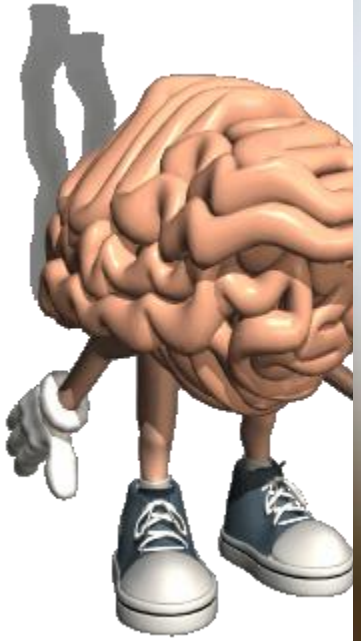
How to Interpret SPRINT

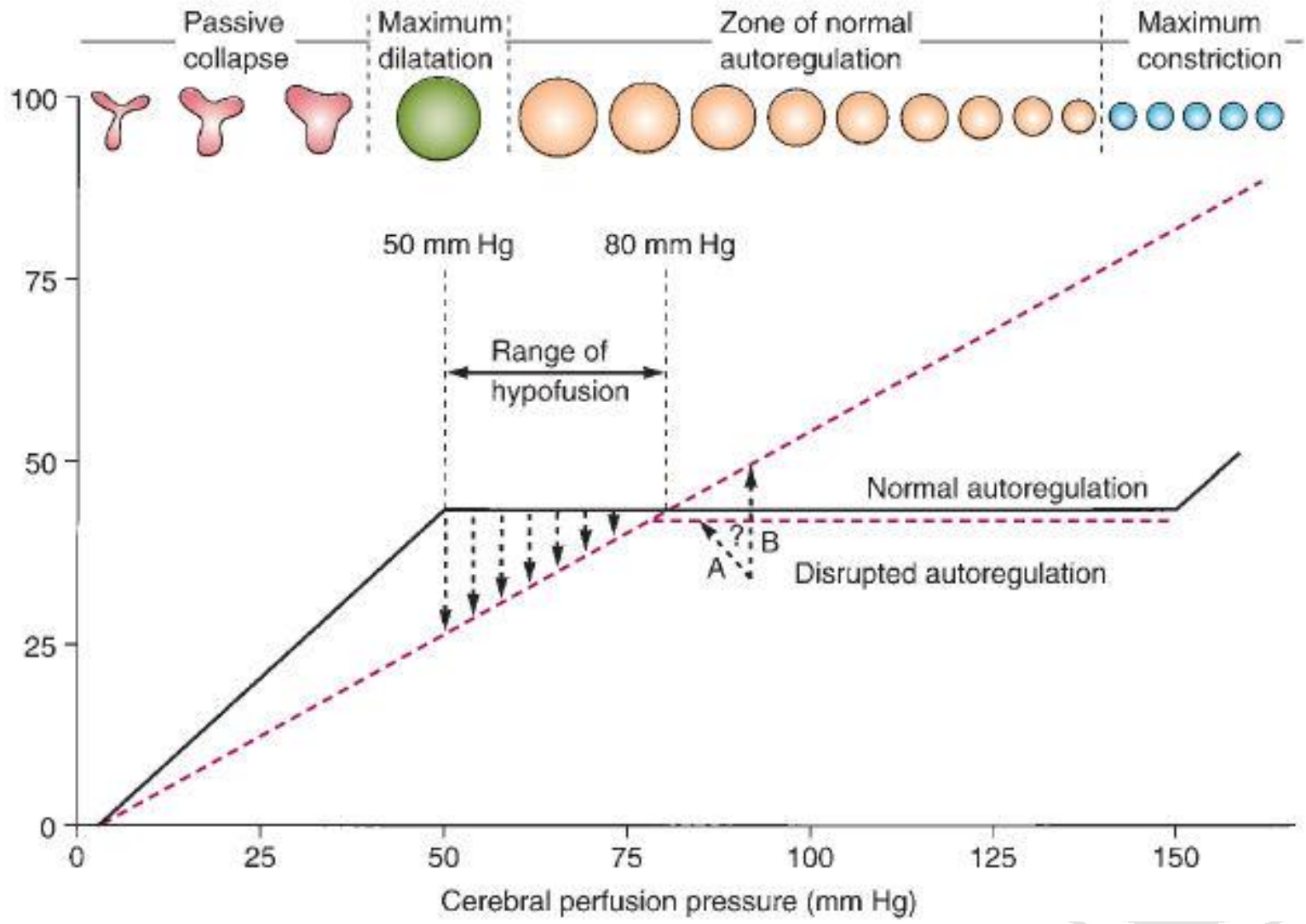
서울아산병원 신경과
권 순 억

Blood Flow

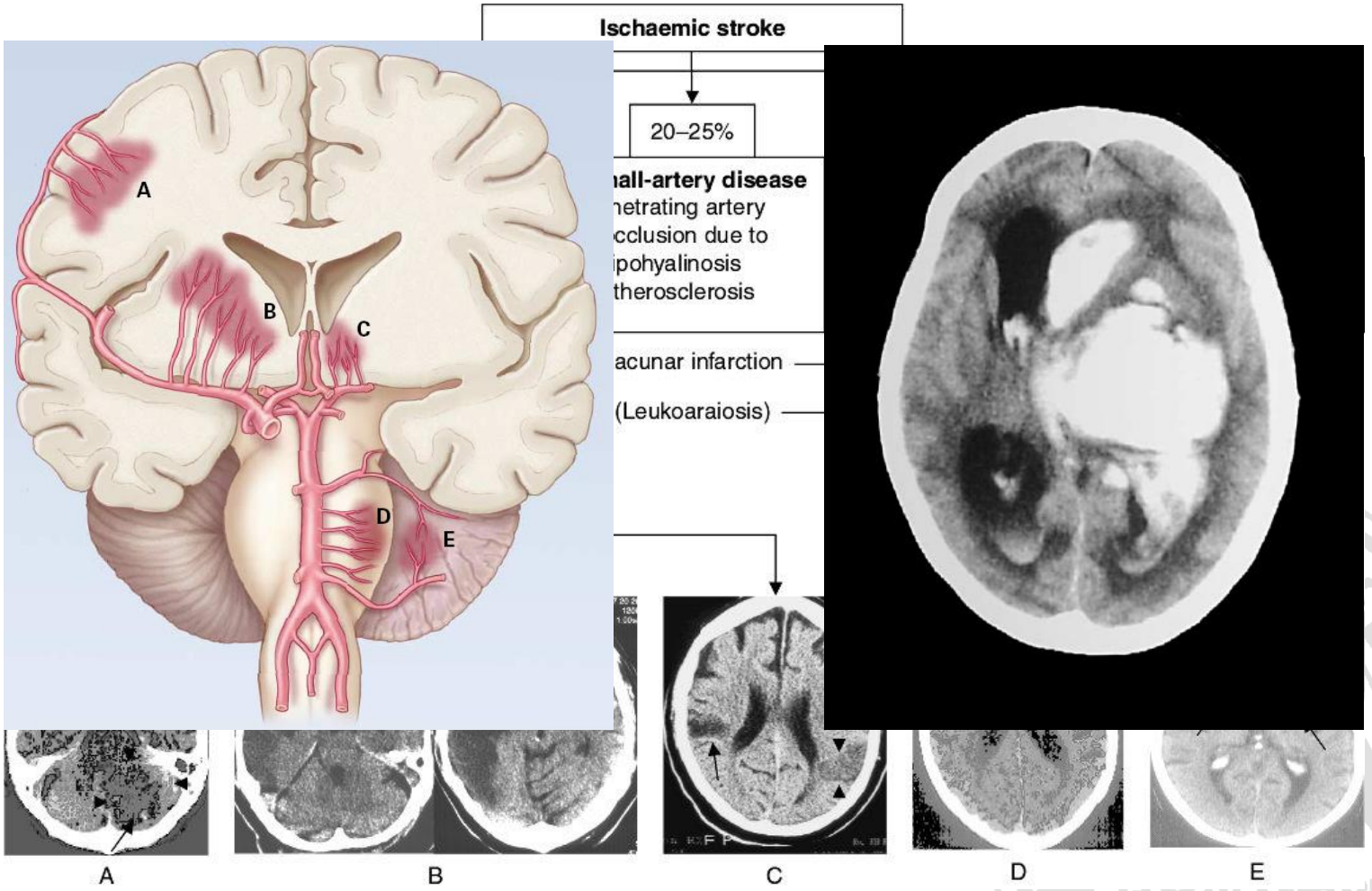
- Cerebral blood flow : 15% of cardiac output



Cerebral Autoregulation

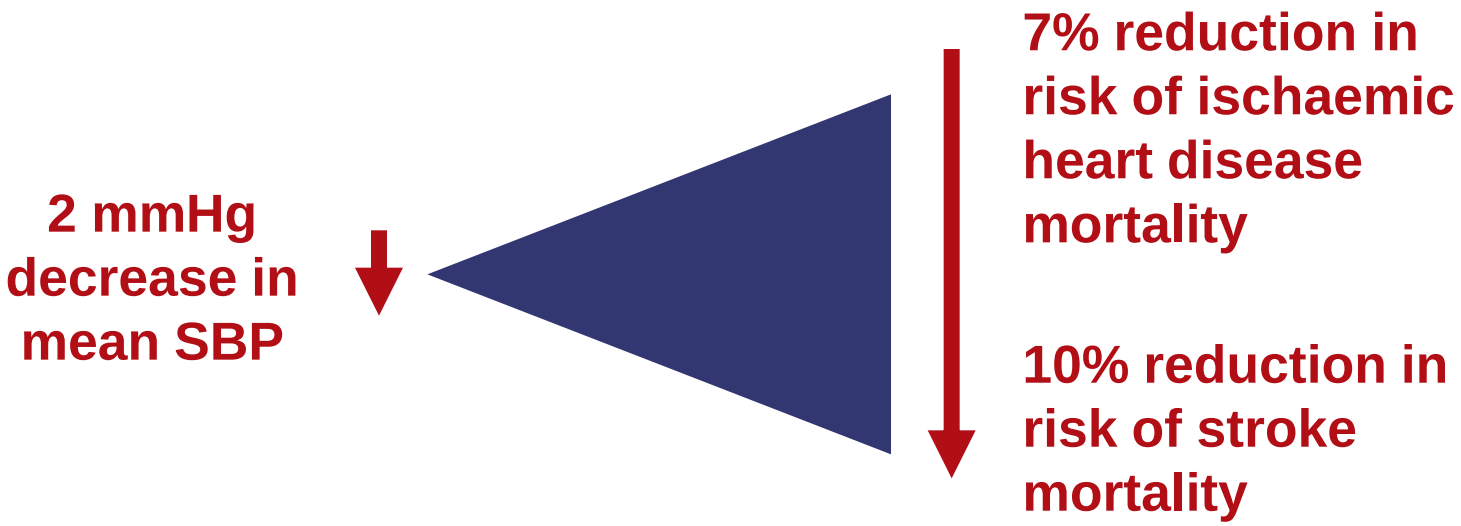


Hypertension and Stroke



Blood Pressure Reduction of 2 mmHg Decreases the Risk of Cardiovascular Events by 7–10%

- Meta-analysis of 61 prospective, observational studies
- 1 million adults
- 12.7 million person-years



Lewington et al. Lancet 2002;360:1903–13

Population attributable risk of common risk factors for stroke vs. MI

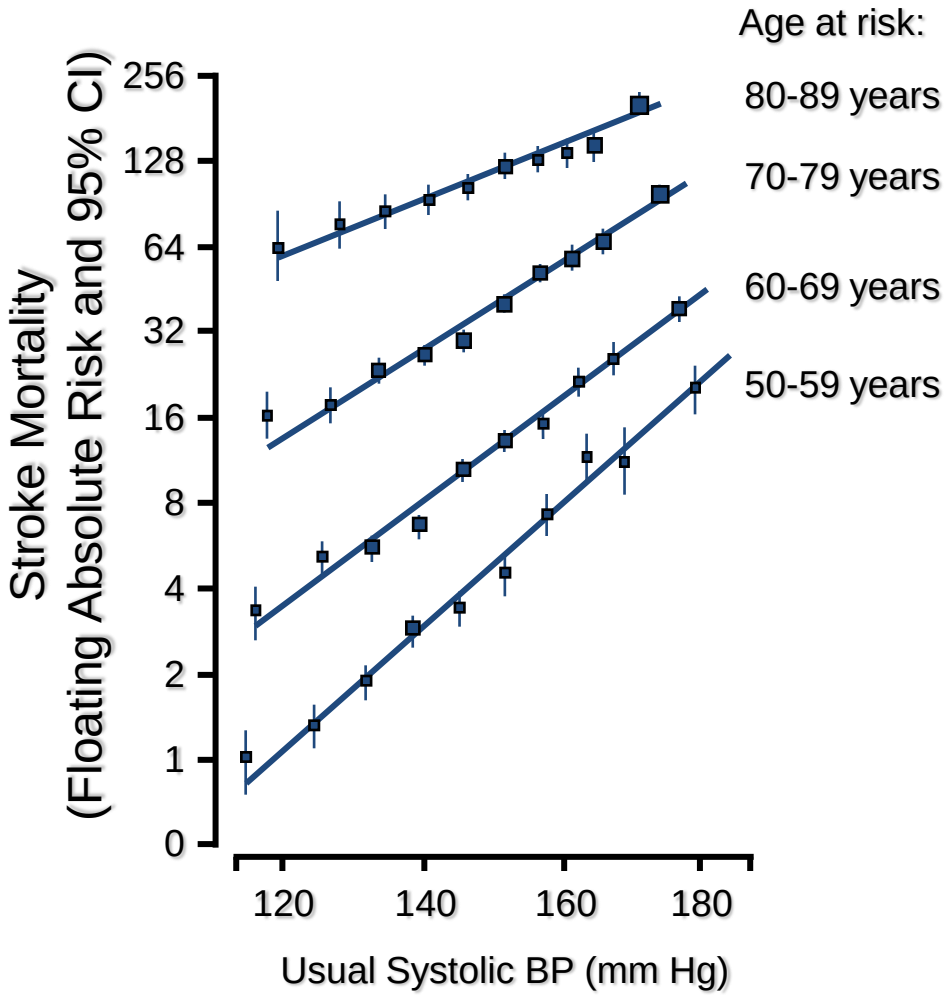
	INTERSTROKE (all stroke; 3000 cases, 3000 controls)[3*]		INTERHEART (acute myocardial infarction; 15 152 cases, 14 820 controls)[4†]
Hypertension	34·6% (30·4–39·1)	>	17·9% (15·7–20·4)
Diabetes	5·0% (2·6–9·5)		9·9% (8·5–11·5)
Alcohol intake	3·8% (0·9–14·4)		6·7% (2·0–20·2)
Psychosocial factors			
All psychosocial factors	..		32·5% (25·1–40·8)
Psychosocial stress	4·6% (2·1–9·6)		..
Depression	5·2% (2·7–9·8)		..
Cardiac causes	6·7% (4·8–9·1)		..
Ratio of apolipoproteins B to A1	24·9% (15·7–37·1)		49·2% (43·8–54·5)

Hypertension is the most important RF in stroke

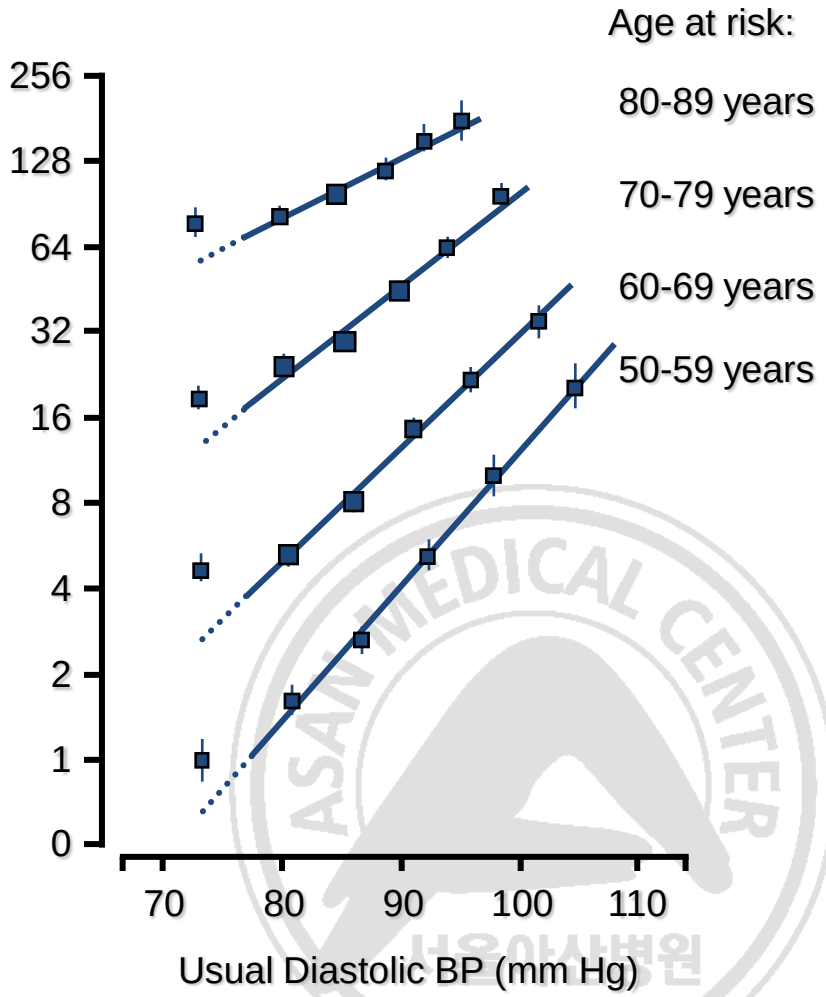
The Lower is Better for Stroke?

Stroke Mortality vs Usual BP by Age

Systolic Blood Pressure

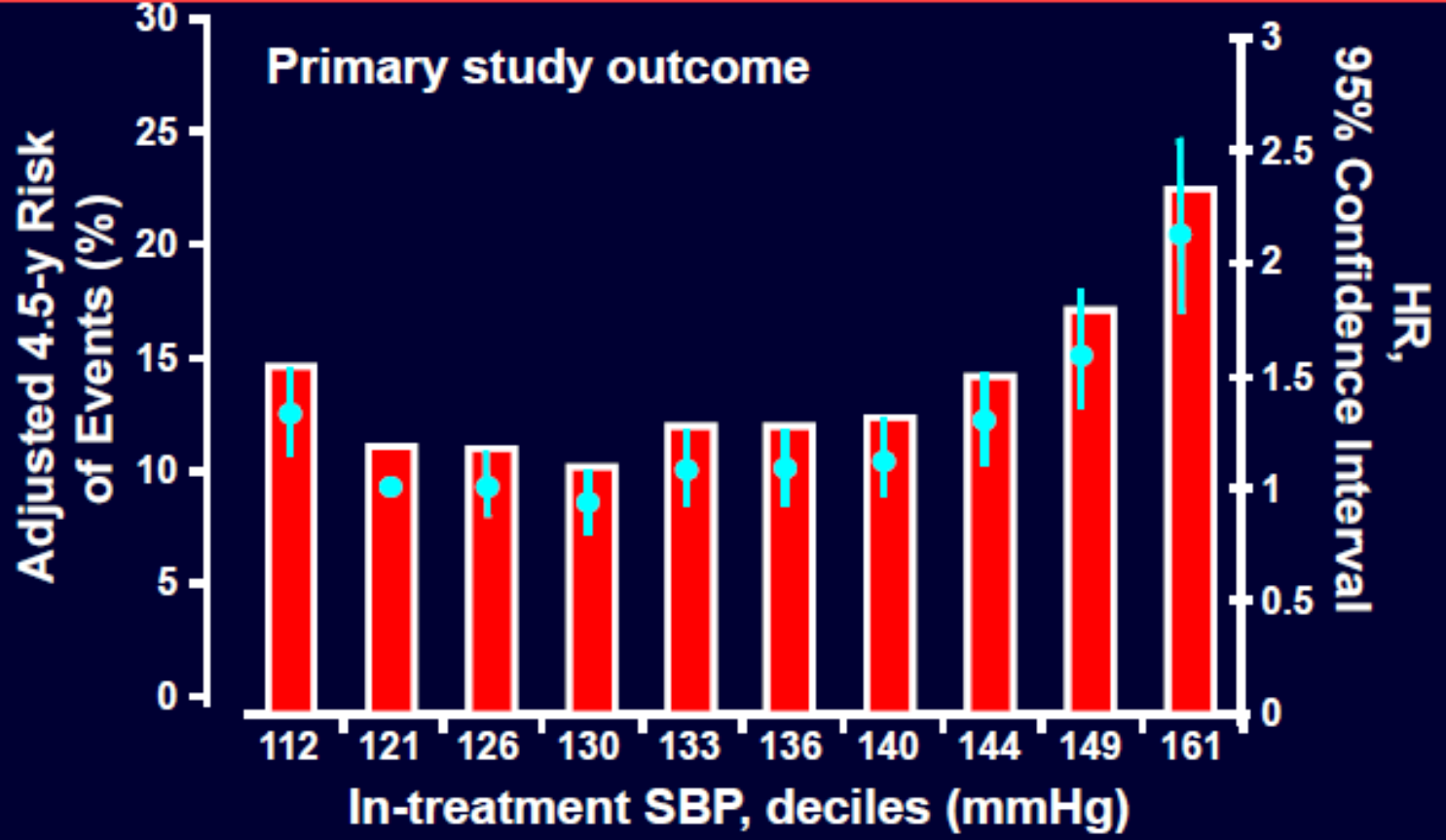


Diastolic Blood Pressure



Prospective Studies Collaboration. *Lancet*. 2002;360:1903-1913.

ONTARGET: Relationships Between Outcome Risks and In-Trial BP

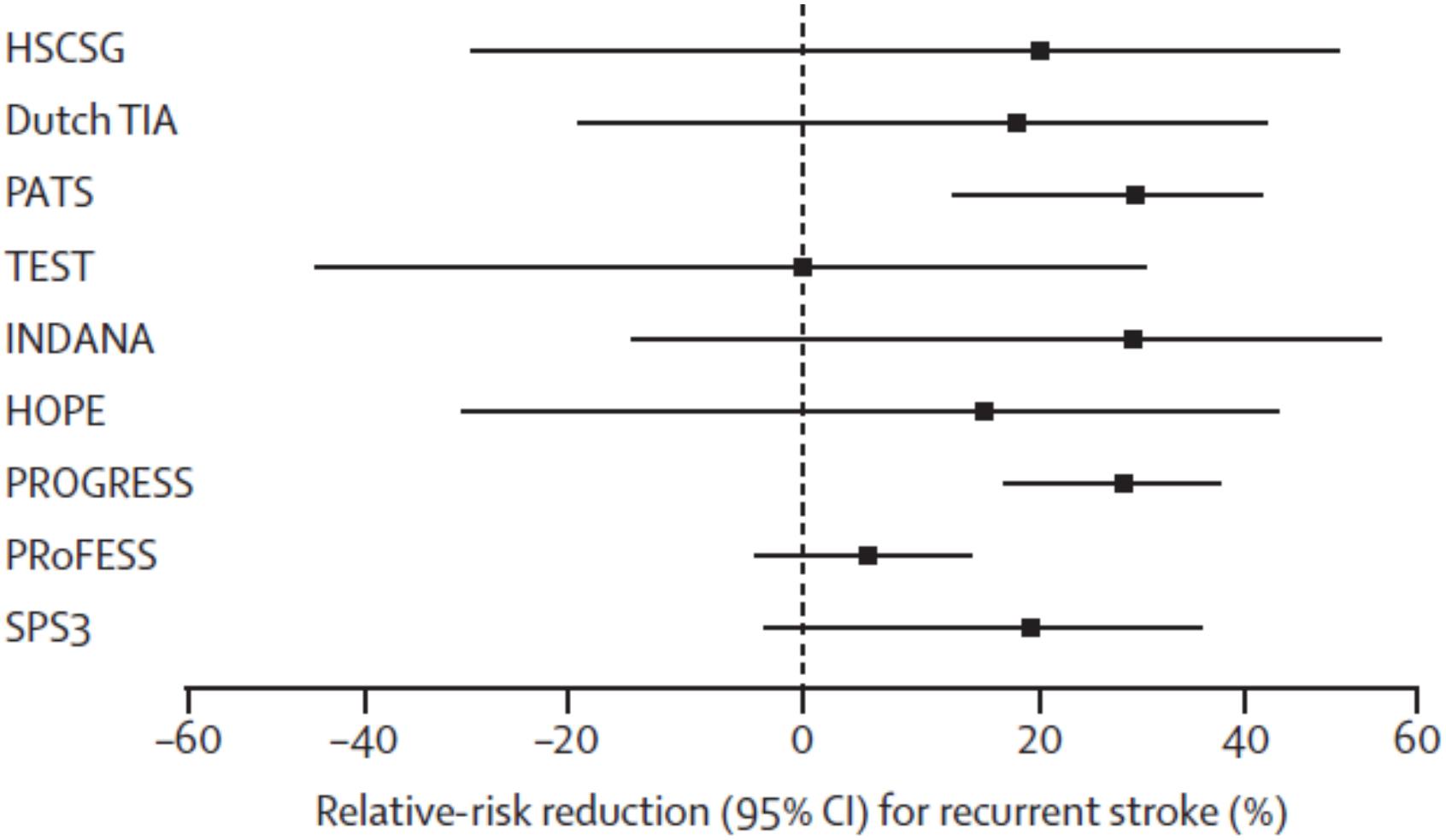


- **J-shaped curve** (nadir ≈ 130 mm Hg) for primary outcome[a], MI, CV mortality (not stroke)
- **Continual risk increase (no J-shaped curve) for stroke**
- **Suggests increased risk of events in patients with extensive vascular disease when BP is decreased below a critical level**

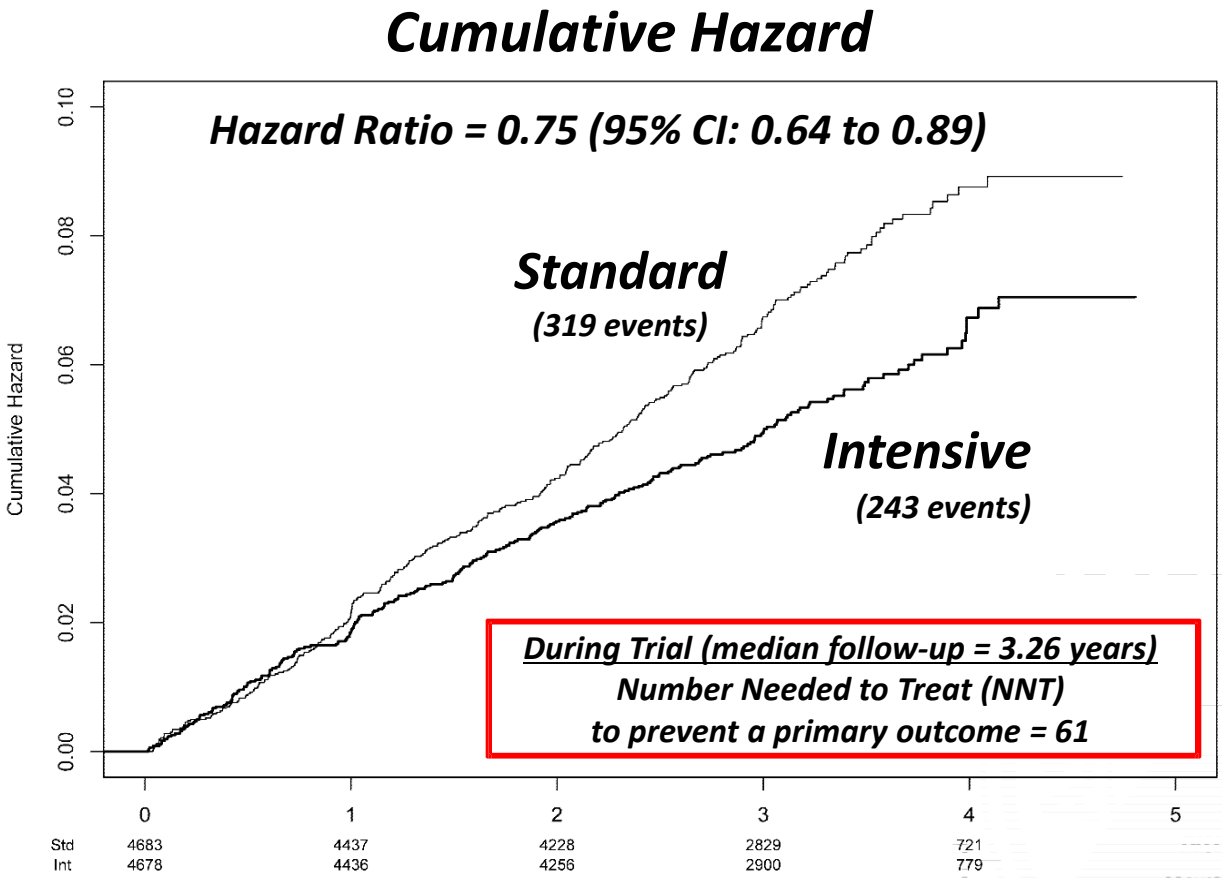
Composite of cardiovascular death, MI, stroke, or hospitalization for congestive heart failure (CHF).

Sleight P, et al. *J Hypertens*. 2009;27:1360-1369.

RCTs of long-term BP lowering for Secondary Stroke Prevention



Primary Outcome of SRPINT



SPRINT
Systolic Blood Pressure Intervention Trial

SPRINT Primary Outcome and its Components

Event Rates and Hazard Ratios

	Intensive		Standard			
	No. of Events	Rate, %/year	No. of Events	Rate, %/year	HR (95% CI)	P value
Primary Outcome	243	1.65	319	2.19	0.75 (0.64, 0.89)	<0.001
All MI	97	0.65	116	0.78	0.83 (0.64, 1.09)	0.19
Non-MI ACS	40	0.27	40	0.27	1.00 (0.64, 1.55)	0.99
All Stroke	62	0.41	70	0.47	0.89 (0.63, 1.25)	0.50
All HF	62	0.41	100	0.67	0.62 (0.45, 0.84)	0.002
CVD Death	37	0.25	65	0.43	0.57 (0.38, 0.85)	0.005

ORIGINAL ARTICLE

Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus

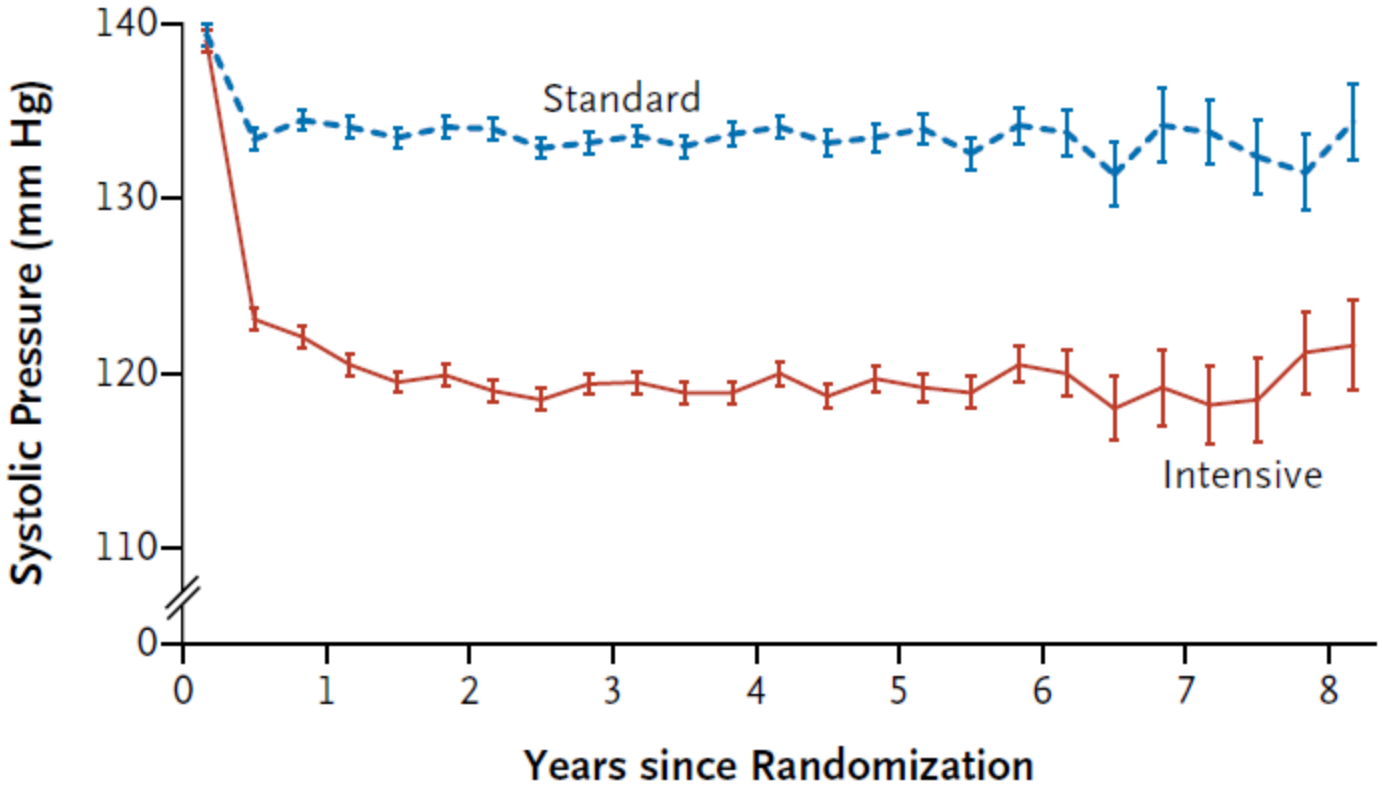
The ACCORD Study Group*

N Engl J Med 2010.

Intensive vs Standard BP

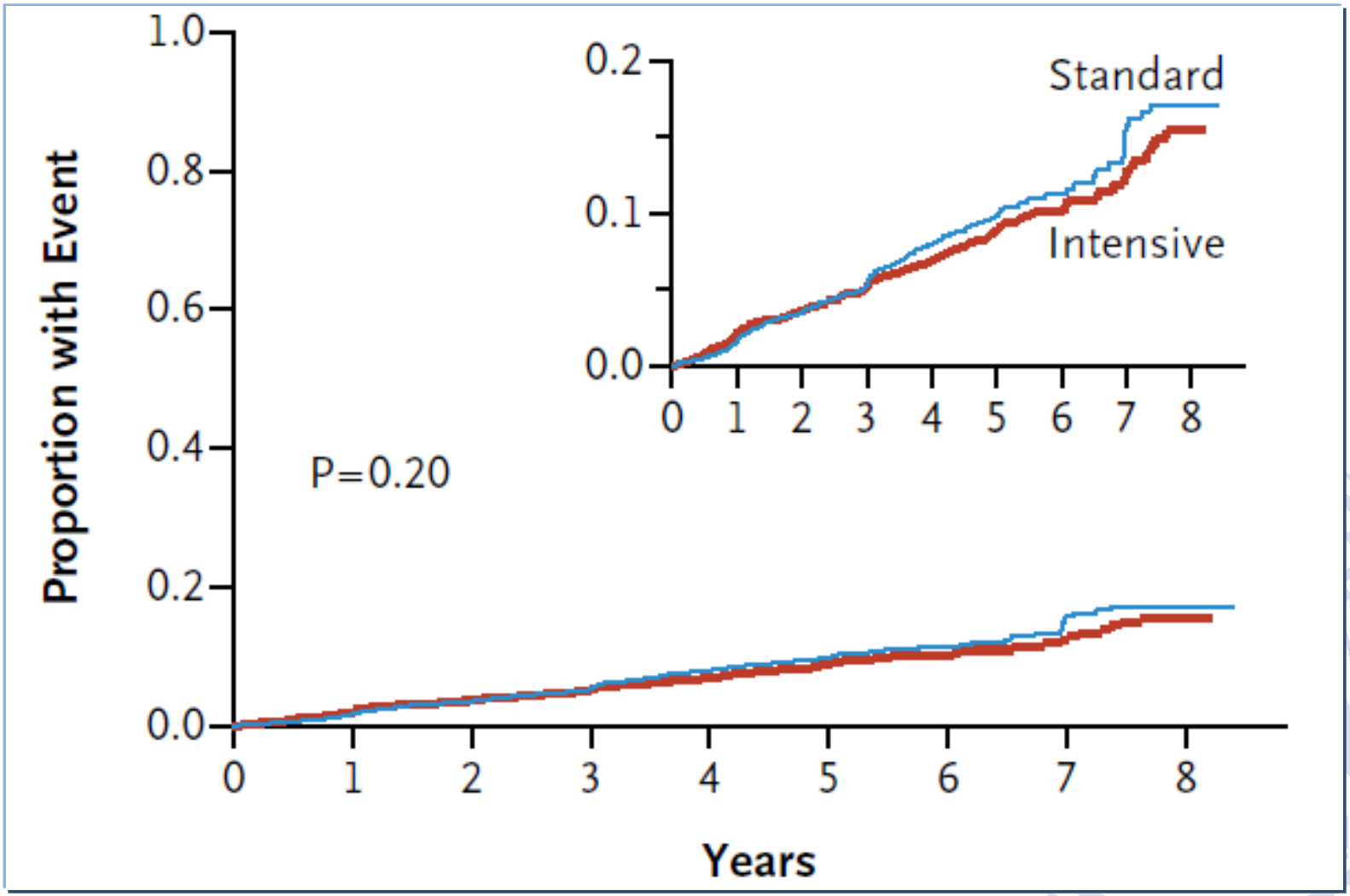
- Intensive BP lowering : less than 120mmHg
- Standard BP lowering : less than <140mmHg

Mean SBP Level

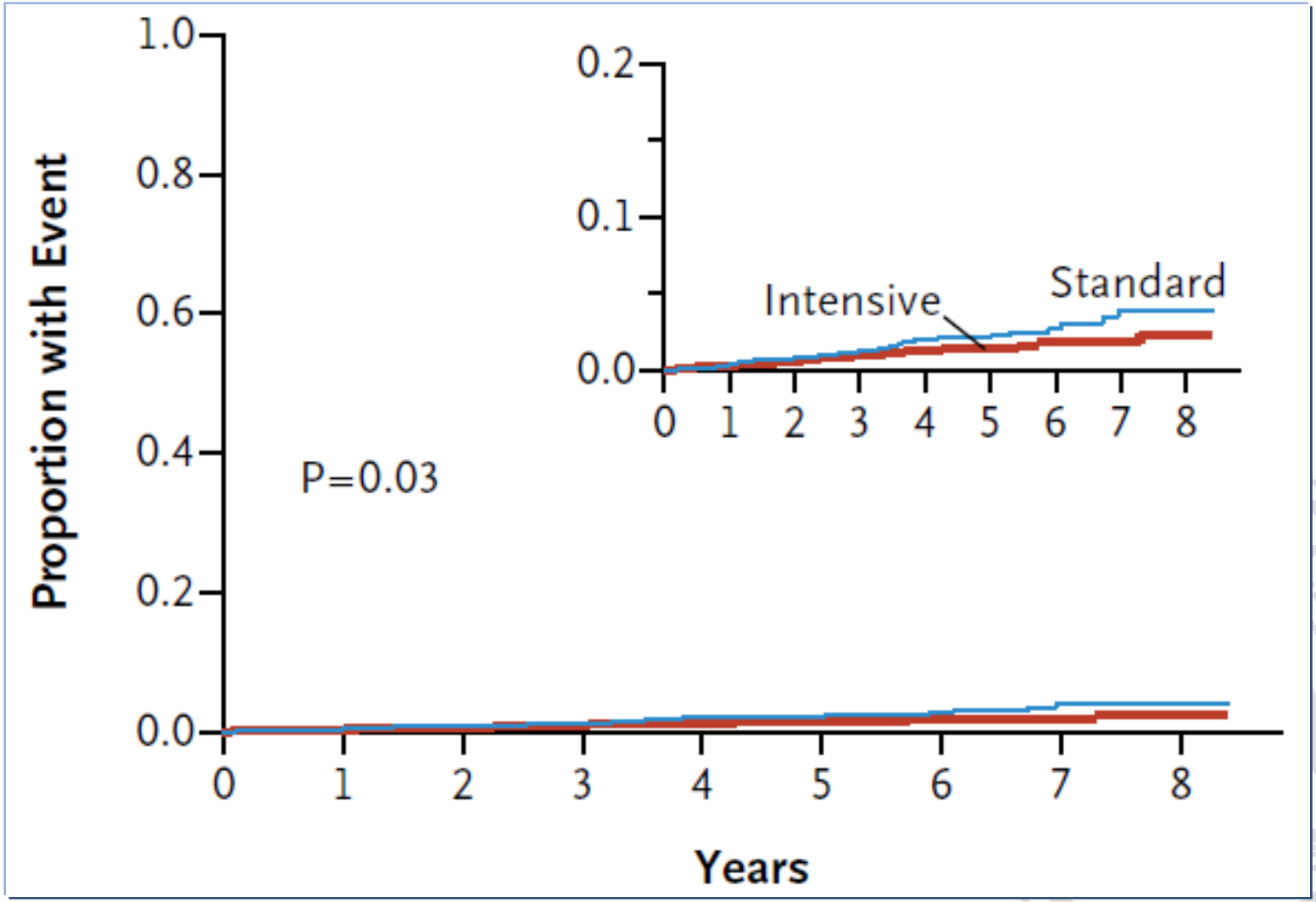


Mean No. of Medications Prescribed								
Intensive	3.2	3.4	3.4	3.5	3.5	3.5	3.4	3.4
Standard	1.9	2.1	2.1	2.2	2.2	2.3	2.3	2.3

Overall CV Events



Nonfatal Stroke



Outcomes

Outcome	Intensive Therapy (N=2363)		Standard Therapy (N=2371)		Hazard Ratio (95% CI)	P Value
	no. of events	*%/yr*	*no. of events*	*%/yr*		
Primary outcome*	208	1.87	237	2.09	0.88 (0.73–1.06)	0.20
Prespecified secondary outcomes						
Nonfatal myocardial infarction	126	1.13	146	1.28	0.87 (0.68–1.10)	0.25
Stroke						
Any	36	0.32	62	0.53	0.59 (0.39–0.89)	0.01
Nonfatal	34	0.30	55	0.47	0.63 (0.41–0.96)	0.03
Death						
From any cause	150	1.28	144	1.19	1.07 (0.85–1.35)	0.55
From cardiovascular cause	60	0.52	58	0.49	1.06 (0.74–1.52)	0.74
Primary outcome plus revascularization or nonfatal heart failure	521	5.10	551	5.31	0.95 (0.84–1.07)	0.40
Major coronary disease event†	253	2.31	270	2.41	0.94 (0.79–1.12)	0.50
Fatal or nonfatal heart failure	83	0.73	90	0.78	0.94 (0.70–1.26)	0.67

Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial

*The SPS3 Study Group**

Summary

Background Lowering of blood pressure prevents stroke but optimum target levels to prevent recurrent stroke are unknown. We investigated the effects of different blood-pressure targets on the rate of recurrent stroke in patients with recent lacunar stroke.

Methods In this randomised open-label trial, eligible patients lived in North America, Latin America, and Spain and had recent, MRI-defined symptomatic lacunar infarctions. Patients were recruited between March, 2003, and April, 2011, and randomly assigned, according to a two-by-two multifactorial design, to a systolic-blood-pressure target of 130–149 mm Hg or less than 130 mm Hg. The primary endpoint was reduction in all stroke (including ischaemic strokes and intracranial haemorrhages). Analysis was done by intention to treat. This study is registered with ClinicalTrials.gov, number NCT 00059306.

Findings 3020 enrolled patients, 1519 in the higher-target group and 1501 in the lower-target group, were followed up for a mean of 3·7 (SD 2·0) years. Mean age was 63 (SD 11) years. After 1 year, mean systolic blood pressure was 138 mm Hg (95% CI 137–139) in the higher-target group and 127 mm Hg (95% CI 126–128) in the lower-target group. Non-significant rate reductions were seen for all stroke (hazard ratio 0·81, 95% CI 0·64–1·03, p=0·08), disabling or fatal stroke (0·81, 0·53–1·23, p=0·32), and the composite outcome of myocardial infarction or vascular death (0·84, 0·68–1·04, p=0·32) with the lower target. The rate of intracerebral haemorrhage was reduced significantly (0·37, 0·15–0·95, p=0·03). Treatment-related serious adverse events were infrequent.

Interpretation Although the reduction in stroke was not significant, our results support that in patients with recent lacunar stroke, the use of a systolic-blood-pressure target of less than 130 mm Hg is likely to be beneficial.

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This online publication has been corrected. The corrected version first appeared at thelancet.com on August 9, 2013

See Comment page 482

*Members listed at end of paper

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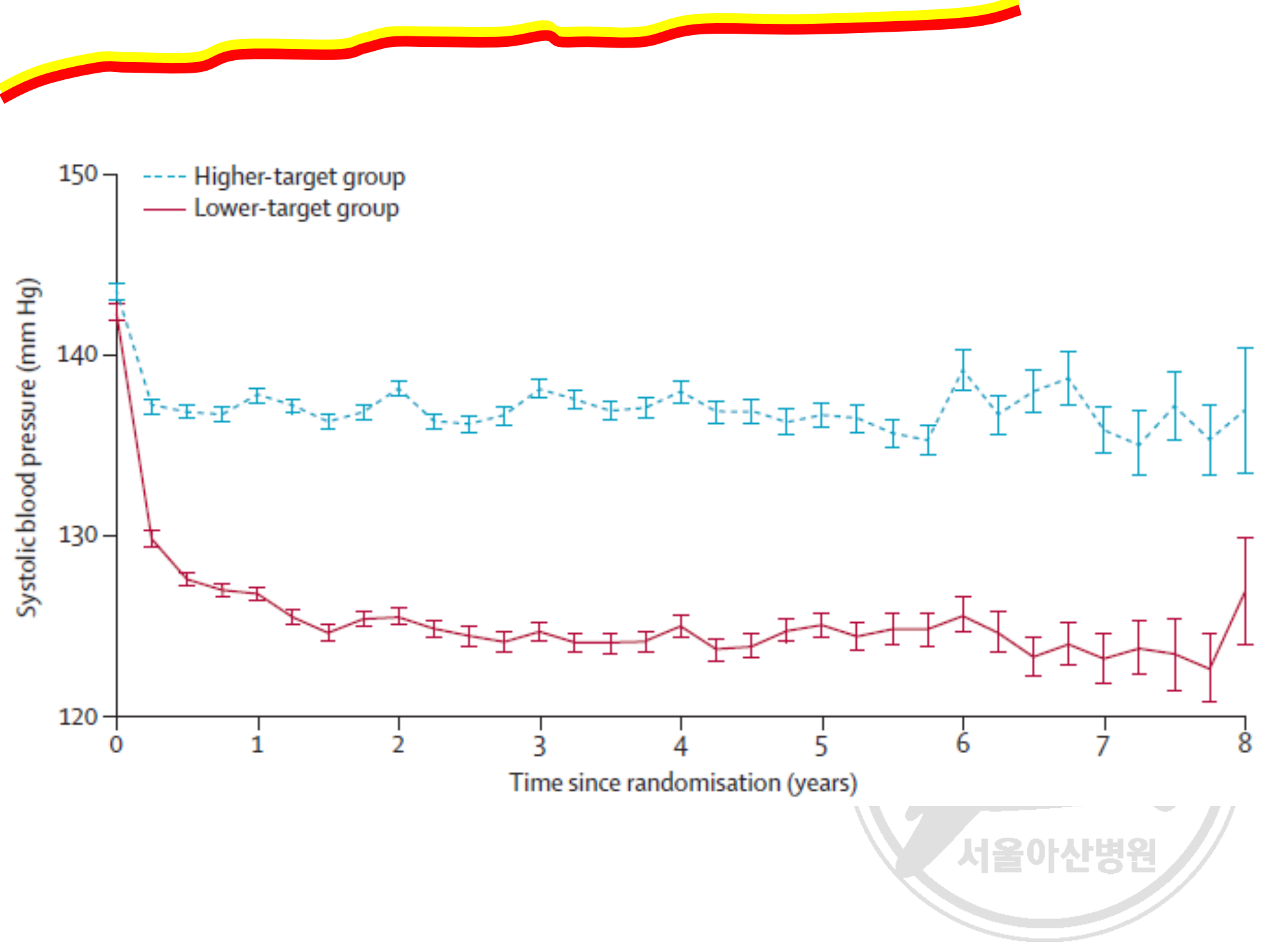
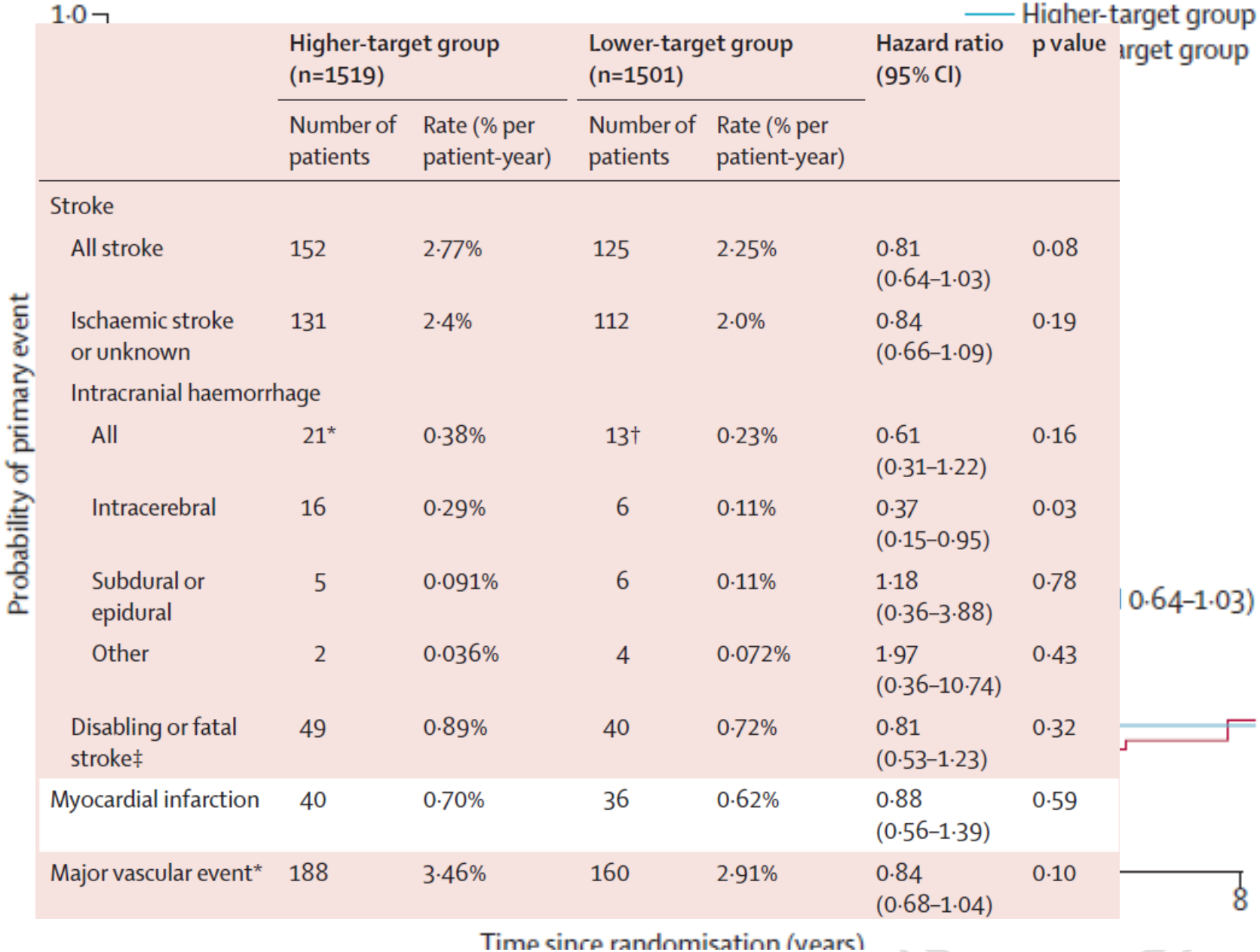

Higher-target group
Lower-target group
Systolic blood pressure (mm Hg)
150
140
130
120
0
1
2
3
4
5
6
7
8
Time since randomisation (years)

	Higher-target group (n=1519)		Lower-target group (n=1501)		Hazard ratio (95% CI)	p value
	Number of patients	Rate (% per patient-year)	Number of patients	Rate (% per patient-year)		
Stroke						
All stroke	152	2·77%	125	2·25%	0·81 (0·64–1·03)	0·08
Ischaemic stroke or unknown	131	2·4%	112	2·0%	0·84 (0·66–1·09)	0·19
Intracranial haemorrhage						
All	21*	0·38%	13†	0·23%	0·61 (0·31–1·22)	0·16
Intracerebral	16	0·29%	6	0·11%	0·37 (0·15–0·95)	0·03
Subdural or epidural	5	0·091%	6	0·11%	1·18 (0·36–3·88)	0·78
Other	2	0·036%	4	0·072%	1·97 (0·36–10·74)	0·43
Disabling or fatal stroke‡	49	0·89%	40	0·72%	0·81 (0·53–1·23)	0·32
Myocardial infarction	40	0·70%	36	0·62%	0·88 (0·56–1·39)	0·59
Major vascular event*	188	3·46%	160	2·91%	0·84 (0·68–1·04)	0·10



Difference between the 3 trials

ACCORD

SPS3

SPRINT

Major Inclusion Criteria

- *≥50 years old*
- *Systolic blood pressure : 130 – 180 mm Hg (treated or untreated)*
- *Additional cardiovascular disease (CVD) risk*
  - *Clinical or subclinical CVD (excluding stroke)*
  - *Chronic kidney disease (CKD), defined as eGFR 20 – <60 ml/min/1.73m²*
  - *Framingham Risk Score for 10-year CVD risk ≥ 15%*
  - *Age ≥ 75 years*

At least one

SPRINT
Systolic Blood Pressure Intervention Trial

Major Exclusion Criteria

- *Stroke*
- *Diabetes mellitus*
- *Polycystic kidney disease*
- *Congestive heart failure (symptoms or EF < 35%)*
- *Proteinuria >1g/d*
- *CKD with eGFR < 20 mL/min/1.73m^2 (MDRD)*
- *Adherence concerns*

Mean Ages At Random

SPRINT : 67.9±9.4years old

SPS3 : 63 years old

ACCORD : 62.2±6.9 years old

Rate of MACE

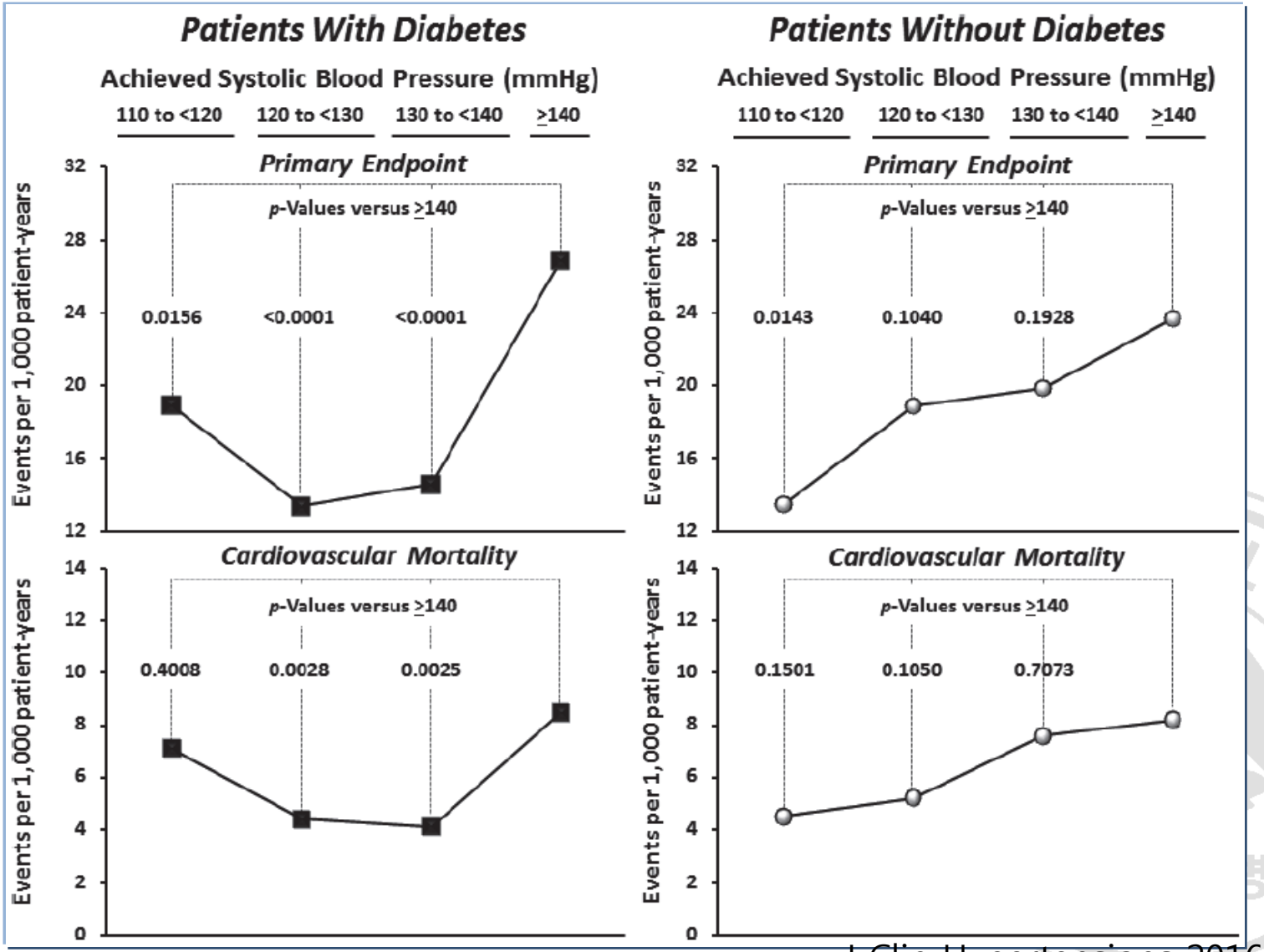
	SPRINT (2015)		SPS3 (2013)		ACCORD (2010)	
	Intensive	Control	Intensive	Control	Intensive	Control
Composite	1.65%/y	2.19%/y	2.91%/y[2]	3.46%/y	1.87%/y	2.09%/y
MI	0.65%/y	0.78%/y	0.62%/y	0.70%/y	1.13%/y[1]	1.28%/y[1]
ACS	0.27%/y	0.27%/y				
Stroke	0.41%/y	0.47%/y	2.25%/y	2.77%/y	0.32%/y	0.53%/y
Heart failure	0.41%/y	0.67%/y			0.73%/y	0.78%/y
Vascular death	0.25%/y	0.43%/y	0.61%/y	0.70%/y	0.52%/y	0.49%/y
Major Coronary event					2.31%/y	2.41%/y

1; nonfatal MI in ACCORD, 2; major vascular events in SPS3 trial included stroke, myocardial infarction or vascular death

Difference in Population

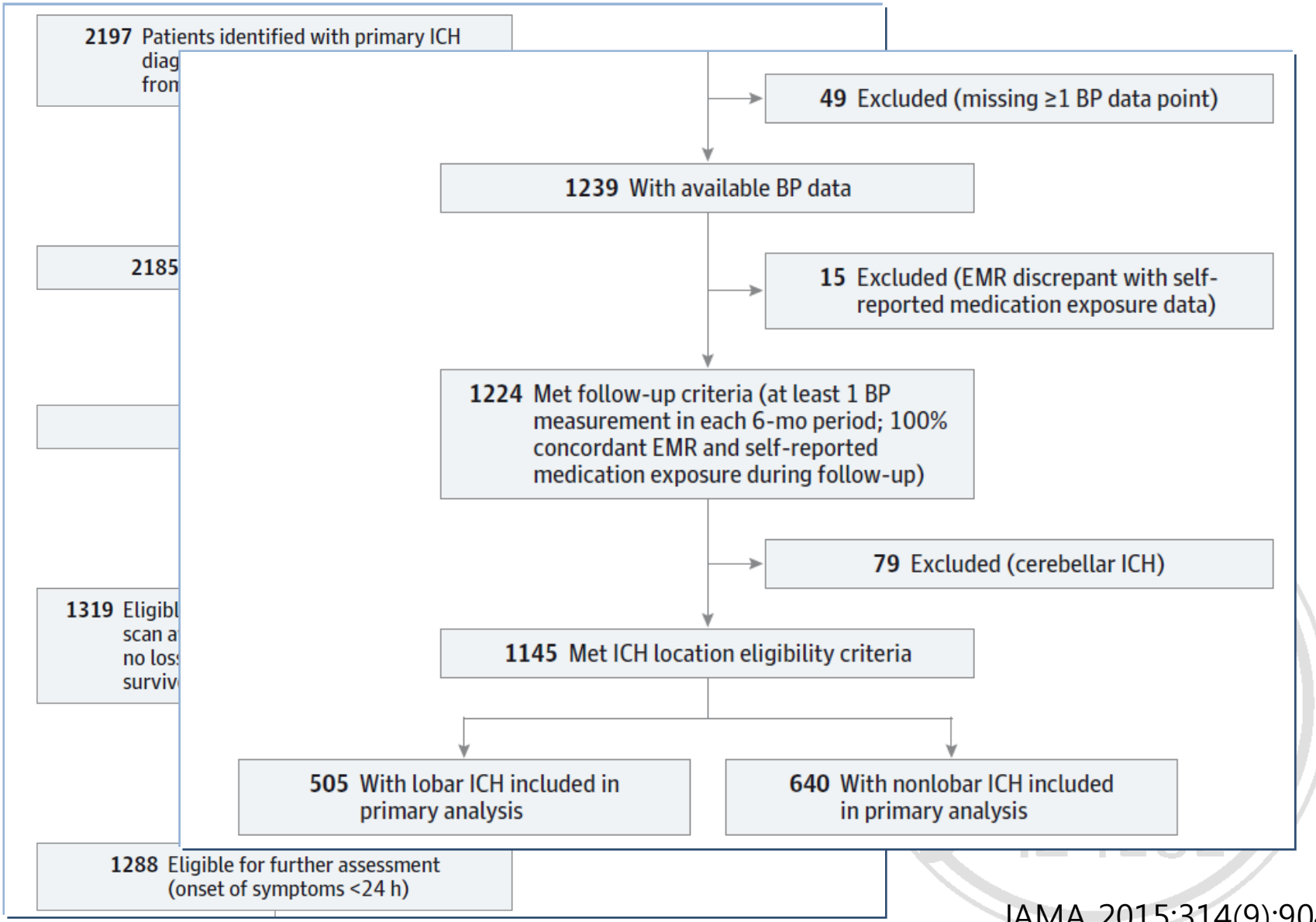
- ACCORD : diabetic patients
- SPS3: ischemic stroke patients (lacunar stroke)

ACCOMPLISH post-hoc



J Clin Hypertensions 2016;18:299

BP control & Risk of Recurrent ICH



JAMA 2015;314(9):904

Table 3. Bivariable and Multivariable Analysis of Factors Associated With Recurrent ICH[a]

Variable	Analysis			
	Bivariable		Multivariable	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Lobar ICH (n = 505)				
Lobar ICH prior to index event	5.01 (2.24-11.21)	<.001	4.22 (1.40-15.71)	<.001
Antiplatelet agent use (after index ICH)[b]	2.77 (1.03-7.48)	.046	2.89 (1.32-6.30)	.008
Warfarin use (after index ICH)[b]	4.78 (1.02-22.49)	.049	5.64 (0.85-37.39)	.08
Education ≥10 y	0.66 (0.50-0.87)	.004	0.70 (0.52-0.95)	.02
Inadequate BP control[c]	3.19 (1.42-7.16)	.005	3.53 (1.65-7.54)	.001
Nonlobar ICH (n = 640)				
Nonlobar ICH prior to index event	3.01 (1.51-6.01)	.002	2.78 (1.52-5.09)	<.001
Antiplatelet agent use (after index ICH)[b]	1.71 (0.98-2.98)	.06	1.56 (0.98-2.48)	.06
Warfarin use (after index ICH)[b]	3.12 (0.62-13.43)	.18	2.88 (0.46-18.16)	>.20
Ischemic heart disease	2.33 (1.19-4.56)	.01	2.48 (1.26-4.90)	.009
Race				
White	1 [Reference]		1 [Reference]	
African American	2.67 (1.26-5.66)	.01	2.91 (1.37-6.17)	.006
Education (≥10 y)	0.60 (0.42-0.86)	.005	0.56 (0.36-0.88)	.01
Inadequate BP control[c]	3.99 (1.16-13.76)	.03	4.23 (1.02-17.52)	.048

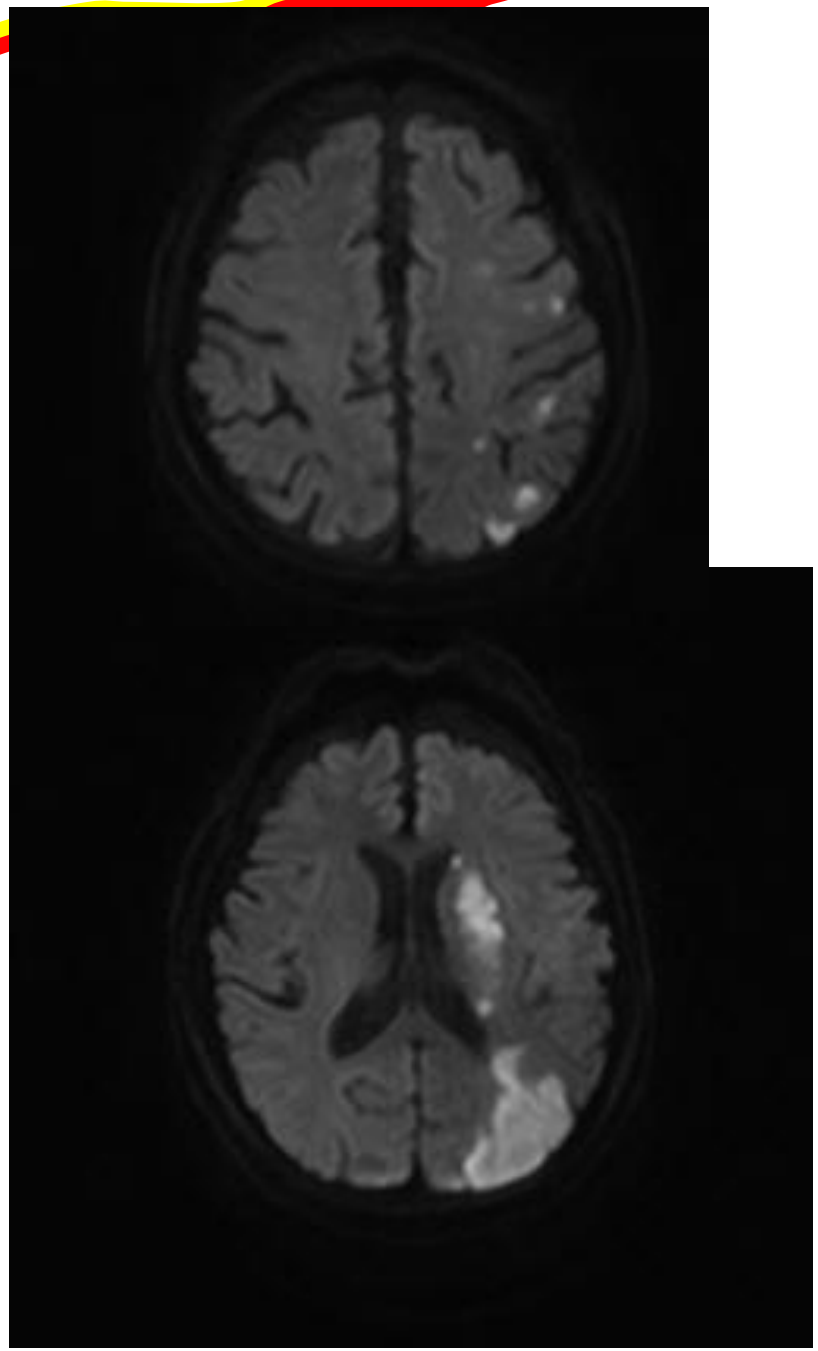
JAMA 2015;314(9):904

Table 4. Multivariable Analyses: BP and Recurrence of ICH

	Recurrent ICH			
	Lobar (n = 505)[a]		Nonlobar (n = 640)[b]	
BP Exposure Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Inadequate BP control[c]	3.53 (1.65-7.54)	.001	4.23 (1.02-17.52)	.048
Hypertension stage[d]				
Normotension	1 [Reference]		1 [Reference]	
Prehypertension	2.76 (1.32-5.82)	.007	3.06 (1.07-8.78)	.04
Hypertension stage 1	3.90 (1.36-11.17)	.01	3.88 (1.31-11.61)	.02
Hypertension stage 2	5.21 (2.74-9.91)	<.001	6.23 (0.90-42.97)	.06
Continuous BP values (for 10-mm Hg increase)[e]				
Systolic	1.33 (1.02-1.76)	.04	1.54 (1.03-2.30)	.04
Diastolic	1.36 (0.90-2.10)	.15	1.21 (1.01-1.47)	.05

JAMA 2015;314(9):904

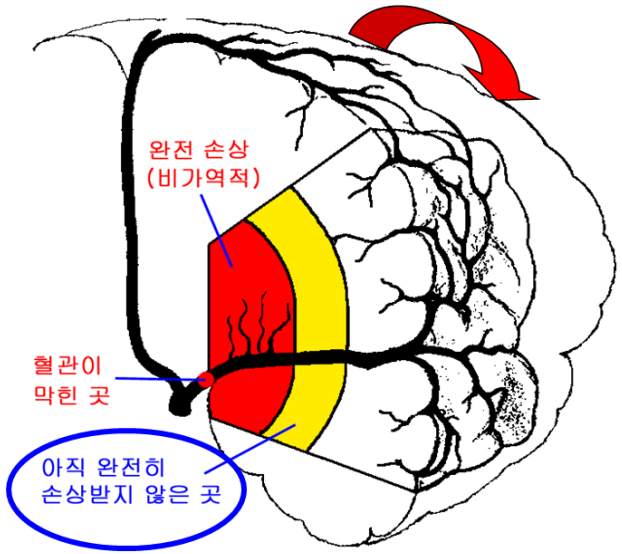
Stroke is not single diseases but a syndrome including various cerebro-vascular status



Effect of Low BP on ICAS

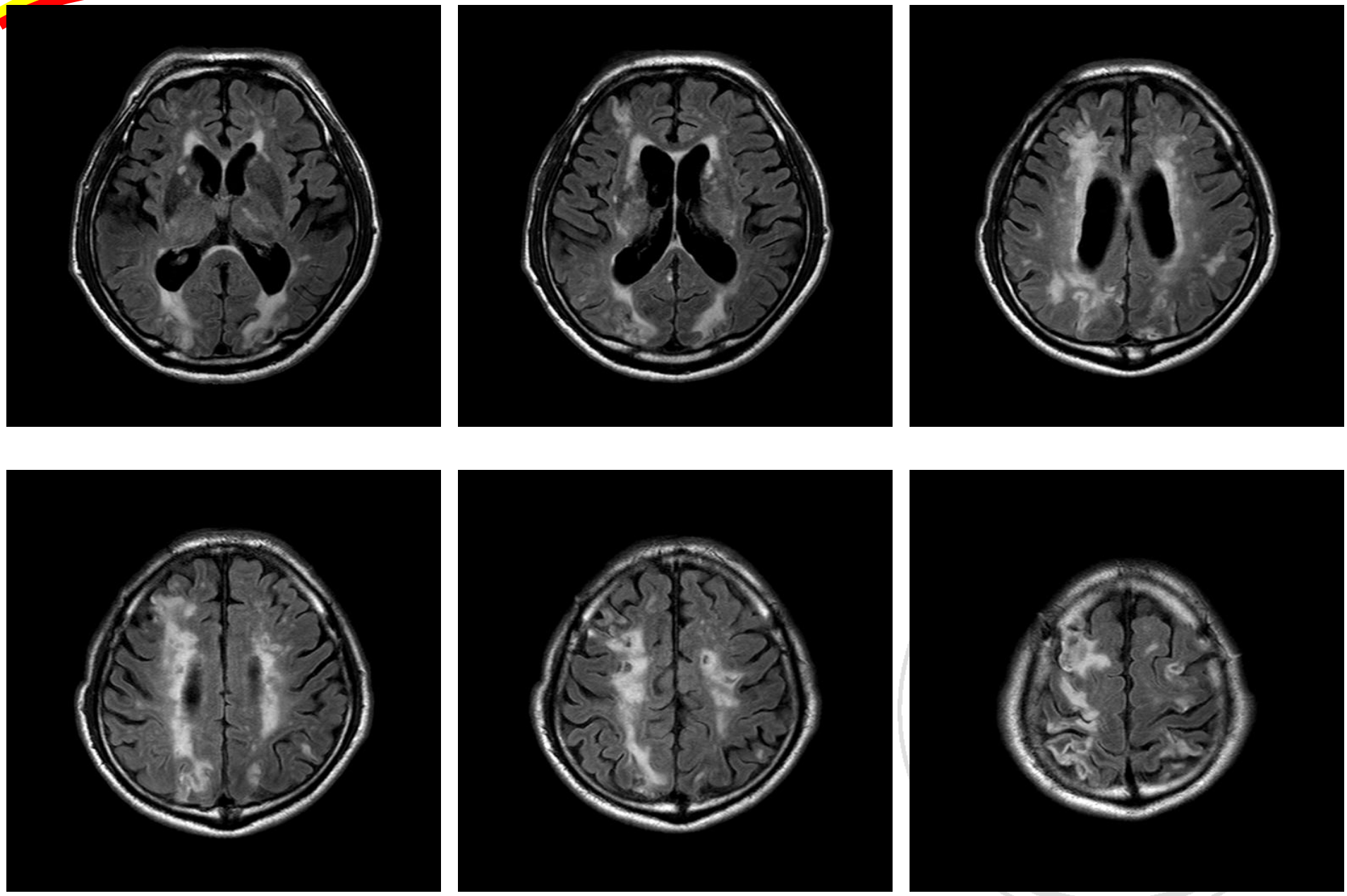
Disadvantage

- Acute - Infarct growth
- Chronic - Borderzone hypoperfusion



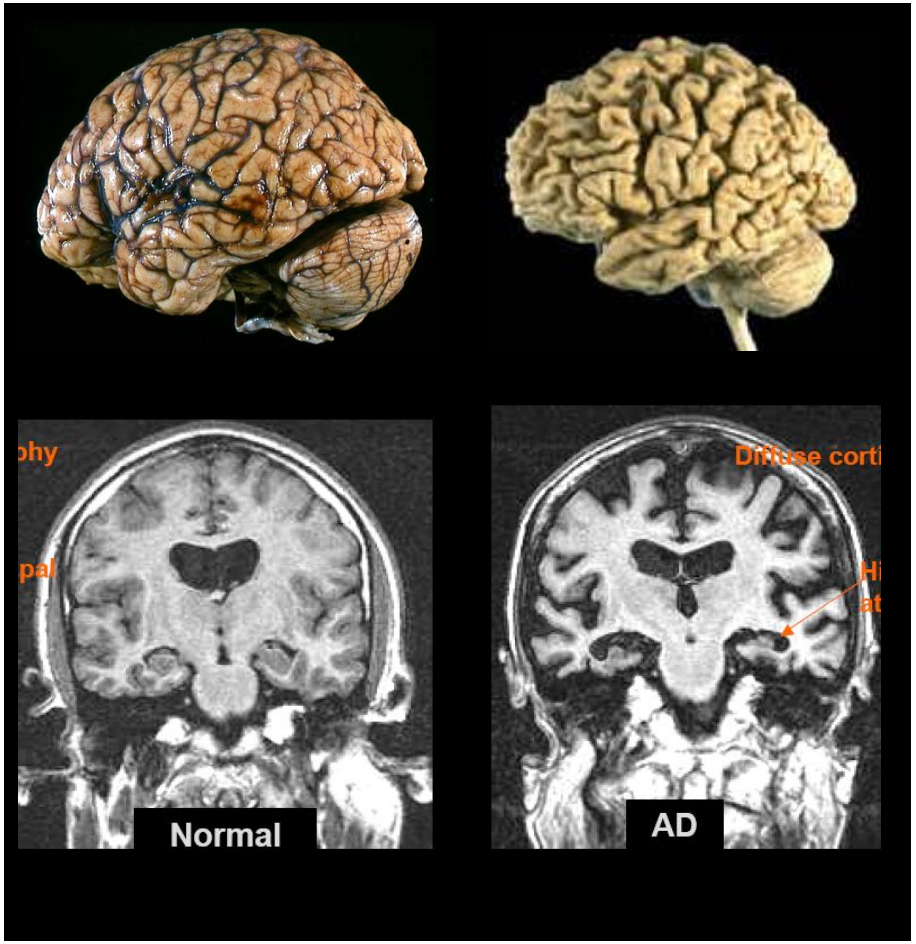
Advantage

- Acute
  - Brain edema ↓
  - Hemorrhagic transformation ↓
  - Preventing further vascular damage ↓ → early recurrent or progressing stroke ↓
- Chronic
  - Microangiopathy ↓
  - Systemic benefit



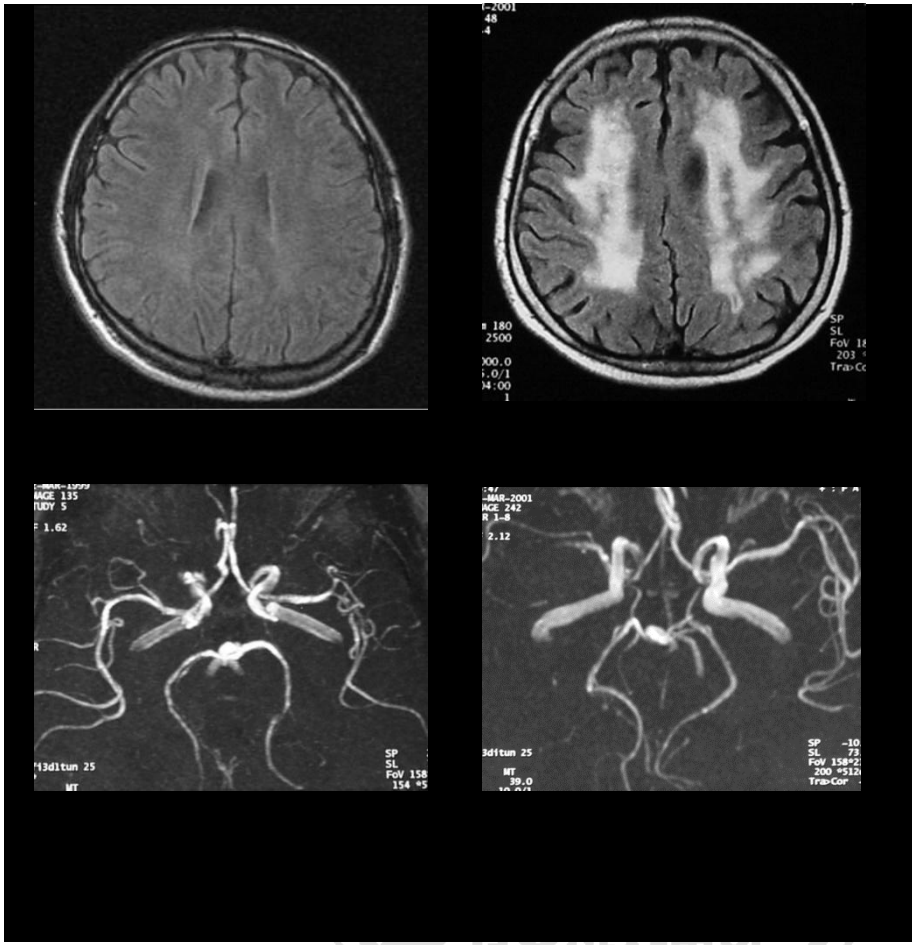
Neurodegenerative Dementia

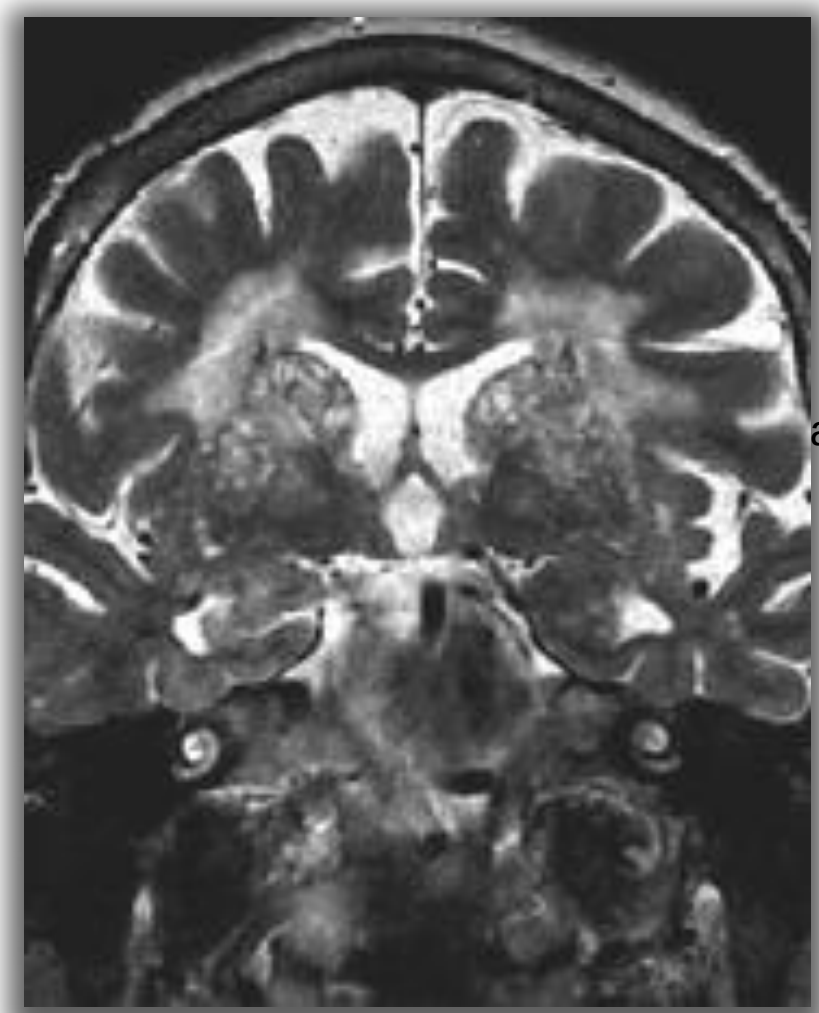
Alzheimer's Disease



Vascular Dementia

Post-Stroke Dementia



- 
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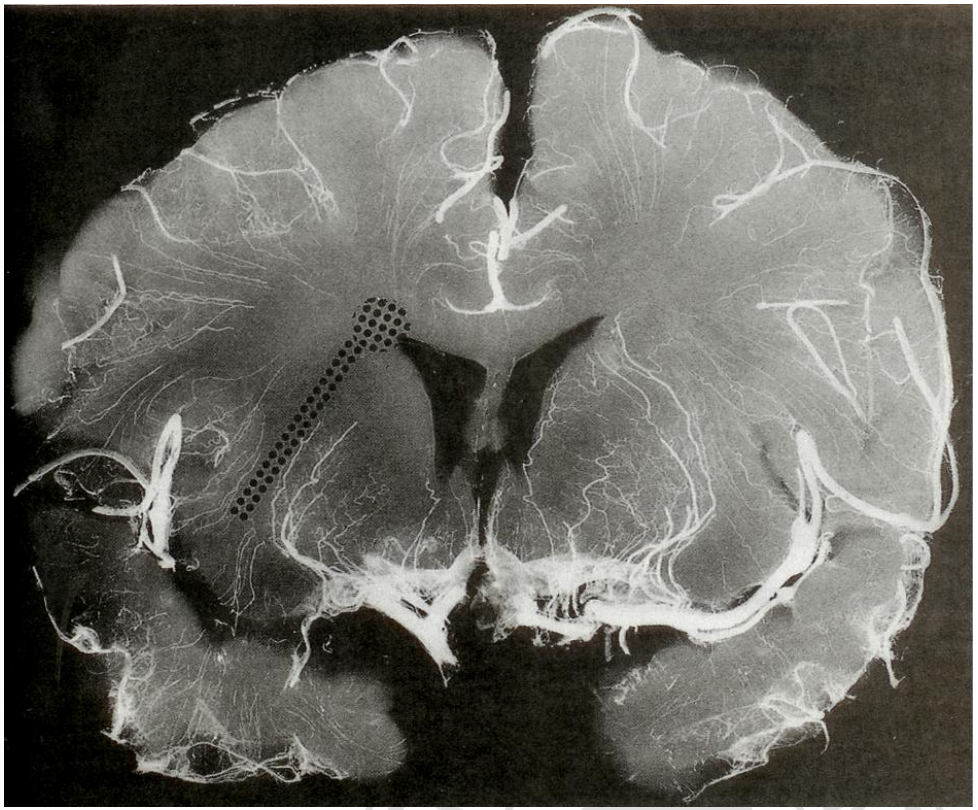
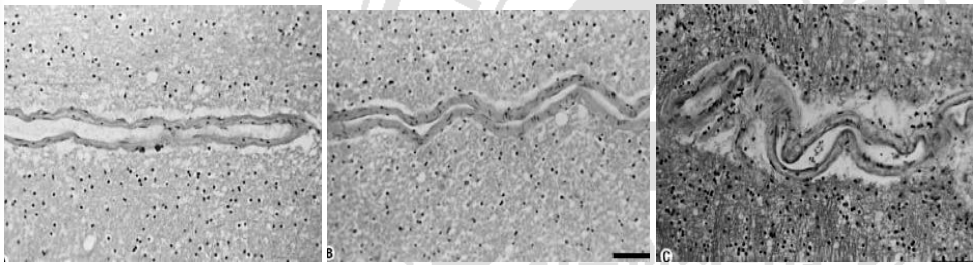
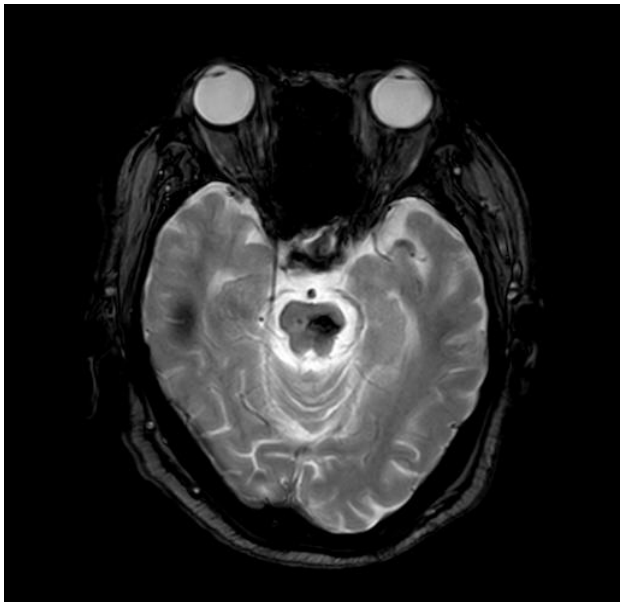
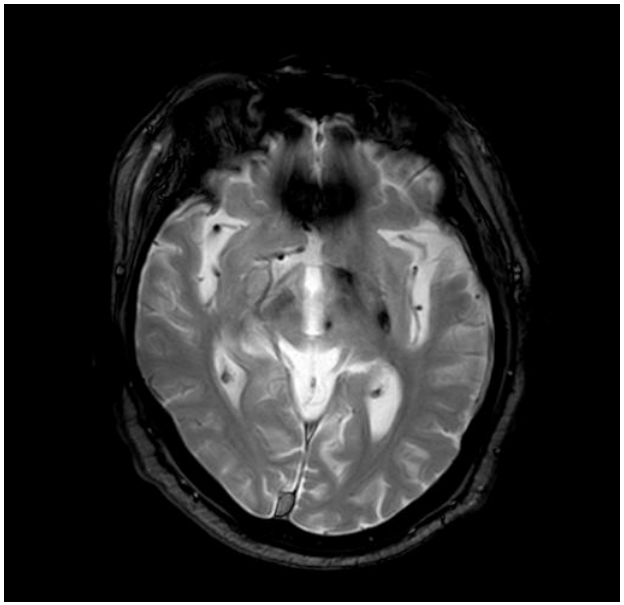
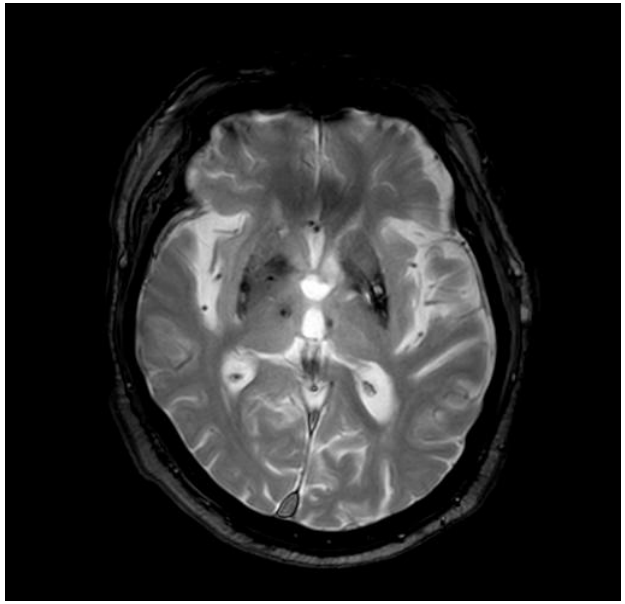
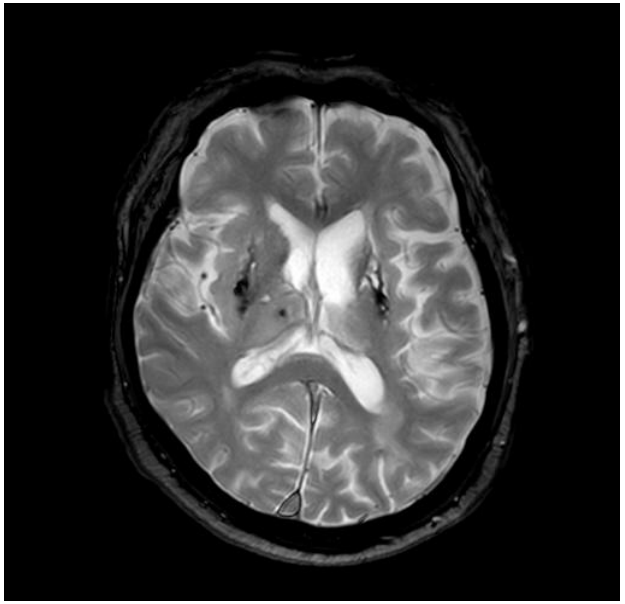
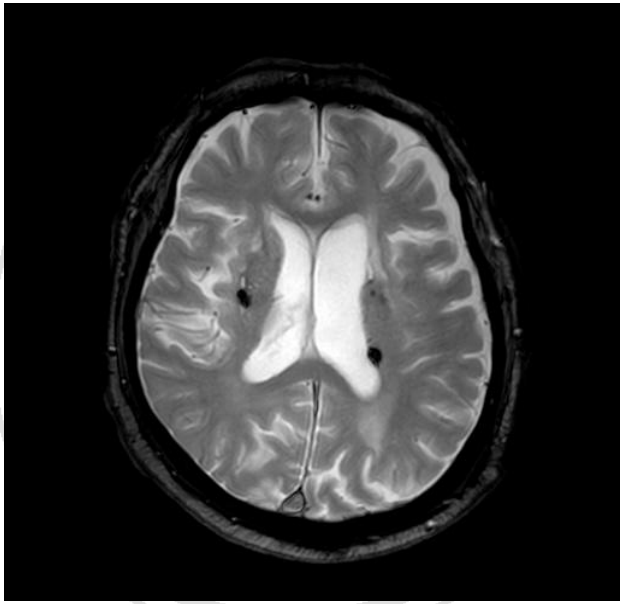


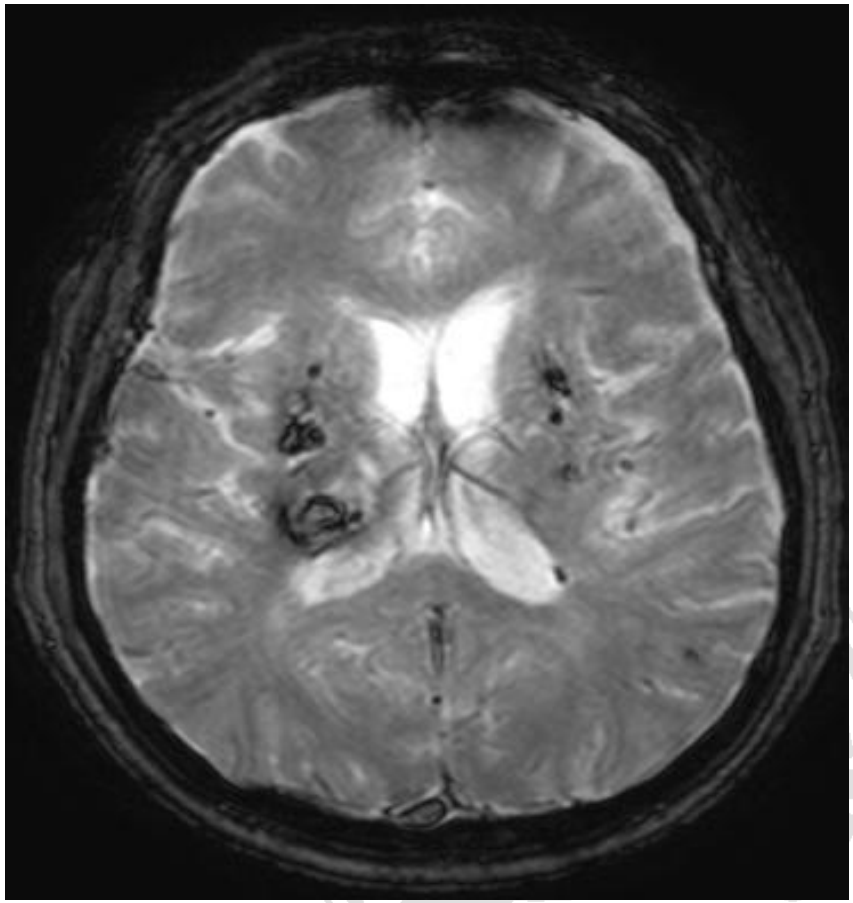


Silent Microbleeds (SMBs)

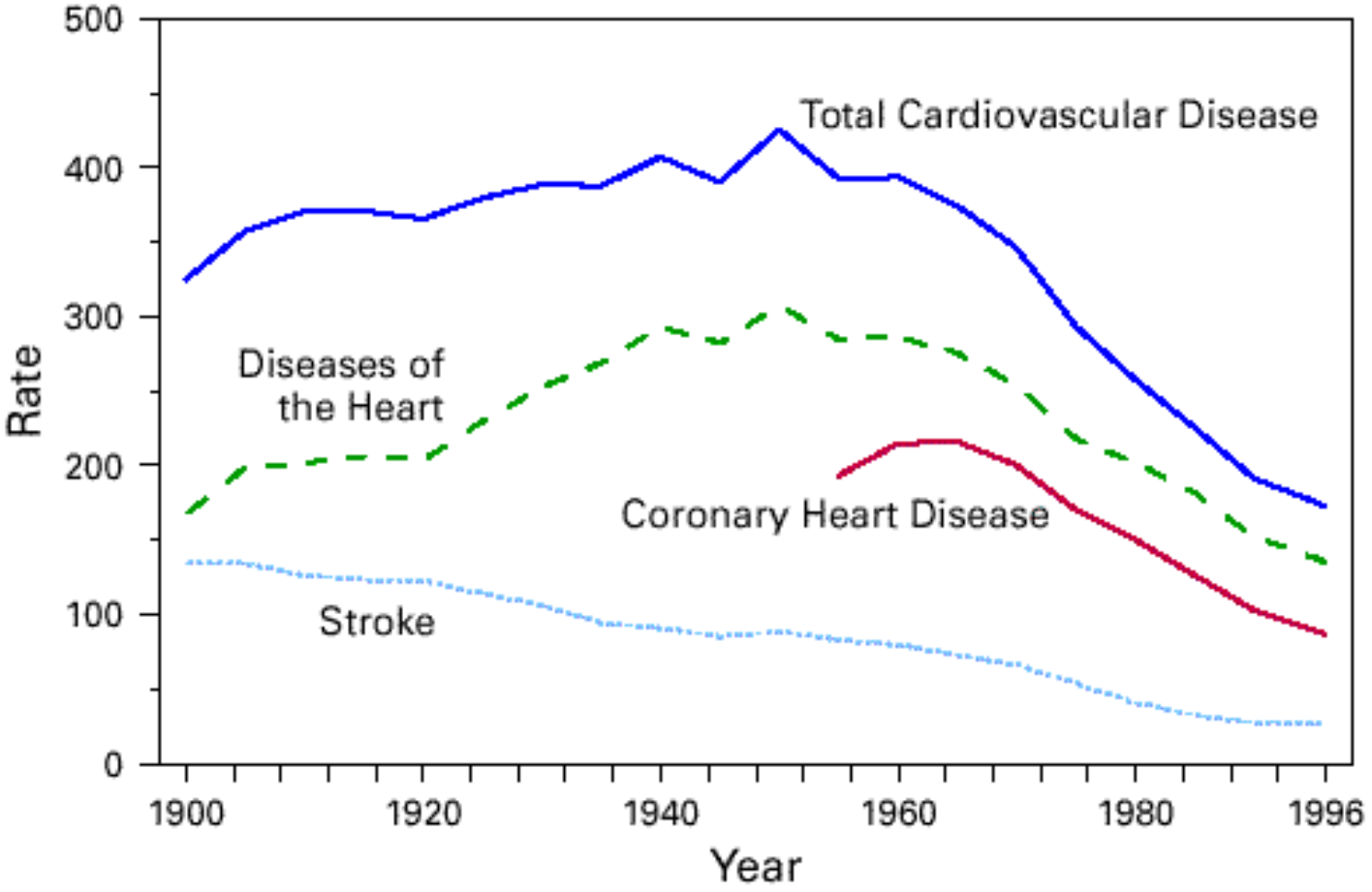
- Visualized typically by **GRE** sequence
- **Small round signal loss lesion (< 5 mm)**
- Throughout the whole brain area

- **Surrogate marker for symptomatic ICH**



Different Epidemiology of Cardiovascular diseases between in Korea &in Western

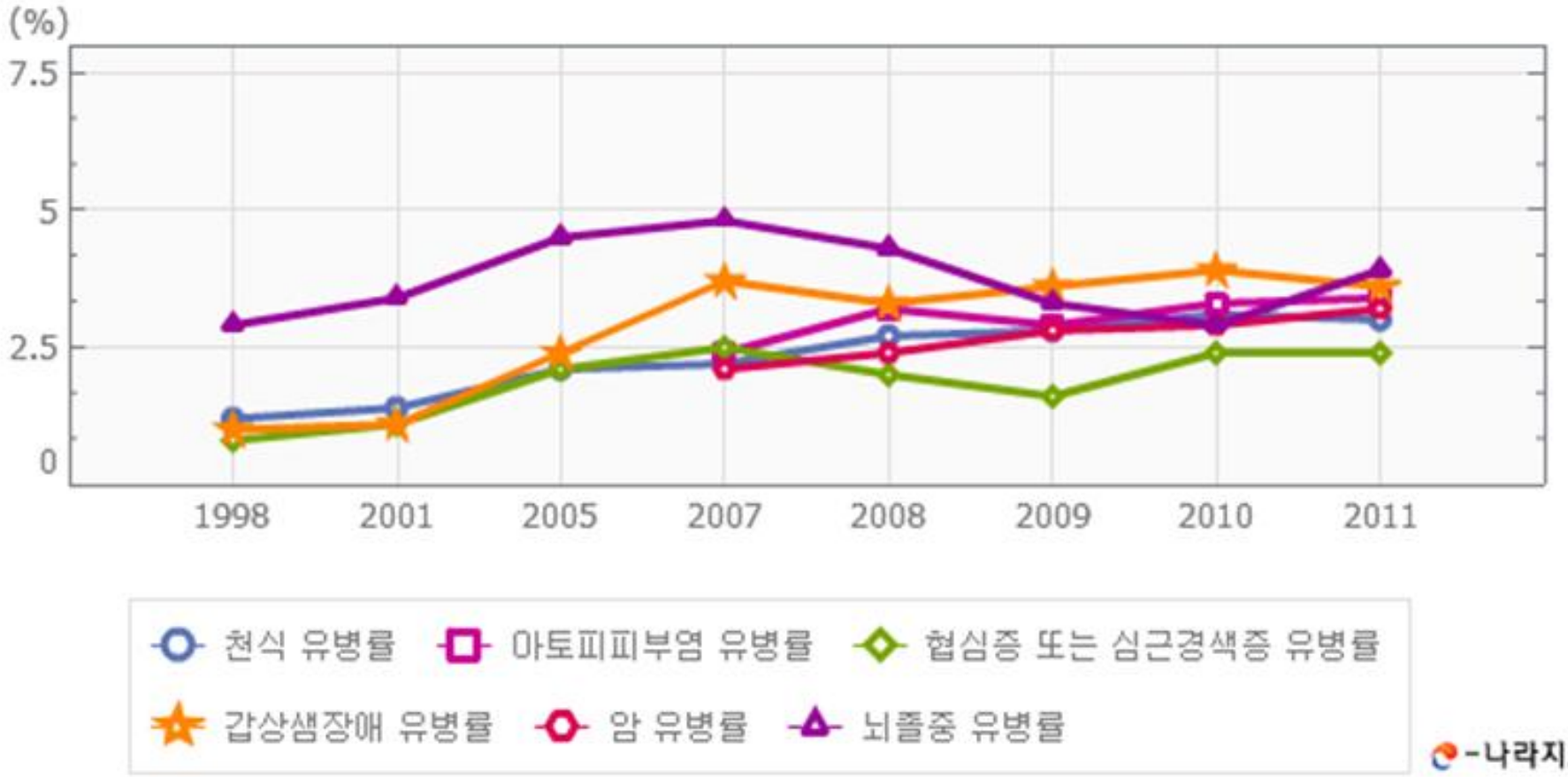
FIGURE 1. Age-adjusted death rates* for total cardiovascular disease, diseases of the heart, coronary heart disease, and stroke,† by year — United States, 1900–1996



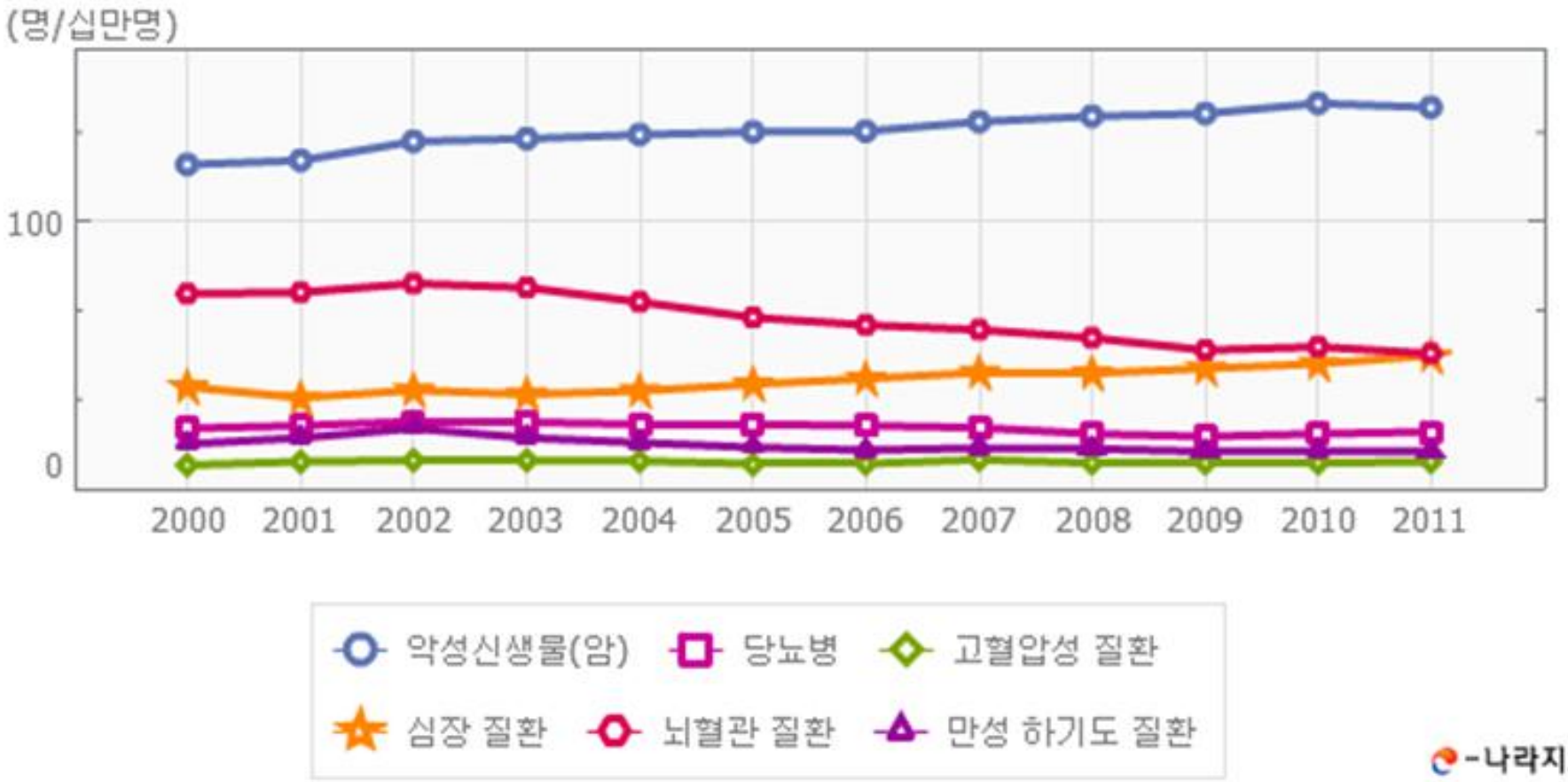
*Per 100,000 population, standardized to the 1940 U.S. population.
†Diseases are classified according to *International Classification of Diseases* (ICD) codes in use when the deaths were reported. ICD classification revisions occurred in 1910, 1921, 1930, 1939, 1949, 1958, 1968, and 1979. Death rates before 1933 do not include all states. Comparability ratios were applied to rates for 1970 and 1975.

Source: Adapted from reference 1; data provided by the National Heart, Lung and Blood Institute, National Institutes of Health.

만성질환 유병률(건강설문)



만성질환 사망률



Summary

- Hypertension is the most important risk factor of stroke
- In Korea, the burden of stroke is much bigger than it of coronary diseases compared to western countries.
- Stroke includes various cerebro-vascular status

Conclusion

- SPRINT did not include the patients with history of stroke
- Majority of SPRINT population is white or black
- No evidence for Asian stroke patients
- Intensive BP control will be helpful for Healthy population with mild hypertension