

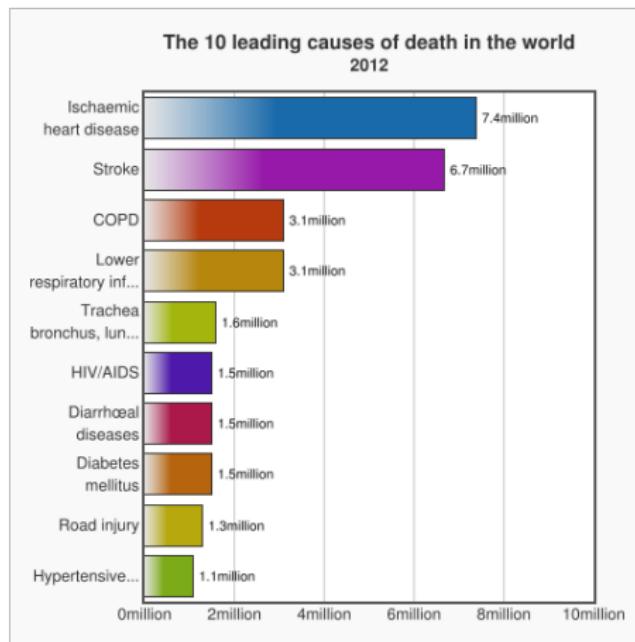
2018 한국지질동맥경화학회 춘계학술대회
Management of Insignificant Arterial Stenosis



Kwang-Yeol Park

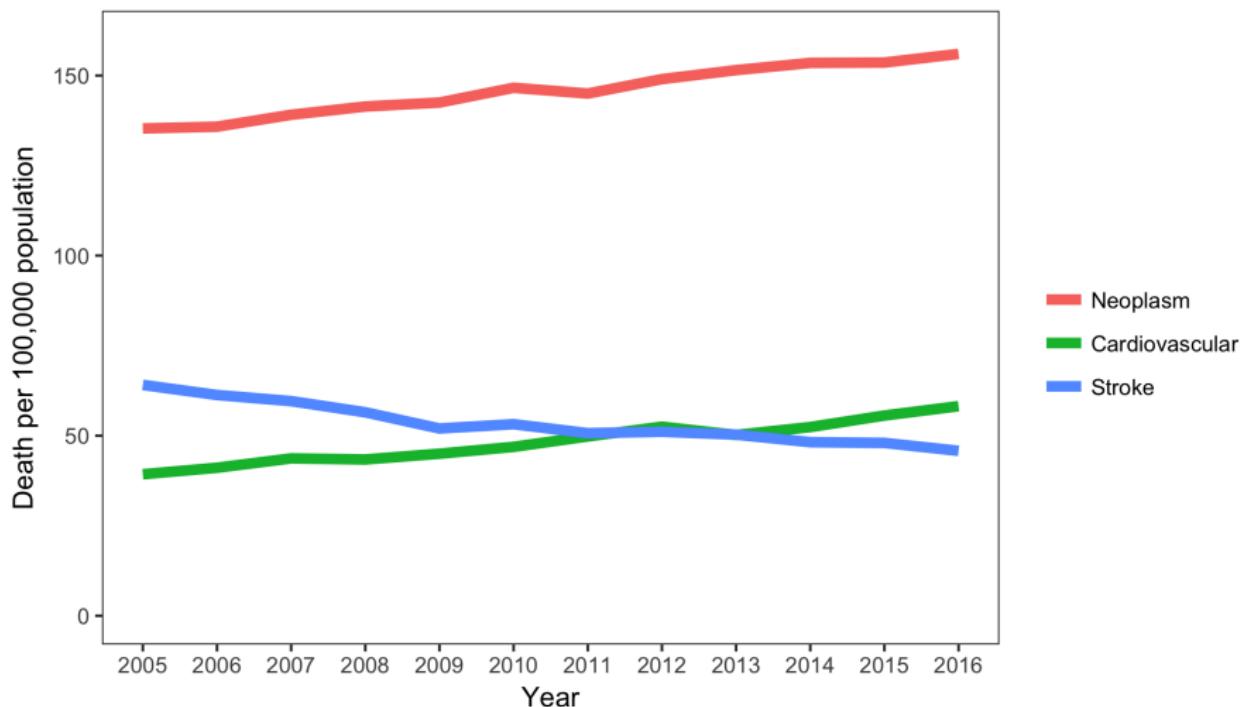
Dep. of Neurology, Chung-Ang University, Seoul South Korea

Global burden of vascular disease



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

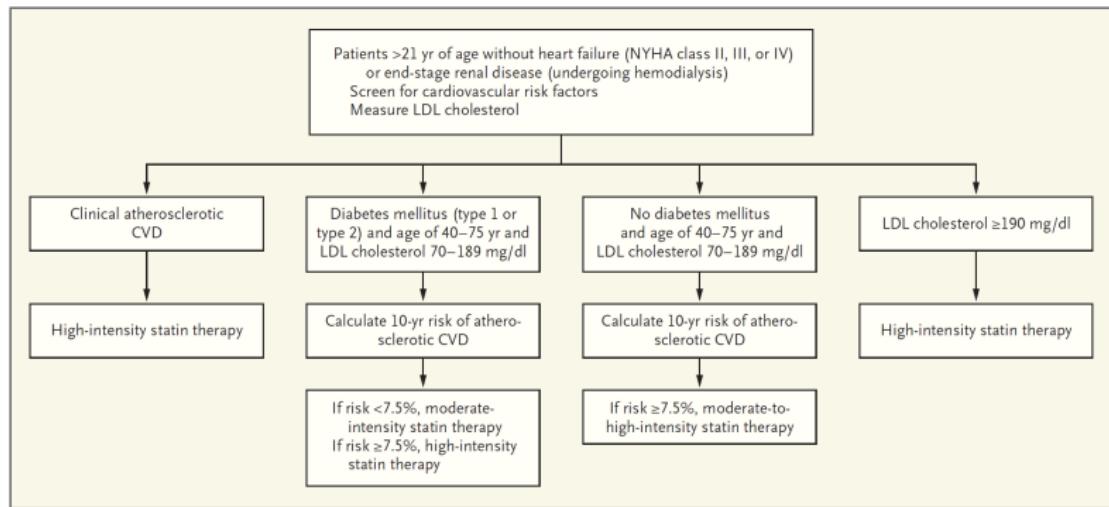
Secular trend of mortality in Korea



http://www.index.go.kr/potal/main/EachDtIPageDetail.do?idx_cd=1012 accessed on Apr 10, 2018

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

my.americanheart.org/cvriskcalculator



Stone NJ, et al. JACC. 2013; Keaney JF, et al. N Engl J Med. 2013

Very high-risk

Subjects with any of the following:

- Documented cardiovascular disease (CVD), clinical or unequivocal on imaging. Documented CVD includes previous myocardial infarction (MI), acute coronary syndrome (ACS), coronary revascularisation (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG)) and other arterial revascularization procedures, stroke and transient ischaemic attack (TIA), and peripheral arterial disease (PAD). Unequivocally documented CVD on imaging is what has been shown to be strongly predisposed to clinical events, such as significant plaque on coronary angiography or carotid ultrasound.
- DM with target organ damage such as proteinuria or with a major risk factor such as smoking, hypertension or dyslipidaemia.
- Severe CKD (GFR <30 mL/min/1.73 m²).
- A calculated SCORE ≥10% for 10-year risk of fatal CVD.

Chain of Events

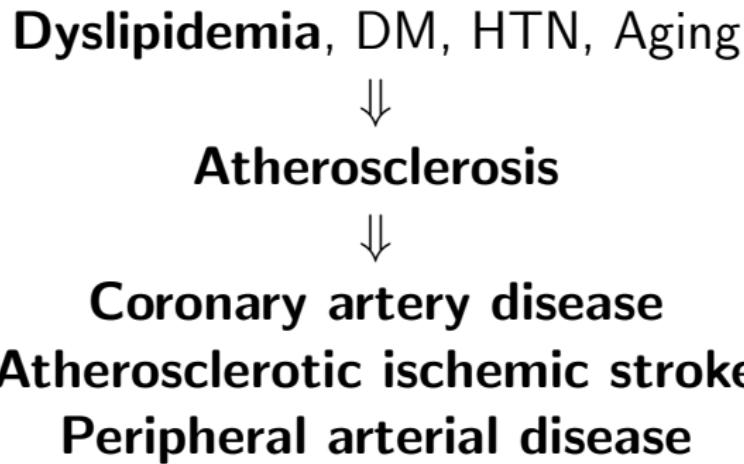


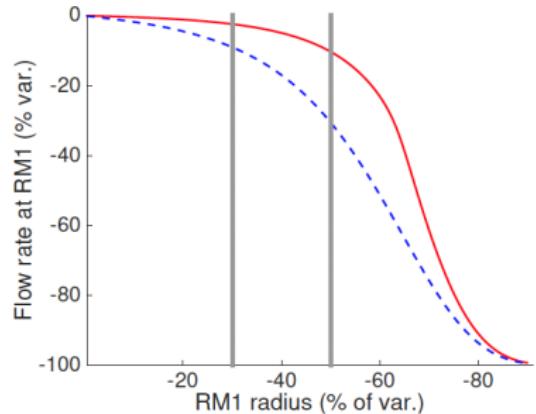
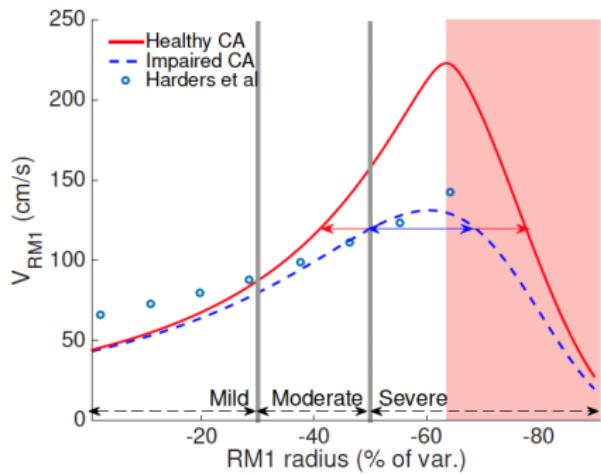
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- 1 What is insignificant arterial stenosis?
- 2 Statin for insignificant arterial stenosis
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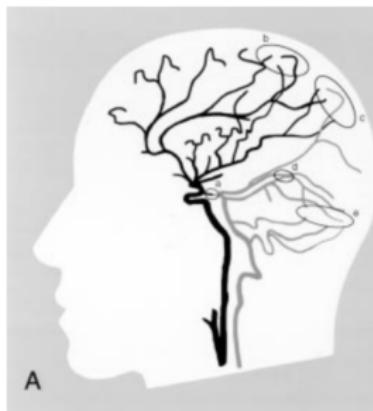
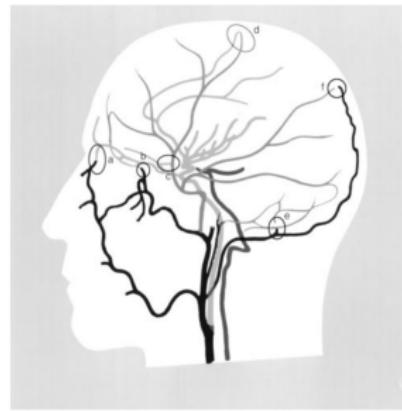
Significance of arterial stenosis

- Symptomatic vs. Asymptomatic
- Arterial stenosis brings about decreased flow.
- $Blood\ Flow = Area \times Mean\ Velocity$
- Cerebral autoregulation
- Diameter of the arteries
- Collateral flow

Flow rate at MCA(M1) during vasospasm



Collateral flow in the brain



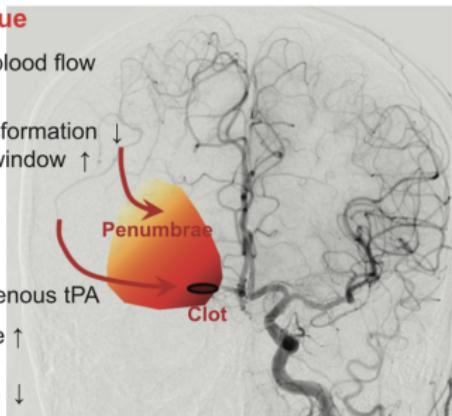
Liebeskind DS. Stroke 2003;34:2279-2284

Collateral flow in the brain

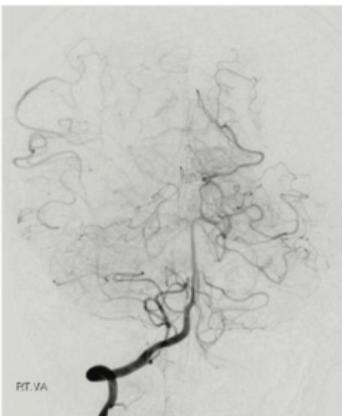
Collateral flow to

(a) Penumbral tissue

- Maintain cerebral blood flow
- Infarct growth ↓
Hemorrhagic transformation
Therapeutic time window ↑



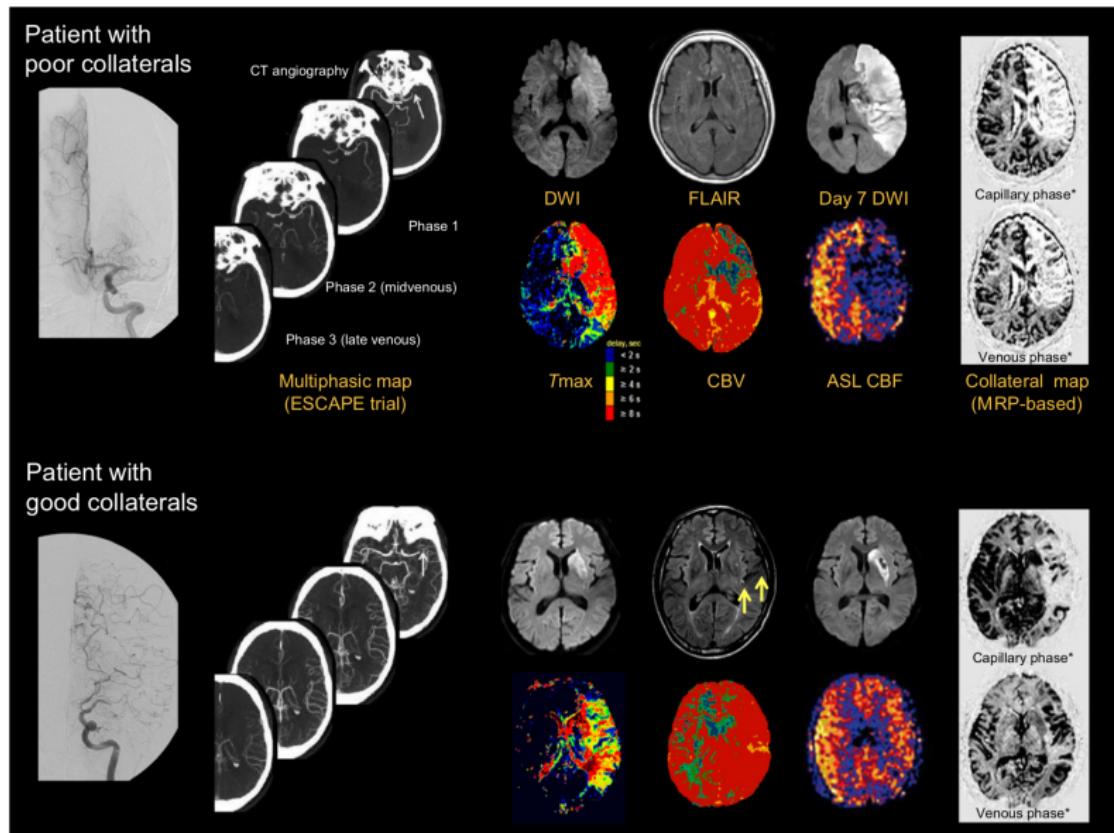
Contralateral carotid injection



Vertebral injection

(b) Clot

- Deliver endo/exogenous tPA
- Recanalization rate ↑
Reocclusion ↓
Instent thrombosis ↓



Significance of arterial stenosis

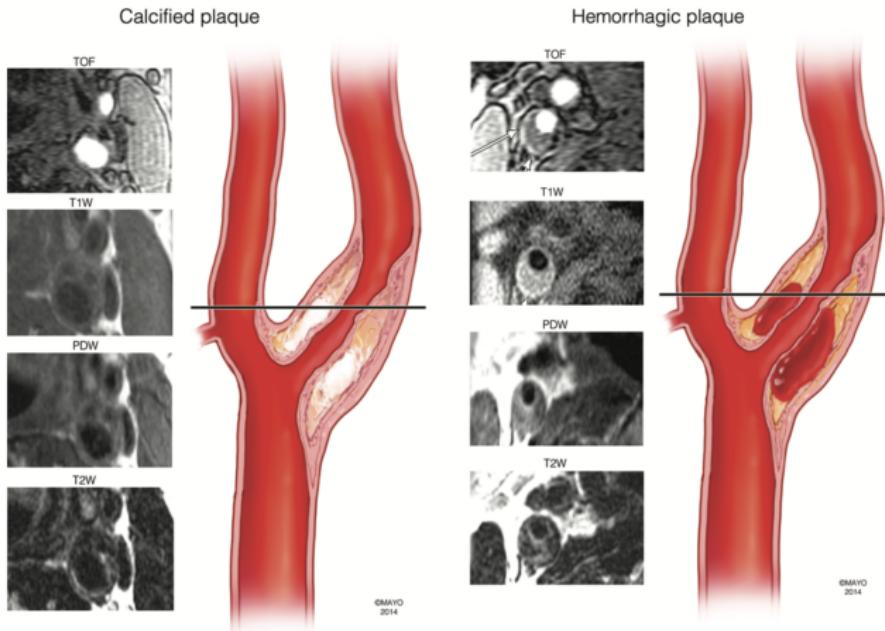
- Symptomatic vs. Asymptomatic
- Arterial stenosis brings about decreased flow.
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- Collateral flow
- Morphology

Morphology of plaque

TABLE 1. Summary of histopathological features of atheromatous plaques

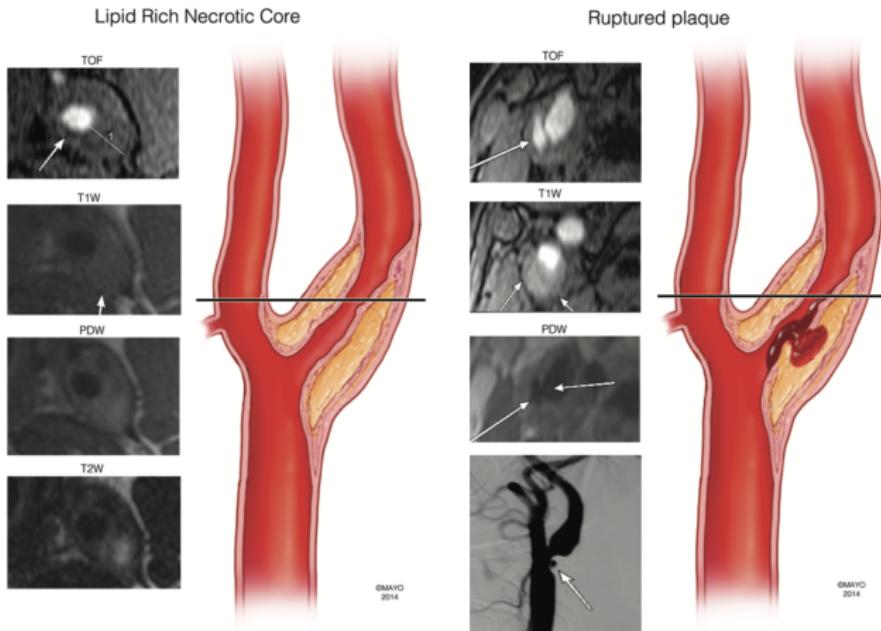
| AHA Plaque Type | Histopathological Findings | Symptomatic Status |
|-----------------|---|----------------------|
| Type I | Isolated deposition of macrophages & foam cells. | Asymptomatic |
| Type II | Fatty streak lesion w/ mainly intracellular lipid accumulation. | Asymptomatic |
| Type III | Deposition of intracellular lipids w/in the plaque. | Asymptomatic |
| Type IV | Dense accumulation of extracellular lipid (i.e., lipid core). Inflammatory cell infiltration. No fibrous tissue formation, no surface defects or thrombosis. | Possibly symptomatic |
| Type V | Fibrous cap overlying necrotic lipid core. Inflammation w/in plaque & in the vasa vasorum of the artery wall. Prone to hematoma, thrombus formation, & fissuring. | Possibly symptomatic |
| Type VI | Fissuring & ulceration of plaque. Necrotic lipid core. Intraplaque hemorrhage & thrombus. Inflammation w/in the plaque. | Probably symptomatic |

Morphology of plaque



Brinjikji W et al J Neurosurg 2016

Morphology of plaque

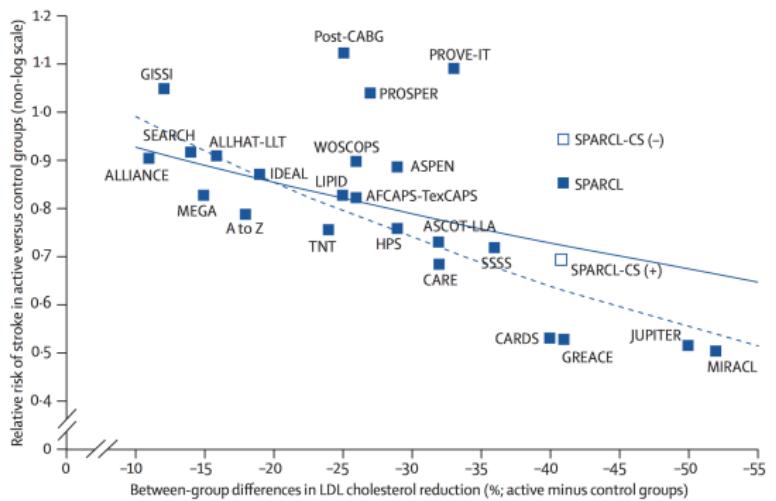


Brinjikji W et al J Neurosurg 2016

Significance of arterial stenosis

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Stroke incidence and LDL-C reduction

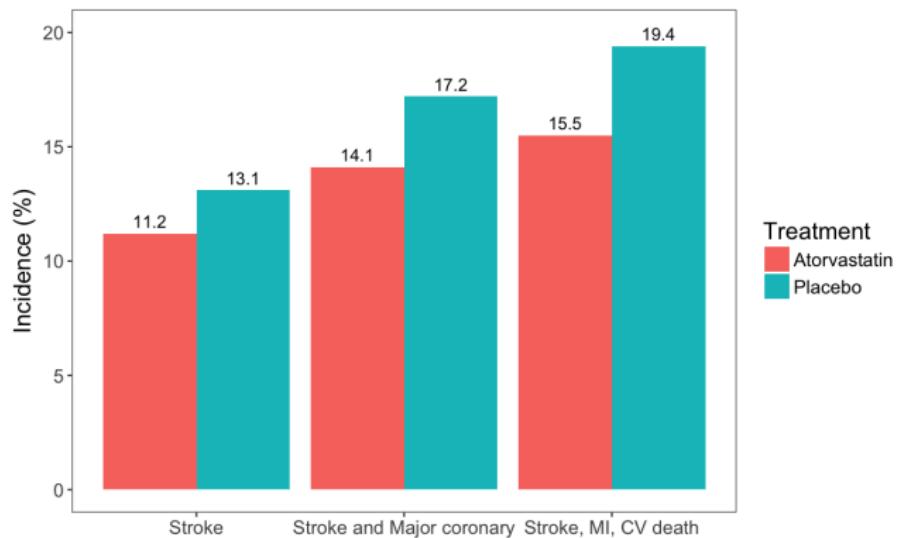


Estimates of relative risk reduction

- 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

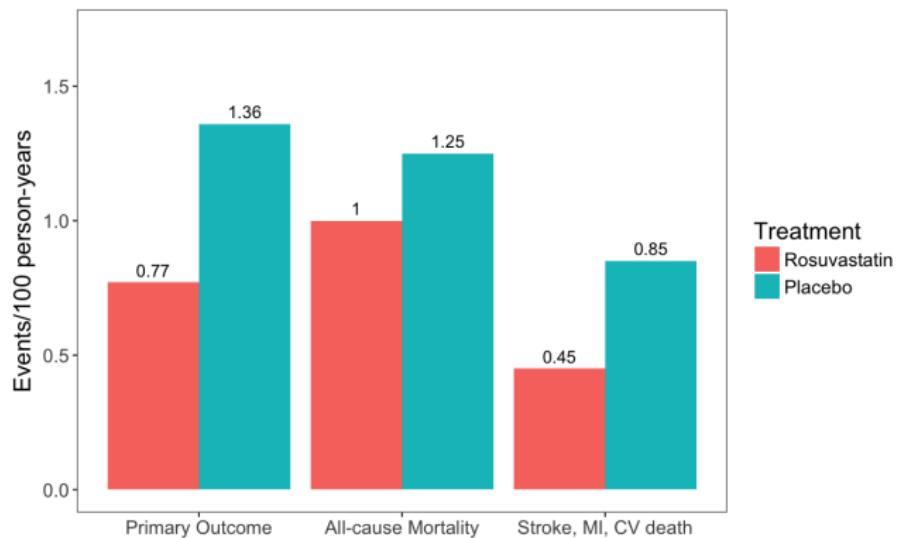
Amarenco et al. Lancet Neurol 2009;8:453-463.

SPARCL: Atorvastatin 80mg vs. placebo



SPARCL investigator. N Engl J Med 2006; 355:549-559

JUPITER: Rosuvastatin 20mg vs. placebo



Ridker PM et al. N Engl J Med 2008

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)

2016 ESC/EAS 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 33 Recommendations for lipid-lowering drugs for primary and secondary prevention of stroke

| Recommendations | Class ^a | Level ^b | Ref ^c |
|--|--------------------|--------------------|------------------|
| 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.

^aClass of recommendation.

^bLevel of evidence.

^cReference(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.^{422,428} Statin pre-treatment 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.⁴²⁹ 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.⁴²²

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 Yamaguchi¹⁴, for the J-STARS collaborators

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

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

³Hiroshima City Rehabilitation Hospital, Hiroshima, Japan

⁴National Cerebral and Cardiovascular Center, Suita, Japan

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

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

⁷Department of Neurology, Tokyo Saiseikai Central Hospital, Tokyo, Japan

⁸Seirai Rehabilitation Hospital, Fukuoka, Japan

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

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

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

¹²Federation 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

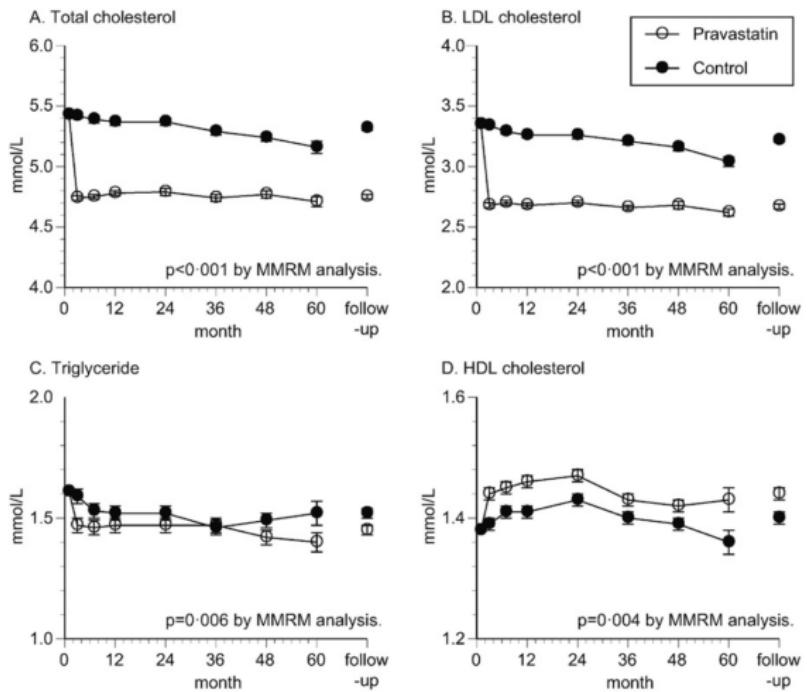
Primary Endpoint: Stroke Recurrence

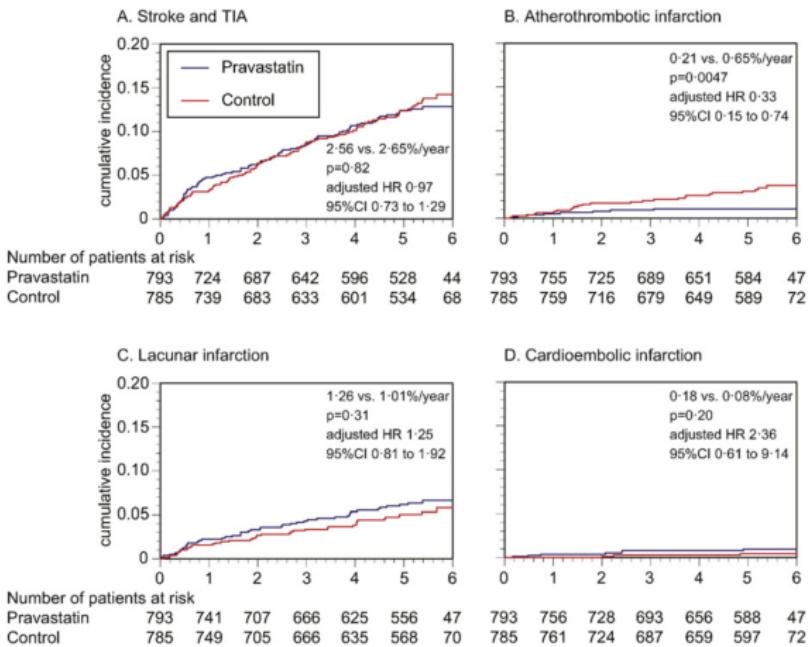
A total of 1578 patients were enrolled and completed follow-up.
(originally this study was designed to recruit 3000 patients).

| | Daily dose of different statins | | | | |
|--------------|---------------------------------|-------|-------|-------|-------|
| | 5 mg | 10 mg | 20 mg | 40 mg | 80 mg |
| Pravastatin | 15% | 20% | 24% | 29% | 33% |
| Simvastatin | 23% | 27% | 32% | 37% | 42% |
| Atorvastatin | 31% | 37% | 43% | 49% | 55% |
| Rosuvastatin | 38% | 43% | 48% | 53% | 58% |

Shaded boxes indicate regimens that can produce about a halving or more in LDL cholesterol concentrations (largely irrespective of patient characteristics, including presenting concentrations of cholesterol). The 2016 cost for generic atorvastatin 40 mg daily in the UK is about £2 per 28 days of treatment,¹⁸⁴ rosuvastatin 20 mg daily currently costs about £25 per month,¹⁸⁵ but it became available as a generic in the USA during 2016.

Table 3: Average relative reductions in LDL cholesterol concentrations with different doses of commonly used statins^{160,163}



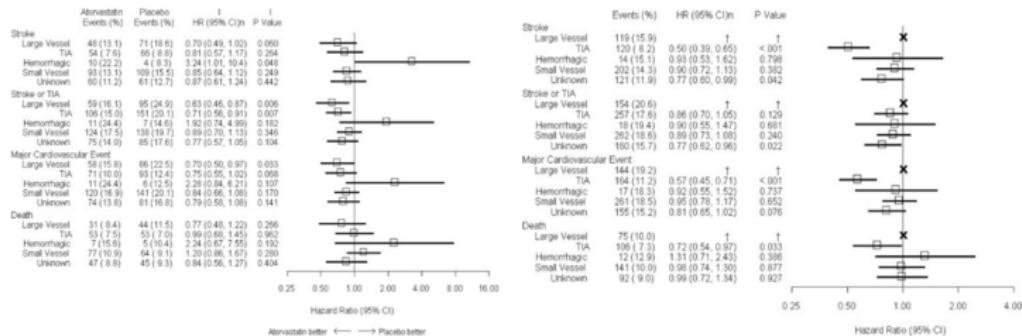


Statin in Lacunar infarction ?

The Answer is “Maybe Yes”

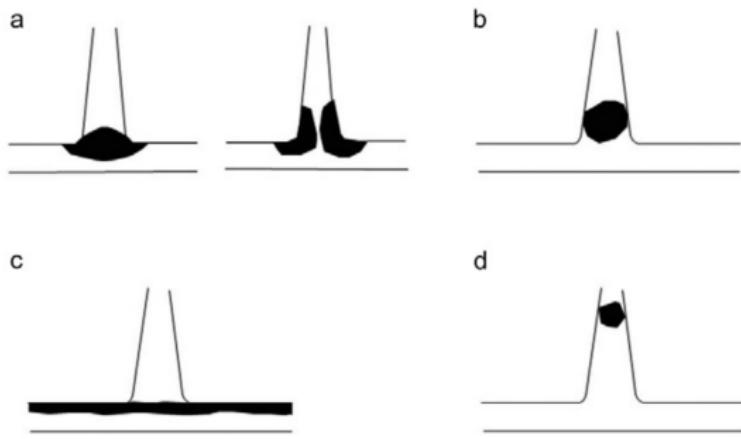
Results of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Trial by Stroke Subtypes

Pierre Amarenco, MD; Oscar Benavente, MD; Larry B. Goldstein, MD; Alfred Callahan III, MD;
 Henrik Silleßen, 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



Statin therapy for 5 years in 10,000 patients

Table: Benefit of statin therapy

| 2 mmol/L reduction in LDL-C | Prevention of MVE |
|-----------------------------|-------------------|
| in high risk group | 1000 |
| in low risk group | 500 |

MVE means major vascular events.

Table: Adverse effects of statin therapy

| | Occurrence of adverse events |
|--------------------|------------------------------|
| Myopathy | 5 |
| New onset DM | 50 - 100 |
| Hemorrhagic stroke | 5 - 10 |

Collins R. et al. Lancet 2016

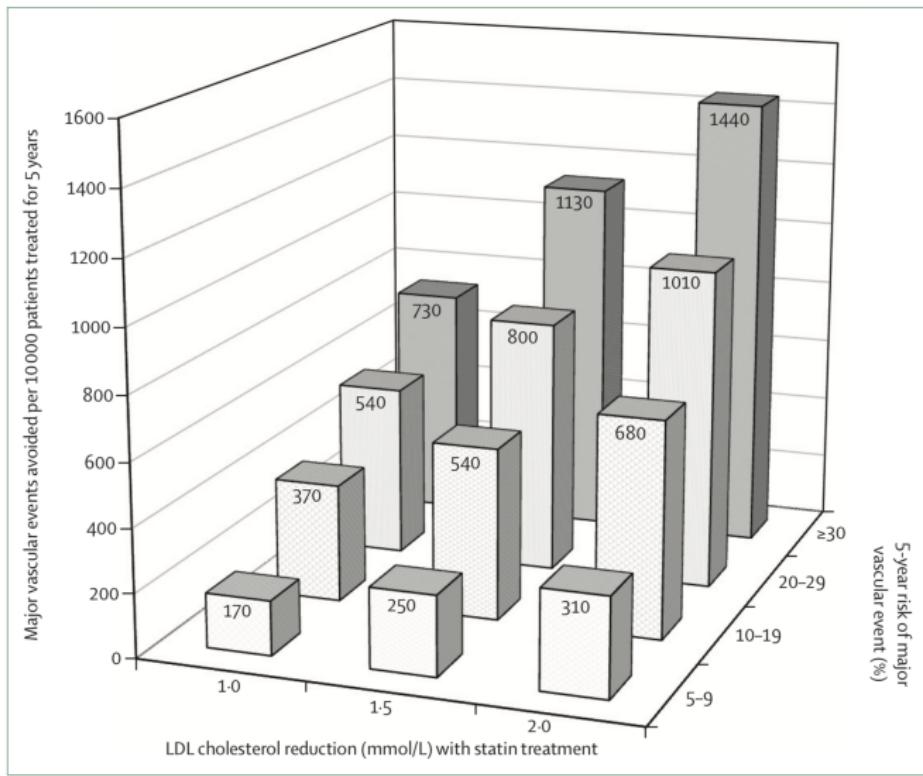


Figure 5: Predicted absolute reductions in risks of major vascular events (after the first year) by lowering LDL cholesterol with statin therapy for 5 years in people at different levels of absolute risk

Collins R. et al. Lancet 2016

Stroke has diverse etiologies

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

Arteriolosclerosis

- Hypertensive SVD
- Age-related SVD
- Associated with Aging, diabetes, and hypertension
- Pathology**
 - Lipohyalinosis
 - Microatheroma
 - Microaneurysm

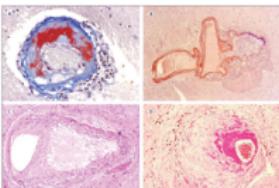
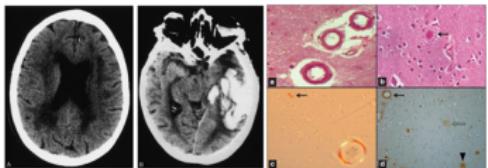


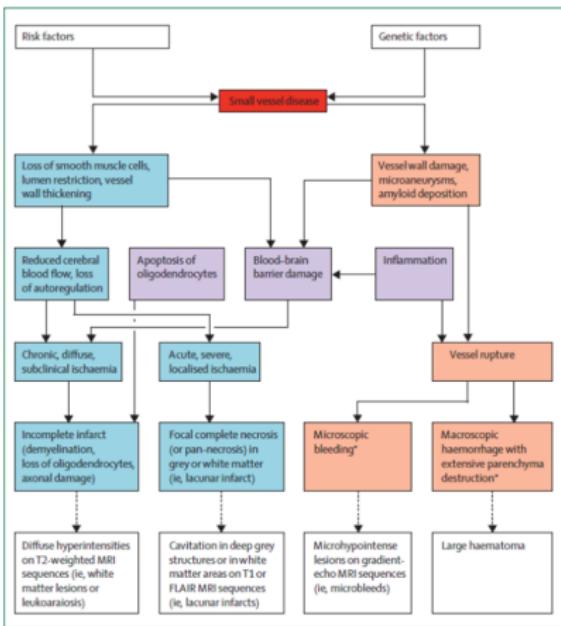
Figure 1 Histological features of small vessel disease. The top row shows the right anterior cerebral artery of a 70-year-old asymptomatic patient who died after developing massive intracranial haemorrhage. The bottom row shows the same vessel from a 70-year-old patient with a history of hypertension and a previous stroke. Pathology includes lipohyalinosis and microaneurysms.

Cerebral Amyloid Angiopathy

- Progressive accumulation of congophilic amyloid protein
- Small to medium sized arteries in the leptomeningeal space and cortex
- AD and general elderly population (as frequent as 50% in the ninth decade)



Pantoni L. Lancet Neurol 2010; 9: 689–701



Various manifestations of SVD

| | Recent small subcortical infarct | White matter hyperintensity | Lacune | Perivascular space | Cerebral microbleed |
|------------------|----------------------------------|-----------------------------|-------------------------------|--------------------------------------|---|
| Example image | | | | | |
| Schematic | | | | | |
| Usual diameter | ≤20 mm | Variable | 3-15 mm | ≤2 mm | ≤10 mm |
| Comment | Best identified on DWI | Located in white matter | Usually have hyperintense rim | Most linear without hyperintense rim | Detected on GRE seq, round or ovoid, blooming |
| DWI | ↑ | ↔ | ↔/(↓) | ↔ | ↔ |
| FLAIR | ↑ | ↑ | ↓ | ↓ | ↔ |
| T2 | ↑ | ↑ | ↑ | ↑ | ↔ |
| T1 | ↓ | ↔/(↓) | ↓ | ↓ | ↔ |
| T2*-weighted GRE | ↔ | ↑ | ↔(↓ if haemorrhage) | ↔ | ↓↓ |
| ↑ | Increased signal | ↓ | Decreased signal | ↔ | Iso-intense signal |

Figure 2: MRI findings for lesions related to small vessel disease

Wardlaw JM et al. Lancet Neurol 2013; 12: 822–38

Cerebral Microbleeds and Recurrent Stroke Risk

Systematic Review and Meta-Analysis of Prospective Ischemic Stroke and Transient Ischemic Attack Cohorts

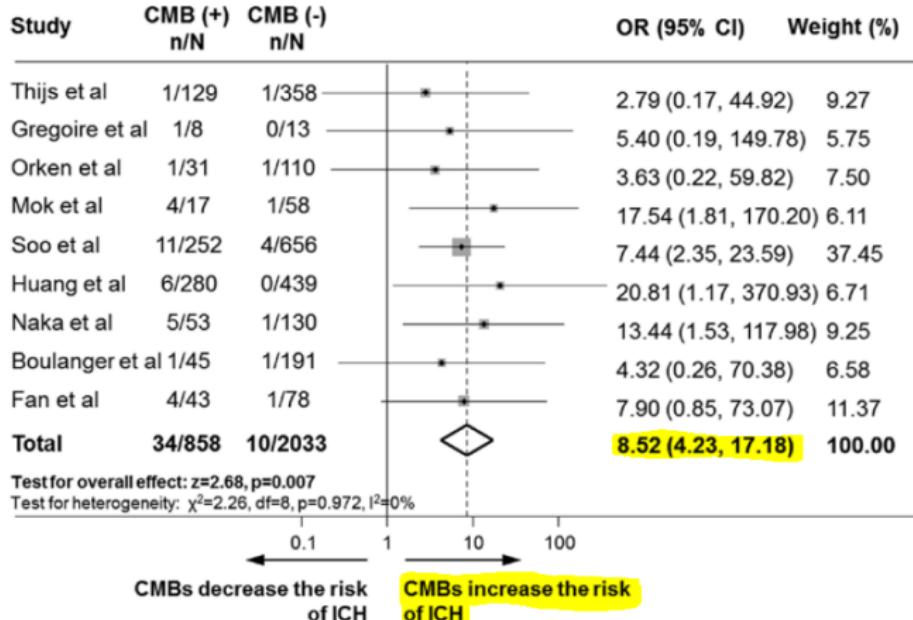
Andreas Charidimou, MSc; Puneet Kakar, MD; Zoe Fox, PhD; David J. Werring, PhD

Background and Purpose—To evaluate cerebral microbleeds (CMBs) and future stroke risk (including intracerebral hemorrhage [ICH]) in patients with ischemic stroke (IS) or transient ischemic attack.

Materials and Methods—A systematic review and meta-analysis of prospective cohorts with recent IS/transient ischemic attack. We critically appraised studies and calculated pooled odds ratios (ORs), using the Mantel-Haenszel fixed-effects method, for ICH or recurrent IS, in patients with versus without CMBs.

Results—We pooled data from 10 cohorts, including 3067 patients. CMBs were associated with a significant increased risk of any recurrent stroke (OR, 2.25; 95% confidence interval [95% CI], 1.70–2.98; $P<0.0001$), ICH (OR, 8.52; 95%CI, 4.23–17.18; $P=0.007$), and IS (OR, 1.55; 95%CI, 1.12–2.13; $P<0.0001$). When stratified by study population ethnicity (Asian versus Western [mainly white European]), the association of CMBs with ICH was significant for Asian cohorts (5 studies; n=1915; OR, 10.43; 95%CI, 4.59–23.72; $P<0.0001$) but borderline and of lower magnitude for Western cohorts (4 studies; n=885; OR, 3.87; 95%CI, 0.91–16.4; $P=0.066$). By contrast, there was a significant association of CMBs with recurrent IS in Western (3 studies; n=899) but not Asian cohorts (4 studies; n=1357; OR, 2.23; 95%CI, 1.29–3.85; $P=0.004$ compared with OR, 1.30; 95%CI, 0.88–1.93; $P=0.192$, respectively).

Conclusions—There is consistent evidence of an increased risk of recurrent stroke after IS or transient ischemic attack in patients with CMBs. The risk for spontaneous ICH appears to be greater than the risk for recurrent IS. Our findings also suggest that the balance of risk for ICH versus IS differs between Asian and Western cohorts. (*Stroke*. 2013;44: 995–1001.)



Charidimou A et al. Am J Cardiol 2013;112:1230e1234

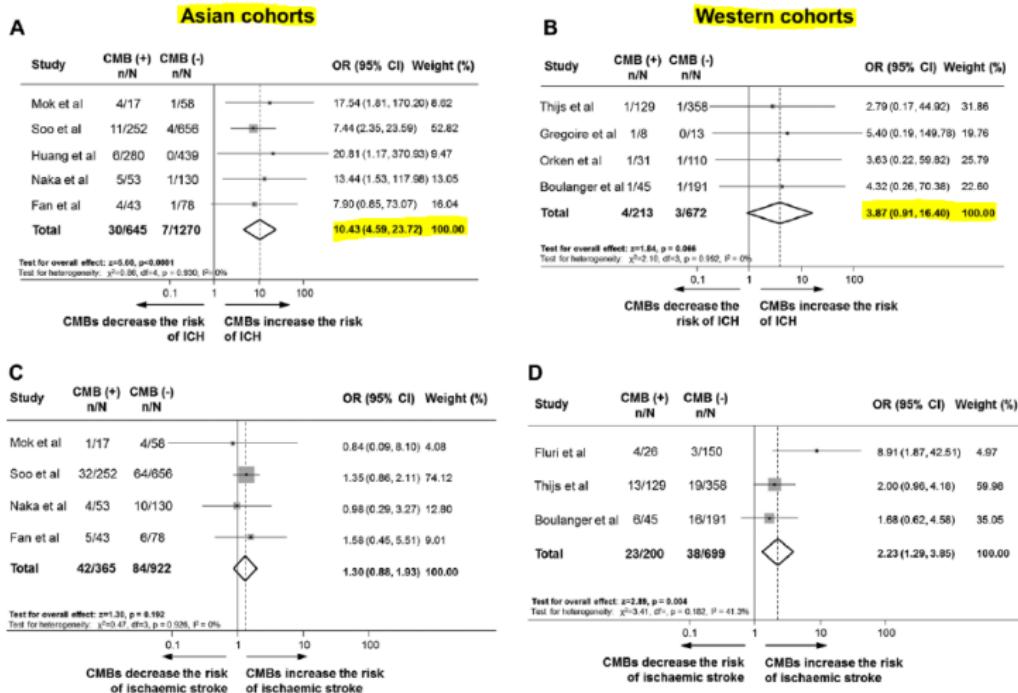
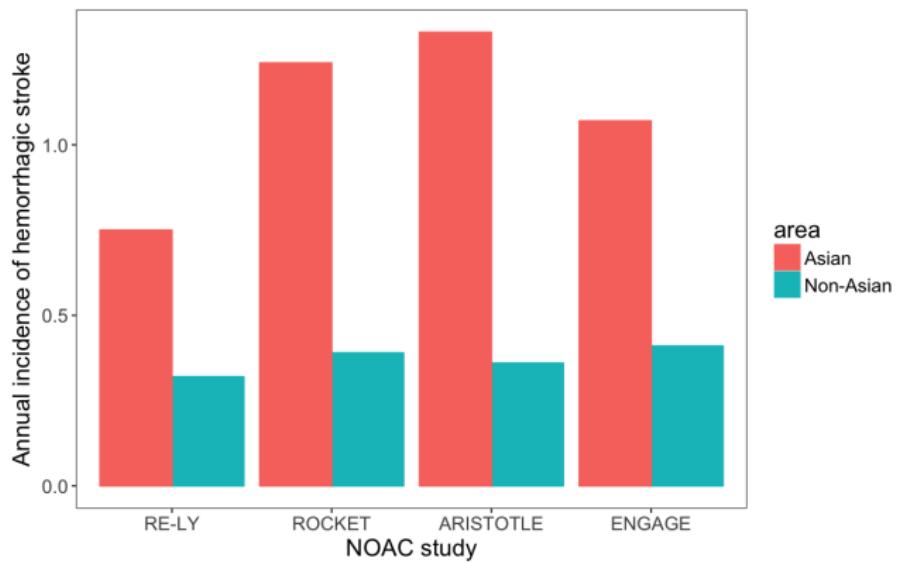


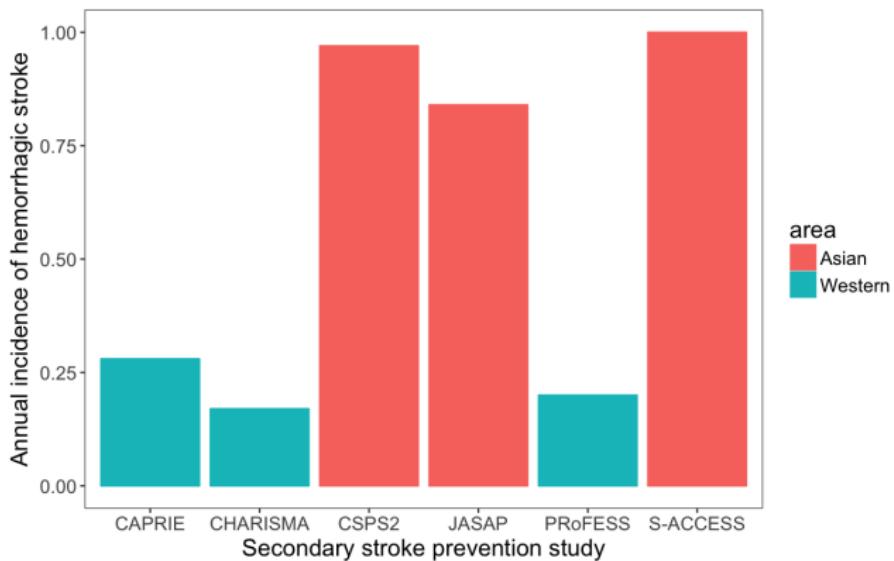
Figure 4. Meta-analysis of the risk of spontaneous intracerebral hemorrhage (ICH; A and B) and ischemic stroke (C and D) stratified by the dominant ethnicity of subjects included in each cohort as Asian or Western (white), with and without cerebral microbleeds (CMBs).

Hemorrhagic stroke on warfarin



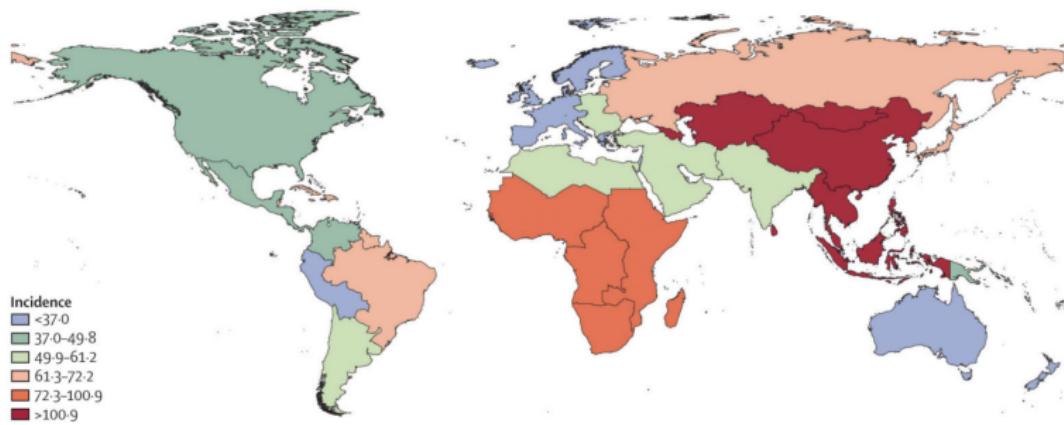
Lip GYH et al, Int J Cardiol 2015;180:246

Incidence of Cerebral Hemorrhage with Aspirin



1. Kim JS, et al. Int J Stroke 2015;10 Suppl 1:1-9.

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



Lancet Glob Health. 2013 Nov; 1(5): e259-e281.

Take-Home Message

- The decision on the significance of atherosclerotic stenosis should be made individually.
 - Statin is an effective treatment option for preventing subsequent vascular disease in patients with insignificant atherosclerotic stenosis.
-
- The use of statin should be decided after considering the risk of atherosclerotic disease and the risk of adverse effects.
 - The intensity of statin, the level of LDL cholesterol and the risk of adverse events such as hemorrhagic stroke should be considered.