# SATURN

## StATins Use in intRacerebral hemorrhage patieNts

**MAY 28, 2020**

**PI/SC WEBINAR**

NIH StrokeNet PREVENTION | TREATMENT | RECOVERY

National Institutes of Health

National Institute of Neurological Disorders and Stroke

U01NS102289

SATURN

# SATURN TEAM

Ashkan Shoamanesh
PI, Canada

Sharon Yeatts
PI, Statistician

Pooja Khatri
PI, StrokeNet

Sarah Marchina
Project Manager, BIDMC

Kimberlee Bernstein
Project Manager, NCC

Aaron Perlmutter
NDMC Monitoring Manager

Katie Stever
NDMC Data Manager

Logan Sirline
StrokeNet NDMC
Project Manager

Magdy Selim
Lead Pi

NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

SATURN

# Agenda


- Sites start-up status
- Reopening enrollment
- Rationale for SATURN

  *What to tell our Cardiology colleagues and PCPs?*
- Tips for enrollment and consent

  *Remote consent & Protocol Amendment V4*
- SAEs, outcome events, and follow-up procedures
- Open discussion and questions

# Sites Start Up Status

NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

SATURN

# Status (5/26/20)

- cIRB/REB Approved sites = 76
- Fully executed CTAs = 94
- Sites with both cIRB/CTA = 69


- Readiness Calls Completed = 52
- Readiness Calls Scheduled = 56
- Site Released to Enroll = 23*

**Release of new sites pending cIRB approval of v4 site documents*

- Pending CTAs = 40
- Pending cIRB/REB = 58


- Pending CTA and cIRB/REB = **17 USA**; 16 Canada

NIH StrokeNet PREVENTION | TREATMENT | RECOVERY

SATURN

# Reopening Enrollment

NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

SATURN

# Required Steps

- SATURN Received cIRB approval to Reopen Enrollment. Distributed to sites.

Does your institution allow enrollment in clinical trials? If on case-by-case basis, are you able to submit a petition?

- SATURN amendment approved protocol and ICF v4; added options for remote consent and telehealth follow up visits.

Sites who have submitted to the cIRB- Have received your approved ICF v4?

Yes – Please notify local IRB as required. Upload IDC v4 and approval letter to WebDCU & update COVID Impact Assessment Survey to confirm that you can start enrollment (taking measures to minimize participant & staff exposure; using remote assessments/visits when feasible; verify that study procedures would not interfere with clinical procedures put in place to care for COVID-19 patients)

- Sites who have not yet submitted to the cIRB- will need to complete the ICF v4 template with your site specific edits for your cIRB submission and will receive initial approval under protocol/ICF v4.

- Will your site be using remote consent?

Yes –Update COVID Impact Assessment Survey to indicate your site will utilize remote consent procedures. Work with the NCC on amendment to edit your ICF to include e-consent if applicable and add remote consent SOP to your site. NCC will make submission to cIRB on your behalf.

Approved- Please notify local IRB as required. Upload IDC v4 and amendment approval letter to WebDCU & update COVID Impact Assessment Survey if applicable

No – Update COVID Impact Assessment Survey to confirm that you will not use remote consent procedures. Notify NCC PM Kim Bernstein to submit cIRB amendment on your behalf indicating you will not use remote consent at your site.

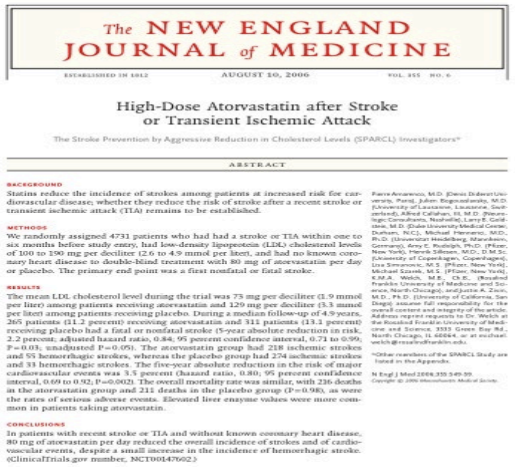
Approved- Please notify local IRB as required. Upload amendment approval letter to WebDCU & update COVID Impact Assessment Survey if applicable

- Sites with cIRB approved IDCv4 documents and approved remote consent amendments with local approval to reopen enrollment may be released to enroll!

**Sites will receive an email notification from WebDCU once enrollment may begin.

# Study Background and Rationale

# SPARCL RESULTS



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 10, 2006 VOL. 355 NO. 6

**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

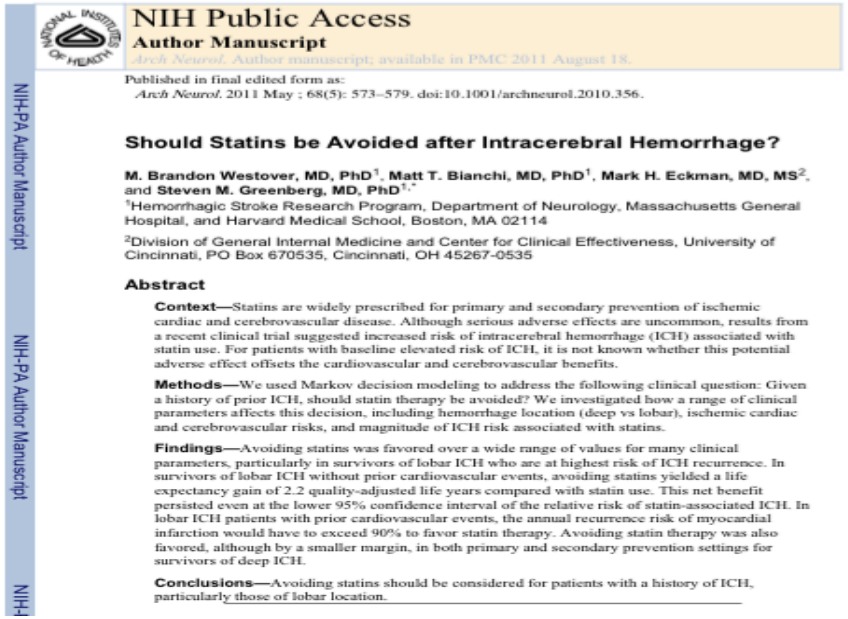
- Overall incidence of ICH was 1.8%, BUT
  - ICH was significantly higher in the atorvastatin group vs. the placebo group (2.3% vs. 1.4%)
  - Relative risk of ICH on statin = 1.68 (95% CI: 1.09-2.59), compared with placebo
  - The risk for ICH was independent of the effects of statin therapy on cholesterol 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

| | Atorvastatin | Placebo |
|---|---|---|
| Stroke/TIA | 24% | 15% |
| MACE | 23% | 12% |
| Vascular death | 16% | 10% |

NIH StrokeNet PREVENTION | TREATMENT | RECOVERY

SATURN

# DECISION ANALYSIS RESULTS



NIH Public Access
Author Manuscript
*Arch Neurol*. Author manuscript; available in PMC 2011 August 18.

Published in final edited form as:
*Arch Neurol*. 2011 May ; 68(5): 573–579. doi:10.1001/archneurol.2010.356.

**Should Statins be Avoided after Intracerebral Hemorrhage?**

**M. Brandon Westover, MD, PhD**[1], **Matt T. Bianchi, MD, PhD**[1], **Mark H. Eckman, MD, MS**[2], and **Steven M. Greenberg, MD, PhD**[1,*]
[1]Hemorrhagic Stroke Research Program, Department of Neurology, Massachusetts General Hospital, and Harvard Medical School, Boston, MA 02114
[2]Division of General Internal Medicine and Center for Clinical Effectiveness, University of Cincinnati, PO Box 670535, Cincinnati, OH 45267-0535

**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 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

# THE CONTROVERSY

## Continued Statin Treatment After Acute Intracranial Hemorrhage

### Fighting Fire With Fire

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

EDITORIAL

JAMA Neurology November 2014 Volume 71, Number 11

## Statin Use and Brain Hemorrhage

### Real Risk or Unfounded Fear?

Marco A. Gonzalez-Castellon, MD; Randolph S. Marshall, MD, MS

## Statin Therapy Should be Discontinued in Patients With Intracerebral Hemorrhage

Larry B. Goldstein, MD

Comments and Opinions

## Statin Treatment in Patients With Intracerebral Hemorrhage

Matthias Endres, MD; Christian H. Nolte, MD; Jan F. Scheitz, MD

## Statin Therapy Should Not be Discontinued in Patients With Intracerebral Hemorrhage

Alejandro Bustamante, MD; Joan Montaner, MD, PhD

EDITORIAL

## Cholesterol levels, statins, and spontaneous intracerebral hemorrhage

### An interesting but complicated story

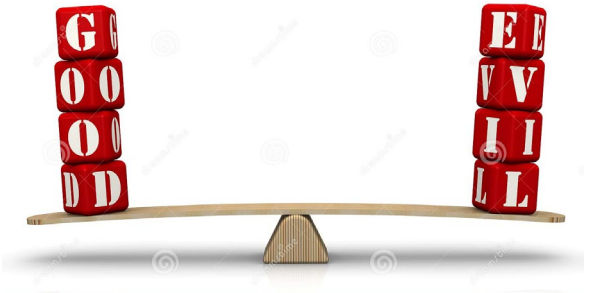
Guido J. Falcone, MD, ScD, MPH, and M. Edip Gurol, MD, MSc

*Neurology*® 2018;91:197-198. doi:10.1212/WNL.0000000000005898

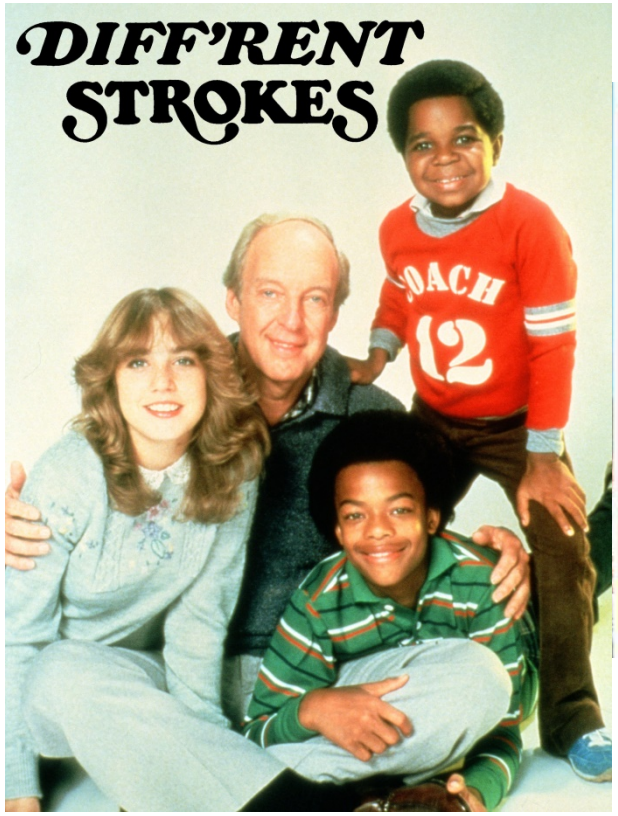
# THE REASONINGS …..

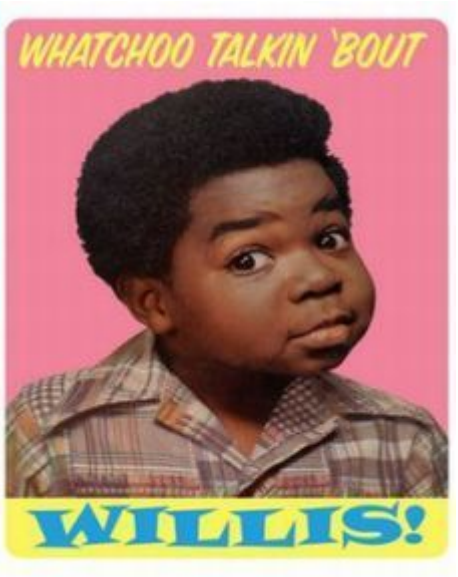
- Statins and aggressive reduction of LDL have been shown to reduce the risks of MACE and ischemic stroke
- Several meta-analyses do not suggest that statins are associated with increased risk of ICH
- Recent studies suggest that aggressive reduction of LDL does not significantly increase ICH risk
- Some retrospective observational studies suggest statins are not associated with increased risk of recurrent ICH
- Retrospective observational studies suggest that pre-ICH statin use is associated with improved outcomes and that cessation of statin during hospitalization is associated with worse outcomes and increased mortality after ICH.

- Some observational studies suggest that hypercholesterolemia is protective against ICH, and that low LDL (<70 mg/dL) is associated with increased risk for hemorrhagic stroke (ICH & SAH)
- The protective effects of hypercholesterolemia against ICH is reduced by statins particularly in lobar regions & in patients carrying ApoE4/E4 and Apo E2/E4 genotypes
- Few studies have shown that statin use is associated with the presence and number of cerebral microbleeds on brain MRI
- SPARCLE post-hoc analysis
- Markov decision analysis



# THE PROBLEMS WITH THIS REASONING…




# Example 1: Statins increase cardiovascular mortality!

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Statin Use and Reduced Cancer-Related Mortality

Sune F. Nielsen, Ph.D., Børge G. Nordestgaard, M.D., D.M.Sc.
and Stig E. Bojesen, M.D., Ph.D., D.M.Sc.

From the Department of Clinical Biochemistry, Herlev Hospital, Copenhagen University Hospital, Herlev, and the Faculty of Health Sciences, University of Copenhagen, Copenhagen — both in Denmark. Address reprint requests to Dr. Bojesen at the Department of Clinical Biochemistry, 54M1, Herlev Hospital, Copenhagen University Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark, or at stig.egil.bojesen@regionh.dk.

N Engl J Med 2012;367:1792-802.
DOI: 10.1056/NEJMoa1201735


ABSTRACT

**BACKGROUND**

A reduction in the availability of cholesterol may limit the cellular proliferation required for cancer growth and metastasis. We tested the hypothesis that statin use begun before a cancer diagnosis is associated with reduced cancer-related mortality.

**METHODS**

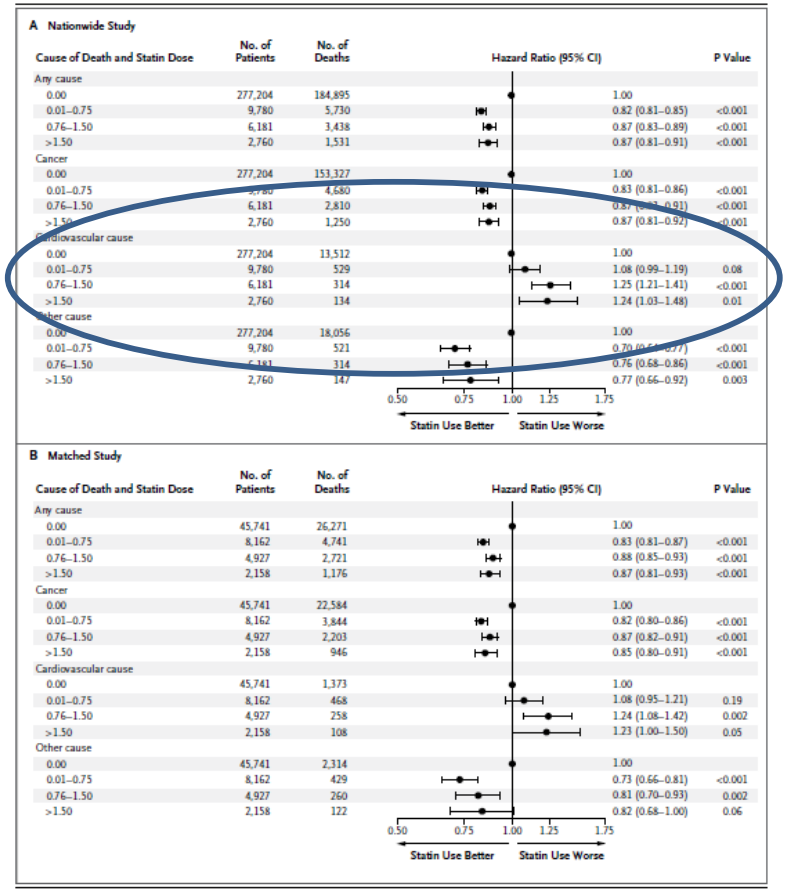
We assessed mortality among patients from the entire Danish population who had received a diagnosis of cancer between 1995 and 2007, with follow-up until December 31, 2009. Among patients 40 years of age or older, 18,721 had used statins regularly before the cancer diagnosis and 277,204 had never used statins.

**RESULTS**

Multivariable-adjusted hazard ratios for statin users, as compared with patients who had never used statins, were 0.85 (95% confidence interval [CI], 0.83 to 0.87) for death from any cause and 0.85 (95% CI, 0.82 to 0.87) for death from cancer. Adjusted hazard ratios for death from any cause according to the defined daily statin dose (the assumed average maintenance dose per day) were 0.82 (95% CI, 0.81 to 0.85) for a dose of 0.01 to 0.75 defined daily dose per day, 0.87 (95% CI, 0.83 to 0.89) for 0.76 to 1.50 defined daily dose per day, and 0.87 (95% CI, 0.81 to 0.91) for higher than 1.50 defined daily dose per day; the corresponding hazard ratios for death from cancer were 0.83 (95% CI, 0.81 to 0.86), 0.87 (95% CI, 0.83 to 0.91), and 0.87 (95% CI, 0.81 to 0.92). The reduced cancer-related mortality among statin users as compared with those who had never used statins was observed for each of 13 cancer types.

**CONCLUSIONS**

Statin use in patients with cancer is associated with reduced cancer-related mortality. This suggests a need for trials of statins in patients with cancer.




NIH PREVENTION | TREATMENT | RECOVERY

SATURN

# Example 2: Physicians/Prescription biases..

## 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.**)

### Conclusion

Although statin use, especially continued or new use of statins, was associated with improved outcomes in ICH patients, this effect may merely reflect the physician/healthcare team's view of whether the person will survive and not a predictor of survival. We were unable to identify a substantial effect of statin use on long-term survival, outcomes, and hematoma volume or hematoma growth.

The NEW ENGLAND JOURNAL of MEDICINE

SOUNDING BOARD

# The Magic of Randomization versus the Myth of Real-World Evidence

Rory Collins, F.R.S., Louise Bowman, M.D., F.R.C.P., Martin Landray, Ph.D., F.R.C.P., and Richard Peto, F.R.S.

Nonrandomized observational analyses of large electronic patient databases are being promoted as an alternative to randomized clinical trials as a source of "real-world evidence" about the efficacy and safety of new and existing treatments.[1-3] For drugs or procedures that are already being used widely, such observational studies may involve exposure of large numbers of patients. Consequently, they have the potential to detect rare adverse effects that cannot plausibly be attributed to bias, generally because the relative risk is large (e.g., Reye's syndrome associated with the use of aspirin, or rhabdomyolysis associated with the use of statin therapy).[4] Nonrandomized clinical observation may also suffice to detect large beneficial effects when good outcomes would not otherwise be expected (e.g., control of diabetic ketoacidosis with insulin treatment, or the rapid shrinking of tumors with chemotherapy).

However, because of the potential biases inherent in observational studies, such studies cannot generally be trusted when — as is often the case — the effects of the treatment of interest are actually null or only moderate (i.e., less than a twofold difference in the incidence of the health outcome between using and not using the treatment).[4-6] In those circumstances, large observational studies may yield misleading associations of a treatment with health outcomes that are statistically significant but noncausal, or that are mistakenly null when the treatment really does have clinically important effects. Instead, randomized, controlled trials of adequate size are generally required to ensure that any moderate benefits or moderate harms of a treatment are assessed reliably enough to guide patient care appropriately (Box 1).[5-7]

Reliance on nonrandomized observational studies risks inadequate assessments of both safety and efficacy because the potential biases with respect to both can be appreciable. For example, the treatment that is being assessed may well have been provided more or less often to patients who had an increased or decreased risk of various health outcomes. Indeed, that is what would be expected in medical practice, since both the severity of the disease being treated and the presence of other conditions may well affect the choice of treatment (often in ways that cannot be reliably quantified). Even when associations of various health outcomes with a particular treatment remain statistically significant after adjustment for all the known differences between patients who received it and those who did not receive it, these adjusted associations may still reflect residual confounding because of differences in factors that were assessed only incompletely or not at all (and therefore could not be taken fully into account in adjusted analyses). Modeling studies indicate that potential biases in observational studies may well be large enough to lead to the false conclusion that a treatment produces benefit or harm, with none of a range of statistical strategies capable of adjusting with certainty for bias. Those findings are consistent with findings from reviews that compared estimates of treatment effects from observational studies with estimates from randomized trials, with examples in which results for the same intervention were similar but also many in which the results were importantly different.[8-12]

Such discrepancies are illustrated by a database analysis involving the entire Danish population that found that the relative risk of death from cancer was 15% lower (95% confidence interval, 13 to 18) among patients who had taken statin therapy for only a few years than among those who had not taken statin therapy, even after statistical adjustment for what was



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!

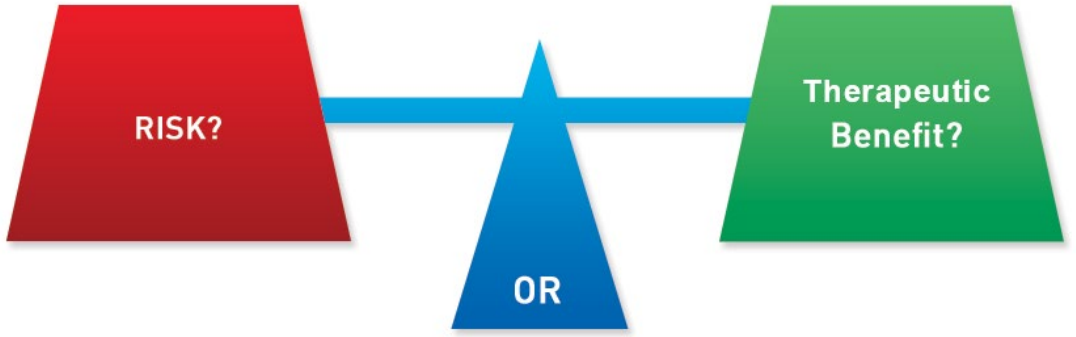
NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

SATURN

# Other Considerations..

- Exclusion criteria in SATURN are tailored to exclude patients who are most likely to benefit from statin therapy

- Use of non-statin lipid lowering agents is permitted
  - Omega-3 fatty acids (fish oil)
  - Ezetimibe

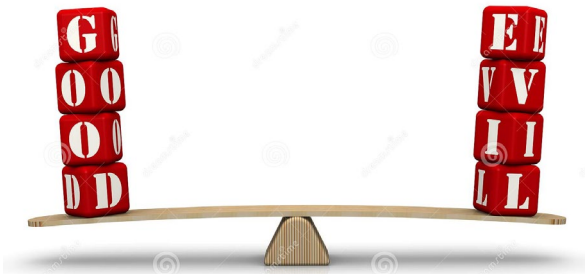


# Study Objectives

# Primary Objectives

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

- To determine the effects of discontinuation vs. continuation of statins on the occurrence of any of the following major adverse cardio- and cerebrovascular events:
  - 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

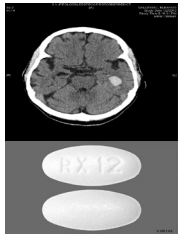


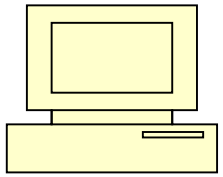
# Secondary Objectives

- 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 major adverse cardio- and cerebrovascular events vary by sex or ethnicity

# Study Procedures

# Study Assessments Flowchart



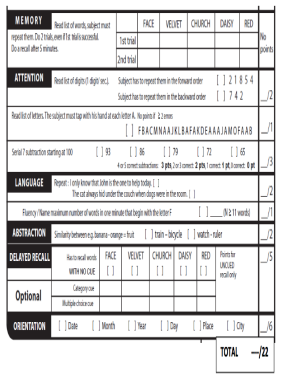


| Screening | Randomization | APOE | Discharge | 1, 2, 3, 6, 9, 12, 18, 24 months* |
|---|---|---|---|---|
| ✓ Inclusion<br>✓ Exclusion | ✓ ICH score<br>✓ NIHSS |  | ✓ mRS<br>✓ NIHSS | ✓ Recurrent symptomatic ICH; MACE; SAEs; mRS; TMoCA; QoL (EQ-5D); Review of prescription refills; BP reporting |

**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.*

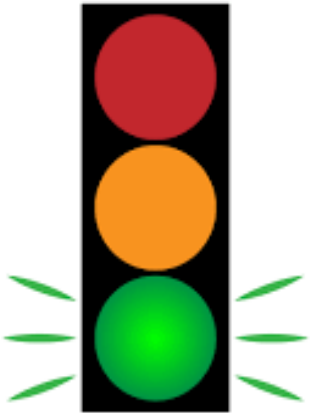
*Each subject will be followed for 24 months, including those who experience a recurrent ICH, to standardize the timing of final assessments of quality of life and functional/cognitive outcomes among all participants.*

***MACE = Major adverse cardio- and cerebro-vascular events*



# Inclusion Criteria

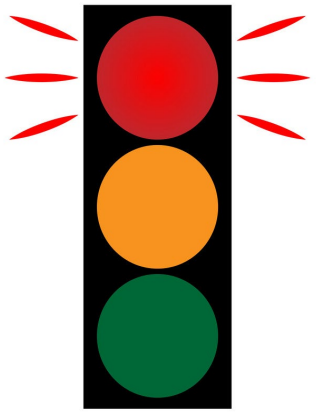
1. Age ≥50 years
2. Spontaneous lobar ICH*, confirmed by CT or MRI scan
3. Patient was taking a statin drug prior to the onset of the qualifying/index ICH
4. Randomization to one of the two treatment strategies can be carried out within 7 days of the onset of the qualifying ICH
5. Patient or surrogate 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, caudate, or internal capsule.

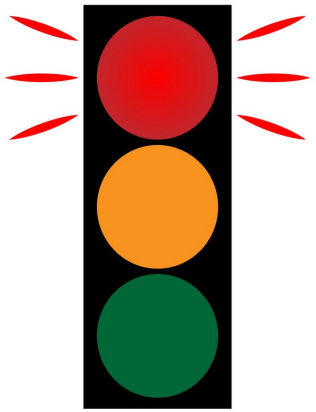
# Exclusion Criteria

1. Suspected secondary cause for the qualifying ICH, such as an underlying vascular abnormality or tumor, trauma, venous infarction, or hemorrhagic transformation of an ischemic infarct.
2. History of recent myocardial infarction (attributed to coronary artery disease) or unstable angina within the previous 3 months
3. Diabetic patients with history of myocardial infarction or coronary revascularization
4. History of familial hypercholesterolemia
5. Patients receiving PCSK-9 inhibitors
6. Inability to obtain informed consent
7. Women of childbearing potential
8. Pre-morbid mRS >3
9. ICH score >3 upon presentation



# Exclusion Criteria

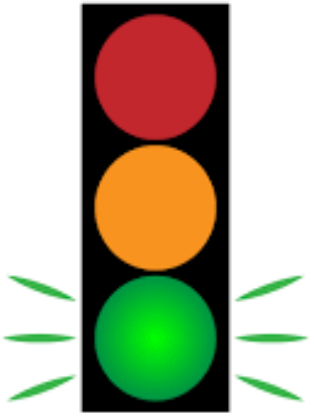
10. Known diagnosis of severe dementia
11. Life expectancy of less than 24 months due to co-morbid terminal conditions
12. Indication that withdrawal of care will be implemented for the qualifying ICH
13. Contraindications to continuation/resumption of statin therapy, such as significant elevations of serum creatinine kinase and/or liver transaminases, and rhabdomyolysis
14. 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, such as unable to adhere to the protocol specified visits/assessments.
15. Concurrent participation in another research protocol for investigation of experimental therapy



# Exclusion Criteria

**Please note the following ARE NOT exclusion criteria**

- **Surgery**
- **Anticoagulation**
- **Atrial fibrillation**



## Are you participating in ASPIRE?

# SATURN

# VS.

# ASPIRE

## ASPIRE

- First-ever ICH
- Predominantly, deep ICH, but lobar ICH with "low-risk" cerebral amyloid angiopathy can be enrolled
  - < 5 microbleeds on MRI
  - No superficial siderosis
- Patients must have non-valvular atrial fibrillation & $CHA_2DS_2$-$VAS_c$ score ≥ 2
- Patients with ICH caused by a ruptured AVM can be enrolled once AVM is secured

## SATURN

- First or recurrent ICH
- Only patients with lobar ICH (any) can be enrolled
- Patients with valvular or non-valvular atrial fibrillation (regardless of $CHA_2DS_2$-$VAS_c$ score) or need for oral anticoagulation can be enrolled
- Any patient with secondary ICH cannot be enrolled

**You must develop an enrollment strategy for these competing trials which ensures unbiased screening of subjects to each trial**

NIH StrokeNet PREVENTION | TREATMENT | RECOVERY

SATURN

# Obtaining Informed Consent

- IRB approved informed consent is required from all subjects or their legally authorized representative (LAR) prior to participating in the study
- Potential subjects or their LARs should be given ample opportunity to ask questions and to consider their decision. They should be given a copy of the **"Provider Study Information Sheet"** and instructed to contact their primary care physician to discuss the study further before signing the consent form
- Investigators should be available to answer the provider's questions if needed

**Q & A:**

- How to contact PCP? ---- *Anyway you like*
- Is PCP approval required? ---- *Strongly encouraged, but ultimately up to the subject/LAR*
- What about subjects who do not have a PCP? ---- *Post-discharge primary provider is required*
- Remote consent? ---- *Fax, video, e-mail; ultimately needs the original; adequate documentation*

# Important Reminders

- Ask the subject or LAR to provide the contact information for someone else such as a family member or caregiver that we could contact for follow up if needed. Ideally, an English-speaking person if the subject or LAR are non-English speaking
- Ask the subject or LAR for the name and contact information of the subject's Primary Healthcare Provider
- Provide the subject or LAR with the **"Study Participant Information Sheet/Card"**, which outlines what to expect during follow-up phone calls
- BP monitoring & treatment is important for prevention of recurrent stroke, including ICH

# Post Enrollment Procedures and Assessments

# Blood Sample Collection

- Once the subject is randomized, a blood sample (2 tubes) should be collected for genomic analysis
- Blood should be collected in purple-top tubes
  - Universal precautions practices must be followed during blood collection & handling
  - Do not fill all the way to the way to the purple top. Only fill the vial ¾ full
  - Store the samples upright
  - Store & ship at room temperature on the day of collection. Otherwise, store in a refrigerator at 4 degrees Celsius and ship on ice within 72 hours during weekends/holidays

# Monitoring & Reporting Adverse/Outcome Events

- Once the central assessors uncover any adverse event that meets the definition of a SAE such as a major adverse cardiovascular event, ischemic stroke, or recurrent ICH during the follow-up phone calls, they will enter these events into WebDCU™ within 24 hours or the following business day

- This will generate an e-mail notification to inform the local site PI & study coordinator to complete the AE CRF within 72 hours. Once completed this will trigger notification to the study statistician and independent Medical Safety Monitor to review the CRF.

- The Medical Safety Monitor will make an initial assessment of the reported event(s). If the Medical Safety Monitor requests additional materials/records to assist him with event adjudication, an e-mail notification of this request will be sent to the site investigators and central assessors to coordinate their efforts to obtain the necessary materials and upload them into WebDCU™ within 7 days.

- If participants or their caregivers notify the local site study team of the occurrence of an adverse event or any hospitalization prior to scheduled follow-up phone calls by the central assessors, the local team is expected to enter these events into WebDCU™ within 24 hours or the following business day.

# Questions


- Overall Study Principal Investigator
  Magdy Selim, MD, PhD
  mselim@bidmc.harvard.edu
  Tel: +1-617-632-8913
- NCC Project Manager
  Kimberlee Bernstein, BS, CCRP
  gammk@ucmail.uc.edu
  Tel: +1-513-558-3970
- BIDMC Project Manager
  Sarah Marchina, PhD
  smarchin@bidmc.harvard.edu
  Tel: +1-617-632-8949


SATURN@bidmc.harvard.edu

**24/7 Clinical Hotline**
For urgent questions call +1-617-667-7000 & ask to page beeper #39636 re: the SATURN Trial

NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

SATURN