Use of Statins after ICH

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Disclosures

- Co-Chair and Canadian National PI of SATURN trial (NIH-StrokeNet) and Co-PI of SATURN MRI substudy (NIA)

Objectives

- Discuss the clinical dilemma surrounding the use of statins in patients with ICH
  - Epidemiologic data correlating cholesterol levels and ICH
  - Mendelian randomization analyses
  - RCTs
- Review alternative lipid lowering therapies in this population
- Highlight the ongoing SATURN RCT

Statins in Vascular Prevention

	ACEI (HOPE)	Lipid lowering (1 mmol/L)	DAPT (PEGASUS; ticagrelor 60 mg BID)	BP lowering (10 mmHg)	COMPASS Rivaroxaban 2.5 mg BID + ASA
Composite of efficacy outcomes	–18%	–21%	–16%	–20%	–24%
Death	–14%	–9%	–17%*	–13%	–18%
Stroke	–23%	–15%	–25%	–27%	–42%
MI	–18%	–24%	–16%	–17%	–14%*
MALE	–11%*	–	–35%	–	–46%

*Not significant

ACEI, angiotensin-converting-enzyme inhibitor; ASA, acetylsalicylic acid; BID, twice daily; BP, blood pressure; DAPT, dual antiplatelet therapy; MALE, major adverse limb event; MI, myocardial infarction

Eikelboom JW *et al. N Engl J Med* 2017; 377:1319-30. Ettehad D *et al. Lancet* 2016; 387:957-67. CTT Collaboration. *Lancet* 2015; 385:1397-405. Collins R *et al. Lancet* 2016; 388:2532-61. Dagenais GR *et al. Lancet* 2006; 368:581-8. HOPE Investigators. *N Engl J Med* 2000; 342:145-53. Bonaca MP *et al. N Engl J Med* 2015; 372:1791-800. Bonaca MP *et al. J Am Coll Cardiol* 2016; 67:2719-28.

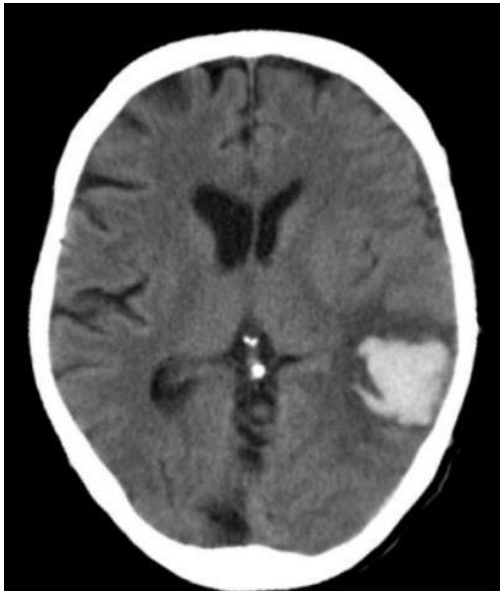
Statin use in Canada

- 10% of Canadians are taking statins
  - 1 in 4 should be as per CCS guidelines

Brown C. *CMAJ :* 2016;188:325

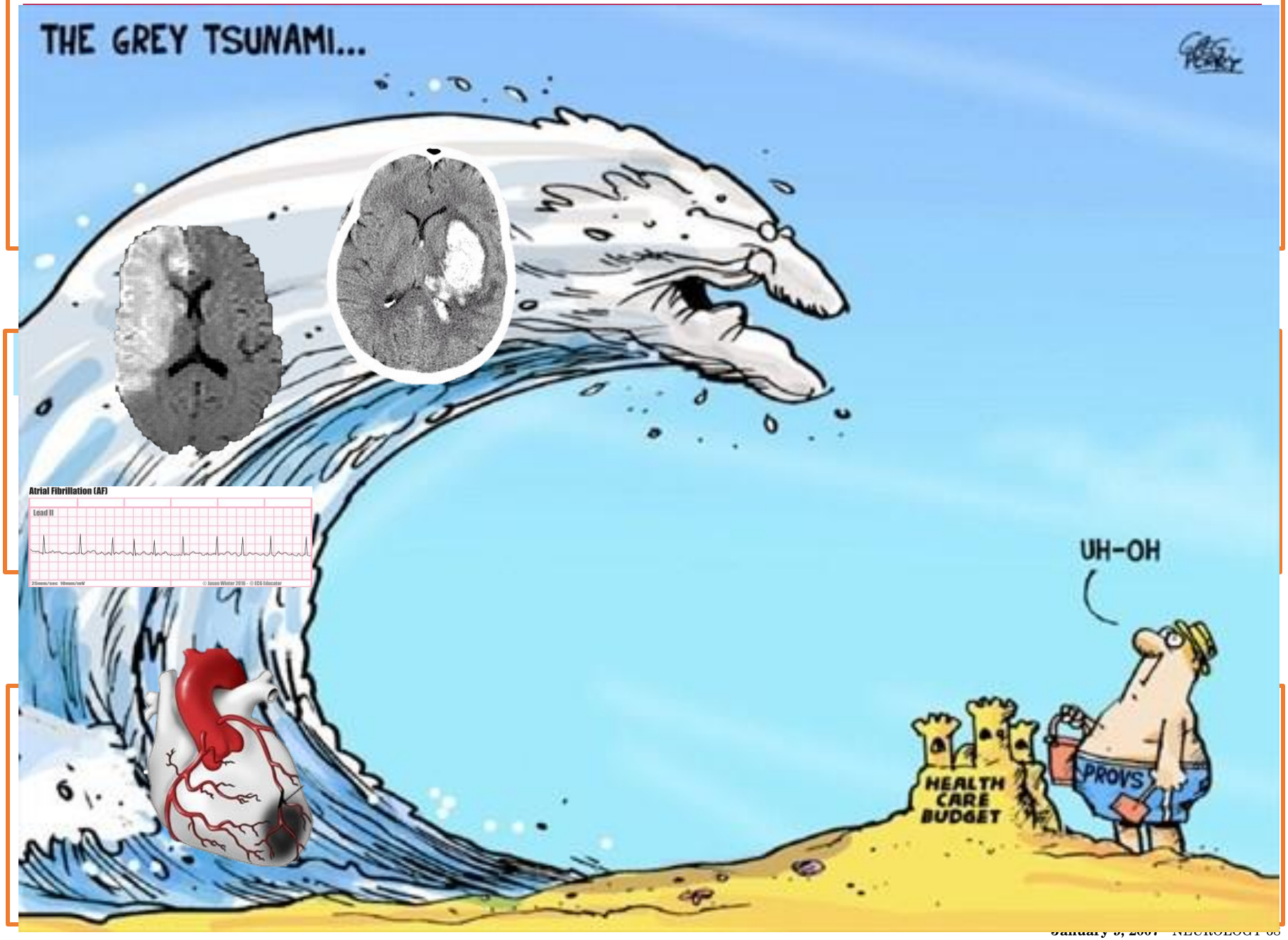
ICH cohort

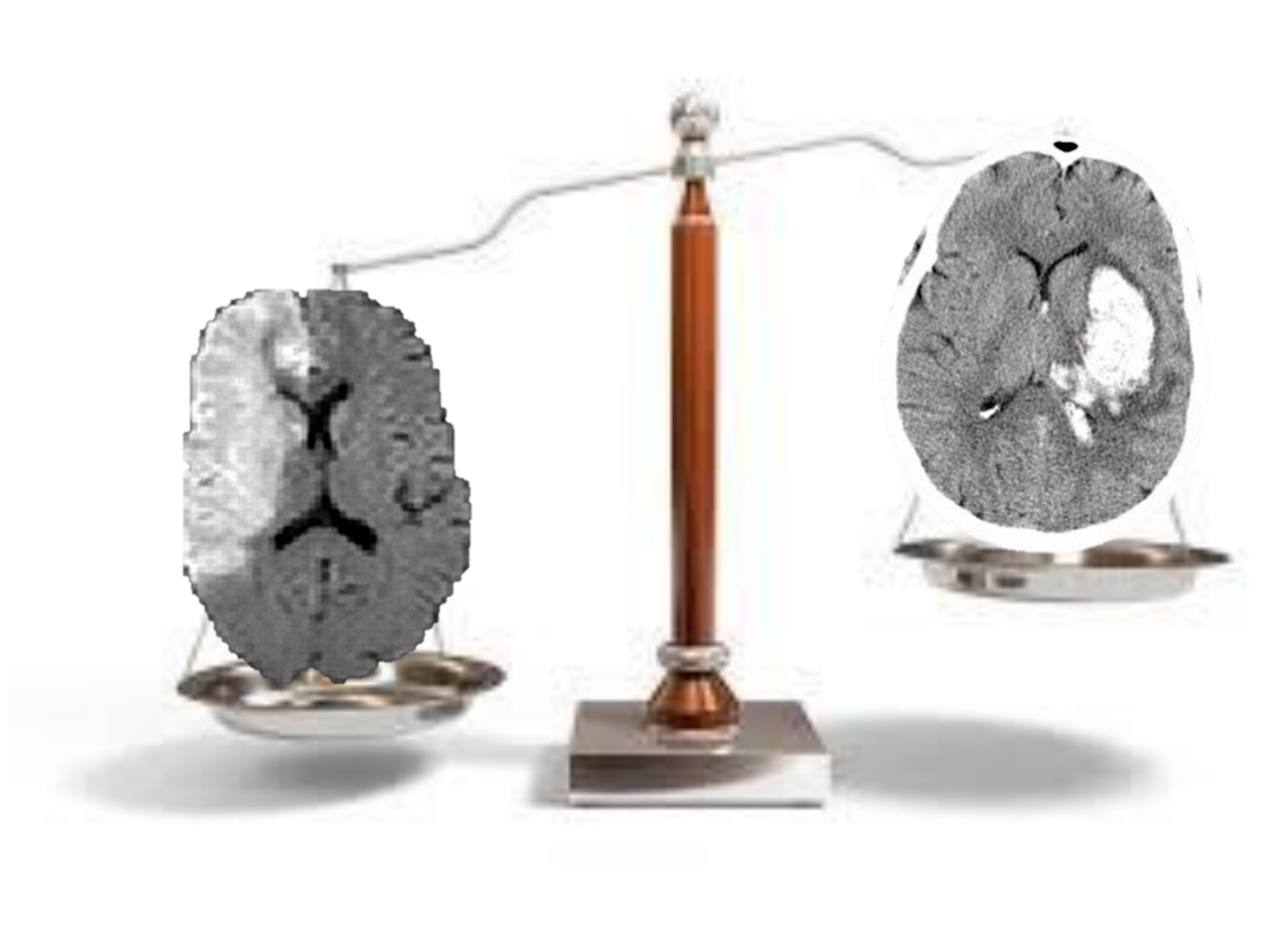
N=89, mean age: 72
Hamilton Health Sciences



Atrial fibrillation	21%
CAD/MI	17%
Ischemic stroke	10%
TIA	9%
Antithrombotic therapy	26%
Statin therapy	**35%**
Indication for antithrombotic therapy	43%

Beshara et al. Manuscript in submission


THE GREY TSUNAMI...
Atrial Fibrillation (AF)
Lead II
UH-OH
HEALTH CARE BUDGET
PROVS



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*

- N=4731 (1998-2001)
- Stroke or TIA within 1-6 months prior to study entry
- Patients with ICH included if deemed to be at risk for ischemic stroke or CAD
- LDL between 2.6 – 4.9 mmol/L
- No CAD/No cardioembolic stroke
- Randomized (1:1) Atorvastatin 80 mg daily or Placebo

Entry event — no. (%)		
Stroke	1655 (70.0)	1613 (68.2)
Ischemic	1595 (67.4)	1559 (65.9)
Hemorrhagic	45 (1.9)	48 (2.0)
Other type or not determined	15 (0.6)	6 (0.3)
TIA	708 (29.9)	752 (31.8)
Unknown	2 (0.1)	1 (<0.1)

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Median follow-up of 4.9 years

Table 2. Estimates of the Hazard Ratio for the Primary and Secondary Efficacy Outcome Measures.

Outcome*	Atorvastatin (N=2365)	Placebo (N=2366)	Unadjusted P Value†	Prespecified Adjusted Model‡	
				HR (95% CI)	P Value
	no. (%)				
Primary outcome					
Nonfatal or fatal stroke§	265 (11.2)	311 (13.1)	0.05	0.84 (0.71–0.99)	0.03
Nonfatal stroke	247 (10.4)	280 (11.8)	0.14	0.87 (0.73–1.03)	0.11
Fatal stroke	24 (1.0)	41 (1.7)	0.04	0.57 (0.35–0.95)	0.03
Secondary outcomes					
Stroke or TIA	375 (15.9)	476 (20.1)	<0.001	0.77 (0.67–0.88)	<0.001
TIA	153 (6.5)	208 (8.8)	0.004	0.74 (0.60–0.91)	0.004
Major coronary event§	81 (3.4)	120 (5.1)	0.006	0.65 (0.49–0.87)	0.003
Death from cardiac causes	40 (1.7)	39 (1.6)	0.90	1.00 (0.64–1.56)	1.00
Nonfatal myocardial infarction	43 (1.8)	82 (3.5)	0.001	0.51 (0.35–0.74)	<0.001
Resuscitation after cardiac arrest	1 (<0.1)	1 (<0.1)	—	—	—
Major cardiovascular event	334 (14.1)	407 (17.2)	0.005	0.80 (0.69–0.92)	0.002
Acute coronary event	101 (4.3)	151 (6.4)	0.001	0.65 (0.50–0.84)	0.001
Any coronary event	123 (5.2)	204 (8.6)	<0.001	0.58 (0.46–0.73)	<0.001
Revascularization¶	94 (4.0)	163 (6.9)	<0.001	0.55 (0.43–0.72)	<0.001
Any cardiovascular event	530 (22.4)	687 (29.0)	<0.001	0.74 (0.66–0.83)	<0.001
Death	216 (9.1)	211 (8.9)	0.77	1.00 (0.82–1.21)	0.98
Death from cardiovascular disease	78 (3.3)	98 (4.1)	0.14	0.78 (0.58–1.06)	0.11
Death from cancer	57 (2.4)	53 (2.2)	0.67	1.05 (0.72–1.53)	0.80
Death from infection	26 (1.1)	20 (0.8)	—	—	—
Accidental or violent death	11 (0.5)	6 (0.3)	—	—	—
Death from other causes	23 (1.0)	15 (0.6)	—	—	—
Unclassified deaths	21 (0.9)	19 (0.8)	—	—	—

* Only the first event for each patient is counted.
† Unadjusted P values were calculated by the log-rank test.
‡ Treatment hazard ratios (HRs) and P values are from the Cox regression model with adjustment for geographic region, entry event, time since entry event, sex, and age at baseline. CI denotes confidence interval.
§ Numbers of patients in the outcome subgroups do not total the number for the overall outcome because some patients had multiple events or the outcome could not be subclassified.
¶ Revascularization includes coronary, carotid, and peripheral revascularization.

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

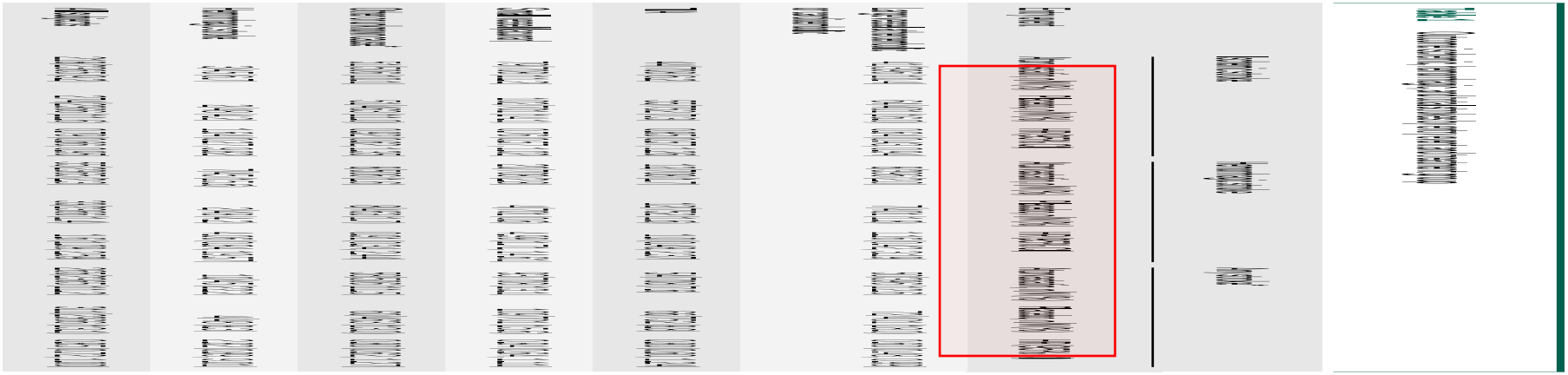
High-Dose Atorvastatin after Stroke or Transient Ischemic Attack

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

HR 1.67 (95% CI 1.08 – 2.55) for ICH

Hemorrhagic stroke in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels study

Neurology® 2008;70:2364–2370

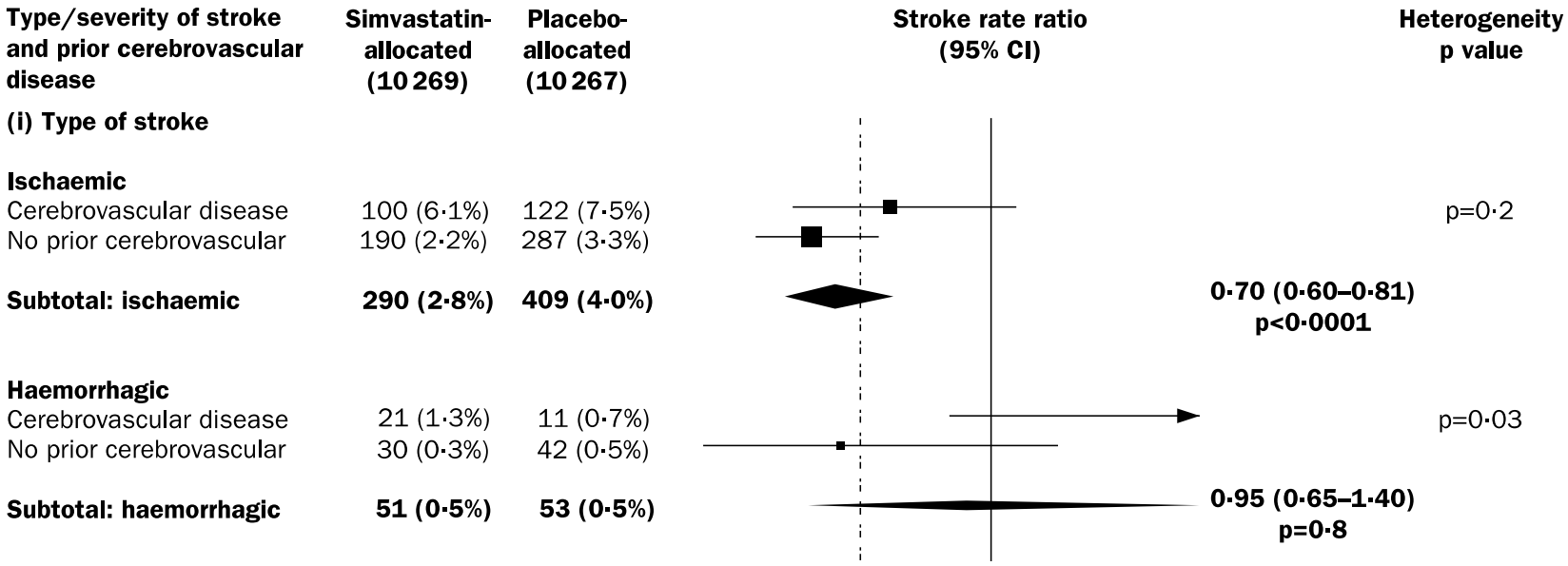


Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20 536 people with cerebrovascular disease or other high-risk conditions

*Heart Protection Study Collaborative Group**

Lancet 2004; **363:** 757–67

3280 cerebrovascular disease
17256 With other arterial disease or DM
ICH excluded
Simva 40 vs. placebo



Type/severity of stroke and prior cerebrovascular disease	Simvastatin-allocated (10 269)	Placebo-allocated (10 267)	Stroke rate ratio (95% CI)	Heterogeneity p value
(i) Type of stroke				
Ischaemic				
Cerebrovascular disease	100 (6·1%)	122 (7·5%)		p=0·2
No prior cerebrovascular	190 (2·2%)	287 (3·3%)		
Subtotal: ischaemic	**290 (2·8%)**	**409 (4·0%)**	**0·70 (0·60–0·81) p<0·0001**	
Haemorrhagic				
Cerebrovascular disease	21 (1·3%)	11 (0·7%)		p=0·03
No prior cerebrovascular	30 (0·3%)	42 (0·5%)		
Subtotal: haemorrhagic	**51 (0·5%)**	**53 (0·5%)**	**0·95 (0·65–1·40) p=0·8**	

PREVENTIVE MEDICINE 9, 722–740 (1980)

Multivariate Analysis of Risk Factors for Stroke

Eight-Year Follow-Up Study of Farming Villages in Akita, Japan

HIROTSUGU UESHIMA,* MINORU IIDA,* TAKASHI SHIMAMOTO,* MASAMITSU KONISHI,* KATSUHIKO TSUJIOKA,† MASATO TANIGAKI,* NORIYUKI NAKANISHI,* HIDEKI OZAWA,‡ SABURO KOJIMA,§ AND YOSHIO KOMACHI**

ANALYSIS OF RISK FACTORS FOR ALL STROKE,[a] HEMORRHAGE, AND INFARCTION, DISCRIMINANT COEFFICIENTS OF STANDARD UNIT CALCULATED BY MULTIPLE LOGISTIC FUNCTION FOR 1720 NONSTROKE AND EACH TYPE OF STROKE CASES, MALE AND FEMALE, AGED 40–69 YEARS AT TIME OF INITIAL EXAMINATION

	All stroke[a] $N = 94$		Hemorrhage $N = 28$		Infarction $N = 57$	
Variables	Coefficients	t values	Coefficients	t values	Coefficients	t values
1. Sex	−0.268	−2.396[b]	−0.280	−1.396	−0.276	−1.939
2. Age	0.624	5.409[c]	0.483	2.357[b]	0.775	5.299[c]
3. Obesity index	0.023	0.212	0.107	0.538	0.030	0.214
4. Systolic BP	0.952	7.942[c]	1.248	5.880[c]	0.819	5.446[c]
5. Urinary sugar	0.044	0.407	0.033	0.167	0.025	0.183
6. Urinary albumin	−0.002	−0.015	0.139	0.706	−0.059	−0.422
7. Cholesterol	−0.134	−1.161	−0.443	−2.131[b]	0.043	0.291
8. Total protein	0.202	1.716	0.358	1.681	0.177	1.177
Constant	−3.699		−5.344		−4.256	

[a] All stroke includes hemorrhage, infarction, and unclassified cases.
[b] Significance, $P < 0.05$.
[c] Significance, $P < 0.001$.

can, angiography, computerized axial
phy (CAT), etc. Moreover, in fatal cases,
autopsy it may be difficult to distinguish ac-
between subarachnoid hemorrhage, due to
aneurysm, primary hypertensive in-
al hemorrhage and secondary hemorrhage
omboembolic cerebral infarction especially if
s been extensive destruction of brain and
structures. With ischemic cerebral infarction,
hard to be sure whether infarction is due to
sis or embolism.
e these difficulties, studies have been carried
under way often in conjunction with studies

that of Whites in the United States. In fig
tality data for the year 1970 are show
several populations with rates age-adjuste
the age of the Hawaiian population in 19

When the ABCC mortality data were
with those for the Hawaii and California
the same age groups, it was found that s
tality in Japan was 3 times that of the
American cohorts.[10] Stroke prevalence als
pared in the 3 study sites and the
remarkably similar to the mortality ratio

A comparison of strokes found at first ex
subdivided into those due to infarction an

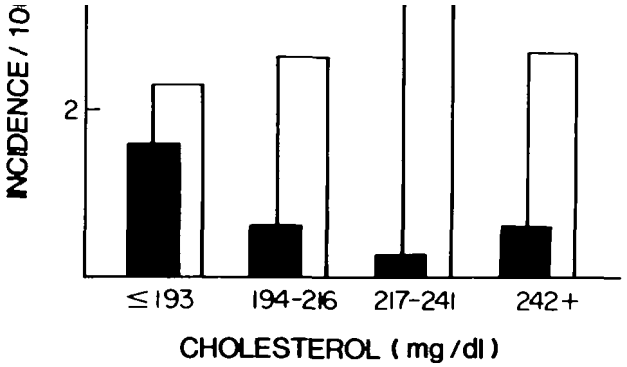


FIGURE 7. *Incidence of stroke by quartile of serum cholesterol.*

193 mg/dl = 5 mmol/L

It appears to be a universal finding among all stroke epidemiology studies that the single most important risk factor for stroke, whether of cerebral infarction or of intracranial hemorrhage, is hypertension. In addition, Paffenbarger, et al.,[37] in a study of California longshoremen, found heart disease and abnormal glucose metabolism as factors increasing stroke mor-

e United States. In figure

International Journal of Epidemiology 2003;**32**:563–572
DOI: 10.1093/ije/dyg106

Cholesterol, coronary heart disease, and stroke in the Asia Pacific region

Asia Pacific Cohort Studies Collaboration

Individual level meta-analysis
N=352,033; 2 million person years of follow-up

Each 1-mmol/l increase in total cholesterol

- 35% increased risk of coronary death
- 25% increased risk of fatal or non-fatal ischaemic stroke
- 20% decreased risk of fatal haemorrhagic stroke

Different Risk Factors for Different Stroke Subtypes

Association of Blood Pressure, Cholesterol, and Antioxidants

Jaana M. Leppälä, MD; Jarmo Virtamo, MD; Rainer Fogelholm, MD;
Demetrius Albanes, MD; Olli P. Heinonen, MD

TABLE 2. Crude Incidence per 10 000 Person-Years and Adjusted Relative Risk (95% CI) of Stroke Subtypes by Systolic and Diastolic Blood Pressure, Serum Total and HDL Cholesterol, and Smoking at Beginning of Follow-Up

	Subarachnoid Hemorrhage				Intracerebral Hemorrhage				Cerebral Infarction			
Risk Factor	N	I	RR	(95% CI)	N	I	RR	(95% CI)	N	I	RR	(95% CI)
Systolic blood pressure												
≤139 mm Hg	21	2.7	1.00	...	26	3.3	1.00	...	243	30.8	1.00	...
140–159 mm Hg	36	6.5	2.57	(1.49–4.44)	43	7.8	2.20	(1.34–3.61)	292	52.7	1.54	(1.29–1.83)
≥160 mm Hg	28	9.4	3.86	(2.14–6.94)	43	14.4	3.78	(2.28–6.25)	272	91.2	2.38	(1.99–2.85)
Diastolic blood pressure												
≤89 mm Hg	30	3.3	1.00	...	37	4.0	1.00	...	339	37.0	1.00	...
90 –99 mm Hg	30	6.0	1.89	(1.13–3.16)	40	8.0	2.10	(1.34–3.31)	282	56.3	1.54	(1.31–1.81)
≥100 mm Hg	25	11.1	3.54	(2.04–6.17)	35	15.6	4.17	(2.58–6.74)	186	82.6	2.27	(1.88–2.73)
Serum total cholesterol												
≤4.9 mmol/L	12	5.7	1.00	...	25	11.9	1.00	...	104	49.4	1.00	...
5.0–5.9 mmol/L	35	7.0	1.20	(0.62–2.32)	47	9.3	0.77	(0.47–1.26)	235	46.7	1.00	(0.79–1.26)
6.0–6.9 mmol/L	19	3.6	0.60	(0.29–1.24)	30	5.6	0.46	(0.27–0.78)	241	45.2	0.97	(0.77–1.22)
≥7.0 mmol/L	19	4.8	0.78	(0.38–1.62)	10	2.5	0.20	(0.10–0.42)	226	57.3	1.25	(0.99–1.57)
Serum HDL cholesterol												
≤0.84 mmol/L	14	8.3	1.00	...	11	6.6	1.00	...	127	75.6	1.00	...
0.85–1.14 mmol/L	29	4.4	0.50	(0.26–0.95)	47	7.2	1.24	(0.64–2.41)	341	52.2	0.75	(0.61–0.93)
1.15–1.44 mmol/L	33	6.5	0.69	(0.36–1.33)	30	5.9	1.05	(0.52–2.15)	205	40.3	0.59	(0.46–0.74)
≥1.45 mmol/L	9	2.9	0.26	(0.11–0.62)	24	7.7	1.33	(0.62–2.85)	133	42.9	0.59	(0.45–0.77)
Smoking												

(*Stroke*. 1999;30:2535-2540.)

ARTICLE

Lipid levels and the risk of hemorrhagic stroke among women

Pamela M. Rist, ScD, Julie E. Buring, ScD, Paul M Ridker, MD, MPH, Carlos S. Kase, MD, Tobias Kurth, MD, ScD,* and Kathryn M. Rexrode, MD, MPH*

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Dr. Rist
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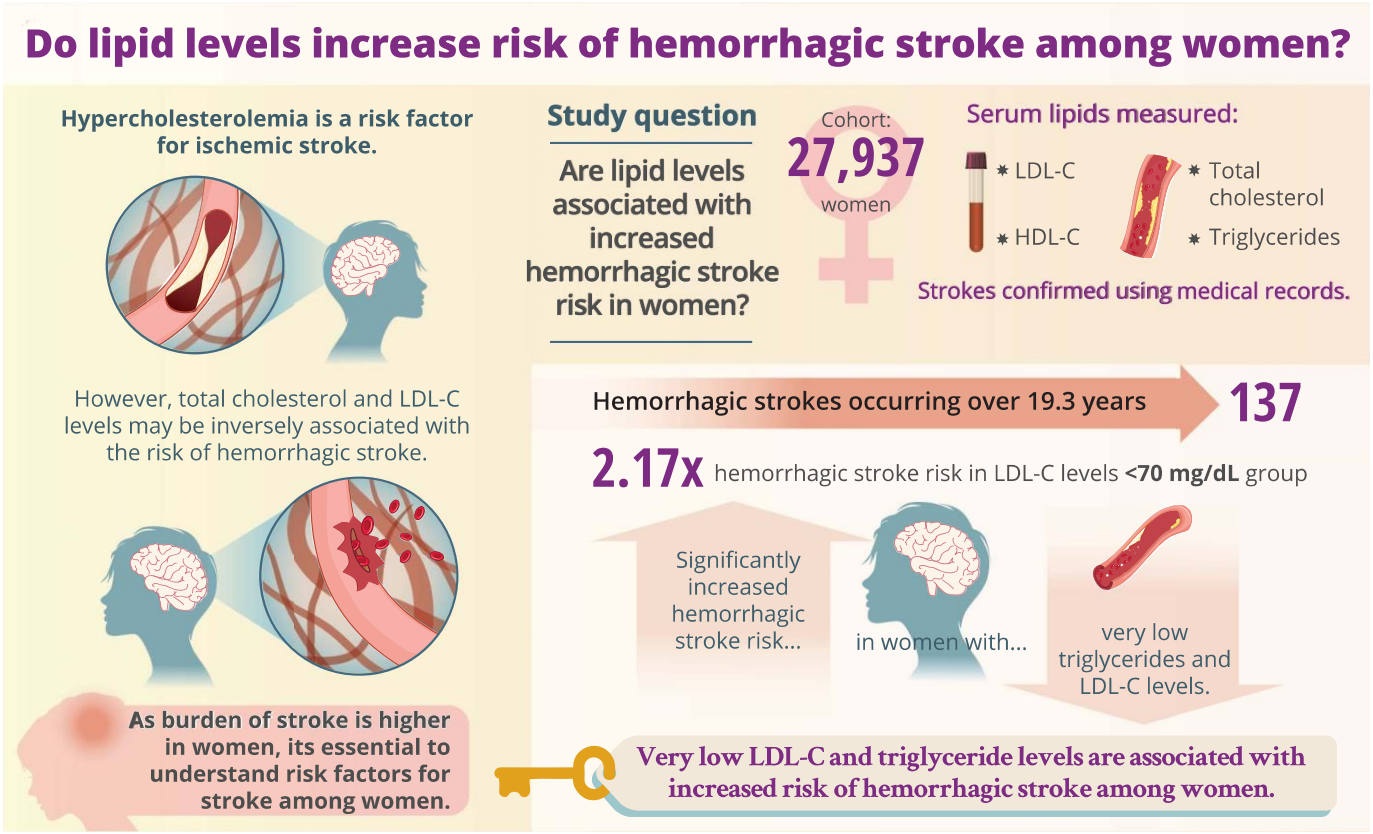
Neurology® 2019;92:e2286-e2294. doi:10.1212/WNL.0000000000007454



ARTICLE

Low-density lipoprotein cholesterol and risk of intracerebral hemorrhage

A prospective study

Chaoran Ma, MD, M. Edip Gurol, MD, MSc, Zhe Huang, MD, PhD, Alice H. Lichtenstein, DSc, Xiuyan Wang, MD, Yuzhen Wang, MD, Samantha Neumann, BSc, Shouling Wu, MD, PhD, and Xiang Gao, MD, PhD

Neurology® 2019;93:e445-e457. doi:10.1212/WNL.0000000000007853

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Dr. Gao
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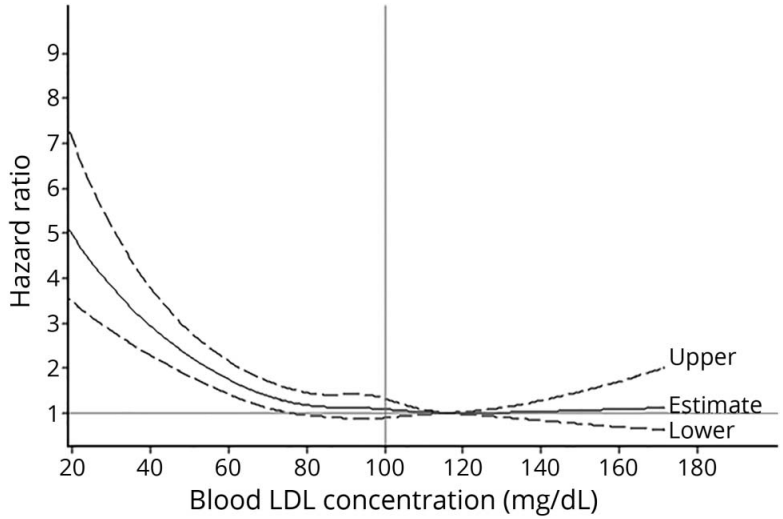
or Dr. Wu
drwusl@163.com

Figure Hazard ratios for intracerebral hemorrhage according to updated cumulative average blood LDL cholesterol from 2006 to 2012 among 96,043 Kailuan participants



Inconsistencies

Hemorrhagic stroke in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels study

Neurology® 2008;70:2364–2370

Table 3 Multivariable Cox regression model evaluating the effect of post-randomization time-varying LDL cholesterol on the risk of hemorrhagic stroke, adjusting for significant baseline characteristics

	Hazard ratio (95% CI)	*p* Value
Male gender	2.21 (1.20, 4.09)	0.01
Age, 10 y increment	1.40 (1.08, 1.81)	0.01
Entry event = hemorrhagic stroke	8.38 (3.78, 18.56)	<0.001
LDL cholesterol (quartiles, atorvastatin group)	—	0.77
LDL cholesterol <52 mg/dL (1st quartile, 12 events)*	—	—
LDL cholesterol 52 to 65 mg/dL (2nd quartile, 18 events)	1.26 (0.60, 2.64)	0.54
LDL cholesterol 66 to 92 mg/dL (3rd quartile, 13 events)	0.97 (0.44, 2.17)	0.94
LDL cholesterol ≥93 mg/dL (4th quartile, 45 events)	1.37 (0.63, 2.98)	0.43

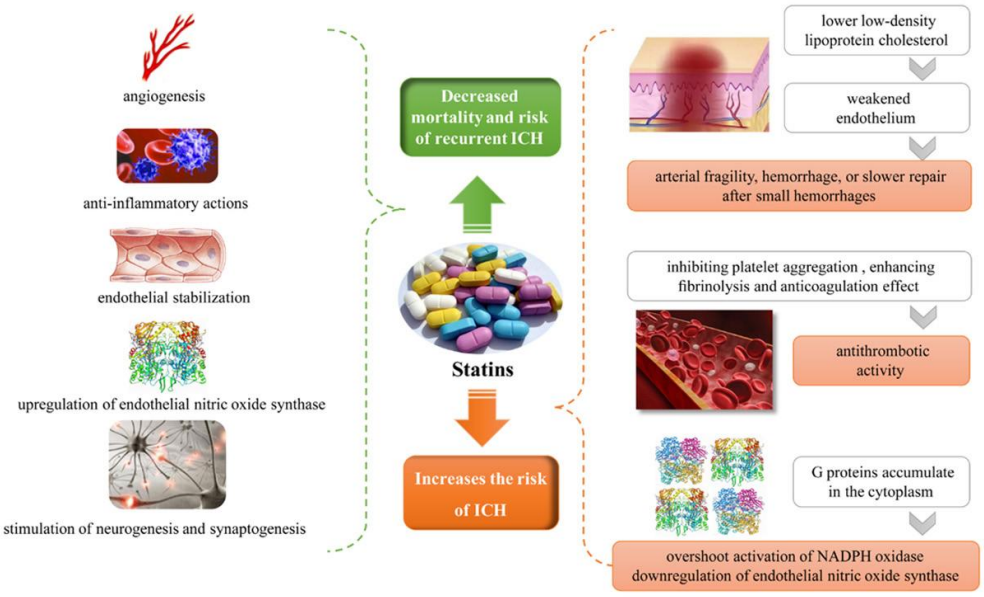
Brief Review

Statins and Blood Coagulation

Anetta Undas, Kathleen E. Brummel-Ziedins, Kenneth G. Mann

Arterioscler Thromb Vasc Biol. 2005;25:287-294

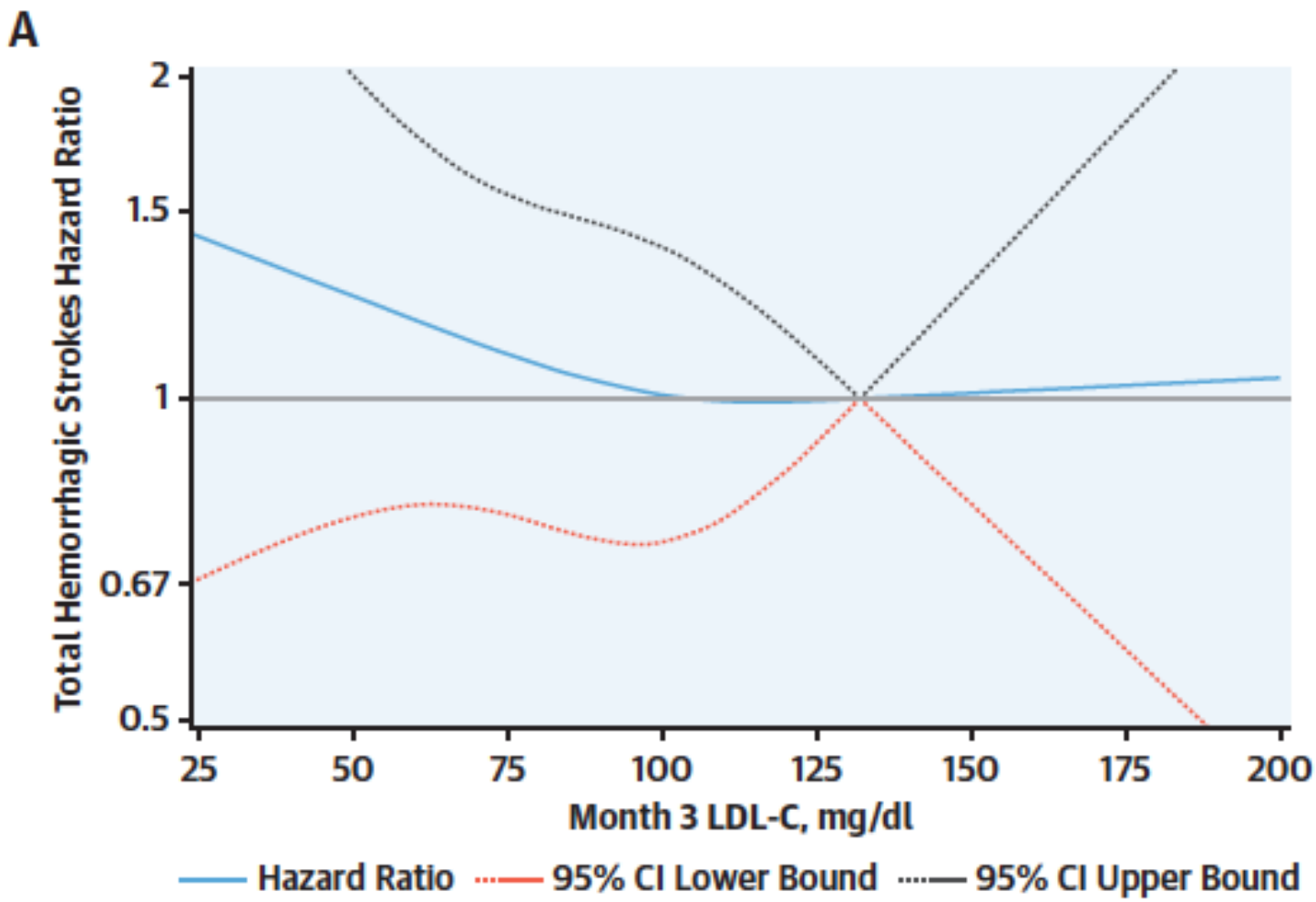
The dose-dependent pleiotropic effects of statin therapy



Summary of the Outcome Studies on Major Effects of Statin Use on Blood Coagulation

Process/Reaction	Effect	Evidence (References)
Tissue factor expression	Decrease	Established (13–22)
FVII production/FVII activation	Decrease	Unlikely (23–26, 28)
Thrombin generation	Decrease	Highly suggestive (27, 29–31, 34–39)
FV activation	Decrease	Suggestive (39)
Fibrinogen cleavage	Decrease	Suggestive (37, 39)
FXIII activation	Decrease	Suggestive (39)
Fibrinogen synthesis	No change	Suggestive (35–39, 49–52)
Thrombomodulin expression	Increase	Suggestive (63, 64)
Inactivation of FVa	Increase	Suggestive (39)
TFPI production/activity	Decrease	Inconsistent (36, 69–71)

FIGURE 1 Hemorrhagic and Nonhemorrhagic Strokes



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Retrospective cohort study, Taiwan National Health Insurance Research Database

N= 2676

High-Dose Atorvastatin after Stroke or Transient Ischemic Attack

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

Death	216 (9.1)	211 (8.9)	0.77	1.00 (0.82–1.21)	0.98

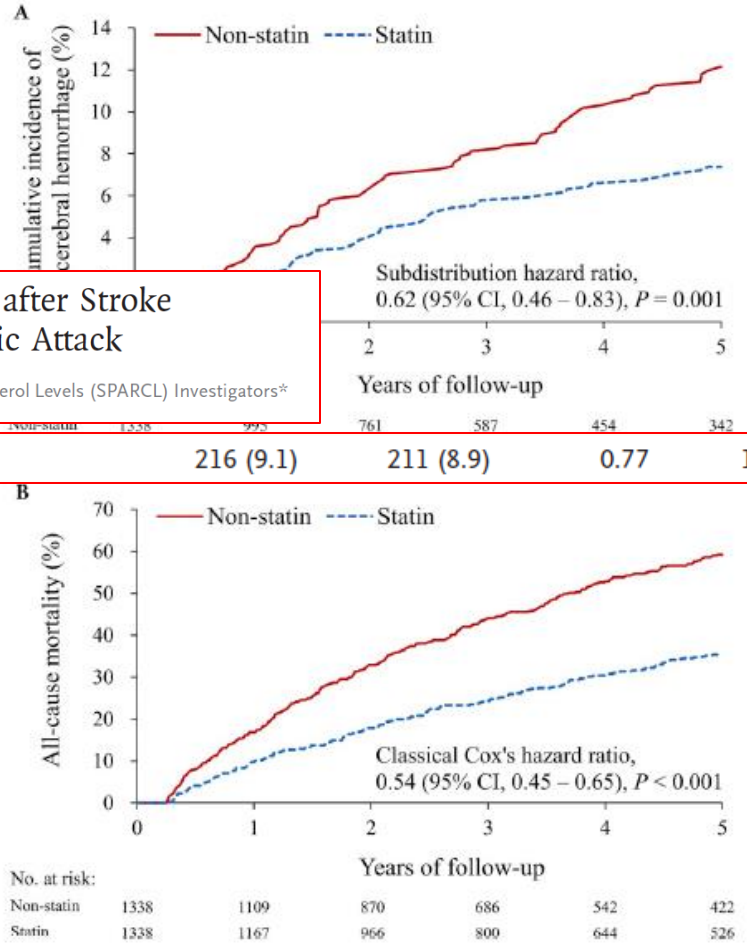

Fig. 2. Cumulative incidence of intracerebral hemorrhage (A) and unadjusted event rate of all-cause mortality (B) during 5 years of follow-up.

Atherosclerosis 288(2019)137–145

Limitations of observational data

- Healthy user?
  - Healthier patients are more likely to initiate and continue taking statins
  - Statin adherents more likely to adhere to other medications and healthier lifestyle

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Comparison of Two LDL Cholesterol Targets after Ischemic Stroke

P. Amarenco, J.S. Kim, J. Labreuche, H. Charles, J. Abtan, Y. Béjot, L. Cabrejo, J.-K. Cha, G. Ducrocq, M. Giroud, C. Guidoux, C. Hobeanu, Y.-J. Kim, B. Lapergue, P.C. Lavallée, B.-C. Lee, K.-B. Lee, D. Leys, M.-H. Mahagne, E. Meseguer, N. Nighoghossian, F. Pico, Y. Samson, I. Sibon, P.G. Steg, S.-M. Sung, P.-J. Touboul, E. Touzé, O. Varenne, É. Vicaut, N. Yelles, and E. Bruckert, for the Treat Stroke to Target Investigators*

DOI: 10.1056/NEJMoa1910355

- N=2860,Stroke within 3 months/TIA within 3 weeks
- LDL <1.8 vs. 2.3 to 2.8 mmol/L
- Established atherosclerotic disease
- **ICH and lacunar stroke excluded**
  - **31 ICH events vs. 88 in SPARCL**

Table 2. Hazard Ratios for Adjudicated Clinical End Points.

End Points	Lower-Target Group (N=1430)	Higher-Target Group (N=1430)	Hazard Ratio (95% CI)	P Value
Primary end point				
Major cardiovascular event — no. (%)	121 (8.5)	156 (10.9)	0.78 (0.61–0.98)*	0.04
Death from cardiovascular causes	17 (1.2)	24 (1.7)	—	
Fatal cerebral infarction or stroke of undetermined origin	3 (0.2)	6 (0.4)	—	
Fatal myocardial infarction	1 (0.1)	1 (0.1)	—	
Other cardiovascular death	7 (0.5)	6 (0.4)	—	
Sudden death of undetermined origin	6 (0.4)	11 (0.8)	—	
Nonfatal cerebral infarction or stroke of undetermined origin	81 (5.7)	100 (7.0)	—	
Nonfatal acute coronary syndrome	15 (1.0)	23 (1.6)	—	
Urgent coronary revascularization	5 (0.3)	6 (0.4)	—	
Urgent carotid revascularization	3 (0.2)	3 (0.2)	—	
Secondary end points				
Myocardial infarction or urgent coronary revascularization — no. (%)	20 (1.4)	31 (2.2)	0.64 (0.37–1.13)	0.12†
Cerebral infarction or urgent revascularization of carotid or cerebral artery — no. (%)	88 (6.2)	109 (7.6)	0.81 (0.61–1.07)	
Cerebral infarction or TIA — no. (%)	120 (8.4)	139 (9.7)	0.87 (0.68–1.11)	
Any revascularization procedure — no./total no. (%)‡	94/1430 (6.6)	99/1430 (6.9)	0.93 (0.70–1.24)	
Carotid artery	17/94 (18)	23/99 (23)	—	
Coronary artery	44/94 (47)	51/99 (52)	—	
Peripheral artery	33/94 (35)	25/99 (25)	—	
Death — no. (%)				
Cardiovascular cause	22 (1.5)	32 (2.2)	0.69 (0.40–1.18)	
Any cause	88 (6.2)	93 (6.5)	0.97 (0.73–1.30)	
Cerebral infarction or intracranial hemorrhage — no. (%)	103 (7.2)	126 (8.8)	0.82 (0.63–1.07)	
Intracranial hemorrhage — no. (%)	18 (1.3)	13 (0.9)	1.38 (0.68–2.82)	
Newly diagnosed diabetes — no. (%)§	103 (7.2)	82 (5.7)	1.27 (0.95–1.70)	

* The hazard ratio for the primary end point was adjusted for the index event (stroke or transient ischemic attack [TIA]), the time since the index event, sex, and age. Missing values for covariates were handled with the use of a multiple-imputation technique in 37 patients (1.3%). The unadjusted hazard ratio was 0.77 (95% confidence interval [CI], 0.61 to 0.97; P=0.03). Confidence intervals have not been adjusted for multiple comparisons and cannot be used to infer treatment effects.

† P values for additional secondary end points were not calculated after there was no significant between-group difference for the first end point on hierarchical testing.

‡ The percentage of patients who underwent each revascularization procedure has been rounded because the overall denominator of patients in each category is less than 100.

§ Patients in whom diabetes had not been diagnosed at baseline were categorized by investigators as having newly diagnosed diabetes if they had at least two measures of fasting glucose of 126 mg per deciliter (7.0 mmol per liter) or more or a glycated hemoglobin value of 6.5% or more at a follow-up visit. This classification was not adjudicated.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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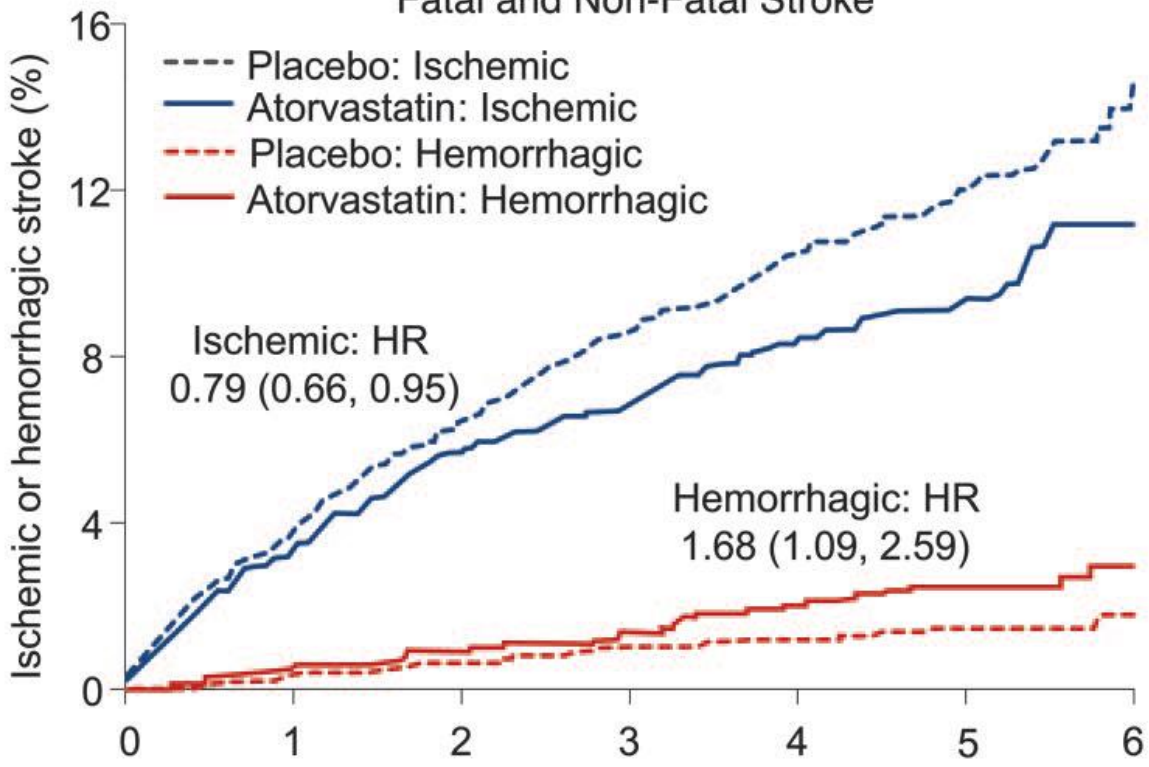


Figure 1. Low-Density Lipoprotein (LDL) Cholesterol Levels over Time.
Shown are median values in the two study groups; I bars indicate 95% confidence intervals. Below the graph, the absolute and percentage reductions in LDL cholesterol level in the evolocumab group are compared with those in the placebo group and are presented as least-squares means or means (details are provided in the Methods section in the Supplementary Appendix). To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.

locumab =13,784)	Placebo (N=13,780)	Hazard Ratio (95% CI)	P Value*
no. of patients (%)			
14 (9.8)	1563 (11.3)	0.85 (0.79–0.92)	<0.001
16 (5.9)	1013 (7.4)	0.80 (0.73–0.88)	<0.001
7 (1.5)	262 (1.9)	0.79 (0.66–0.95)	0.01
1 (1.2)	226 (1.6)	0.75 (0.62–0.92)	
9 (0.21)	25 (0.18)	1.16 (0.68–1.98)	
3 (0.09)	14 (0.10)	0.93 (0.44–1.97)	

- Statin survivors (LDL ~2.3 on moderate-high dose statin at baseline)
- ICH excluded
- Length of follow-up 26 months

Genetically Elevated LDL Associates with Lower Risk of Intracerebral Hemorrhage

Guido J. Falcone, MD, ScD, MPH,[1†] Elayna Kirsch, BA,[1†] Julian N. Acosta, MD,[1]

ANN NEUROL 2020;88:56–66

TABLE 5. MR Analysis of Genetically Instrumented Lipid Levels and Risk of ICH

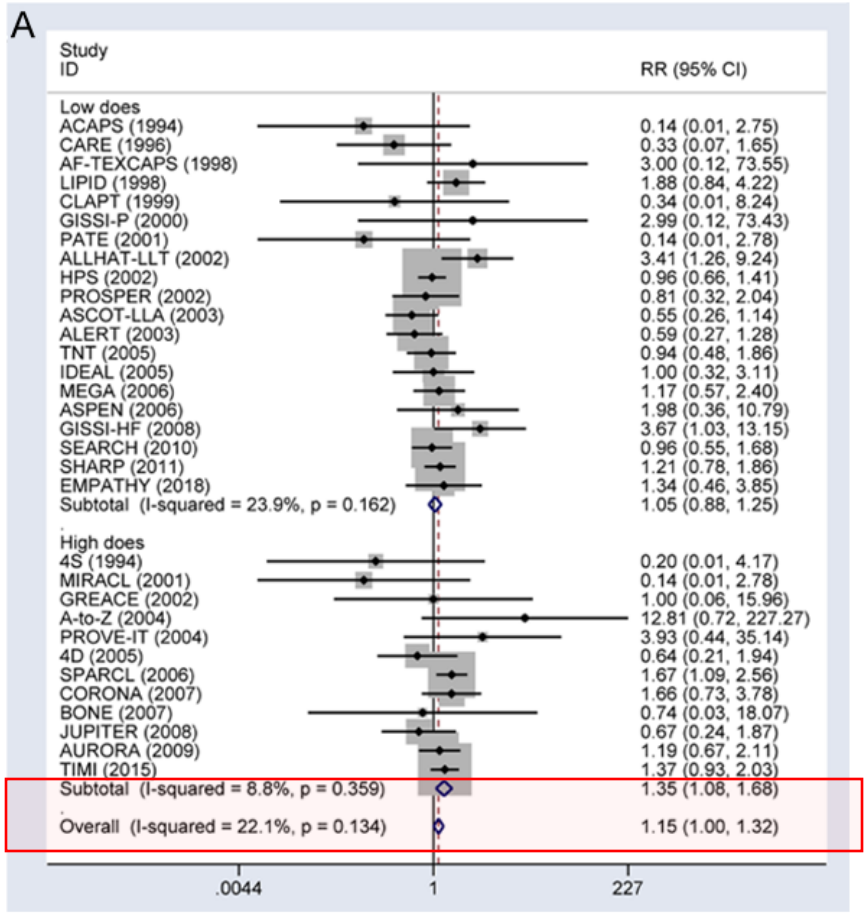
MR method	Instrument	Total cholesterol OR (95% CI)	*p*	LDL cholesterol OR (95% CI)	*p*
Ratio method	Polygenic risk score using on individual level data	0.77 (0.6–0.98)	0.03	0.59 (0.42–0.82)	0.002
IVW	Multiple SNPs using summary level data	0.84 (0.72–0.99)	0.04	0.65 (0.52–0.82)	<0.001

Am J Transl Res 2020;12(2):463-477
www.ajtr.org /ISSN:1943-8141/AJTR0100829

Original Article

Significnt reduction in the LDL cholesterol increases the risk of intracerebral hemorrhage: a systematic review and meta-analysis of 33 randomized controlled trials

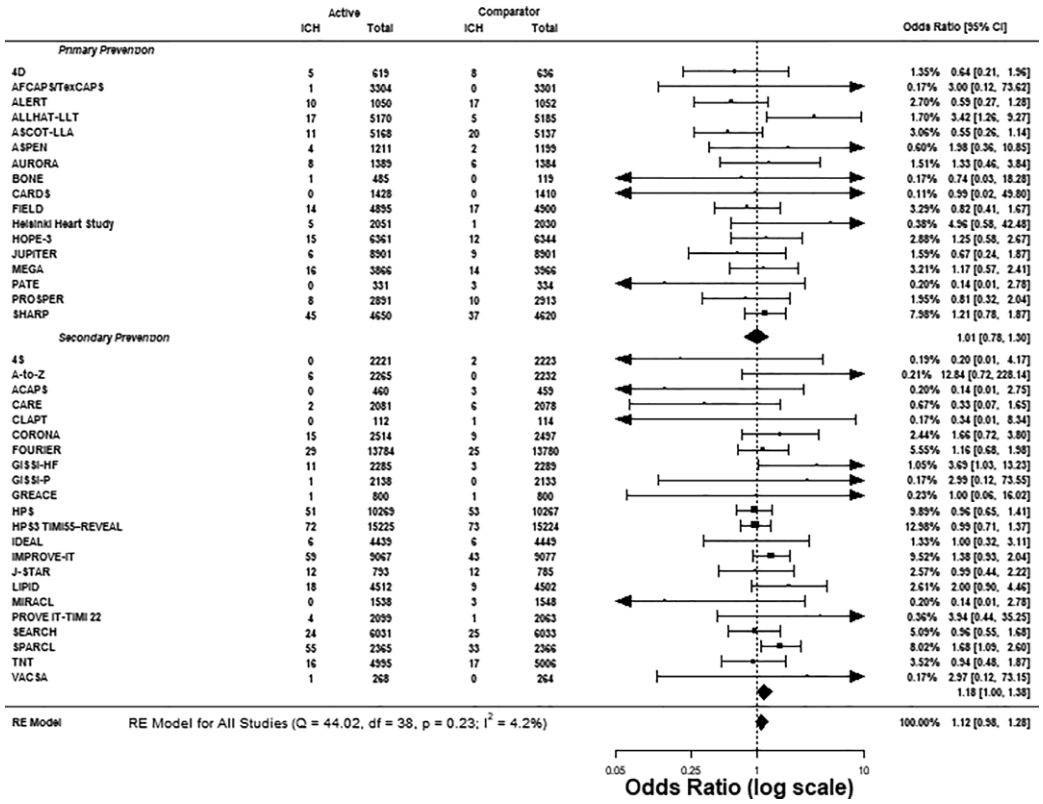
Yao Cheng[2*], Longwei Qiao[3*], Zhibiao Jiang[4*], Xiaofeng Dong[5*], Hongxuan Feng[5], Qian Gui[5], Yaojuan Lu[6], Yuting Liang[1]



Lipid Lowering Therapy, Low-Density Lipoprotein Level and Risk of Intracerebral Hemorrhage – A Meta-Analysis

Conor Judge, MB, BEng,*,†,‡ Sarah Ruttledge, MB,* Maria Costello, MB,*
Robert Murphy, MB,* Elaine Loughlin, MB,* Alberto Alvarez-Iglesias, PhD,*
John Ferguson, PhD,* Sarah Gorey, MB,* Aoife Nolan, PhD,*
Michelle Canavan, MB, PhD,* Martin O'Halloran, BEng, PhD,† and
Martin J. O'Donnell, MB, PhD*

Journal of Stroke and Cerebrovascular Diseases, Vol. 28, No. 6 (June), 2019: pp 1703-1709



Secondary prevention defined as either cardiac or stroke

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

Ther Adv Neurol Disord
2019, Vol. 12: 1–14
DOI: 10.1177/1756286419864830

Ru Jian Jonathan Teoh, Chi-Jung Huang, Chi Peng Chan, Li-Yin Chien, Chih-Ping Chung, Shih-Hsien Sung, Chen-Huan Chen, Chern-En Chiang and Hao-Min Cheng

Secondary prevention confined to stroke patients

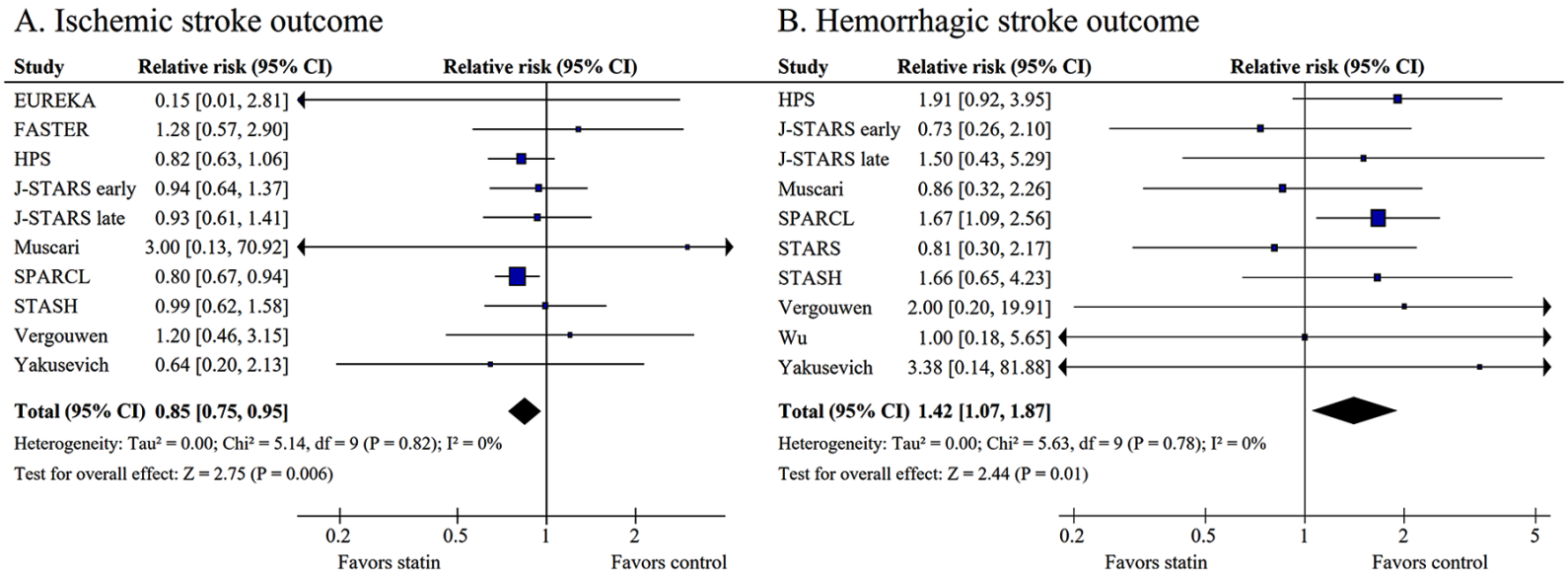


Figure 1. Effects of statin on the risk of ischemic and hemorrhagic stroke in patients with ischemic stroke, transient ischemic attack, or intracerebral hemorrhage. CI, confidence interval; df, degrees of freedom.

Genetically Elevated LDL Associates with Lower Risk of Intracerebral Hemorrhage

Guido J. Falcone, MD, ScD, MPH,[1†] Elayna Kirsch, BA,[1†] Julian N. Acosta, MD,[1]

ANN NEUROL 2020;88:56–66

TABLE 7. Location-Specific Results for ICH risk

	Lobar ICH n = 539 cases			Nonlobar ICH n = 704 cases		
Lipid trait	**OR (95% CI)**	***p***	**Meta-analysis heterogeneity *p***	**OR (95% CI)**	***p***	**Meta-analysis heterogeneity *p***
Polygenic risk score analysis[a]						
Total cholesterol	0.89 (0.80–0.99)	0.03	0.42	0.94 (0.85–1.08)	0.20	0.96
LDL cholesterol	0.81 (0.73–0.89)	<0.001	0.96	0.90 (0.82–0.99)	0.04	0.99
Mendelian randomization analysis[b]						
Total cholesterol	0.70 (0.51–0.96)	0.03	–	0.73 (0.62–1.11)	0.20	–
LDL cholesterol	0.41 (0.27–0.64)	<0.001	–	0.66 (0.44–0.97)	0.04	–

[a]Inverse variance fixed effects meta-analysis of logistic regression results for intracerebral hemorrhage (ICH) across Genetics of Cerebral Hemorrhage with Anticoagulation (GOCHA), International Stroke Genetics Consortium ICH (ISGC-ICH) genomewide association study (GWAS), and Genetic and Environmental Risk Factors for Hemorrhagic Stroke (GERFHS). For each study, the logistic regression model used ICH risk as the dependent variable and a polygenic risk score as the independent variable, adjusting for age, sex, and 4 principal components. The PRS were normalized and entered to the model as a continuous predictor. The OR represents the change in the odds of ICH per each additional SD of the PRS.

[b]Mendelian randomization results of genetically instrumented cholesterol levels using a polygenic risk score as the instrument. Each lipid fraction-specific analysis utilized the ratio method, taking the effect estimates for ICH ~ PRS (numerator) and lipid level ~ PRS (denominator).

CI = confidence intervals; ICH = intracerebral hemorrhage; LDL = low-density lipoprotein.; OR = odds ratio; PRS = polygenic risk score.

Original Contribution

Apolipoprotein E, Statins, and Risk of Intracerebral Hemorrhage

Daniel Woo, MD, MS; Ranjan Deka, PhD; Guido J. Falcone, MD, MPH; Matthew L. Flaherty, MD; Mary Haverbusch, RN, BSN; Sharyl R. Martini, MD, PhD; Steven M. Greenberg, MD, PhD; Alison M. Ayres, BA; Laura Sauerbeck, RN, MS; Brett M. Kissela, MD, MS; Dawn O. Kleindorfer, MD; Charles J. Moomaw, PhD; Christopher D. Anderson, MD; Joseph P. Broderick, MD; Jonathan Rosand, MD, MS; Carl D. Langefeld, PhD; Jessica G. Woo, PhD, MHSA

(*Stroke*. 2013;44:00-00.)

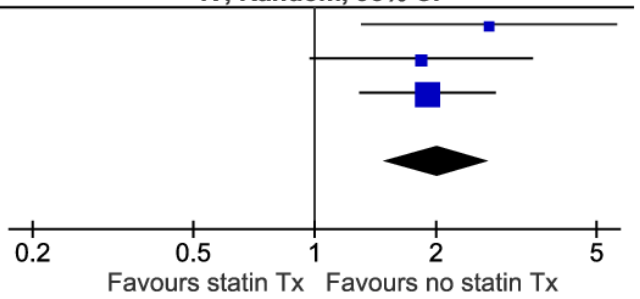
Statins and Lobar CMBs

c

Study or Subgroup	Statin treatment Events	Total	No statin treatment Events	Total	Weight	Odds Ratio IV, Random, 95% CI
Haussen et al, 2012	23	40	41	123	17.2%	2.71 [1.30, 5.62]
Martí-Fàbregas et al, 2018	23	193	19	277	22.6%	1.84 [0.97, 3.48]
Romero et al, 2014	49	606	60	1359	60.2%	1.90 [1.29, 2.81]
Total (95% CI)		**839**		**1759**	**100.0%**	**2.01 [1.48, 2.72]**
Total events	95		120			

Heterogeneity: Tau² = 0.00; Chi² = 0.79, df = 2 (P = 0.68); I² = 0%

Test for overall effect: Z = 4.51 (P < 0.00001)



Katsanos et al. 2020 Under review

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

Results of Base Case Decision Analysis

Prior ICH Location	Setting Effectiveness (QALYs)	No Statin	Statin RR 1.68
Lobar ICH	Primary prevention	6.8	4.6
	Prior MI	6.2	4.4
	Prior ischemic stroke	6.0	4.2
Deep ICH	Primary prevention	13.0	12.2
	Prior MI	11.2	11.0
	Prior ischemic stroke	10.6	10.3

For statin therapy to be favored, the RR of ICH would need to be less than or equal to 1.03 for primary prevention, 1.07 for secondary prevention after MI, and 1.06 for secondary prevention after ischemic stroke.

Other lipid lowering agents

- **Ezetimibe:** reduces LDL 15-20%. 20% RRR on MACE
- **Niacin:** reduces LDL by 12%/triglycerides 29%. 26% RRR in stroke
- **Icosapent ethyl:** 18% reduction in triglyceride. No evidence for benefit as monotherapy. Suggestion of perhaps excess bleeding and pleiotropic antiplatelet effect.
- **Fibrates:** No benefit as monotherapy. Pleiotropic antithrombotic therapies, including inhibition of tissue factor.

Canadian Stroke Best Practice Recommendations: Management of Spontaneous ICH

- There is no role for statin therapy in the secondary prevention of ICH. Statin therapy should not be initiated for secondary prevention of intracerebral hemorrhage [Evidence Level C].

- For intracerebral hemorrhage patients who have a clear concomitant indication for cholesterol lowering treatment, statin therapy should be individualized and should take into account the patient's overall thrombotic risk as well as the possibility of increased ICH risk with statin therapy.

Clinical Considerations

- An ongoing clinical trial (SATURN) addressing this question may potentially inform clinical decision-making for these patients. Until these results are available, decisions regarding statin therapy should be made based on risk/benefit ratio in consultation with an expert in cerebrovascular disease.

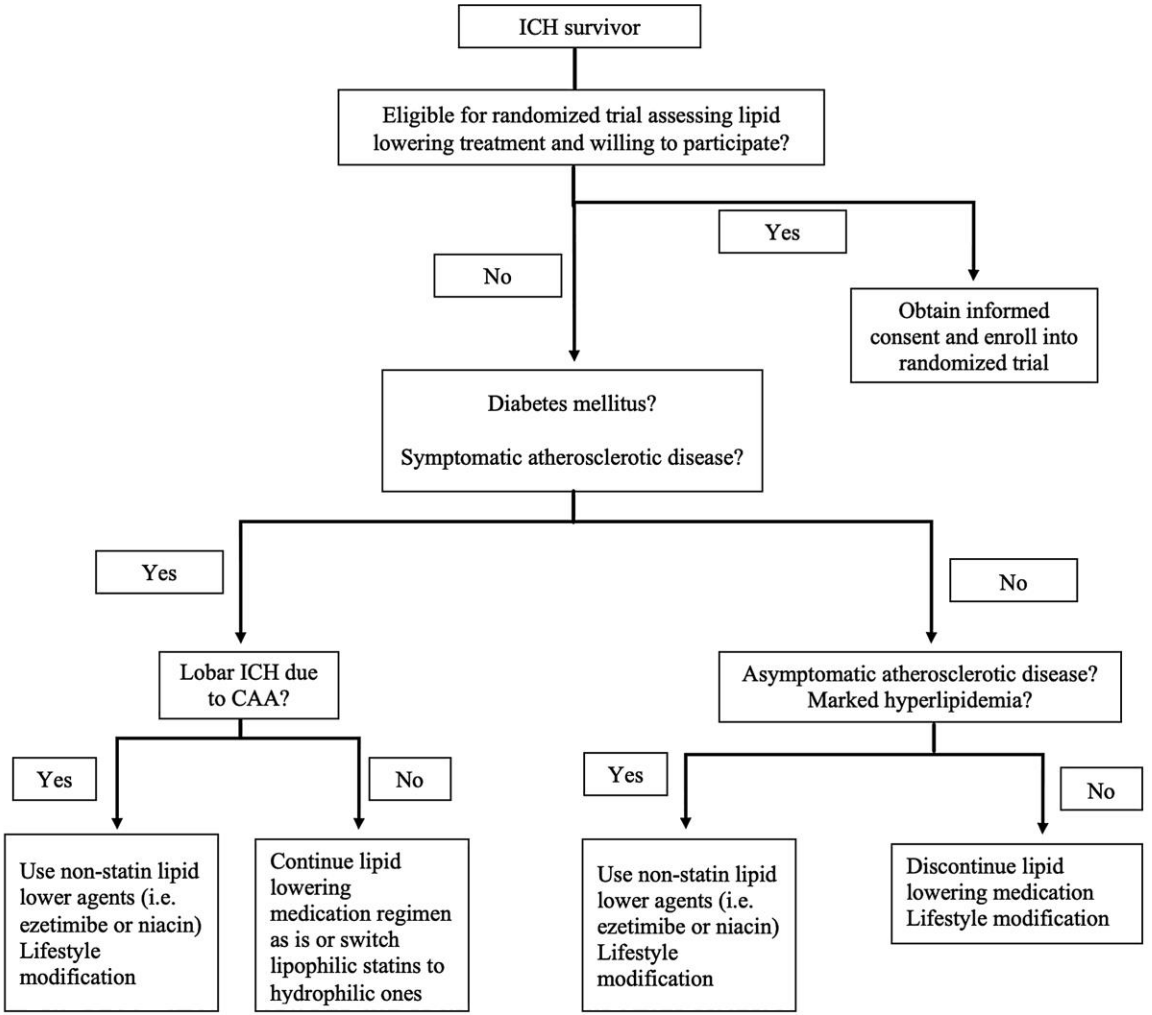
Shoamanesh et al. Int J Stroke. 2020

Stroke

FOCUSED UPDATES

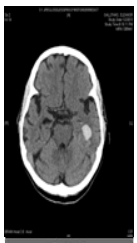
Use of Lipid-Lowering Drugs After Intracerebral Hemorrhage

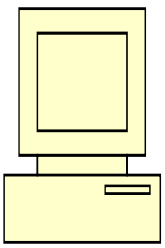
Ashkan Shoamanesh, MD; Magdy Selim, MD, PhD



Stroke. 2022;53:2161–2170. DOI: 10.1161/STROKEAHA.122.036889

Study Procedures





Randomization

D/C

1, 2, 3, 6, 9, 12, 18, 24 months*

Screening

APOE

- ✓ Inclusion
- ✓ Exclusion

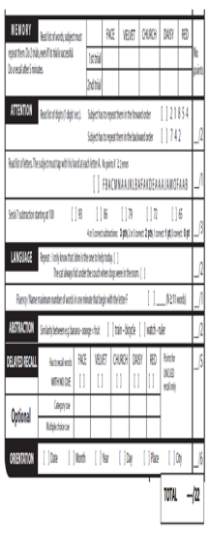
- ✓ ICH score
- ✓ NIH

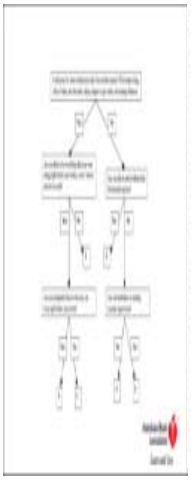
- ✓ mRS
- ✓ NIHSS

- ✓ MACCE; SAEs; mRS;
TMoCA; QoL (EQ-5D); Review of prescription refills; Pill count; BP reporting

*All follow-up assessmen[illegible]rmed 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.





ORIGINAL ARTICLE

Statin treatment and accrual of covert cerebral ischaemia on neuroimaging: a systematic review and meta-analysis of randomized trials

A. H. Katsanos[a], V.-A. Lioutas[b], A. Charidimou[c], L. Catanese[a], K. K. H. Ng[a], K. Perera[a], D. de Sa Boasquevisque[a], G. Tsivgoulis[d,e], E. E. Smith[f], M. Sharma[a], M. H. Selim[b] and A. Shoamanesh[a]

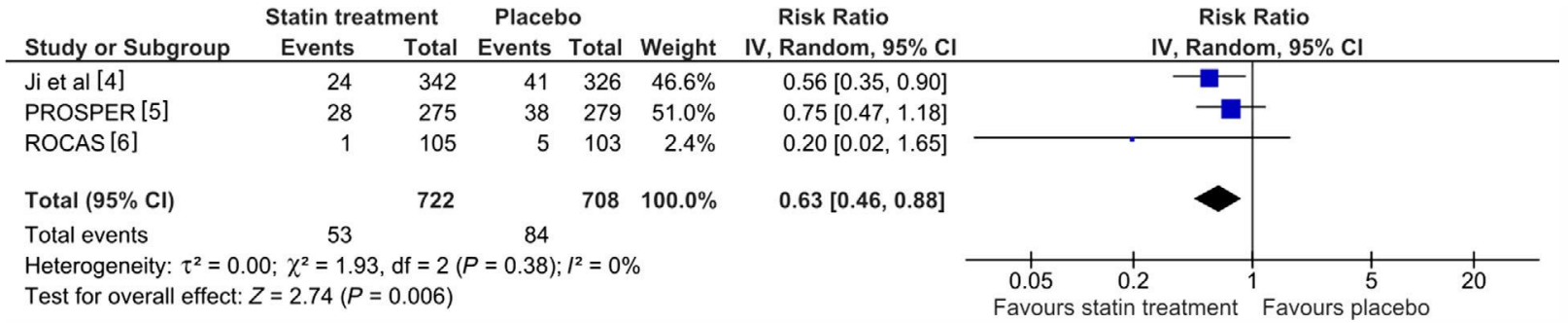
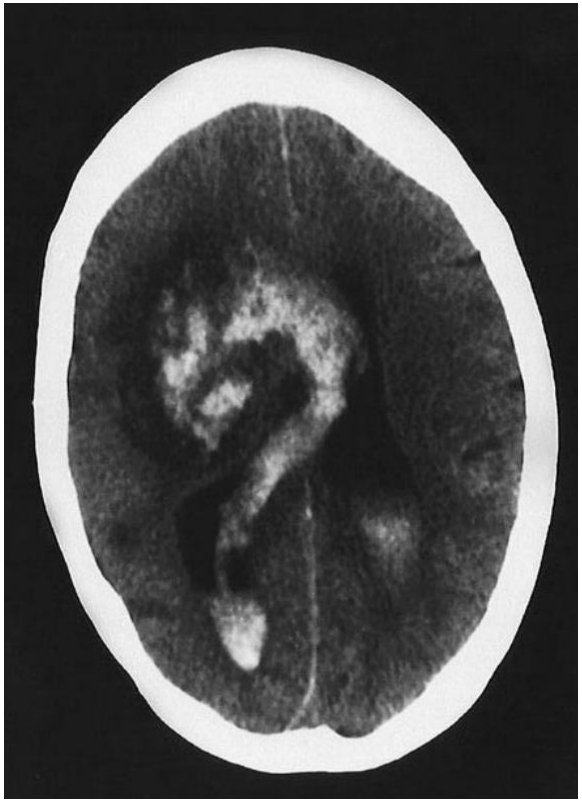


Figure 1 Risk of incident covert brain ischaemic infarcts in follow-up neuroimaging between individuals randomized to statin treatment or placebo. [Colour figure can be viewed at wileyonlinelibrary.com]

Conclusion

- Statins and lower cholesterol levels have been associated with greater risk of ICH – and likely play a causal role
  - Mendelian randomization and RCT meta-analyses
- The heterogeneity in the literature likely reflects heterogeneity in populations, study design, and residual confounding
- By targeting a lobar ICH population at high risk of recurrence, SATURN will likely be a landmark trial that answers the unresolved clinical question of statin continuation post ICH.

Questions?



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