A COhort of antithrombotic use and Optimal INR Level in patients with non-valvular atrial fibrillation in Thailand (COOL AF Thailand)

CONTEMPORARY REVIEW

Stroke prevention in atrial fibrillation—An Asian stroke perspective

Heart Rhythm 2013;10:1082–1088

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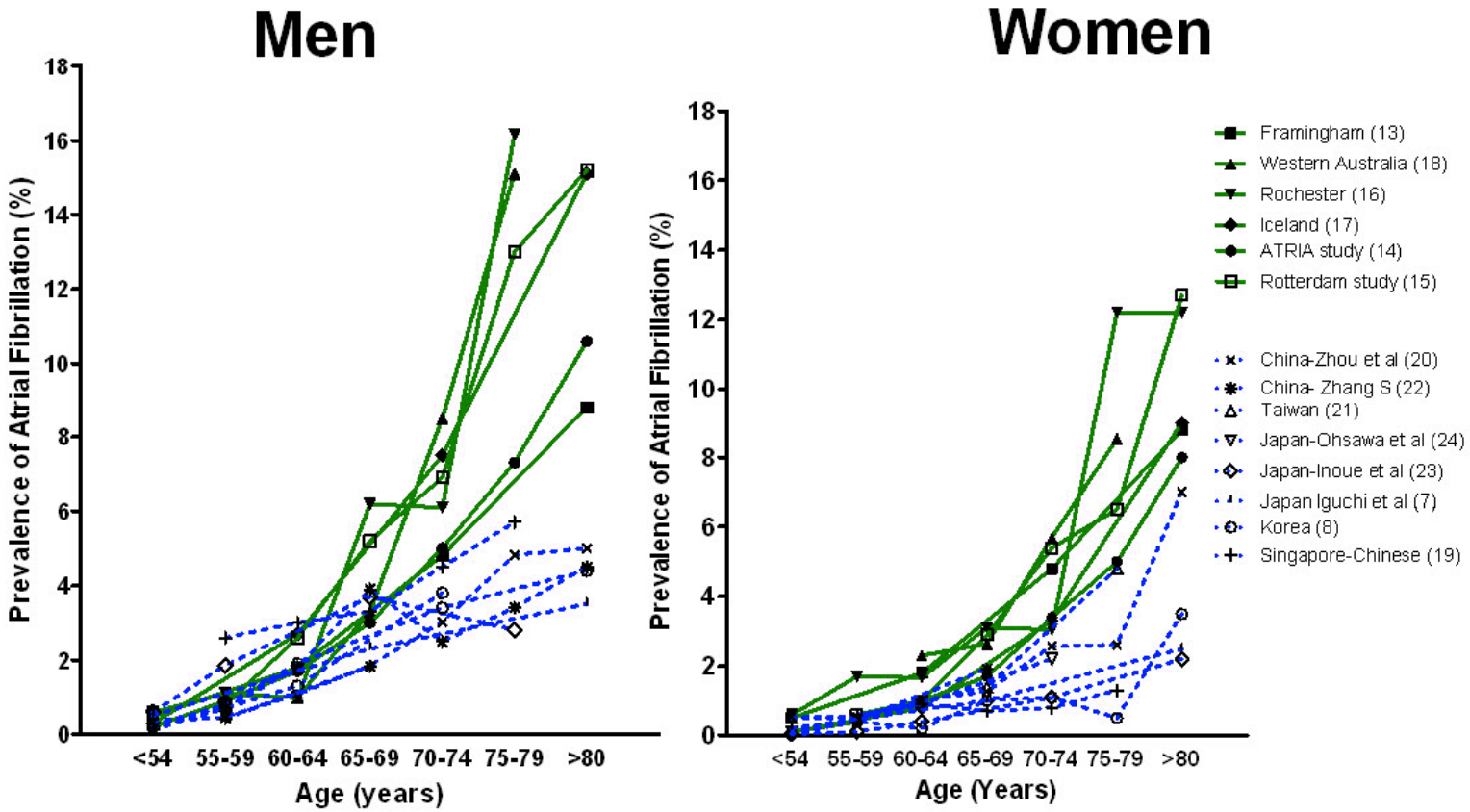
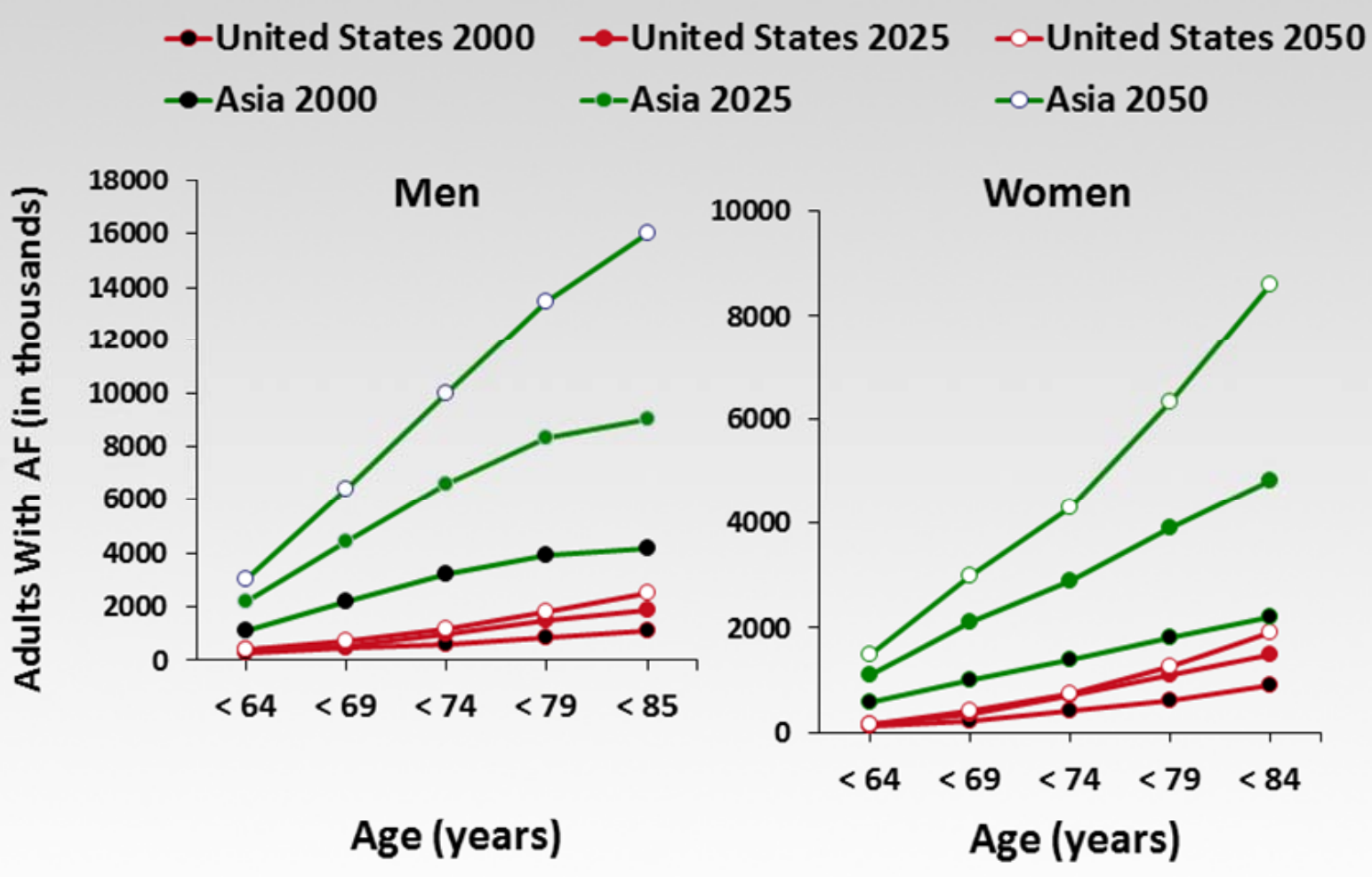


Prevalence of Atrial Fibrillation

Number of AF Patients Predicted to More Than Double by 2050



United Nations Department of Economic and Social Affairs, Population Division.
http://esa.un.org/unpd/wpp/unpp/panel_population.htm

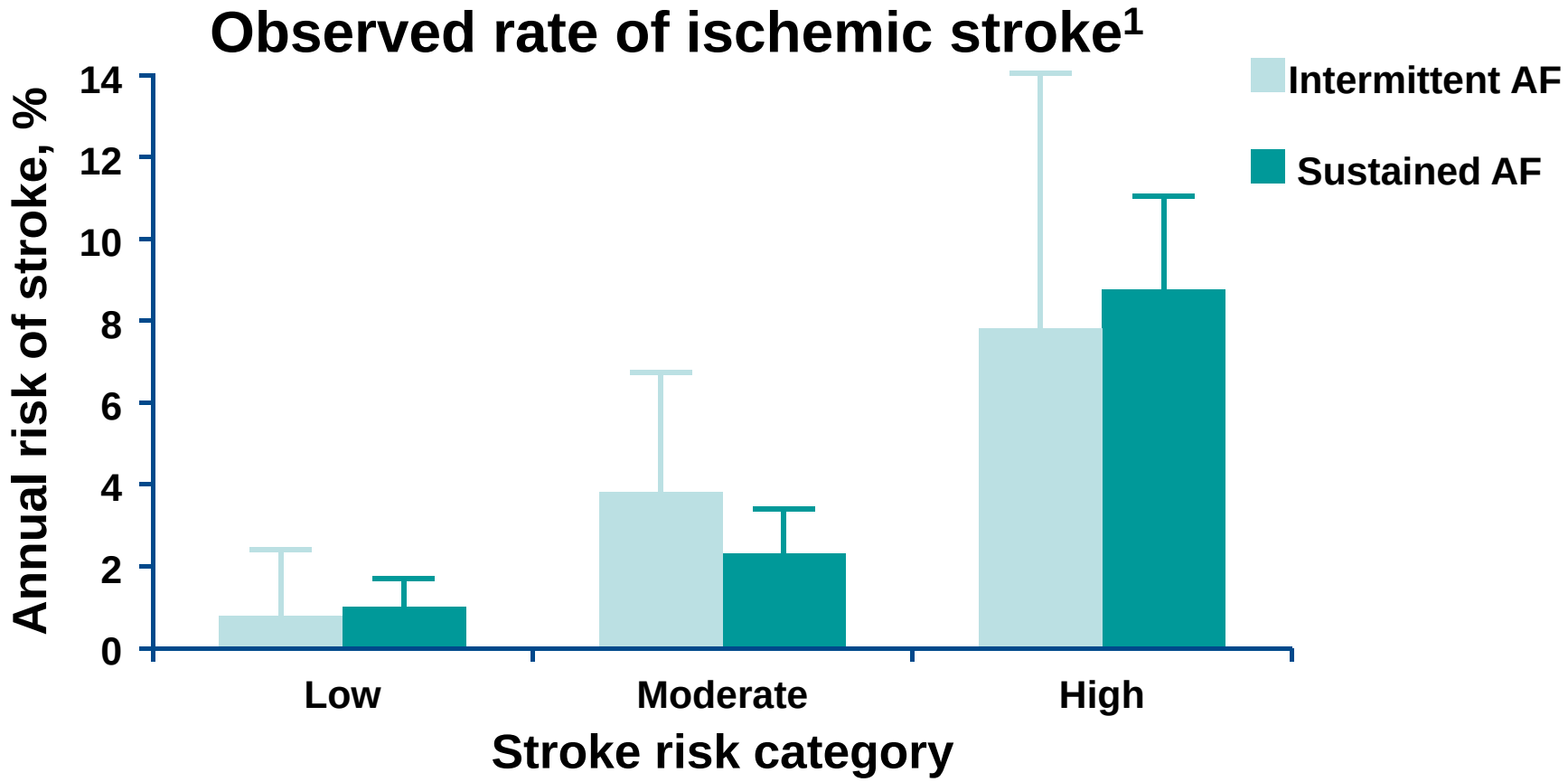
AF and Stroke Risk

Study Location	Mean Age (yrs)	Stroke (% per yr)		Relative Risk
		AF	No AF	
China[a]	71	5.3	-	-
Japan[b]	65	5.0	0.90	5.6
Taiwan[c]	70	4.9	0.45	8.4
United States[d]	70	4.1	0.74	5.6
United Kingdom[e]	60	1.8	0.26	6.9

a. Ma CS, et al. *Chin J Cardiol (Chin)*. 2012;107:1014-1018.
b. Nakayama T, et al. *Stroke*. 1997;28(1):45-52.
c. Chien KL, et al. *Int J Cardiol*. 2010;139(2):173-180.
d. Wolf PA, et al. *Stroke*. 1991;22(8):983-988.
e. Onundarson PT, et al. *Eur Heart J*. 1987;8(5):521-527.

Stroke risk persists even in asymptomatic/intermittent AF

- The risk of stroke with asymptomatic or intermittent AF is comparable to that with permanent AF[1,2]



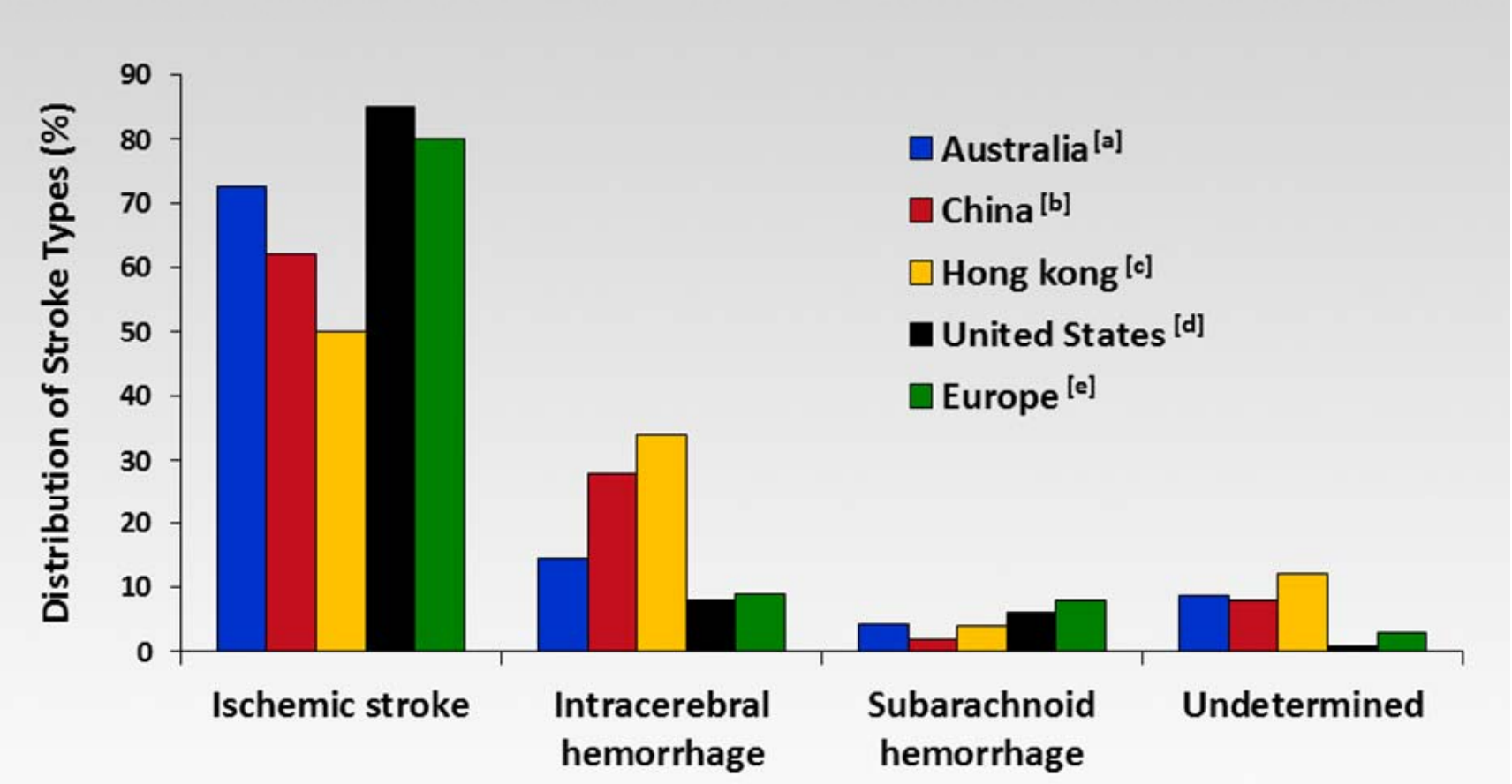
1. Hart RG et al. J Am Coll Cardiol 2000;35:183–7;
2. Flaker GC et al. Am Heart J 2005;149:657–63

Atrial fibrillation and Stroke Risk

Study	Mean age, years	Stroke (% per year)		Relative risk
		AF	No AF	
Ma, China	71	5.3	-	-
Shibata, Japan	65	5.0	0.90	5.6
Lee, Taiwan	70	4.9	0.45	8.4
Framingham, USA	70	4.1	0.74	5.6
Whitehall, UK	60	1.8	0.26	6.9

Ma et al. Chin J Cardiol 2012; 107: 1014-1018.
Shibata et al. Stroke 1997; 28: 45–52.
Lee et al. Int J Cardiol 2010; 139: 173-180.
Wolf et al. Stroke 1991; 22: 983–988.
Onundarson et al. Eur Heart J 1987; 8: 521–527.

Stroke Subtypes by Different Geographic Regions



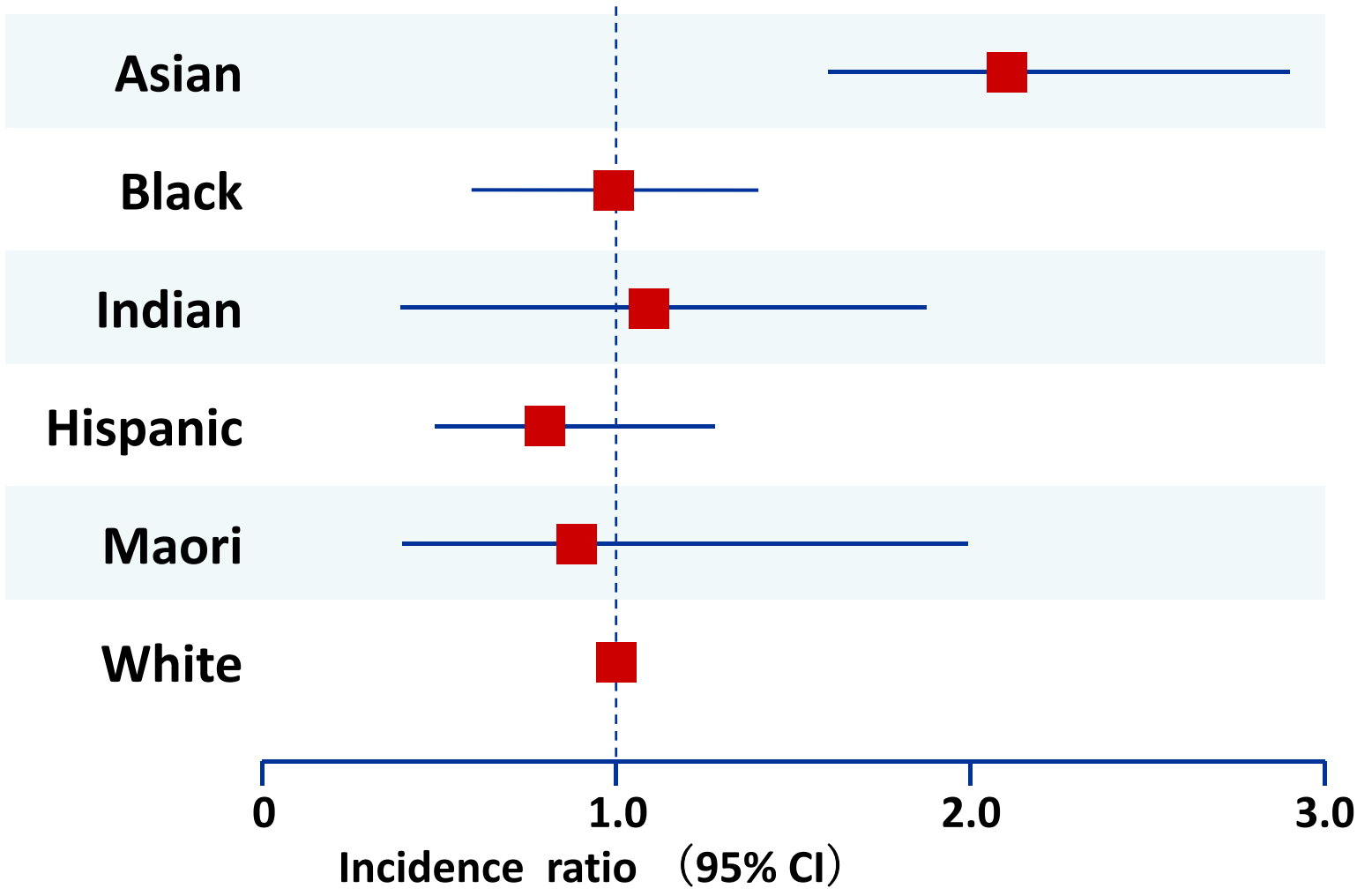
a. Thrift AG, et al. *Neuroepidemiology*. 2009;32(1):11-18.
b. Zhang LF, et al. *Stroke*. 2003;34(9):2091-2096.
c. Chau PH, et al. *Cerebrovasc Dis*. 2011;31(2):138-146.
d. Gross CR, et al. *Stroke*. 1984;15(2):249-255.
e. Sivenius J, et al. *Stroke*. 1985;16(2):188-192.

Reduction of risk of thromboembolism in AF

- Warfarin vs placebo 62% (48-72%)
- ASA vs placebo 22% (2-38%)
- Warfarin vs ASA 36% (14-52%)

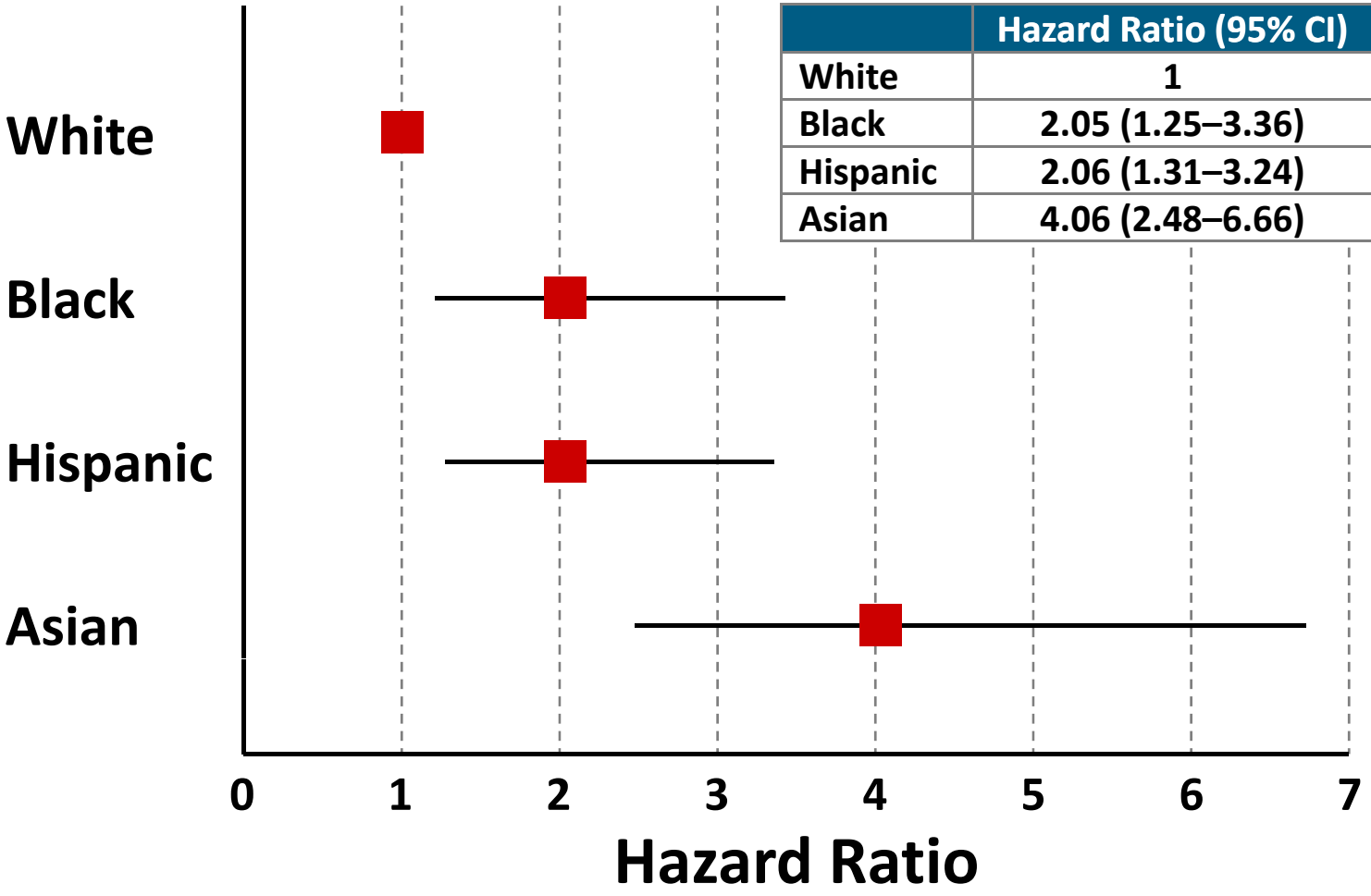
Lip GY, et al. BMJ 2002; 325: 1022-5

Incidence Ratios of Cerebral Hemorrhage in Different Ethnic Groups (Meta-analysis)



van Asch CJ, et al. *Lancet Neurol.* 2010;9(2):167-176.

Adjusted Hazard Ratio for Intracranial Hemorrhage on warfarin treatment



	Hazard Ratio (95% CI)	p Value
White	1	-
Black	2.05 (1.25–3.36)	0.005
Hispanic	2.06 (1.31–3.24)	0.002
Asian	4.06 (2.48–6.66)	<0.0001

Multiethnic cohort of 18,867 patients hospitalized with first-time AF (January 1995 – December 2000)

Shen AY, et al: J Am Coll Cardiol 50: 309-315, 2007

	Western countries	Thailand
CYP2C9*2 and CYP2C9*3	5-10%[1,2]	5%[3]
VKORC1 A haplotypes	37%[4]	63.6%[3]

1.Guruprasad P Aithal et al . Association of polymorphisms in the CYP2C9 with warfarin dose requirement and risk of bleeding complications. The Lancet Vol. 353. February 27, 1999.
2. Janis Taube et al Influence of CYP2C9 polymorphisms on warfarin sensitivity and risk of over-anticoagulation in patients on long-term treatment. Blood. 2000;96:1816-19.
3. Kuanprasert S et al. Prevalence of CYP2C9 and VKORC1 mutation in patients with VHD in northern Thailand. J Med Assoc Thai. 2009 Dec;92(12): 1597-601.
4. Mark J. Rieder et al. Effect of VKORC1 Haplotypes on Transcriptional Regulation and Warfarin Dose. N Engl J Med 2005;352:2285-93.

Why Are Asian Patients at Higher Bleeding Risk? Potential Explanations

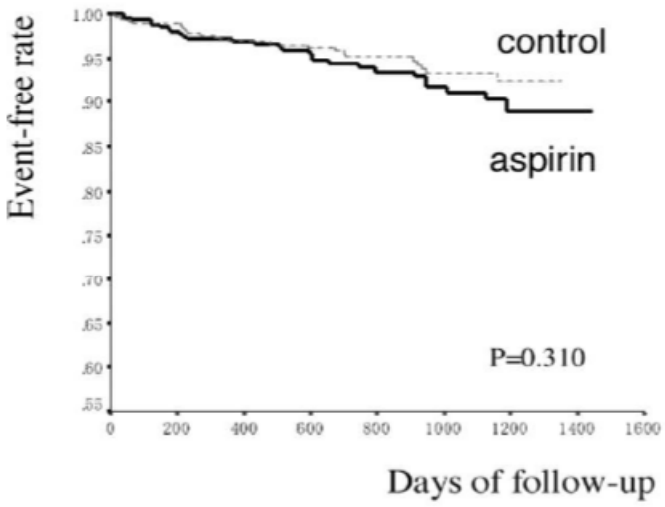
- INR instability; difficulties regulating INR[a]
- Differences in the prevalence of certain polymorphisms in genes that influence warfarin pharmacokinetics and pharmacodynamics[b]
  - Cytochrome P450 2CY—In patients on warfarin, the variant CYP2C9 genotype has conferred an increased risk for major hemorrhage.[c]
  - Vitamin K epoxide reductase
- Different vascular properties of Asian patients

a. Kim JH, et al. *Yonsei Med J.* 2009;50(1):83-88.
b. Medi C, et al. *Stroke*. 2010;41(11):2705-2713.
c. Shen AY, et al. *CNS Drugs*. 2008;22(10):815-825.

The Japan AF Stroke Prevention Trial: - JAST Trial -

Primary Endpoint:

CV Death, stroke, TIA

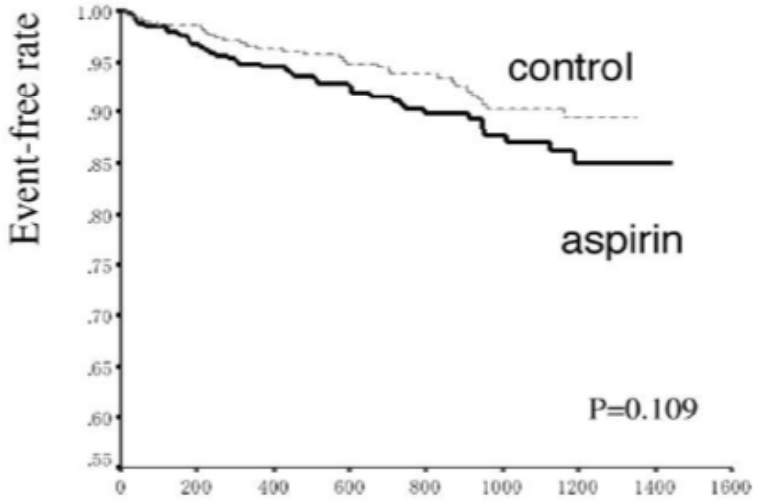


No. at risk

445	400	352	307	240	175	73	0
426	366	316	267	203	143	65	3

Primary & Secondary Endpoints:

+ all-cause-mortality, hemorrhage, per. embolism



No. at risk

445	400	352	307	240	175	73	0
426	366	316	267	203	143	65	3

In addition, treatment with aspirin caused a marginally increased risk of major bleeding (7 patients; 1.6%) compared with the control group (2 patients; 0.4%; Fisher exact test *P*0.101)

Sato et al. Stroke 2006; 37:447-501

Stroke risk assessment with $CHADS_2$

$CHADS_2$ risk criteria	Score
Prior stroke or TIA	2
Age >75 yr	1
Hypertension	1
Diabetes mellitus	1
Heart failure	1

Total $CHADS_2$ score	Adjusted stroke risk, %/yr (95% CI)	
0	1.9	(1.2–3.0)
1	2.8	(2.0–3.8)
2	4.0	(3.1–5.1)
3	5.9	(4.6–7.3)
4	8.5	(6.3–11.1)
5	12.5	(8.2–17.5)
6	18.2	(10.5–27.4)

CI = confidence interval; TIA = transient ischaemic attack

Fuster V et al. Circulation 2006;114:e257–354; Gage BF et al. JAMA 2001;285:2864–70

Stroke risk assessment with CHA_2DS_2-VASc

CHA_2DS_2-VASc criteria	Score
Congestive heart failure/ left ventricular dysfunction	1
Hypertension	1
Age ≥75 yrs	2
Diabetes mellitus	1
Stroke/transient ischemic attack/TE	2
Vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque)	1
Age 65–74 yrs	1
Sex **c**ategory (i.e. female gender)	1

Total score	Patients (n=7329)	Adjusted stroke rate (%/year)*
0	1	0.0
1	422	1.3
2	1230	2.2
3	1730	3.2
4	1718	4.0
5	1159	6.7
6	679	9.8
7	294	9.6
8	82	6.7
9	14	15.2

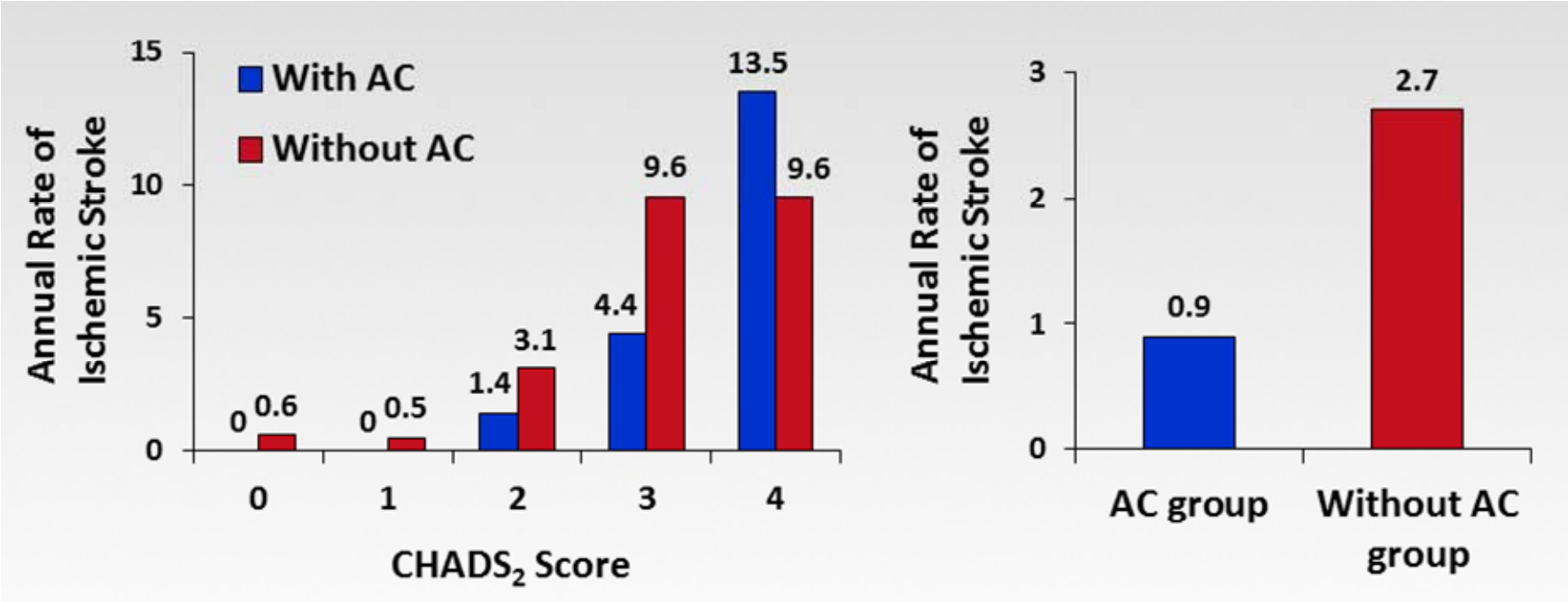
***Theoretical rates without therapy; assuming that warfarin provides a 64% reduction in stroke risk, based on Hart RG et al. 2007.**

TE = thromboembolism

Lip G et al. Chest 2010;137:263-72; Lip G et al. Stroke 2010; 41:2731–8; Camm J et al. Eur Heart J 2010; 31: 2369–429; Hart RG et al. Ann Intern Med 2007;146:857–67

$CHADS_2$ Score Effectively Determines Stroke Risk in Japanese Patients With NVAF

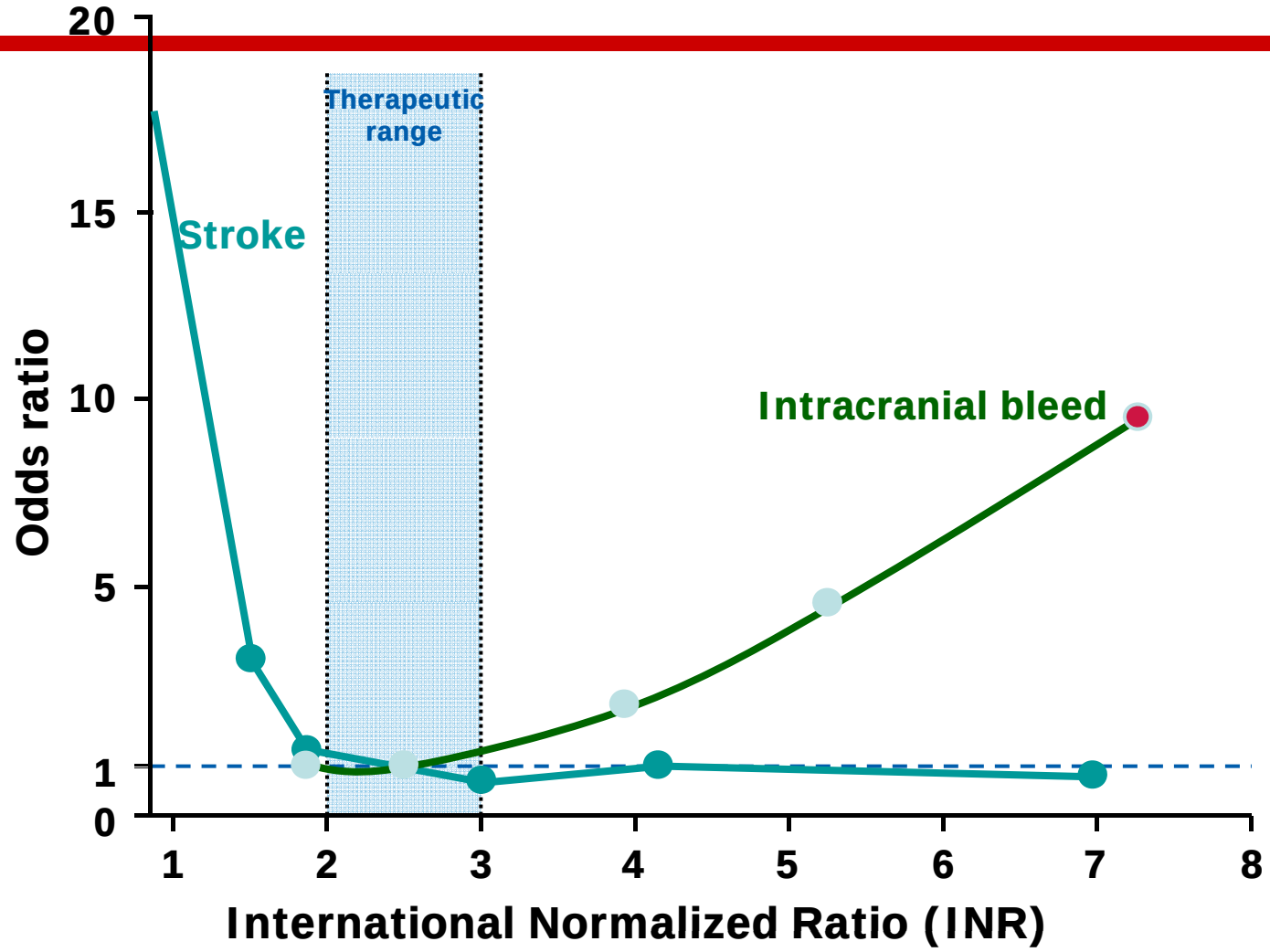
- In a study of 334 Japanese NVAF patients, $CHADS_2$ score was identified as a useful predictor of ischemic stroke.



AC = anticoagulation; NVAF = nonvalvular atrial fibrillation

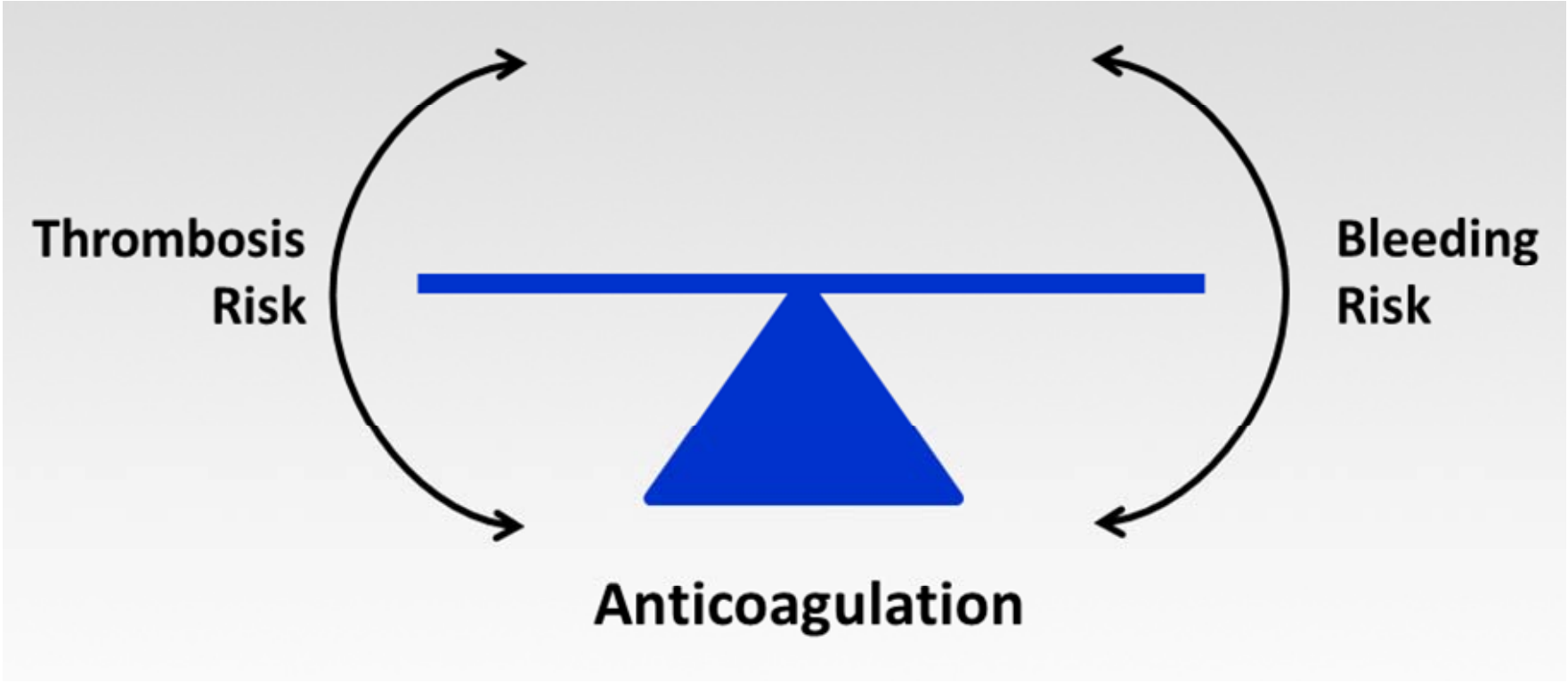
Komatsu T, et al. *Int Heart J.* 2010;51(1):24-29.

VKAs have a narrow therapeutic window

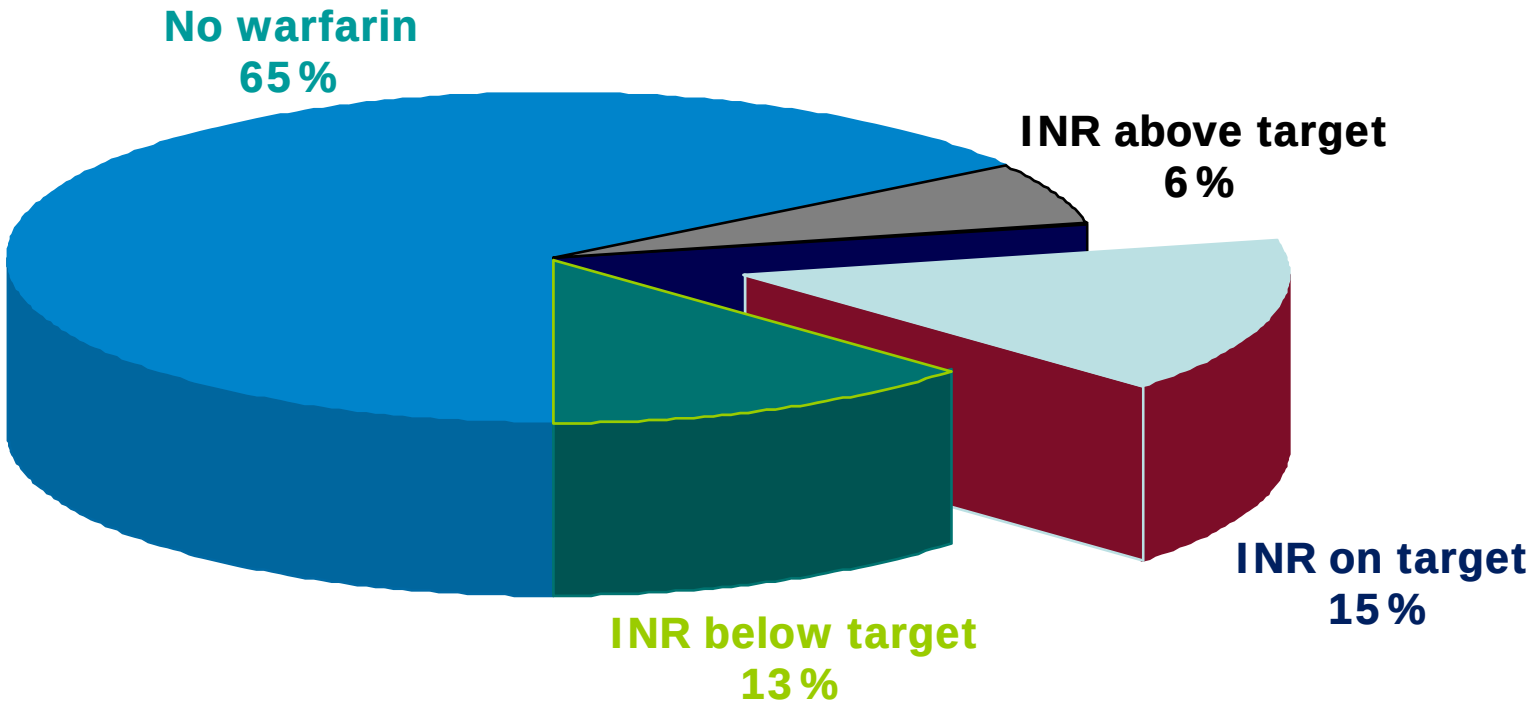


Fuster V et al. Circulation 2006;114:e257–e354

Anticoagulation Use: A Balance Between Stroke Prevention and Risk for Bleeding



In the small proportion of patients with AF receiving warfarin, the INR is often outside the therapeutic range



Samsa GP et al. Arch Intern Med 2000;160:967–73

Major Bleeding risk assessment with HAS-BLED

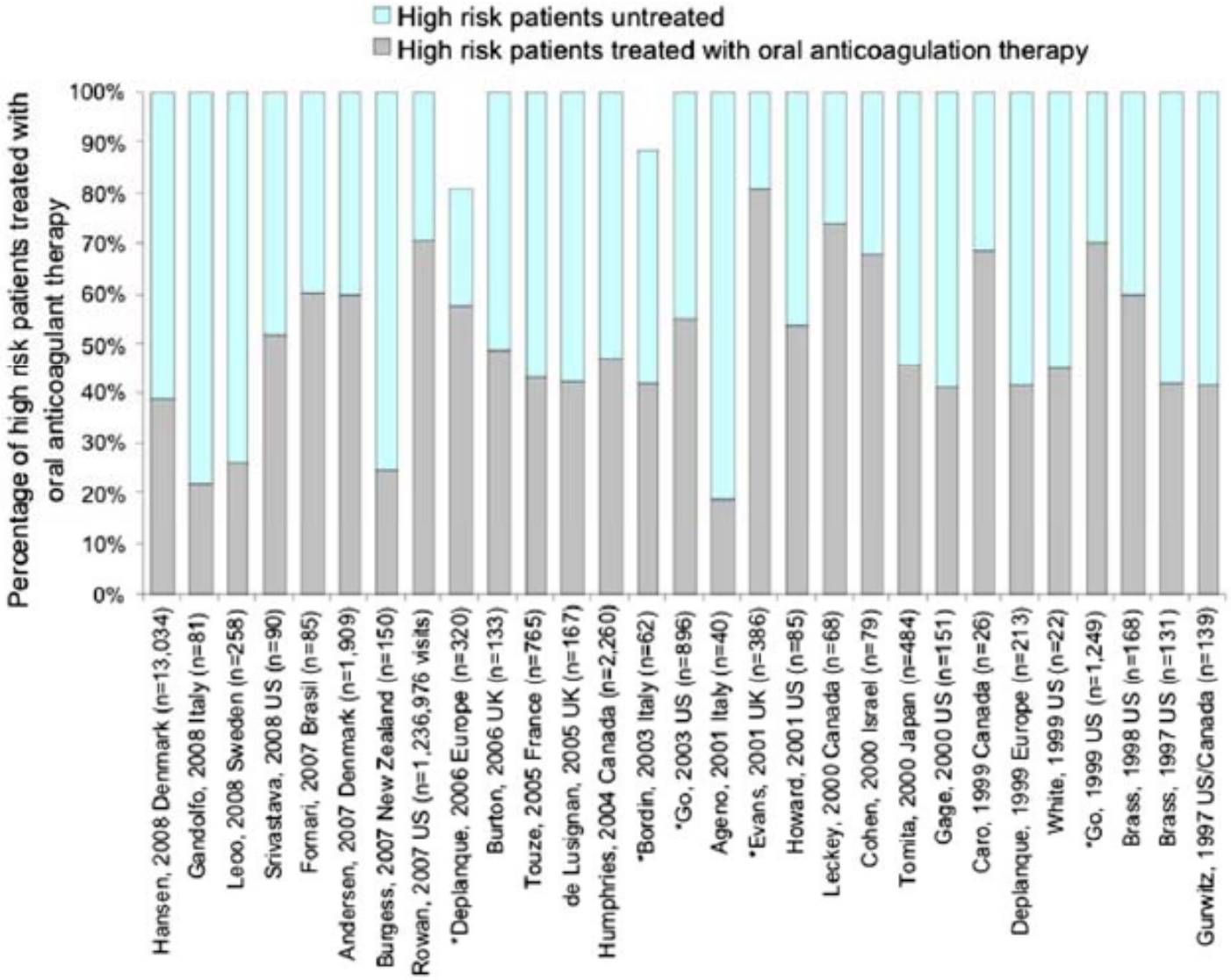
HAS-BLED risk criteria	Score
Hypertension	1
Abnormal renal or liver function (1 point each)	1 or 2
Stroke	1
Bleeding	1
Labile INRs	1
Elderly (e.g. age >65 yrs)	1
Drugs or alcohol (1 point each)	1 or 2

HAS-BLED total score	N	Number of bleeds	Bleeds per 100 patient-yrs*
0	798	9	1.13
1	1286	13	1.02
2	744	14	1.88
3	187	7	3.74
4	46	4	8.70
5	8	1	12.5
6	2	0	0.0
7	0	–	–
8	0	–	–
9	0	–	–

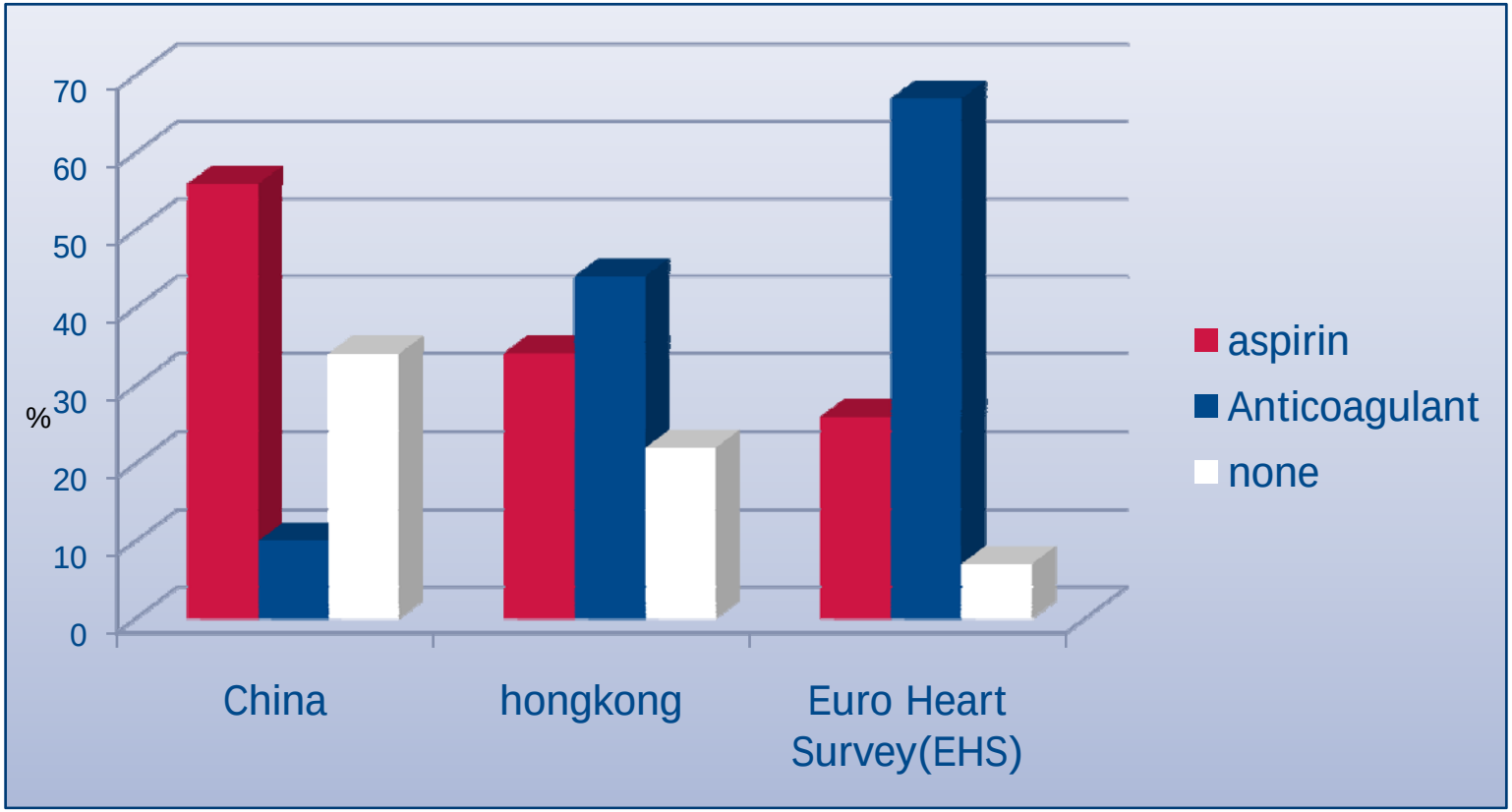
Pisters R et al. Chest. 2010; [Epub ahead of print];
ESC guidelines: Camm J et al. Eur Heart J 2010;31:2369–429

***P value for trend = 0.007**

Patients with atrial fibrillation and prior stroke/transient ischemic attack



Stroke Prevention in AF in China[1], Hong Kong[2], Europe[3]



1. Y. Sun et al.: Investigation of stroke risk in native Chinese. Clin. Cardiol. 2009:32, 2,76-81.
2. Leung CS, Tam KM: Antithrombotic treatment of atrial fibrillation in a regional hospital in Hong Kong. *Hong Kong Med J 2003;9(3):*179–185
3. Nieuwlaat R, Capucci A, Camm AJ, Olsson SB, Andresen D,et al., European Heart Survey Investigators: Atrial fibrillation management: a prospective survey in ESC member countries: the Euro Heart Survey on Atrial Fibrillation. *Eur Heart J 2005;26(22):*2422–2434

การใช้ยาต้านการแข็งตัวของเลือดในผู้ป่วยนอกที่มีภาวะหัวใจเต้นผิดจังหวะชนิด Nonvalvular Atrial Fibrillation

สุพร กุละพัฒน์, พ.บ.★ กนกพจน์ มีวัฒนา, พย.บ.★★

Warfarin Use among Ambulatory Patients with Nonvalvular Atrial Fibrillation

Suporn Kulapatnana, M.D. Kanokpoj Meewatana, B.N.S.

RESULTS: Nineteen (22.6%) of 84 patients were prescribed warfarin and only 15 (29.4%) of 51 patients with at least one or more risk factors for stroke and no contraindications were received warfarin. Specialty of attending physician was significantly predicted underuse of warfarin (p=0.002). Nine (47.3%) of 19 patients who received warfarin stopped warfarin. Warfarin discontinuation was mainly due to nonadherence with drug.

Patterns and Adherence to Guidelines of Antithrombotic Therapy in Thai Patients with Nonvalvular Atrial Fibrillation

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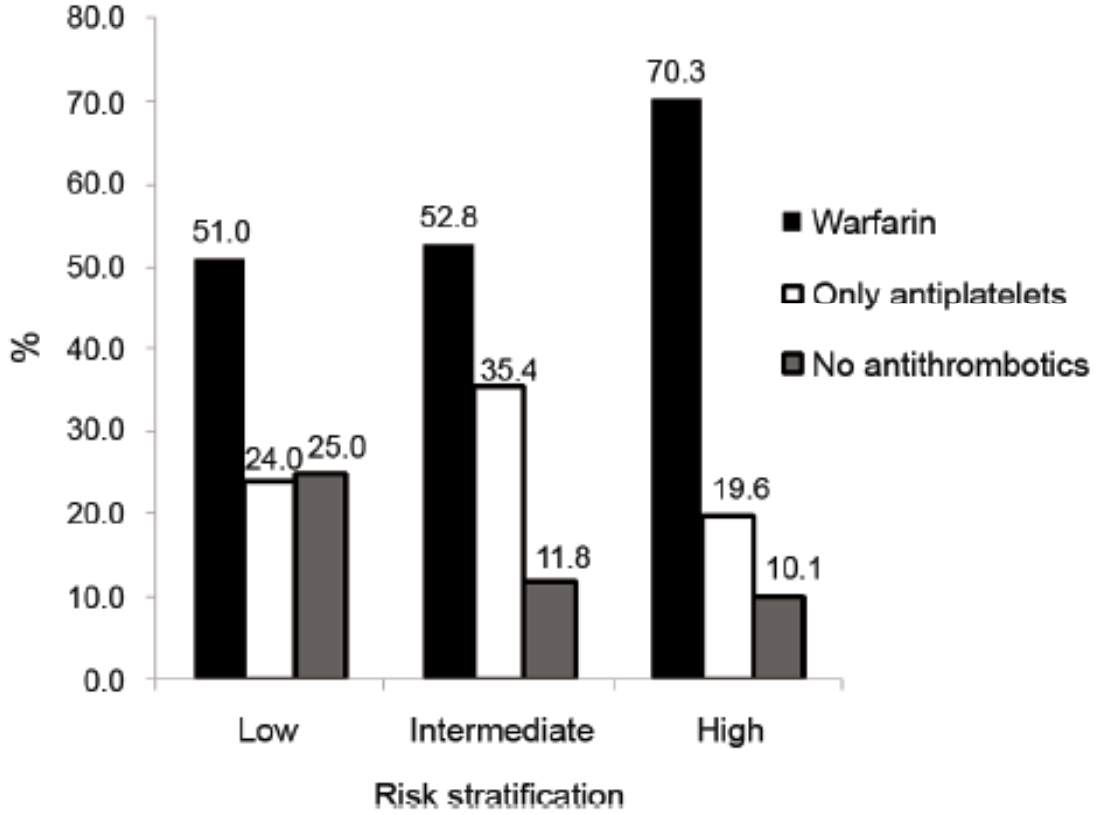
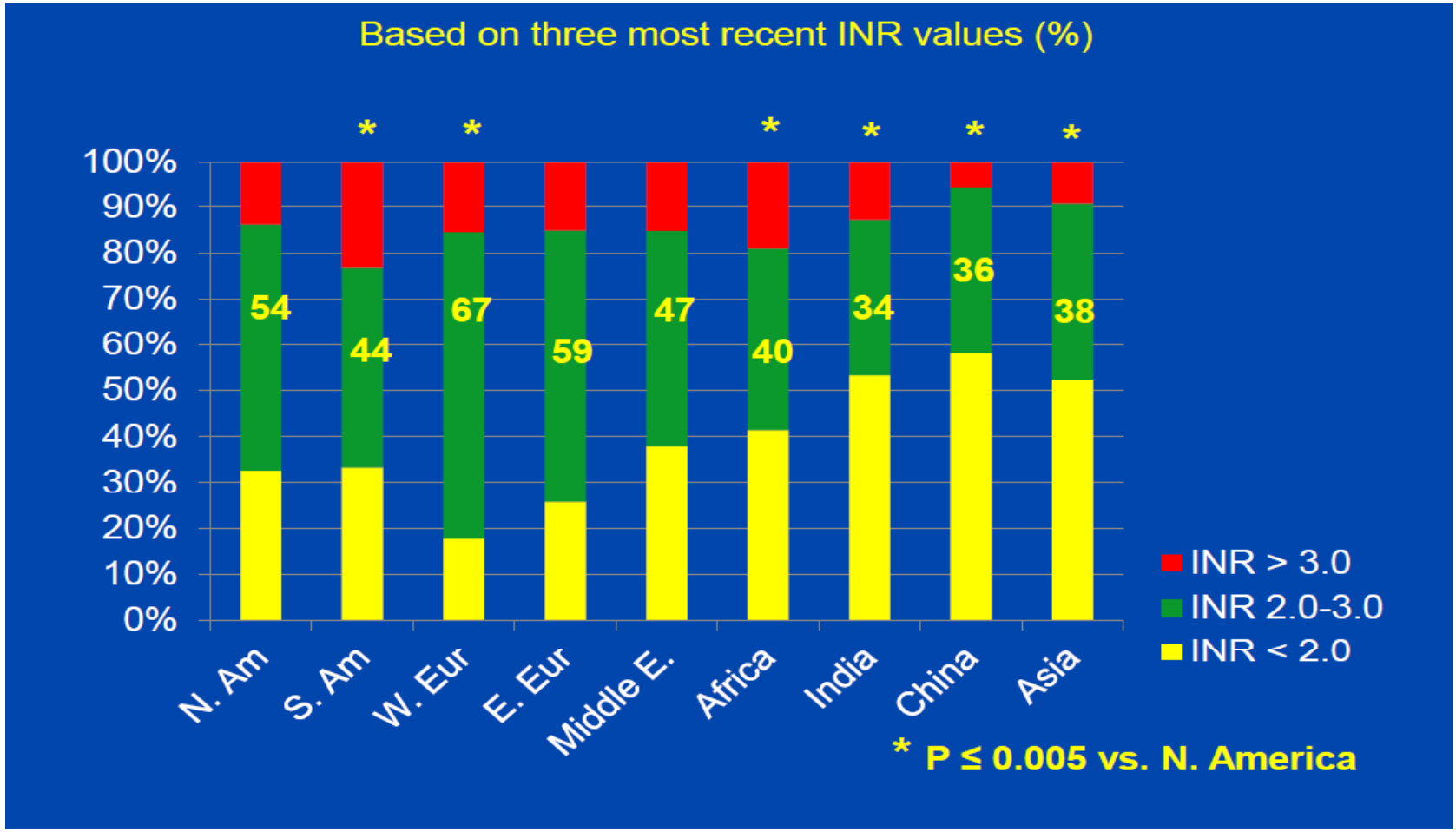
** Center of Pharmaceutical Outcomes Research, and Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Naresuan University, Phitsanulok, Thailand*



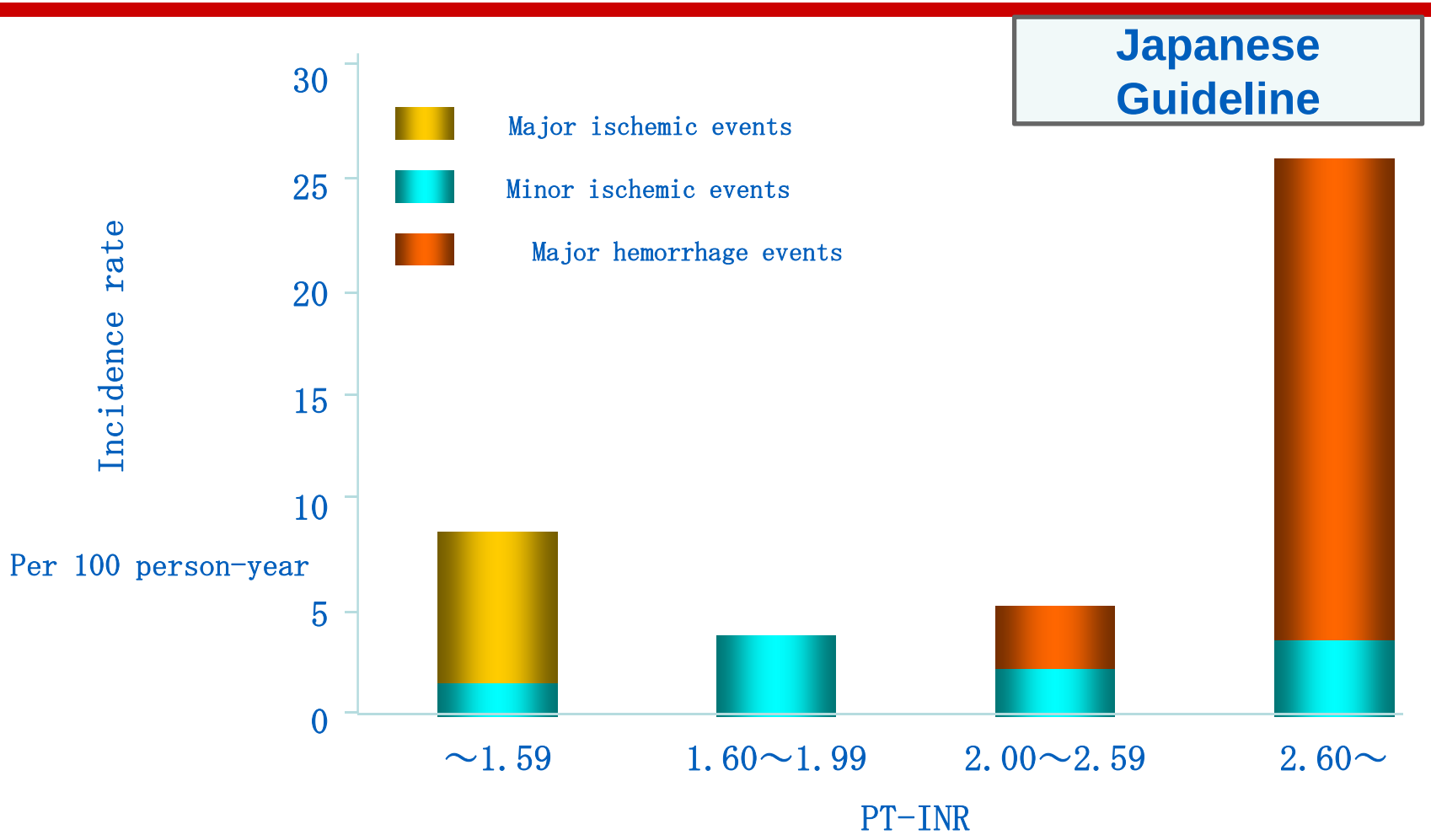
J Med Assoc Thai 2013; 96 (1): 91-8

INR Control by Region



Author/year	Country	Patients	Antithrombotic strategy	Conclusion
Sato/2006	Japan	NVAF n=871	Aspirin 150 to 200 mg/d vs. placebo	A low dosage of aspirin was neither effective nor safe
Hu/2006	China	NVAF n=828	Adjusted-dose warfarin (INR 2–3) vs. aspirin (150 to 160 mg/d)	Adjusted-dose warfarin was superior to aspirin
Yamaguchi/ 2000	Japan	NVAF n=115	Low-intensity warfarin (INR 1.5 to 2.1) vs. (INR 2.2 to 3.5)	Annual rate of ischemic stroke did not differ significantly, but low-intensity warfarin was safer
Suzuki/2007	Japan	NVAF n=667	Target INR value was set at 1.6–2.6	Incidence of major bleeding was 2.38%, which is higher than in Western patients INR ≥2.27 was an independent risk factor for major bleeding
Chen/2012	China	NVAF n=786	Warfarin INR 1.6-2 vs warfarin INR 2.1-2.6 vs aspirin 200 mg/d	Warfarin INR 1.6-2 similar to INR 2.1-2.6 and better than aspirin

Intensity of anticoagulation and incidence rates of ischemic and hemorrhagic events



Yasaka M, et al., Intern. Med. 40, 1183-1188, 2001

Optimal INR level of Thai atrial fibrillation patients who were receiving warfarin for stroke prevention in Siriraj Hospital

Komsing Methavigul, MD, and Warangkna Boonyapisit, MD

Division of Cardiology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand

- A first retrospective study in Thailand.
- A total of 230 patients with AF in Siriraj Hospital.
- Between January 2005 to December 2009.
- The optimal INR level was the lowest ischemic stroke and bleeding complication.

Komsing Methavigul et al. The Optimal INR Level in Thai Atrial Fibrillation Patients. Poster presentation on APSC2013 Congress on 19th APCC.

Optimal INR level of Thai atrial fibrillation patients who were receiving warfarin for stroke prevention in Siriraj Hospital

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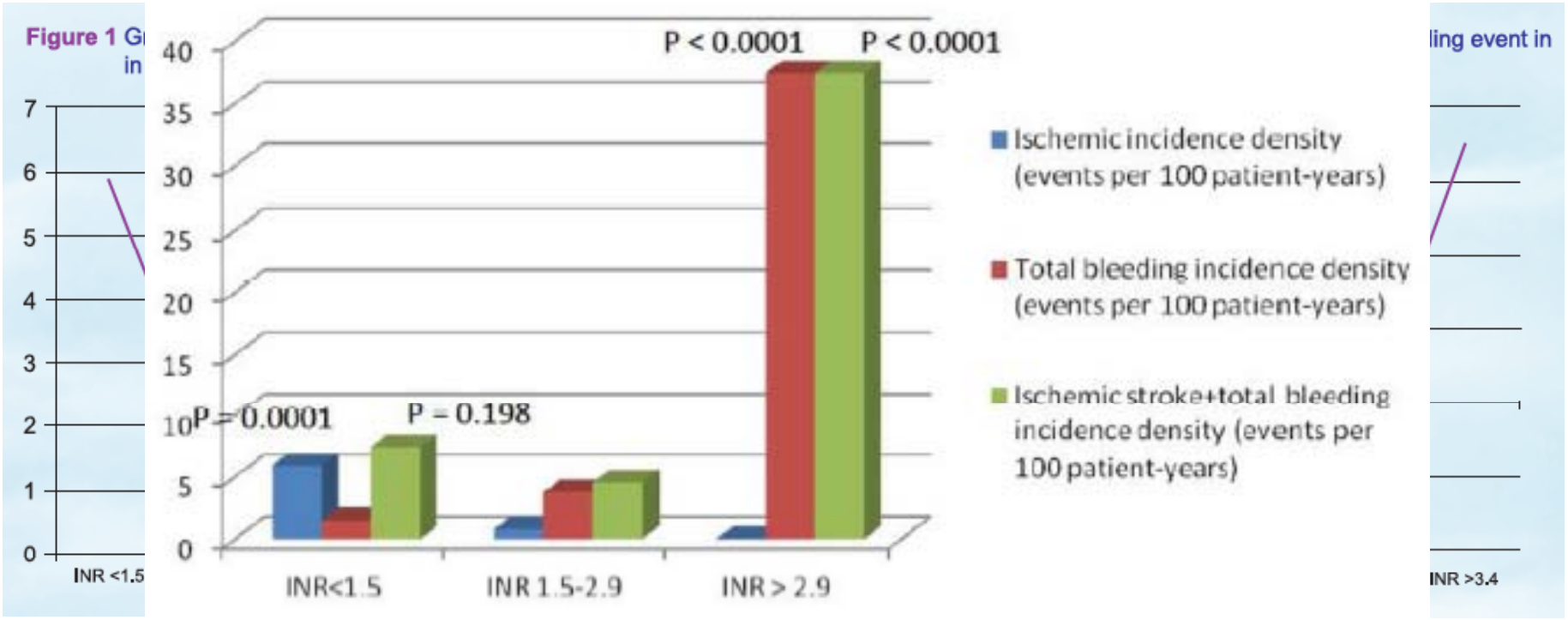


The optimal INR level was 1.5 to 2.9 in Thailand.

Komsing Methavigul et al. The Optimal INR Level in Thai Atrial Fibrillation Patients. Poster presentation on APSC2013 Congress on 19th APCC).

Background (1)

- Atrial fibrillation is the common cardiac arrhythmia in clinical practices.
- One of therapeutic goals is prevention of thromboembolism.
- Warfarin is the most effective anticoagulant for prevention of thromboembolism in AF.

Background (2)

- The main adverse reaction is bleeding.
- The optimal INR is 2-3 evaluated in several trials in US and European countries.
- But less evidence in Asian countries.

Objectives

- To determine pattern of antithrombotic use in Thailand
- To determine the optimal INR level in patients with AF in Thailand who receive warfarin

Study design

- Multicenter prospective registry study (25-30 sites).
- patients with non-valvular AF
- The estimated sample size is 5,000 patients.
- Outcome measurement 1) prevalence and appropriateness of warfarin use 2) is the optimal INR level in patients with NVAF in Thailand who received warfarin: as indicated by efficacy endpoint (ischemic stroke) and safety endpoint (bleeding events).

Major Impact/Output/Outcomes

- Know about the optimal INR in patients with non-valvular AF will lead to
  - ✓ Reduction of major or minor bleeding → cost saving for treatment of complication from warfarin.
  - ✓ Reduction of ischemic stroke → disease prevention.
  - ✓ Expectation of changing the Thai CPG in the future.

Method: Population

- Thai AF patients were enrolled.
- Patients will be followed up for 3 years.
- 6 groups is classified by INR : < 1.5, 1.5-1.9, 2.0-2.4, 2.5-2.9, 3.0-3.4, >3.4 .

Method: Inclusion criteria

- Age ≥ 18 years old
- Non-valvular AF

Method: Exclusion criteria

- Prior ischemic stroke or prior major or minor bleeding before enrolment
- Thrombocytopenia or MPD, or hyperviscosity syndrome, chronic DIC or APS
- Ischemic stroke due to HIT
- Prosthetic heart valve or valvular repair
- Significant valvular heart disease
- Only detectable AF from permanent pacemaker, AICD, or CRT

Method: Sample size calculation (2)

INR	<1.5	1.5-1.9	2.0-2.4	2.5-2.9	3.0-3.4	>3.4
P_i	0.074	0.034	0.051	0.057	0.158	0.560
n_i	0.18	0.28	0.27	0.14	0.06	0.07

- P_i = Proportion of ischemic stroke or bleeding events in 1^{st} to 6^{th} group of INR
- n_i = Proportion of person time in 1^{st} to 6^{th} group of INR
- Assuming prevalence of warfarin use in Thai AF patients = 50%.

Method: Sample size calculation (5)

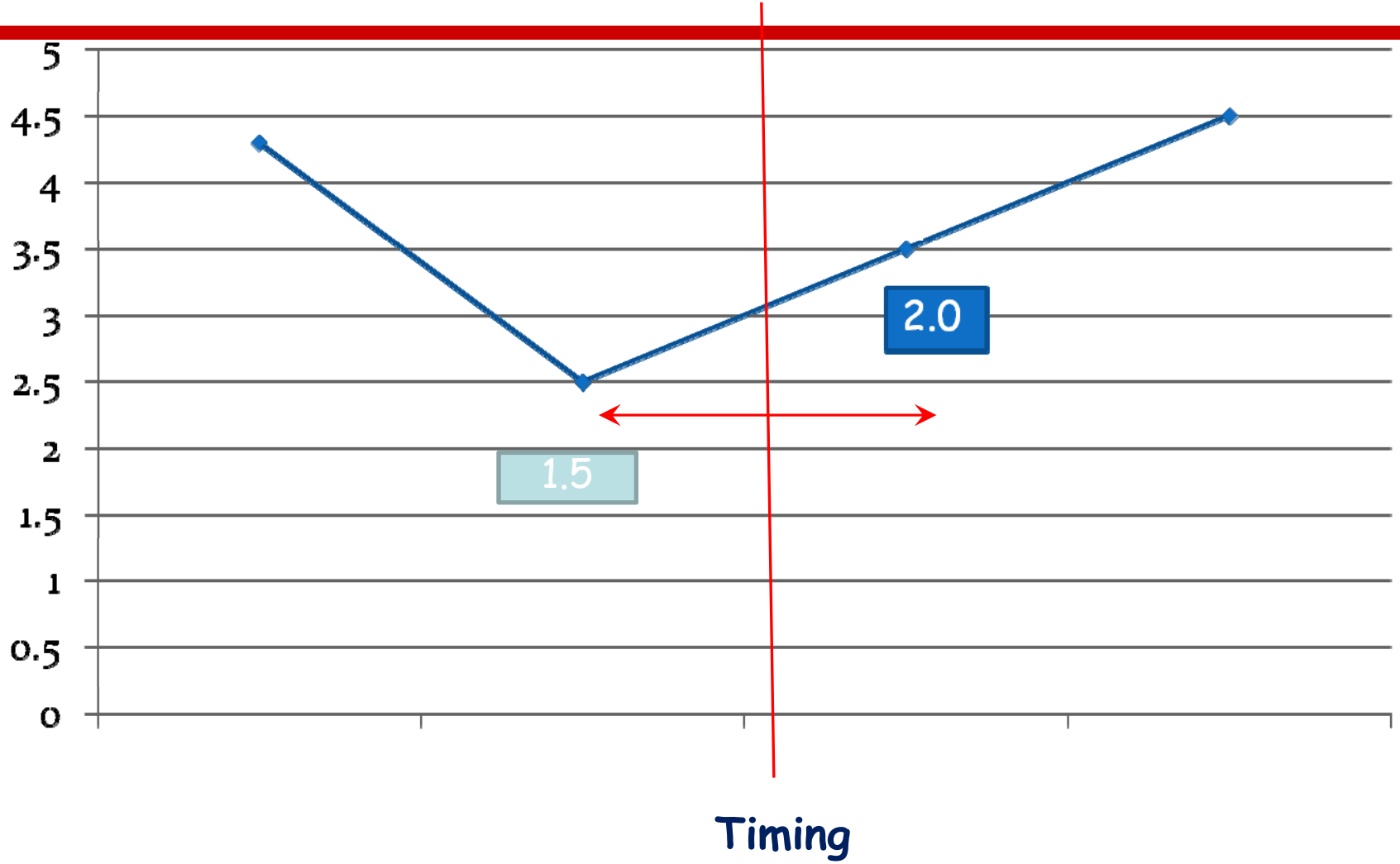
- Assuming prevalence of warfarin use in Thai AF patients (with $CHA_2DS_2VASc >= 1$) = 50%.
- Total N = 4040
- After adding the proportion of patients with $CHA_2DS_2VASc = 0$, the estimated sample size is 5000

Method: Data collection (2)

- Classify into 6 groups of INR:
  - INR < 1.5
  - INR 1.5-1.9
  - INR 2.0-2.4
  - INR 2.5-2.9
  - INR 3.0-3.4
  - INR > 3.4

- Record INR during ischemic stroke or bleeding complication.

INR level



Method: Data collection (3)

- Other data are collected:
  - Age/Sex
  - Comorbidity : liver cirrhosis, CKD, hyper- or hypothyroidism, diabetes, hypertension, dyslipidemia, and CAD
  - Echocardiographic findings: LVEF, apical aneurysm, LA size
  - Incidence of ischemic stroke, major or minor bleeding
  - Antiplatelet medication combine with warfarin
  - Reason for no warfarin therapy

Method: Clinical end point

- The optimal INR level in patients with NVAF in Thailand.
- The optimal INR level was defined as the lowest ischemic stroke and bleeding complication.

Data analysis

- Descriptive statistics:
  - Categorical data such as sex, underlying diseases is presented as percentage
  - Numerical data such as age, LVEF, LA size is presented as mean±S.D. if normal distribution or median if no normal distribution
-
- Inferential statistics: Chi-square or Fisher's exact test

Clinical application

- Prevalence of warfarin therapy in Thai patients with NVAF.
- Optimal INR level in Thai patients with NVAF.
- Change in CPG in the use of antithrombotic agent in Thai population