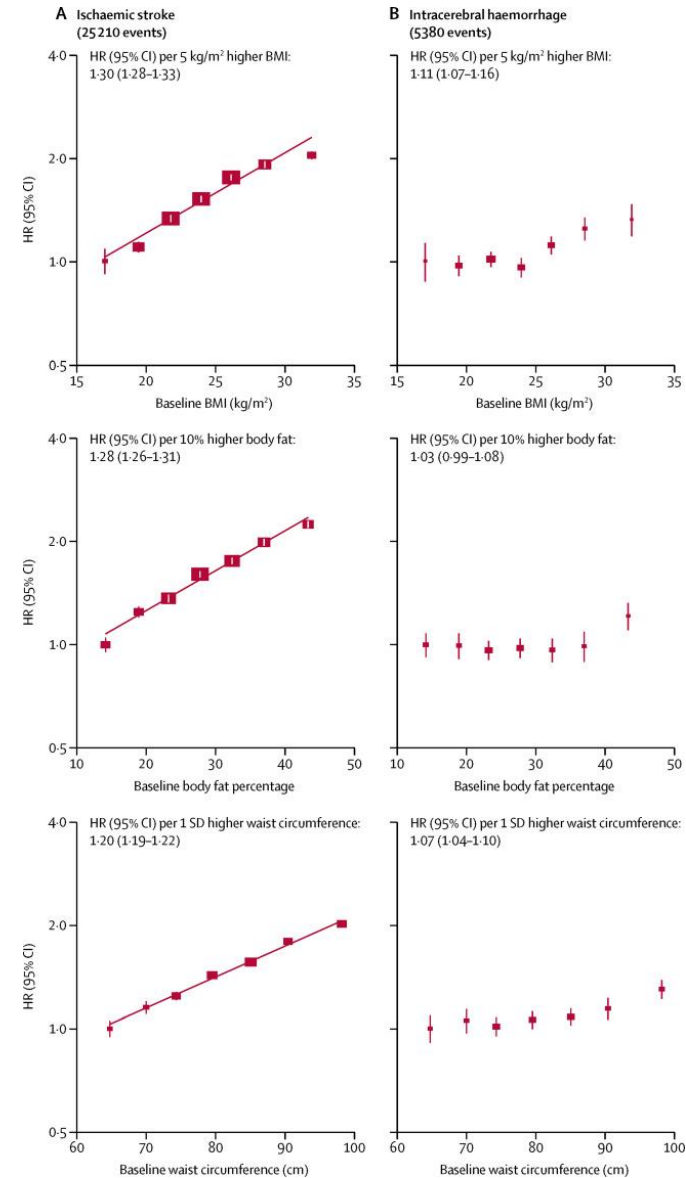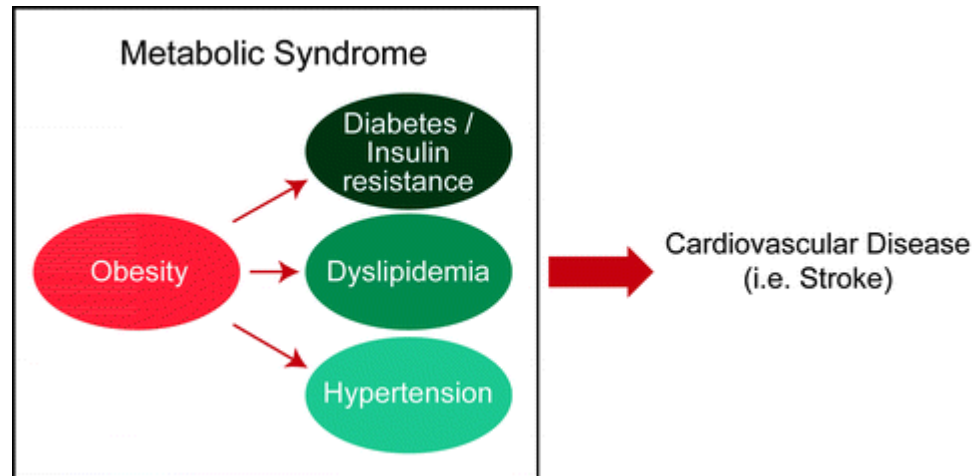# Cutting edge treatment of complications of obesity; Cutting edge treatment of stroke

Asan Medical Center, University of Ulsan
Stroke center
Department of Neurology
Bum Joon Kim MD

Obesity

- Associated with stroke risk
  - BMI < **Central obesity**
  - Elder population < **Middle age**
  - Both Ischemic and hemorrhagic stroke

Lancet Glob Health 2018; 6: e630–40

Weight loss and stroke

Weight Loss After Stroke

A Population-Based Study From the Lund Stroke Register

Ann-Cathrin Jönsson, **Ingrid Lindgren**, **Bo Norrving** and **Arne Lindgren**

Other version(s) of this article ∨

Abstract

Background and Purpose— Data on the prevalence and indicators of weight loss in population-based groups of stroke survivors are scarce. We aimed to find the predictors and indicators of weight loss >3 kg as a possible marker of malnutrition after stroke.

Methods— We registered weight at baseline, after 4 months, and 1 year later in 305 survivors from a population-based cohort of first-ever stroke patients. Characteristics of the patients were registered at baseline and follow-ups, including glycosylated hemoglobin at baseline and follow-up II, eating difficulties at both follow-ups, and screening for depression at follow-up II. We used univariate and multivariate analyses to find baseline predictors and follow-up indicators related to weight loss >3 kg from baseline.

Results— Among the 305 patients, 60% were male, the mean age was 72.5 years, and mean body mass index was 25.8 kg/m^2. The main stroke types were cerebral infarction (89%), intracerebral hemorrhage (7%), and subarachnoid hemorrhage (4%). Weight loss >3 kg was found in 74 (24%) patients (mean, −6.6 kg) after 4 months and in 79 patients (26%; mean, −8.3 kg) 1 year later. Severe stroke and elevated glycosylated hemoglobin levels were baseline predictors of weight loss >3 kg. Indicators associated with short-term weight loss (at follow-up I) were eating difficulties, low prealbumin value, and dependence (Barthel Index), whereas indicators associated with long-term weight loss (follow-up II) were eating difficulties, hemorrhagic stroke, and low prealbumin value.

Conclusions— Weight loss >3 kg after stroke indicates the need for closer observation regarding nutritional status. Monitoring of body weight may be useful, particularly among patients with severe stroke, eating difficulties, low prealbumin values, and impaired glucose metabolism.
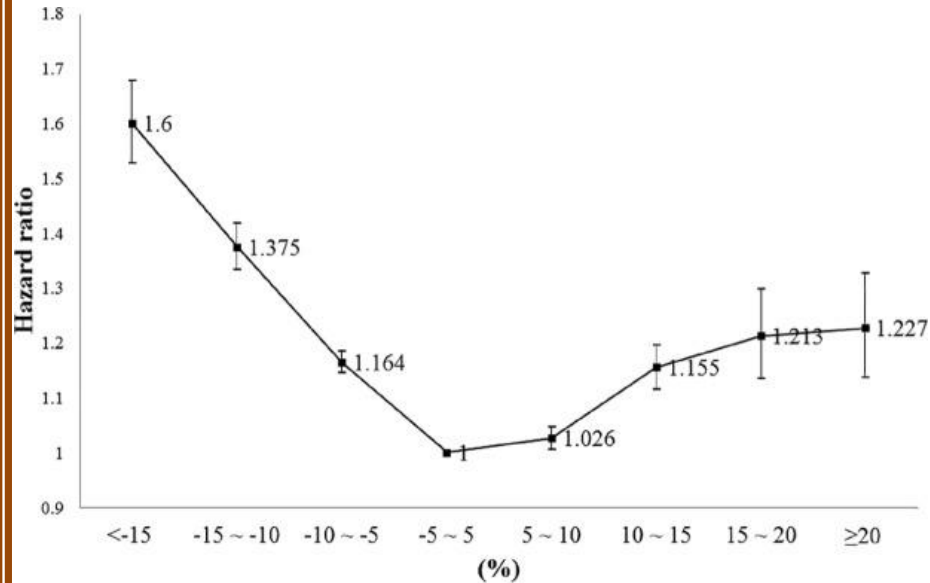
Obesity paradox

- Less mortality in those with obesity after stroke

  - Obese stroke patients, compared with low or normal weight patients, may experience
    - 1) **stroke subtypes associated with lower recurrence risk** or

    - 2) receive more aggressive therapy

    - 3) survival bias; obese patients who have survived until their event may be somehow healthier individuals

Obesity and SVO

Visceral fat accumulation is associated with cerebral small vessel disease

K Yamashiro [1], R Tanaka, Y Tanaka, N Miyamoto, Y Shimada, Y Ueno, T Urabe, N Hattori

Affiliations + expand

Abstract

Background and purpose: Obesity is associated with the risk of coronary artery disease and stroke. Visceral fat plays a significant role in the atherogenic effects of obesity. Whether visceral fat accumulation, as measured by computed tomography (CT), is an independent risk factor for the presence of cerebral small vessel disease (SVD) was investigated.

Methods: This study comprised 506 Japanese subjects 35-74 years of age (mean 55.3 years) without a history of symptomatic cerebrovascular disease who underwent health screening tests, including brain magnetic resonance imaging, carotid echography and measurements of the visceral fat area (VFA) and subcutaneous fat area (SFA) on abdominal CT. Visceral fat accumulation was defined as VFA ≥ 100 cm(2) . Logistic regression analysis was performed to examine the associations between visceral fat accumulation and cerebral SVD such as white matter lesions (WMLs) and silent lacunar infarction (SLI).

Results: The prevalence of WMLs and SLI but not carotid plaque were significantly higher in subjects with VFA ≥ 100 cm(2) than those with VFA < 100 cm(2) . A VFA ≥ 100 cm(2) was associated with WMLs and SLI independent of age, cardiovascular risk factors and other measurements of obesity, such as waist circumference and body mass index. A large waist circumference was independently associated with SLI. SFA, the combination of VFA and SFA, and body mass index were not associated with WMLs or SLI.

Conclusions: Visceral fat accumulation was independently associated with the presence of cerebral SVD in subjects without a history of symptomatic cerebrovascular disease.

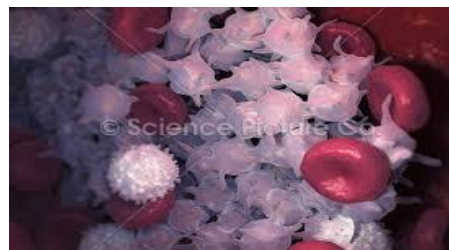### Table 3. Association of Obesity and IR With Incident Lacunes, by Size

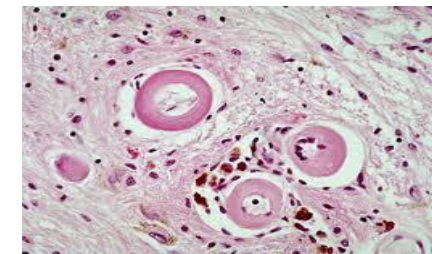|	Incident Lacunes, 3–7 mm		Incident Lacunes, >7 to 20 mm	
	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval
Insulin*	1.13	0.89–1.42	1.16	0.89–1.51
HOMA-IR*	1.19	0.96–1.46	1.23	0.97–1.55
Body mass index*	1.00	0.75–1.33	1.18	0.87—1.58
Waist circumference*	1.07	0.82–1.41	1.34	1.00–1.81
Waist:hip ratio*	1.33	1.00–1.80	1.43	1.02–2.00
Triglycerides*	1.32	1.09–1.60	1.21	0.97–1.50
High-density lipoprotein*	0.73	0.53–1.02	0.67	0.45–1.00
Systolic blood pressure*†	1.22	0.94–1.60	1.28	0.96–1.71
MetS†	1.85	1.09–3.14	3.34	1.78–6.30
IR score*†	1.34	1.01–1.79	1.62	1.16–2.25

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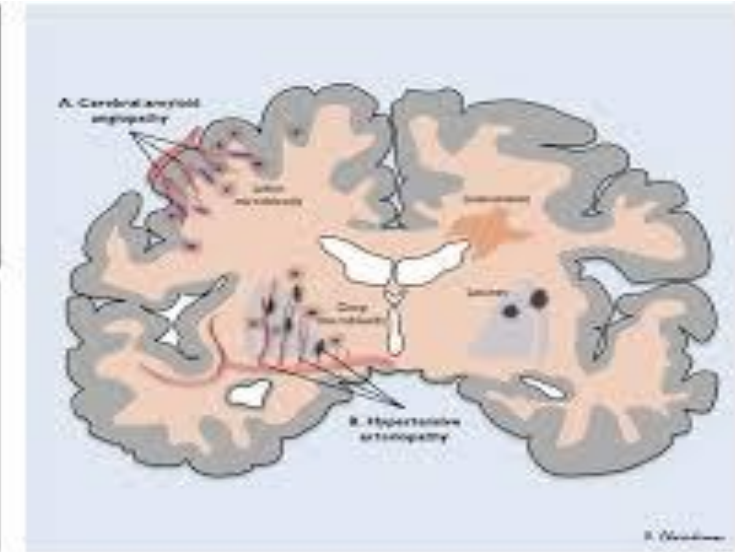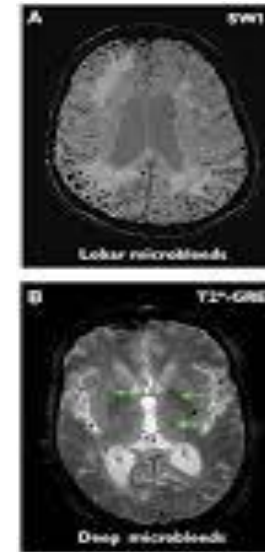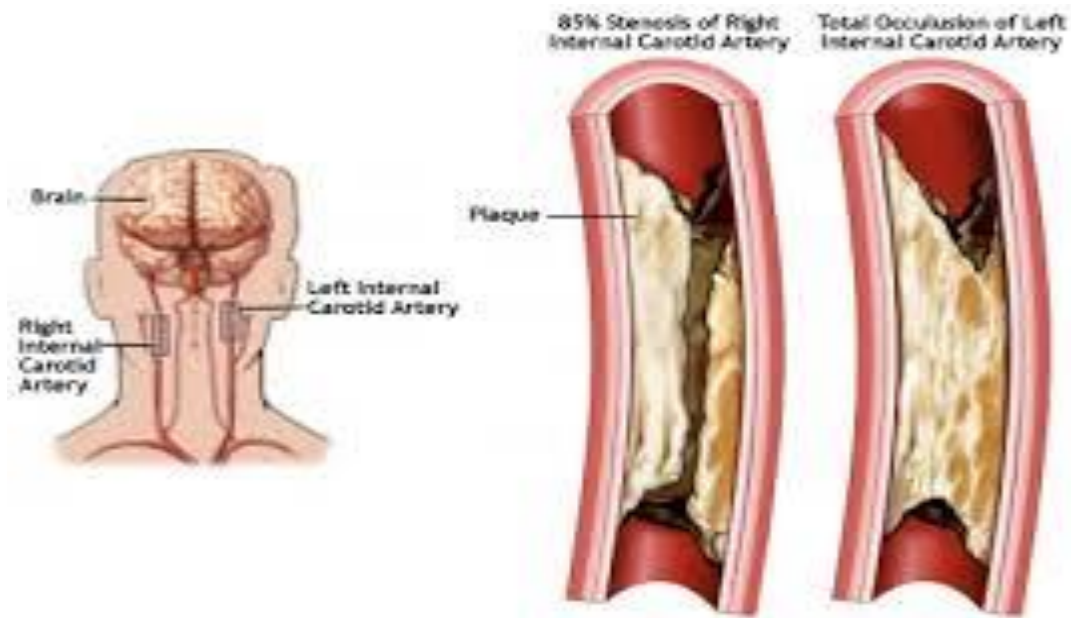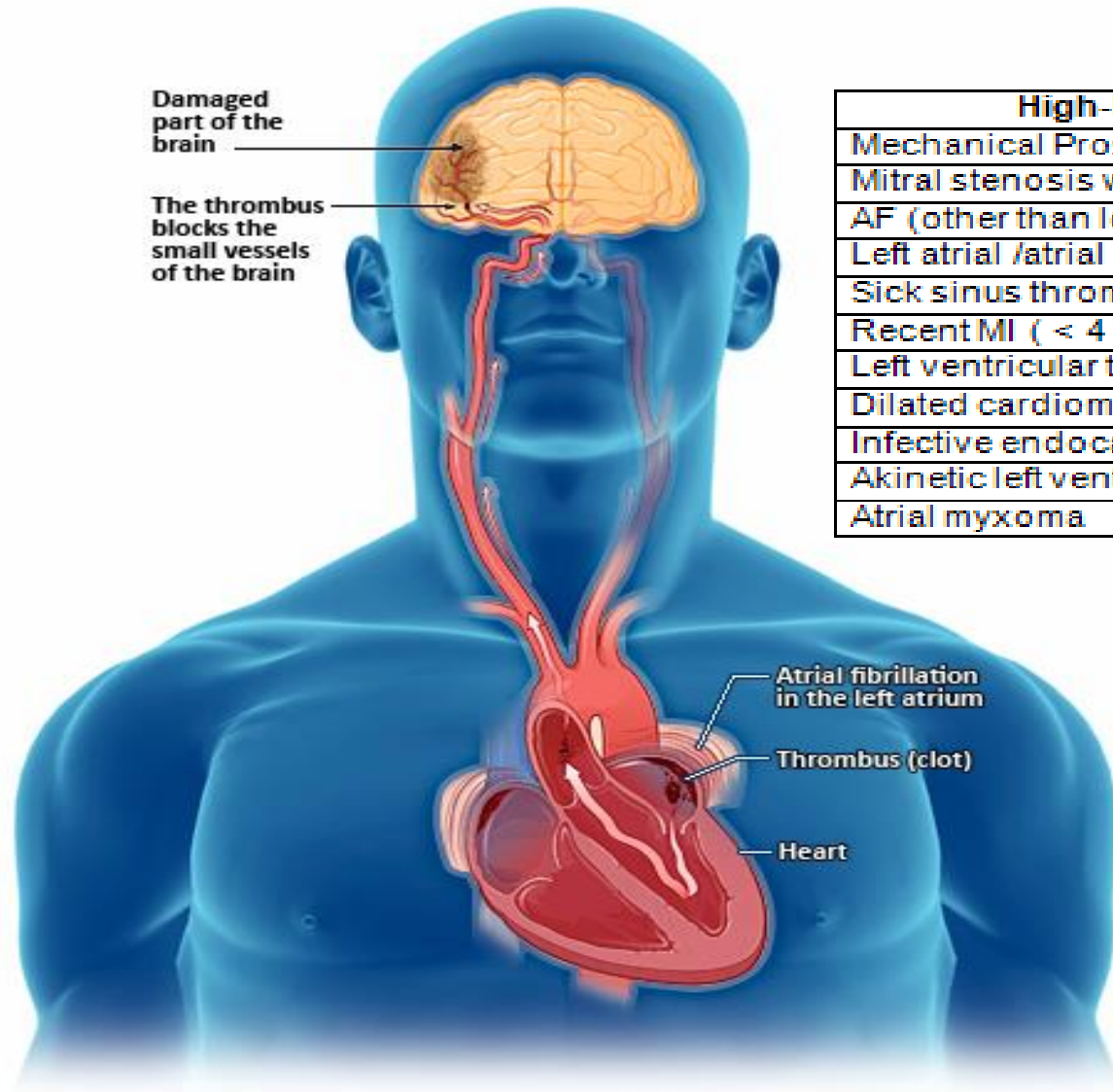
Large artery atherosclerosis
- artery to artery embolization
- in situ thrombosis
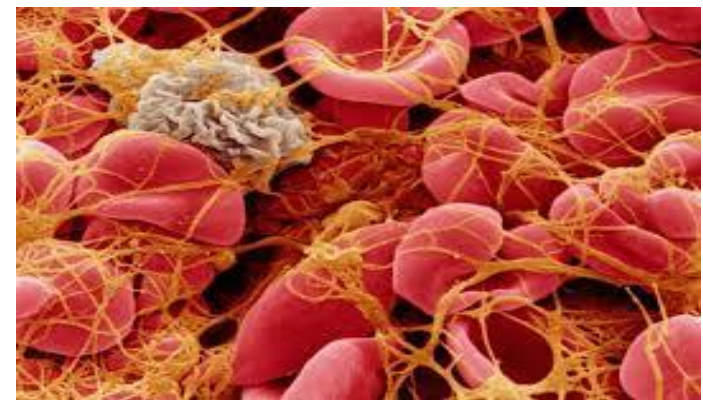- hemodynamic
- local branch occlusion

Small artery occlusion
- lipohyalinosis
- microatheroma
- branch atheromatous disease

Damaged part of the brain

The thrombus blocks the small vessels of the brain

Atrial fibrillation in the left atrium

Thrombus (clot)

Heart

High-Risk Sources	Medium-Risk Sources
Mechanical Prosthetic valve	Mitral valve prolapse
Mitral stenosis with AF	Mitral annulus calcification
AF (other than lone AF)	Mitral stenosis without AF
Left atrial /atrial appendage thrombus	Left atrial turbulence (smoke)
Sick sinus thrombus	Atrial septal aneurysm
Recent MI (< 4 weeks)	Patent foramen ovale
Left ventricular thrombus	Atrial flutter
Dilated cardiomyopathy	Lone AF
Infective endocarditis	Bioprosthetic cardiac valve
Akinetic left ventricular segment	Nonbacterial thrombotic endocarditis
Atrial myxoma	MI (> 4 weeks and 6 < weeks)

- IV thrombolysis

Administration of t-PA to a stroke patient (intravenous injection)

tPA for Stroke
THE STORY OF A CONTROVERSIAL DRUG
Justin A. Zivin, M.D., Ph.D.
John Galbraith Simmons

1. Blood clot formation
2. tPA injected intravenously
t-PA
3. Blood clots dissolving
4. Restored blood flow

mRS: NINDS rt-PA

	0-1	2-3	4-5	Death
Treatment	39	21	23	17
Control	26	25	27	21

Percentage of Patients
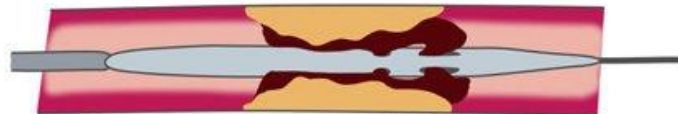
- Endovascular treatment

Thrombectomy

Catheter aspiration thrombectomy

Blood clot is removed using suction

Mechanical thrombectomy

Blood clot is broken up into small pieces and removed

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But may differ in secondary stroke prevention

- Antiplatelet agents

- Acute stage

CHANCE
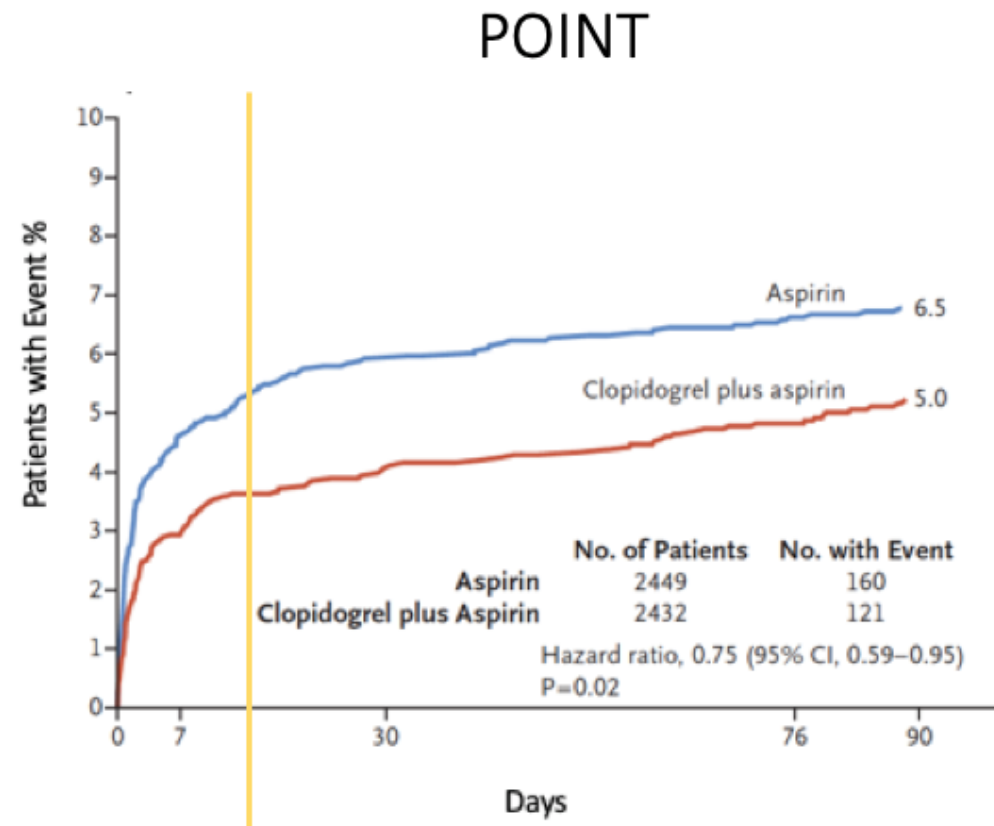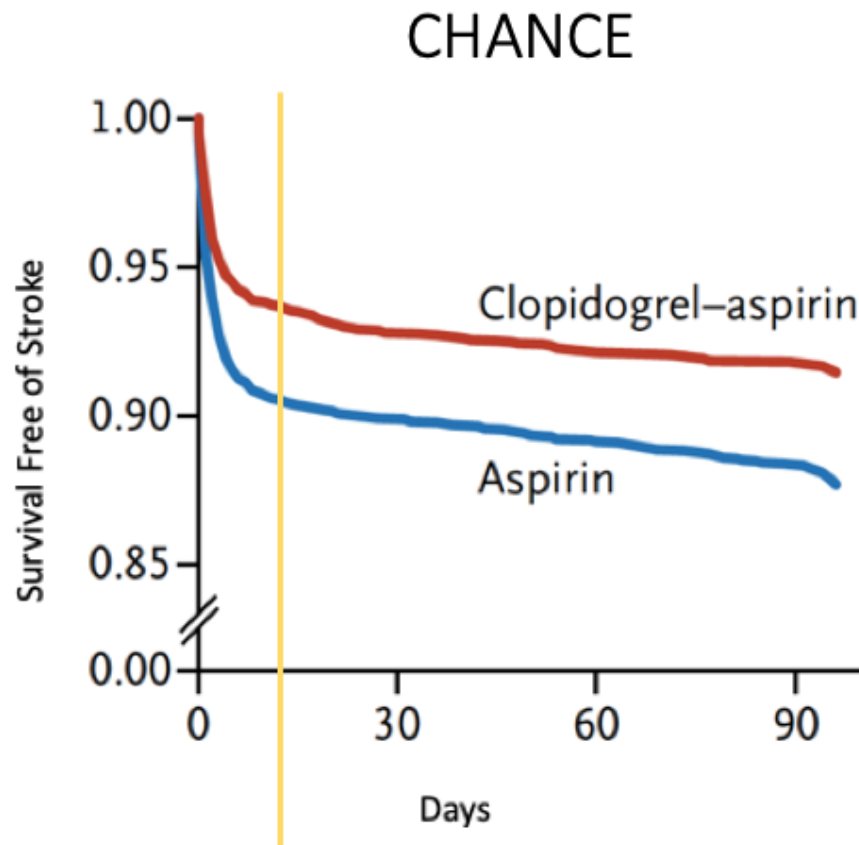
POINT

Antiplatelet agent for secondary prevention

Table 4. Composite and Individual Primary and Secondary End Points.

End Point	Clopidogrel plus Aspirin (N=7802)	Placebo plus Aspirin (N=7801)	Relative Risk (95% CI)*	P Value
	no. (%)			
Efficacy end points				
Primary efficacy end point	534 (6.8)	573 (7.3)	0.93 (0.83–1.05)	0.22
Death from any cause	371 (4.8)	374 (4.8)	0.99 (0.86–1.14)	0.90
Death from cardiovascular causes	238 (3.1)	229 (2.9)	1.04 (0.87–1.25)	0.68
Myocardial infarction (nonfatal)	146 (1.9)	155 (2.0)	0.94 (0.75–1.18)	0.59
Ischemic stroke (nonfatal)	132 (1.7)	163 (2.1)	0.81 (0.64–1.02)	0.07
Stroke (nonfatal)	150 (1.9)	189 (2.4)	0.79 (0.64–0.98)	0.03
Secondary efficacy end point†	1301 (16.7)	1395 (17.9)	0.92 (0.86–0.995)	0.04
Hospitalization for unstable angina, transient ischemic attack, or revascularization	866 (11.1)	957 (12.3)	0.90 (0.82–0.98)	0.02
Safety end points				
Severe bleeding	130 (1.7)	104 (1.3)	1.25 (0.97–1.61)	0.09
Fatal bleeding	26 (0.3)	17 (0.2)	1.53 (0.83–2.82)	0.17
Primary intracranial hemorrhage	26 (0.3)	27 (0.3)	0.96 (0.56–1.65)	0.89
Moderate bleeding	164 (2.1)	101 (1.3)	1.62 (1.27–2.08)	<0.001

* CI denotes confidence interval.
† The secondary efficacy end point was the first occurrence of myocardial infarction, stroke, death from cardiovascular causes, or hospitalization for unstable angina, a transient ischemic attack, or a revascularization procedure (coronary, cerebral, or peripheral).

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SPS3

Ischemic Stroke

AP Group
1: Aspirin + Clopidogrel
2: Aspirin + Placebo

- Aspirin = 125 (2.4 %/yr)
- Aspirin + Clopidogrel = 105 (2.1 %/yr)

HR: 0.85 (0.66, 1.1). p value: 0.21

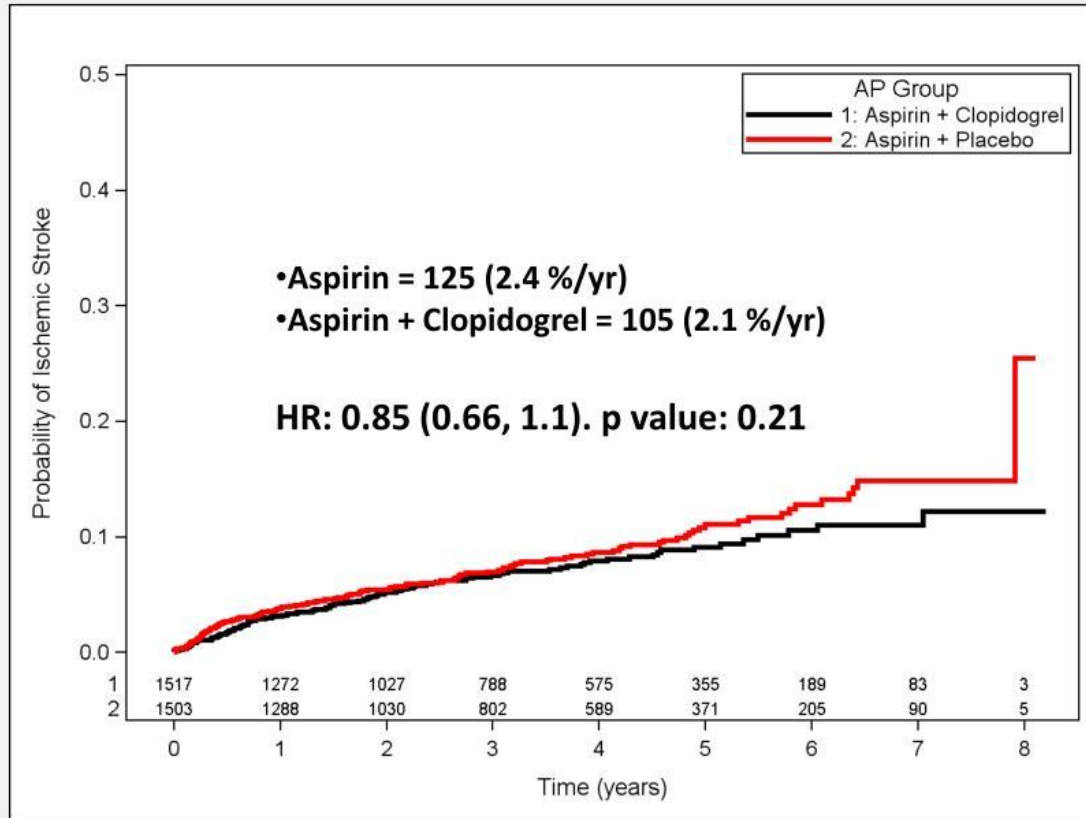| | 1517 | 1272 | 1027 | 788 | 575 | 355 | 189 | 83 | 3 |
| | 1503 | 1288 | 1030 | 802 | 589 | 371 | 205 | 90 | 5 |

Table 3. Safety Outcomes.*

Outcome	Aspirin plus Placebo (N=1503)		Aspirin plus Clopidogrel (N=1517)		Hazard Ratio (95% CI)	P Value
	no.	rate (%/yr)	no.	rate (%/yr)		
All major hemorrhages	56	1.1	105	2.1	1.97 (1.41–2.71)	<0.001
Intracranial hemorrhages†	15*	0.28	22	0.42	1.52 (0.79–2.93)	0.21
Intracerebral	8	0.15	15	0.28	1.92 (0.82–4.54)	0.14
Subdural or epidural	6	0.11	7	0.13	1.23 (0.41–3.64)	0.72
Other	4	0.07	2	0.04	0.53 (0.10–2.89)	0.46
Extracranial bleeding	42	0.79	87	1.7	2.15 (1.49–3.11)	<0.001
Gastrointestinal‡	28	0.52	58	1.1	2.14 (1.36–3.36)	<0.001
Fatal hemorrhages	4	0.07	9	0.17	2.29 (0.70–7.42)	0.17
Intracranial	4	0.07	7	0.13	1.78 (0.52–6.07)	0.36
Extracranial	0	0	2	0.04	—	—

* A time-to-first-event model was used for each outcome category; rates are annualized. All adjudications were performed centrally by the SPS3 adjudication committee. CI denotes confidence interval.
† In the group taking aspirin plus placebo, two events were adjudicated as both intracerebral and other, and one event was adjudicated as both intracerebral and subdural. In the group taking aspirin plus clopidogrel, one event was adjudicated as both intracerebral and other, and one event was adjudicated as both intracerebral and subdural.
‡ The site of bleeding was determined by an investigator at the local study center.

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Prevention of cardiovascular events in Asian patients with ischaemic stroke at high risk of cerebral haemorrhage (PICASSO): a multicentre, randomised controlled trial

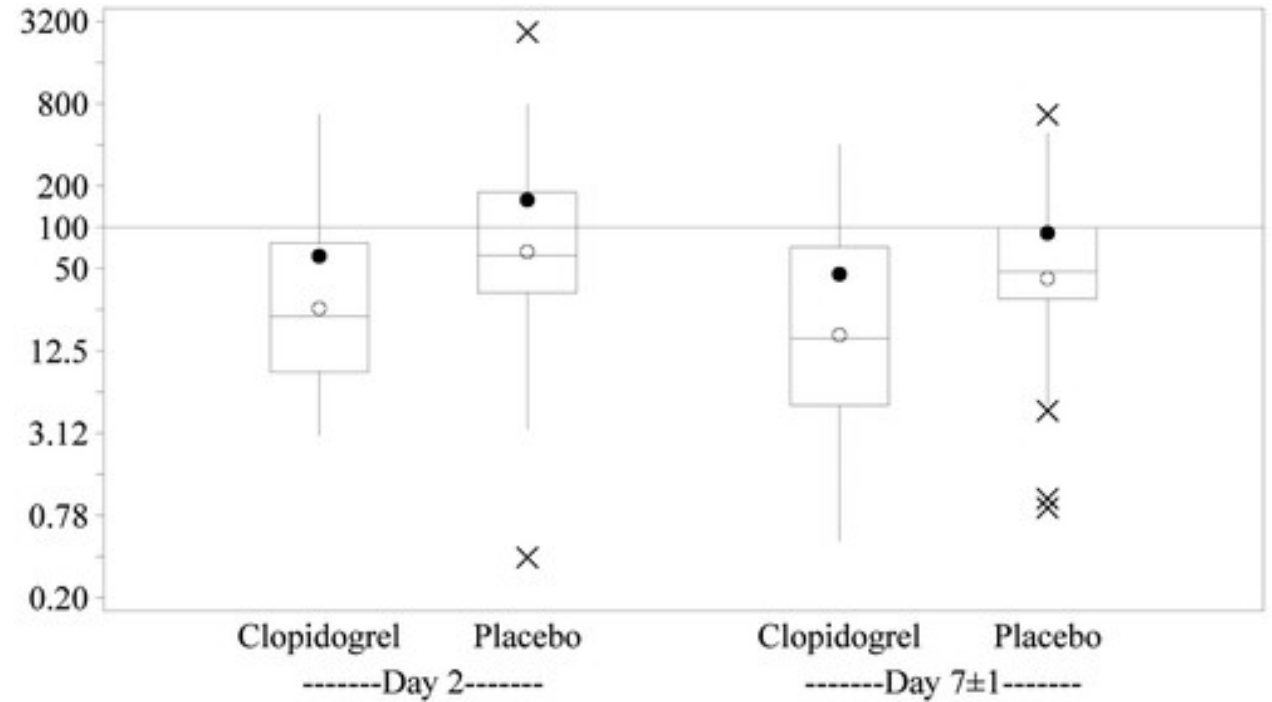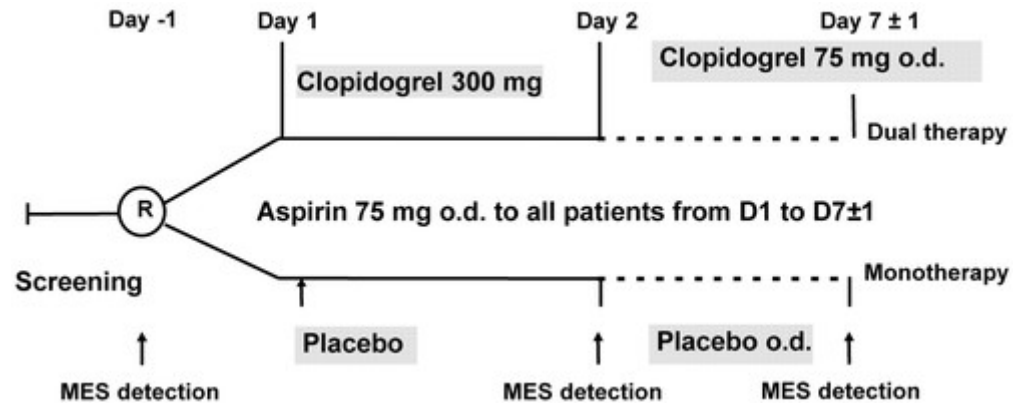Bum Joon Kim, MD [*] • Eun-Jae Lee, MD [*] • Prof Sun U Kwon, MD �✉ • Jong-Ho Park, MD • Prof Yong-Jae Kim, MD • Prof Keun-Sik Hong, MD • et al.   Show all authors • Show footnotes
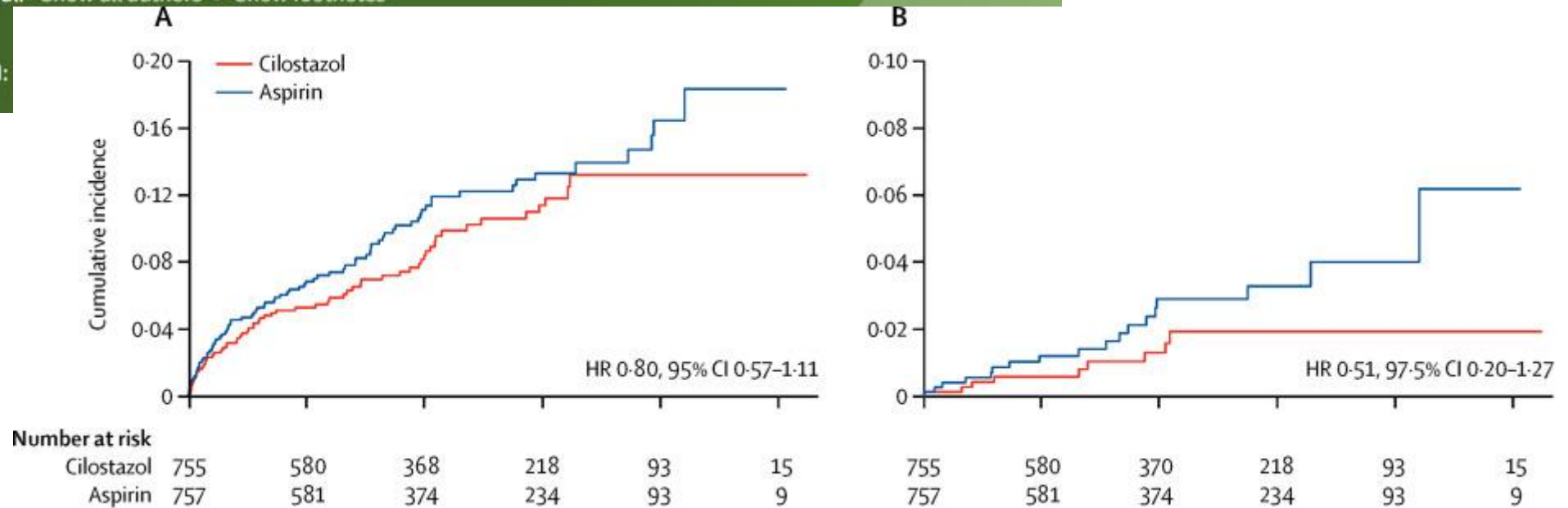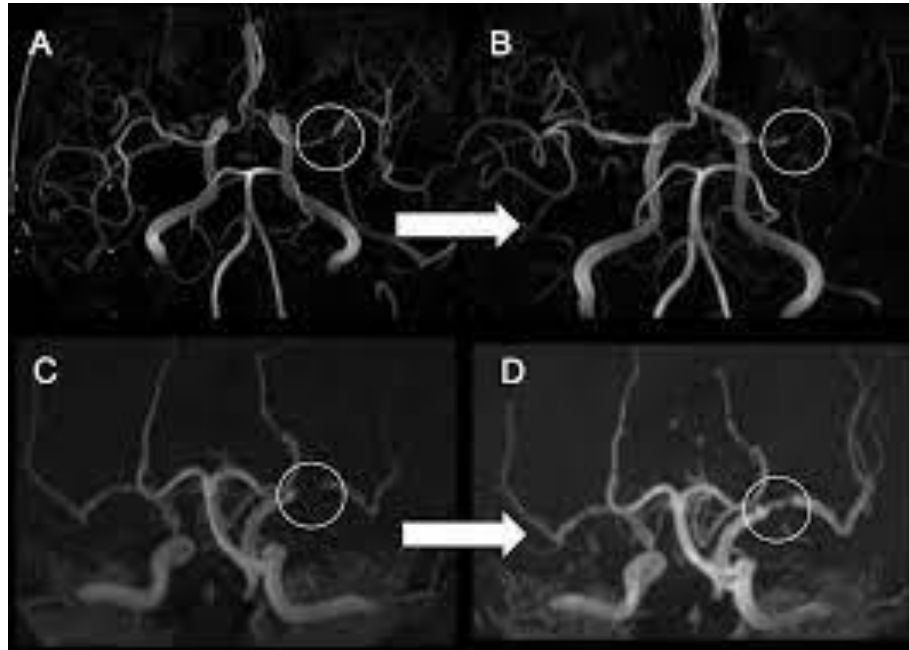
Large artery atherosclerosis

- ECAS – carotid disease (CARESS study)

Stroke Mechanisms Associated With Each Symptomatic Vessel (n=925*)

	Artery-to-Artery Embolism	In Situ Thrombo-occlusion	Local Branch Occlusion	Hemodynamic Impairment	Mixed	Total
ACA	20 (39.2)	24 (47.1)	1 (2.0)	0	6 (11.7)	51
MCA	172 (50.6)	67 (19.7)	53 (15.6)	3 (0.9)	45 (13.2)	340
Distal ICA	43 (69.4)	5 (8.1)	1 (1.6)	2 (3.2)	11 (17.7)	62
PCA	21 (36.8)	16 (28.1)	13 (22.8)	0	7 (12.3)	57
BA	14 (16.9)	6 (7.2)	53 (63.9)	0	10 (12.0)	83
Distal VA	34 (53.1)	7 (10.9)	17 (26.6)	0	6 (9.4)	64
Proximal ICA	214 (92.6)	2 (0.9)	0	3 (1.3)	12 (5.2)	231
Proximal VA	34 (91.9)	0	0	0	3 (8.1)	37
ICAS	304 (46.3)	125 (19.0)	138 (21.0)	5 (0.8)	85 (12.9)	657
ECAS	248 (92.5)	2 (0.7)	0	3 (1.1)	15 (5.6)	268
Anterior	449 (65.5)	98 (14.3)	56 (8.2)	8 (1.2)	74 (10.8)	685
Posterior	103 (42.9)	29 (12.1)	82 (34.2)	0	26 (10.8)	240
Anterior ICAS	235 (51.8)	96 (21.1)	56 (12.3)	5 (1.1)	62 (13.7)	454
Posterior ICAS	69 (34.0)	29 (14.3)	82 (40.4)	0	23 (11.3)	203

- ICAS
  - More various pathomechanism

Stroke Mechanisms Associated With Each Symptomatic Vessel (n=925*)

	Artery-to-Artery Embolism	In Situ Thromobo-occlusion	Local Branch Occlusion	Hemodynamic Impairment	Mixed	Total
ACA	20 (39.2)	24 (47.1)	1 (2.0)	0	6 (11.7)	51
MCA	172 (50.6)	67 (19.7)	53 (15.6)	3 (0.9)	45 (13.2)	340
Distal ICA	43 (69.4)	5 (8.1)	1 (1.6)	2 (3.2)	11 (17.7)	62
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Anterior ICAS	235 (51.8)	96 (21.1)	56 (12.3)	5 (1.1)	62 (13.7)	454
Posterior ICAS	69 (34.0)	29 (14.3)	82 (40.4)	0	23 (11.3)	203

Overall change in the symptomatic stenosis was significantly favorable (less progression and more regression) in the cilostazol group (P0.049 by 2 trend test, post hoc analysis)
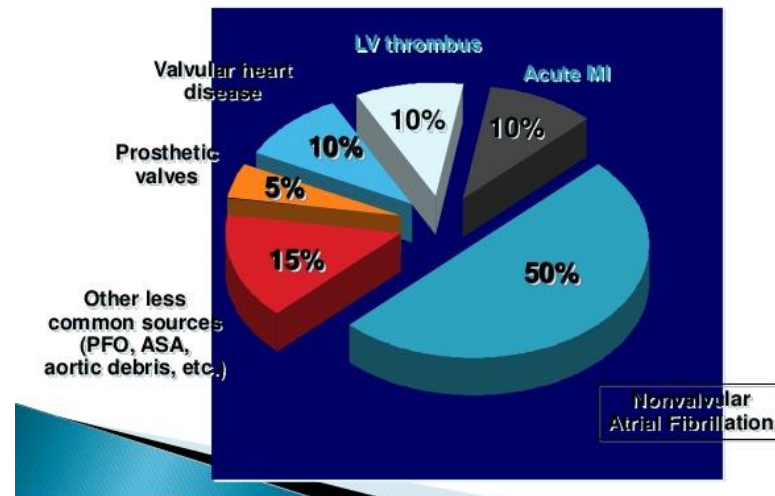
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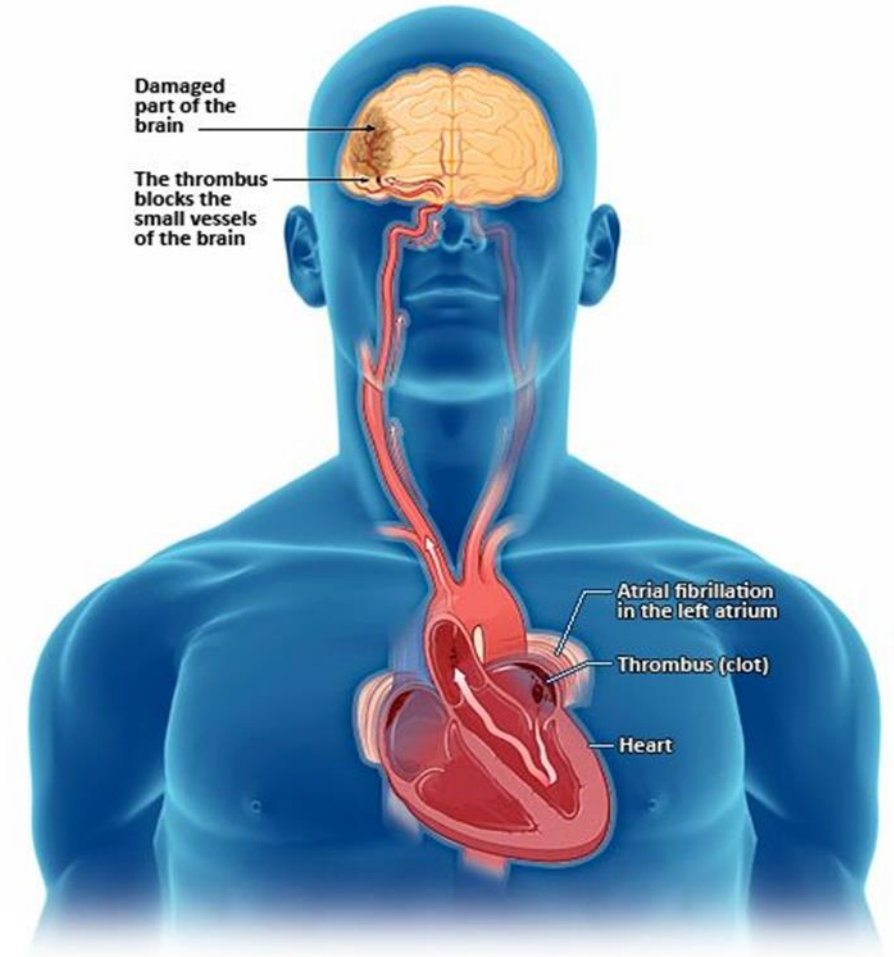
Cardioembolism

- **Cardioembolic stroke**
  - Sudden occlusion of major vessel by clot from heart
  - Large infarction, high severity
  - Poor prognosis

| High-Risk Sources	Medium-Risk Sources
Mechanical Prosthetic valve	Mitral valve prolapse
Mitral stenosis with AF	Mitral annulus calcification
AF (other than lone AF)	Mitral stenosis without AF
Left atrial /atrial appendage thrombus	Left atrial turbulence (smoke)
Sick sinus thrombus	Atrial septal aneurysm
Recent MI (< 4 weeks)	Patent foramen ovale
Left ventricular thrombus	Atrial flutter
Dilated cardiomyopathy	Lone AF
Infective endocarditis	Bioprosthetic cardiac valve
Akinetic left ventricular segment	Nonbacterial thrombotic endocarditis
Atrial myxoma	MI (> 4 weeks and 6 < weeks)

Anticoagulation

NOACs

Warfarin vs. Placebo **2,900 Patients**	NOACs vs. Warfarin **71,683 Patients**

6 Trials of Warfarin vs. Placebo 1989 - 1993

ROCKET AF (Rivaroxaban) 2010

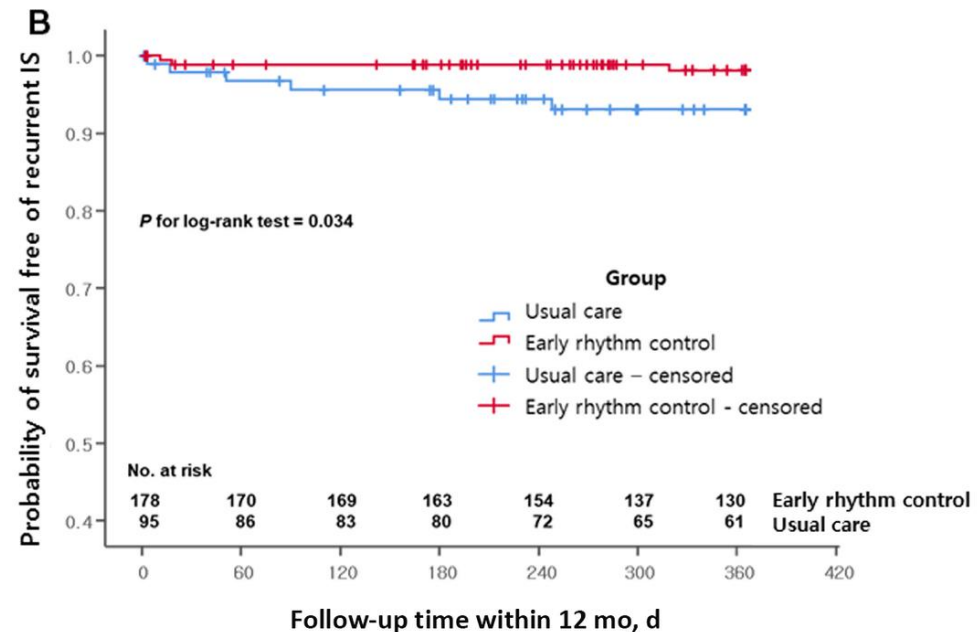**ENGAGE AF-TIMI 48 (Edoxaban) 2013**

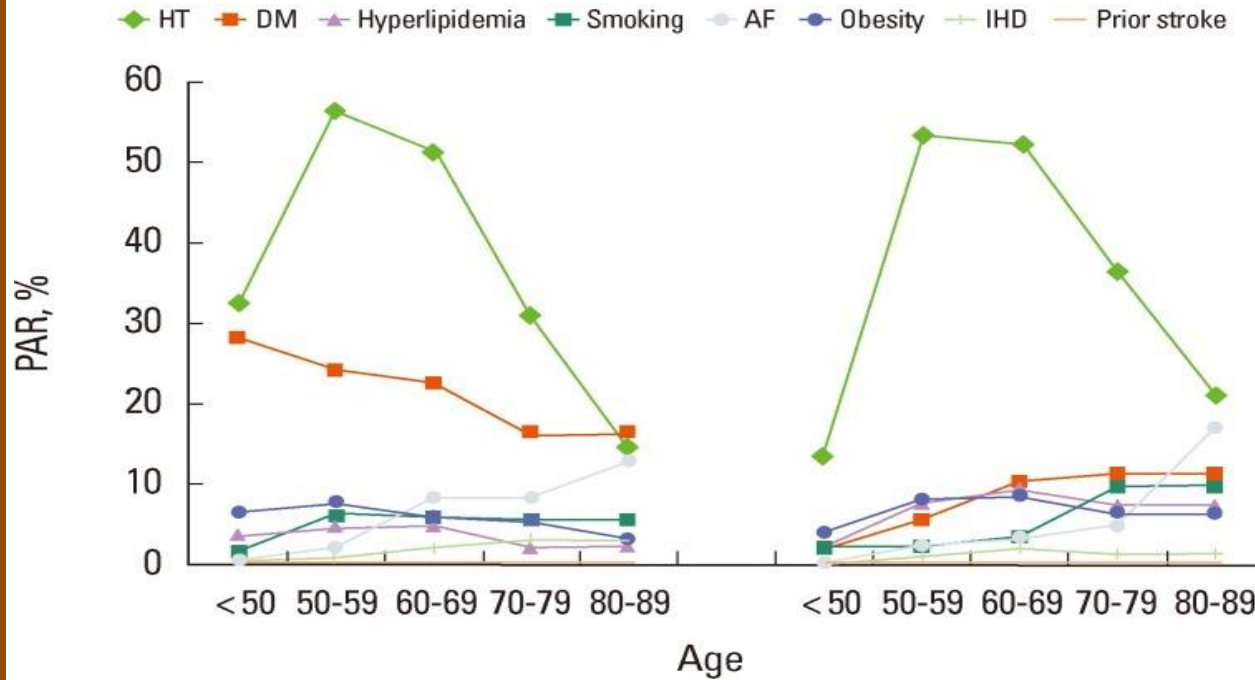**RE-LY (Dabigatran) 2009**

ARISTOTLE (Apixaban) 2011
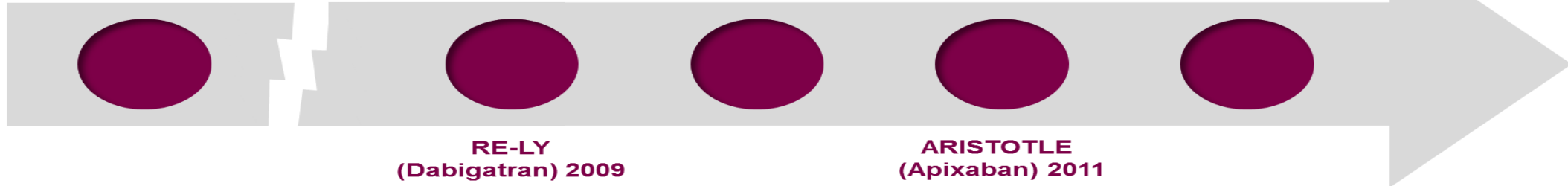
Warfarin
- needs monitoring
- interaction with food
- interaction with other medication
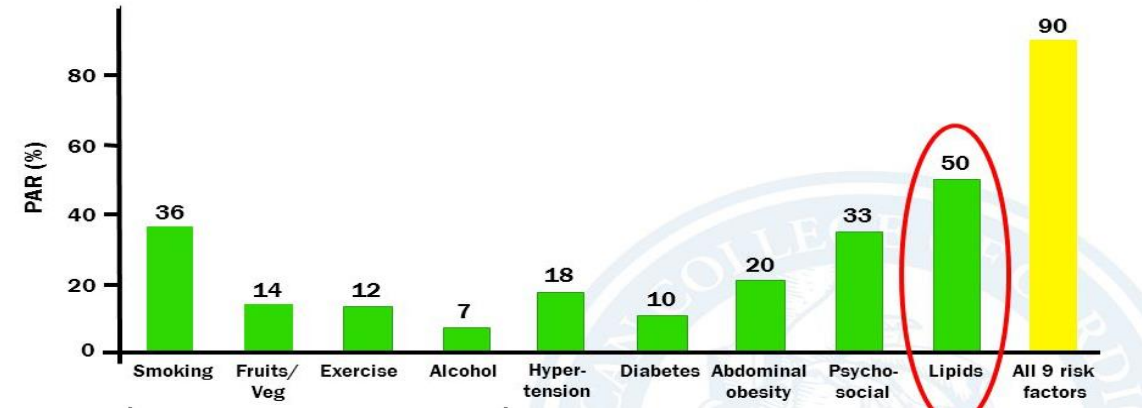- relatively high risk of bleeding

Beyond anticoagulation

B

P for log-rank test = 0.034

Probability of survival free of recurrent IS

Group
- Usual care
- Early rhythm control
- Usual care – censored
- Early rhythm control - censored

No. at risk							
178	170	169	163	154	137	130	Early rhythm control
95	86	83	80	72	65	61	Usual care

Follow-up time within 12 mo, d

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Blood pressure control


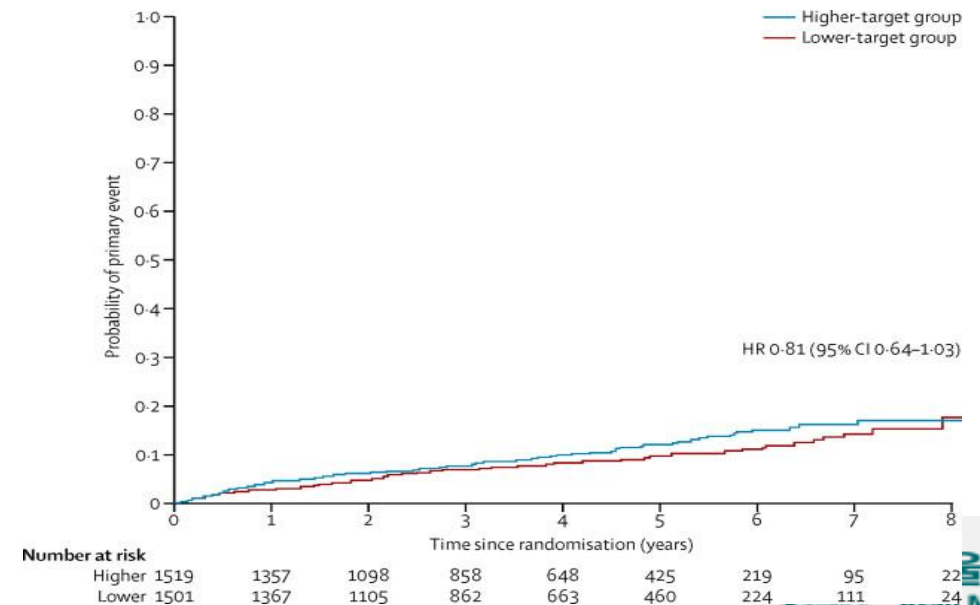PAR for ischemic stroke by sex

Population attributable risk of MI

- Hypertension is the most important population attributable risk factor in stroke patients

- Both in men and women, and in most ages.
- Up to 60 % of strokes are attributable to hypertension

- Patients with **lacunar infarction** defined by MR
- 2x2 factorial design
  - BP arm: Open label trial
  - 130-139 vs. less than 130
- **Primary endpoint**
  - Reduction in stroke
   - Ischemic and hemorrhagic

138

127
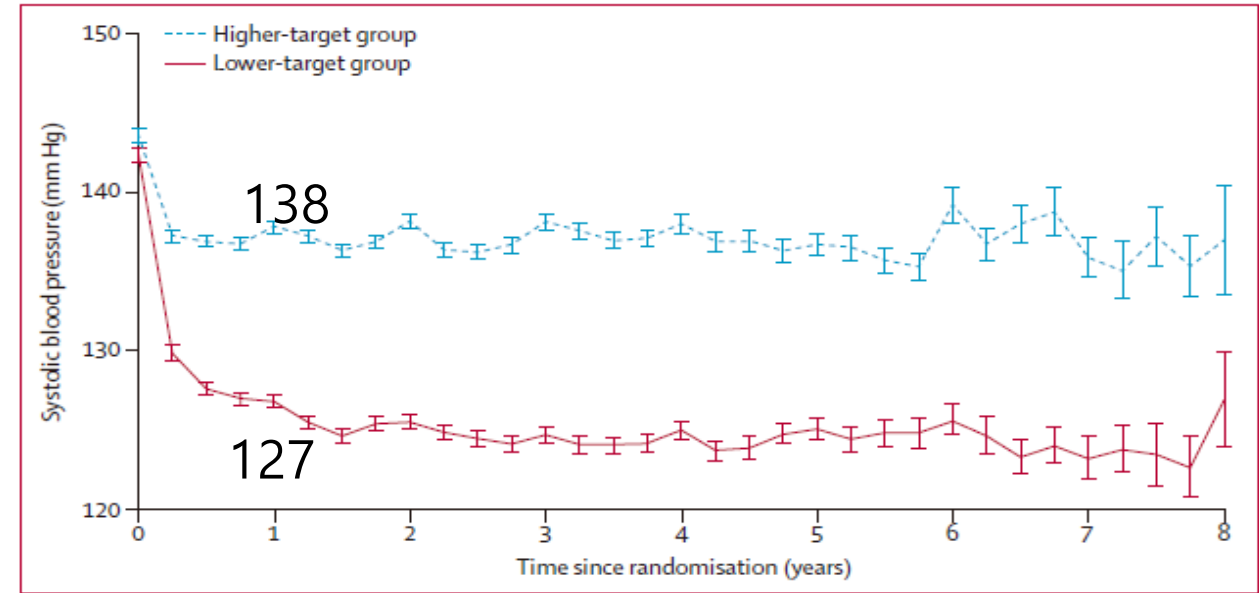
	Higher-target group (n=1519)	Lower-target group (n=1501)
Age (years)	63 (10·8)	63 (10·7)
Men	990 (65%)	912 (61%)
Blood pressure at entry (mm Hg)		
Systolic	144 (19)	142 (19)
Diastolic	79 (11)	78 (10)
Body-mass index (kg/m²)	29·2 (7·5)	29·0 (6·1)
History of hypertension	1137 (75%)	1127 (75%)
Diabetes mellitus	553 (36%)	553 (37%)
Ischaemic heart disease	173 (11%)	144 (10%)
Previous clinical stroke or TIA	211 (14%)	237 (16%)
Current tobacco smoker	308 (20%)	309 (21%)

HR 0·81 (95% CI 0·64–1·03)

Number at risk

Higher	1519	1357	1098	858	648	425	219	95	22
Lower	1501	1367	1105	862	663	460	224	111	24

울아산병원
Asan Medical Center

SPS3 trial main result

	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
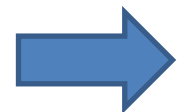
Patients with small vessel occlusion (Lacunar infarction) BP lowering under 130 reduced ICH and may be beneficial

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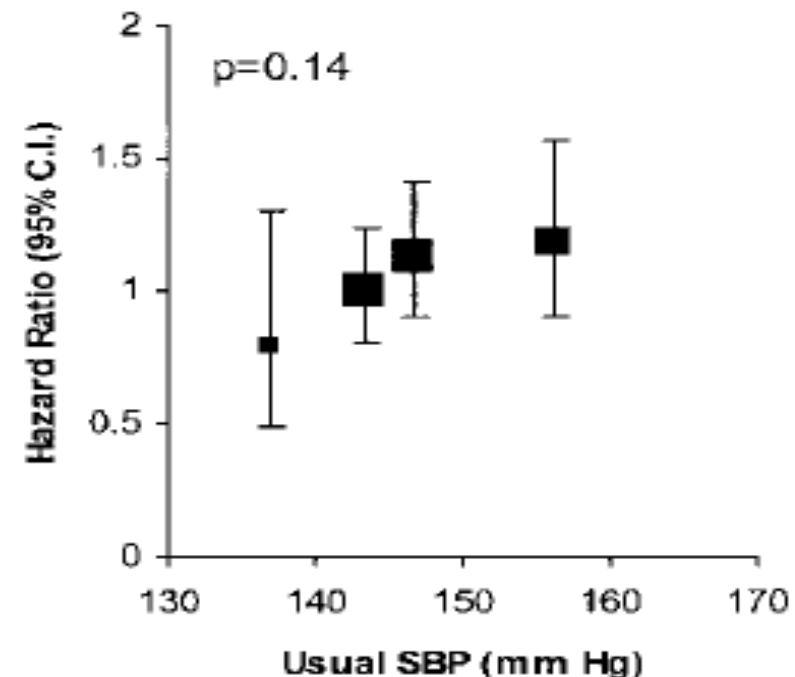
Carotid disease

(b) NASCET

p=0.02
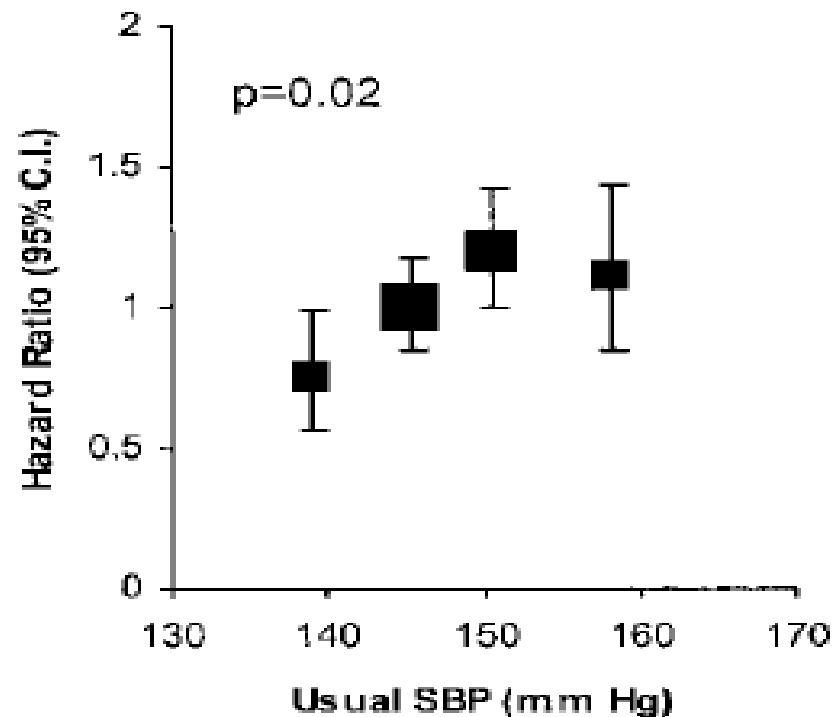
Events:	47	148	124	57
Patient-years:	1060	2428	1652	822

Degree of ipsilateral stenosis (%)

50−69%	38	39
30−49%	43	42
<30%	19	19

(c) ECST

p=0.14

Events:	16	81	78	53
Patient-years:	658	2557	2067	1310

Stenosis of symptomatic carotid artery

0–29%	240 (13%)	179 (15%)
30–49%	390 (22%)	261 (22%)
50–69%	582 (32%)	377 (31%)
70–99%	586 (32%)	389 (32%)
Occluded	9 (0·5%)	5 (0·4%)

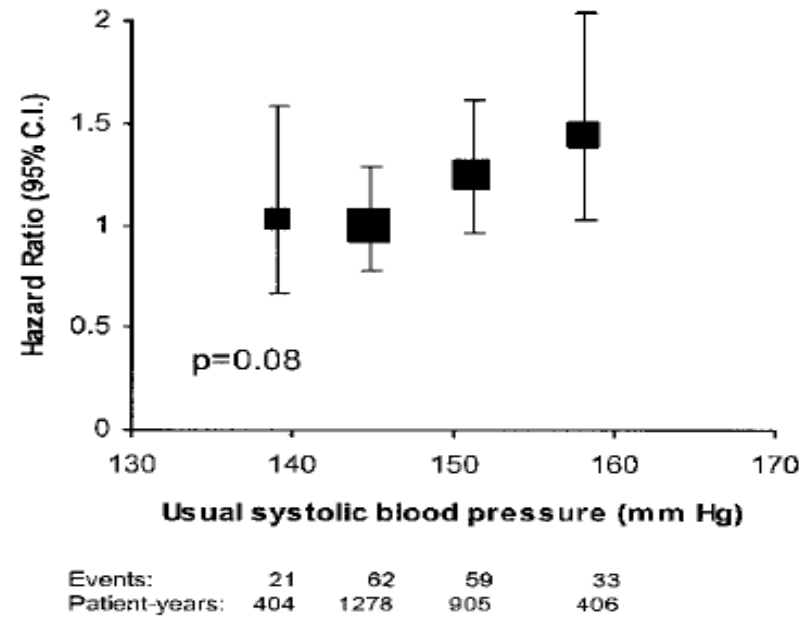Lowering BP to SBP 140 mmHg can be beneficial in those with carotid disease, But need consideration for stenosis degree

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Carotid disease

(a) Both stenoses <70%
p=0.009
Events: 32, 140, 124, 65
Patient-years: 1151, 3341, 2478, 1416

(b) One stenosis ≥70%
p=0.08
Events: 21, 62, 59, 33
Patient-years: 404, 1278, 905, 406

(c) Both stenoses ≥70%
p=0.04
Events: 5, 13, 5, 6
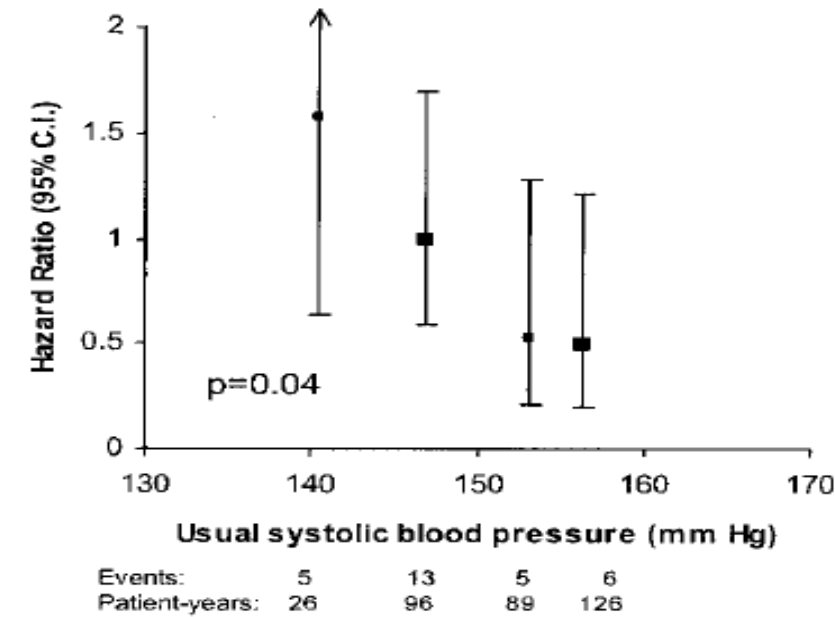Patient-years: 26, 96, 89, 126
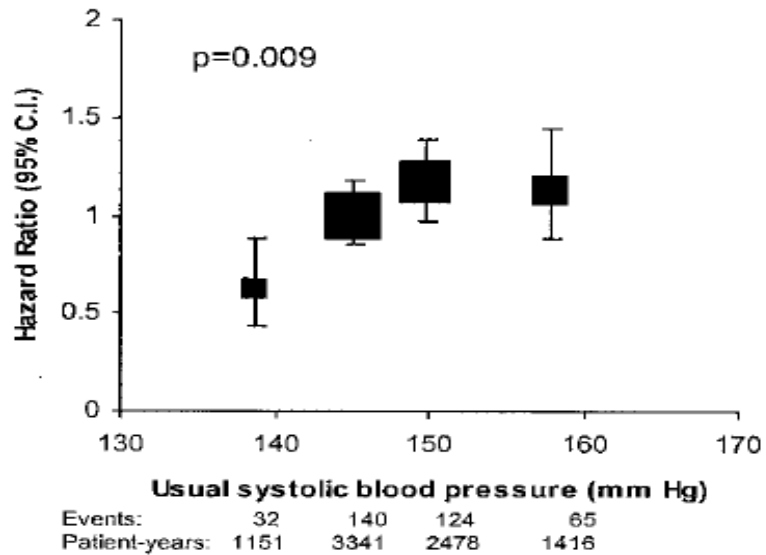
TABLE 3. HRs (95% CI) for the Risk of Stroke in Patients C to Severity of Carotid Disease Within the Prespecified Blood

Stenosis Group	SBP, mm Hg		
	<130	130–149	150–1(
Bilateral <70%	1 (0.69–1.44)	1 (0.84–1.19)	1 (0.83–1
Unilateral ≥70%	1.90 (1.24–2.89)	1.18 (0.92–1.51)	1.27 (0.99–
P	0.025	0.30	0.13
Bilateral ≥70%	5.97 (2.43–14.68)	2.54 (1.47–4.39)	0.97 (0.4–
P	<0.001	0.001	0.95

HRs are derived from a Cox proportional-hazards model, are stratified by age, sex, and previous coronary heart disease. Patients with bilateral <7
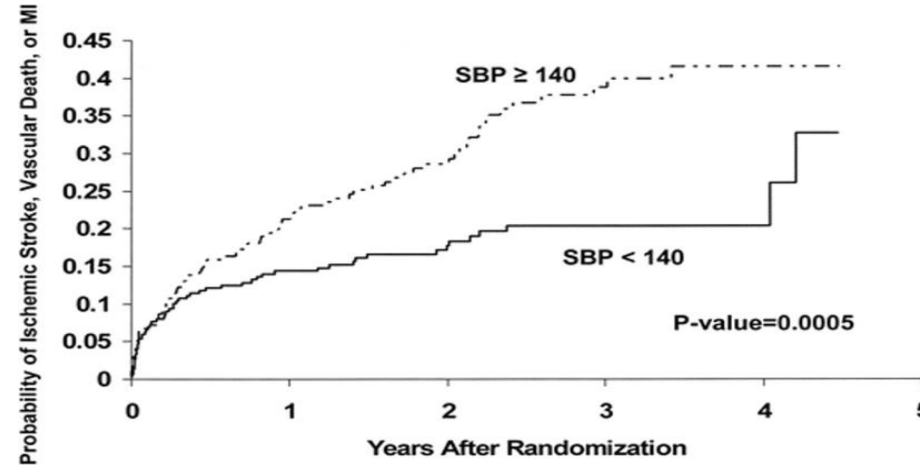
In those with Carotid stenosis less than 70%
SBP can be lowered to 140 mm Hg

In those with 70% stenosis
Unilateral: 150 mmHg
Bilateral: > 150 mmHg

Stroke. 2003;34:2583-2592
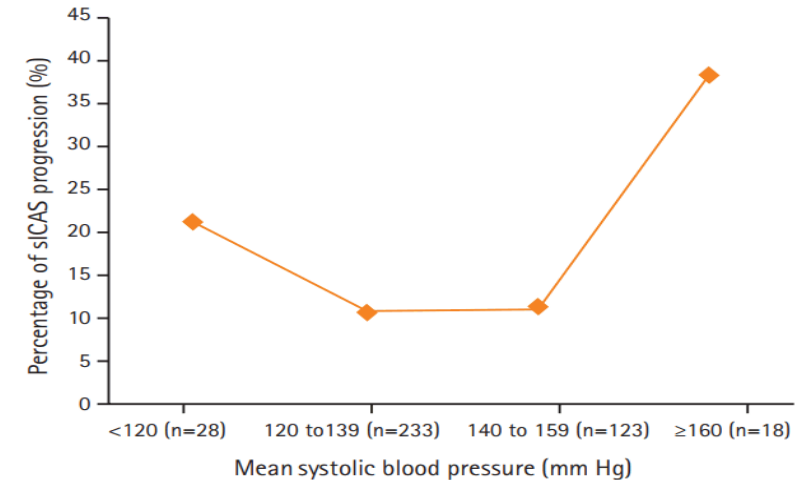
- **WASID**
  - SBP < 140 mmHg vs. SBP > 140 mmHg
  - increased risk of recurrent stroke (adjusted HR, 1.63, 95% CI 1.11–2.40) and major cardiovascular events (1.79, 1.27–2.52)
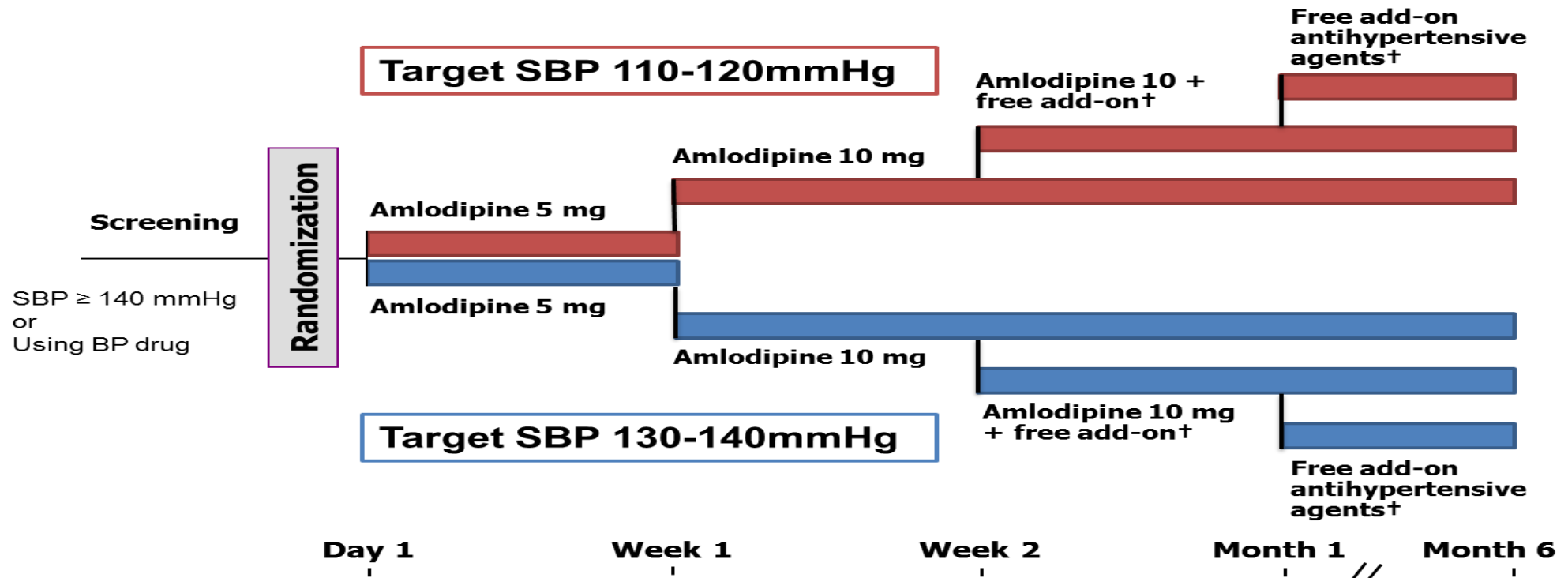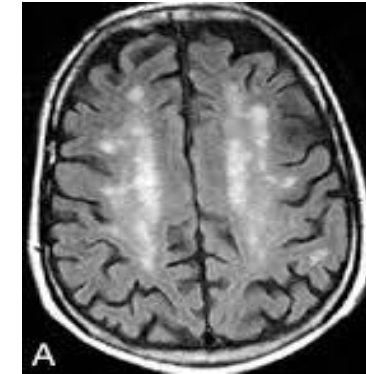

- TOSS-2

sICAS outcome	Mean SBP category (mm Hg)				P^*
	<120 (n=28)	120 to 139 (n=233)	140 to 159 (n=123)	≥160 (n=18)	
Regression	9 (32.1)	62 (26.6)	37 (30.1)	1 (5.6)	0.009
Quiescence	13 (46.4)	146 (62.7)	72 (58.5)	10 (55.6)	
Progression	6 (21.4)	25 (10.7)	14 (11.4)	7 (38.9)	

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ICAS

Target SBP 110-120mmHg

Free add-on antihypertensive agents†

Amlodipine 10 + free add-on†

Amlodipine 10 mg

Amlodipine 5 mg

Screening

SBP ≥ 140 mmHg
or
Using BP drug

Randomization

Amlodipine 5 mg

Amlodipine 10 mg

Amlodipine 10 mg + free add-on†

Free add-on antihypertensive agents†

Target SBP 130-140mmHg

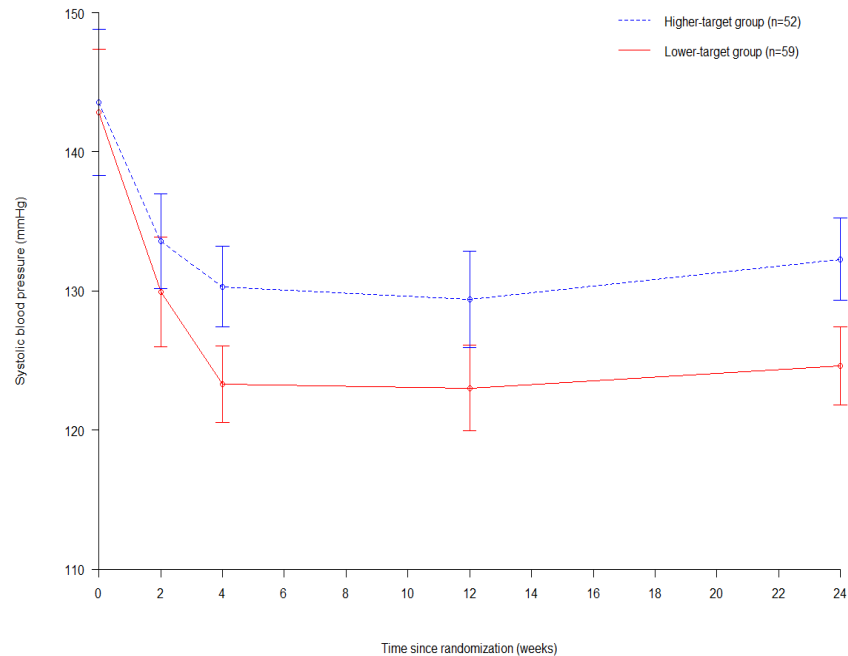**Day 1**   **Week 1**   **Week 2**   **Month 1**   **Month 6**
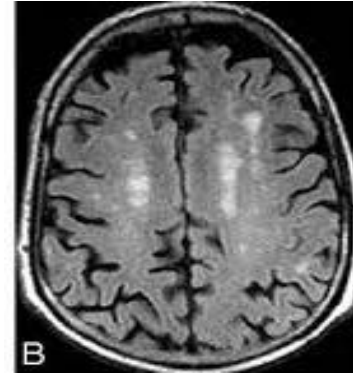
Free add-on† - ARB/ACEI, diuretics or beta blockers except CCB
* If SBP is below target range, skip or reduce BP lowering drug (amlodipine first)

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STABLE ICAS

Higher-target group (n=52)
Lower-target group (n=59)

	Aggressive BP control (n = 59)	Modest BP control (n = 52)	Difference†	P
WML volume in whole forebrain (cc)				
Screening	11.2 (24.3)	10.4 (19.4)		0.8549[a]
24 weeks	16.1 (39.3)	12.6 (20.0)		0.5445[a]
Volume change*	4.9 (18.3)	2.2 (8.2)	2.8 (14.5)	0.4658[b]
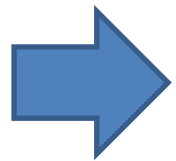
Failed to prove non-inferiority of intensive BP lowering in Stable ICAS patients.

How about BPV ? (STABLE ICAS trial)

Figure 1. Study profile.
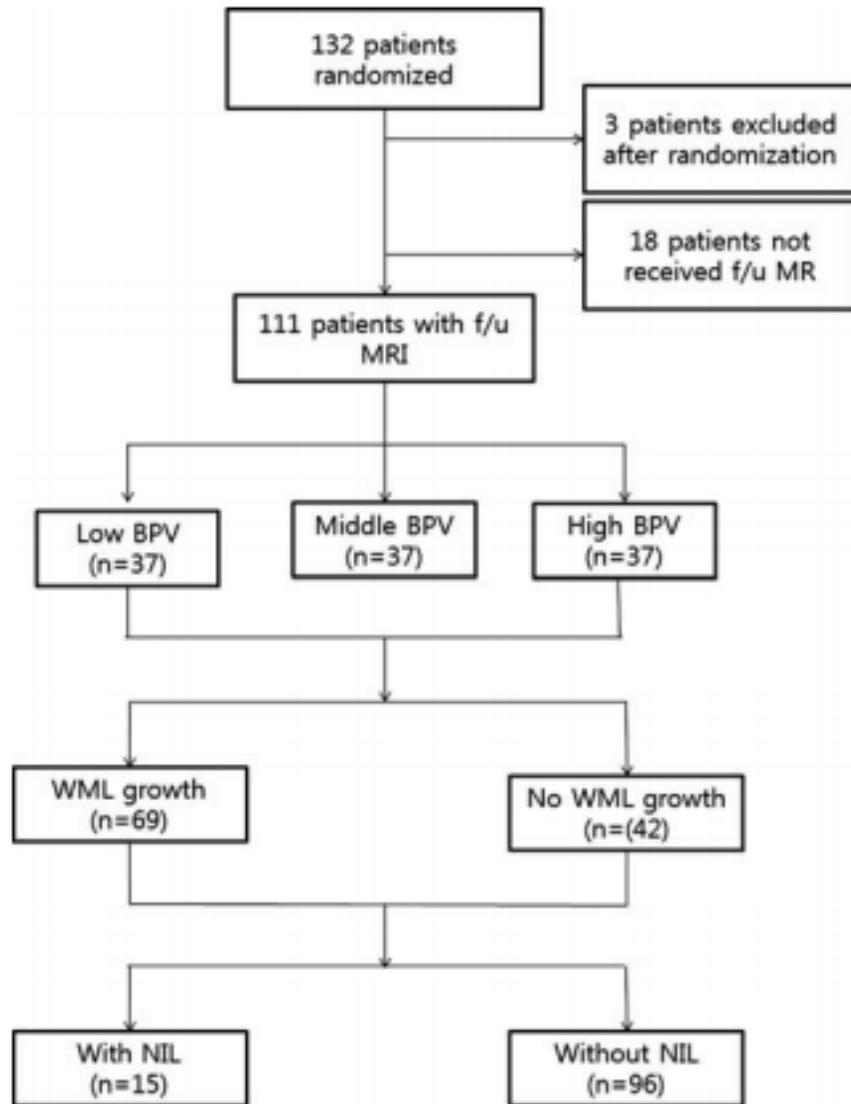
	Low BPV (n = 37)	Middle BPV (n = 37)	High BPV (n = 37)	P
Age, years	61.7 [9.9]	65.4 [8.7]	64.3 [9.4]	0.23
Male	19 (51.4)	24 (64.9)	22 (59.5)	0.48
Diabetes	14 (37.8)	16 (43.2)	19 (51.4)	0.24
Hyperlipidemia	26 (70.3)	16 (43.2)	15 (40.5)	0.01
Coronary artery disease	3 (8.1)	2 (5.4)	1 (2.7)	0.31
Smoking	15 (40.5)	19 (51.4)	21 (56.8)	0.17
Intensive BP control	16 (43.2)	21 (56.8)	22 (59.5)	0.16
Mean home BP				
Mean home SBP, mm Hg	130 [7]	134 [14]	137 [12]	0.03
Mean home DBP, mm Hg	78 [8]	78 [10]	82 [8]	0.09
BPV				
WML (whole forebrain)				
Initial WML, cm^3	6.2 [7.6]	6.9 [12.7]	19.4 [33.9]	0.03
Follow-up WNL, cm^3	7.2 [11.3]	8.2 [12.7]	28.1 [50.0]	0.02
WML growth volume, cm^3	0.9 [7.5]	1.3 [5.0]	8.6 [22.8]	0.02
WML growth	17(50)	21 (61.8)	31 (83.8)	0.001
WML growth > 10% baseline	14 (37.8)	19 (51.4)	28 (75.7)	0.001
WML (ipsilesional forebrain)				
WML growth volume, cm^3	0.9 [7.5]	1.3 [5.0]	8.6 [22.8]	0.02
WML growth	17(50)	21 (61.8)	31 (83.8)	0.001
WML (contralesion forebrain)				
WML growth volume, cm^3	0.05 [0.30]	0.03 [0.12]	0.02 [0.60]	0.732
WML growth	2 (5.4%)	6 (16.2%)	9 (24.3%)	0.024
New ischemic lesion	2 (5.4)	2 (5.4)	11 (29.7)	0.002

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- Data extraction from ASCOT and ALLHAT

Table 4 Recurrent Stroke Outcomes by BPV-SD Quartile, in the Cohorts of Patients Who Had a History of Stroke or TIA (Table view)

	ASCOT (N=2046)		ALLHAT (N=2173)			Pooled (N=4219)
	Amlodipine (n=1014)	Atenolol (n=1032)	Amlodipine (n=604)	Chlorthalidone (n=990)	Lisinopril (n=579)	
First quartile						
No. of patients	334	178	163	277	104	1056
Recurrent stroke/TIA	31 (9.3%)	23 (12.9%)	6 (3.7%)	15 (5.4%)	9 (8.7%)	84 (8.0%)
Second quartile						
No. of patients	297	214	165	244	134	1054
Recurrent stroke/TIA	24 (8.1%)	22 (10.3%)	11 (6.7%)	22 (9.0%)	11 (8.2%)	90 (8.5%)
Third quartile						
No. of patients	220	292	136	246	161	1055
Recurrent stroke/TIA	30 (13.6%)	31 (10.6%)	10 (7.4%)	15 (6.1%)	10 (6.2%)	96 (9.1%)
Fourth quartile						
No. of patients	163	348	140	223	180	1054
Recurrent stroke/TIA	26 (16.0%)	65 (18.7%)	9 (6.4%)	27 (12.1%)	16 (8.9%)	143 (13.6%)
Totals						
No. of patients	1014	1032	604	990	579	4219
Recurrent stroke/TIA	111 (10.9%)	141 (13.7%)	36 (6.0%)	79 (8.0%)	46 (7.9%)	413 (9.8%)
1st vs 4th BPV quartilea	$P=0.029$	$P=0.094$	$P=0.272$	$P=0.007$	$P=0.946$	$P<0.001$
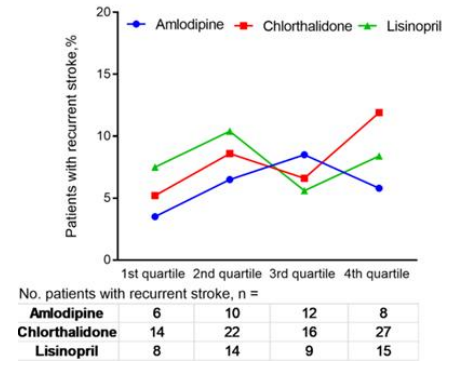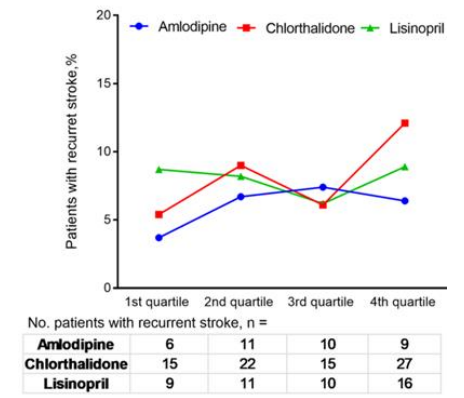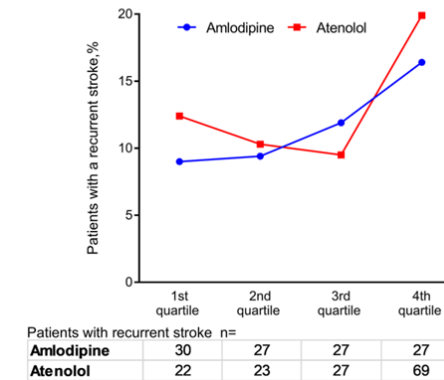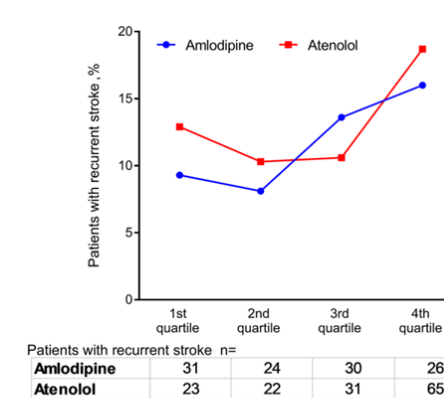
The risk of recurrent stroke increases with BPV regardless to medication type
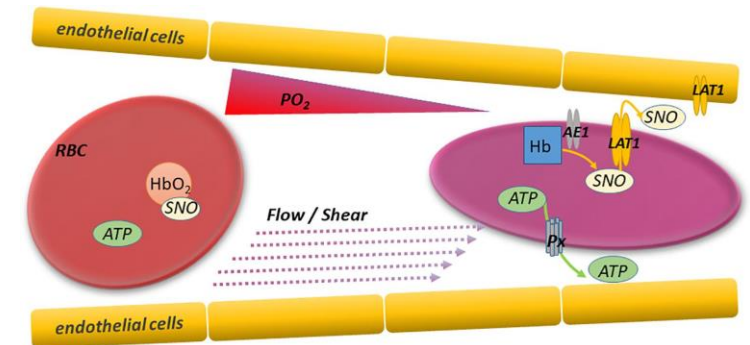
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Diabetes

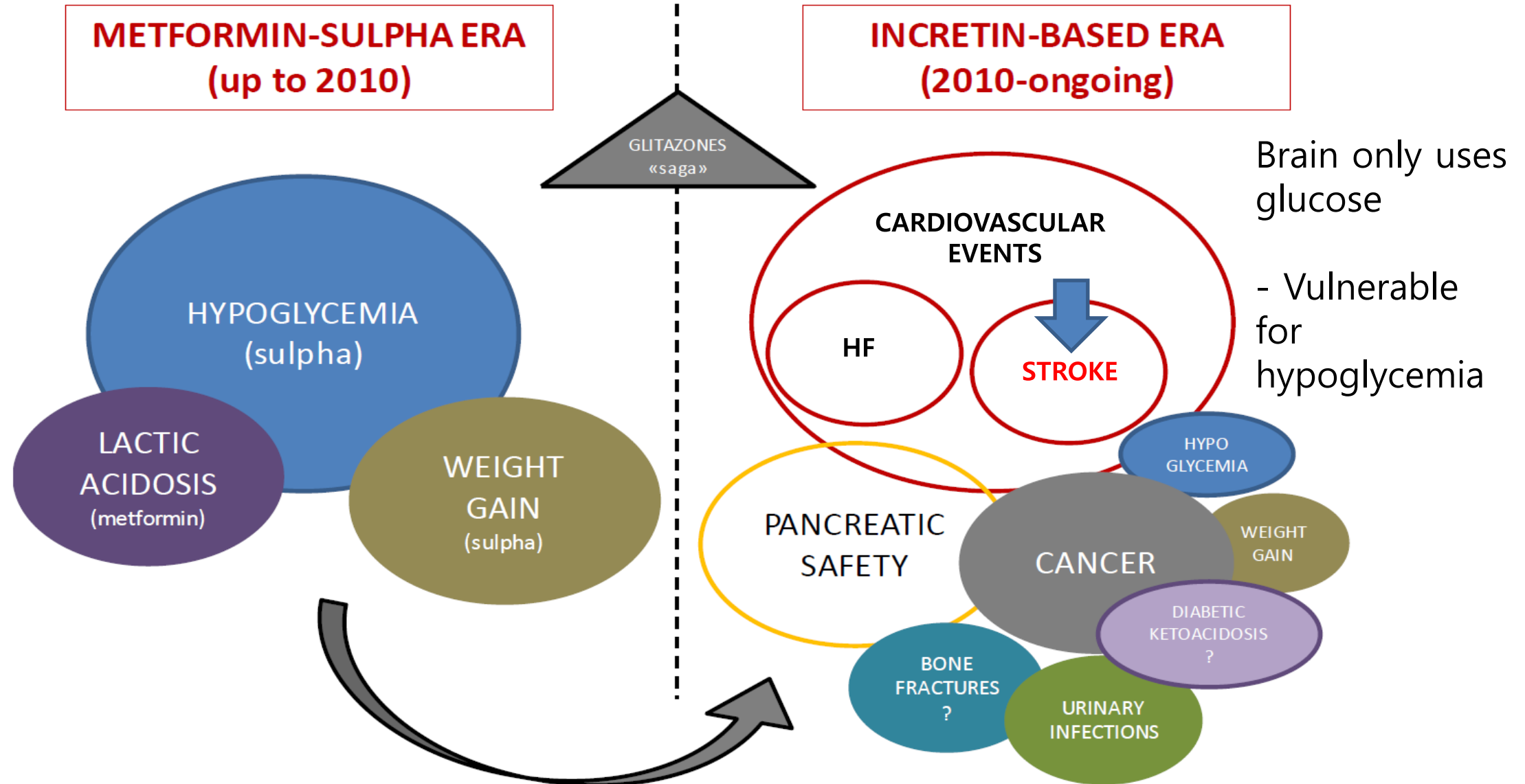- Of 20 % of stroke patients have DM

- DM accelerates atherosclerosis disease
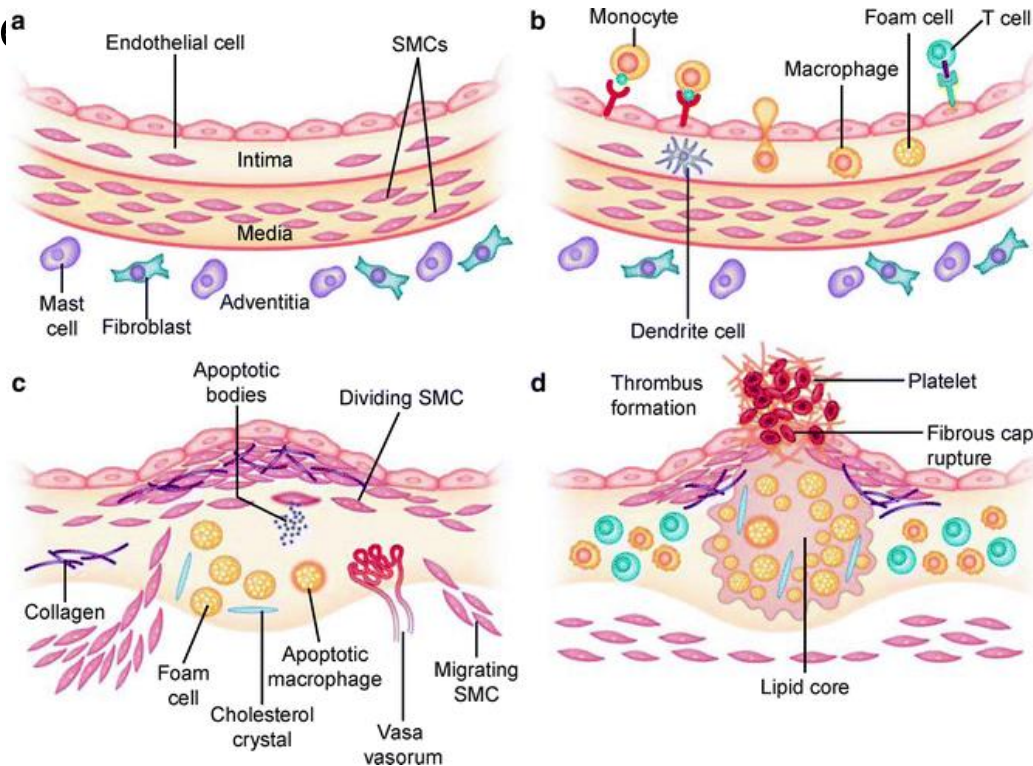
DM and small vessel

Metabolic syndrome associated with ICAS ➡ High viscosity reduces RBC deformability
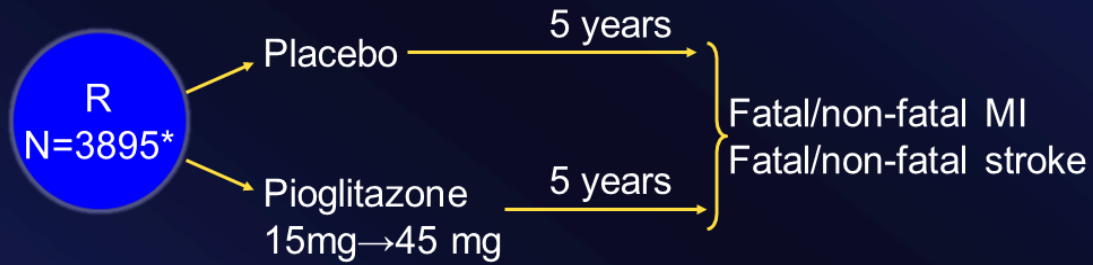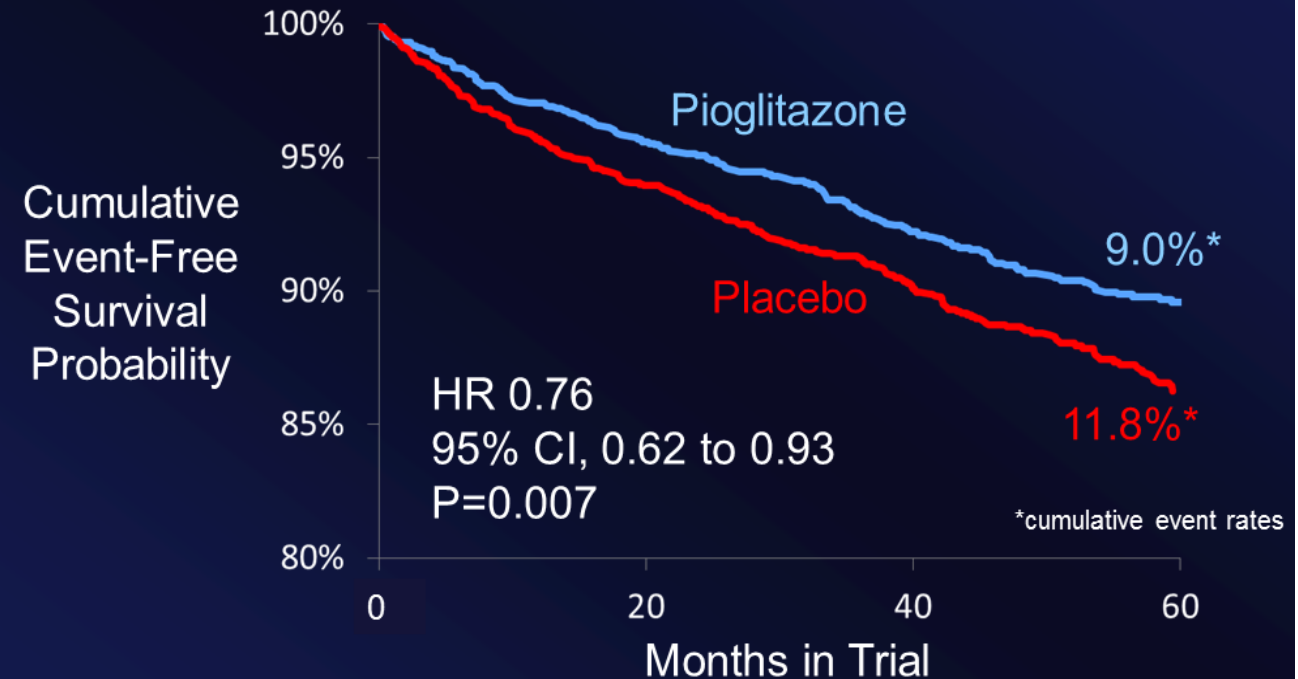
Turning Point

Parisotto, et al., J Pharmacovigil 2016, 4:4

IRIS study

Figure 1: IRIS Trial Design

Eligibility: Recent TIA or Ischemic Stroke
Non-Diabetic
Insulin Resistant (HOMA > 3.0)
No CHF

R
N=3895*

Placebo — 5 years

Pioglitazone 15mg→45 mg — 5 years

Fatal/non-fatal MI
Fatal/non-fatal stroke

*90% power to detect a 20% RRR from 27% in the placebo group to 22% in the pioglitazone group at an alpha level of 0.05

Viscoli CM *et al. Am Heart J* 2014;168:823-829

ClinicalTrials.gov Identifier: NCT00091949

Figure 2: IRIS Primary Outcome

Cumulative Event-Free Survival Probability

Pioglitazone — 9.0%*

Placebo — 11.8%*

HR 0.76
95% CI, 0.62 to 0.93
P=0.007

*cumulative event rates

Months in Trial

Kernan WN, *et al. N Engl J Med* 2016;374:1321-1331.

➡ However, problem of weight gain, increase in fracture

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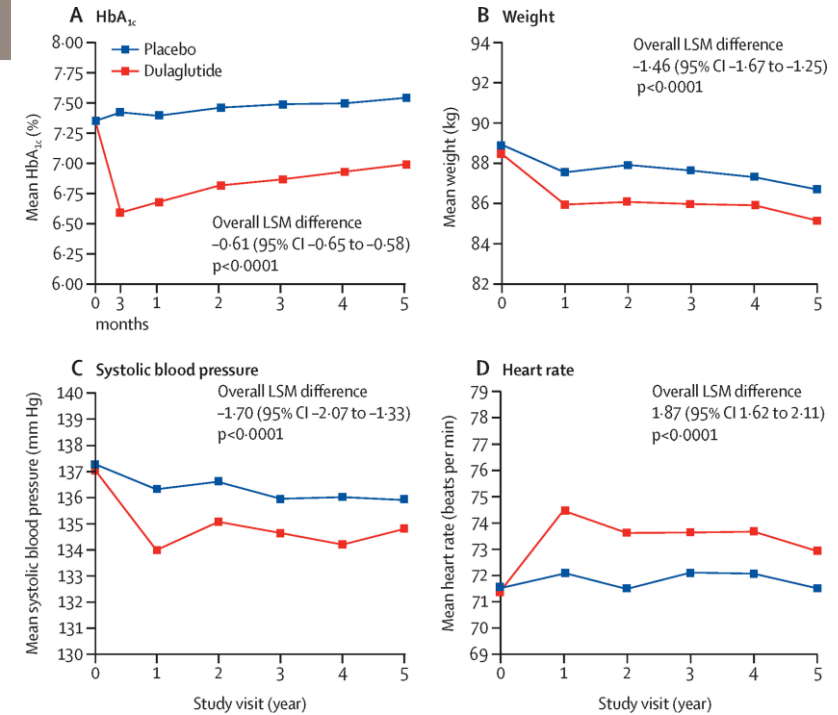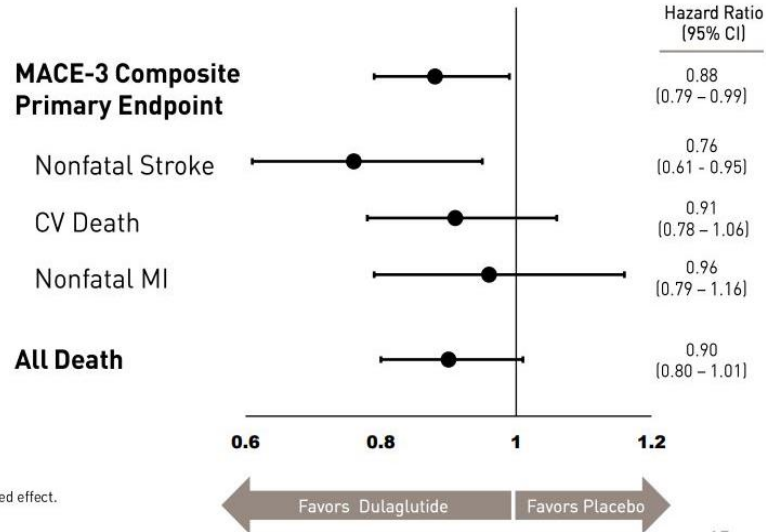
REWIND study

PRIMARY MACE 3 RESULT

Dulaglutide significantly reduced the risk of Major Adverse Cardiovascular Events (MACE 3: CV death, non-fatal MI or non-fatal stroke) by 12% vs. placebo

p-Value: 0.026
Hazard Ratio (95% CI): 0.88 (0.79, 0.99)

PLACEBO
DULAGLUTIDE
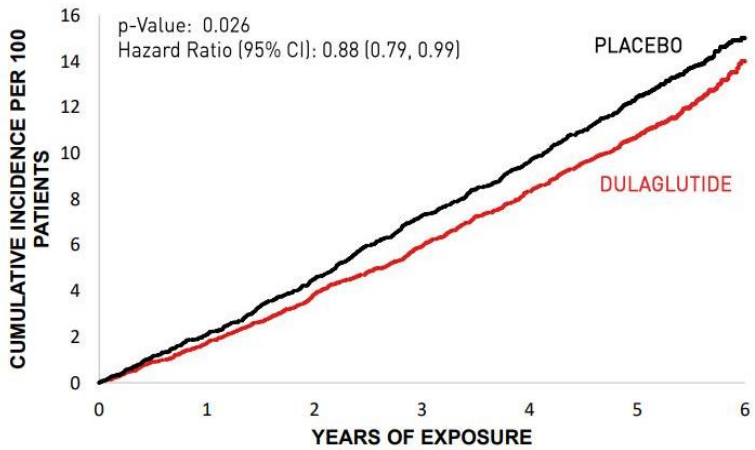
Note: Hazard Ratio and its CI and p-value obtained from Cox Proportional Hazards Regression Model with treatment as a fixed effect.
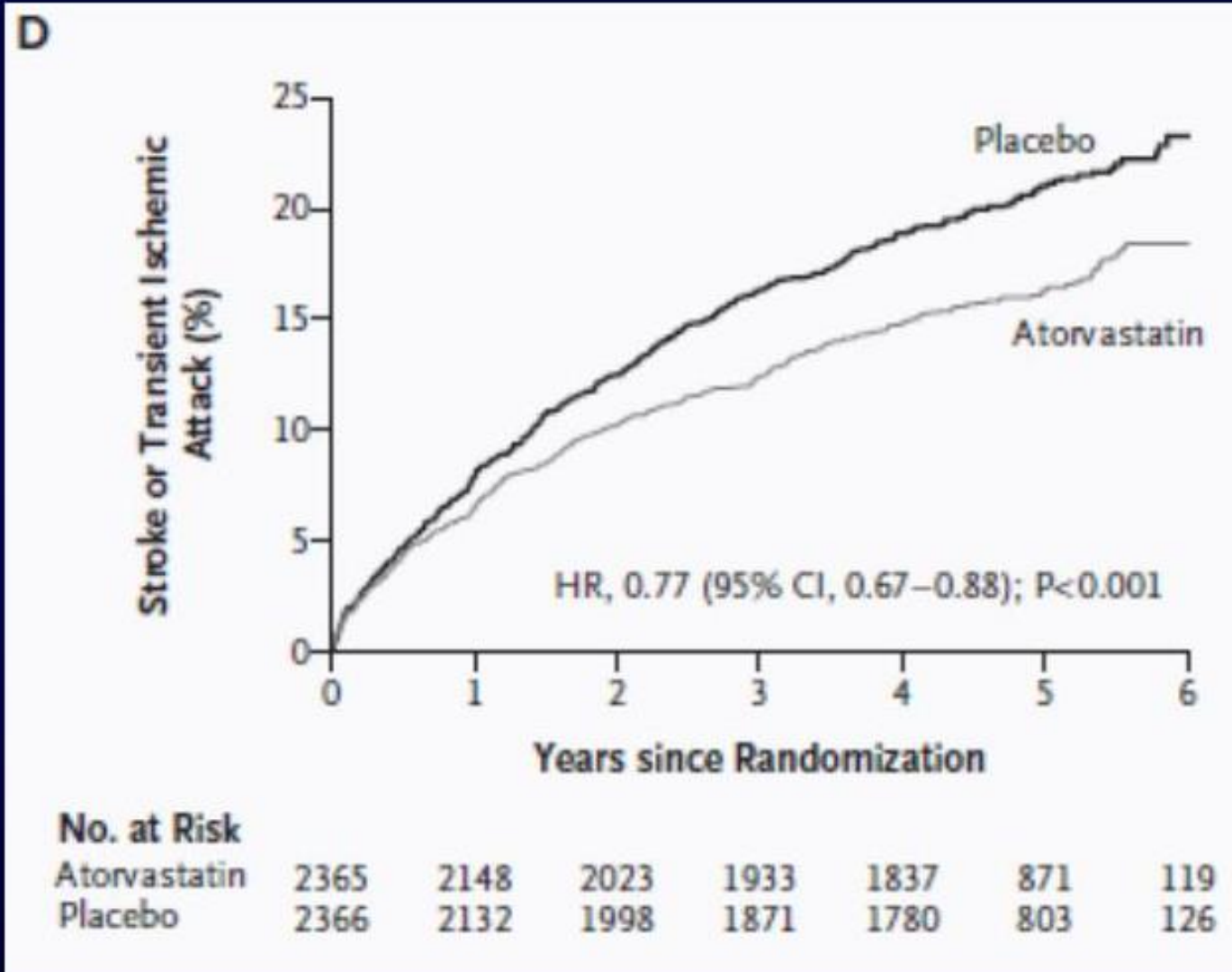Gerstein et al. Lancet 2019.

CV OUTCOMES

Consistent effect across three components of MACE, greatest difference observed in Nonfatal Stroke

	Hazard Ratio (95% CI)
MACE-3 Composite Primary Endpoint	0.88 (0.79 – 0.99)
Nonfatal Stroke	0.76 (0.61 - 0.95)
CV Death	0.91 (0.78 – 1.06)
Nonfatal MI	0.96 (0.79 – 1.16)
All Death	0.90 (0.80 – 1.01)

Favors Dulaglutide — Favors Placebo

A HbA1c

Overall LSM difference −0·61 (95% CI −0·65 to −0·58) p<0·0001

B Weight

Overall LSM difference −1·46 (95% CI −1·67 to −1·25) p<0·0001

C Systolic blood pressure

Overall LSM difference −1·70 (95% CI −2·07 to −1·33) p<0·0001

D Heart rate

Overall LSM difference 1·87 (95% CI 1·62 to 2·11) p<0·0001

Injection

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Lipid

Amarenco P, Bogousslavsky J, Callahan A, 3rd, et al. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med 2006;355:549-59.

Statin use in the acute phase may positively influence short- and long-term outcome

|	Statin use in the acute phase		Adjusted analysis	
Multivariate analysis: Efficacy and safety of statin use in the acute phase of stroke				
	Yes (n = 839)	No (n = 1,233)	OR (95% CI)	*p* Value
Short-term efficacy (at 7 days)				
Neurologic improvement	632/832 (76.0)	773/1,223 (63.2)	1.68 (1.26–2.25)	<0.001
Major neurologic improvement	422/832 (50.7)	500/1,223 (40.9)	1.43 (1.11–1.85)	0.006
Long-term efficacy (at 30 months)				
Favorable functional outcome	523/746 (70.1)	576/1,098 (52.5)	1.63 (1.18–2.26)	0.003
Excellent functional outcome	402/746 (53.9)	438/1,098 (39.9)	1.28 (0.94–1.73)	0.121
Short-term safety (at 7 days)				
Neurologic deterioration	42/832 (5.0)	176/1,223 (14.4)	0.31 (0.19–0.53)	<0.001
sICH	10/832 (1.2)	47/1,222 (3.8)	0.52 (0.20–1.34)	0.176
Long-term safety (at 30 months)				
Death	43/746 (5.8)	166/1,098 (15.1)	0.48 (0.28–0.82)	0.007

sICH, symptomatic intracerebral hemorrhage

Ref. Cappellari M, et al. Neurology 2013;80:655–661.

2019 AHA/ASA Guidelines
for the Early Management of Patients With Acute Ischemic Stroke

In-Hospital Institution of Secondary Stroke Prevention

< Treatment of Hyperlipidemia >

Timing	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. For patients with AIS who qualify for statin treatment, in-hospital initiation of statin therapy is reasonable.	IIa	C-LD

Ref. Powers WJ, et al. Stroke. 2019;50:e344–e418.
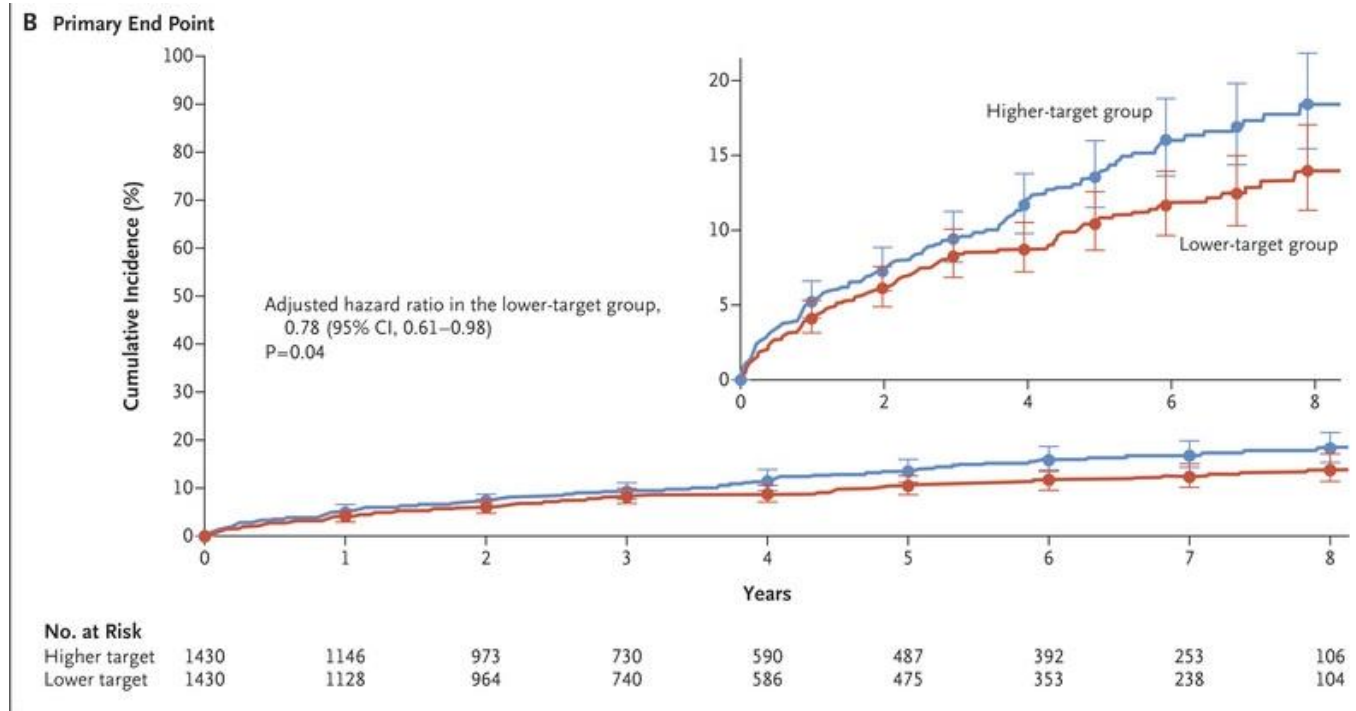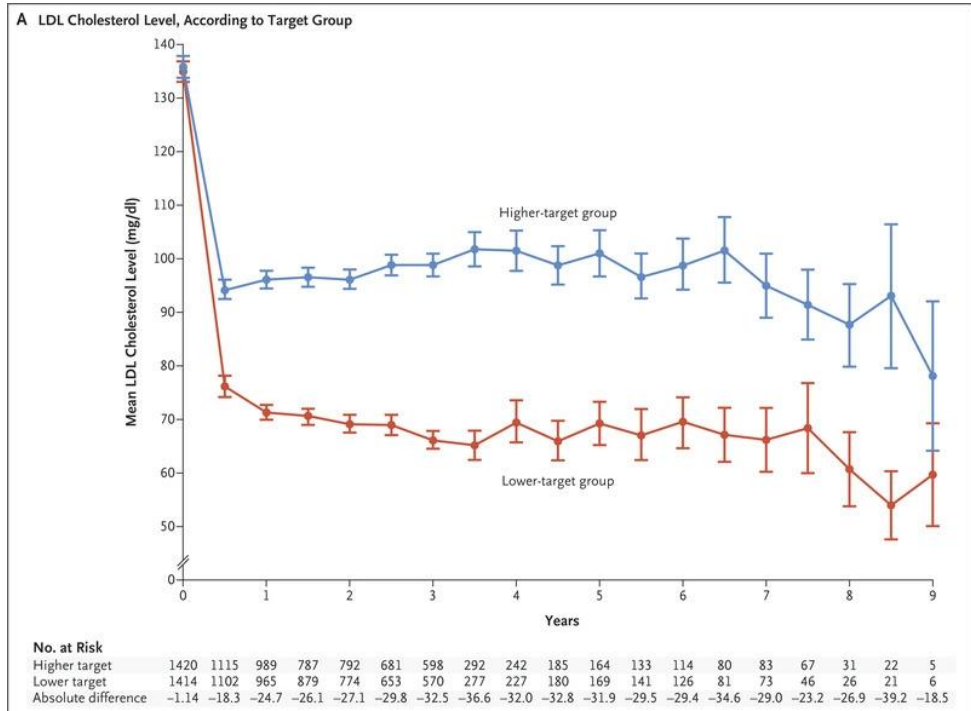
Controlling LDL cholesterol under 70mg/dl reduces cardiovascular event in stroke patients

Conclusion

- Obesity is associated with stroke

- Stroke is a disease of heterogeneous mechanism

- Different approach may be needed according to stroke mechanisms
  - LAA
    - DAPT → mono antiplatelet agent (Considering risk benefit)
    - Lowering BP under 140mmHg is reasonable, but with individual approach
    - Acute stage: high potent statin, → LDL under 70mg/dl

  - SVO
    - DAPT → mono antiplatelet (with less bleeding complication)
    - Lowering BP under 130 mmHg is reasonable
    - LDL lowering may be considered