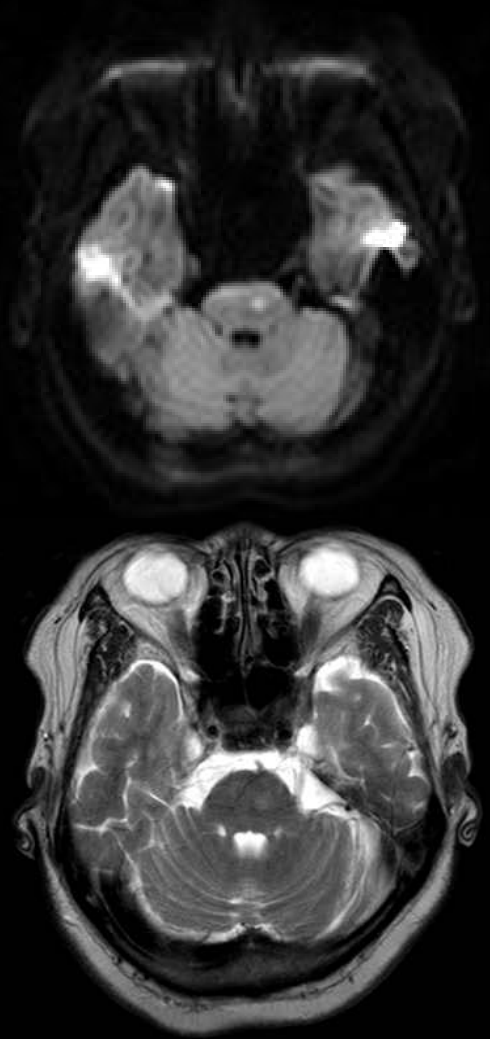
Antiplatelet Therapy in Atrial Fibrillation

Sun U. Kwon, MD, PhD
Department of Neurology
Asan Medical Center, University of Ulsan

60 Yr with Dizziness

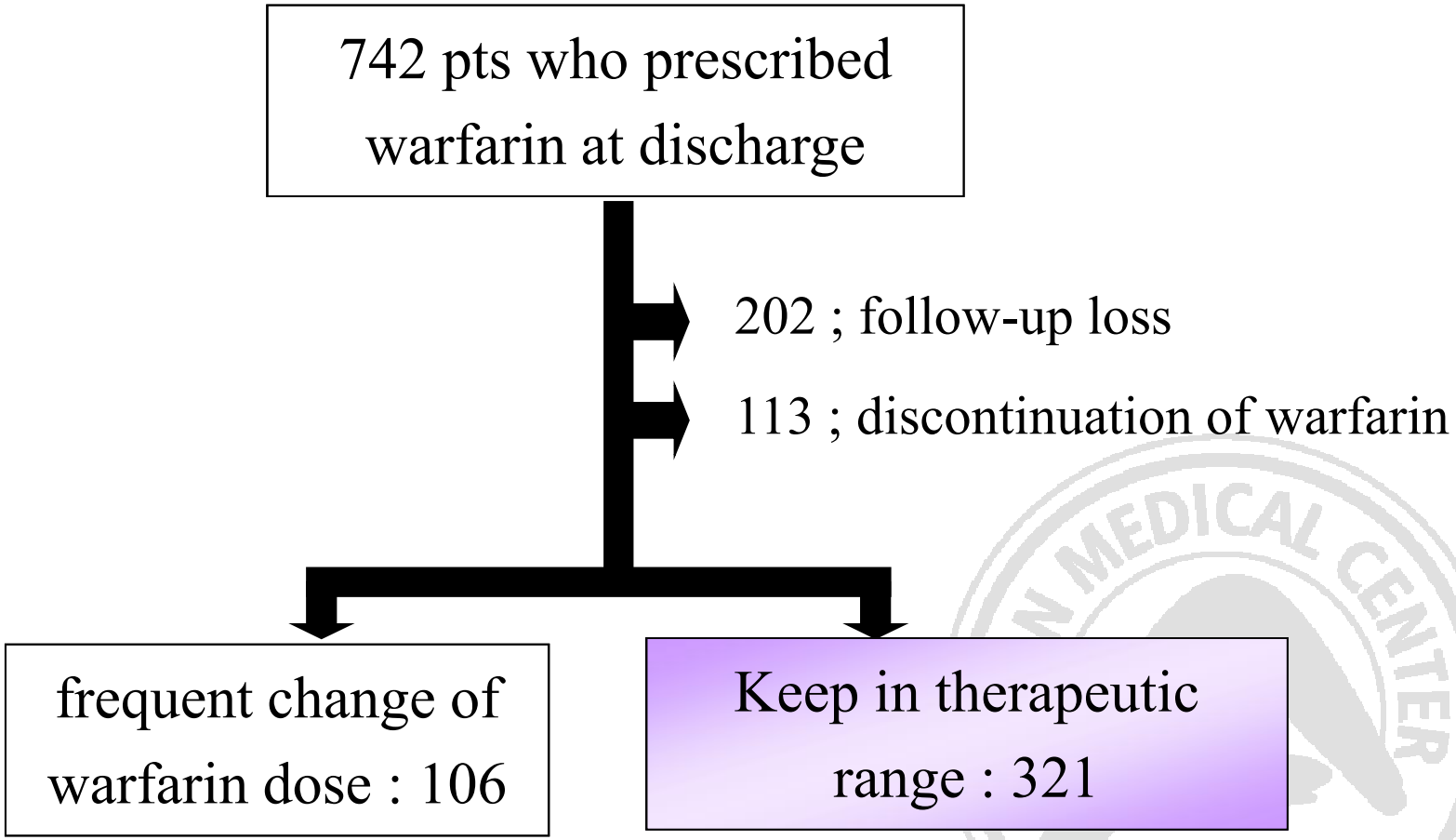
Risk Factors: DM, Hypertension and Atrial fibrillation



Medications

Date	Warfarin Dose	INR	New Dose
Dec 7, 2007	3.5mg/day	2.35	3.5mg/day
Dec 28, 2007	3.5mg/day	3.62	2.5mg/day
Jan 14, 2008	2.5mg/day	1.57	3.5mg/day
Jan 28, 2008	3.5mg/day	2.56	3.5mg/day
Feb 21, 2008	3.5mg/day	1.42	4.5mg/day
Mar 10, 2008	4.5mg/day	1.58	5.0mg/day
Mar 24, 2008	5.0mg/day	3.62	4.0mg/day
Apr 14, 2008	4.0mg/day	3.82	3.0mg/day
Apr 28, 2008	3.0mg/day	2.20	3.0mg/day
May 19, 2008	3.0mg/day	3.90	2.0mg/day
Jun 7, 2008	2.0mg/day	1.36	Stop Warfarin

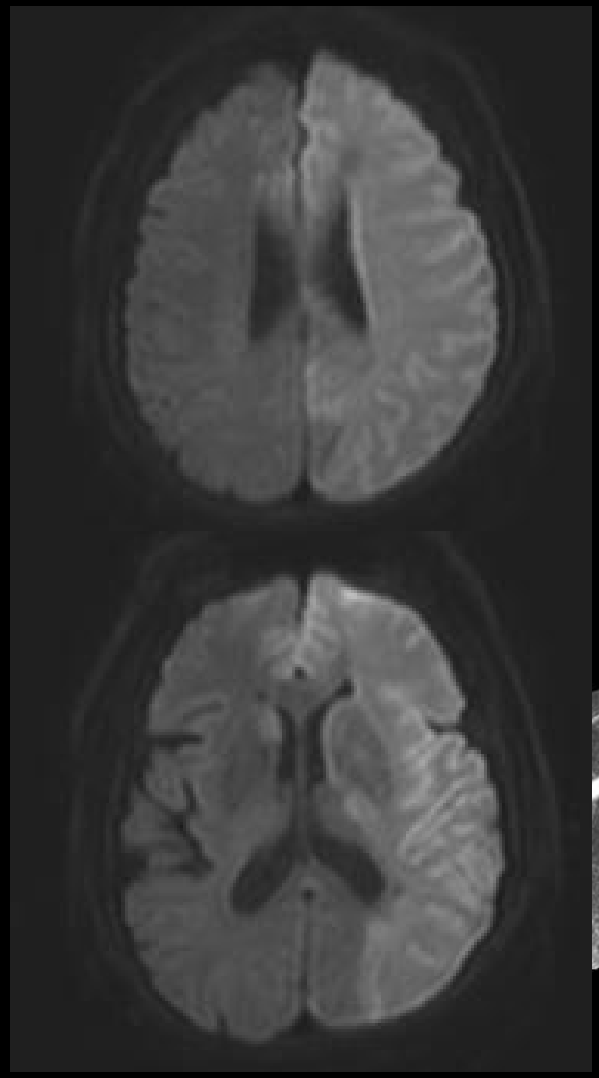
A Quarter of Patients Required Frequent Dose Change



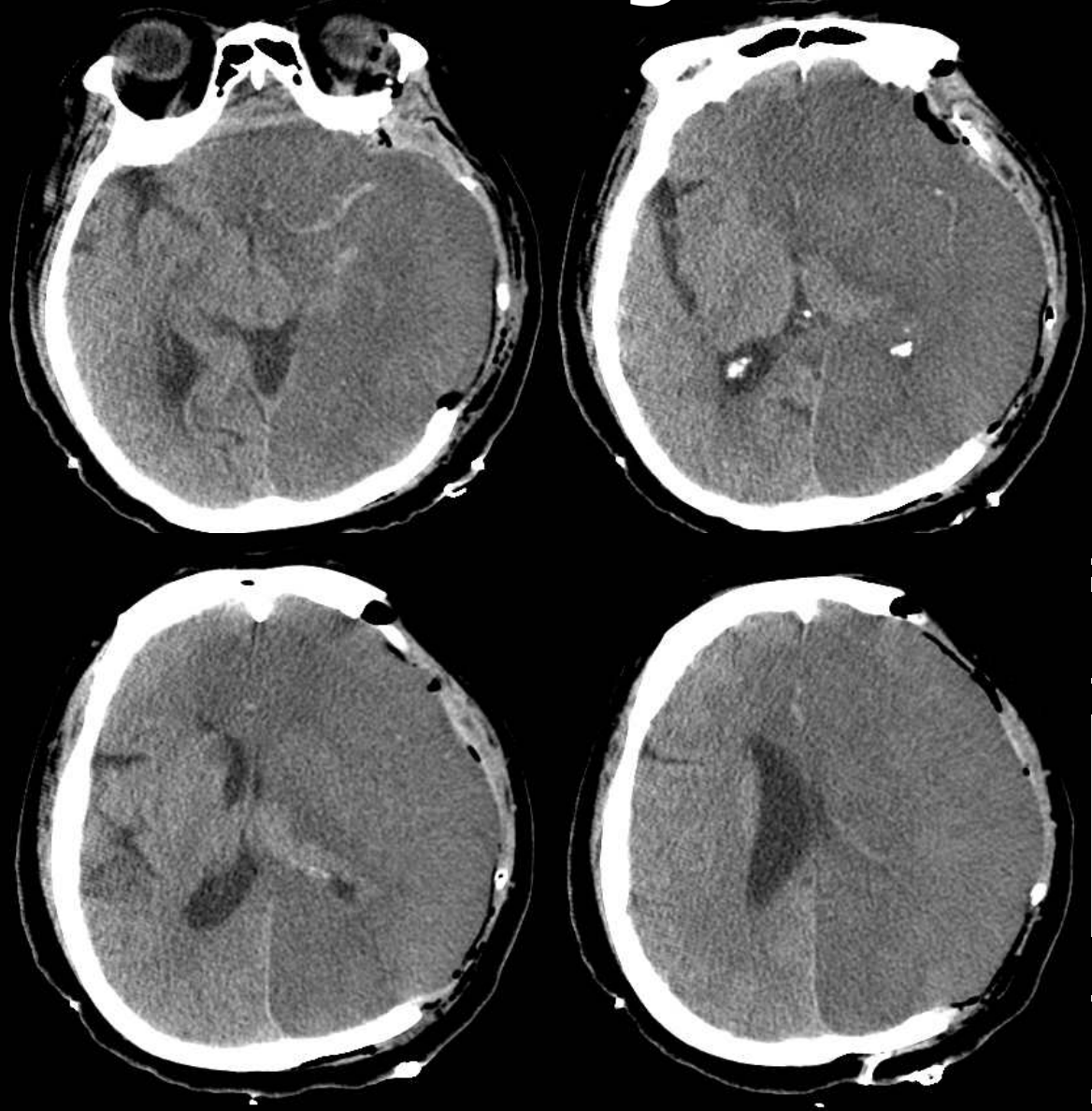
Yoo SH and Kwon SU, Eur J Neurol 2009;16:1100

Aug 26, 2009

Sudden right hemiplegia and global aphasia During Aspirin 300mg



Death due to large Infarction



ICAL CENTER
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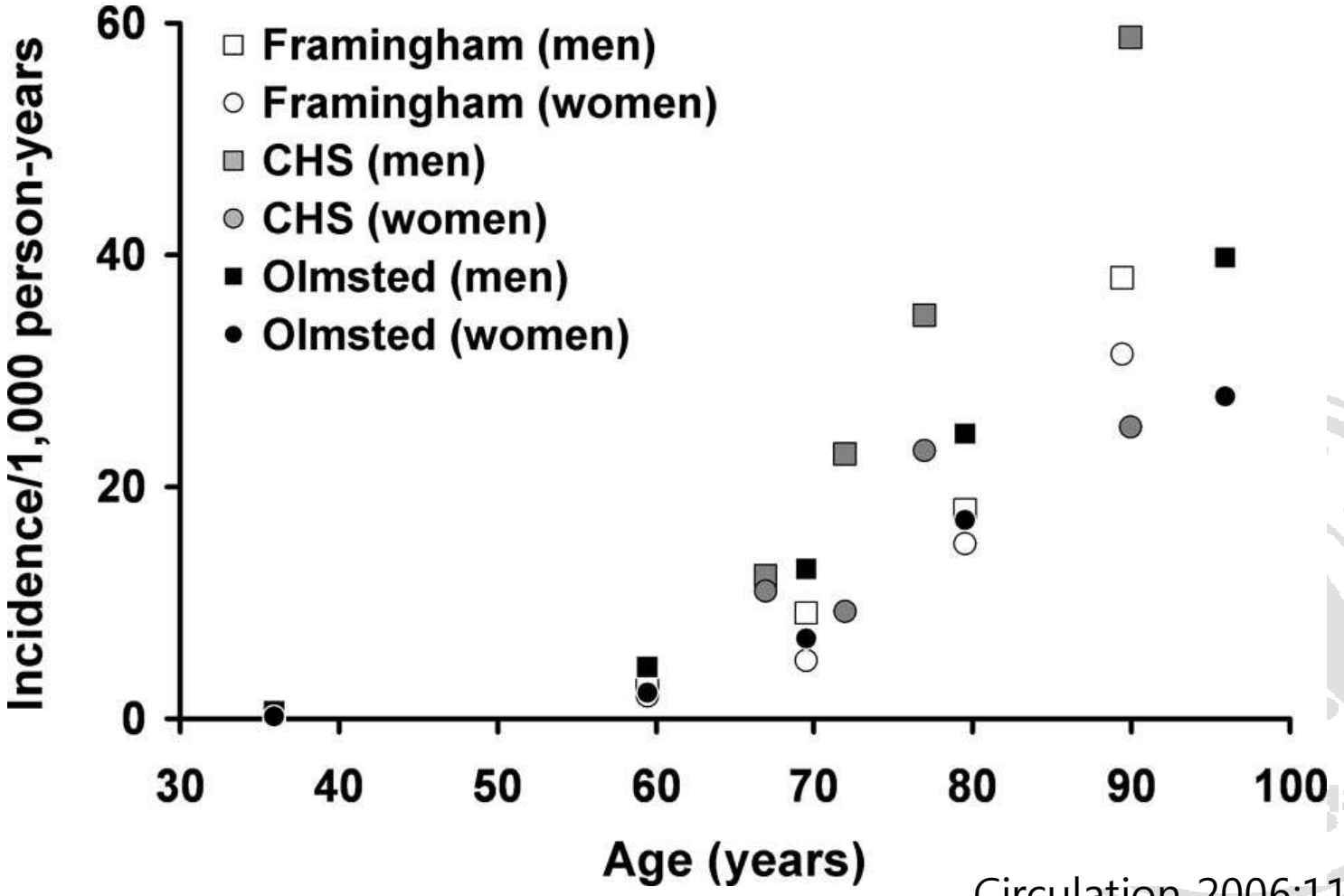
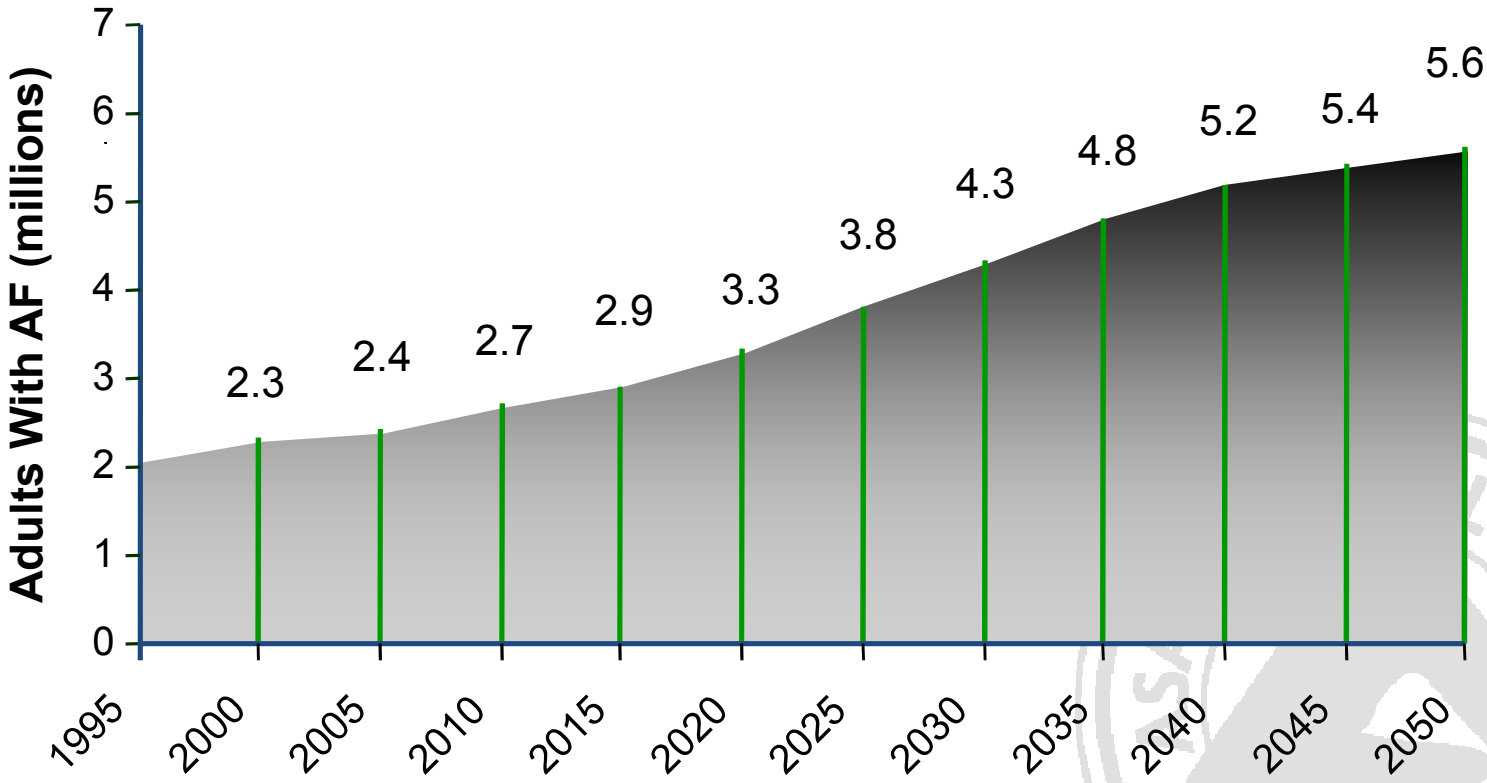
Af increases with Aging

Incidence of Af by age in the Framingham Heart Study



Circulation 2006;114:119

Prevalence of Af is Increasing

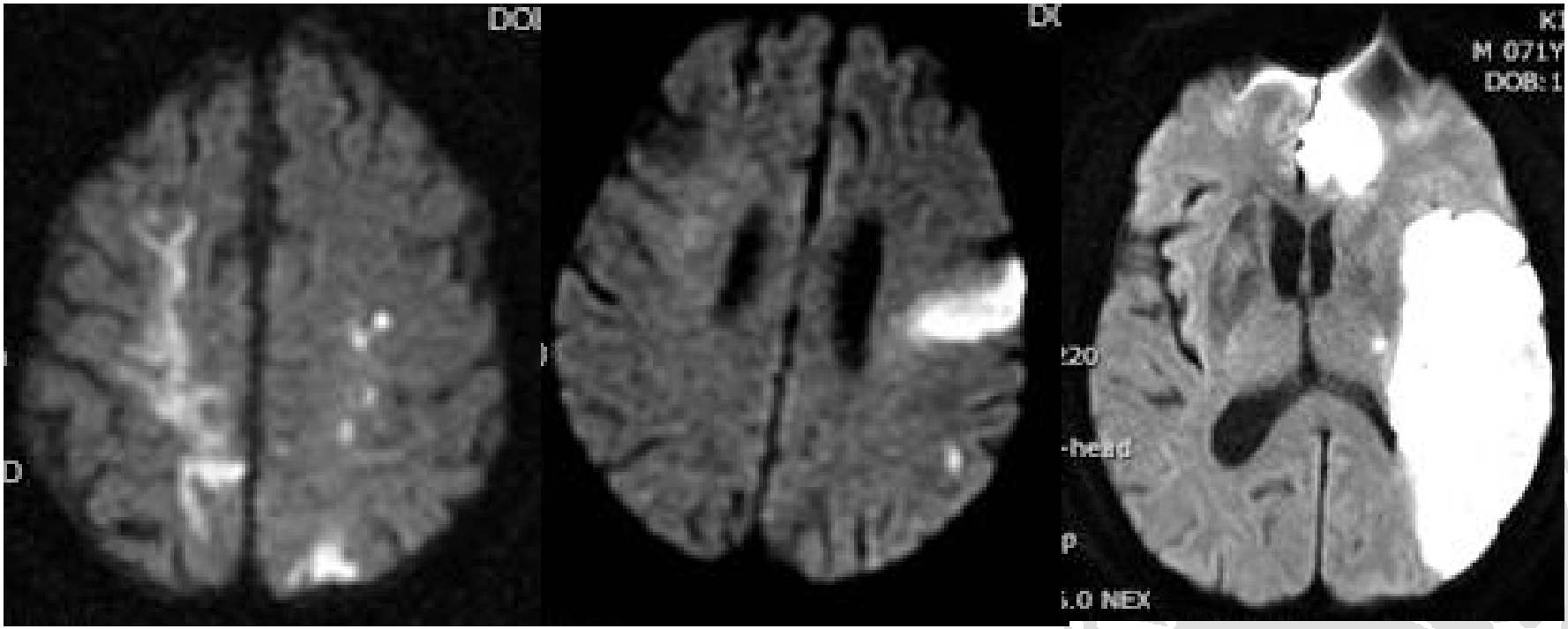


1. Lamassa M *et al. Stroke* 2001; 32: 392-398.
2. Kannel WB *et al. Am J Cardiol* 1998; 82: 2N-9N.

Stroke with AF

- 15-20% of ischemic stroke, and increasing
- Multiple lesions, multivascular territory
- More women, more older
- More larger infarct and poorer outcome
- Higher risk of recurrence
- More bleeding

Multiple Infarct is Common



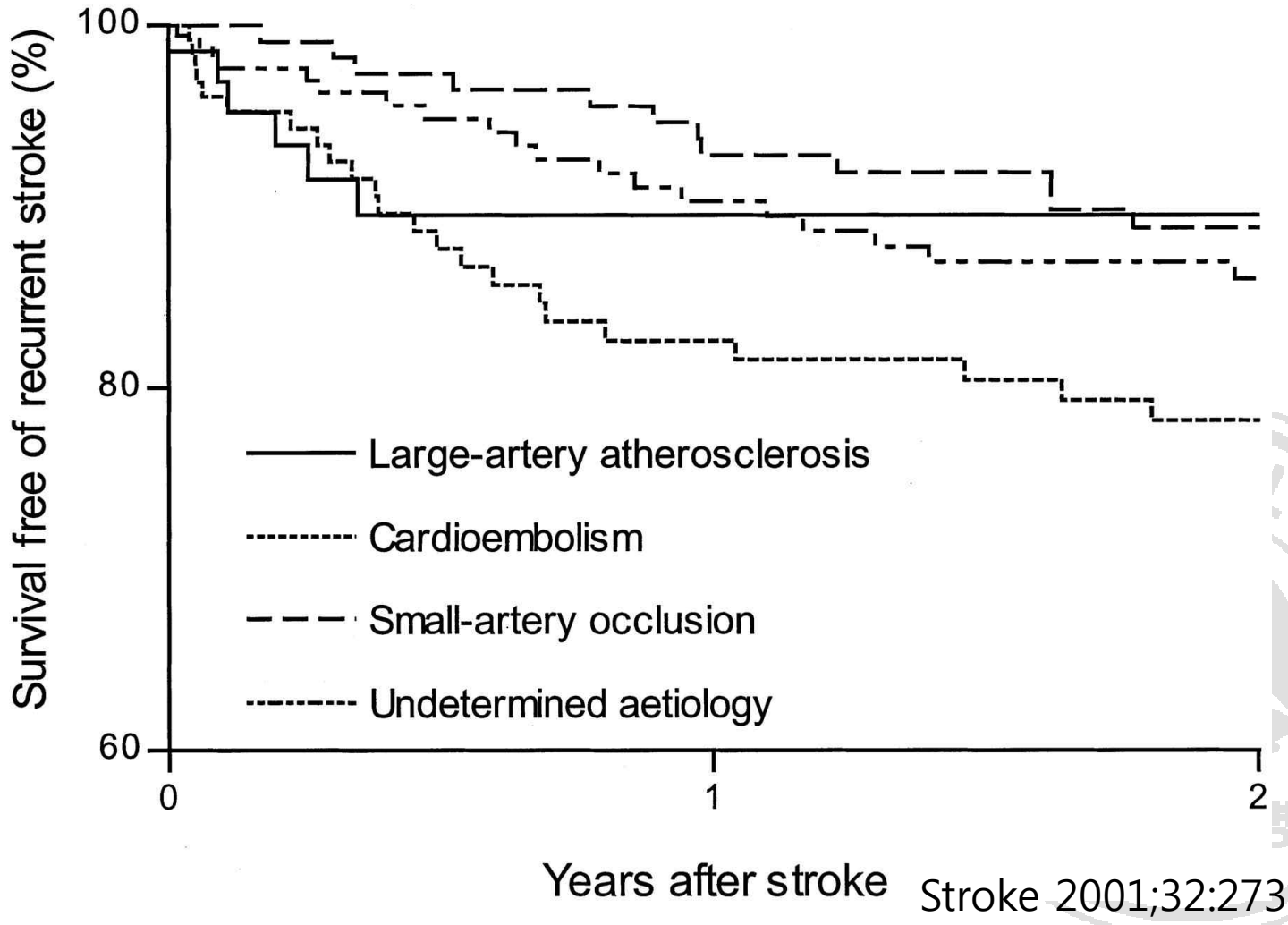
Poorer Clinical Outcome

	Delayed AC	Immediate AC	
N (%)	82 (31 %)	179 (69%)	261
Two Weeks outcome			
Recurrent Ischemic Stroke, n(%)	1 (1.2%)	6 (3.4%)	7 (3%)
Symptomatic ICH, n(%)	9 (11%)	6 (3%)	15 (6%)
Death, n(%)	18 (22%)	5 (3%)	23 (9%)
Three months outcome			
Favorable(012), n(%)	15 (18%)	96 (54%)	111 (43%)
mortality, n(%)	25 (30%)	20 (11%)	45 (17%)

Park KY & Kwon SU, ACSR 2008

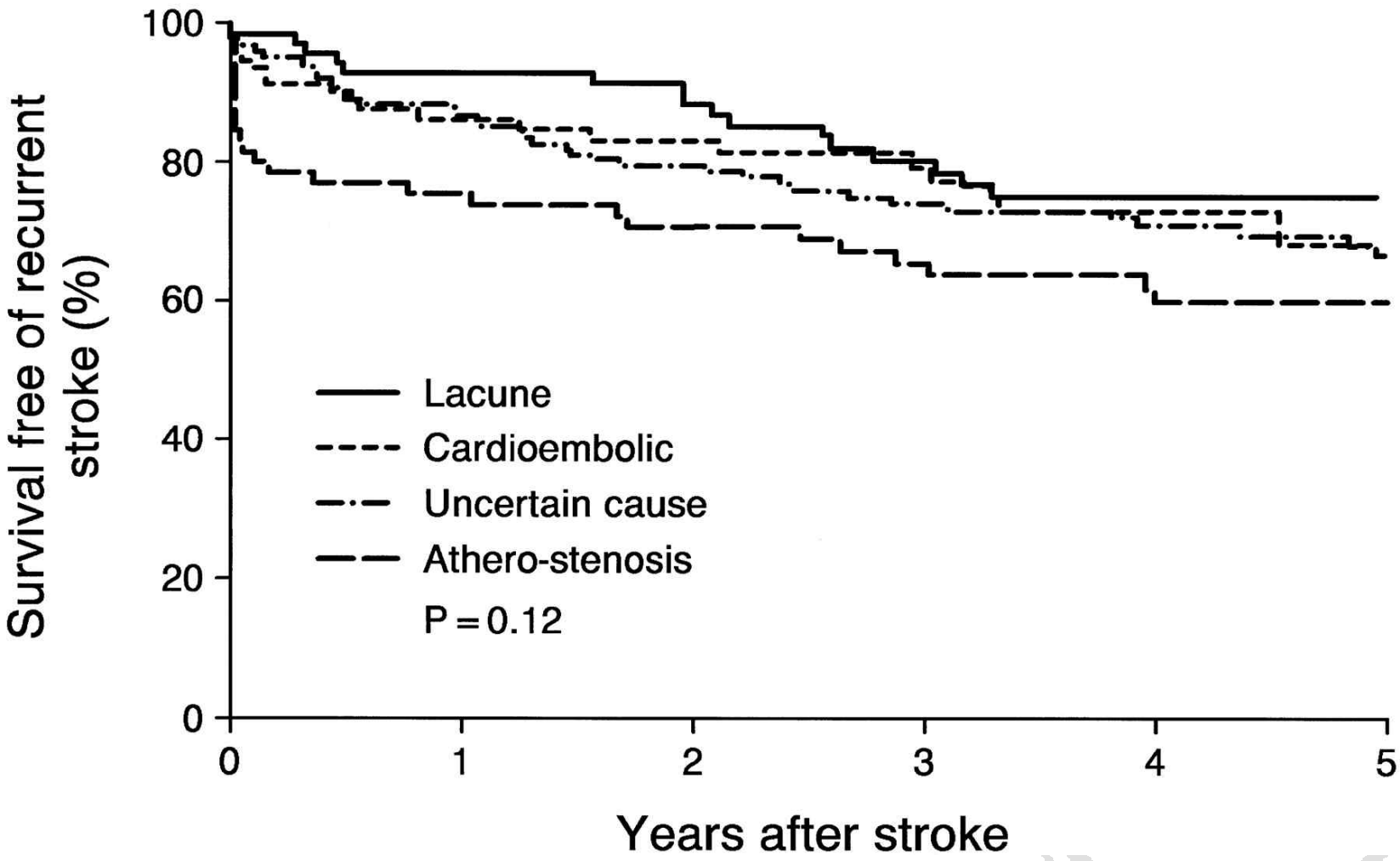
Higher Recurrent Rate

Erlangen Stroke Project : community-based stroke register in Germany



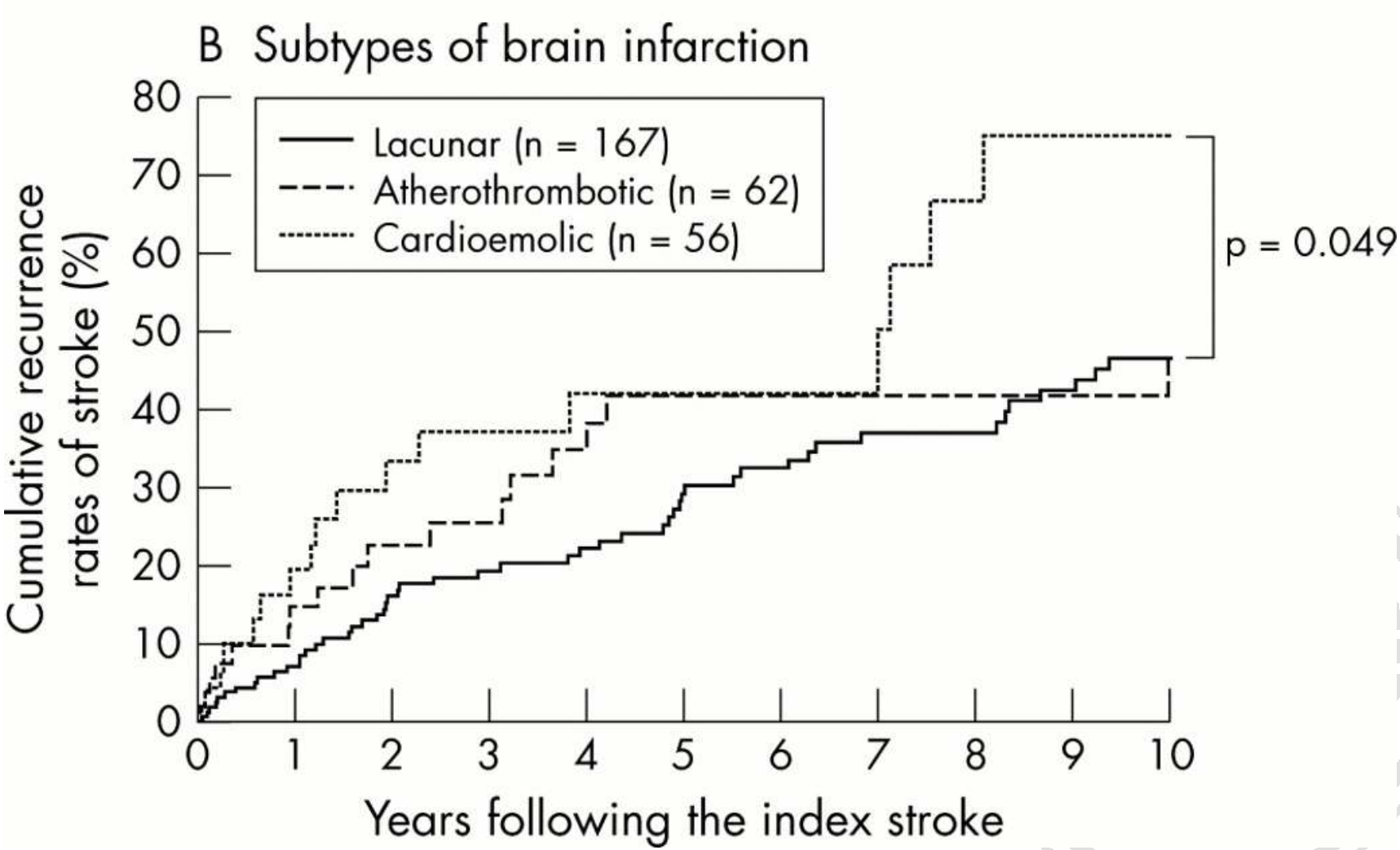
Stroke 2001;32:2735

Higher Recurrence in USA



Stroke 2000;31:1062

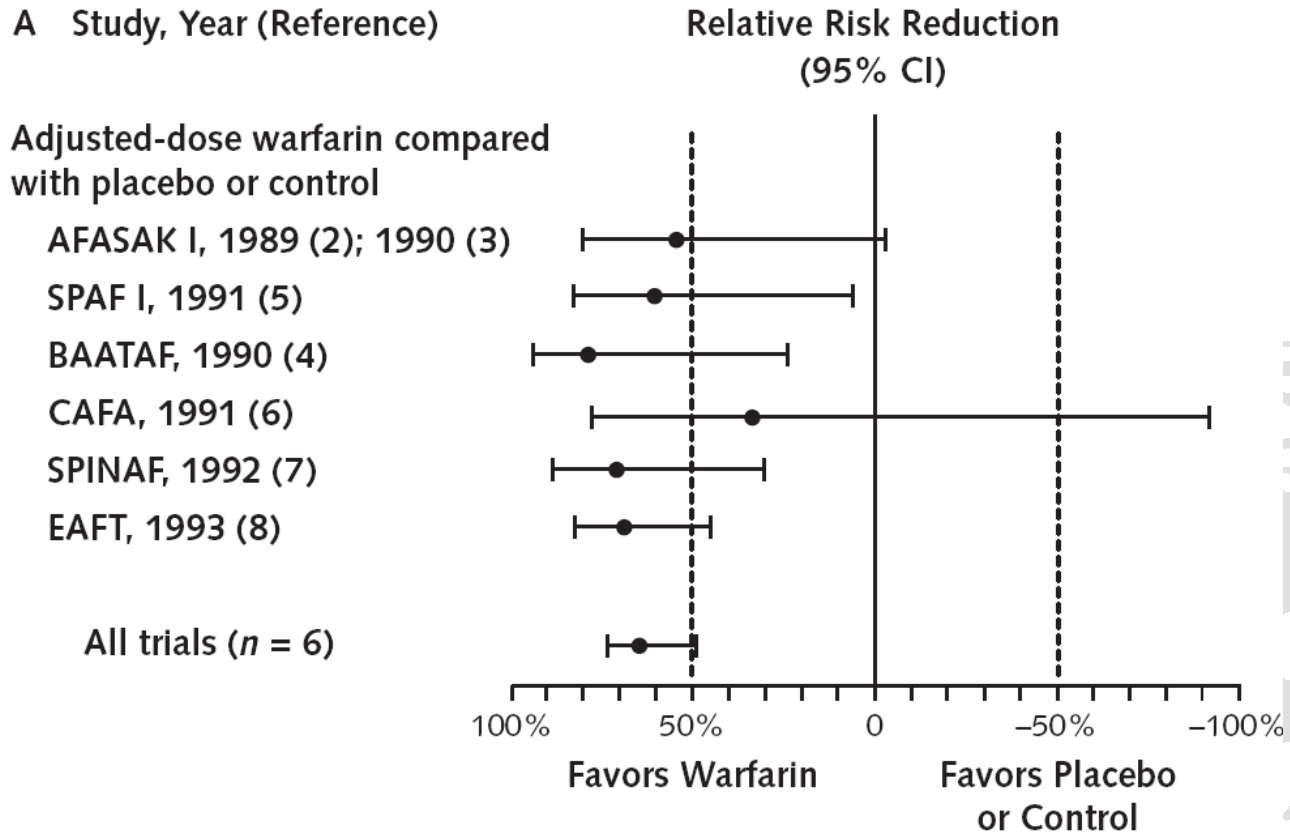
Higher Recurrent Rate in Japan



JNNP 2005;76:368-372

Warfarin vs Placebo

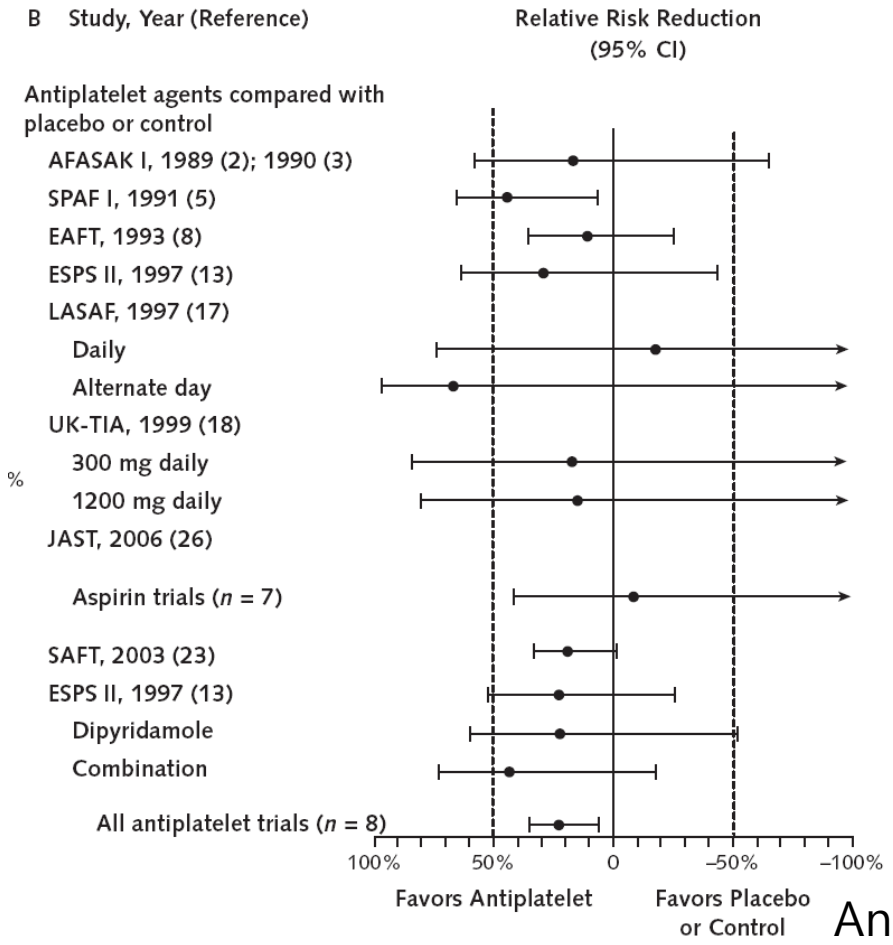
In 2990 pt in 6 trials, Adjusted-dose warfarin **reduced 64% stroke**
ARR was 2.7%/yr for primary and 8.4%/yr for secondary prevention



Ann Intern Med 2007;146:857

Antiplatelets vs Placebo

In 3990 pts in 7 trials, antiplatelet agents reduced **19 % in stroke**
ARR was 0.8%/yr for primary and 2.5%/yr for secondary prevention



Ann Intern Med 2007;146:857

Stroke Risk Stratification of Af

$CHADS_2$ Criteria	Risk score
Congestive heart failure	1 point
Hypertension	1 point
Age 75 years or older	1 point
Diabetes mellitus	1 point
Prior **S**troke or TIA	**2** point

Current Guideline of AHA

- Antithrombotic therapy to prevent thromboembolism is recommended for all patients with Af, except those with lone Af or contraindication (LOE: A)
- Oral anticoagulation is recommended for patients with more than 1 moderate risk. (LOE: A)
- Aspirin, 81-325mg, is recommended as an alternative to anticoagulation in low-risk patients and in those with contraindications to oral anticoagulation. (LOE: A)

Circulation 2008

Risk Factor for Stroke in Af

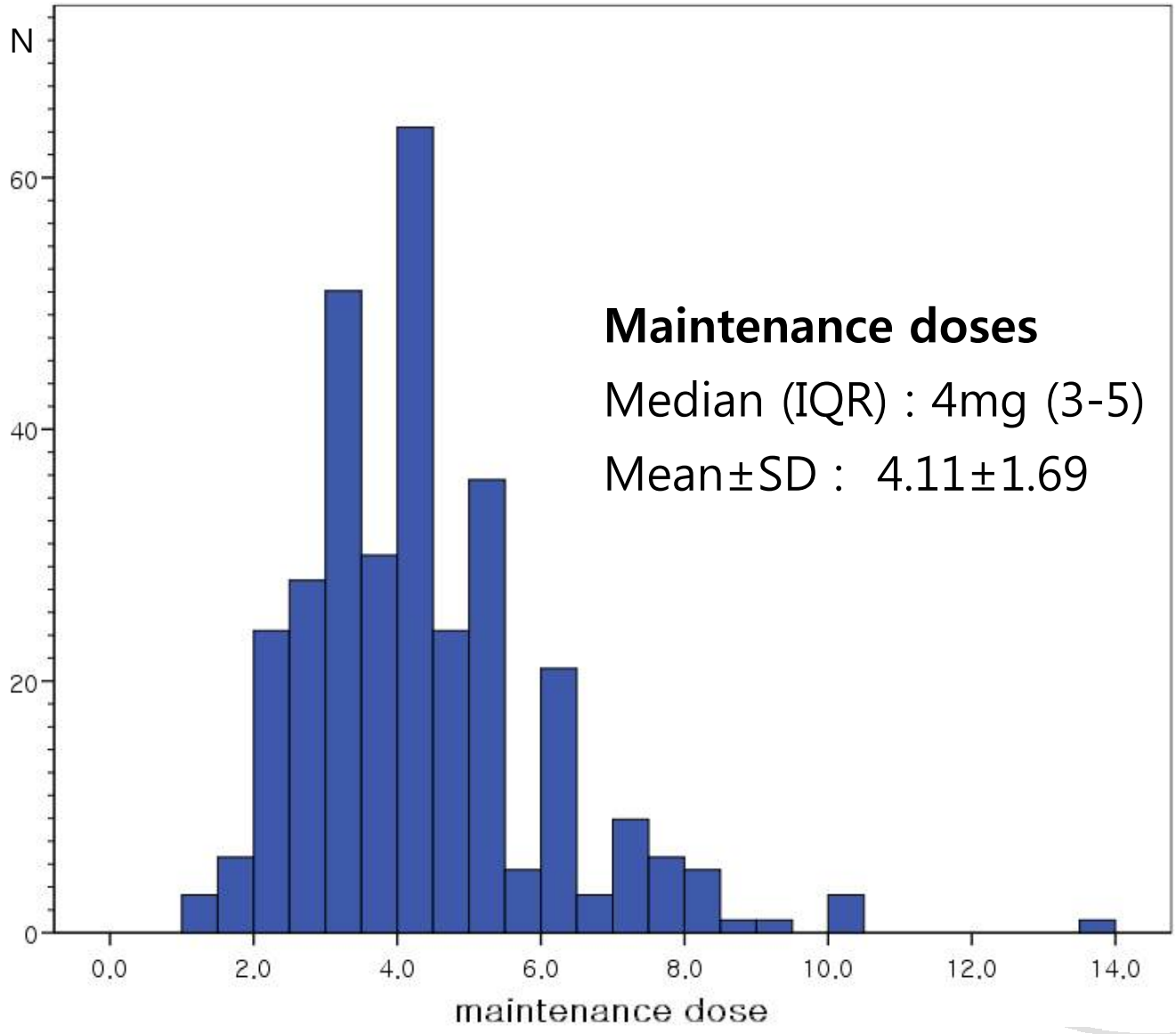
Weak RF	Moderate RF	High RF
Female	Age > 75	Prior stroke, TIA or systemic embolism
Age 65-74	Hypertension	
Coronary disease	Heart failure	
thyrotoxicosis	LVEF 35% or less	
	DM	

Circulation 2008

Limitation of Warfarin

- Complicated drug interaction
- Certain risk of bleeding complications
- Wide inter-individual variation of the dose to maintain therapeutic range
- Require regular monitoring
- The intensity of anticoagulation is unpredictable sometimes

Maintenance Dose of Warfarin



Antiplatelet Therapy in AF

- Increased platelet activation in AF
- Aspirin reduces stroke in AF by 22%
- Addition of clopidogrel to aspirin achieves greater suppression of platelet activity
- Addition of clopidogrel to aspirin reduces vascular events in ACS, with acceptable risk of bleeding

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

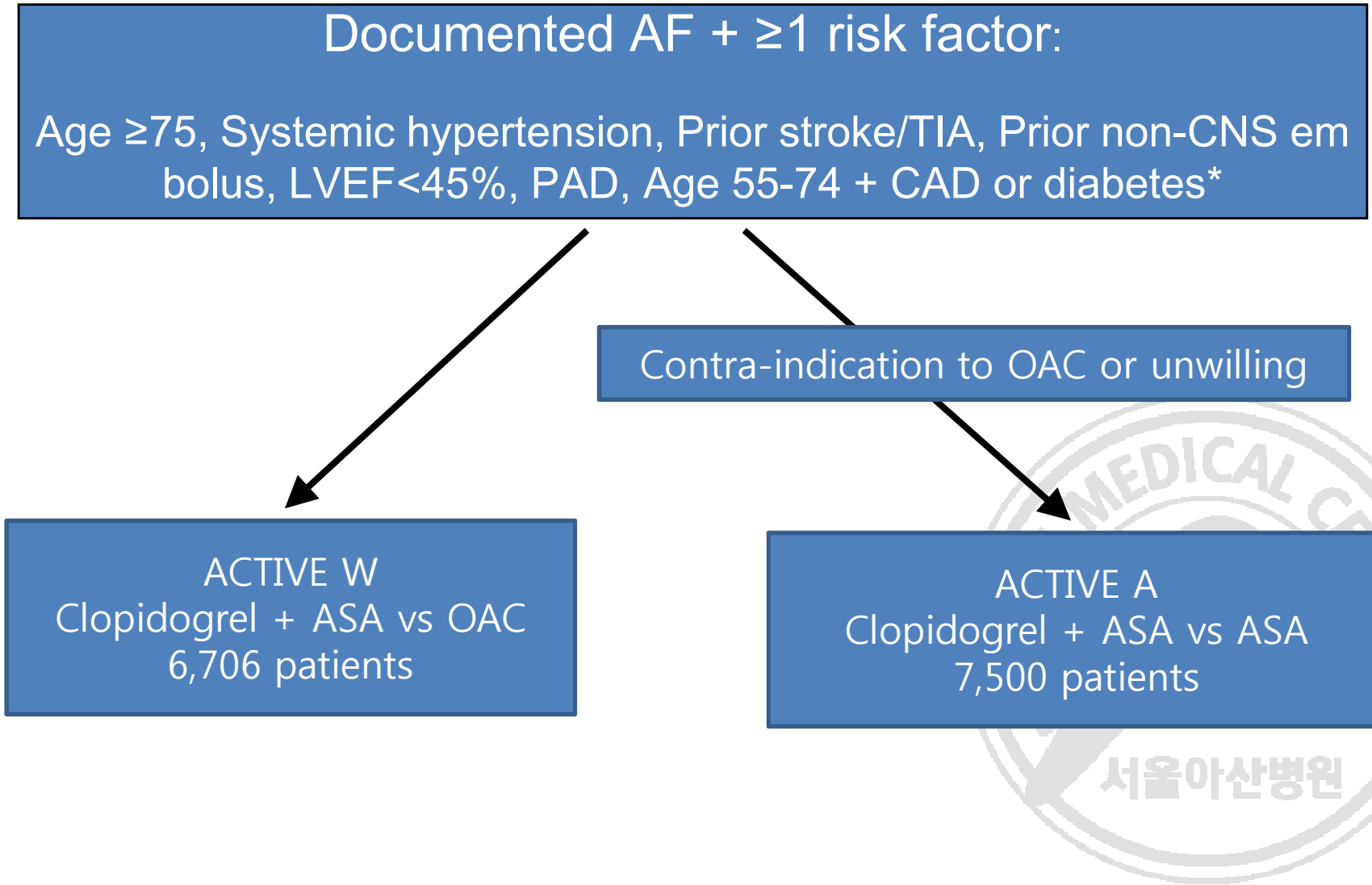
Effect of Clopidogrel Added to Aspirin in Patients with Atrial Fibrillation

The ACTIVE Investigators*

Hypothesis :In patients with AF, unsuitable for warfarin therapy, addition of clopidogrel to aspirin will reduce the risk of major vascular events, at acceptable risk of major bleeding

N Engl J Med 2009;360

Design of ACTIVE



Design of ACTIVE A

- Double blind placebo controlled trial
- 580 centers in 33 countries
- Aspirin (75-100mg/day) was given to all patients
- Randomized into Clopidogrel (75mg/day) or matching placebo
- Primary outcome
  - Composite of major vascular events
  - Stroke, MI, non-CNS systemic embolism, vascular death

Reason for Enrollment in ACTIVE A

Relative risk factor for bleeding	23%
Physician assessment that patient is not appropriate for oral anticoagulation	50%
Patient preference only	26%

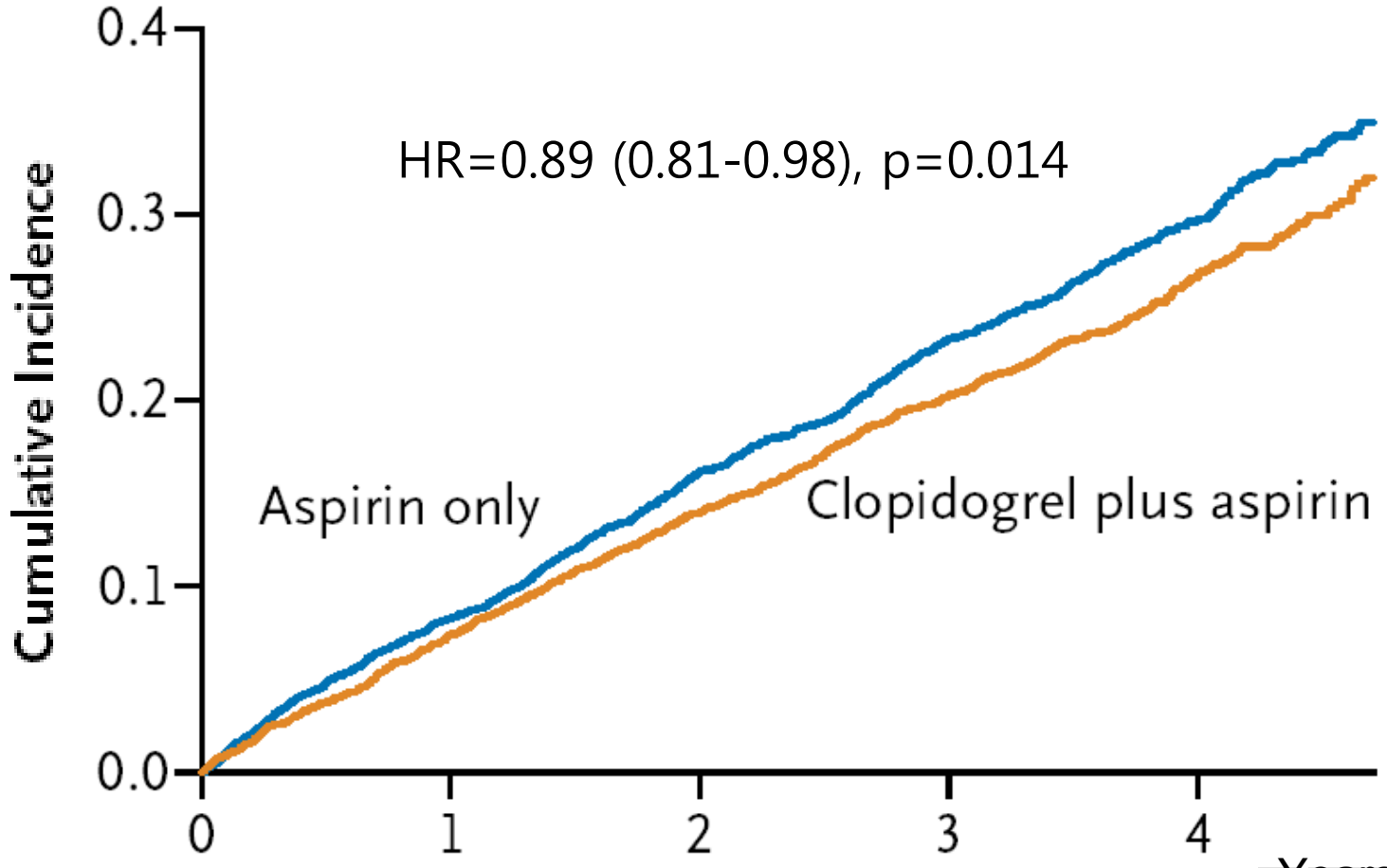
* Inability to comply with INR monitoring, predisposition to falling or head trauma, persistent BP >160/100, previous serious bleeding on VKA, severe alcohol abuse <2 years, peptic ulcer disease, thrombocytopenia, need for chronic NSAID

Baseline Characteristics

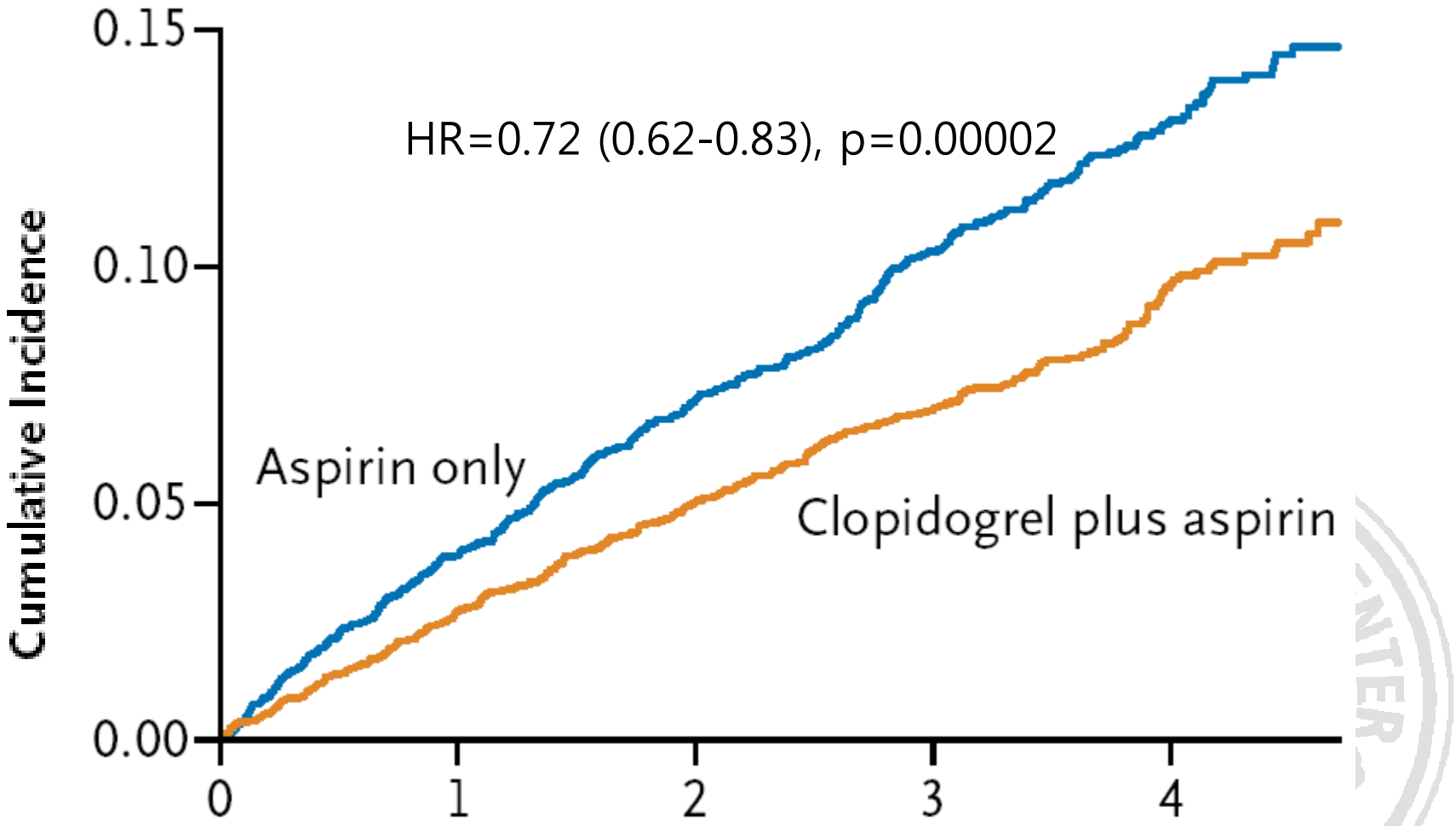
	Clopidogrel + Aspirin N=3772	Aspirin N=3782
Age- yr	70.9±10.2	71.1±10.2
Systolic BP	136.3±19.0	136.2±19.1
Heart rate — beats/min	75.2±14.5	74.8±14.4
CHADS2 0	105 (2.8%)	101 (2.7%)
1	1360 (36.1%)	1338 (35.4%)
2	1263 (33.5%)	1315 (34.8%)
3 or more	937 (24..8%)	924 (24.4%)
Male sex	2212 (58.6%)	2185 (57.8%)
Hypertension	3217 (85.3%)	3210 (84.9%)
Ischemic heart diseases	987 (26.2%)	1081 (28.6%)
DM	734 (19.5%)	728 (19.2%)
CHF	1240 (32.9%)	1256 (33.2%)

Primary Endpoint

Stroke, MI, Systemic embolism, Vascular death



Stroke

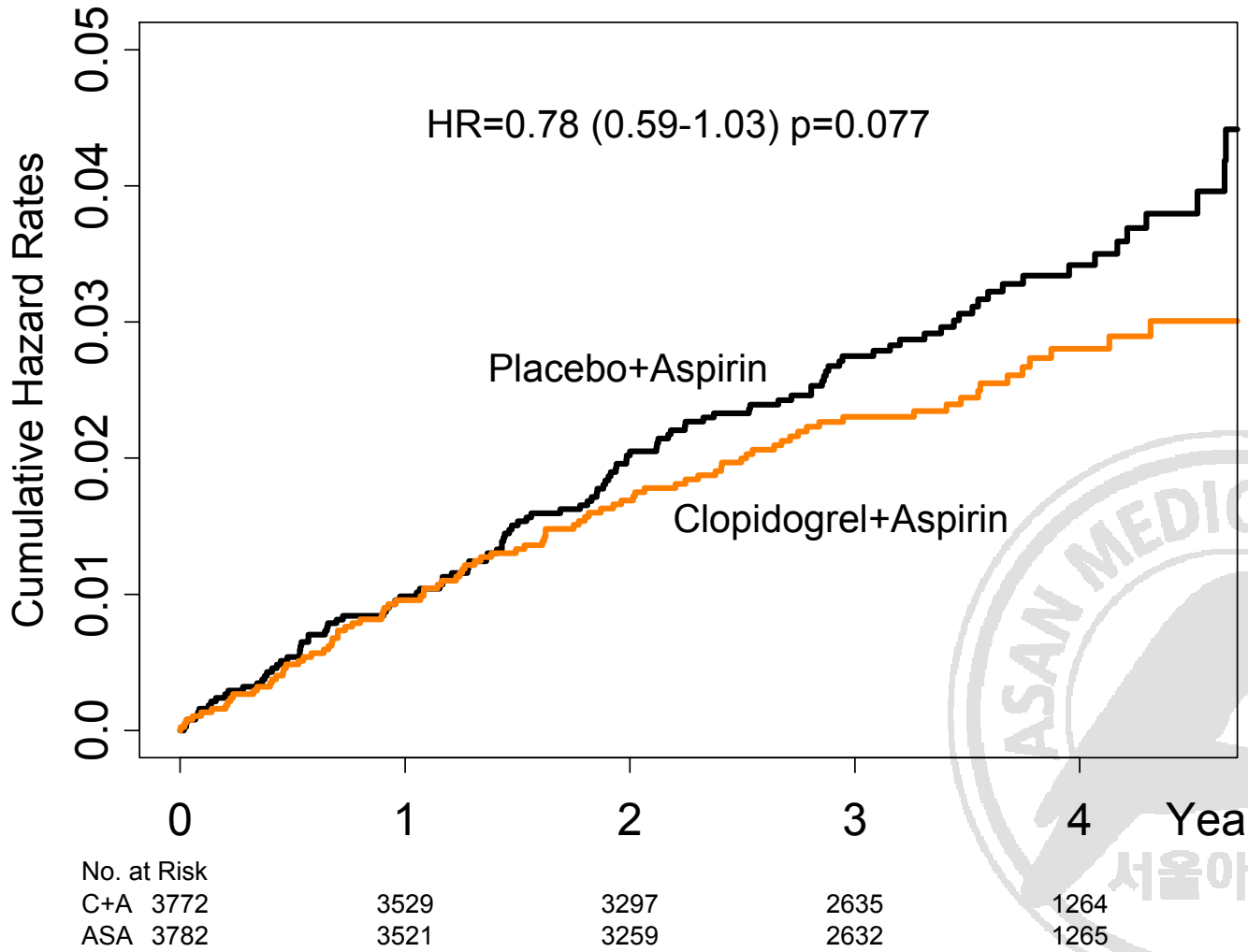


No. at Risk					
Clopidogrel plus aspirin	3772	3456	3180	2522	1179
Aspirin only	3782	3426	3103	2460	1156

Components of Primary Outcomes

Outcome	Clopidogrel + Aspirin		Aspirin		Clopidogrel + Aspirin versus Aspirin		
	#	rate/ year	#	rate/ year	RR	95% CI	P
Primary	832	6.8	924	7.6	0.89	0.81-0.98	0.014
Stroke	**296**	**2.4**	**408**	**3.3**	**0.72**	**0.62-0.83**	**<0.001**
MI	**90**	**0.7**	**115**	**0.9**	**0.78**	**0.59-1.03**	**0.08**
Vascular Death	600	4.7	599	4.7	1.0	0.89-1.12	0.97
Other embolism	54	0.4	56	0.4	0.96	0.66-1.40	0.84

Myocardial Infarction



Stroke Subtype & Severity

Outcome	Clopidogrel + Aspirin		Aspirin		Clopidogrel + Aspirin vs. Aspirin		
	#	rate/ year	#	rate/ year	RR	95% CI	P
Ischemic/Uncertain	268	2.1	388	3.2	0.68	0.59-0.80	<0.001
Hemorrhagic	30	0.2	22	0.2	1.37	0.79-2.37	0.27
Non-disabling (mod. Rankin 0-2)	107	0.9	153	1.2	0.70	0.54-0.89	0.004
Disabling or fatal (mod. Rankin 3-6)	198	1.6	267	2.1	0.74	0.62-0.89	0.001

Bleeding Events

Outcome	Clopidogrel + Aspirin		Aspirin		Clopidogrel + Aspirin vs. Aspirin		
	#	rate/ year	#	rate/ year	RR	95% CI	P
Major	251	2.0	162	1.3	1.57	1.29-1.92	<0.001
Severe	190	1.5	122	1.0	1.57	1.25-1.98	<0.001
Fatal	42	0.3	27	0.2	1.56	0.96-2.53	0.07
Intra-cranial	54	0.4	29	0.2	1.87	1.19-1.94	0.006
Extra-cranial	200	1.6	134	1.1	1.51	1.21-1.88	<0.001

Conclusions

- Maintenance of therapeutic range of oral anticoagulation is difficult in a significant portion of patients
- Addition of clopidogrel to aspirin in high risk of AF patient, unsuitable for warfarin
  - **Reduces major vascular events**
  - **Primarily due to a reduction in stroke**
  - **With an increase in major bleeding**
- It provides an important benefit to many patients at an acceptable risk