BP and Lipid management
Focusing on ischemic stroke

馬偕紀念醫院神經內科
陳律安醫師
2020/08/09

Hypertension :

the strongest risk factor for stroke

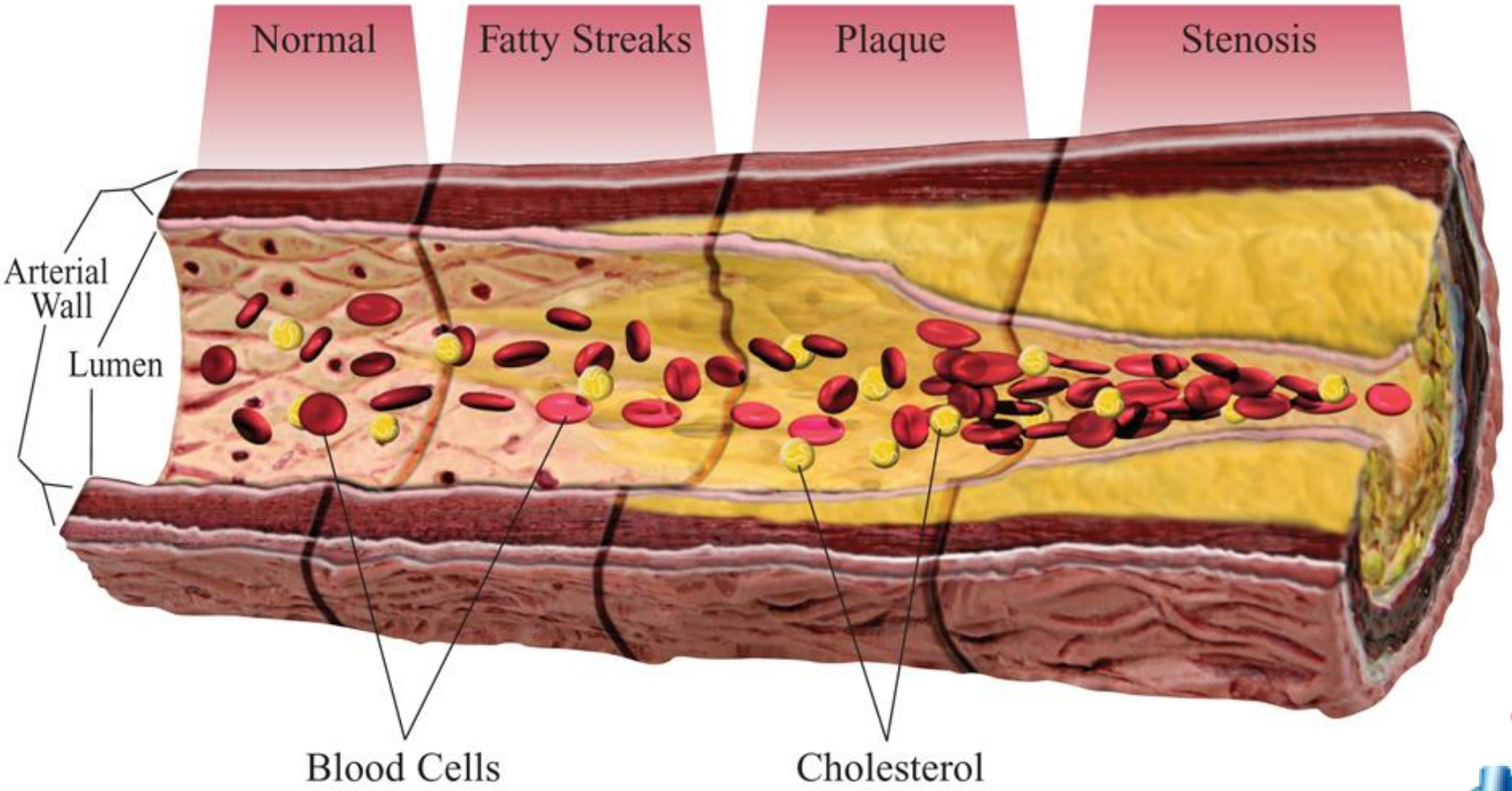
INTERSTROKE study

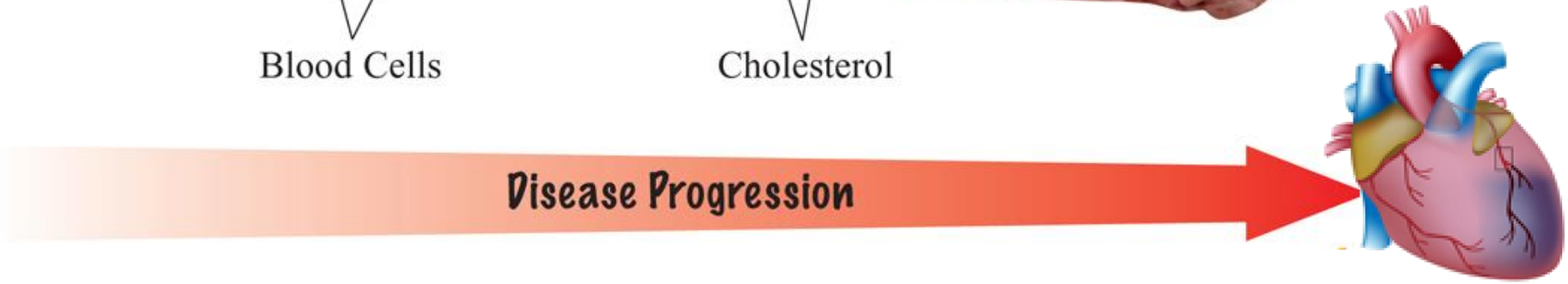
The association between cholesterol and stroke is …….?

Lancet Neurol 2009; 8: 453


Stroke
Cholesterol

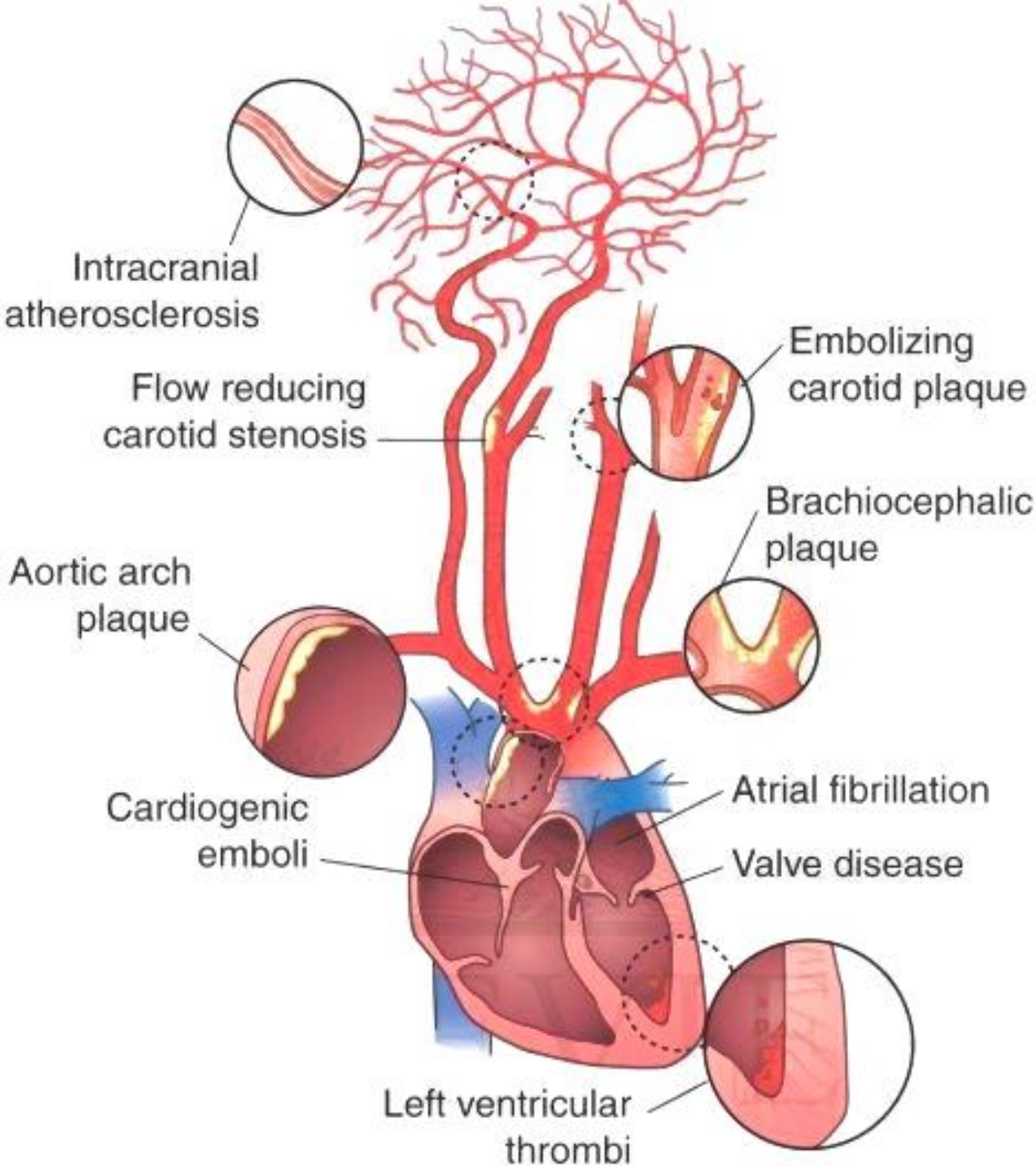
Artery with Atherosclerosis





Stroke

Stroke Heterogeneity


Intracranial atherosclerosis
Flow reducing carotid stenosis
Embolizing carotid plaque
Brachiocephalic plaque
Aortic arch plaque
Cardiogenic emboli
Atrial fibrillation
Valve disease
Left ventricular thrombi

我們將會討論

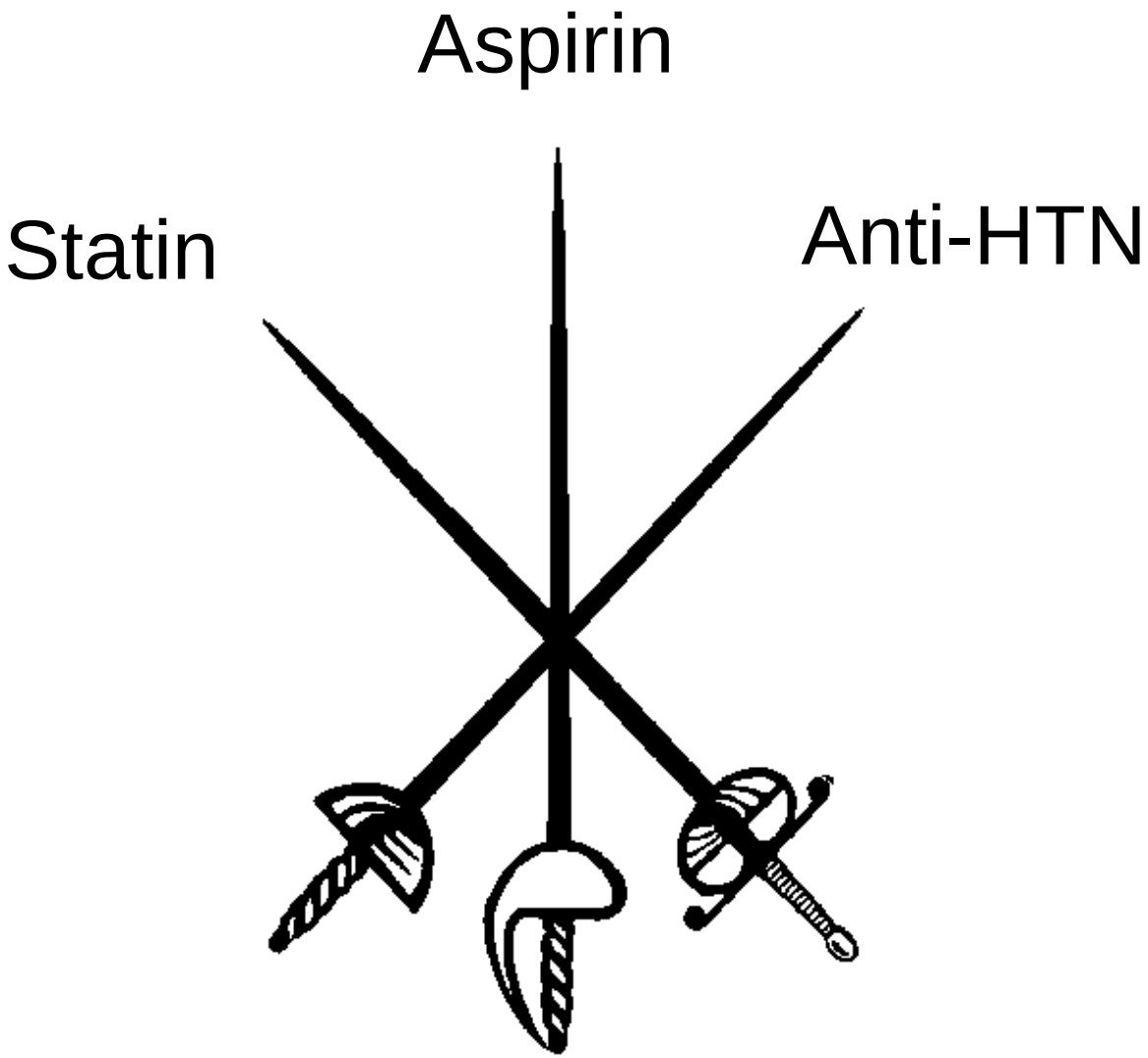
BP / Lipid management in stroke patient

1. Acute phase
2. Secondary prevention
3. What are the “targets”

我們將會討論

BP / Lipid management in stroke patient

1. Acute phase
2. Secondary prevention
3. What are the “targets”



Lancet Neurol 2009; 8: 453

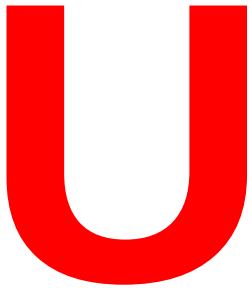
急性中風期

急性中風期血壓

過高或過低的血壓，均是預後不良之指標

(Class I, Level of Evidence A)

Best outcome at SBP 140 ~ 180 mm Hg



台灣腦中風防治指引2008

Lancet Neurol 2009; 8: 938

ESO Guideline

建議避免急速降壓 (Class Ⅱ，Level C)。

血壓過度升高 (>220/120 mmHg)者、有嚴重心臟衰竭、主動脈剝離或高血壓腦病者，建議謹慎降壓 (Class Ⅳ，GCP)

American Heart Association | American Stroke Association

AHA/ASA guidelines

Restarting antihypertensives at 24 hours in previously hypertensive neurologically stable patients unless contraindicated

Stroke. 2009;40:2251

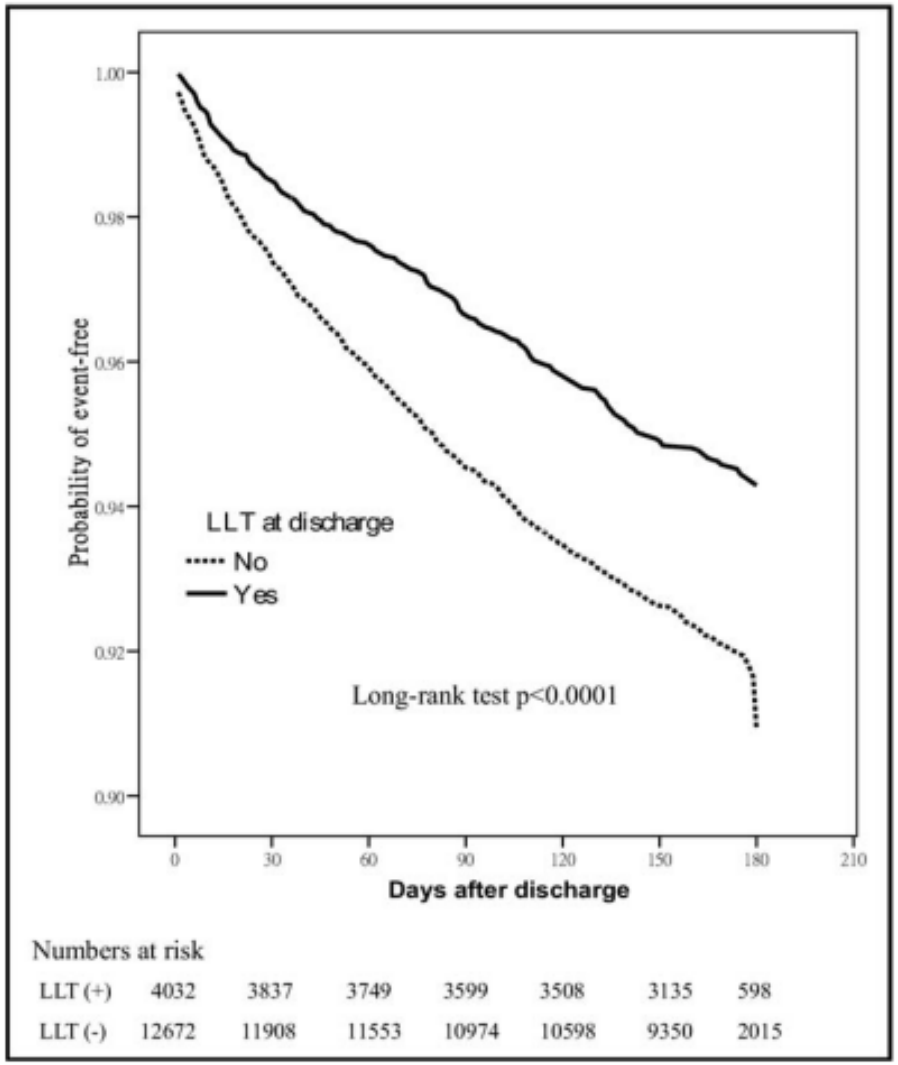
急性中風期膽固醇

中風入院的高血脂病人，之前大多沒有達到良好的血脂控制

Dose it matter ?

Neurology 2007 ;68:660

Effect of In-Hospital Initiation of Lipid-Lowering Therapy on Six-Month Outcomes in Patients With Acute Ischemic Stroke or Transient Ischemic Attack



24%病人在中風住院期間使用statin

六個月後的預後較好

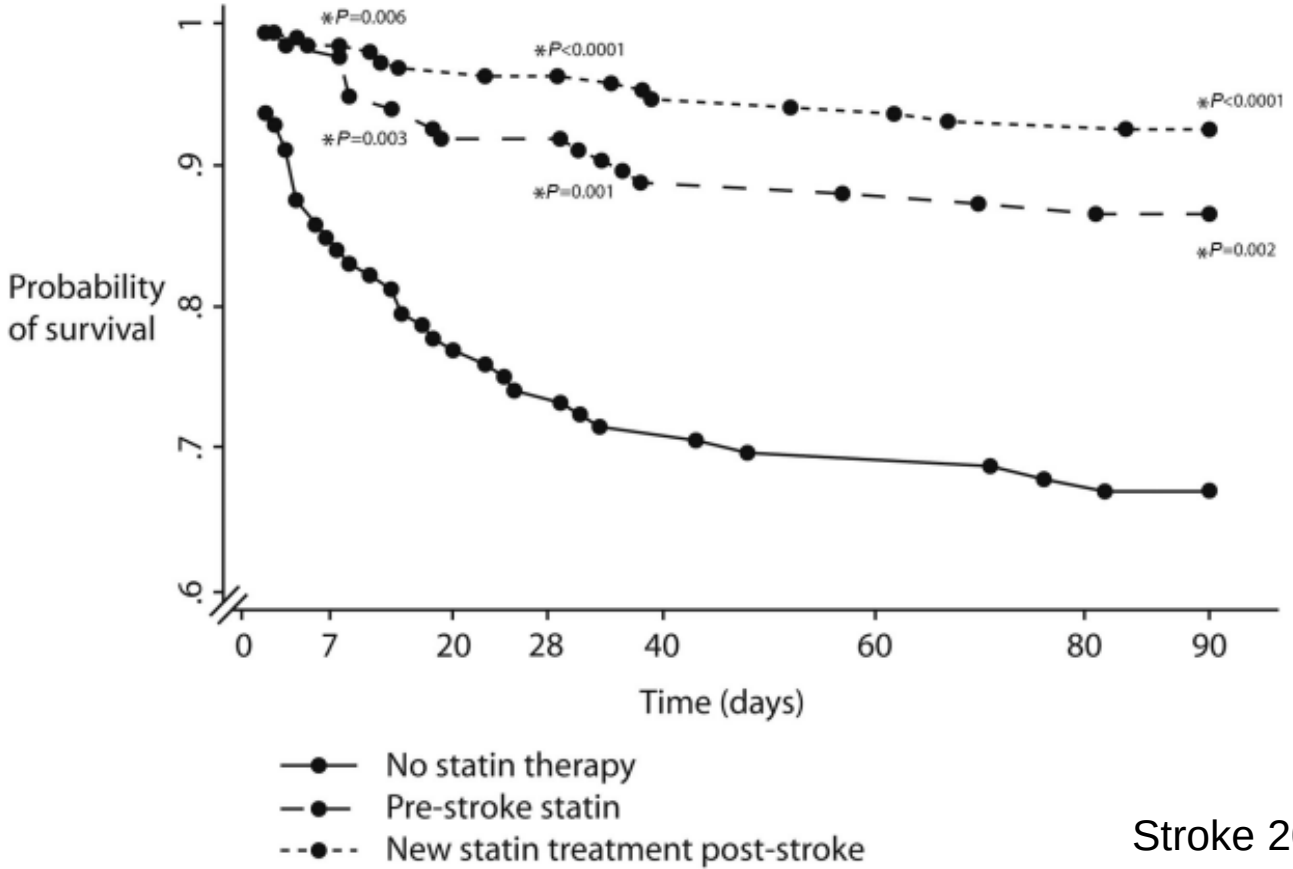
Taiwan Stroke Society
台灣腦中風學會
中風登錄平台

Am J Cardiol 2010;105:1490

Association Between Acute Statin Therapy, Survival, and Improved Functional Outcome After Ischemic Stroke

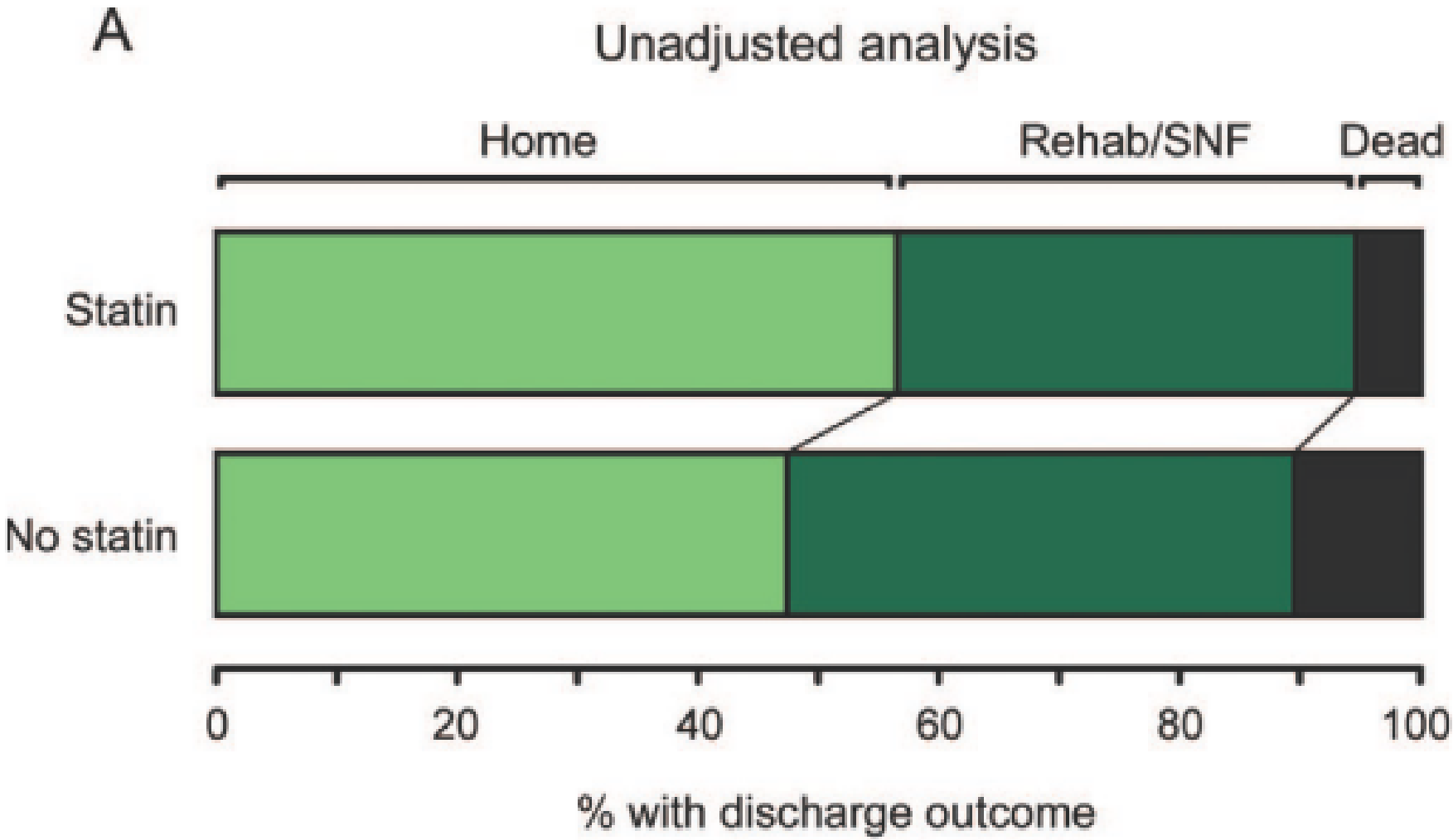
The North Dublin Population Stroke Study

在中風時已用Statin，或中風時開始使用預後都比沒有用Statin的好



Stroke 2011;42:1021

Figure 1 Statin use is associated with a greater likelihood of discharge to home and reduced chances of in-hospital death



Neurology 2012;78:1678

Never too late

我們將會討論

BP / Lipid management in stroke patient

1. Acute phase
2. Secondary prevention
3. Continuous use of statin

腦中風後的次級預防

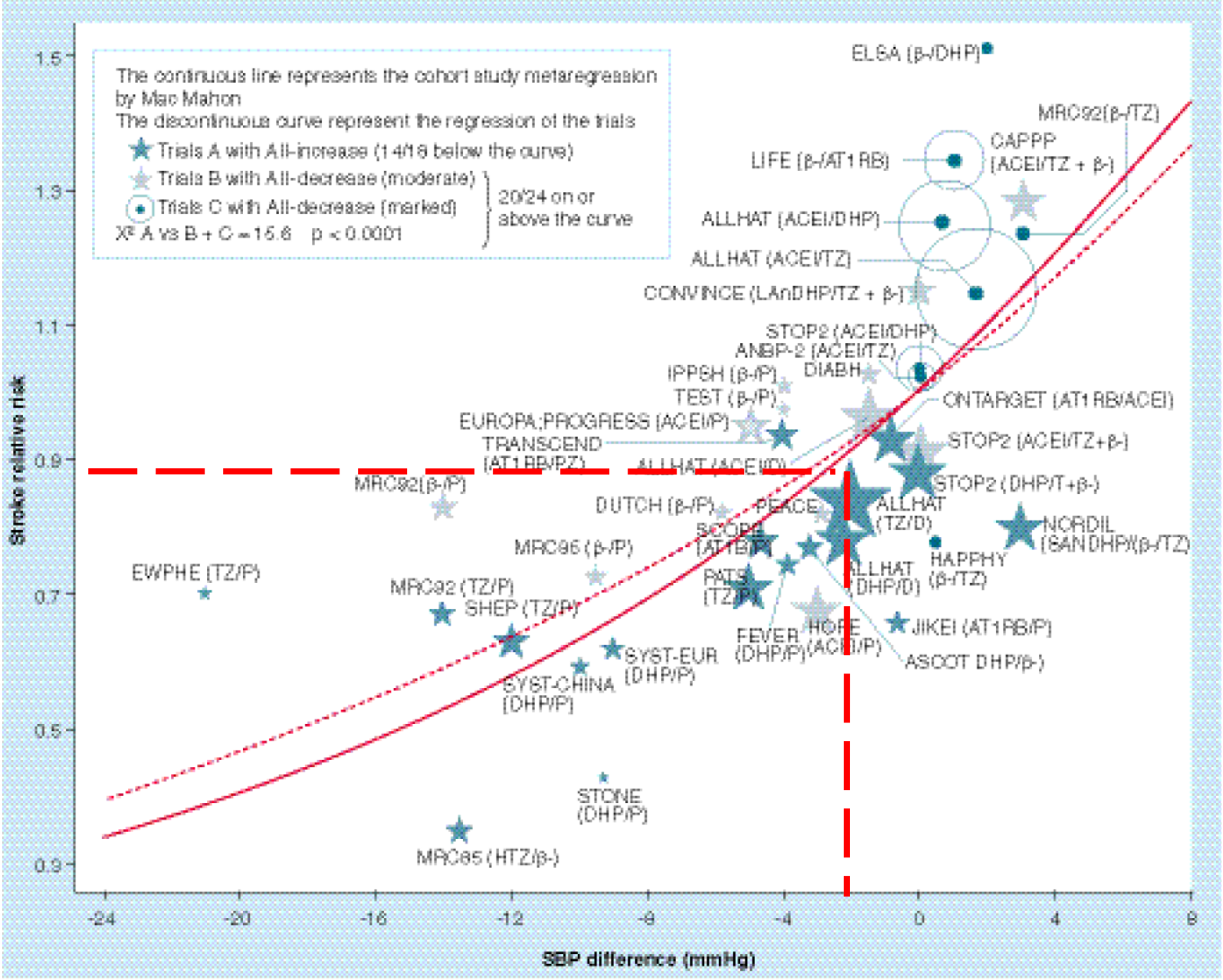
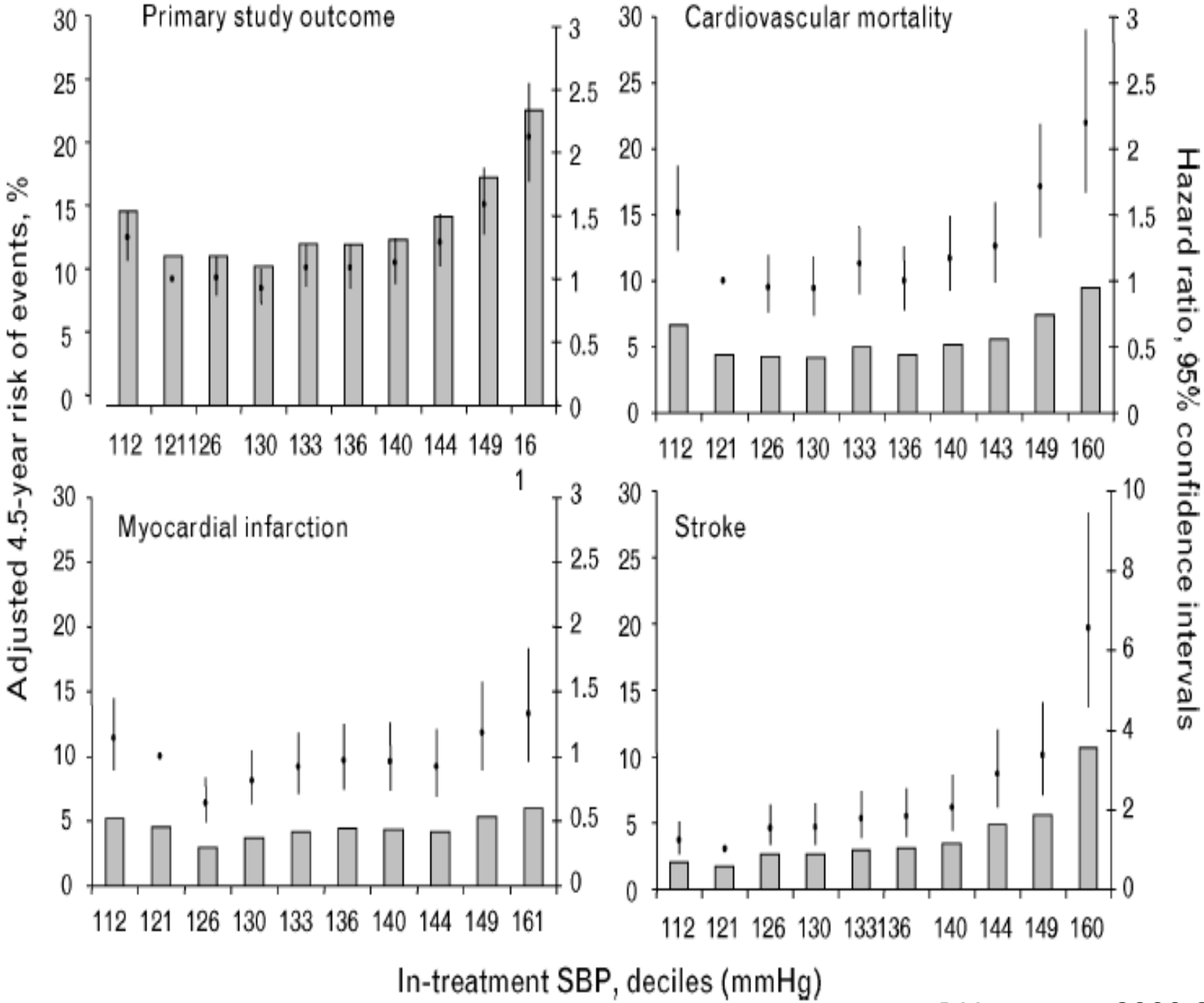


Figure 2. Relationship between stroke relative risk and SBP difference in cohort and trial studies.
ACEI: Angiotensin converting enzyme inhibitor; AII: Angiotensin II; AT1B: AT1 blocker; β-: β-blocker; D: Doxazosin; DHP: Dihydropyridine; HTZ: High-dose thiazide; LA: Long-acting; nDHP: Non-dihydropyridine; P: Placebo; SA: Short-acting; SBP: Systolic blood presure; TZ: Low-dose thiazide.



J Hypertens 2009;27:1360

- Q: Which BP-Lowering Agent Is Most Effective?

Table 8. Recommended combinations

Clinical conditions	Single drug	2-drug combinations	3-drug combinations*
Target organ damage			
Left ventricular hypertrophy	ARB	ARB + D	ARB + CCB + D
Microalbuminuria	ACEI, ARB	ACEI + CCB, ARB + CCB, ACEI + D, ARB + D	ACEI + CCB + D, ARB + CCB + D
Asymptomatic atherosclerosis	CCB	ACEI + CCB, ARB + CCB	ACEI + CCB + D, ARB + CCB + D
Clinical events			
History of myocardial infarction	BB, ACEI, ARB	ACEI + BB, ARB + BB	ACEI + BB + D, ARB + BB + D
Coronary heart disease	BB, ACEI, ARB, CCB (long-acting)	BB + CCB, ACEI + CCB, ARB + CCB, ACEI + BB, ARB + BB	ACEI + CB + CCB, ARB + BB + CCB
Heart failure	BB, ACEI, ARB, D†	ACEI + BB, ARB + BB, ACEI + D†, ARB + D†, BB + D†	ACEI + BB + D†, ARB + BB + D†
Stroke	ACEI, ARB, D, CCB	ACEI + CCB, ARB + CCB, ACEI + D, ARB + D	ACEI + CCB + D, ARB + CCB + D

2010 台灣心臟學會(TSOC)高血壓臨床指引

All BP-lowering agents may diminish recurrent stroke risk

再次中風之預防

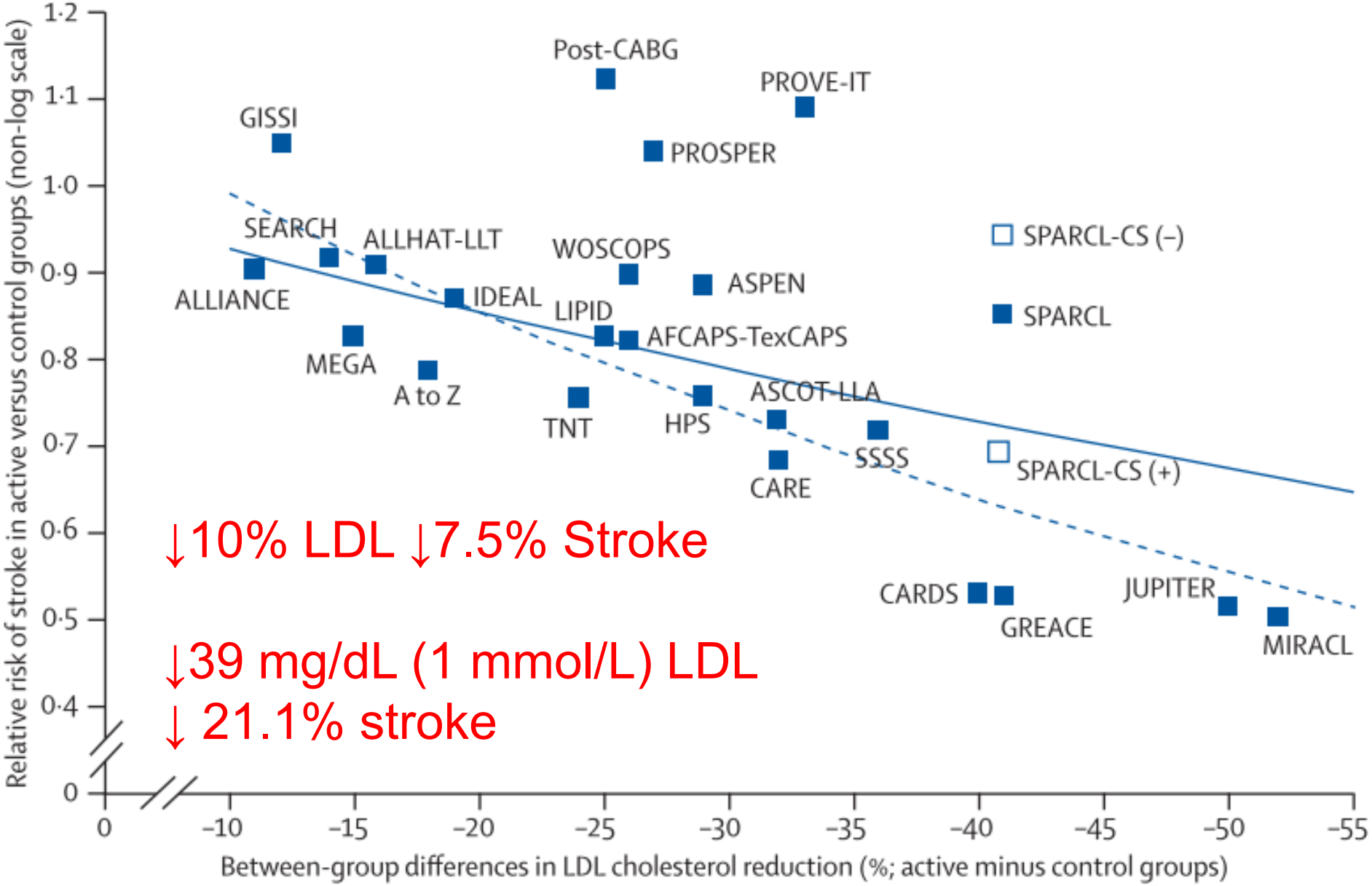
PROGRESS study

- Diuretic（Indapamide）+ ACEI（Perindopril）
  有效地降低中風發生率達28%

Class I, Level of Evidence A

台灣腦中風防治指引2008

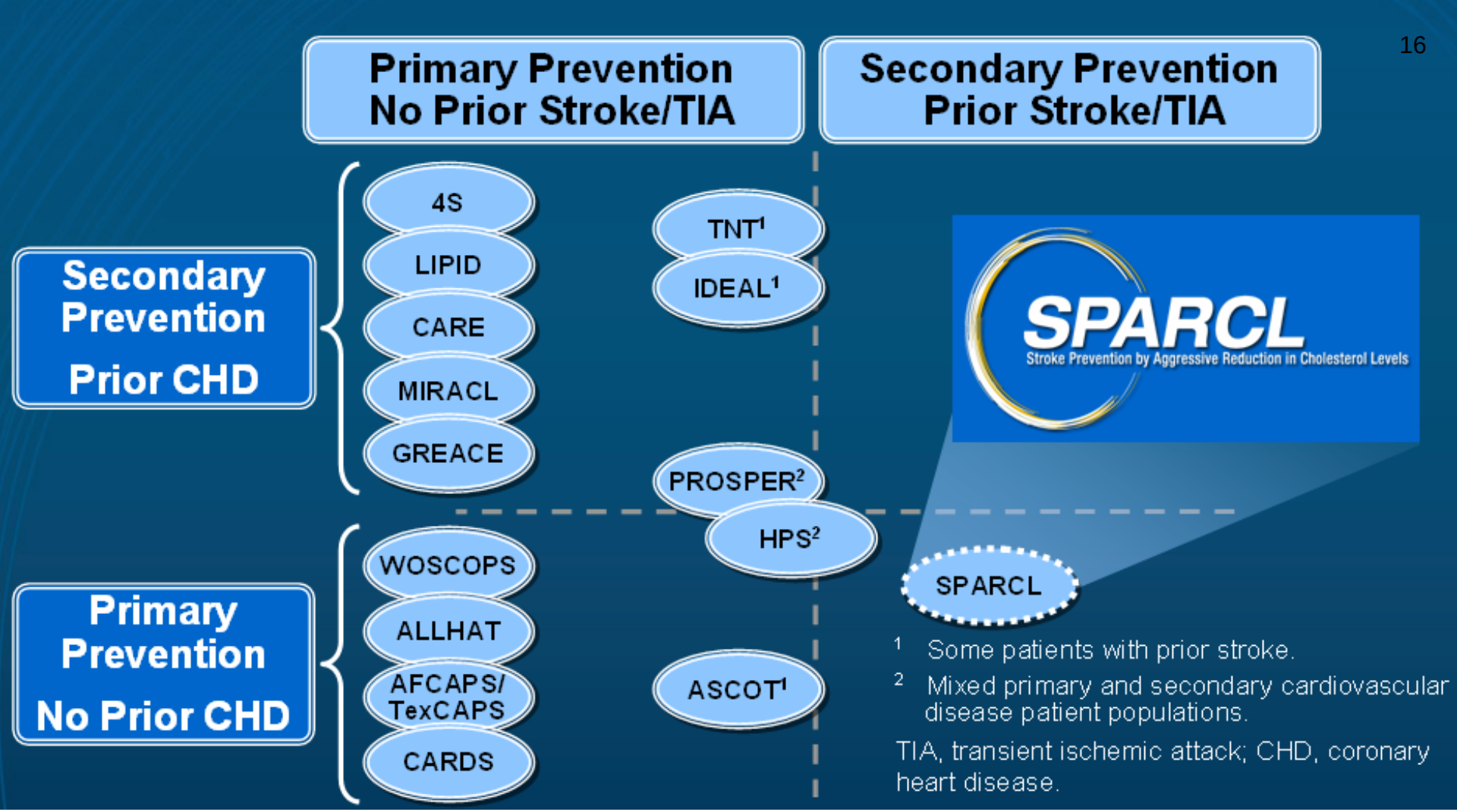
LDL-Cholesterol and Stroke



↓10% LDL ↓7.5% Stroke

↓39 mg/dL (1 mmol/L) LDL
↓ 21.1% stroke

Lancet Neurol 2009; 8: 453



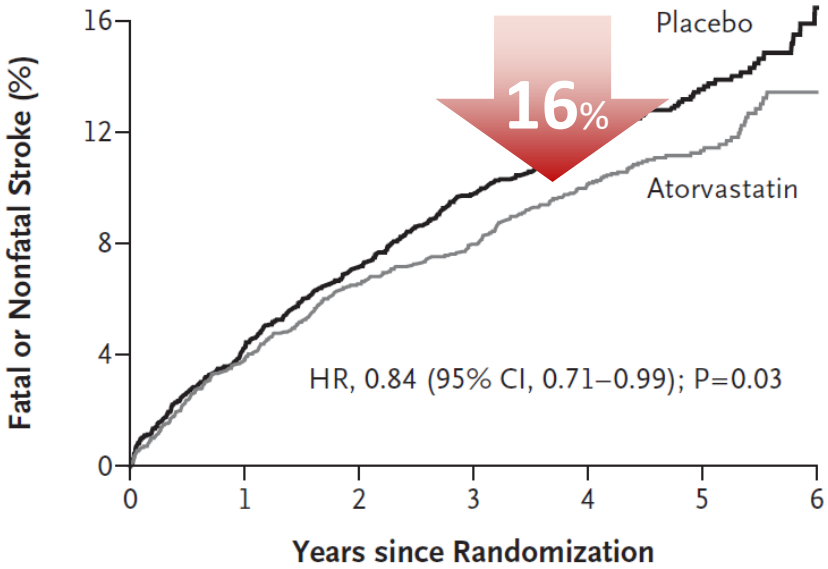
SPARCL試驗首次證實了statin可預防腦中風復發，服用Atovastatin中風之復發率減少達23%

台灣腦中風防治指引2008

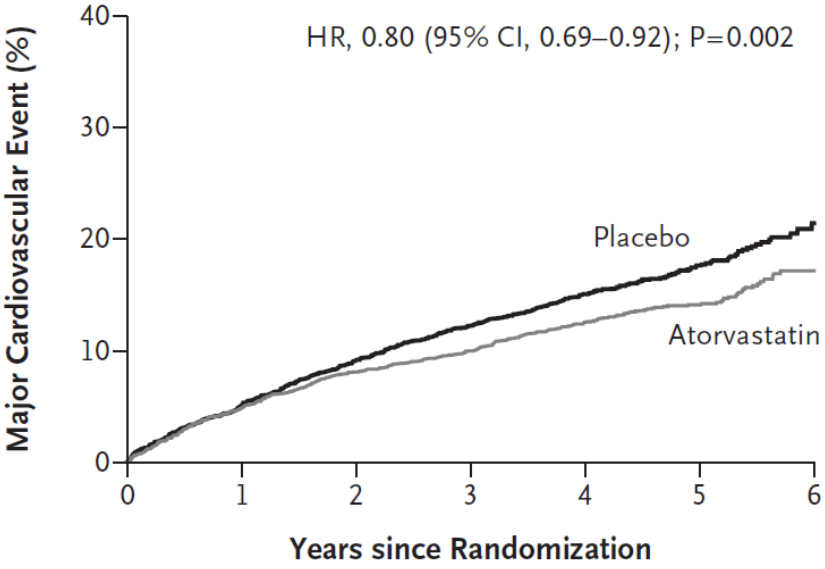
SPARCL trial: study result

Atorvastatin 80 mg reduced the incidence of fatal or nonfatal stroke by 16% in patients with a recent stroke or TIA.

First occurrence of a fatal or nonfatal stroke



First occurrence of any major coronary event



CI, confidence interval; HR, hazard ratio; TIA, transient ischemic attack.

Amarenco P, et al. N Engl J Med 2006;355:549-59.

我們將會討論

BP / Lipid management in stroke patient

1. Acute phase
2. Secondary prevention
3. What are the “targets”

2017 Focused Update of Hypertension Guidelines of TSOC and THS Recommend a New Aggressive BP Target

New BP targets

Categories	Targets (mmHg)	COR	LOE
Primary prevention	<140/90	I	B
Secondary prevention			
Diabetes	<130/80	I	B
CHD	**<120/NA[AOBP]**	**I**	**B**
Stroke	**<140/90**	**I**	**A**
CKD	**<120/NA[AOBP]**	**I**	**B**
Elderly (age ≥75 years)	**<120/NA[AOBP]**	**I**	**B**
Patients receiving antithrombotics for stroke prevention	**<130/80**	**I**	**B**

A new **more aggressive BP target** for patients with **CHD and CKD, and age ≥ 75 years.**

AOBP, unattended automated office blood pressure; BP, blood pressure; CHD, coronary heart disease; CKD, chronic kidney disease; COR, class of recommendation; LOE, level of evidence; NA., not available; THS, Taiwan Hypertension Society; TSOC, Taiwan Society of Cardiology.

Chiang CE, et al. Acta Cardiol Sin. 2017 May;33(3):213-225.

腦中風危險因子防治指引：高血壓 2015

2.1 建議

1. 中風的初級預防，建議將血壓降至140/90mmHg以下。(Class I, Level of Evidence A)
2. 降壓藥物選擇方面，成功的降血壓，會比選用特定藥物來的重要，治療原則建議因人因病而異。(Class I, Level of Evidence A)

3.3 要給那一種血壓藥

有中風病史或暫時性腦缺血發作的病人應該給那一種類血壓藥，需先考量病人需使用單一種血壓藥物或複方藥物來達到血壓合適之控制。

1. 單一藥物(monotherapy)：目前沒有強烈證據支持那一種類之血壓用藥比其他種類之血壓用藥更適合當做中風病人之單一起始用藥。某些臨床研究指出[(19)-(21)]，Beta-blockers比起Angiotensin receptor inhibitors、CCB，並無法降低中風風險，因此除非有強烈之適應症，不然Beta-blockers不應當做預防再次中風之單一降壓藥物。在一篇統合分析研究[(22)]，受試者是在中風後數天至數月進入研究並接受追蹤2至5年，確認了控制血壓可顯著降低再次中風之風險(相對風險顯著降低22%)。使用利尿劑的受試者(單獨使用或合併Angiotensin receptor inhibitors)，發現可以顯著降低再次中風機率，但此種情形卻未見於單獨使用Renin-angiotensin system inhibitors、Beta-blockers或Calcium channel blockers，惟此結果統計的效力有限。

3.4 中風病人之血壓治療目標

中風病人血壓治療目標的決定必須先考量病人是否有嚴重的顱外或顱內大血管狹窄。

1. 有嚴重的顱外或顱內大血管狹窄：詳見本指引第五章之嚴重顱外或顱內的大血管狹窄之血壓控制。降血壓應溫和，不一定要降超過 10/5mmHg，在治療過程中一定要注意有無低血壓或神經症狀。
2. 無嚴重的顱外或顱內大血管狹窄：詳見本指引第九章之指引內容原則。合適之血壓控制目標與降幅仍然未有明確數值，治療應個別化。所有病人都應考慮至少降壓 10/5mmHg，若是病人起始血壓小於 120/70mmHg，則不降低血壓。

5.1 建議

1. 高血壓病患併有嚴重的大血管狹窄，若沒有雙側顱外頸動脈狹窄>70%或血流動力學的變化，建議血壓控制目標為<140/90mmHg (Class I, Level of Evidence B)。
2. 嚴重大血管狹窄之高血壓病患併有血流動力學的變化或雙側顱外頸動脈狹窄>70%時，血壓控制目標不宜太低，建議收縮壓130-150mmHg。如需降血壓時，速度不要太快並應監測病患症狀。若因降血壓藥物造成腦血流不足而出現症狀，血壓控制應維持在沒有症狀的血壓(Class IIa, Level of Evidence B)。

Cholesterol Levels and Risk of Hemorrhagic Stroke

A Systematic Review and Meta-Analysis

- Total cholesterol level is inversely associated with risk of hemorrhagic stroke.
- Higher level of LDL seems to be associated with lower risk of hemorrhagic stroke.

Stroke. 2013;44:1833

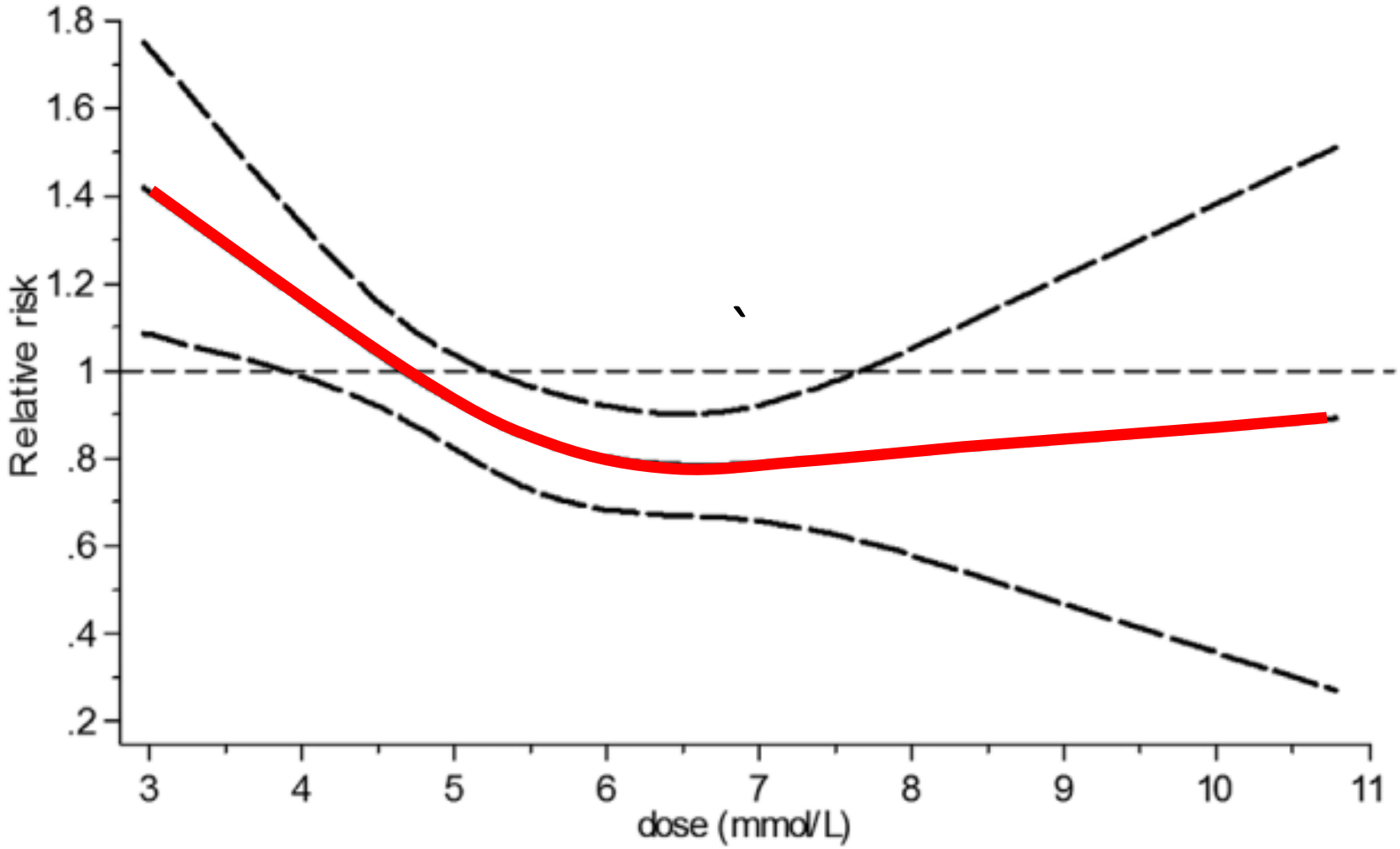


Figure 3. Relative risk (solid line) with 95% CI (long dashed lines) for the association of total cholesterol level with risk of hemorrhagic stroke in a restricted cubic spline random-effects model.

Stroke. 2013;44:1833

Taiwan lipid guidelines

For patients with ischemic stroke or TIA presumed to be of **atherosclerotic origin**, **intensive statin therapy** is recommended. The goal of **LDL-C < 100 mg/dL** is suggested.

Disease category	LDL-C target
• ACS • Stable CAD • PAD + CAD	<70 mg/dL
• ACS + DM	<55 mg/dL
• Ischemic stroke/TIA • DM • PAD	<100 mg/dL

ACS, acute coronary syndrome; CAD, coronary artery disease; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; PAD, peripheral arterial disease; TIA, transient ischemic attack.

Li YH, et al. J Formos Med Assoc 2017;116:217-48.

LDL < 70 or 100 ?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 18, 2015 VOL. 372 NO. 25

Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes

- IMPROVE-IT study
- 13.3% reduction in total cholesterol at one year was associated with a hazard ratio (HR) of 0.86 for total stroke

Outcome	Simvastatin Monotherapy (N=9077)	Simvastatin–Ezetimibe (N=9067)	Hazard Ratio (95% CI)	P Value
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

NEJM 2015;372:2387-97

Treat Stroke to Target Trial

ClinicalTrials.gov

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

Verified December 2013 by Assistance Publique - Hôpitaux de Paris

Sponsor:
Assistance Publique - Hôpitaux de Paris

ClinicalTrials.gov Identifier:
NCT01252875

First received: December 2, 2010
Last updated: December 9, 2013
Last verified: December 2013

Estimated Enrollment:	3760
Study Start Date:	March 2010
Estimated Study Completion Date:	September 2018
Estimated Primary Completion Date:	September 2018 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
LDL-C to100 mg/dL (+/-10 mg/dL) Target : 100 mg/dL (+/-10 mg/dL): Patients recruited in this arm will receive statin +/-other lipid lowering therapy in order to reach a LDL-C concentration of 100 mg/dL(+/-10 mg/dL).	Procedure: Target : 100 mg/dL (+/-10 mg/dL) Statin +/- other lipid lowering therapy during 3 years, Target : LDL-C =100 mg/dL (+/-10 mg/dL), recording recurrent non fatal stroke, non fatal MI, and vascular death and others endpoints such as new onset diabetes, hemorrhagic strokes. Other Name: treat to target
LDL-C < 70 mg/dL 70 mg/dL: Patients recruited in this arm will receive statin +/-other lipid lowering therapy in order to reach a LDL-C concentration of less than 70 mg/dL.	Procedure: 70 mg/dL Statin +/-lipid lowering therapy during eight and a half years maximum, Target : LDL-C concentration of less than 70 mg/dL, recording recurrent of non fatal stroke, non fatal IM, and vascular death and others endpoints such as: new onset diabetes, hemorrhagic strokes. Other Name: treat to target

http://clinicaltrials.gov/show/NCT01252875

TST trial (Treat Stroke to Target) : comparison of two LDL-C targets after ischemic stroke

≥18 y/o
Had an ischemic stroke <3 months previously (Rankin Scale: 0-3)
Had history of atherosclerotic disease
Had level of LDL-C ≥70 mg/dL if on statin, or ≥100 mg/dL if statin naïve.

Statin ± ezetimibe
LDL-C lowering target

<70 mg/dL
n=1,430

90 ~ 100 mg/dL
n=1,430

Primary endpoint

Composite primary end point of major CV events

(included ischemic stroke, MI, new symptoms leading to urgent coronary or carotid revascularization, or death from CV causes)

Secondary endpoint

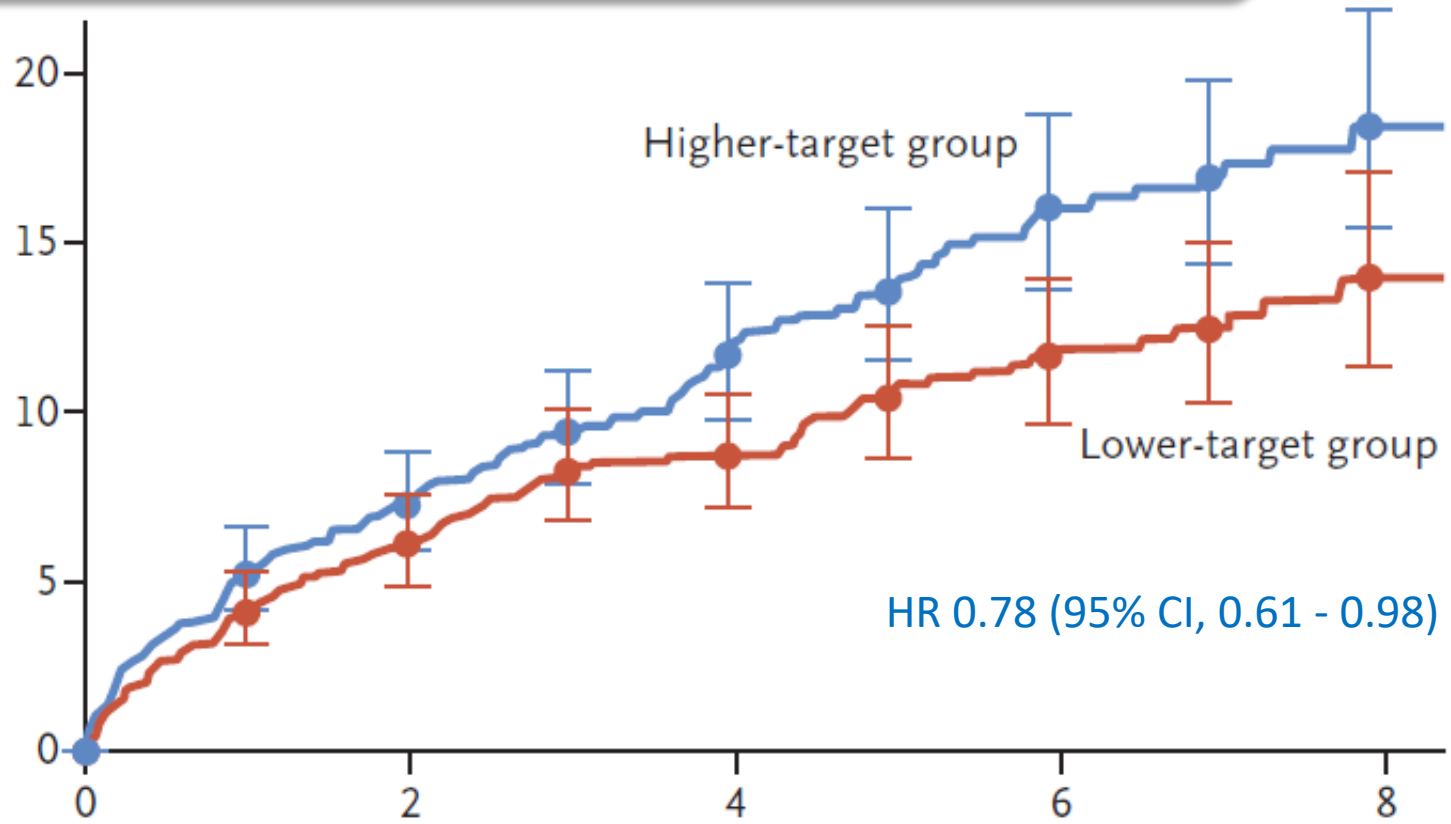
MI or urgent coronary revascularization after the onset of new symptoms; cerebral infarction or urgent revascularization of a carotid or cerebral artery after TIA; cerebral infarction or TIA; any revascularization of a coronary, cerebral, or peripheral artery; CV death; death from any cause; cerebral infarction or ICH; ICH; newly diagnosed diabetes; and a composite of the primary end point or ICH

CV, cardiovascular; ICH, intracranial hemorrhage; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; TIA, transient ischemic attack.

Amarenco P, et al. N Engl J Med 2020;382(1):9.

TST trial: cumulative incidence of the composite primary end point of major CV events

Patients who achieved lower target had a lower risk of subsequent CV events than those who achieved higher target.



CI, confidence interval; CV, cardiovascular; HR, hazard ratio.

Amarenco P, et al. N Engl J Med 2020;382(1):9.

TST trial: HRs for adjudicated clinical outcomes

End Points	Lower-Target Group (N= 1430)	Higher-Target Group (N= 1430)	Hazard Ratio (95% CI)	P Value
Secondary end points				
Myocardial infarction or urgent coronary revascularization — no. (%)	20 (1.4)	31 (2.2)	0.64 (0.37–1.13)	0.12†
Cerebral infarction or urgent revascularization of carotid or cerebral artery — no. (%)	88 (6.2)	109 (7.6)	0.81 (0.61–1.07)	
Cerebral infarction or TIA — no. (%)	120 (8.4)	139 (9.7)	0.87 (0.68–1.11)	
Any revascularization procedure — no./total no. (%)‡	94/1430 (6.6)	99/1430 (6.9)	0.93 (0.70–1.24)	
Carotid artery	17/94 (18)	23/99 (23)	—	
Coronary artery	44/94 (47)	51/99 (52)	—	
Peripheral artery	33/94 (35)	25/99 (25)	—	
Death — no. (%)				
Card				
Any				
Cerebral				
Intracranial hemorrhage — no. (%)	18 (1.3)	13 (0.9)	1.38 (0.68–2.82)	
Newly diagnosed diabetes — no. (%)§	103 (7.2)	82 (5.7)	1.27 (0.95–1.70)	

The incidence of ICH and newly diagnosed diabetes did not differ significantly between the two groups.

CI, confidence interval; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; TIA, transient ischemic attack.

Amarenco P, et al. N Engl J Med 2020;382(1):9.

2020台灣腦中風學會腦血管疾病血脂異常治療指引

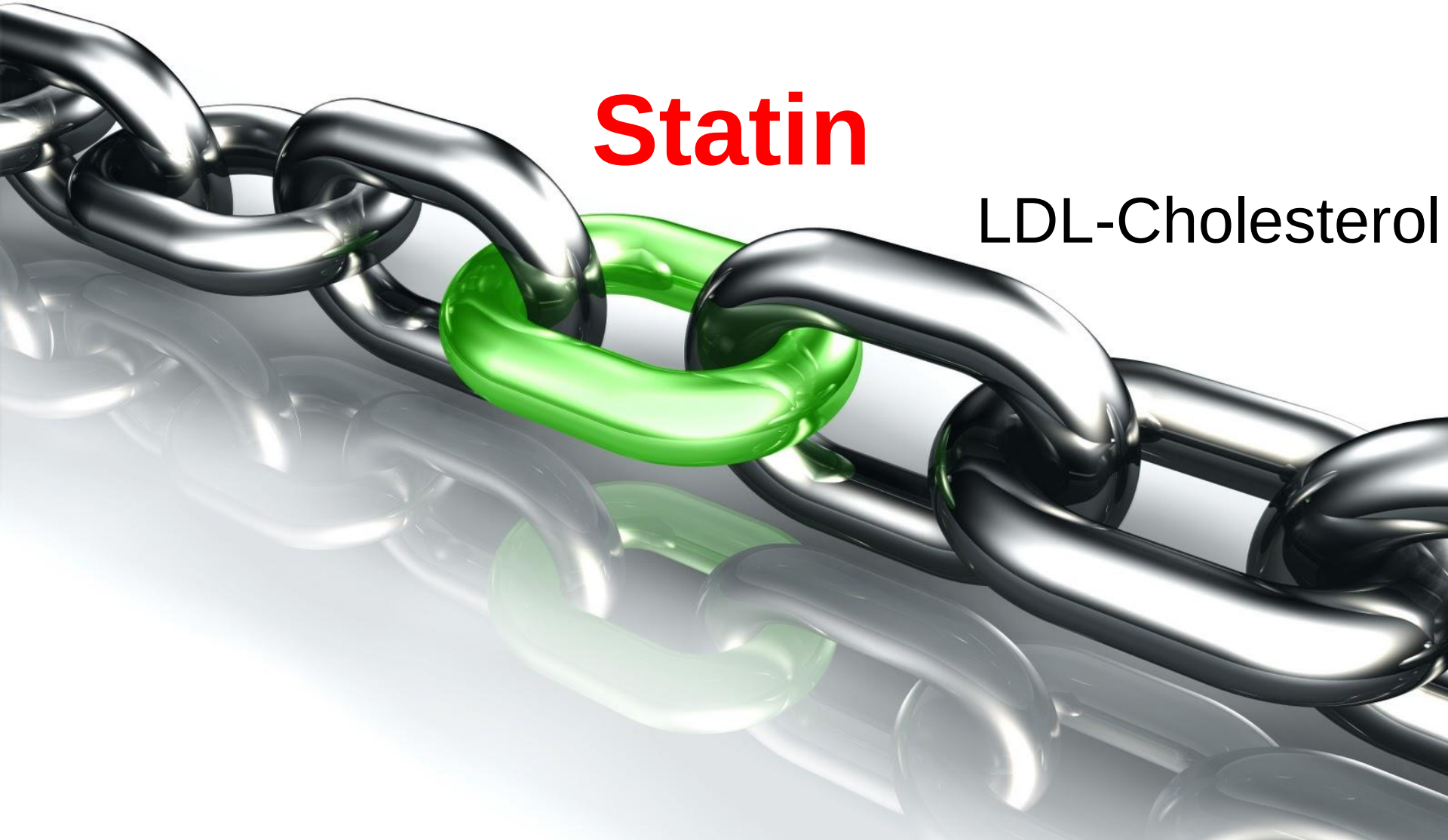
- 有腦中風病史且有急性冠心症的病患合併使用ezetimibe與statin比起單用statin，可降低再次腦中風的風險。(COR IIa、LOE B-R).
- 對於缺血性腦中風或TIA的病人合併有動脈粥狀硬化性心血管疾病，為了達到治療目標LDL-C <70 mg/dL，可考慮於statin之外加上ezetimibe。(COR IIb、LOE B-R)
- 對於症狀性頸動脈狹窄或顱內動脈狹窄病人，控制LDL-C <70 mg/dL。
- 對於無症狀頸動脈狹窄或顱內動脈狹窄病人，控制LDL-C <100 mg/dL。

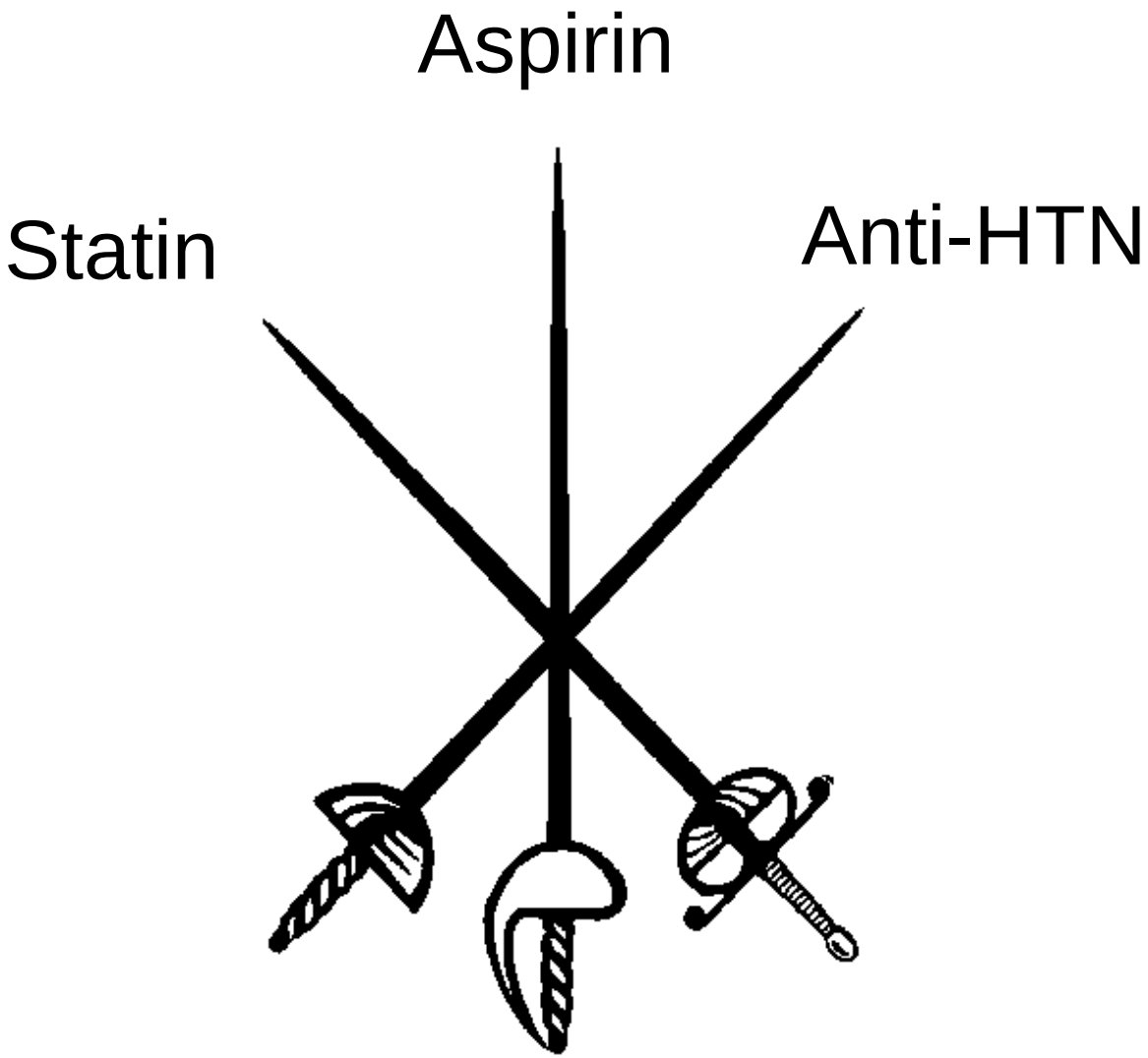
Hypertension : the strongest risk factor for all stroke

INTERSTROKE study


Stroke
Cholesterol

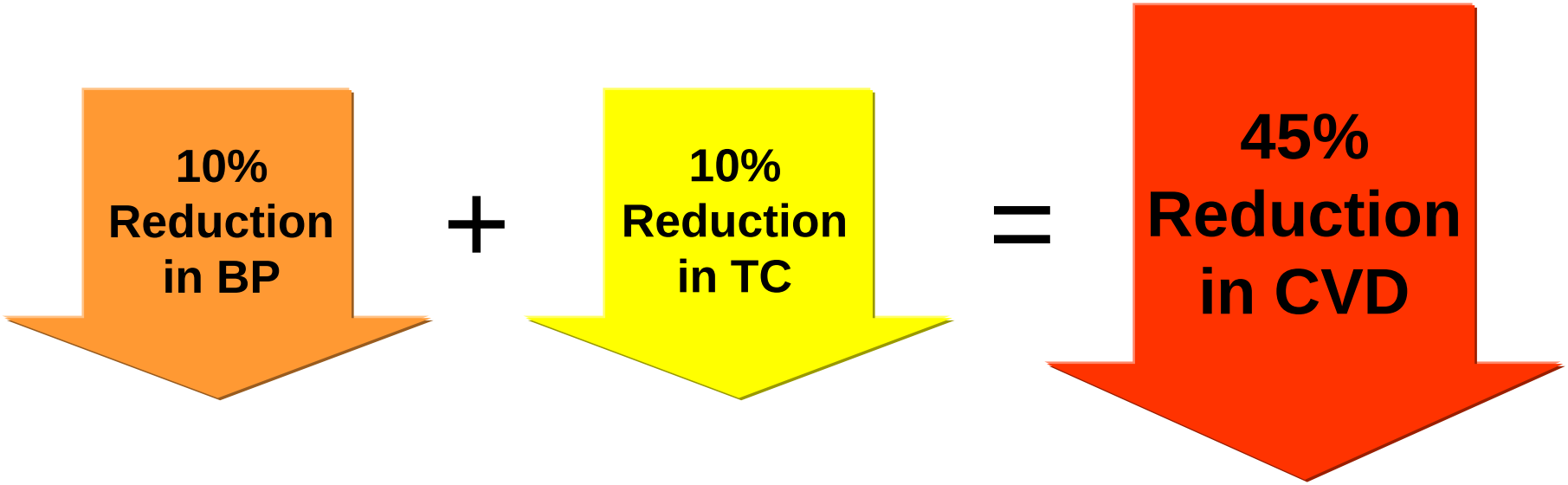
Atherosclerotic
ischemic stroke





Lancet Neurol 2009; 8: 453

Start Earlier and Together



Eur Heart J. 2004;25:484.

Caduet®

Aspirin