The optimal anticoagulant treatment for Asian in SPAF

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Associate Professor

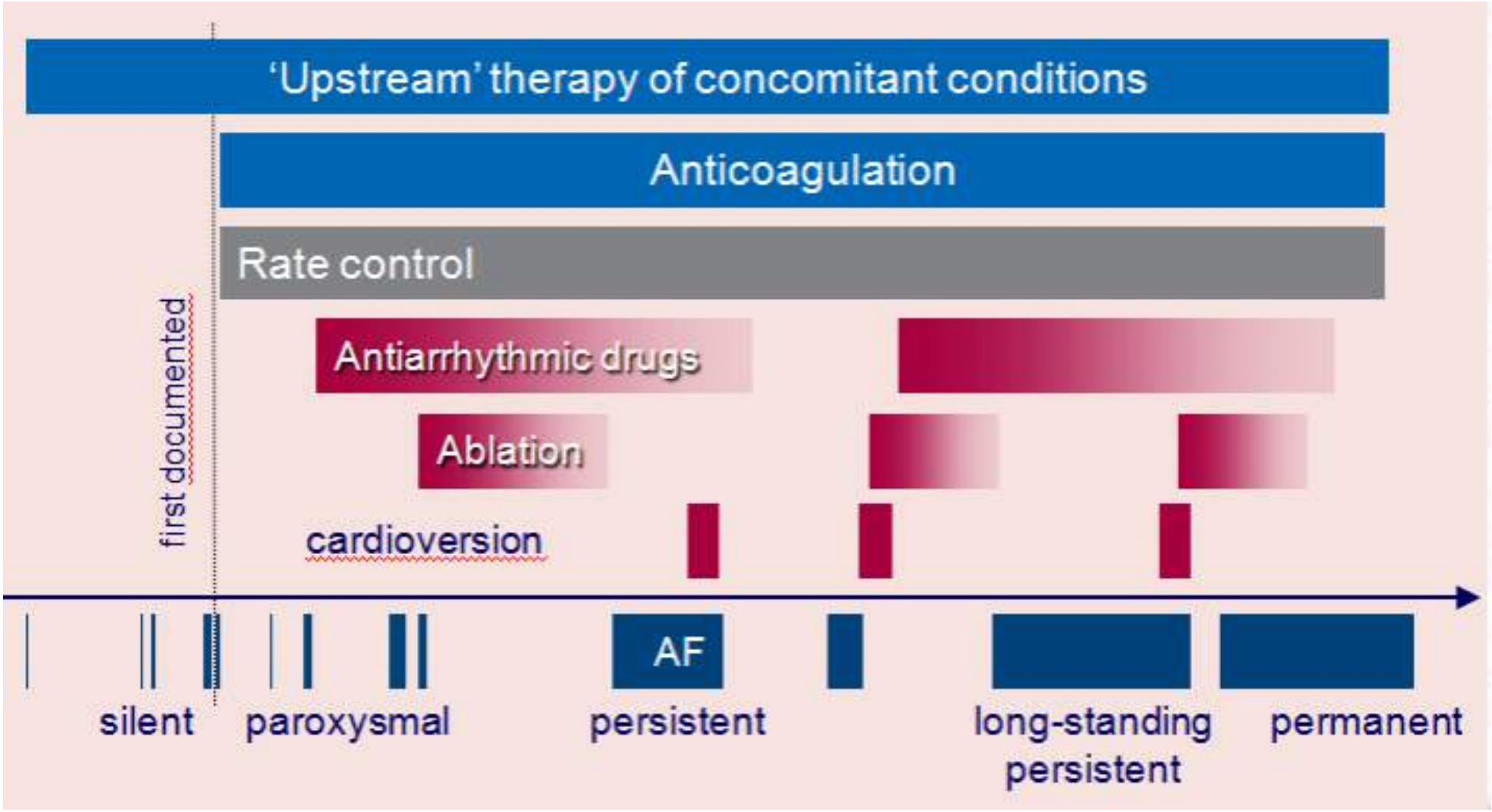
2019/2/17

台灣血脂衛教協會

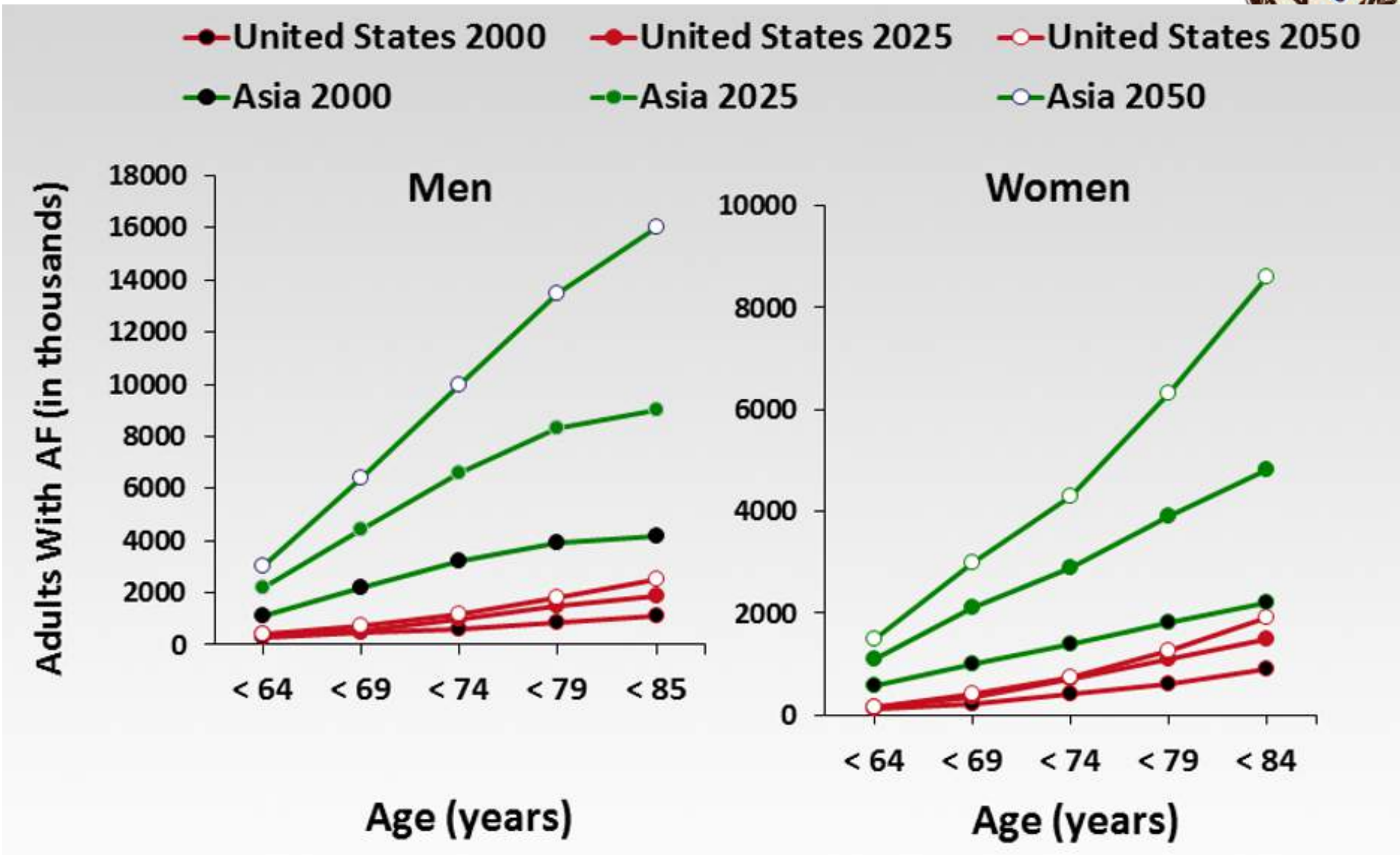
Outline

- Association between Af & Stroke
- Drug Prevention for Stroke in Af patients
- From Warfarin to NOAC:
  Evolution of Af Guideline
- NOAC (focus on edoxaban)
  - ENGAGE-AF study
  - ENGAGE-AF subgroup (East Asia) studies
- How about Real Word Data?
- Take Home message

Natural time course of AF



Number of AF patients predicted to more than double by 2050



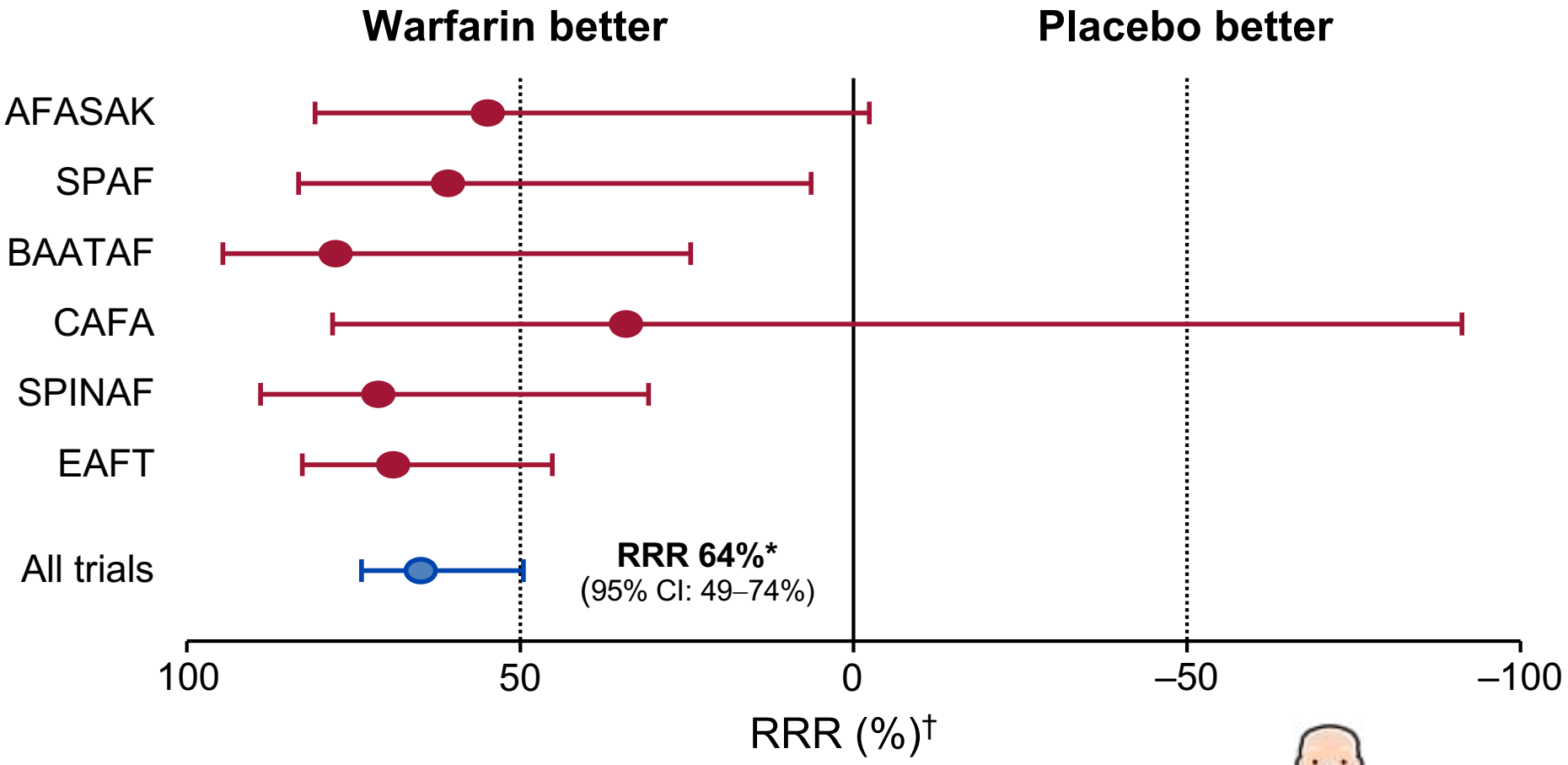
United Nations Department of Economic and Social Affairs, Population Division.
http://esa.un.org/unpd/wpp/unpp/panel_population.htm

中風為心房顫動最嚴重的併發症

- 中風為心房顫動的最常見併發症，造成沉重的疾病與死亡負擔
- 心房顫動會使中風的風險增加大約5倍[1]
- 若無有效的治療以預防血栓的形成，心律不整病患幾乎每年每20人就有一人發生中風(5%) [2]
- AF為栓塞性中風的首要原因[3]
- 心房顫動患者的死亡率為心律正常者的兩倍[4]

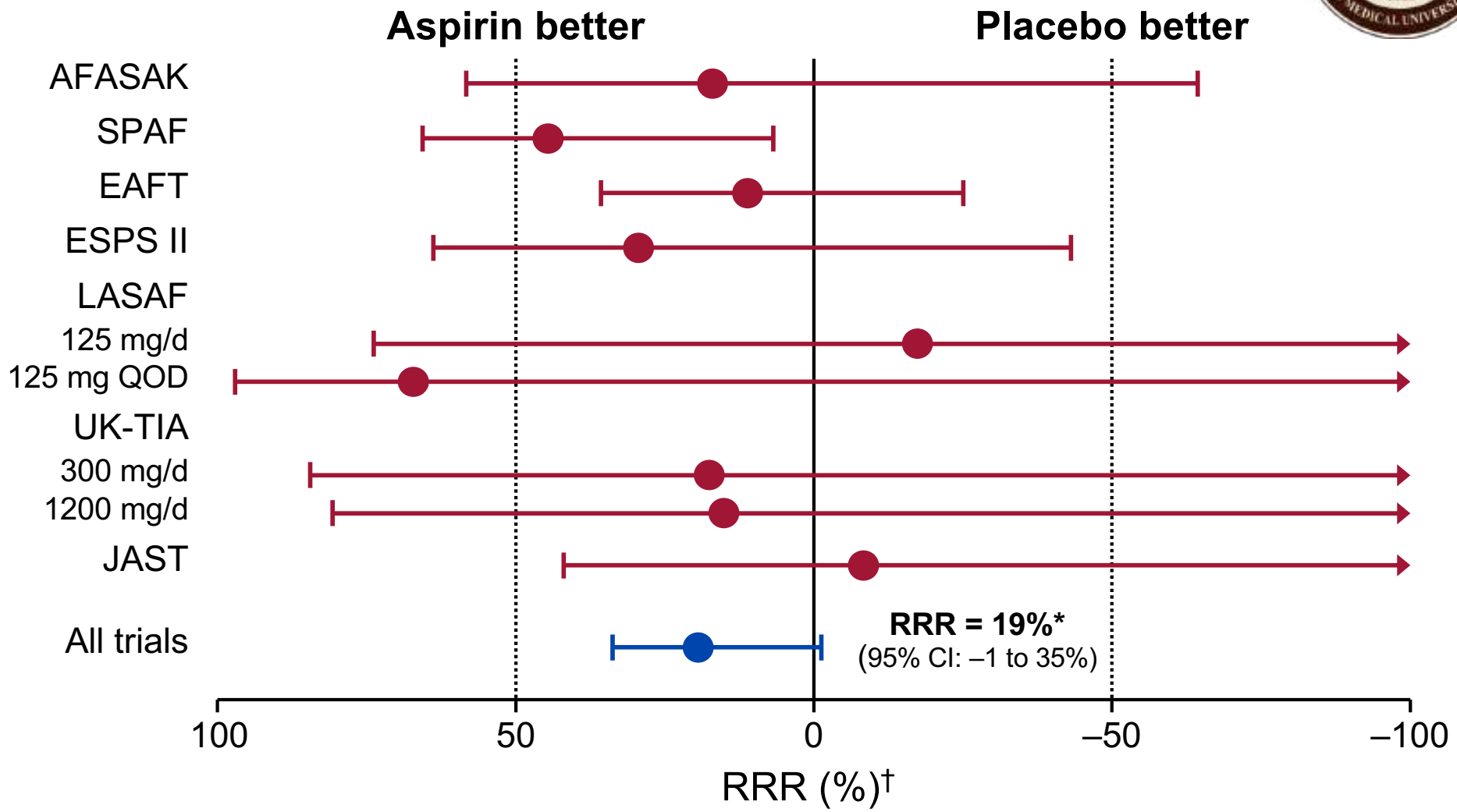
1. Savelieva I et al. Ann Med 2007;39:371–91;
2. Atrial Fibrillation Investigators. Arch Intern Med 1994;154:1449–57;
3. Atrial fibrillation; available at http://www.americanheart.org/presenter.jhtml?identifier=4451; accessed Feb 2010
4. Benjamin EJ et al. Circulation 1998;98:946–52

相較於安慰劑，warfarin可明顯降低中風風險



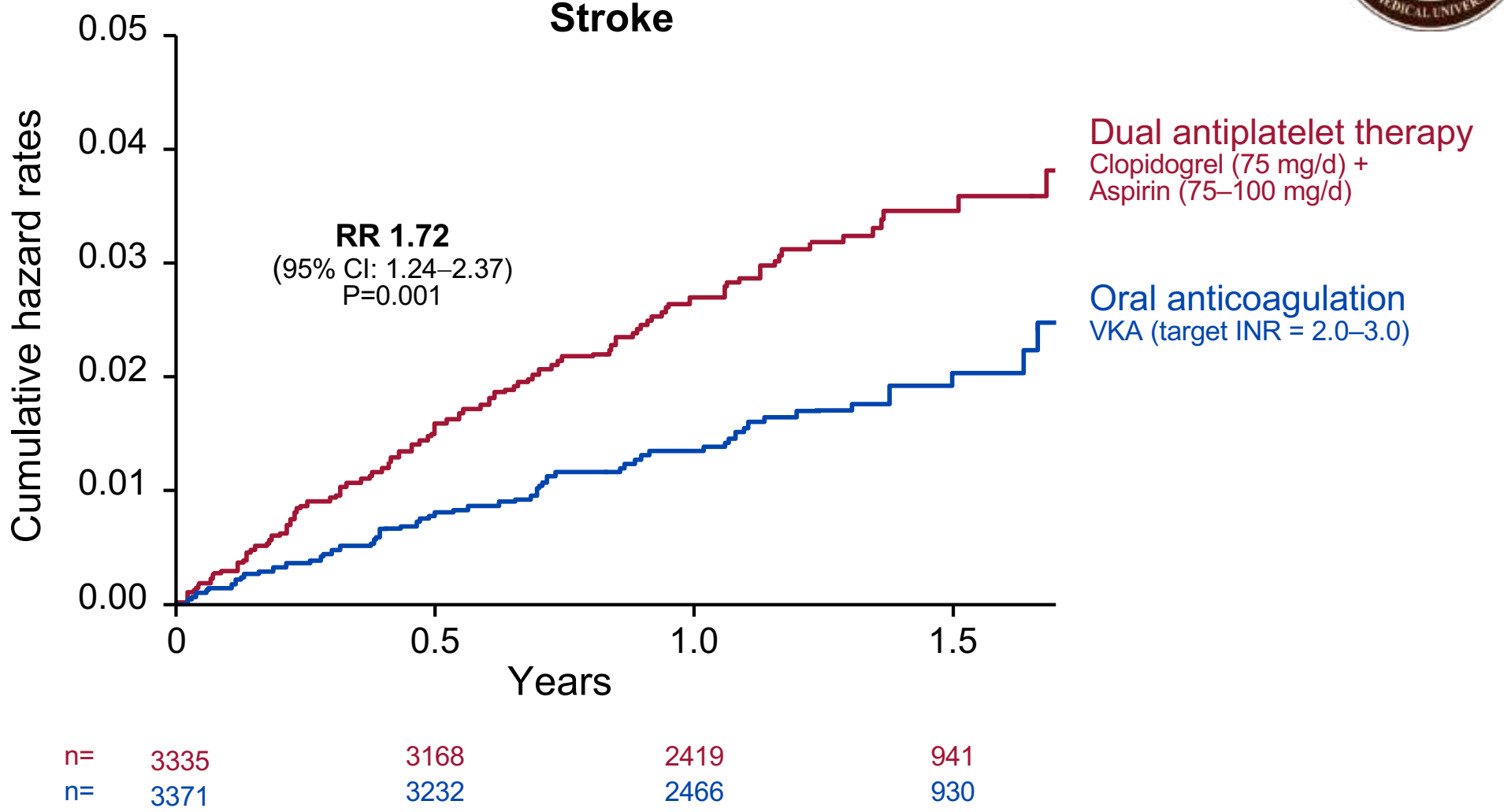
Random effects model; Error bars = 95% CI; *P>0.2 for homogeneity; †RRR for all strokes (ischaemic and haemorrhagic)
Hart RG et al. Ann Intern Med 2007;146:857–67

阿斯匹靈對心房顫動病患中風預防的功效極為有限



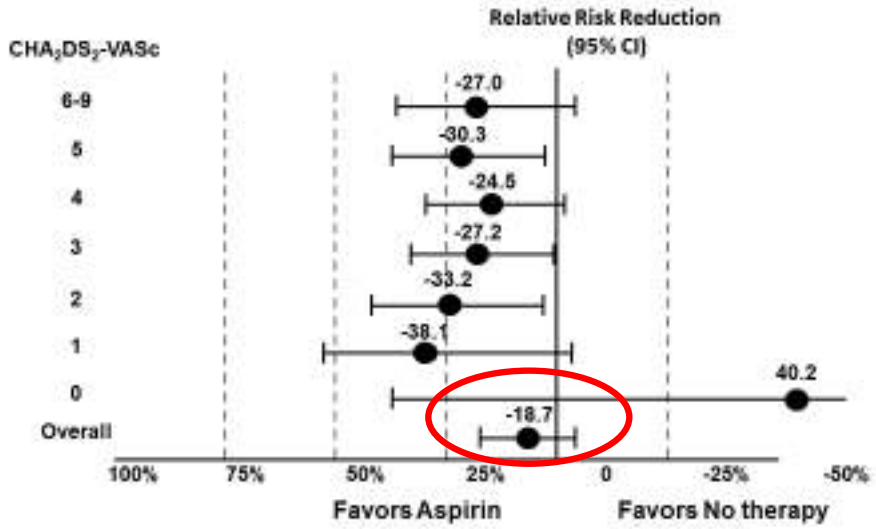
Random effects model; Error bars = 95% CI; *P>0.2 for homogeneity; †RRR for all strokes (ischaemic and haemorrhagic)
Hart RG et al. Ann Intern Med 2007;146:857–67

口服抗凝血療法在綜合主要評估指標(中風、全身性栓塞、心肌梗塞或血管原因之死亡)上的療效明顯優於雙重抗血小板療法

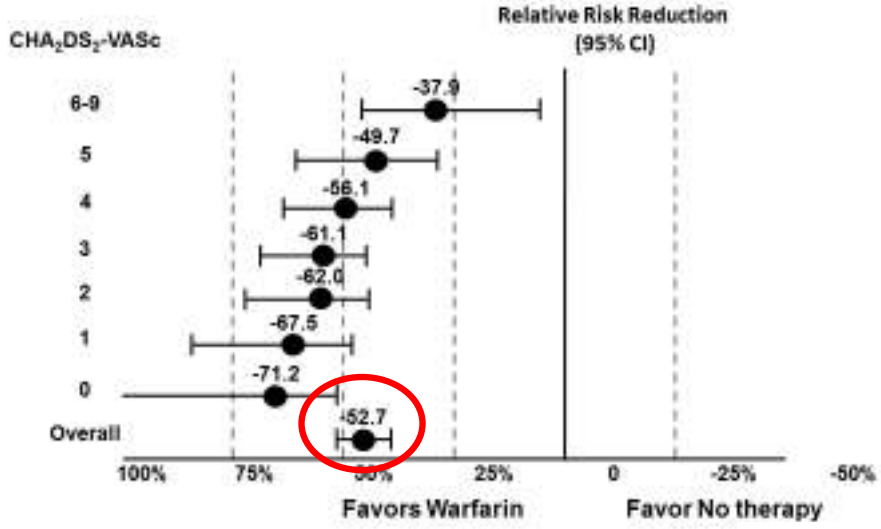


ACTIVE Investigators. Lancet 2006;151:1903–12

Warfarin and Aspirin reduce ischemic stroke in Chinese AF patients of similar magnitude as in Caucasians



Benefit of Aspirin



Benefit of Warfarin

Heart Rhythm 2014 Aug;11(8):1401-8

AF 患者的中風風險評估 - $CHADS_2$ score

Risk factor	Points
Congestive heart failure	+1
Hypertension	+1
Age ≥75 years	+1
Diabetes mellitus	+1
Previous stroke/TIA/thromboembolism	+2

Risk category	Score
Low	0
Intermediate	1
Moderate to high	≥2

$CHADS_2$	Stroke rate (95 %CI)*
6	18.2 (10.5–27.4)
5	12.5 (8.2–17.5)
4	8.5 (6.3–11.1)
3	**5.9** (4.6–7.3)
2	**4.0** (3.1–5.1)
1	**2.8** (2.0–3.8)
0	**1.9** (1.2–3.0)

Gage BF *et al. Circulation* 2004;110:2287–2292; Fuster V *et al. Circulation* 2006;114:e257–354;
Singer DE *et al. Chest* 2008;133:546S–592S

AF 患者的中風風險評估- CHA_2DS_2-VASc

Item	Points
Previous stroke TIA or systemic embolism	2
Age ≥75 years	2
Congestive heart failure*	1
Hypertension	1
Diabetes mellitus	1
Age 65–74 years	1
Female gender	1
Vascular disease	1

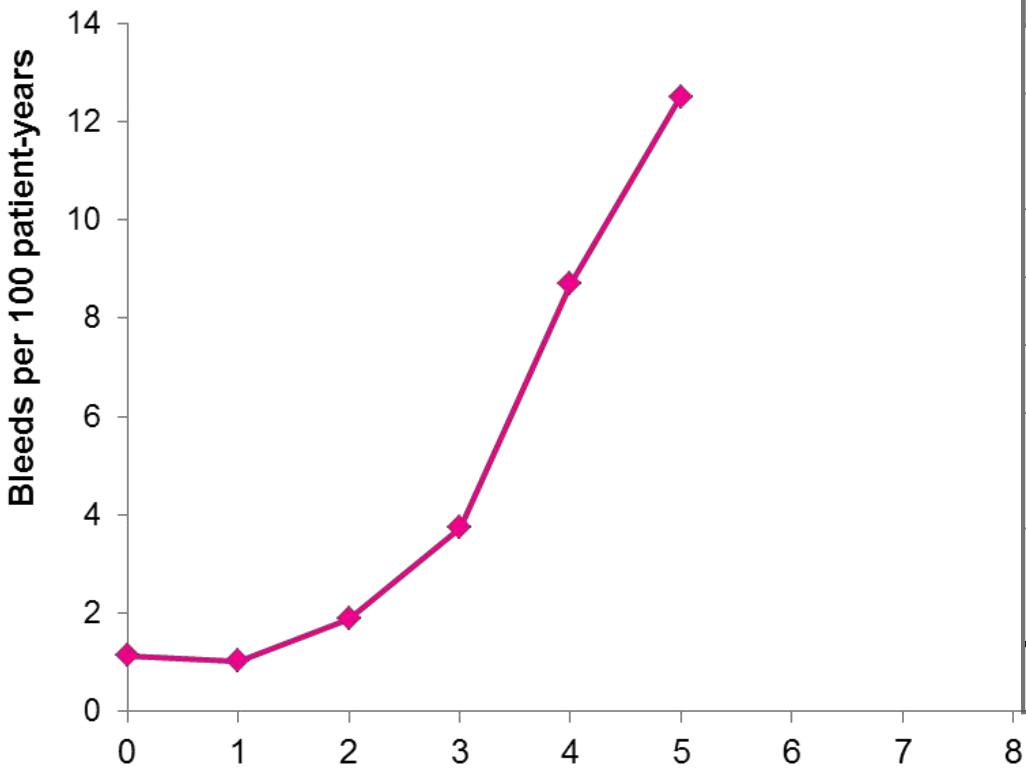
Add points together

CHA_2DS_2-VASc	1-year stroke rate
9	23.64%
8	22.38%
7	21.50%
6	19.74%
5	15.26%
4	9.27%
3	5.92%
2	3.71%
1	2.01%
0	0.78%

*Or moderate-to-severe left ventricular systolic dysfunction (left ventricular ejection fraction ≤40%)

Olesen JB *et al*. *BMJ* 2011;342:d124; Camm AJ *et al*. *Eur Heart J* 2010;31:2369–2429

HAS-BLED Bleeding Risk Stratification



Risk factor	Points
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 years)	1
Drug or alcohol use (1 point each)	1 or 2
Maximum score	9

- **A score ≥3 is considered 'high risk'** and indicates that caution and regular review is needed during anticoagulant or antiplatelet therapy[2]
- **Higher stroke risk = Higher bleeding risk**

1. Pisters *et al*, 2010; 2. Camm *et al*, 2010

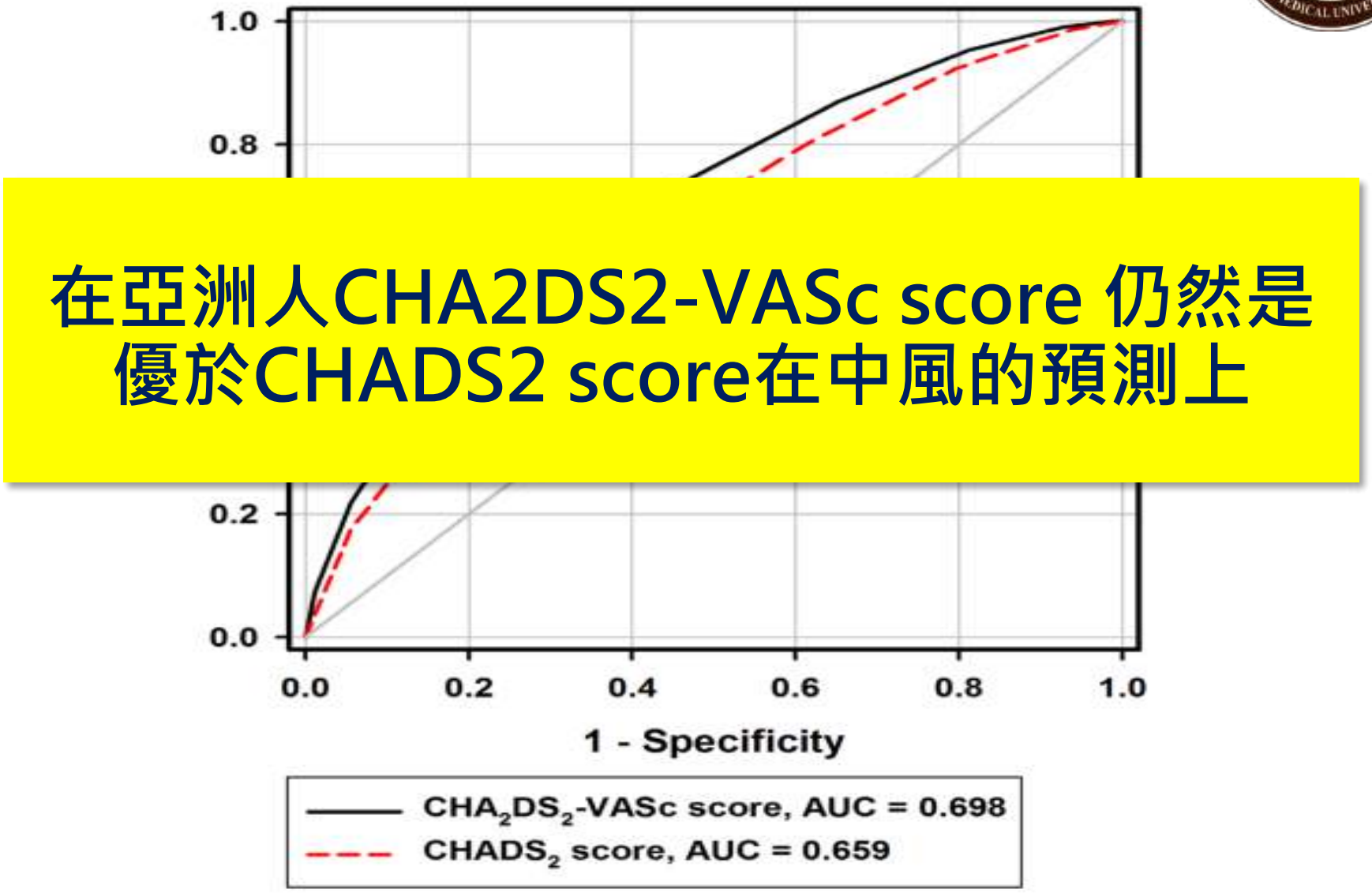
ARTICLE IN PRESS

Comparisons of $CHADS_2$ and CHA_2DS_2-VASc scores for stroke risk stratification in atrial fibrillation: Which scoring system should be used for Asians?

Tze-Fan Chao, MD,[*†] Chia-Jen Liu, MD,[‡§] Ta-Chuan Tuan, MD,[*†] Su-Jung Chen, MD,[§¶] Kang-Ling Wang, MD,[*†] Yenn-Jiang Lin, MD,[*†] Shih-Lin Chang, MD,[*†] Li-Wei Lo, MD,[*†] Yu-Feng Hu, MD,[*†] Tzeng-Ji Chen, MD,[**] Chern-En Chiang, MD, PhD,[*†††‡‡] Shih-Ann Chen, MD[*†]

Heart Rhythm 2015;0:1–8

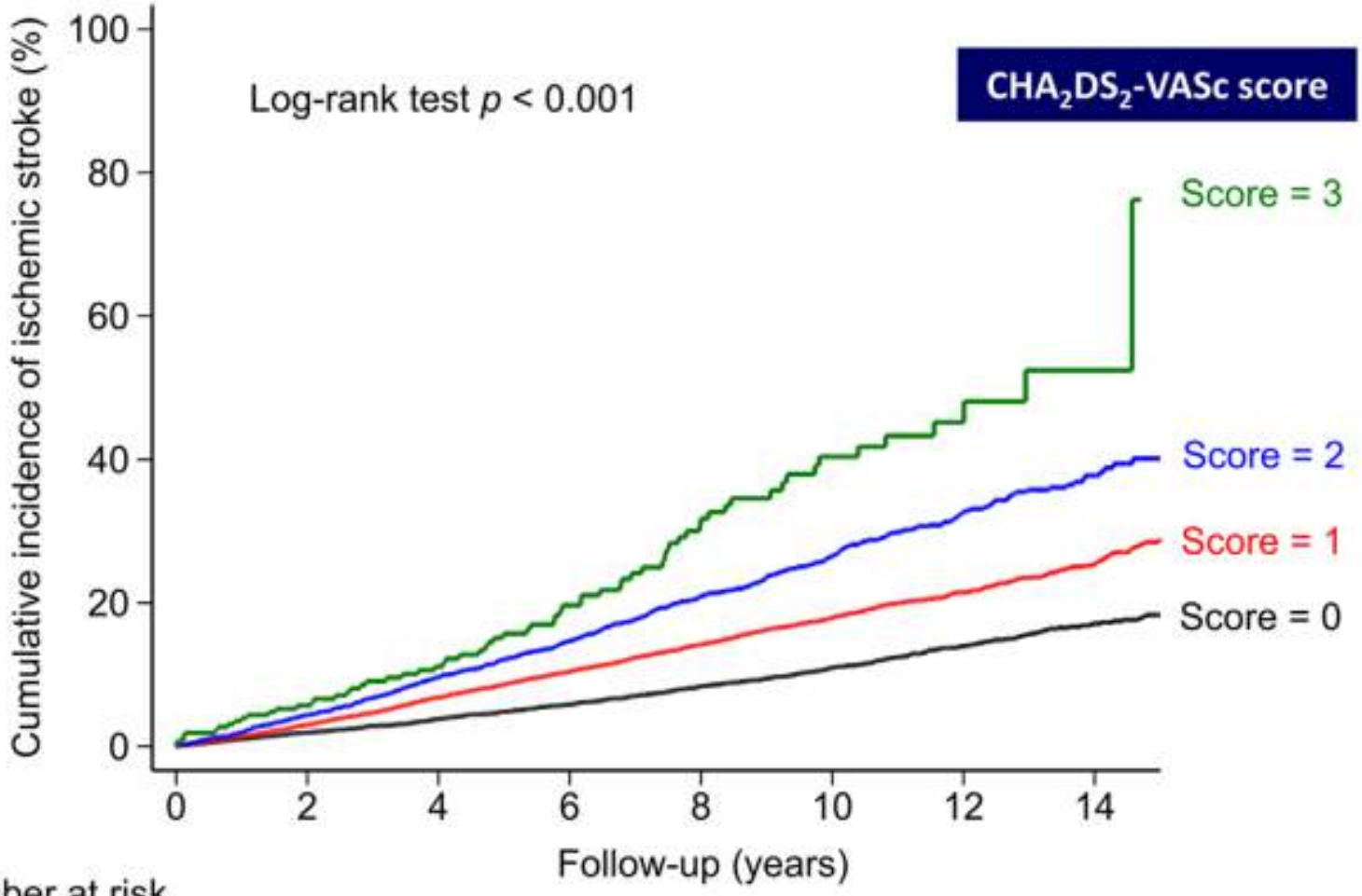
ROC curves of CHADS2 and CHA2DS2-VASc scores in predicting ischemic stroke



在亞洲人CHA2DS2-VASc score 仍然是優於CHADS2 score在中風的預測上

Heart Rhythm 2015;0:1–8

Kaplan–Meier curves of atrial fibrillation patients with a CHADS2score of 0 stratified based on CHA2DS2-VASc scores



Number at risk

Score = 3	269	205	166	118	78	46	19	3
Score = 2	3,464	2,543	1,978	1,559	1,132	765	397	128
Score = 1	12,137	9,003	7,142	5,614	4,089	2,798	1,535	624
Score = 0	9,416	7,223	5,871	4,623	3,426	2,339	1,267	527

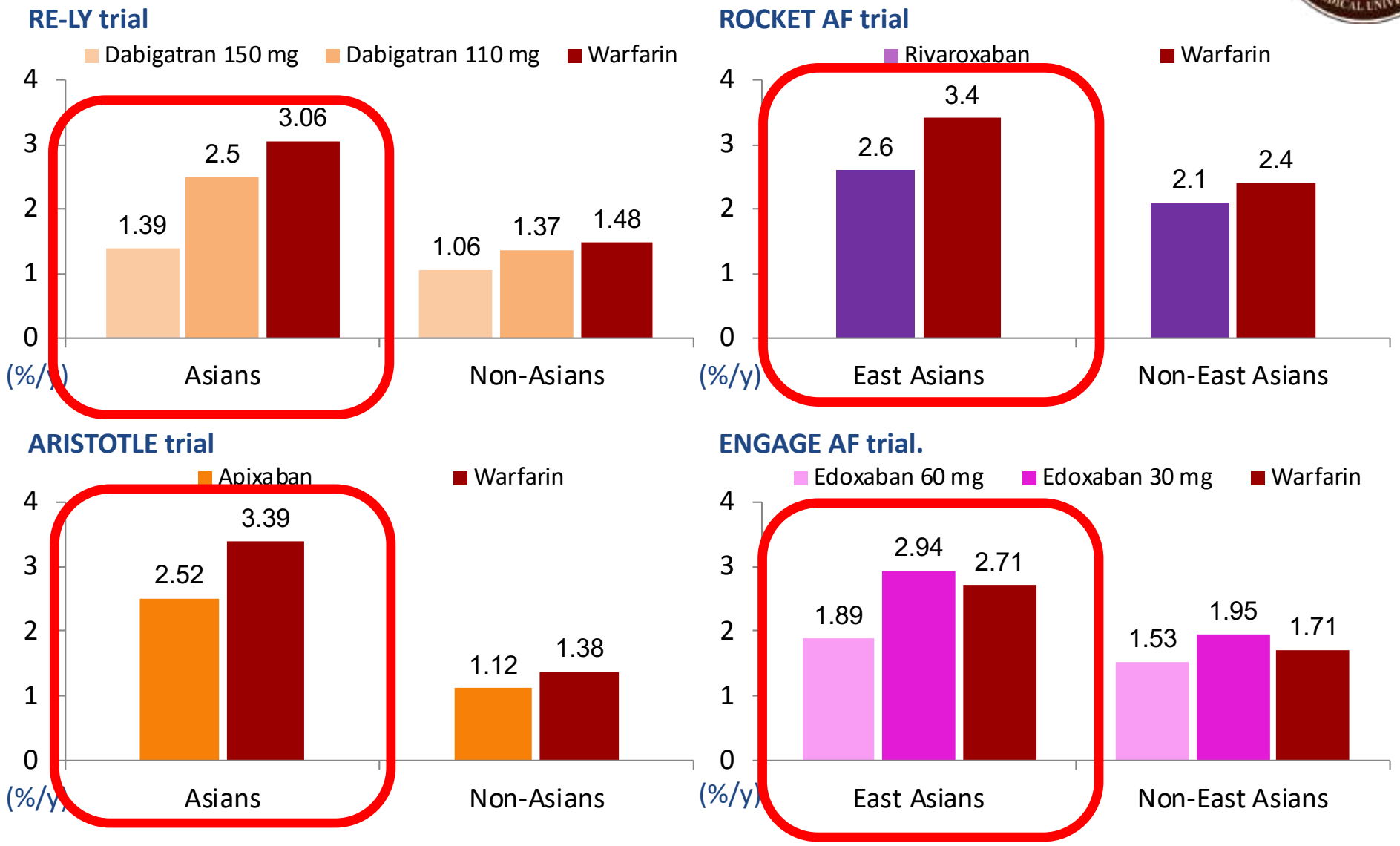
Heart Rhythm 2015;0:1–8

The Scope of AF and Stroke rate

Study	Mean age	Stroke (% per year)		Relative risk
		AF	No AF	
Framingham, USA	70	4.1	0.74	5.6x
Shibata, Japan	65	5.0	0.90	5.6x
Reykjavik, Iceland	52	1.6	0.23	7.1x
Whitehall, UK	60	1.8	0.26	6.9x
Taiwan	70	3.8-4.9	0.45	8.4-10.8X

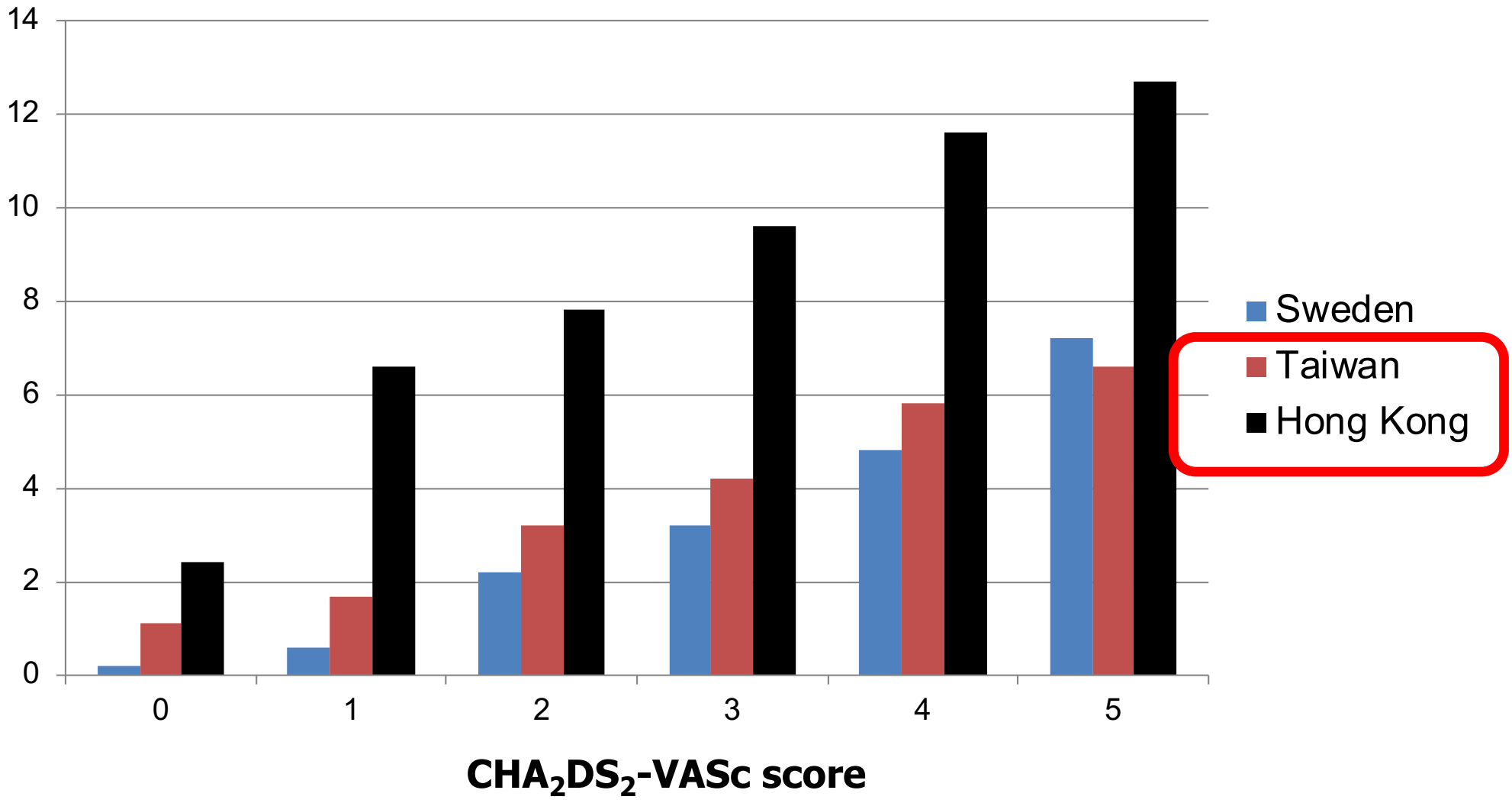
Am J Manag Care. 2004;10:S297-S306
王敏如 林立人 高雅慧 2008
Int J Cardiol 2008. e-published.

Higher Risk of Stroke/Systemic Embolization Events in Asians



2016 AF Guidelines of THRS/TSOC. Journal of the Formosan Medical Association (2016).

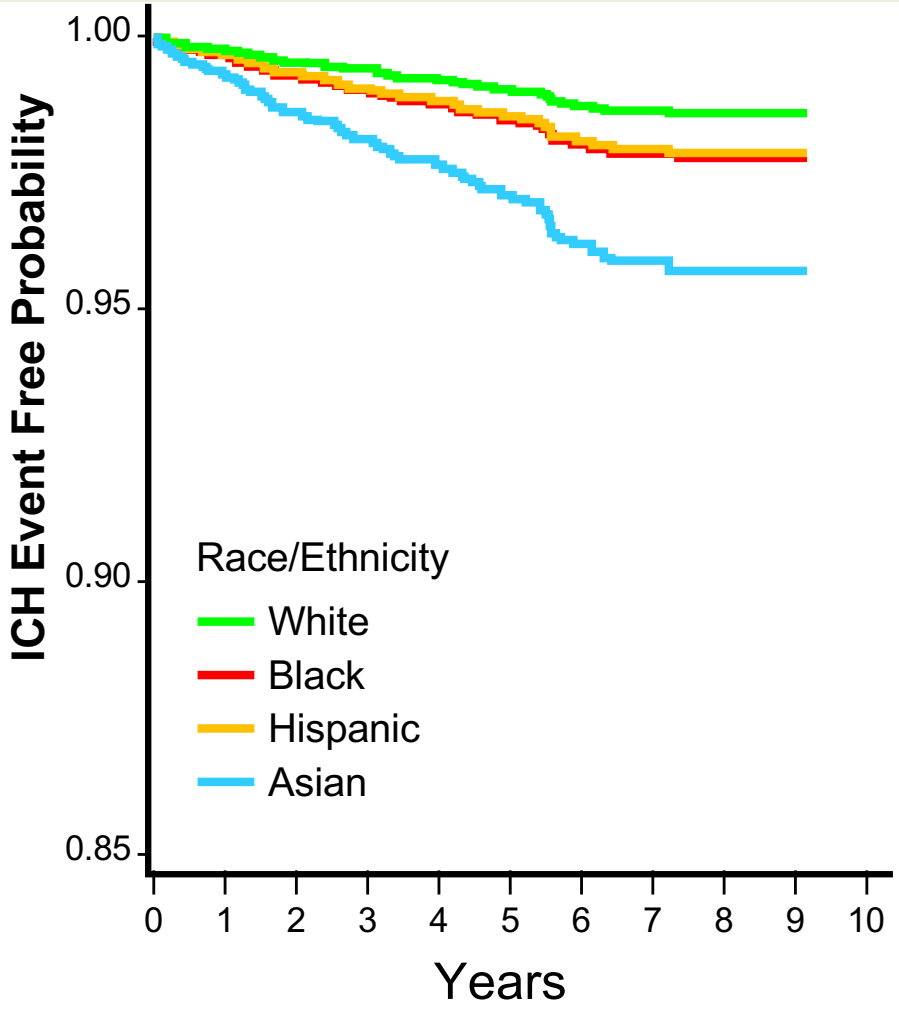
Higher stroke rate in Asians with same CHA_2DS_2-VASc score

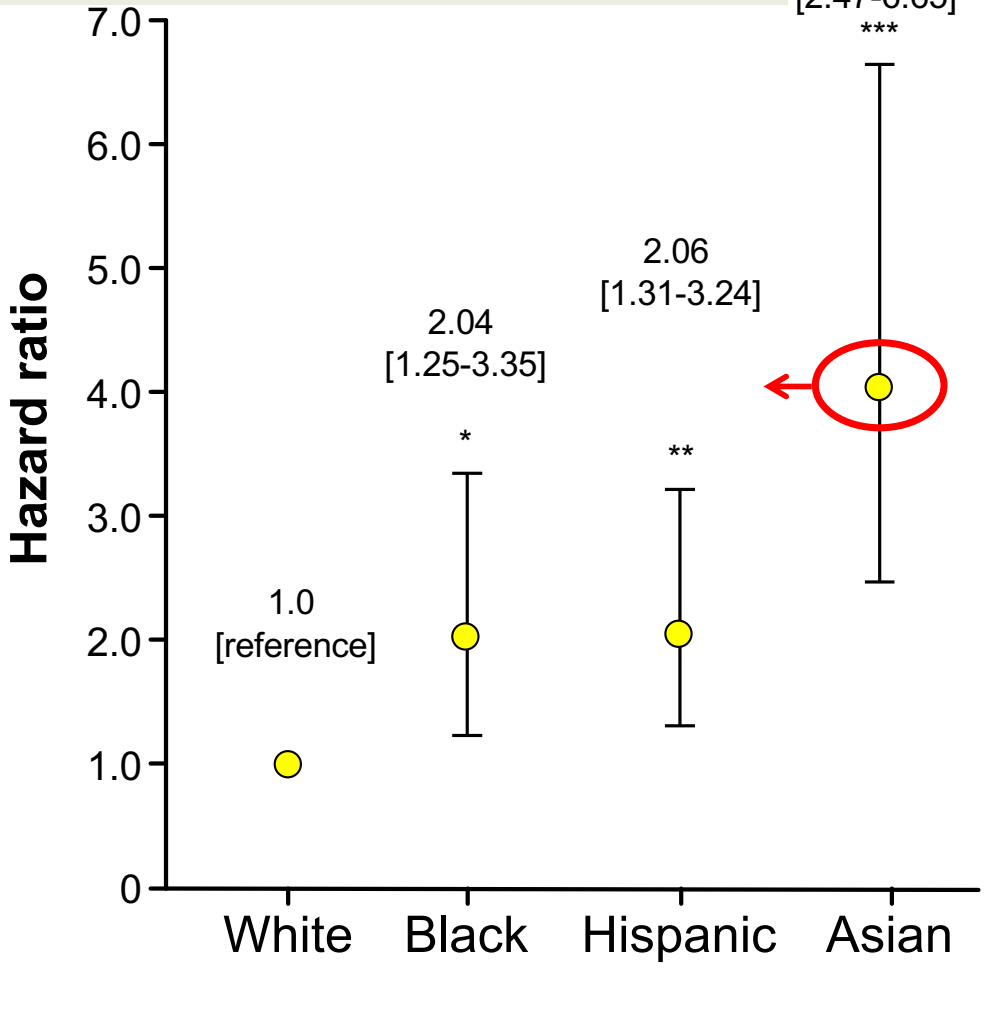


Friberg et al. Eur Heart J 2012;33:1500
Heart Rhythm 2014 Aug;11(8):1401-8
J Am Coll Cardiol 2014;64:1658-65

Asians are prompt to ICH comparing to Caucasians

Asians are prone to ICH and VKA induced ICH is more severe

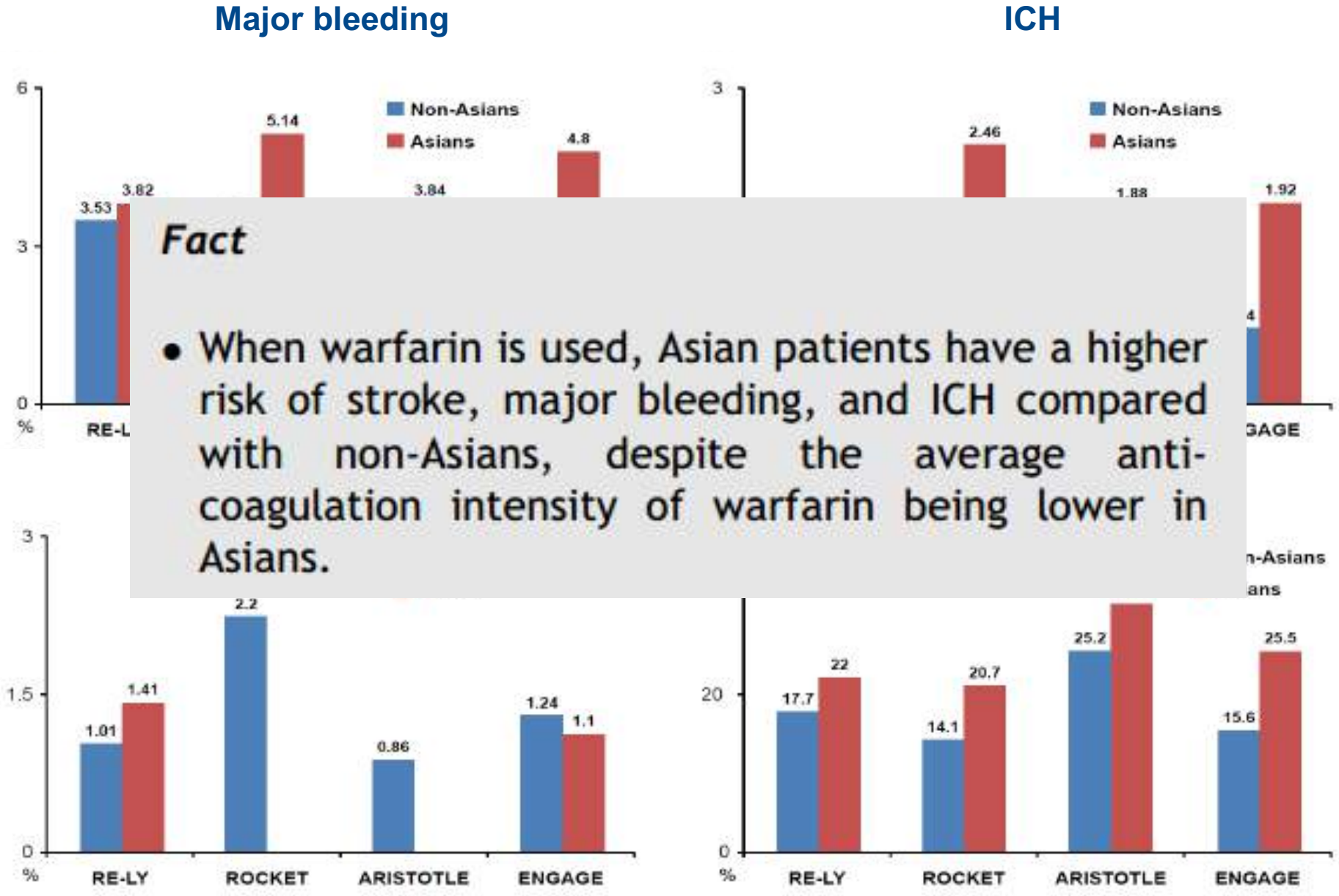




*:p=0.005（vs White）、**:p=0.002（vs White）、***:p＜0.0001（vs White）

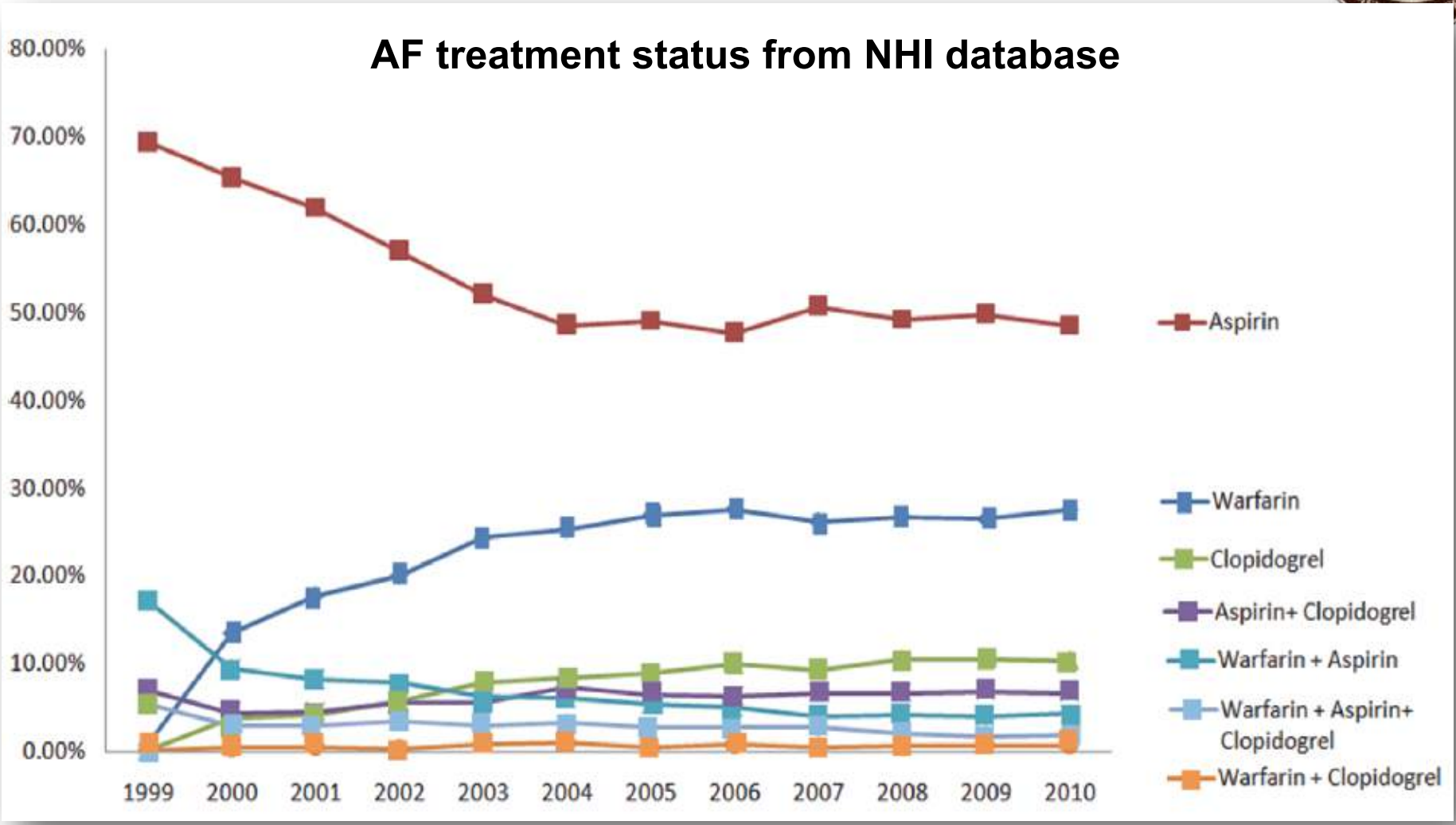
Source: Shen AY, et al. J Am Coll Cardiol. 2007 Jul 24;50(4):309-15.

Bleeding risks of warfarin were higher in Asia



Int J Cardiol. 2015 Feb 1;180:246-54

Over use of antiplatelet and under use of anticoagulant in Taiwan



NHIRD = National Health Insurance Research Database
Chen PC et al. PLoS One. 2015 Apr 29;10:e0125257.

Archives of Cardiovascular Disease (2014) 107, 77–87

ELSEVIER MASSON

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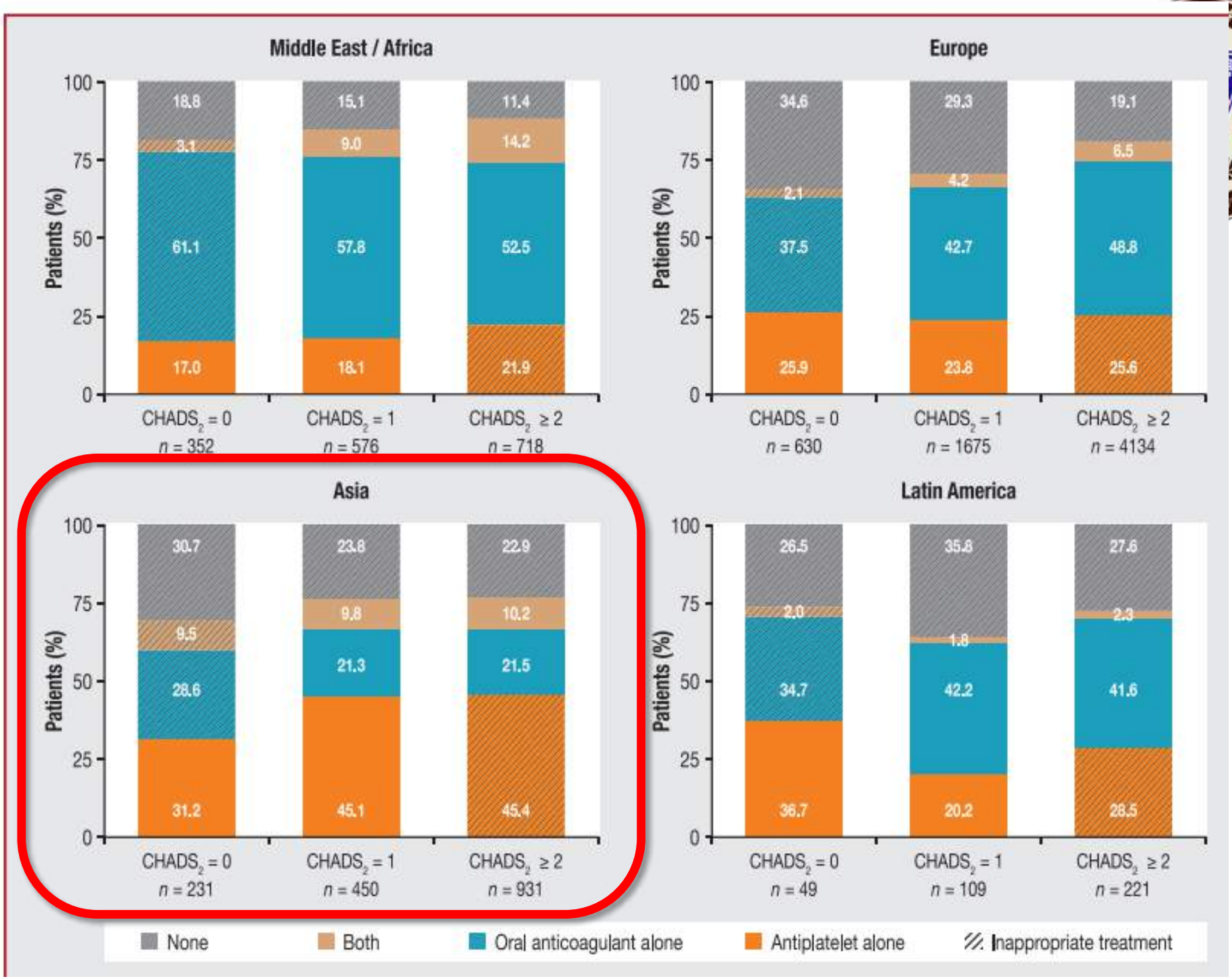
CLINICAL RESEARCH

Use of antithrombotics in atrial fibrillation in Africa, Europe, Asia and South America: Insights from the International RealiseAF Survey

Utilisation des antithrombotiques dans la fibrillation atriale en Afrique, Europe, Asie et Amérique du Sud : de l'enquête internationale RealiseAF

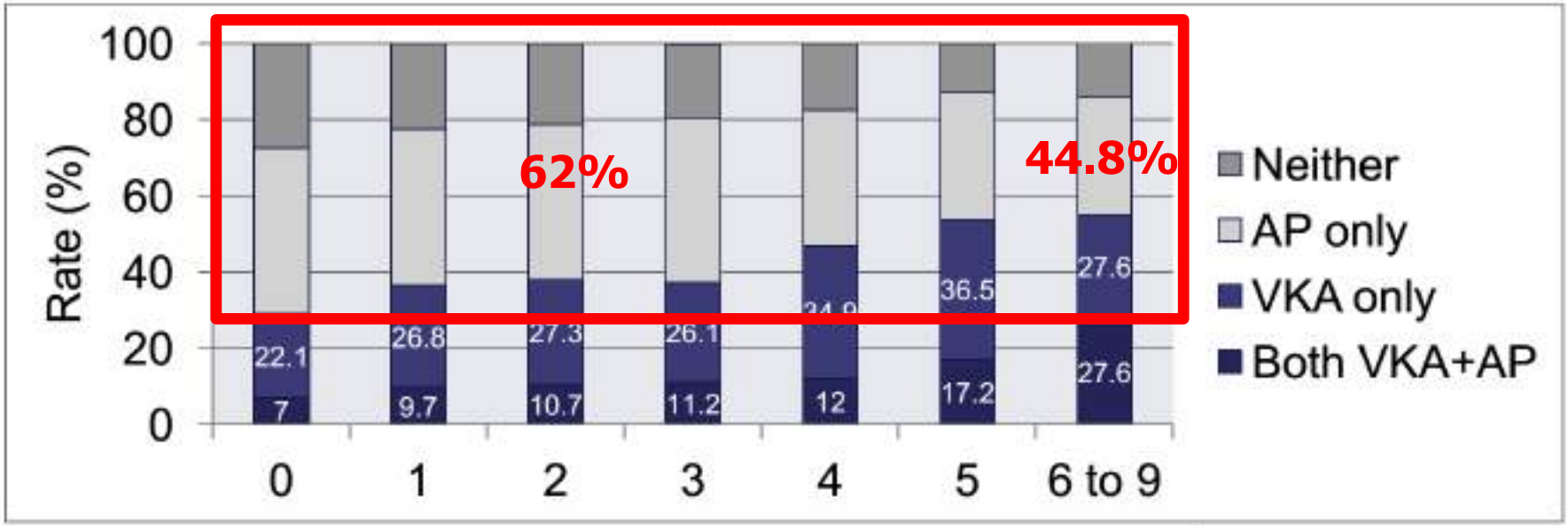
Habib Gamra[a,*], Jan Murin[b], Chern-En Chiang[c], Lisa Naditch-Brûlé[d], Sandrine Brette[e], Philippe Gabriel Steg[f,g,h,i], on behalf of the RealiseAF investigators



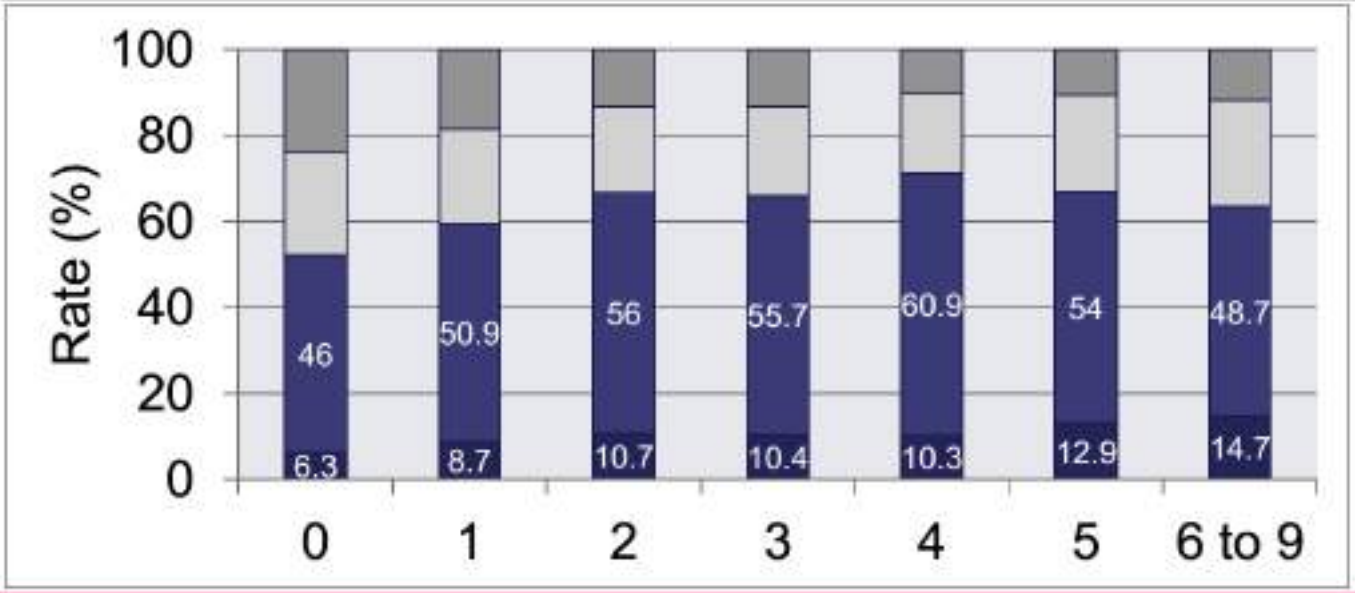
Archives of Cardiovascular Disease (2014) 107, 77—87

Results: antithrombotic use according to CHA_2DS_2-VASc score

Asia
(n=2580)



Europe
(n=6529)



Warfarin 治療的上的限制極多而導致50%以上的病患無法使用妥善的治療

- Unpredictable response
- Narrow therapeutic window (INR range 2.0–3.0)
- Slow onset/ offset of action

VKA therapy has several limitations that make it difficult to use in practice

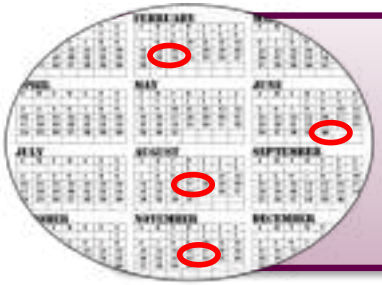
- Numerous food–drug interactions
- Numerous drug–drug interactions
- Warfarin resistance

Routine coagulation monitoring → Frequent dose adjustments

INR = International normalized ratio; VKA = vitamin K antagonist.

Ansell J, et al. *Chest* 2008;133;160S-198S. Umer Ushman MH, et al. *J Interv Card Electrophysiol* 2008;22:129-137.
Nutescu EA, et al. *Cardiol Clin* 2008;26:169-187.

Several reasons for lower TTRs in Asia have been suggested:



Less frequent monitoring

Oh et al Int J. Cardiol; 2016; 223:543-547

Lower INR target in Japan AF Guidelines

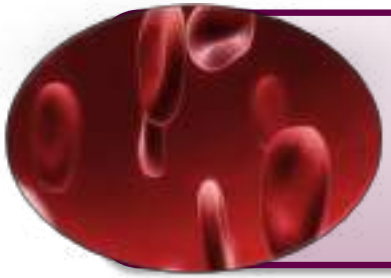
JSC Joint Working Group; Circ J 2014; 78: 1997-2021

Interactions with diet and herbal medicines

Chan HT et al J Card Pharm 2011;58(1):87-90

Less structured OAC management

Lip GY et al Int J Cardiol 2015; 180:246-254



Bleeding / ICH concern

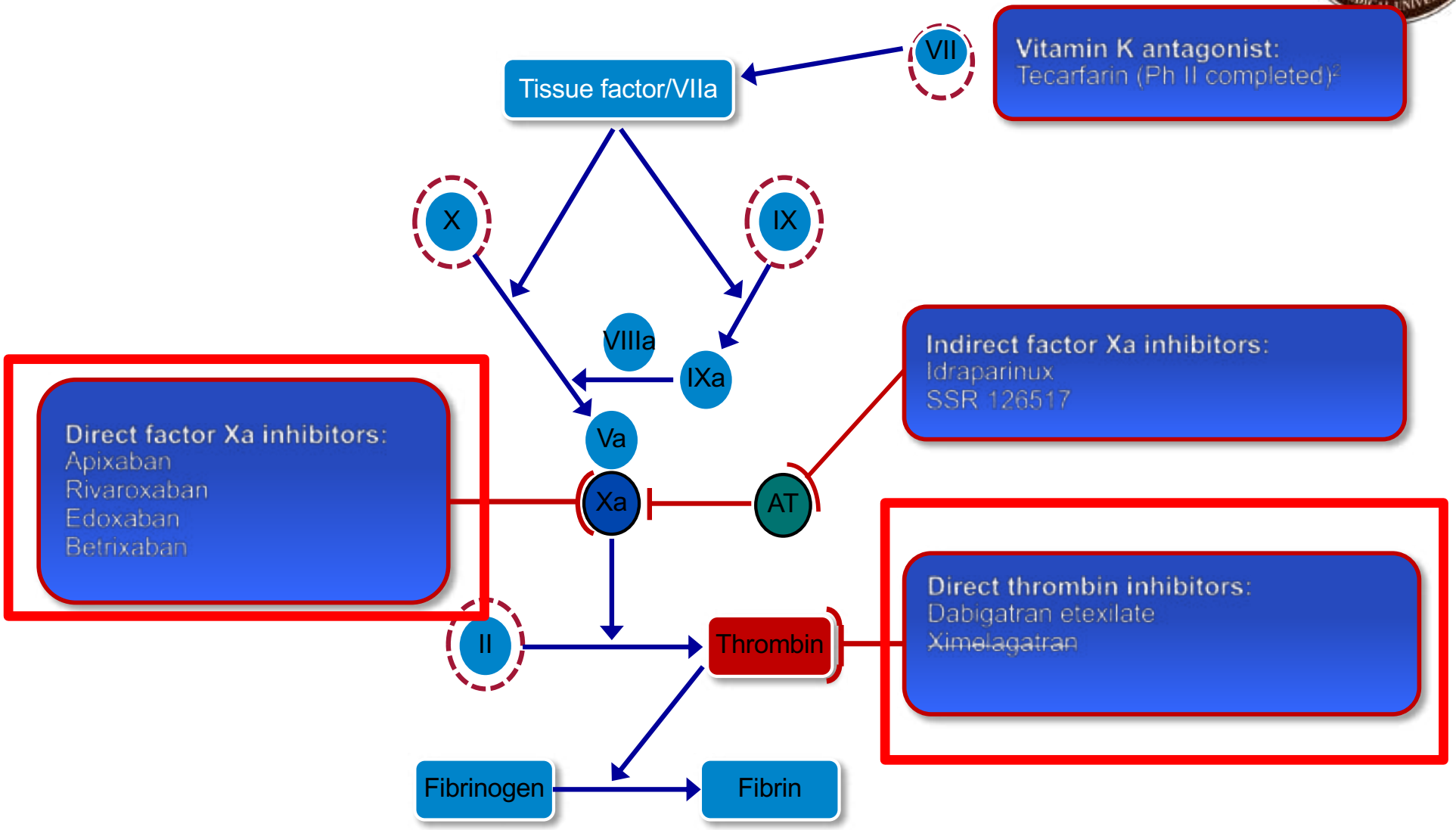
Shen AY et al. JACC 2007;50:309-315

Genetics

Takahashi H. et al. Clin Pharm Ther 2003; 73-253-263

D'Andrea et al. Blood 2005; 105-645-649

新型抗血栓藥物的作用標的



The war of NOAC

Edoxaban

RE-LY®: **R**andomized **E**valuation of **L**ong-term anticoagulant therap**Y**

- 18,113 patients randomized during 2 years[1,2]
- 951 centres in 44 countries
- 50% of enrolled patients were naïve to previous oral anticoagulant
- December 2005 to March 2009
- Median duration of follow-up: 2 years

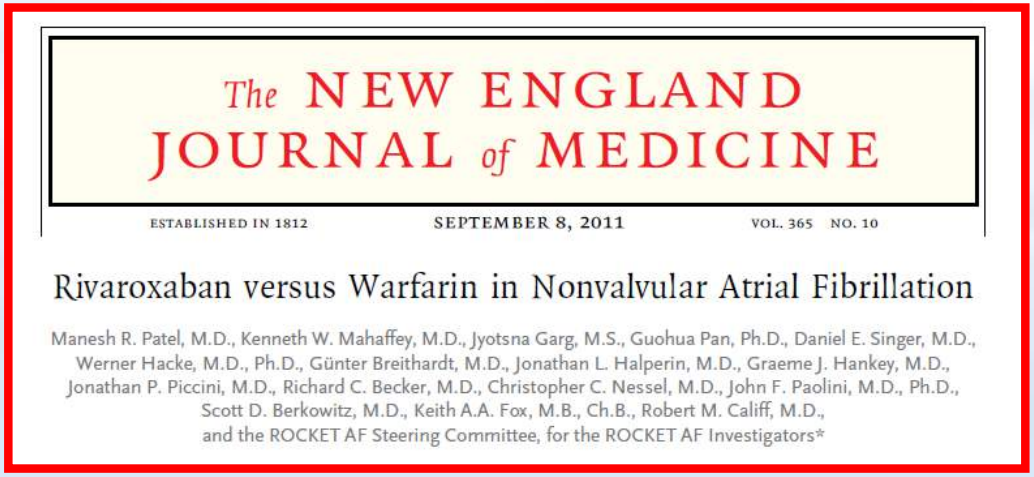
RELY®

Study of stroke prevention in atrial fibrillation

1. Ezekowitz MD et al. Am Heart J 2009;157:805–10;
2. Connolly SJ et al. N Engl J Med 2009;361:1139–51;
3. Connolly SJ et al. N Engl J Med 2010; 363:1875–1876

ROCKET AF

Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 8, 2011 VOL. 365 NO. 10

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Manesh R. Patel, M.D., Kenneth W. Mahaffey, M.D., Jyotsna Garg, M.S., Guohua Pan, Ph.D., Daniel E. Singer, M.D., Werner Hacke, M.D., Ph.D., Günter Breithardt, M.D., Jonathan L. Halperin, M.D., Graeme J. Hankey, M.D., Jonathan P. Piccini, M.D., Richard C. Becker, M.D., Christopher C. Nessel, M.D., John F. Paolini, M.D., Ph.D., Scott D. Berkowitz, M.D., Keith A.A. Fox, M.B., Ch.B., Robert M. Califf, M.D., and the ROCKET AF Steering Committee, for the ROCKET AF Investigators*

Patel MR *et al. N Engl J Med* 2011;365:883–891

Xarelto® rivaroxaban

Apixaban versus ASA: results from AVERROES

Apixaban versus warfarin: results from ARISTOTLE

Subject to local country prior approval BMS/Pfizer, as per relevant SOP and local country rules, slide may be used with external audiences in local country BMS/Pfizer arranged

Effective anticoagulation with factor Xa next generation in AF – TIMI 48

Engage AF TIMI 48

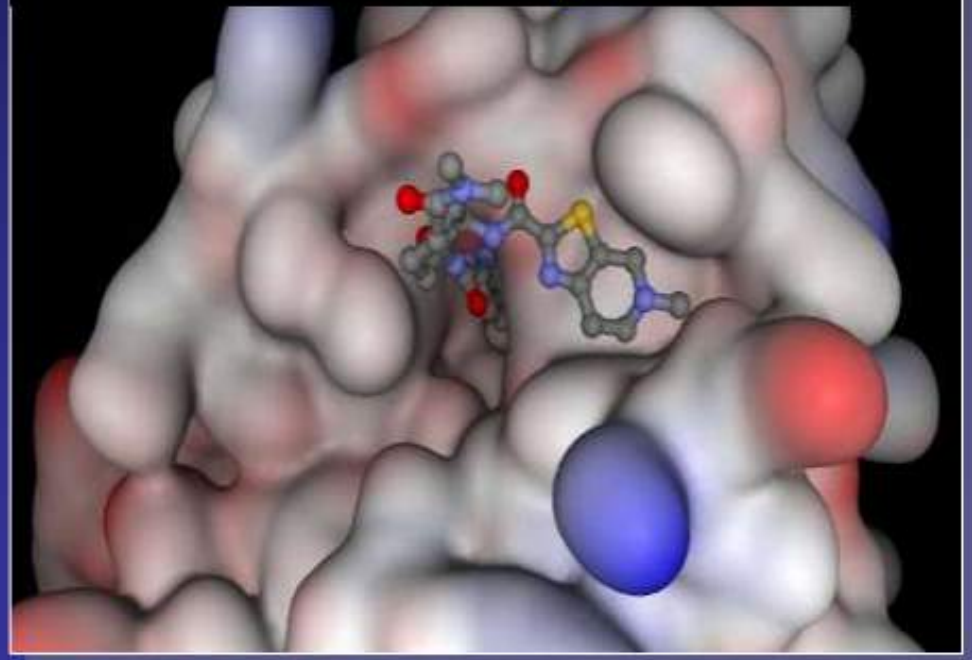
Direct oral FXa inhibitor

62% oral bioavailability

Peak 1-2h

$t_{1/2}$ ~10-14h

Edoxaban seated in Factor Xa catalytic center



Once daily

~50% renal clearance

Dose↓ 50%[2] if:
- CrCl 30-50 mL/m
- Weight ≤ 60kg
- Strong P-gp inhib

There are currently 4 NOACs which have been studied vs warfarin for stroke prevention in AF:

	Warfarin[1,2]	Dabigatran[3]	Rivaroxaban[4]	Apixaban[5]	Edoxaban[6]
Mechanism of action	Inhibitor of vitamin K-dependent factors	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Oral bioavailability	>95%	~6.5%	80–100%	~50%	~62%
Pro-drug	No	Yes	No	No	No
Food effect	Yes (foods high in vitamin K)	No	Yes (20 mg and 15 mg doses need to be taken with food)	No	No
T_{max}	within 4 h‡	0.5–2 h	2–4 h	3–4 h	1–2 h
Renal clearance	8%	85%	~33%*	~27%	50%
Mean half-life ($t_{1/2}$)	40 h	12–14 h†	5–9 h (young) 11–13 h (elderly)	12 h	10–14 h

The information in this table is based on the SmPCs for apixaban, rivaroxaban, dabigatran and edoxaban.

Please refer to the label information in your country of practice for further information.

Edoxaban approval status may vary from country to country.

*Direct renal excretion as unchanged active substance. The remaining 66% undergoes metabolic degradation, of which half is excreted renally.
†Prolonged in patients with impaired renal function.
‡Time to peak effect is up to 4–5 days.[2]

1. Warfarin SmPC. Available at http://www.ema.europa.eu; 2. Weitz & Gross. Hematology Am Soc Hematol Educ Program 2012;2012:536-40; 3. Dabigatran SmPC. Available at http://www.ema.europa.eu; 4. Rivaroxaban SmPC. Available at http://www.ema.europa.eu; 5. Apixaban SmPC. Available at http://www.ema.europa.eu; 6. Edoxaban SmPC. Available at http://www.ema.europa.eu.

NOAC 健保適應症	Boehringer Pradaxa (Dabigatran) 普栓達 150/110mg	Bayer Xarelto (Rivaroxaban) 拜瑞妥 20/15/10mg	Boehringer Eliquis (Apixaban) 艾必可擬 5mg	第一三共 Lixiana (Edoxaban) 里先安 60/30mg
機轉	Direct thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
心房顫動	每日2次 RE-LY	每日1次 ROCKET-AF	每日2次 ARISTOLE	每日1次 ENGAGE-TIMI48
深層靜脈栓塞+肺栓塞		前3周每日2次15mg，之後半年每日1次20mg	前7日每日2次每次2顆，之後半年每日2次每次1顆	須先經非腸道抗凝劑5日，之後半年每日1次每次1顆
人工髖/膝關節預防靜脈血栓症(有相關病史)	75mg每日至多2粒	10mg每日1次每日1粒		
GFR	≥30	≥15	≥15	15≤GFR<95
解毒劑	專案 Praxbind (Idarucizumab)	研究中 Andexanet Alfa Ciraparantag	研究中 Andexanet Alfa Ciraparantag	研究中 Ciraparantag

NOAC stroke prevention in AF studies: ROCKET and ENGAGE excluded lower risk patients

Data for overall study group (all study arms)	RE-LY[1,2]	ROCKET AF[3]	ARISTOTLE[4]	AVERROES[5]	ENGAGE AF-TIMI 48[6,7]
Age (mean)*	72	73§	70§	70	72§
Gender (men)	64.0%	60.0%	65.0%	59.0%	62.0%
CHADS$_2$ score, mean*	2.1	3.5	2.1	2.0	2.8
0 or 1	31.9%	<1.0%	34.0%	36.2%	–
2	35.6%	13.0%	35.8%	35.7%	77.4%†
3–6	32.5%	87%	30.2%	28.0%	22.6%‡
TTR in the warfarin group (mean % of the study period)	64.4%	55.0%	62.2%	N/A	64.9%

*Data calculated for the entire study group
§Median age
†CHADS$_2$ score ≤3; ‡ CHADS$_2$ score 4–6

There are no adequate and well-controlled head-to-head clinical trials comparing efficacy and safety of apixaban to any of the other NOACs.

Edoxaban approval status and label may vary from country to country.

1. Connolly et al. N Engl J Med 2009;361:1139–51; 2. Connolly et al. N Engl J Med 2010;363:1875–6; 3. Patel et al. N Engl J Med 2011;365:883–91; 4. Granger et al. N Engl J Med 2011;365:981–92; 5. Connolly et al. N Engl J Med 2011;364:806–17; 6. Giugliano et al. N Engl J Med 2013;369:2093–104; 7. EMA Lixiana assessment report, 23 April 2015.

Properties of an ideal anticoagulant versus currently available agents

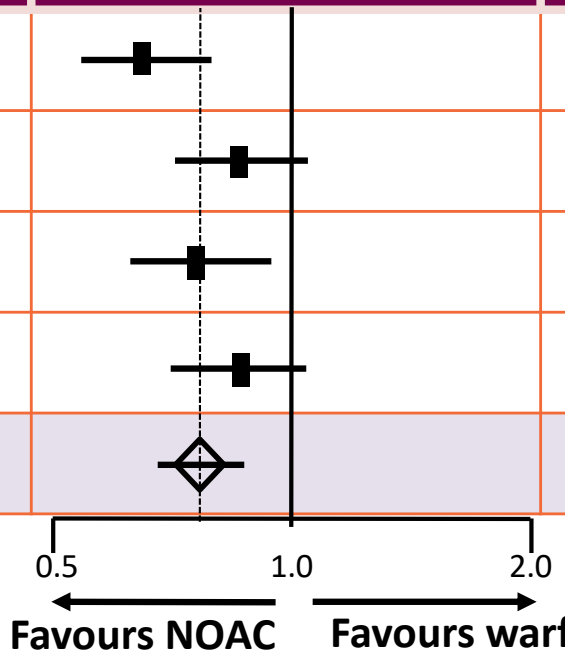
理想口服凝血藥的特性

	Oral	No significant food/drug interactions	Predictable response	No routine coagulation monitoring	Fixed dosing	No risk of HIT
IDEAL	✓	✓	✓	✓	✓	✓
LMWH		✓	✓	✓	✓	
UFH		✓				
Fondaparinux		✓	✓	✓	✓	✓
VKAs	✓					✓
Rivaroxaban	✓	✓	✓	✓	✓	✓
Dabigatran	✓	✓	✓	✓	✓	✓
Apixaban	✓	✓	✓	✓	✓	✓
Edoxaban	✓	✓	✓	✓	✓	✓

Meta-analysis: Efficacy of NOACs vs warfarin for stroke prevention in patients with NVAF[1]

Stroke or SE

Study	NOAC (events)	Warfarin (events)	RR (95% CI)	RR (95% CI)	*P* value
RE-LY (150 mg)	134 / 6,076	199 / 6,022		**0.66** (0.53–0.82)	0.0001
ROCKET AF (20 mg)	269 / 7,081	306 / 7,090		**0.88** (0.75–1.03)	0.12
ARISTOTLE (5 mg)	212 / 9,120	265 / 9,081		**0.80** (0.67–0.95)	0.012
ENGAGE AF (60 mg)	296 / 7,035	337 / 7,036		**0.88** (0.75–1.02)	0.10
Combined (random)	**911 / 29,312**	**1107 / 29,229**		**0.81** (0.73–0.91)	<0.0001



Data are n/N, unless otherwise indicated.
Heterogeneity: I^2=47%, P=0.13

Adapted from Ruff et al. 2014

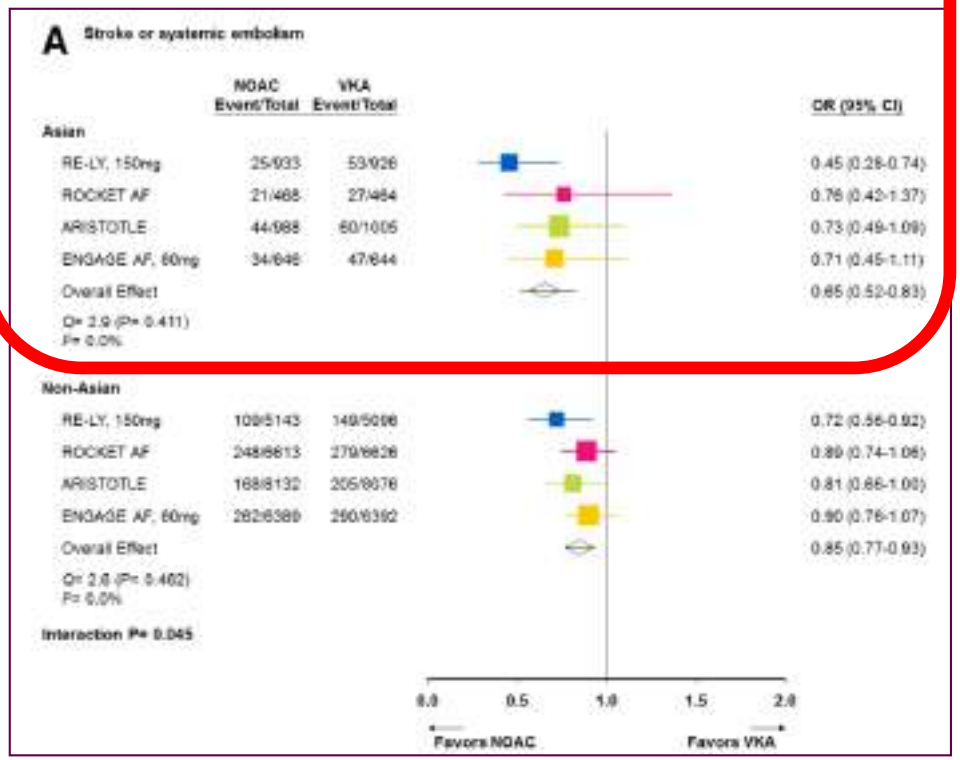
There are no adequate and well-controlled head-to-head clinical trials comparing efficacy and safety of apixaban to any of the other NOACs. Hence, the analysis presented does not imply a comparison of efficacy, safety, or product interchangeability

Edoxaban approval status and label may vary from country to country.

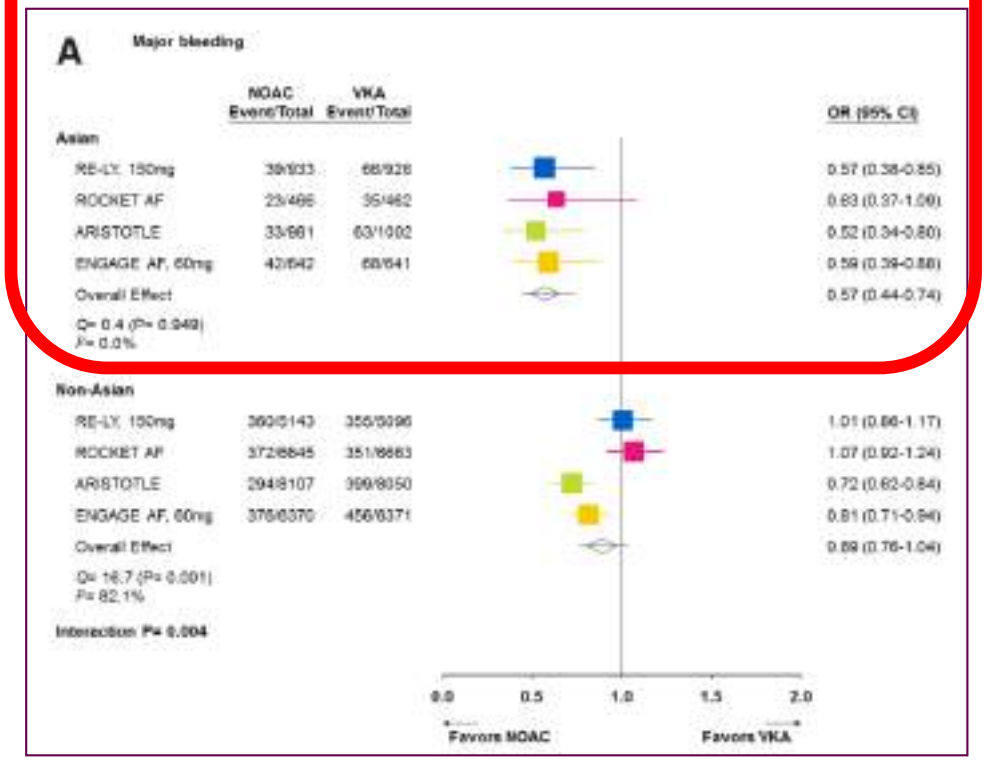
1. Ruff et al. Lancet 2014;383:955-62.

Meta-analysis of major NOAC trials: Asian and non-Asian populations[1]

Primary efficacy endpoint:
Stroke or systemic embolism



Primary safety endpoint:
Major bleeding



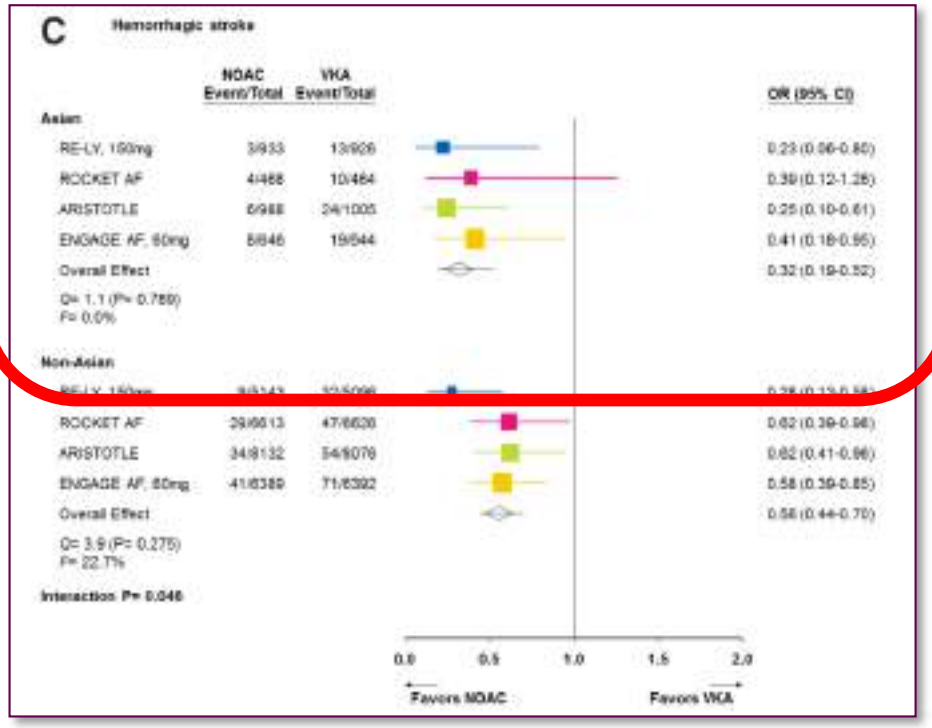
Figures adapted from Wang et al. 2015

There are no adequate and well-controlled head-to-head clinical trials comparing efficacy and safety of apixaban to any of the other NOACs. Hence, the analysis presented does not imply a comparison of efficacy, safety, or product interchangeability

Wang et al. Stroke 2015;46:2555-61.

The rate of haemorrhagic stroke was consistently lower for all NOACs vs warfarin in Asian patients[1]

Key Secondary endpoint:
Haemorrhagic Stroke (ICH)



Adapted from Wang et al. 2015

Key observations from the meta-analysis:

- The efficacy and safety of standard dose NOACs over VKA were typically greater for Asian patients versus non-Asian patients[1]
- Standard dose NOACs also were more effective in reducing haemorrhagic stroke in Asian vs non-Asian patients[1]

There are no adequate and well-controlled head-to-head clinical trials comparing efficacy and safety of apixaban to any of the other NOACs. Hence, the analysis presented does not imply a comparison of efficacy, safety, or product interchangeability

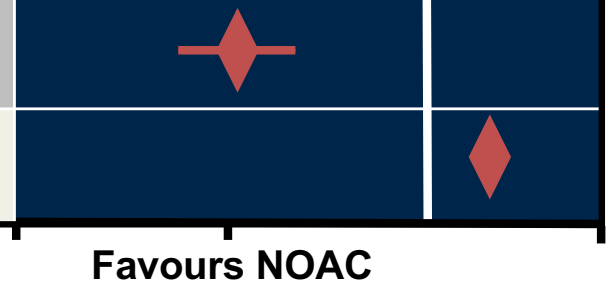
1. Wang et al. Stroke 2015;46:2555-61.

NOAC 4-trial Meta-analysis Full Dose

Efficacy vs. Safety

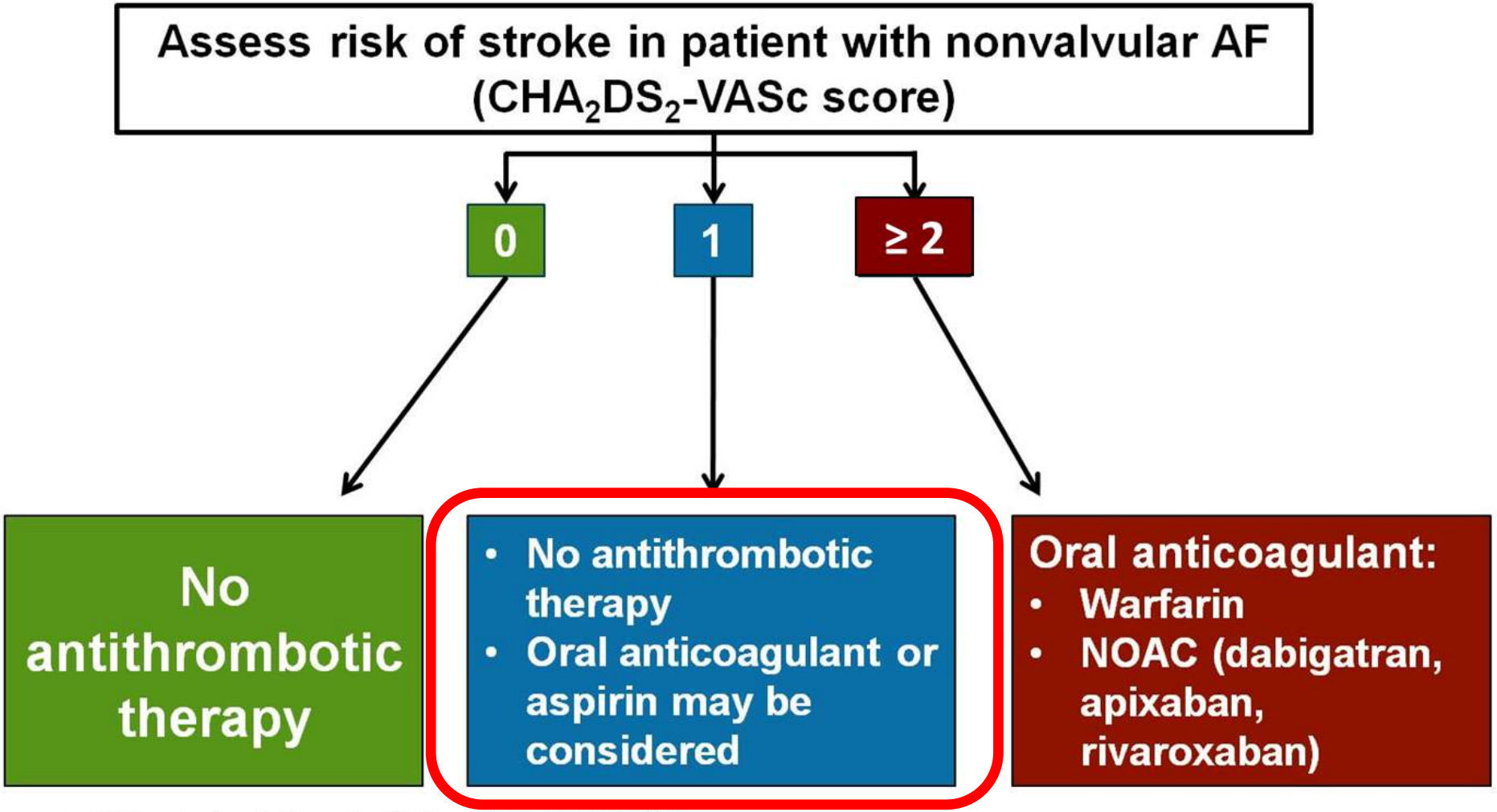
Result	Pooled NOAC Events /Total	Pooled Warfarin Events /Total	Risk Ratio	95% CIs	p	* Edoxaban is not approved for clinical use in AF
Safety						
Intra-cranial hemorrhage	204 /29287	425 /29211	0.48	0.39-0.59	<0.0001	
Gastrointestinal bleeding	751 /29287	591 /29211	1.25	1.01-1.55	0.043	

NOAC比起warfarin能減少ICH和出血性中風風險但可能會增加GI出血機率



Ruff C, et al. Lancet 2014 Mar 15;383(9921):955-62.

2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation



January CT, et al. *J Am Coll Cardiol*. 2014.[19]

European Heart Journal Advance Access published August 27, 2016

European Heart Journal
doi:10.1093/eurheartj/ehw210

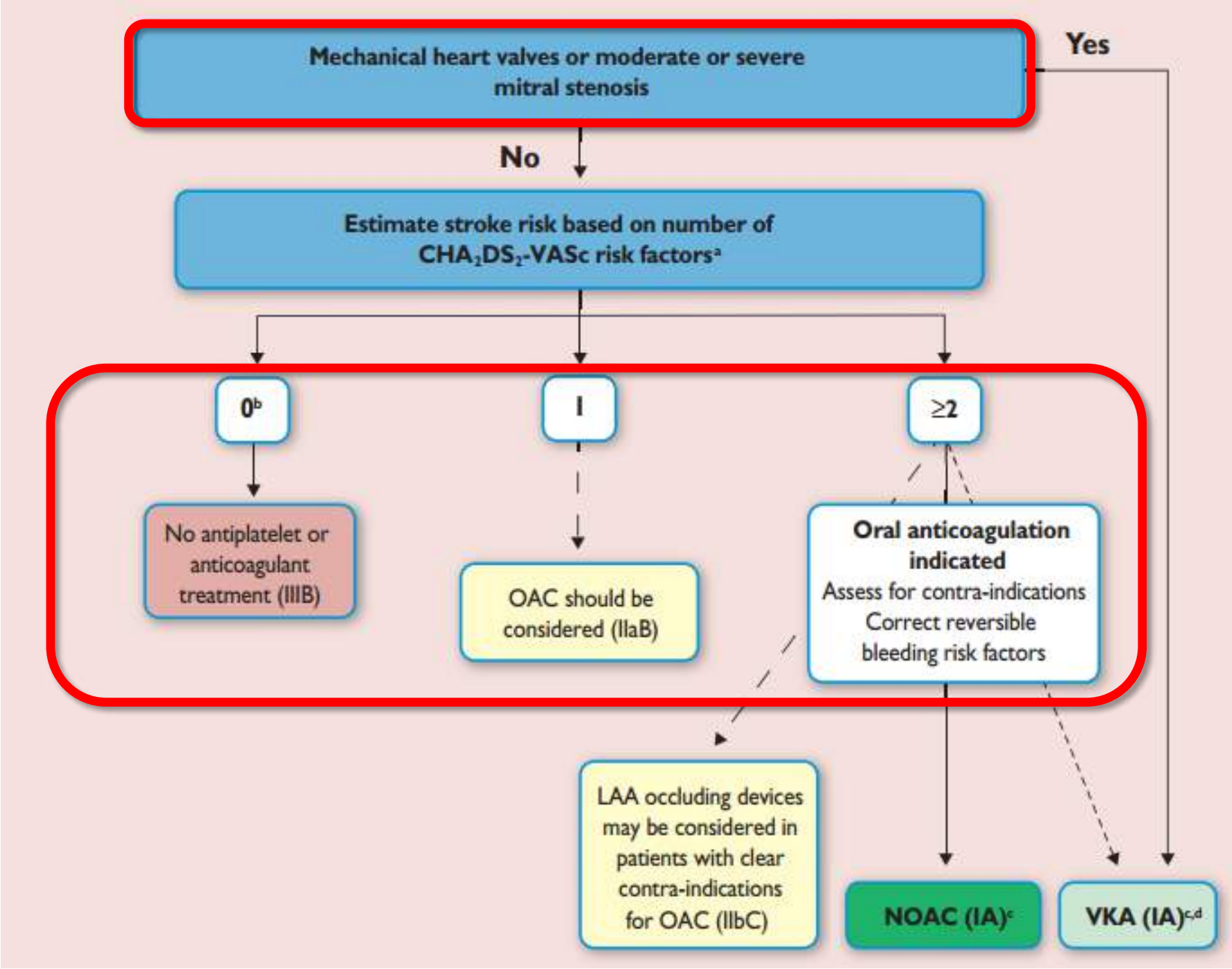
ESC GUIDELINES

2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

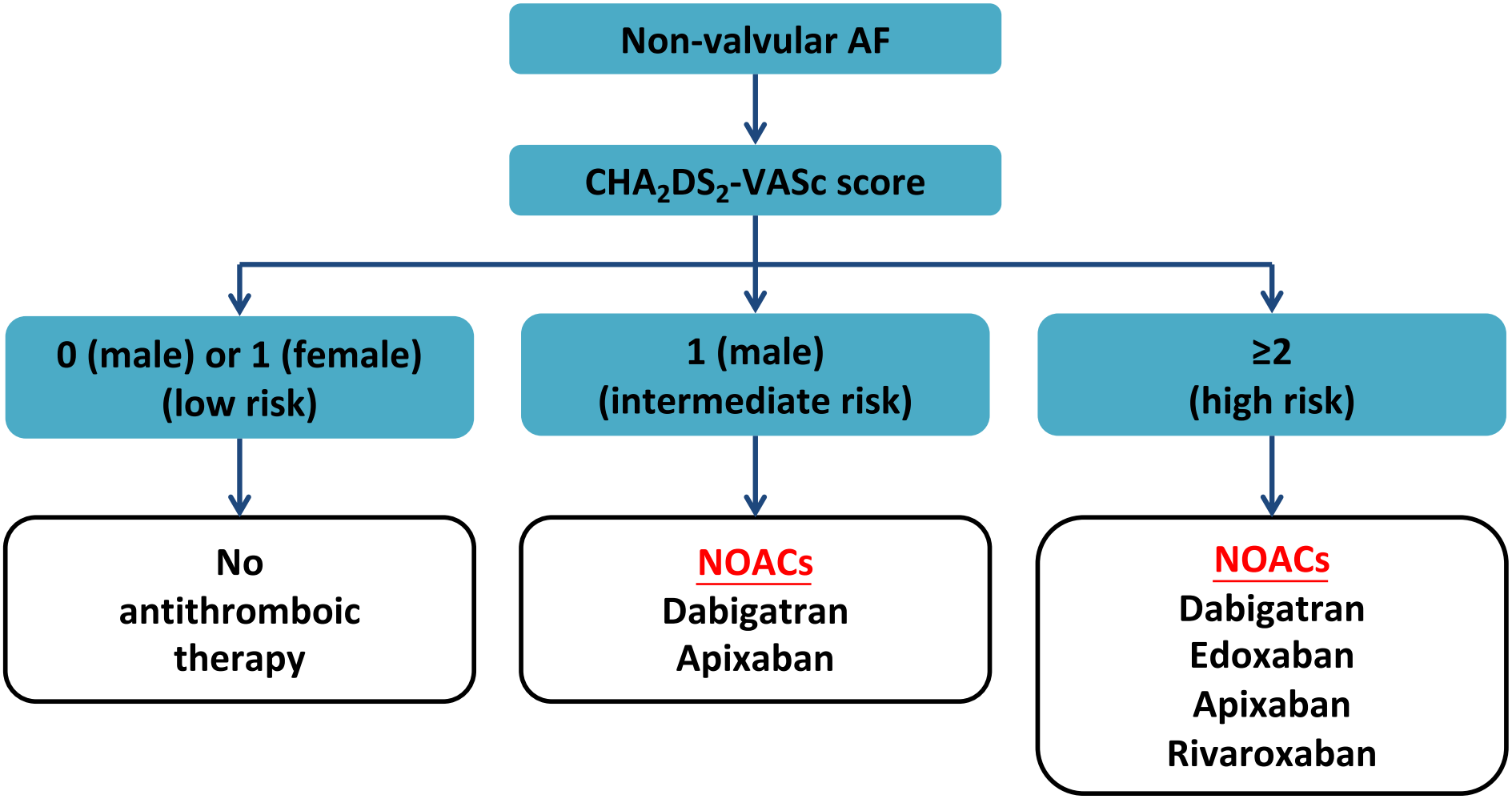
The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC)

Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC

Endorsed by the European Stroke Organisation (ESO)


Mechanical heart valves or moderate or severe mitral stenosis
Yes
No
Estimate stroke risk based on number of CHA2DS2-VASc risk factors[a]
0[b]
1
≥2
No antiplatelet or anticoagulant treatment (IIIB)
OAC should be considered (IIaB)
Oral anticoagulation indicated
Assess for contra-indications
Correct reversible bleeding risk factors
LAA occluding devices may be considered in patients with clear contra-indications for OAC (IIbC)
NOAC (IA)[c]
VKA (IA)[c,d]

Management Algorithm for Stroke Prevention in Asians



AF = atrial fibrillation; NOAC = non-vitamin K antagonist oral anticoagulant.

2016 AF Guidelines of THRS/TSOC. Journal of the Formosan Medical Association (2016).

Efficacy and Safety Endpoints of NOACs in Asians

	Stroke/ SEE	Ischemic stroke	Hemorrhage stroke	MI	All-cause death	CV death	Major bleeding	Intracranial hemorrhage	GI bleeding	Bleeding of any cause
Dabigatran[a] 150 mg	V	V	V			NR	V	V		V
Dabigatran[a] 110 mg			V			NR	V	V		V
Rivaroxaban								V	NR	
Apixaban			V			NR	V	V	NR	V
Edoxaban 60 mg			V		V	V	V	V		V
Edoxaban 30 mg			V				V	V		V

GI = gastrointestinal; NOACs = non-vitamin K antagonist oral anticoagulants; NR = not reported; SEE = systemic embolization events;
V = p value less than 0.05 when compared with warfarin.
[a] China, Japan, South Korea, Taiwan, Hong Kong, Philippines, Singapore, Malaysia, Thailand, India.
[b] China, South Korea, Taiwan, Hong Kong.
[c] China, Japan, South Korea, Taiwan, Hong Kong, Philippines, Singapore, Malaysia.
[d] China, Japan, South Korea, Taiwan.

Chiang et al. J Formos Med Assoc. **2016** Nov;115(11):893-952

January CT, et al.
2019 Focused Update on Atrial Fibrillation

2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society

Developed in Collaboration With the Society of Thoracic Surgeons

COR	LOE	Recommendations
I	A	**1. For patients with AF and an elevated CHA_2DS_2-VASc score of 2 or greater in men or 3 or greater in women, oral anticoagulants are recommended. Options include:** **• Warfarin (LOE: A) (S4.1.1-5–S4.1.1-7)** **• Dabigatran (LOE: B) (S4.1.1-8)** **• Rivaroxaban (LOE: B) (S4.1.1-9)** **• Apixaban (LOE: B) (S4.1.1-10), or** **• Edoxaban (LOE: B-R) (S4.1.1-11)** **MODIFIED**: This recommendation has been updated in response to the approval of edoxaban, a new factor Xa inhibitor. More precision in the use of CHA_2DS_2-VASc scores is specified in subsequent recommendations. The LOEs for warfarin, dabigatran, rivaroxaban, and apixaban have not been updated for greater granularity as per the new LOE system. (Section 4.1. in the 2014 AF Guideline) The original text can be found in Section 4.1 of the 2014 AF guideline. Additional information about the comparative effectiveness and bleeding risk of NOACs can be found in Section 4.2.2.2.
I	B	
I	B	
I	B-R	
I	A	**2. NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) are recommended over warfarin in NOAC-eligible patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) (S4.1.1-8–S4.1.1-11).** **NEW**: Exclusion criteria are now defined as moderate-to-severe mitral stenosis or a mechanical heart valve. When the NOAC trials are considered as a group, the direct thrombin inhibitor and factor Xa inhibitors were at least noninferior and, in some trials, superior to warfarin for preventing stroke and systemic embolism and were associated with lower risks of serious bleeding.

IIb	C- LD	15. **For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) and a CHA_2DS_2-VASc score of 1 in men and 2 in women, prescribing an oral anticoagulant to reduce thromboembolic stroke risk may be considered (S4.1.1-31–S4.1.1-35).** **MODIFIED**: Exclusion criteria are now defined as moderate-to-severe mitral stenosis or a mechanical heart valve, and evidence was added to support separate risk scores by sex. LOE was updated from C to C-LD. (Section 4.1. in the 2014 AF Guideline)
III: No Benefit	C-EO	16. **In patients with AF and end-stage CKD or on dialysis, the direct thrombin inhibitor dabigatran or the factor Xa inhibitors rivaroxaban or edoxaban are not recommended because of the lack of evidence from clinical trials that benefit exceeds risk (S4.1.1-8–S4.1.1-11, S4.1.1-36–S4.1.1-38).** **MODIFIED**: New data have been included. Edoxaban received FDA approval and has been added to the recommendation. LOE was updated from C to C-EO. (Section 4.1. in the 2014 AF Guideline)
III: Harm	B-R	17. **The direct thrombin inhibitor dabigatran should not be used in patients with AF and a mechanical heart valve (S4.1.1-39).** **MODIFIED**: Evidence was added. LOE was updated from B to B-R. Other NOACs are addressed in the supportive text. (Section 4.1. in the 2014 AF Guideline)

I	B-NR	3. **Idarucizumab is recommended for the reversal of dabigatran in the event of life-threatening bleeding or an urgent procedure (S4.3-2).** **NEW**: New evidence has been published about idarucizumab to support LOE B-NR.
IIa	B-NR	4. **Andexanet alfa can be useful for the reversal of rivaroxaban and apixaban in the event of life-threatening or uncontrolled bleeding (S4.3-3, S4.3-4).** **NEW**: New evidence has been published about andexanet alfa to support LOE B-NR.

4.4.1. Percutaneous Approaches to Occlude the LAA

Recommendation for Percutaneous Approaches to Occlude the LAA

Referenced studies that support the new recommendation are summarized in Online Data Supplement 4.

COR	LOE	Recommendation
IIb	B-NR	1. **Percutaneous LAA occlusion may be considered in patients with AF at increased risk of stroke who have contraindications to long-term anticoagulation (S4.4.1-1–S4.4.1-5).** **NEW**: Clinical trial data and FDA approval of the Watchman device necessitated this recommendation.

Effective a**N**ticoa**G**ulation with factor x**A** next **GE**neration in **A**trial **F**ibrillation

Study Design

21,105 PATIENTS
AF on electrical recording within last 12 m
$CHADS_2$ ≥2

RANDOMIZATION
1:1:1 randomization is stratified by $CHADS_2$ score 2–3 versus 4–6 and need for edoxaban dose reduction*

Double-blind, Double-dummy

Warfarin (INR 2.0–3.0)	High-dose Edoxaban 60* mg QD	Low-dose Edoxaban 30* mg QD

*Dose reduced by 50% if:
- CrCl 30–50 mL/min
- weight ≤60 kg
- strong P-gp inhibitor

1º Efficacy EP = Stroke or SEE
2º Efficacy EP = Stroke or SEE or CV mortality
1º Safety EP = Major Bleeding (ISTH criteria)

Non-inferiority
Upper 97.5% CI <1.38

CI = confidence interval; CrCl = creatinine clearance; ISTH=International Society on Thrombosis and Haemostasis; P-gp = P-glycoprotein; SEE=systemic embolic event

Ruff CR et al. Am Heart J 2010; 160:635-41.

Baseline Characteristics

Median age [IQR]	72 [64, 78]
Female sex	38%
Paroxysmal atrial fibrillation	25%
$CHADS_2$ (mean ± SD)	2.8 ± 1.0
$CHADS_2 \geq 3$	53%
$CHADS_2 \geq 4$	23%
Prior CHF	57%
Hypertension	94%
Age ≥ 75 years	40%
Diabetes mellitus	36%
Prior stroke or TIA	28%
Dose reduced at randomization	25%
Prior VKA experience	59%
Aspirin at randomization	29%
Amiodarone at randomization	12%

No differences across treatment groups

CHF=congestive heart failure; IQR=interquartile range; TIA=transient ischemic attack; VKA=vitamin K antagonist

Population/Analysis Definitions

Populations	Analyses
mITT*, On-Treatment†	Primary efficacy (Non-inferiority)
Intent-to-Treat (ITT) All randomized	Superiority All events
Safety, On-Treatment†	Principal Safety Major Bleeding (ISTH definition)

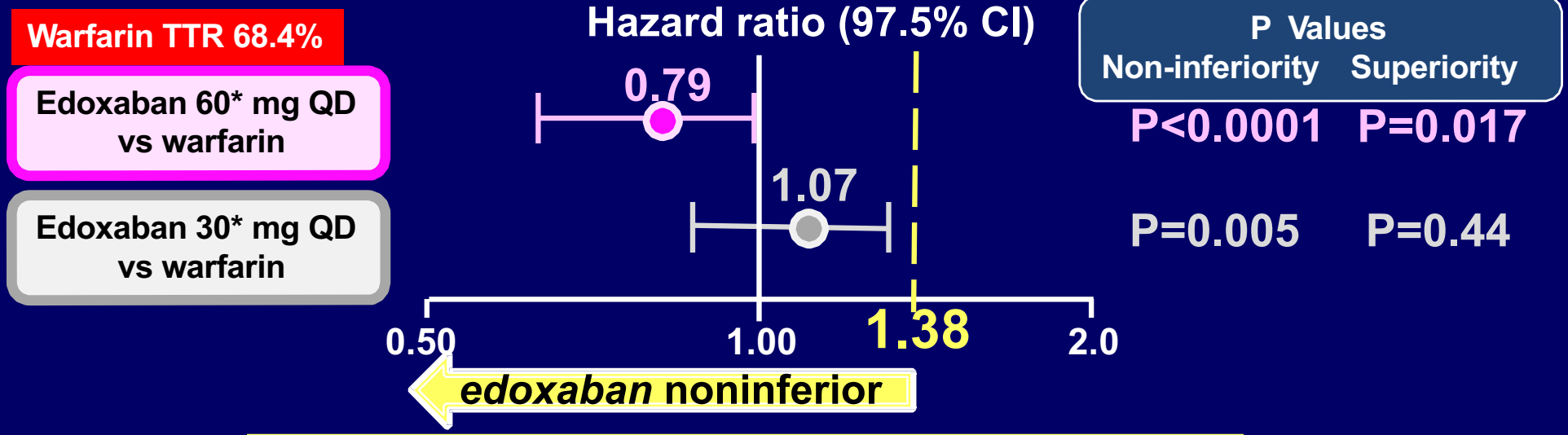
* mITT = All patients who took at least 1 dose

† On-Treatment = 1st dose → last dose +3 days or end of double-blind treatment

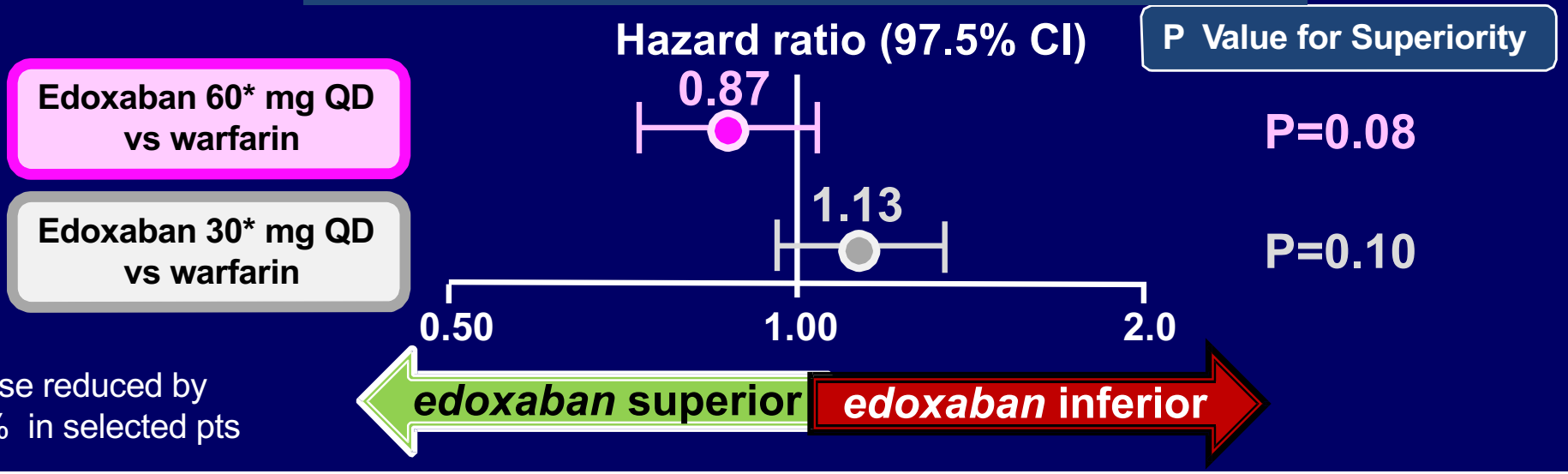
ISTH=International Society on Thrombosis and Haemostasis

Primary Endpoint: Stroke / SEE
(2.8 years median f/u)

Noninferiority Analysis (mITT, On Treatment)



Superiority Analysis (ITT, Overall)



*Dose reduced by 50% in selected pts

Key Secondary Outcomes

Engage AF TIMI 48

	Edoxaban 60* mg QD vs warfarin	Edoxaban 30* mg QD vs warfarin	Warfarin TTR 68.4%	HR (95% CI)	E-60	E-30
Hem. Stroke	0.54	0.33			<0.001	<0.001
Ischemic Stroke	1.00	1.41			0.97	<0.001
2° EP: Stroke, SEE, CV death	0.87	0.95			0.005	0.32
Death or ICH	0.87	0.82			0.004	<0.001
All-cause mortality	0.92	0.87			0.08	0.006
CV death	0.86	0.85			0.013	0.008
Myocardial infarction	0.94	1.19			0.60	0.13

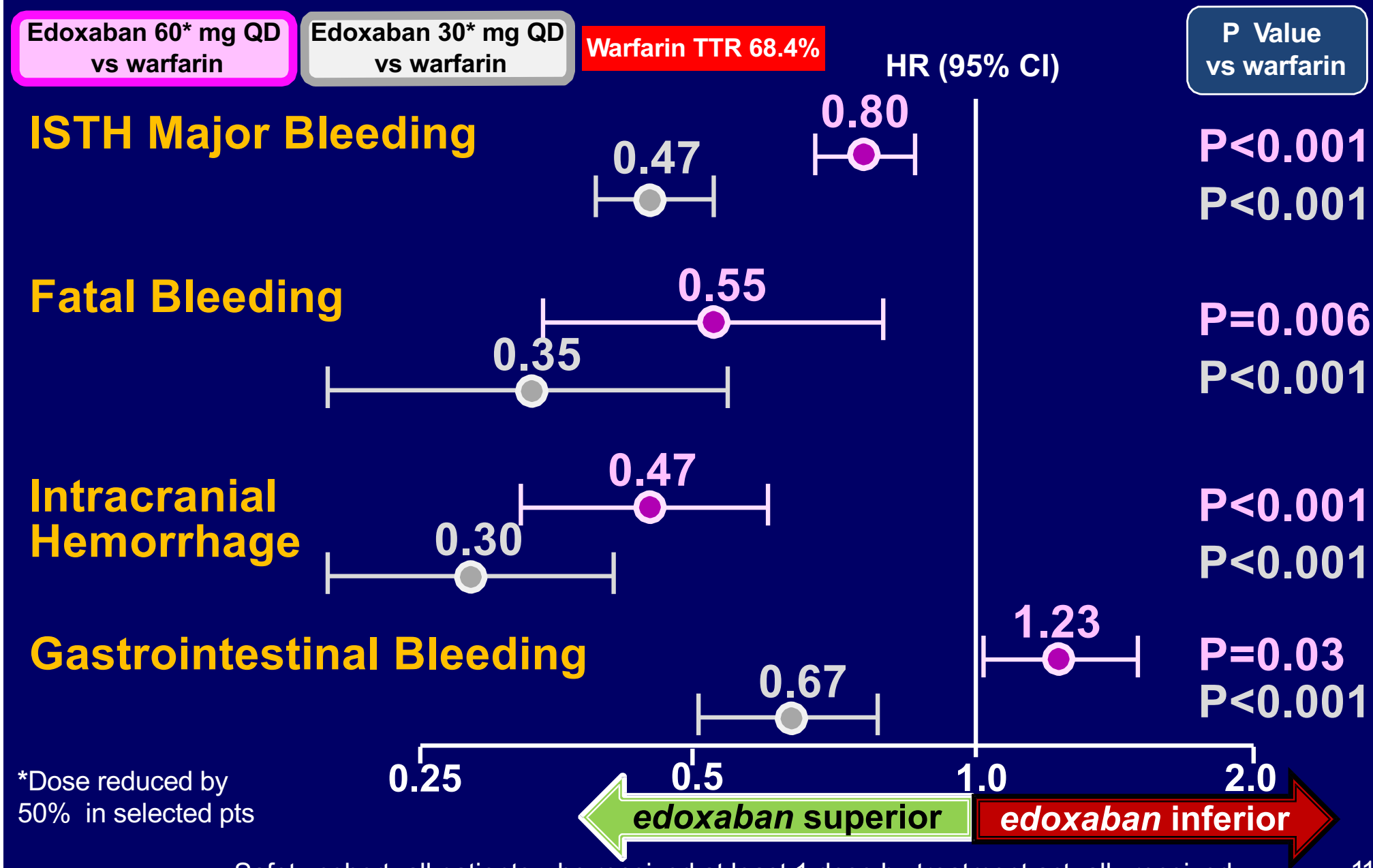
warfarin

0.25 0.5 1.00 2.0

edoxaban superior | *edoxaban* inferior

*Dose reduced by 50% in selected pts

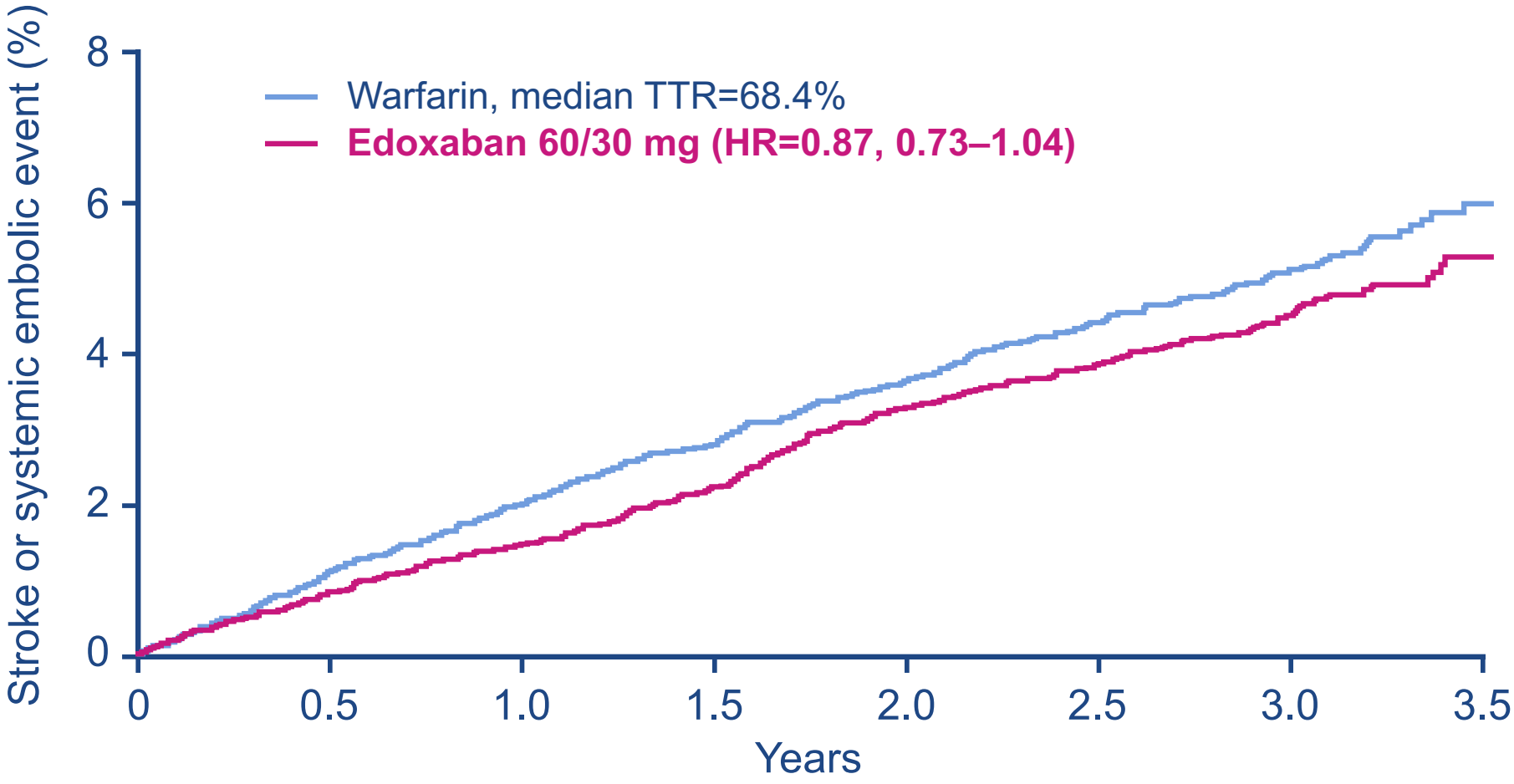
Main Safety Results
- Safety Cohort on Treatment -



*Dose reduced by 50% in selected pts

Safety cohort=all patients who received at least 1 dose by treatment actually received

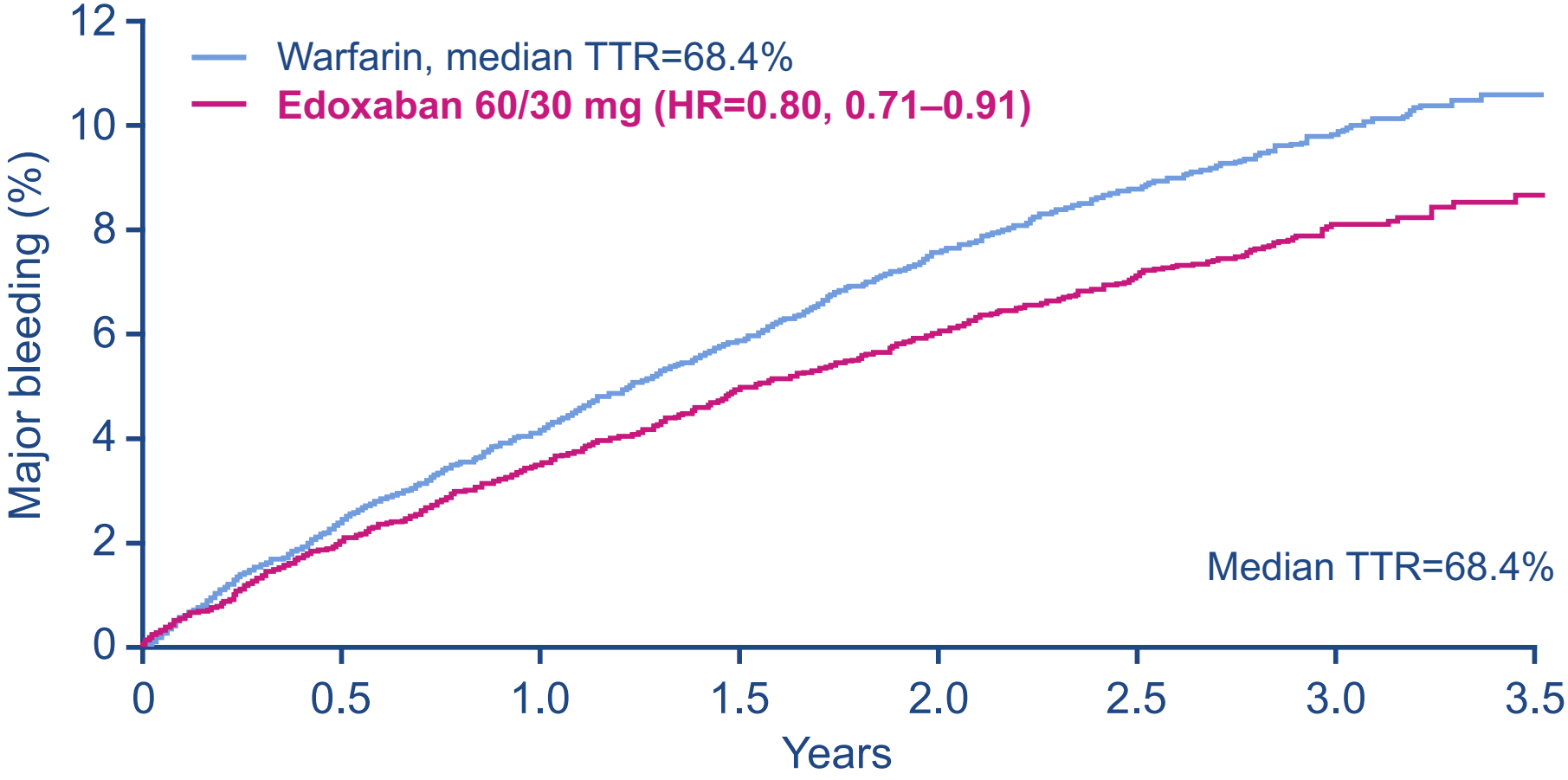
Kaplan-Meier of primary efficacy outcome ITT population



No.at risk								
Warfarin	7036	6798	6615	6406	6225	4593	2333	536
Edoxaban (60)	7035	6816	6650	6480	6283	4659	2401	551

Giugliano et al. N Engl J Med 2013; DOI: 10.1056/NEJMoa1310907

Kaplan-Meier of principal safety outcome



No.at risk								
Warfarin	7012	6166	5630	5278	4941	3446	1687	370
Edoxaban (60)	7012	6039	5594	5232	4910	3471	1706	345

Giugliano et al. N Engl J Med 2013; DOI:

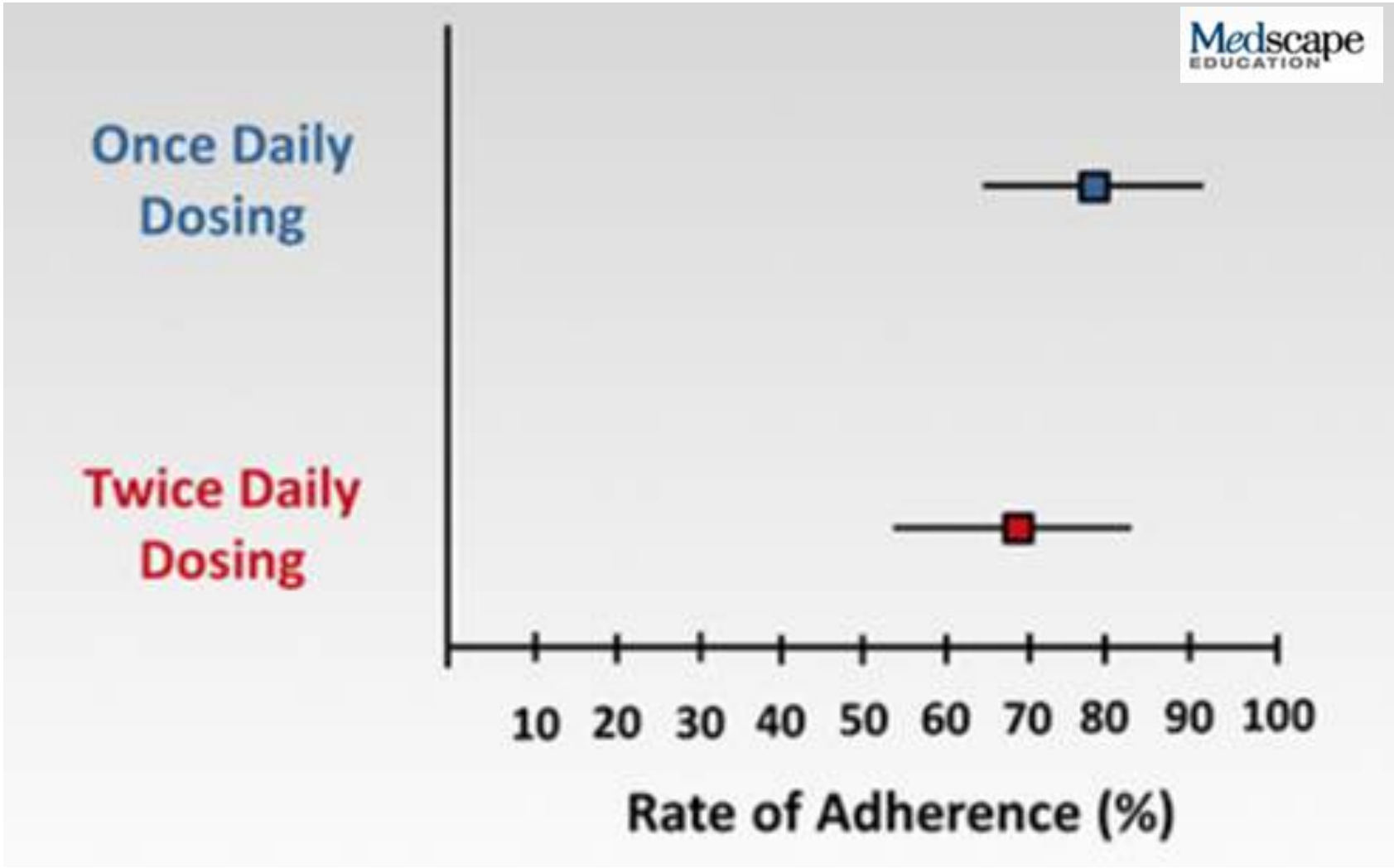
ENGAGE-AF study
Conclusions

- **Both 60 mg and 30 mg edoxaban dose** regimens were **non-inferior to well-managed warfarin** for the prevention of stroke and SEE.
- Compared with warfarin, edoxaban was associated with a **consistent and dose-related reduction in bleeding** e.g. major, intracranial and life-threatening bleeding.
- **Once-daily edoxaban**, with patient-specific dose-reduction, could offer patients and healthcare providers a new, effective, safe and convenient therapeutic option, with the benefits of superior safety compared with high-quality standard therapy with warfarin.

AF = atrial fibrillation; SEE = systemic embolic event.

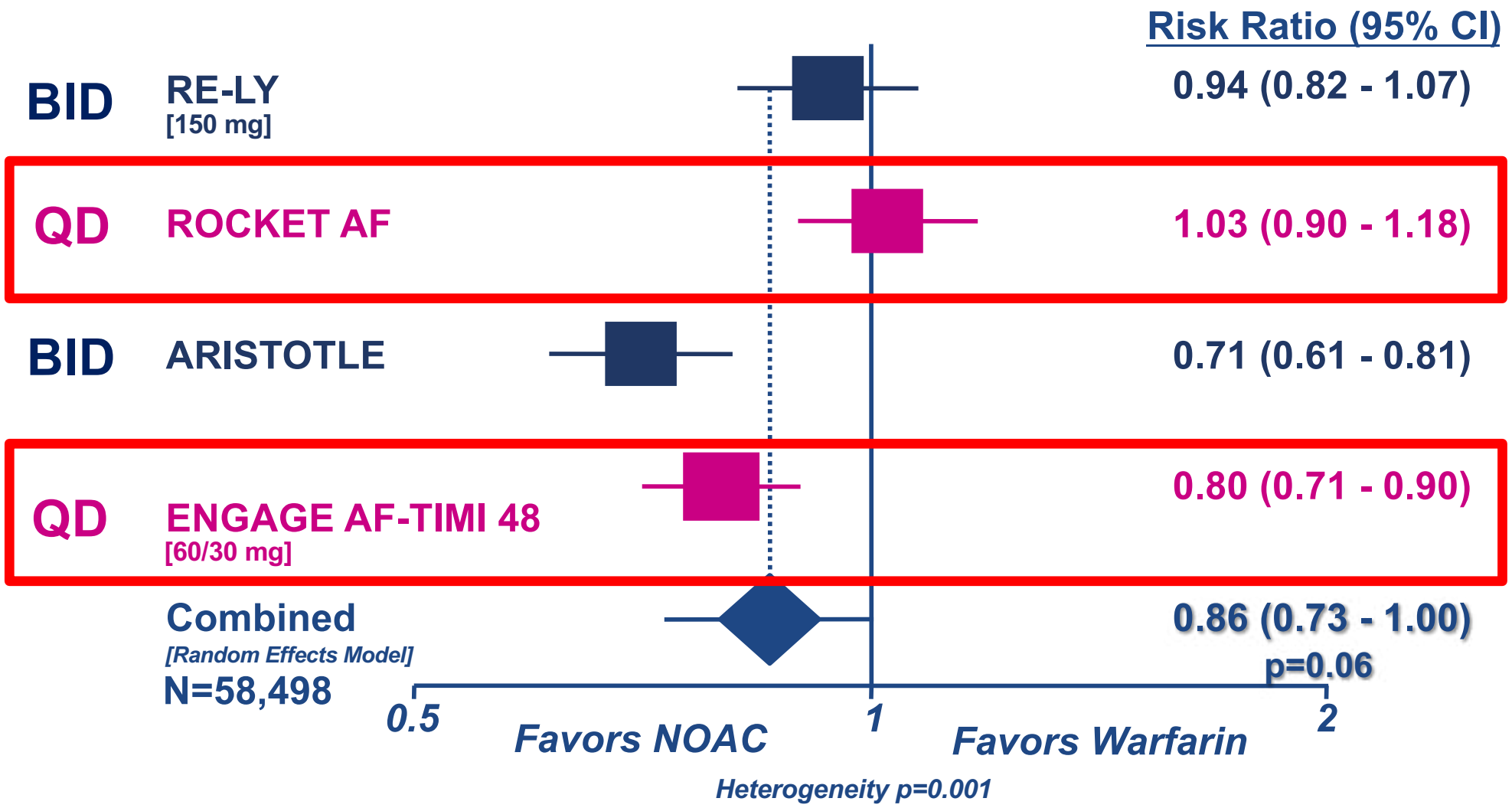
Giugliano et al. N Engl J Med 2013; DOI: 10.1056/NEJMoa1310907

Adherence to Medication According to Dosing Frequency



Osterberg L and Blaschke T. NEJM 2005;353:487-497

Major Bleeding for Once-daily NOACs in RCTs



Ruff CT, et al. Lancet 2014 Mar 15;383(9921):955-62

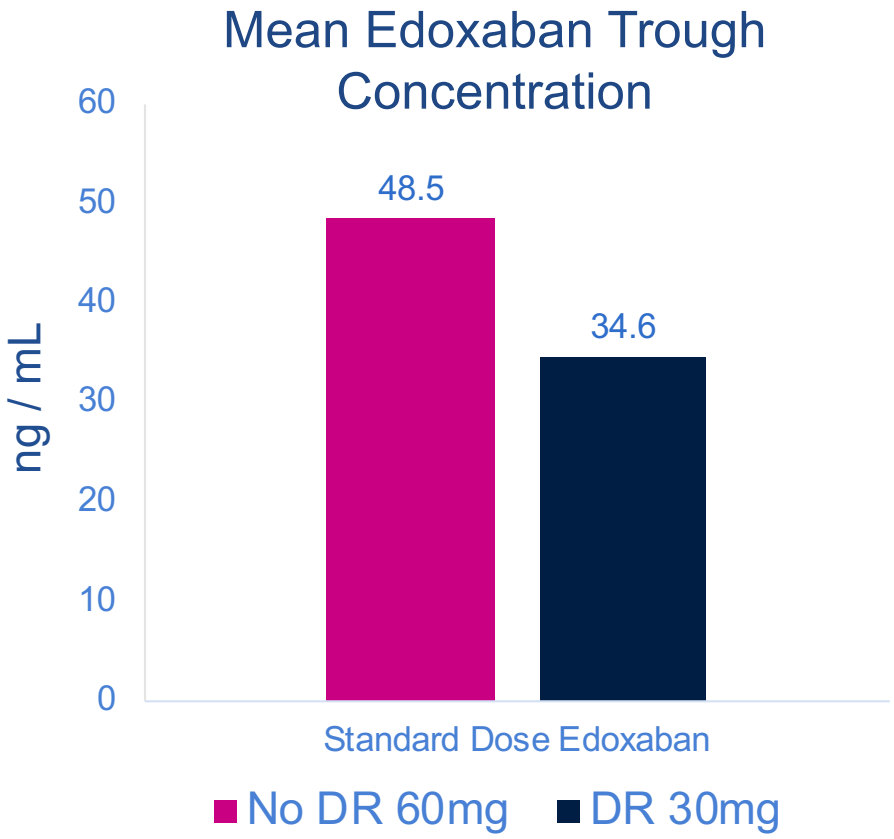
THE LANCET

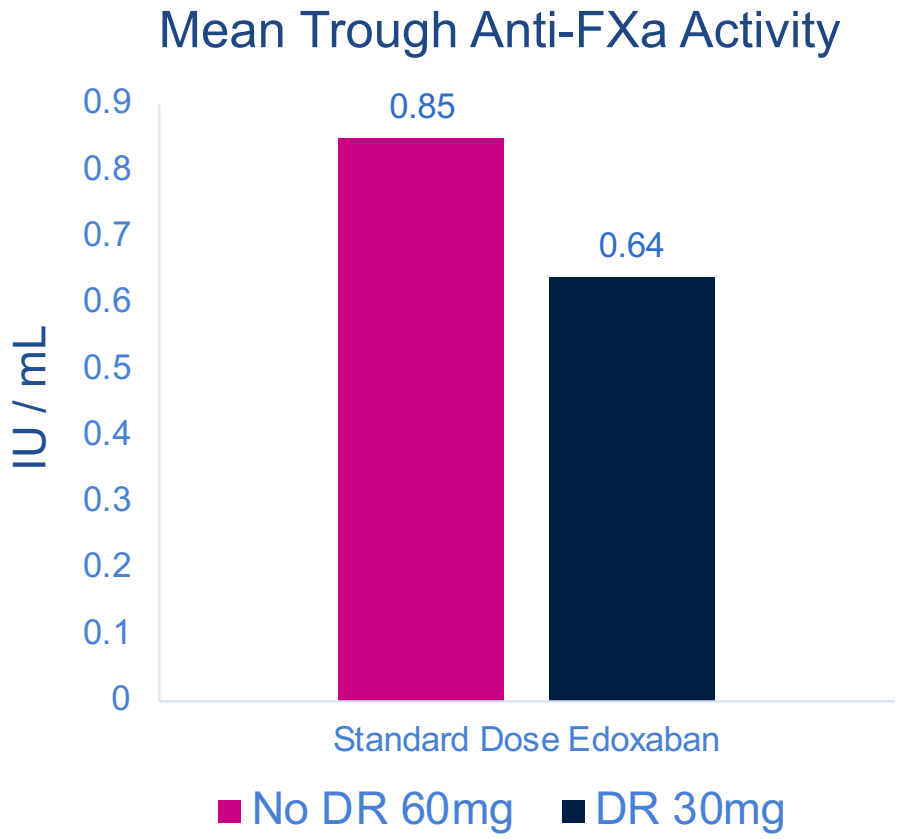
Association between edoxaban dose, concentration, anti-Factor Xa activity, and outcomes: an analysis of data from the randomised, double-blind ENGAGE AF-TIMI 48 trial

Christian T Ruff , Robert P Giugliano, Eugene Braunwald, David A Morrow, Sabina A Murphy, Julia F Kuder, Naveen Deenadayalu, Petr Jarolim, Joshua Betcher, Minggao Shi, Karen Brown, Indravadan Patel, Michele Mercuri, Elliott M Antman

Published:March 10, 2015
DOI:https://doi.org/10.1016/S0140-6736(14)61943-7

Edoxaban Concentration & Anti-FXa Activity

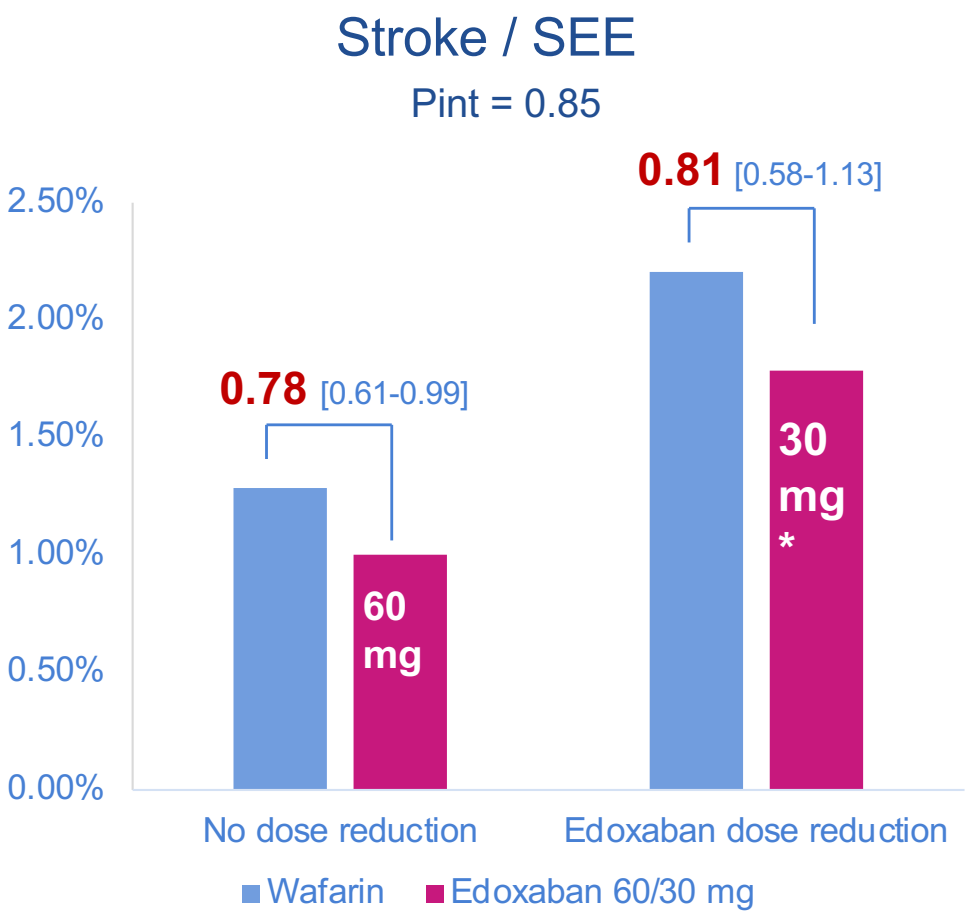


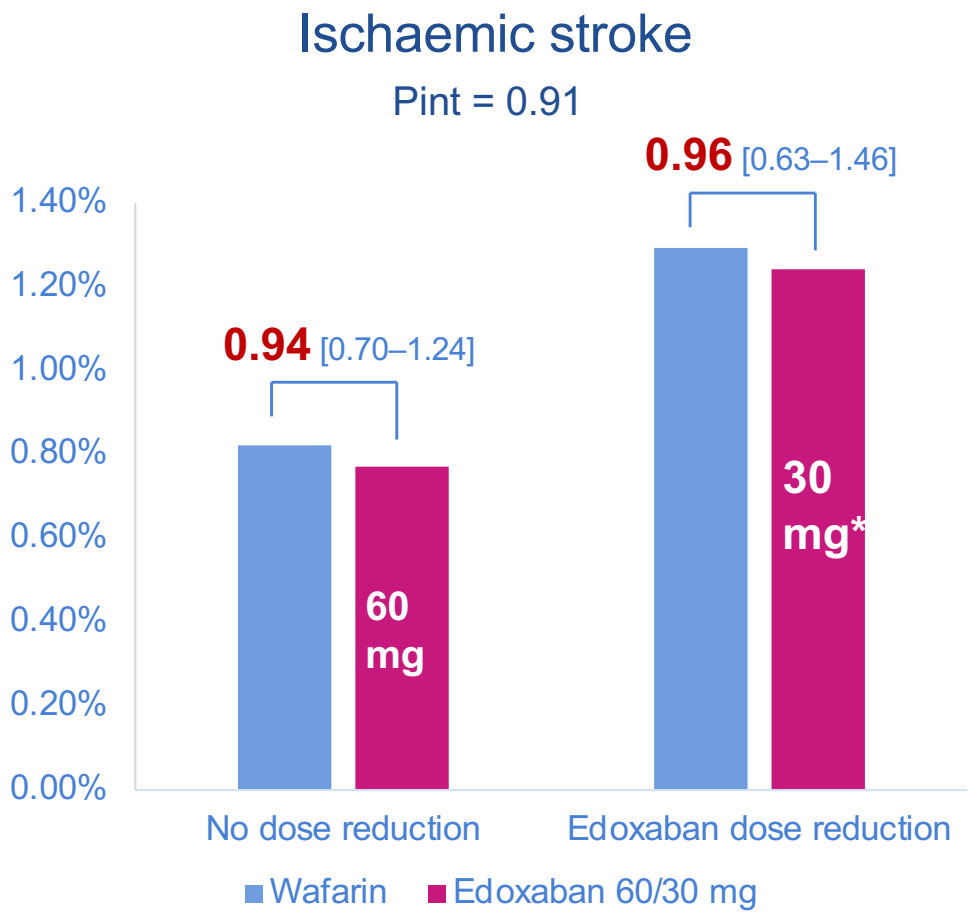


DR, dose reduction

Ruff CT, et al. Lancet. 2015 Jun 6;385(9984):2288-95.

Efficacy of edoxaban compared with warfarin stratified by dose reduction status

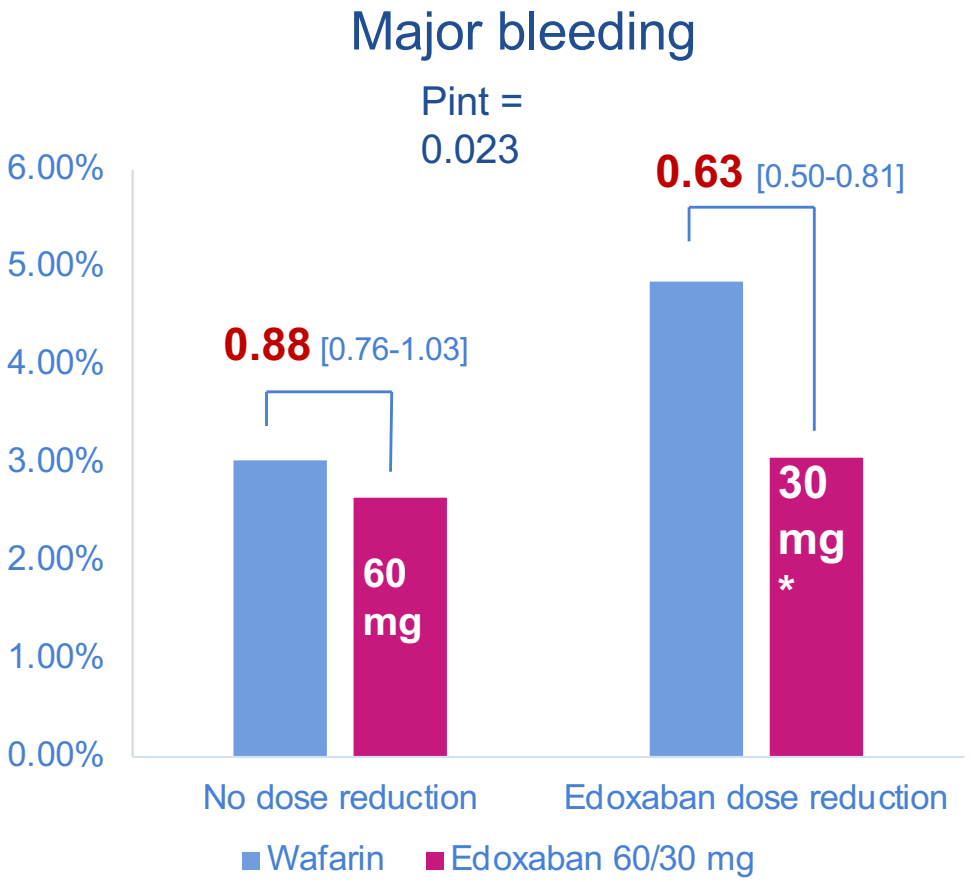


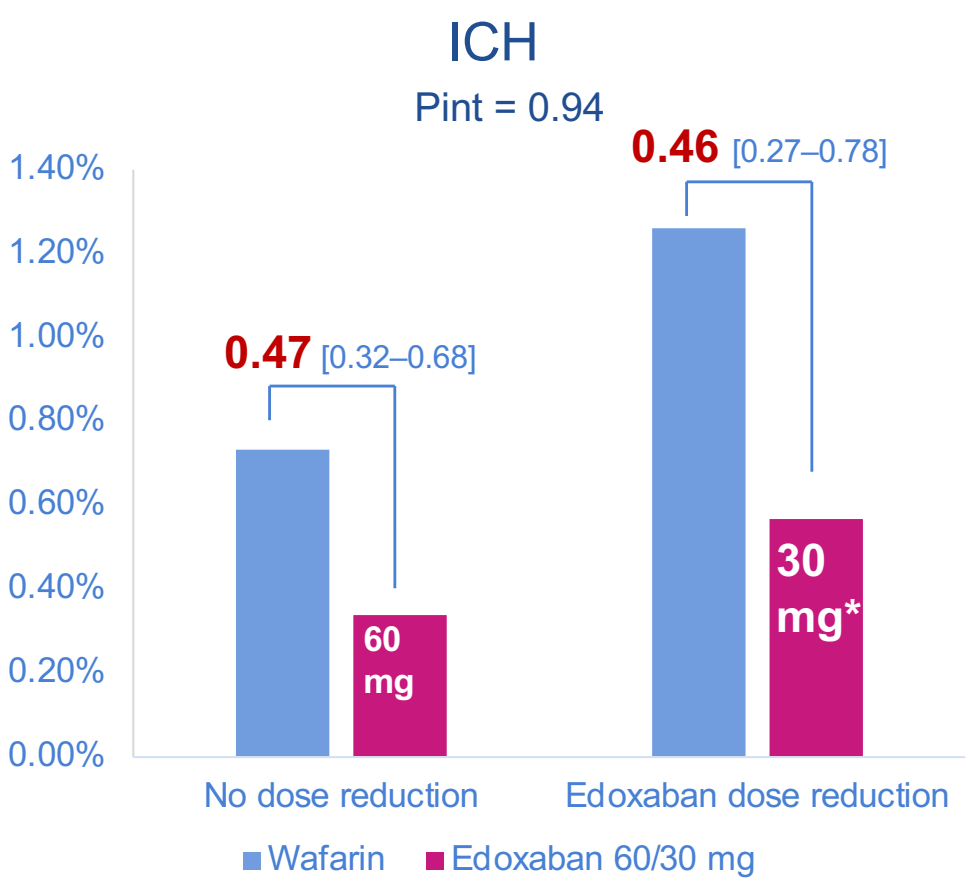


* If patient meet the dose reduction criteria in ENGAGE AF-TIMI 48

Christian T Ruff et al. Lancet 2015;385(9984):2288-2295

Safety of edoxaban compared with warfarin stratified by dose reduction status

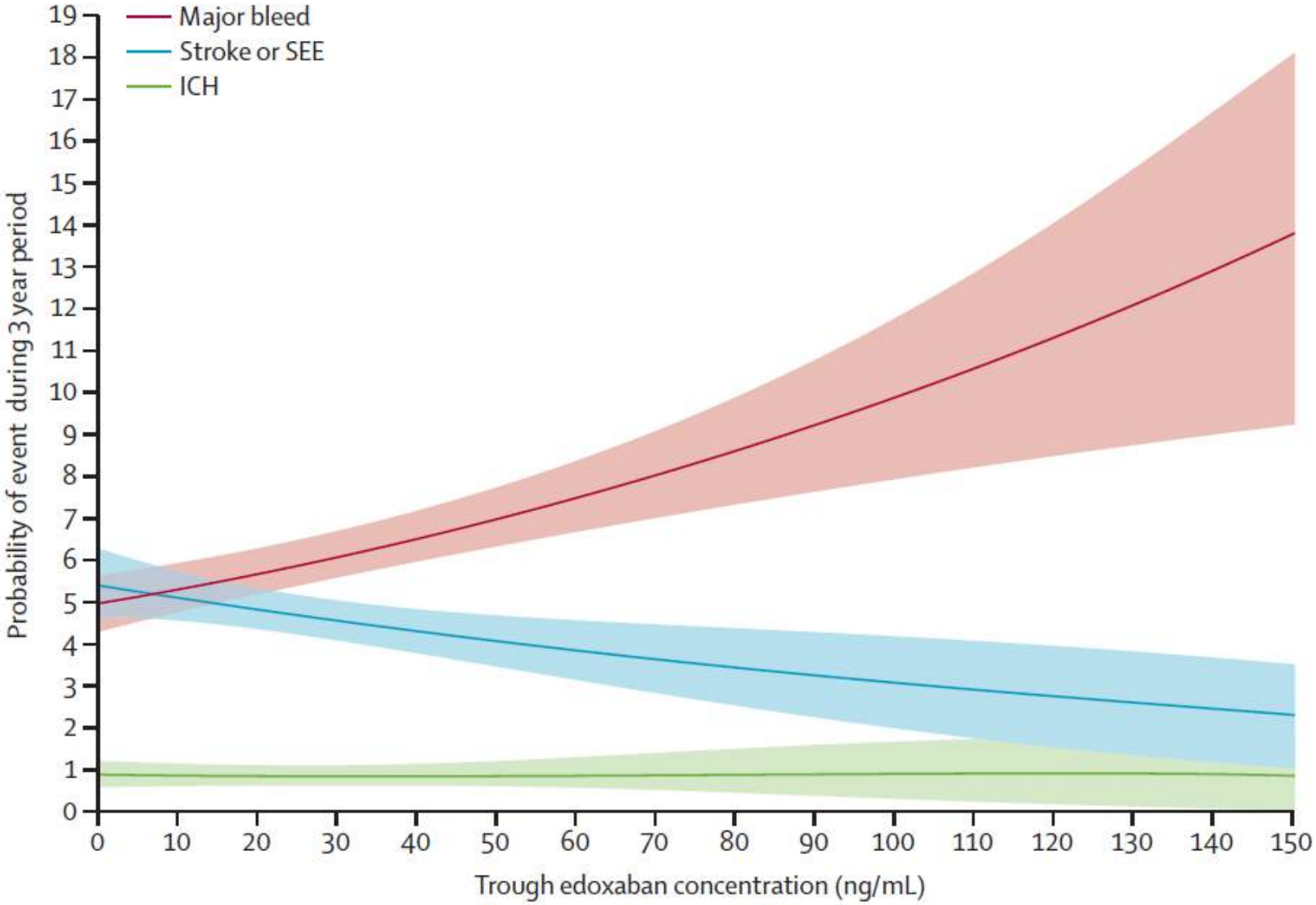




* If patient meet the dose reduction criteria in ENGAGE AF-TIMI 48

Christian T Ruff et al. Lancet 2015;385(9984):2288-2295 efficace

Probability of Edoxaban Concentration vs. Outcomes



ICH, intracranial hemorrhage; SEE, systemic embolic event.

Ruff CT, et al. Lancet. 2015 Jun 6;385(9984):2288-95

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

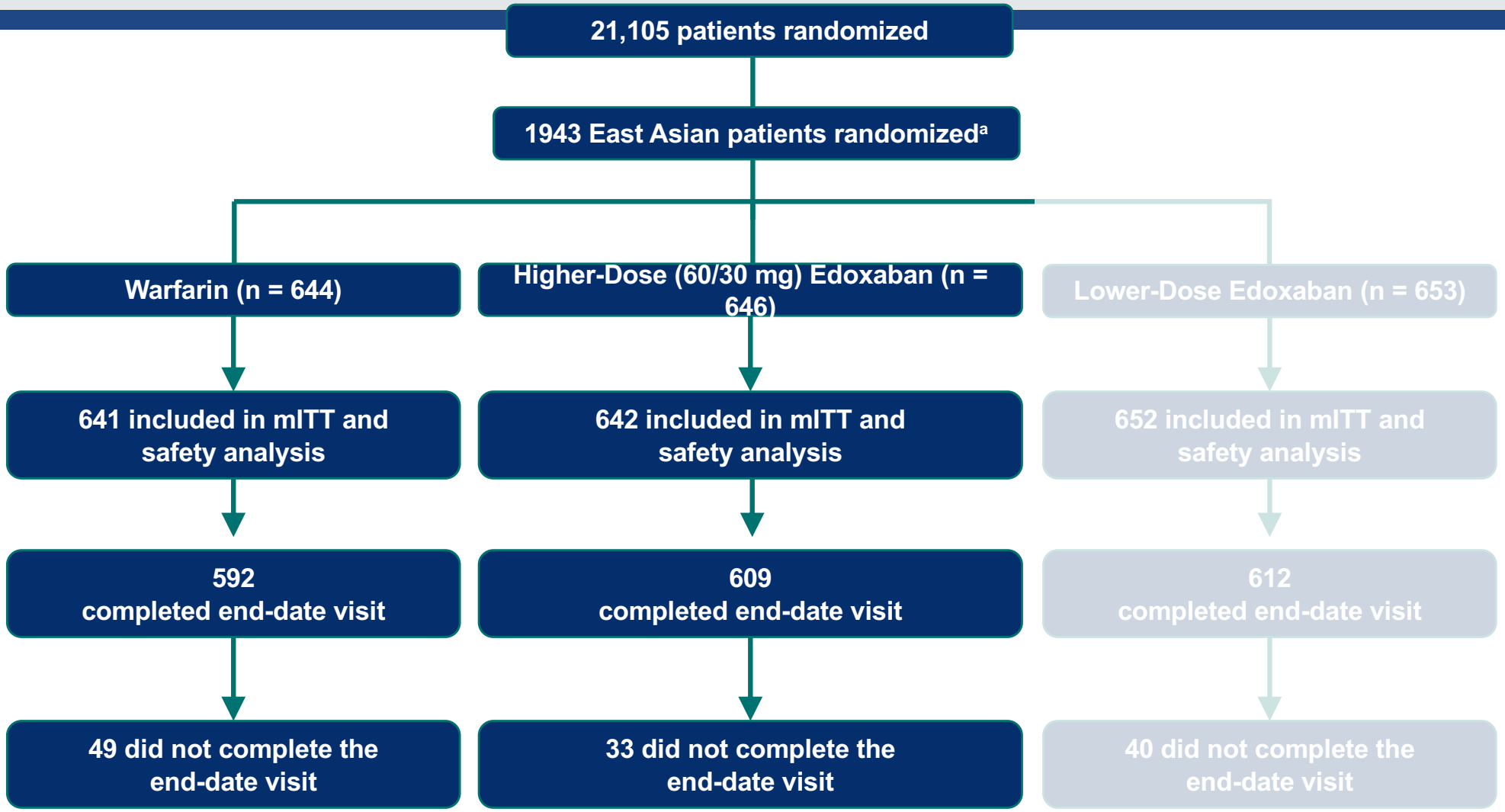
ORIGINAL ARTICLE
Arrhythmia/Electrophysiology

Edoxaban vs. Warfarin in East Asian Patients With Atrial Fibrillation

– An ENGAGE AF-TIMI 48 Subanalysis –

Takeshi Yamashita, MD, PhD; Yukihiro Koretsune, MD; Yuejin Yang, MD, PhD; Shih-Ann Chen, MD; Namsik Chung, MD, PhD; Yuichi J. Shimada, MD; Tetsuya Kimura; Koichi Miyazaki; Kenji Abe; Michele Mercuri, MD, PhD; Christian T. Ruff, MD; Robert P. Giugliano, MD

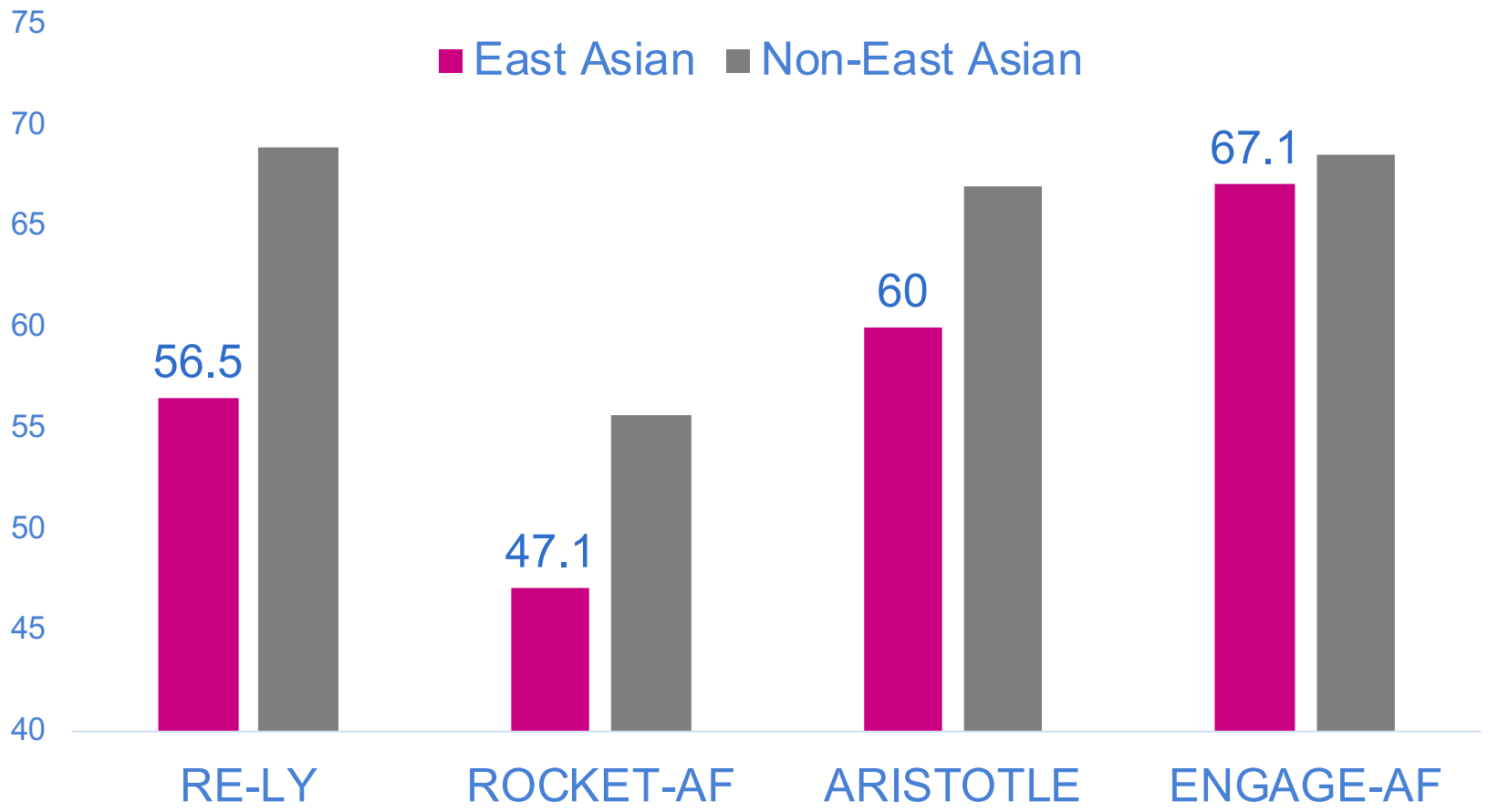
Patient Disposition



[a] Of the 1943 East Asian patients randomized, 1010 were from Japan, 469 were from China, 234 were from Taiwan, and 230 were from South Korea.
mITT = modified intent-to-treat.

Yamashita T, et al. *Circ J*. 2016; 80(4):860-9.

median TTR for Warfarin-treated Patients in East-Asian



Stroke 44 (2013) 1891–1896.
Stroke 45 (2014) 1739–1747.
Am Heart J. 2014 Sep;168(3):303-
Circ J. 2016;80(4):860-9.

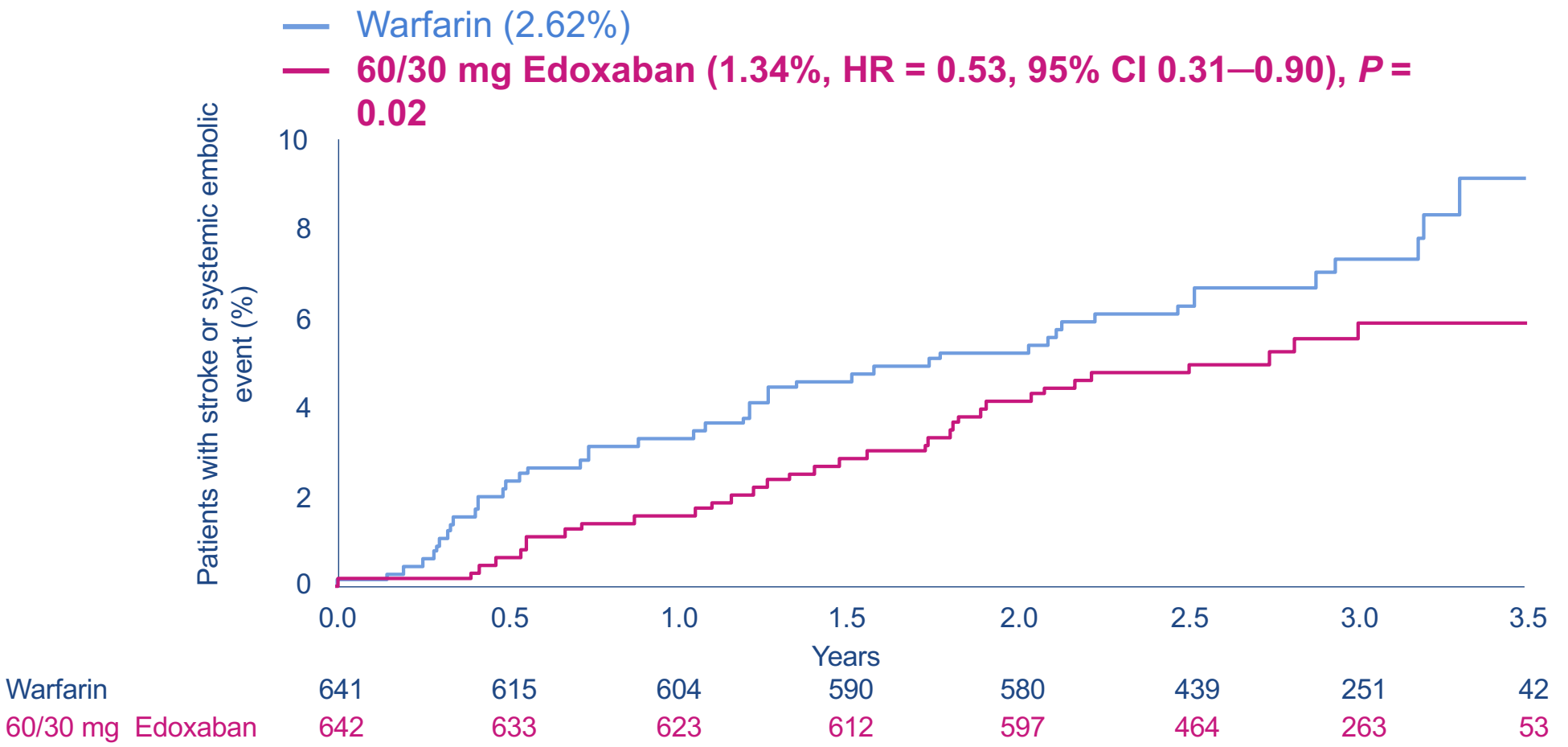
Baseline Demographics and Characteristics

	East Asian (n = 1,943)	Non-East Asian (n = 19,162)	*P*-value
Age (y), mean ± SD	70.1 ± 8.7	70.7 ± 9.5	0.0085
Females, n (%)	545 (28.0)	7495 (39.1)	<0.0001
Weight (kg), mean ± SD	67.0 ± 12.6	85.6 ± 20.0	<0.0001
Paroxsymal atrial fibrillation, n (%)	373 (19.2)	4993 (26.1)	<0.0001
$CHADS_2$ score, mean ± SD	2.9 ± 1.0	2.8 ± 1.0	0.17
≤3, n (%)	1487 (76.5)	14850 (77.5)	0.33
4–6, n (%)	456 (23.5)	4312 (22.5)	
Dose reduction at randomization, n (%)	912 (**46.9**)	4444 (23.2)	<0.0001
CrCl ≤50 mL/min, n (%)	583 (30.0)	3491 (18.2)	<0.0001
Weight ≤60 kg, n (%)	594 (30.6)	1489 (7.8)	<0.0001
Use of verapamil or quinidine, n (%)	128 (6.6)	633 (3.3)	<0.0001
Previous use of VKA for ≥60 days, n (%)	1153 (59.3)	11288 (58.9)	0.71
Medication at time of randomization, n (%)			
Aspirin	543 (27.9)	5637 (29.4)	0.17
Thienopyridine	60 (3.1)	427 (2.2)	0.016
Amiodarone	85 (4.4)	2407 (12.6)	<0.0001
Digoxin or digitalis preparation	576 (29.6)	5751 (30.0)	0.74

$CHADS_2$ = Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes, prior Stroke or transient ischemic attack; CrCl = creatinine clearance; SD = standard deviation; VKA = vitamin K antagonist.

Yamashita T, et al. *Circ J*. 2016; 80(4):860-9.

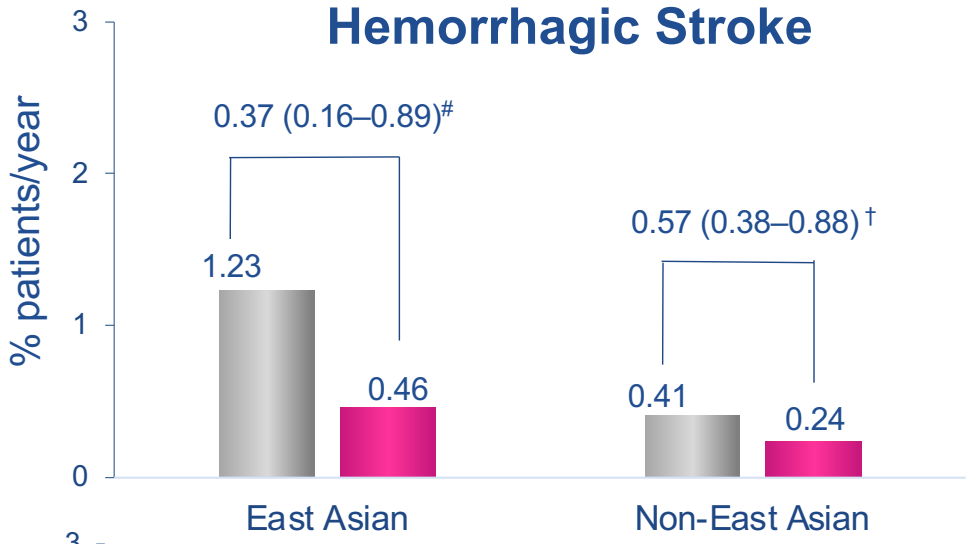
Primary Efficacy Endpoint (East Asian, mITT Population, On-treatment)

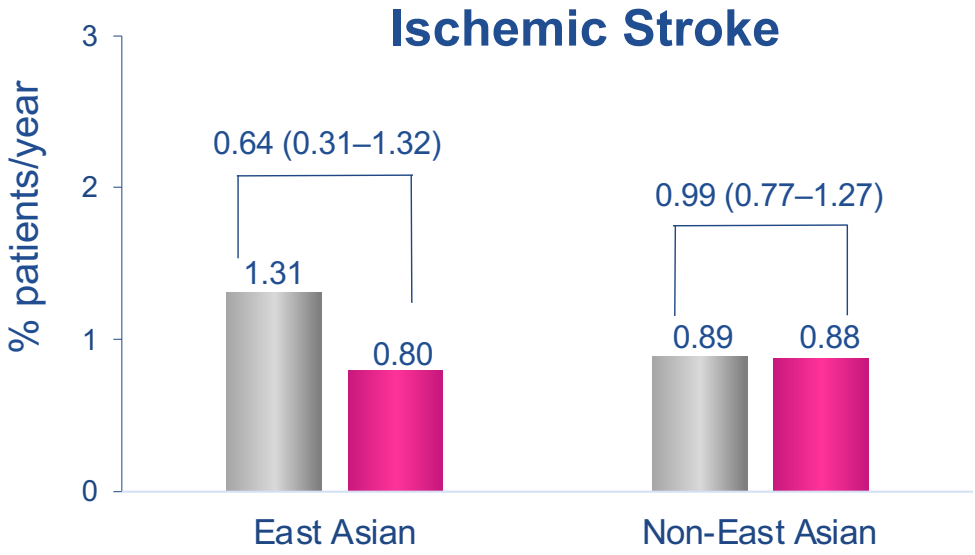


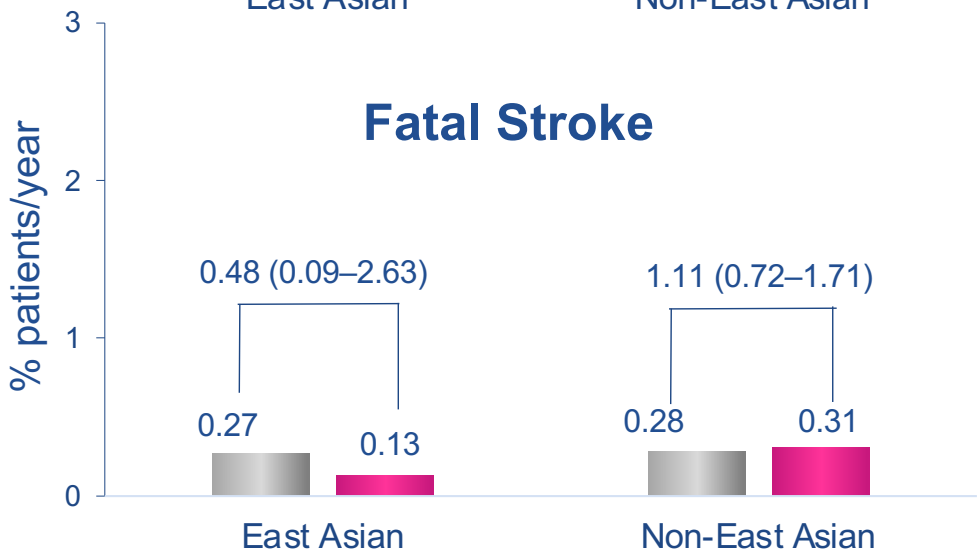
CI = confidence interval; HR = hazard ratio; mITT = modified intent-to-treat.

Yamashita T, et al. *Circ J*. 2016; 80(4):860-9.

Rates of Stroke







- Warfarin
  East Asian, n = 641; Non-East Asian, n = 6,371
- **Higher-Dose Edoxaban (60/30 mg)**
  East Asian, n = 642; Non-East Asian, n = 6,370

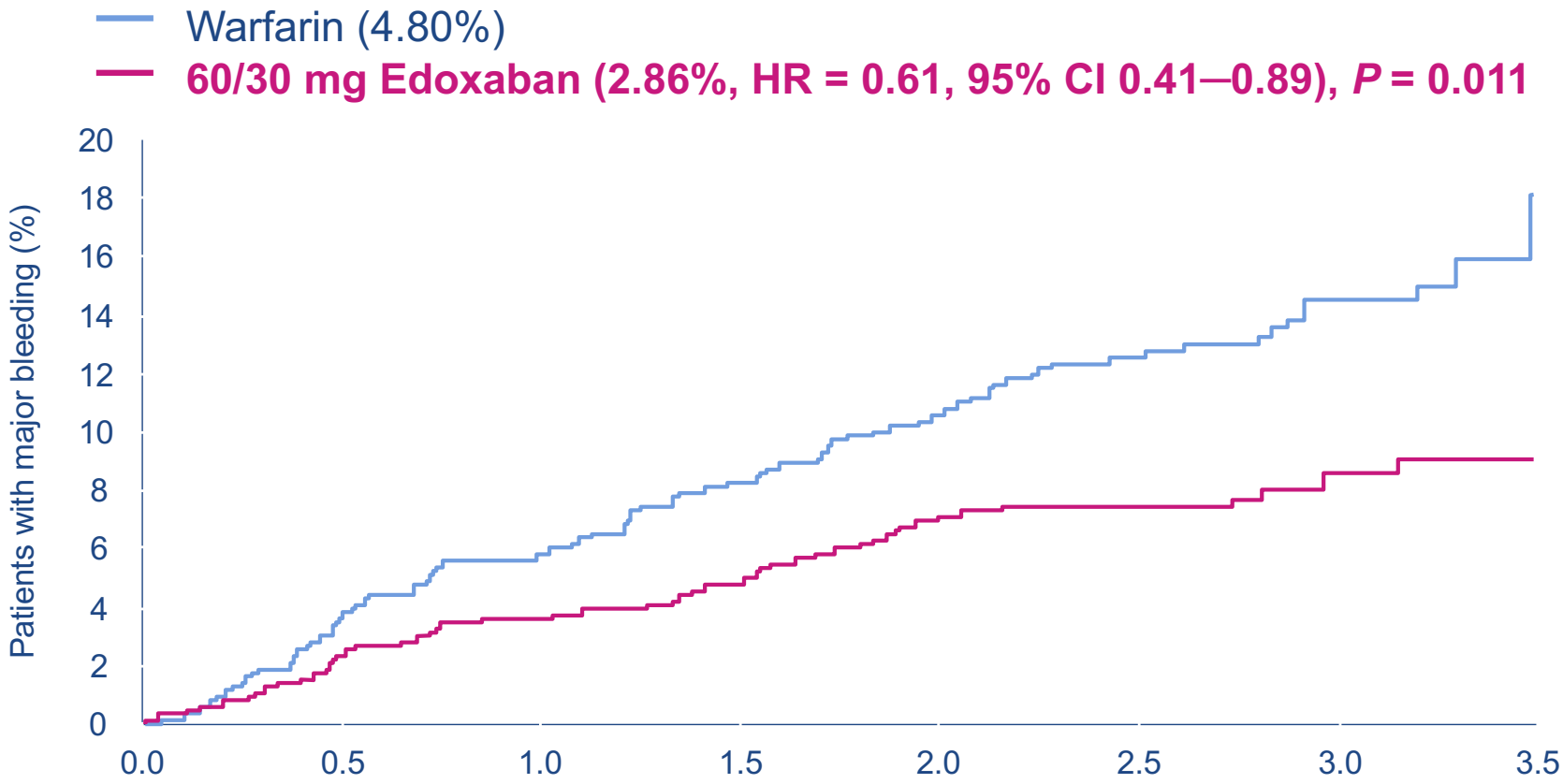
Text indicates hazard ratio for edoxaban dose vs warfarin and 95% confidence intervals. mITT = modified intent-to-treat.
†$P \leq 0.01$, #$P = 0.03$

Yamashita T, et al. *Circ J*. 2016; 80(4):860-9.

Efficacy Endpoints

	East Asian			Non-East Asian		
	Warfarin	Edoxaban 60/30 mg		Warfarin	Edoxaban 60/30 mg	
	n (% patients/ year)	n (% patients/ year)	HR† (95% CI), P-value	n (% patients/ year)	n (% patients/ year)	HR† (95% CI), P-value
Primary Endpoint						
mITT, on treatment period‡	38 (2.62)	20 (1.34)	0.53 (0.31–0.90), **0.02**	194 (1.38)	162 (1.16)	0.84 (0.68–1.04), 0.10
Stroke (mITT)	36 (2.48)	18 (1.20)	0.50 (0.28–0.88), **0.02**	183 (1.30)	156 (1.12)	0.86 (0.69–1.06), 0.16
SEE (mITT)	2 (0.14)	2 (0.13)	1.09 (0.16–7.51), 0.93	11 (0.08)	6 (0.04)	0.55 (0.20–1.49), 0.24
Secondary Endpoint						
Stroke, SEE, or death from CV causes	70 (4.02)	44 (2.44)	0.61 (0.42–0.89), **0.01**	761 (4.47)	684 (4.00)	0.89 (0.80–0.99), 0.03
MACE	76 (4.38)	48 (2.67)	0.61 (0.43–0.88), **0.01**	850 (5.04)	779 (4.59)	0.91 (0.82–1.00), 0.05
Stroke, SEE, or death	88 (5.05)	58 (3.22)	0.64 (0.46–0.90), **0.01**	958 (5.63)	891 (5.20)	0.92 (0.84–1.01), 0.08
Other Endpoint						
Death, any cause	50 (2.77)	32 (1.73)	0.63 (0.40–0.98), **0.04**	789 (4.51)	741 (4.23)	0.93 (0.85–1.03), 0.19
Death, CV causes	32 (1.77)	15 (0.81)	0.46 (0.25–0.84), **0.01**	579 (3.31)	515 (2.94)	0.89 (0.79–1.00), 0.04

Primary Safety Endpoint (East Asian)

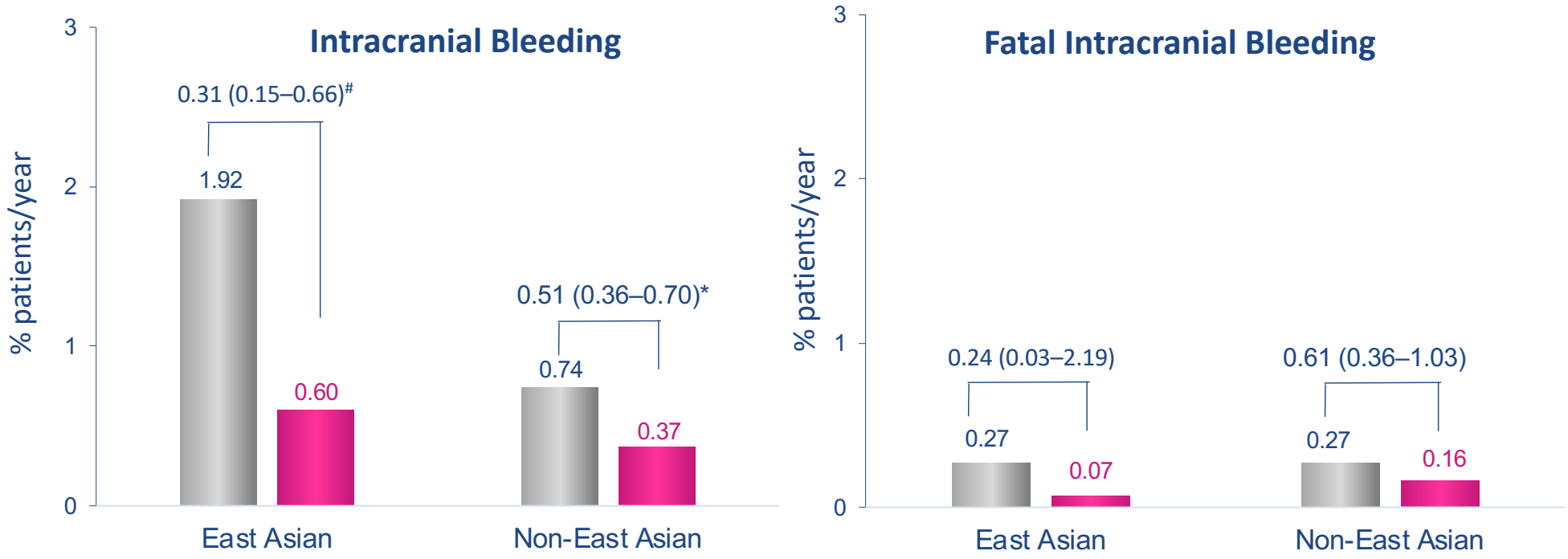


Number at Risk								
Warfarin	641	607	587	567	548	406	234	35
Higher-Dose Edoxaban	642	621	610	599	576	448	250	50

CI = confidence interval; HR = hazard ratio.

Yamashita T, et al. *Circ J*. 2016; 80(4):860-9.

Annualized Rates of Intracranial and Fatal Intracranial Bleeding (Safety Population)



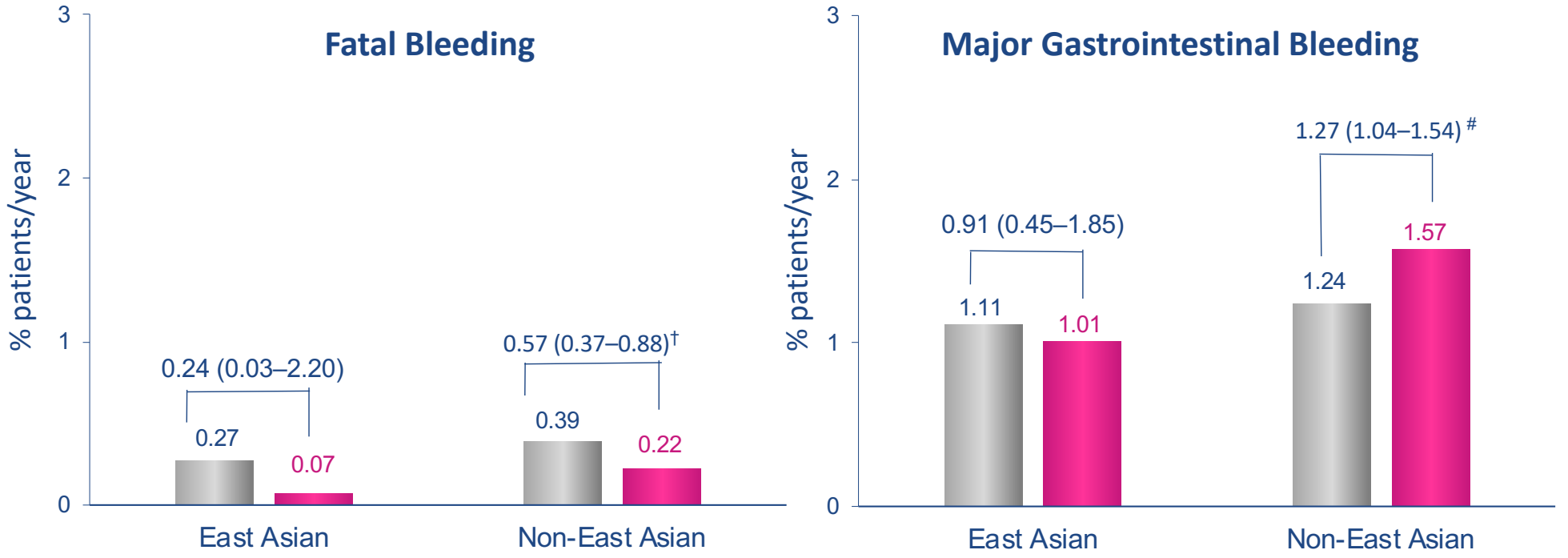
- Warfarin: East Asian, n = 641; Non-East Asian, n = 6371
- 60/30 mg Edoxaban: East Asian, n = 642; Non-East Asian, n = 6370

Text indicates hazard ratio for edoxaban dose vs warfarin and 95% CI. Data are from the on-treatment period.
*$P < 0.001$, #$P = 0.002$.
CI = confidence interval.

Yamashita T, et al. *Circ J*. 2016; 80(4):860-9.

Annualized Rates of Fatal and Gastrointestinal Bleeding (Safety Population)

Fewer GI Bleeding in East Asian



- Warfarin: East Asian, n = 641; Non-East Asian, n = 6371
- 60/30 mg Edoxaban: East Asian, n = 642; Non-East Asian, n = 6370

Text indicates hazard ratio for edoxaban dose vs warfarin and 95% CI. Data are from the on-treatment period.
†*P* = 0.012, # P=0.021
CI = confidence interval.

Yamashita T, et al. *Circ J*. 2016; 80(4):860-9.

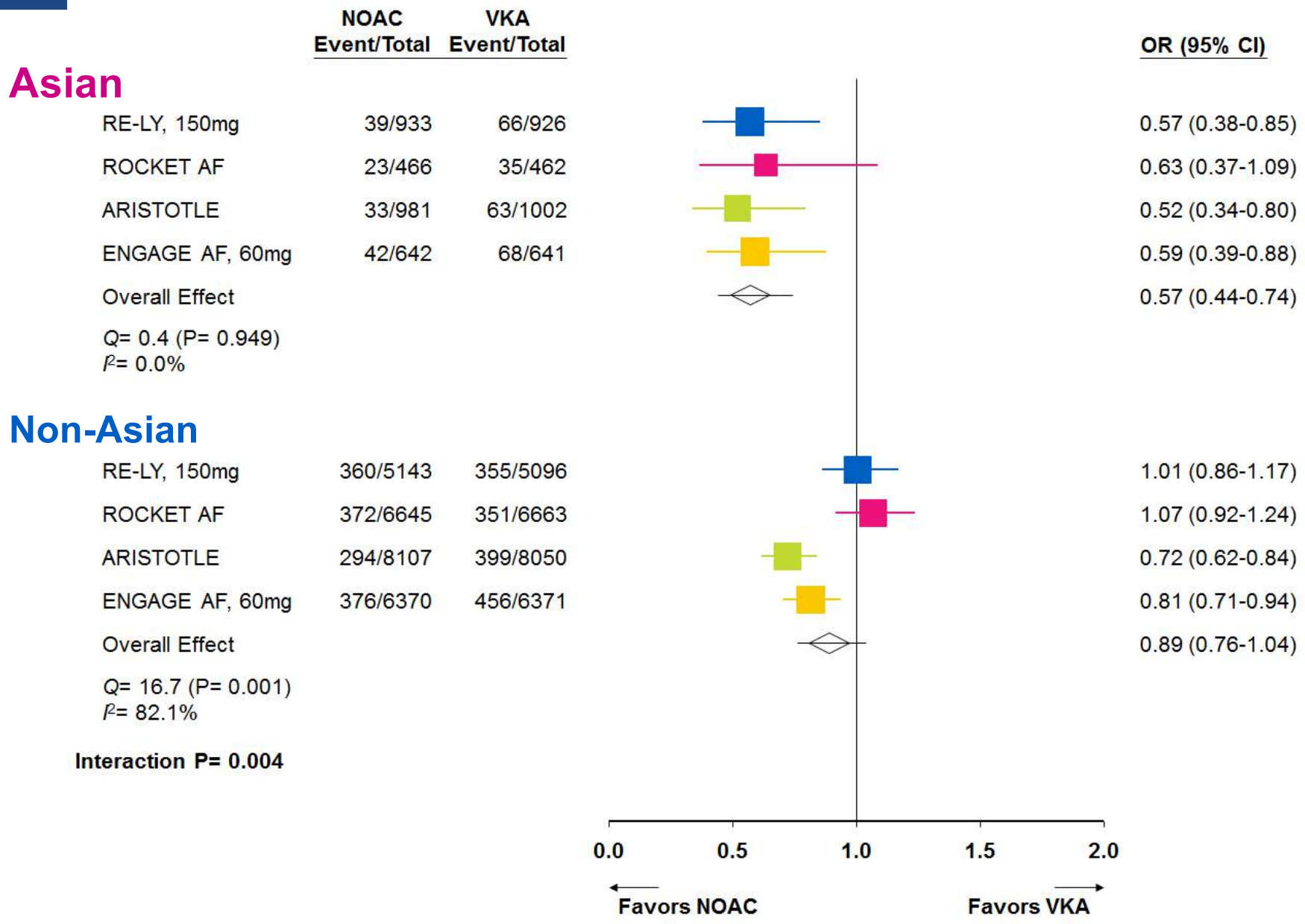
ENGAGE-AF study East Asia subgroup Conclusions

- In East Asian patients with AF, both doses of once-daily edoxaban:
  - Reduced stroke and SEE similar to warfarin, with significantly lower rates observed with higher-dose edoxaban for the on-treatment analysis.
  - Significantly reduced major bleeding and intracranial hemorrhage compared with warfarin.
  - Achieved results consistent with those outside East Asia

AF = atrial fibrillation; SEE = systemic embolic event.

Yamashita T, et al. *Circ J*. 2016; 80(4):860-9.

The only one once-daily NOAC with significantly decreased major bleeding - Asian analysis from RCT



6:2555-2561.

TSOC AF Guideline Recommendation

Table 12 Efficacy and safety endpoints of different NOACs in Asians.[85–88,148]

	Stroke/ SEE	Ischemic stroke	Hemorrhagic stroke	Myocardial infarction	All-cause death	CV death	Major bleeding	Intracranial hemorrhage	GI bleeding	Bleeding of any cause
Dabigatran [a] 150 mg	V	V	V			NR	V	V		V
Dabigatran [a] 110 mg			V			NR	V	V		V
Rivaroxaban [b]								V	NR	
Apixaban [c]			V			NR	V	V	NR	V
Edoxaban [d] 60 mg			V		V	V	V	V		V
Edoxaban [d] 30 mg			V				V	V		V

GI = gastrointestinal; NOACs = non-vitamin K antagonist oral anticoagulants; NR = not reported; SEE = systemic embolization events; V = *p* value less than 0.05 when compared with warfarin.

[a] China, Japan, South Korea, Taiwan, Hong Kong, Philippines, Singapore, Malaysia, Thailand, India.

[b] China, South Korea, Taiwan, Hong Kong.

[c] China, Japan, South Korea, Taiwan, Hong Kong, Philippines, Singapore, Malaysia.

[d] China, Japan, South Korea, Taiwan. Modified from Lip et al[149] with permission.

Journal of the Formosan Medical Association (2016) 115, 893e952

NHIA Reimbursement Criteria for SPAF/VTE

限用於非瓣膜性心房纖維顫動病患 且須符合下列條件之一

(1)曾發生中風或全身性栓塞。
(2)左心室射出分率小於40%。
(3)有症狀之心臟衰竭：收案前依紐約心臟協會衰竭功能分級為第二級或以上。
(4)年齡75歲(含)以上。
(5)年齡介於65歲至74歲且合併有糖尿病、高血壓或冠狀動脈疾病。
(6)每日1次，每次限1顆。

排除標準

(1)病人曾有嚴重心臟瓣膜疾病
(2)14 天內發生中風。
(3)收案前6個月內發生嚴重中風
(4)有增加出血風險的情況。
(5)肌酸酐清除率小於15mL/min，或大於95mL/min。
(6)活動性肝病和懷孕。

治療深部靜脈血栓與肺栓塞

(1)須經影像學或血管超音波檢查診斷。
(2)接受至少5日非經腸道抗凝血劑注射治療後，開始每日1次，每次限1顆，每6個月評估一次。

Lixiana 全民健康保險藥品給付規定

LIXIANA 30mg –
If with One or More Criteria of BCD

Body Weight<60kg

CrCL <50 ml/min

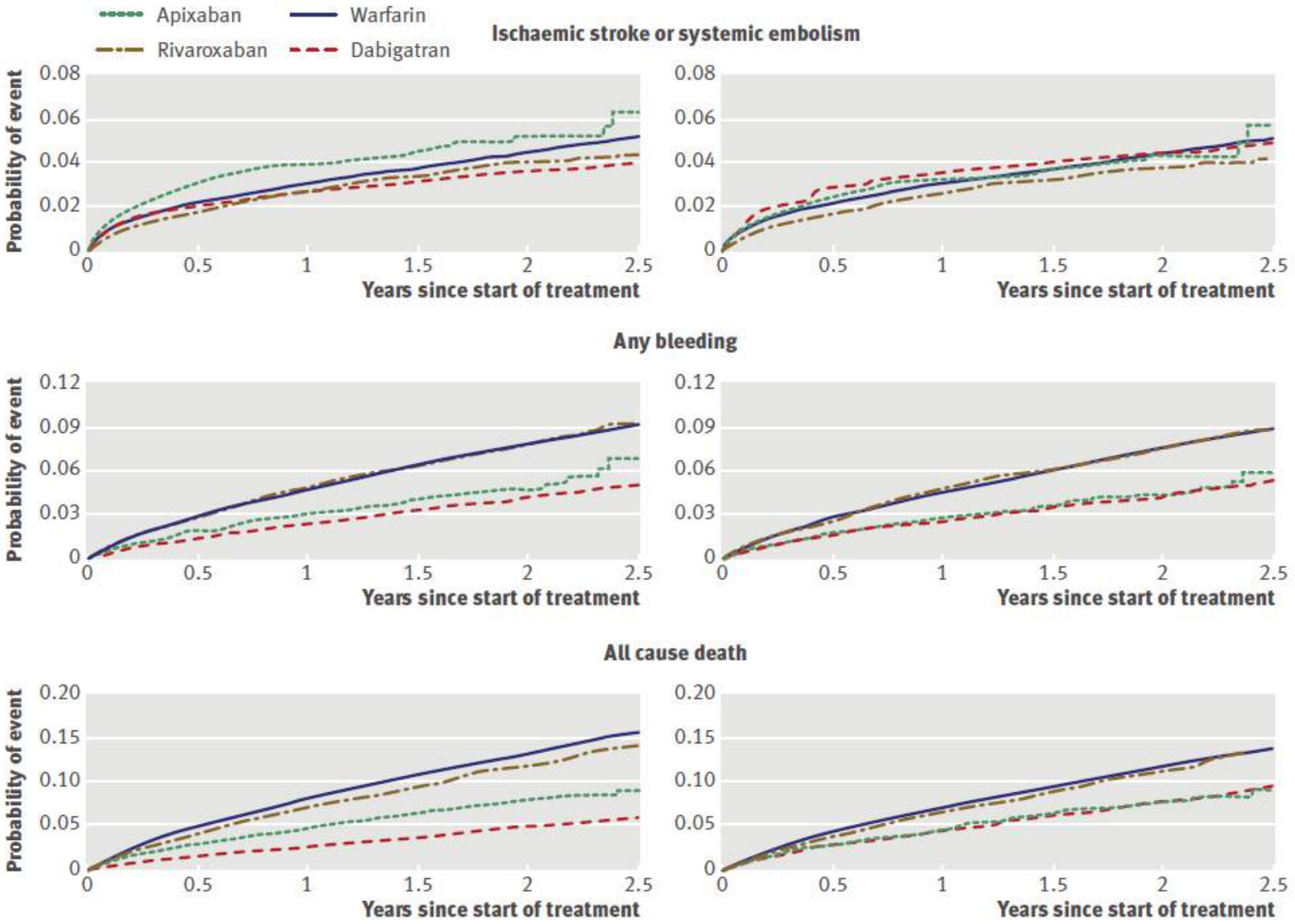
Drug:
Cyclosporine, Dronedarone
Erythromycin, Ketoconazole

Lixiana Package Insert

How to apply clinical trial data to real world practice?

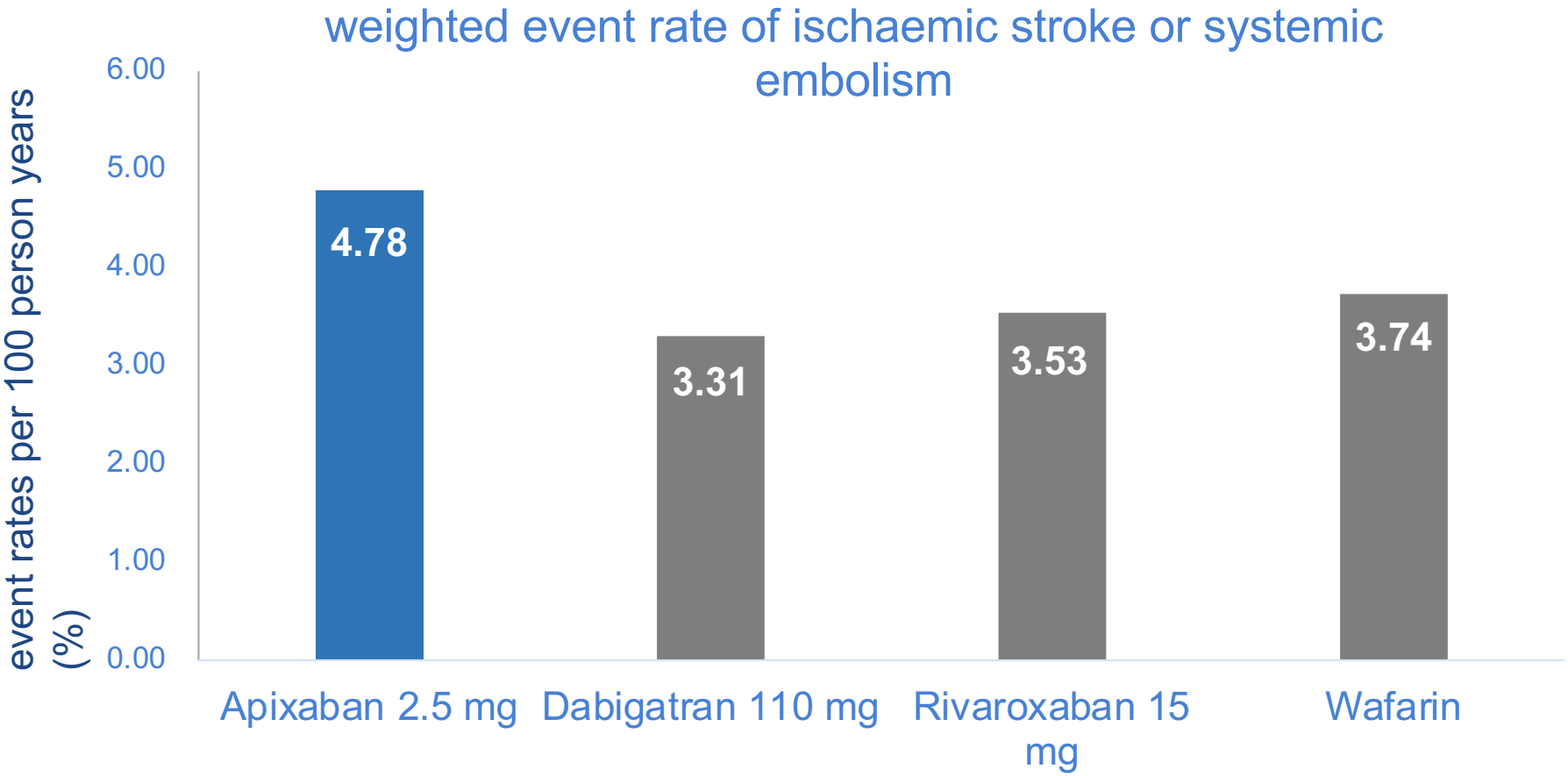
Real World Data

Any bleeding or major bleeding were significantly lower for apixaban and dabigatran than for rivaroxaban or warfarin



BMJ 2016;353:i3189

Apixaban 2.5 mg twice a day was associated with a trend towards higher rates of ischaemic stroke/systemic embolism compared with warfarin



BMJ 2017;356:j510

Edoxaban in Asian Patients With Atrial Fibrillation

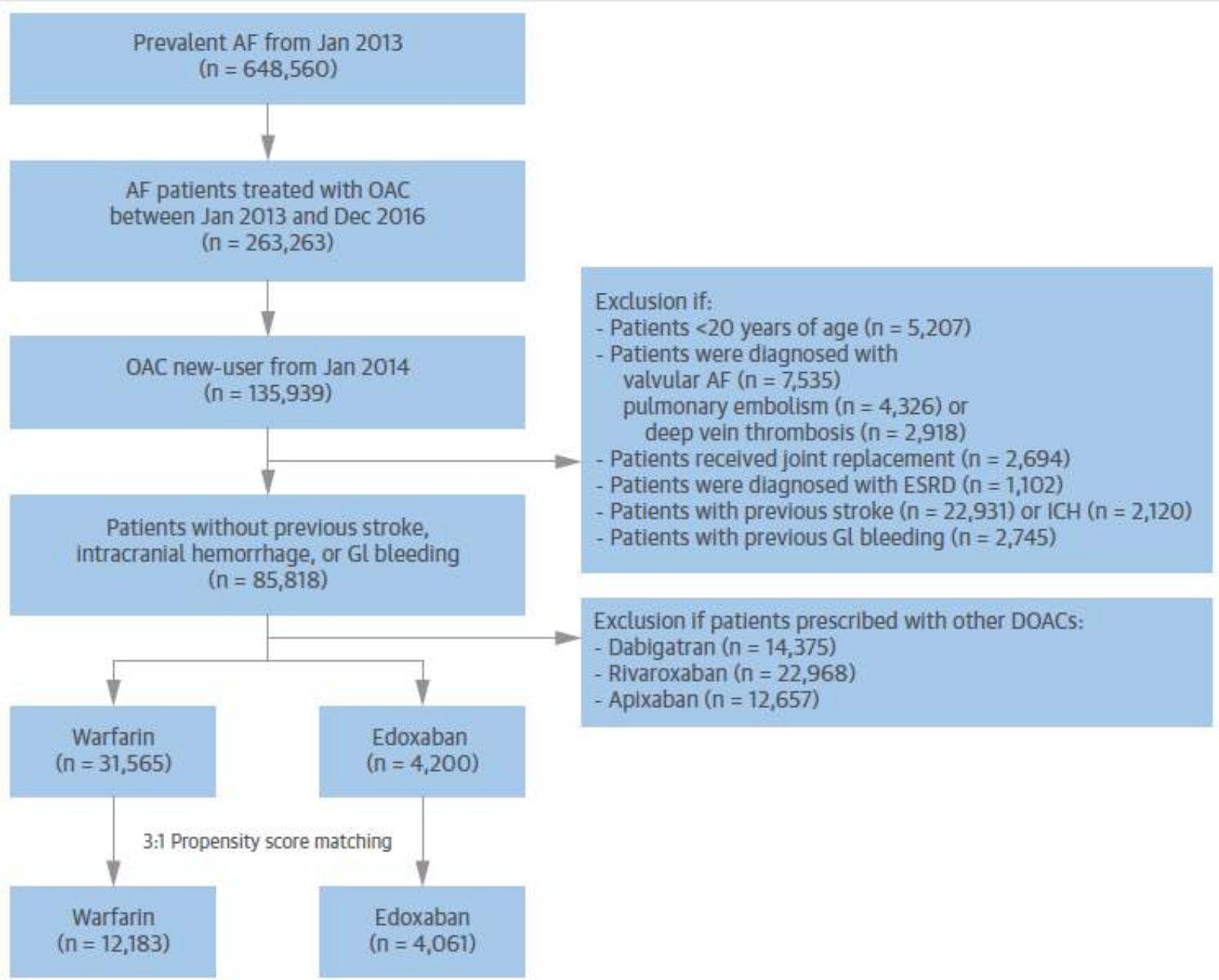
Effectiveness and Safety

So-Ryoung Lee, MD,[a] Eue-Keun Choi, MD, PhD,[b] Kyung-Do Han, PhD,[c] Jin-Hyung Jung, BSc,[c] Seil Oh, MD, PhD,[b] Gregory Y.H. Lip, MD[d,e,f]

First real-world evidence for Lixiana

Lee et al. JACC August 21, 2018: 838-53

Study Population Enrollment Flow



Lee et al. JACC August 21, 2018: 838-53

Baseline Characteristics Before and After Propensity Score Matching

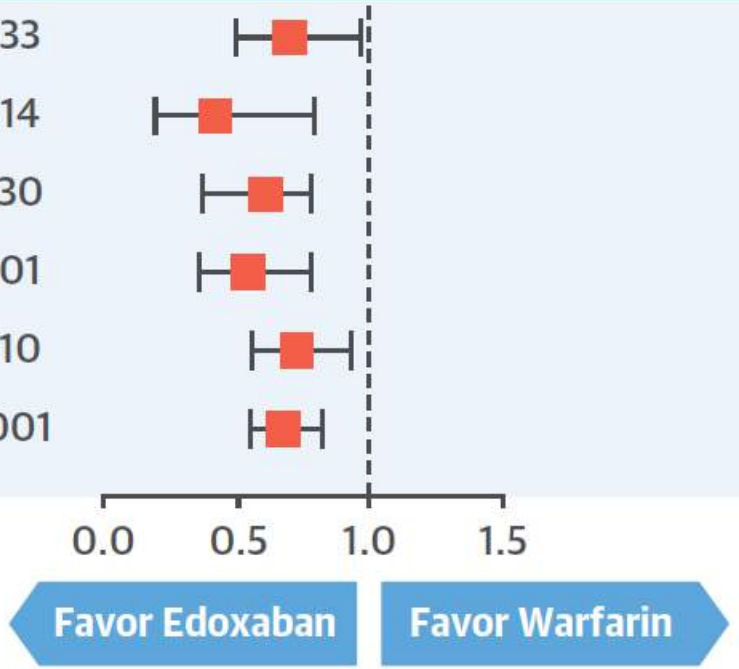
	Before Propensity Score Matching			After Propensity Score Matching		
	Warfarin (n = 31,565)	Edoxaban (n = 4,200)	ASD	Warfarin (n = 12,183)	Edoxaban (n = 4,061)	ASD
Age, yrs						
Mean ± SD	66.3 ± 12.9	70.8 ± 10.0	0.393	70.7 ± 10.5	70.3 ± 9.8	0.033
Median (IQR)	68 (58-76)	72 (65-78)		72 (64-78)	72 (65-77)	
<65	13,304 (42.2)	992 (23.6)		3,156 (25.9)	992 (24.4)	
65-74	8,957 (28.4)	1,606 (38.2)		4,386 (36.0)	1,602 (39.5)	
≥75	9,304 (29.5)	1,602 (38.1)		4,641 (38.1)	1,467 (36.1)	
Men	1,9385 (61.4)	2,271 (54.1)	0.149	6,889 (56.6)	2,247 (55.3)	0.024
CHA_2DS_2-VASc score						
Mean ± SD	3.27 ± 1.97	3.24 ± 1.62	0.014	3.25 ± 1.72	3.22 ± 1.63	0.017
Median (IQR)	3 (2-5)	3 (2-4)		3 (2-4)	3 (2-4)	
0-1	6,479 (20.5)	561 (13.4)		1,929 (15.8)	559 (13.8)	
2-3	11,533 (36.5)	1,885 (44.9)		5,057 (41.5)	1,828 (45.0)	
≥4	13,553 (42.9)	1,754 (41.8)		5,197 (42.7)	1,674 (41.2)	
$CHADS_2$ score						
Mean ± SD	1.82 ± 1.33	1.63 ± 1.16	0.154	1.72 ± 1.22	1.62 ± 1.17	0.079
Median (IQR)	2 (1-3)	2 (1-2)		2 (1-2)	2 (1-2)	
Hypertension	21,569 (68.3)	2,824 (67.2)	0.023	8,517 (69.9)	2,735 (67.4)	0.055
Diabetes mellitus	6,590 (20.9)	845 (20.1)	0.019	2,443 (20.1)	831 (20.5)	0.010
Dyslipidemia	11,783 (37.3)	1,660 (39.5)	0.045	4,793 (39.3)	1,602 (39.5)	0.002
Heart failure	12,246 (38.8)	948 (22.6)	0.357	2,970 (24.4)	948 (23.3)	0.024
Previous MI	1,421 (4.5)	97 (2.3)	0.121	239 (2.0)	97 (2.4)	0.029
PAD	4,923 (15.6)	710 (16.9)	0.035	1,815 (14.9)	677 (16.7)	0.049
COPD	6,590 (20.9)	748 (17.8)	0.078	2,080 (17.1)	736 (18.1)	0.028

Values are n (%), unless otherwise indicated.

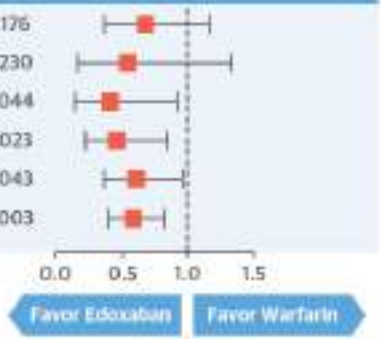
Lee et al. JACC August 21, 2018: 838-53

Edoxaban Versus Warfarin: Hazard Ratios of 6 Study Outcomes

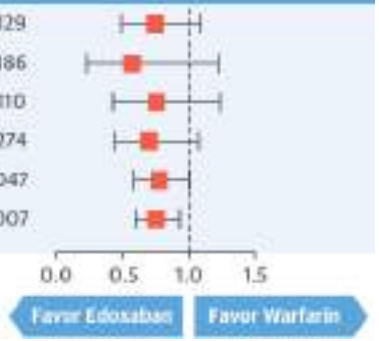
Edoxaban, Total vs. Warfarin	HR (95% CI)	p Value
Ischemic stroke	0.693 (0.487-0.959)	0.033
Intracranial hemorrhage (ICH)	0.407 (0.182-0.785)	0.014
Hospitalization for GI bleeding	0.597 (0.363-0.930)	0.030
Hospitalization for major bleeding	0.532 (0.352-0.773)	0.001
All-cause death	0.716 (0.549-0.918)	0.010
Ischemic stroke + ICH + all-cause death	0.667 (0.542-0.812)	<0.001



Edoxaban 60 mg vs. Warfarin	HR (95% CI)	p Value
Ischemic stroke	0.669 (0.356-1.153)	0.176
ICH	0.532 (0.159-1.326)	0.230
Hospitalization for GI bleeding	0.402 (0.140-0.913)	0.044
Hospitalization for major bleeding	0.452 (0.211-0.847)	0.023
All-cause death	0.603 (0.356-0.959)	0.043
Ischemic stroke + ICH + all-cause death	0.580 (0.394-0.825)	0.003



Edoxaban 30 mg vs. Warfarin	HR (95% CI)	p Value
Ischemic stroke	0.733 (0.481-1.076)	0.129
ICH	0.565 (0.217-1.215)	0.186
Hospitalization for GI bleeding	0.744 (0.421-1.228)	0.110
Hospitalization for major bleeding	0.693 (0.430-1.062)	0.274
All-cause death	0.764 (0.575-0.997)	0.047
Ischemic stroke + ICH + all-cause death	0.737 (0.585-0.917)	0.007



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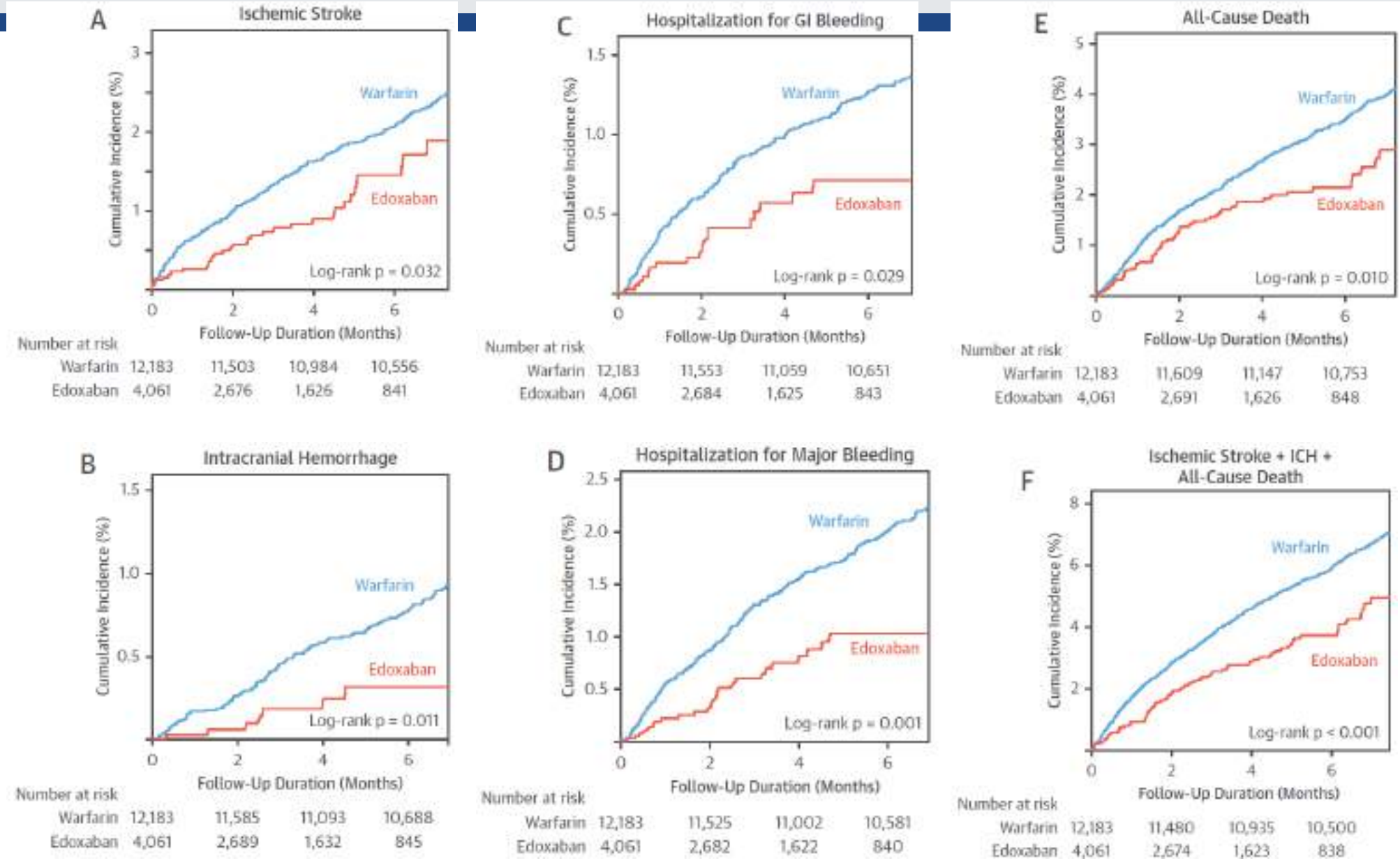
Cumulative Incidence of 6 Study Outcomes



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HR of Ischemic Stroke, ICH, All-Cause Death, and Composite Outcome

*P for interaction

	Ischemic Stroke	Intracranial Hemorrhage	All-Cause Death	Ischemic Stroke + ICH + All-Cause Death
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Total	0.693 (0.487-0.959)	0.407 (0.182-0.785)	0.716 (0.549-0.918)	0.667 (0.542-0.812)
Age	P* = 0.226	P* = 0.465	P* = 0.924	P* = 0.782
<65	0.923 (0.341-2.112)	0.717 (0.112-2.589)	0.978 (0.328-2.368)	0.790 (0.393-1.446)
65-74	0.520 (0.252-0.963)	0.569 (0.169-1.428)	0.882 (0.522-1.414)	0.711 (0.479-1.021)
≥75	0.750 (0.470-1.141)	0.208 (0.034-0.670)	0.725 (0.520-0.984)	0.678 (0.518-0.872)
Sex	P* = 0.891	P* = 0.341	P* = 0.364	P* = 0.675
Male	0.719 (0.428-1.139)	0.265 (0.064-0.716)	0.872 (0.610-1.215)	0.677 (0.511-0.881)
Female	0.704 (0.426-1.102)	0.621 (0.214-1.439)	0.656 (0.436-0.952)	0.656 (0.491-0.861)
CHA_2DS_2-VASc	P* = 0.042	P* = 0.445	P* = 0.598	P* = 0.127
0-2	1.565 (0.687-3.241)	0.568 (0.135-1.626)	0.776 (0.428-1.312)	0.884 (0.565-1.329)
≥3	0.601 (0.402-0.866)	0.344 (0.120-0.770)	0.762 (0.564-1.009)	0.644 (0.508-0.807)
CrCl	P* = 0.661		P* = 0.816	P* = 0.986
≤50 (mL/min)	0.918 (0.141-3.430)	N/A	0.707 (0.209-1.798)	0.611 (0.211-1.409)
>50 (mL/min)	0.616 (0.390-0.929)	0.466 (0.194-0.948)	0.651 (0.437-0.936)	0.623 (0.470-0.812)

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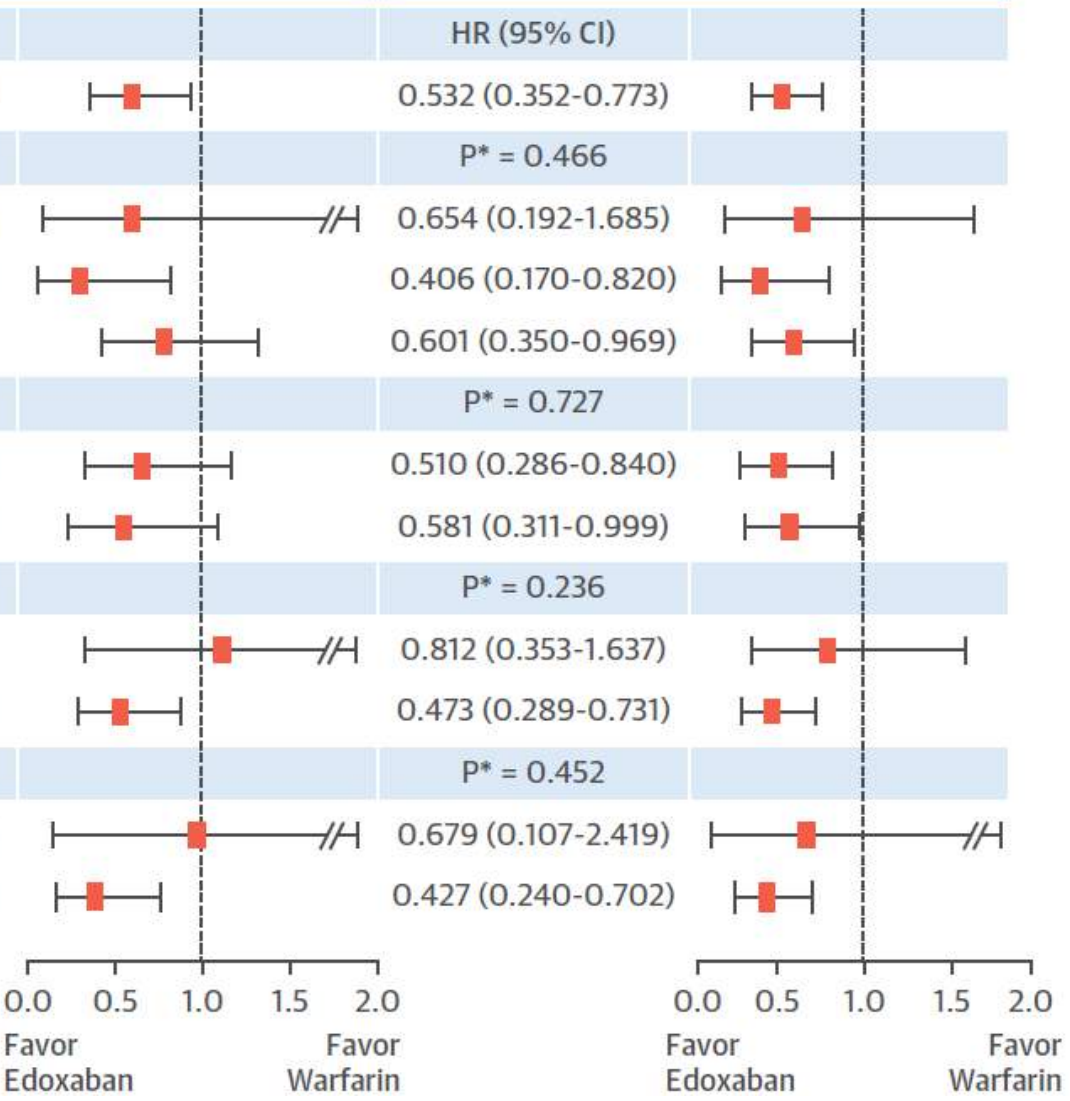
HRs of Hospitalization for GI Bleeding and Major Bleeding

*P for interaction

	Hospitalization for GI Bleeding	Hospitalization for Major Bleeding
	HR (95% CI)	HR (95% CI)
Total	0.597 (0.363-0.930)	0.532 (0.352-0.773)
Age	P* = 0.234	P* = 0.466
<65	0.601 (0.094-2.198)	0.654 (0.192-1.685)
65-74	0.301 (0.073-0.825)	0.406 (0.170-0.820)
≥75	0.784 (0.435-1.317)	0.601 (0.350-0.969)
Sex	P* = 0.906	P* = 0.727
Male	0.660 (0.341-1.165)	0.510 (0.286-0.840)
Female	0.552 (0.244-1.086)	0.581 (0.311-0.999)
CHA_2DS_2-VASc	P* = 0.205	P* = 0.236
0-2	1.109 (0.336-2.774)	0.812 (0.353-1.637)
≥3	0.531 (0.298-0.878)	0.473 (0.289-0.731)
CrCl (mL/min)	P* = 0.262	P* = 0.452
≤50	0.960 (0.148-3.566)	0.679 (0.107-2.419)
>50	0.398 (0.177-0.775)	0.427 (0.240-0.702)



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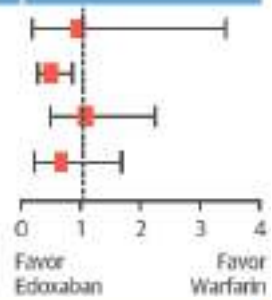
HRs of Ischemic Stroke, ICH, and Composite Outcome

*P for interaction

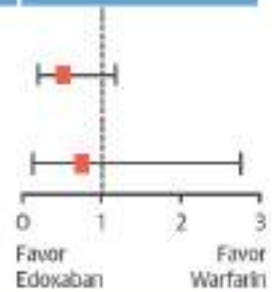
A

Ischemic Stroke					
	No. of events (IR, %/year)		HR (95% CI)	P*	
CrCl (mL/min)	Edoxaban	Warfarin			
30-50	2 (5.39)	21 (4.85)	0.918 (0.141-3.430)	0.457	
>50-80	12 (2.25)	143 (3.77)	0.474 (0.246-0.830)		
>80-95	8 (3.69)	49 (2.96)	1.065 (0.454-2.217)		
>95	4 (2.20)	40 (3.04)	0.644 (0.189-1.668)		



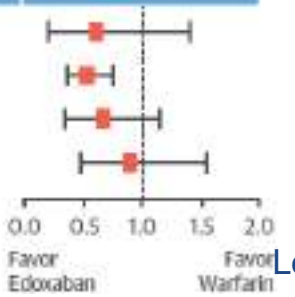
B

Intracranial Hemorrhage					
	No. of events (IR, %/year)		HR (95% CI)	P*	
CrCl (mL/min)	Edoxaban	Warfarin			
30-50	0 (0.0)	11 (2.50)	N/A	N/A	
>50-80	5 (0.94)	67 (1.75)	0.502 (0.173-1.156)		
>80-95	0 (0.0)	21 (1.26)	N/A		
>95	2 (1.09)	16 (1.21)	0.730 (0.112-2.745)		



C

Ischemic Stroke + ICH + All-Cause Death					
	No. of events (IR, %/year)		HR (95% CI)	P*	
CrCl (mL/min)	Edoxaban	Warfarin			
30-50	5 (13.4)	73 (16.9)	0.611 (0.211-1.409)	0.531	
>50-80	33 (6.19)	359 (9.52)	0.537 (0.366-0.762)		
>80-95	13 (5.99)	122 (7.39)	0.669 (0.355-1.161)		
>95	14 (7.71)	97 (7.40)	0.900 (0.483-1.560)		



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Real world data
Conclusions

- This study showed that edoxaban was associated with a **lower risk of ischemic stroke, ICH, hospitalization for GI bleeding, hospitalization for major bleeding, all-cause death, and the composite outcome of ischemic stroke + ICH + all-cause death** than warfarin.
- The results demonstrated the effectiveness and safety of edoxaban 60 mg, and this was **consistent with a previous meta-analysis** that reported that regular doses of DOACs were effective and safe enough in Asian patients, perhaps even more than among the non-Asian population.
- In this study, **44% of patients prescribed 30-mg edoxaban did not meet the dose reduction criteria**, which might have affected the outcomes of our study.
- These benefits were consistent across various high-risk subgroups, **including patients with high CrCl (>95 ml/min).**

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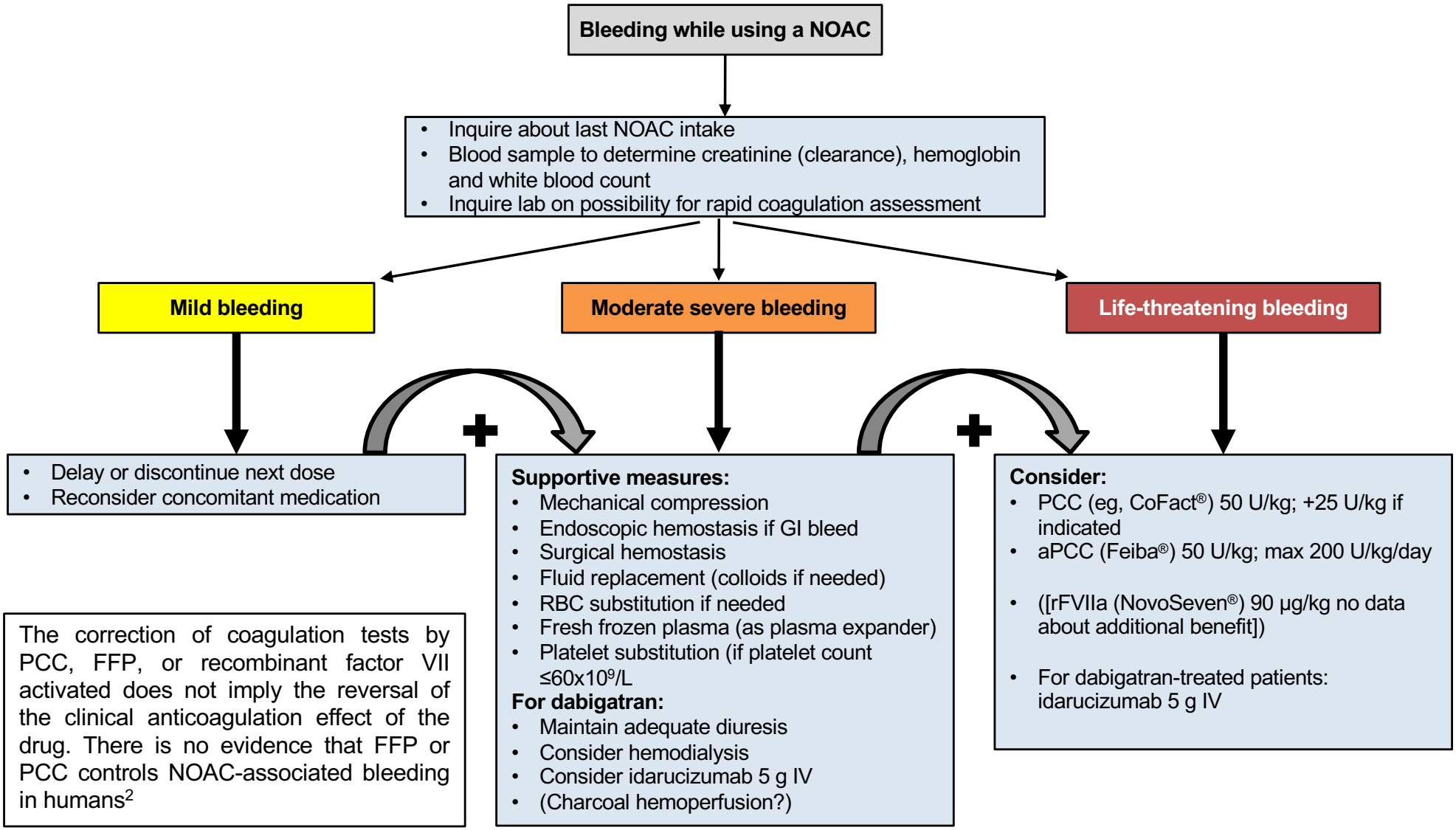
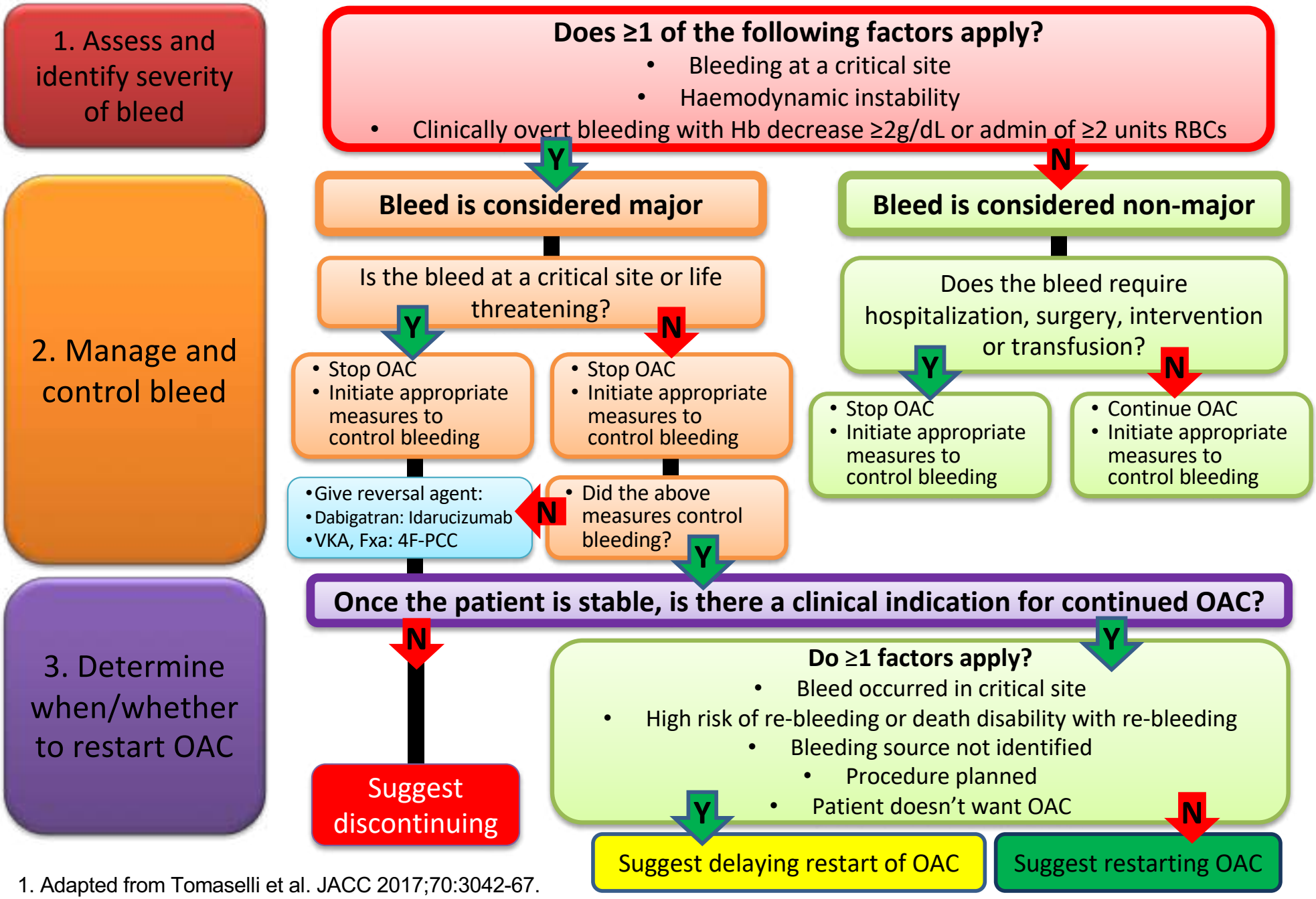
EHRA: Management of bleeding in patients treated with NOACs[1]



1. Adapted from Heidbuchel et al. Europace 2015;17:1467-507.
2. Raval et al. Circulation 2017;135:e604-e633.

2017 ACC expert consensus on OAC bleeding management[1]

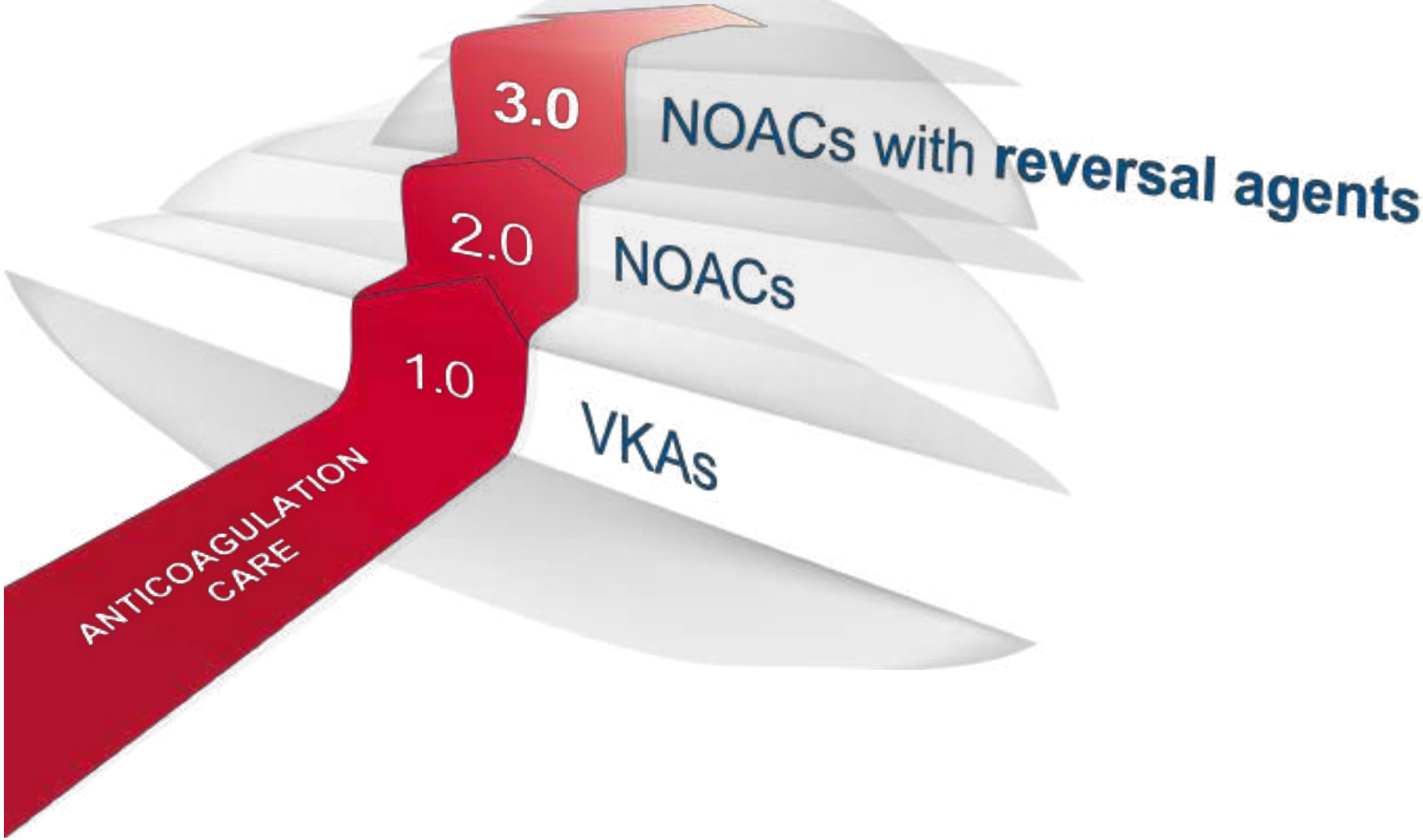


1. Adapted from Tomaselli et al. JACC 2017;70:3042-67.

Innovation: availability of specific reversal agents marks the next phase in anticoagulation care

3.0 Innovation

Specific reversal agents mark the next phase in anticoagulation care



NOAC antidotes

Andexanet[1] (PRT064445)	• Antidote for factor Xa inhibitors • Recombinant modified human factor Xa decoy protein that binds factor Xa inhibitors in the active site
Ciraparantag[2] (PER977)	• Antidote for factor Xa inhibitors, direct thrombin inhibitors, low molecular-weight heparins, and fondaparinux • Synthetic small molecule; reversal effect through direct binding to anticoagulant
Idarucizumab[3] (BI 655075)	• Antidote for direct thrombin inhibitors • Monoclonal antibody fragment

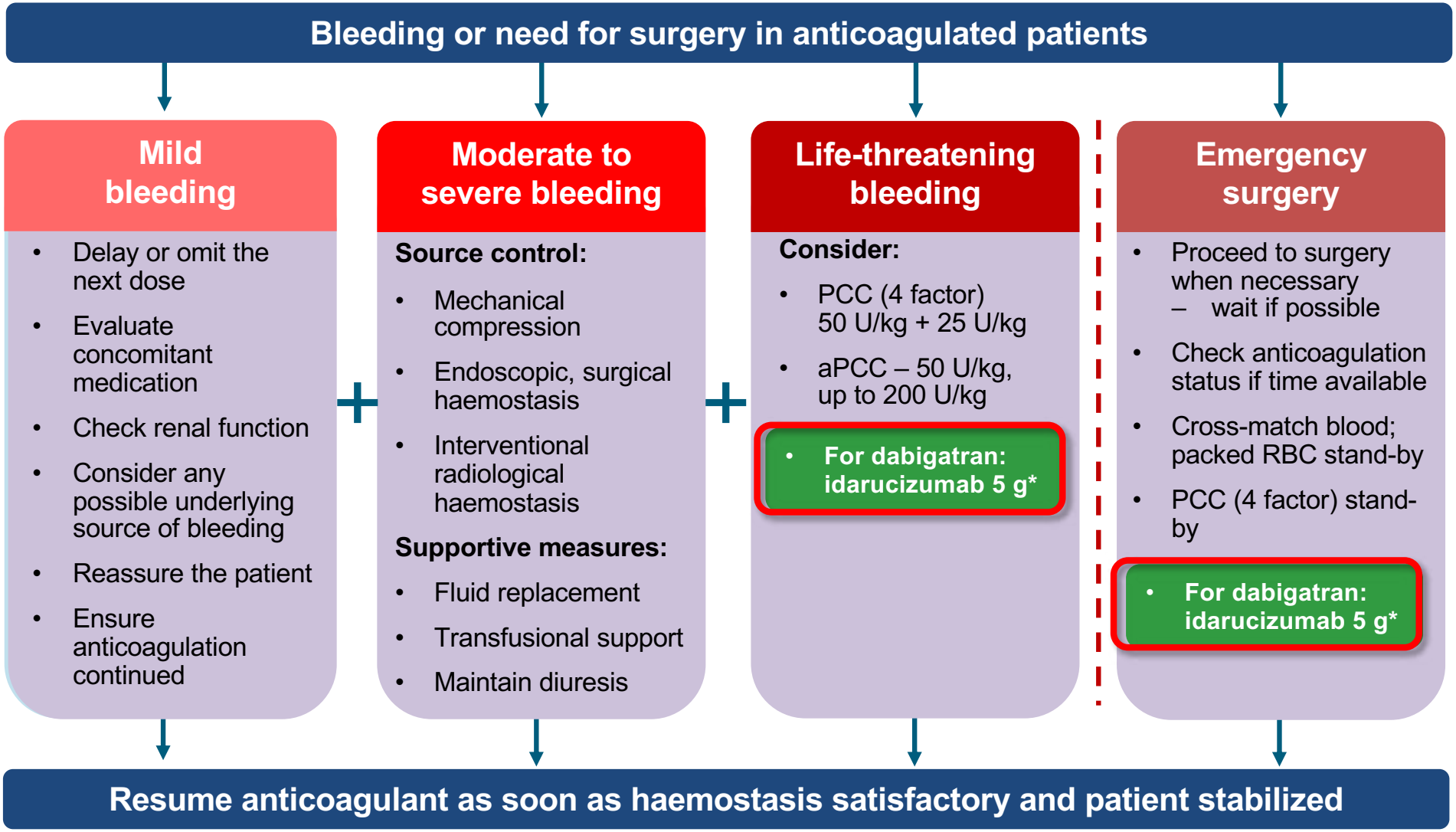
1. Siegal et al. N Engl J Med 2015;373:2413-24.
2. Milling & Katz. Am J Med 2016;129(11 Suppl):S80-S88.
3. Pollack CV Jr et al. N Engl J Med 2015;373:511-20.

RE-VERSE AD: key results in a cohort of multi-morbid elderly patients presenting with life-threatening emergencies

1. 5 g of idarucizumab resulted in immediate, complete, and sustained reversal of dabigatran anticoagulation
2. Median time to cessation of assessable extracranial bleeding in Group A was 2.5 hours after reversal
3. Median time to surgery after reversal was 1.6 hours, with 'normal' intraoperative haemostasis in 93% of Group B patients
4. No safety concerns identified to date

Pollack C et al. N Engl J Med 2017

Idarucizumab is recommended to reverse dabigatran anticoagulation in patients requiring emergency surgery or with life-threatening bleeding



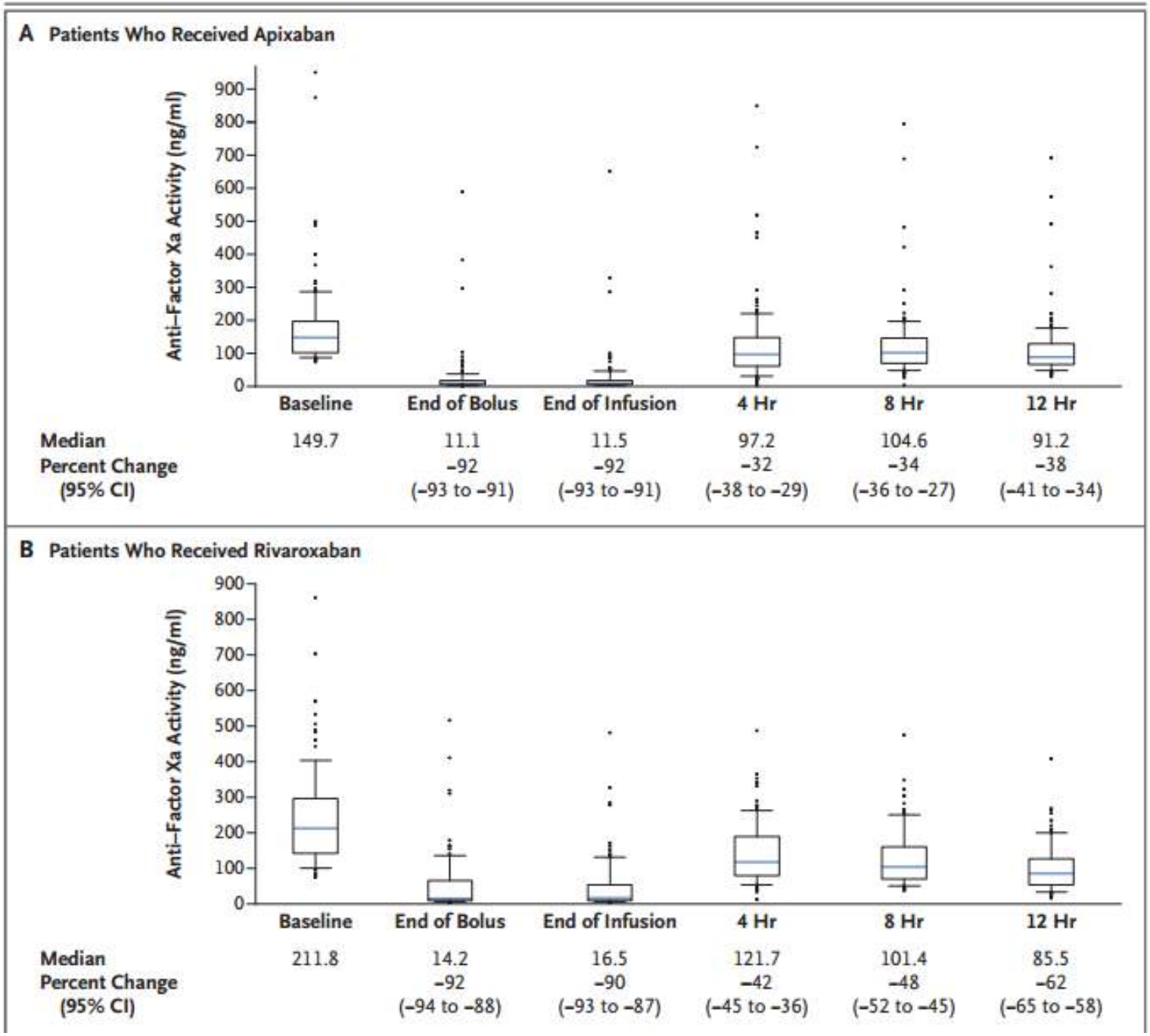
*Idarucizumab is the preferred treatment to reverse dabigatran; PCC, prothrombin complex concentrate; RBC, red blood cell; Anticoagulation Education Task Force White Paper: Ageno W et al. Thromb Haemost 2016

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors

S.J. Connolly, M. Crowther, J.W. Eikelboom, C.M. Gibson, J.T. Curnutte, J.H. Lawrence, P. Yue, M.D. Bronson, G. Lu, P.B. Conley, P. Verhamme, J. Schmidt, S. Middeldorp, A.T. Cohen, J. Beyer-Westendorf, P. Albaladejo, J. Lopez-Sendon, A.M. Demchuk, D.J. Pallin, M. Concha, S. Goodman, J. Leeds, S. Souza, D.M. Siegal, E. Zotova, B. Meeks, S. Ahmad, J. Nakamya, and T.J. Milling, Jr., for the ANNEXA-4 Investigators*


A Patients Who Received Apixaban
Anti–Factor Xa Activity (ng/ml)
900
800
700
600
500
400
300
200
100
0
Baseline
End of Bolus
End of Infusion
4 Hr
8 Hr
12 Hr
Median
Percent Change
(95% CI)
149.7
11.1
–92
(–93 to –91)
11.5
–92
(–93 to –91)
97.2
–32
(–38 to –29)
104.6
–34
(–36 to –27)
91.2
–38
(–41 to –34)
B Patients Who Received Rivaroxaban
Anti–Factor Xa Activity (ng/ml)
900
800
700
600
500
400
300
200
100
0
Baseline
End of Bolus
End of Infusion
4 Hr
8 Hr
12 Hr
Median
Percent Change
(95% CI)
211.8
14.2
–92
(–94 to –88)
16.5
–90
(–93 to –87)
121.7
–42
(–45 to –36)
101.4
–48
(–52 to –45)
85.5
–62
(–65 to –58)

ANNEXA-4 study Conclusions

- In patients with **acute major bleeding** associated with the **use of a factor Xa inhibitor**, treatment with **andexanet markedly reduced anti–factor Xa activity, and 82% of patients had excellent or good hemostatic efficacy at 12 hours**, as adjudicated according to prespecified criteria.

Take Home message (1)

- Afib patients with **CHA2DS2-VASc score ≧2**
  - OAC or NOAC is suggested (non-vulvular AF)
- All NOACs have good efficacy for stroke prevention and **reduce hemorrhagic stroke (except rivaroxaban) / ICH** in RCTs
- Asian populations has **higher stroke and bleeding risk** than non-Asian populations.
- The use of **warfarin** caused **high-risk of hemorrhage in Asian** patients. NOACs offer proven safety and efficacy benefits for stroke prevention in patients with AF.

Take Home message (2)

- **Edoxaban (60/30) regimens** was non-inferior to warfarin for efficacy and reduced in bleeding than warfarin in **ENGAGE-AF study**
- **Real world data** showed edoxaban has **lower risk of ischemic stroke, ICH, hospitalization for GI bleeding, hospitalization for major bleeding, all-cause death, and the composite outcome of ischemic stroke + ICH + all-cause death** than warfarin.
- **Dose reduction criteria:** **B**W < 60kg / **C**rCL < 50 ml/min / **D**rug interaction
- **Once-daily edoxaban** has better drug adherence / compliance than twice-daily dose NOACs

NOAC是上天賜給全洲人最好的一個禮物

for Afib / VTE / CAD, PAD