

## Statin in Lipid Management: The Role of Rosuvastatin

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### Case Scenario

- Mrs. Su
- 79 y/r female
- DM, HCVD, Hyperlipidemia
- Lipid profile:

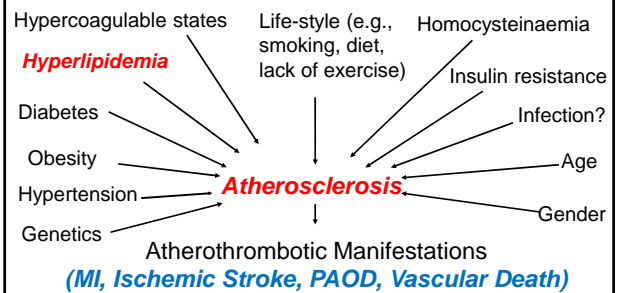
Date	TC level	LDL-C level
9706	266	180
9804	228	158
9809	257	181
10106	158	85
10210	139	70
10403	159	83

Crestor →

What's the role of cholesterol in atherosclerosis?

## What is the Interrelationship Between Lipid and Ischemic Stroke?

### Risk Factors for Atherothrombosis

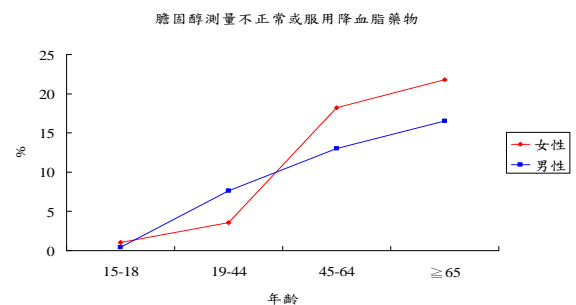


American Heart Association. Heart and Stroke Facts: 1997 Statistical Supplement; Wolf. Stroke 1990;21(suppl 2):II-4-II-6; Laurila et al. Arterioscler Thromb Vasc Biol 1997;17:2910-2913; Grau et al. Stroke 1997;28:1724-1729; Graham et al. JAMA 1997;277:1775-1781; Brigden. Postgrad Med 1997;101(5):249-262.

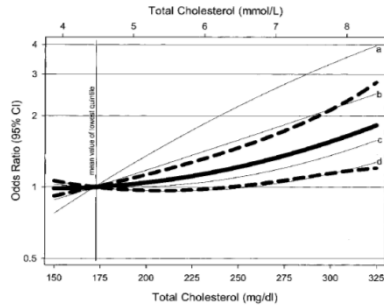
### Pathogenesis of Atherosclerosis: Role of Lipids

- Increased expression of cell adhesion molecules.
- Foam cell formation.
- Endothelial dysfunction.
- Engender and maintain chronic inflammation.
- Destabilise plaques.
- Pro-thrombotic.

### Prevalence of Hyperlipidemia in Taiwan



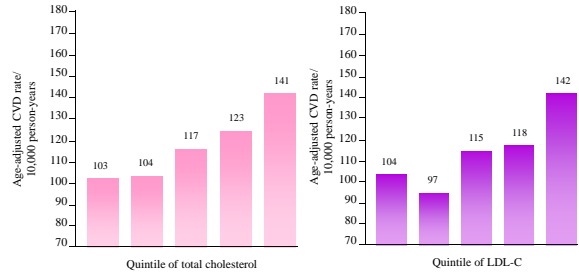
### Total Cholesterol and Ischemic Stroke



a: atherosclerosis  
b: lacunar stroke  
c: other stroke  
d: cardioembolic

Tirschwell D et al. Neurology 2004; 63:1868-75

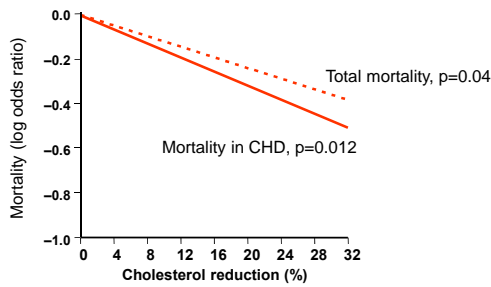
### Cholesterol Levels Linked To Increased Risk of Cerebrovascular Disease (CVD)



Koren-Morag N et al. Arch Intern Med. 2002;162:993-999.

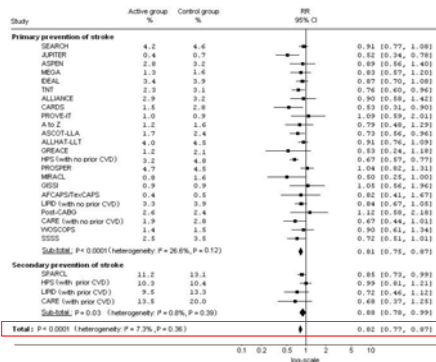
### Benefit of Lowering Cholesterol

Meta-analysis of 38 primary and secondary prevention trials, with more than 98,000 patients in total



Gould AL et al. Circulation 1998;97:946-952

### Statin and Stroke: Meta-analysis



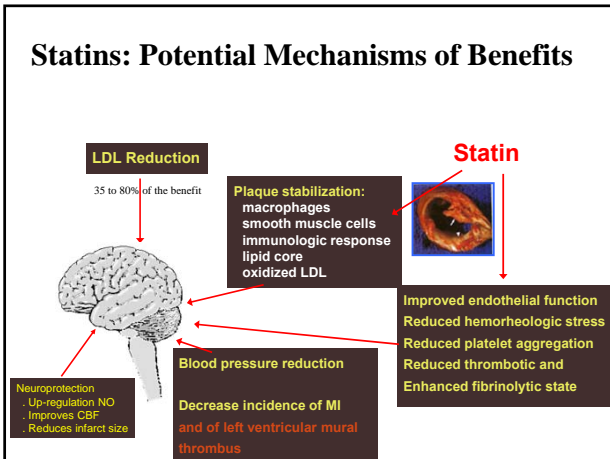
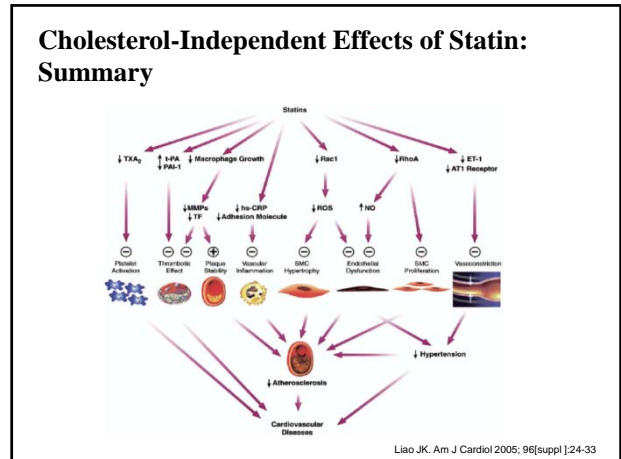
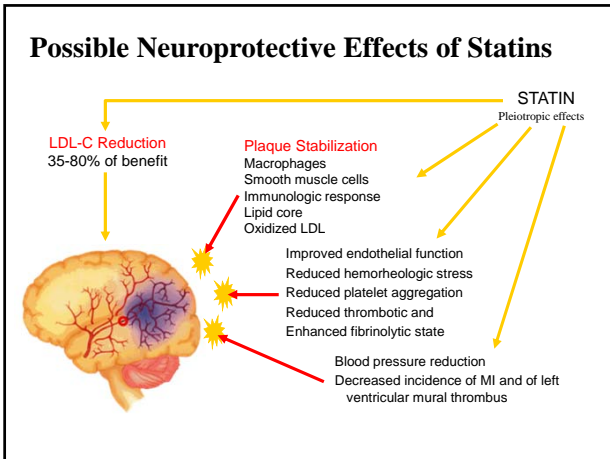
N total=165 732

Amarenco P, Labreuche J. Lancet Neurol. 2009; 8:453-63

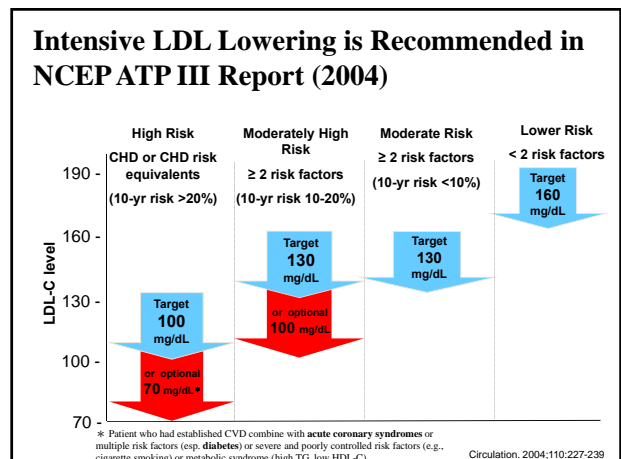
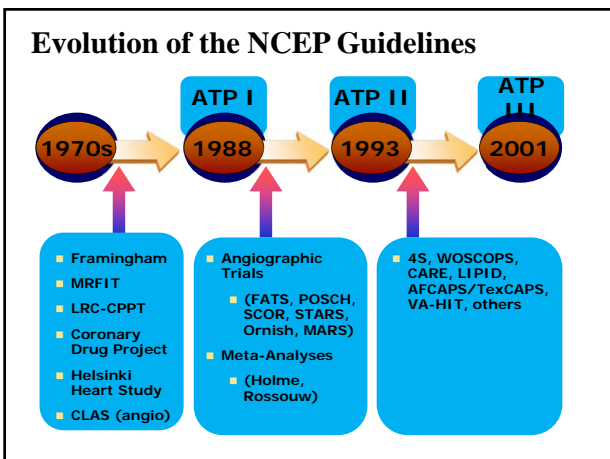
### Mechanisms by Which Statins Reduce Stroke Incidence

### Statin: Mechanisms of Action

- Lipid lowering is not the entire answer
  - Benefits seen in patients with relatively normal levels
- Plaque stabilization
- Anticoagulant effects (fibrinogen, PAI-1)
- Reduces C-reactive protein
- Improves cerebral vasomotor reactivity
- Modulates brain nitric oxide system
- Possible neuro-protective effect in acute strokes



## Guidelines to “Guide” Lipid Management

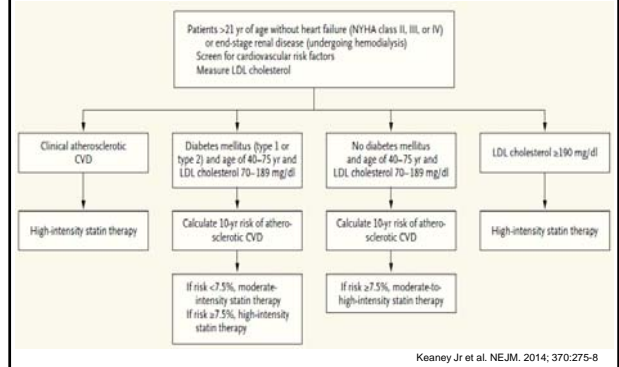


### 2013 ACC / AHA Guidelines

#### 4 Major Statin Benefit Groups

1. **Clinical ASCVD** (ACS or history of MI, stable or unstable angina, revascularisation, **stroke**, TIA, or PAD presumed to be of atherosclerotic origin)
2. **LDL-C  $\geq$  190 mg/dL**
3. **Diabetes aged 40-75 y with LDL-C 70-189 mg/dL**
4. **Estimated 10-year ASCVD risk  $\geq$  7.5 % with LDL-C 70-189 mg/dL (and age 40-75 y)**

### 2013 ACC/AHA Guideline for Use of Statin Therapy in Patients at Increased CV Risk

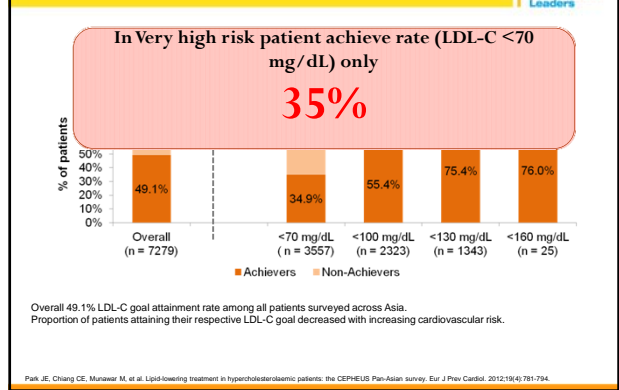


### 2013 ACC / AHA Guidelines

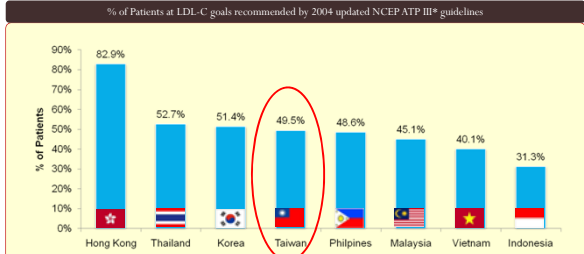
#### High-, Moderate- and Low-intensity statin therapy

High-intensity	Moderate-intensity	Low-intensity
↓ LDL-C $\geq$ 50 %	↓ LDL-C 30 - 50 %	↓ LDL-C < 30 %
Atorva (40) - 80 mg Rosuva 20 (40) mg	Atorva 10-(20) mg Rosuva 5 (10) mg Simva 20 - 40 mg Prava 40 (80) mg Fluva 80 mg	Simva 10 mg Prava 10 - 20 mg Fluva 20 - 40 mg

### Proportion of Patients Attaining Their 2004 Updated NCEP ATP III-Recommended LDL-C Goals



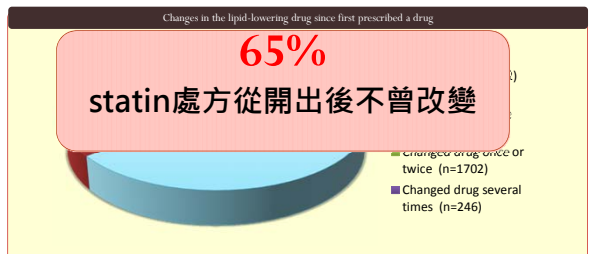
### Percentage of Patients at LDL-C goals recommended by the 2004 updated NCEP ATP III\* guidelines



\*For patients in Hong Kong the treatment goal attainment rate was 82.9% while patients in other countries had very low LDL-C attainment rate (31.3 – 52.7%).

Pak JE, Chiang CE, Munawar M, et al. Lipid-lowering treatment in hypercholesterolemic patients: the CEPHEUS Pan-Asian survey. Eur J Prev Cardiol. 2012;19(4):781-794.

### Changes in the lipid-lowering drug since first prescribed a drug

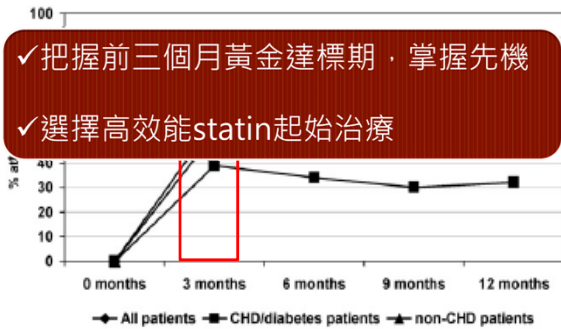


•For 64.1% of patients, initial treatment remained the same.

Pak JE, Chiang CE, Munawar M, et al. Lipid-lowering treatment in hypercholesterolemic patients: the CEPHEUS Pan-Asian survey. Eur J Prev Cardiol. 2012;19(4):781-794.

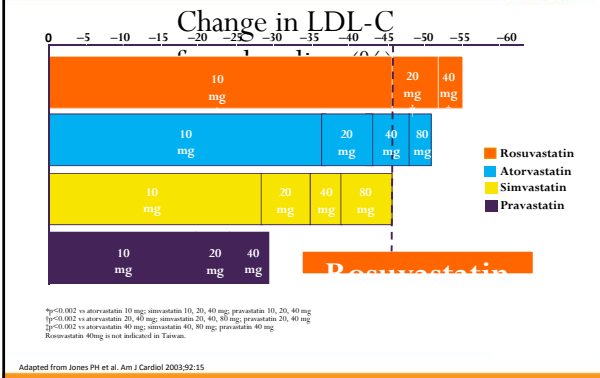
達標兩大關鍵:

- ✓ 把握前三個月黃金達標期，掌握先機
- ✓ 選擇高效能statin起始治療



Curr Med Res Opin. 2008 Jul; 24(7): 1951-63

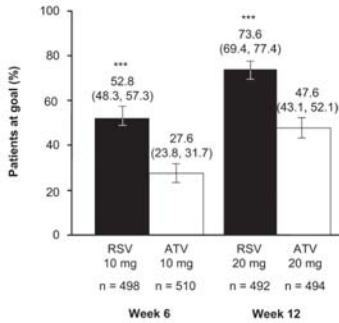
選擇高效能statin協助病患一次達標



\*p<0.002 vs atorvastatin 10 mg; simvastatin 10, 20, 40 mg; pravastatin 10, 20, 40 mg  
 †p<0.002 vs atorvastatin 20, 40 mg; simvastatin 20, 40, 80 mg; pravastatin 20, 40 mg  
 ‡p<0.002 vs atorvastatin 40 mg; simvastatin 40, 80 mg; pravastatin 40 mg  
 Rosuvastatin 40mg is not indicated in Taiwan.

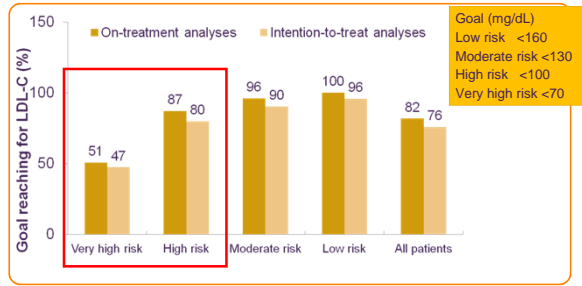
Adapted from Jones PH et al. Am J Cardiol 2003;92:15

CRESTOR can help more patients to achieve LDL-C goal (established CHD or CHD equivalent)



\*\*\*p<.001 versus atorvastatin during same time point (e.g. 6 weeks)  
 Mean baseline LDL-C: 188 to 189 mg/dL  
 Adapted from Faergeman O, et al. Cardiology. 2008; 111:219-228

Over 80% of high risk patients reach LDL-C goal <100mg/dl with CRESTOR 10mg/day



Overall more than 75% of patients reached therapeutic goals with rosuvastatin therapy.

Adapted from Chiang CE, et al. J Chin Med Assoc. 2008;71:113-118.

CRESTOR藥物交互作用可能性較低

不同於某些statins藥物，CRESTOR與經由CYP 450 3A4代謝的藥物產生藥物交互作用的可能性較低

明顯經由 CYP450 3A4 代謝作用

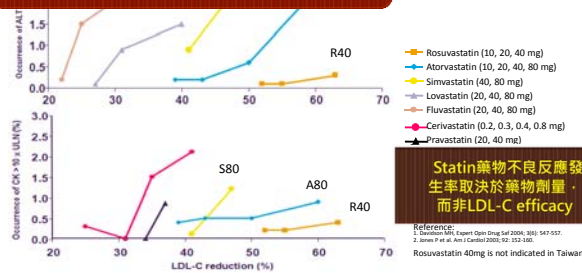
Statin	Interaction with CYP450 3A4
CRESTOR	no
atorvastatin	yes
simvastatin	yes
pravastatin	no

Reference:  
 1. Mc Taggart F et al. Am J Cardiol. 2001; 87(suppl): 288-328  
 2. Cairns MJ et al. Am J Cardiol. 2001; 87(suppl): 61c-68c

Safety of Intensive-Dose Statin

Percentage changes in liver and muscle enzymes by percent LDL-C reduction<sup>1</sup>

Low dose, high potency will be better



Statin藥物不良反應發生率取決於藥物劑量，而非LDL-C efficacy

Reference:  
 1. Danesh M, et al. Expert Opin Drug Saf. 2006; 5(4): 547-557.  
 2. Jones PH et al. Am J Cardiol 2003;92:15-20  
 Rosuvastatin 40mg is not indicated in Taiwan.

# Conclusions

- ## Conclusions
- Total cholesterol, especial the LDL-C, is one of the major risk factor in ischemic stroke
  - Statin agents are very successful for reducing all types of vascular events
  - The efficacy of statin agents appears to be independent of lipid levels
  - Most stroke patients should receive a statin agent

### Comparison with other Statins

Parameter	Rosuva	Atorva	Prava	Fluva	Simva
Half-life, h	19 (任何時間服用)	3-14 (任何時間服用)	1.8 (睡前服用)	1 (晚上服用)	3 (晚上服用)
Metabolic enzyme (S, substrate; I, inhibitor)	2C9,2C19 (none)	3A4(S)	Sulfation (none)	2C9(I)	3A4(S)
Food effect on bioavailability	None	↓13%	↓30%	↓15-25%	None
Hepatoselectivity (log ratio)	3.3	2.2	3.3	1.3	0.54
LDL-C reduction, %	10 mg 46%	10mg 37%	10mg 20%	80mg 30%	20mg 35%
	20mg 52%	20mg 43%	20mg 24%		40mg 39%
	40mg 55%	40mg 48%	40mg 30%		80mg 46%
HDL-C increase%	7.7%~10%	5.7%~2%	3.2%~5.5%	3.2%~5.5%	5.3%~6.8%
TG reduction, %	20%~26%	20%~28%	8%~13%	8%~13%	11%~18%
Price, NT\$	30.8 (10mg)	28.9 (10mg) 49.1 (40mg)	36.6 (40mg)	27 (80mg)	32 (40mg)
	0.67	0.78-1.02	1.22	0.9	0.82
Elimination, % Urine Feces	10 90	4 96	20 70	5 95	13 80

New NHIA guideline (2013/8/1~)

**最主要的改變：**

1. 心血管疾病或糖尿病患者，起始治療LDL-C由  $\geq 130\text{mg/dl}$  降為  $\geq 100\text{mg/dl}$ ，目標  $< 100\text{mg/dl}$
2. 已刪除達到治療目標需 “減量至最低有效劑量”

心血管疾患定義：  
 (一) 冠狀動脈粥狀硬化病人：心絞痛病人，有心導管證實或缺血性心電圖變化或負荷性試驗陽性反應者(附檢查報告)  
 (二) 缺血性腦血管疾病病人包含：  
 1. 腦梗塞。  
 2. 暫時性腦缺血患者(TIA)。(診斷須由神經科醫師確立)  
 3. 有症狀之頸動脈狹窄。(診斷須由神經科醫師確立)

危險因子定義：  
 1. 高血壓  
 2. 男性  $\geq 45$  歲，女性  $\geq 55$  歲或停經者  
 3. 曾有缺血性心臟病病史(男性  $\geq 55$  歲，女性  $\geq 65$  歲)  
 4. HDL-C  $< 40\text{mg/dl}$   
 5. 吸菸(因吸菸而符合起步治療原則之個案，若未戒菸而要求藥物治療，應以自費治療)。

Source: Taiwan NHIA

醫策會2010年BTS(Breakthrough Series)專案  
 提升急性缺血性腦中風照護

評核指標10: 出院時使用降血脂藥物

分子: 急性缺血性中風及TIA病人LDL>100mg/dl出院時使用降血脂藥物病人數

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分母: 急性缺血性中風及TIA病人LDL>100mg/dl出院病人數

x 100%

