

The novel strategy to improve cardiovascular outcomes in primary prevention of stroke



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Stroke and Dyslipidemia

Stroke in Korea

Dyslipidemia fact sheet in Korea

Lipid lowering agents for ischemic stroke

Guidelines

Role of Weak Statin ?

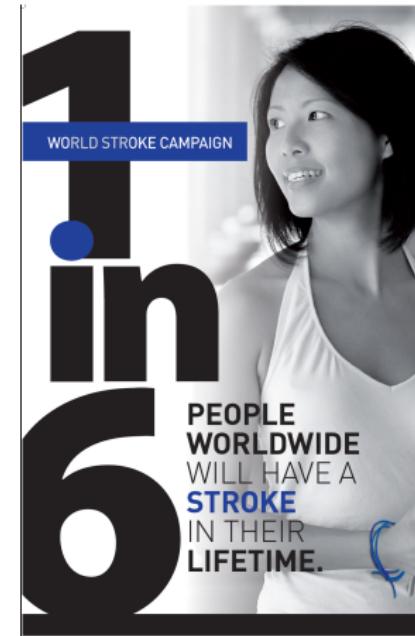
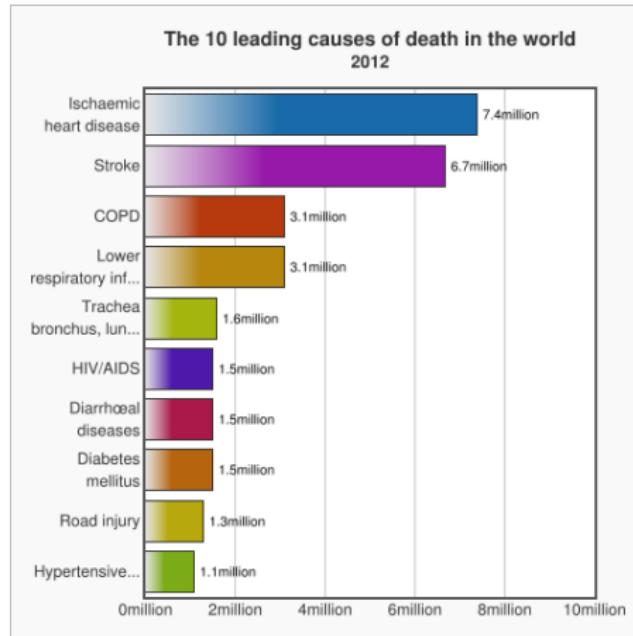
Statin in Lacunar Infarction ?

LDL-C or Statin?

Statin in Intermediate-Risk Patients ?

Summary

Global burden of stroke



Future life expectancy in 35 industrialised countries: projections with a Bayesian model ensemble



Vassilis Kontis*, James E Bennett*, Colin D Mather, Guangguan Li, Kyle Foreman, Majid Ezzati

Summary

Background Projections of future mortality and life expectancy are needed to plan for health and social services and

Lancet 2012; 380: 1323–35

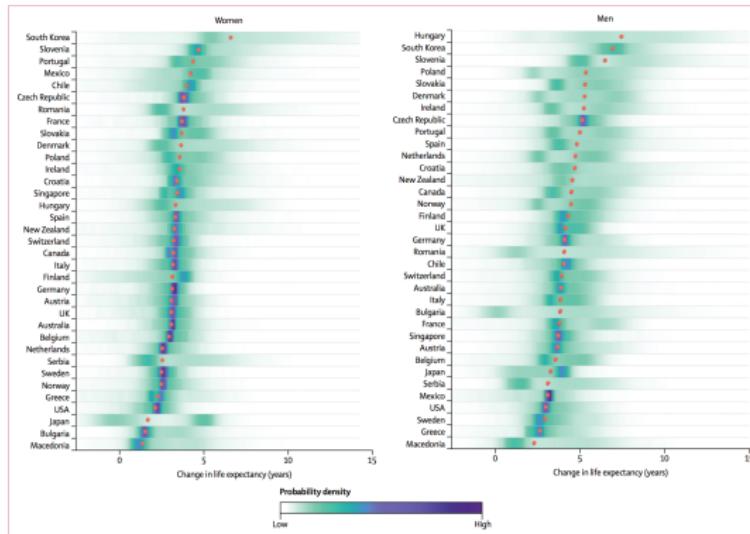
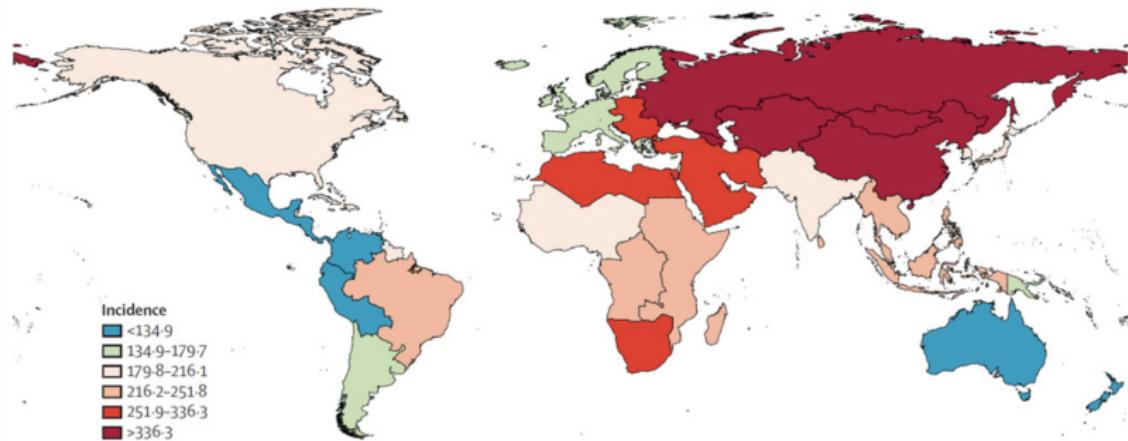


Figure 1: Posterior distribution of projected change in life expectancy at birth from 2010 to 2030
Red dots show the posterior medians. Countries are ordered vertically by median projected increase from largest (at the top) to smallest (at the bottom).

There is a **90% probability that life expectancy at birth among South Korean women in 2030 will be higher than 86 · 7 years, and a 57% probability that it will be higher than 90 years.**

There is a **greater than 95% probability that life expectancy at birth among men in South Korea, Australia, and Switzerland will surpass 80 years in 2030, and a greater than 27% probability that it will surpass 85 years.**

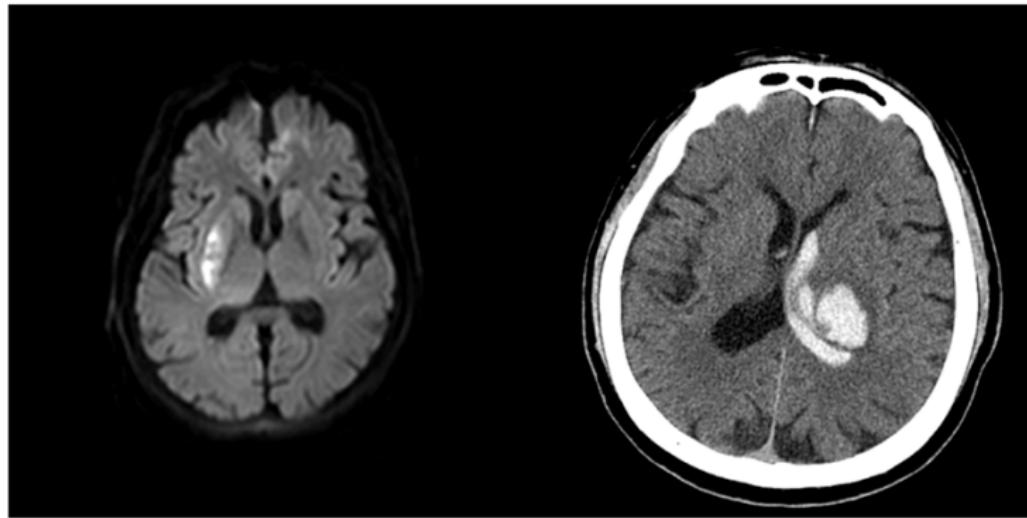
Age-standardised stroke incidence per 100 000 person-years for 2010



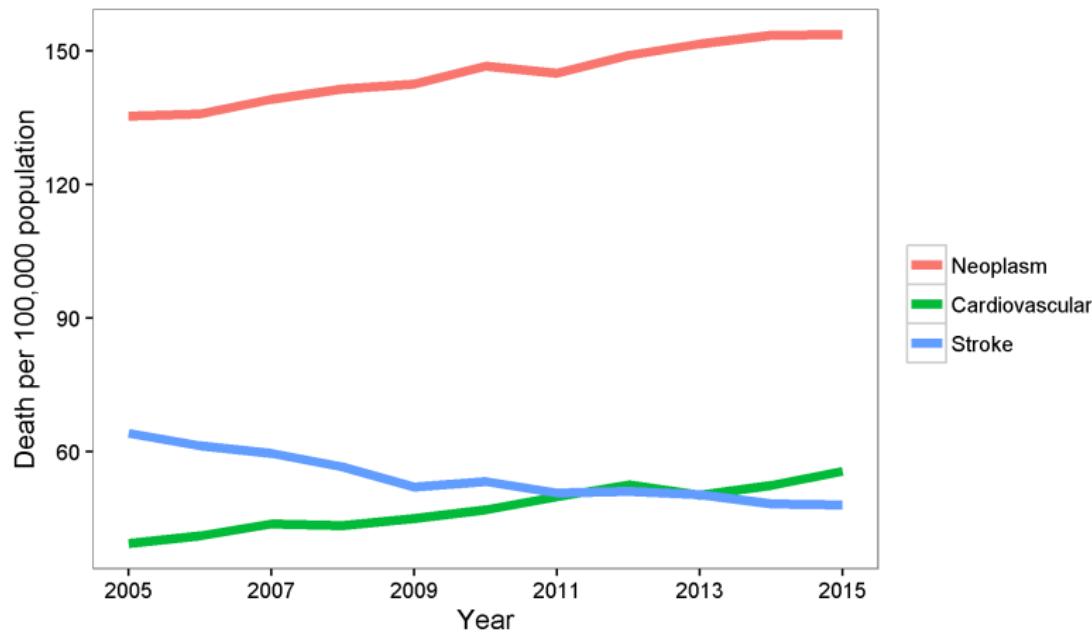
Statin in Stroke

└ Stroke and Dyslipidemia

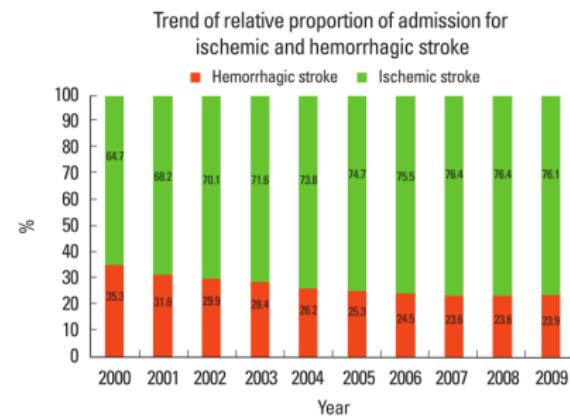
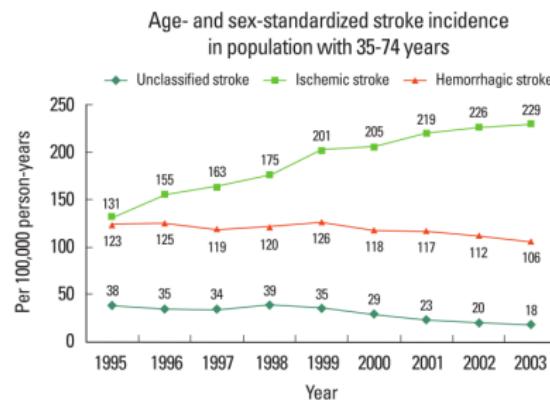
└ Stroke in Korea



Secular trend of mortality in Korea



Incidence of stroke is increasing



Etiologies of stroke

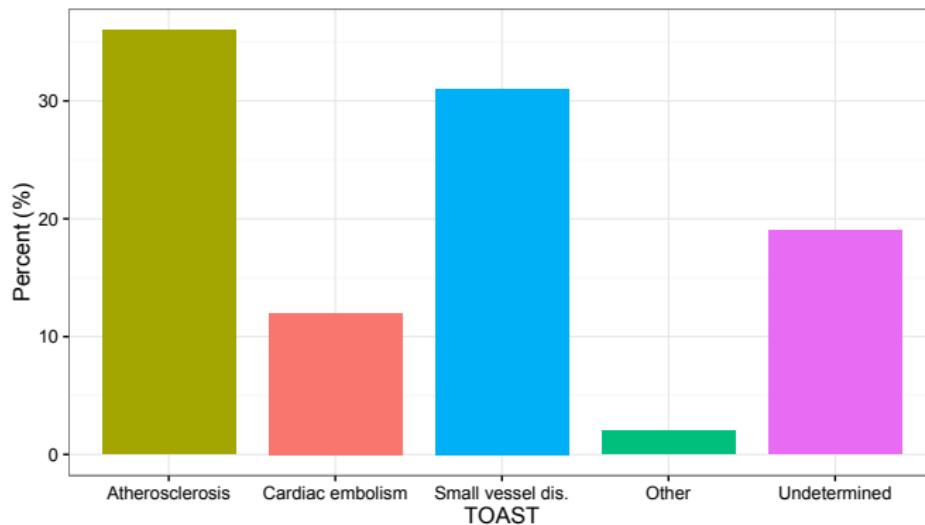
Ischemic Stroke

- ▶ Atherosclerosis
- ▶ Small artery occlusion
- ▶ Cardiac disease causing embolism
- ▶ Other causes such as moyamoya disease

Hemorrhagic Stroke

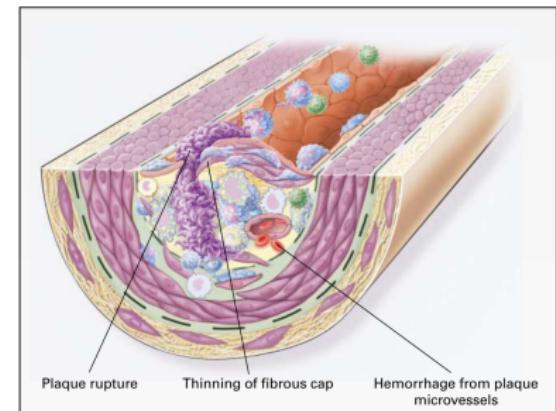
- ▶ Hypertensive hemorrhage
- ▶ Cerebral amyloid angiopathy
- ▶ Arteriovenous malformations
- ▶ Subarachnoid hemorrhage

Ischemic stroke in Korea: Analysis of 10,861 cases in Korean Stroke Registry



Atherosclerosis: Leading cause of ischemic stroke

- ▶ Artery wall thickens as a result of invasion and accumulation of white blood cells with cholesterol fatty substances, calcium and fibrin.
- ▶ Intima of medium and large sized systemic arteries are involved.



Risk factors for Stroke

Non-modifiable factors

1. Age
2. Sex
3. Race
4. Family history

Modifiable factors

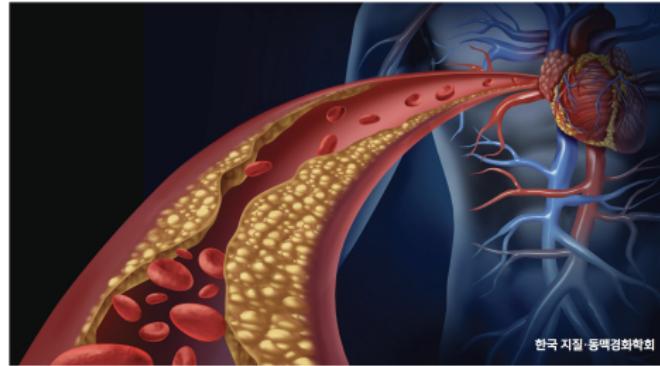
1. Hypertension
2. Diabetes
3. **Dyslipidemia**
4. Smoking
5. Carotid disease
6. Cardiac disease such as atrial fibrillation
7. Obesity
8. Inactivity

Statin in Stroke

└ Stroke and Dyslipidemia

└ Dyslipidemia fact sheet in Korea

DYSLIPIDEMIA FACT SHEET IN KOREA 2015

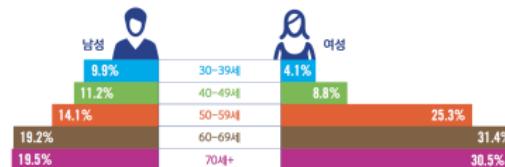


고LDL콜레스테롤혈증

- 고LDL콜레스테롤혈증은 연령에 따라 증가하는 추세를 보이는데 60대 이상 성인에서 남자는 5명 중 1명, 여자는 3명 중 1명으로 많음.
- 여성의 경우 50대가 되면 30대보다 6배, 40대보다 3배가량 급증.

**1
3**

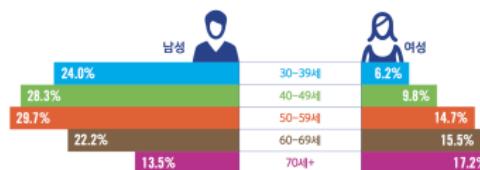
60대 이상 여성



고증성지방혈증

×4

30대 남성



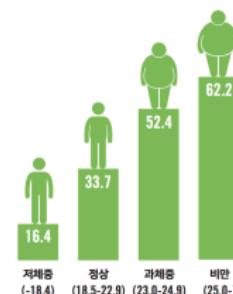
비만도에 따른 이상지질혈증

- 정상 체중 범위에서도 3명 중 1명이 이상지질혈증을 동반하며
과체중 이상 비만하거나 복부비만이 있으면 절반 이상이 이상지질혈증을 가지고 있음.
- 특히 복부비만이 있는 경우에 3명 중 2명이 이상지질혈증을 동반하고 있음.

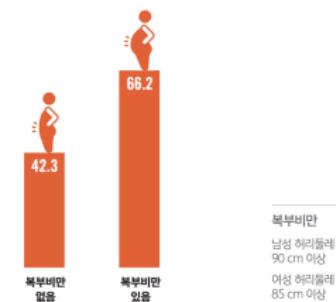
**2
3**

복부비만인 경우

비만도(체질량지수)에 따른 유병률(%)



복부비만에 따른 유병률(%)

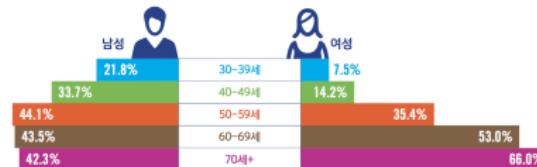


대사증후군의 유병률

- 30세 이상 성인 3명 중 1명이 대사증후군임. 남성은 50대까지 여성보다 2~3배 더 많고 여성은 50대에 2배로 급증한 후 지속적으로 증가함.

**1
—
3**

30세 이상 성인



다음 5가지 중 3가지 이상에 해당하면 대사증후군으로 정의

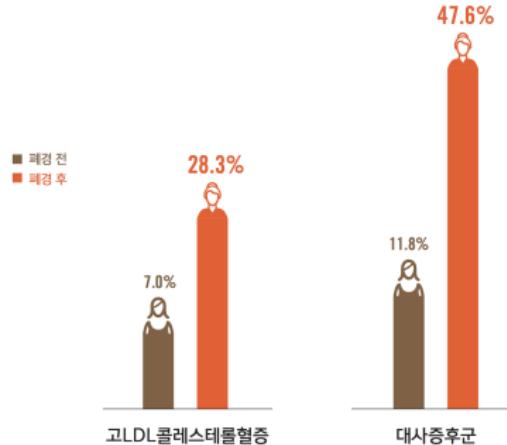
복부비만, 골짜기당 100 mg/dL 이상 혹은 당뇨병 기왕력, 혈압 130/85 mmHg 이상 혹은 고혈압 기왕력,
증상지방 150 mg/dL 이상, HDL콜레스테롤 40mg/dL 미만(남자) 혹은 50 mg/dL 미만(여자)

폐경에 따른
고LDL콜레스테롤혈증 및
대사증후군 유병률

×4

폐경 후

- 고LDL콜레스테롤혈증 및 대사증후군이 폐경 전에 비해 폐경 후 4배까지 증가함.



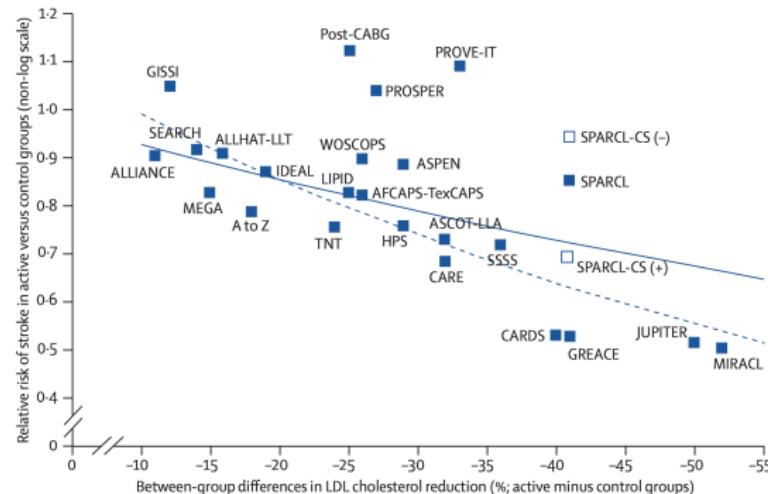
혈청지질 수준

 189
 192

- 30세 이상 성인의 총콜레스테롤 평균 수치는 남성 189 mg/dL, 여성 192 mg/dL 이다.

지질 종류	평균	분위수						
		5	10	25	50	75	90	95
남성								
총콜레스테롤	189	133	145	166	187	209	233	249
중성지방	172	54	66	90	130	194	286	385
HDL콜레스테롤	45	30	33	37	43	50	57	63
LDL콜레스테롤	114	63	72	93	113	134	155	168
여성								
총콜레스테롤	192	139	149	168	189	215	241	258
중성지방	121	44	52	70	101	150	210	267
HDL콜레스테롤	50	35	37	43	50	57	64	70
LDL콜레스테롤	118	73	81	96	116	140	160	175

Stroke incidence and LDL-C reduction



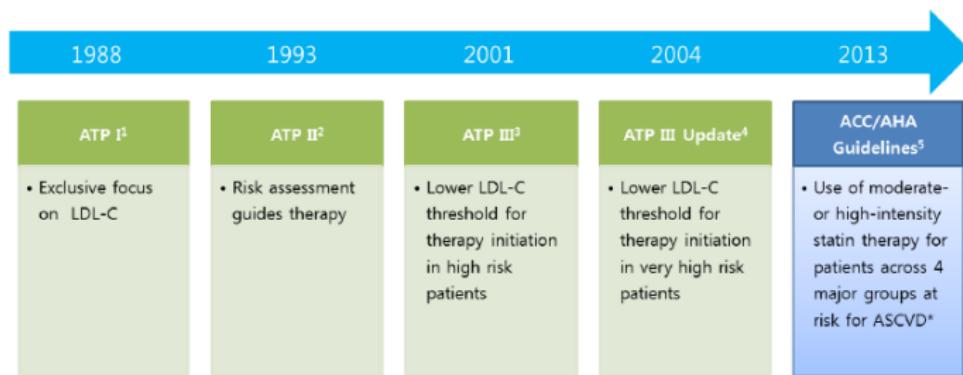
Estimates of relative risk reduction

- 10% LDL reduction: relative risk reduction 7.5% (2.3-12.5) overall
relative risk reduction 13.5% (7.7-18.8) for primary prevention of stroke
- 1 mmol/L (39 mg/dL) LDL reduction: relative risk reduction 21.1% (6.3-33.5) overall
relative risk reduction 35.9% (21.7-47.6) for primary prevention of stroke

Statin in Stroke

└ Lipid lowering agents for ischemic stroke

└ Guidelines



1. NCEP. *Arch Intern Med*. 1988;148:36-59. 2. NCEP ATP II. *Circulation*. 1994;89:1333-445. 3. NCEP ATP III. *Circulation*. 2002;106:3143.

4. Grundy SM, et al. *Circulation*. 2004;110:227-239. 5. Stone NJ, et al. *J Am Coll Cardiol*. 2013. doi:10.1016/j.jacc.2013.11.002. Available at: <http://content.onlinelibrary.wiley.com/article.aspx?articleId=1770217>. Accessed November 13, 2013.

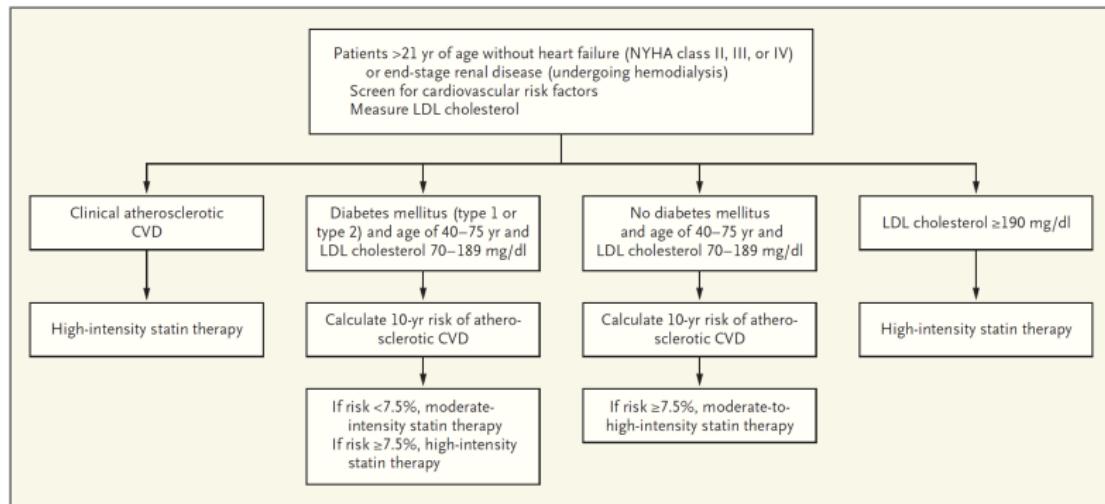
Statin in Stroke

└ Lipid lowering agents for ischemic stroke

└ Guidelines

2013 ACC/AHA Guideline on the Tx of Blood Chol. to Reduce Atherosclerotic CV Risk in Adults

my.americanheart.org/cvriskcalculator



Statin in Stroke

└ Lipid lowering agents for ischemic stroke

└ Guidelines

2013 ACC/AHA Guideline on the Tx of Blood Chol. to Reduce Atherosclerotic CV Risk in Adults

Table 1. High-Intensity and Moderate-Intensity Statin Therapy, According to 2013 American College of Cardiology–American Heart Association (ACC-AHA) Cholesterol Guidelines.

High-intensity statin therapy

Daily dose lowers LDL cholesterol level by approximately $\geq 50\%$ on average

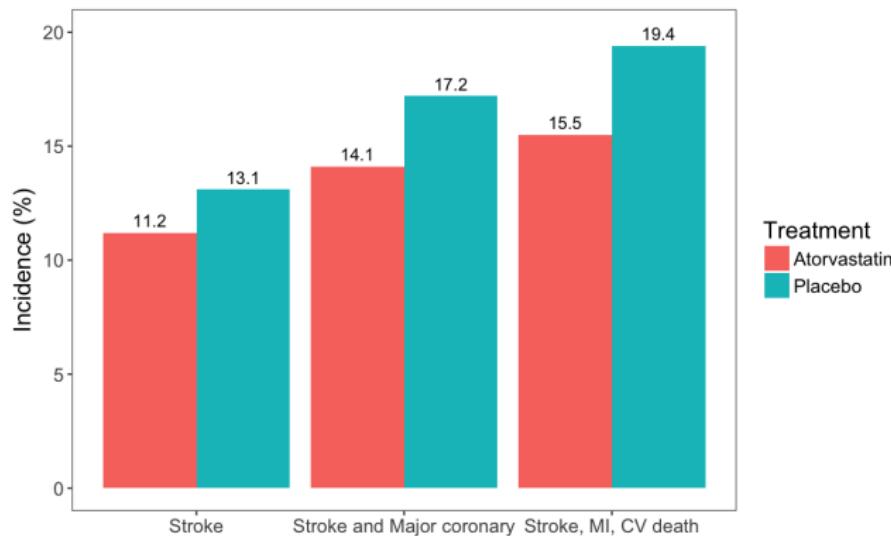
Recommended: atorvastatin, 40 to 80 mg; rosuvastatin, 20 to 40 mg

Moderate-intensity statin therapy

Daily dose lowers LDL cholesterol level by approximately 30 to $< 50\%$ on average

Recommended: atorvastatin, 10 to 20 mg; rosuvastatin, 5 to 10 mg; simvastatin, 20 to 40 mg; pravastatin, 40 to 80 mg; lovastatin, 40 mg; extended-release fluvastatin, 80 mg; fluvastatin, 40 mg twice a day; pitavastatin, 2 to 4 mg

SPARCL: Atorvastatin 80mg vs. placebo

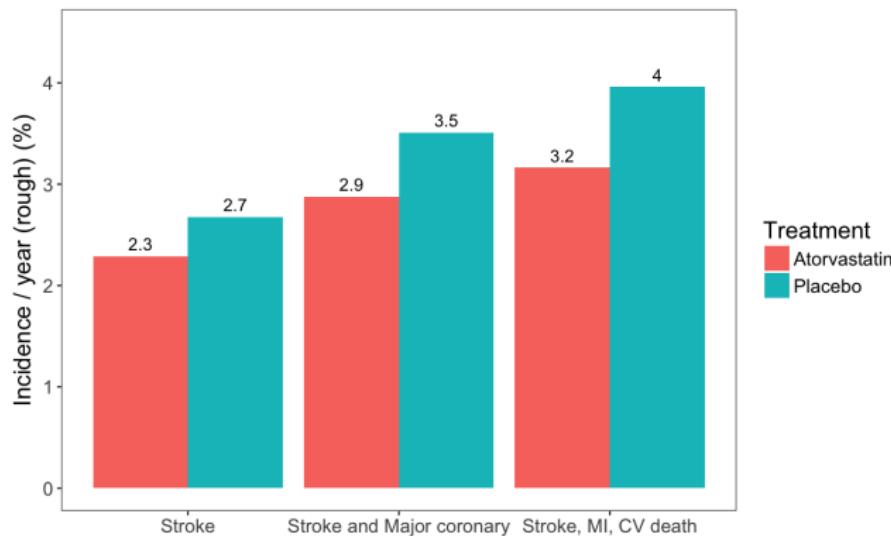


Statin in Stroke

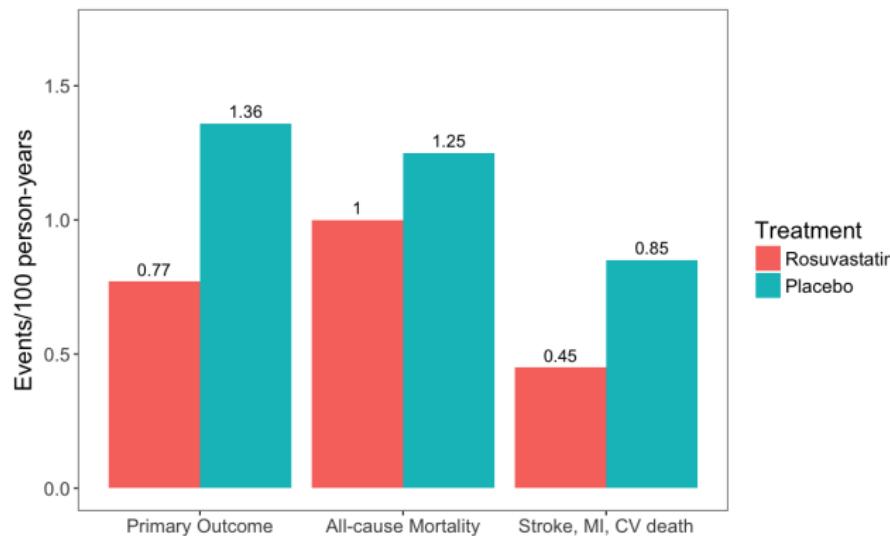
└ Lipid lowering agents for ischemic stroke

└ Guidelines

SPARCL: Atorvastatin 80mg vs. placebo



JUPITER: Rosuvastatin 20mg vs. placebo



The Japan Statin Treatment Against Recurrent Stroke (J-STARS): a multicenter, randomized, open-label, parallel-group study

EMBARGOED FOR 11:30 am CT, FRIDAY, FEB. 13, 2015

Masayasu Matsumoto¹, Naohisa Hosomi¹, Yoji Nagai², Tatsuo Kohriyama³, Shiro Aoki¹, Chiaki Yokota⁴, Kazuo Kitagawa⁵, Yasuo Terayama⁶, Makoto Takagi⁷, Setsuro Ibayashi⁸, Masakazu Nakamura⁴, Hideki Origasa⁹, Masanori Fukushima², Etsuro Mori¹⁰, Kazuo Minematsu⁴, Shinichiro Uchiyama¹¹, Yukito Shinohara¹², Takenori Yamaguchi⁴; for the J-STARS collaborators

1)Department of Clinical Neuroscience and Therapeutics, Hiroshima University Graduate School of Biomedical and Health Sciences, Hiroshima, Japan

2)Foundation for Biomedical Research and Innovation Translational Research Informatics Center, Kobe, Japan

3)Hiroshima City Rehabilitation Hospital, Hiroshima, Japan

4)National Cerebral and Cardiovascular Center, Suita, Japan

5)Department of Neurology, Tokyo Women's Medical University School of Medicine, Tokyo, Japan

6)Department of Neurology, Iwate Medical University, Morioka, Japan

7)Department of Neurology, Tokyo Seiseikai Central Hospital, Tokyo, Japan

8)Seirai Rehabilitation Hospital, Fukuoka, Japan

9)Division of Biostatistics and Clinical Epidemiology, University of Toyama Graduate School of Medicine and Pharmaceutical Sciences, Toyama, Japan

10)Department of Behavioral Neurology and Cognitive Neuroscience, Tohoku University Graduate School of Medicine, Sendai, Japan

11)Clinical Research Center, International University of Health and Welfare, Center for Brain and Cerebral Vessels, Sanno Hospital and Sanno Medical Center, Tokyo, Japan

12)Federation of National Public Service Personnel Mutual Aid Associations Tachikawa Hospital, Tokyo, Japan

Design of J-STARS

Randomized Controlled Trial
PROBE method

Enrollment Criteria

- Ischemic Stroke
1 month~3 yrs ago
- TC 180~240mg/dl
- >45 yrs, <80 yrs

Exclusion Criteria

- Cardioembolic Stroke

Pravastatin
10mg/day

Non-Statin

5-6 years Follow-up

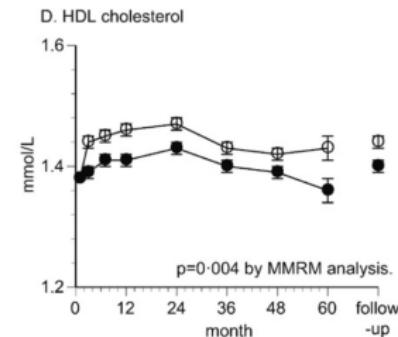
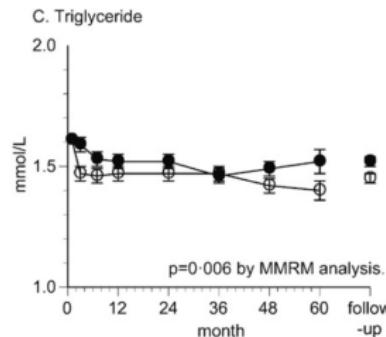
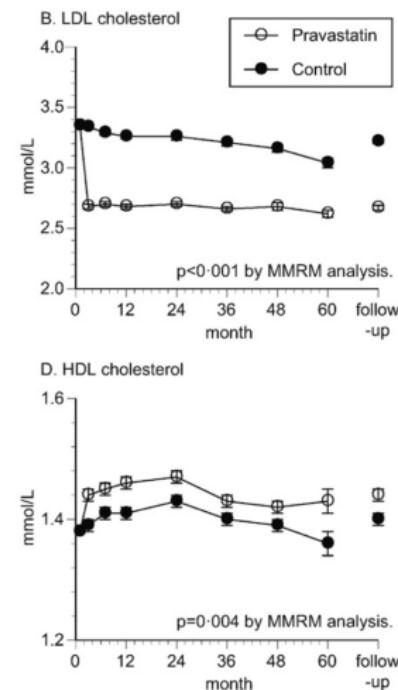
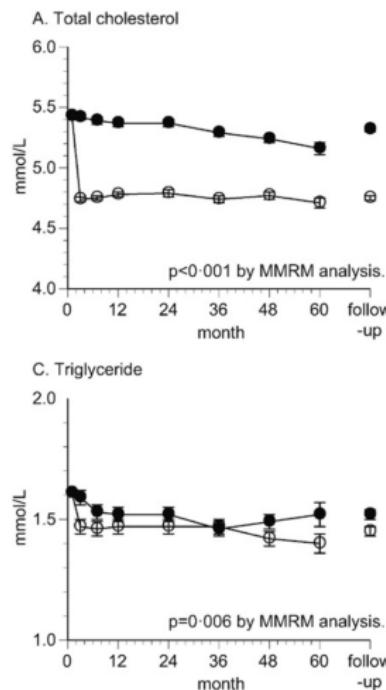
Primary Endpoint: Stroke Recurrence

A total of 1578 patients were enrolled and completed follow-up.
(originally this study was designed to recruit 3000 patients).

Statin in Stroke

Lipid lowering agents for ischemic stroke

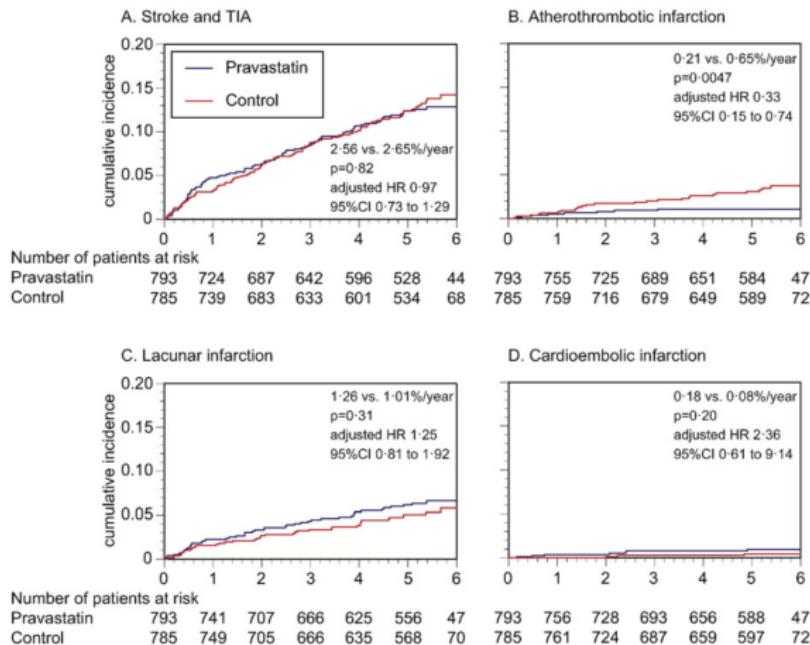
Role of Weak Statin ?



Statin in Stroke

Lipid lowering agents for ischemic stroke

Role of Weak Statin ?



Statin in Stroke

└ Lipid lowering agents for ischemic stroke

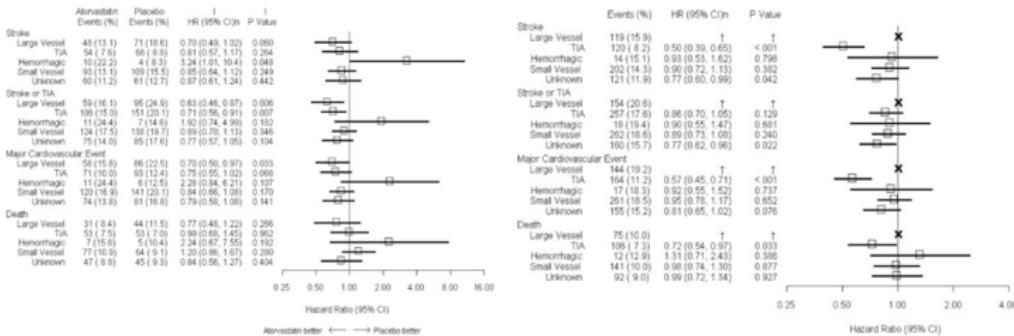
└ Statin in Lacunar Infarction ?

Statin in Lacunar infarction ?

The Answer is “Maybe Yes”

Results of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Trial by Stroke Subtypes

Pierre Amarenco, MD; Oscar Benavente, MD; Larry B. Goldstein, MD; Alfred Callahan III, MD;
Henrik Sillesen, MD, DMSc; Michael G. Hennerici, MD, PhD; Steve Gilbert, PhD;
Amy E. Rudolph, PhD; Lisa Simunovic, MS; Justin A. Zivin, MD, PhD;
K. Michael A. Welch, MB, ChB, FRCP; on behalf of the SPARCL Investigators



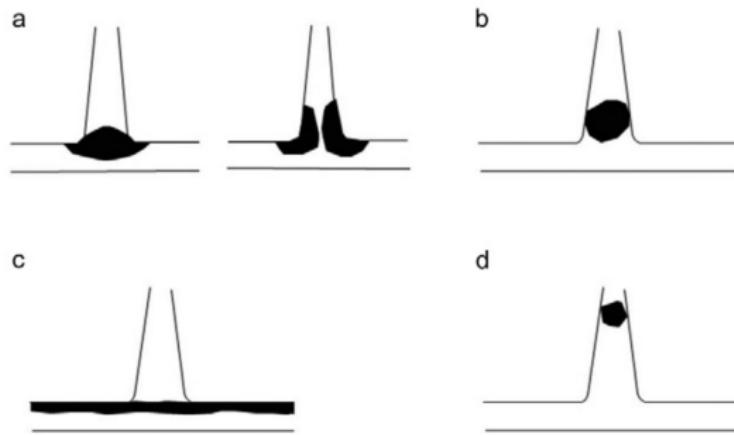
Conclusions—Atorvastatin 80 mg/d is similarly efficacious in preventing strokes and other cardiovascular events, irrespective of baseline ischemic stroke subtype. (*Stroke*. 2009;40:1405-1409.)

Statin in Stroke

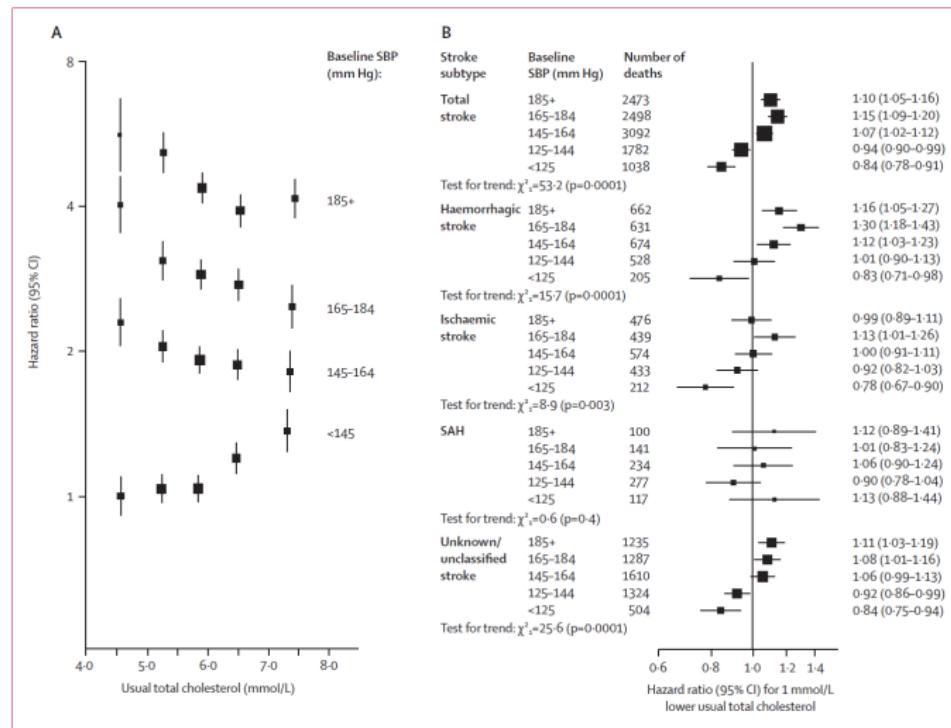
└ Lipid lowering agents for ischemic stroke

└ Statin in Lacunar Infarction ?

Statin might be useful in branchatheromatous disease



Hypertension should be strictly controlled

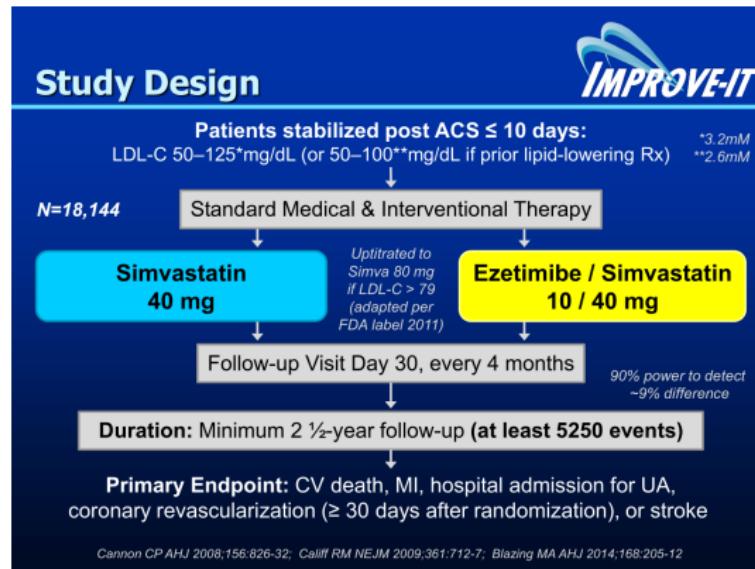


Statin in Stroke

└ Lipid lowering agents for ischemic stroke

└ LDL-C or Statin?

IMPROVE-IT

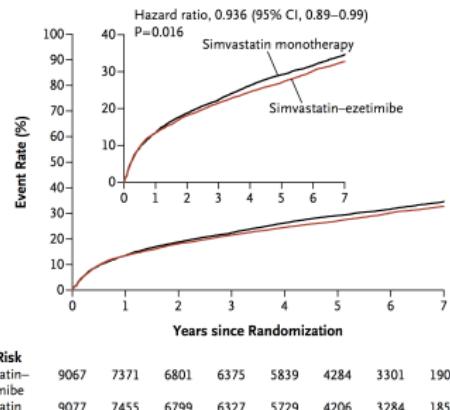


Statin in Stroke

└ Lipid lowering agents for ischemic stroke

└ LDL-C or Statin?

Drugs	LDL-C	Primary outcome	Stroke, MI, CV death
Simvastatin-ezetimibe	53.7 mg/dL	32.7%	20.4 %
Simvastatin	69.5 mg/dL	34.7%	22.2 %



Statin in Stroke

Lipid lowering agents for ischemic stroke

LDL-C or Statin?

Outcome	Simvastatin Monotherapy (N=9077)	Simvastatin– Ezetimibe (N=9067)	Hazard Ratio (95% CI)	P Value
no. of patients (%)				
Primary end point: death from cardiovascular causes, major coronary event, or nonfatal stroke	2742 (34.7)	2572 (32.7)	0.936 (0.89–0.99)	0.016
Secondary end points				
Death from any cause, major coronary event, or nonfatal stroke	3246 (40.3)	3089 (38.7)	0.95 (0.90–1.0)	0.03
Death from coronary heart disease, nonfatal MI, urgent coronary revascularization ≥ 30 days	1448 (18.9)	1322 (17.5)	0.91 (0.85–0.98)	0.02
Death from cardiovascular causes, nonfatal MI, hospitalization for unstable angina, all revascularization ≥ 30 days, nonfatal stroke	2869 (36.2)	2716 (34.5)	0.95 (0.90–1.0)	0.04
Tertiary end points†				
Death from any cause	1231 (15.3)	1215 (15.4)	0.99 (0.91–1.07)	0.78
Death from cardiovascular causes	538 (6.8)	537 (6.9)	1.00 (0.89–1.13)	1.00
Death from coronary heart disease	461 (5.8)	440 (5.7)	0.96 (0.84–1.09)	0.50
Any MI	1118 (14.8)	977 (13.1)	0.87 (0.80–0.95)	0.002
Nonfatal MI	1083 (14.4)	945 (12.8)	0.87 (0.80–0.95)	0.002
Fatal MI	49 (0.7)	41 (0.5)	0.84 (0.55–1.27)	0.41
Any stroke	345 (4.8)	296 (4.2)	0.86 (0.73–1.00)	0.05
Ischemic stroke	297 (4.1)	236 (3.4)	0.79 (0.67–0.94)	0.008
Hemorrhagic stroke	43 (0.6)	59 (0.8)	1.38 (0.93–2.04)	0.11

Statin in Stroke

└ Lipid lowering agents for ischemic stroke

 └ LDL-C or Statin?

Treat Stroke to Target (TST) Trial

- ▶ The aim of this study is the evaluation of two usual care strategies after stroke or TIA : achieved **target LDL-C of 100 mg/dL (+/-10 mg/dL) or less than 70 mg/dL.**

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Trial record 19 of 12993 for: **Treat to target**

+ Previous Study | Return to List | Next Study +

Treat Stroke to Target (TST)

This study is currently recruiting participants. (see Contacts and Locations)

Verified March 2017 by Assistance Publique - Hôpitaux de Paris

Sponsor:
Assistance Publique - Hôpitaux de Paris

Collaborators:
Pfizer
AstraZeneca
Merck Sharp & Dohme Corp.

ClinicalTrials.gov Identifier: NCT01252875

First received: February 7, 2010
Last updated: March 6, 2017
Last verified: March 2017
History of Changes

<https://clinicaltrials.gov/> accessed on Apr 15, 2017

Statin in Stroke

└ Lipid lowering agents for ischemic stroke

└ Statin in Intermediate-Risk Patients ?

HOPE-3



Intermediate-Risk Population



Inclusion Criteria (Target Risk 1.0%/yr)

Women \geq 60 yrs, men \geq 55 yrs with at least one additional Risk Factor

- Increased WHR
- Dysglycemia
- Smoking
- Mild renal dysfunction
- Low HDL
- Family history of CHD

Exclusion Criteria:

CVD or indication(s) or contraindication(s) to study drugs

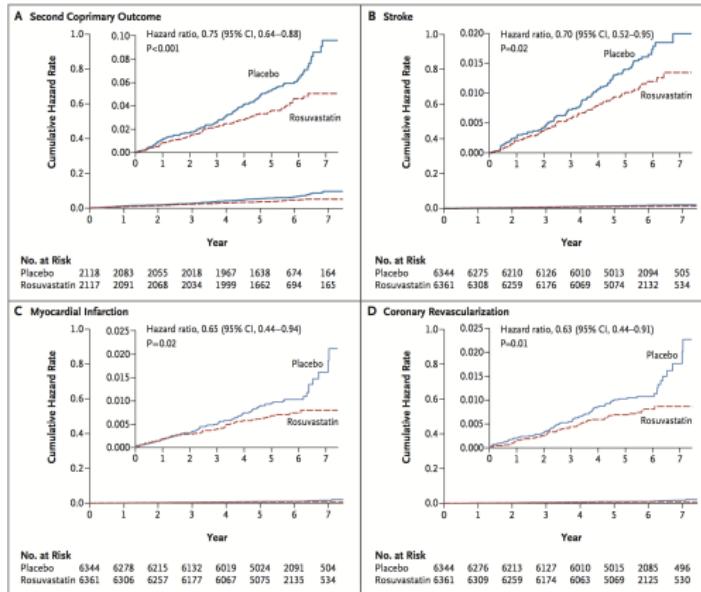
No strict BP or LDL-C criteria for entry
Uncertainty principle

Statin in Stroke

└ Lipid lowering agents for ischemic stroke

└ Statin in Intermediate-Risk Patients ?

HOPE-3

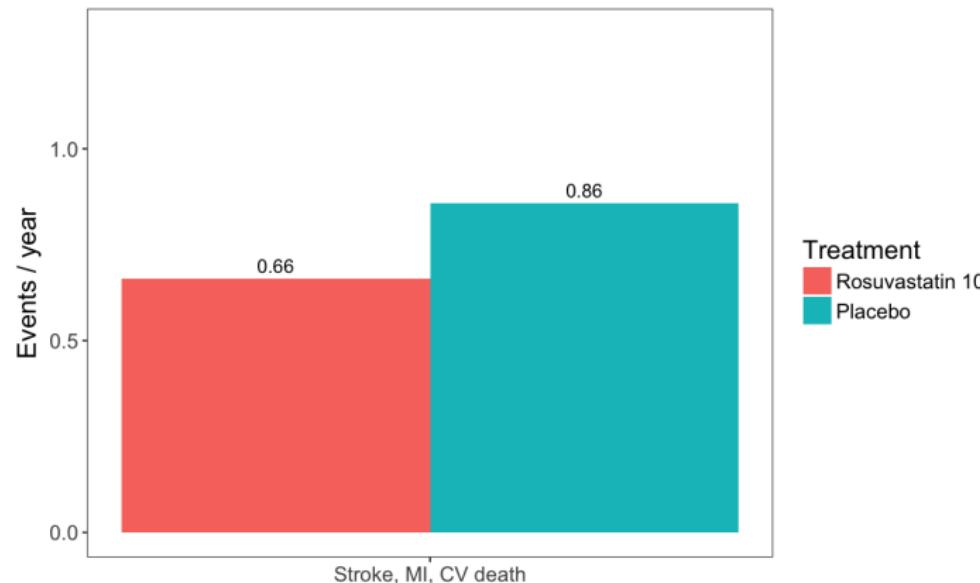


Statin in Stroke

└ Lipid lowering agents for ischemic stroke

└ Statin in Intermediate-Risk Patients ?

HOPE-3



Take-Home Message

- ▶ Stroke is the third leading cause of death in Korea and atherosclerosis is one of the major causes of stroke.
- ▶ Lipid lowering agents have been shown to be effective for reducing the burden of stroke in primary and secondary prevention.