



# Anticoagulation in Patients with Atrial Fibrillation

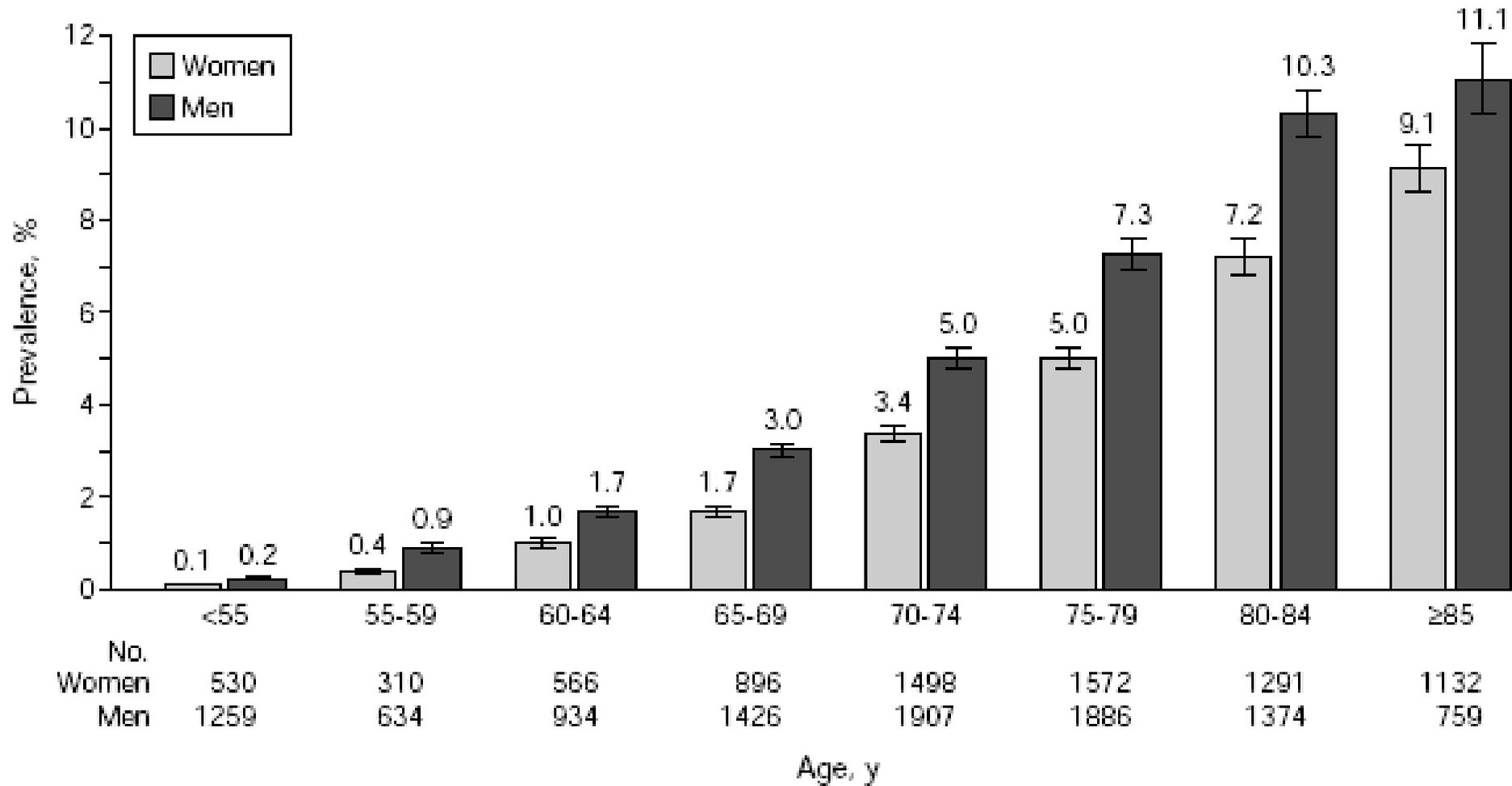
**Kim Sung-Hwan, MD**

Seoul St. Mary's Hospital

The Catholic University of Korea

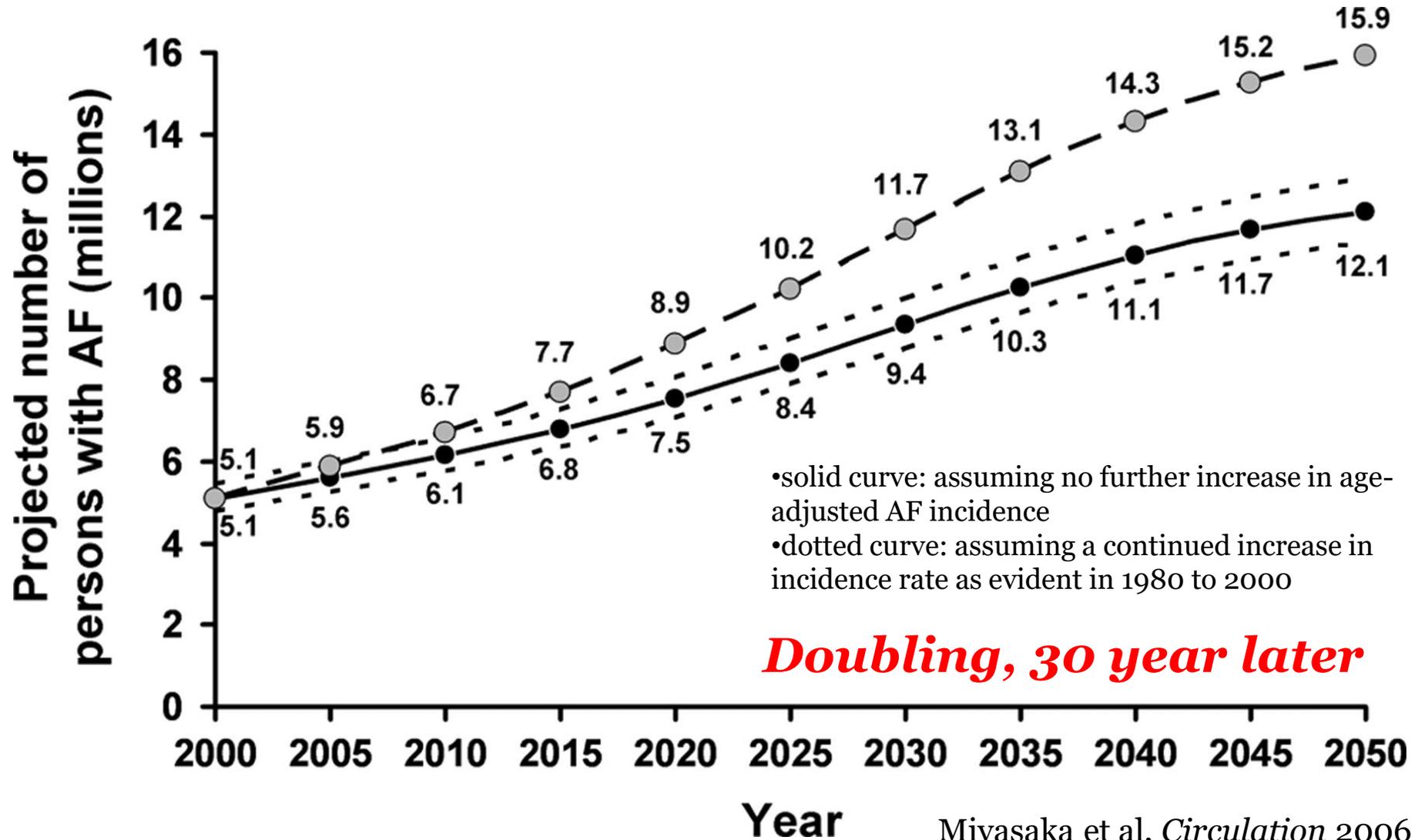


# Prevalence of Atrial Fibrillation



Go et al, *JAMA* 2001

# Increasing !



Miyasaka et al, *Circulation* 2006

# Treatment Strategy for AF

## **1) Anticoagulation or Not**

2) Rhythm vs. Rate

3) LA appendage closure

# Anticoagulation guideline for AF

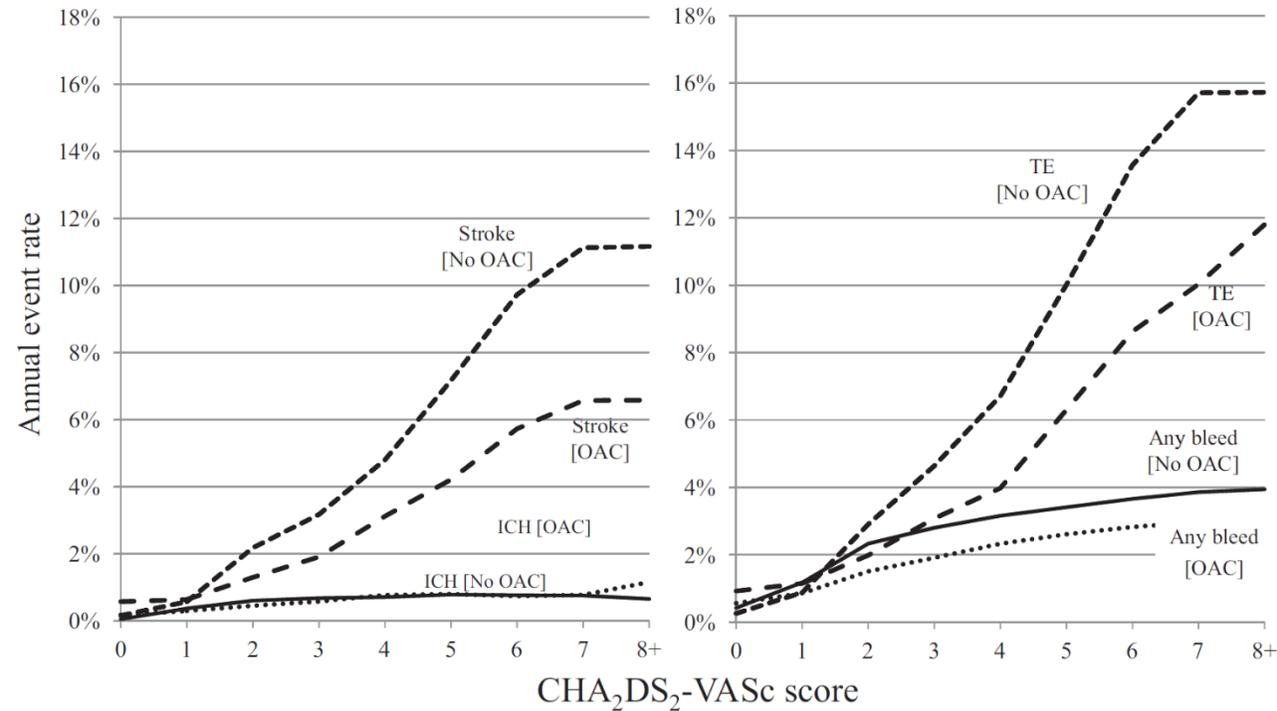
- Mitral stenosis, hypertrophic cardiomyopathy, and mechanical valve
  - ⇒ High risk of thrombus
  - ⇒ Absolute indication of anticoagulation
  
- The others
  - ⇒ as CHADS-VA score

# Why we need anticoagulation for atrial fibrillation ?



# Warfarin effects (1)

- Swedish AF cohort. N=182,678



Swedish AF Cohort. Friberg et al. *Circulation* 2012

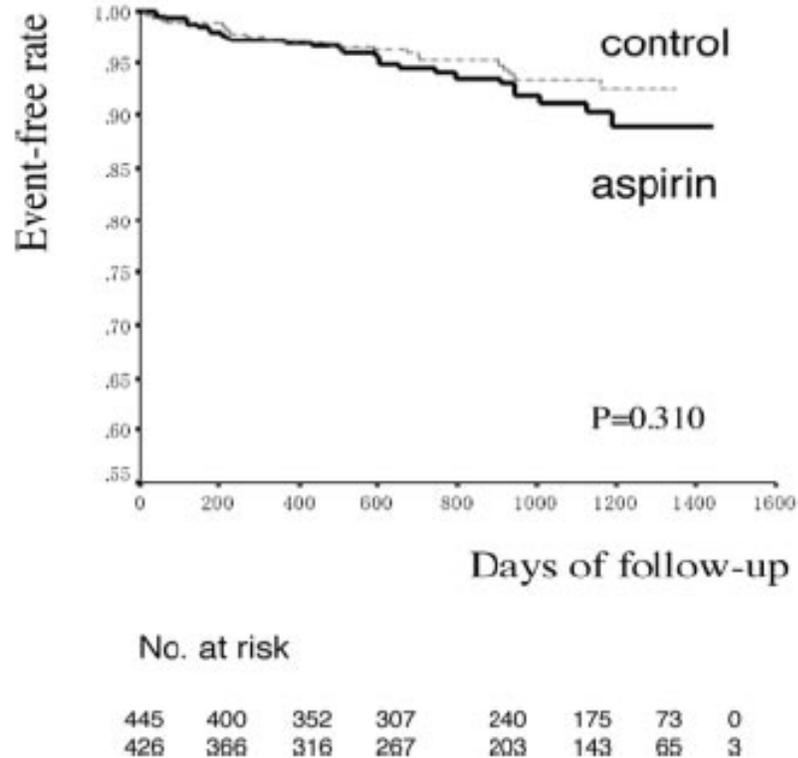
# How about aspirin ?

- Relatively low-risk patients with AF
  - Japanese, non-valvular, CHADS  $\leq 2$  (?)
- aspirin vs. placebo
- Age 65, HT 40%, DM 14%, s/p stroke 2.5%, HF 9%
- End point: CV death + ischemic stroke + TIA
  
- **Early termination !**

JAFST trial, *Stroke* 2006



# No effect but bleeding



**TABLE 2. Primary and Secondary End Points**

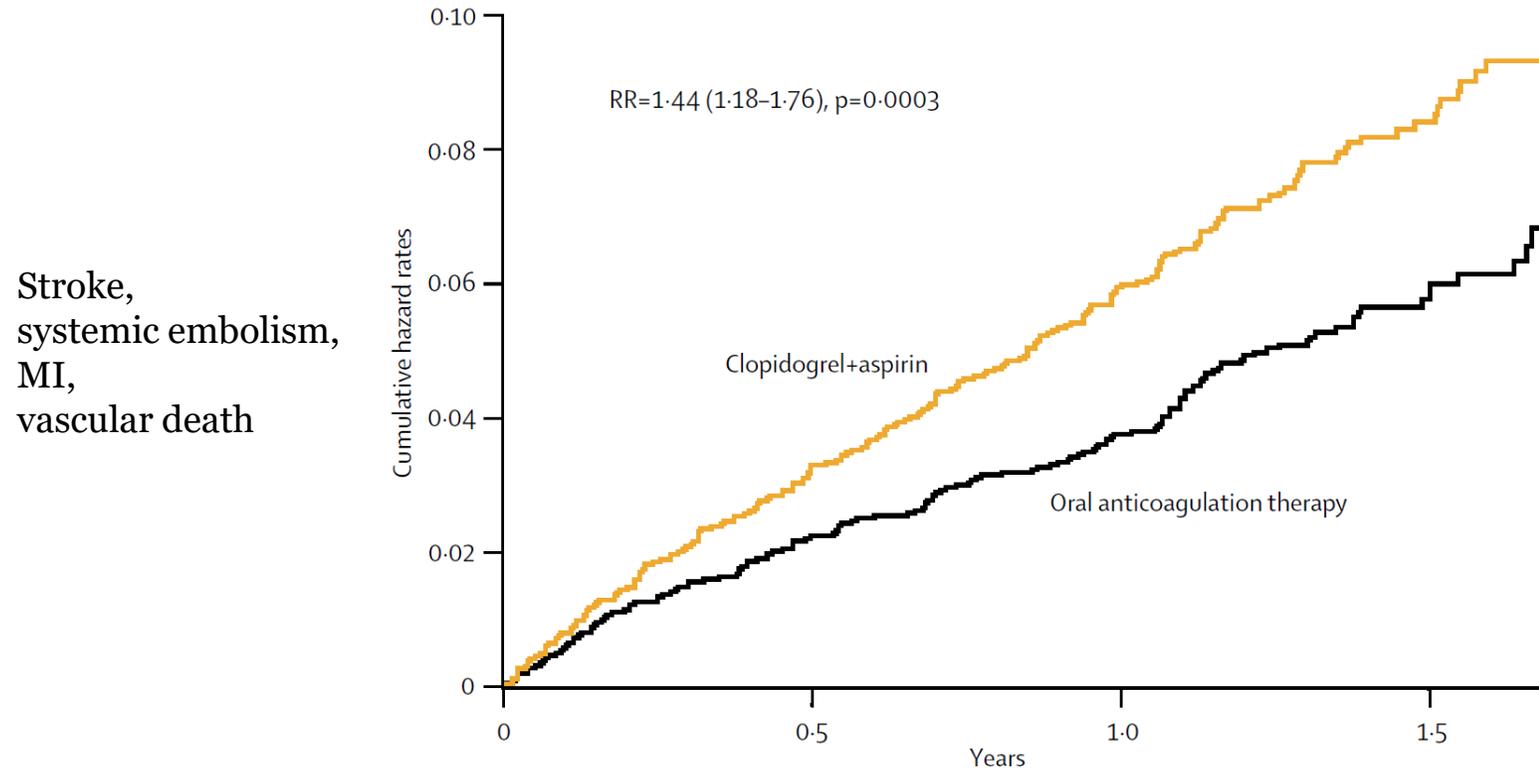
	Aspirin (n=426)	Control (n=445)	P Value
Primary end points	27	23	0.458
Cardiovascular death	3	3	1.000*
Stroke	17	18	0.967
Cardiogenic embolism	14	12	0.609
Thrombotic infarction	3	2	0.959*
Lacunar infarction	0	4	0.135*
TIA	7	2	0.101*
Secondary end points	14	9	0.254
Noncardiovascular death	7	6	0.720
Peripheral emboli	0	1	1.000*
Major bleeding	7†	2‡	0.101*

\*Fisher test; †includes 2 subdural bleedings, thalamic bleeding, subarachnoidal bleeding, urinary tract bleeding, gastric bleeding, and respiratory bleeding; ‡include subarachnoidal bleeding and thalamic bleeding.

JAFST trial, *Stroke* 2006

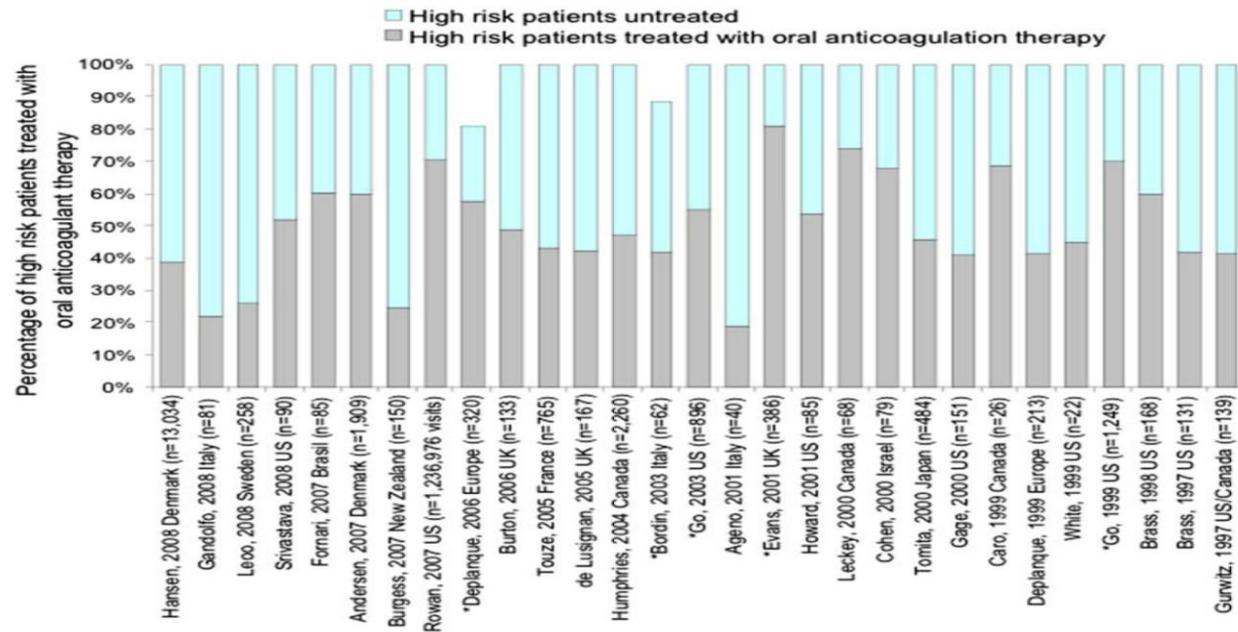
# Warfarin effects (2)

- Aspirin + Clopidogrel vs. Warfarin



ACTIVE W trial. *Lancet* 2006

# Significant underuse of warfarin



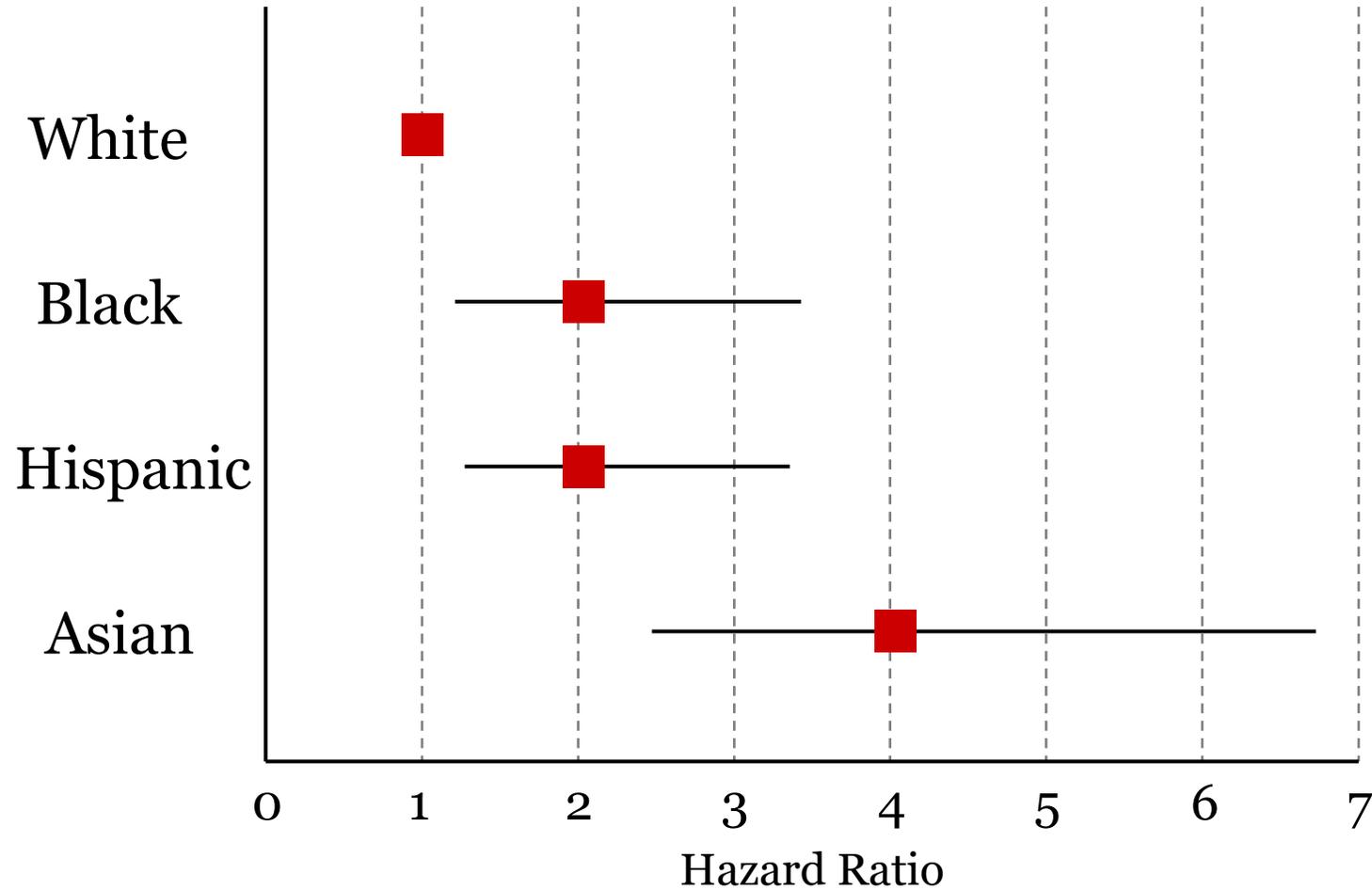
Warfarin was prescribed in only 50% of AF patients at high risk of stroke in real world practice

Ogilvie et al. *Am J Med.* 2010

# Underuse of Warfarin

- Diverse drug/food interaction
- Blood sampling for prothrombin time

# The risk of Intracranial hemorrhage during warfarin



Shen AY, et al: *J Am Coll Cardiol* 2007

# Oral anticoagulants other than warfarin



# Non-vitamin K Oral AntiCoagulant

(or Direct Oral AntiCoagulant, DOAC)

- Dabigatran (=Pradaxa<sup>®</sup>)
- Rivaroxaban (=Xarelto<sup>®</sup>)
- Apixaban (=Eliquis<sup>®</sup>)
- Edoxaban (=Lixiana<sup>®</sup>)

# The Indications of Warfarin

**Atrial fibrillation  
without MS**

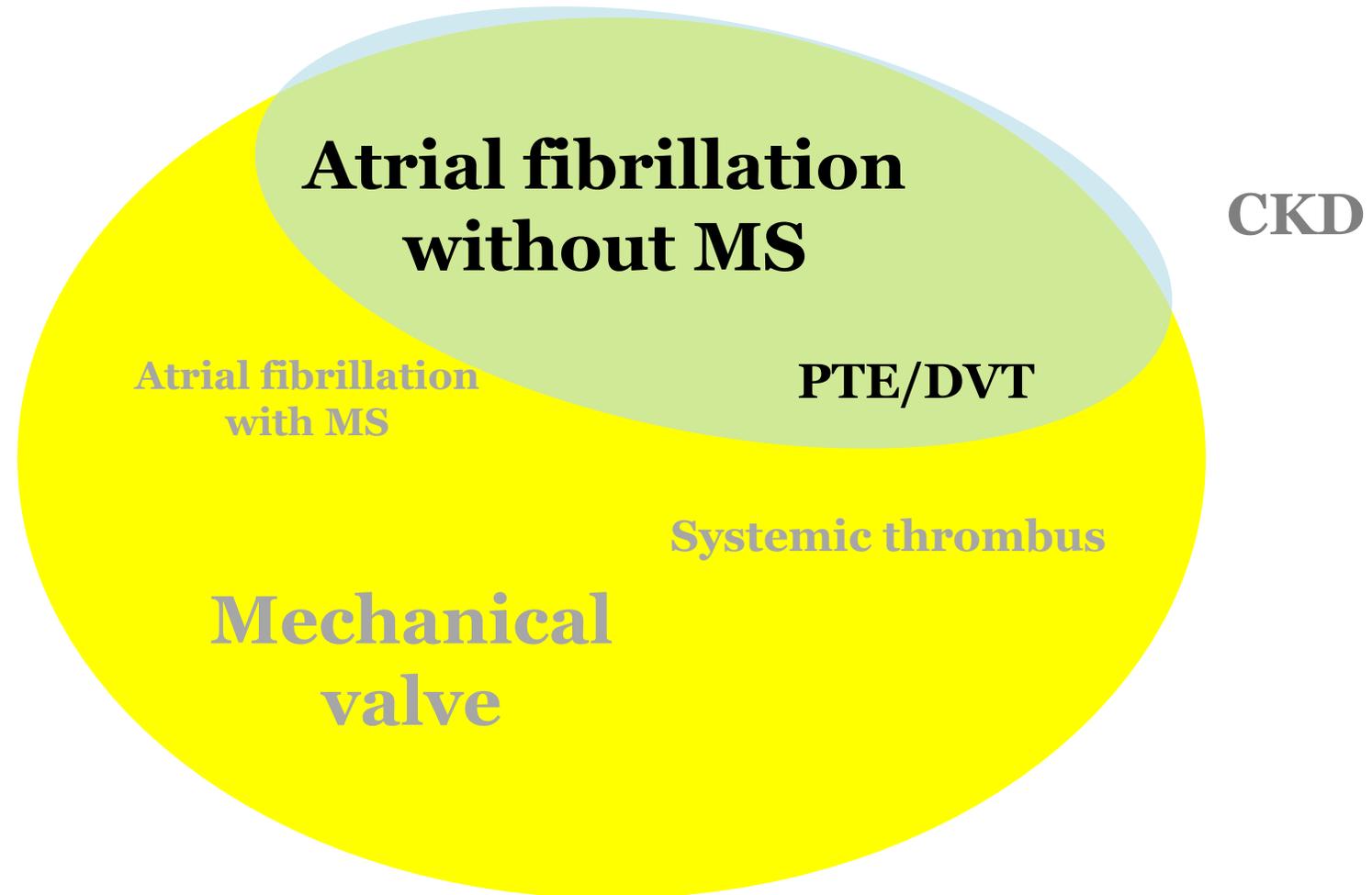
**Atrial fibrillation  
with MS**

**PTE/DVT**

**Systemic thrombus**

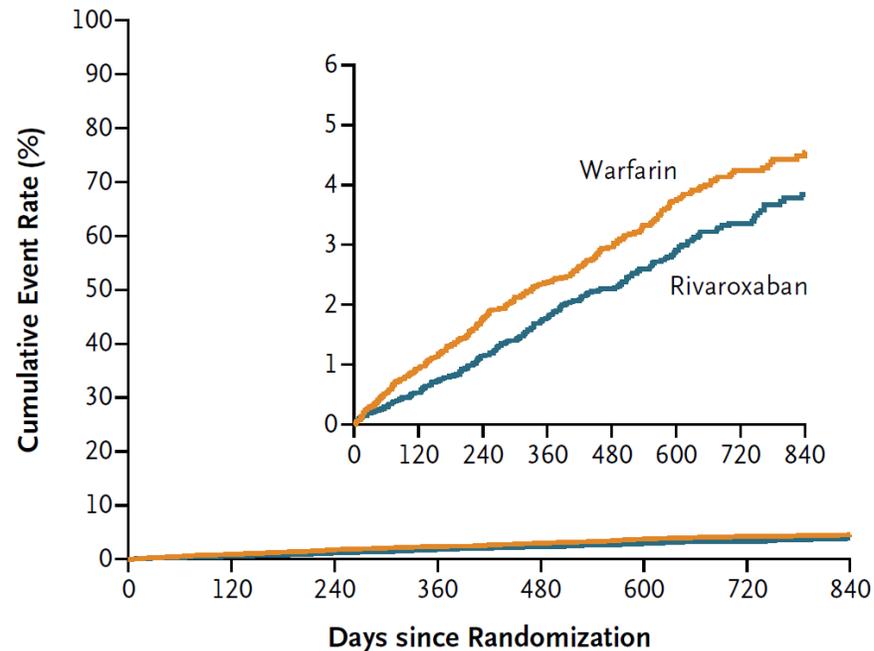
**Mechanical  
valve**

# The indications of NOAC, so far



# Stroke/embolism - Rivaroxaban

- AF without mitral stenosis, N=14,264, Rivaroxaban vs. Warfarin
- Stroke/systemic embolism is decreased



ROCKET AF trial. Patel et al. *N Engl J Med* 2011

# Bleeding - Rivaroxaban

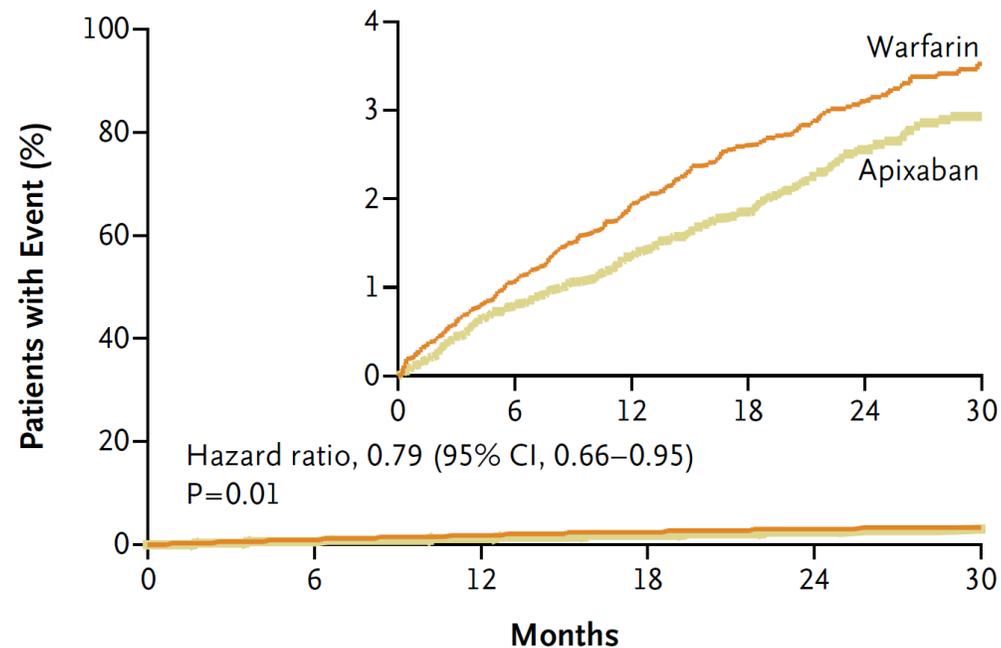
- Major bleeding : similar with warfarin
- Intracranial hemorrhage is significantly decreased

ROCKET AF trial. Patel et al. *N Engl J Med* 2011



# Stroke/embolism - Apixaban

- AF without MS, N=18,201, Apixaban vs. Warfarin
- Stroke/embolism: 21% decrease compared to warfarin



ARISTOTLE trial. Granger et al. *N Engl J Med* 2011

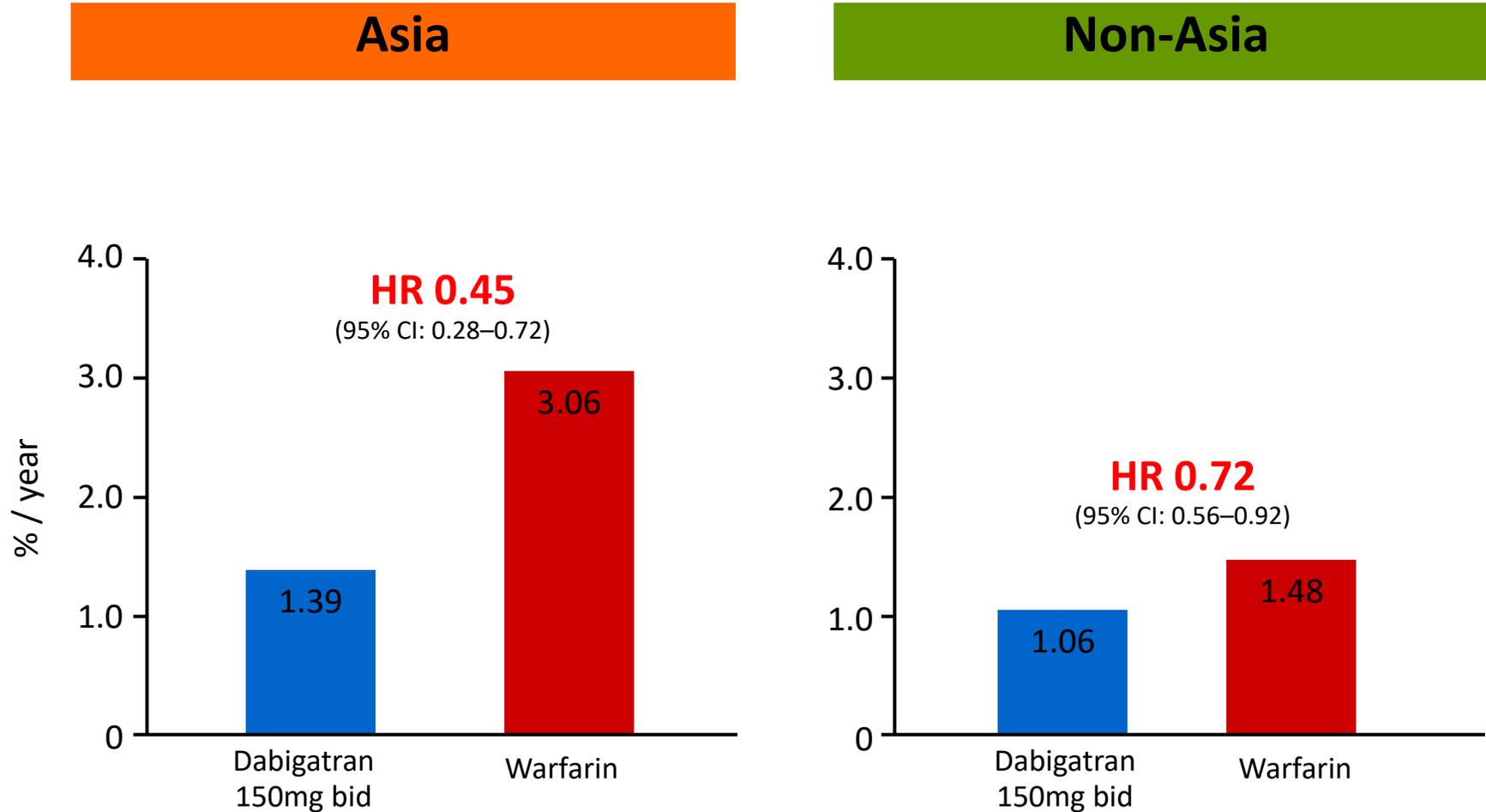
# Bleeding - Apixaban

- Major bleeding: 31% decrease compared to warfarin
- Intracranial hemorrhage: 58% decrease compared to warfarin

ARISTOTLE trial. Granger et al. *N Engl J Med* 2011

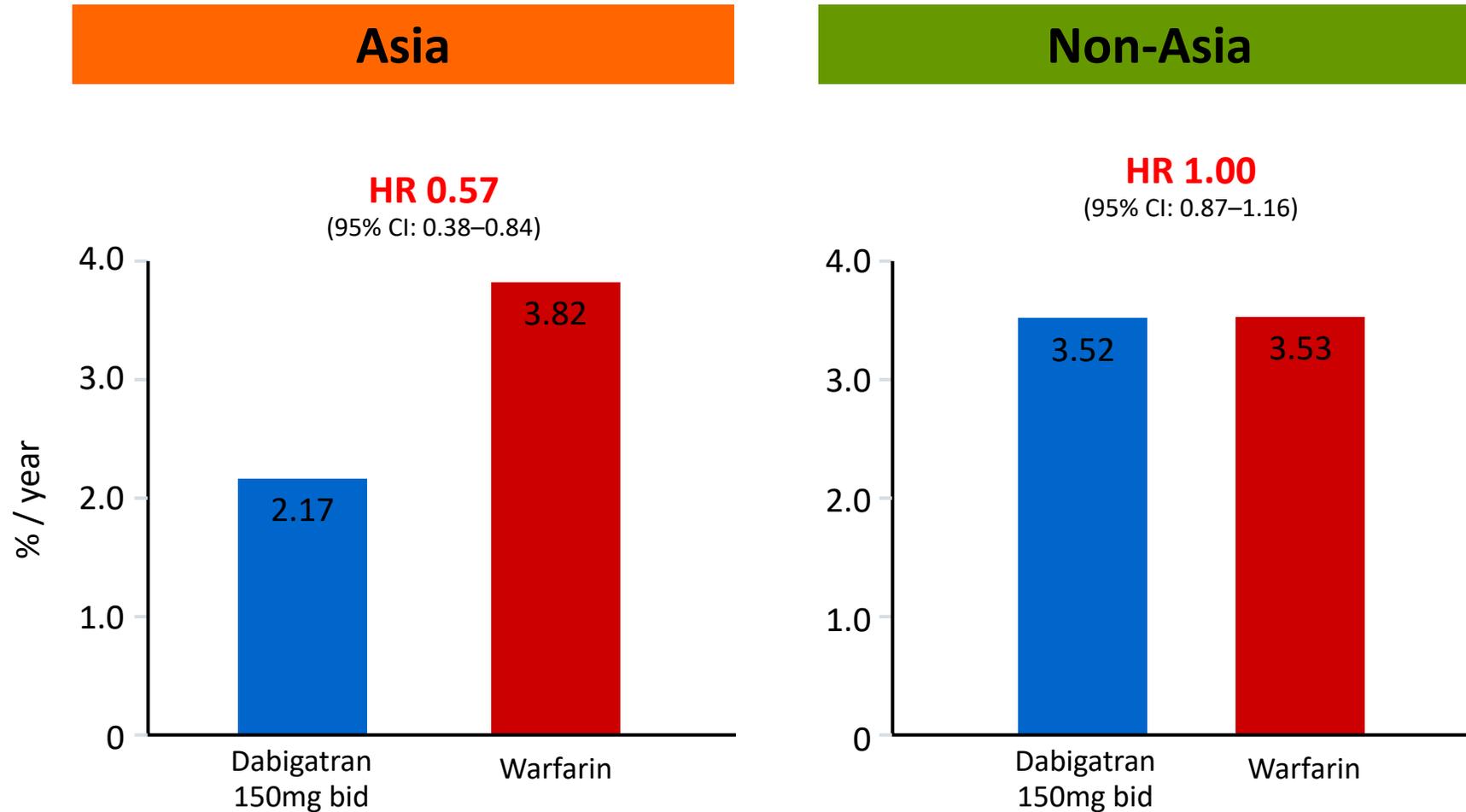


# Stroke/embolism - Dabigatran



RE-LY trial subgroup study. *Stroke* 2013

# Major bleeding - Dabigatran



RE-LY trial subgroup study. *Stroke* 2013

# CHA<sub>2</sub>DS<sub>2</sub>-VASc score?

- **C**ongestive heart failure (1)
- **H**ypertension (1)
- **A**ge (>75) (2)
- **D**iabetes (1)
- **S**troke (2)
- **V**ascular disease (1); OMI, PAOD, aortic plaque
- **A**ge (65~74) (1)
- **S**ex (female) (1)

# Update of European Guideline

- Past
  - as CHADS-VASc
  - Male: 2 or higher
  - Female: 3 or higher
- Current (2024~)
  - as CHADS-VA
  - 2 or higher

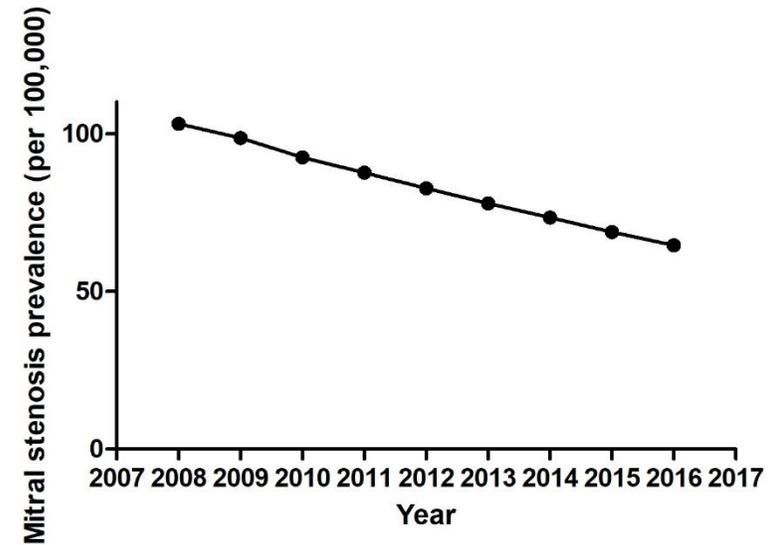
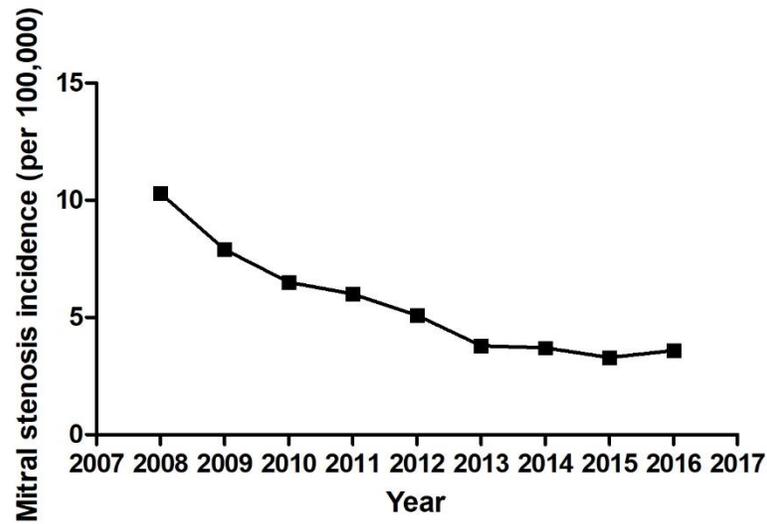
# Anticoagulation as CHA<sub>2</sub>DS<sub>2</sub>-VA score

- In case of AF **without mitral stenosis**
- ESC 2024
  - 0 point: no
  - 1 point: case by case
  - **≥2 point: NOAC or warfarin**

# **Anticoagulation in Patients with AF and Mitral Stenosis**

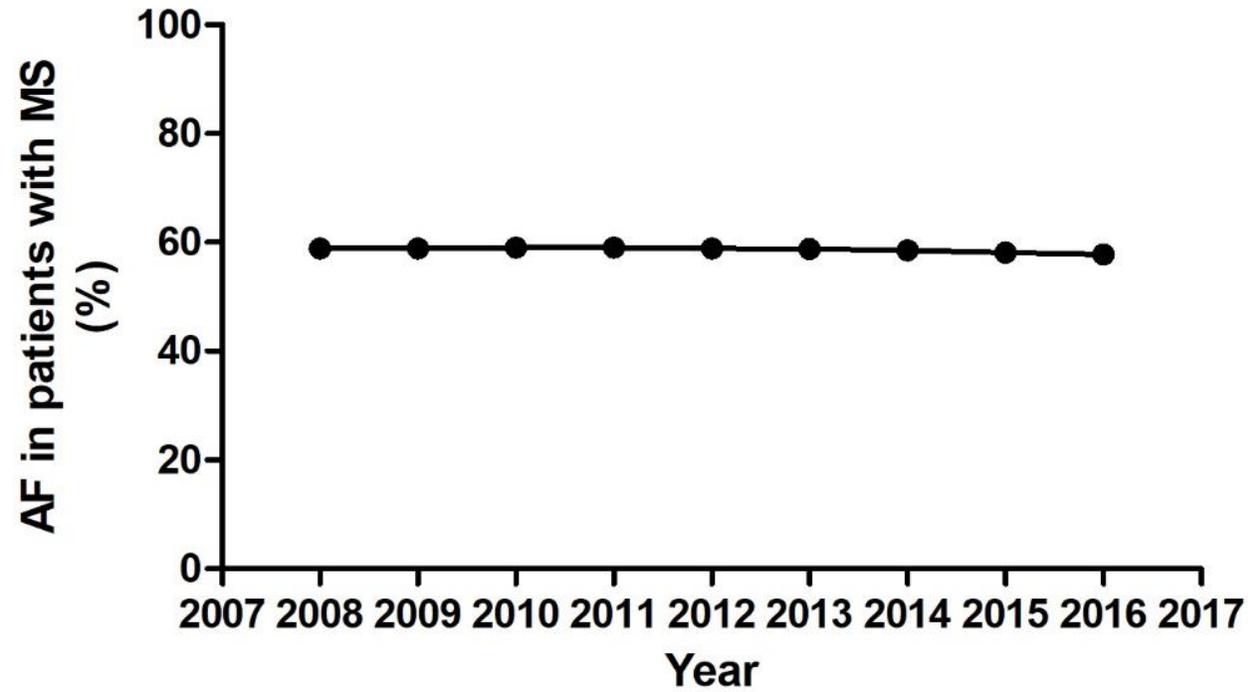


# Epidemiology of Mitral Stenosis in Korea



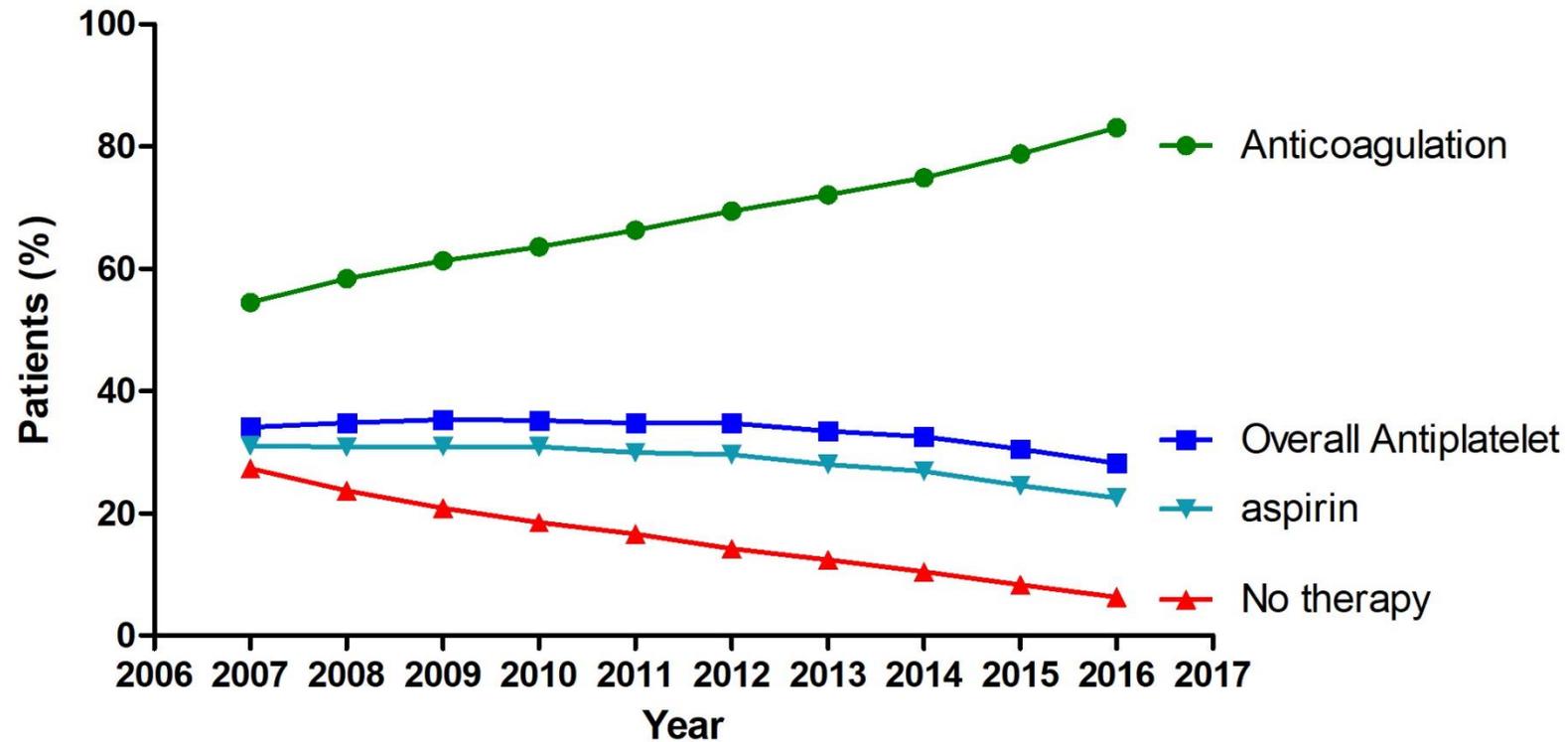
Kim JY, Kim SH et al. *Heart* 2020

# AF in patients with MS



Kim JY, Kim SH et al. *Heart* 2020

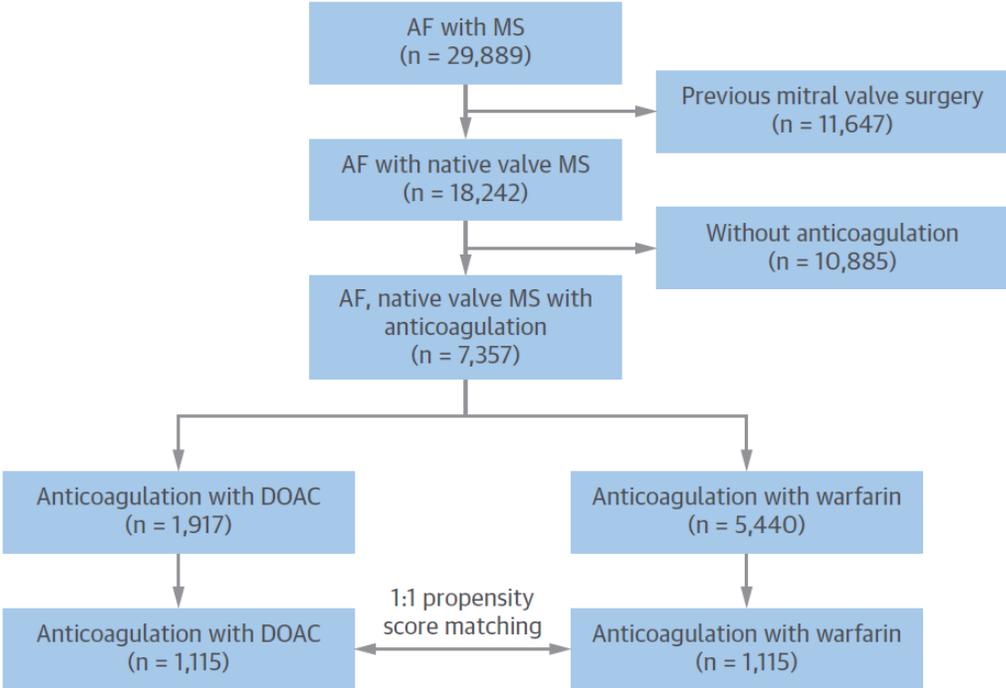
# Anticoagulation status in patients with AF and MS



Kim JY, Kim SH et al. *Heart* 2020

# Some physicians have prescribed NOAC for MS

- Off-label use? Unawareness ?



Kim JY, Kim SH et al. *JACC* 2019

# Baseline characteristics

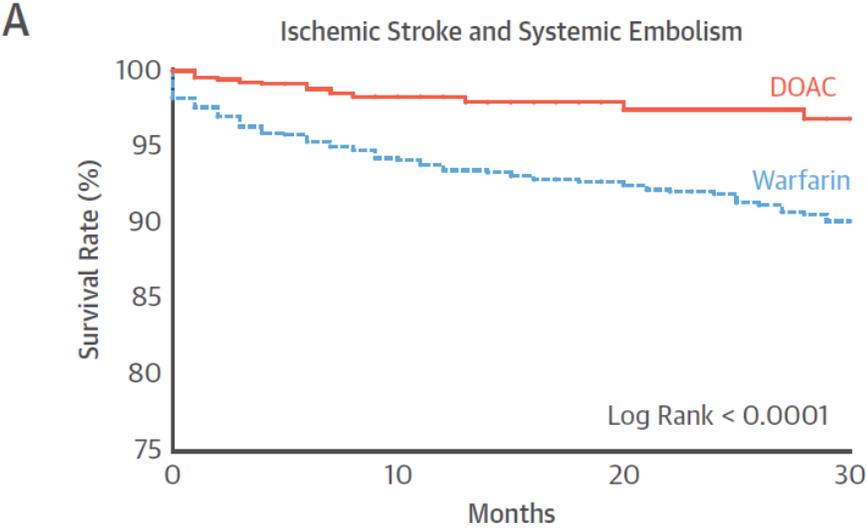
	DOAC (n = 1,115)	Warfarin (n = 1,115)	Standardized Difference	p Value
Age, yrs	69.2 ± 10.9	70.2 ± 10.2	0.0947	
<65	311 (27.9)	318 (28.5)	0.0192	0.90
65-74	401 (36.0)	404 (36.2)		
≥75	403 (36.1)	393 (35.3)		
Female	775 (69.5)	773 (69.3)	0.0039	0.93
Hypertension	1,076 (96.5)	1,080 (96.9)	0.0200	0.64
Diabetes mellitus	759 (68.1)	760 (68.2)	0.0019	0.96
Previous stroke	518 (46.5)	521 (46.7)	0.0054	0.90
Congestive heart failure	832 (74.6)	838 (75.2)	0.0124	0.77
Previous vascular disease	625 (56.1)	623 (55.9)	0.0036	0.93
Dyslipidemia	810 (72.7)	808 (72.5)	0.0040	0.92
COPD	265 (23.7)	267 (24.0)	0.0042	0.92
CKD	80 (3.59)	73 (6.55)	0.0248	0.56

Values are mean ± SD or n (%).

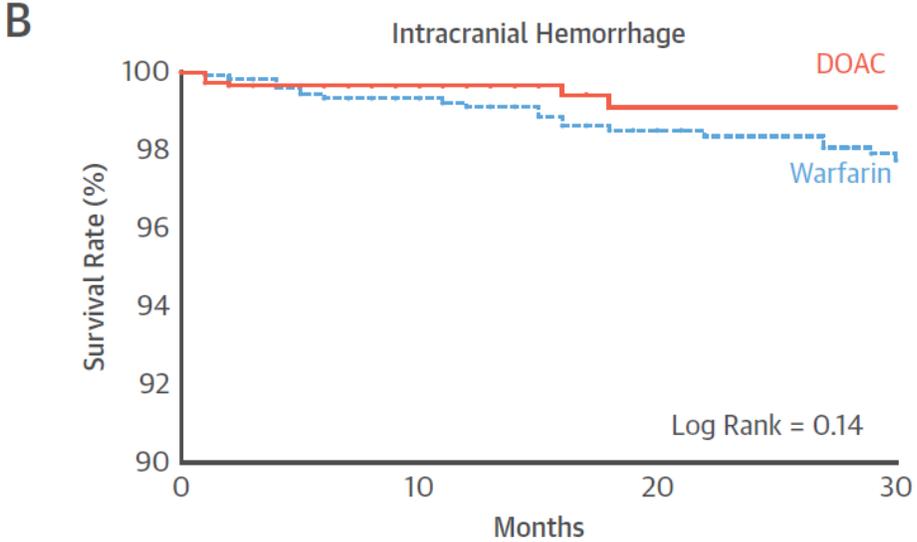
CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; DOAC = direct oral anticoagulants.

Kim JY, Kim SH et al. *JACC* 2019

# Less events (stroke and bleeding)



Number at Risk				
	0	10	20	30
DOAC	1,115	703	192	140
Warfarin	1,115	853	701	560



Number at Risk				
	0	10	20	30
DOAC	1,115	718	199	150
Warfarin	1,115	905	759	620

Kim JY, Kim SH et al. *JACC* 2019

# Main findings

- This is the first study of NOAC for AF with MS
- NOAC would be feasible even for MS
- Provide evidence for future randomized trial

Kim JY, Kim SH et al. *JACC* 2019



# INVICTUS trial

ORIGINAL ARTICLE

## Rivaroxaban in Rheumatic Heart Disease–Associated Atrial Fibrillation

S.J. Connolly, G. Karthikeyan, M. Ntsekhe, A. Haileamlak, A. El Sayed, A. El Ghamrawy, A. Damasceno, A. Avezum, A.M.L. Dans, B. Gitura, D. Hu, E.R. Kamanzi, F. Maklady, G. Fana, J.A. Gonzalez-Hermosillo, J. Musuku, K. Kazmi, L. Zühlke, L. Gondwe, C. Ma, M. Paniagua, O.S. Ogah, O.J. Molefe-Baikai, P. Lwabi, P. Chillo, S.K. Sharma, T.T.J. Cabral, W.M. Tarhuni, A. Benz, M. van Eikels, A. Krol, D. Pattath, K. Balasubramanian, S. Rangarajan, C. Ramasundarahettige, B. Mayosi,\* and S. Yusuf, for the INVICTUS Investigators†

ABSTRACT



# ERTEMIS trial, prospective RCT

- Inclusion
  - AF (any type)
  - MS (any degree)
- Exclusion
  - Mechanical valve
  - CrCl < 15 ml/min
- Efficacy end point
  - Stroke, systemic embolism
- Safety end point
  - Major bleeding

# Process

- **N=240** (edoxaban vs. warfarin, 1:1)
- Edoxaban group: drug provided (free)
- 2 yr FU
- Estimated event rate
  - Stroke/systemic embolism: 3.5% vs. 7%
  - ICH: 1% vs. 2%

# Summary

- AF without mitral stenosis
  - CHADS-VA score 2 points or more
  - NOAC > warfarin
  
- AF with mitral stenosis
  - Absolute indication for anticoagulation
  - Warfarin is recommended so far, but randomized trial is going for the question (DOAC vs. warfarin).

Any question?

[sunghwan@catholic.ac.kr](mailto:sunghwan@catholic.ac.kr)

