Lipid Target in Patients with Ischemic Stroke or TIA

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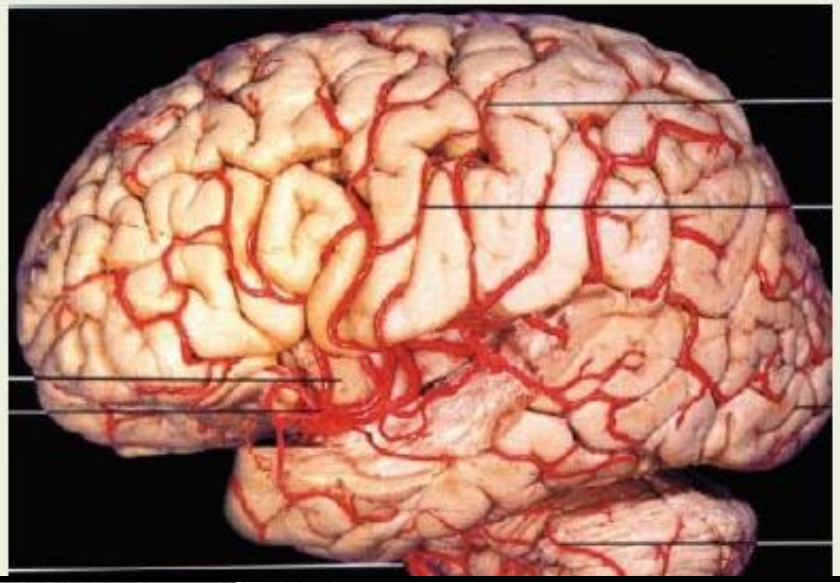
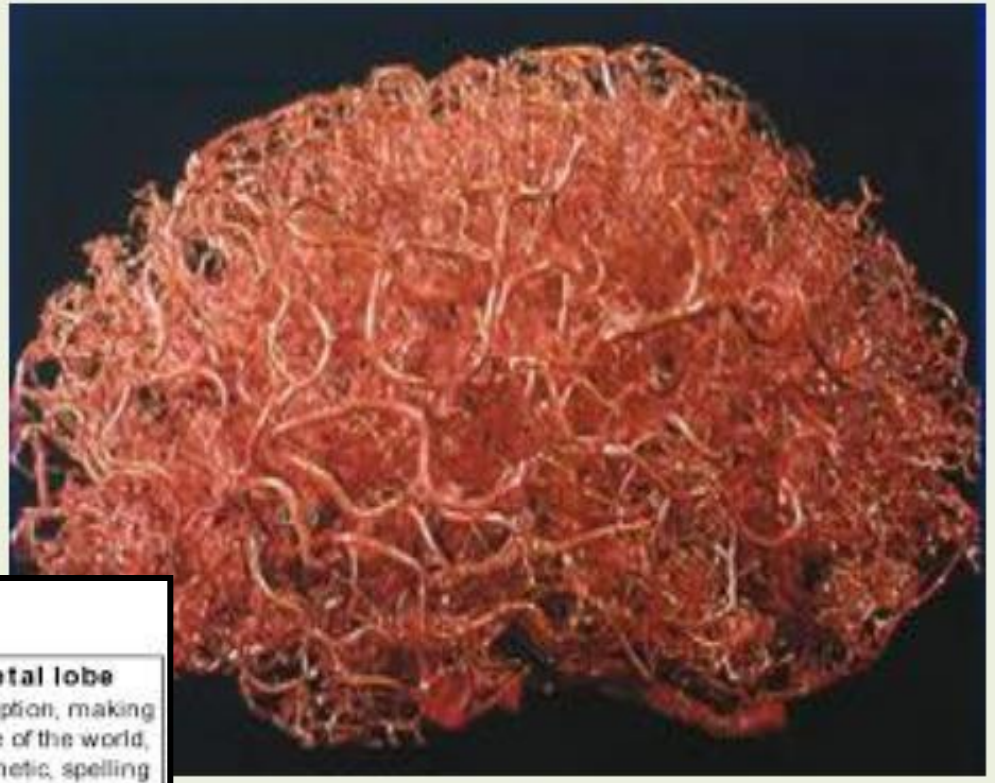
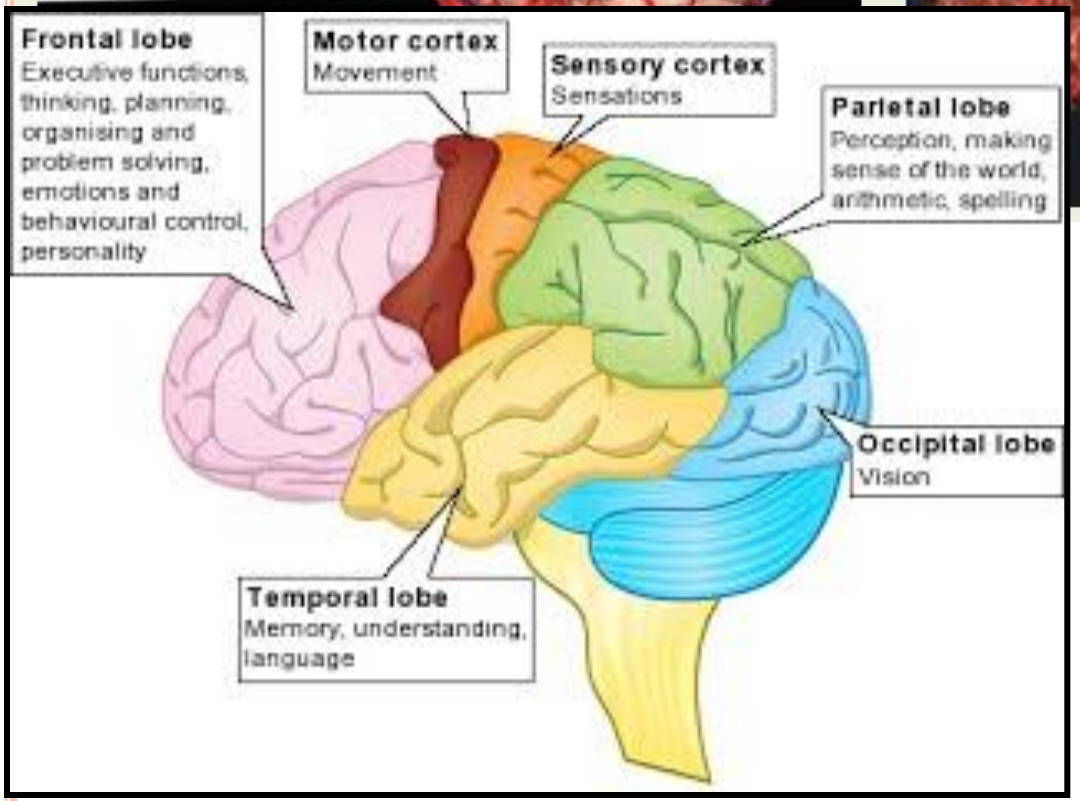
台大醫院神經部腦中風中心
March 23, 2017



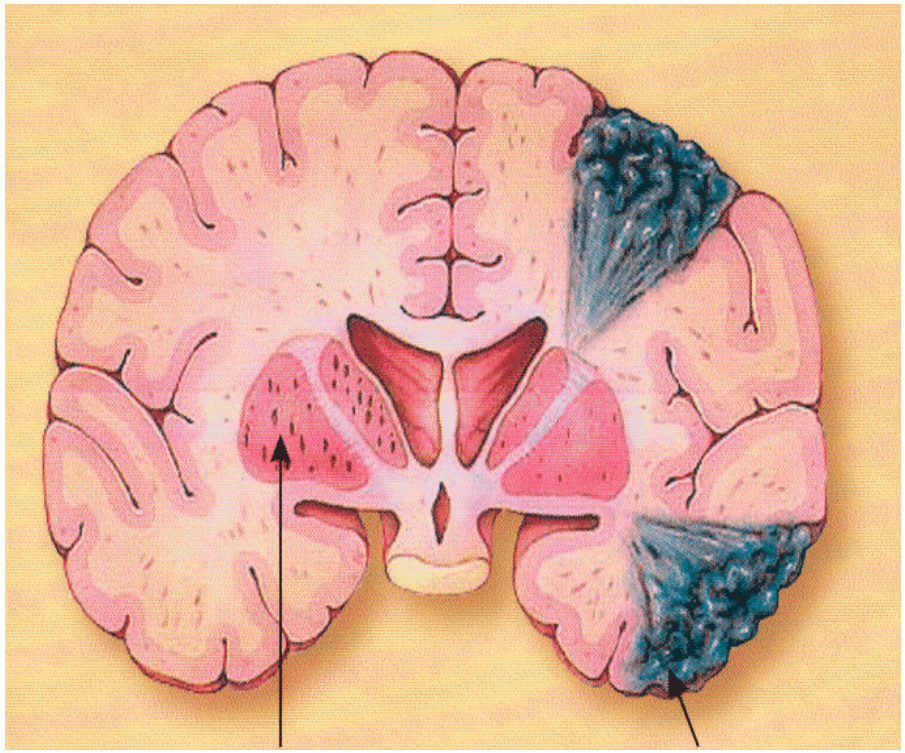


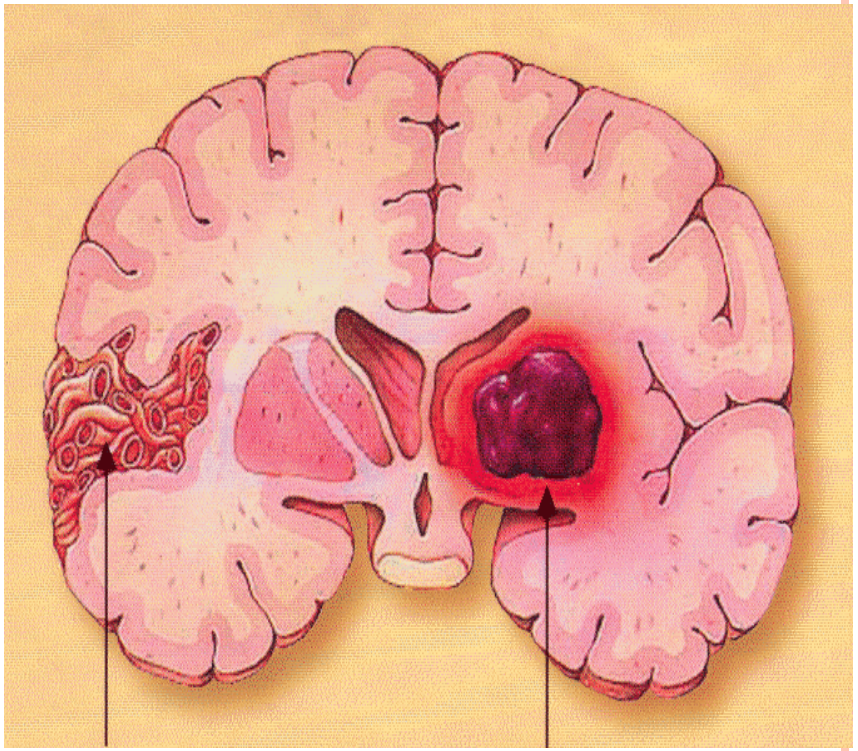


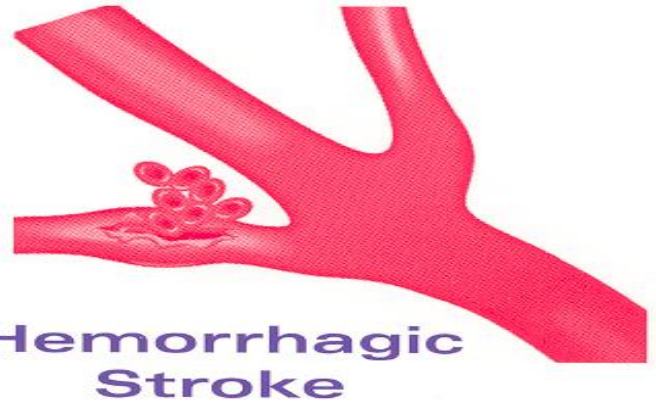
Brain, Vasculature, & Function

J Young Invetigators 2008 & ECMS School Counseling

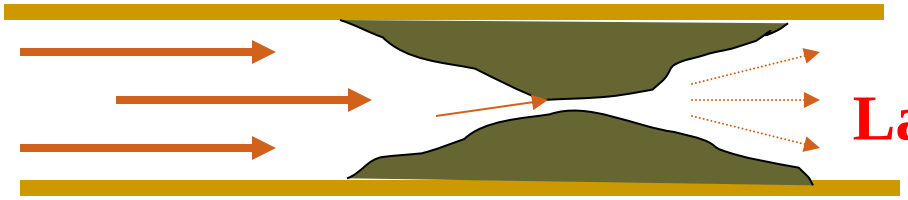
Stroke Subtypes



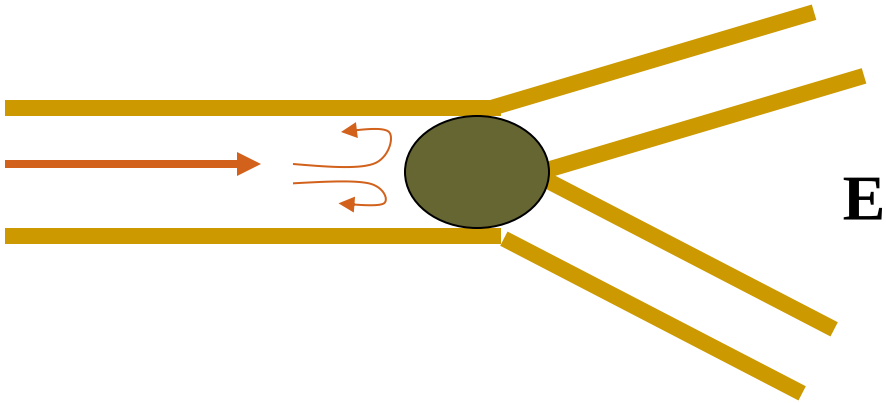




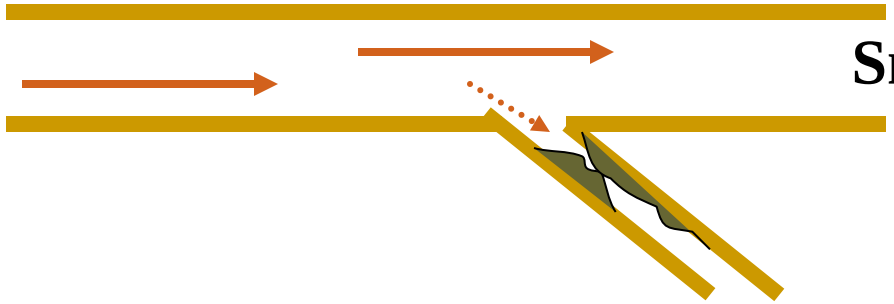
Classification of Ischemic Stroke



Large artery atherothrombosis

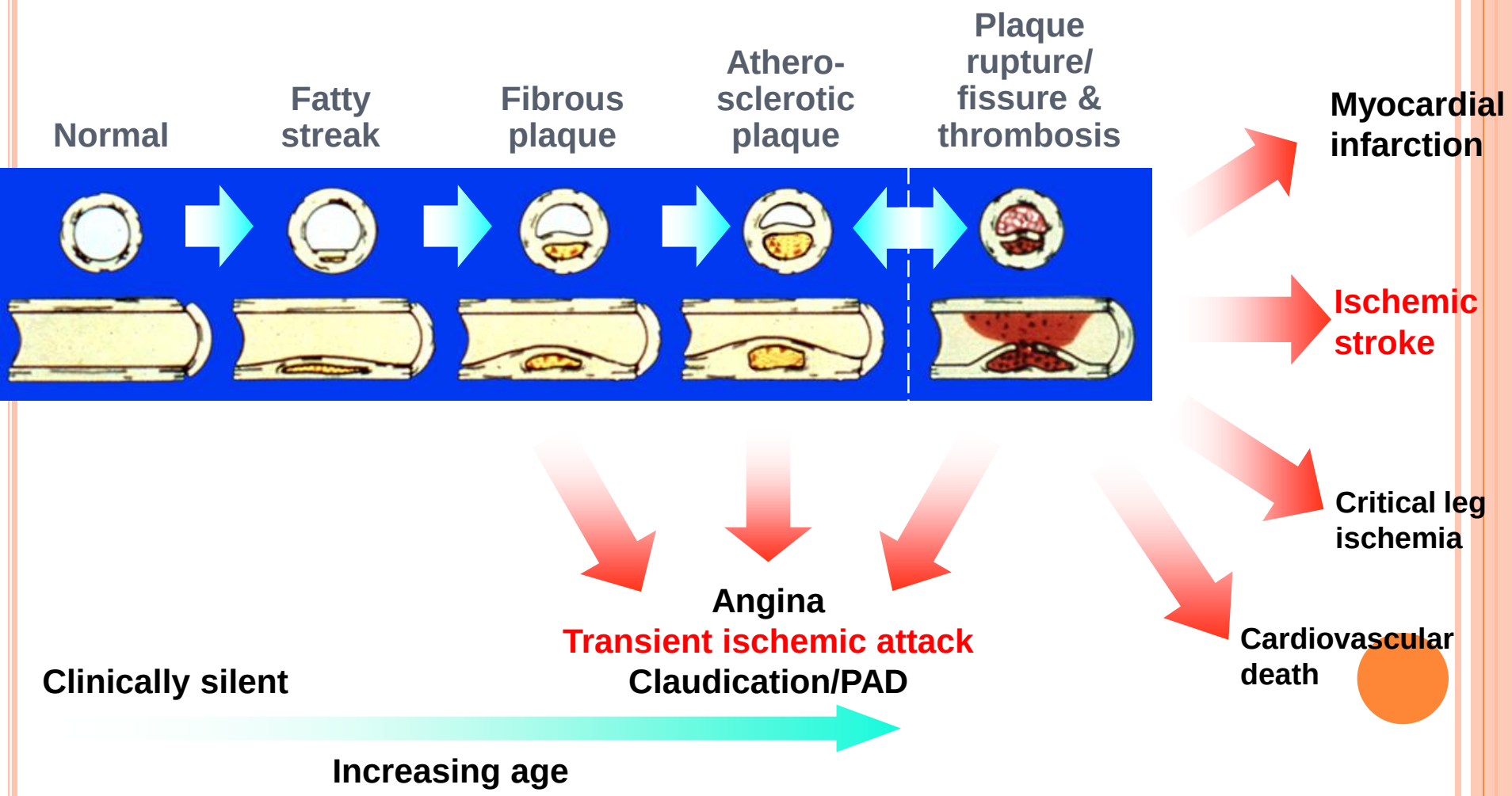


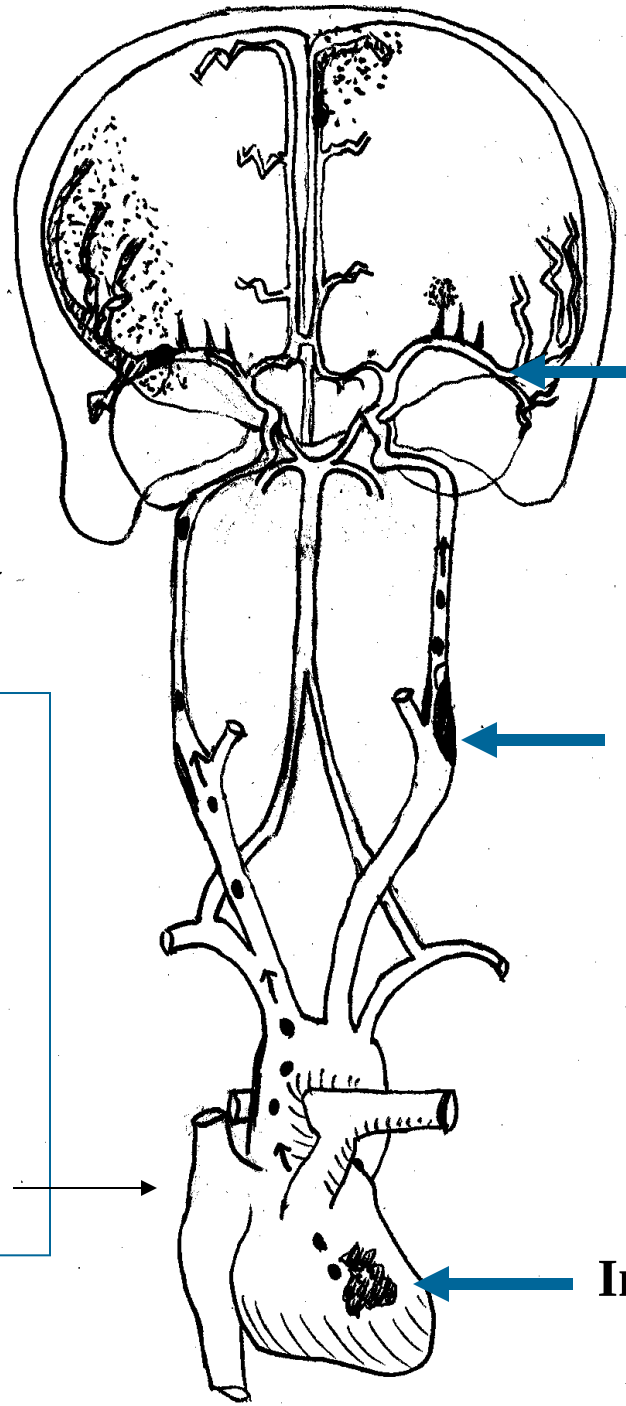
Embolic stroke



Small artery occlusion

Atherothrombosis: a Progressive Process

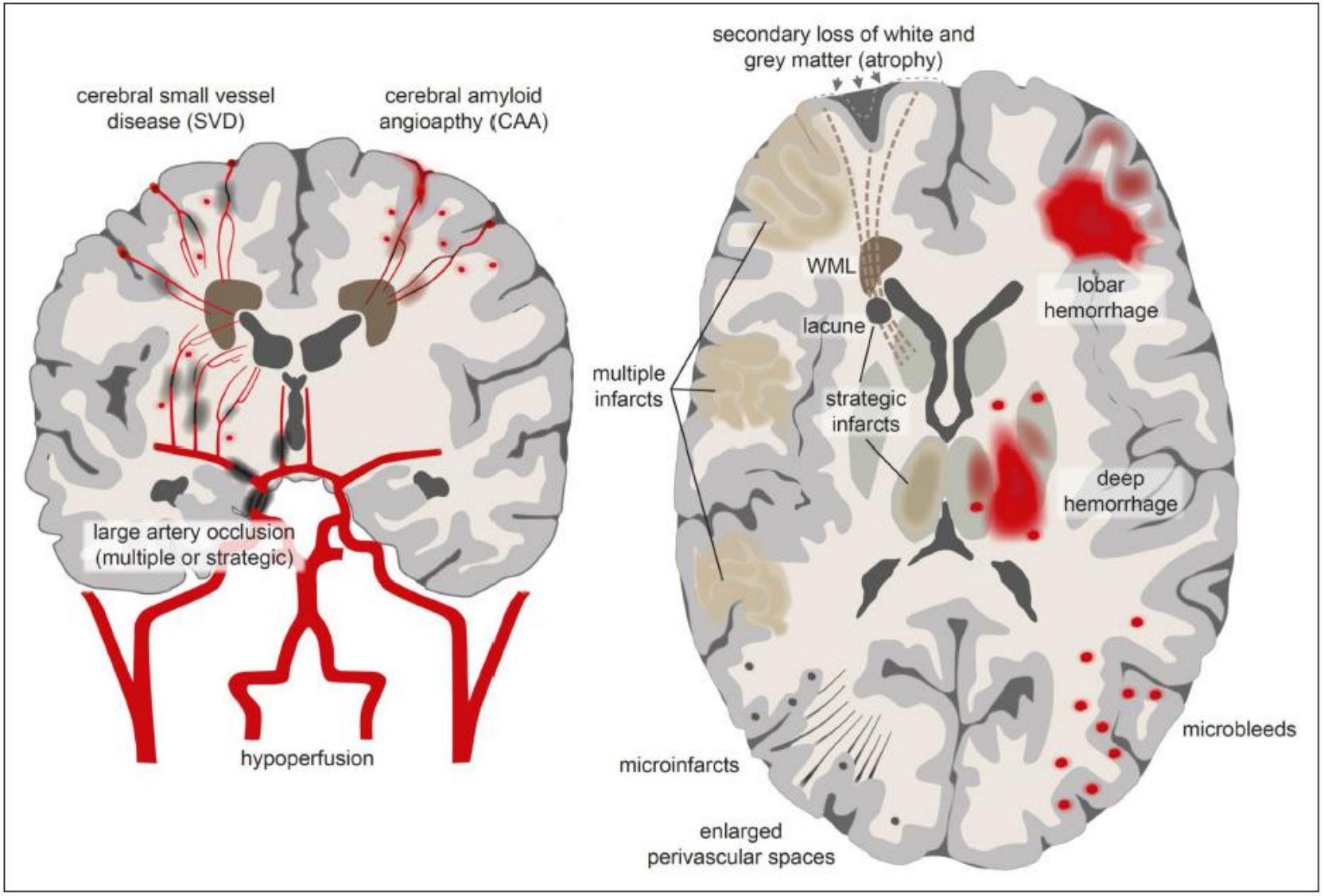




Heart Disease

1. **AF**
2. **VHD**
3. **Cardiomyopathy**
4. **Coronary disease**
5. **Septum defect**

Small Vessel Disease: HT, smoking, gene..



***Circulation Research*. 2017**

Other specific causes of ischemic stroke

Coagulopathy
- Protein C
  - *arterial infarct*
  - *cerebral venous thrombosis*
- Protein S
  - *arterial infarct*
  - *cerebral venous thrombosis*
- Polycythemia vera
- Antiphospholipid syndrome
- Trousseau's syndrome
- Idiopathic thrombocytopenic purpura
- Aplastic anemia
- Hemolytic anemia
- Myeloproliferative disorder
- Leukemia or lymphoma

Dissection
- VA dissection
- ICA dissection
- MCA dissection
- CCA dissection due to aortic arch aneurysm

Post-irradiation vasculopathy

Nephrotic syndrome

SLE with or without nephrotic syndrome

Cerebral venous thrombosis

Giant aneurysm

Infection
- Syphilis
- Tuberculosis
- Cryptococcus
- Mucomycosis

Migrainous stroke

Arteritis
- Isolated CNS angitis
- Takayasu's arteritis
- Moyamoya disease

Hypereosinophilic syndrome

Hypovolemic shock

Post-trauma infarct

Genetic disease: MELAS/CADASIL

Behcet's disease

Post-renal transplant

Cryptogenic Stroke

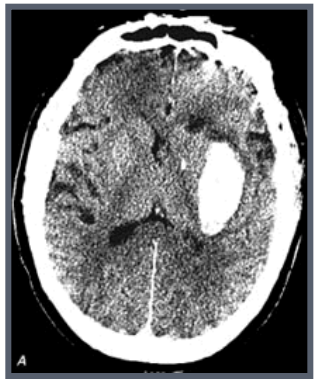
- Brain infarction that is not attributable to a source of definite CE, LAA, SVO despite a standard vascular, cardiac, and serologic evaluation.

- **Stroke of undetermined etiology**
  - **Two or more causes identified**
  - **Negative evaluation**
  - **Incomplete evaluation**

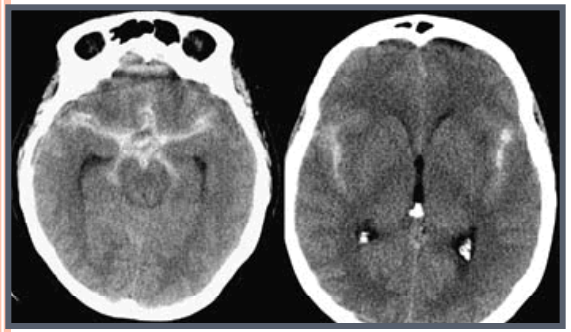
AHA website

Stroke Subtype in Taiwan
NTUH Stroke Registry 1995-2002

Hemorrhagic stroke (28%)

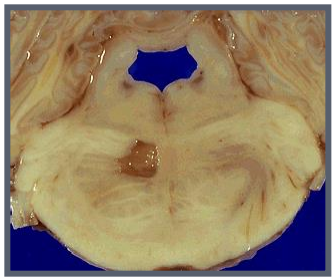


Intracerebral hemorrhage (23%)

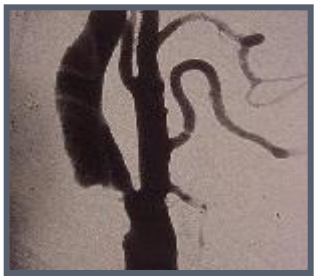


SAH (5%)

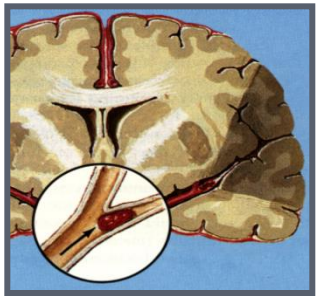
Ischemic stroke (74%)



Lacunar small vessel disease (31%)



Atherothrombotic disease (15%)



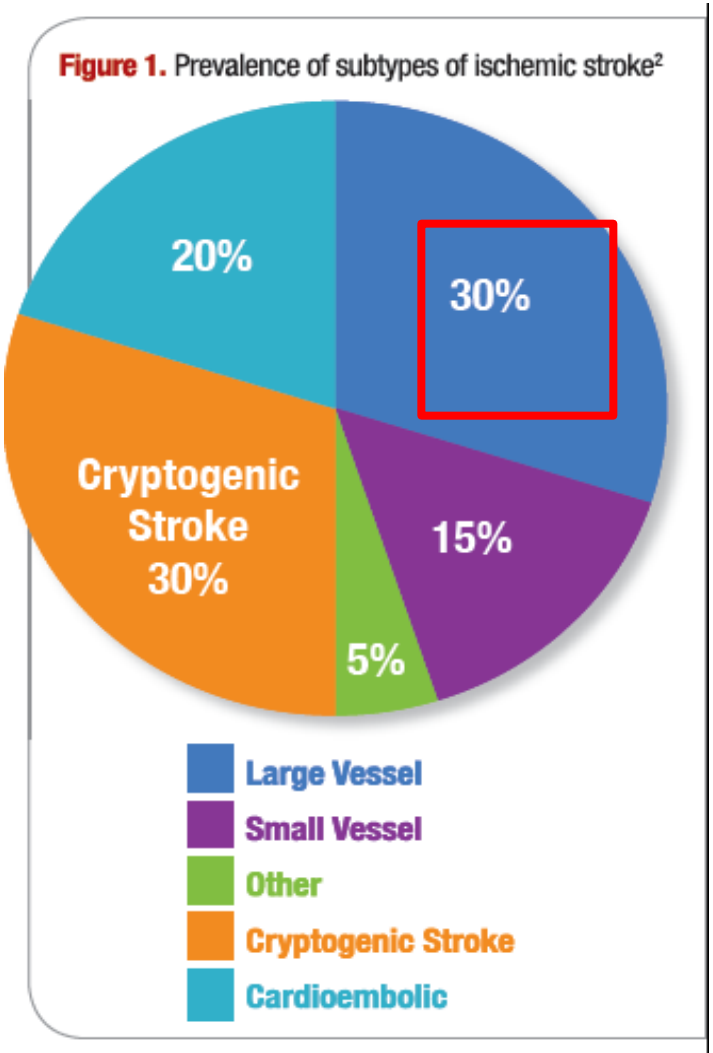
Embolism (19%)

Cryptogenic (29%)

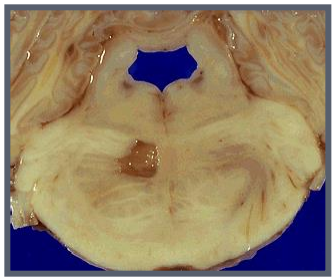
Stroke Subtype in Taiwan & the U.S

Taiwan Stroke Registration & AHA

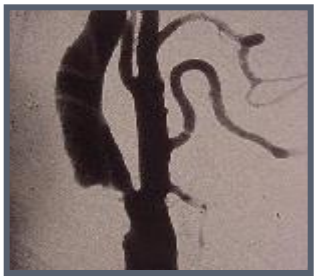
Ischemic stroke (87%)



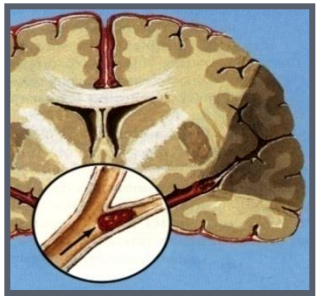
Ischemic stroke (81%)



Lacunar small vessel disease (38%)



Atherothrombotic disease (28%)



Embolism (11%)

Cryptogenic (22%)

2010 Circulation

Table 2. Key Variables in Different Stroke Types

Items	Ischemic Stroke/TIA n=24 695	ICH n=4913	SAH n=846
Age (median, IQR)	69.9 (59.6–77.9)	62.2 (51.9–73.7)	57.6 (47.4–70.4)
Sex			
Male (%)	59.8	65.7	40.7
Body mass index	24.3 (22.0–26.8)	23.9 (21.5–26.7)	23.5 (21.2–26.0)
Arrival time (hour)* (median, IQR)	5.5 (1.8–19.7)	2.1 (0.9–5.2)	2.7 (0.9–7)
Length of stay (day) (median, IQR)	8 (5–15)	13 (7–29)	17 (7–33)
MRI (%)	61.4	10.8	11.0
CT (%)	92.1	98.6	99.3
NIHSS (admission) (median, IQR)	5 (2–9)	10 (4–21)	4 (0–18)
Medical history (%)			
Atrial fibrillation	16.5	6.4	5.4
Previous stroke/TIA	34.1	24.1	8.4
CAD/prior MI	13.6	6.9	4.7
Carotid stenosis	10.6	. . .	. . .
Diabetes mellitus	45.4	37.0	37.2
Hypertension	79.2	84.9	65.3
Dyslipidemia	49.4	29.4	20.5

Table 3. Performance Measures in Acute Stroke Care and Prevention From 2006 to 2008 in the Taiwan Stroke Registry

Performance/Safety Measures (%)	2006	2007	2008	Total	Trend Test β (SE), P Value
Performance measures					
IV tPA for 2 hours*	7.67	8.55	10.42	8.84	0.17 (0.09), 0.0581#
Antithrombotics during hospitalization†	92.39	94.54	94.76	94.14	0.21 (0.04), <0.001#
Antithrombotics at discharge‡	85.57	85.09	86.60	85.54	0.04 (0.03), 0.1012#
Anticoagulation for atrial fibrillation§	32.12	27.71	26.14	28.28	−0.15 (0.05), 0.0060#
Lipid-lowering drug at discharge‖	37.00	38.97	39.54	38.69	0.05 (0.03), 0.0629#
Safety measure					
Symptomatic ICH after IV tPA therapy	6.78	9.41	7.00	8.21	−0.03 (0.27), 0.9078#
Composite measure, mean±SD	74.00±4.59	74.20±5.82	73.19±6.32	73.12±5.33	0.02 (0.01), 0.0581**

*Patients with ischemic stroke presenting within 2 hours of symptom onset who received IV tPA within 3 hours of symptom onset.

†Antithrombotics (antiplatelet or anticoagulant) prescription for patients with ischemic stroke or TIA during hospitalization.

‡Antithrombotic (antiplatelet or anticoagulant) prescription for patients with ischemic stroke or TIA at discharge.

§Warfarin prescription for patients with ischemic stroke or TIA with atrial fibrillation at discharge.

‖Lipid-lowering drug prescription for patients with ischemic stroke or TIA with low-density lipoprotein >100 mg/dl or patients taking lipid lowering agents on admission.

#Trends of performance/safety measures from 2006 to 2008 were tested by the logistic regression model.

**Composite measure by the linear regression model using generalized estimating equations accounting for within-hospital correlation.[11]

SE indicates standard error.

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REVIEW ARTICLE

2017 Taiwan lipid guidelines for high risk patients☆

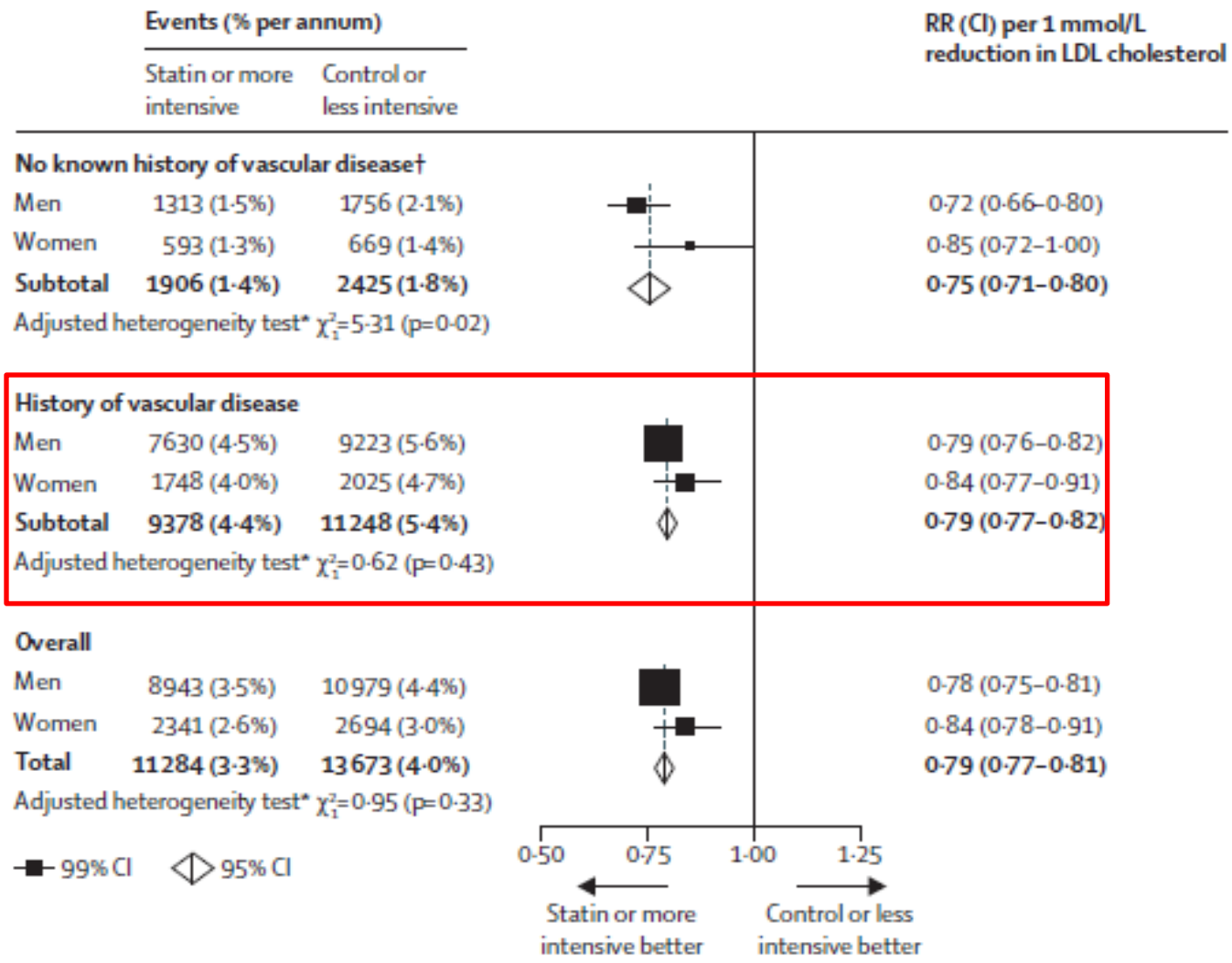
Yi-Heng Li [a], Kwo-Chang Ueng [b,c], Jiann-Shing Jeng [d], Min-Ji Charng [e,f], Tsung-Hsien Lin [g,h], Kuo-Liong Chien [i,j], Chih-Yuan Wang [j], Ting-Hsing Chao [a], Ping-Yen Liu [a], Cheng-Huang Su [k,l], Shih-Chieh Chien [k], Chia-Wei Liou [m], Sung-Chun Tang [d], Chun-Chuan Lee [k], Tse-Ya Yu [n], Jaw-Wen Chen [e,f,o], Chau-Chung Wu [j], Hung-I Yeh [k,l,*], for The Writing Group of 2017 Taiwan Lipid Guidelines for High Risk Patients

Recommendation for Ischemic Stroke, TIA and Carotid Stenosis From Taiwan Lipid Guideline

- **Statin in Stroke Prevention**
- **Statin in Acute Stroke**
- **Statin in Carotid Stenosis**

Efficacy and Safety of LDL-Lowering Therapy :

Meta-analysis of 27 Trials with 174 000 Individuals

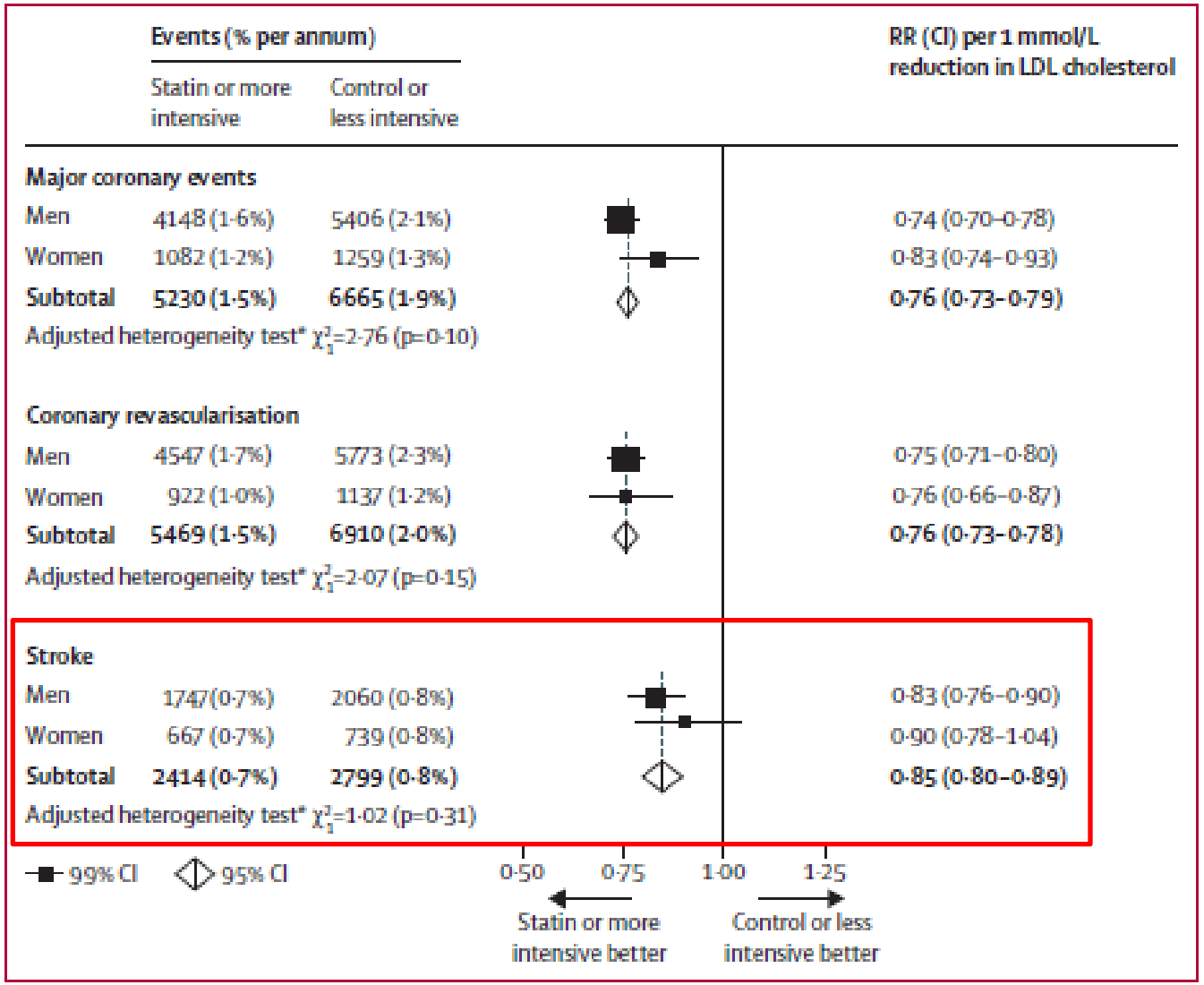


Effects on major vascular events per 1.0 mmol/L reduction in LDL cholesterol

***Lancet* 2015;385:1397-405.**

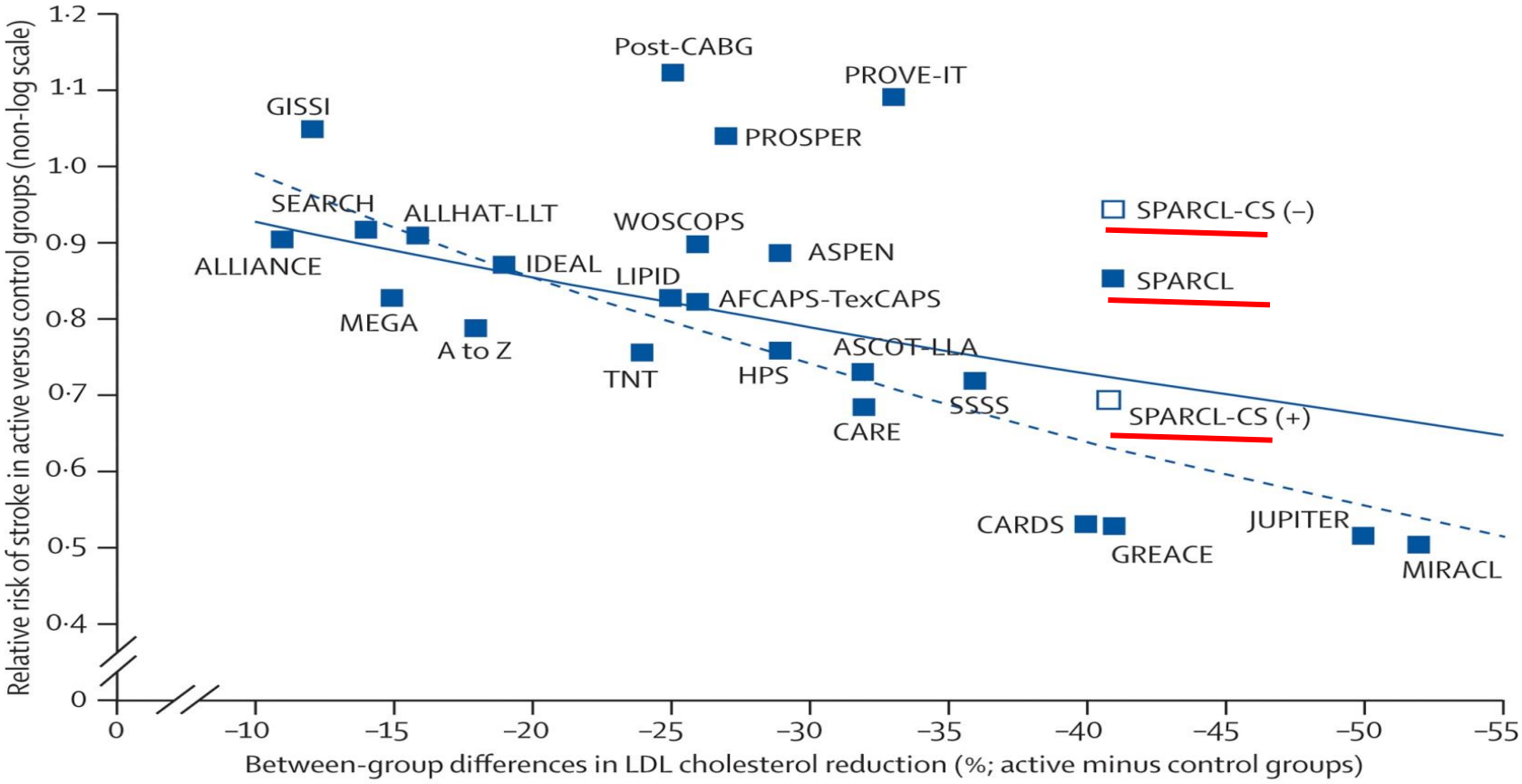
Efficacy and Safety of LDL-Lowering Therapy :

Meta-analysis of 27 Trials with 174 000 Individuals



Effects on major vascular events per 1.0 mmol/L reduction in LDL cholesterol ***Lancet* 2015;385:1397-405.**

Association Between LDL Cholesterol Reduction and Stroke Incidence Among the Major Statin Trials



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

Lancet Neurol. 2009;8:45363.

SPARCL

Only trial to date for lipid control in secondary stroke prevention

Patient Population

- 205 sites worldwide
- Previously documented stroke or TIA within 6 months
- No history of CHD
- LDL-C levels ≥100 mg/dL and ≤190 mg/dL

4,731 Patients

Double-Blind Period

- **Atorvastatin 80 mg/day**
- **Placebo**

Primary End Point
Time to the First Occurrence of a Fatal or Nonfatal Stroke

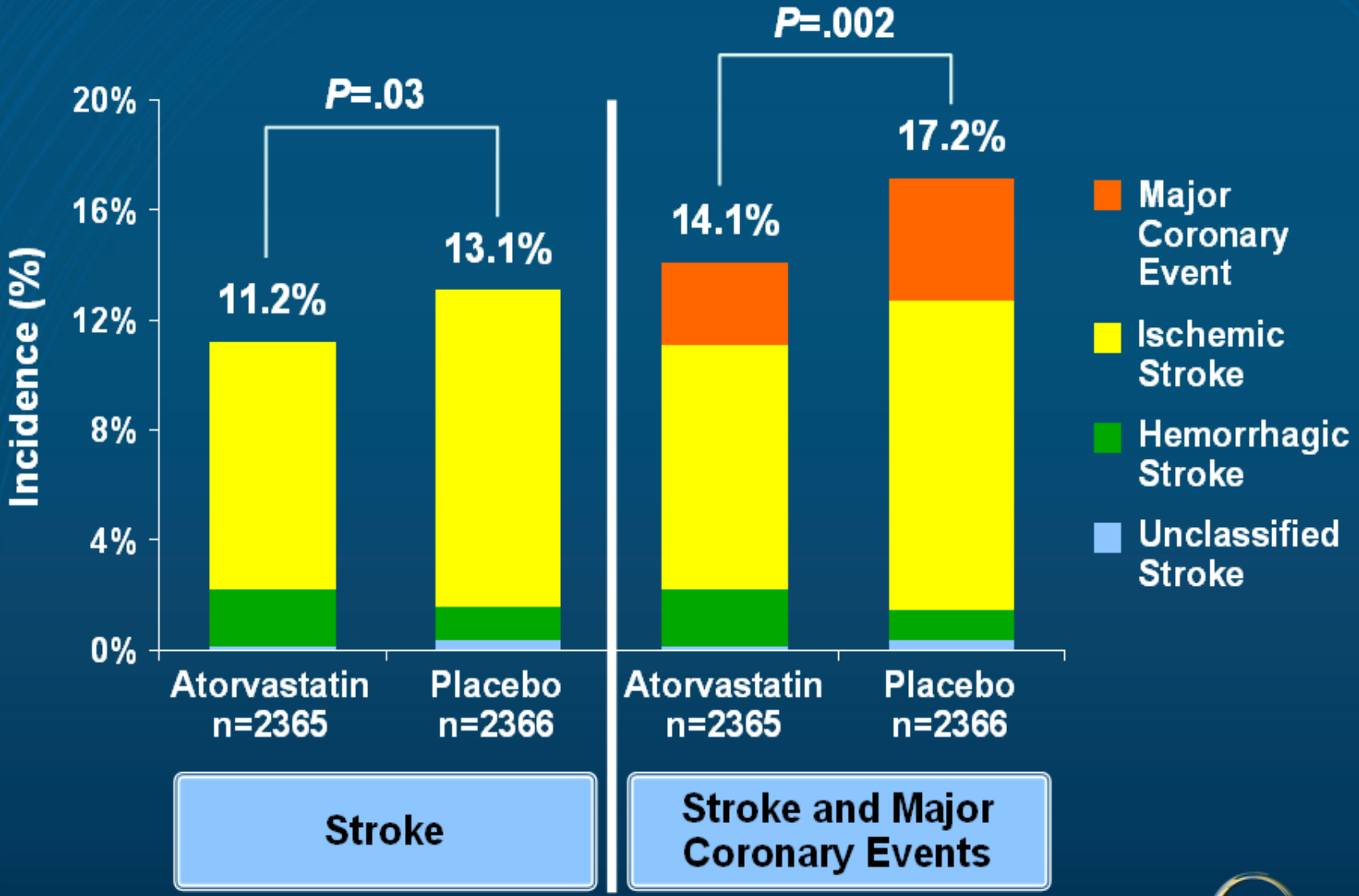
TIA, transient ischemic attack; CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol.

The SPARCL Investigators. *Cerebrovasc Dis*. 2003;16:389-395.
The SPARCL Investigators. *N Engl J Med*. 2006;355:549-559.

SPARCL
Stroke Prevention by Aggressive Reduction in Cholesterol Levels

SPARCL

Outcome events: stroke and major coronary events



The SPARCL Investigators. *N Engl J Med*. 2006;355:549-559.

SPARCL

Post-Hoc Analysis of Ischemic and Hemorrhagic Stroke

	Atorvastatin (n=2365) n (%)	Placebo (n=2366) n (%)	HR (95% CI)*	*P*-value
Prespecified Analysis				
Primary Endpoint	265 (11.2)	311 (13.1)	0.84 (0.71, 0.99)	.03
Fatal Stroke	24 (1.0)	41 (1.7)	0.57 (0.35, 0.95)	.03
Non-fatal Stroke	247 (10.4)	280 (11.8)	0.87 (0.73, 1.03)	.11
Post-Hoc Analysis				
Ischemic	218 (9.2)	274 (11.6)	0.78 (0.66, 0.94)	.01
Hemorrhagic	55 (2.3)	33 (1.4)	1.66 (1.08, 2.55)	.02

* Treatment effect from Cox proportional hazards models with pre-specified adjustment for geographical region, entry event, time since entry event, gender, and baseline age.

HR, hazard ratio; CI, confidence interval.

The SPARCL Investigators. *N Engl J Med*. 2006;355:549-559.

SPARCL

Comments and Opinions

(*Stroke*. 2018;49:240-246.

Statin Treatment in Patients With Intracerebral Hemorrhage

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

Ever since the publication of the SPARCL trial (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) in 2006, neurologists became aware of the fact that statins may increase the risk for future intracerebral hemorrhage (ICH) in patients with previous ischemic stroke or ICH.[1,2] At the same time, observational studies reported an increased risk for hemorrhagic transformation or even symptomatic bleeding in ischemic stroke patients undergoing thrombolysis who were pretreated with statins.[3,4] As a con-

Statin Therapy and ICH Risk

~ A Meta-analysis Of 31 Randomized Controlled Trials

- 91,588 subjects in active group and 91,215 in control group.

- No significant difference in incidence of ICH (OR, 1.08; 95% CI, 0.88 –1.32; P=0.47).
  - ICH risk was not related to the degree of LDL reduction or achieved LDL cholesterol.
  - Decrease in total stroke (OR, 0.84; 95% CI, 0.78–0.91; P<0.0001) and all-cause mortality (OR, 0.92; CI, 0.87– 0.96; P=0.0007).

Stroke. 2012;43:2149-56.

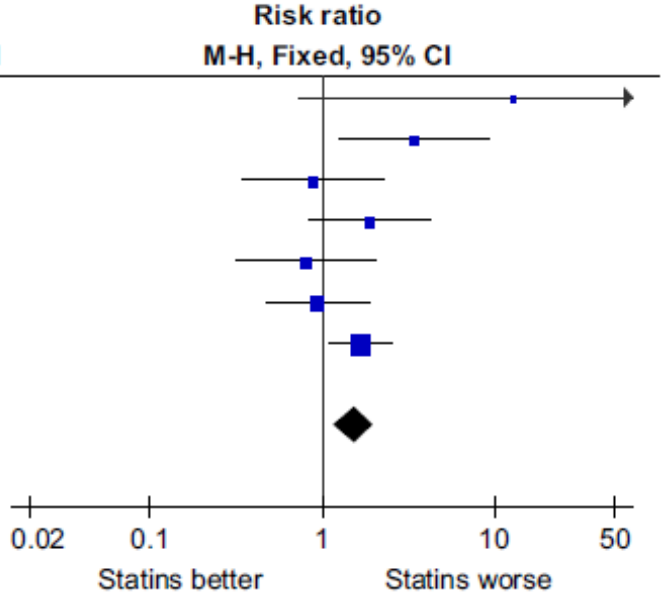
High-dose Statin Therapy and ICH Risk

- High dose of statins was defined as atorvastatin 80 mg, simvastatin 80 mg, pravastatin 40 mg, rosuvastatin 20 mg per day.
- Seven RCTs involving 31,099 subjects receiving high-dose statin and 31,105 subjects.

	Active		Control			Risk ratio
Study or subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
ATOZ 2004	6	2265	0	2232	0.6%	12.81 [0.72, 227.27]
ALLHAT 2002	17	5170	5	5185	6.0%	3.41 [1.26, 9.24]
JUPITER 2008	8	8901	9	8901	10.8%	0.89 [0.34, 2.30]
LIPID 1998	17	4512	9	4502	10.8%	1.88 [0.84, 4.22]
PROSPER 2002	8	2891	10	2913	11.9%	0.81 [0.32, 2.04]
TNT 2005	16	4995	17	5006	20.4%	0.94 [0.48, 1.86]
SPARCL 2006	55	2365	33	2366	39.5%	1.67 [1.09, 2.56]
Total (95% CI)		**31099**		**31105**	**100.0%**	**1.53 [1.16, 2.01]**
Total events	127		83			

Heterogeneity: $\chi^2 = 10.01$, df = 6 (P = 0.12); $I^2 = 40\%$

Test for overall effect: $Z = 3.02$ (P = 0.002)



~ Increased risk of ICH in subjects with higher dose of statin therapy.

Acta Neurol Scand. 2016;134:22-8.

Other Lipid-lowering Drugs For Stroke Prevention

- Hypertriglyceridemia increases stroke risk.
- HDL-C level is strongly inversely associated with cardiovascular disease from observational studies

- However, a meta-analysis showed there was no significant effect on stroke outcomes for **niacin** (OR=0.96, 95% CI=0.75-1.22, P=0.72), **fibrates** (OR=1.01, 95% CI=0.90-1.13, P=0.84), or **CETP inhibitors** (OR=1.14, 95% CI=0.90-1.45, P=0.29), and on other cardiovascular events.

Keene D, et al. *BMJ* 2014;349:g4379.

Statin in Stroke Prevention Recommendation

- For patients with ischemic stroke or TIA presumed to be of atherosclerotic origin or accompanied with other comorbid ASCVD, intensive statin therapy is recommended. The goal of LDL-C <100 mg/dL is suggested ***(COR I; LOE A)***.

- For patients with stroke or TIA presumed to be of non-atherosclerotic origin and no accompanied with other comorbid ASCVD, the benefit of intensive statin therapy is uncertain ***(COR IIb; LOE C)***.

Recommendation for Ischemic Stroke, TIA and Carotid Stenosis From Taiwan Lipid Guideline

- Statin in Stroke Prevention
- Statin in Acute Stroke
- Statin in Carotid Stenosis

In-hospital Initiation of Lipid-lowering Therapy in Patients with Acute Ischemic Stroke/TIA in Taiwan

- Taiwan Stroke Registry:
  - From 2006/05 to 2008/07, 16704 acute ischemic stroke or TIA patients
  - No previous lipid-lowering therapy, survival to discharge.
  - End-points: recurrent stroke, ischemic heart disease, and death at 6 mon

Multivariate Cox proportional hazards analyses for composite end point at 6 months

Variable	HR	95% CI	p Value
Age (per year)	1.02	1.02–1.03	<0.0001
Diabetes (yes vs no)	1.41	1.25–1.60	<0.0001
National Institutes of Health Stroke Scale score at admission (per 1 unit)	1.05	1.09–1.50	<0.0001
Arial fibrillation (yes vs no)	1.28	1.09–1.50	0.002
LLT at discharge (yes vs no)	0.78	0.61–0.98	0.013

Yeh PS, et al. Am J Cardiol 2010;105:1490-4.

In-hospital Initiation of Statin in Patients with Acute Ischemic Stroke in U.S.

- Patients ≥65 years enrolled in the GWTG-Stroke Registry.
- Two-year follow-up on statin versus not on statin
- During 2007~2011, 77 468 patients who were not taking statin at admission were hospitalized with ischemic stroke
- 71% were discharged on statin therapy.

- Statin therapy
  - Lower cardiovascular events (HR, 0.91; 95%CI, 0.87-0.94)
  - Lower all-cause mortality and readmission.
  - No increased hemorrhagic stroke (HR, 0.94; 95%CI, 0.72-1.23).

***Circulation* 2015;132:1404-13.**

Statin Use in Patients with ICH

- A meta-analysis of 16 studies shows pre-ICH statin use do not increase mortality (OR=0.90, 95% CI=0.63-1.28), and has a better 3-month functional outcome (OR=1.49, 95% CI=1.01-2.19), as compared to pre-ICH no statin use.

Jung JM, et al. *Int J Stroke* 2015; 10:10-7.

- One study from Taiwan's National Health Insurance database showed ICH patients who have taken statins during hospitalization or within 3 months after discharge were associated with lower all-cause mortality and without increased recurrent ICH.

Chen PS, et al. *Eur J Neurol* 2015;22:773-80.

Statin in Acute Ischemic Stroke or TIA Recommendation

- For patients with acute ischemic stroke or TIA, early initiation of statin therapy if indicated is recommended ***(COR IIa; LOE B)***.

- For patients with acute ischemic stroke, hemorrhagic stroke or TIA, discontinuation of pre-stroke statin therapy is not recommended ***(COR III; LOE C)***.

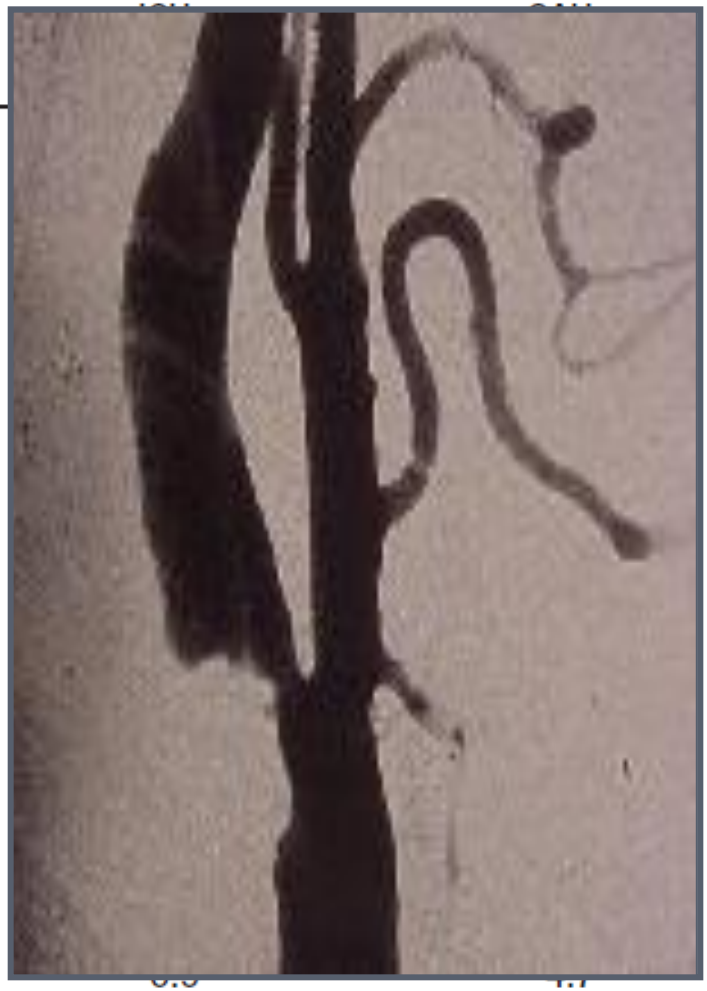
Recommendation for Ischemic Stroke, TIA and Carotid Stenosis From Taiwan Lipid Guideline

- Statin in Stroke Prevention
- Statin in Acute Stroke
- Statin in Carotid Stenosis

Carotid Stenosis

Table 2. Key Variables in Different Stroke Types

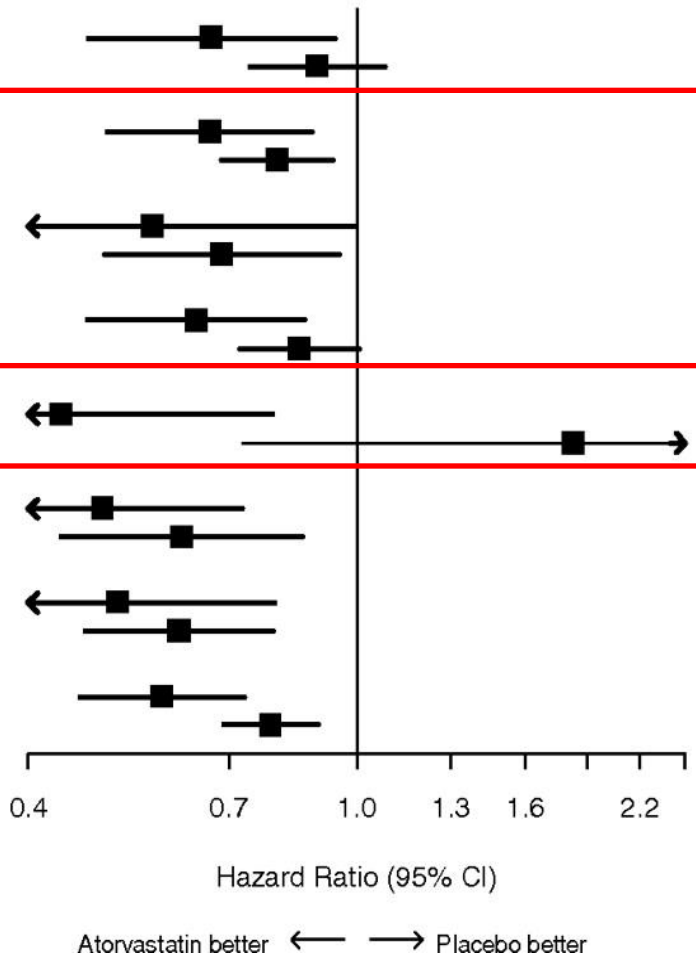
Items	Ischemic Stroke/TIA n=24 695		
Age (median, IQR)	69.9 (59.6–77.9)		
Sex			
Male (%)	59.8		
Body mass index	24.3 (22.0–26.8)		
Arrival time (hour)* (median, IQR)	5.5 (1.8–19.7)		
Length of stay (day) (median, IQR)	8 (5–15)		
MRI (%)	61.4		
CT (%)	92.1		
NIHSS (admission) (median, IQR)	5 (2–9)		
Medical history (%)			
Atrial fibrillation	16.5		
Previous stroke/TIA	34.1		
CAD/prior MI	13.6		
Carotid stenosis	10.6	. . .	. . .
Diabetes mellitus	45.4	37.0	37.2
Hypertension	79.2	84.9	65.3
Dyslipidemia	49.4	29.4	20.5



SPARCL :

~ Treatment effect of atorvastatin on primary and secondary end points in patients with and without carotid stenosis (CS)

	Atorvastatin Events (%)	Placebo Events (%)	HR	Treatment P Value	Heterogeneity P Value
Stroke					
With CS	55 (11.2)	83 (16.1)	0.67	0.021	0.151
Without CS	210 (11.2)	228 (12.3)	0.90	0.256	
Stroke or TIA					
With CS	79 (16.0)	118 (23.0)	0.66	0.005	0.268
Without CS	296 (15.8)	358 (19.3)	0.80	0.005	
Major Coronary Event					
With CS	19 (3.9)	33 (6.4)	0.57	0.049	0.597
Without CS	62 (3.3)	87 (4.7)	0.69	0.024	
Major Cardiovascular Event					
With CS	70 (14.2)	108 (21.0)	0.64	0.004	0.119
Without CS	264 (14.1)	299 (16.1)	0.85	0.059	
Carotid Revascularization					
With CS	16 (3.2)	37 (7.2)	0.44	0.006	0.010
Without CS	13 (0.7)	7 (0.4)	1.83	0.199	
Any Revascularization					
With CS	38 (7.7)	76 (14.8)	0.49	<0.001	0.398
Without CS	56 (3.0)	87 (4.7)	0.61	0.005	
Any Coronary Event					
With CS	31 (6.3)	59 (11.5)	0.51	0.003	0.544
Without CS	92 (4.9)	145 (7.8)	0.61	<0.001	
Any Cardiovascular Event					
With CS	119 (24.1)	194 (37.7)	0.58	<0.001	0.029
Without CS	403 (21.5)	491 (26.5)	0.79	<0.001	



Stroke. 2008;39:3297-3302

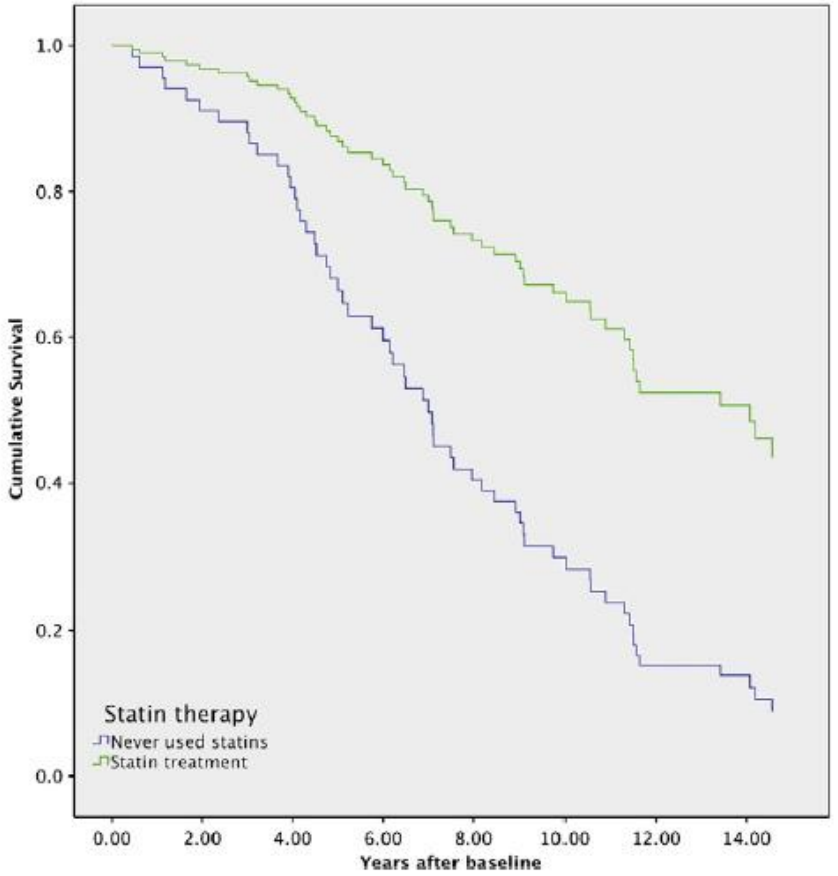
Statins Use in Patients with Carotid Artery Stenosis

- In a review of 17 studies including 11,391 asymptomatic carotid artery stenosis patients, the 5-year all-cause mortality was 23.6%.

Giannopoulos A, et al. Eur J Vasc Endovasc Surg 2015;50:573-82.

- Treatment with statins improved long-term survival in patients with carotid stenosis.

Wörlund SM, et al. *Int J Cardiol* 2013;168:624-6.



Statin in Carotid Stenosis Recommendation

- For patients with symptomatic carotid stenosis (>50%), aggressive medical therapy, including antiplatelets, well BP and lipid control, and risk factor modification, is recommended. The goal of LDL-C <100 mg/dL is highly recommended ***(COR I; LOE A)***.

- For patients with asymptomatic carotid stenosis (>50%) and evidence for other clinical ASCVD, aggressive medical therapy, including antiplatelets, well BP and lipid control, is recommended. The goal of LDL-C <100 mg/dL is recommended ***(COR IIa; LOE B)***.

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

ASCVD: Atherosclerotic cardiovascular disease

6.8. Statins	COR	LOE
1. Among patients already taking statins at the time of onset of ischemic stroke, continuation of statin therapy during the acute period is reasonable.	IIa	B-R
2. High-intensity statin therapy should be initiated or continued as first-line therapy in women and men ≤75 years of age who have clinical ASCVD*, unless contraindicated.	I	A
3. In individuals with clinical ASCVD* in whom high-intensity statin therapy would otherwise be used, when high-intensity statin therapy is contraindicated or when characteristics predisposing to statin-associated adverse effects are present, moderate-intensity statin should be used as the second option if tolerated.	I	A

AHA/ASA Guideline

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

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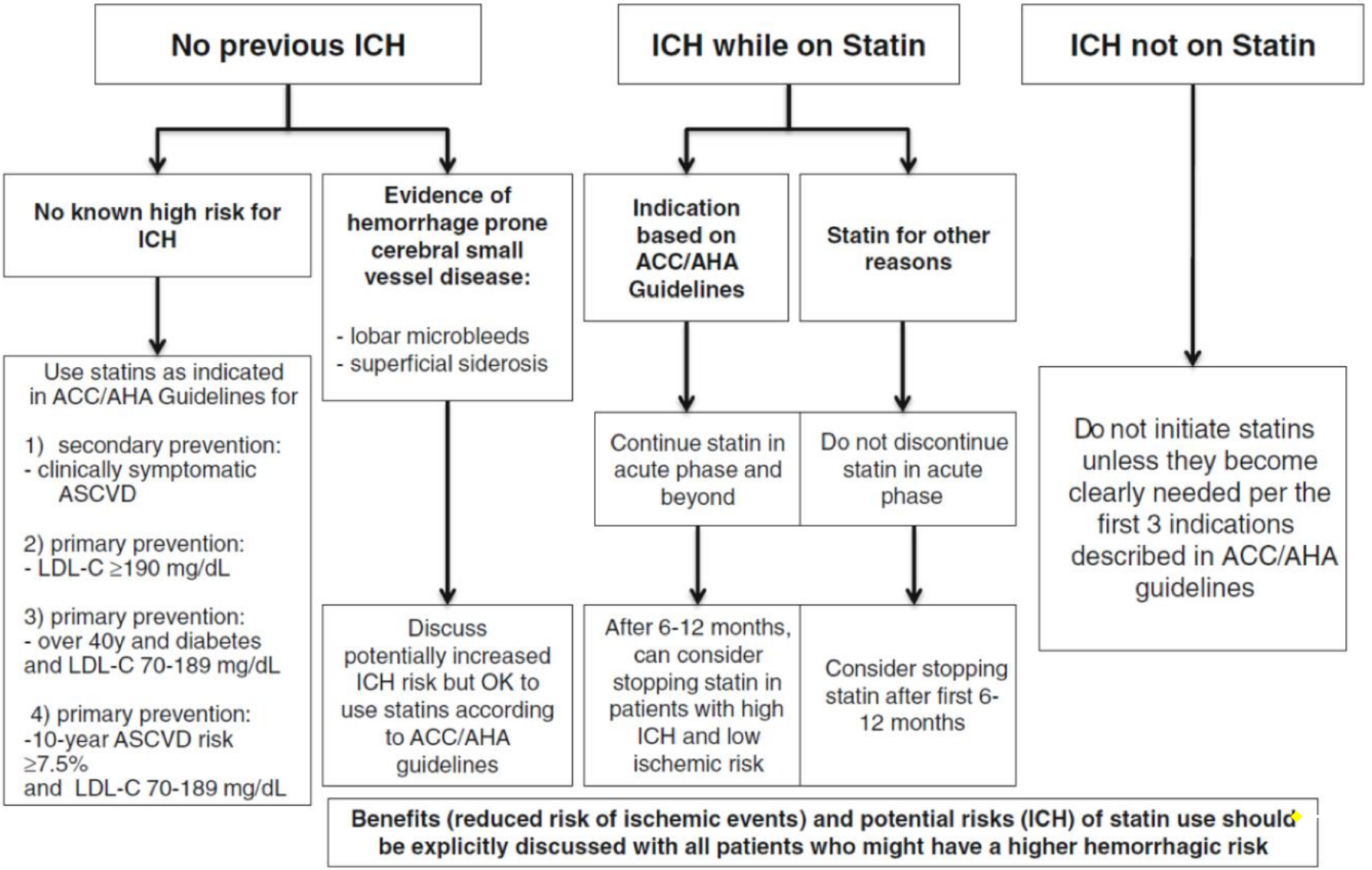
4. In individuals with clinical ASCVD* >75 years of age, it is reasonable to evaluate the potential for ASCVD risk-reduction benefits and for adverse effects and drug–drug interactions and to consider patient preferences when initiating a moderate- or high-intensity statin. It is reasonable to continue statin therapy in those who are tolerating it.	IIb	C-EO
5. Patients with ischemic stroke and other comorbid ASCVD should be otherwise managed according to the 2013 ACC/AHA cholesterol guidelines, which include lifestyle modification, dietary recommendations, and medication recommendations.	I	A
6. For patients with an AIS who qualify for statin treatment, in-hospital initiation of statin therapy is reasonable.	IIa	C-LD

Drug Choice? High versus Moderate?

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Lowers LDL-C, on average, by approximately ≥50 %	Lowers LDL-C, on average, by approximately 30% to <50%	Lowers LDL-C, on average, <30%
Atorvastatin (40)**–80 mg** **Rosuvastatin 20** *(40)* **mg**	**Atorvastatin 10** *(20)* **mg** **Rosuvastatin** *(5)* **10 mg** **Simvastatin 20–40 mg** **Pravastatin 40** *(80)* **mg** **Lovastatin 40 mg** *Fluvastatin XL 80 mg* **Fluvastatin 40 mg bid** *Pitavastatin 2-4 mg*	*Simvastatin 10 mg* **Pravastatin 10-20 mg** **Lovastatin 20 mg** *Fluvastatin 20-40 mg bid* *Pitavastatin 1 mg*

Statins in Intracerebral Hemorrhage



Lauer et al., Curr Atheroscle Rep, 2015

Recommendation for Statin in Stroke Patients

- Ischemic stroke or TIA presumed to be of atherosclerotic origin or accompanied with other comorbid ASCVD, intensive statin therapy with LDL-C <100 mg/dL is recommended. ***(COR I; LOE A)***.
- Early initiation of statin therapy if indicated in acute ischemic stroke or TIA is recommended ***(COR IIa; LOE B)***.
- For patients with acute ischemic stroke, hemorrhagic stroke or TIA, discontinuation of pre-stroke statin therapy is not recommended ***(COR III; LOE C)***.
- For patients with symptomatic carotid stenosis (>50%), aggressive medical therapy, including antiplatelets, well BP and lipid control, and risk factor modification, is recommended. The goal of LDL-C <100 mg/dL is highly recommended ***(COR I; LOE A)***.

Thanks For Your Attention