

# Statin for Stroke Prevention



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## Stroke in Korea

### Lipid lowering agents for ischemic stroke

Guidelines

Role of Weak Statin ?

Statin in Lacunar Infarction ?

LDL-C or Statin?

### Summary

## 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

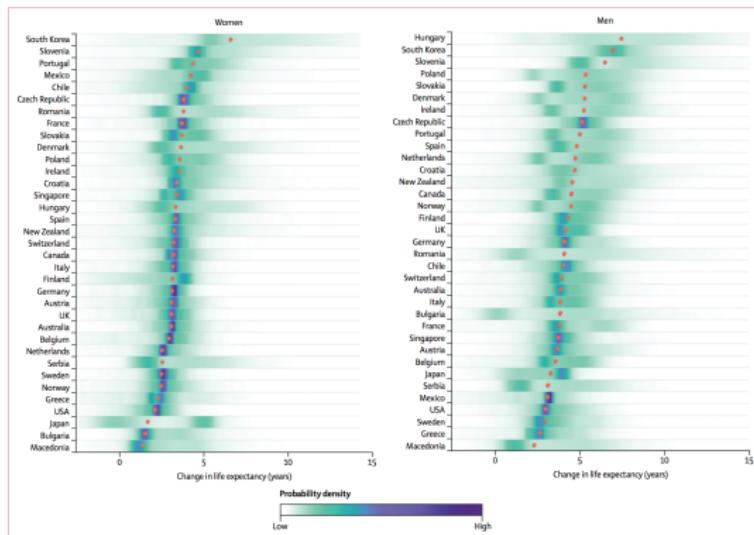
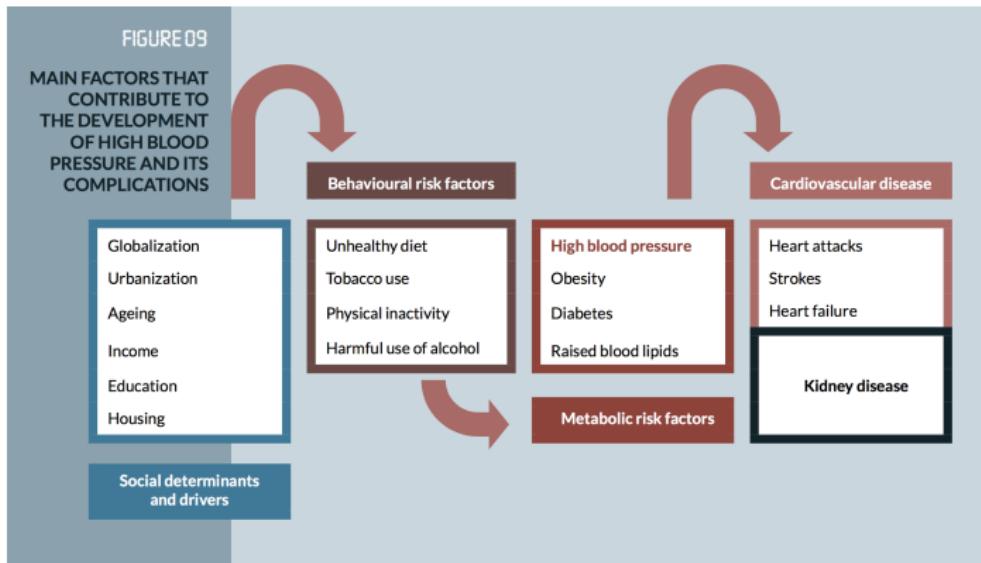


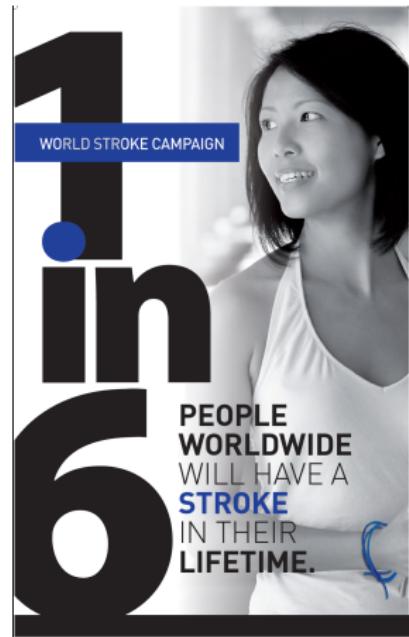
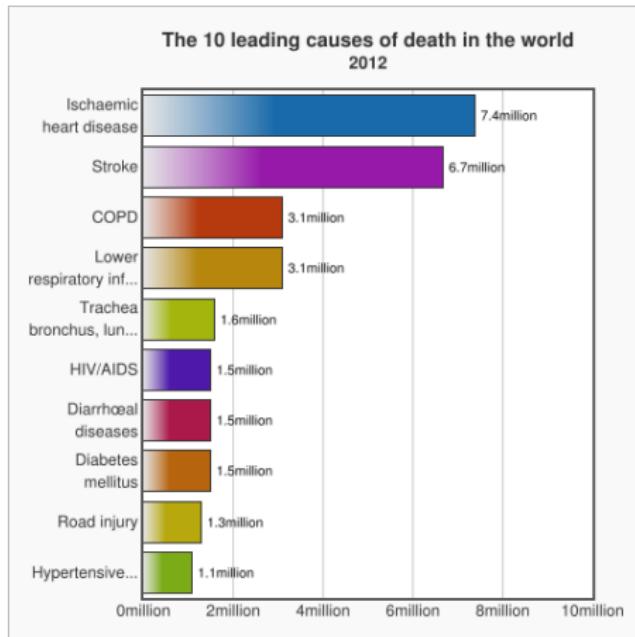
Figure 1: Posterior distribution of projected change in life expectancy at birth from 2010 to 2030  
Red dots show the posterior medians. Countries are ordered vertically by median projected increase from largest (at the top) to smallest (at the bottom).

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.**



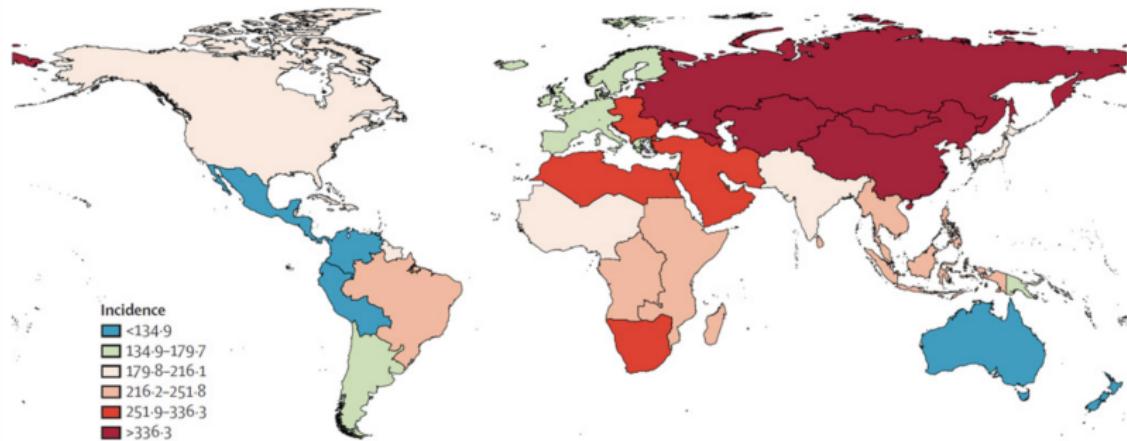
## Global burden of stroke



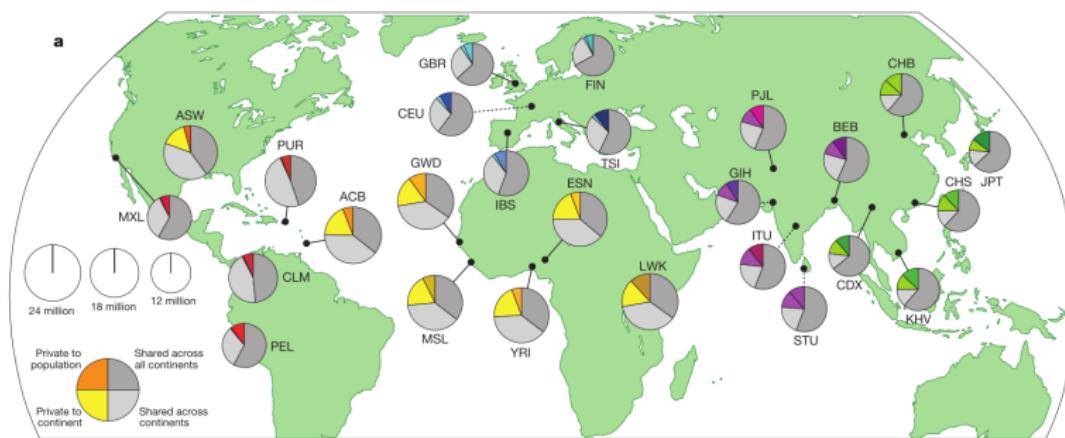
<http://www.who.int/mediacentre/factsheets/fs310/en/> accessed on Jan 16, 2016

<http://www.worldstrokecampaign.org/get-involved/2015-08-20-01-49-19/campaign-posters.html>

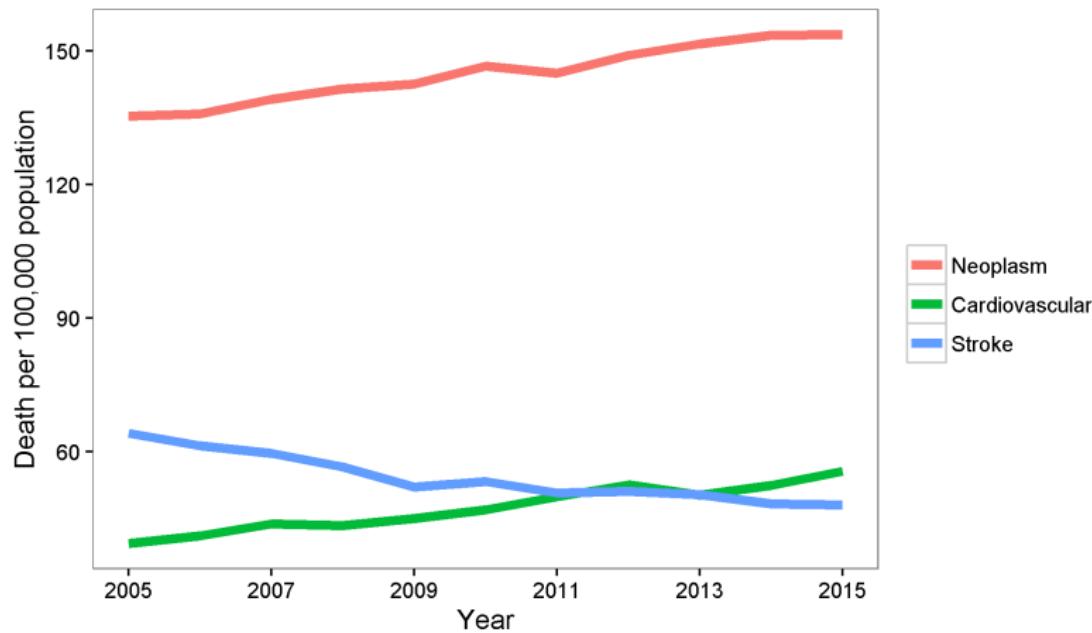
## Age-standardised stroke incidence per 100 000 person-years for 2010



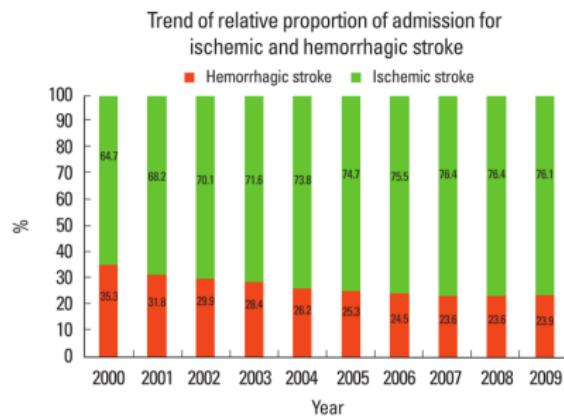
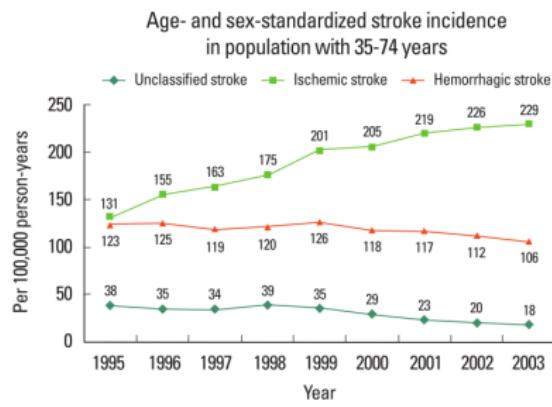
# A global reference for human genetic variation



## Secular trend of mortality in Korea



# Incidence of stroke is increasing



## Etiologies of stroke

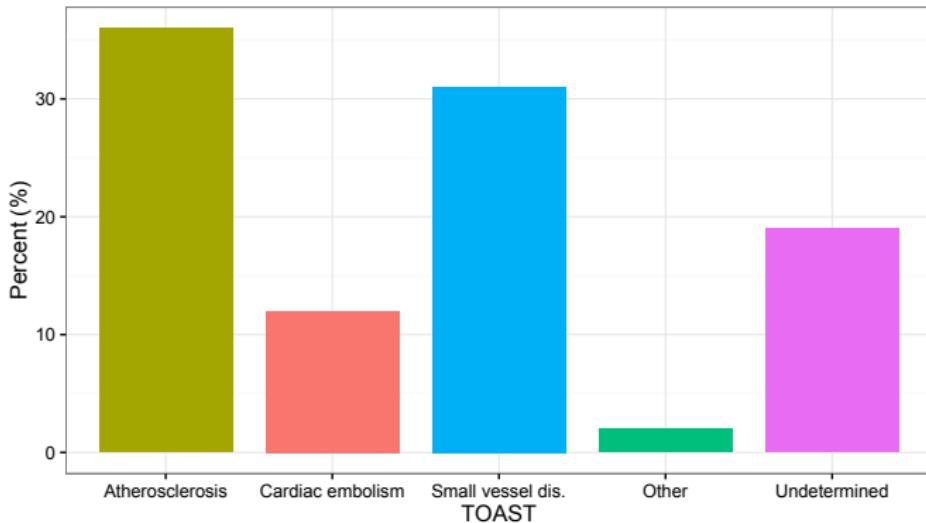
### Ischemic Stroke

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

### Hemorrhagic Stroke

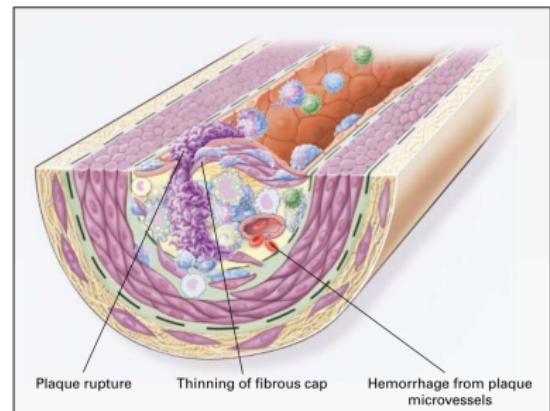
- ▶ Hypertensive hemorrhage
- ▶ Cerebral amyloid angiopathy
- ▶ Arteriovenous malformations
- ▶ Subarachnoid hemorrhage

# 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

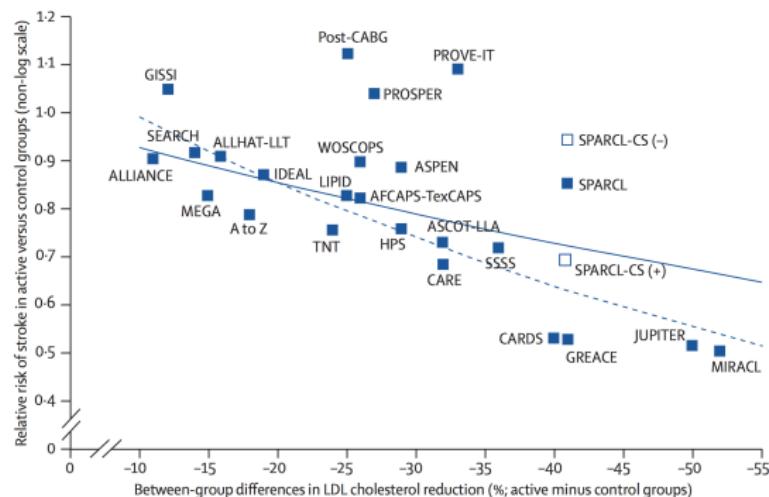
### Non-modifiable factors

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

# Stroke incidence and LDL-C reduction



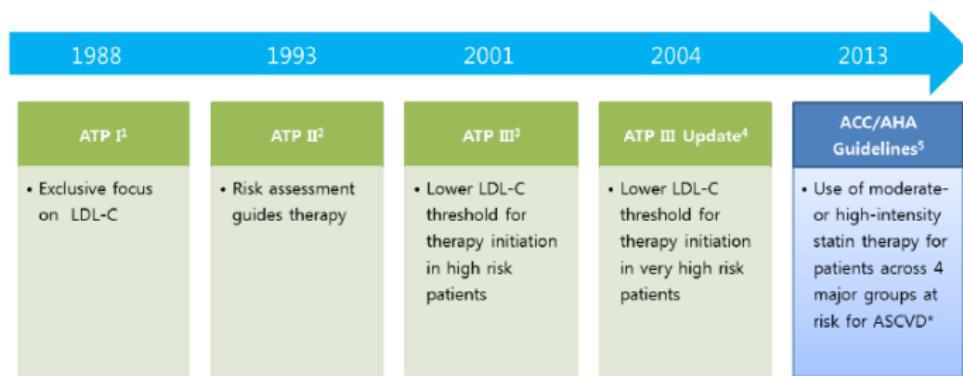
### Estimates of relative risk reduction

- 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 for Stroke Prevention

└ 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 for Stroke Prevention

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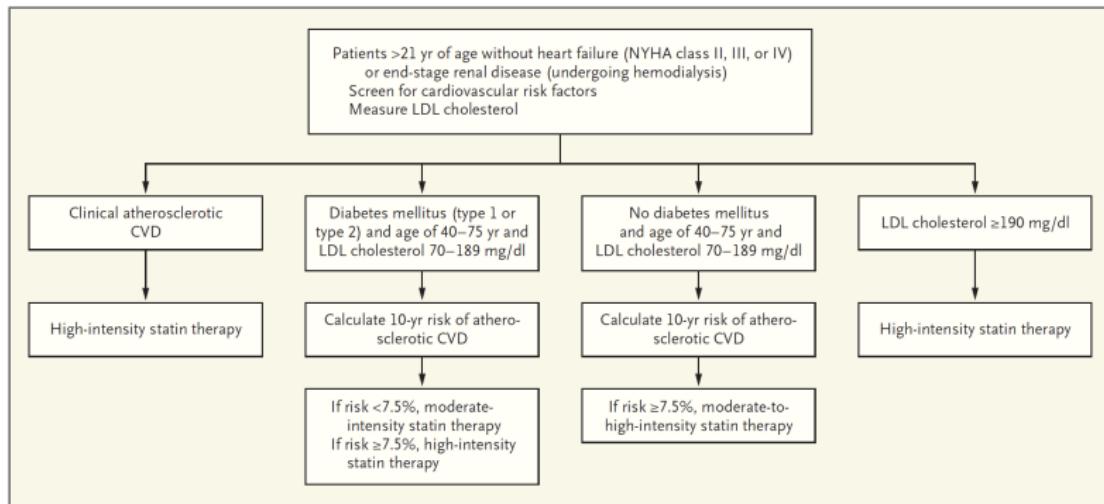
└ Guidelines

## Guidelines

- 2013 American College of Cardiology/American Heart Association (ACC/AHA)
- 2014 United Kingdom's National Institute for Health and Care Excellence (NICE)
- 2016 Canadian Cardiovascular Society (CCS), U.S. Preventive Services Task Force (USPSTF), and European Society of Cardiology/European Atherosclerosis Society (ESC/EAS)
- 2018 American Stroke Association (Secondary Prevention)

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

[my.americanheart.org/cvriskcalculator](http://my.americanheart.org/cvriskcalculator)



## 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

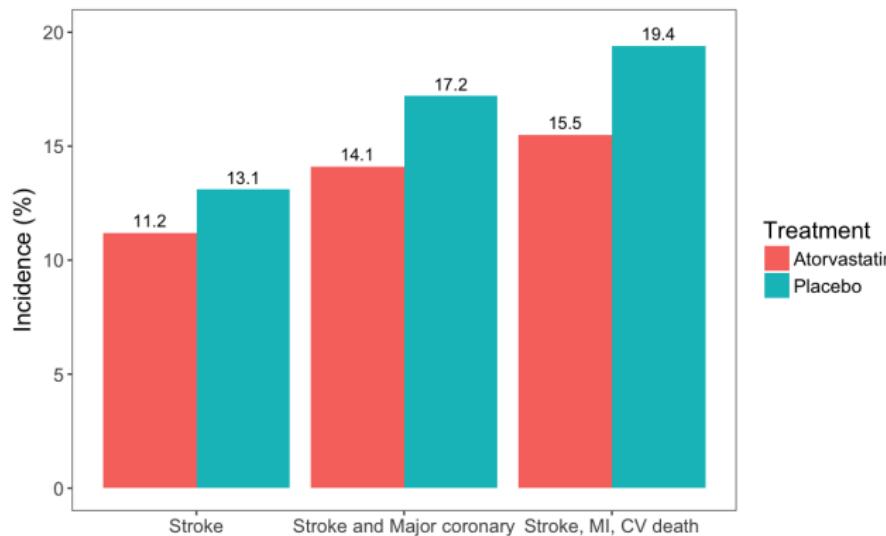
Recommended: atorvastatin, 40 to 80 mg; rosuvastatin, 20 to 40 mg

### Moderate-intensity statin therapy

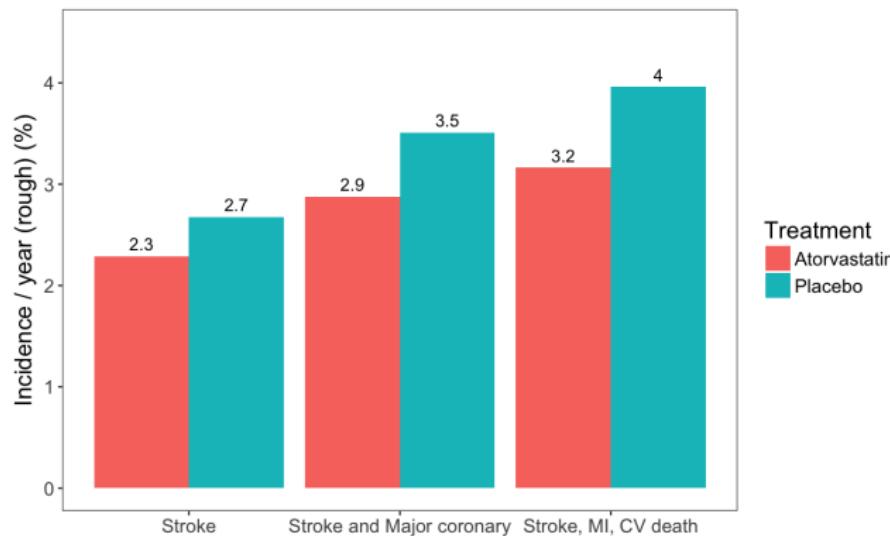
Daily dose lowers LDL cholesterol level by approximately 30 to  $< 50\%$  on average

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

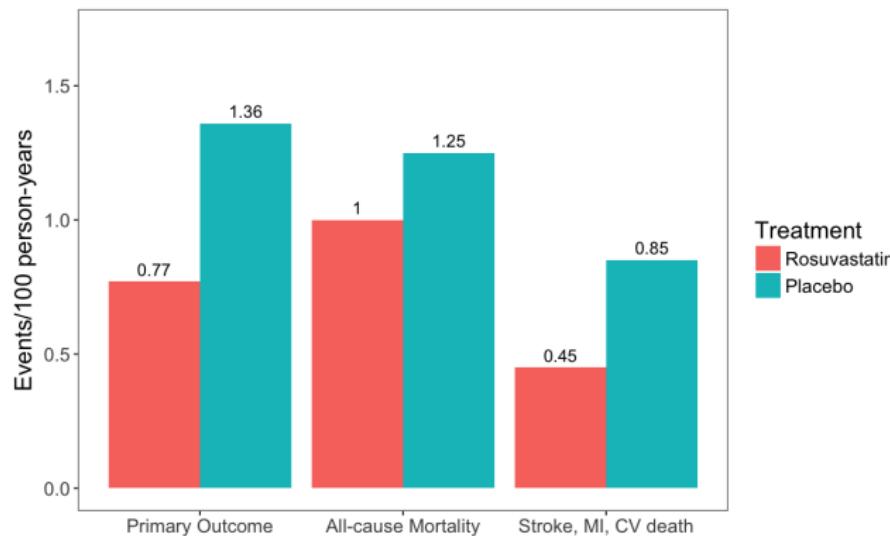
## SPARCL: Atorvastatin 80mg vs. placebo



## SPARCL: Atorvastatin 80mg vs. placebo



## JUPITER: Rosuvastatin 20mg vs. placebo



Statin for Stroke Prevention

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## Recent guideline



European Heart Journal (2016) **37**, 2999–3058  
doi:10.1093/eurheartj/ehw272

**ESC/EAS GUIDELINES**

## **2016 ESC/EAS Guidelines for the Management of Dyslipidaemias**

**The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)**

**Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR)**

**Authors/Task Force Members: Alberico L. Catapano\* (Chairperson) (Italy),**

# Treatment goal

**Table 10** Treatment targets and goals for cardiovascular disease prevention

<b>Smoking</b>	No exposure to tobacco in any form.
<b>Diet</b>	Healthy diet low in saturated fat with a focus on whole grain products, vegetables, fruit and fish.
<b>Physical activity</b>	2.5–5 h moderately vigorous physical activity per week or 30–60 min most days.
<b>Body weight</b>	BMI 20–25 kg/m <sup>2</sup> , waist circumference <94 cm (men) and <80 cm (women).
<b>Blood pressure</b>	<140/90 mmHg <sup>a</sup>
<b>Lipids</b> <b>LDL-C is the primary target<sup>b</sup></b>	<p><b>Very high-risk:</b> LDL-C &lt;1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline<sup>b</sup> is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL).</p> <p><b>High-risk:</b> LDL-C &lt;2.6 mmol/L (100 mg/dL) or a reduction of at least 50% if the baseline<sup>b</sup> is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL).</p> <p><b>Low to moderate risk:</b> LDL-C &lt;3.0 mmol/L (115 mg/dL).</p> <p>Non-HDL-C secondary targets are &lt;2.6, 3.4 and 3.8 mmol/L (100, 130 and 145 mg/dL) for very high-, high- and moderate-risk subjects, respectively.</p> <p>HDL-C: no target, but &gt;1.0 mmol/L (40 mg/dL) in men and &gt;1.2 mmol/L (48 mg/dL) in women indicates lower risk.</p> <p>TG: no target but &lt;1.7 mmol/L (150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors.</p>
<b>Diabetes</b>	HbA1c: <7% (<53 mmol/mol).

## Reason: Treatment goal

- ▶ Systematic reviews confirming the dose-dependent reduction in CVD with LDL-C lowering;  
the greater the LDL-C reduction, the greater the CV risk reduction
- ▶ The benefits related to LDL-C reduction are not specific for statin therapy.
- ▶ The use of goals can also aid patient–doctor communication.

# Treatment goal

**Table 33 Recommendations for lipid-lowering drugs for primary and secondary prevention of stroke**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Ref <sup>c</sup>
Statin therapy to reach established treatment goals is recommended in patients at high or very high CV risk for primary prevention of stroke.	I	A	64, 65, 422, 426
Lipid-lowering therapy is recommended in patients with other manifestations of CVD for primary prevention of stroke.	I	A	63–65, 422, 426
Intensive statin therapy is recommended in patients with a history of non-cardioembolic ischaemic stroke or TIA for secondary prevention of stroke	I	A	422, 428

CVD = cardiovascular disease; TIA = transient ischaemic attack.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>Reference(s) supporting recommendations.

## 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

## Treatment goal

### 9.12.2 Secondary prevention of stroke

Following stroke or TIA, patients are at risk not only of recurrent cerebrovascular events, but also of other major CV events, including MI. Secondary prevention therapy with statins reduces the risk of recurrent stroke (by 12%), MI and vascular death.<sup>422,428</sup> Statin pretreatment at TIA onset was associated with reduced recurrent early stroke risk in patients with carotid stenosis in a pooled data analysis, supporting an as-early-as-possible initiation of statins after stroke.<sup>429</sup> However, the aetiology of stroke may influence the response to statins, and those patients with evidence of atherosclerosis underlying their cerebrovascular events appear to benefit most, while those with haemorrhagic stroke may not benefit.<sup>422</sup>

Statin for Stroke Prevention

└ Lipid lowering agents for ischemic stroke

└ Guidelines

## AHA/ASA Guideline

# 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke

**A Guideline for Healthcare Professionals From the American Heart  
Association/American Stroke Association**

*Reviewed for evidence-based integrity and endorsed by the American Association of Neurological  
Surgeons and Congress of Neurological Surgeons*

*Endorsed by the Society for Academic Emergency Medicine*

## Statin for Stroke Prevention

└ Lipid lowering agents for ischemic stroke

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CLASS III: No Benefit (MODERATE) <i>(Generally, LOE A or B use only)</i>	Benefit = Risk
Suggested phrases for writing recommendations: <ul style="list-style-type: none"><li>■ Is not recommended</li><li>■ Is not indicated/useful/effective/beneficial</li><li>■ Should not be performed/administered/other</li></ul>	
CLASS III: Harm (STRONG)	Risk > Benefit
Suggested phrases for writing recommendations: <ul style="list-style-type: none"><li>■ Potentially harmful</li><li>■ Causes harm</li><li>■ Associated with excess morbidity/mortality</li><li>■ Should not be performed/administered/other</li></ul>	

## Statin for Stroke Prevention

└ Lipid lowering agents for ischemic stroke

└ Guidelines

### 6.5. Cholesterol

6.5. Cholesterol	COR	LOE	New, Revised, or Unchanged
1. Routine measurement of blood cholesterol levels in all patients with ischemic stroke presumed to be of atherosclerotic origin who are not already taking a high-intensity statin is not recommended.	III: No Benefit	B-R	New recommendation.
2. Measurement of blood cholesterol levels in patients with ischemic stroke presumed to be of atherosclerotic origin who are already taking an optimized regimen of statin therapy may be useful for identifying patients who would be candidates for outpatient proprotein convertase subtilisin/kexin type 9 inhibitor treatment to reduce the risk of subsequent cardiovascular death, MI, or stroke.	IIb	B-R	New recommendation.

## **Statin for Stroke Prevention**

- └ Lipid lowering agents for ischemic stroke
- └ Guidelines

The “2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults” recommend statin therapy for secondary prevention for adults with clinical atherosclerotic cardiovascular disease (ASCVD), including stroke presumed to be of atherosclerotic origin. No data were identified for treatment or titration to a specific low-density lipoprotein cholesterol (LDL-C) goal.<sup>7</sup> The **2016 European Society of Cardiology/European Atherosclerosis Society guidelines** for the management of dyslipidemias and the 2014 guidelines from the UK National Institute for Health Care Excellence also contain recommendations based on clinical factors and not blood cholesterol measurements.<sup>305,306</sup> Thus, statin therapy can be recommended in patients with stroke presumed to be of atherosclerotic origin without measurement of blood cholesterol. For patients with ischemic stroke that is presumed to be the result of nonatherosclerotic disease such as arterial dissection, measurement of blood cholesterol may be of value because the primary prevention guidelines are based on LDL-C levels.<sup>7</sup> It is of note that the 2012 Canadian Cardiovascular

# 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 Matsumoto<sup>1</sup>, Naohisa Hosomi<sup>1</sup>, Yoji Nagai<sup>2</sup>, Tatsuo Kohriyama<sup>3</sup>, Shiro Aoki<sup>1</sup>, Chiaki Yokota<sup>4</sup>, Kazuo Kitagawa<sup>5</sup>, Yasuo Terayama<sup>6</sup>, Makoto Takagi<sup>7</sup>, Setsuro Ibayashi<sup>8</sup>, Masakazu Nakamura<sup>4</sup>, Hideki Origasa<sup>9</sup>, Masanori Fukushima<sup>2</sup>, Etsuro Mori<sup>10</sup>, Kazuo Minematsu<sup>4</sup>, Shinichiro Uchiyama<sup>11</sup>, Yukito Shinohara<sup>12</sup>, Takenori Yamaguchi<sup>4</sup>; 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

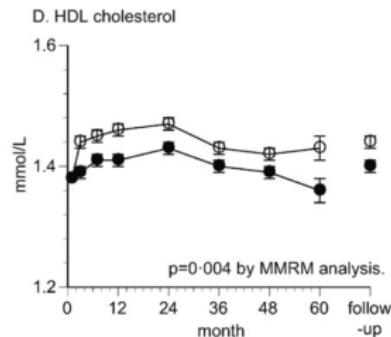
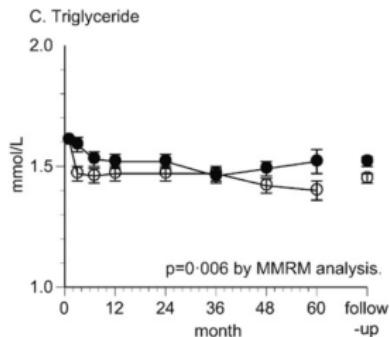
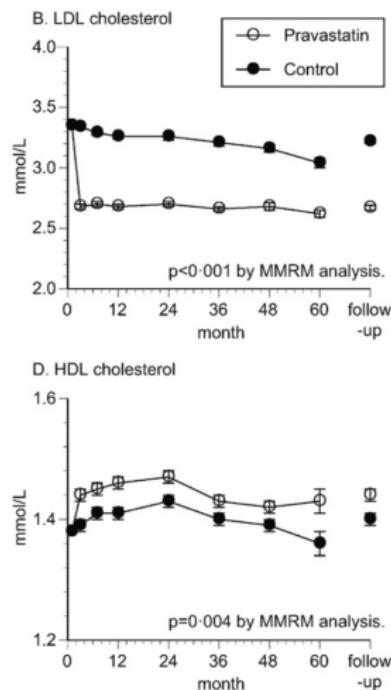
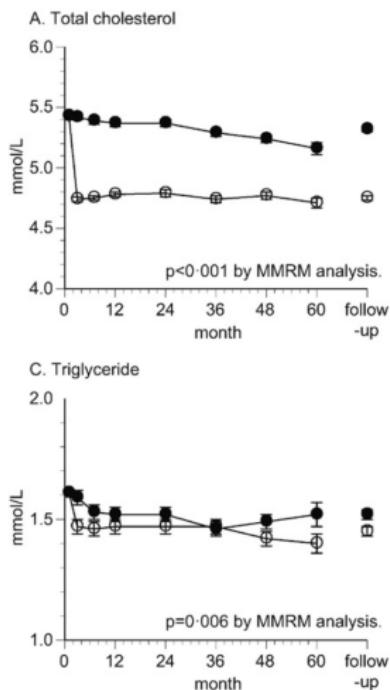
Primary Endpoint: Stroke Recurrence

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

# Statins for Stroke Prevention

## Lipid lowering agents for ischemic stroke

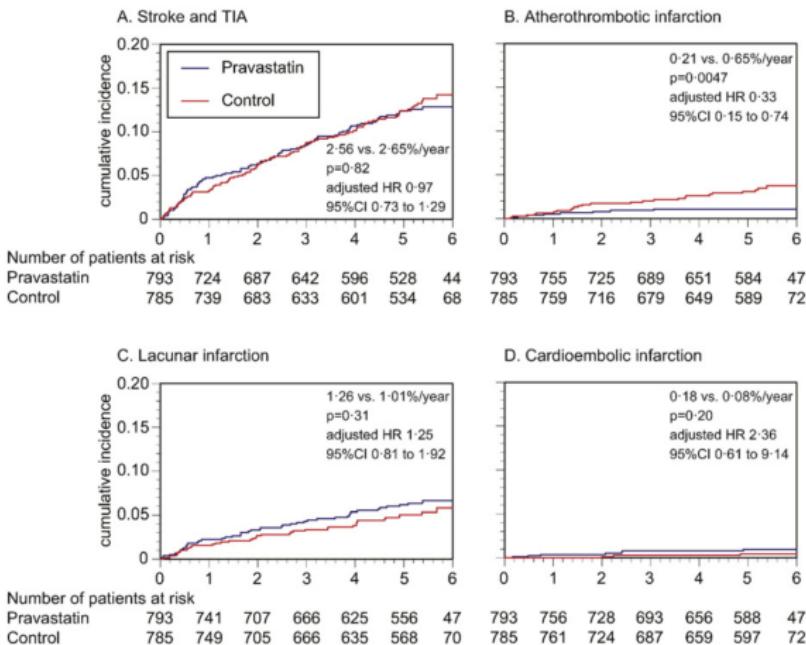
### Role of Weak Statin ?



# Statins for Stroke Prevention

## Lipid lowering agents for ischemic stroke

### Role of Weak Statin ?

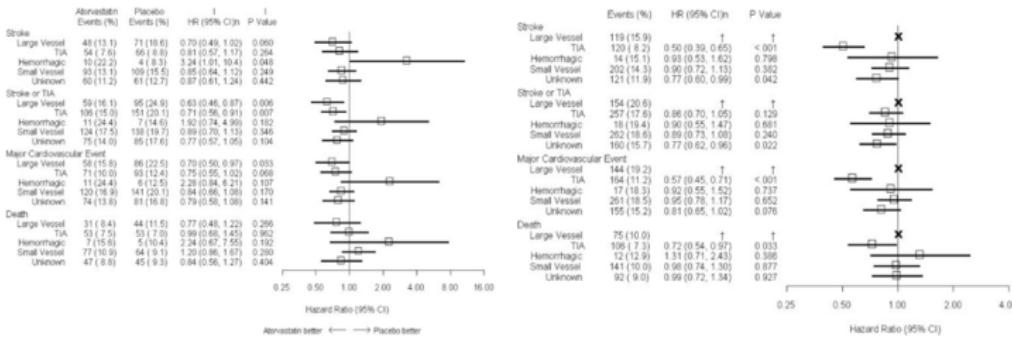


# Statin in Lacunar infarction ?

## The Answer is “Maybe Yes”

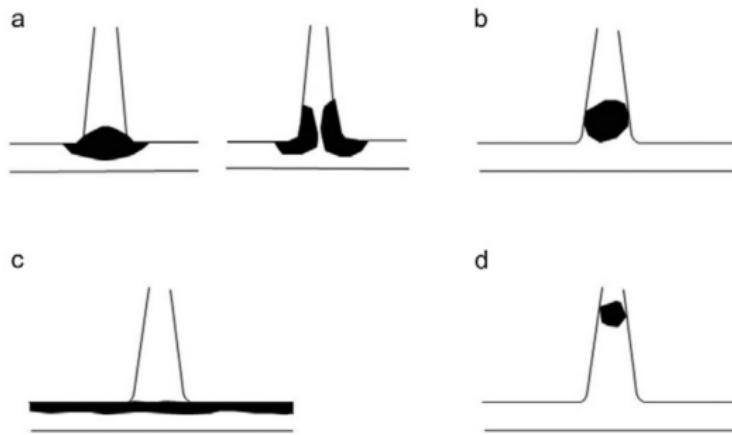
### Results of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Trial by Stroke Subtypes

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

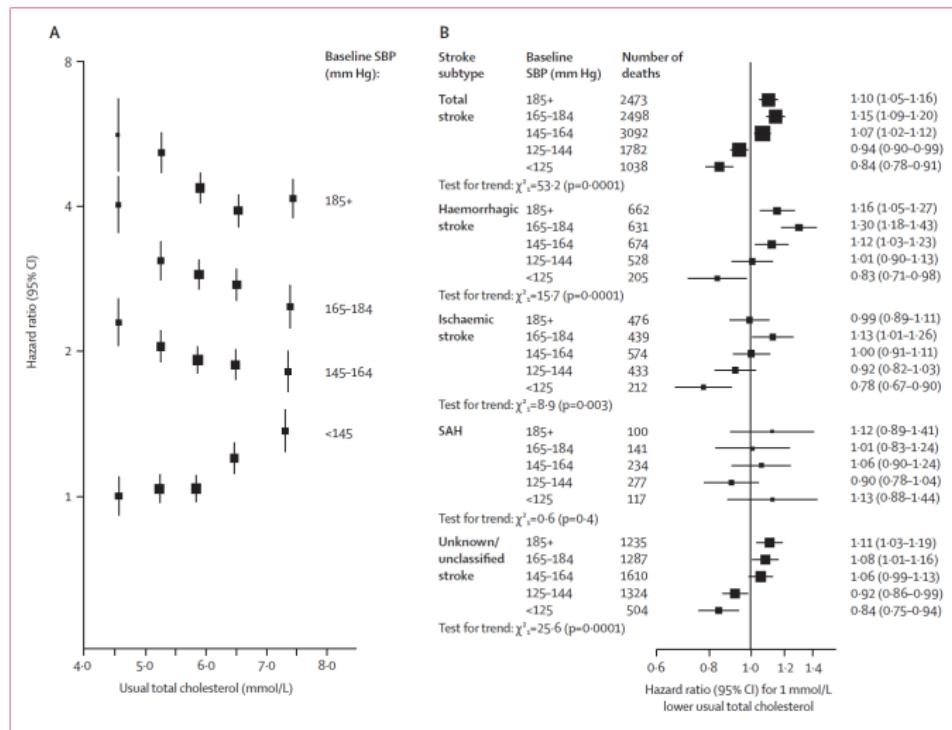


**Conclusions**—Atorvastatin 80 mg/d is similarly efficacious in preventing strokes and other cardiovascular events, irrespective of baseline ischemic stroke subtype. (*Stroke*. 2009;40:1405-1409.)

## Statin might be useful in branchatheromatous disease



# Hypertension should be strictly controlled

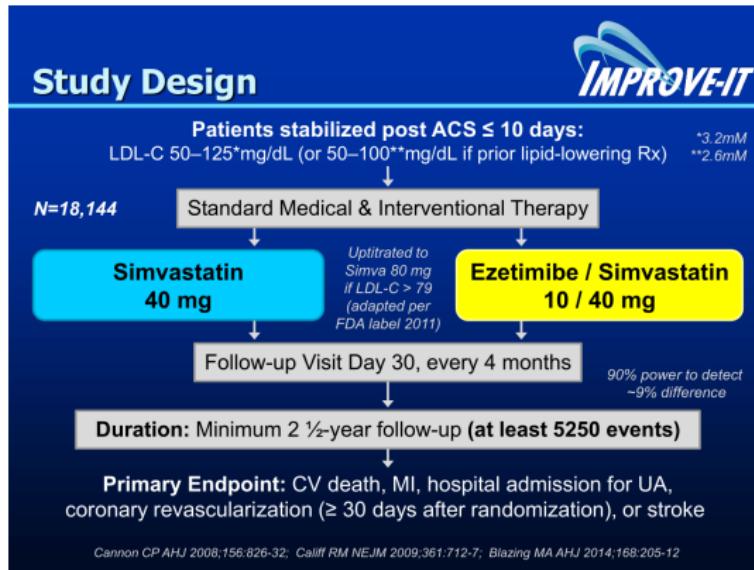


## Statin for Stroke Prevention

└ Lipid lowering agents for ischemic stroke

└ LDL-C or Statin?

# IMPROVE-IT

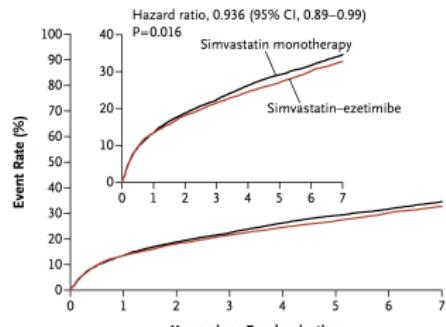


## Statins for Stroke Prevention

└ 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 %



No. at Risk	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
Simvastatin-ezetimibe	9067	7371	6801	6375	5839	4284	3301	1906
Simvastatin	9077	7455	6799	6327	5729	4206	3284	1857

## Statins for Stroke Prevention

### 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
<i>no. of patients (%)</i>				
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 $\geq 30$ 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 $\geq 30$ 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

└ 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: December 2, 2010  
Last updated: March 6, 2017  
Last verified: March 2017  
History of Changes



## 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.
- ▶ High intensity statin should be used in patients with ischemic stroke of presumed atherosclerosis origin.