Statins and Stroke

Keun-Sik Hong, MD/PhD

Department of Neurology, Stroke Center, Ilsan Paik Hospital,
Inje University

Disclosure related to this topic

- Lecture honoraria
  - Pfizer Korea
  - Chong Kun Dang Pharm
- Research grant
  - Pfizer Korea

Topics

- Statins for primary and secondary stroke prevention

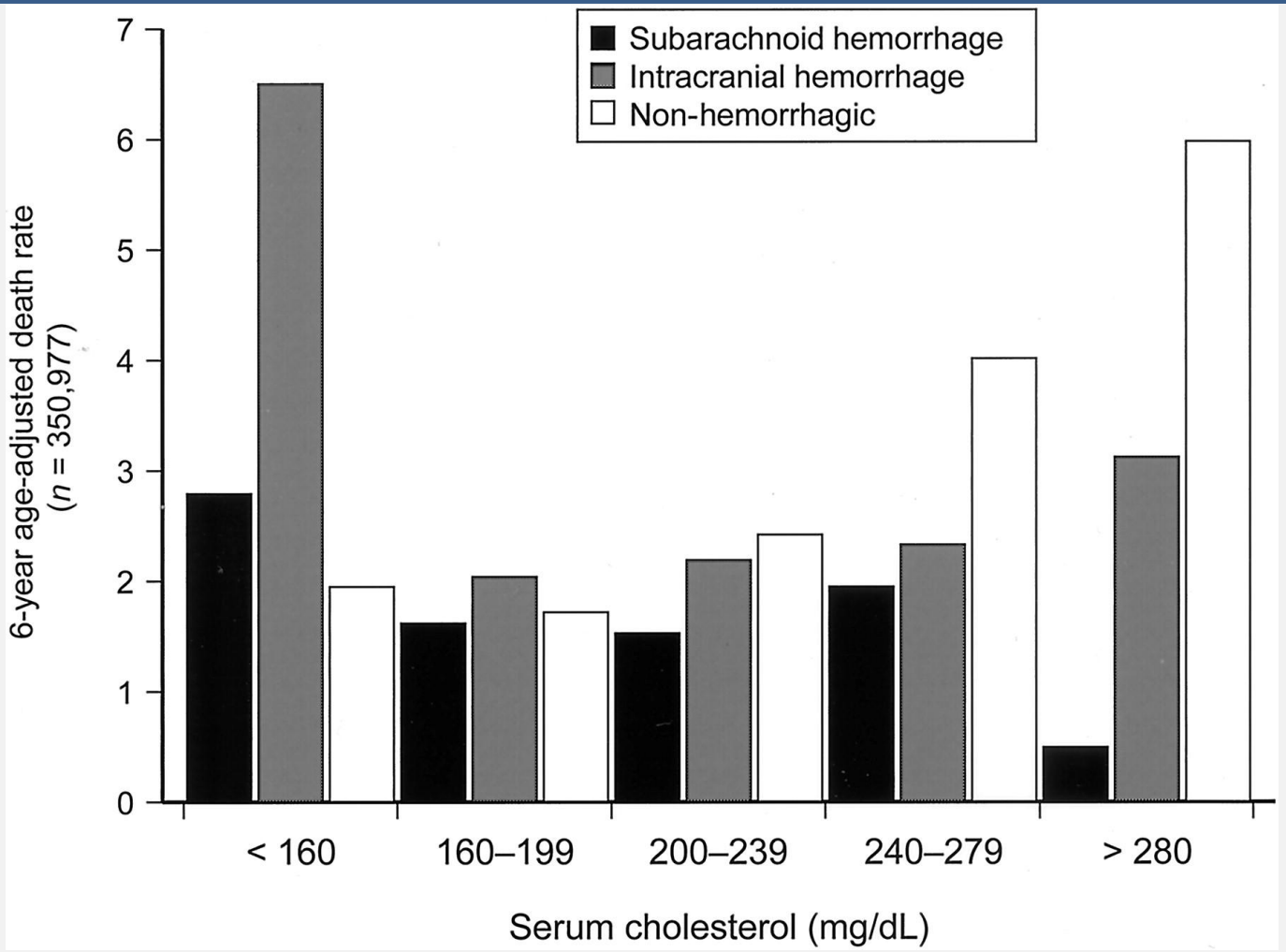
- Statins and acute ischemic stroke

Dyslipidemia

- Well-established and modifiable risk factor for stroke

- Statin benefit
  - Secondary as well as Primary Stroke Prevention

MRFIT: stroke death and cholesterol

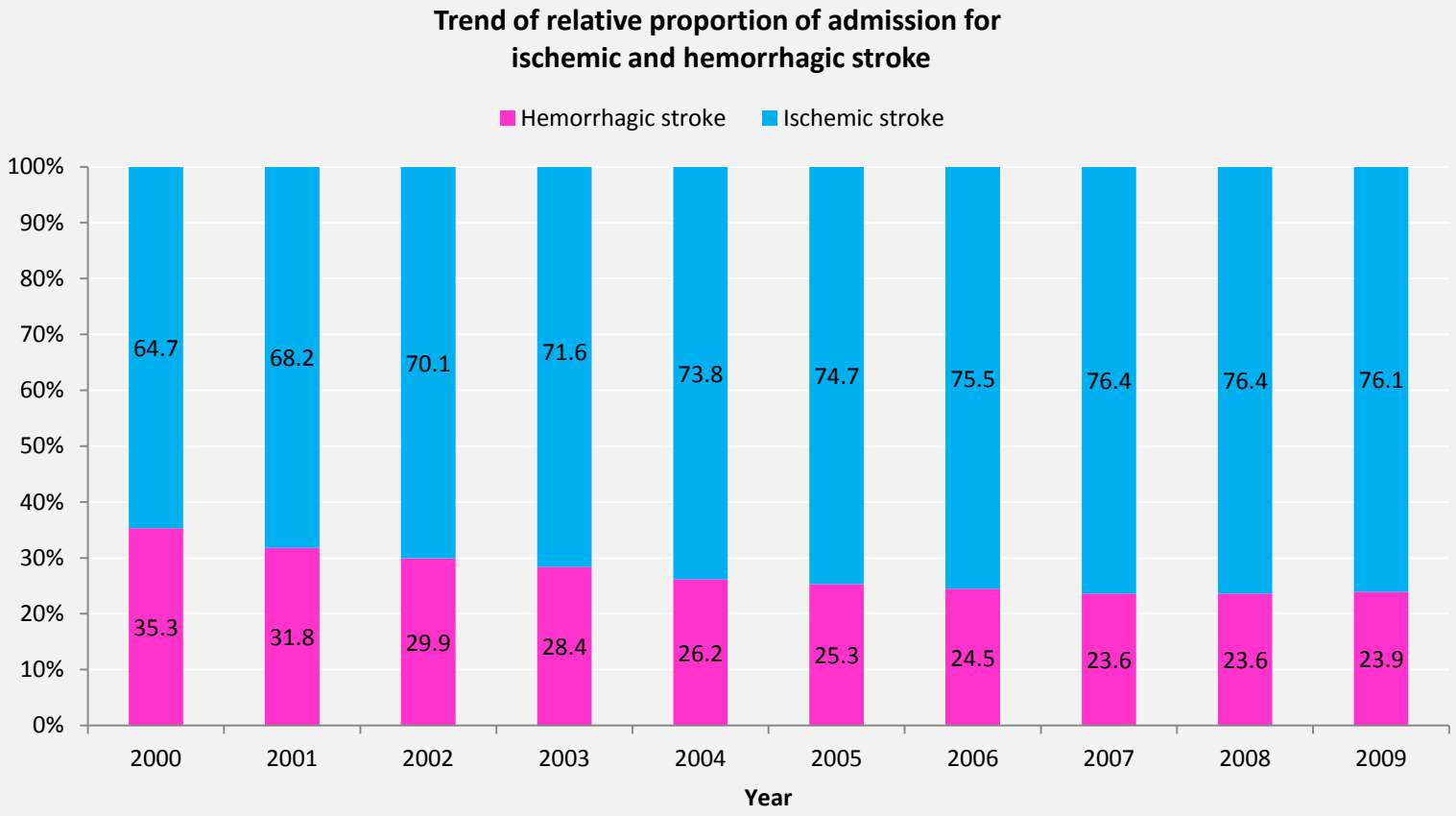


MRFIT: multiple risk factor intervention trial

6 years of follow-up in 350,977 men, 35 to 57 years of age

Ischemic stroke as a major stroke type in Korea

- Ischemic stroke has increased during the first decade of the 21st century
- Ischemic stroke accounts for >75% of all strokes



Hong, KS et al. Stroke Statistics in Korea Part I. JOS 2013;15:2-20; Data from Korean HIRA

INTERSTROKE

- Case-control study: 3000 acute stroke vs. 3000 control
- 22 countries worldwide

Risk factor	All stroke		Ischemic stroke	
	OR (99% CI)	PAR, % (99% CI)	OR (99% CI)	PAR, % (99% CI)
Hypertension (self-reported, self-reported or >160/90)	2.64 (2.26—3.08) 3·89 (3·33–4·54)	34.6 (30.4-39.1) 51·8 (47·7–55·8)	2·37 (2·00–2·79) 3·14 (2·67–3·71)	31·5 (26·7–36·7) 45·2 (40·3–50·0)
Regular physical activity	0.69 (0.53—0.90)	28.5 (14.5-48.5)	0·68 (0·51–0·91)	29·4 (14·5–50·5)
Waist-to-hip ratio (T2 vs T1, T3 vs T1))	1·42 (1·18–1·71) 1·65 (1·36–1·99)	26.5 (18.8-36.0)	1·34 (1·10–1·64) 1·69 (1·38–2·07)	26·0 (17·7–36·5)
Ratio of apolipoprotein B to A1 (T2 vs T1, T3 vs T1)	**1·13 (0·90–1·42) 1·89 (1·49–2·40)**	**24.9 (15.7-37.1)**	**1·30 (1·01-1·67) 2·40 (1·86–3·11)**	**35·2 (25·5–46·3)**
Smoking	2.09 (1.75—2.51)	18.9 (15.3-23.1)	2·32 (1·91–2·81)	21·4 (17·5–25·8)
Dietary risk score (T2 vs T1, T3 vs T1)	1.35 (1.11—1.61) 1·35 (1·11–1·64)	18.8 (11.2-29.7)	1·29 (1·06–1·57) 1·34 (1·09–1·65)	17·3 (9·4–29·6)
Cardiac causes	2.38 (1.77—3.20)	6.7 (4.8-9.1)	2·74 (2·03–3·72)	8·5 (6·4–11·2)
Depression	1.35 (1.10—1.66)	5.2 (2.7-9.8)	1·47 (1·19–1·83)	6·8 (3·9–11·4)
Diabetes	1.36 (1.10—1.68)	5.0 (2.6-9.5)	1·60 (1·29–1·99)	7·9 (5·1–12·3)
Psychosocial stress	1.30 (1.06—1.60)	4.6 (2.1-9.6)	1·30 (1·04–1·62)	4·7 (2·0–10·2)
Alcohol intake (1-30 drinks/month, >30 drinks)	0·90 (0·72–1·11) 1·51 (1·18–1·92)	3.8 (0.9-14.4)	0·79 (0·63–1·00) 1·41 (1·09–1·82)	1·0 (0·0–83·8)

O'Donnell et al. Lancet 2010;376:112-123

Statin trials

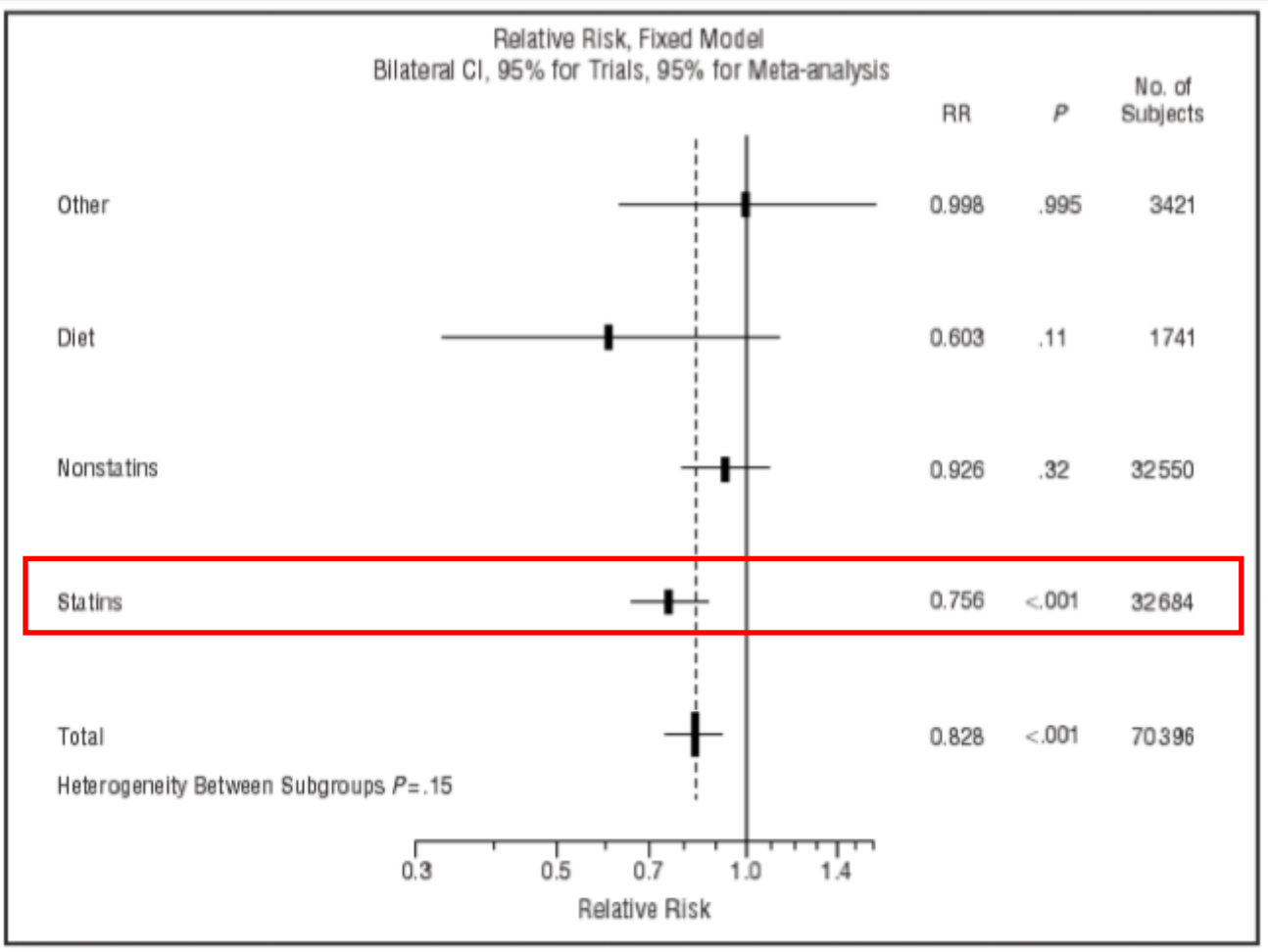
Non-stroke population in majority

SPARCL: secondary stroke prevention

Statins Save Stroke

Lipid-lowering therapies
Differential effects on stroke prevention

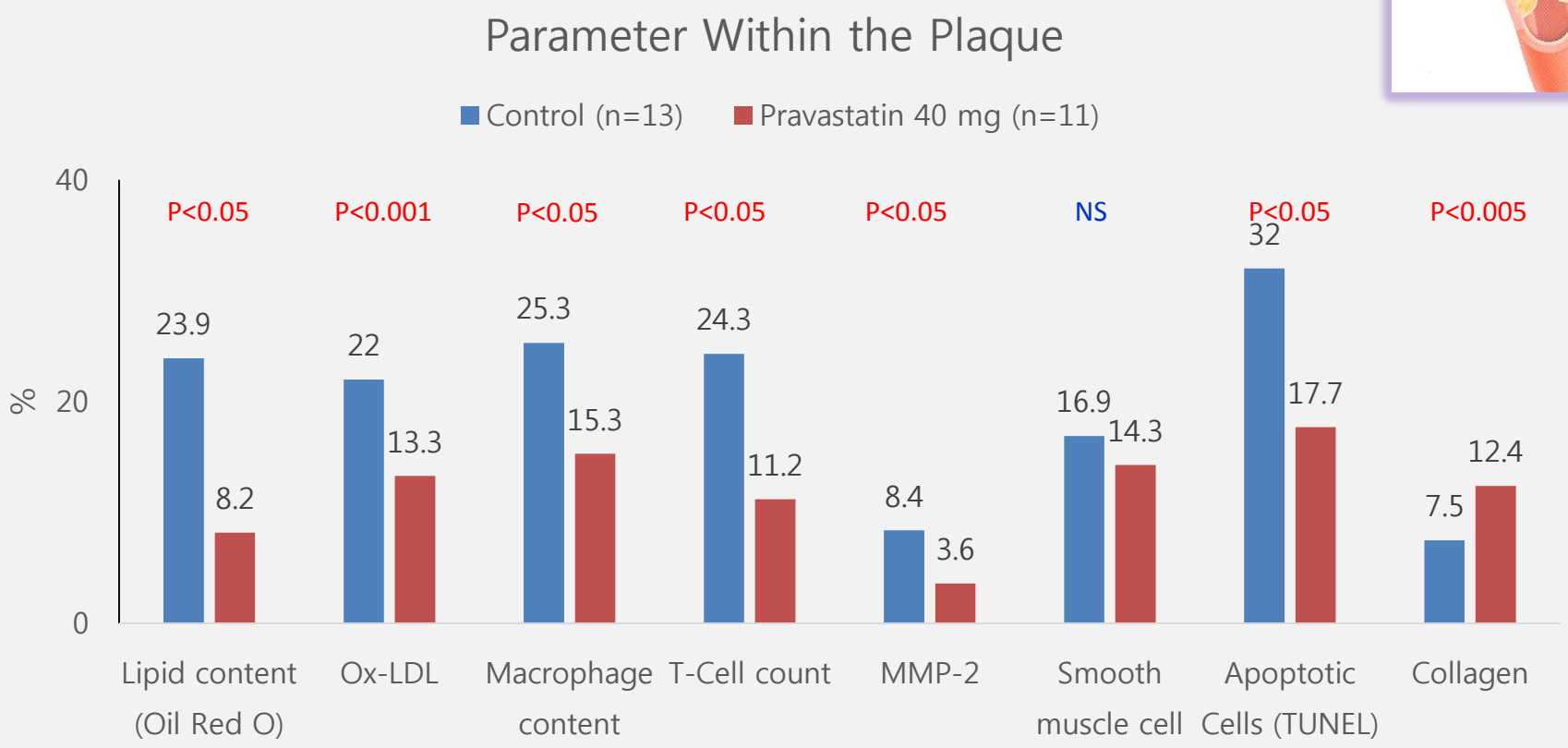
Meta-analysis by the type of treatment on stroke incidence in patients with CHD



Corvol JC. Arch Intern Med 2003;163:669-676.

Carotid plaque stabilization

Carotid plaque specimen removed by CEA

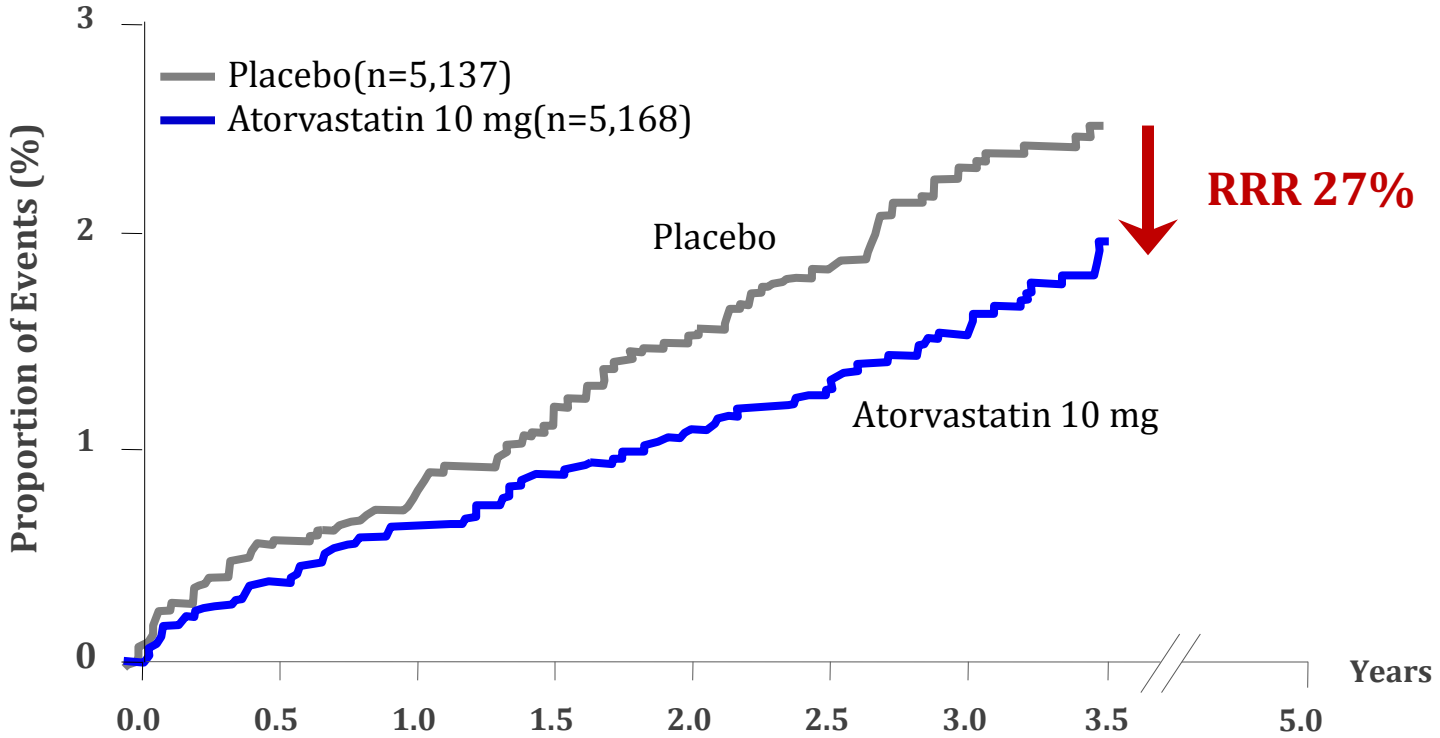


Crisby et al. Circulation 2001:103:926

ASCOT-LLA study, HT and 3 or more RFs

- 10,305 hypertensive patients with no Prior CHD
- Atorvastatin 10 mg versus Placebo

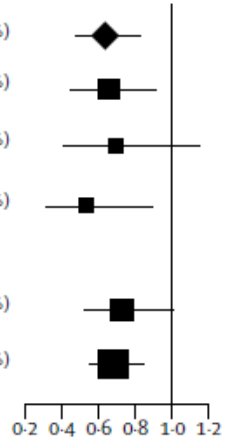
Stroke: 0.73 [0.56–0.96], p=0.024



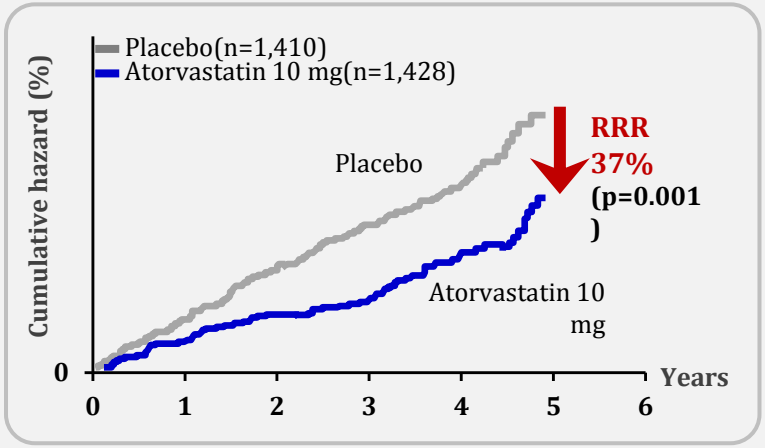
Adapted from Sever PS, et al. Lancet 2003; 361: 1149–58.

CARDS: atorvastatin 10 mg/day in T2DM
48% relative risk reduction in stroke

	Number of patients with an event (%) Placebo	Atorvastatin 10 mg	Hazard ratio (95% CI)	p
Primary endpoint	127 (9·0%)	83 (5·8%)	0·63 (0·48–0·83)	0·001
Acute coronary events	77 (5·5%)	51 (3·6%)	0·64 (0·45–0·91)	
Coronary revascularisation	34 (2·4%)	24 (1·7%)	0·69 (0·41–1·16)	
Stroke	39 (2·8%)	21 (1·5%)	0·52 (0·31–0·89)	
Secondary endpoint				
Death from any cause	82 (5·8%)	61 (4·3%)	0·73 (0·52–1·01)	0·059
Any acute cardiovascular disease event	189 (13·4%)	134 (9·4%)	0·68 (0·55–0·85)	0·001

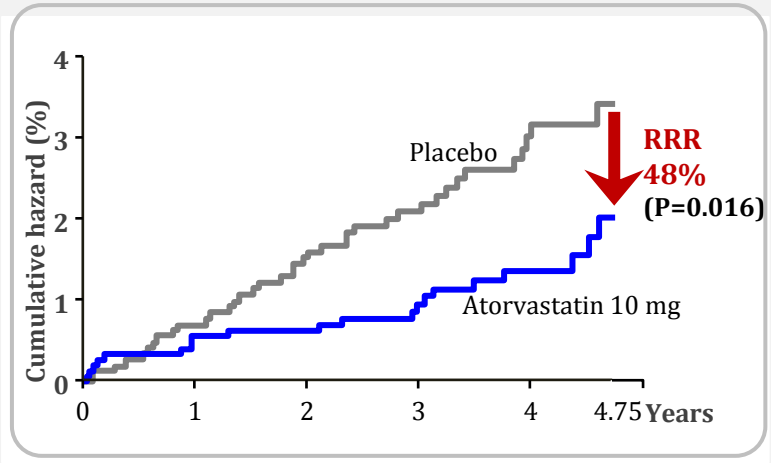


Primary endpoint: major cardiovascular event



Secondary endpoint: Stroke

RRR of ischemic stroke = 55% (P=0.017)

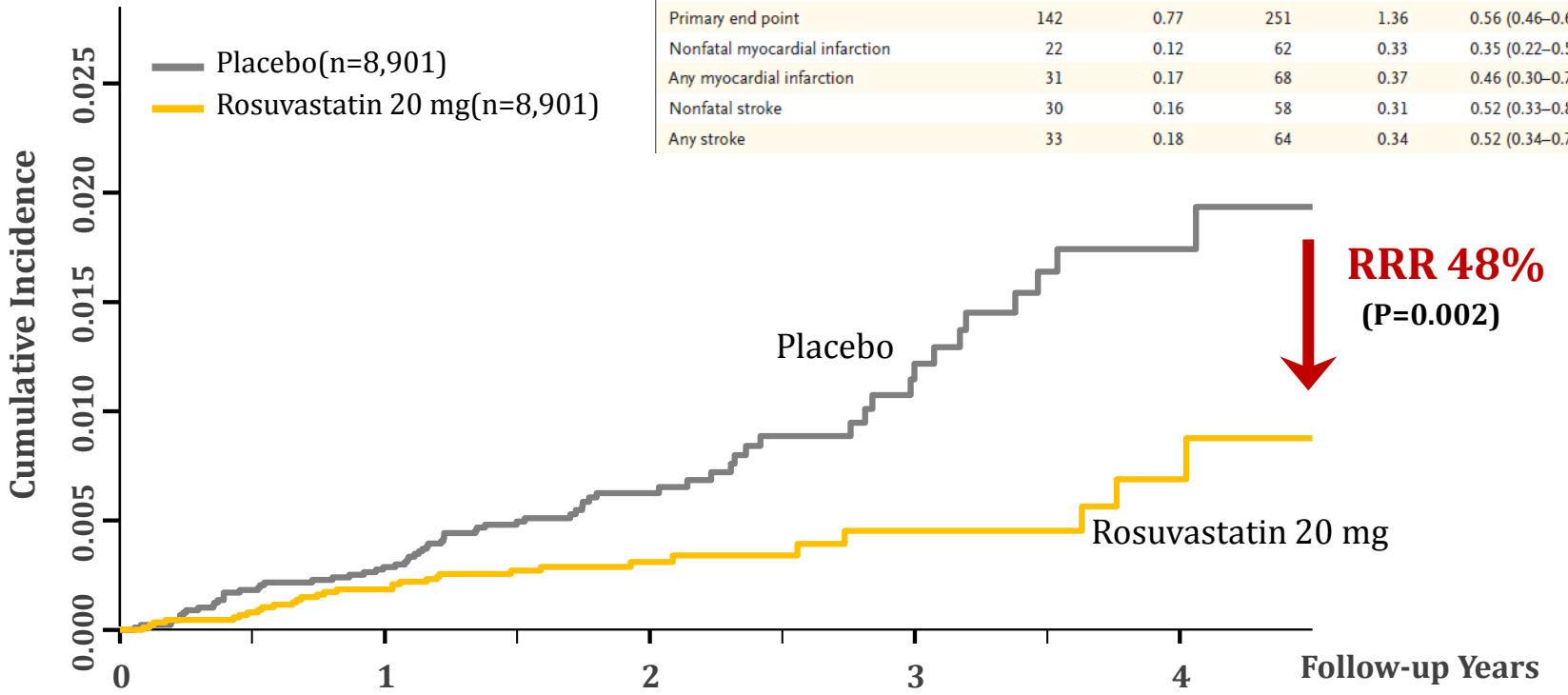


JUPITER: rosuvastatin 20 mg/day 48% reduction in risk of stroke

17,802 healthy adults with no Prior CVD, no DM, LDL <130 mg/dL, hsCRP >2 mg/L
Rosuvastatin 20 mg versus Placebo

Table 3. Outcomes According to Study Group.

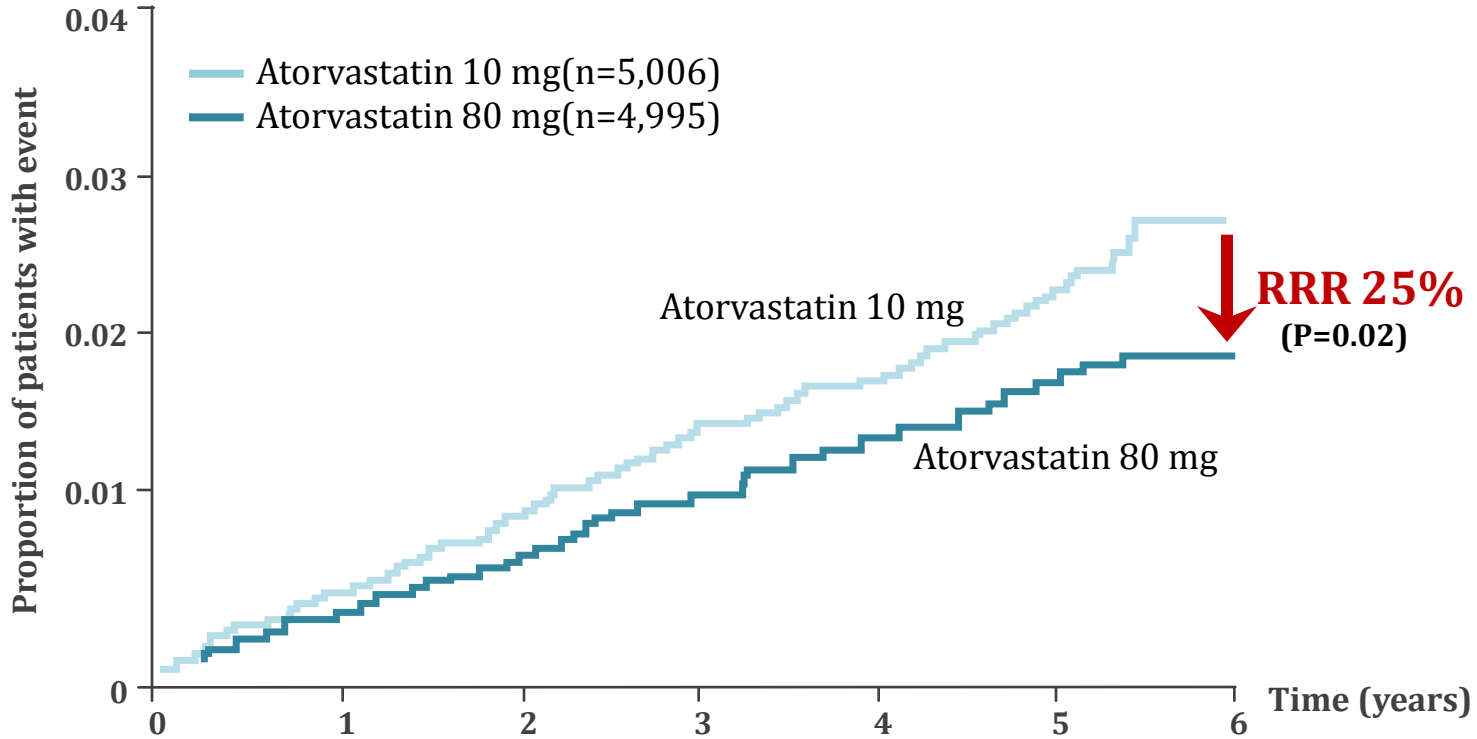
End Point	Rosuvastatin (N=8901)		Placebo (N=8901)		Hazard Ratio (95% CI)	P Value
	No. of Patients	Rate per 100 person-yr	No. of Patients	Rate per 100 person-yr		
Primary end point	142	0.77	251	1.36	0.56 (0.46–0.69)	<0.00001
Nonfatal myocardial infarction	22	0.12	62	0.33	0.35 (0.22–0.58)	<0.00001
Any myocardial infarction	31	0.17	68	0.37	0.46 (0.30–0.70)	0.0002
Nonfatal stroke	30	0.16	58	0.31	0.52 (0.33–0.80)	0.003
Any stroke	33	0.18	64	0.34	0.52 (0.34–0.79)	0.002



Adapted from Ridker PM, et al, NEJM 2008;359:2195-207.

TNT study, Stable CHD
atorvastatin 80 mg/day vs 10 mg/day

- 10,001 patients with CHD randomized Atorvastatin 10 mg or 80 mg
- 25% reduction in risk of stroke with atorvastatin 80 mg/day vs 10 mg/day



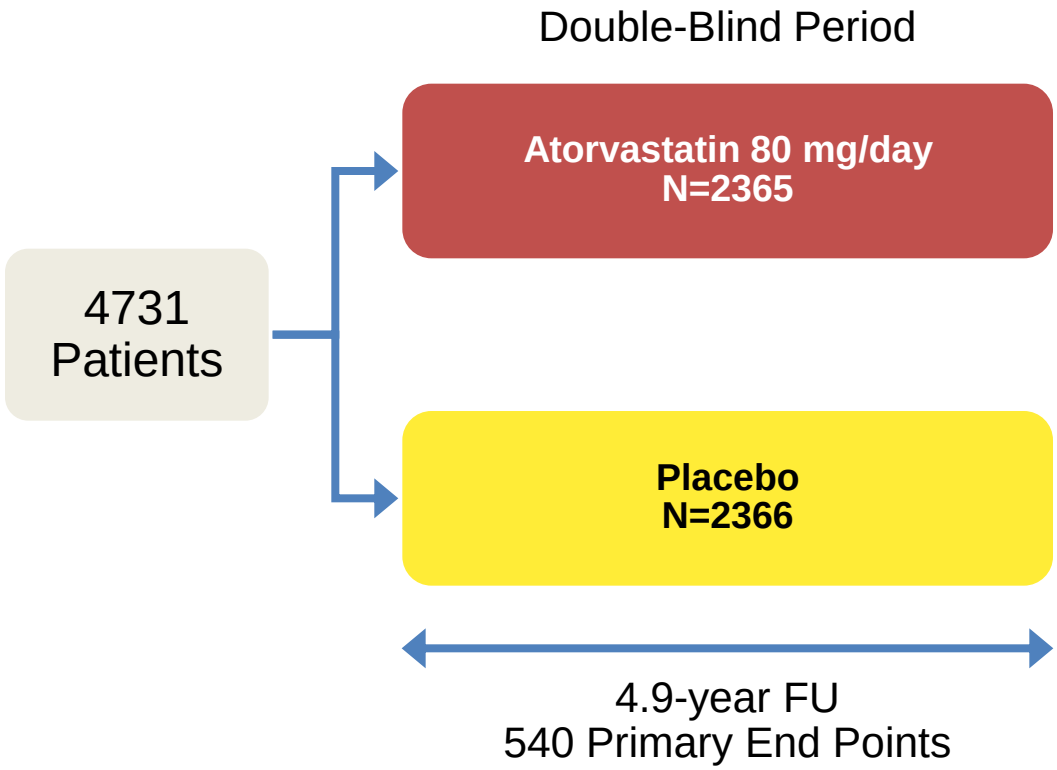
*TNT = Treating to New Targets; RRR = relative risk reduction.

LaRosa JC, et al. N Engl J Med 2005;352:1425-1435.

SPARCL: Study Design
Statin for 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

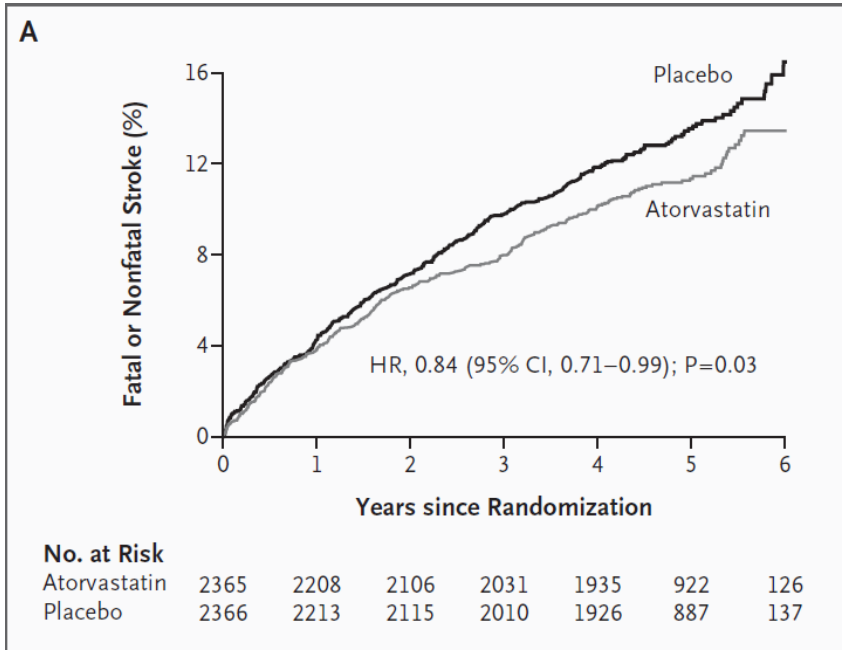


Primary End Point
Time to the First Occurrence of a Fatal or Nonfatal Stroke

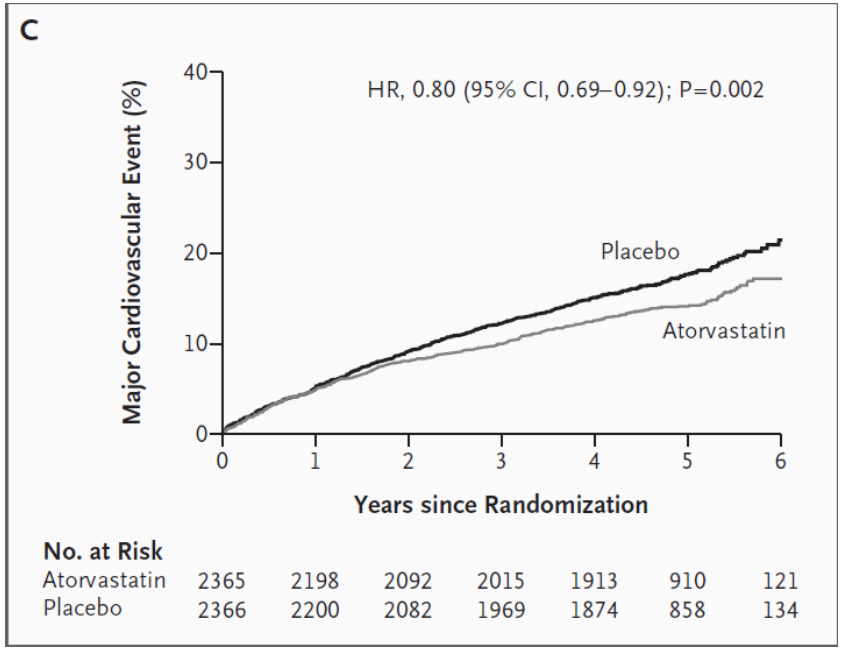
SPARCL Investigators. *N Engl J Med*. 2006;355:549–559.

SPARCL Trial
Statin Preventing Recurrent Stroke as well as Major CVD

Stroke



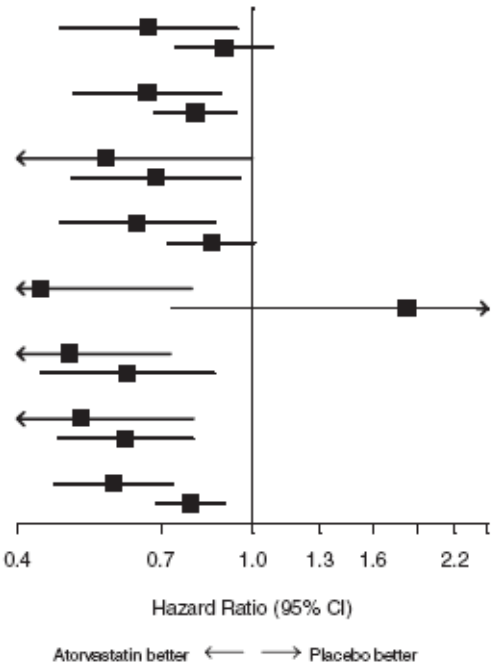
Stroke and MI



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

Greater benefit in SPARCL Trial : Carotid stenosis

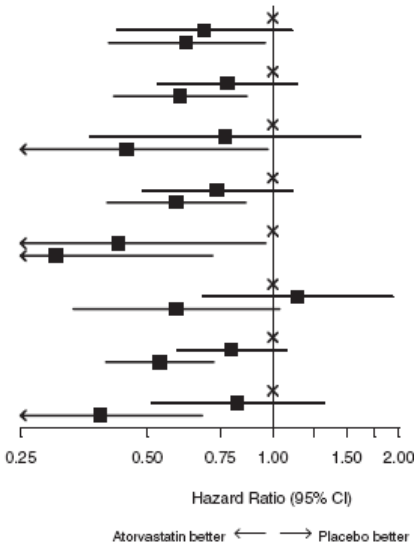
	Atorvastatin Events (%)	Placebo Events (%)	HR	Treatment P Value	Heterogeneity P Value
Stroke					
With CS	55 (11.2)	83 (16.1)	0.67	0.021	0.151
Without CS	210 (11.2)	228 (12.3)	0.90	0.256	
Stroke or TIA					
With CS	79 (16.0)	118 (23.0)	0.66	0.005	0.268
Without CS	296 (15.8)	358 (19.3)	0.80	0.005	
Major 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	



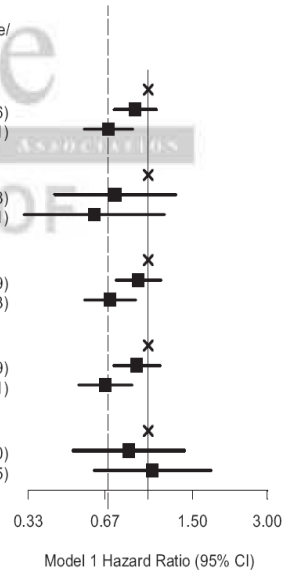
Sillesen H et al. Stroke 2008:39:3297

Intensive lowering, further risk reduction SPARCL

	Events (%)	HR	LDL P Value	Global P Value
Stroke				
>100 mg/dL	85 (16.1)	1.00		
70-100 mg/dL	21 (11.3)	0.69	0.124	0.054
<70 mg/dL	28 (10.7)	0.62	0.031	
Stroke or TIA				
>100 mg/dL	120 (22.7)	1.00		
70-100 mg/dL	34 (18.3)	0.78	0.201	0.020
<70 mg/dL	38 (14.5)	0.60	0.007	
Major Coronary Event				
>100 mg/dL	33 (6.3)	1.00		
70-100 mg/dL	9 (4.8)	0.77	0.489	0.123
<70 mg/dL	8 (3.1)	0.45	0.043	
Major Cardiovascular Event				
>100 mg/dL	110 (20.8)	1.00		
70-100 mg/dL	29 (15.6)	0.74	0.146	0.017
<70 mg/dL	35 (13.4)	0.59	0.007	
Carotid Revascularization				
>100 mg/dL	38 (7.2)	1.00		
70-100 mg/dL	7 (3.8)	0.43	0.040	0.006
<70 mg/dL	6 (2.3)	0.30	0.007	
Any Coronary Event				
>100 mg/dL	50 (9.5)	1.00		
70-100 mg/dL	20 (10.8)	1.15	0.610	0.110
<70 mg/dL	16 (6.1)	0.59	0.066	
Any Cardiovascular Event				
>100 mg/dL	191 (36.2)	1.00		
70-100 mg/dL	55 (29.6)	0.80	0.143	<0.001
<70 mg/dL	57 (21.8)	0.54	<0.001	
Any Revascularization				
>100 mg/dL	71 (13.4)	1.00		
70-100 mg/dL	23 (12.4)	0.82	0.423	0.004
<70 mg/dL	15 (5.7)	0.39	<0.001	



	Events	Model 1: p-value/ HR (95% CI)	Model 2: p-value/ HR (95% CI)	Model 3: p-value/ HR (95% CI)
All Stroke				
>=0% Increase	210	0.0063	0.0122	0.0009
<50% Decrease	237	0.89 (0.73, 1.08)	0.90 (0.74, 1.09)	0.87 (0.71, 1.06)
>=50% Decrease	129	0.69 (0.55, 0.87)	0.71 (0.57, 0.89)	0.65 (0.52, 0.81)
Fatal Stroke				
>=0% Increase	23	0.2967	0.3391	0.2385
<50% Decrease	27	0.74 (0.42, 1.29)	0.75 (0.43, 1.31)	0.73 (0.42, 1.28)
>=50% Decrease	15	0.61 (0.32, 1.17)	0.63 (0.33, 1.20)	0.58 (0.30, 1.11)
Non-Fatal Stroke				
>=0% Increase	192	0.0130	0.0224	0.0020
<50% Decrease	218	0.91 (0.74, 1.12)	0.92 (0.75, 1.13)	0.89 (0.72, 1.09)
>=50% Decrease	117	0.70 (0.55, 0.89)	0.72 (0.57, 0.92)	0.66 (0.52, 0.83)
Ischemic Stroke				
>=0% Increase	182	0.0063	0.0111	0.0010
<50% Decrease	204	0.90 (0.73, 1.12)	0.92 (0.74, 1.13)	0.88 (0.71, 1.09)
>=50% Decrease	106	0.67 (0.52, 0.86)	0.69 (0.54, 0.89)	0.63 (0.49, 0.81)
Hemmorhagic Stroke				
>=0% Increase	26	0.6536	0.6390	0.6928
<50% Decrease	34	0.84 (0.50, 1.40)	0.85 (0.51, 1.41)	0.84 (0.50, 1.40)
>=50% Decrease	28	1.04 (0.61, 1.78)	1.07 (0.62, 1.82)	1.02 (0.60, 1.75)

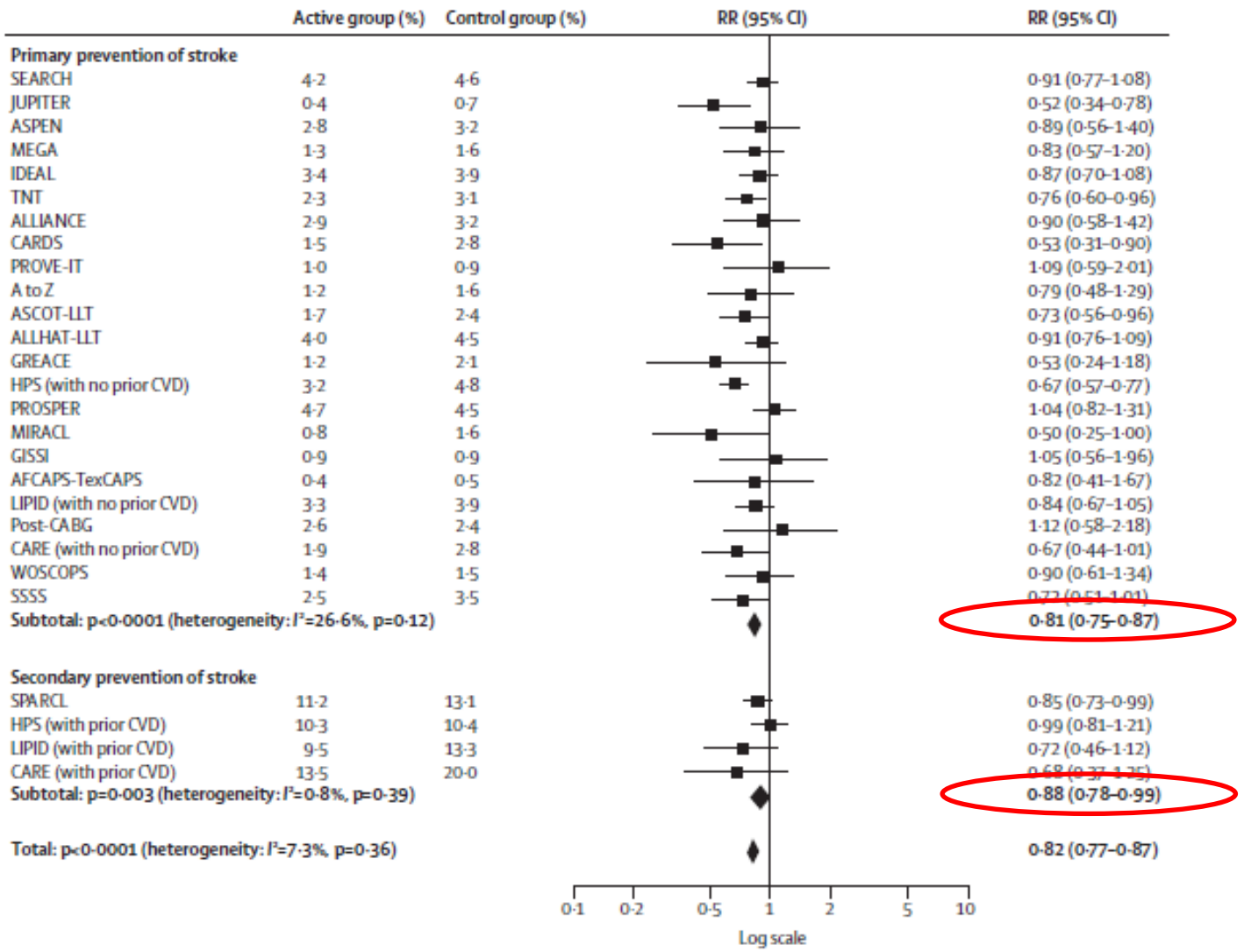


Sillesen H et al. Stroke 2008:39:3297

Amarenco P et al. *Stroke* 2007; 38: 3198-3204

Statin Benefits
: Secondary as well as Primary Stroke Prevention

N total=165,732: Statins reduce the stroke by 18%



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

Further LDL-C reduction, further stroke reduction

Estimates of relative risk reduction from 24 trials (n=165,792)

10% LDL reduction

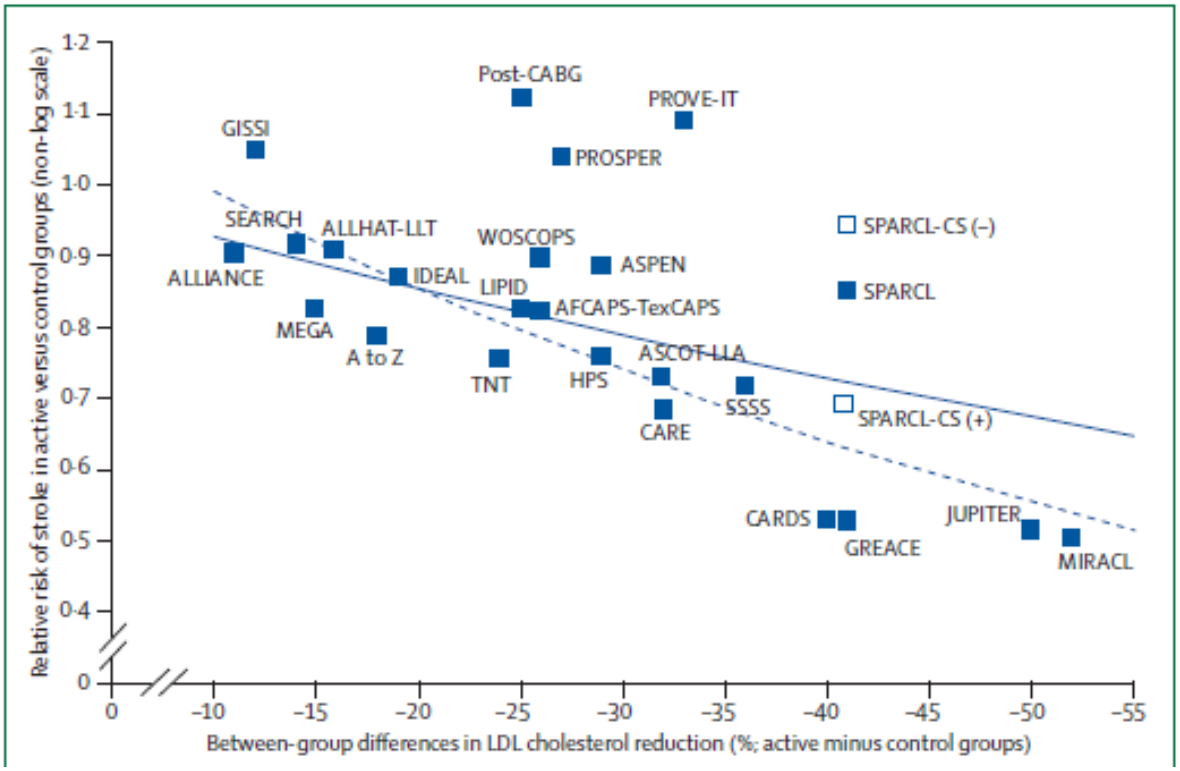
relative risk reduction 7·5% (2·3–12·5) overall

relative risk reduction 13·5% (7·7–18·8) for primary prevention of stroke

1 mmol/L (39 mg/dL) LDL reduction

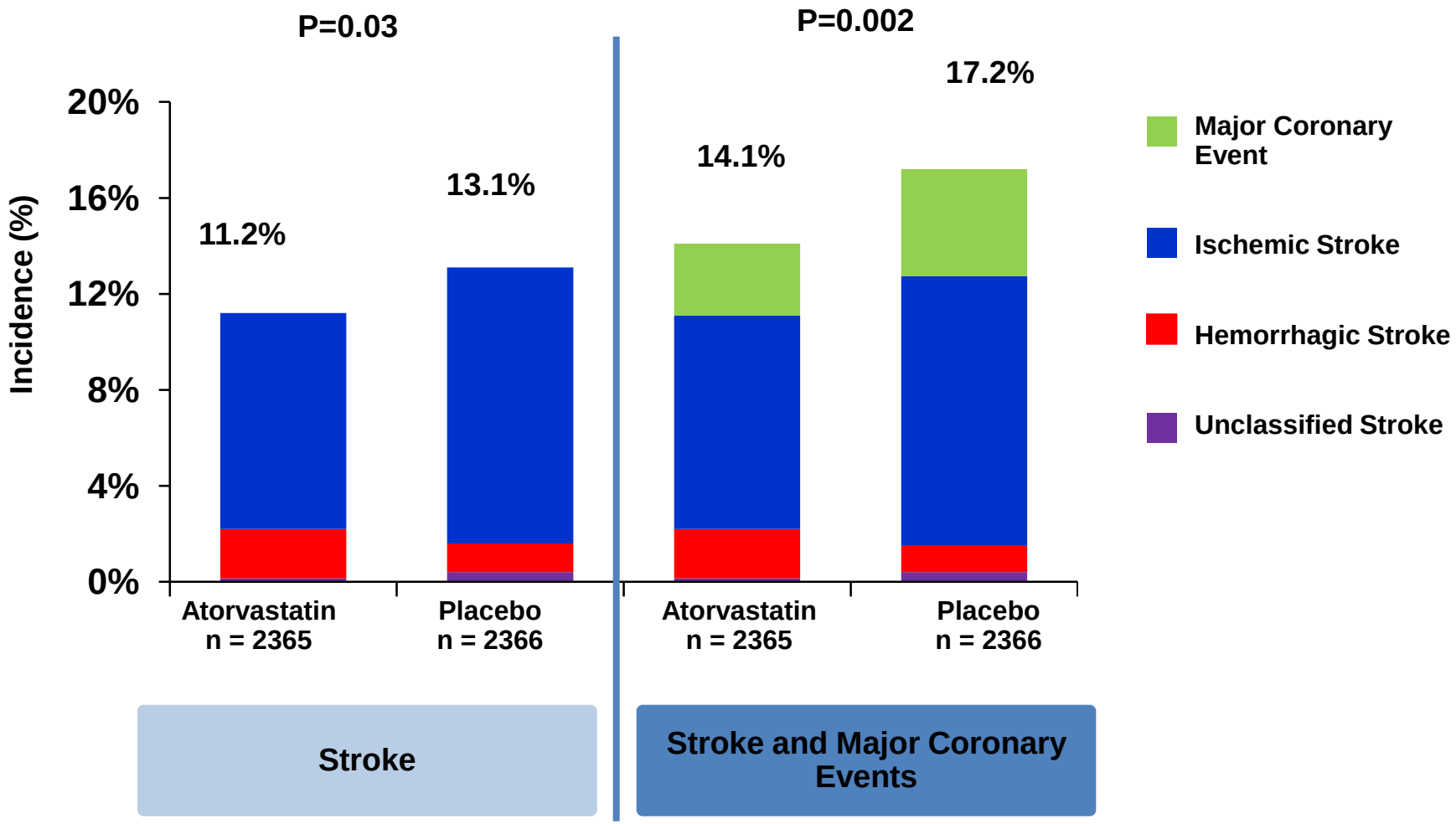
relative risk reduction 21·1% (6·3–33·5) overall

relative risk reduction 35·9% (21·7–47·6) for primary prevention of stroke



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

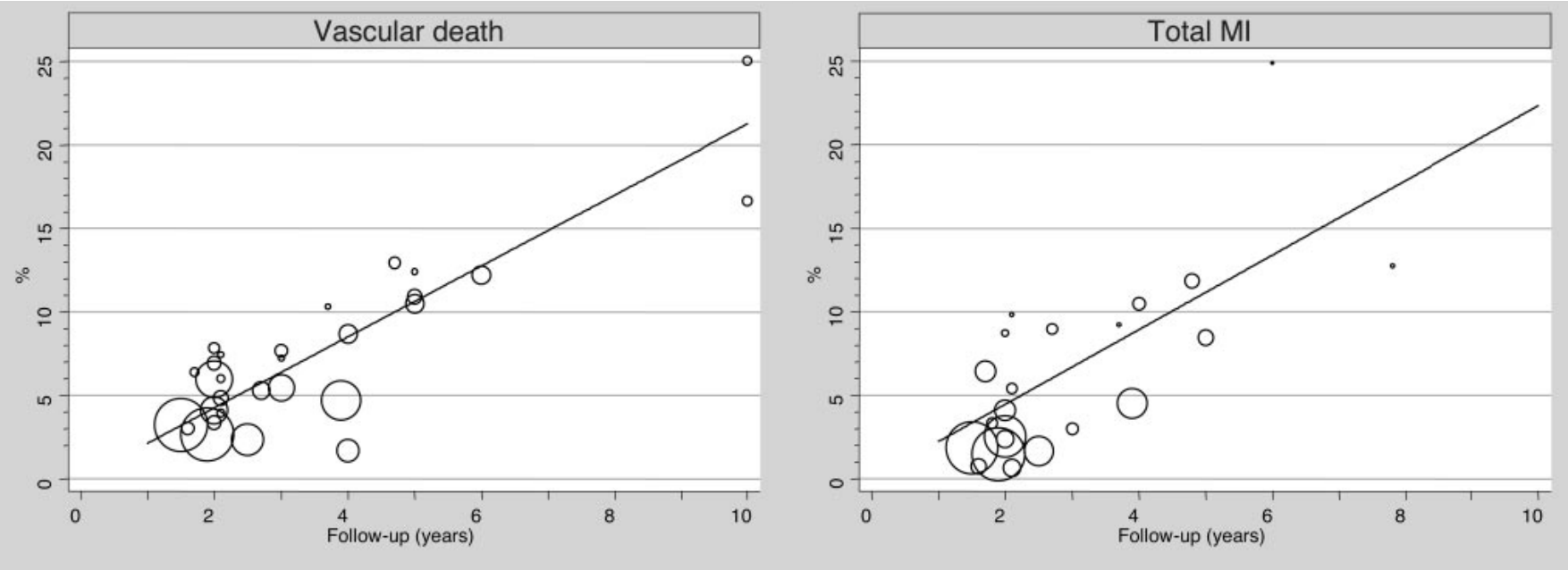
Weighting the Benefit and Risk
High dose atorvastatin in Stroke Population



Amarenco P, et al. *Exp Op Pharmacotherapy. 2007*

Accumulating Risk of MI and CV death after stroke/TIA

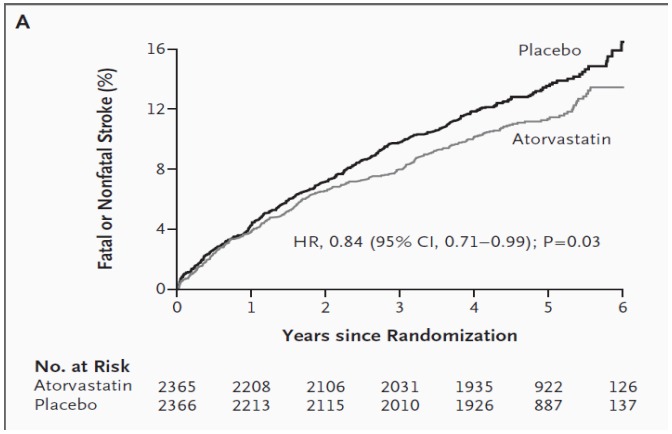
- Meta-analysis of 39 studies (n=65,996, mean FU=3.5 y)
  - Annual risk: linear time course over 10 years
    - 2.2% (CI 95%, 1.7-2.7) for total MI
    - 2.1% (CI 95%, 1.9-2.4) for nonstroke vascular death
  - 10-year risk > 20% for both of MI and CV death



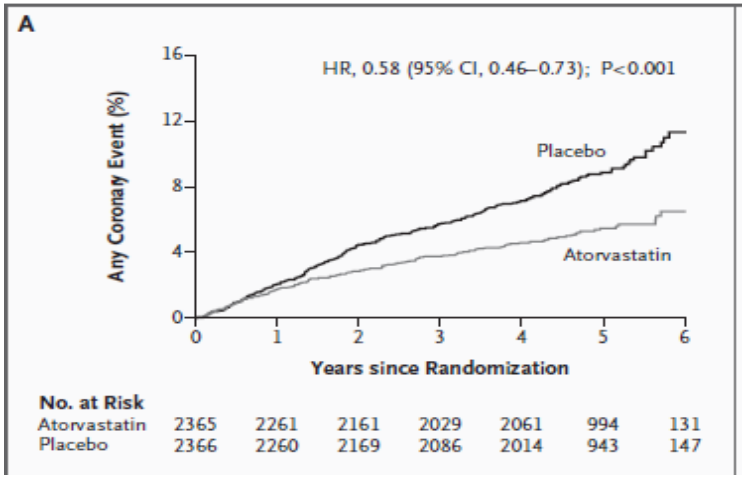
Touze´ E et al. Stroke. 2005;36:2748

Magnitude of Benefit with Atorvastatin Greater for Coronary Event than Stroke Event in Stroke Population

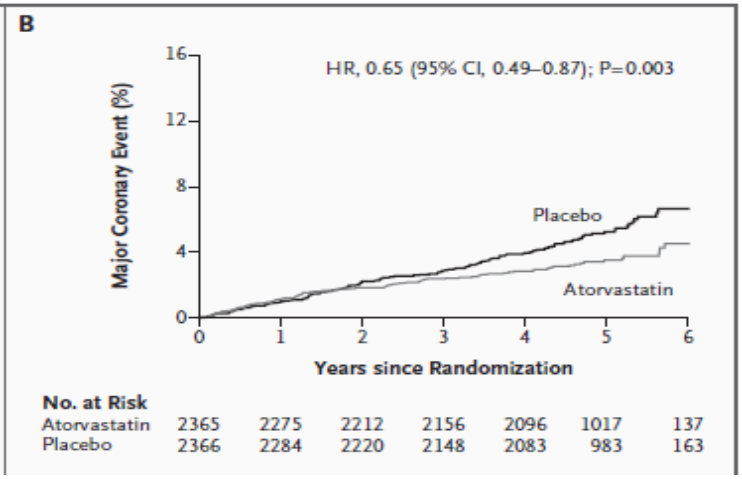
Stroke



Any Coronary Event



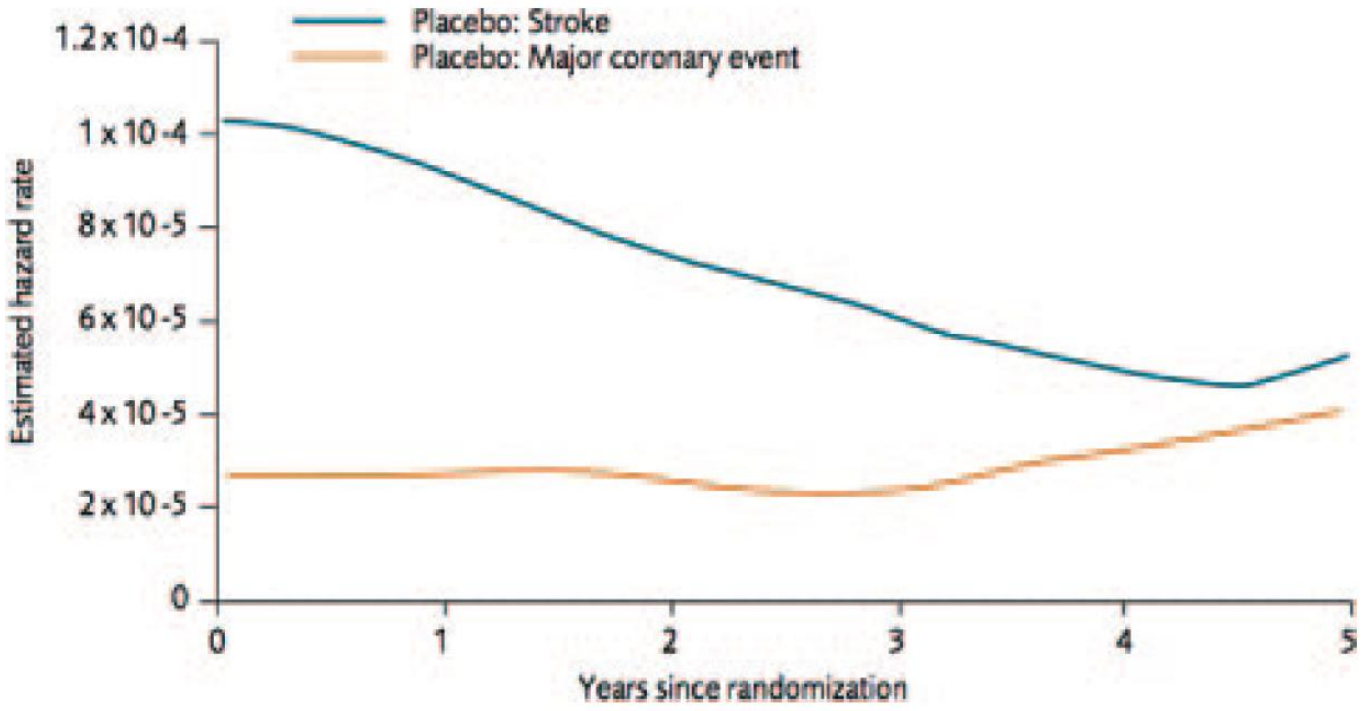
Major Coronary Event



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

The more time that goes by, the more often events accumulate in a wide range of vascular beds

SPARCL trial post-hoc analysis



Amarenco P et al. Stroke 2010:41:426

Pleiotropic effects in acute ischemia

- Potential Benefits in Acute Ischemia of Brain and Heart
  - Anti-inflammatory action
  - Antithrombotic action and facilitation of clot lysis
  - Endothelial NO synthetase upregulation
  - Plaque stabilization: LDL oxidation reduction
  - Angiogenesis: smooth muscle cell migration and proliferation

- In acute cerebral ischemia
  - Angiogenesis, neurogenesis, and synaptogenesis
  - Potentially neuroprotective and neurorestorative in brain ischemia

- Concerns on statins in acute cerebral ischemia
  - Intracerebral hemorrhage related to antiplatelet and profibrinolytic effects

Guidelines: statins in ACS/PCI

- ACS
  - High-intensity statin therapy should be initiated or continued in all patients with STEMI and no contraindications (2013 ACCF/AHA: Class I, LOE B)
  - Statins, regardless of baseline LDL-C, to UA/NSTEMI patients before discharge (2011 ACCF/AHA: Class I, LOE A)
  - High dose statin therapy be initiated during the first 1–4 days of hospitalization for the index ACS (LDL-C target <70 mg/dL) (2011 ESC/EAS).

- Before PCI
  - Administration of a high-dose statin is reasonable before PCI to reduce the risk of periprocedural MI. (2011 ACCF/AHA, Class IIa/LOE A/B)

Statins trial for Acute ischemic stroke

- SPARCL
  - Randomization at 1 to 6 months after stroke
- No large trials testing statins for acute ischemic stroke
  - Statin withdrawal during acute ischemic stroke
  - FASTER: simvastatin, clinical endpoint

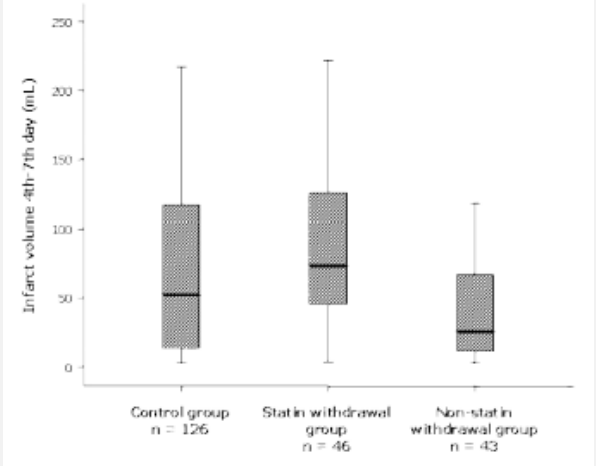
Statin withdrawal in AIS

- Patients with hemispheric ischemic stroke within 24 hours
- 89 patients on chronic pre-stroke statin treatment randomized
  - 46 withdrawal for the first 3 days vs 43 atorvastatin 20 mg/day
  - 126 control: no prestroke statin

Table 2 Unadjusted and adjusted ORs of death or dependency and END in patients with and without statin withdrawal

(mRS >2)	Statin-withdrawal group, n (%)	Non-statin-withdrawal group, n (%)	OR (95% CI)	Adjusted OR (95% CI)*
Primary outcome event†	27 (60.0)	16 (39.0)	2.39 (1.02, 5.62)	4.66 (1.46, 14.91)
Early neurologic deterioration	30 (65.2)	9 (20.9)	7.08 (2.73, 18.37)	8.67 (3.05, 24.63)

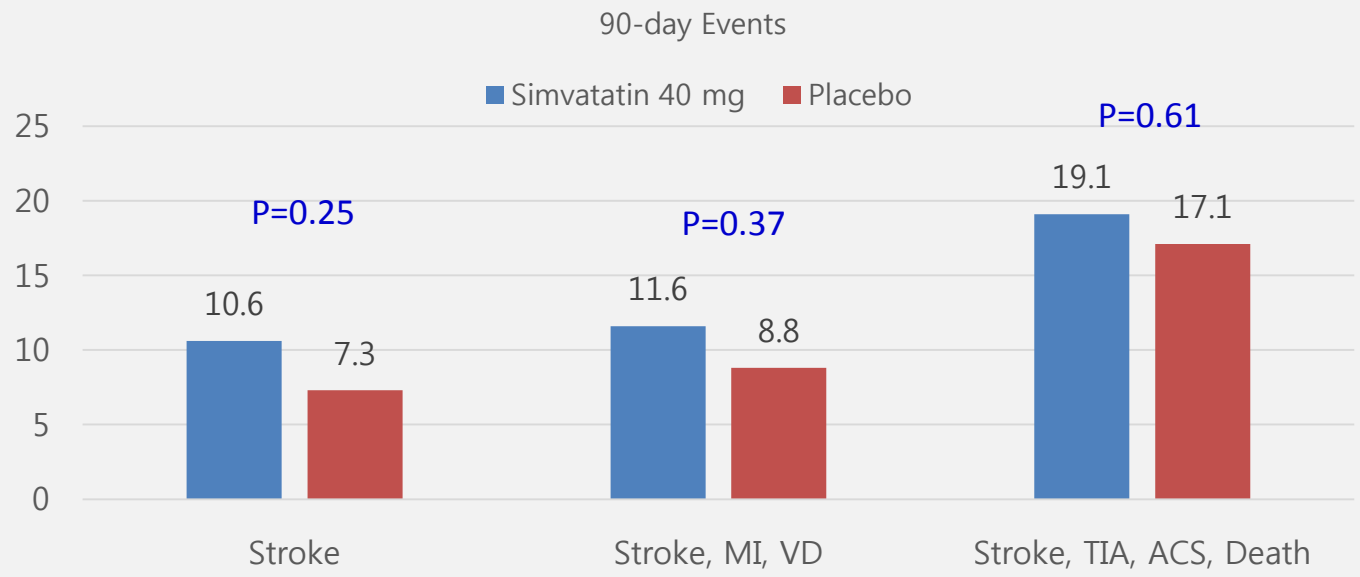
Figure 2 Infarct volume by groups



Blanco M et al. Neurology 2007; 69: 904

FASTER

- Simvastatin 40 mg vs. placebo within 24 hours of minor AIS or TIA
  - Vascular event prevention rather than neuroprotection
- Original enrollment plan
  - 500 patients to test trial feasibility for the main trial with a target enrollment of 7500 patients
- Early terminated after enrolling only 392 patients
  - Substantially underpowered study



Kennedy J et al. Lancet Neurol 2007; 6: 961

2013 ASA Guidelines

- Among patients already taking statins at the time of onset of ischemic stroke, continuation of statin therapy during the acute period is reasonable (Class IIa; Level of Evidence B). (New recommendation)

- No specific recommendations
  - Neither ‘When to start?’ nor ‘How intensive?’

JoS JOURNAL OF STROKE

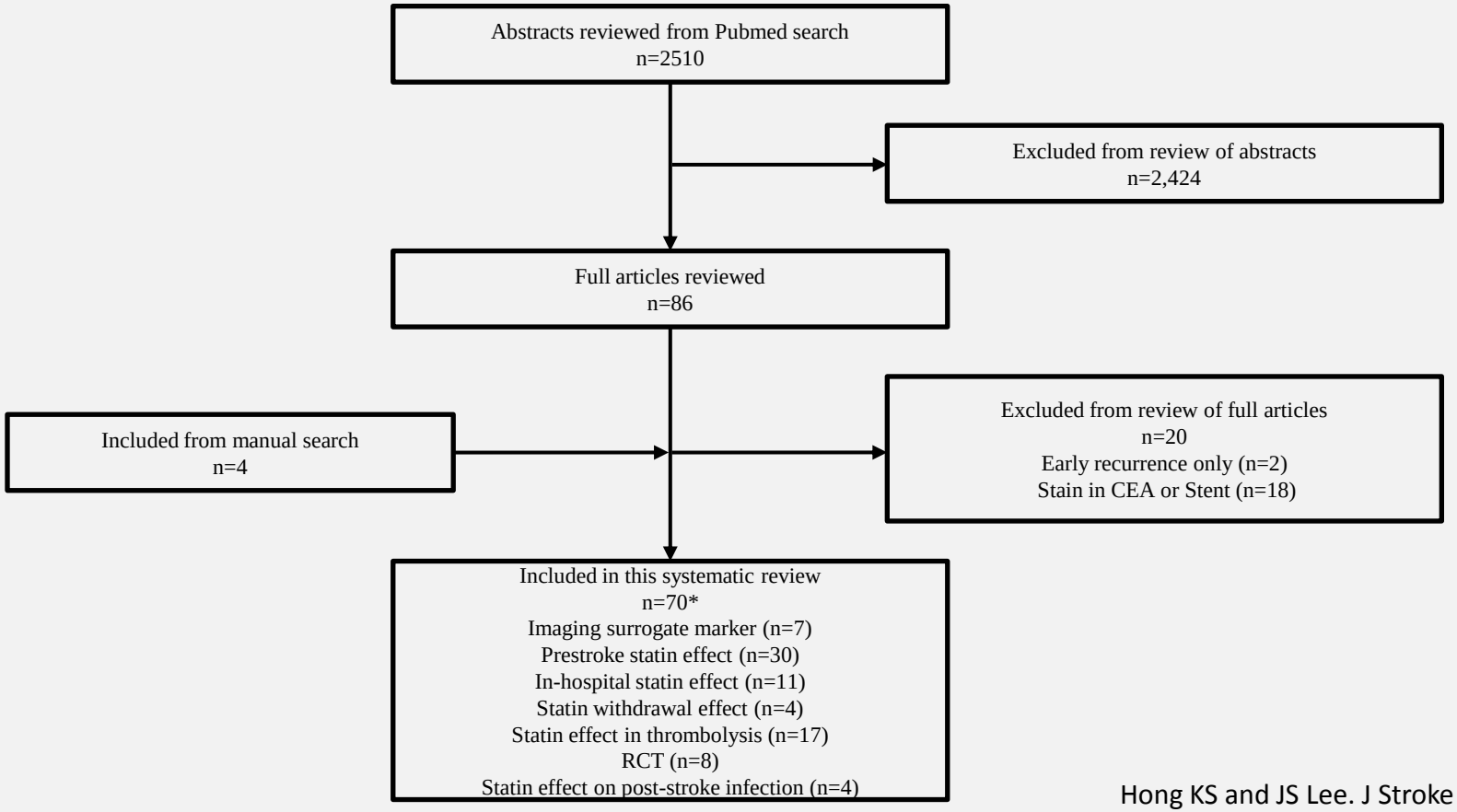
Journal of Stroke 2015;17(3):282-301
http://dx.doi.org/10.5853/jos.2015.17.3.282

Systematic Review

Statins in Acute Ischemic Stroke: A Systematic Review

Keun-Sik Hong,[a] Ji Sung Lee[b]

[a]Department of Neurology, Inje University Ilsan Paik Hospital, Goyang, Korea
[b]Clinical Research Center, Asan Medical Center, Seoul, Korea



Hong KS and JS Lee. J Stroke 2015;17:282-301

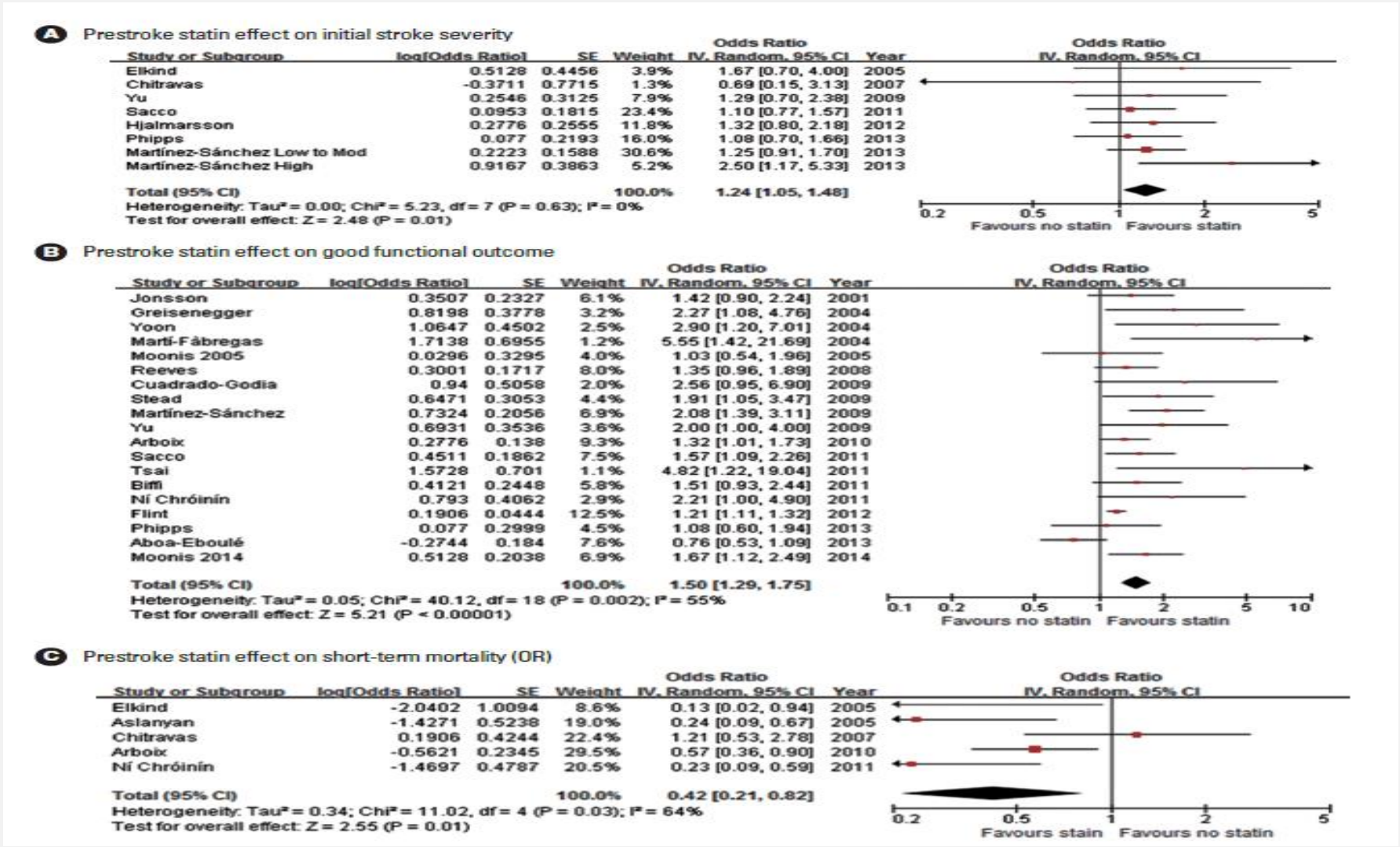
Prestroke statin effect in acute ischemic stroke
Neuroimaging studies in humans

- Smaller infarct volume in patients with MCA
- More extensive arterial collaterals
- Greater reperfusion in hyperacute ischemic stroke
- Greater recanalization in a cohort of ischemic stroke patients undergoing acute intervention

Shook SJ et al. J Neuroimaging 2006; Ovbiagele B et al. Neurology 2007; Lee et al. CVD 2014

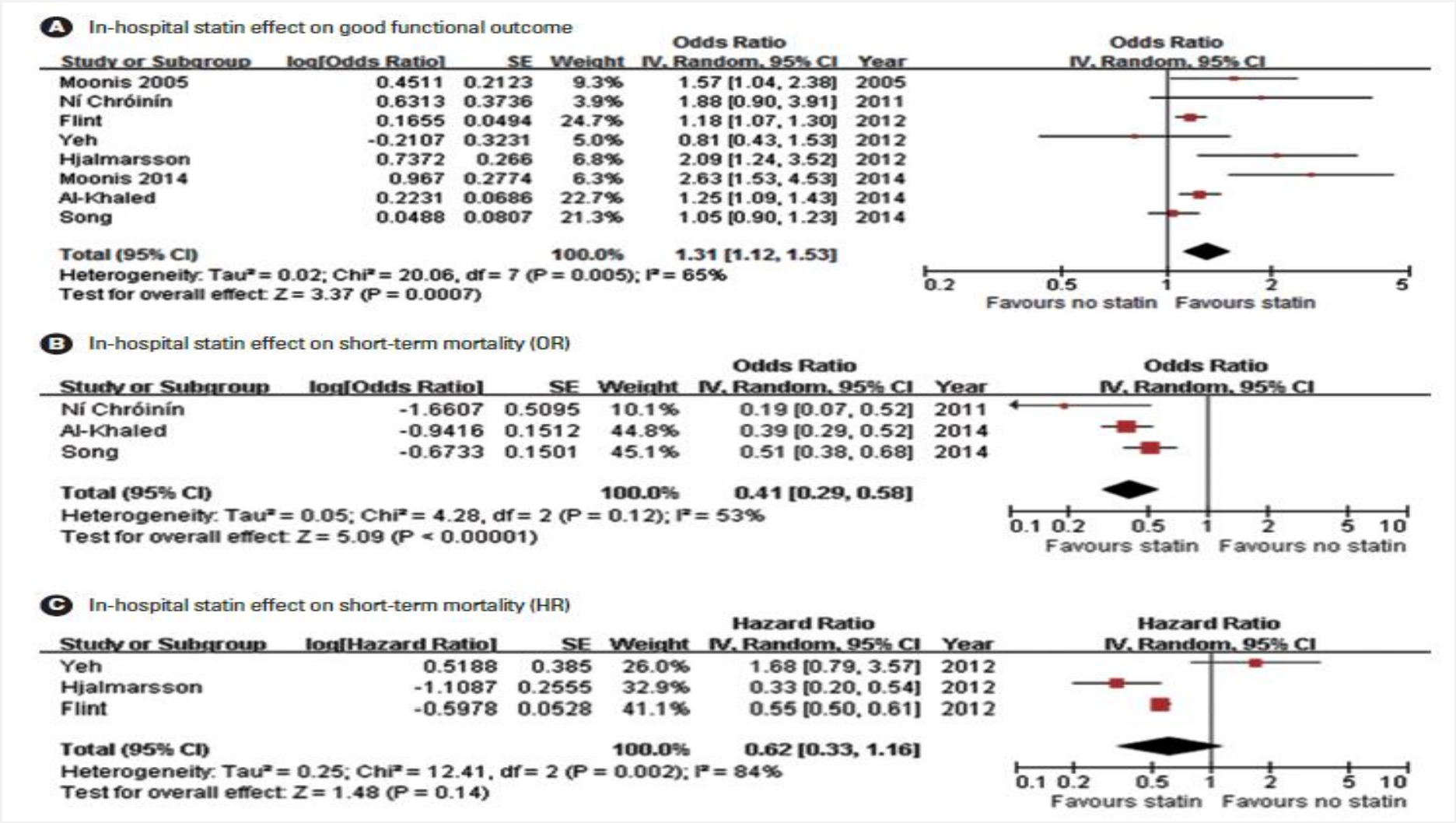
Andria F et al. Stroke 2011; Georgiadis AL et al. J Neuroimaging 2009

Prestroke statin effect



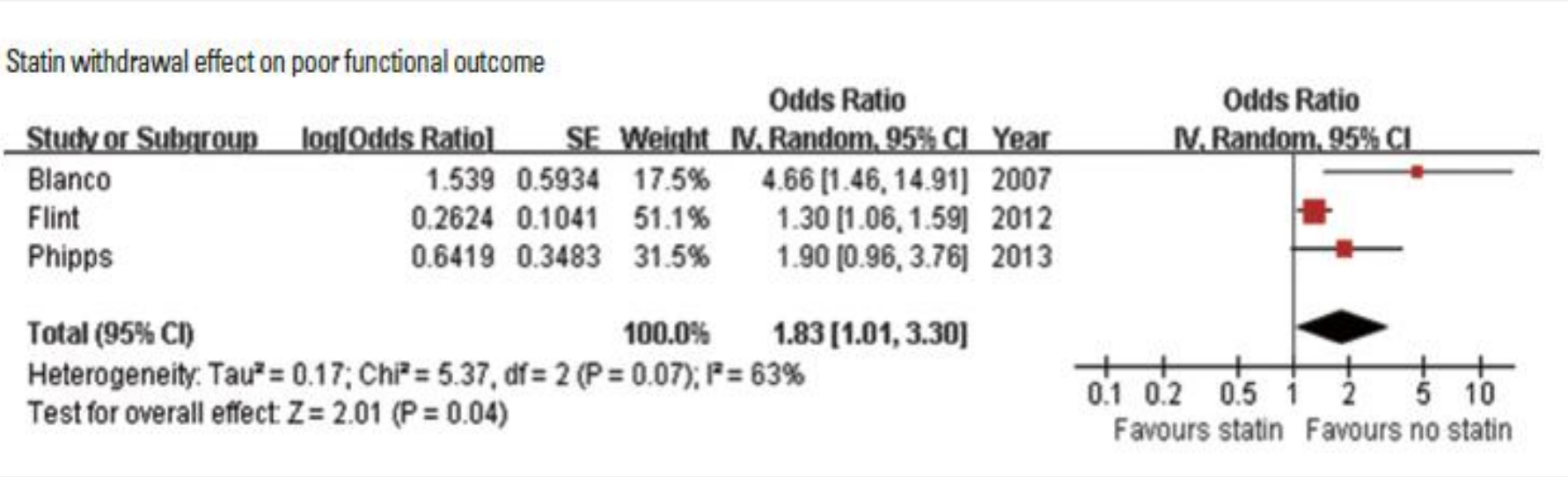
Hong KS & JS Lee. J Stroke 2015;17:282-301

In-hospital statin effect



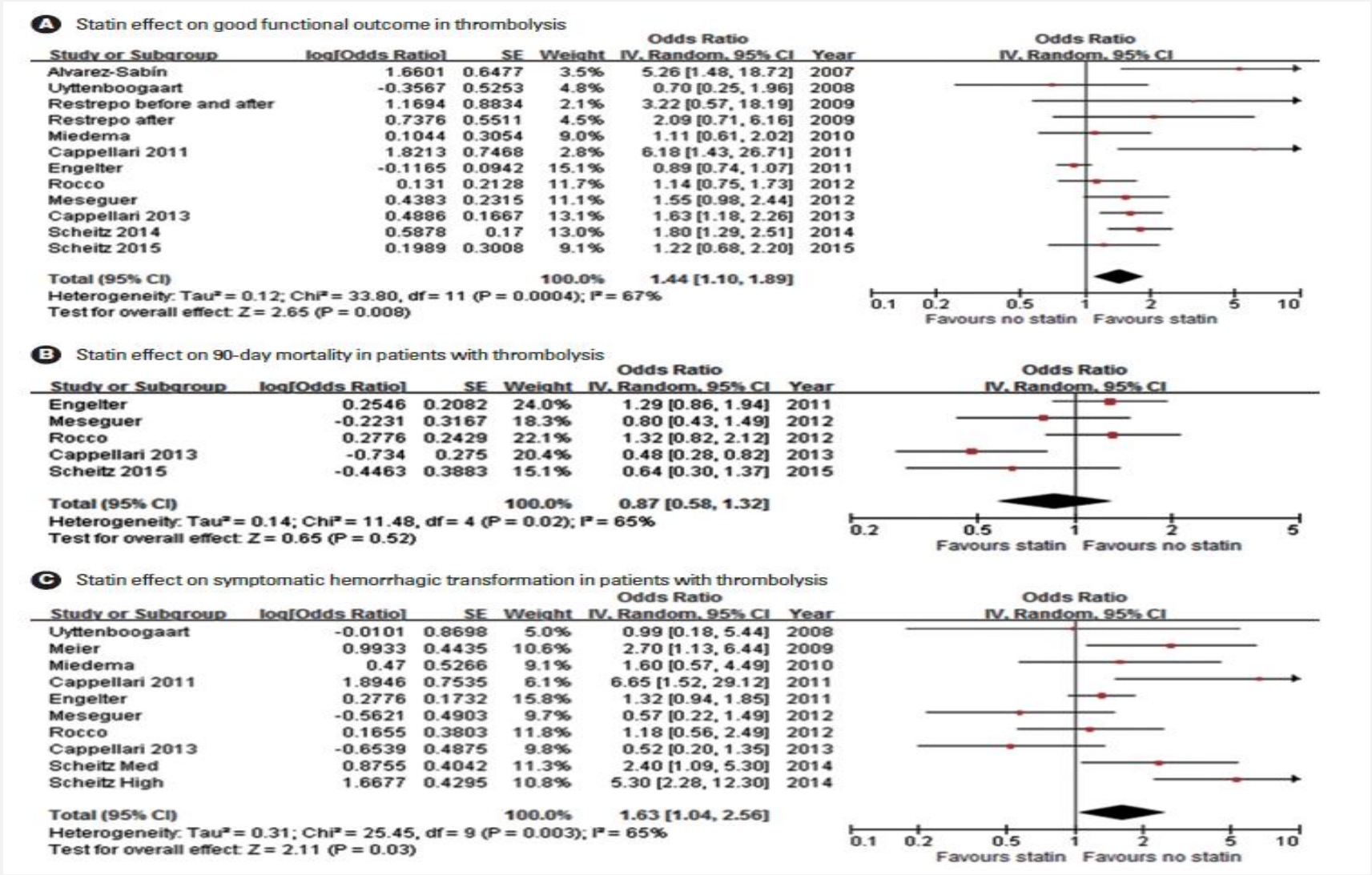
Hong KS & JS Lee. J Stroke 2015;17:282-301

Statin withdrawal effect



Hong KS & JS Lee. J Stroke 2015;17:282-301

Statin effect in patients with thrombolysis



A Statin effect on good functional outcome in thrombolysis

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Year
Alvarez-Sabín	1.6601	0.6477	3.5%	5.26 [1.48, 18.72]	2007
Uyttenboogaart	-0.3567	0.5253	4.8%	0.70 [0.25, 1.96]	2008
Restrepo before and after	1.1694	0.8834	2.1%	3.22 [0.57, 18.19]	2009
Restrepo after	0.7376	0.5511	4.5%	2.09 [0.71, 6.16]	2009
Miedema	0.1044	0.3054	9.0%	1.11 [0.61, 2.02]	2010
Cappellari 2011	1.8213	0.7468	2.8%	6.18 [1.43, 26.71]	2011
Engelter	-0.1165	0.0942	15.1%	0.89 [0.74, 1.07]	2011
Rocco	0.131	0.2128	11.7%	1.14 [0.75, 1.73]	2012
Meseguer	0.4383	0.2315	11.1%	1.55 [0.98, 2.44]	2012
Cappellari 2013	0.4886	0.1667	13.1%	1.63 [1.18, 2.26]	2013
Scheitz 2014	0.5878	0.17	13.0%	1.80 [1.29, 2.51]	2014
Scheitz 2015	0.1989	0.3008	9.1%	1.22 [0.68, 2.20]	2015
Total (95% CI)			100.0%	1.44 [1.10, 1.89]	

Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 33.80$, df = 11 (P = 0.0004); $I^2 = 67\%$
Test for overall effect: Z = 2.65 (P = 0.008)

Odds Ratio IV, Random, 95% CI
0.1 0.2 0.5 1 2 5 10
Favours no statin Favours statin

B Statin effect on 90-day mortality in patients with thrombolysis

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Year
Engelter	0.2546	0.2082	24.0%	1.29 [0.86, 1.94]	2011
Meseguer	-0.2231	0.3167	18.3%	0.80 [0.43, 1.49]	2012
Rocco	0.2776	0.2429	22.1%	1.32 [0.82, 2.12]	2012
Cappellari 2013	-0.734	0.275	20.4%	0.48 [0.28, 0.82]	2013
Scheitz 2015	-0.4463	0.3883	15.1%	0.64 [0.30, 1.37]	2015
Total (95% CI)			100.0%	0.87 [0.58, 1.32]	

Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 11.48$, df = 4 (P = 0.02); $I^2 = 65\%$
Test for overall effect: Z = 0.65 (P = 0.52)

Odds Ratio IV, Random, 95% CI
0.2 0.5 1 2 5
Favours statin Favours no statin

C Statin effect on symptomatic hemorrhagic transformation in patients with thrombolysis

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Year
Uyttenboogaart	-0.0101	0.8698	5.0%	0.99 [0.18, 5.44]	2008
Meier	0.9933	0.4435	10.6%	2.70 [1.13, 6.44]	2009
Miedema	0.47	0.5266	9.1%	1.60 [0.57, 4.49]	2010
Cappellari 2011	1.8946	0.7535	6.1%	6.65 [1.52, 29.12]	2011
Engelter	0.2776	0.1732	15.8%	1.32 [0.94, 1.85]	2011
Meseguer	-0.5621	0.4903	9.7%	0.57 [0.22, 1.49]	2012
Rocco	0.1655	0.3803	11.8%	1.18 [0.56, 2.49]	2012
Cappellari 2013	-0.6539	0.4875	9.8%	0.52 [0.20, 1.35]	2013
Scheitz Med	0.8755	0.4042	11.3%	2.40 [1.09, 5.30]	2014
Scheitz High	1.6677	0.4295	10.8%	5.30 [2.28, 12.30]	2014
Total (95% CI)			100.0%	1.63 [1.04, 2.56]	

Heterogeneity: $Tau^2 = 0.31$; $Chi^2 = 25.45$, df = 9 (P = 0.003); $I^2 = 65\%$
Test for overall effect: Z = 2.11 (P = 0.03)

Odds Ratio IV, Random, 95% CI
0.1 0.2 0.5 1 2 5 10
Favours statin Favours no statin

Hong KS & JS Lee. J Stroke 2015;17:282-301

Prestroke statin on initial stroke severity and discharge outcomes: Analysis of Korean registry data (CRCS-5)

- 8,340 patients with acute ischemic stroke
  - 964 (11.6%) prestroke statin users vs 7376 (88.4%) non-users

- Prestroke statins effect in Korean stroke patients
  - Primary endpoint: neuroprotective?
    - Initial stroke severity, NIHSS
  - Secondary endpoints: neurorestorative?
    - Discharge functional outcome adjusted for initial stroke severity
      - Proportion of mRS 0-2
      - mRS shift analysis

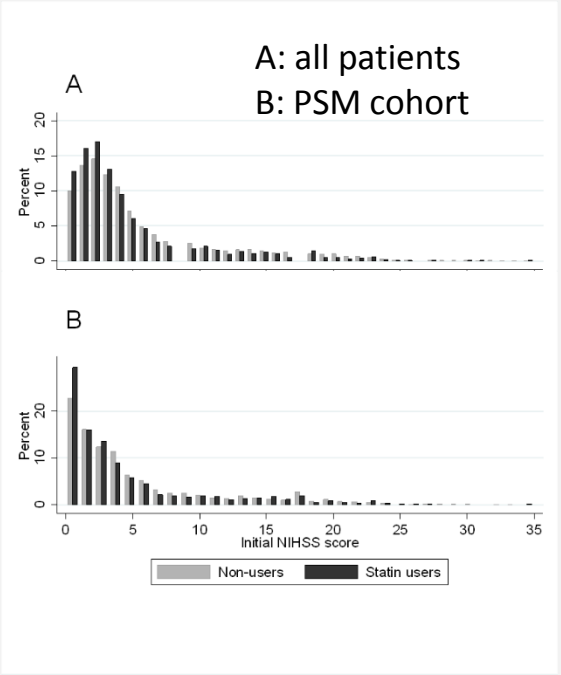
Choi JC + Hong KS et al. BMC Neurology (2015) 15:120

Pre-stroke statin on admission NIHSS

- Pre-stroke statin, lesser stroke severity at presentation
  - Neuroprotective effect during ischemia?

Comparisons of initial NIHSS scores between statin users and non-users for unmatched and PS-matched cohorts

	Statin users	Non-users	Difference	P-value
Unmatched cohort				
Unadjusted	4.6 (4.3–4.9)	5.4 (5.3–5.6)	0.8 (0.5–1.2)	<0.001
Adjusted*	5.7 (5.2–6.3)	6.4 (5.9–6.9)	0.7 (0.2–1.1)	0.002
PS-matched cohort				
PS-matched †‡	5.2 (4.7–5.7)	5.7 (5.4–6.0)	0.5 (0.02–1.0)	0.043



Choi JC + Hong KS et al. BMC Neurology (2015) 15:120

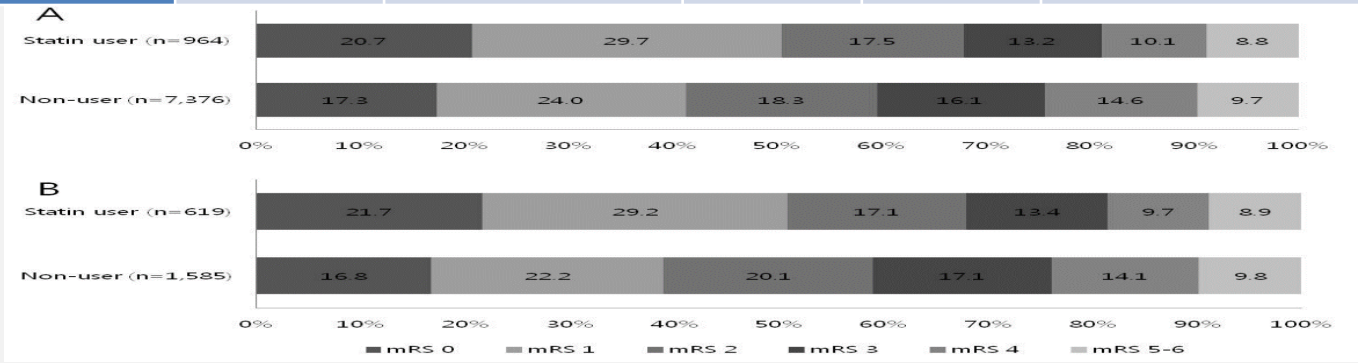
Pre-stroke statin on discharge functional outcome

- Pre-stroke statin, better early functional outcome after adjusting all covariates including initial stroke severity
  - Neurorestorative effect after ischemia?

	Binary mRS 0-2 outcome (good outcome)			Ordinal outcome†		
	OR	95% CI	p-value	OR	95% CI	p-value
Crude analysis, unmatched cohort	1.44	(1.25–1.66)	<0.001	1.37	(1.21–1.54)	<0.001
Multivariable analysis, unmatched cohort	1.54	(1.25–1.91)	<0.001	1.29	(1.10–1.50)	0.001
PS- matched analysis§ ||	1.44	(1.15–1.82)	0.002	1.32	(1.12–1.56)	0.001
PS-stratification, deciles¶	1.57	(1.25–1.97)	<0.001	1.29	(1.10–1.52)	0.002

A: all patients

B: PSM cohort



Choi JC + Hong KS et al. BMC Neurology (2015) 15:120

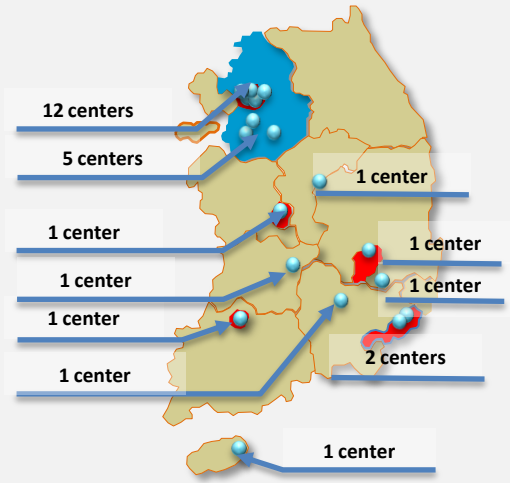
Statin prescription at discharge after hospitalization for AIS/TIA

- Stroke hospitalization as a window of opportunity
  - To assure statin initiation
  - To promote statin adherence

- USA Get With The Guidelines Stroke database (n=173,284)
  - Overall statin prescription rate at discharge, 83.5% in 2005-2007

Guideline-Based Statin Prescription (GBSP) in Korea ROLLERKOST Study

- 27 centers
  - 4407 patients with AIS from
  - 174 neurologists surveyed



Statin prescription at discharge: 76.6%

	Overall	Higher-level knowledge group	Lower-level knowledge group
Patients treated	4407	2528 (57.4%)	1879 (42.6%)
GBSP rate	**78.6%**	**81.6%**	**74.7%**

- Absolute difference in GBSP rate
  - 6.9%, unadjusted p<0.0001
- Multivariable analysis
  - Higher-level knowledge group for GBSP: OR=1.40 (1.01-1.96), p=0.045

Hong KS et al. JCN 2013;9:214

In summary

- Statins for primary and secondary stroke prevention
  - Confirmed from RCTs and meta-analyses

- Statin benefit in acute ischemic stroke
  - No confirmatory data from well-designed RCTs
  - No signal of harm, but strong signal of benefit
  - Hospitalization for acute cerebral ischemia
    - Good opportunity to assure statin initiation and to increase statin adherence

Thank you for your attention