What Asian Data on Stroke Prevention in Atrial Fibrillation Says

Asan Medical center, Ulsan University

Kee-Joon Choi, MD, PhD

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1. Antithrombotic therapy in patients with AF in Asia
   - Why are OACs underused in Asia?
2. NOAC for stroke prevention in Asian AF patients
   - in RE-LY
   - in ROCKET-AF and ARISTOTLE

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2. NOAC for stroke prevention in Asian AF patients
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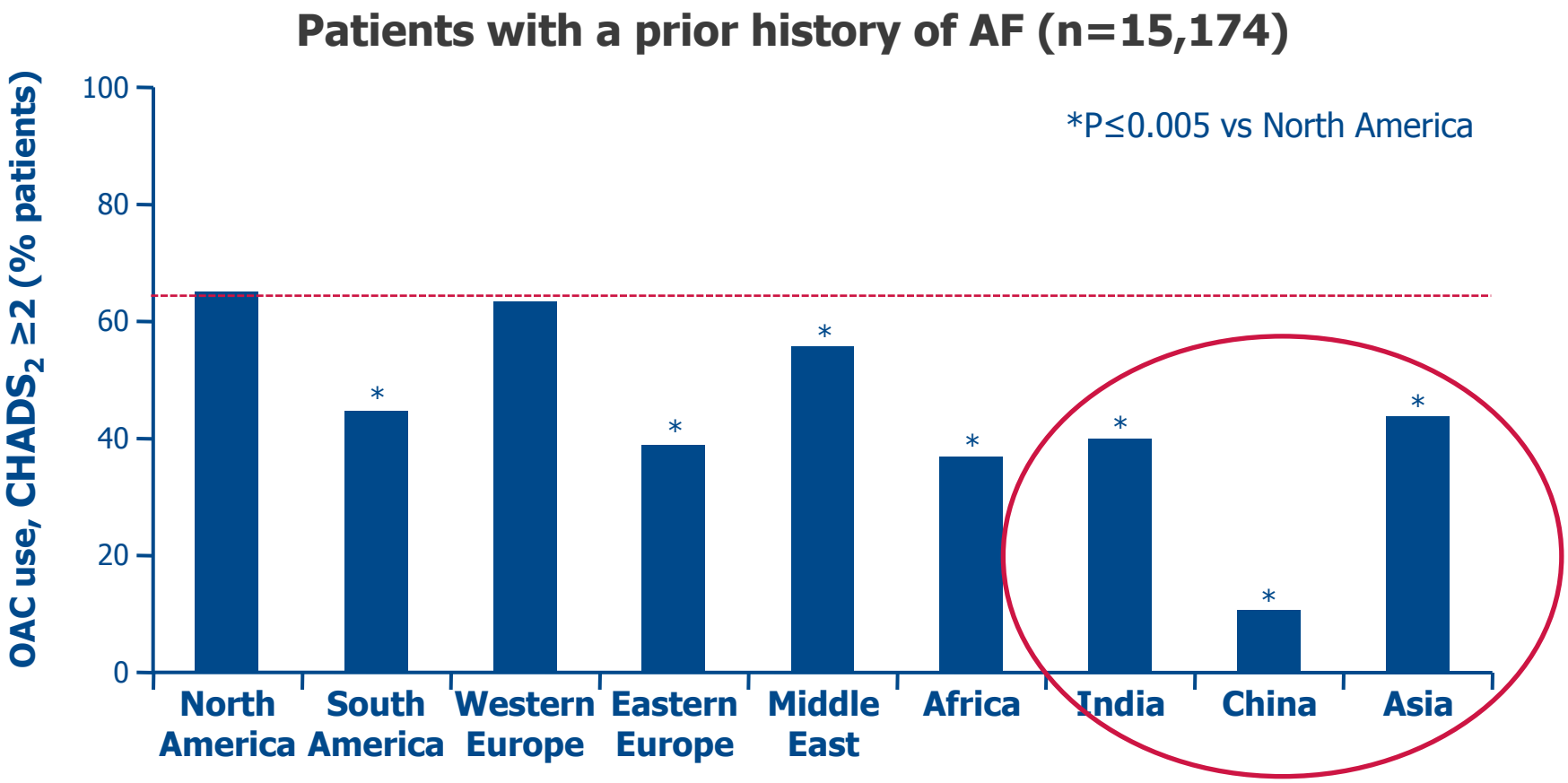
Global AF registry: *use of OACs* is lower in Asia vs Western countries



Healey J et al. ESC 2011; e-slides available at http://spo.escardio.org/eslides/view.aspx?eevtid=48&fp=1355; accessed August 2013

GARFIELD registry: use of OACs in patients with AF at risk of stroke is lower in Asia vs Europe

	$CHADS_2$ score 0		$CHADS_2$ score 1		$CHADS_2$ score ≥2	
	Asia (n=351)	Europe (n=408)	Asia (n=1078)	Europe (n=2174)	Asia (n=1151)	Europe (n=3947)
VKA + AP, %	6.6	7.1	9.2	8.7	15.2	12.2
VKA only, %	23.9	47.8	25.3	54.6	32.7	56.9
AP only, %	41.9	23.8	44.3	21.2	35.4	20.1
Neither, %	27.6	21.3	21.1	15.5	16.8	10.8

- VKA was used in 39.9% of all Asian patients and 41.4% of those **with $CHADS_2$ score ≥1** (vs 66.3% and **67.0%**, respectively, in Europe)

AP = antiplatelet

Goto S et al. ESC 2012; abstract 4043

Why are OACs underused in Asia?

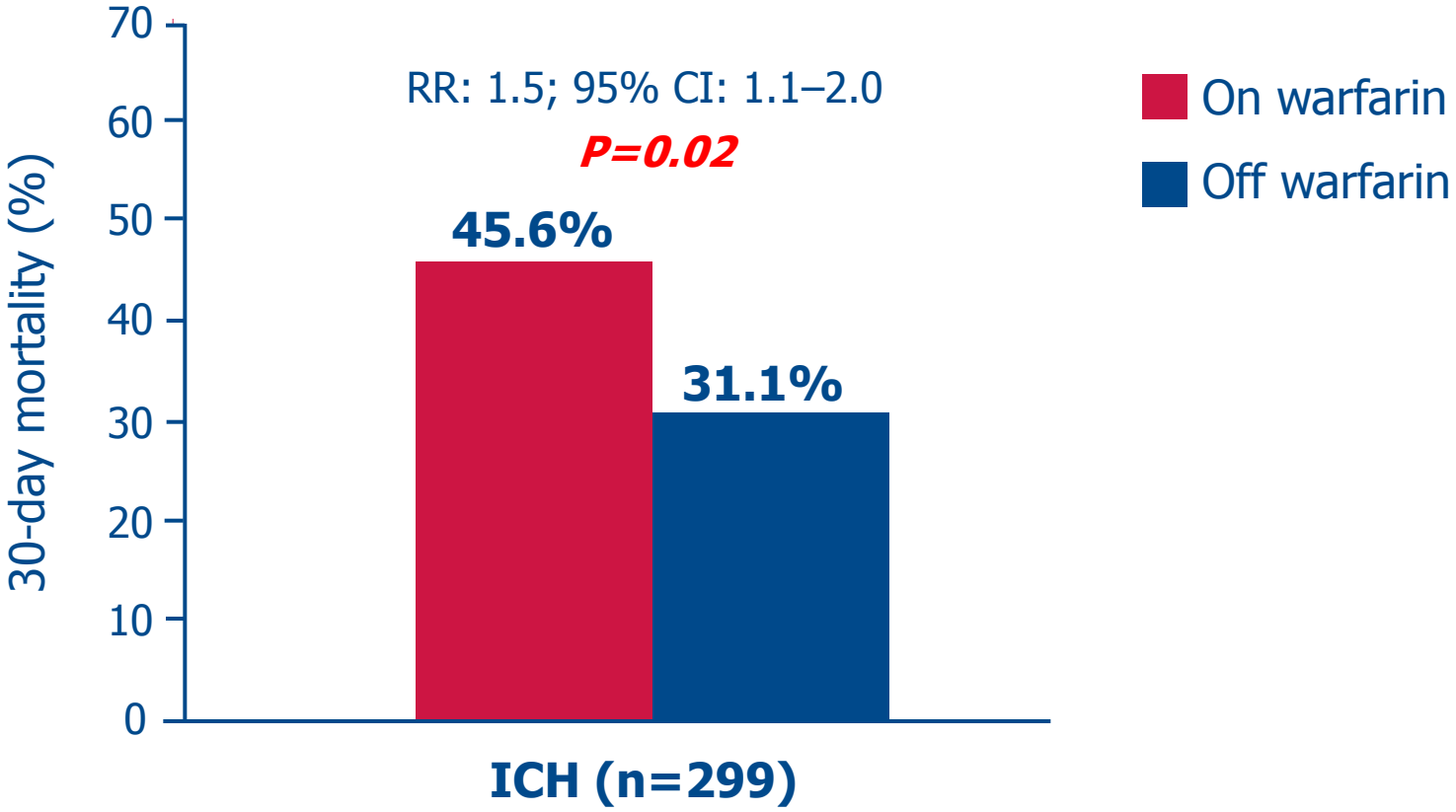
ICH is the most feared complication of antithrombotic therapy

- Can be life-threatening
- Of patients with ICH:
  - ~10% are on warfarin
  - ~25% are on ASA
- ICH risk with traditional antithrombotics:
  - Increased ~40% with ASA
  - Doubled with warfarin (INR 2.0–3.0)
    - Annual ICH rates 0.3–0.6% with OACs in recent reports

*Compared with placebo

Hart RG et al. Stroke 2005;36:1588–93

VKAs can increase the likelihood of suffering an ICH, as well as the mortality associated with it

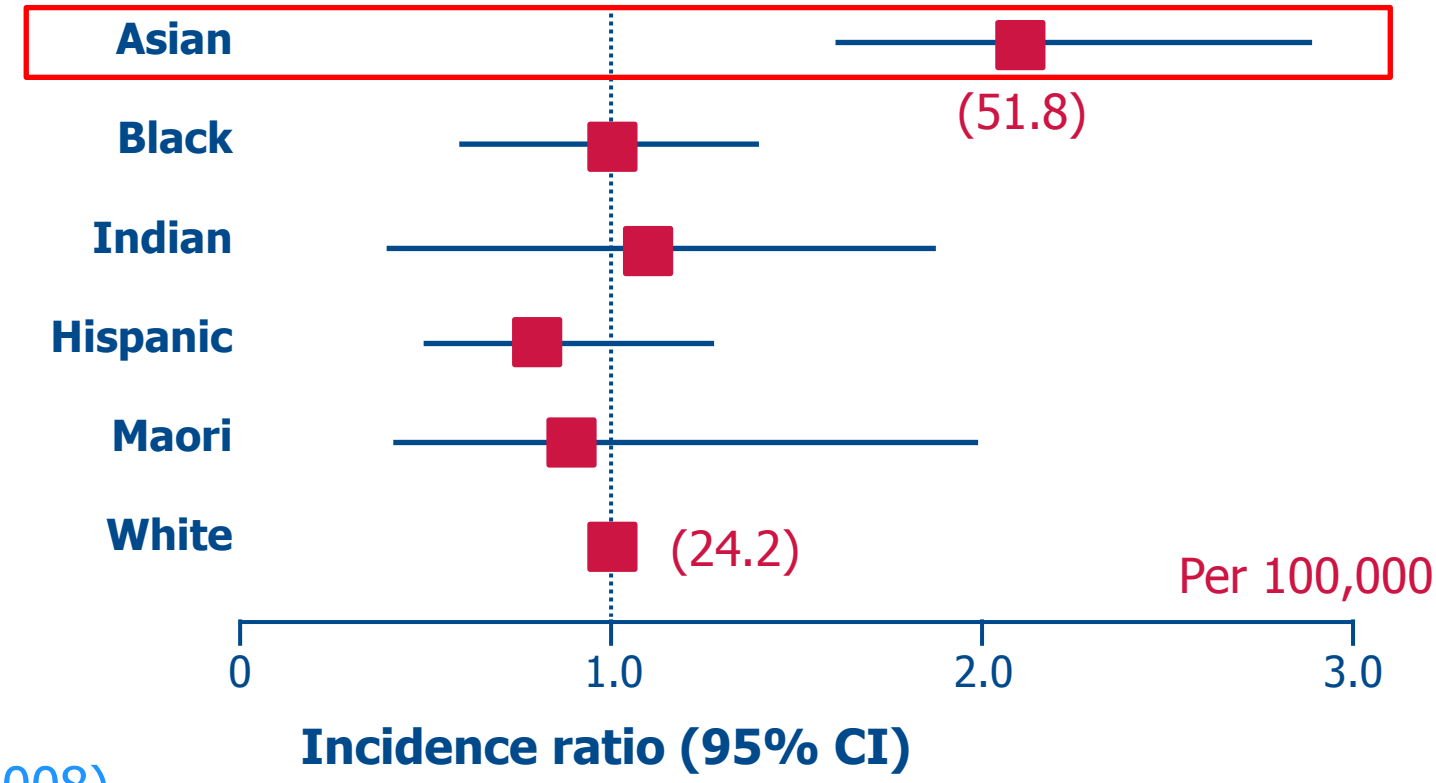


RR = relative risk

Fang MC et al. Stroke 2012;43:1795–9

Incidence of ICH is higher in Asian vs. other ethnicities

- Meta-analysis of 36 studies, including 8145 patients with ICH

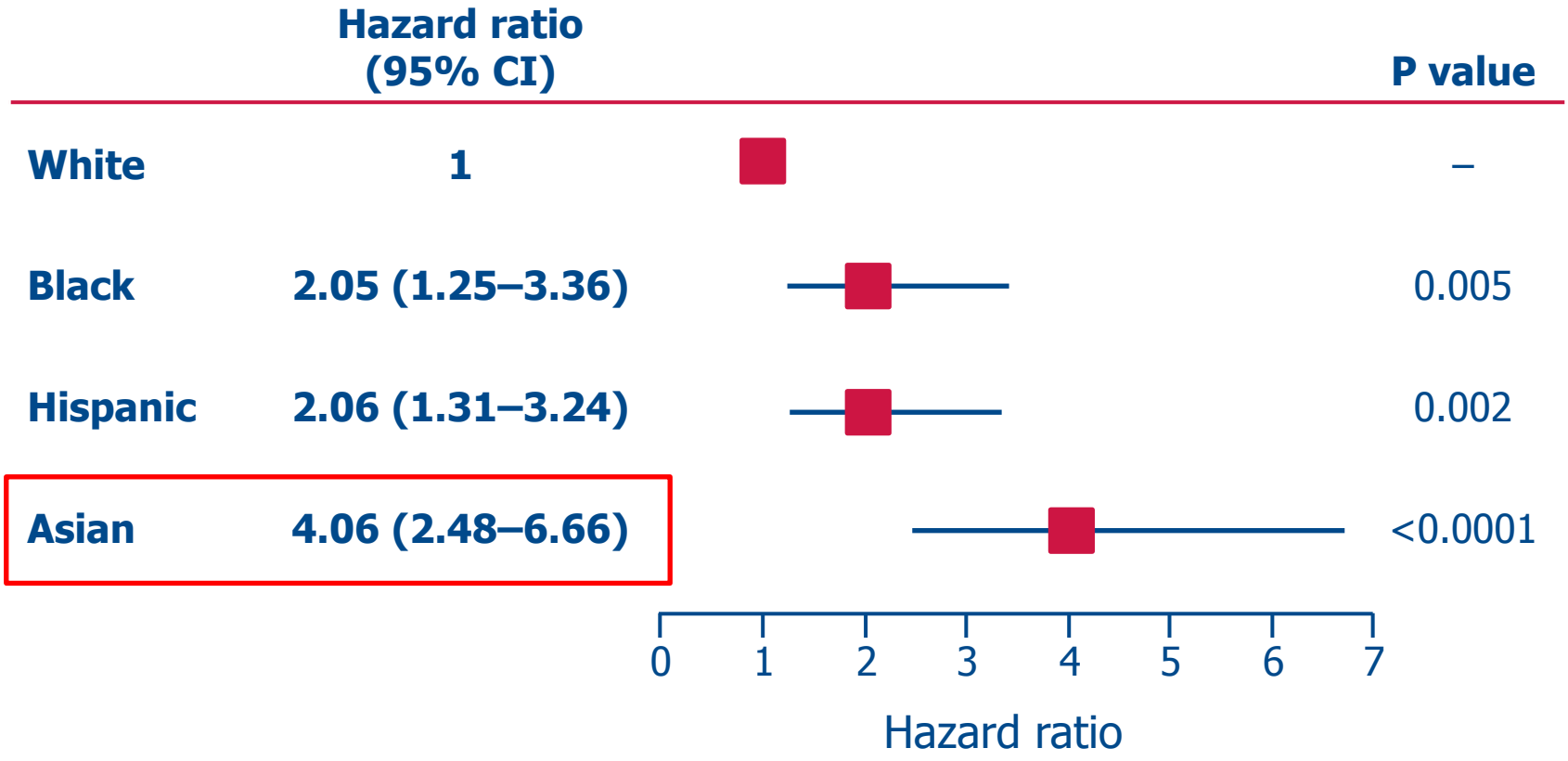


(1980-2008)

Van Asch CJ et al. Lancet Neurol 2010;9:167–76

Incidence of ICH in patients receiving warfarin is higher in Asian vs other ethnicities

- Retrospective analysis of 18,867 patients hospitalized with first-time AF in California, USA -173 ICH events over 3.3y



Shen AY et al. J Am Coll Cardiol 2007;50:309–15

Why are Asian patients at higher bleeding risk?

- INR instability; difficulties regulating INR[1]
  - Non-compliance, food, drug interactions
- Different ethnic prevalence rates of gene polymorphisms that influence warfarin PK and PD[2]
  - Vitamin K epoxide reductase (VKORC1)
    - Different dose requirements between racial groups possibly related to the prevalence of VKORC1 variants[3]
  - Cytochrome P450 2CY
    - CYP2C9 genotype confers increased risk of major haemorrhage[3]

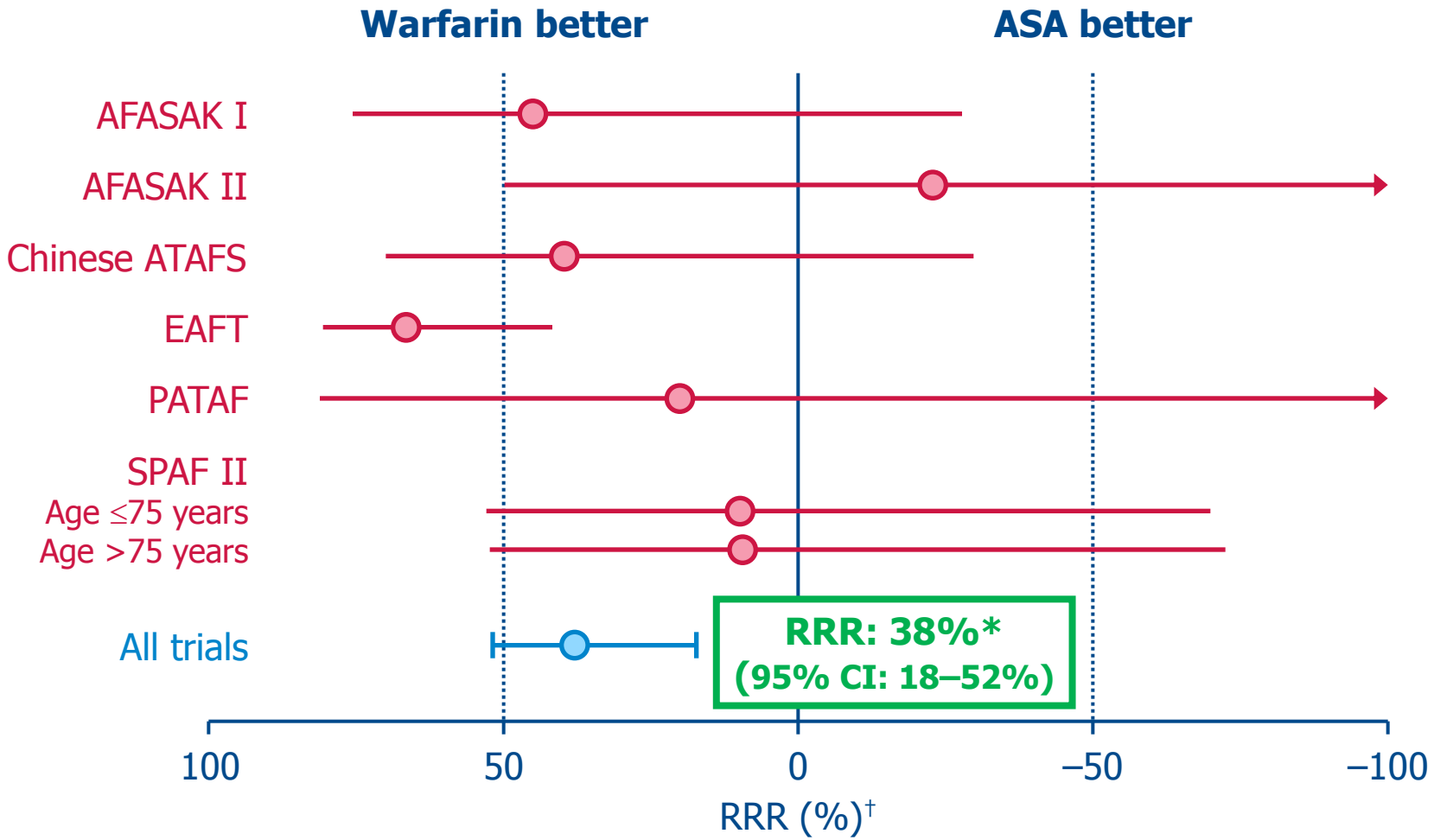
CYP = cytochrome P450

1. Kim JH et al. Yonsei Med J 2009;50:83–8;

2. Medi C et al. Stroke 2010;41:2705–13;

3. Limdi NA et al. Pharmacotherapy. 2008;28:1084–97

ASA inferior to warfarin for stroke prevention in AF



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

Chinese patients: ASA inferior to warfarin in stroke prevention with lower bleeding risk

- 704 patients with AF randomized to ASA or warfarin (INR 2.0–3.0)

	ASA	Warfarin
Death or ischaemic stroke, %	6.0	2.7
	0.44 (0.198–0.960); P=0.03	
Thromboembolism, %	10.6	5.4
	0.48 (0.269–0.858); P=0.01	
Stroke, death, peripheral artery embolism, TIA, acute MI, serious bleeding, %	**13.0**	**8.4**
	P=0.047	
Bleeding, %	2.4	6.9
	P<0.05	

MI = myocardial infarction

Hu DY et al. Zhonghua Xin Xue Guan Bing Za Zhi 2006;34:295–8

In Japanese patients at low risk of stroke, ASA was no more effective than placebo

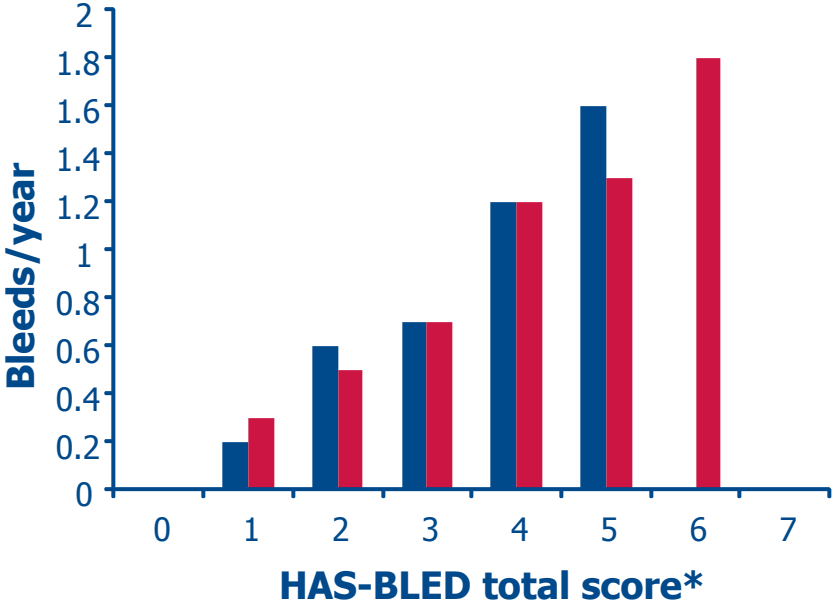
- Patients with AF randomized to ASA or no antithrombotic treatment
- **No significant difference in efficacy or safety endpoints**

	ASA (n=426)	Control (n=445)	P value
Primary endpoint, n (%/year)	**27 (3.1)**	**23 (2.4)**	**0.458**
Cardiovascular death	3	3	1.000*
Stroke	**17**	**18**	**0.967**
Cardiogenic embolism	14	12	0.609
Thrombotic infarction	3	2	0.959*
Lacunar infarction	0	4	0.135
TIA	7	2	0.101*
Secondary endpoints, n	14	9	0.254
Non-cardiovascular death	7	6	0.720
Peripheral emboli	0	1	1.000*
Major bleeding	**7†**	**2‡**	**0.101***

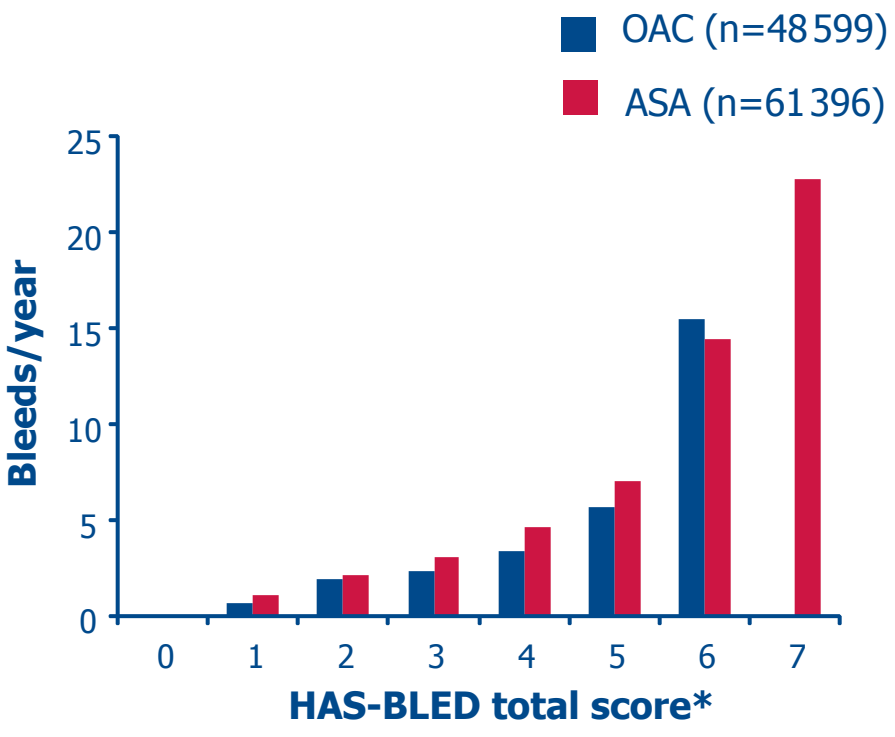
*Fisher test; †Includes two subdural bleeds, thalamic bleeding, subarachnoid bleed, urinary tract bleed, gastric bleed, and respiratory bleed; ‡Includes subarachnoid bleed and thalamic bleed; Sato H et al. Stroke 2006;37:447–51

Risk of major and intracranial bleeding not significantly different between ASA and OACs

Intracranial bleeding



Major bleeding



In the Swedish Atrial Fibrillation cohort study (n=182 678)

*Modified HAS-BLED score used in this study: score 0–2 indicates low bleeding risk; ≥3 indicates high bleeding risk

Friberg L et al. Eur Heart J 2012:33:1500–10;
Pisters R et al. Chest 2010;138:1093–100

No difference in overall bleeding events with ASA vs warfarin

- Prescriptions database analysis of 82,854 patients with AF prescribed antithrombotic therapy in Denmark

Events, %/patient-year, HR (95% CI)	ASA	Warfarin
Fatal/non-fatal bleeding	**3.7**	**3.9**
	0.93 (0.88–0.98)	
Fatal bleeding	0.4	0.2
	1.37 (1.13–1.65)	
Non-fatal bleeding	3.3	3.6
	0.84 (0.80–0.89)	
ICH	**0.5**	**0.6**
	0.78 (0.68–0.89)	
GI bleeding	1.5	0.9
	1.28 (1.17–1.41)	

GI = gastrointestinal

Hansen ML et al. Arch Intern Med 2010;170:1433–41

ASA no longer has a role in stroke prevention in patients with AF owing to significant limitations

- Global studies have shown limited efficacy and no safety advantage with ASA in stroke reduction[1–3]
  - Efficacy: no consistent difference vs placebo and inferior to warfarin
  - Safety: no consistent difference in major bleeding vs warfarin
- Similar results shown in studies of Asian populations[4–8]

1. Hart RG et al. Ann Intern Med 2007;146:857–67;
2. Friberg L et al. Eur Heart J 2012:33:1500–10;
3. Pisters R et al. Chest 2010;138:1093–100;
4. Sato H et al. Stroke 2006;37:447–51;
5. Guo Y et al, Int J Cardiol;S0167-5273:01308-3 [e-pub ahead of print];
6. Lee et al. J Cardiovasc Electrophysiol 2010; 21:501–7;
7. Hu DY et al. Zhonghua Xin Xue Guan Bing Za Zhi 2006;34:295–8;
8. Chen K-P et al. Chin Med J 2012;125:4355–60

CONTENTS

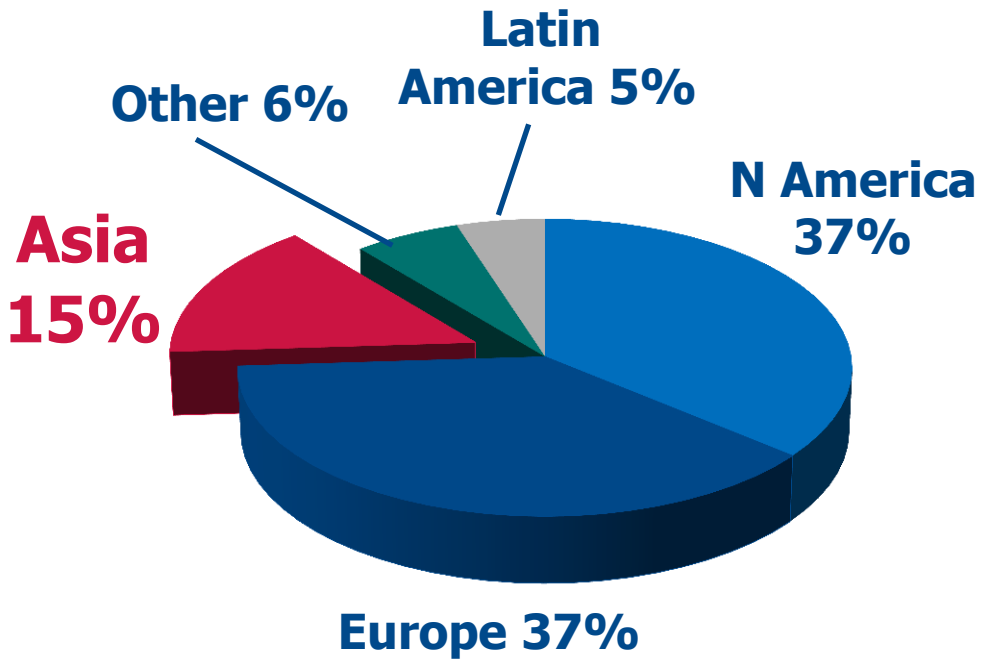
Efficacy and safety of dabigatran versus warfarin in patients with atrial fibrillation: Analysis in Asian population in RE-LY trial

Hori M et al. Stroke 2013;44:1891–6

RE-LY® Asian population analysis: recruitment by region (N=18 113)

Patients (n)

- East Asia 1648
  - China 541
  - Hong Kong 90
  - Japan 326
  - South Korea 336
  - Taiwan 355
- South Asia 1134
  - India 578
  - Malaysia 185
  - Philippines 157
  - Singapore 59
  - Thailand 155
- **Total** **2782**



Hori M et al. Stroke 2013;44:1891–6

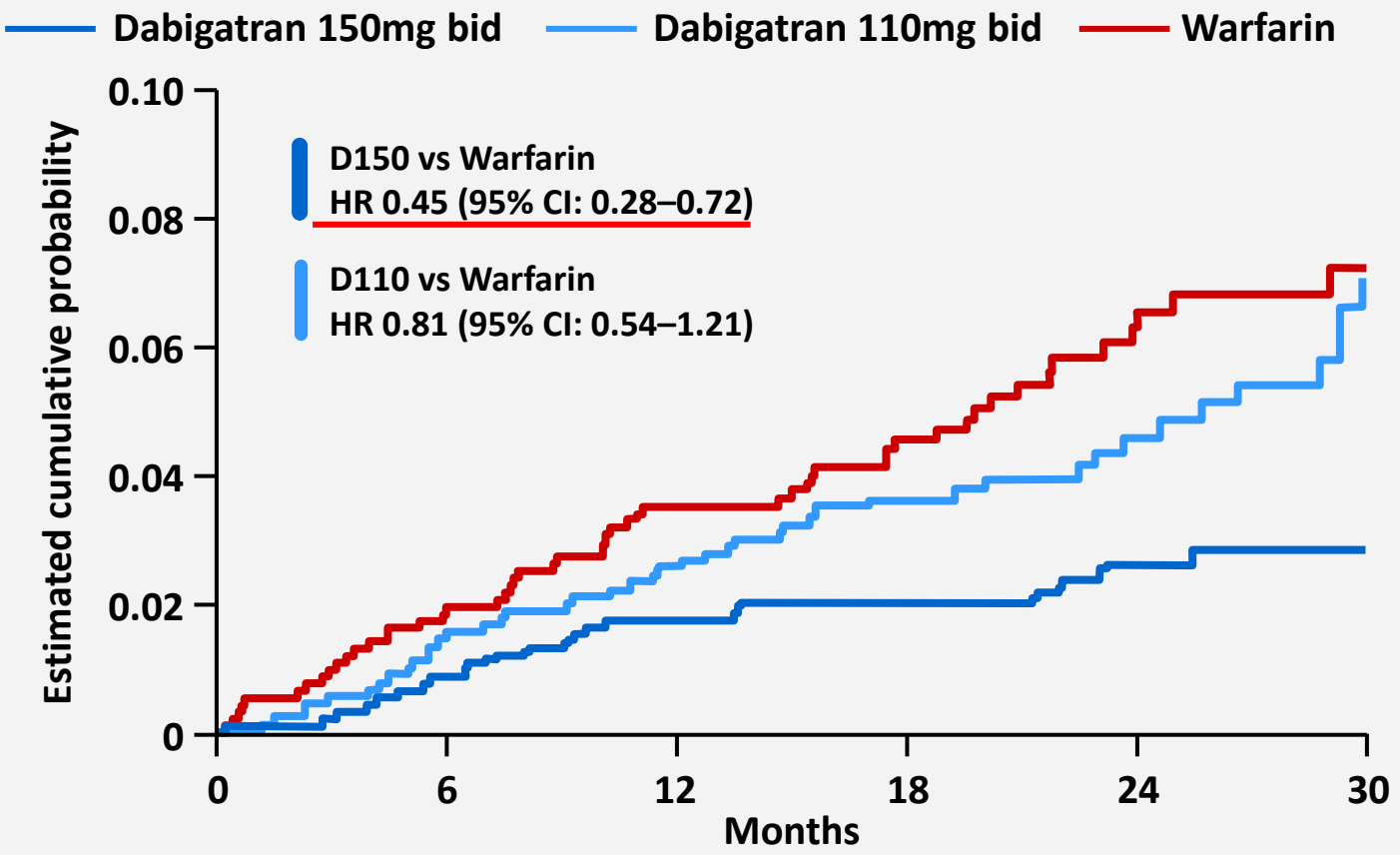
RE-LY® Asian population analysis: time in therapeutic range

- Mean TTR was lower in Asian patients than non-Asian patients
- Asian patients were less likely to be above, and more likely to be below, the therapeutic range than non-Asian patients

	Asia (n=880)			Non-Asia (n=4909)		
INR	<2.0	**2.0–3.0**	>3.0	<2.0	**2.0–3.0**	>3.0
Mean	35.4	**54.5**	10.1	19.8	**66.2**	14.0
Median	30.8	**56.5**	8.1	15.4	**68.9**	11.6

Hori M et al. Stroke 2013;44:1891–6

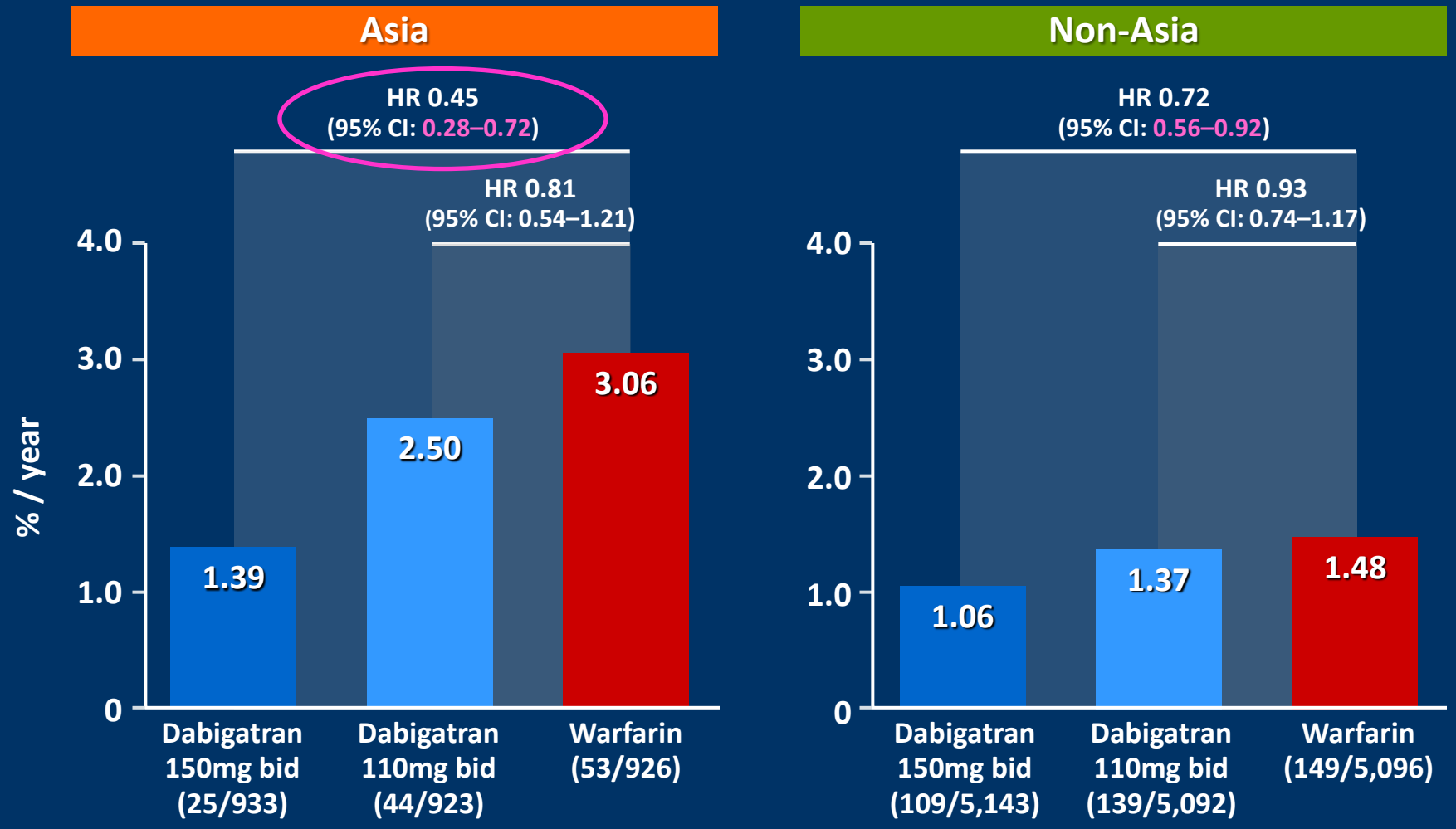
1. Efficacy outcome : Stroke or Systemic Embolism in Asia



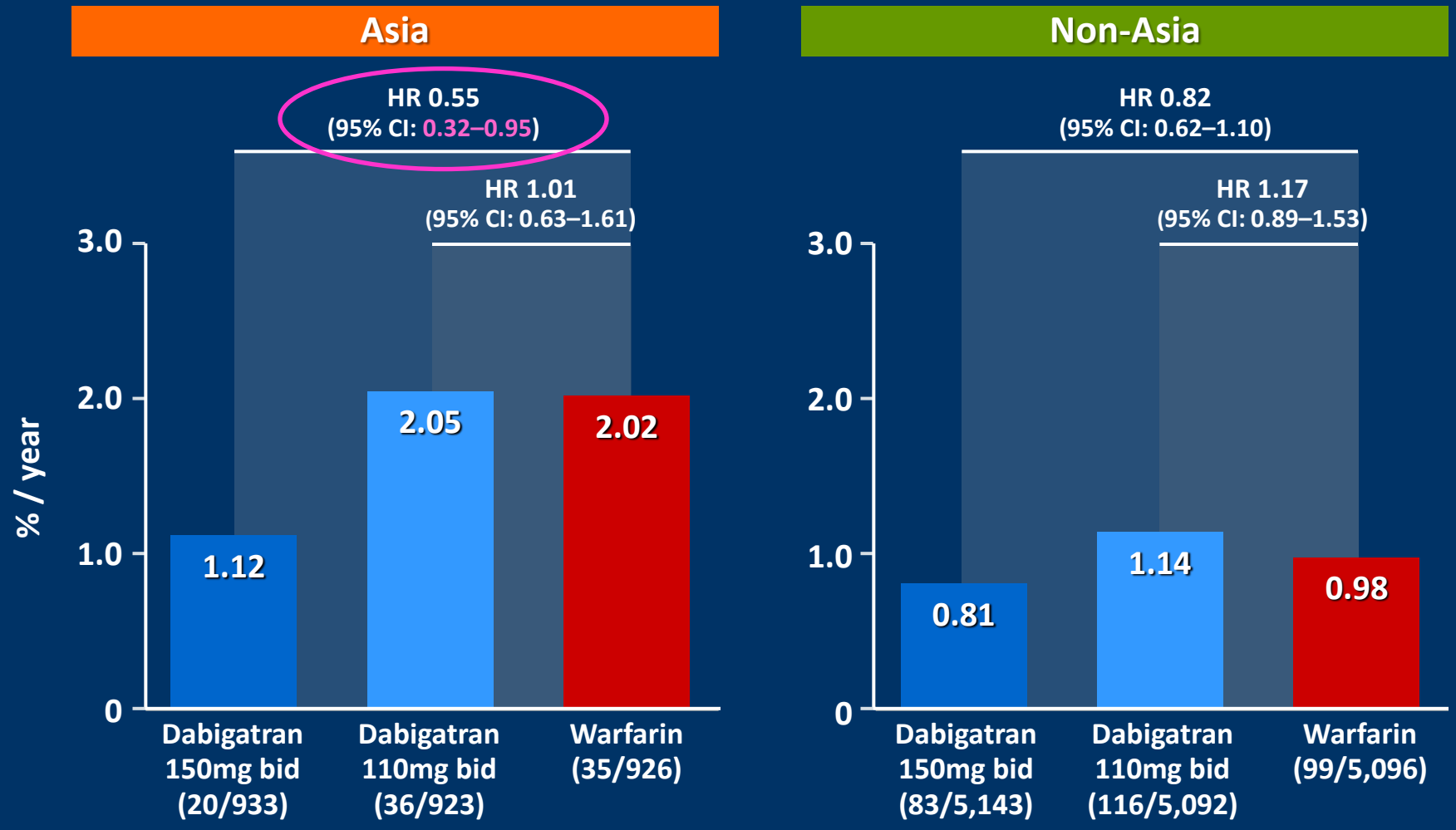
Subjects at risk						
DE 150mg bid	933	906	875	697	420	237
DE 110mg bid	923	888	866	683	401	216
Warfarin	926	886	858	664	382	198

Hori M et al. Stroke 2013;44:1891–6

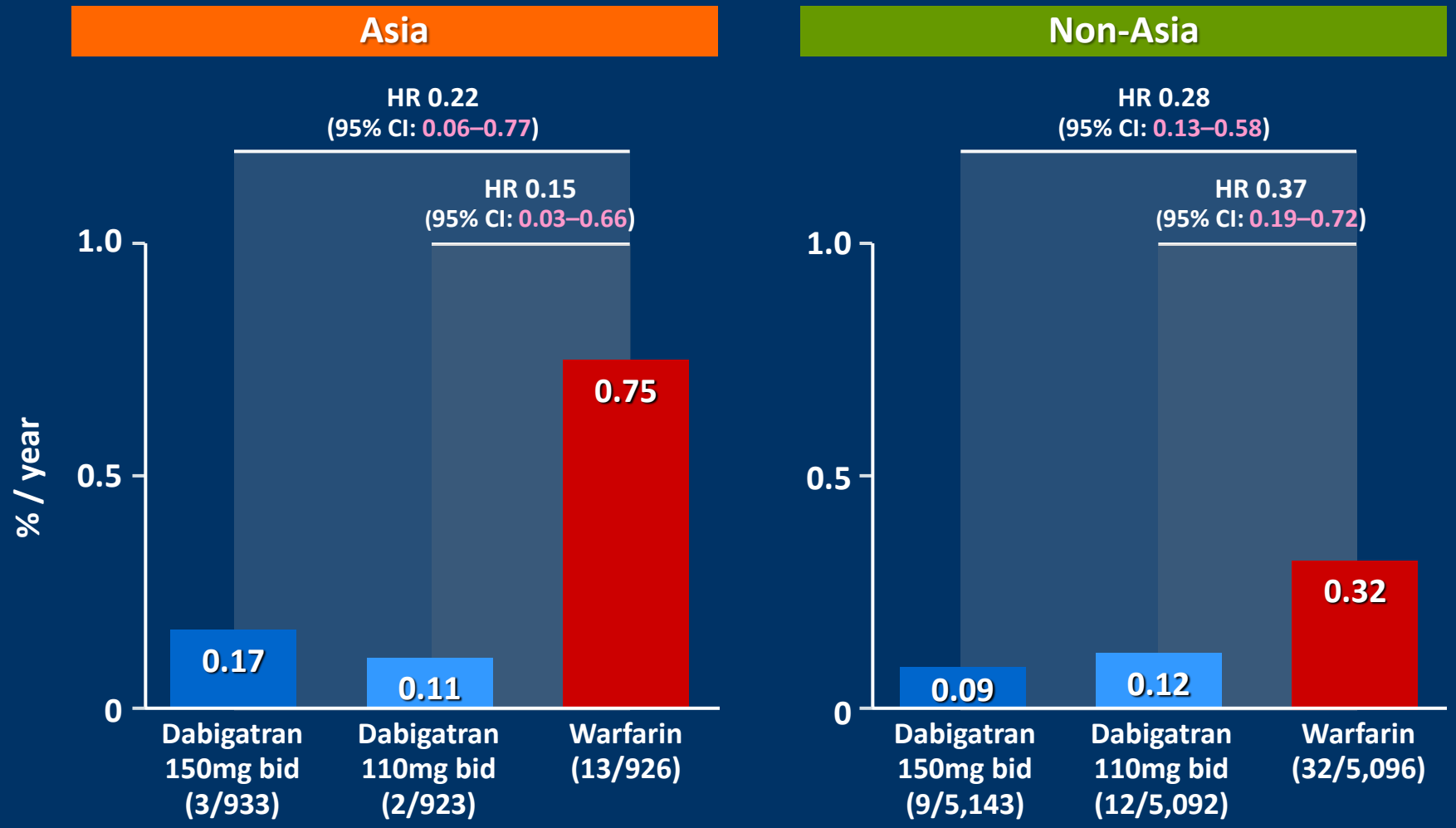
Primary Endpoint (Stroke or Systemic Embolism)



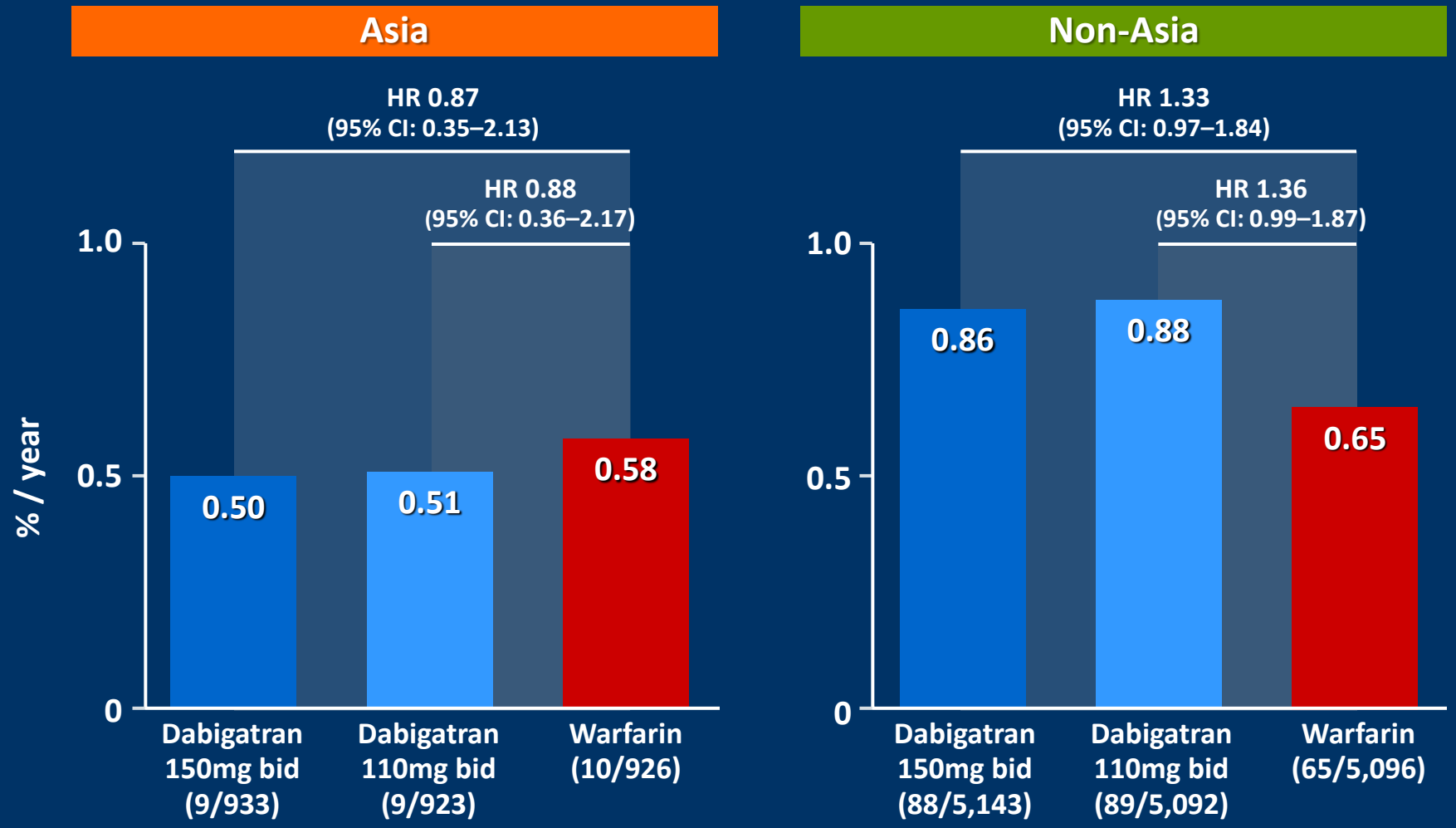
Ischemic Stroke



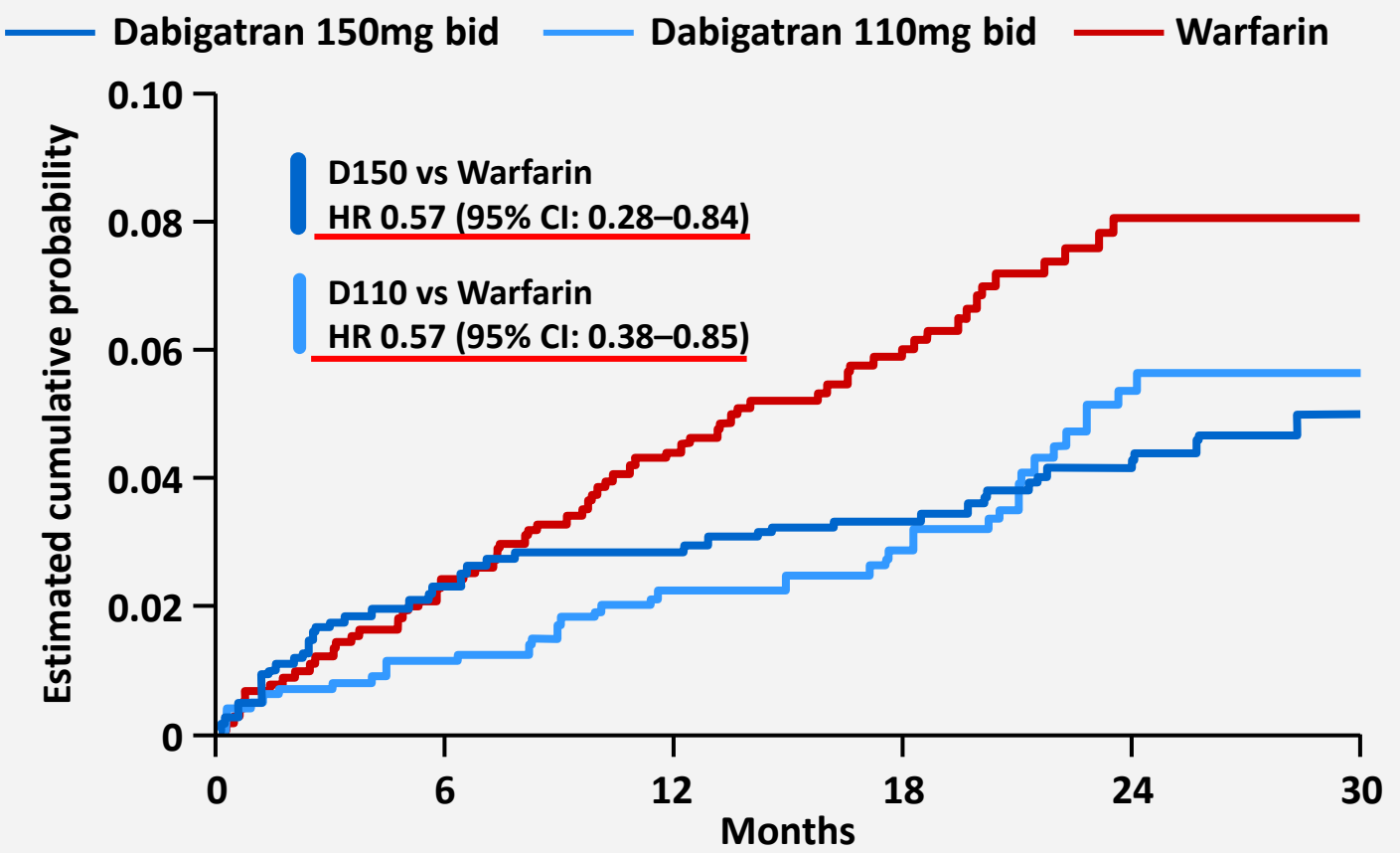
Hemorrhagic Stroke



Myocardial Infarction



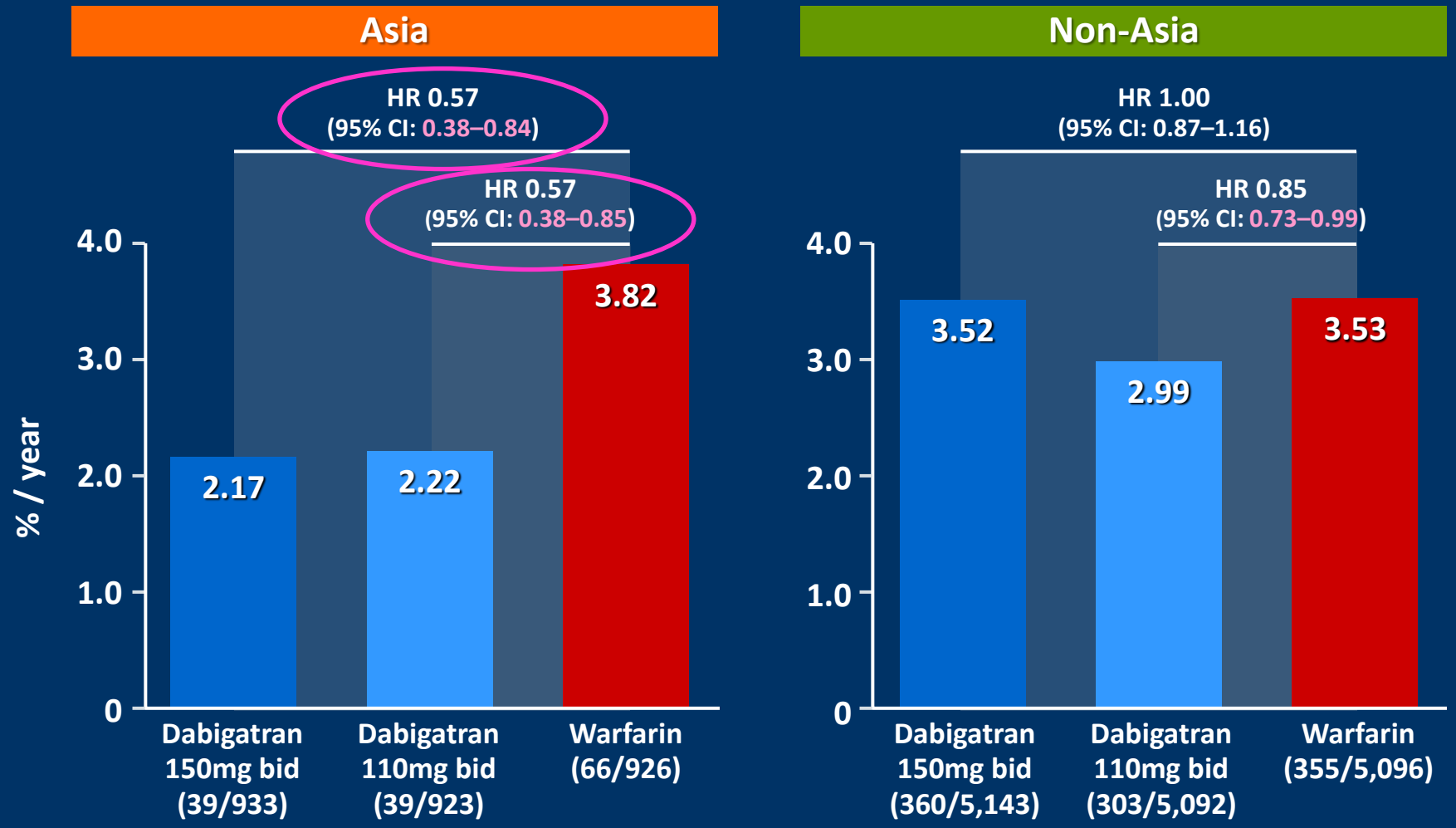
2. Safety outcome : Major Bleeding in Asia



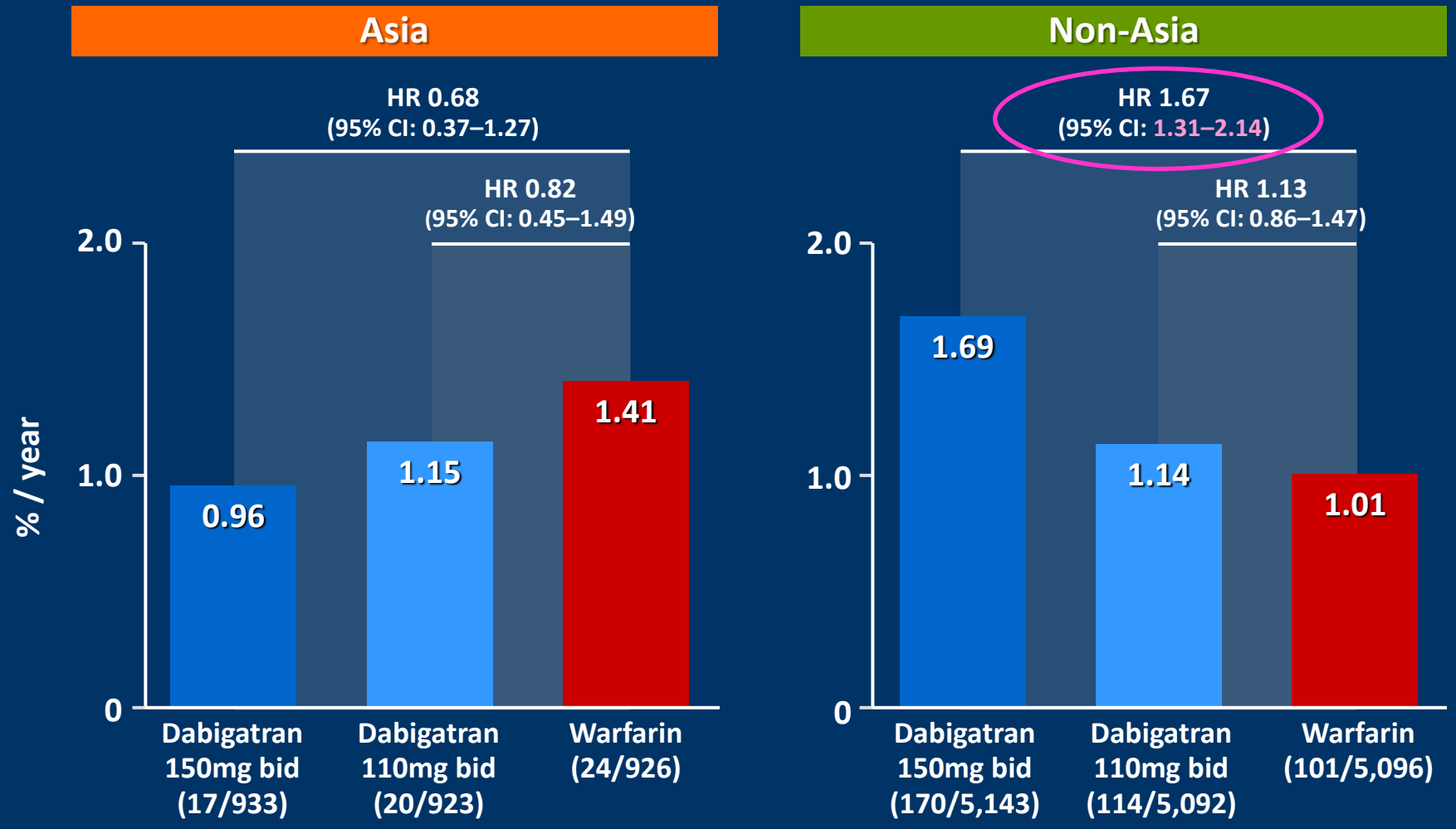
Subjects at risk						
DE 150mg bid	933	896	869	693	419	237
DE 110mg bid	923	889	863	685	400	219
Warfarin	926	884	850	658	374	191

Hori M et al. Stroke 2013;44:1891–6

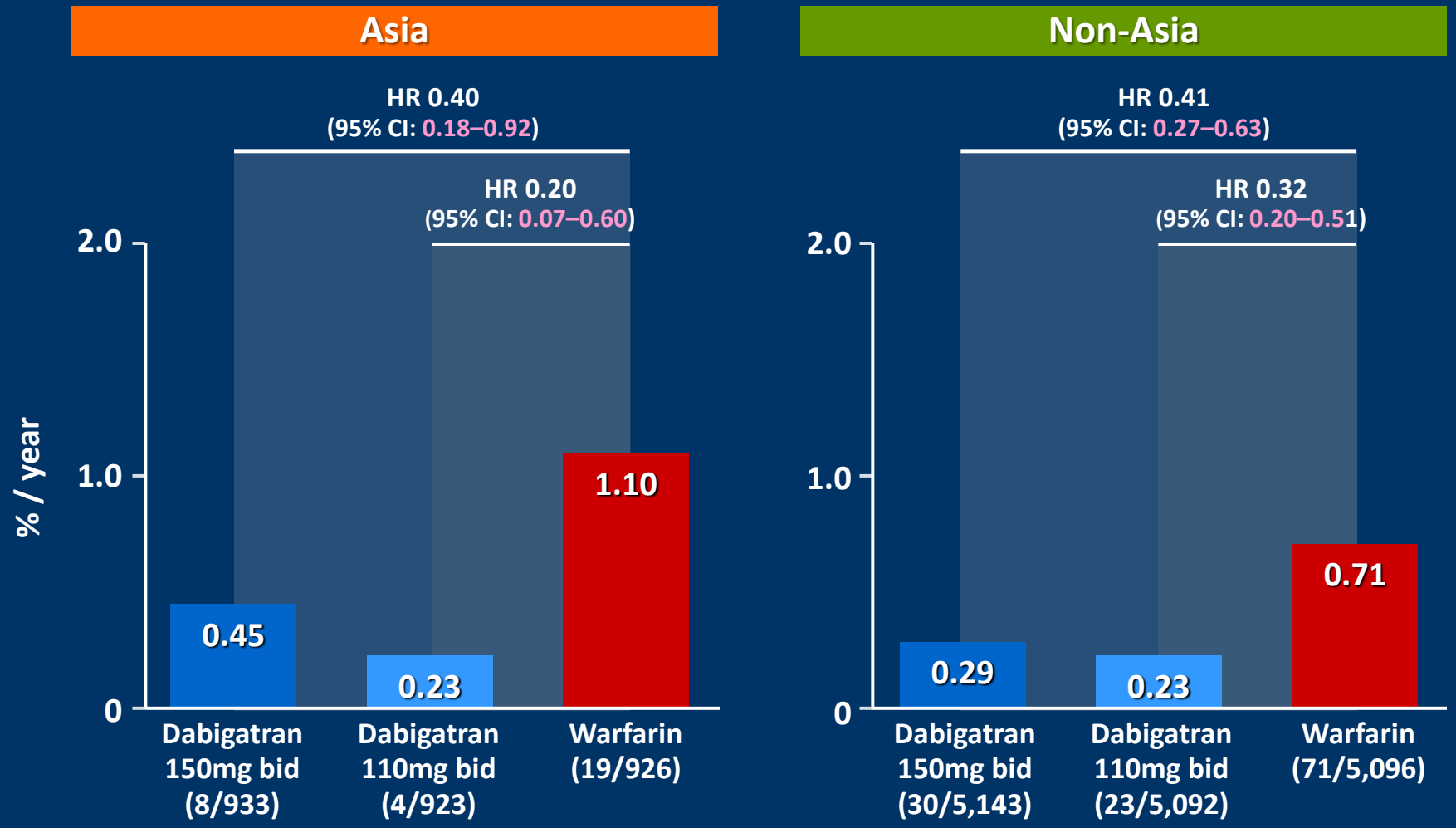
Major Bleeding



GI Major Bleeding



Intracranial Bleeding



Asian data in RE-LY : Summary 1

1. Although Asian patients had considerably more time below therapeutic range and were younger than non-Asian patients, there was a trend for more bleeding in Asians on warfarin.
2. The underlying cause of this higher bleeding rate in Asians may be associated with Asian sensitivity to warfarin, probably due to ethnic differences.

Asian data in RE-LY : Summary 2

3. The effects of dabigatran against stroke or systemic embolism are comparable in Asian and non-Asian patients for both doses of dabigatran compared to warfarin.
4. Dabigatran *reduced the risk of major bleeding in Asians more than in non-Asians*.
5. Dabigatran reduced numerically the incidence of MI and GI bleeding in Asians, compared to warfarin (not consistent with the result in non-Asians)

ROCKET AF East Asia cohort: stroke/SE

- Efficacy in a subgroup of patients from China, Korea, Taiwan, and Hong Kong (N=932/14,254) was consistent with that of the total study population

	Rivaroxaban		Warfarin		Rivaroxaban vs warfarin			
	n/N	%/year	n/N	%/year	HR	(95% CI)	P value non-inf.	P value superi.
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[2]	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
ITT = intention to treat

1. Patel MR et al. N Engl J Med 2011;365:883–91; **2.** Wong L et al. Presented January 2013

ROCKET AF East Asia cohort: major and non-major clinically relevant bleeding

- Safety in a subgroup of patients from China, Korea, Taiwan, and Hong Kong was consistent with that of the total study population

	Rivaroxaban		Warfarin		Rivaroxaban vs warfarin		
Cohort	**n/N**	**Event rate (%/year)**	**n/N**	**Event rate (%/year)**	**HR**	**(95% CI)**	**P value**
ROCKET AF overall[1]	1475/ 7111	**14.9**	1449/ 7125	**14.5**	**1.03**	(0.96–1.11)	0.44
ROCKET AF East Asia cohort[2]	121/ 466	**20.9**	122/ 462	**20.7**	**1.01**	(0.79–1.30)	0.929

All bleeding events based on the first event in the safety population during treatment (first dose to 2 days after last dose of study medication)

1. Patel MR et al. N Engl J Med 2011;365:883–91; **2.** Wong L et al. Presented January 2013

ARISTOTLE : East Asian data

Greater Reductions in Hemorrhagic Stroke and Major or CRNM bleeding among East Asians

Endpoint	East Asia (n=1,993)			Other Regions of the World (n=16,202)			Interaction P Value
	Apixaban	Warfarin	HR (95 % CI)	Apixaban	Warfarin	HR (95 % CI)	
	Rate/yr (n)	Rate/yr (n)	Apixaban vs. Warfarin	Rate/yr (n)	Rate/yr (n)	Apixaban vs. Warfarin	
Stroke or SE	2.52 (44)	3.39 (60)	0.743 (0.504-1.097)	1.12 (168)	1.38 (205)	0.810 (0.661-0.993)	0.6977
Hemorrhagic Stroke	**0.34 (6)**	**1.33 (24)**	**0.253 (0.103-0.618)**	**0.23 (34)**	**0.36 (54)**	**0.623 (0.406-0.957)**	**0.0745**
MI	0.45 (8)	0.39 (7)	1.170 (0.424-3.226)	0.54 (82)	0.64 (95)	0.853 (0.635-1.147)	0.5634
All-cause death	2.86 (52)	2.81 (52)	1.020 (0.695-1.499)	3.60 (551)	4.08 (617)	0.884 (0.788-0.992)	0.4901
Major Bleeding	2.02 (33)	3.84 (63)	0.526 (0.345-0.802)	2.14 (294)	3.00 (399)	0.717 (0.617-0.834)	0.1743
Major or CRNM bleeding	**3.46 (56)**	**7.16 (114)**	**0.486 (0.353-0.669)**	**4.14 (557)**	**5.87 (763)**	**0.708 (0.634-0.789)**	**0.0301**
Any Bleeding	20.47 (278)	31.27 (387)	0.675 (0.579-0.78)	17.80 (2078)	25.19 (2673)	0.720 (0.680-0.763)	0.4026
Intracranial hemorrhage	0.67 (11)	1.88 (31)	0.359 (0.180-0.714)	0.30 (41)	0.67 (91)	0.440 (0.304-0.636)	0.5953

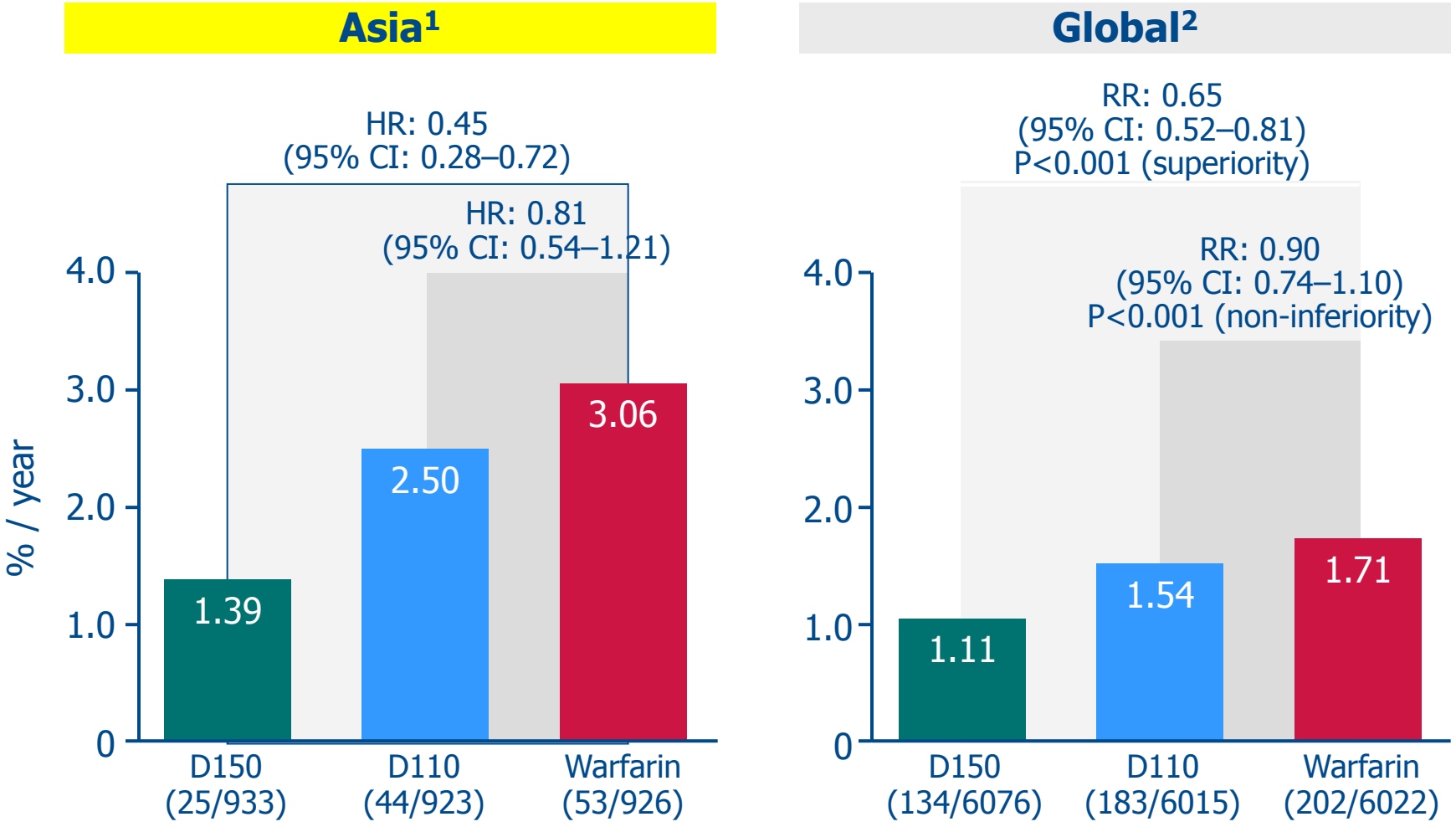
European Heart Journal (2013) 34 (Abstract Supplement), 1039

Asian Data on Stroke Prevention in Atrial Fibrillation : summary

- An increased risk of haemorrhagic events in Asian patients can result in underuse of OACs
- **ASA**, more frequently used in Asia, is not as effective as OACs in the prevention of stroke in AF with no major safety advantage
- Dabigatran and other NOACs provides superior prevention of stroke along with a reduced risk of major bleeding and ICH compared with warfarin in Asian patients with AF


Thank You !

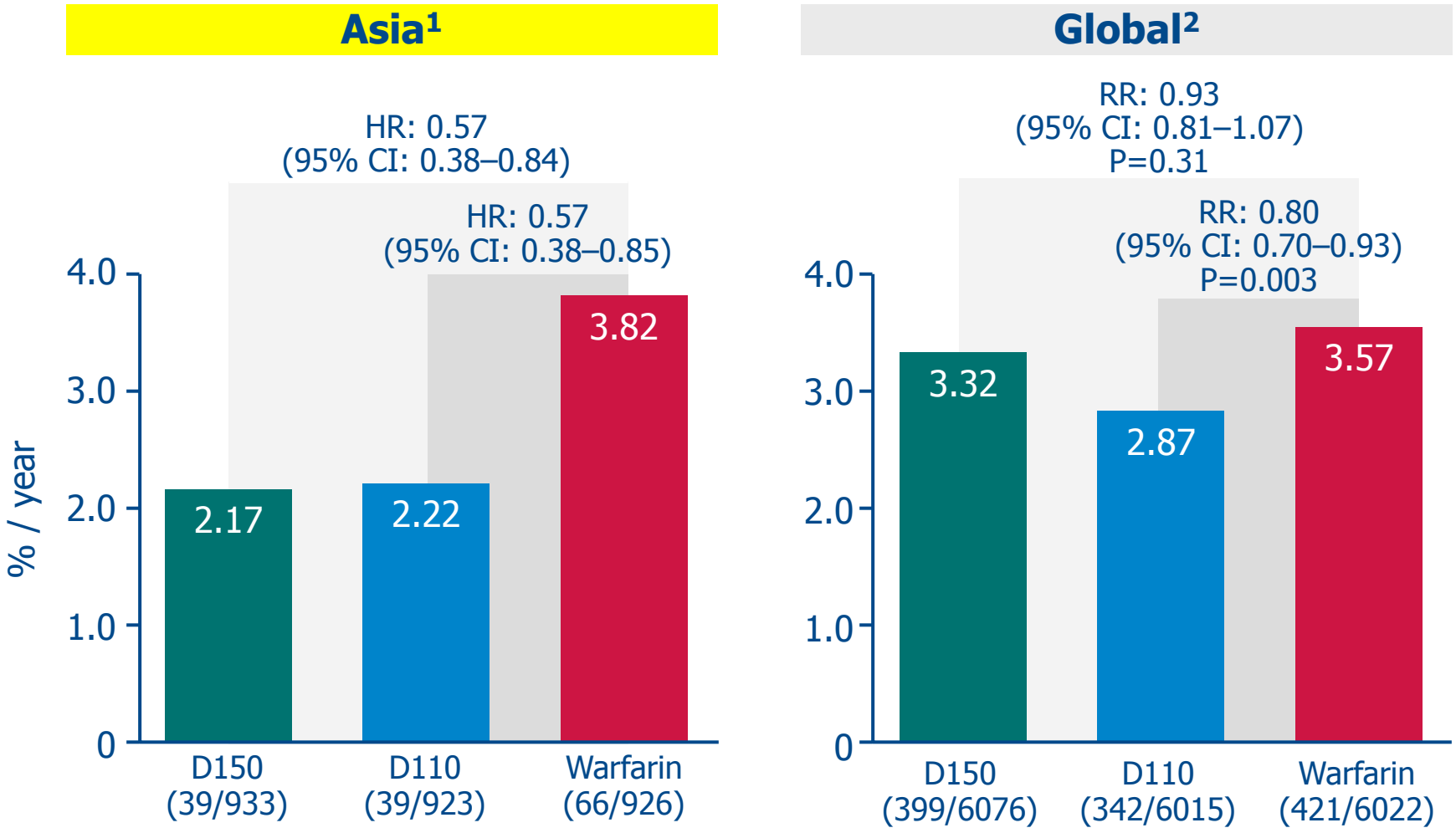
RE-LY® Asian population analysis: stroke or systemic embolism



Interaction: D150 vs warfarin P=0.09; D110 vs warfarin P=0.56

1. Hori M et al. Stroke 2013;44:1891–6; **2.** Connolly SJ et al. N Engl J Med 2010;363:1875–6

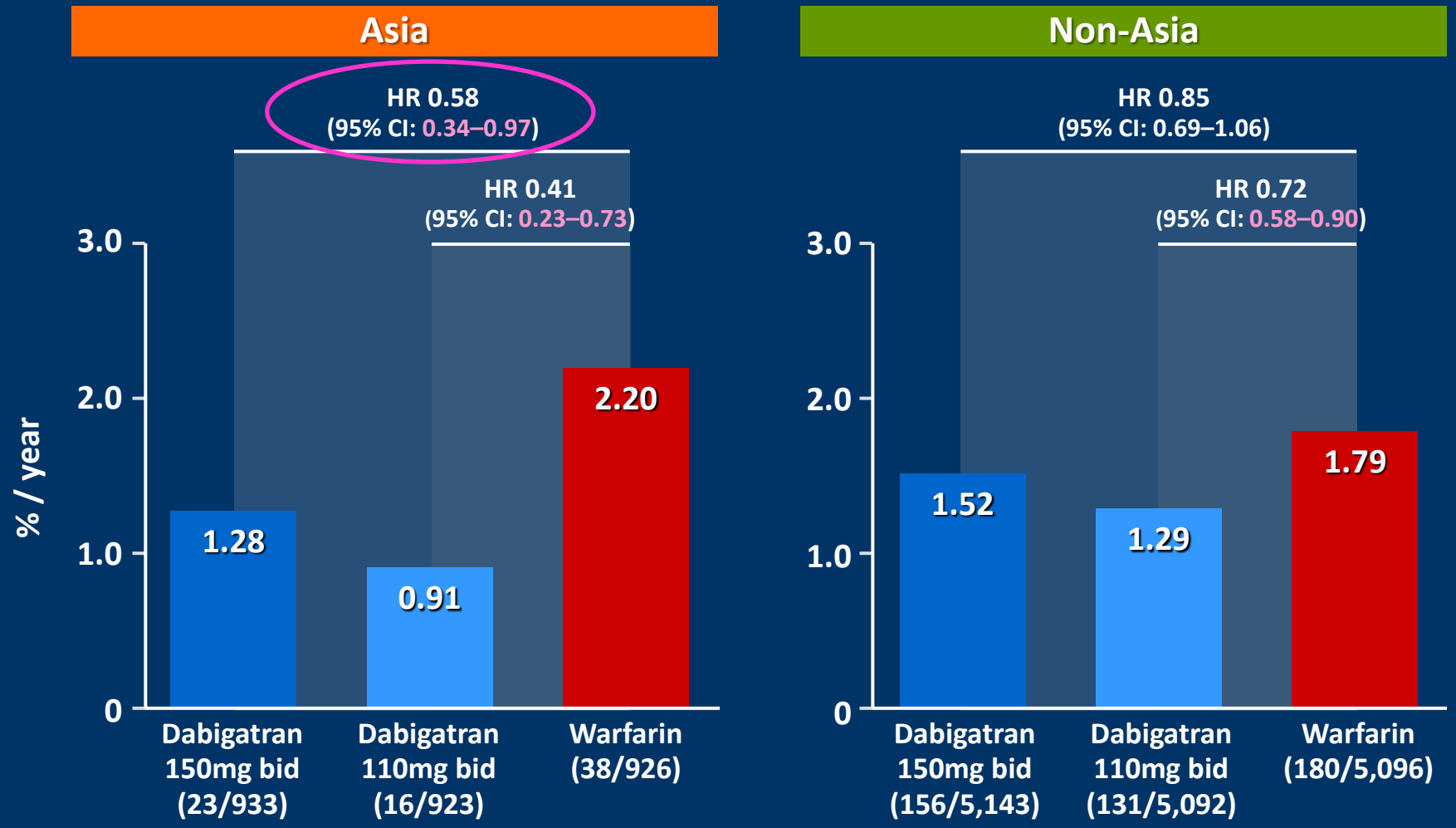
RE-LY® Asian population analysis: major bleeding



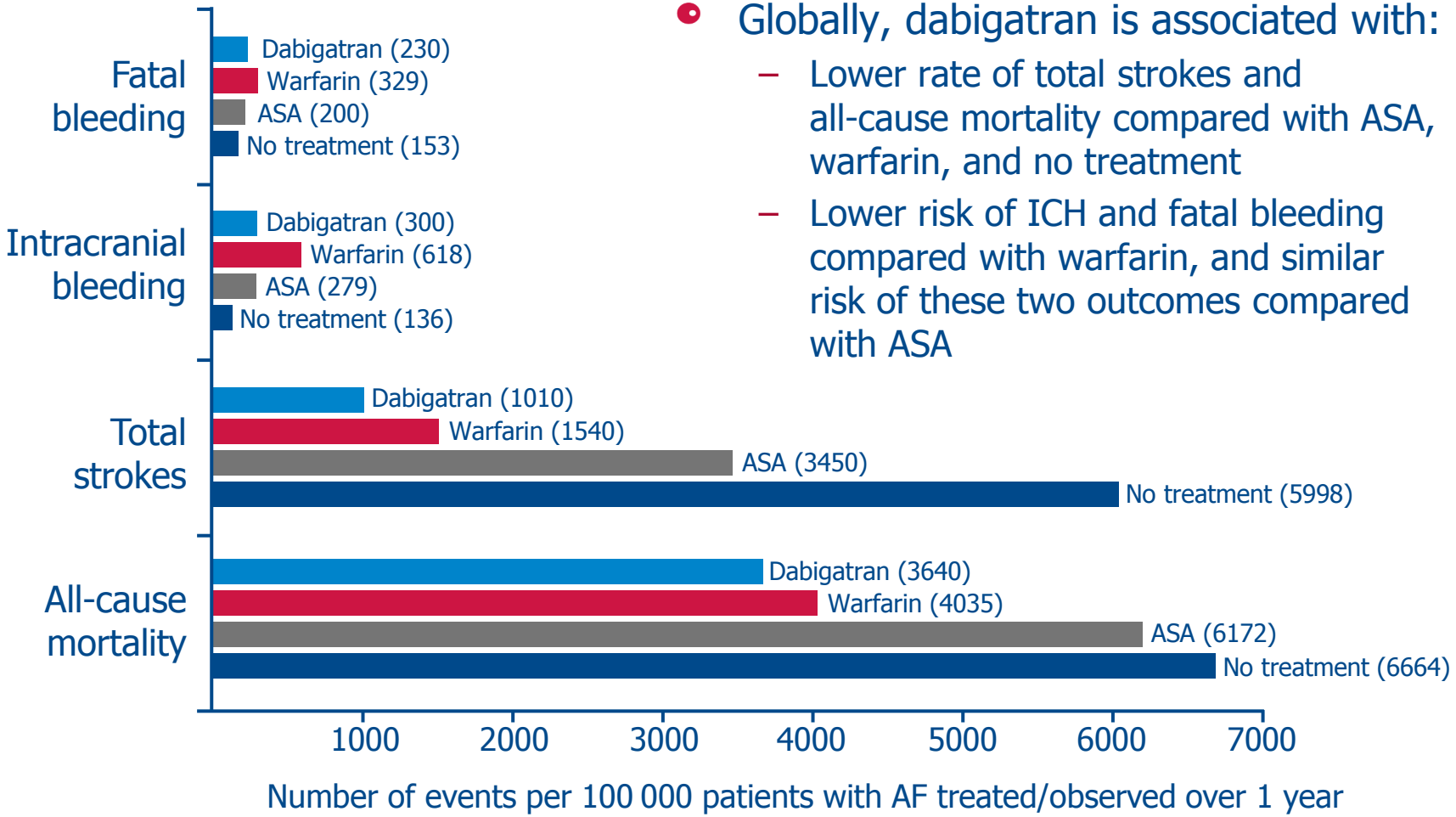
Interaction: D150 vs warfarin P= 0.008; D110 vs warfarin P=0.07

1. Hori M et al. Stroke 2013;44:1891–6; **2.** Connolly SJ et al. N Engl J Med 2010;363:1875–6

Life Threatening Bleeding



Global stroke prevention data



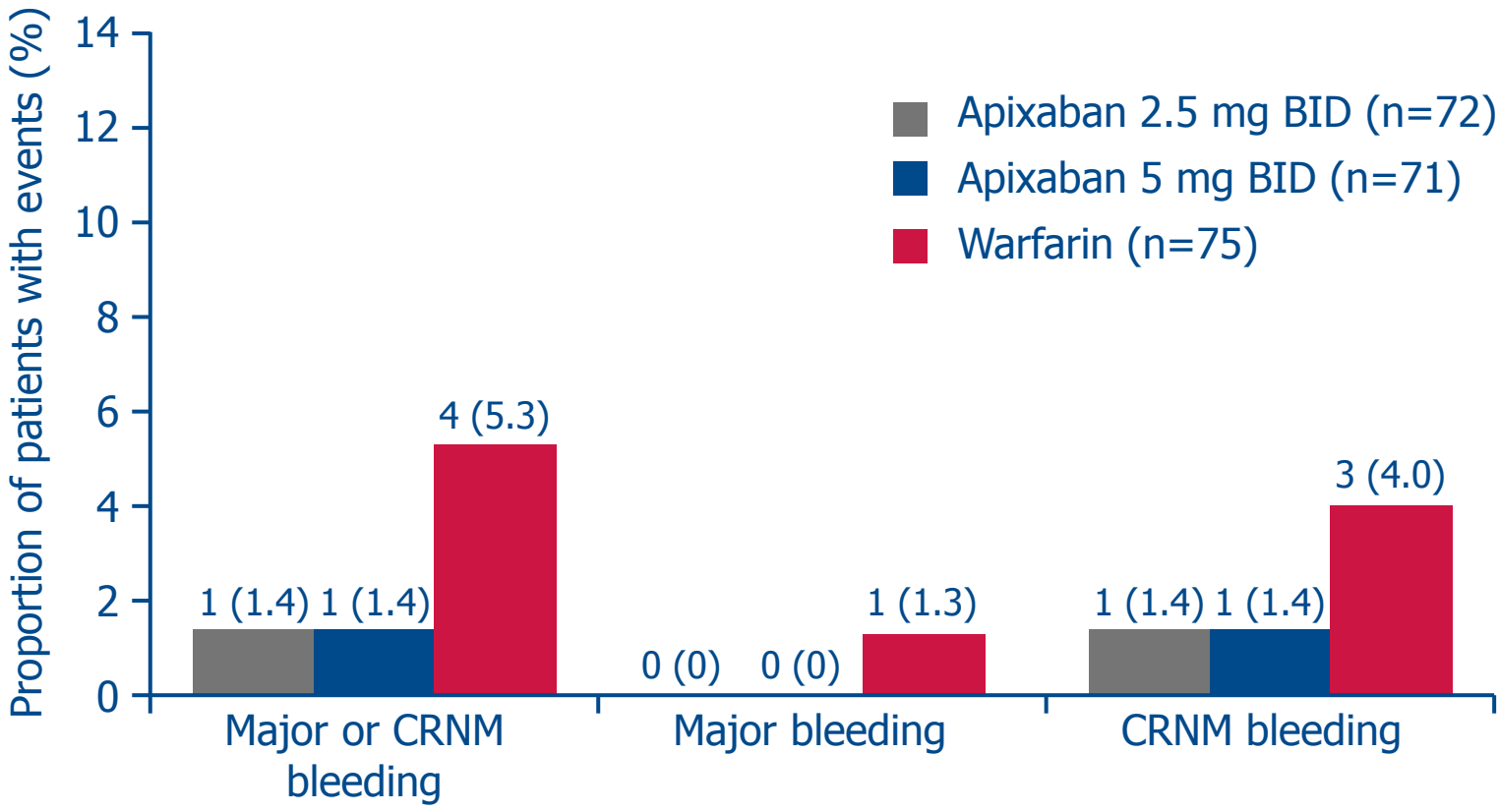
- Globally, dabigatran is associated with:
  - Lower rate of total strokes and all-cause mortality compared with ASA, warfarin, and no treatment
  - Lower risk of ICH and fatal bleeding compared with warfarin, and similar risk of these two outcomes compared with ASA

Data are estimates derived from contemporary global randomized controlled trials of ASA and dabigatran and from a meta-analysis of randomized controlled trials of ASA or warfarin vs placebo/no treatment in AF

Eikelboom et al. J Thromb Haemost 2012;10:966–8

ARISTOTLE-J: safety in Japanese patients with AF

- Phase II study showed that apixaban 2.5 mg and 5 mg BID were well tolerated, with lower bleeding rates vs warfarin over 12 weeks



CRNM = Clinically relevant non-major

Ogawa S et al. Circ J 2011;75:1852–9