台灣血脂衛教協會
Taiwan Association of Lipid Educators

Holistic Care for the Patients with Cardiovascular Diseases: Controversies and Issues in 2013

Debate

Which one is better – Factor IIa or Xa inhibitor?

Factor IIa inhibitor is better

日期：103 年 01 月 26 日 (週日) 14:30 - 15:30

地點：高醫啟川大樓 6F 第一會議室

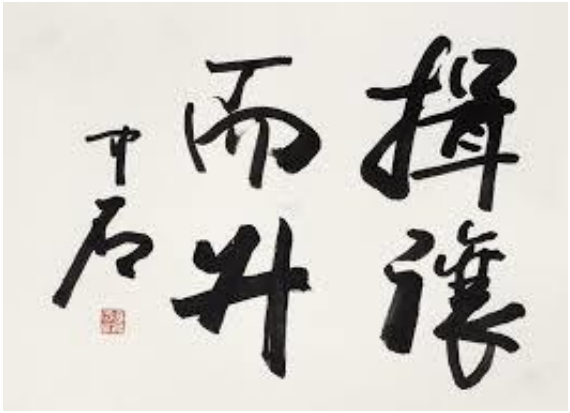
講者：台大醫院新竹分院 心臟內科 趙嘉倫

台大醫院 新竹分院

Presenter Disclosures

- **Research grant: none**
- **Speaking or consulting: honorarium from BI**
- **Stockholding: none**

論語八佾第三 子曰：「君子無所爭。必也射乎！揖讓而升，下而飲。其爭也君子。」



Outline

- **NOACs vs. Warfarin**
- Dabigatran vs. Rivaroxaban
- Dabigatran vs. Apixaban
- Dabigatran vs. Edoxaban
- Review of specific conditions
- Conclusion

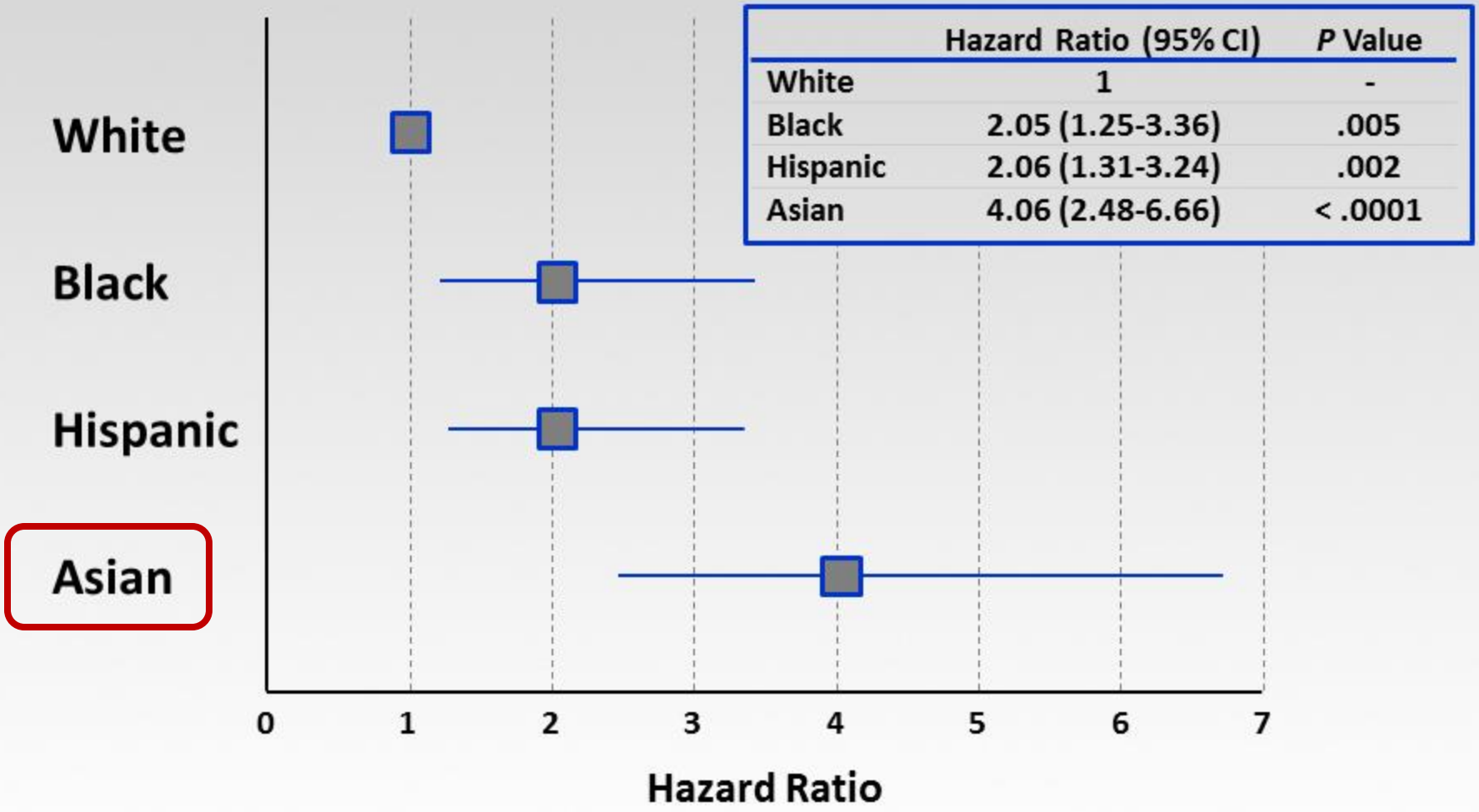
AF and Stroke Risk

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.

Incidence of ICH in Different Ethnic Groups on Warfarin:

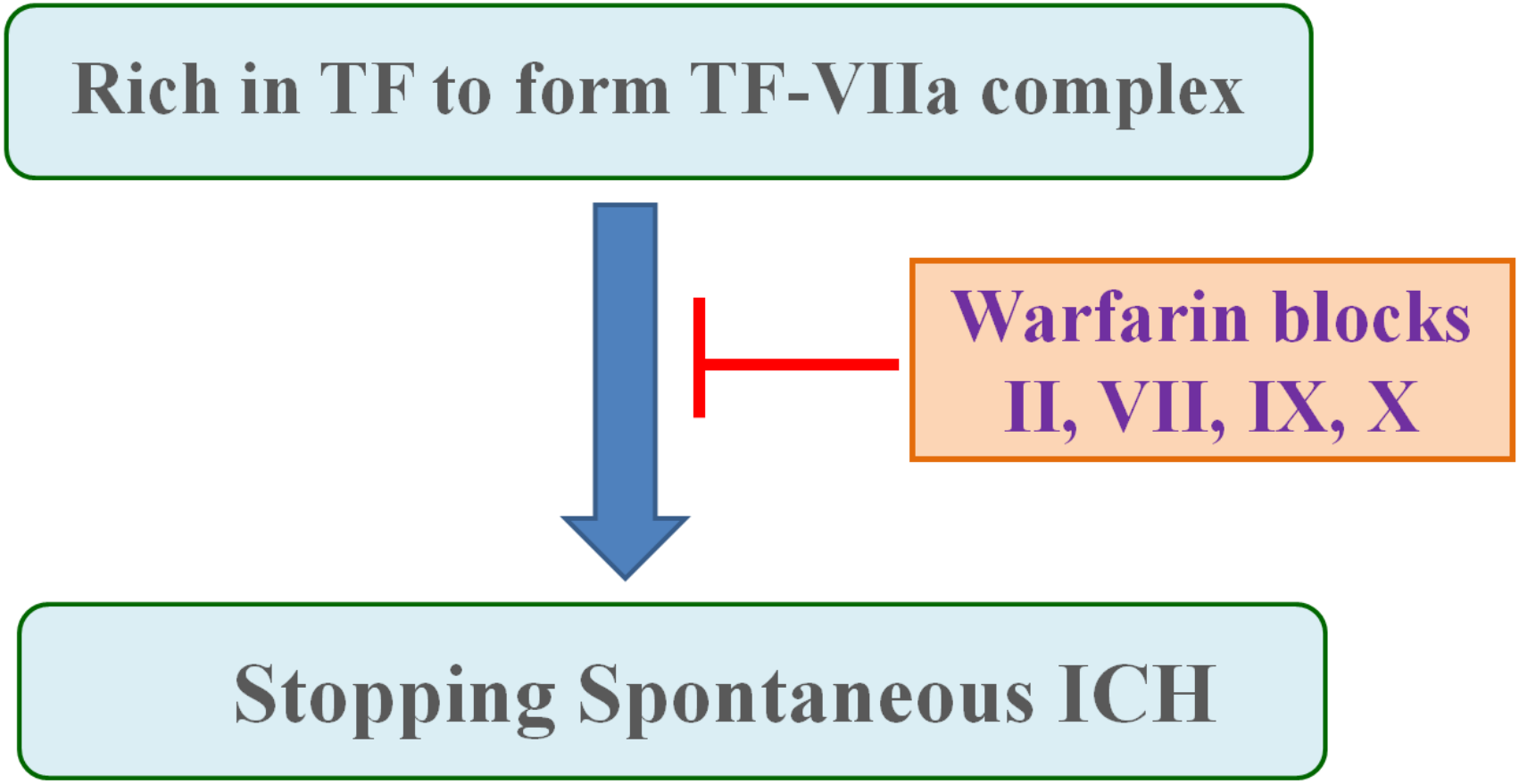
Multiethnic Cohort of 18,867 Patients Hospitalized With First-time AF (January 1995-December 2000)



	Hazard Ratio (95% CI)	*P* Value
White	1	-
Black	2.05 (1.25-3.36)	.005
Hispanic	2.06 (1.31-3.24)	.002
Asian	4.06 (2.48-6.66)	< .0001

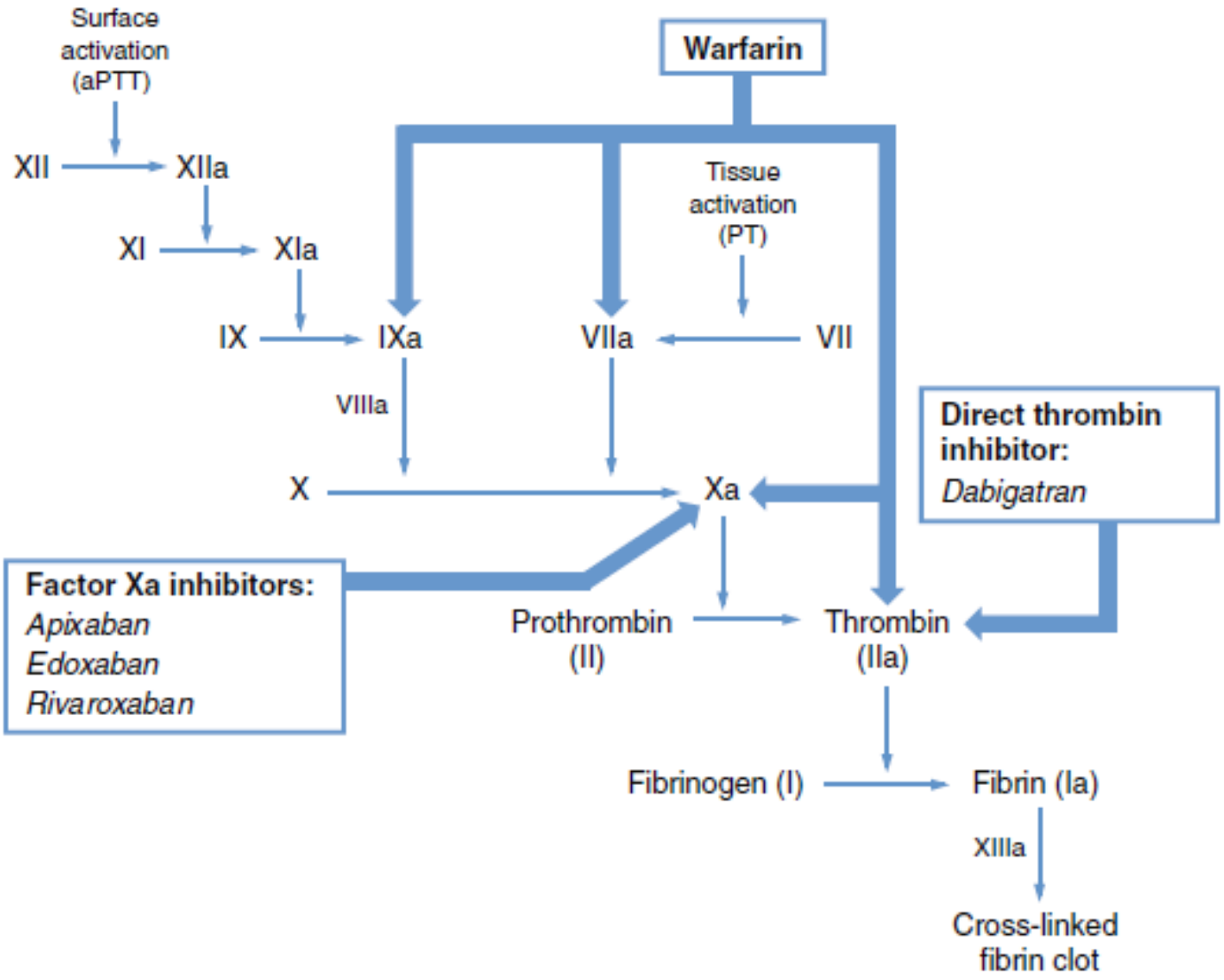
Shen AY, et al. *J Am Coll Cardiol*. 2007;50(4):309-315.

The Brain is Sensitive to Warfarin!



Circulation 2011;123:2363–2372.

Anticoagulant Sites of Action



Int Arch Med 2013;6;46

Characteristics of New Oral Anticoagulants

Table 1. Characteristics of Oral Anticoagulants Under Development in Japan[8,31]

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target factor	Thrombin	Xa	Xa	Xa
$t_{1/2}$ (h)	12–14	9–13	8–15	6–11[31]
t_{max} (h)	0.5–2	2–4	1–4	1–1.5[31]
Bioavailability	6.5% (humans)	67–86% (animals)	49% (humans)	60% (animals)
Protein binding	35%	92–95%	87%	40–59%
Metabolism	Glucuronidation	CYP3A4/2J2[8]	CYP3A4[8]	CYP3A
Renal excretion	80%	33%	25%	35–39%
Prodrug	Yes	No	No	No
Company	Boehringer Ingelheim	Bayer/ Johnson & Johnson	Bristol-Myers Squibb/ Pfizer	Daiichi Sankyo

Circ J 2011; 75: 1539–1547.

Study Designs in Trials of NOACs

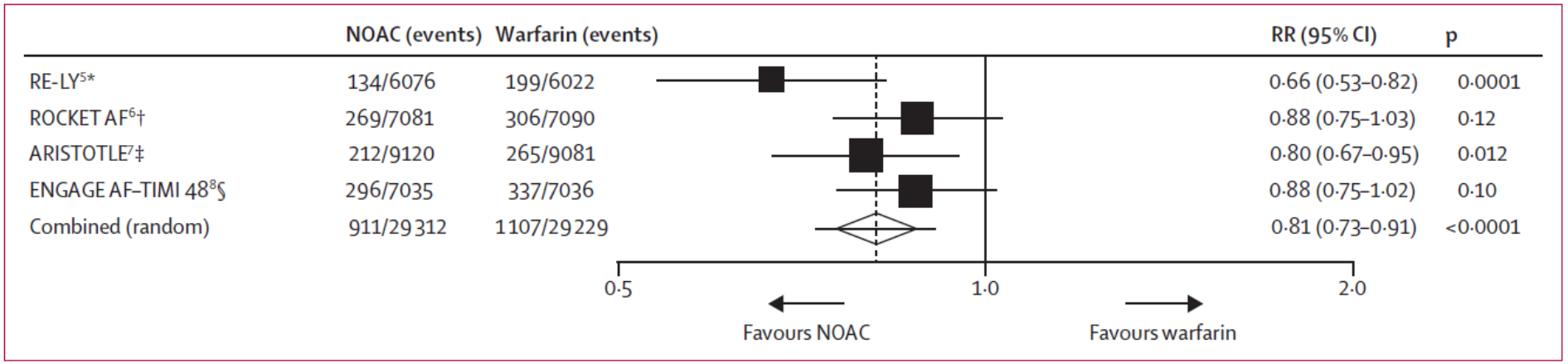
	RE-LY [41]	ROCKET-AF [52]	ARISTOTLE [49]	ENGAGE AF-TIMI 48 [51]
Study treatments	DABI 110 mg or 150 mg BID vs WARF	RIVA 20 mg/d vs WARF	APIX 5 mg BID vs WARF	EDOX 60 mg or 30 mg/d vs WARF
Dose adjusted[a]	No	20 → 15 mg/d	5 → 2.5 mg BID	60 → 30, 30 → 15 mg/d
Design	Prospective randomized, open-label, blinded endpoint (PROBE)	Double-blind	Double-blind	Double-blind
Inclusion criteria	Nonvalvular AF in last 6 mo and ≥1 of following:	Nonvalvular AF and history of stroke, TIA, systemic embolism, or ≥2 of following:	Nonvalvular AF or AFL in last 12 mo *plus* ≥1 of following:	AF in last 12 mo and prior stroke or TIA or ≥2 of following:
	• Previous stroke or TIA	• HF or LVEF ≤35%	• Previous stroke, TIA, or systemic embolism	• History of HF
	• LVEF <40%	• Age ≥75 y	• Symptomatic HF in last 3 mo	• Age ≥75 y
	• NYHA class ≥ II HF in last 6 mo	• Hypertension	• LVEF ≤40%	• Hypertension
	• Age ≥75 y or 65–74 y *plus* diabetes, hypertension, or CAD	• Diabetes	• Age ≥75 y	• Diabetes
			• Hypertension requiring treatment	
			• Diabetes	

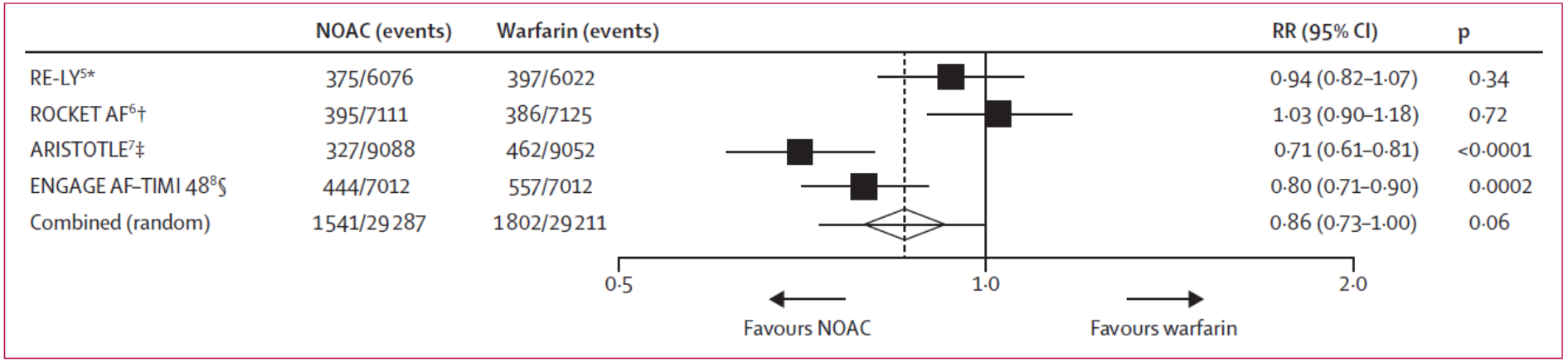
Int Arch Med 2013;6;46

RIVA 15 mg QD: CrCl 30-49 ml/min

APIX 2.5 mg BID: age ≧ 80 yrs, BW ≦ 60 kg, or Cr ≧ 1.5 mg/dL (two or more)

Meta-analysis of Randomised Trials





Interpretation: NOACs showed a favorable risk-benefit profile with significant reductions in stroke, ICH, and mortality, and with similar major bleeding as warfarin, ……..

Lancet Dec 4, 2013

Outline

- NOACs vs. Warfarin: NOACs better
- Dabigatran vs. Rivaroxaban
- Dabigatran vs. Apixaban
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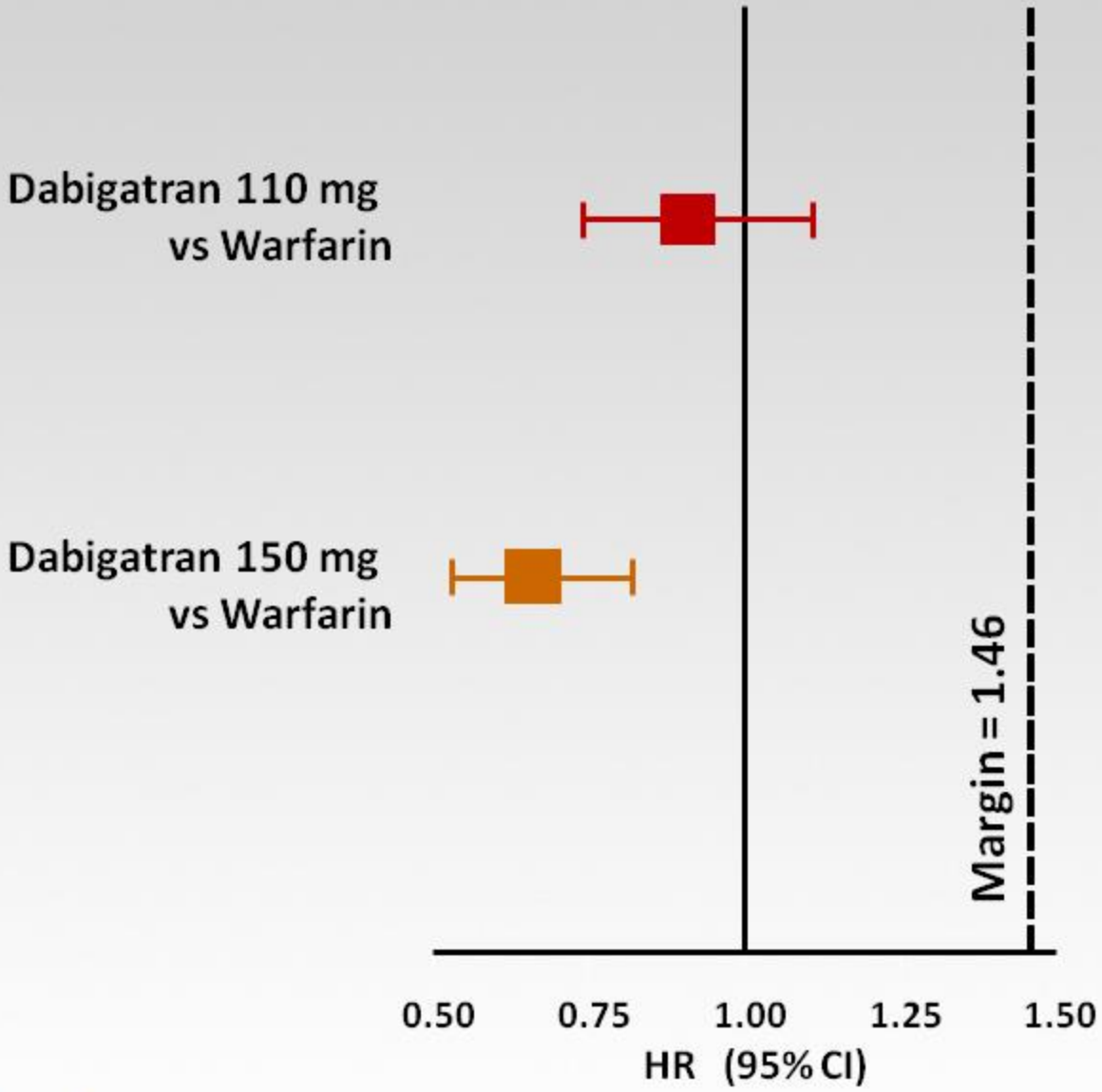
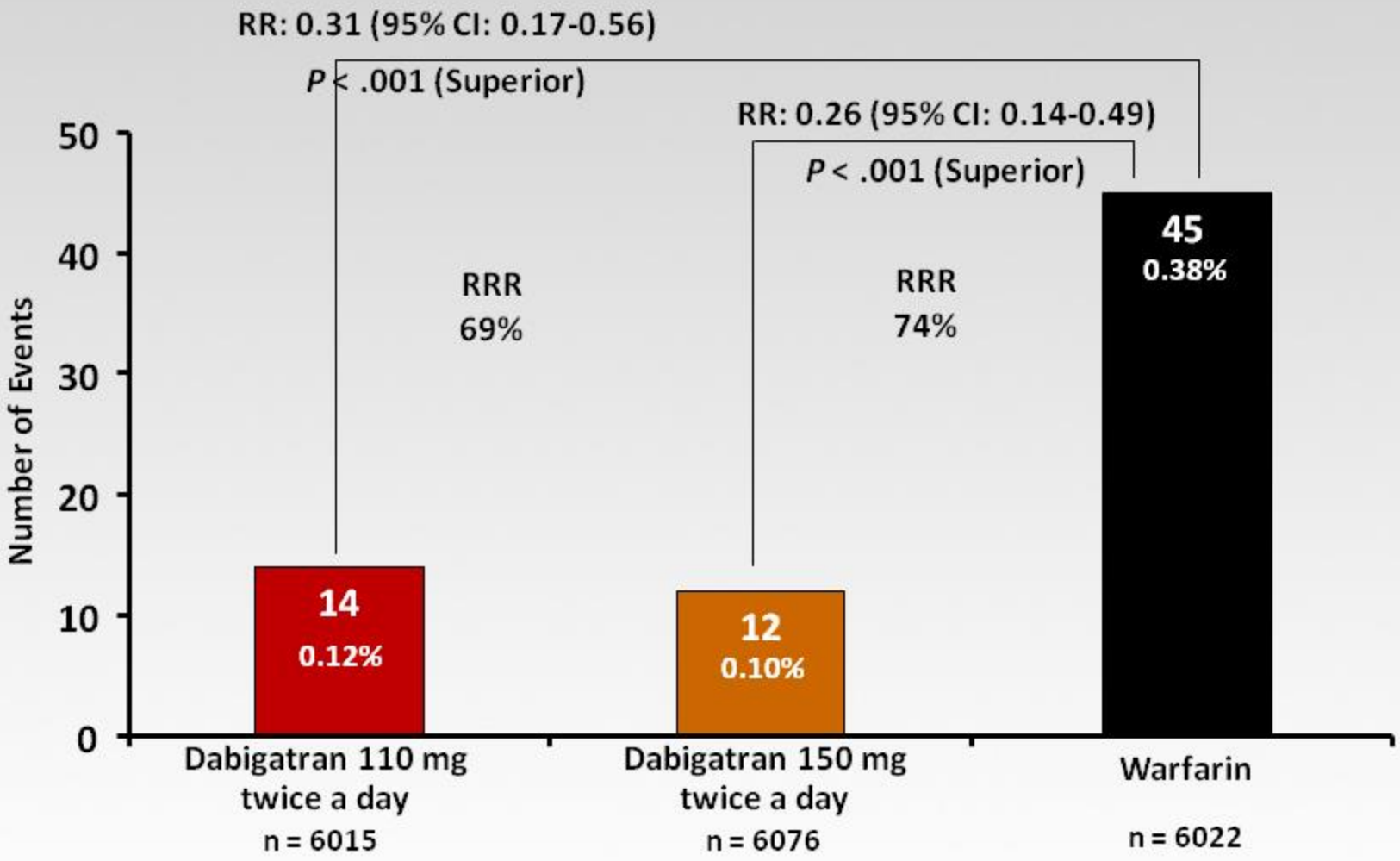
Stroke or Systemic Embolism



	Noninferiority *P* value	Superiority *P* value
Dabigatran 110 mg vs Warfarin	< .001	.29
Dabigatran 150 mg vs Warfarin	< .001	< .001

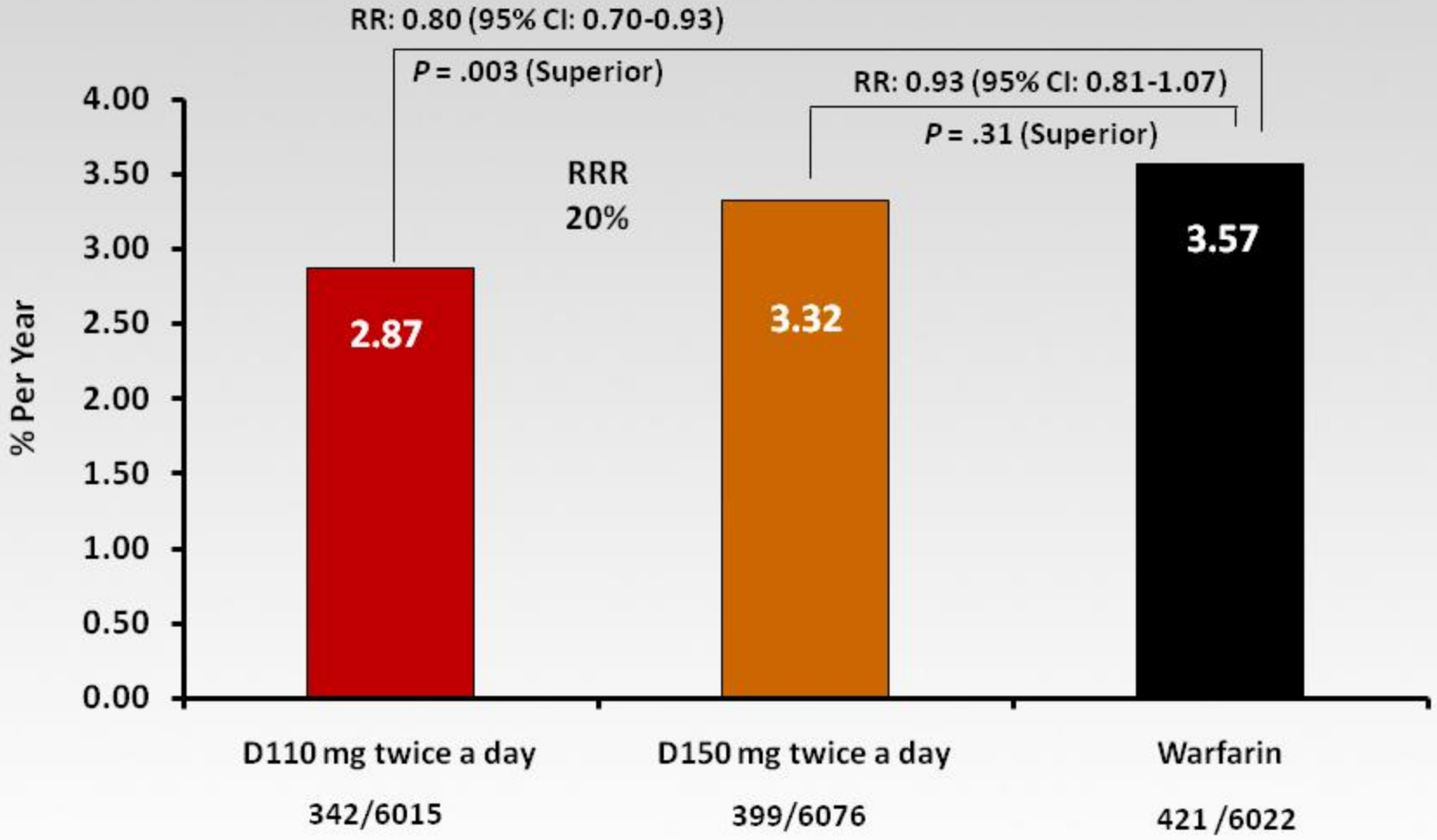
Connolly SJ, et al. *N Engl J Med.* 2009; 361:1139-1151.

RE-LY: Hemorrhagic Stroke



Connolly SJ, et al. *N Engl J Med.* 2009;361:1139-1151.

RE-LY Safety: Major Bleeding



Connolly SJ, et al. *N Engl J Med.* 2009; 361:1139-1151.

Major Bleeding and Components

Characteristic	D110 mg	D150 mg	Warfarin	*P* value D110 vs W	*P* value D150 vs W
Number of patients (n)	6015	6076	6022		
Major bleeding	2.87	3.32	3.57	.003	.31
• Life threatening	1.24	1.49	1.85	< .001	.03
• Non-life threatening	1.83	2.06	1.92	.65	.39
• Gastrointestinal	1.15	1.56	1.07	.52	.001

Data represents %/year

Connolly SJ, et al. *N Engl J Med.* 2009; 361:1139-1151.

Efficacy and Safety of Pradaxa versus Warfarin in Patients with Atrial Fibrillation

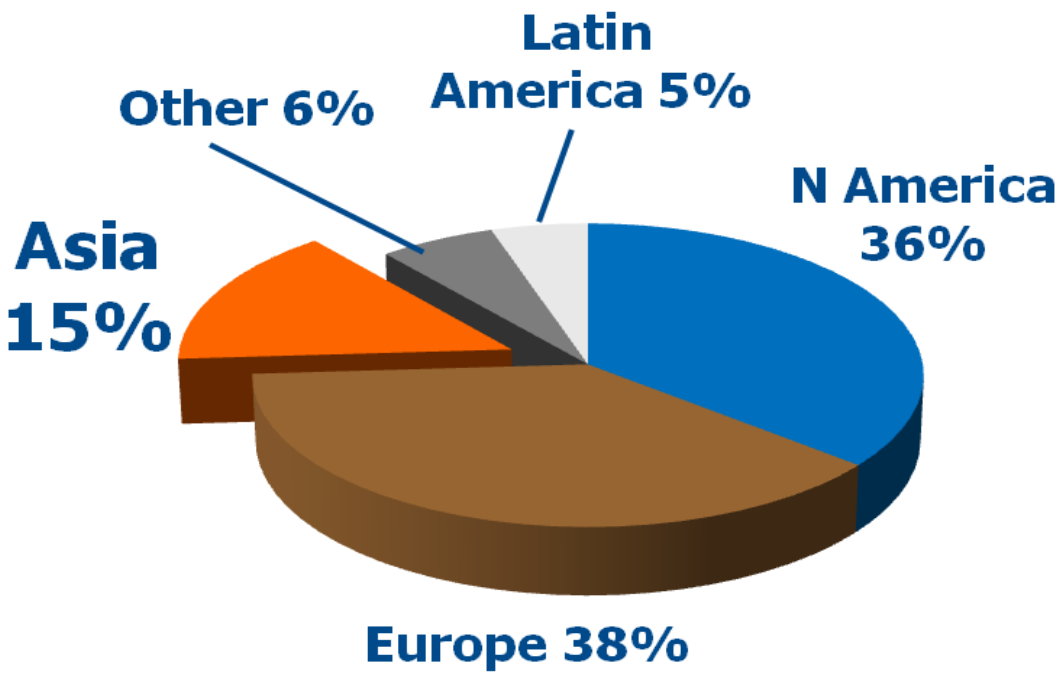
Analysis in Asian Population in RE-LY Trial

RELY® ASIA

RE-LY® recruitment by region (n=18,113)

Patients (n)

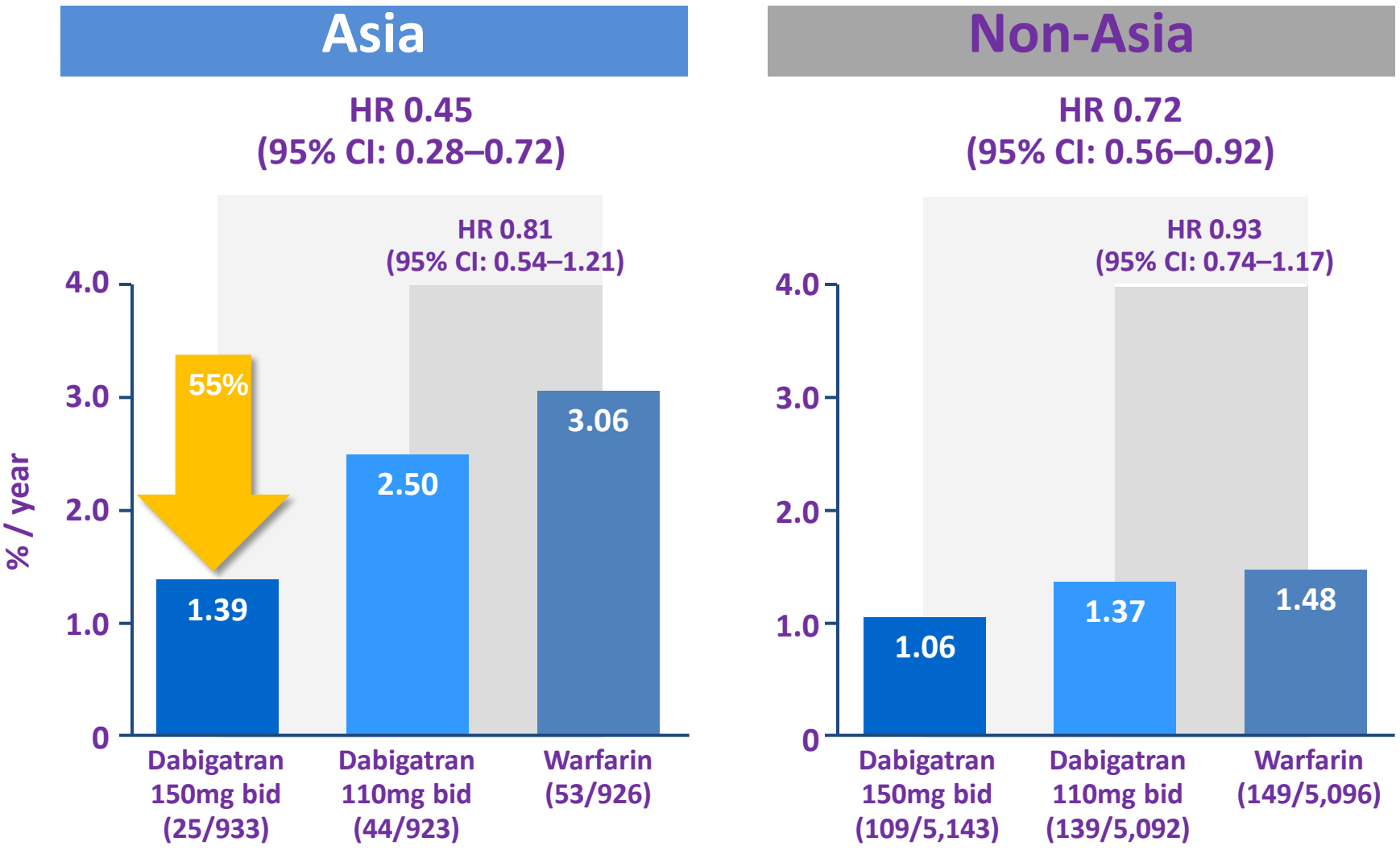
- East Asia 1,648
  - China 541
  - Hong Kong 90
  - Japan 326
  - South Korea 336
  - Taiwan 355
- South Asia 1,134
  - India 578
  - Malaysia 185
  - Philippines 157
  - Singapore 59
  - Thailand 155
- Total 2,782



Hori M, et al. Presented at the 2nd Asia Pacific Stroke Conference in Tokyo, Japan. September 2012.

Analysis in Asian Populations in RE-LY Trial

Primary Endpoint (Stroke or Systemic Embolism)

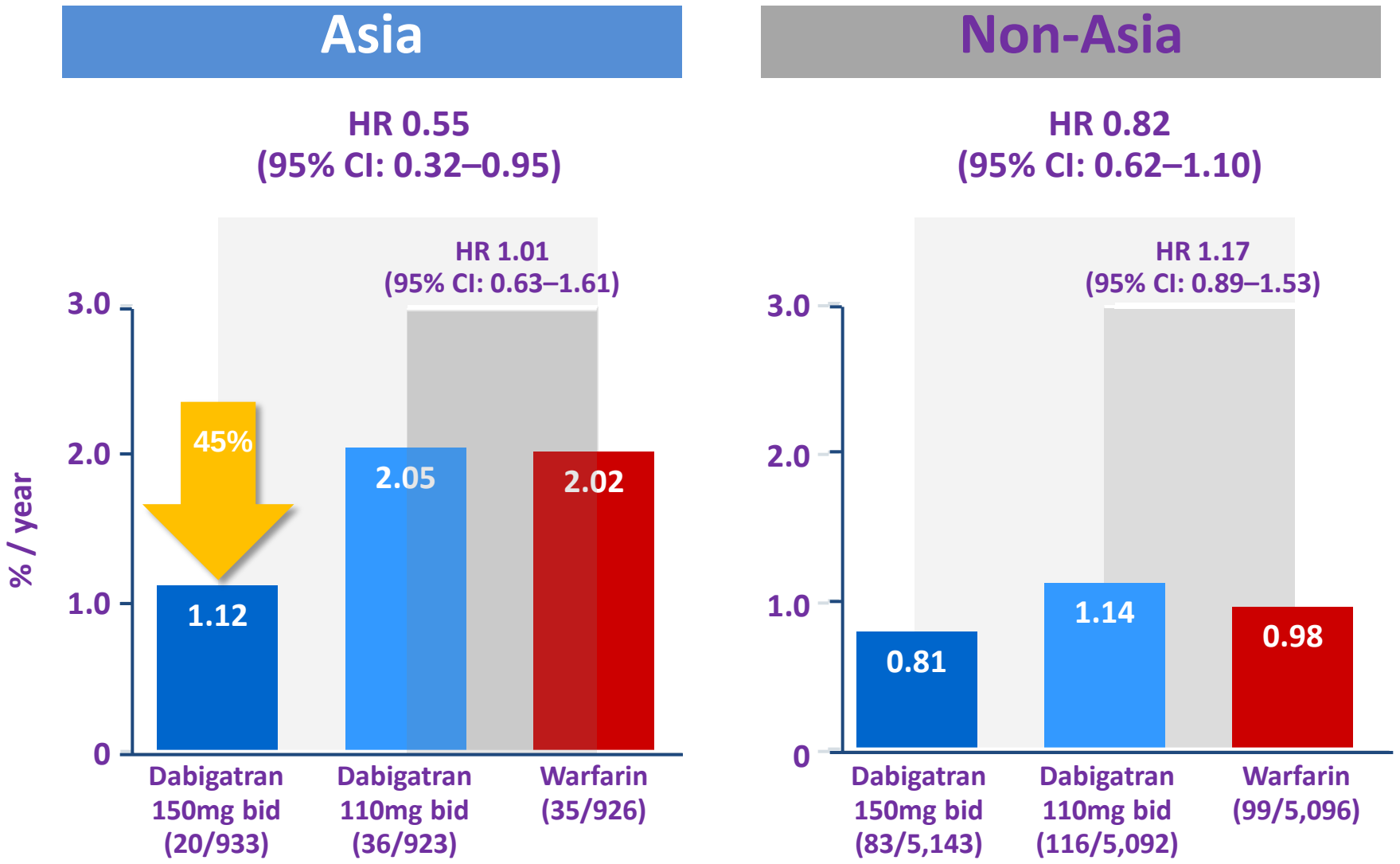


Interaction: Dabigatran 150mg bid vs Warfarin p= 0.0853, Dabigatran 110mg bid vs Warfarin p= 0.5597

Stroke. 2013;44:1891-1896

Analysis in Asian Populations in RE-LY Trial

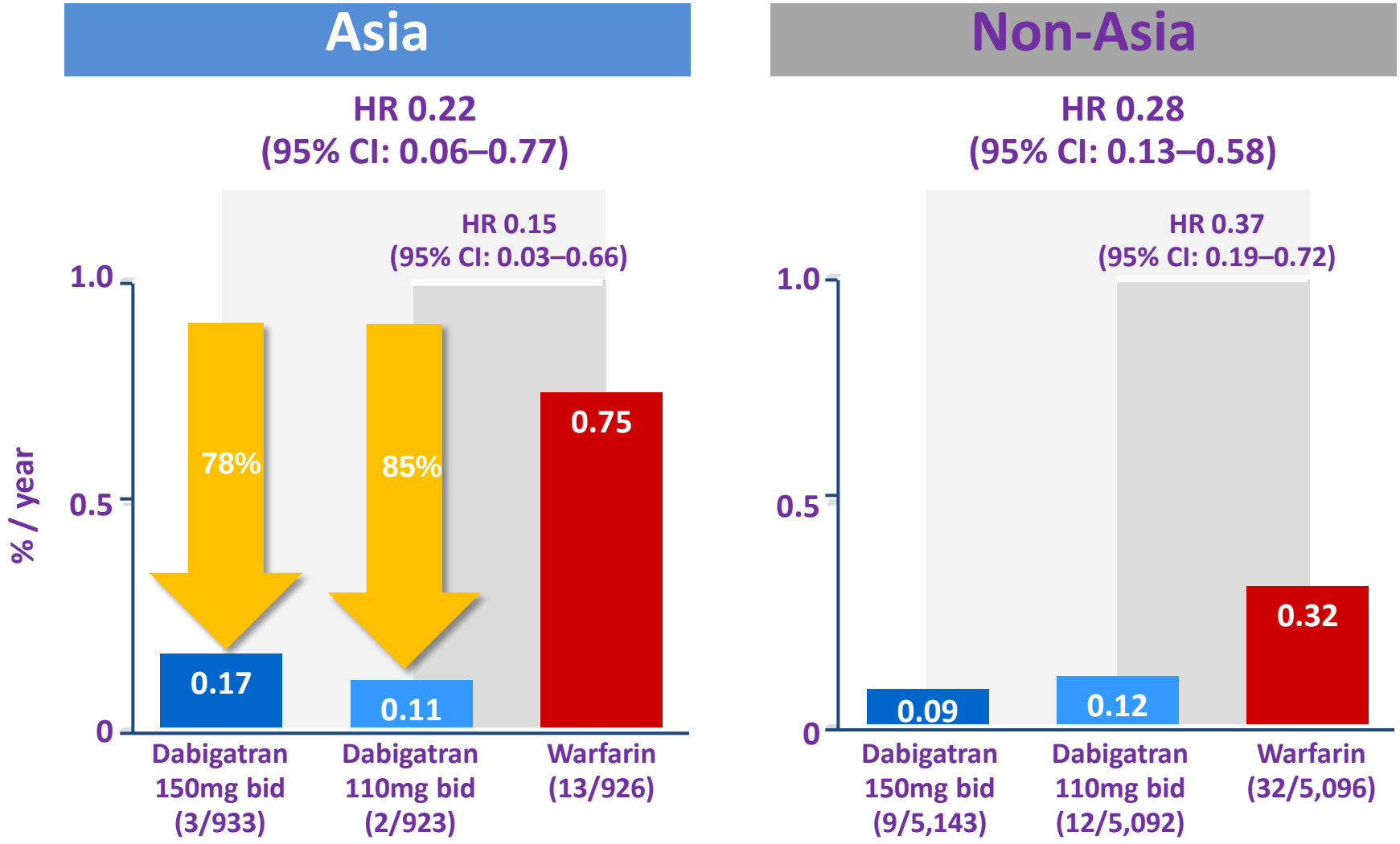
Ischemic Stroke



Stroke. 2013;44:1891-1896

Analysis in Asian Populations in RE-LY Trial

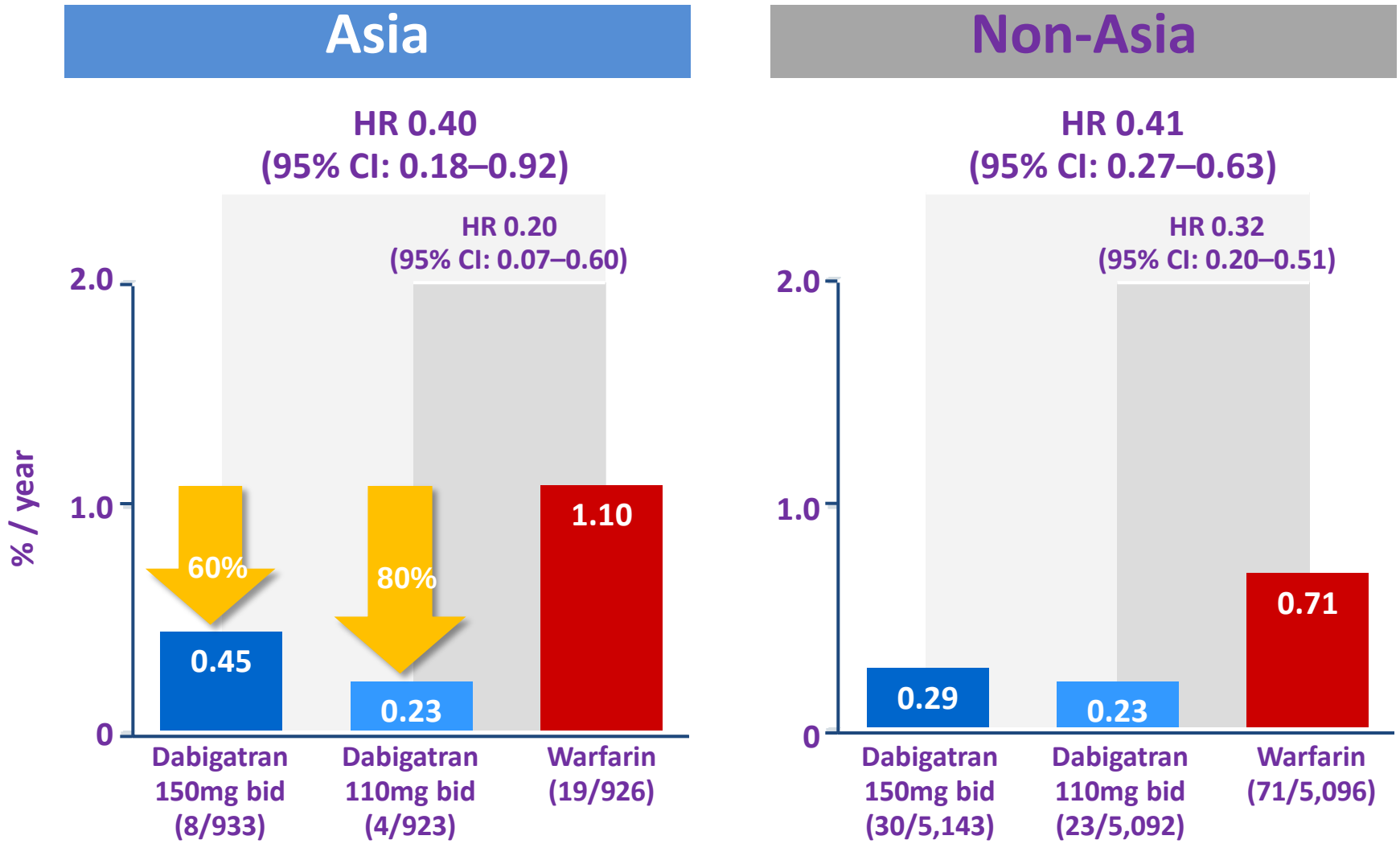
Hemorrhagic Stroke



Stroke. 2013;44:1891-1896

Analysis in Asian Populations in RE-LY Trial

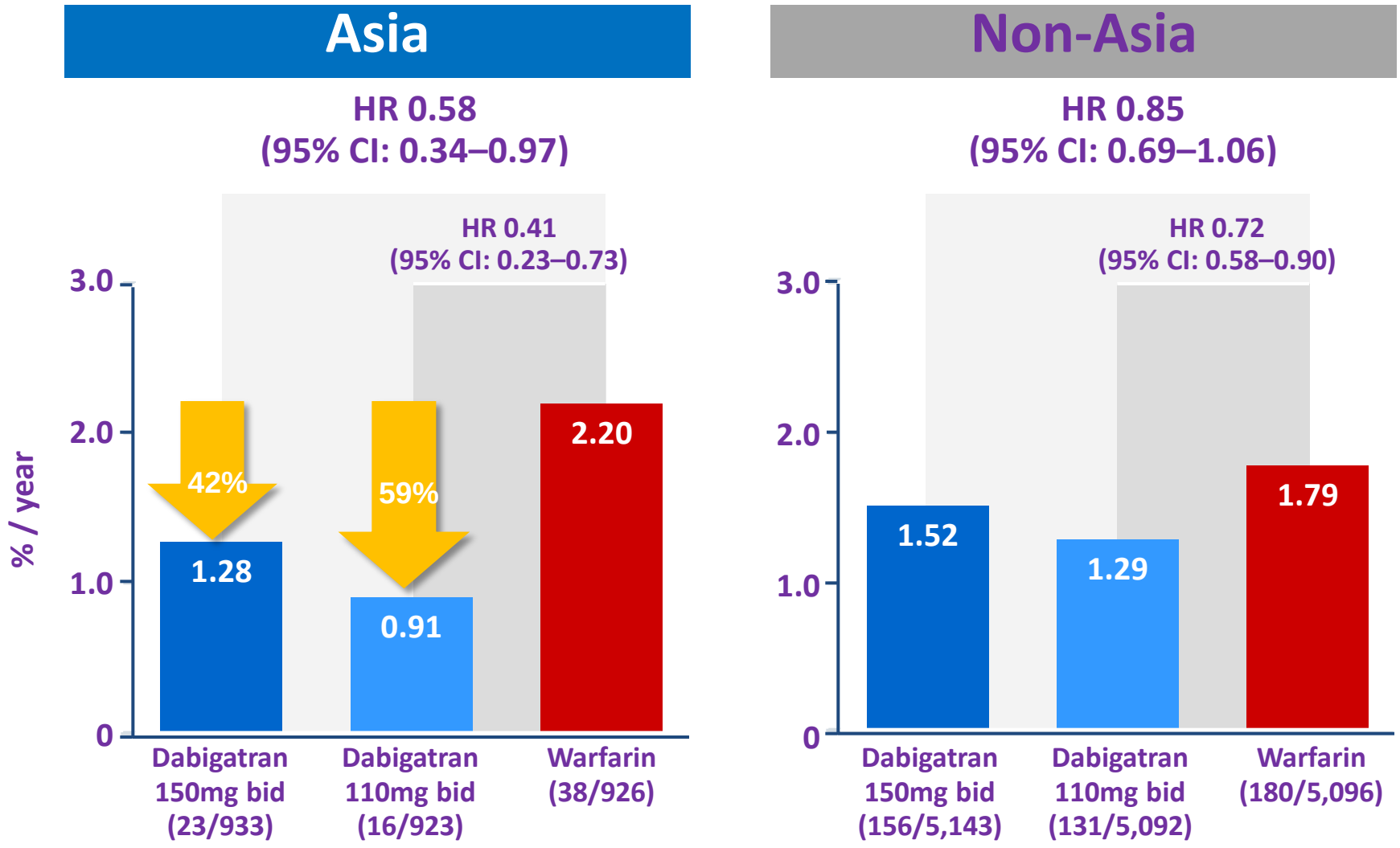
Intracranial Bleeding



Stroke. 2013;44:1891-1896

Analysis in Asian Populations in RE-LY Trial

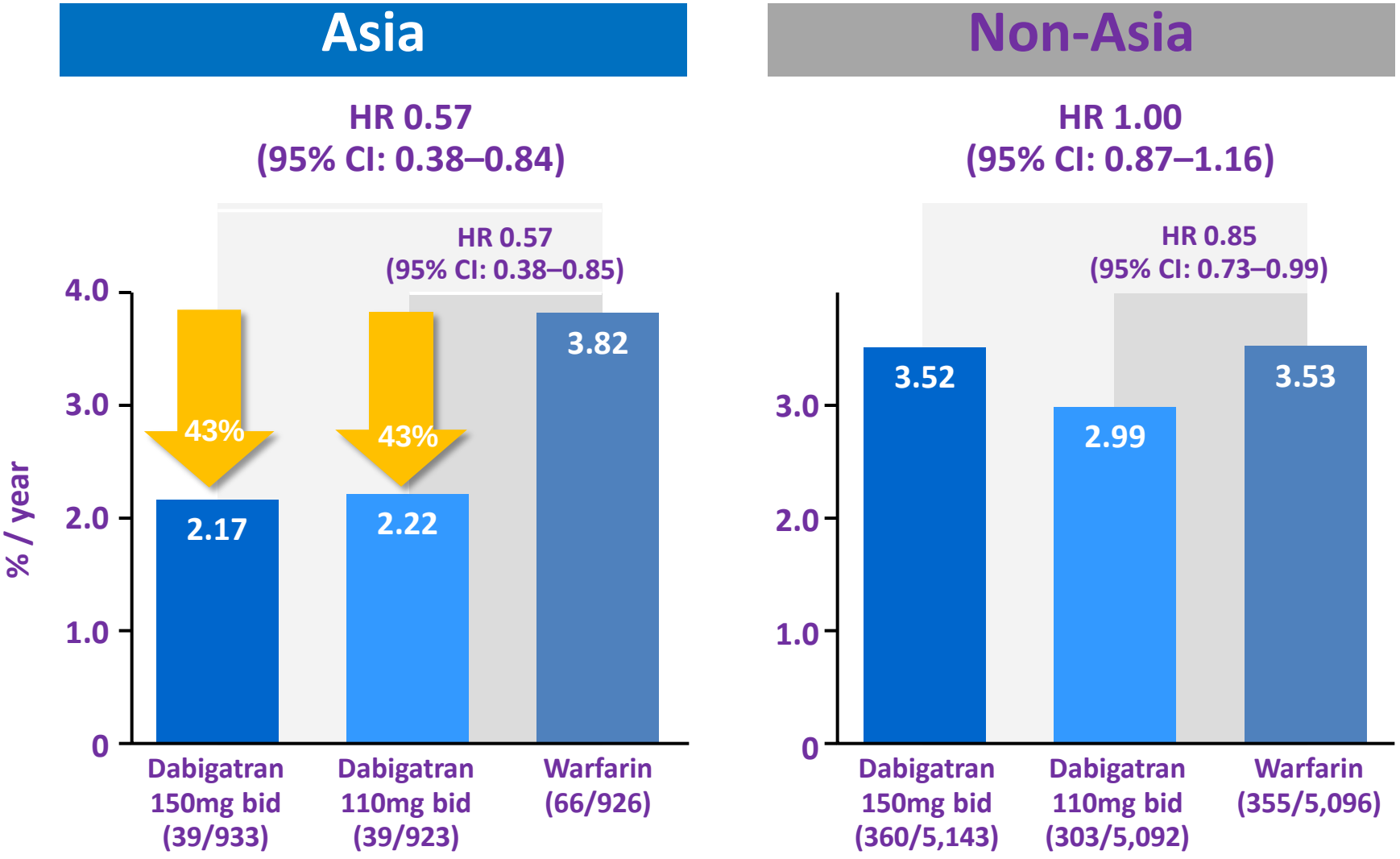
Life Threatening Bleeding



Stroke. 2013;44:1891-1896

Analysis in Asian Populations in RE-LY Trial

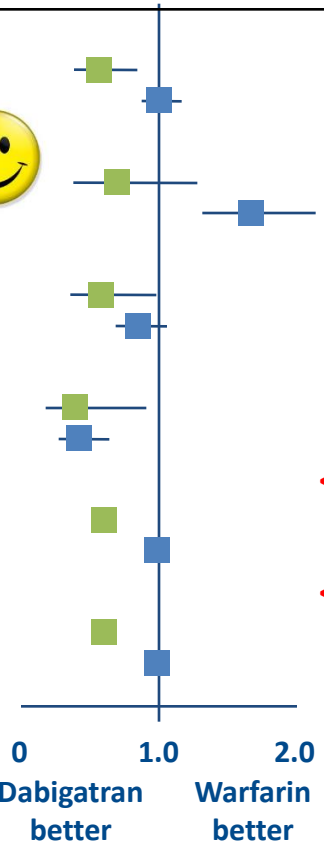
Major Bleeding

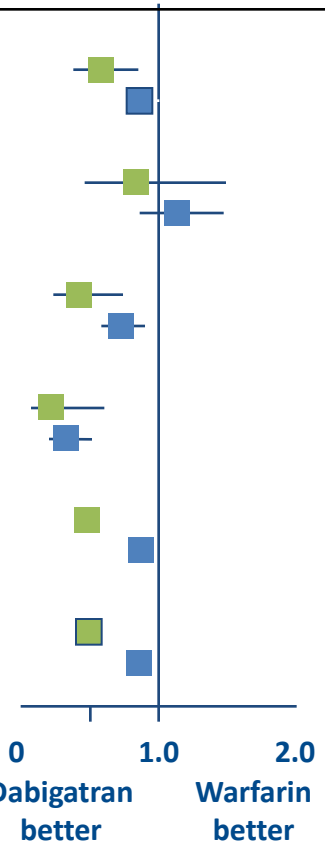


Stroke. 2013;44:1891-1896

Safety outcomes (Asia vs. non-Asia)

	Rate (%/year)			Dabigatran 150mg bid vs. Warfarin		Dabigatran 110mg bid vs. Warfarin	
	Dabigatran		Warfarin				
	150mg bid	110mg bid		HR (95%CI)	Interaction p value	HR (95%CI)	Interaction p value
Major bleeding					0.0079		0.0705
Asia	2.17	2.22	3.82				
Non-Asia	3.52	2.99	3.53				
GI major bleeding					0.0089		0.3379
Asia	0.96	1.15	1.41				
Non-Asia	1.69	1.14	1.01				
Life threatening bleeding					0.1749		0.0738
Asia	1.28	0.91	2.20				
Non-Asia	1.52	1.29	1.79				
Intracranial bleeding					0.9509		0.4561
Asia	0.45	0.23	1.10				
Non-Asia	0.29	0.23	0.71				
Minor bleeding					<0.0001		<0.0001
Asia	12.43	10.12	19.66				
Non-Asia	15.27	13.69	15.81				
Major or minor bleeding					<0.0001		<0.0001
Asia	13.99	11.72	22.03				
Non-Asia	17.02	15.27	17.74				





Asia: n=2,782; Non-Asia: n=15,331

Hori M, et al. *Stroke. 2013;44:1891-1896*

Primary Endpoint of Stroke or Systemic Embolism: Non-inferiority Analysis

		Non Inferiorirty p vs warfarin
RE-LY		ITT Analysis
Dabigatran 110 mg	1.53% per year	p<0.001
Dabigatran 150 mg	1.11% per year	p<0.001
Warfarin	1.69% per year	
Rocket AF		Per Protocol Analysis
Rivaroxaban 20mg	2.12% per year	p<0.001
Warfarin	2.42% per year	

No ITT analysis is available for non-inferiority in Rocket AF. An on treatment or per-protocol analysis is generally performed in the assessment of non-inferiority. If numerous patients come off of study drug, this biases the trial towards a non-inferior result in an ITT analysis. This is the basis for performing a per-protocol analysis in a non-inferiority assessment.

Rocket AF Investigators, AHA 2010; Connolly SJ, et al. N Engl J Med. 2009;361:1139-1151

Primary Endpoint of Stroke or Systemic Embolism: Superiority Analysis

		Superiority p vs warfarin ITT Analysis
RE-LY		
Dabigatran 110 mg	1.53% per year	p=0.34
Dabigatran 150 mg	1.11% per year	p<0.001
Warfarin	1.69% per year	
Rocket AF		
Rivaroxaban 20mg	2.12% per year	p=0.117*
Warfarin	2.42% per year	

*In an on treatment analysis in Rocket AF Stoke or SE rates were 1.70% / yr for rivaroxaban and 2.15% / yr for warfarin, p=0.015. No on treatment analysis is available from RE-LY.

Rocket AF Investigators, AHA 2010; Connolly SJ, et al. N Engl J Med. 2009;361:1139-1151

Ischemic Stroke

RELY		HR		ITT P-value
Dabigatran 110 mg	1.34% / yr	1.20		0.35
Dabigatran 150 mg	0.92% / yr	0.76		0.03
Warfarin	1.20% / yr			

Rocket AF			
Rivaroxaban 20 mg	1.62% / yr	0.99	0.92*
Warfarin	1.64% / yr		

*In an on treatment analysis in Rocket AF Ischemic Stoke rates were 1.34% / yr for rivaroxaban and 1.42% / yr for warfarin, p=0.58. No on treatment analysis is available from RE-LY.

Rocket AF Investigators, AHA 2010; Connolly SJ, et al. *N Engl J Med*. 2009;361:1139-1151

Hemorrhagic Stroke

RELY		HR	ITT P-value
Dabigatran 110 mg	0.12% / yr	0.31	<0.001
Dabigatran 150 mg	0.10% / yr	0.26	<0.001
Warfarin	0.38% / yr		

Rocket AF			
Rivaroxaban 20 mg	0.26% / yr	0.59	0.012*
Warfarin	0.44% / yr		

*In an on treatment analysis in Rocket AF Hemorrhagic Stoke rates were 0.26% / yr for rivaroxaban and 0.44% / yr for warfarin, p=0.024. No on treatment analysis is available from RE-LY.

Rocket AF Investigators, AHA 2010; Connolly SJ, et al. *N Engl J Med*. 2009;361:1139-1151

Major Bleeding

RE-LY		HR		ITT P-value
Dabigatran 110 mg	2.71% / yr	0.8		0.003
Dabigatran 150 mg	3.11% / yr	0.93		0.31
Warfarin	3.36			

150 mg Dabigatran vs 110 mg Dabigatran = HR of 1.16 (1.00–1.34) p = 0.052

Rocket AF			On Treatment P-value
Rivaroxaban 20 mg	3.60% / yr	0.92	0.58*
Warfarin	3.45% / yr		

*There is no ITT analysis of safety in Rocket AF. There is no on treatment analysis of safety from RE-LY.

Rocket AF Investigators, AHA 2010; Connolly SJ, et al. *N Engl J Med*. 2009;361:1139-1151

Conclusions: RE-LY vs Rocket AF Regarding Stroke

Dabigatran 150 mg reduced the risk of hemorrhagic stroke (HR 0.26, $p<0.001$) as did rivaroxaban (HR 0.59, $p=0.024$).

Both drugs were therefore safer.

Dabigatran 150 mg also reduced the risk of ischemic stroke (HR=0.76, $p=0.03$) while rivaroxaban did not ($p=0.58$) (dabigatran was associated with thrombotic efficacy)

Rocket AF Investigators, AHA 2010; Connolly SJ, et al. N Engl J Med. 2009;361:1139-1151

ROCKET AF

Primary Efficacy Endpoint: East Asia Cohort versus the Overall Population

Analysis method	Rivaroxaban		Warfarin		Rivaroxaban vs warfarin			
	n/N	%/year	n/N	%/year	HR	(95% CI)	*p*-value (a)	*p*-value (b)
ROCKET AF overall[1]	269/ 7081	2.1	306/ 7090	2.4	0.88	(0.75, 1.03)	<0.001	0.12
ROCKET AF East Asia cohort	21/468	2.6	27/464	3.4	0.78	(0.44, 1.39)	0.016	0.401

Based on ITT population until site notification
p-value (a) non-inferiority
p-value (b) superiority

The efficacy of Rivaroxaban is no better than warfarin in Asia groups.

L.TW.GM.03.2012.0084

1. Patel *et al*, 2011

ROCKET AF

Principal Safety Outcome Analysis: ROCKET AF East Asia Cohort

	Rivaroxaban (N=466)		Warfarin (N=462)		Rivaroxaban vs warfarin		
	n/%	Event rate (%/year)	n/%	Event rate (%/year)	HR	(95% CI)	*p*-value
Major bleeding	23 (4.9)	3.44	35 (7.6)	5.14	0.67	(0.39, 1.13)	0.132
≥2 g/dl Hb drop	20 (4.3)	2.99	20 (4.3)	2.93	1.02	0.55, 1.89)	0.954
Transfusion (≥2 units)	8 (1.7)	1.18	15 (3.3)	2.19	0.54	(0.23, 1.28)	0.161
Critical organ bleeding	5 (1.1)	0.73	18 (3.9)	2.61	0.28	(0.10, 0.75)	0.012*
Bleeding causing death	1 (0.2)	0.15	7 (1.5)	1.01	0.14	(0.02, 1.16)	0.069
Intracranial haemorrhage	4 (0.9)	0.59	17 (3.7)	2.46	0.24	(0.08, 0.71)	0.010*
Non-major clinically relevant bleeding	103 (22.1)	17.43	93 (20.1)	15.50	1.12	(0.85, 1.49)	0.411

Rivaroxaban doesn't reduce major bleeding in Asia groups.

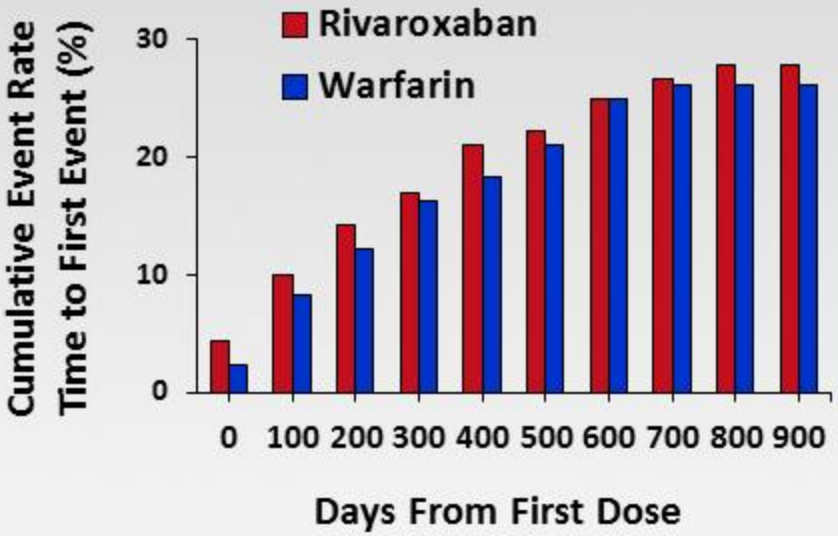
L.TW.GM.03.2012.0084

Rivaroxaban vs Warfarin in Japanese Patients With AF

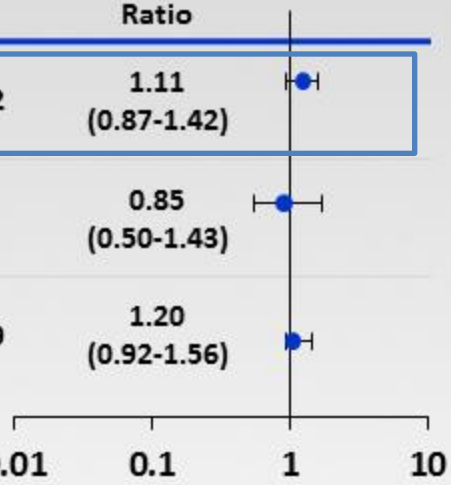
J-ROCKET AF Study*

Hazard ratio (95% CI): 1.11 (0.78-1.42)

P for noninferiority < .001 (one-sided)



Outcome	Rivaroxaban (n=639) Event Rate (5/year)	Warfarin (n=639) Event Rate (5/year)	Hazard Ratio
Major or CRNM bleeding	18.04	16.42	1.11 (0.87-1.42)
Major bleeding	3.00	3.59	0.85 (0.50-1.43)
CRNM bleeding	15.42	12.99	1.20 (0.92-1.56)



Rivaroxaban is no better than warfarin.

J-ROCKET AF = Japanese Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; CRNM = clinically relevant nonmajor

Arrhythmia & EP

Hori M, et al. *Circ J.* 2012;76(9):2104-2111.

theheart.org from WebMD

Medscape EDUCATION

Summary

	Dabigatran 150mg	Dabigatran 110mg	Rivaroxaban 15/20 mg
Total population			
All stroke and systemic embolism	Superior	Non-inferior	Non-inferior
Ischemic stroke	Superior	Non-inferior	Non-inferior
Major bleeding	Non-inferior	Superior	Non-inferior
Total bleeding	Superior	Superior	Non-inferior
Asian			
All stroke and systemic embolism	Superior	Non-inferior	Non-inferior
Ischemic stroke	Superior	Non-inferior	Non-inferior
Major bleeding	Superior	Superior	Non-inferior
Total bleeding	Superior	Superior	Non-inferior

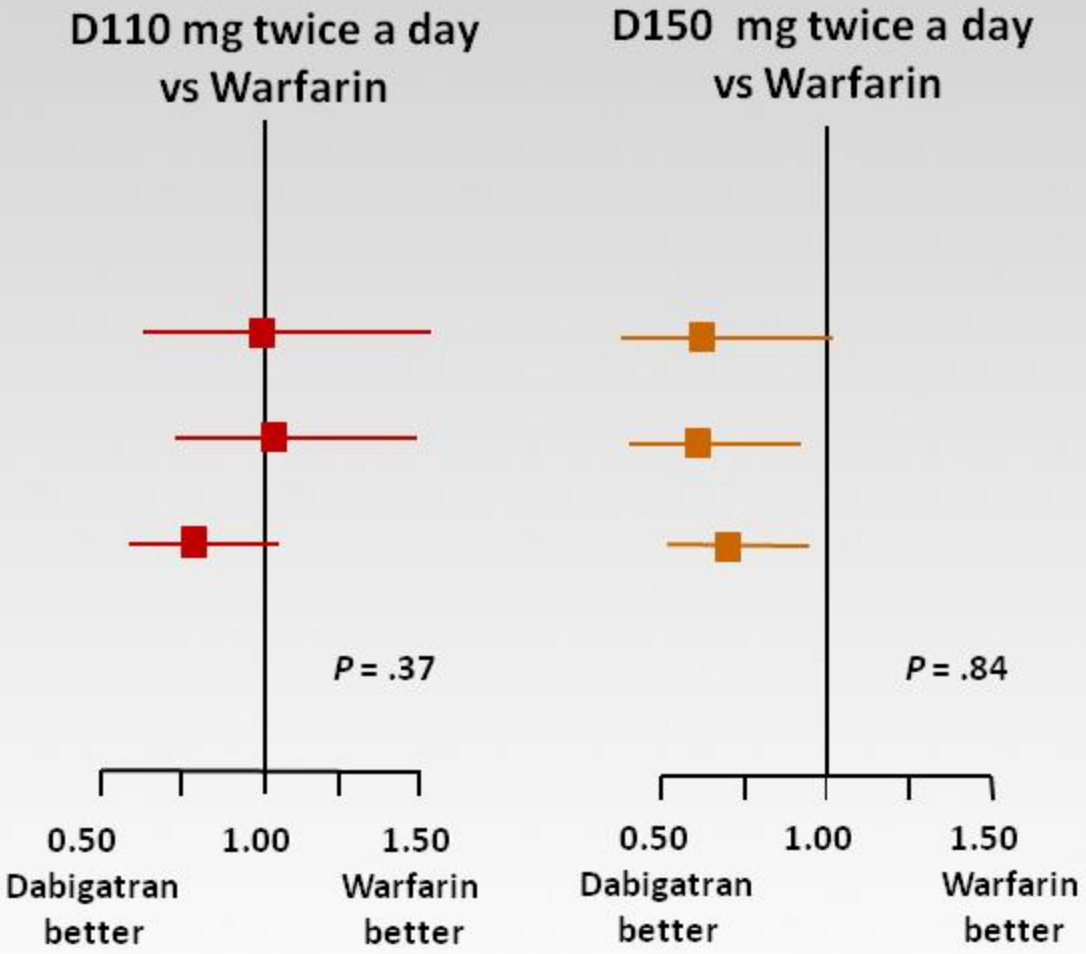
Rocket AF was a Higher Risk Patient Population

- Low risk CHADS 0-1: 32.4% in RE-LY; none in Rocket AF
- High risk CHADS 3 or more: just over 32% in RE-LY; over 85% in Rocket AF
- Age: about 71.5 yrs old in RE-LY, 73 yrs old in Rocket AF
- Prior stroke TIA embolism: about 20% in RE-LY, 55% in Rocket AF
- Warfarin naïve: about half in RE-LY, 37.5% in Rocket AF

Rocket AF Investigators, AHA 2010; Connolly SJ, et al. N Engl J Med. 2009;361:1139-1151

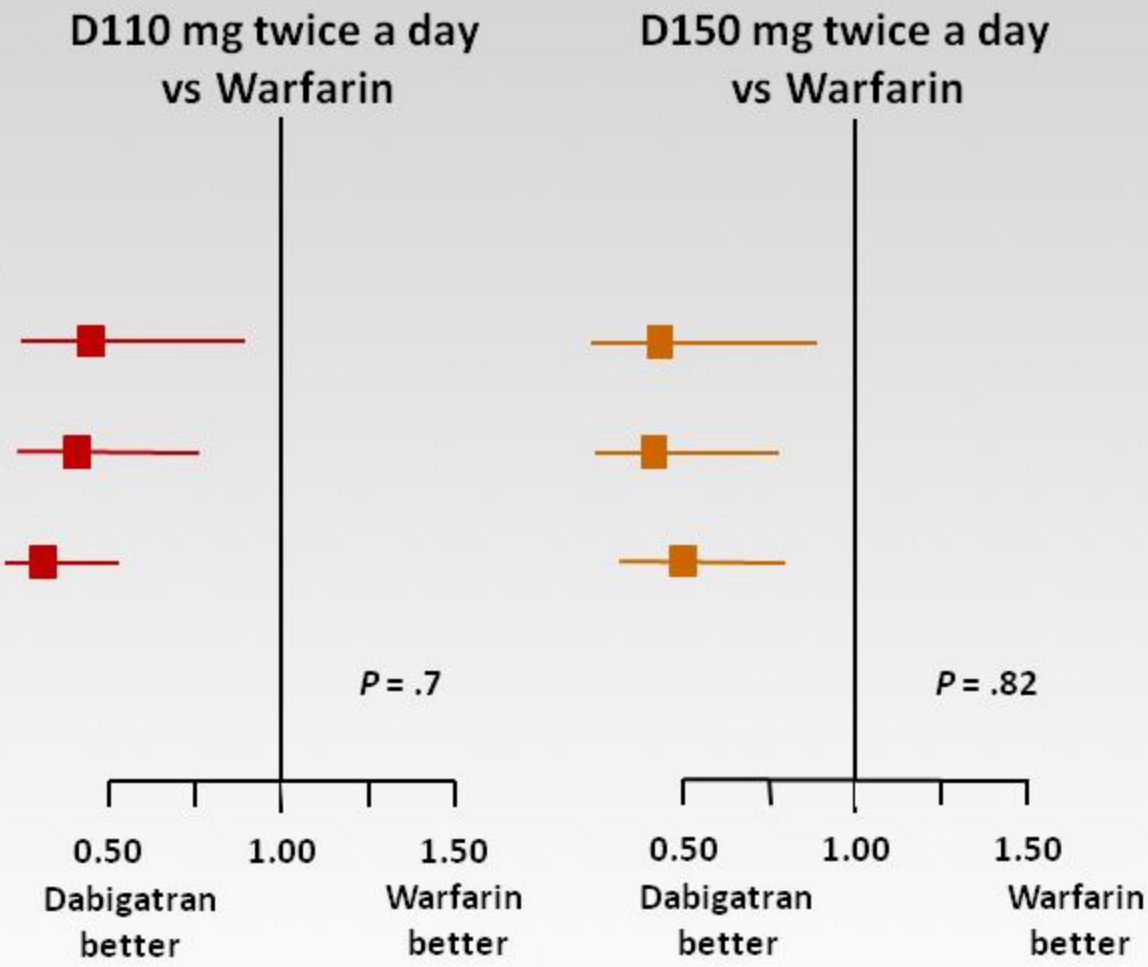
$CHADS_2$ and Stroke and Systemic Embolism

	Annual rate, %		
$CHADS_2$	D110	D150	WARFARIN
0-1	1.06	0.65	1.08
2	1.45	0.84	1.38
3-6	2.12	1.88	2.73



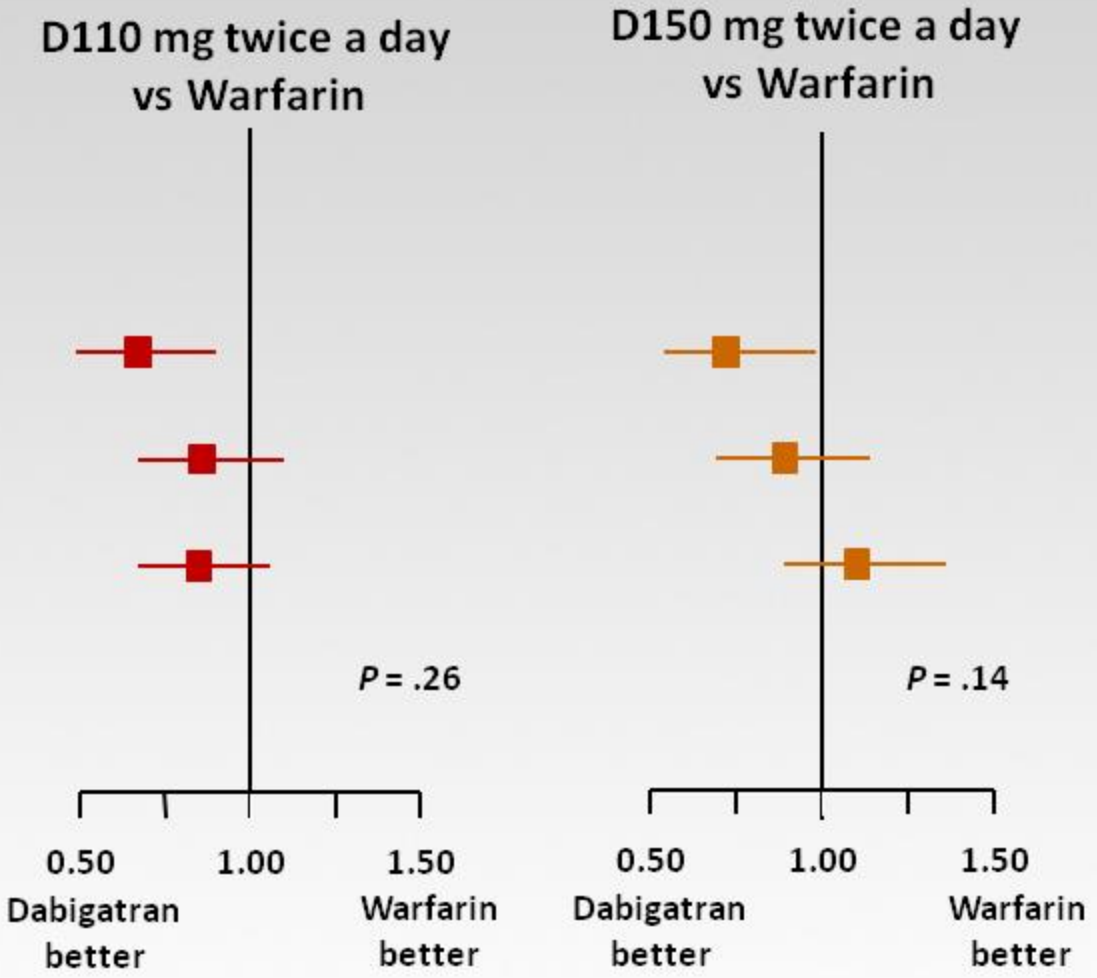
$CHADS_2$ and Intracranial Bleeding

	Annual rate, %		
$CHADS_2$	D110	D150	WARFARIN
0-1	0.20	0.20	0.54
2	0.22	0.26	0.69
3-6	0.26	0.52	1.07

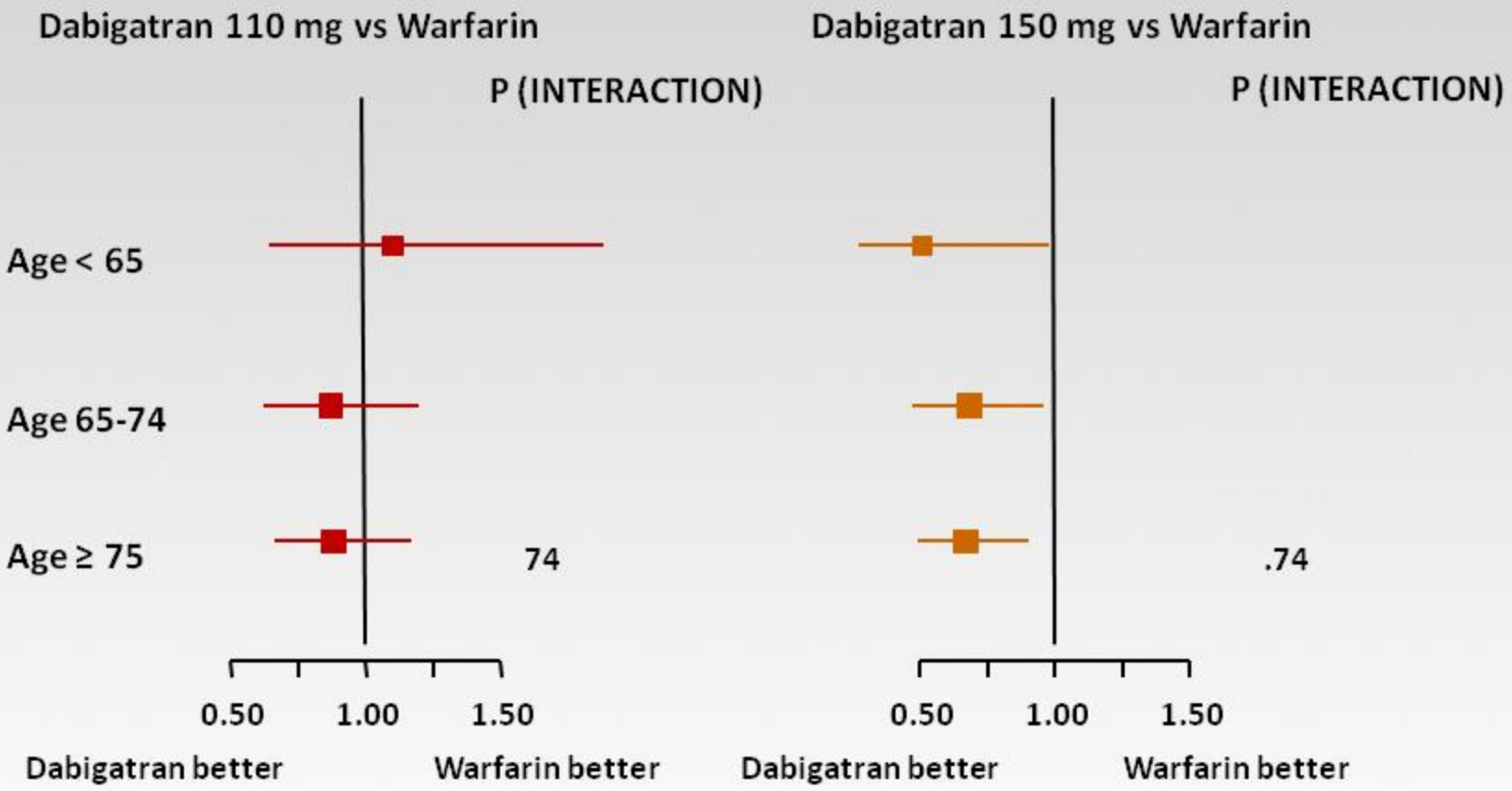


$CHADS_2$ and Major Bleeding

$CHADS_2$	Annual rate, % D110	D150	WARFARIN
0-1	1.86	2.11	2.84
2	2.98	3.03	3.3
3-6	3.8	4.85	4.6

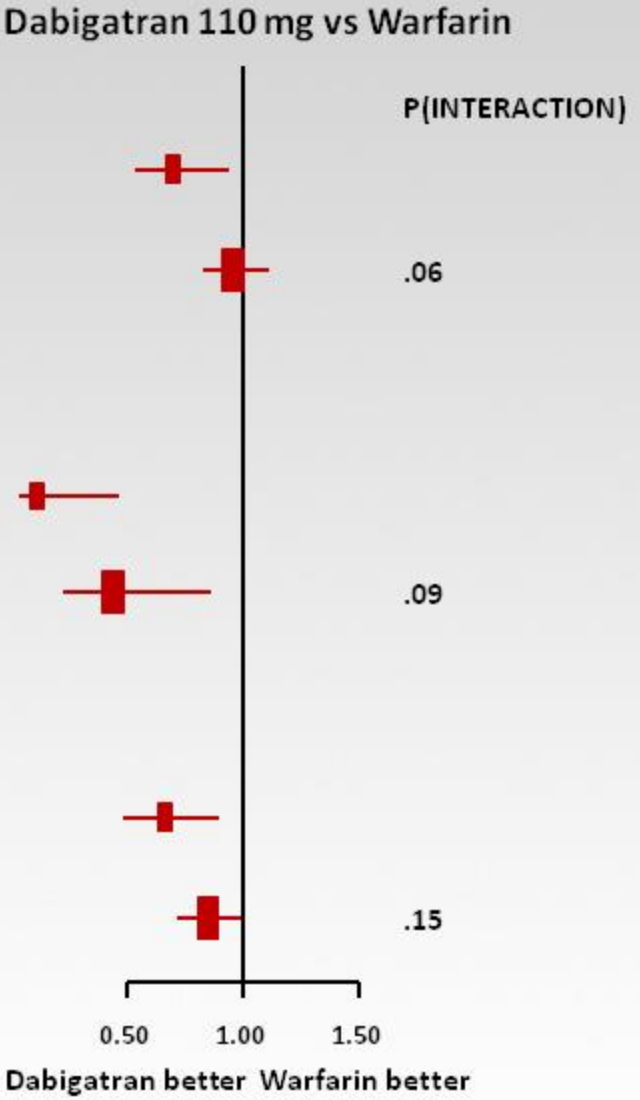


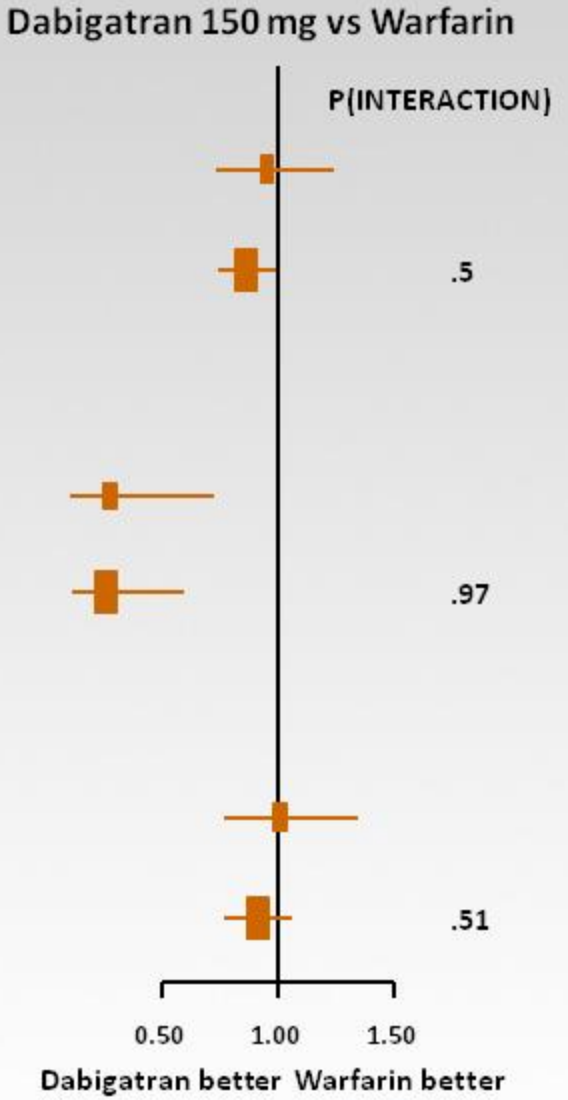
Age and Stroke and Non-Central Nervous System Embolism



Prior Stroke Subgroup Analysis

	Rate (% per year) D110	D150	WAR	P(INTERACTION)
All death				
Prior stroke/TIA	3.24	4.39	4.58	
No prior stroke/TIA	3.87	3.45	4.02	.06
Hemorrhagic stroke				
Prior stroke/TIA	0.08	0.2	0.77	
No prior stroke/TIA	0.13	0.07	0.29	.09
Major bleeding				
Prior stroke/TIA	2.74	4.14	4.15	
No prior stroke/TIA	2.91	3.1	3.42	.15





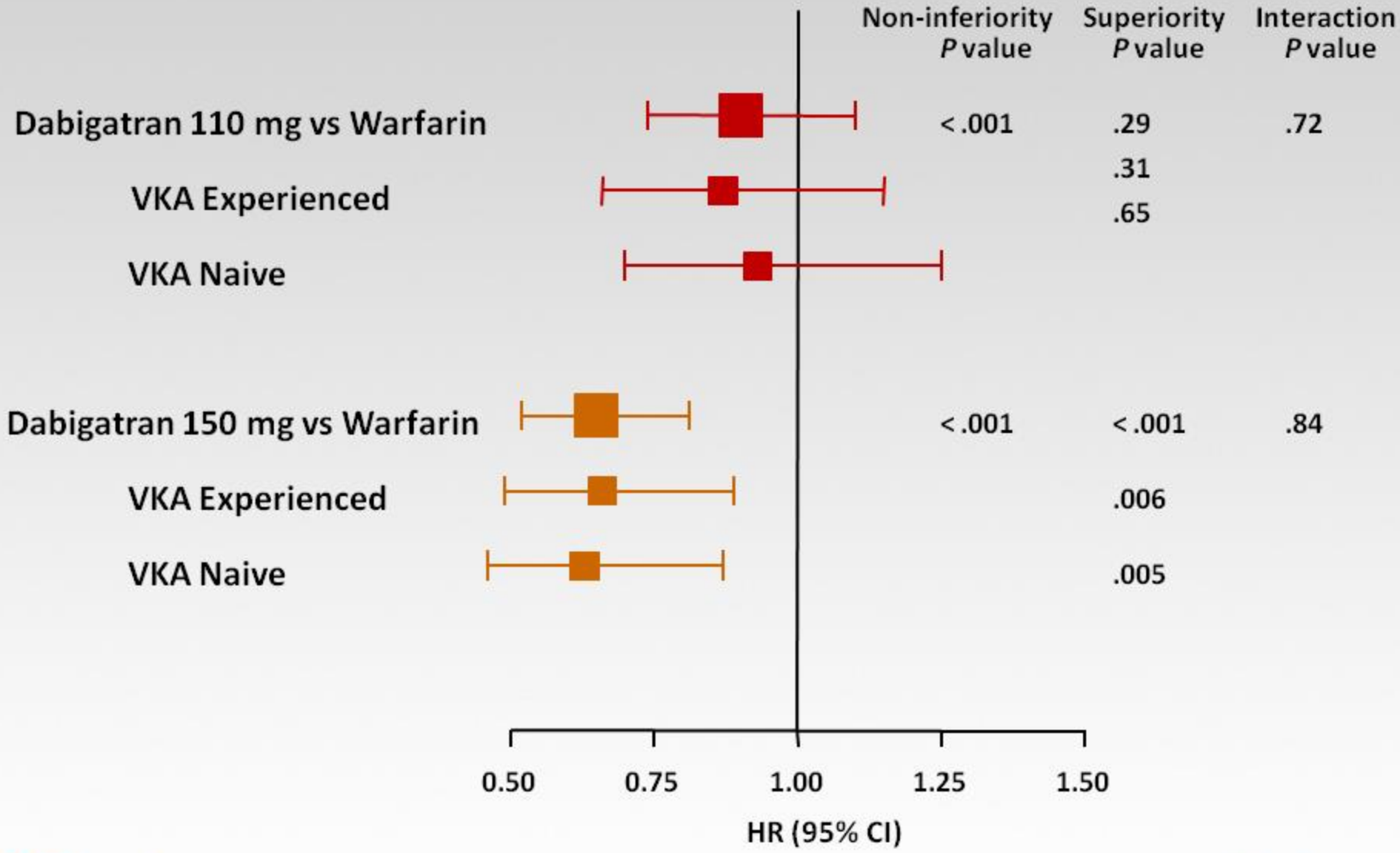
Thrombosis

Diener HC, et al. ASA International Stroke Conference 2010.

theheart.org from WebMD

Medscape EDUCATION

Primary Outcome: Warfarin Naive



Outline

- NOACs vs. Warfarin: NOACs better
- Dabigatran vs. Rivaroxaban: DABI better
- Dabigatran vs. Apixaban
- Dabigatran vs. Edoxaban
- Review of specific conditions
- Conclusion

Baseline Characteristics in 3 Trials

Characteristic	RE-LY	ROCKET-AF	ARISTOTLE
Number of patients	18,113	14,264	18,201
Lost to follow-up (n)	20	32	69
Median Follow-up (years)	2	1.9	1.8
$CHADS_2$ score (mean)	2.1	3.5	2.1
0 or 1	31.9%	0	33.9%
2	35.6%	13.0%	35.8%
3-6	32.5%	86.9%	30.2%
Age (years)	71 (mean)	73 (median)	70 (median)
Female sex (%)	36	40	35
Previous stroke or TIA (%)	20	55	19
Aspirin use (%)	40	37	31
Mean TTR for warfarin (%)	64	55	62
Creatinine clearance			
≤30 ml/min	0	0	1.5%
30–50 ml/min	19.4%	20.7%	18.1%
>50 ml/min	80.6%	79.6%	82.9%

http://www.slideshare.net/satanicala/novel-oral-anticoagulants-for-stroke-prevention-in-patients-with-atrial-fibrillation

Key Findingsin 3 Trials

Outcome	Dabigatran 110 mg vs. warfarin RR (95% CI)	Dabigatran 150 mg vs. warfarin RR (95% CI)	Rivaroxaban vs. warfarin HR (95% CI)	Apixaban vs. warfarin HR (95% CI)
Stroke or systemic embolism	0.90 (0.74–1.10)	0.65 (0.52–0.81) ↓	PPOT 0.79 (0.66-0.96) ↓ ITT 0.88 (0.75-1.03) ↔	0.79 (0.66–0.95) ↓
Ischemic stroke	1.11 (0.88–1.39)	0.76 (0.59–0.97) ↓	NA	0.92 (0.74–1.13)
Hemorrhagic stroke	0.31 (0.17–0.56) ↓	0.26 (0.14–0.49) ↓	0.59 (0.37–0.93) ↓	0.51 (0.35–0.75) ↓
Major bleeding	0.80 (0.70–0.93) ↓	0.93 (0.81–1.07)	1.04 (0.90–1.20)	0.69 (0.60–0.80) ↓
Intracranial hemorrhage	0.30 (0.19–0.45) ↓	0.41 (0.28–0.60) ↓	0.67 (0.47–0.93) ↓	0.42 (0.30–0.58) ↓
All-cause mortality	0.91 (0.80–1.03)	0.88 (0.77–1.00)	0.92 (0.82–1.03)	0.89 (0.80–0.99) ↓
Myocardial infarction	1.29 (0.96–1.75)	1.27 (0.94–1.71)	0.81 (0.63–1.06)	0.88 (0.66–1.17)
Gastrointestinal bleeding	1.08 (0.85–1.38)	1.48 (1.18–1.85) ↑	NA	0.89 (0.70–1.15)

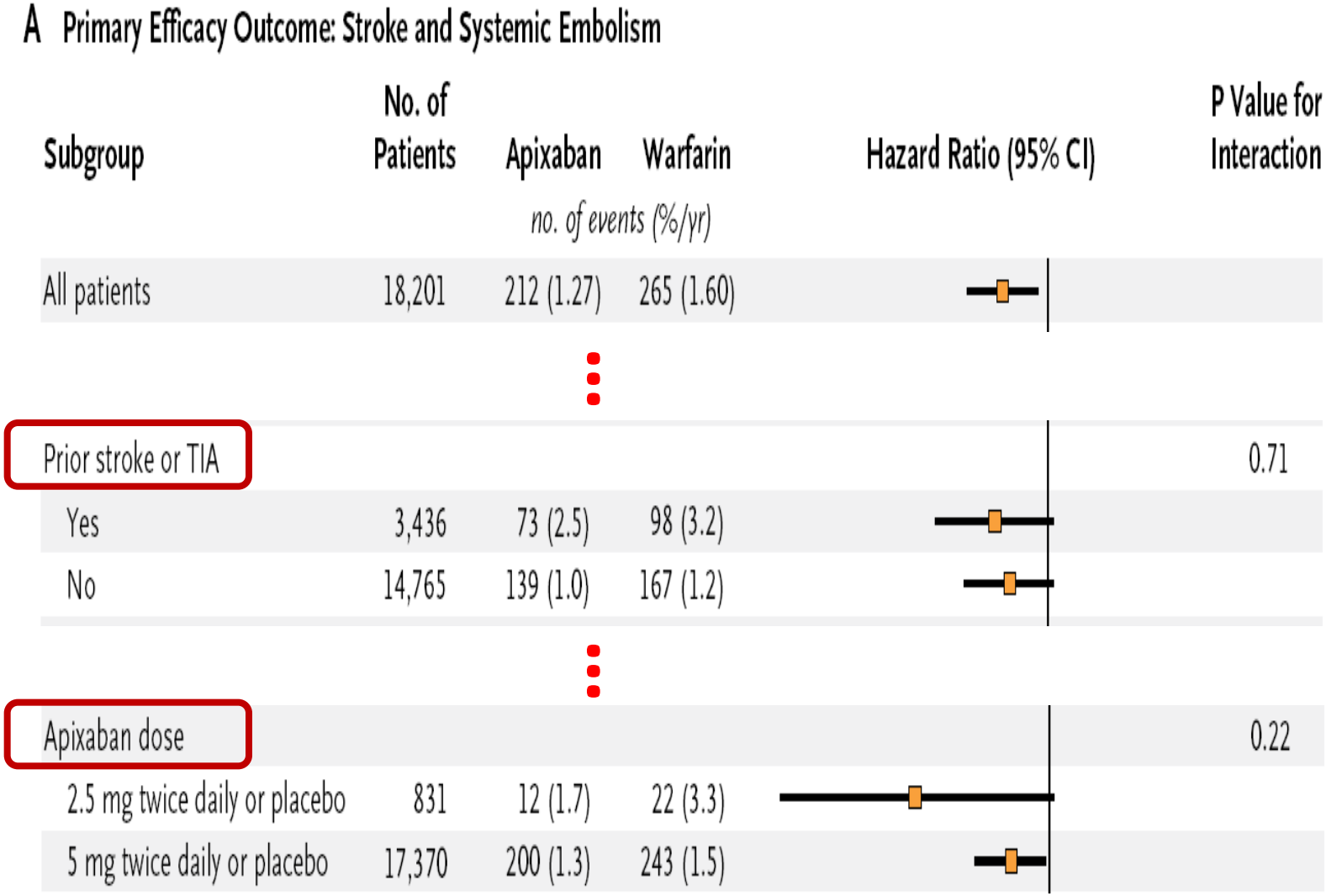
http://www.slideshare.net/satanicala/novel-oral-anticoagulants-for-stroke-prevention-in-patients-with-atrial-fibrillation

ARISTOTLE – not Significant in Ischemic Stroke

Table 2. Efficacy Outcomes.*

Outcome	Apixaban Group (N=9120)		Warfarin Group (N=9081)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate	Patients with Event	Event Rate		
	no.	*%/yr*	*no.*	*%/yr*		
Primary outcome: stroke or systemic embolism	212	1.27	265	1.60	0.79 (0.66–0.95)	0.01
Stroke	199	1.19	250	1.51	0.79 (0.65–0.95)	0.01
Ischemic or uncertain type of stroke	162	0.97	175	1.05	0.92 (0.74–1.13)	0.42
Hemorrhagic stroke	40	0.24	78	0.47	0.51 (0.35–0.75)	<0.001
Systemic embolism	15	0.09	17	0.10	0.87 (0.44–1.75)	0.70
Key secondary efficacy outcome: death from any cause	603	3.52	669	3.94	0.89 (0.80–0.998)	0.047
Other secondary outcomes						
Stroke, systemic embolism, or death from any cause	752	4.49	837	5.04	0.89 (0.81–0.98)	0.02
Myocardial infarction	90	0.53	102	0.61	0.88 (0.66–1.17)	0.37
Stroke, systemic embolism, myocardial infarction, or death from any cause	810	4.85	906	5.49	0.88 (0.80–0.97)	0.01
Pulmonary embolism or deep-vein thrombosis	7	0.04	9	0.05	0.78 (0.29–2.10)	0.63

ARISTOTLE – Major Prespecified Groups



N Engl J Med 2011;365:981-92.

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Efficacy and Safety of the Novel Oral Anticoagulants in Atrial Fibrillation : A Systematic Review and Meta-Analysis of the Literature

Circulation 2012 Nov 13;126(20):2381

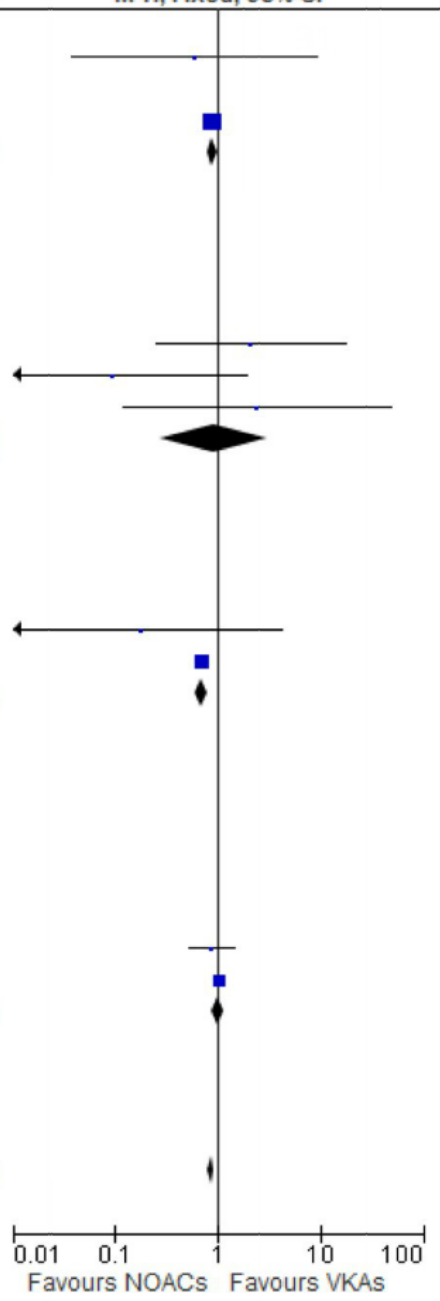
Background	• NOACs were at least noninferior to vitamin K antagonists, but a clear superiority in overall and vascular mortality was not consistently proven
Methods	• **Meta-analysis of phase II and phase III RCT** comparing NOACs (non-VKA oral anticoagulants) with warfarin in patients with atrial fibrillation • NOACs: **apixaban, dabigatran, edoxaban, rivaroxaban**
Results	• 12 RCT enrolling a total of 54875 patients 3 involved dabigatran 4 involved rivaroxaban 2 involved apixaban 3 involved edoxaban

Subgroup analysis of major bleeding

Apixaban and dabigatran reduced major bleeding events

Whereas neither rivaroxaban nor edoxaban reduced bleeding

Study or Subgroup	NOACs Events	NOACs Total	VKAs Events	VKAs Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.6.1 Dabigatran						
NCT01136408 (D)	1	104	1	62	0.1%	0.60 [0.04, 9.36]
PETRO	0	166	0	70		Not estimable
RE-LY	741	12091	421	6022	38.8%	0.88 [0.78, 0.98]
Subtotal (95% CI)		**12361**		**6154**	**38.9%**	**0.88 [0.78, 0.98]**
Total events	742		422			
Heterogeneity: Chi² = 0.08, df = 1 (P = 0.78); I² = 0%						
Test for overall effect: Z = 2.25 (P = 0.02)						
1.6.2 Edoxaban						
WEITZ	6	713	1	250	0.1%	2.10 [0.25, 17.39]
CHUNG	0	159	2	75	0.2%	0.10 [0.00, 1.95]
YAMASHITA	2	260	0	125	0.0%	2.41 [0.12, 49.90]
Subtotal (95% CI)		**1132**		**450**	**0.4%**	**0.91 [0.27, 3.04]**
Total events	8		3			
Heterogeneity: Chi² = 3.15, df = 2 (P = 0.21); I² = 36%						
Test for overall effect: Z = 0.15 (P = 0.88)						
1.6.3 Apixaban						
ARISTOTLE-J	0	143	1	75	0.1%	0.18 [0.01, 4.27]
ARISTOTLE	327	9088	462	9052	31.9%	0.70 [0.61, 0.81]
Subtotal (95% CI)		**9231**		**9127**	**32.1%**	**0.70 [0.61, 0.81]**
Total events	327		463			
Heterogeneity: Chi² = 0.73, df = 1 (P = 0.39); I² = 0%						
Test for overall effect: Z = 4.99 (P < 0.00001)						
1.6.4 Rivaroxaban						
NCT00973245 (R1)	0	75	0	27		Not estimable
NCT00973323 (R2)	0	50	0	26		Not estimable
J-ROCKET-AF	26	639	30	639	2.1%	0.87 [0.52, 1.45]
ROCKET-AF	395	7111	386	7125	26.6%	1.03 [0.89, 1.18]
Subtotal (95% CI)		**7875**		**7817**	**28.7%**	**1.01 [0.89, 1.16]**
Total events	421		416			
Heterogeneity: Chi² = 0.38, df = 1 (P = 0.54); I² = 0%						
Test for overall effect: Z = 0.20 (P = 0.84)						
Total (95% CI)		**30599**		**23548**	**100.0%**	**0.86 [0.80, 0.93]**
Total events	1498		1304			
Heterogeneity: Chi² = 18.58, df = 8 (P = 0.02); I² = 57%						
Test for overall effect: Z = 4.03 (P < 0.0001)						
Test for subgroup differences: Chi² = 14.27, df = 3 (P = 0.003), I² = 79.0%						



Circulation 2012 Nov 13;126(20):238:

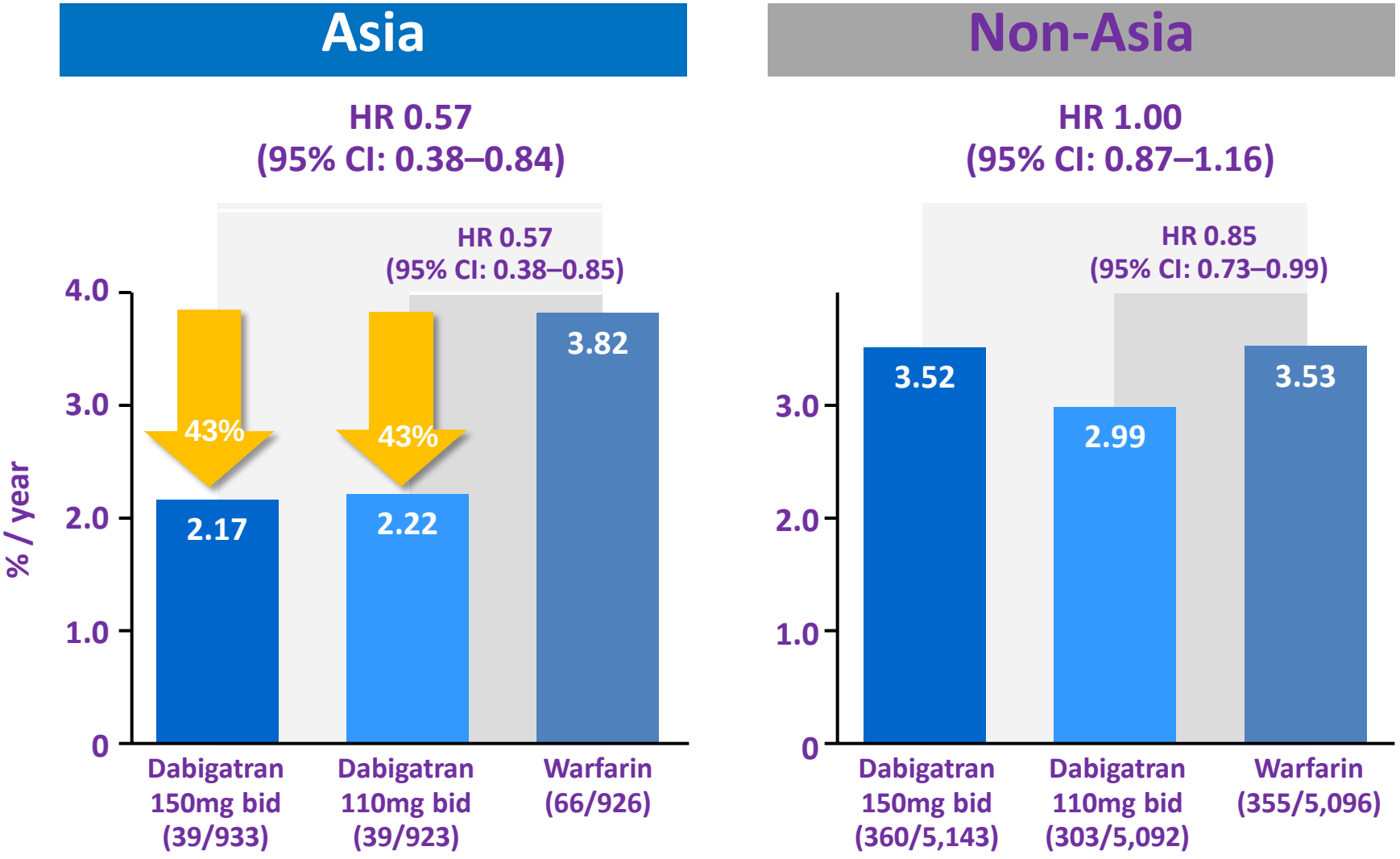
Total (1/2)	Dabigatran 150	Dabigatran 110	Rivaroxaban	Apixaban	Edoxaban 60	Edoxaban 30
Stroke or SE	1	2	2	1	1	2
Ischemic stroke	1	2	(2)	2	2	3
Hemorrhagic stroke	1	1	1	1	1	1
Intracranial hemorrhage	1	1	1	1	(1)	(1)
Major bleeding	1*	1	2	1	1	1
Myocardial infarction	2	2	2	2	2	2
All-cause mortality	2	2	2	1	2	1
Total	9	11	12	9	10	13

Total (2/2)	DABI 150	DABI 110	RIVA 20	APIX 5	APIX 2.5	EDOX 60	EDOX 30
Stroke or SE	1	2	2	1	2	1	2
Ischemic stroke	1	2	(2)	2	(2)	2	3
Hemorrhagic stroke	1	1	1	1	(1)	1	1
Intracranial hemorrhage	1	1	1	1	(1)	(1)	(1)
Major bleeding	1*	1	2	1	(1)	1	1
Myocardial infarction	2	2	2	2	(2)	2	2
All-cause mortality	2	2	2	1	(2)	2	1
Total	9	11	12	9	11	10	13

APIX 2.5 BID:
831 pts only

Analysis in Asian Populations in RE-LY Trial

Major Bleeding



Stroke. 2013;44:1891-1896

Efficacy and Safety of Apixaban Compared with Warfarin for Stroke Prevention in Atrial Fibrillation in East Asia with Atrial Fibrillation

S. Goto1, J. Zhu2, L. Lisheng2, BH. Oh3, D. Wojdyla4, M. Hanna5, J. Horowitz6, L. Wallentin7, D. Xavier8, JH. Alexander4

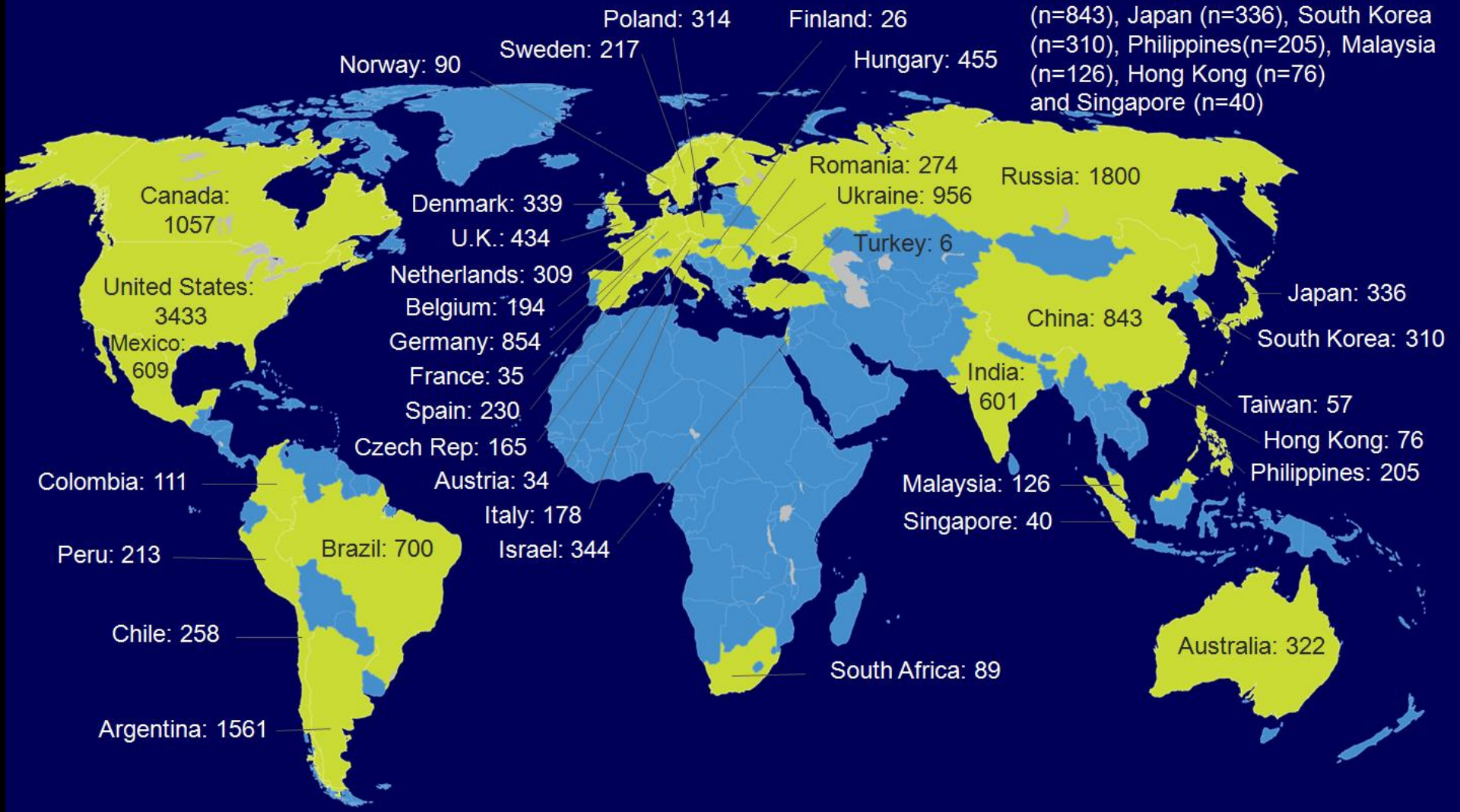
(1) Tokai University School of Medicine, Isehara, Japan (2) Fuwai Hospital, Beijing, China, People's Republic of (3) Seoul National University Hospital, Seoul, Korea, Republic of (4) Duke Clinical Research Institute, Duke University Medical Center, Durham, United States of America (5) Bristol-Myers Squibb, Princeton, United States of America (6) University of Adelaide, Adelaide, Australia (7) Uppsala University, UCR-Uppsala Clinical Research Center, Uppsala, Sweden (8) St. John's Research Institute, Bangolore, India

Global Collaboration

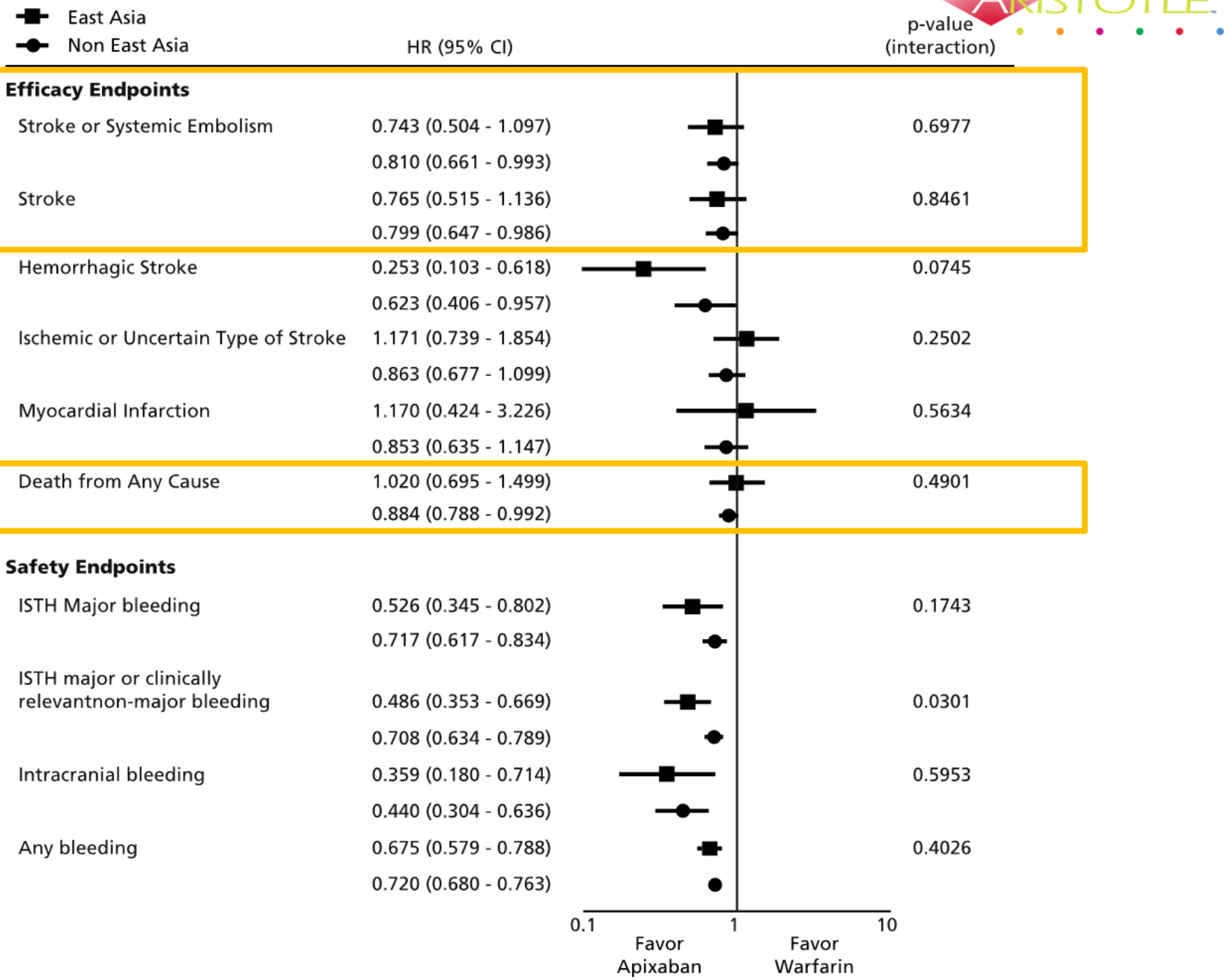
39 countries, 1034 sites, 18,201 patients

ARISTOTLE

1,993 patients were recruited from East Asian countries including China (n=843), Japan (n=336), South Korea (n=310), Philippines(n=205), Malaysia (n=126), Hong Kong (n=76) and Singapore (n=40)



Bristol-Myers Squibb and Pfizer


East Asia
Non East Asia
HR (95% CI)
p-value (interaction)
Efficacy Endpoints
Stroke or Systemic Embolism
0.743 (0.504 - 1.097)
0.6977
0.810 (0.661 - 0.993)
Stroke
0.765 (0.515 - 1.136)
0.8461
0.799 (0.647 - 0.986)
Hemorrhagic Stroke
0.253 (0.103 - 0.618)
0.0745
0.623 (0.406 - 0.957)
Ischemic or Uncertain Type of Stroke
1.171 (0.739 - 1.854)
0.2502
0.863 (0.677 - 1.099)
Myocardial Infarction
1.170 (0.424 - 3.226)
0.5634
0.853 (0.635 - 1.147)
Death from Any Cause
1.020 (0.695 - 1.499)
0.4901
0.884 (0.788 - 0.992)
Safety Endpoints
ISTH Major bleeding
0.526 (0.345 - 0.802)
0.1743
0.717 (0.617 - 0.834)
ISTH major or clinically relevantnon-major bleeding
0.486 (0.353 - 0.669)
0.0301
0.708 (0.634 - 0.789)
Intracranial bleeding
0.359 (0.180 - 0.714)
0.5953
0.440 (0.304 - 0.636)
Any bleeding
0.675 (0.579 - 0.788)
0.4026
0.720 (0.680 - 0.763)
0.1
1
10
Favor Apixaban
Favor Warfarin

Asia (1/2)	Dabigatran 150	Dabigatran 110	Rivaroxaban	Apixaban	Edoxaban 60	Edoxaban 30
Stroke or SE	1	2	2	2	2	2
Ischemic stroke	1	2	(2)	2	NA	NA
Hemorrhagic stroke	1	1	(1)	1	NA	NA
Intracranial hemorrhage	1	1	1	1	NA	NA
Major bleeding	1	1	2	1	NA	NA
Myocardial infarction	2	2	(2)	2	NA	NA
All-cause mortality	2	2	(2)	2	NA	NA
Total	9	11	12	11	NA	NA

Asia (2/2)	DABI 150	DABI 110	RIVA 20	APIX 5	APIX 2.5	EDOX 60	EDOX 30
Stroke or SE	1	2	2	(2)	(2)	2	2
Ischemic stroke	1	2	(2)	2	NA	NA	NA
Hemorrhagic stroke	1	1	(1)	1	NA	NA	NA
Intracranial hemorrhage	1	1	1	1	NA	NA	NA
Major bleeding	1	1	2	1	NA	NA	NA
Myocardial infarction	2	2	(2)	2	NA	NA	NA
All-cause mortality	2	2	(2)	(2)	NA	NA	NA
Total	9	11	12	11	NA	NA	NA

Outline

- NOACs vs. Warfarin: NOACs better
- Dabigatran vs. Rivaroxaban: DABI better
- Dabigatran vs. Apixaban: DABI better (Asian)
- Dabigatran vs. Edoxaban
- Review of specific conditions
- Conclusion

Baseline Characteristics in 4 Trials

	RE-LY[5]			ROCKET-AF[6]		ARISTOTLE[7]		ENGAGE AF-TIMI 48[8]		
	Dabigatran 150 mg (n=6076)	Dabigatran 110 mg (n=6015)	Warfarin (n=6022)	Rivaroxaban (n=7131)	Warfarin (n=7133)	Apixaban (n=9120)	Warfarin (n=9081)	Edoxaban 60 mg (n=7035)	Edoxaban 30 mg (n=7034)	Warfarin (n=7036)
Age (years)	71·5 (8·8)	71·4 (8·6)	71·6 (8·6)	73 (65–78)	73 (65–78)	70 (63–76)	70 (63–76)	72 (64–68)	72 (64–78)	72 (64–78)
≥75 years	40%	38%	39%	43%	43%	31%	31%	41%	40%	40%
Women	37%	36%	37%	40%	40%	36%	35%	39%	39%	38%
Atrial fibrillation type										
Persistent or permanent	67%	68%	66%	81%	81%	85%	84%	75%	74%	75%
Paroxysmal	33%	32%	34%	18%	18%	15%	16%	25%	26%	25%
CHADS2*	2·2 (1·2)	2·1 (1·1)	2·1 (1·1)	3·5 (0·94)	3·5 (0·95)	2·1 (1·1)	2·1 (1·1)	2·8 (0·97)	2·8 (0·97)	2·8 (0·98)
0–1	32%	33%	31%	0	0	34%	34%	<1%	<1%	<1%
2	35%	35%	37%	13%	13%	36%	36%	46%	47%	47%
3–6	33%	33%	32%	87%	87%	30%	30%	54%	53%	53%
Previous stroke or TIA*	20%	20%	20%	55%	55%	19%	18%	28%	29%	28%
Heart failure†	32%	32%	32%	63%	62%	36%	35%	58%	57%	58%
Diabetes	23%	23%	23%	40%	40%	25%	25%	36%	36%	36%
Hypertension	79%	79%	79%	90%	91%	87%	88%	94%	94%	94%
Prior myocardial infarction	17%	17%	16%	17%	18%	15%	14%	11%	12%	12%
Creatinine clearance‡										
<50 mL/min	19%	19%	19%	21%	21%	17%	17%	20%	19%	19%
50–80 mL/min	48%	49%	49%	47%	48%	42%	42%	43%	44%	44%
>80 mL/min	32%	32%	32%	32%	31%	41%	41%	38%	38%	37%
Previous VKA use§	50%	50%	49%	62%	63%	57%	57%	59%	59%	59%
Aspirin at baseline	39%	40%	41%	36%	37%	31%	31%	29%	29%	30%
Median follow-up (years)¶	2·0	2·0	2·0	1·9	1·9	1·8	1·8	2·8	2·8	2·8
Individual median TTR	NA	NA	67 (54–78)	NA	58 (43–71)	NA	66 (52–77)	NA	NA	68 (57–77)

Lancet Dec 4, 2013

Primary Endpoint Events
High-Dose Edoxaban vs Warfarin

Annualized Event Rates (%)	Warfarin (n = 7036)	High-Dose Edoxaban (n = 7035)	HR (97.5% CI)	*P* value
Stroke or embolic event[a]	1.50	1.18	0.79 (0.63-0.99)	< .001[c] .02[d]
Stroke or embolic event[b]	1.80	1.57	0.87 (0.73-1.04)	.08
Hemorrhagic stroke[b]	0.47	0.26	0.54 (0.38-0.77)[e]	< .001
Ischemic stroke[b]	1.25	1.25	1.00 (0.83-1.09)[e]	.97

HR = hazard ratio; CI = confidence interval

[a] Modified intention-to-treat; treatment period

[b] Prespecified superiority analysis/intention-to-treat; overall study period

[c] *P* for noninferiority

[d] *P* for superiority

[e] 95% confidence interval

Primary Endpoint Events
Low-Dose Edoxaban vs Warfarin

Annualized Event Rates (%)	Warfarin (n = 7036)	Low-Dose Edoxaban (n = 7034)	HR 97.5% CI	*P* value
Stroke or embolic event[a]	1.50	1.61	1.07 (0.87-1.31)	.005[c] .44[d]
Stroke or embolic event[b]	1.80	2.04	1.13 (0.96-1.34)	.10
Hemorrhagic stroke[b]	0.47	0.16	0.33 (0.22-0.50)[e]	< .001
Ischemic stroke[b]	1.25	1.77	1.41 (1.19-1.67)[e]	< .001

HR = hazard ratio; CI = confidence interval

[a] Modified intention-to-treat; treatment period

[b] Prespecified superiority analysis/intention-to-treat; overall study period

[c] *P* for noninferiority

[d] *P* for superiority

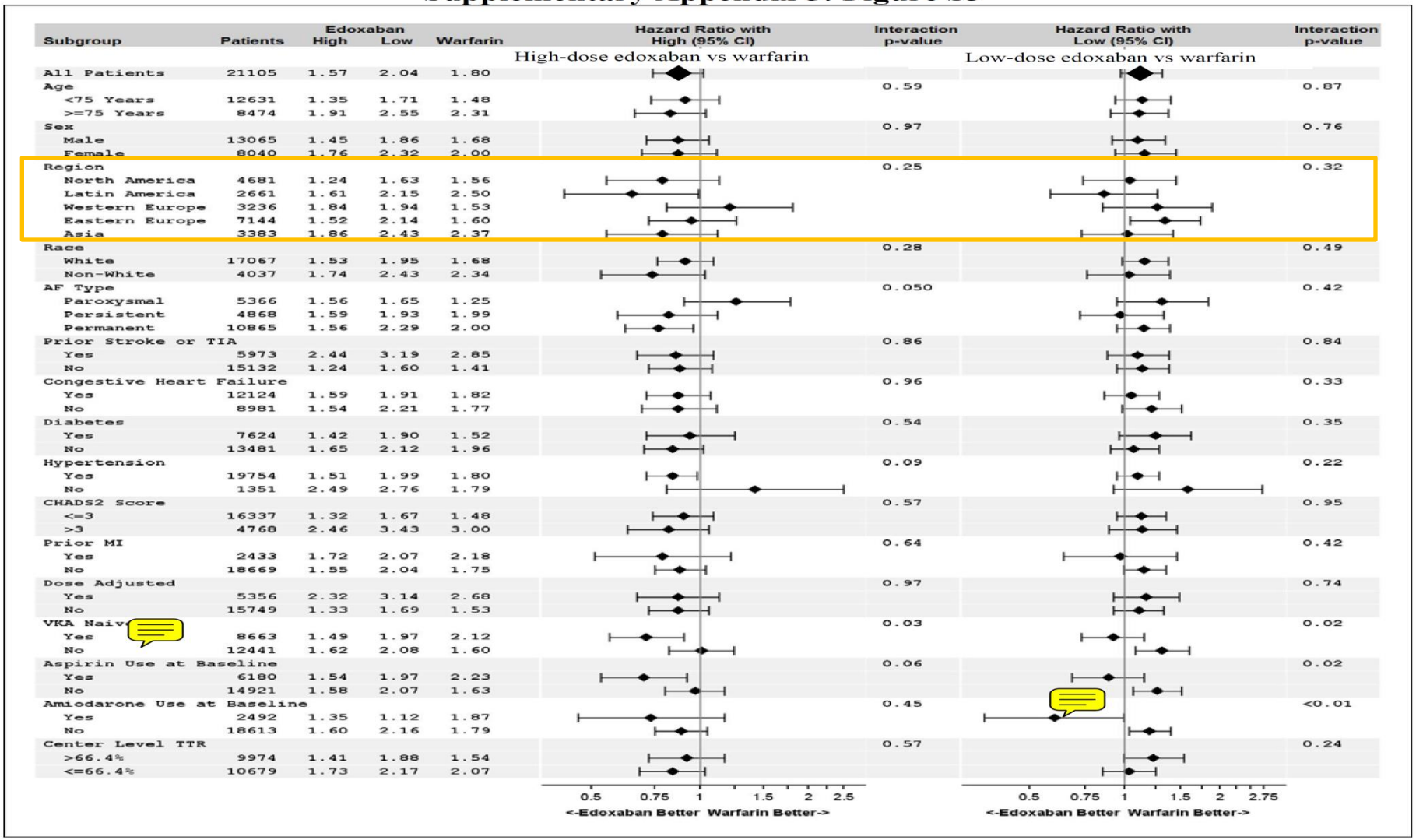
[e] 95% confidence interval

Total (1/2)	Dabigatran 150	Dabigatran 110	Rivaroxaban	Apixaban	Edoxaban 60	Edoxaban 30
Stroke or SE	1	2	2	1	1	2
Ischemic stroke	1	2	(2)	2	2	3
Hemorrhagic stroke	1	1	1	1	1	1
Intracranial hemorrhage	1	1	1	1	(1)	(1)
Major bleeding	1*	1	2	1	1	1
Myocardial infarction	2	2	2	2	2	2
All-cause mortality	2	2	2	1	2	1
Total	9	11	12	9	10	13

Total (2/2)	DABI 150	DABI 110	RIVA 20	APIX 5	APIX 2.5	EDOX 60	EDOX 30
Stroke or SE	1	2	2	1	2	1	2
Ischemic stroke	1	2	(2)	2	(2)	2	3
Hemorrhagic stroke	1	1	1	1	(1)	1	1
Intracranial hemorrhage	1	1	1	1	(1)	(1)	(1)
Major bleeding	1*	1	2	1	(1)	1	1
Myocardial infarction	2	2	2	2	(2)	2	2
All-cause mortality	2	2	2	1	(2)	2	1
Total	9	11	12	9	11	10	13

APIX 2.5 BID:
831 pts only

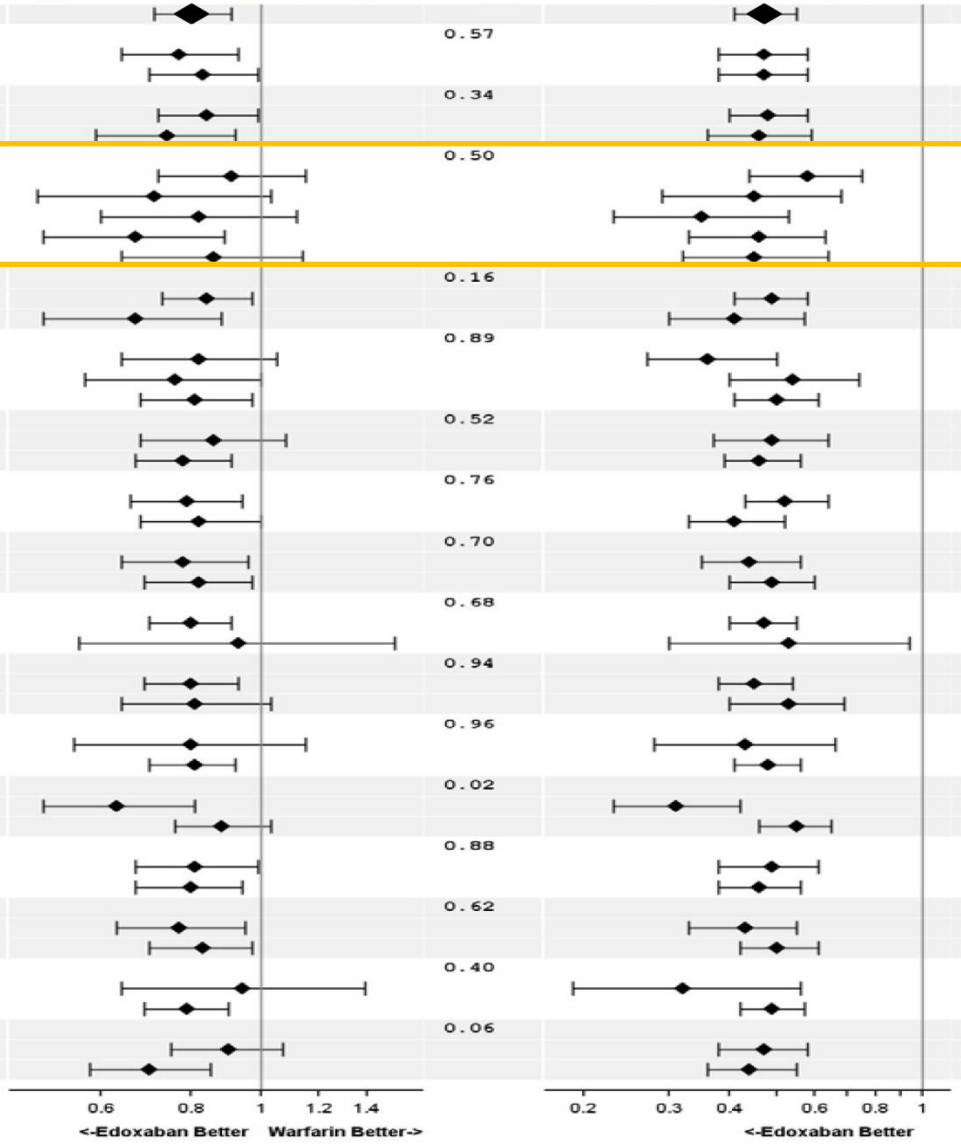
Supplementary Appendix 5: Figure S3



Hazard Ratio of the Primary Efficacy Outcome of Stroke or Systemic Embolism with Edoxaban versus Warfarin, in Pre-specified Subgroups, in the Intention-to-Treat Population During the Overall Study Period. The solid diamonds represent the hazard ratio and horizontal lines are the 95% confidence intervals. VKA-experienced denotes ≥60 days of treatment with a vitamin K antagonist at any time prior to enrollment. The $CHADS_2$ is a score predictive of stroke and is calculated by assigning one point each for a history of congestive heart failure, hypertension requiring treatment, age ≥75 years, or diabetes mellitus, and two points for prior stroke or systemic embolic event.[7] The creatinine clearance was estimated using the Cockcroft-Gault equation.

Supplementary Appendix 6: Figure S4

Subgroup	Patients	Edoxaban High	Edoxaban Low	Warfarin	Hazard Ratio with High (95% CI)	Interaction p-value	Hazard Ratio with Low (95% CI)	Interaction p-value
					High-dose edoxaban vs warfarin		Low-dose edoxaban vs warfarin	
All Patients	21026	2.75	1.61	3.43				
Age						0.57		0.95
<75 Years	12594	2.02	1.23	2.62				
>=75 Years	8432	4.01	2.26	4.83				
Sex						0.34		0.78
Male	13020	2.90	1.66	3.47				
Female	8006	2.48	1.54	3.35				
Region						0.50		0.35
North America	4665	4.07	2.57	4.47				
Latin America	2651	2.65	1.66	3.74				
Western Europe	3220	3.26	1.40	3.98				
Eastern Europe	7121	1.44	0.99	2.17				
Asia	3369	3.51	1.87	4.12				
Race						0.16		0.34
White	17008	2.72	1.58	3.23				
Non-White	4017	2.88	1.76	4.32				
AF Type						0.89		0.15
Paroxysmal	5348	3.06	1.36	3.69				
Persistent	4850	2.42	1.75	3.25				
Permanent	10825	2.75	1.68	3.38				
Prior Stroke or TIA						0.52		0.76
Yes	5950	3.11	1.79	3.65				
No	15076	2.61	1.55	3.35				
Congestive Heart Failure						0.76		0.11
Yes	12086	2.58	1.71	3.28				
No	8940	2.98	1.50	3.63				
Diabetes						0.70		0.52
Yes	7599	3.06	1.74	3.94				
No	13427	2.58	1.54	3.15				
Hypertension						0.68		0.71
Yes	19679	2.72	1.60	3.42				
No	1347	3.17	1.86	3.62				
CHADS2 Score						0.94		0.37
<=3	16276	2.47	1.40	3.09				
>3	4750	3.79	2.45	4.68				
Prior MI						0.96		0.70
Yes	2423	3.09	1.66	3.89				
No	18600	2.71	1.61	3.37				
Dose Adjusted						0.02		<0.01
Yes	5330	3.05	1.50	4.85				
No	15696	2.66	1.65	3.02				
VKA Naive						0.88		0.78
Yes	8624	2.86	1.71	3.53				
No	12401	2.67	1.55	3.36				
Aspirin Use at Baseline						0.62		0.29
Yes	6152	3.62	2.00	4.71				
No	14872	2.41	1.46	2.92				
Amiodarone Use at Baseline						0.40		0.16
Yes	2484	2.79	0.96	2.98				
No	18542	2.74	1.70	3.49				
Center Level TTR						0.06		0.76
>66.4%	9952	3.15	1.62	3.51				
<=66.4%	10628	2.33	1.49	3.35				



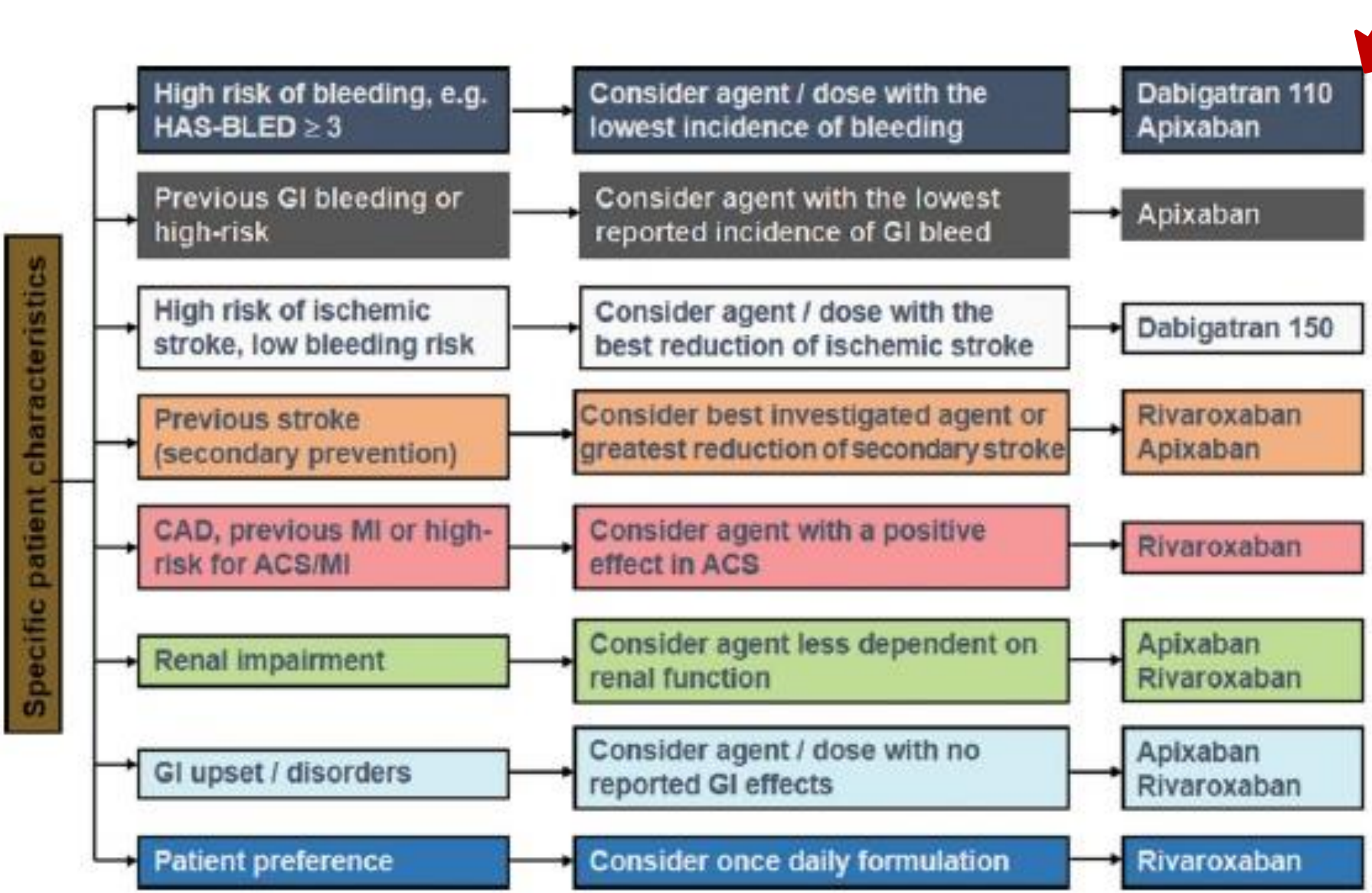
Hazard Ratio of the Principal Safety Outcome of Major Bleeding with Edoxaban versus Warfarin, in Pre-specified Subgroups, in the Safety Population During the On-treatment Period. Major bleeding was as defined by the International Society for Thrombosis and Haemostasis.[10] See Figure S3 legend for explanations of abbreviations.

Asia (1/2)	Dabigatran 150	Dabigatran 110	Rivaroxaban	Apixaban	Edoxaban 60	Edoxaban 30
Stroke or SE	1	2	2	2	2	2
Ischemic stroke	1	2	(2)	2	NA	NA
Hemorrhagic stroke	1	1	(1)	1	NA	NA
Intracranial hemorrhage	1	1	1	1	NA	NA
Major bleeding	1	1	2	1	2	1
Myocardial infarction	2	2	(2)	2	NA	NA
All-cause mortality	2	2	(2)	2	NA	NA
Total	9	11	12	11	NA	NA

Asia (2/2)	DABI 150	DABI 110	RIVA 20	APIX 5	APIX 2.5	EDOX 60	EDOX 30
Stroke or SE	1	2	2	(2)	(2)	2	2
Ischemic stroke	1	2	(2)	2	NA	NA	NA
Hemorrhagic stroke	1	1	(1)	1	NA	NA	NA
Intracranial hemorrhage	1	1	1	1	NA	NA	NA
Major bleeding	1	1	2	1	NA	2	1
Myocardial infarction	2	2	(2)	2	NA	NA	NA
All-cause mortality	2	2	(2)	(2)	NA	NA	NA
Total	9	11	12	11	NA	NA	NA

Outline

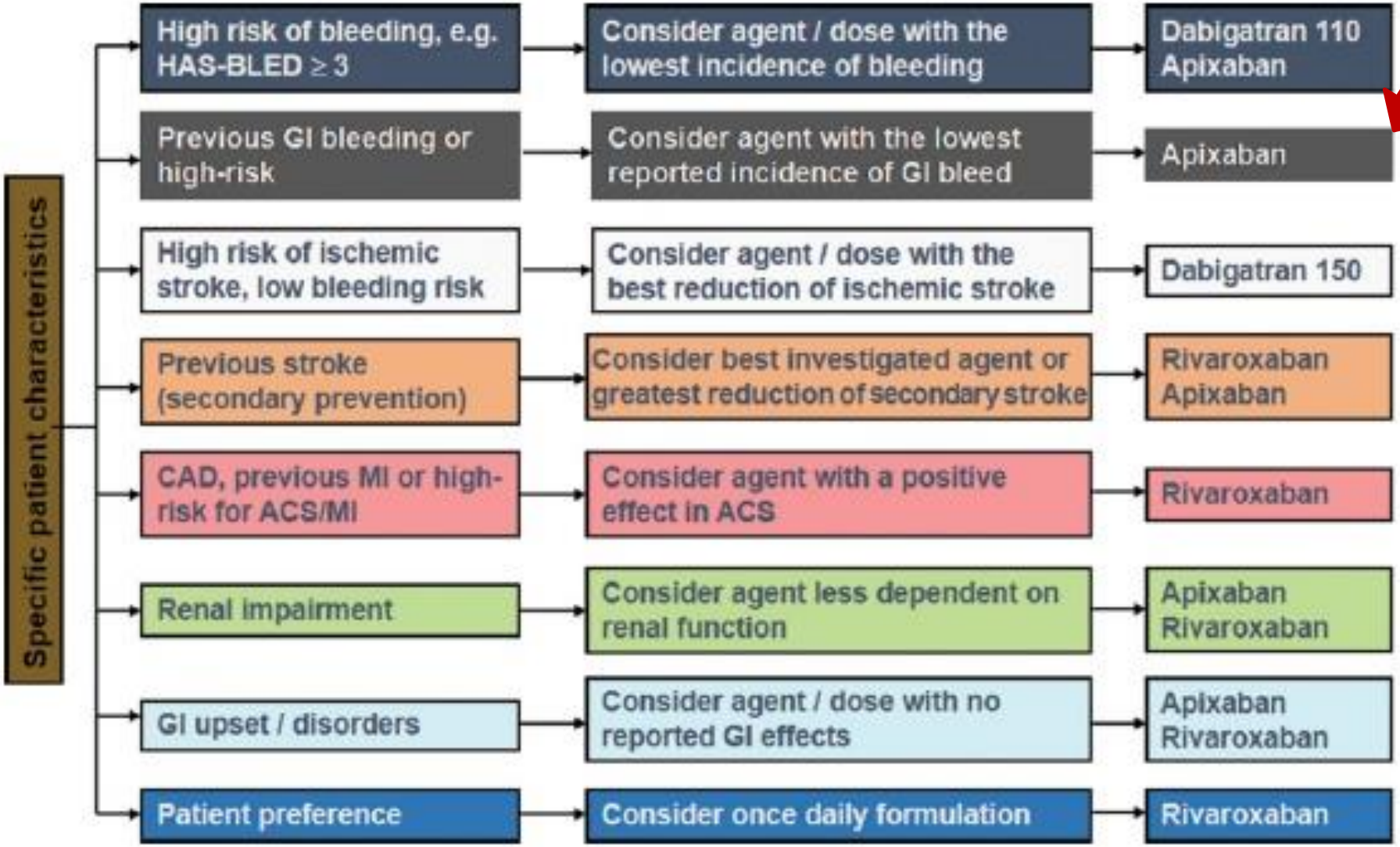
- NOACs vs. Warfarin: NOACs better
- Dabigatran vs. Rivaroxaban: DABI better
- Dabigatran vs. Apixaban: DABI better (Asian)
- Dabigatran vs. Edoxaban: DABI better
- Review of specific conditions
- Conclusion



Clin. Cardiol. (in press)
Savelieva and Camm: Oral anticoagulants in patients with AF
Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.22204

Table 2. Numbers Needed to Treat in Comparison With Warfarin Sodium for the Prevention of Intracranial Hemorrhage

Drug	NNT vs Warfarin Sodium		
	Median	2.5% CrI	97.5% CrI
Dabigatran etexilate mesylate, 110 mg	29.32	6.56	130.20
Dabigatran etexilate mesylate, 150 mg	34.53	7.57	156.80
Rivaroxaban	59.11	10.98	348.10
Apixaban	35.07	7.85	157.20
Aspirin	39.60	−188.60	376.30



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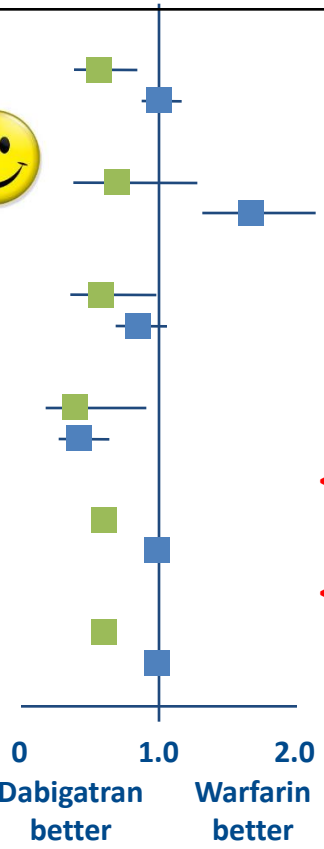
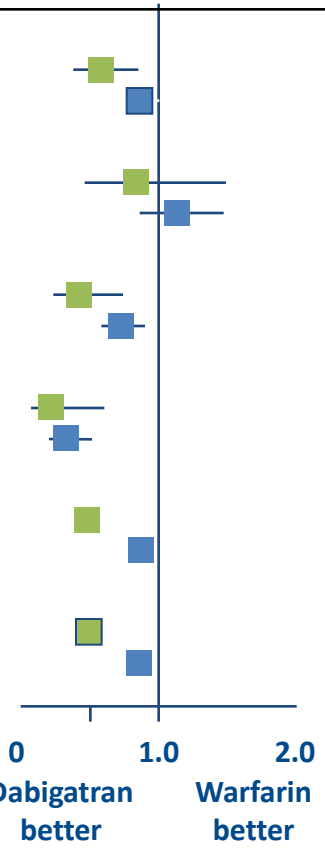
DOI:10.1002/clc.22204

Safety outcomes (Asia vs. non-Asia)

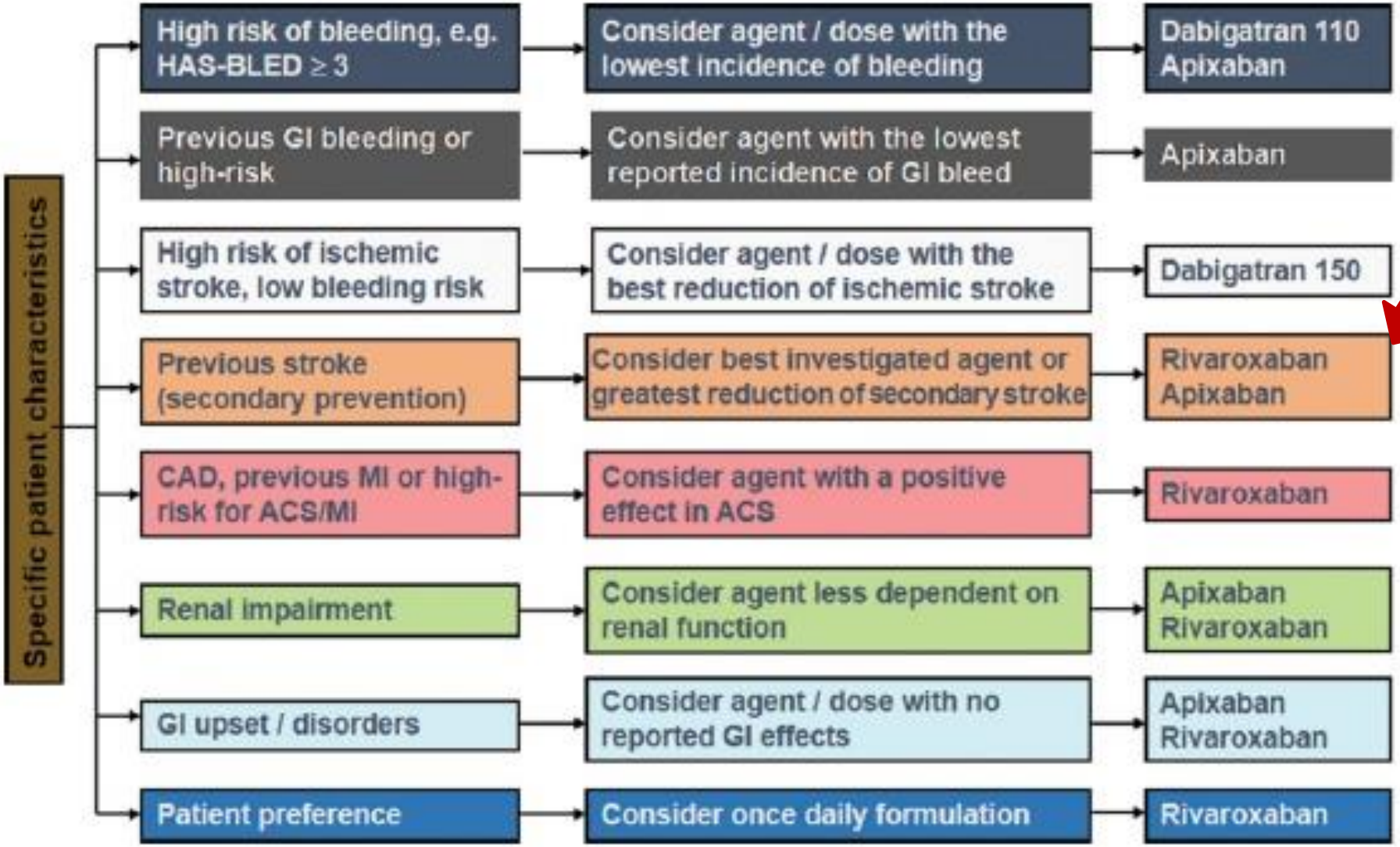
	Rate (%/year)			Dabigatran 150mg bid vs. Warfarin		Dabigatran 110mg bid vs. Warfarin	
	Dabigatran		Warfarin				
	150mg bid	110mg bid		HR (95%CI)	Interaction p value	HR (95%CI)	Interaction p value
Major bleeding					0.0079		0.0705
Asia	2.17	2.22	3.82				
Non-Asia	3.52	2.99	3.53				
GI major bleeding					0.0089		0.3379
Asia	0.96	1.15	1.41				
Non-Asia	1.69	1.14	1.01				
Life threatening bleeding					0.1749		0.0738
Asia	1.28	0.91	2.20				
Non-Asia	1.52	1.29	1.79				
Intracranial bleeding					0.9509		0.4561
Asia	0.45	0.23	1.10				
Non-Asia	0.29	0.23	0.71				
Minor bleeding					<0.0001		<0.0001
Asia	12.43	10.12	19.66				
Non-Asia	15.27	13.69	15.81				
Major or minor bleeding					<0.0001		<0.0001
Asia	13.99	11.72	22.03				
Non-Asia	17.02	15.27	17.74				





Asia: n=2,782; Non-Asia: n=15,331

Hori M, et al. *Stroke. 2013;44:1891-1896*



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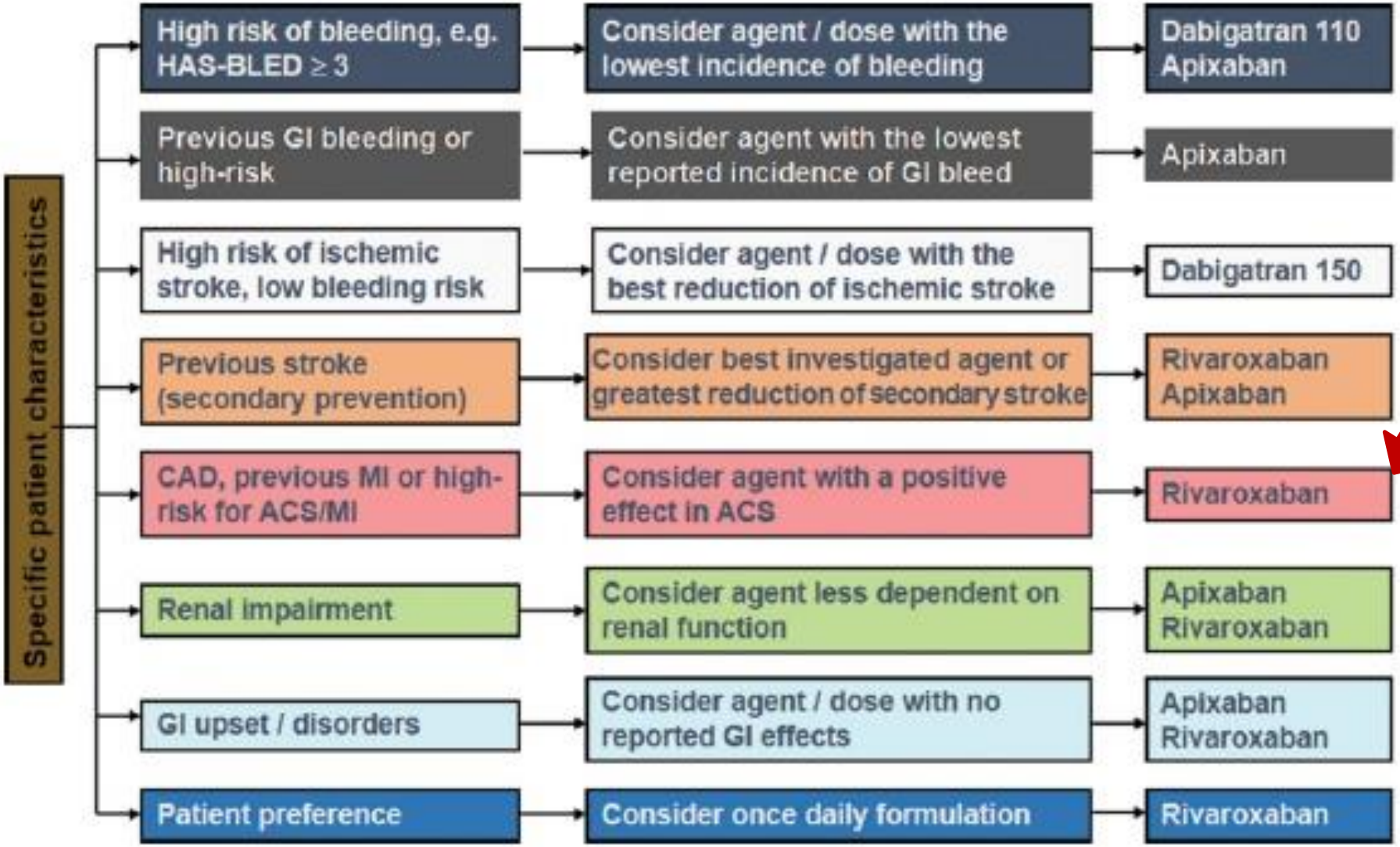
Subgroup analysis in patient with previous stroke or TIA

???

Outcome	Dabigatran 110 mg vs. warfarin RR (95% CI)	Dabigatran 150 mg vs. warfarin RR (95% CI)	Rivaroxaban vs. warfarin HR (95% CI)	Apixaban vs. warfarin HR (95% CI)
Stroke or systemic embolism	0·84 (0·58–1·20)	0·75 (0·52–1·08)	0·94 (0·77–1·16)	0·76 (0·56–1·03)
Major bleeding	0·66 (0·48–0·90) ↓	1·01 (0·77–1·34)	0·97 (0·79–1·19)	0·73 (0·55–0·98) ↓
Hemorrhagic stroke	0·11 (0·03–0·47) ↓	0·27 (0·10–0·72) ↓	0·73 (0·42–1·26)	0·37 (0·21–0·67) ↓

- Outcomes for subgroup of patients with previous stroke or TIA were consistent

http://www.slideshare.net/satanicala/novel-oral-anticoagulants-for-stroke-prevention-in-patients-with-atrial-fibrillation



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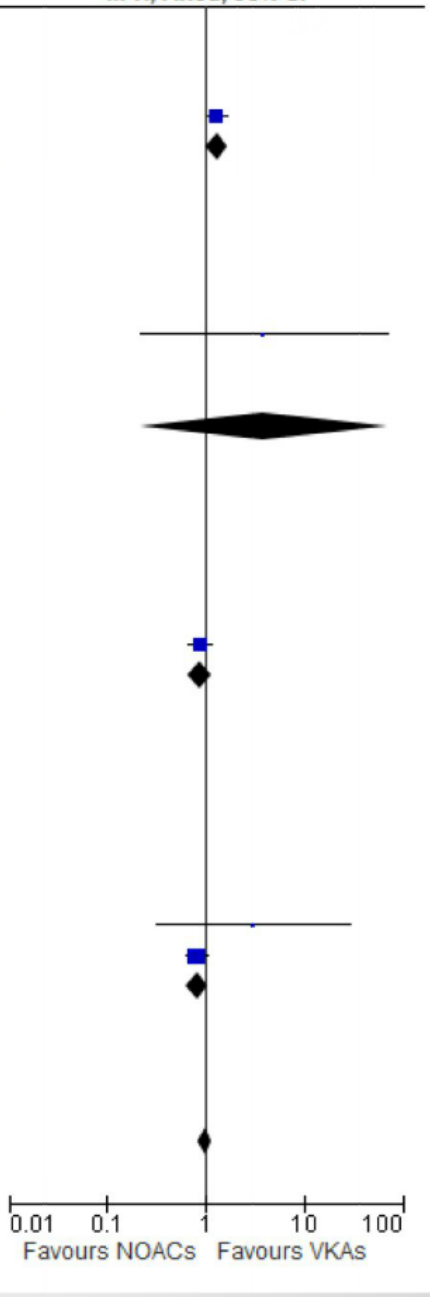
Subgroup analysis of myocardial infarction

Did not find any statistically significant difference between the NOACs and warfarin

Study or Subgroup	NOACs Events	NOACs Total	VKAs Events	VKAs Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.9.1 Dabigatran						
NCT01136408 (D)	0	104	0	62		Not estimable
PETRO	0	166	0	70		Not estimable
RE-LY	195	12091	75	6022	30.4%	1.29 [0.99, 1.69]
Subtotal (95% CI)		**12361**		**6154**	**30.4%**	**1.29 [0.99, 1.69]**
Total events	195		75			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.92 (P = 0.06)						
1.9.2 Edoxaban						
WEITZ	5	713	0	250	0.2%	3.87 [0.21, 69.68]
CHUNG	0	159	0	75		Not estimable
YAMASHITA	0	260	0	125		Not estimable
Subtotal (95% CI)		**1132**		**450**	**0.2%**	**3.87 [0.21, 69.68]**
Total events	5		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.92 (P = 0.36)						
1.9.3 Apixaban						
ARISTOTLE-J	0	148	0	74		Not estimable
ARISTOTLE	90	9120	102	9081	31.0%	0.88 [0.66, 1.16]
Subtotal (95% CI)		**9268**		**9155**	**31.0%**	**0.88 [0.66, 1.16]**
Total events	90		102			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.90 (P = 0.37)						
1.9.4 Rivaroxaban						
NCT00973245 (R1)	0	75	0	27		Not estimable
NCT00973323 (R2)	0	50	0	26		Not estimable
J-ROCKET-AF	3	637	1	637	0.3%	3.00 [0.31, 28.76]
ROCKET-AF	101	7061	126	7082	38.1%	0.80 [0.62, 1.04]
Subtotal (95% CI)		**7823**		**7772**	**38.4%**	**0.82 [0.64, 1.06]**
Total events	104		127			
Heterogeneity: $Chi^2 = 1.29$, df = 1 (P = 0.26); $I^2 = 22\%$						
Test for overall effect: Z = 1.50 (P = 0.13)						
Total (95% CI)		**30584**		**23531**	**100.0%**	**0.99 [0.85, 1.15]**
Total events	394		304			
Heterogeneity: $Chi^2 = 8.89$, df = 4 (P = 0.06); $I^2 = 55\%$						
Test for overall effect: Z = 0.13 (P = 0.89)						
Test for subgroup differences: $Chi^2 = 7.52$, df = 3 (P = 0.06), $I^2 = 60.1\%$						



Circulation 2012 Nov 13;126(20):2381

Myocardial ischaemic events subanalysis: cardiac outcomes

RE-LY trial

- Numerical imbalance in rate of MI that was not statistically significant for either dose of dabigatran vs warfarin

	Annual rate (%)			D110 vs warfarin		D150 vs warfarin	
	D110	D150	W	HR (95% CI)	P value	HR (95% CI)	P value
Total MI	0.82	0.81	0.64	1.29 (0.96–1.75)	0.09	1.27 (0.94–1.71)	0.12
Clinical MI	0.73	0.74	0.56	1.30 (0.95–1.80)	0.10	1.32 (0.96–1.81)	0.09
Silent MI	0.09	0.07	0.08	1.22 (0.50–2.93)	0.66	0.87 (0.34–2.27)	0.72
Fatal MI	0.13	0.11	0.10	1.32 (0.63–2.80)	0.46	1.06 (0.49–2.33)	0.88

D110 = dabigatran 110 mg twice daily; D150 = dabigatran 150 mg twice daily;
MI = myocardial infarction; W = warfarin

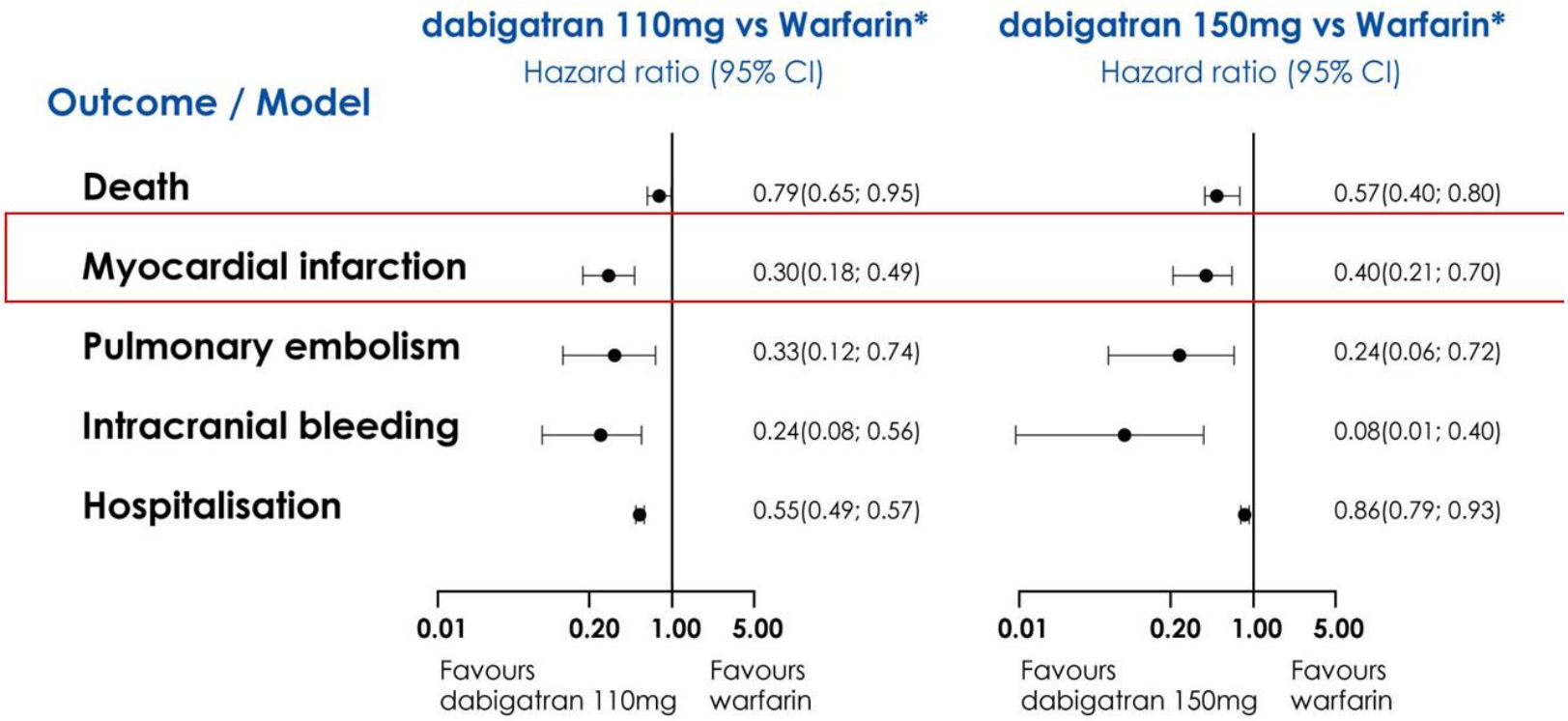
Hohnloser SH et al. Circulation 2012;125:669–76

Stroke and ischaemic events: RELY-ABLE®*

Event	D150 (%/yr)	D110 (%/yr)	HR	95% CI
Stroke or SEE	1.46	1.60	0.91	0.69–1.20
All stroke	1.24	1.38	0.89	0.66–1.21
Ischaemic	1.15	1.24	0.92	0.67–1.27
Haemorrhagic	0.13	0.14	0.89	0.34–2.30
Myocardial infarction	0.69	0.72	0.96	0.63–1.45
Pulmonary embolism	0.13	0.11	1.14	0.41–3.15

*5851 patients followed for mean of 2.3 years after RE-LY (Dabigatran blinded dose continued in RELY-ABLE)
D150 and D110 = dabigatran 150 and 110 mg twice daily, respectively; HR = hazard ratio
SEE = systemic embolic event

丹麥上市後分析顯示，Pradaxa可提供AF病患更安全的中風預防治療



*Patient number: Dabigatran 110mg (N=2,739); Warfarin D110 matched (N=4,940); Dabigatran 150mg (N=2,239); Warfarin D150 matched (N=3,996)

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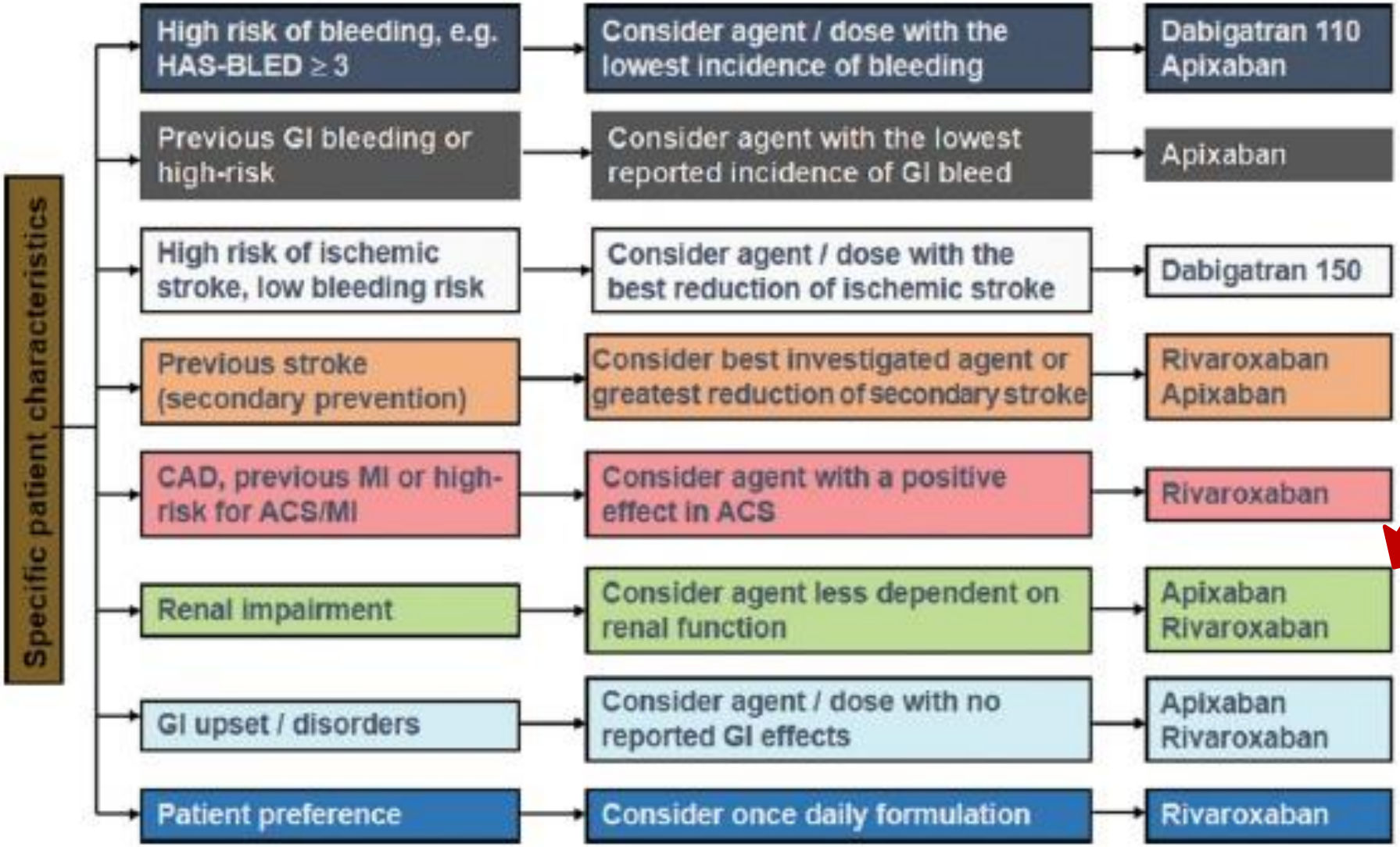

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Comparisons between Novel Oral Anticoagulants and Vitamin K Antagonists in Patients with CKD

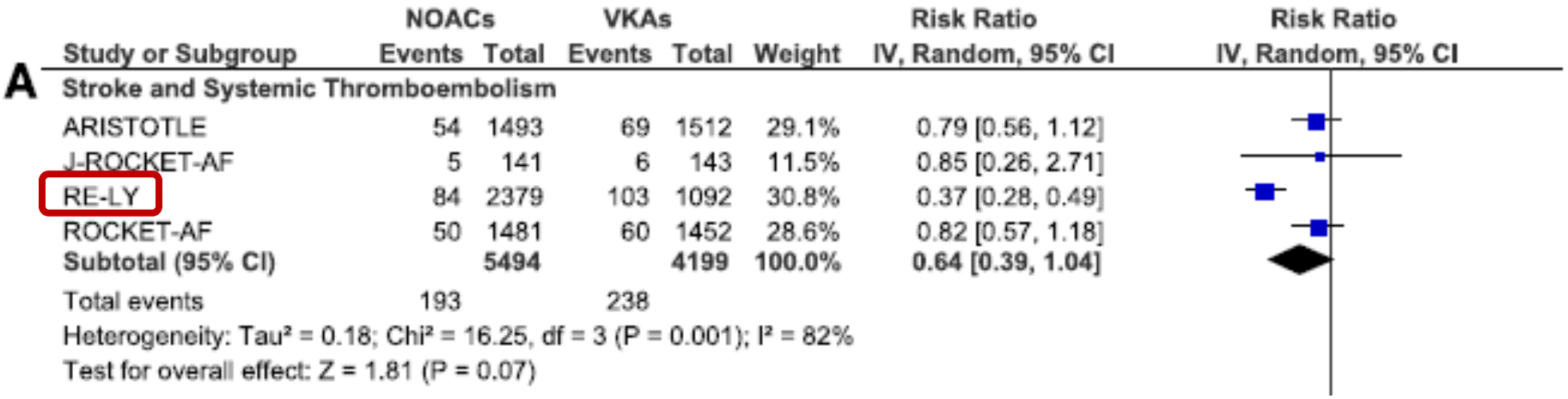


Figure 2. (A) There was no significant difference in the risk of stroke and systemic thromboembolism among participants with a CrCl≤50 ml/min given a NOAC versus a VKA (RR, 0.64; 95% CI, 0.39–1.04). (B) There was no significant difference in the risk of recurrent thromboembolism or thromboembolism-related death among participants with a CrCl≤50 ml/min given a NOAC versus a VKA (RR, 0.97; 95% CI, 0.43–2.15).

Anticoagulants in atrial fibrillation patients with chronic kidney disease

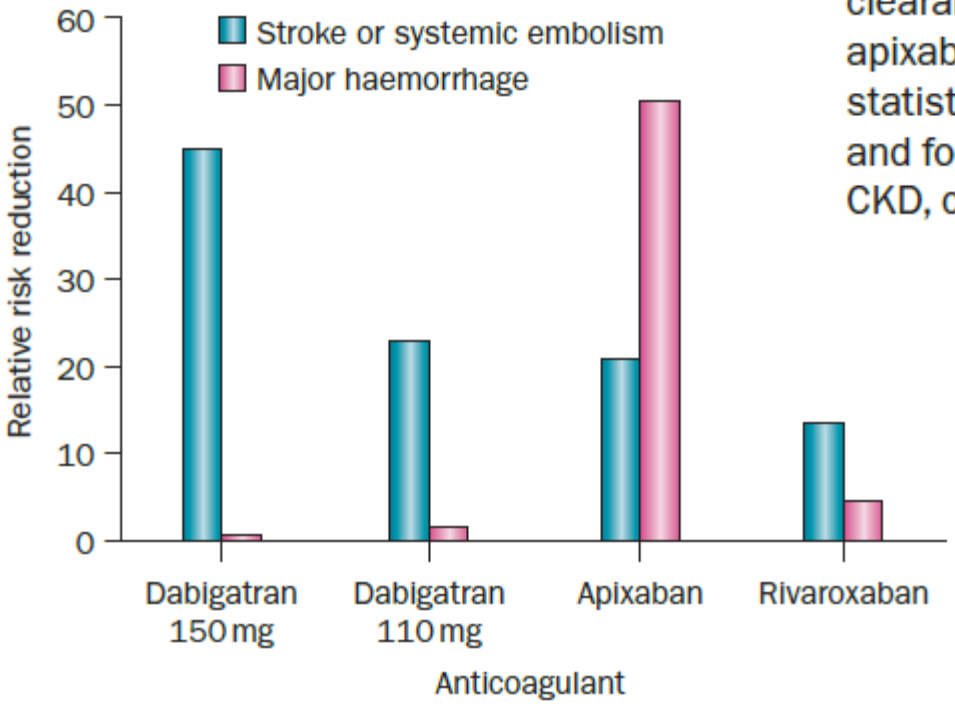


Figure 1 | Relative risk reductions in stroke or systemic embolism and major haemorrhage by novel oral anticoagulants versus warfarin in patients with moderate CKD.[9,12,25] Patients with CKD had estimated creatinine clearances of 30–49 ml/min, except for those treated with apixaban (25–50 ml/min). Risk reductions were statistically significant for dabigatran 150 mg on stroke and for apixaban on major haemorrhage. Abbreviation: CKD, chronic kidney disease.

Nat. Rev. Nephrol. 2012;8:569-578.

Management of bleeding in patients taking new oral anticoagulants

- Warfarin can be reversed with four-factor PCC or FFP in conjunction with vitamin K
- Absence of a reversal agent, but the shorter half-lives provide assurance that drug concentrations will decline relatively rapidly after discontinuation

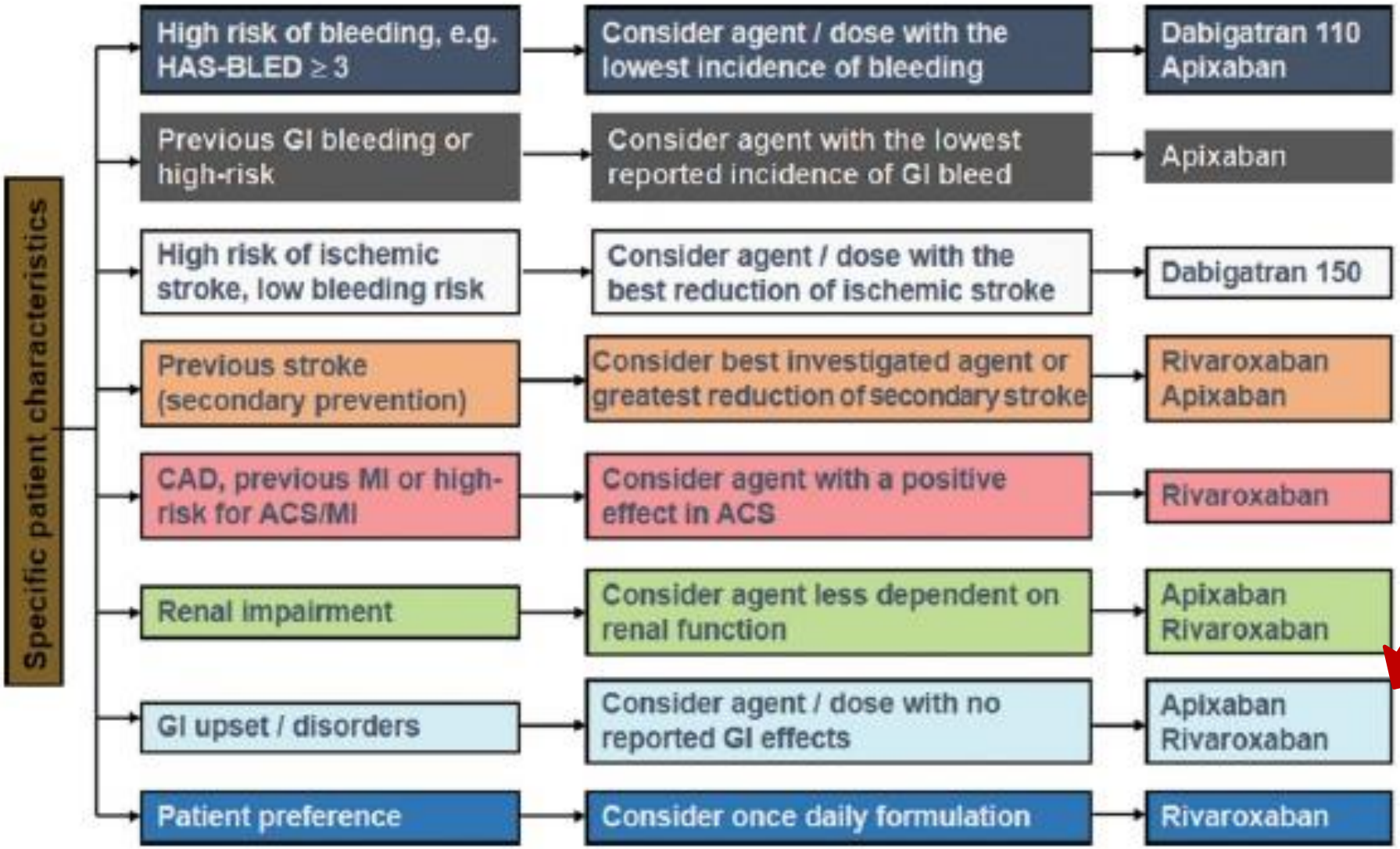
	Dabigatran (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)
Half-life	12–14 h	7–11 h	12 h
Protein binding	35%	95%	87%
Management	• Local and supportive care • Dialyzable ~60% of dabigatran	• Local and supportive care • Possibly PCC, rF VIIa	• Local and supportive care

PCC (prothrombin complex concentrate)

- Consist of four-factor concentrates (II, VII,IX, X)
- In a small human study, PCC 50 unit/kg led immediate and complete reversal of the anticoagulant effect of rivaroxaban

British J Hematol. 2011; 154: 311-24.
Ann Pharmacother. 2011; 45:869-75.
Lancet Neurol. 2012 Dec;11(12):1066-81
Thrombosis. 2012;2012:108983.

FFP= fresh frozen plasma



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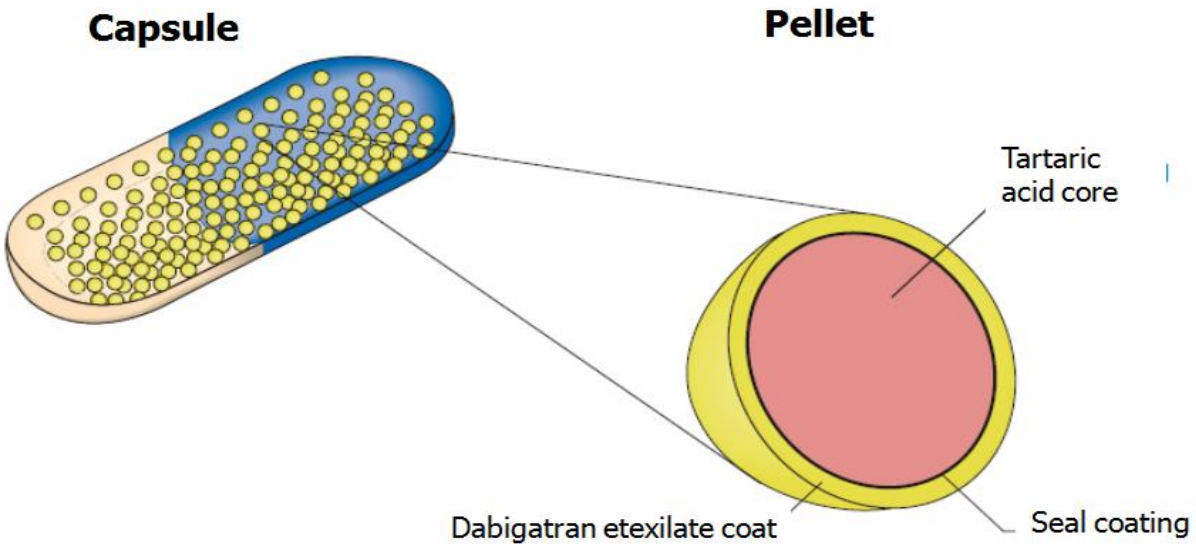


Generation of acidic microenvironment by tartaric acid core

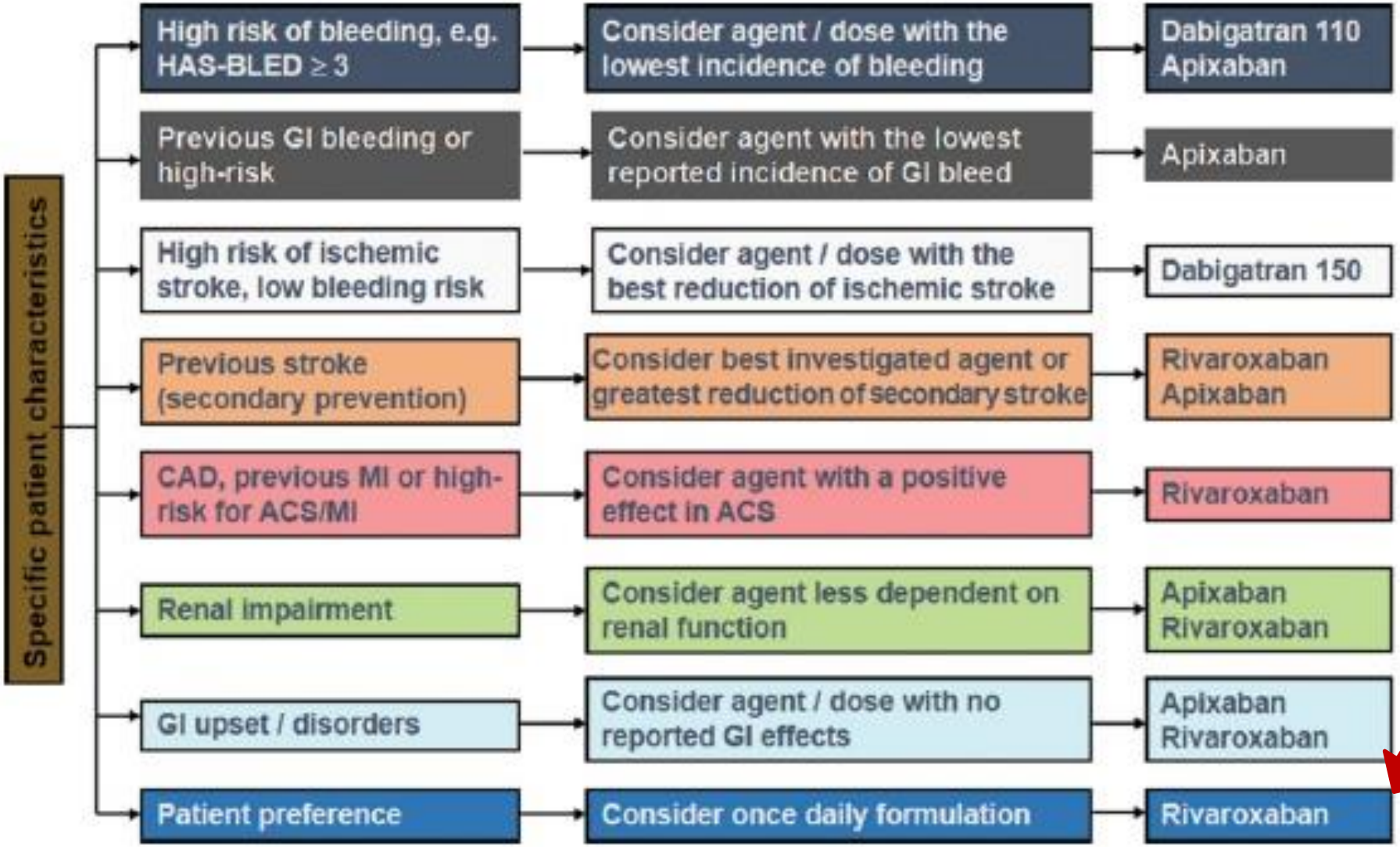
→ Increase of drug dissolution and absorption

→ Ensures that absorption is less affected by variations in gastric pH

Tartaric acid in white wine: 450-1200 mg/glass (0.2 L) -- 2.5 to 6.7 fold higher than that (178 mg) in a single dabigatran 150 mg capsule.

It is important to inform patients that dyspepsia may occur. The administration of dabigatran within meals (breakfast and dinner) can mitigate this effect [22]. The value

Scandinavian Journal of Gastroenterology. 2012; Early Online, 1–8



Clin. Cardiol. (in press)
Savelieva and Camm: Oral anticoagulants in patients with AF
Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.22204

Characteristics of New Oral Anticoagulants

Table 1. Characteristics of Oral Anticoagulants Under Development in Japan[8,31]

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target factor	Thrombin	Xa	Xa	Xa
$t_{1/2}$ (h)	12–14	9–13	8–15	6–11[31]
t_{max} (h)	0.5–2	2–4	1–4	1–1.5[31]
Bioavailability	6.5% (humans)	67–86% (animals)	49% (humans)	60% (animals)
Protein binding	35%	92–95%	87%	40–59%
Metabolism	Glucuronidation	CYP3A4/2J2[8]	CYP3A4[8]	CYP3A
Renal excretion	80%	33%	25%	35–39%
Prodrug	Yes	No	No	No
Company	Boehringer Ingelheim	Bayer/ Johnson & Johnson	Bristol-Myers Squibb/ Pfizer	Daiichi Sankyo

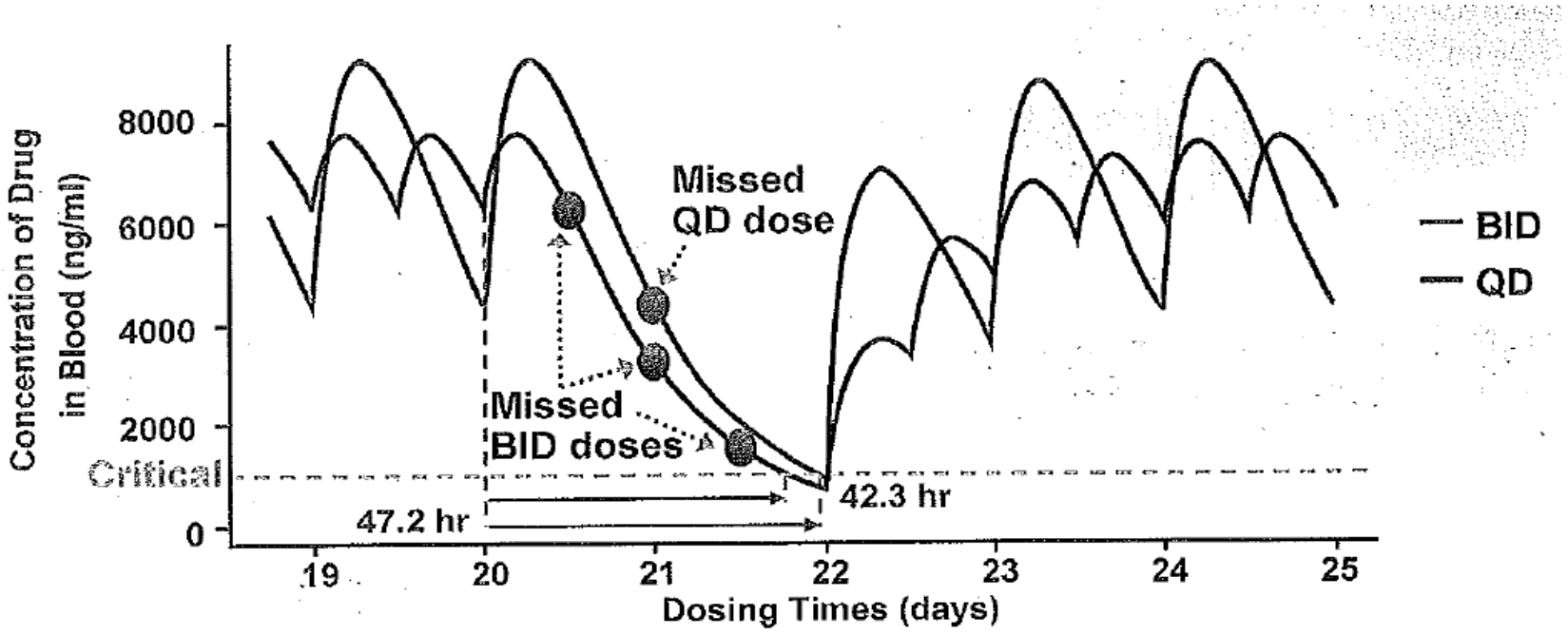
Circ J 2011; 75: 1539–1547.

Dosing and Pharmacokinetic Variations

Plot of drug with ~ 11 hour half-life

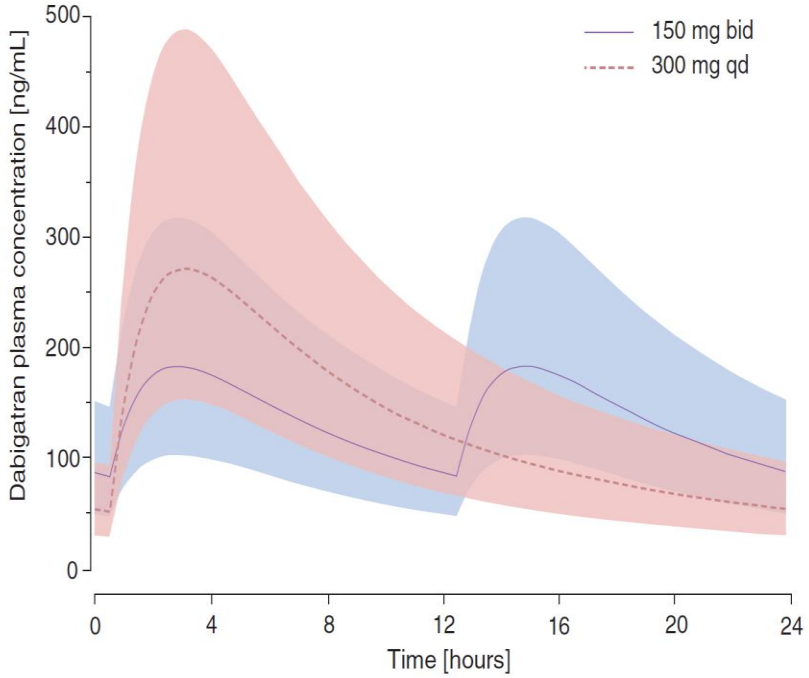
-- Less peak-to-trough variation with BID compared to QD

-- Missing a single QD dose is the pharmacokinetic equivalent to missing three BID doses



Comte L et al. *J Pharmacokinet Pharmacodyn*. 2007;34:549-558.

Twice daily dosing of dabigatran for stroke prevention in AF: a pharmacokinetic justification



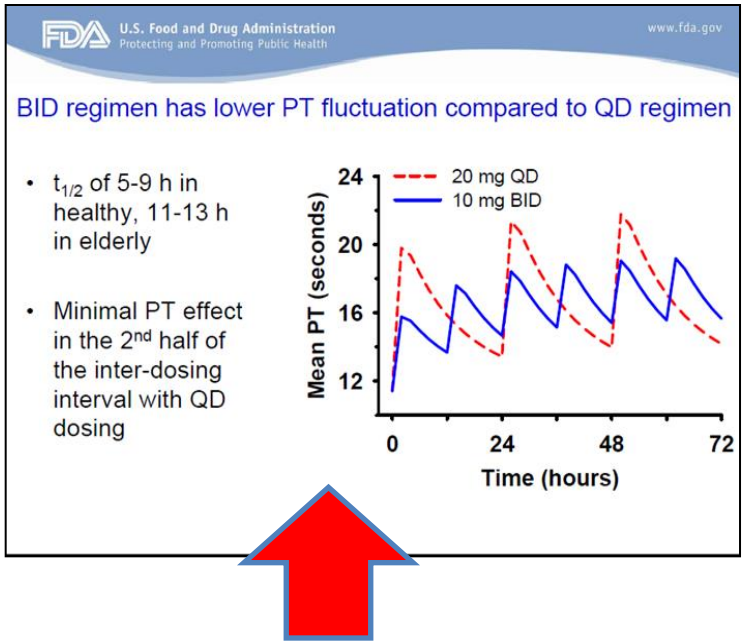
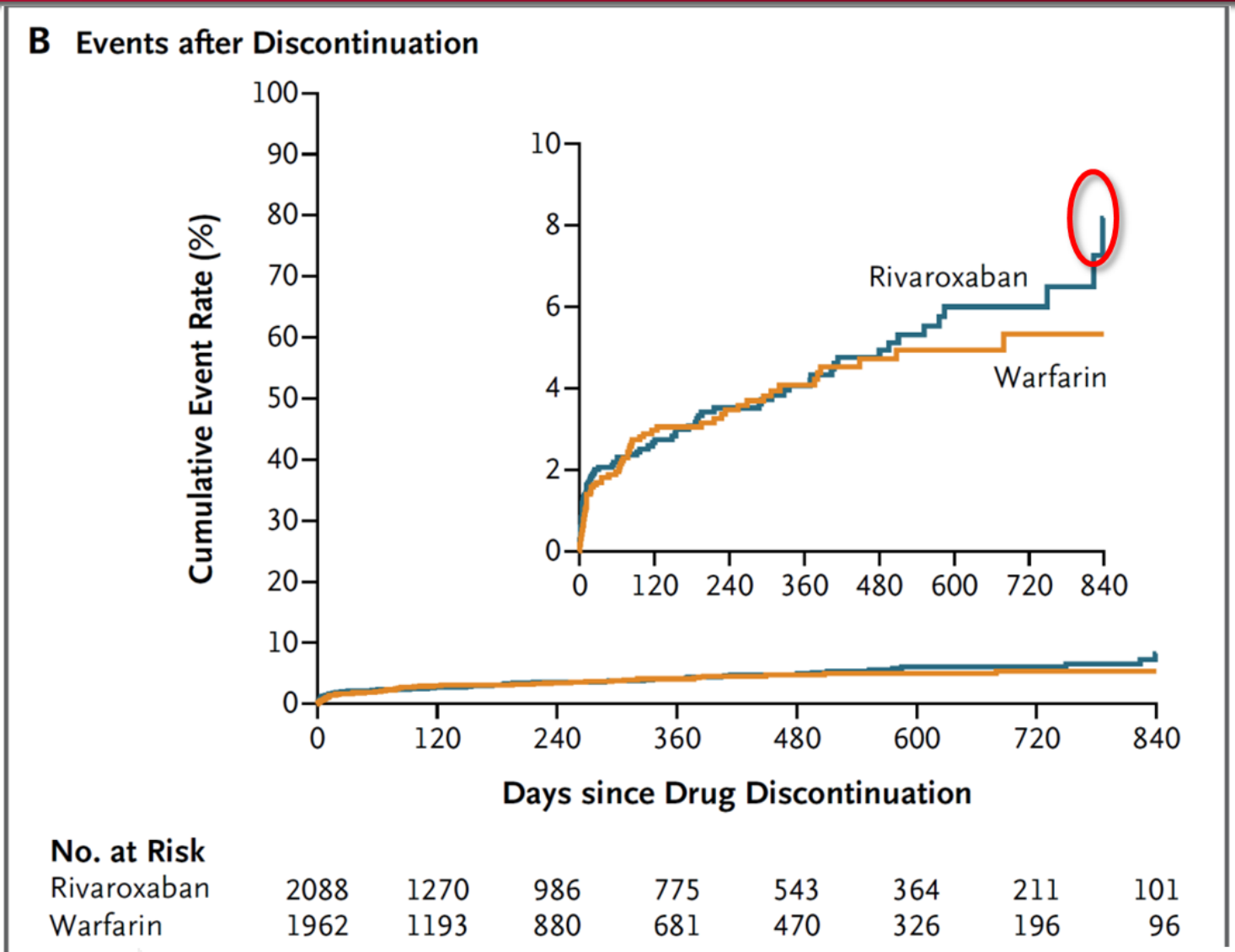


Figure 1. Predicted median concentration (10th–90th percentiles) versus time profiles at steady state after oral administration of dabigatran etexilate 150 mg twice daily (bid) and 300 mg once daily (qd). Data simulated for the typical RE-LY patient with AF (male, 72 years old, Caucasian, weight 80 kg, Cr_{Cl} 68.64 mL/min).

QD設計 –
血中藥物濃度
波動起伏可能
增加出血風險

ROCKET-AF: Rivaroxaban組別停藥後中風及栓塞事件增加



Pradaxa® dabigatran etexilate prevention

Table 3 Stroke or Non–Central Nervous System Embolism Rates and Stroke, Non–Central Nervous System Embolism, Myocardial Infarction, or Vascular Death During Post–Study-Drug Discontinuation Risk Period*

	Events per 100 Patient-Yrs (Total Events)		Rivaroxaban: Warfarin HR (95% CI)	p Value
	Rivaroxaban	Warfarin		
Stroke or non-CNS embolism rates				
All discontinuations and interruptions (before end of study)	16.49 (51)	14.05 (44)	1.21 (0.81–1.81)	0.35
Temporary interruptions	6.20 (9)	5.05 (8)	1.28 (0.49–3.31)	0.62
Permanent discontinuations	25.60 (42)	23.28 (36)	1.10 (0.71–1.72)	0.66
After end of study	6.42 (22)	1.73 (6)	3.72 (1.51–9.16)	0.0044
All discontinuations and interruptions (before end of study) + after end of study events	11.20 (73)	7.57 (50)	1.50 (1.05–2.15)	0.026
Stroke, non-CNS embolism, MI, or vascular death				
All discontinuations and interruptions (before end of study)	46.97 (145)	52.50 (164)	0.92 (0.74–1.15)	0.47
Temporary interruptions	9.66 (14)	10.75 (17)	0.95 (0.47–1.94)	0.89
Permanent discontinuations	80.01 (131)	95.28 (147)	0.84 (0.67–1.07)	0.16
After end of study	9.05 (31)	4.03 (14)	2.24 (1.19–4.22)	0.012
All discontinuations and interruptions (before end of study) + after end of study events	27.02 (176)	26.97 (178)	1.02 (0.83–1.26)	0.85

*Risk period for temporary interruptions is 3 days post-stop to 3 days post-resumption; for permanent discontinuations and end of study is 3–30 days post-stop; for permanent discontinuations and end of study, only patients with ≥3 days follow-up post-stop are included (N=13,650).

CI = confidence interval; CNS = central nervous system; HR = hazard ratio; MI = myocardial infarction.

J Am Coll Cardiol 2013;61:651–8.

XARELTO®
(rivaroxaban) tablets, for oral use

Revised: December 2011
02X12012A

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XARELTO® (rivaroxaban) safely and effectively. See full prescribing information for XARELTO.

XARELTO (rivaroxaban) tablets, for oral use
Initial U.S. Approval: 2011

WARNINGS: (A) DISCONTINUING XARELTO IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION INCREASES RISK OF STROKE, (B) SPINAL/EPIDURAL HEMATOMA

See full prescribing information for complete boxed warning

A. DISCONTINUING XARELTO IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION

Discontinuing XARELTO places patients at an increased risk of thrombotic events. If anticoagulation with XARELTO must be discontinued for a reason other than pathological bleeding, consider administering another anticoagulant (2.1, 5.1, 14.1).

B. SPINAL/EPIDURAL HEMATOMA

Epidur
XAREL
punctu
(5.2, 5.

Monito
impair
necessary (5.3).

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis (5.3).

由於觀察到此現象,FDA在Rivaroxaban的仿單中加註停藥可能會增加中風風險的警語

Events after discontinuation of randomized treatment at the end of the ARISTOTLE trial

Stroke or systemic embolism after stopping study drug at end of trial

Days after last dose	Apixaban to VKA Group		Warfarin to VKA Group	
	n/N	%/year	n/N	%/year
Stroke or systemic embolism				
1-30	21/6791	4.02	5/6569	0.99
1-2	1/6791	2.69	1/6569	2.78
3-7	4/6787	4.31	0/6566	0
8-14	5/6780	3.85	1/6559	0.80
15-30	11/6771	4.18	3/6548	1.18

ARISTOTLE study亦觀察到同樣的情形, 在試驗結束後apixaban轉換為warfarin的過程有較多的中風及栓塞事件發生

FULL PRESCRIBING INFORMATION

WARNING: DISCONTINUING ELIQUIS IN PATIENTS WITHOUT ADEQUATE CONTINUOUS ANTICOAGULATION INCREASES RISK OF STROKE

Discontinuing ELIQUIS places patients at an increased risk of thrombotic events. An increased rate of stroke was observed following discontinuation of ELIQUIS in clinical trials in patients with nonvalvular atrial fibrillation. If anticoagulation with ELIQUIS

FDA在Apixaban的仿單中同樣提醒病人勿輕易停藥,且特別強調這樣的警告是來自於ARISTOTLE臨床試驗中的觀察

FDA認為新型抗凝血劑的使用需特別重視病人的教育,因此Pradaxa的仿單上亦加註病人不可輕易停藥的警語

WARNING: DISCONTINUING PRADAXA IN PATIENTS WITHOUT ADEQUATE CONTINUOUS ANTICOAGULATION INCREASES RISK OF STROKE

See full prescribing information for complete boxed warning.

Discontinuing PRADAXA places patients at an increased risk of thrombotic events. If anticoagulation with PRADAXA must be discontinued for a reason other than pathological bleeding, consider coverage with another anticoagulant. (2.6, 5.1)

與Factor Xa inhibitor不同的是Pradaxa (dabigatran)**並未在臨床試驗中被觀察到有在停藥後中風風險增加的情形**,因此仿單上的警語僅是為了強調病人持續用藥的重要性

Outline

- NOACs vs. Warfarin: NOACs better
- Dabigatran vs. Rivaroxaban: DABI better
- Dabigatran vs. Apixaban: DABI better (Asian)
- Dabigatran vs. Edoxaban: DABI better
- Review of specific conditions: DABI applicable
- Conclusion

Total (1/2)	Dabigatran 150	Dabigatran 110	Rivaroxaban	Apixaban	Edoxaban 60	Edoxaban 30
Stroke or SE	1	2	2	1	1	2
Ischemic stroke	1	2	(2)	2	2	3
Hemorrhagic stroke	1	1	1	1	1	1
Intracranial hemorrhage	1	1	1	1	(1)	(1)
Major bleeding	1*	1	2	1	1	1
Myocardial infarction	2	2	2	2	2	2
All-cause mortality	2	2	2	1	2	1
Total	9	11	12	9	10	13

Total (2/2)	DABI 150	DABI 110	RIVA 20	APIX 5	APIX 2.5	EDOX 60	EDOX 30
Stroke or SE	1	2	2	1	2	1	2
Ischemic stroke	1	2	(2)	2	(2)	2	3
Hemorrhagic stroke	1	1	1	1	(1)	1	1
Intracranial hemorrhage	1	1	1	1	(1)	(1)	(1)
Major bleeding	1*	1	2	1	(1)	1	1
Myocardial infarction	2	2	2	2	(2)	2	2
All-cause mortality	2	2	2	1	(2)	2	1
Total	9	11	12	9	11	10	13

APIX 2.5 BID:
831 pts only

Asia (1/2)	Dabigatran 150	Dabigatran 110	Rivaroxaban	Apixaban	Edoxaban 60	Edoxaban 30
Stroke or SE	1	2	2	2	2	2
Ischemic stroke	1	2	(2)	2	NA	NA
Hemorrhagic stroke	1	1	(1)	1	NA	NA
Intracranial hemorrhage	1	1	1	1	NA	NA
Major bleeding	1	1	2	1	2	1
Myocardial infarction	2	2	(2)	2	NA	NA
All-cause mortality	2	2	(2)	2	NA	NA
Total	9	11	12	11	NA	NA

Asia (2/2)	DABI 150	DABI 110	RIVA 20	APIX 5	APIX 2.5	EDOX 60	EDOX 30
Stroke or SE	1	2	2	(2)	(2)	2	2
Ischemic stroke	1	2	(2)	2	NA	NA	NA
Hemorrhagic stroke	1	1	(1)	1	NA	NA	NA
Intracranial hemorrhage	1	1	1	1	NA	NA	NA
Major bleeding	1	1	2	1	NA	2	1
Myocardial infarction	2	2	(2)	2	NA	NA	NA
All-cause mortality	2	2	(2)	(2)	NA	NA	NA
Total	9	11	12	11	NA	NA	NA

Outline

- NOACs vs. Warfarin: NOACs better
- Dabigatran vs. Rivaroxaban: DABI better
- Dabigatran vs. Apixaban: DABI better (Asian)
- Dabigatran vs. Edoxaban: DABI better
- Review of specific conditions: DABI applicable
- Conclusion:

Factor IIa inhibitor is better!!!

To Be Continued....

台灣血脂衛教協會
Taiwan Association of Lipid Educators

Holistic Care for the Patients with Cardiovascular Diseases: Controversies and Issues in 2013

Debate

Which one is better – Factor IIa or Xa inhibitor?

Factor IIa inhibitor is better

Rebuttal Rebuttal Rebuttal Rebuttal Rebuttal

日期：103 年 01 月 26 日 (週日) 14:30 - 15:30

地點：高醫啟川大樓 6F 第一會議室

講者：台大醫院新竹分院 心臟內科 趙嘉倫

台大醫院 新竹分院


PETRUS

Cannikin Law (木桶定律)

「木桶理論」-- 在一個團隊裡，決定這個團隊戰鬥力強弱的不是那個能力最強、表現最好的人，而恰恰是那個能力最弱、表現最差的落後者。

http://www.twwiki.com/wiki/%E6%9C%A8%E6%A1%B6%E5%AE%9A%E5%BE%8B

請問 Factor Xa inhibitors 中哪一個是最短的木板?

RIVA ?? APIX ?? EDOX??

請問 Factor Xa inhibitors 中要用哪一個跟 Factor IIa inhibitor 相比?

大劑量

Total	DABI 150	RIVA 20	APIX 5	EDOX 60
Stroke or SE	1	2	1	1
Ischemic stroke	1	(2)	2	2
Hemorrhagic stroke	1	1	1	1
Intracranial hemorrhage	1	1	1	(1)
Major bleeding	1*	2	1	1
Myocardial infarction	2	2	2	2
All-cause mortality	2	2	1	2
Total	9	12	9	10

Asia	DABI 150	RIVA 20	APIX 5	EDOX 60
Stroke or SE	1	2	(2)	2
Ischemic stroke	1	(2)	2	NA
Hemorrhagic stroke	1	(1)	1	NA
Intracranial hemorrhage	1	1	1	NA
Major bleeding	1	2	1	NA
Myocardial infarction	2	(2)	2	NA
All-cause mortality	2	(2)	(2)	NA
Total	9	12	11	NA

小劑量

Total	DABI 110	RIVA 15	APIX 2.5	EDOX 30
Stroke or SE	2	NA	2	2
Ischemic stroke	2	NA	(2)	3
Hemorrhagic stroke	1	NA	(1)	1
Intracranial hemorrhage	1	NA	(1)	(1)
Major bleeding	1	NA	(1)	1
Myocardial infarction	2	NA	(2)	2
All-cause mortality	2	NA	(2)	1
Total	11	NA	11	13

Asia	DABI 110	RIVA 15	APIX 2.5	EDOX 30
Stroke or SE	2	NA	(2)	2
Ischemic stroke	2	NA	NA	NA
Hemorrhagic stroke	1	NA	NA	NA
Intracranial hemorrhage	1	NA	NA	NA
Major bleeding	1	NA	NA	NA
Myocardial infarction	2	NA	NA	NA
All-cause mortality	2	NA	NA	NA
Total	11	NA	NA	NA

褚大師：琴棋書畫 樣樣精通

勝 – 理所當然 (因才高八斗)

負 – 非戰之罪 (因事證所趨)

趙小子：吃喝玩樂 處處得逞

：射御書數 個個平凡

勝 – 非辯之功 (因二優於十)

負 – 請多包涵 (因詞不達意)

Conclusion

“Factor IIa inhibitor is better”

Thank you *for your attention!*