) OR (95% CI)	Lobar Only (n=109) OR (95% CI)	Deep Only (n=38) OR (95% CI)	Any Deep [Deep+Mixed] (n=64) OR (95% CI)
Age, y	1.08 (1.06–1.10)	1.07 (1.05–1.09)	1.10 (1.06–1.13)	1.11 (1.08–1.14)
Men vs women	1.82 (1.31–2.51)	1.99 (1.33–2.97)	1.38 (0.72–2.65)	1.57 (0.94–2.63)
Vascular risk factors				
Hypertension stage 1 or higher*	1.71 (1.15–2.54)	1.32 (0.84–2.10)	2.45 (0.99–6.09)	3.13 (1.45–6.78)
Total cholesterol, mg/dL	1.00 (0.99–1.00)	1.00 (0.99–1.01)	0.99 (0.98–1.01)	1.00 (0.99–1.01)
Total cholesterol <10th percentile†	1.91 (1.20–3.03)	1.99 (1.14–3.44)	2.25 (0.93–5.49)	1.76 (0.84–3.70)
LDL-cholesterol <10th percentile†	1.28 (0.75–2.19)	1.69 (0.94–3.06)	0.53 (0.12–2.29)	0.63 (0.22–1.82)
Medication use				
Statin use	1.67 (1.20–2.31)	1.52 (1.02–2.27)	1.83 (0.95–3.54)	1.92 (1.15–3.21)
Aspirin use	1.27 (0.91–1.77)	1.22 (0.81–1.82)	1.93 (0.97–3.83)	1.39 (0.82–2.34)
Antiplatelet use	1.35 (0.96–1.91)	1.20 (0.79–1.83)	2.14 (1.08–4.25)	1.71 (1.00–2.92)
Anticoagulant use	1.72 (0.97–3.03)	1.76 (0.89–3.48)	0.70 (0.16–3.06)	1.54 (0.65–3.65)
APOE				
Any APOE ε4 vs none	1.29 (0.88–1.87)	1.62 (1.05–2.50)	1.01 (0.45–2.24)	0.79 (0.40–1.55)

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Apolipoprotein E, Statins and Risk of Intracerebral Hemorrhage

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Abstract

Background and Purpose—*Apolipoprotein E (ApoE)* genotypes have been associated with lobar intracerebral hemorrhage (ICH). Although HMG-CoA reductase inhibitors (statins) have been associated with an increased risk of ICH, meta-analyses have not consistently shown a statin-induced risk of ICH. Here, we test whether hypercholesterolemia and *ApoE* polymorphisms affect the risk with ICH by statin use.

Methods—The Genetic and Environmental Risk Factors for Hemorrhagic Stroke study is a prospective, demographically-matched case-control study of ICH. A similar study of ICH, Genetic Risks for Medication-Related Hemorrhagic Stroke study, was used as a replication cohort. Subjects were classified as normocholesterolemia (NC), hypercholesterolemia without statin (HC-NS), and hypercholesterolemia with statin use (HC-S). Statistical comparisons were performed using Fisher's Exact Test, chi-square tests, and the Breslow-Day test.

Results—The discovery cohort consisted of 558 ICH cases and 1,444 controls, and the replication cohort consisted of 1,020 ICH cases and 382 controls. The association of lower risk for hypercholesterolemia was not attenuated by statin use. Statin use was observed to confer a higher risk for lobar ICH in those carrying *ApoE4/E4* and *ApoE2/E4* genotypes in both discovery and replication cohorts and combined, showed a trend towards significance (p=0.11 for Statin vs. *ApoE4/E4*).

	Discovery Sample						Replication Sample				
	Lobar ICH			Nonlobar ICH							
	Cases	Controls	*P* Value	Cases	Controls	*P* Value	Lobar ICH	Nonlobar ICH	Controls	*P* Value vs Lobar	*P* Value vs Nonlobar
N	204	508		354	936		481	539	382		
Age, y, mean±SD	66.4±16.2	63.1±15.6	0.01	64.7±15.1	61.3±14.0	0.0001	74.7±10.5	70.9±12.6	74.2±7.8	0.43	<0.0001
Male sex, n (%)	91 (45)	216 (43)	0.61	188 (53)	468 (50)	0.32	240 (50)	308 (57)	211 (55)	0.12	0.57
Black race, n (%)	30 (15)	73 (14)	0.91	82 (23)	227 (24)	0.68					
Hypertension, n (%)	111 (55)	267 (53)	0.61	262 (75)	467 (50)	<0.0001	308 (64)	454 (84)	263 (69)	0.14	<0.0001
Hypercholesterolemia, n (%)	85 (42)	223 (44)	0.59	114 (32)	400 (43)	0.0006	152 (32)	190 (35)	226 (59)	<0.0001	<0.0001
Frequent alcohol use, n (%)	14 (7)	31 (6)	0.68	24 (7)	55 (6)	0.50	12 (3)	29 (7)	9 (2)	0.66	0.004
Previous ischemic stroke, n (%)	16 (8)	6 (1)	<0.0001	39 (11)	24 (3)	<0.0001	64 (13)	66 (12)	33 (9)	0.03	0.08
ApoE genotype, n (%)											
E2/E2	2 (1)	6 (1)		8 (2)	12 (1)		9 (2)	2 (<1)	1 (<1)		
E2/E3	42 (21)	59 (12)		49 (14)	131 (14)		69 (14)	56 (10)	41 (11)		
E2/E4	17 (8)	15 (3)		10 (3)	22 (2)		32 (7)	11 (2)	6 (2)		
E3/E3	85 (42)	297 (59)	<0.0001	195 (55)	550 (59)	0.69	237 (49)	346 (64)	251 (66)	<0.0001	0.67
E3/E4	46 (23)	114 (22)		82 (23)	195 (21)		106 (22)	110 (20)	79 (21)		
E4/E4	12 (6)	17 (3)		10 (3)	26 (3)		28 (6)	14 (3)	4 (1)		

ApoE indicates apolipoprotein E; and ICH, intracerebral hemorrhage.

Table 3. Risk of Lobar ICH by ApoE Carrier Status and Hypercholesterolemia vs No Hypercholesterolemia

	Discovery Sample				Replication Sample			
	Case	Control	OR (CI)	*P* Value	Case	Control	OR (CI)	*P* Value
ApoE2 carriers vs *E3/E3*								
Normocholesterolemia	33 (39%)	53 (24%)	2.06 (1.21–3.51)	0.01	86 (36%)	20 (17%)	2.87 (1.65–4.97)	0.0002
Hypercholesterolemia	28 (46%)	27 (18%)	3.93 (2.04–7.55)	<0.0001	24 (22%)	28 (16%)	1.69 (0.91–3.32)	0.09
ApoE4 carriers vs *E3/E3*								
Normocholesterolemia	42 (45%)	73 (30%)	1.90 (1.17–3.11)	0.01	112 (42%)	40 (29%)	1.82 (1.17–2.83)	0.008
Hypercholesterolemia	33 (50%)	73 (37%)	1.71 (0.98–3.00)	0.08	54 (39%)	49 (25%)	2.00 (1.25–3.21)	0.004

Genetic markers (APOE genotyping) might be useful to make Personalized treatment decisions re: the use vs. avoidance of Statins in lobar ICH patients……

The Multicenter Study on Cerebral Hemorrhage in Italy (MUCH-Italy)

- Compared 3492 consecutive patients having ICH with 3492 age and sex-matched stroke-free control subjects in a case-control analysis, as part of MUCH-Italy

- There was an interaction between total serum cholesterol levels and statin use for the risk of ICH (IOR), 1.09; 95% CI 1.05- 1.12)

- Increasing levels of total serum cholesterol were associated with a decreased risk of ICH within statin strata (OR, 0.87; 95% CI 0.86- 0.88 for every increase of 0.26 mmol/l of total serum cholesterol concentrations)

- Statin use was associated with an increased risk (OR, 1.54; 95% CI 1.31-1.81 of the average level of total serum cholesterol)

- The protective effect of serum cholesterol against ICH was reduced by statins in strictly lobar brain regions more than in non-lobar regions

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Brain and Behavior

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Statin use after intracerebral hemorrhage: a 10-year nationwide cohort study

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Table 3. Multivariable-adjusted relationships between the intensity (high, moderate, and low) of statin use and outcomes.

Characteristics	High (n = 92)	Moderate (n = 545)	Low (n = 89)
Recurrent ICH, n (%)	15 (16.3)	109 (20.0)	11 (12.4)
Multivariable Adjusted OR (95% CI)	1.00 (–)	1.19 (0.69–2.05)	0.66 (0.30–1.44)
Death (all cause), n (%)	10 (10.9)	70 (12.8)	13 (14.6)
Multivariable Adjusted OR (95% CI)	1.00 (–)	0.75 (0.38–1.48)	0.65 (0.28–1.55)
Acute coronary event, n (%)	1 (1.1)	19 (3.5)	3 (3.4)
Multivariable Adjusted OR (95% CI)	1.00 (–)	2.15 (0.28–16.30)	1.69 (0.17–16.68)
Ischemic stroke/Transient ischemic attack, n (%)	58 (63.0)	380 (69.7)	66 (74.2)
Multivariable Adjusted OR (95% CI)	1.00 (–)	1.07 (0.81–1.42)	0.96 (0.67–1.38)

CI, confidence interval; ICH, intracerebral hemorrhage.
High intensity: atorvastatin 40–80 mg, rosuvastatin 20–40 mg; Moderate intensity: atorvastatin 10–20 mg, rosuvastatin 5–10 mg, simvastatin 20–40 mg, pravastatin 40–80 mg, lovastatin 40 mg, fluvastatin XL 80 mg, fluvastatin 40 mg bid, pitavastatin 2–4 mg; Low intensity: simvastatin 10 mg, pravastatin 10–20 mg, lovastatin 20 mg, fluvastatin 20–40 mg, pitavastatin 1 mg.

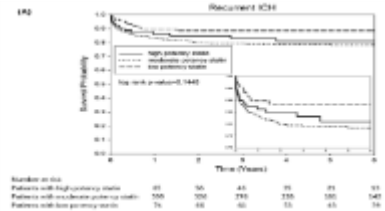
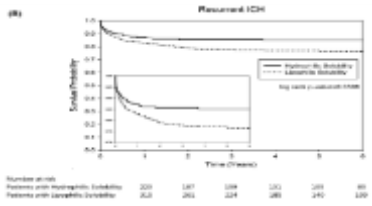
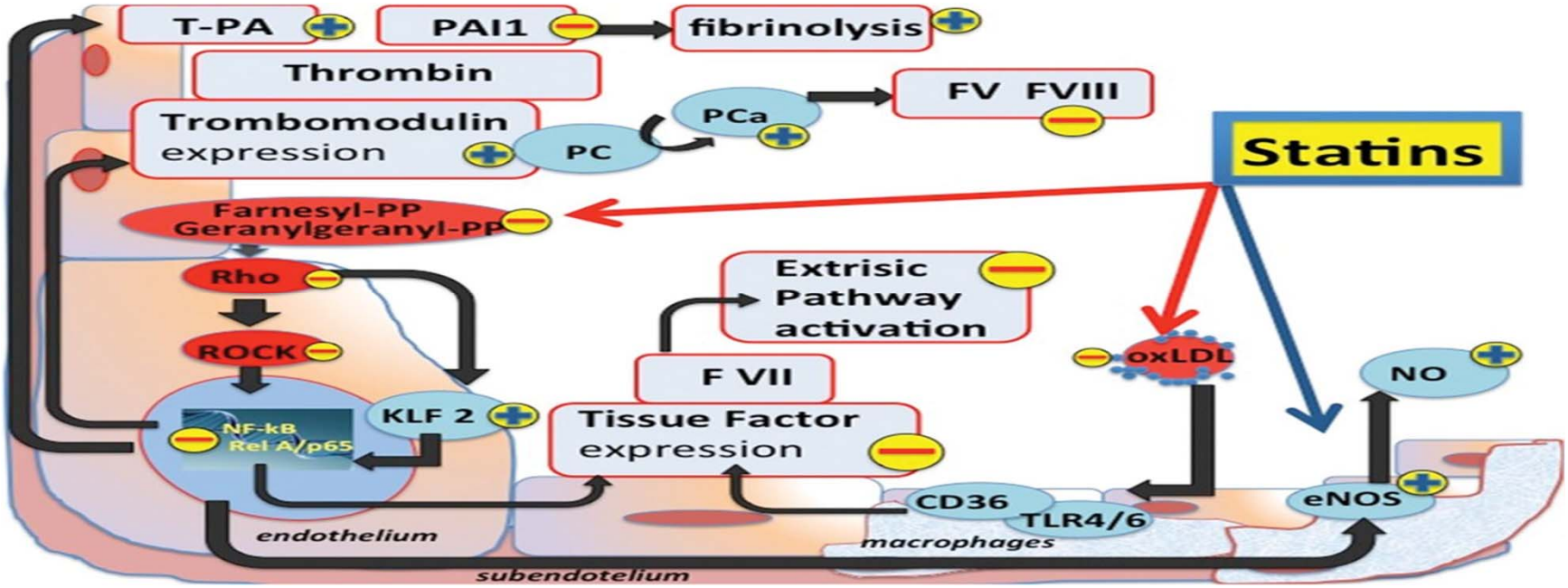


Table 4. Multivariable-adjusted relationships between the solubility (hydrophilic and lipophilic) of statins and outcomes.

Characteristics	Lipophilic (n = 431)	Hydrophilic (n = 295)
Recurrent ICH, n (%)	92 (21.4)	43 (14.6)
Multivariable Adjusted OR (95% CI)	1.00 (–)	0.69 (0.48–0.99)*
Death (all cause), n (%)	56 (13.0)	37 (12.5)
Multivariable Adjusted OR (95% CI)	1.00 (–)	1.15 (0.74–1.78)
Acute coronary event, n (%)	12 (2.8)	11 (3.7)
Multivariable adjusted OR (95% CI)	1.00 (–)	1.33 (0.57–3.15)
Ischemic stroke/Transient ischemic attack, N (%)	298 (69.1)	206 (69.8)
Multivariable adjusted OR (95% CI)	1.00 (–)	1.09 (0.91–1.31)

Hydrophilic solubility: pravastatin, rosuvastatin; Lipophilic solubility: atorvastatin, cerivastatin, fluvastatin, lovastatin, simvastatin.





Statins might increase the propensity for ICH by inhibiting platelets, decreasing thrombus formation, and enhancing fibrinolysis


Statin

Association of Statins and Statin Discontinuation With Poor Outcome and Survival After Intracerebral Hemorrhage

Dar Dowlatshahi, MD, PhD; Andrew M. Demchuk, MD; Jiming Fang, PhD;
Moira K. Kapral, MD, MSc; Mukul Sharma, MD, MSc; Eric E. Smith, MD, MPH;
on behalf of the Registry of the Canadian Stroke Network

Background and Purpose—Studies suggest a protective role for statins after intracerebral hemorrhage, but many failed to assess statin discontinuation, did not include postdischarge outcomes, or did not account for withdrawal of care. We studied the relationship between preintracerebral hemorrhage statin use and in-hospital statin discontinuation on stroke severity and 30-day mortality.

Methods—We analyzed data from the Registry of the Canadian Stroke Network and determined the adjusted ORs for statin use and outcomes, controlling for stroke severity and other covariates.

Results—We analyzed 2466 consecutive patients with intracerebral hemorrhage from 2003 to 2008: median age was 71 years, 53.6% were male, and 30-day mortality rate was 36.5%. Overall, 537 (21.7%) were taking statins before presentation. Compared with nonusers, statin users were less likely to have severe strokes on presentation (54.7% versus 63.3%) but had similar rates of poor outcome (70% versus 67%) and 30-day mortality (36% versus 37%). Statins were discontinued on admission in 158 of 537 (29.4%); these patients were more likely to have severe stroke (65% versus 27%, $P<0.01$), poor outcome (90% versus 62%, $P<0.01$), and to have died by 30 days (71% versus 21%, $P<0.01$). After adjusting for stroke severity, statin discontinuation was still associated with poor outcome (adjusted OR, 2.4; 95% CI, 1.13–4.56) and higher mortality (adjusted OR, 2.0; 95% CI, 1.30–3.04). However, these associations were attenuated and no longer significant after excluding patients treated palliatively.

Conclusions—We found no association between preadmission statin use and outcomes in intracerebral hemorrhage. Statin discontinuation may worsen outcomes or may simply be a marker of worse underlying prognosis. (***Stroke*. 2012;43:1518-1523.**)

Key Words: hemorrhagic stroke ▮ intracerebral hemorrhage ▮ outcome ▮ registry ▮ statin

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J Stroke Cerebrovasc Dis. 2013 Nov;22(8):e541-5. doi: 10.1016/j.jstrokecerebrovasdis.2013.06.015. Epub 2013 Jul 16.

Long-term improvement in outcome after intracerebral hemorrhage in patients treated with statins.

Winkler J1, Shoup JP, Czap A, Staff I, Fortunato G, McCullough LD, Sansing LH.

Abstract

BACKGROUND:

Intracerebral hemorrhage (ICH) is a severe type of stroke for which there is currently no specific medical therapy. We hypothesized that statins reduce immediate inflammatory injury and improve long-term recovery from increased neurogenesis and angiogenesis. We conducted a large retrospective cohort study to assess the influence of statin therapy on patient death and disability at 12 months after ICH.

METHODS:

This was a retrospective analysis of a prospectively collected database at a tertiary care medical center. Patients were grouped based on statin use, and poor outcome was assessed as dead or alive with dependency (modified Barthel Index≤14).

RESULTS:

We compared outcomes in 190 patients exposed to statins to 236 patients who were not exposed to statins. Univariate analysis found that statin use was associated with decreased mortality in-hospital and at 12 months (P=.001). Multivariable analysis found that statin use was associated with a decreased odds of death or disability at 12 months after ICH (odds ratio 0.44; 95% confidence interval 0.21-0.95).

CONCLUSIONS:

Statin use is associated with improved long-term outcome at 12 months after ICH. This finding supports previous clinical studies that have shown the short-term benefits of statin therapy. In addition, this study correlates with

Association of statin use with spontaneous intracerebral hemorrhage

A cohort study

Walid Saliba, MD, MPH, Hedy S. Rennert, MPH, Ofra Barnett-Griness, PhD, Naomi Gronich, MD, Jeremy Molad, MD, Gad Rennert, MD, PhD, and Eitan Auriel, MD, MSc

Neurology® 2018;0:1-10. doi:10.1212/WNL.0000000000005907

Abstract

Objective

To examine the association between statin exposure in a dose-dependent manner and intracerebral hemorrhage (ICH) in a large nationwide study.

Methods

The computerized database of the largest health care provider in Israel was used to identify diagnosed ICH among new users of statins, who started statin treatment between 2005 and 2010. We assessed a dose–response relationship between ICH and statins, using the average atorvastatin equivalent daily dose (AAEDD). Multivariable Cox proportional hazard regression models, adjusted for baseline disease risk score, were applied to estimate the hazard ratio of ICH.

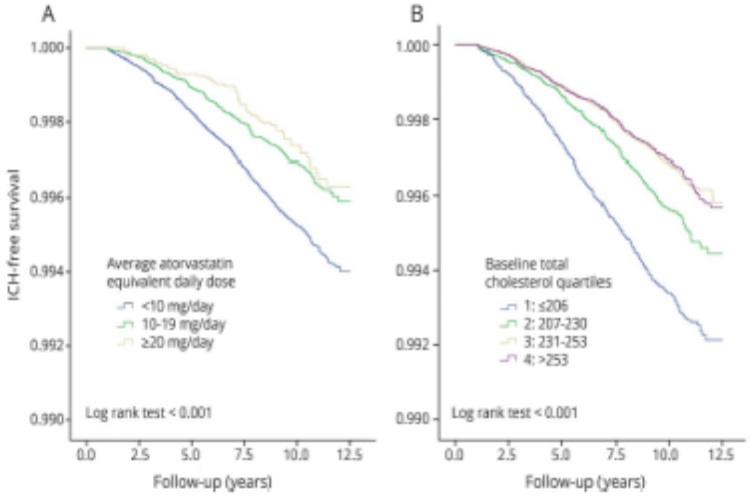
Results

Of the 345,531 included patients, 1,304 were diagnosed with ICH during a median follow-up of 9.5 years (interquartile range 7.6–11.0). Overall, 75.3% of patients had AAEDD <10 mg/d, 19.0% had AAEDD 0–19.9 mg/d, and 5.7% had AAEDD ≥20 mg/d. The corresponding proportions were 81.0%, 15.0%, 4.0% among ICH cases, and 75.3%, 19.0%, 5.7% among non-ICH cases. Compared to those with AAEDD <10 mg/d (reference), the adjusted hazard ratio (HR) for ICH was 0.68 (95% confidence interval [CI] 0.58–0.79) in those with AAEDD 10–19.9 mg/d, and 0.62 (0.47–0.81) in those with AAEDD ≥20 mg/d. Compared to the lowest baseline total cholesterol quartile, the adjusted HR for ICH was 0.71 (95% CI 0.62–0.82), 0.55 (0.47–0.64), and 0.57 (0.49–0.67) in those in the second, third, and highest quartiles, respectively. The results were similar and robust among highly persistent statin users and after controlling for the change in cholesterol level.

Conclusions

This study confirms that the risk of ICH decreases with increasing cholesterol levels, but suggests that statin use might be associated with decreased risk of ICH.

Figure Kaplan-Meier plots for the distribution of time to intracerebral hemorrhage (ICH)



(A) By average atorvastatin equivalent daily dose categories. (B) By baseline total cholesterol quartiles.

Use of Statins and Outcomes in Intracerebral Hemorrhage Patients

Fazeel M. Siddiqui, MD; Carl D. Langefeld, PhD; Charles J. Moomaw, PhD; Mary E. Comeau, MA; Padmini Sekar, MS; Jonathan Rosand, MD; Chelsea S. Kidwell, MD; Sharyl Martini, MD; Jennifer L. Osborne, BSN; Sonja Stutzman, PhD; Christiana Hall, MD; Daniel Woo, MD

Background and Purpose—Statin use may be associated with improved outcome in intracerebral hemorrhage patients. However, the topic remains controversial. Our analysis examined the effect of prior, continued, or new statin use on intracerebral hemorrhage outcomes using the ERICH (Ethnic/Racial Variations of Intracerebral Hemorrhage) data set.

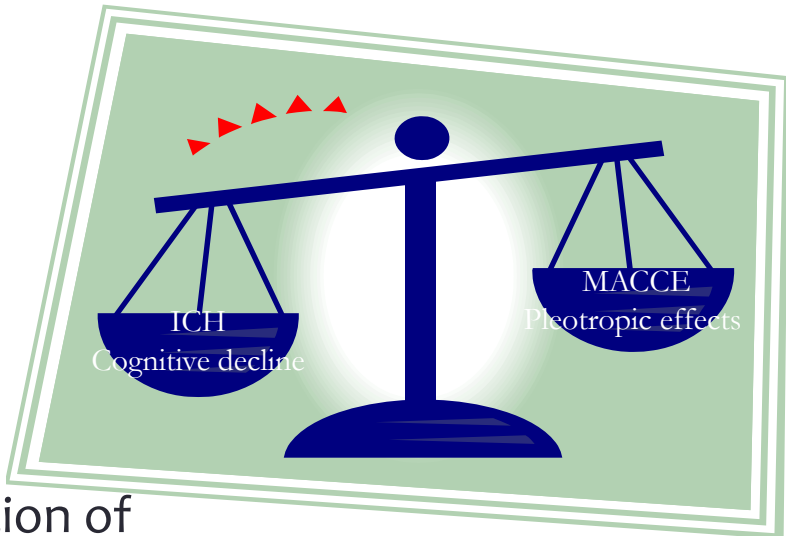
Methods—We analyzed ERICH (a multicenter study designed to examine ethnic variations in the risk, presentation, and outcomes of intracerebral hemorrhage) to explore the association of statin use and hematoma growth, mortality, and 3-month disability. We computed subset analyses with respect to 3 statin categories (prior, continued, or new use).

Results—Two thousand four hundred and fifty-seven enrolled cases (mean age, 62 years; 42% females) had complete data on mortality and 3-month disability (modified Rankin Scale). Among those, 1093 cases were on statins (prior, n=268; continued, n=423; new, n=402). Overall, statin use was associated with reduced mortality and disability without any effect on hematoma growth. This association was primarily driven by continued/new statin use. A multivariate analysis adjusted for age and major predictors for poor outcome showed that continued/new statins users had good outcomes compared with prior users. However, statins may have been continued/started more frequently among less severe patients. When a propensity score was developed based on factors that could influence a physician's decision in prescribing statins and used as a covariate, continued/new statin use was no longer a significant predictor of good outcome.

Conclusions—Although statin use, especially continued/new use, was associated with improved intracerebral hemorrhage outcomes, this effect may merely reflect the physician's view of a patient's prognosis rather than a predictor of survival. **(*Stroke*. 2017;48:2098-2104. DOI: 10.1161/STROKEAHA.117.017358.)**

- Should we resume statins after lobar ICH?

- Under what circumstances?
  - Patient characteristics



  - No consensus
  - No data from RCTs
  - Various opinions based on a combination of observational data, small studies, pathophysiological considerations, and benefit/risk assessment

There are no prospective or randomized data

on the effects of continuation vs. discontinuation of statins after ICH on the risk of ICH recurrence,

incidence of MACCE, or long-term functional outcome and neurological recovery!

Scope of the Problem…..

"We found a bunch of these clogging your arteries. They're cholesterol pills."

A large number of ICH patients are on statin therapy (35% to 52%)

Number of prescriptions of statins is rapidly rising ~ by 500,000 a month!

Number of people taking atorvastatin alone increased from 25 to 56 million after the ACC/AHA 2013 lipid management guidelines!

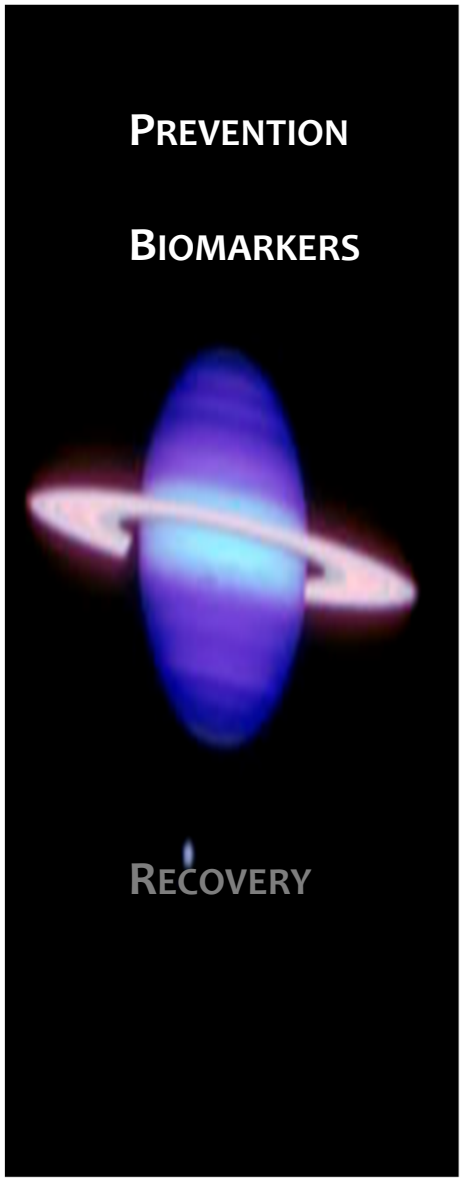
Secondary Prevention of ICH!

- ICH is a frequent cause of morbidity and mortality
  - Mortality up to 40%
  - Most patients are left with serious and permanent disability
- Is it really worth the cost and resources to prevent ICH recurrence?

Secondary Prevention of ICH – YES.

- Up to one-third of ICH patients achieve mRS ≤2 by 90 days, and slightly more by 6 months!

- In the US alone, avoiding statins could potentially lead to 900 to 1120 fewer recurrent ICHs each year --- less expenditure towards recurrent ICH-related care (~ $9,180,000 to $24,192,000) in addition to $13,248,000 to $16,128,000 towards statin costs!



- *To determine whether continuation vs. discontinuation of statin drugs after spontaneous lobar ICH is the best strategy*
- *To assess whether the decision to continue/discontinue statins should be influenced by an individual's APOE genotype*

Primary Objectives

- **EFFICACY -** To evaluate the effects of continuation vs. discontinuation of statins on the risk of symptomatic ICH recurrence during 24 months of follow-up in patients presenting with a spontaneous lobar lCH while taking a statin drug.

- **SAFETY -** To determine the effects of discontinuation vs. continuation of statins on the occurrence of any of the following MACCE during the 24 months follow-up period:
  - Symptomatic ischemic stroke
  - Symptomatic myocardial infarction
  - Newly symptomatic arterial occlusive disease (peripheral, retinal, or carotid)
  - Revascularization procedures for coronary, carotid, or peripheral arterial disease
  - Vascular death

Secondary Objectives

- To examine quality of life, functional, and cognitive outcomes in patients in whom statins are continued vs. discontinued, by repeated assessments of the EQ-5D quality of life questionnaire, modified Rankin Scale (mRS), and Telephone Montreal Cognitive Assessment (T-MoCA) at 3, 6, 9, 12, 18, and 24 months.

- To prospectively examine whether the presence vs. absence of APOE ε4 and APOE ε2 genotypes modifies the effects of statins on the risk of recurrent ICH (i.e., whether APOE genotype can be used as a biological marker to stratify the risk of ICH recurrence in statins-treated patients).

- To determine whether the effects of continuation/ discontinuation of statins on the risk of ICH recurrence and MACCE vary by sex or ethnicity.

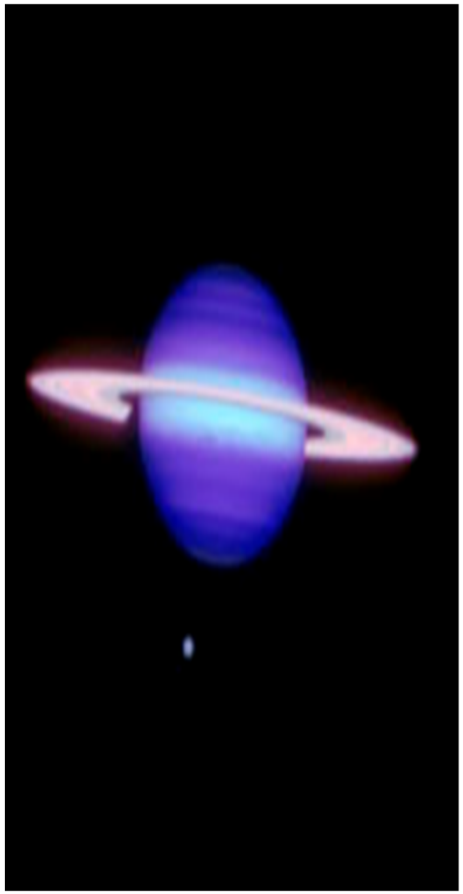
Exploratory Objectives

- To determine whether the risk of ICH recurrence on statin therapy is dose- (intensive vs. non-intensive) or agent- (lipophilic vs. hydrophilic) dependent

- To examine the impact of post-randomization variability in the use of antithrombotics, adequacy of BP control, and use of other concomitant medications such as ACEI & B-blockers on outcomes

- To examine the effects of continuation of statins in patients with possible, probable, or definite CAA vs. no CAA

Study Design



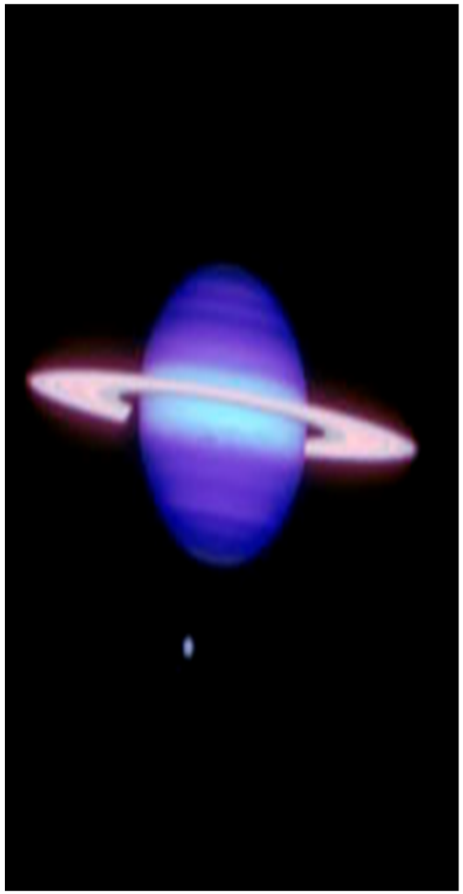
- Pragmatic, prospective, randomized, open-label, and blinded end-point assessment (PROBE) clinical trial.
- 1456 subjects - 140 sites (US, Canada ± UK)

- Patients presenting within 7 days of a spontaneous lobar ICH while taking statins will be randomized to one of two treatment strategies: continuation vs. discontinuation of statin therapy.

- Randomization
  - Ratio = 1:1
  - Covariates: Statin dose/intensity – Indication for statin use (primary vs. secondary prevention) – Use or intent-to-use antithrombotics - Baseline ICH volume (<30 vs. ≥30 ml)

- Participants will undergo repeated structured assessments by phone during the follow-up period.
- All subjects will be followed for 24 months, and will undergo baseline testing for APOE genotype.

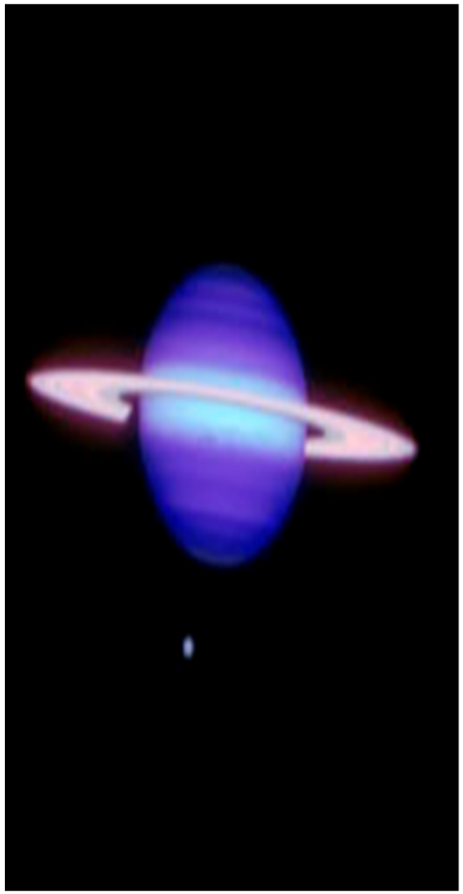
Inclusion Criteria



- Age ≥50 years
- Spontaneous lobar ICH within 7 days prior to recruitment, confirmed by CT or MRI scan*
- Patient was taking a statin drug prior to the onset of the qualifying/index ICH
- Randomization to one of the two treatment strategies can be carried out within 7 days of the onset of the qualifying ICH
- Patient or surrogate after consultation with his/her physicians, agrees to be randomized to statin continuation vs. discontinuation and to provide written informed consent.

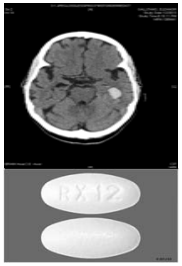
**Lobar ICH will be defined as ICH involving cortical or subcortical locations and situated ≥1 cm from the body of the ipsilateral lateral ventricle and not originating from any of the following deep structures (thalamus, putamen, globus pallidus, or internal capsule)*

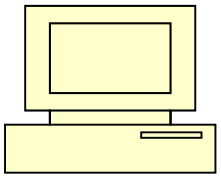
Exclusion Criteria



- Secondary cause for the qualifying ICH
- Baseline mRS >3 and/or ICH score >3
- Patients receiving PCSK-9 inhibitors
- Contraindications to continuation of statin therapy, such as significant elevations of serum creatinine kinase or liver transaminases, or rhabdomyolysis
- Patients known or suspected of not being able to comply with the study protocol due to alcoholism, drug dependency, or other obvious reasons for noncompliance or inability to adhere to the study protocol
- Life expectancy of less than 24 months due to co-morbid terminal conditions
- Concurrent participation in another research protocol for investigation of experimental therapy
- Indication that withdrawal of care will be implemented during hospitalization for the qualifying ICH

Study Procedures

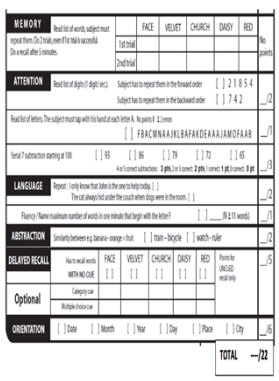


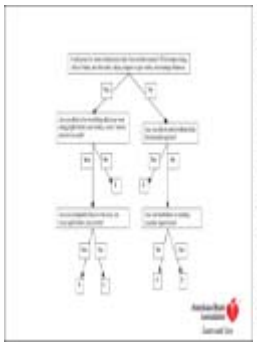


Screening	Randomization	D/C	1, 2, 3, 6, 9, 12, 18, 24 months*
✓ Inclusion ✓ Exclusion	✓ ICH score ✓ NIHSS	✓ mRS ✓ NIHSS	✓ MACCE; SAEs; mRS; TMoCA; QoL (EQ-5D); Review of prescription refills; Pill count; BP reporting

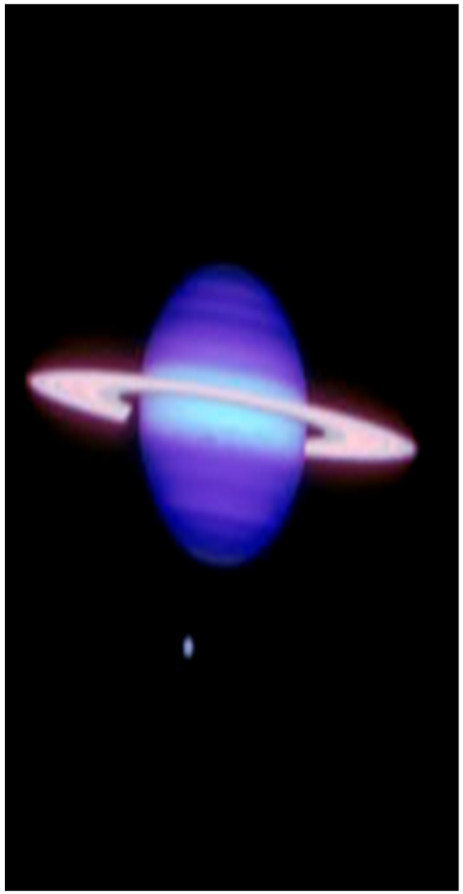
**All follow-up assessments will be performed by centralized evaluators. A central adjudication committee blinded to treatment allocation will adjudicate all outcome events and imaging data.*

Each subject will be followed for 24 months, including those who experience a recurrent ICH, to standardize the timing of final assessments of quality of life and functional/cognitive outcomes among all participants.





Study Outcomes



- Efficacy:
  - Time from randomization to recurrent ICH
  - Pre-specified interim analysis for overwhelming efficacy & futility using O'Brien-Fleming stopping boundary @ midpoint of the trial (~ 2.25 years after enrollment of the first subject)
- Safety:
  - Occurrence of MACCE
  - 3 pre-specified interim analyses using Pocock spending function, after roughly 25%, 50%, and 75% of subjects are randomized
- ITT & On assigned treatment analyses
- Quantification of Risk/Benefit
  - ICH is more likely to result in long-lasting disability compared to MACCE
  - Therefore, a mere increase in MACCE with statin discontinuation may not necessarily offset the benefits of decreased ICH recurrence
  - If discontinuation of statins results in decreased risks of recurrent ICH at the expense of a slight increase in MACCE, but significantly favorable mRS and EQ-5D results compared to statin continuation, then, discontinuation of statins might be deemed the preferable strategy and vice versa

Sample Size/Time Table

- Sample size = 1456 (728 per group)
  - **Assumptions**
    - Annual ICH recurrence rate ~ 7%
    - Annual MACCE rate ~ 8%
    - 85% power to detect HR = 0.6 (i.e. 0.4 reduction in ICH with D/C statins)
    - 10% LTFU & withdrawal of consent
    - 5% crossovers
  - **Study Timeframe**

Start up	Subject Recruitment	Follow-up	Close out
0-6 M	6-48 M	48-72 M	72-78 M

Status

- Reviewed & endorsed by the Canadian Stroke Consortium in June 2016
- Approved for funding in May 2018
- Anticipate to receive funding in Q1 2019
- StrokeNet cIRB (under review)
- NINDS DSMB Protocol Review -- ? December 2018
- Ancillary MRI study is being planned

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