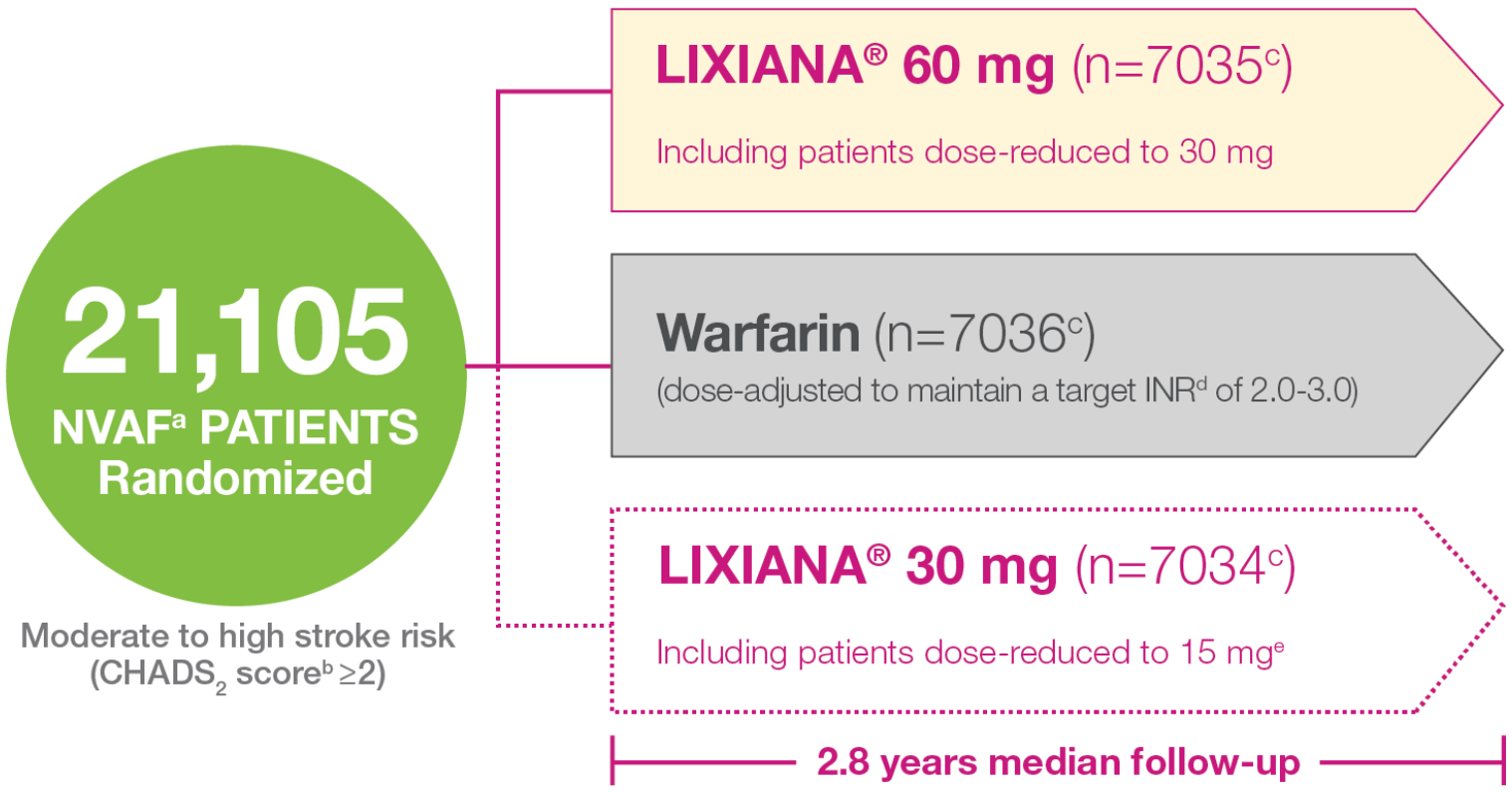
Safe & Convenient Anticoagulation therapy for NVAF patients

Keimyung University Dongsan Medical Center
Hyoung-Seob Park

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

ENGAGE AF-TIMI 48 —the Largest and Longest Clinical Trial Among NOACs'[1,2]



[a] Nonvalvular atrial fibrillation.
[b] A validated measure for assessing stroke risk. The $CHADS_2$ scoring is calculated by assigning 1 point each for a history of congestive heart failure, hypertension, age ≥75 years, or diabetes mellitus and by assigning 2 points for history of stroke or transient ischemic attack.[1]
[c] Twenty-three patients in the LIXIANA® 60/30 mg treatment arm and 24 patients in the warfarin arm did not receive study drug, resulting in 7012 patients included in each arm of the safety analysis, which reflects the on-treatment period.[1] There were 32 patients in the LIXIANA® 30/15 mg treatment arm who did not receive study drug, resulting in 7002 patients in the safety analysis, which reflects the on-treatment period.
[d] International normalized ratio.[1]
[e] The LIXIANA® 30/15 mg dosage is not approved for use.

1. Giugliano RP et al. *N Engl J Med.* 2013;369(22):2093-2104. **2.** Ruff CT et al. *Lancet*. 2014;383(9921):955-962.
3. Giugliano RP et al. *N Engl J Med.* 2013;369(22):Supplemental Appendix.

ENGAGE AF-TIMI 48 Prospectively Accounted for Managing Patients With Clinical Factors That Increase Bleeding Risk

Edoxaban dose was halved from 60 to 30 mg or from 30 to 15 mg QD.

- At randomization:
  - CrCl 30–50 mL/min
  - Body weight ≤60 kg
  - Concomitant use of specific P-gp inhibitor (quinidine, verapamil, dronedarone)*
- During study:
  - CrCl 30–50 mL/min and >20% drop from baseline
  - Body weight ≤60 kg and >10% drop from baseline
  - Concomitant use of specific P-gp inhibitors (quinidine, verapamil, dronedarone)*

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

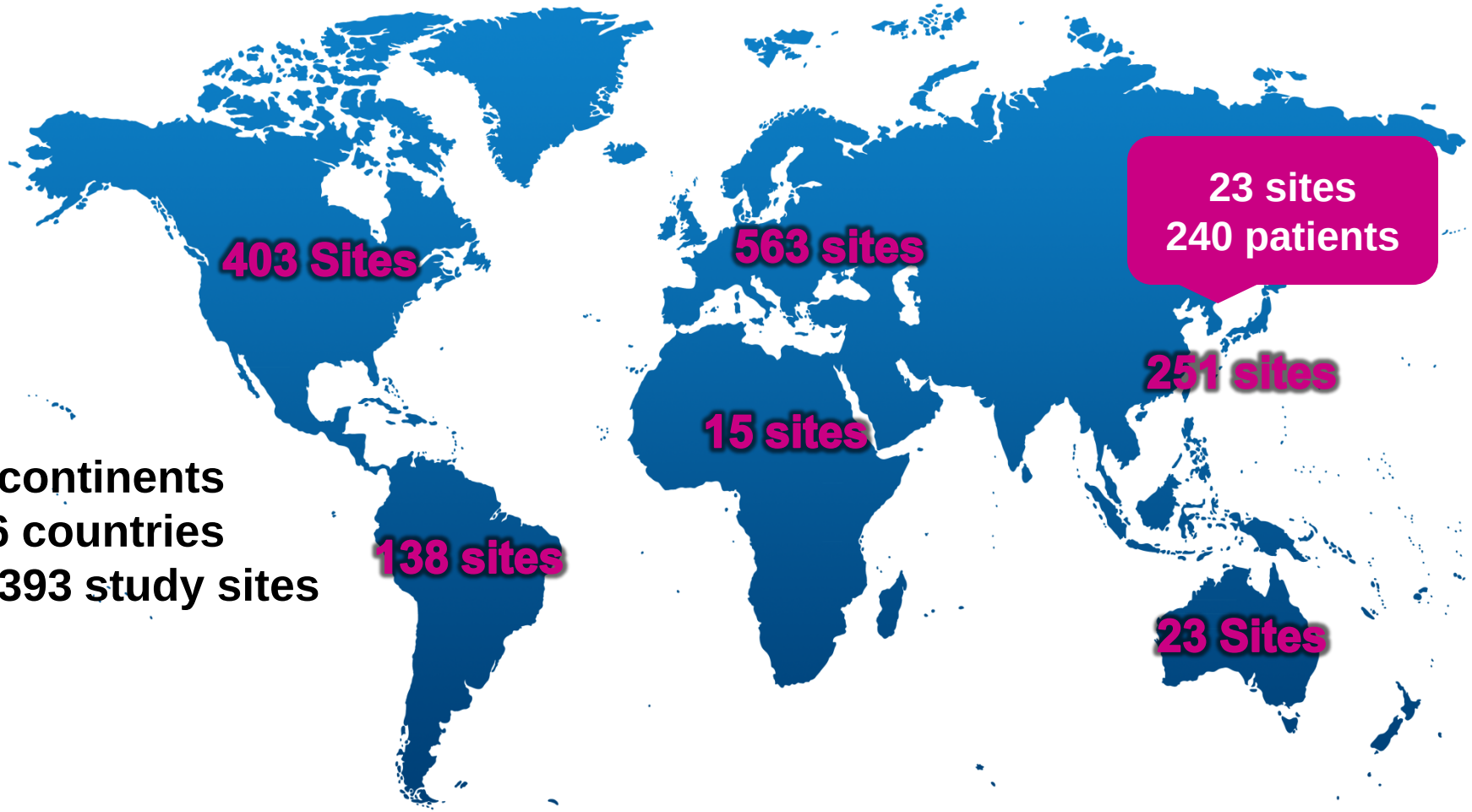
Primary efficacy and principal safety outcome measures

- Primary efficacy
  - Time to first stroke (ischemic or haemorrhagic) or SEE

- Principal safety
  - Major bleeding as defined by ISTH
    - Fatal bleeding, and/or
    - Symptomatic bleeding in a critical area or organ such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or
    - Bleeding causing a fall in haemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells

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

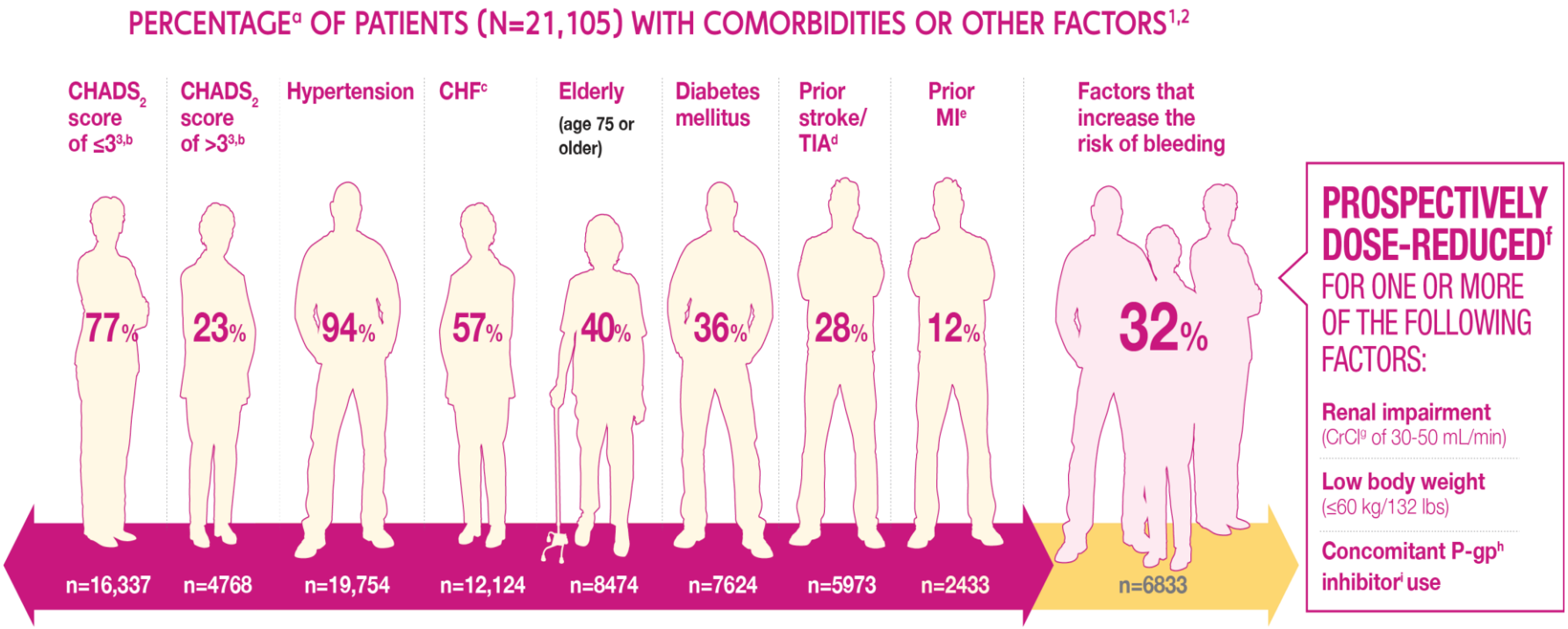
Global participants



6 continents
46 countries
1,393 study sites

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

ENGAGE AF-TIMI 48 Was Designed to Reflect the Broad Range of Patients [1,2]



[a] Percentages are approximate. [b] Mean $CHADS_2$ score in the trial was 2.8. [c] Congestive heart failure. [d] Transient ischemic attack. [e] Myocardial infarction. [f] ~32% of patients (~25% [n=5356] at randomization, and an additional ~7% [n=1477] during the trial) received a dose reduction (half-dose). [g] Creatinine clearance. [h] P-glycoprotein. [i] Verapamil, dronedarone, or quinidine.

1. Giugliano RP et al. *N Engl J Med.* 2013;369(22):2093-2104. **2.** Giugliano RP et al. *N Engl J Med.* 2013;369(22):Supplemental Appendix.

LIXIANA® 60/30mg is approved and 30/15mg is not approved

	HD edoxaban *vs* warfarin			LD edoxaban *vs* warfarin		
	No dose reduction, HR (95% CI)	Dose reduced, HR (95% CI)	$p_{interaction}$	No dose reduction, HR (95% CI)	Dose reduced, HR (95% CI)	$p_{interaction}$
Stroke or SEE	0·78 (0·61–0·99)	0·81 (0·58–1·13)	0·85	1·07 (0·86–1·34)	1·07 (0·79–1·46)	0·99
Ischaemic stroke	0·94 (0·70–1·24)	0·96 (0·63–1·46)	0·91	1·43 (1·11–1·85)	1·79 (1·25–2·58)	0·32
All-cause mortality	0·94 (0·76–1·17)	0·85 (0·62–1·17)	0·59	0·79 (0·63–0·99)	0·94 (0·69–1·28)	0·37
Major bleed	0·88 (0·76–1·03)	0·63 (0·50–0·81)	0·023	0·55 (0·46–0·65)	0·31 (0·23–0·42)	0·002
Fatal bleed	0·61 (0·35–1·07)	0·46 (0·23–0·92)	0·54	0·51 (0·28–0·91)	0·15 (0·05–0·43)	0·044
ICH	0·47 (0·32–0·68)	0·46 (0·27–0·78)	0·94	0·40 (0·27–0·60)	0·11 (0·04–0·28)	0·011
GI bleed	1·32 (1·06–1·65)	1·00 (0·67–1·47)	0·21	0·70 (0·54–0·91)	0·57 (0·36–0·89)	0·43

HD=higher dose. LD=low dose. HR=hazard ratio. SEE=systemic embolic event. ICH=intracranial haemorrhage. GI=gastrointestinal.

Table 2: **Relative efficacy and safety of edoxaban compared with warfarin stratified by dose reduction status**

Lancet. 2015;385(9984):2288-95.

Patients Characteristics

Characteristic	Warfarin (n=7,036)	Edoxaban 60/30 mg (n=7,035)
Median age [IQR], years	72 [64–78]	72 [64–78]
Female sex , n (%)	2,641 (37.5)	2,669 (37.9)
Region, n (%)		
North America	1,562 (22.2)	1,559 (22.2)
Latin America	888 (12.6)	886 (12.6)
Western Europe	1,078 (15.3)	1,079 (15.3)
Eastern Europe	2,381 (33.8)	2,383 (33.9)
Asia Pacific and South Africa	1,127 (16.0)	1,128 (16.0)
Paroxysmal atrial fibrillation, n (%)	1,778 (25.3)	1,753 (24.9)
Qualifying risk factors, n (%)		
Age ≥75 years	2,820 (40.1)	2,848 (40.5)
Prior stroke or transient ischemic attack	1,991 (28.3)	1,976 (28.1)
Chronic heart failure	4,048 (57.5)	4,097 (58.2)
Diabetes mellitus	2,521 (35.8)	2,559 (36.4)
Hypertension requiring treatment	6,588 (93.6)	6,591 (93.7)

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

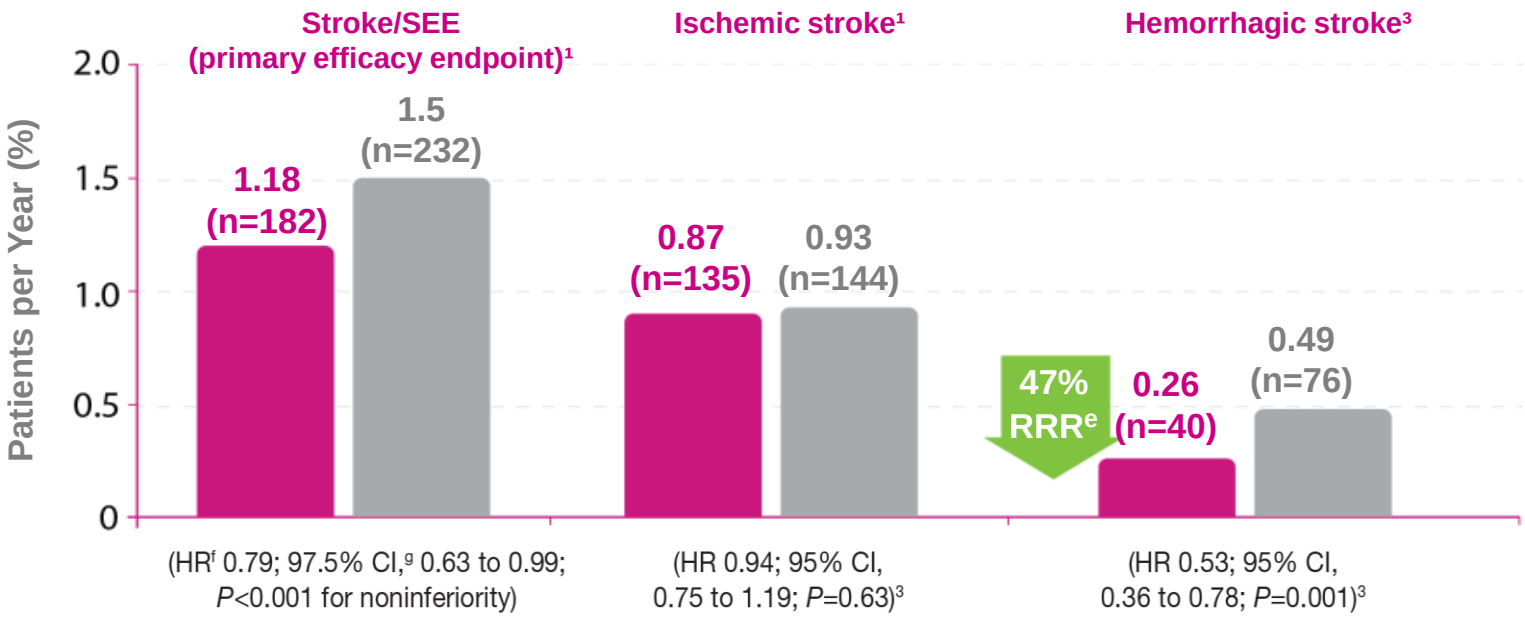
Patients Characteristics

Characteristic	Warfarin (n=7,036)	Edoxaban 60/30 mg (n=7,035)
$CHADS_2$, mean±SD, n (%)	2.8±1.0	2.8±1.0
≤3	5,445 (77.4)	5,422 (77.1)
4–6	1,591 (22.6)	1,613 (22.9)
Dose reduction at randomization*, n (%)	1,787 (25.4)	1,784 (25.4)
Creatinine clearance 30–50 mL/min	1,361 (19.3)	1,379 (19.6)
Weight ≤60 kg	701 (10.0)	684 (9.7)
Verapamil or quinidine	243 (3.5)	258 (3.7)
Previous vitamin K antagonist for ≥60 days, n (%)	4,138 (58.8)	4,140 (58.8)
Medications at time of randomization, n (%)		
Aspirin	2,092 (29.7)	2,070 (29.4)
Thienopyridine	164 (2.3)	174 (2.5)
Amiodarone	827 (11.8)	866 (12.3)
Digoxin or digitalis preparations	2,176 (30.9)	2,078 (29.5)

*Patients with CrCl 30–50 mL/min, body weight ≤60 kg or those receiving concomitant strong P-gp inhibitors (verapamil, quinidine or dronedarone) at randomization received a 50% reduction in the dose of edoxaban to maintain similar exposure to the patient with out these factors

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

Once-daily LIXIANA® Was Comparable to Warfarin in Reducing Stroke/SEE Risk[1]



[a] Time from first dose of study drug to last dose plus 3 days.
[b] Systemic embolic events.
[c] LIXIANA® 60 mg was noninferior to warfarin for the primary endpoint of stroke/SEE.
[d] Includes patients taking LIXIANA® 60 mg and those dose-reduced to 30 mg.
[e] Relative risk reduction.
[f] Hazard ratio.
[g] Confidence interval.

1. Giugliano RP et al. *N Engl J Med*. 2013;369(22):2093-2104. 2. SAVAYSA [package insert]. Parsippany, NJ: Daiichi Sankyo, Inc; 2014 .
3. ENGAGE AF-TIMI 48 CSR.

Once-daily LIXIANA® Was Comparable to Warfarin in Reducing Stroke/SEE Risk[1]

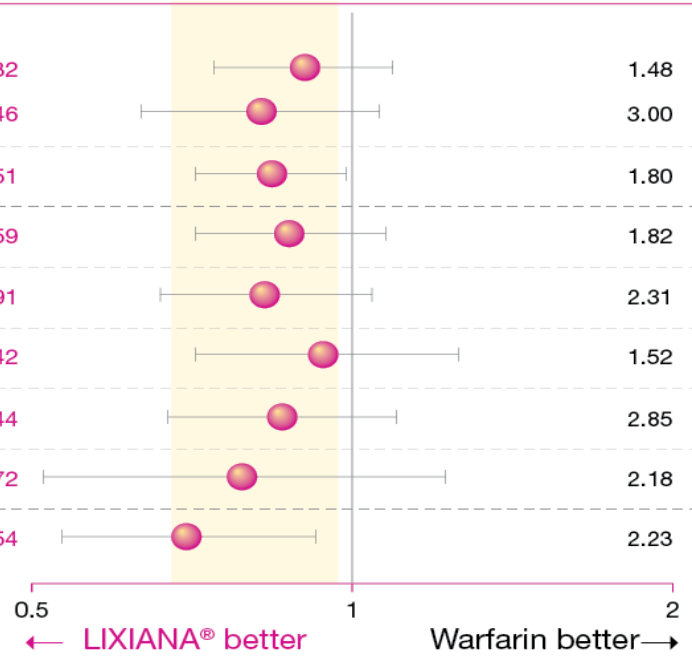
Outcome	Warfarin (n=7,036)		Edoxaban 60/30 mg (n=7,035)		Edoxaban 60/30 mg versus warfarin	
	n	%/yr	n	%/yr	HR (95% CI)	P
Stroke, SEE, CV death	831	4.43	728	3.85	0.87 (0.78–0.96)	0.005
MACE	926	4.98	827	4.41	0.88 (0.81–0.97)	0.01
Stroke, SEE or death	1046	5.57	949	5.01	0.90 (0.82–0.98)	0.02
Death or ICH	926	4.88	817	4.27	0.87 (0.79–0.96)	0.004
Death or disabling stroke	878	4.61	812	4.24	0.92 (0.83–1.01)	0.08
All-cause mortality	839	4.35	773	3.99	0.92 (0.83–1.01)	0.08
CV death	611	3.17	530	2.74	0.86 (0.77–0.97)	0.013
Myocardial infarction	141	0.75	133	0.70	0.94 (0.74–1.19)	0.60

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

Once-daily LIXIANA® Demonstrated Consistent Efficacy Results Across a Broad Range of NVAF Patients[1,2]

Stroke and SEE across major subpopulations (overall study period)[1,3]

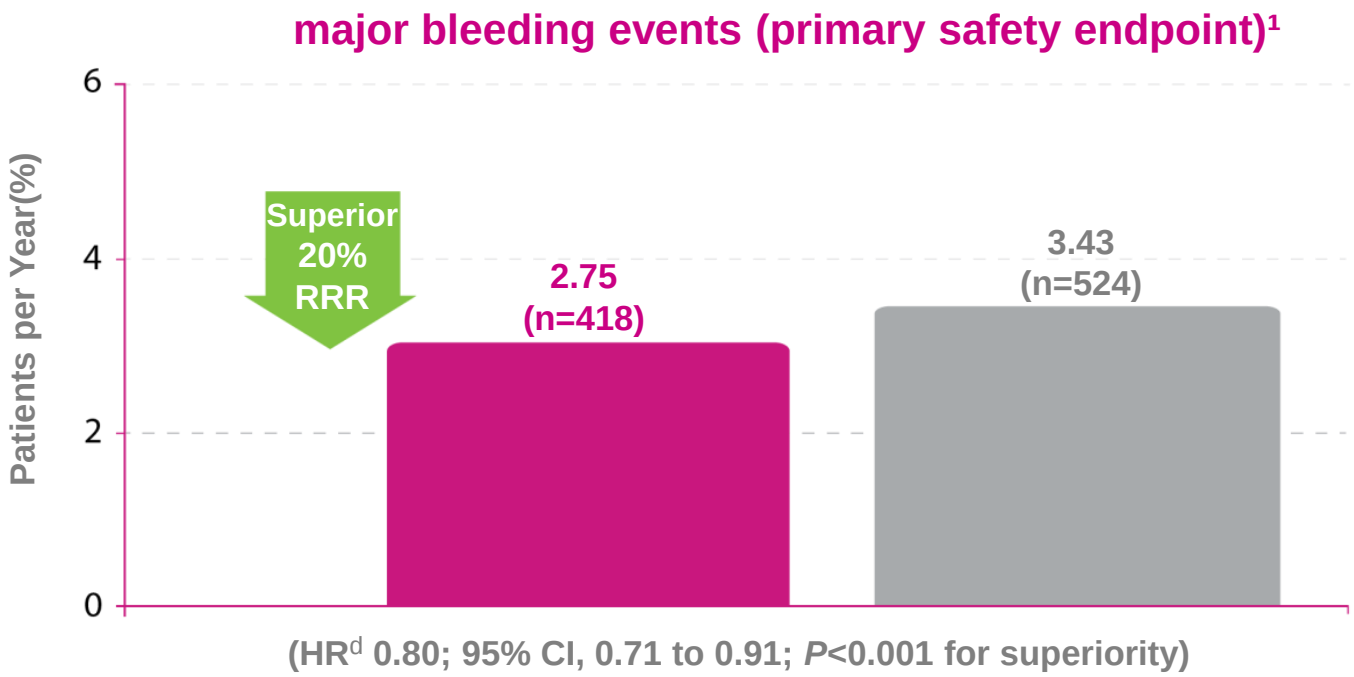
Subgroups	Patients (n)[b]	LIXIANA®[c] % of patients with event/yr	Warfarin % of patients with event/yr
$CHADS_2$ score[f]			
≤3	16,337	1.32	1.48
>3	4768	2.46	3.00
Hypertension	19,754	1.51	1.80
CHF	12,124	1.59	1.82
Elderly (≥75 yrs)	8474	1.91	2.31
Diabetes	7624	1.42	1.52
Prior stroke/TIA	5973	2.44	2.85
Prior MI	2433	1.72	2.18
Concomitant aspirin use at baseline	6180	1.54	2.23



[a] Events that occurred from randomization to end of treatment period.
[b] Reflects combined number of patients from all 3 treatment arms.
[c] Includes patients taking LIXIANA® 60 mg and those dose-reduced to 30 mg.
[d] Hazard ratio.
[e] Confidence interval.
[f] A validated measure for assessing stroke risk. The $CHADS_2$ scoring is calculated by assigning 1 point each for a history of congestive heart failure, hypertension, age ≥75 years, or diabetes mellitus and by assigning 2 points for history of stroke or transient ischemic attack.

1. Giugliano RP et al. *N Engl J Med*. 2013;369(22):Supplemental Appendix. **2.** Giugliano RP et al. *N Engl J Med*. 2013;369(22):2093-2104.

Once-daily LIXIANA® Was Superior to Warfarin in Reducing Major Bleeding Risk[1]



[a] Time from first dose of study drug to last does plus 3 days
[b] Includes patients talking LIXIANA 60 mg and those dose-reduced to 30mg
[c] Relative risk reduction [d] Hazard ratio [e] Confidence interval

1. Giugliano RP et al. *N Engl J Med*. 2013;369(22):2093-2104. **2.** Ruff CT et al. *Am Heart J.* 2010;160(4):635-641.
3. LIXIANA Summary of Product Characteristics 2014. Daiichi Sankyo Europe GmbH

Once-daily LIXIANA® Was Associated With Significantly Lower Rates of bleeding Compared With Warfarin[1]

Key bleeding outcomes in ENGAGE AF-TIMI 48 (On-treatment period[a])[1]

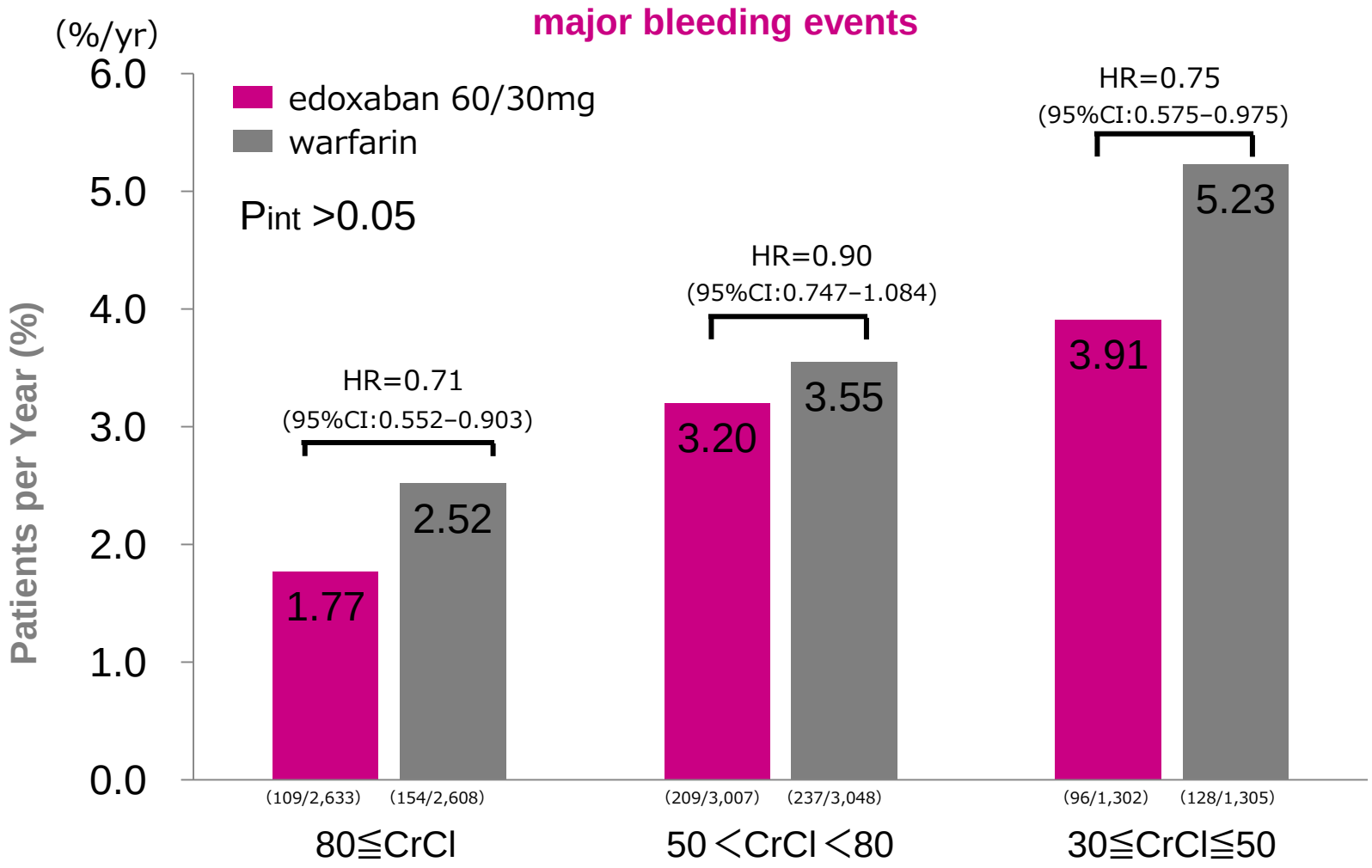
	LIXIANA®[b] (n=7012)	Warfarin (n=7012)	Relative Risk Reduction	HR[c] and 95% CI[d]
Intracranial bleeding	**0.39** (n=61)	0.85 (n=132)	53%	HR, 0.47; 95% CI, 0.34 to 0.63; *P*<0.001
Life-threatening bleeding	**0.40** (n=62)	0.78 (n=122)	49%	HR, 0.51; 95% CI, 0.38 to 0.70; *P*<0.001
Fatal bleeding	**0.21** (n=32)	0.38 (n=59)	45%	HR, 0.55; 95% CI, 0.36 to 0.84; *P*=0.006

- The rate of major gastrointestinal bleeding was higher in patients taking LIXIANA® compared with those taking warfarin (1.51% per year vs 1.23% per year, respectively; HR, 1.23; 95% CI, 1.02 to 1.50; *P*=0.03)[1]

[a] Time from first dose of study drug to last does plus 3 days
[b] Includes patients talking LIXIANA 60 mg and those dose-reduced to 30mg
[c] Hazard ratio [d] Confidence interval

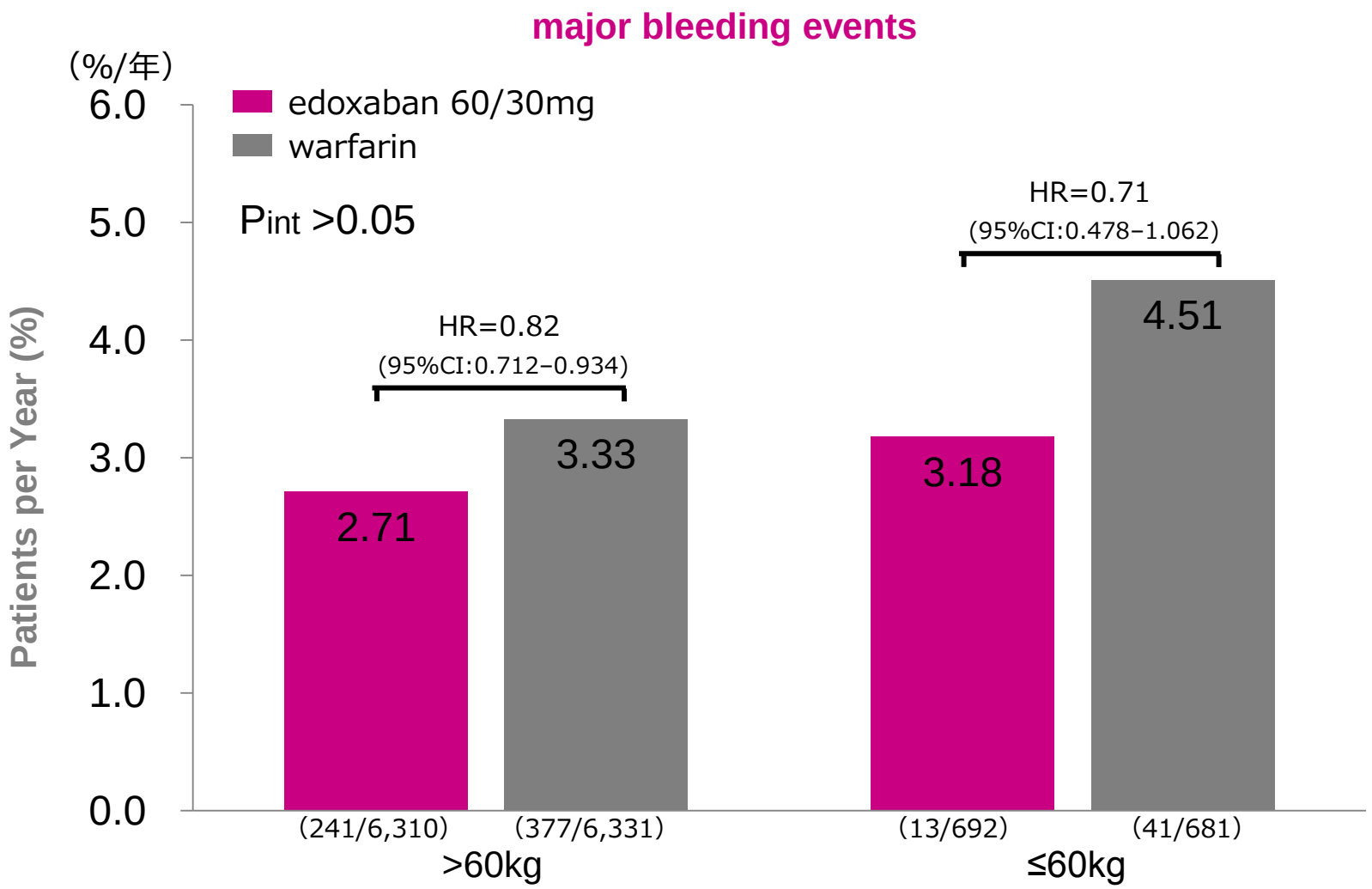
1. Giugliano RP et al. *N Engl J Med*. 2013;369(22):2093-2104.

Once-daily LIXIANA® Was Superior to Warfarin in Reducing the Risk of Major Bleeding in renal impairment pts.



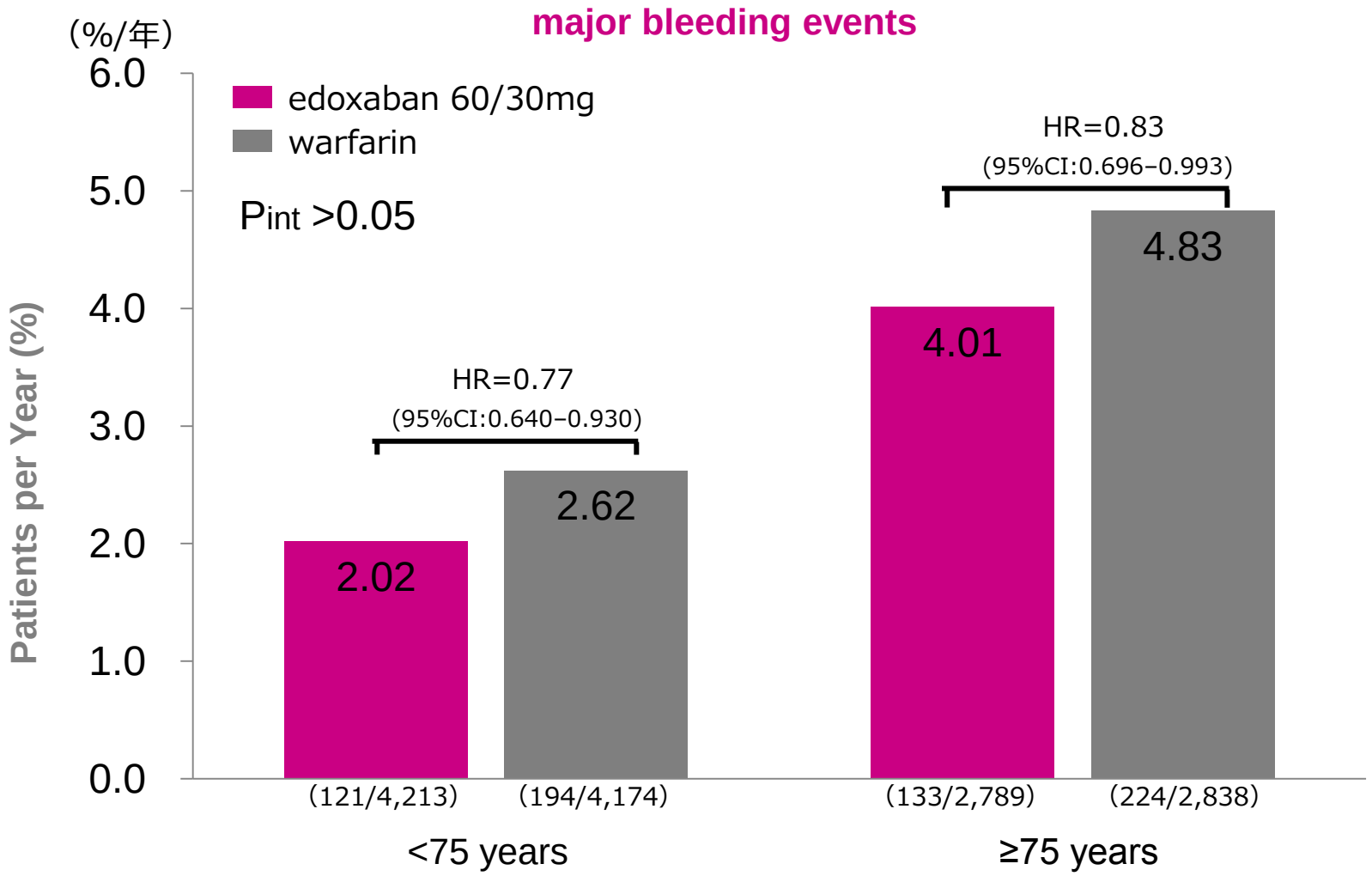
Giugliano et al. N Engl J Med 2013; DOI: 10.1056/NEJMoa1310907

Once-daily LIXIANA® Was Superior to Warfarin in Reducing the Risk of Major Bleeding in low body weight pts.



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

Once-daily LIXIANA® Was Superior to Warfarin in Reducing the Risk of Major Bleeding in elderly pts.



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

Once-daily LIXIANA® Demonstrated Consistent Safety Results Across a Broad Range of NVAF Patients[1]

Major bleeding events across major subpopulations (on-treatment period)[12]

Subgroups	Patients (n)[b]	LIXIANA®[c] % of patients with event/yr	HR[d] and 95% CI[e]	Warfarin % of patients with event/yr
$CHADS_2$ score[f]				
≤3	16,276	2.47		3.09
>3	4750	3.79		4.68
Hypertension	19,679	2.72		3.42
CHF	12,086	2.58		3.28
Elderly (≥75 yrs)	8432	4.01		4.83
Diabetes	7599	3.06		3.94
Prior stroke/TIA	5950	3.11		3.65
Prior MI	2423	3.09		3.89
Concomitant aspirin use at baseline	6152	3.62		4.71

[a] Time from first dose of study drug to last dose plus 3 days.
[b] Reflects combined number of patients from all 3 treatment arms.
[c] Includes patients taking LIXIANA® 60 mg and those dose-reduced to 30 mg.
[d] Hazard ratio.
[e] Confidence interval.
[f] A validated measure for assessing stroke risk. The $CHADS_2$ scoring is calculated by assigning 1 point each for a history of congestive heart failure, hypertension, age ≥75 years, or diabetes mellitus and by assigning 2 points for history of stroke or transient ischemic attack.

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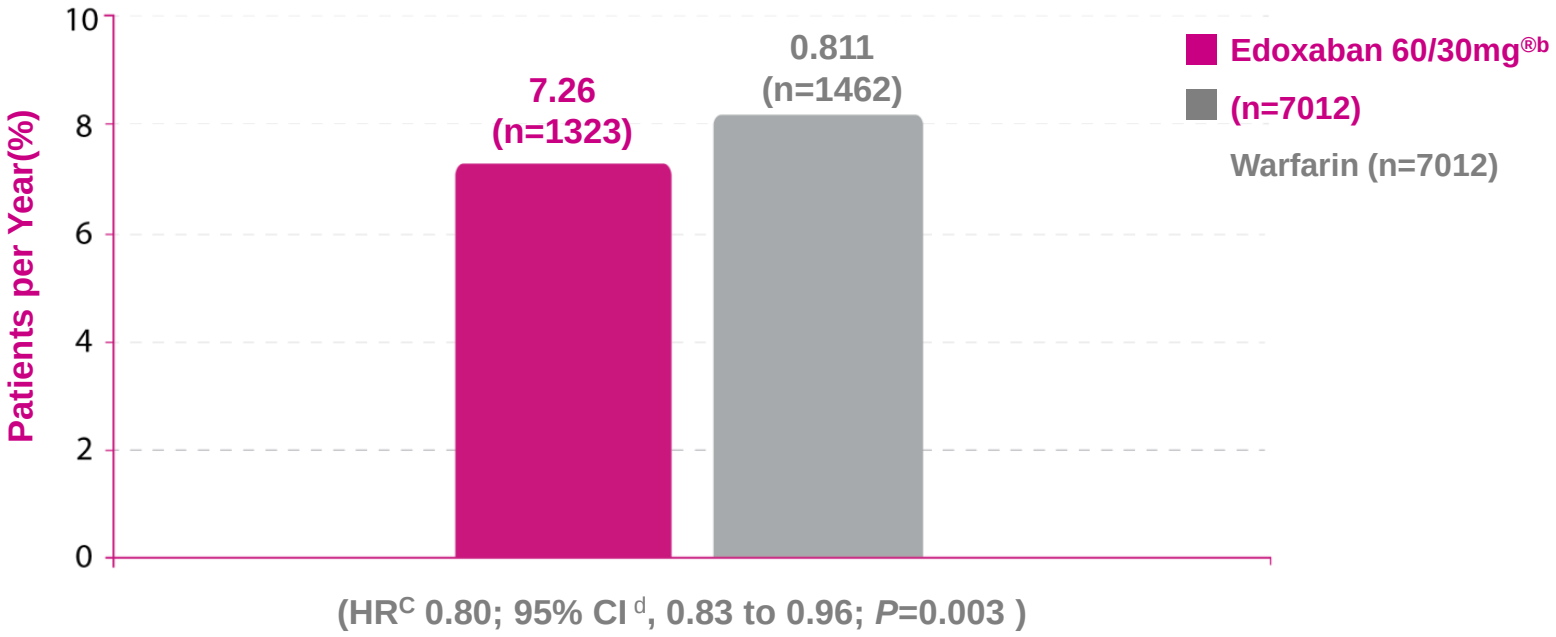
3. Ruff CT et al. *Am Heart J*. 2010;160(4):635-641.

Once-daily LIXIANA® Also Significantly Reduced the Primary Net Clinical Outcome[1]

Net Clinical Outcome (overall study period[a])[1]



[a] Event that occurred from randomization to end of treatment period [b] Includes paients taking LIXIANA 60 mg and those dose reduced to 30mg
[c] Hazard ratio [d] Confidence interval.

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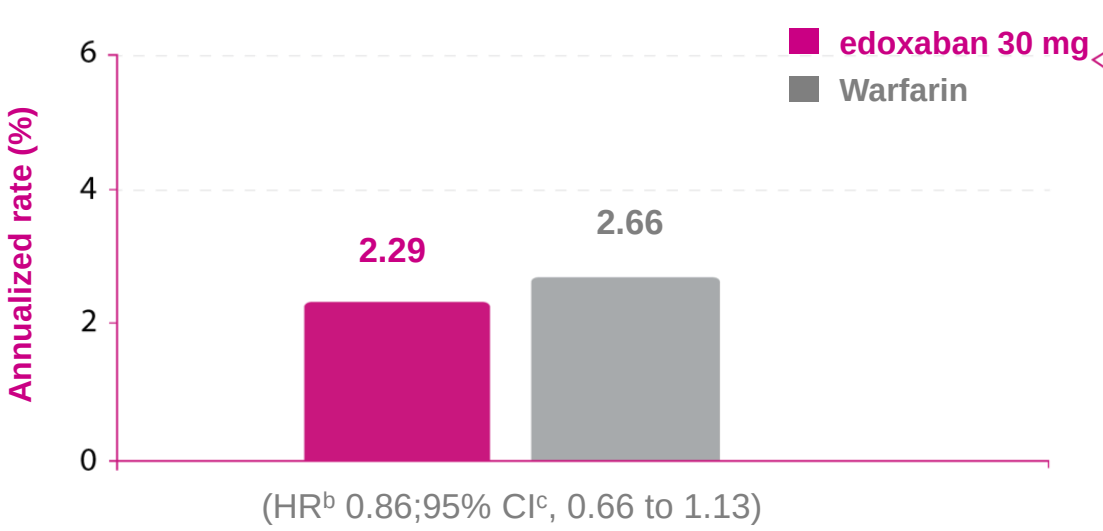
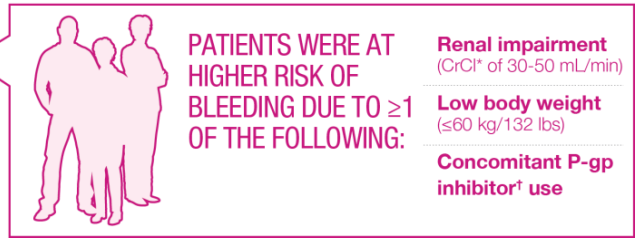
1. Giugliano RP et al. *N Engl J Med*. 2013;369(22):2093-2104.

Proven Efficacy in Patients With Factors That Increase the Risk of Bleeding Who Were Dose-reduced to LIXIANA® 30 mg[1]

Stroke/SEE (overall study period)[1]



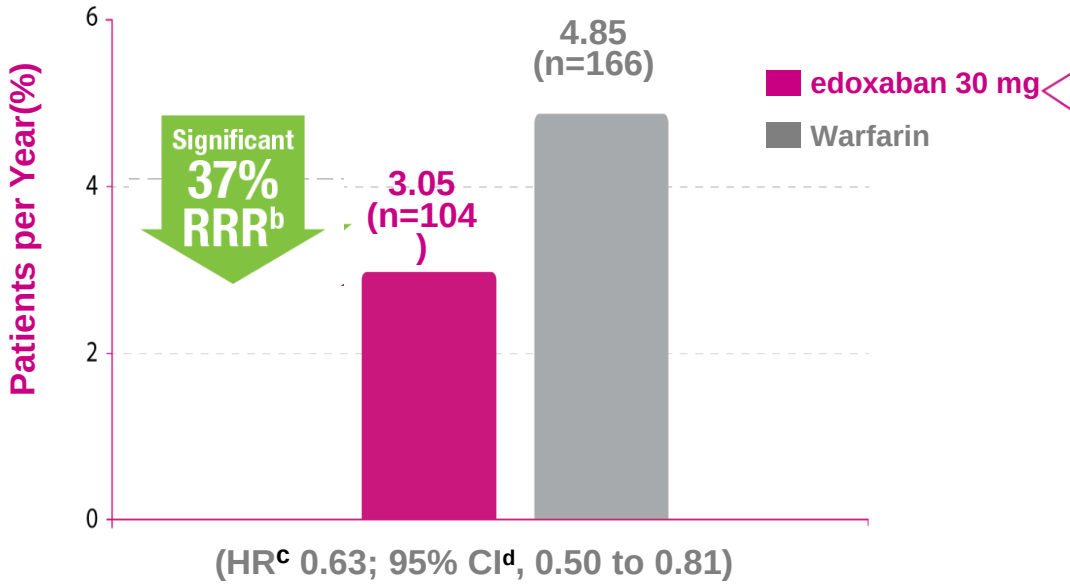


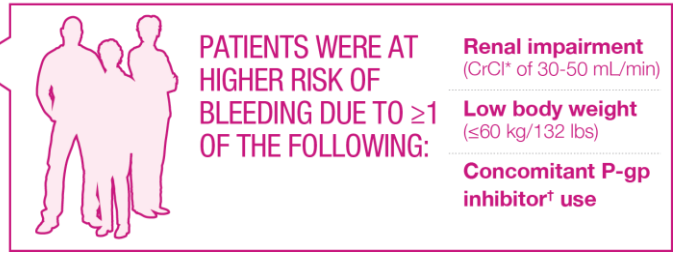
[a] All randomized subjects who received at least 1 dose of randomized drug and did not have any major protocol violations
[b] Hazard ratio [c] Confidence interval
[d] Creatinine clearance.
†Verapamil, dronedarone, or quinidine.

1. LIXIANA Summary of Product Characteristics 2014. Daiichi Sankyo Europe GmbH.

Superior Reduction in Major Bleeding Compared With Warfarin in Patients Who Were Dose-reduced to LIXIANA® 30 mg[1]

Major bleeding (on-treatment period) [1]





a Time from first dose of study drug to last dose plus 3 days. b Relative risk reduction. c Hazard ratio. d Confidence interval.
* Creatinine clearance. † Verapamil, dronedarone, or quinidine.

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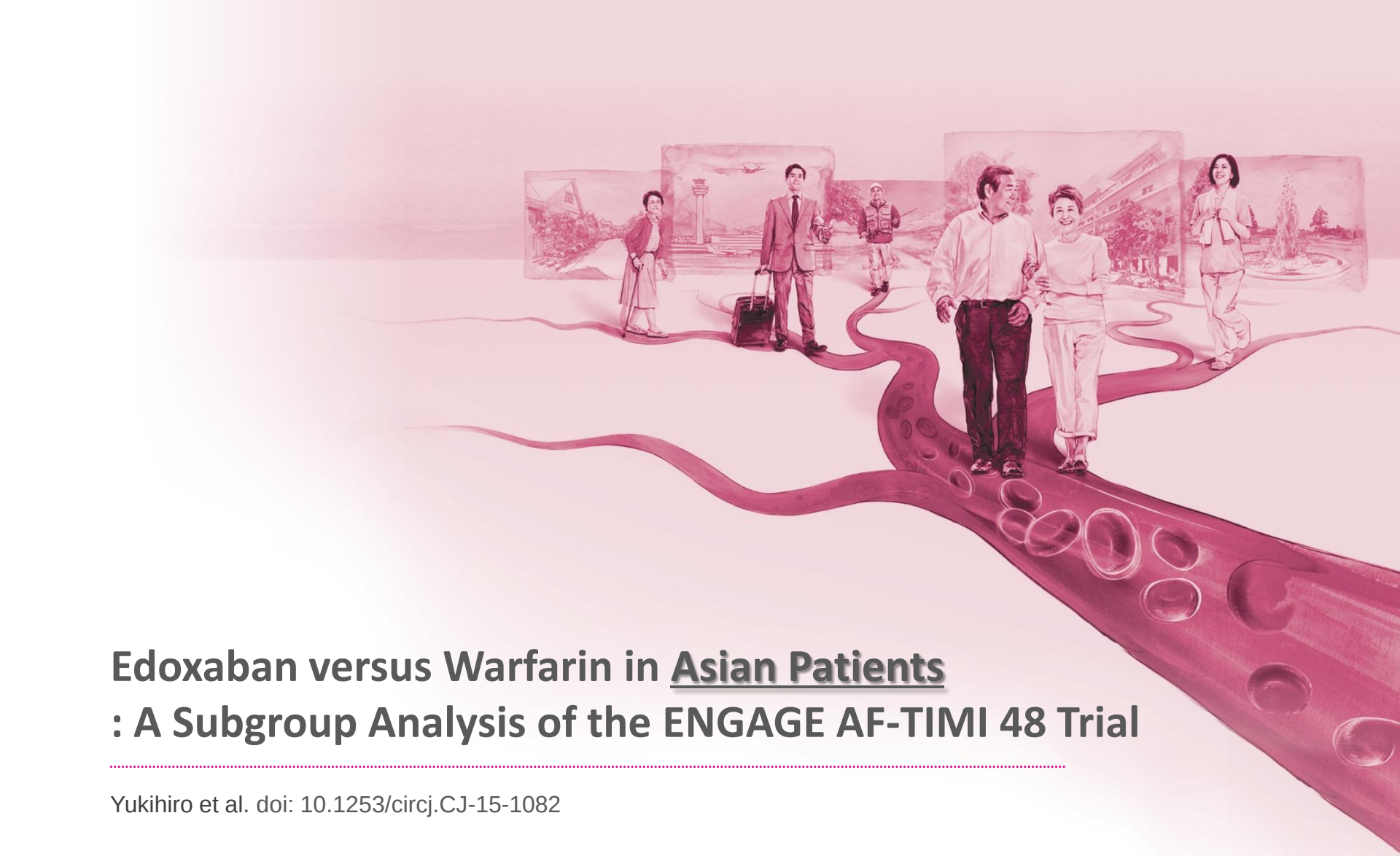
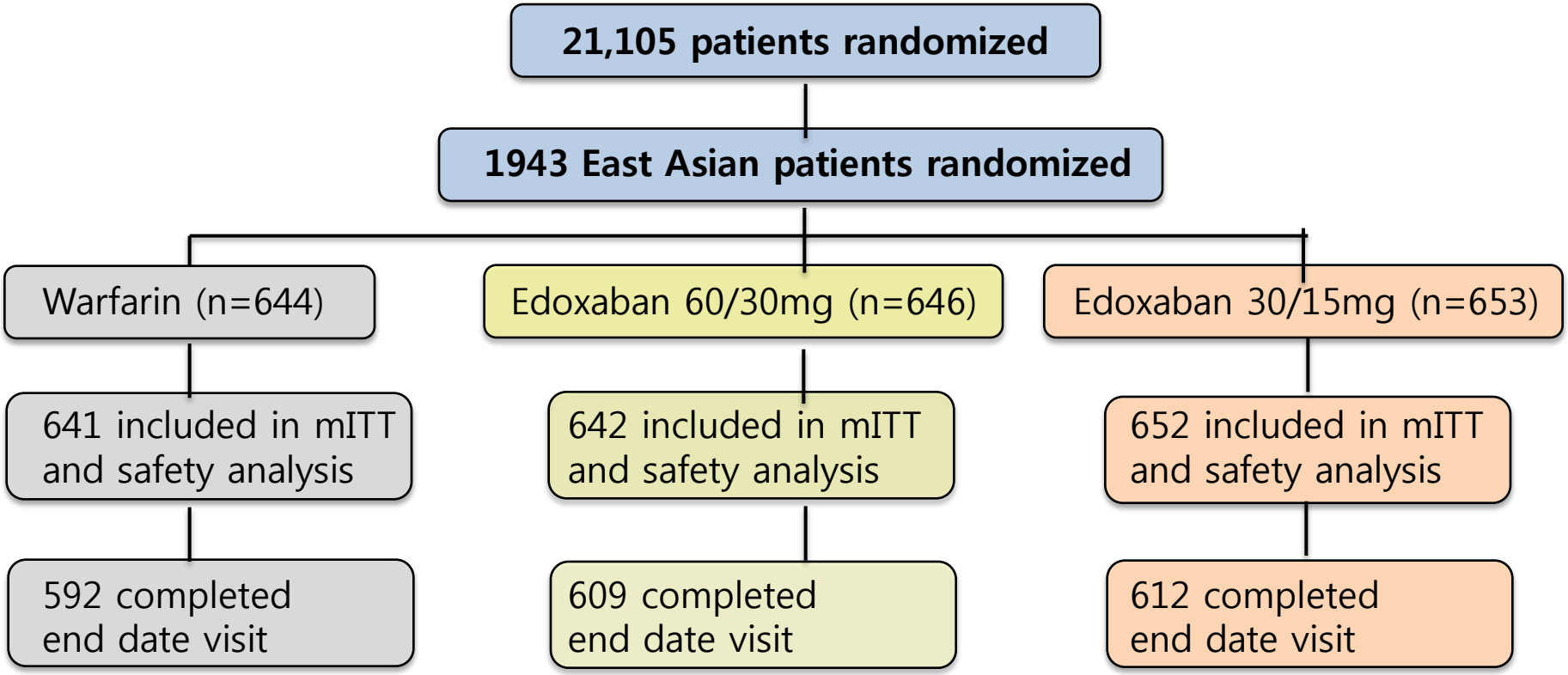


Edoxaban versus Warfarin in Asian Patients : A Subgroup Analysis of the ENGAGE AF-TIMI 48 Trial

Yukihiro et al. doi: 10.1253/circj.CJ-15-1082

Patients disposition



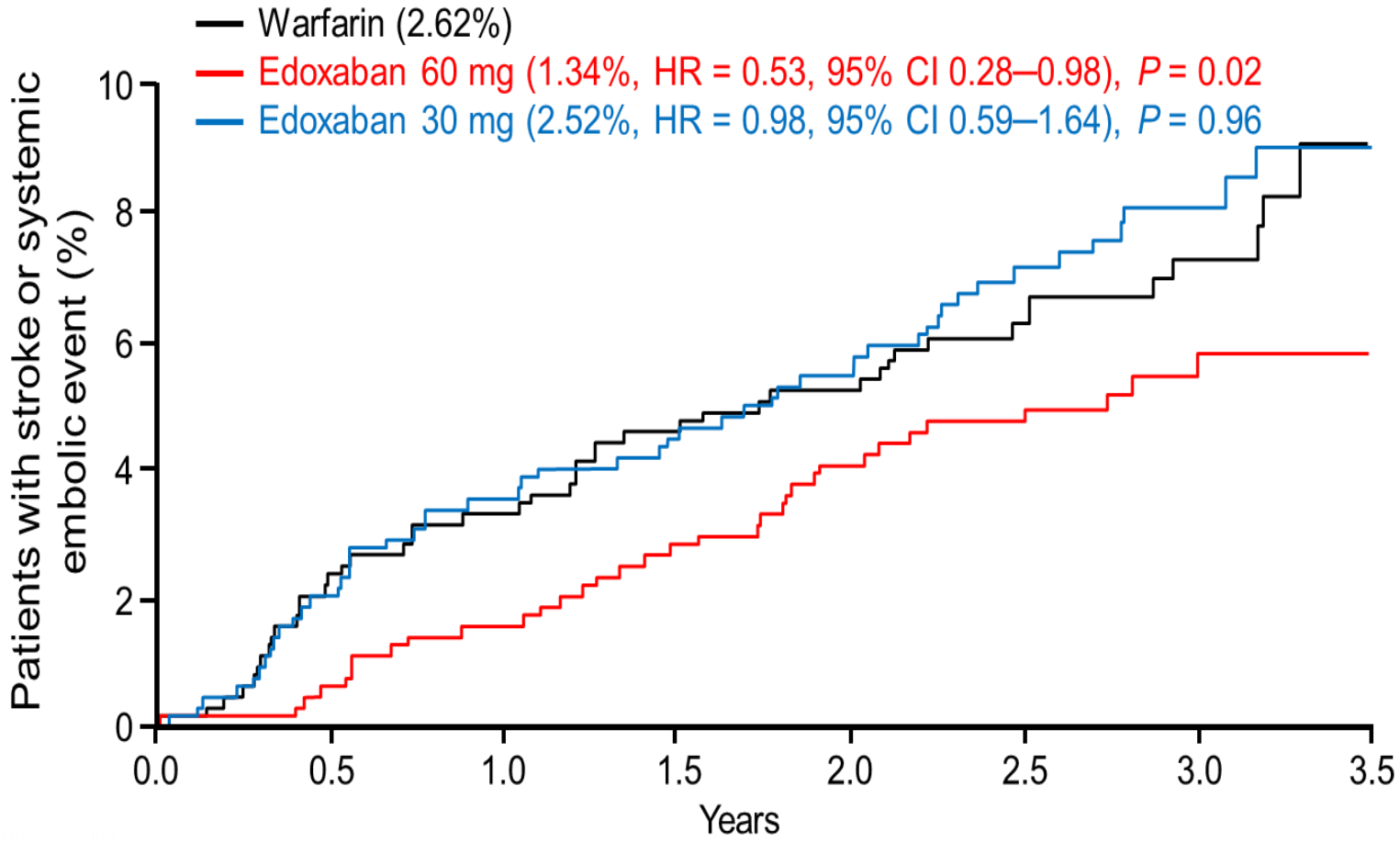
	Japan	China	Korea	Taiwan
Edoxaban 60/30mg	336	150	84	72
Edoxaban 30/15mg	337	152	78	85
warfarin	337	163	64	77

Ref) Yukihiro et al. doi: 10.1253/circj.CJ-15-1082

Baseline Demographics and Characteristics

	East Asian (n=1,943)	Non-East Asian (n=19,162)
Age, y, median	71	72
Females, n (%)	545(28.0)	7495(39.1)
Weight, kg, mean	67.0	85.6
Paroxysmal AF, n (%)	373(19.2)	4993(26.1)
CHADS2 score, mean±SD	2.9±1.0	2.8±1.0
≤3, n (%)	1487(76.5)	14850(77.5)
4-6, n (%)	456(23.5)	4312(22.5)
Dose reduction at randomization, n (%)	912(46.9)	4444(23.2)
CrCl≤50mL/min, n (%)	583(30.0)	3491(18.2)
weight≤60kg, n (%)	594((30.6)	1489(7.8)
Use of verapamil or quinidine, n (%)	128(6.6)	633(3.3)
Previous use of VKA for ≥60days, n (%)	1153(59.3)	11288(58.9)
Medication at time of randomization, n (%)		
Aspirin	543(27.9)	5637(29.4)
Thienopyridine	60(3.1)	427(2.2)
Amiodarone	85(4.4)	2407(12.6)
Digoxine or digitalis preparation	576(29.6)	5751(30.0)

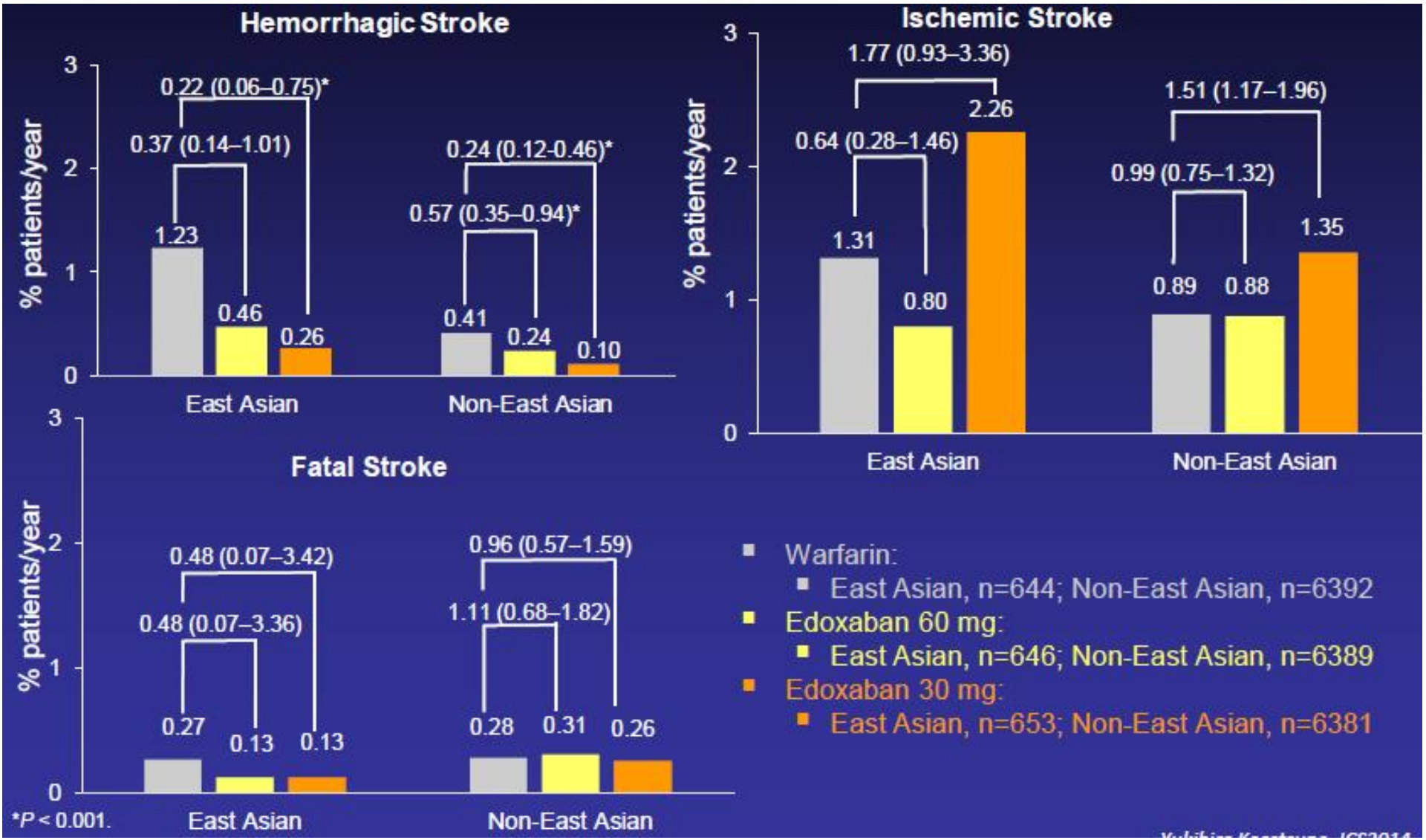
Primary Efficacy Endpoint (East Asian)



Warfarin	644	618	607	593	583	441	253	42
Edoxaban	646	636	626	615	600	467	265	54
Edoxaban	653	635	617	605	594	449	254	46

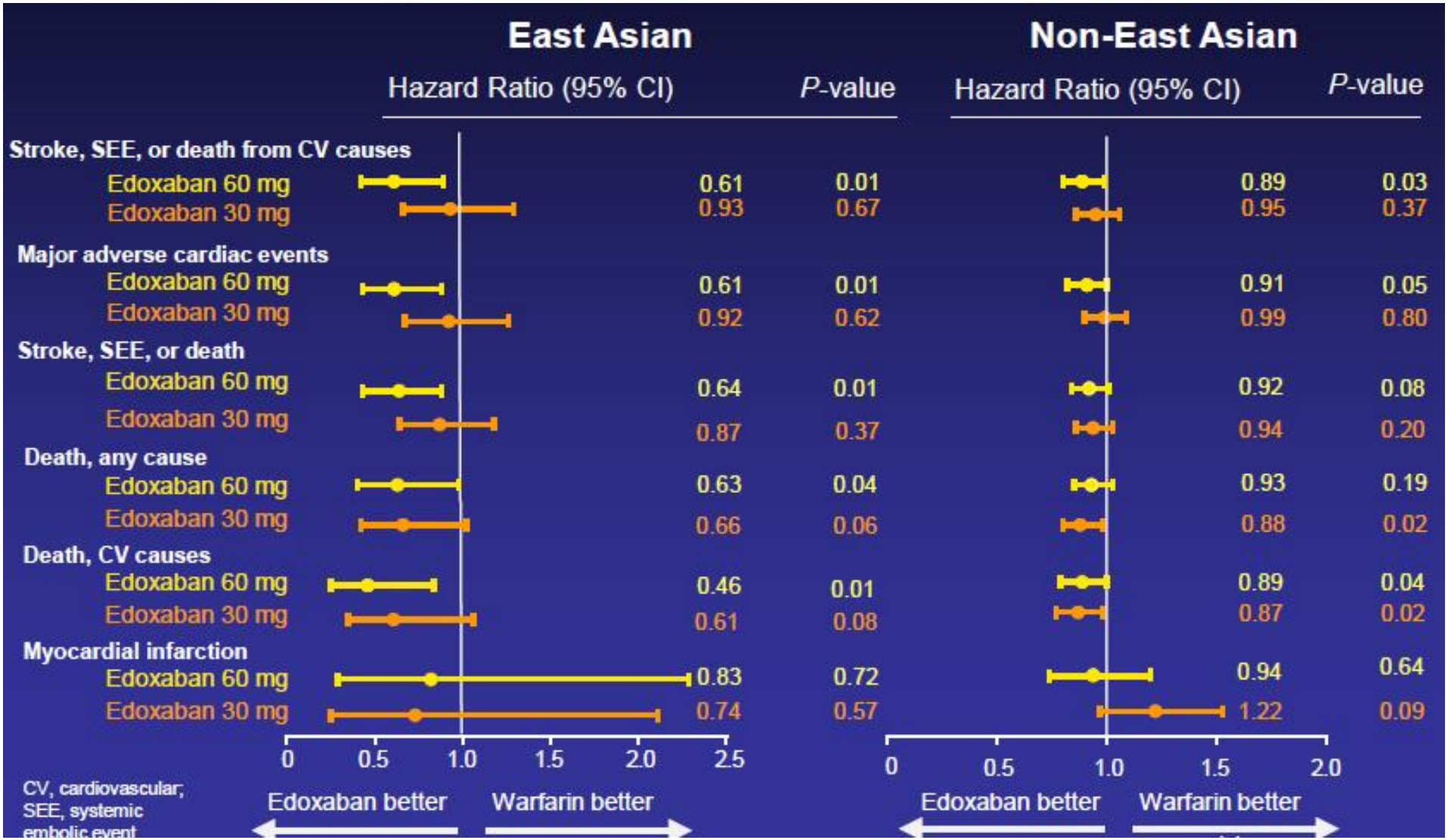
Ref) Yukihiro et al. doi: 10.1253/circj.CJ-15-1082

Rates of Stroke (East Asian)



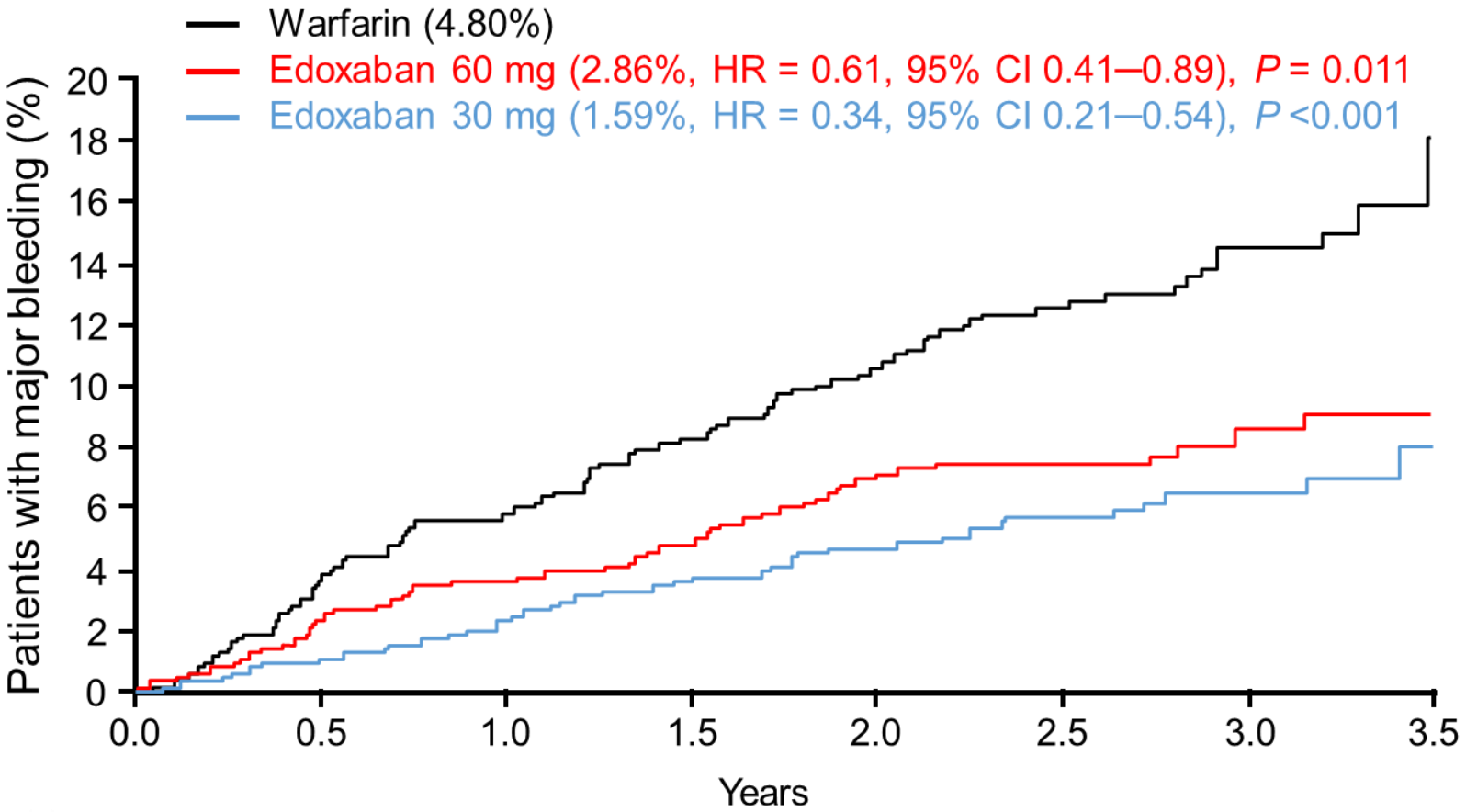
Ref) Yukihiro et al. doi: 10.1253/circj.CJ-15-1082

Secondary Efficacy Endpoint



Ref) Yukihiro et al. doi: 10.1253/circj.CJ-15-1082

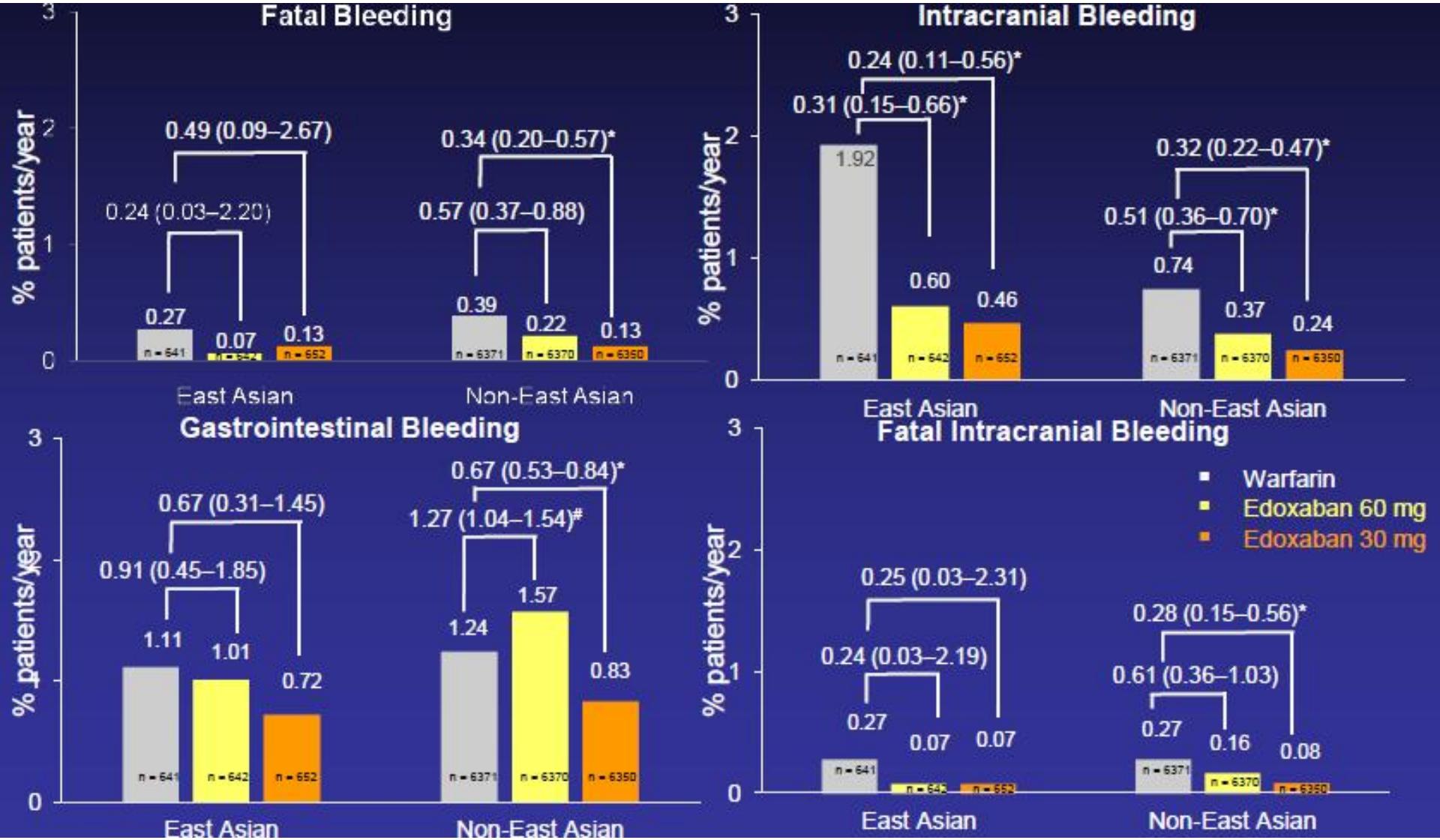
Primary safety Endpoint



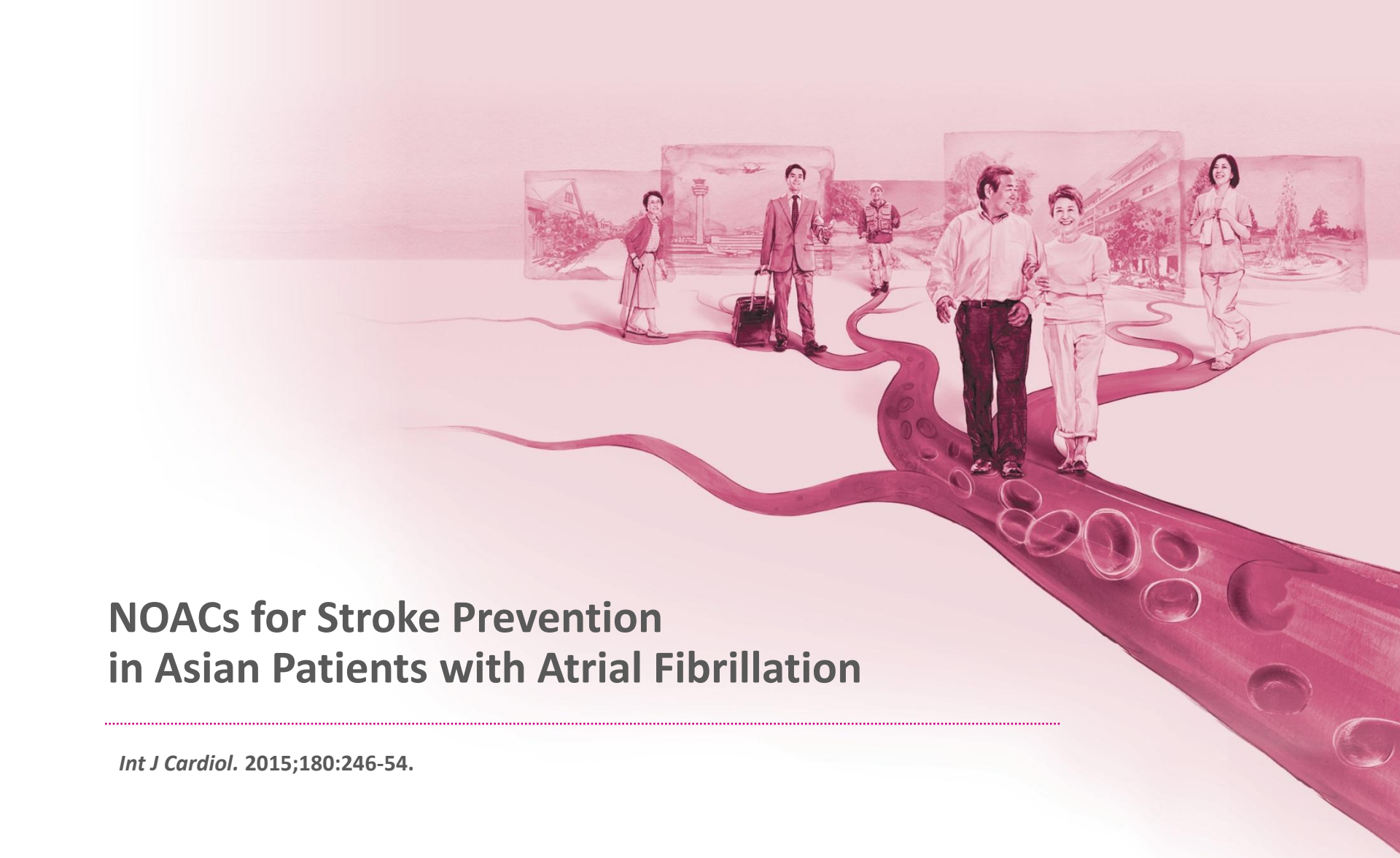
Warfarin	641	607	587	567	548	406	234	35
Edoxaban 60mg	642	621	610	599	576	448	250	50
Edoxaban 30mg	652	640	623	610	598	452	255	45

Ref) Yukihiro et al. doi: 10.1253/circj.CJ-15-1082

Major Bleeding



Ref) Yukihiro et al. doi: 10.1253/circj.CJ-15-1082



NOACs for Stroke Prevention in Asian Patients with Atrial Fibrillation

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

Efficacy Endpoints with NOACs vs Warfarin in Asian vs Non-Asians

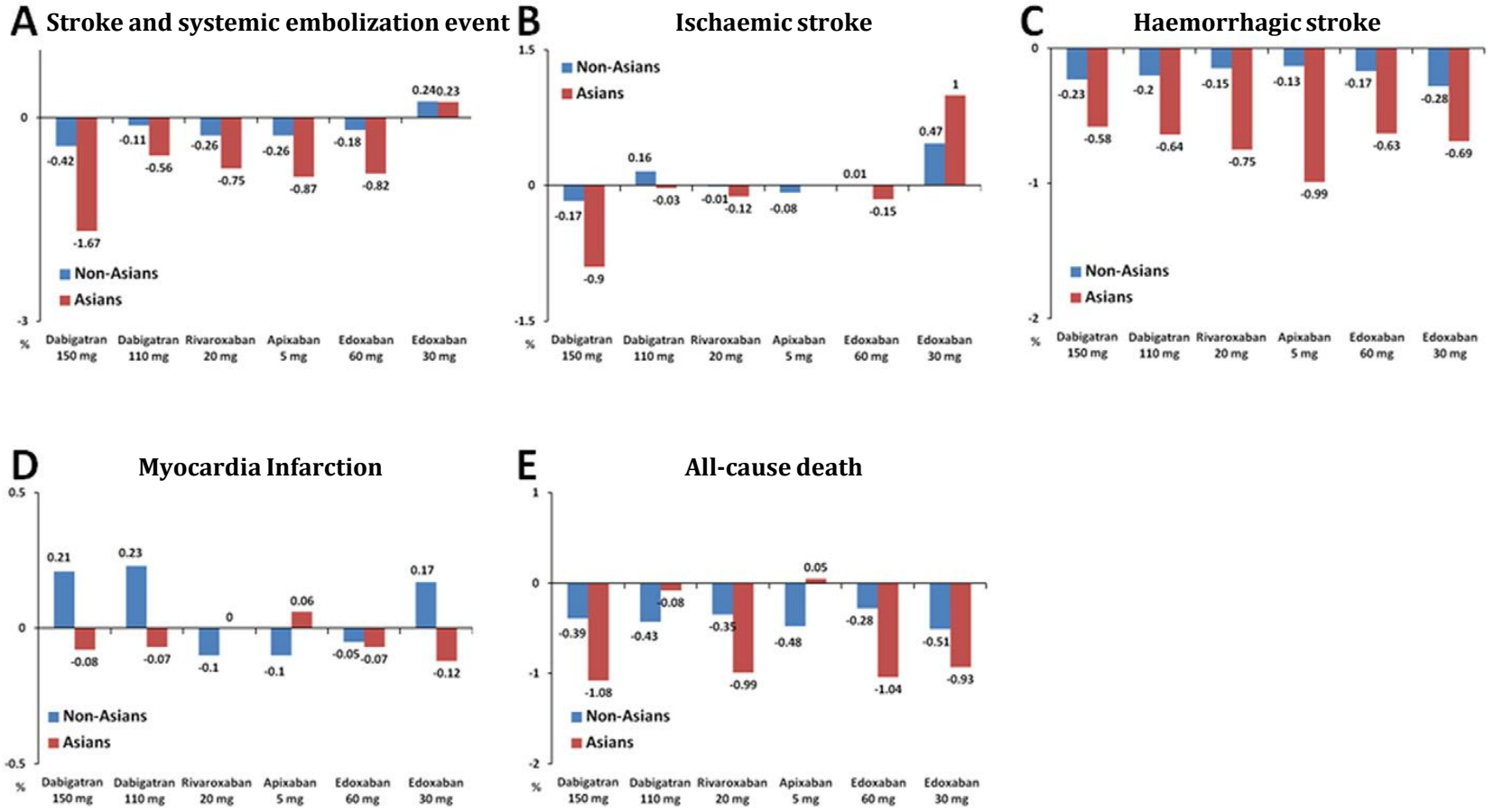


Fig. 5. Absolute risk reductions in efficacy endpoints with NOACs vs warfarin in Asians vs non-Asians, from the randomised trials. In general, the absolute risk reductions were numerically greater in Asians than in non-Asians. A. Stroke and systemic embolization events; B. Ischaemic stroke; C. Haemorrhagic stroke; D. Myocardial infarction; E. All-cause death.

Int J Cardiol. **2015;180:246-54.**

Safety Endpoints with NOAC vs Warfarin in Asians vs. Non-Asians

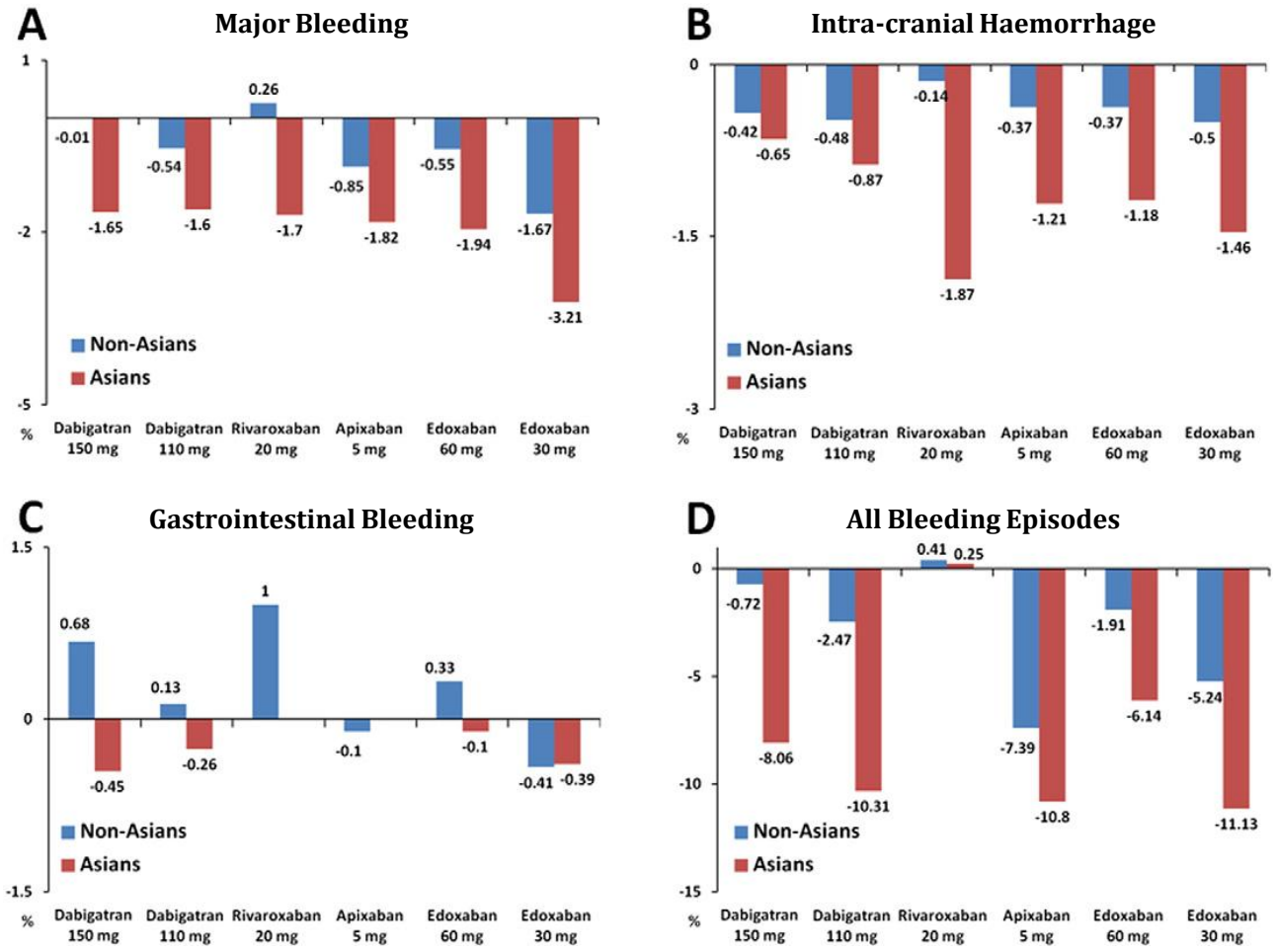


Fig. 7. Absolute risk reductions in safety endpoints with NOACs vs warfarin in Asians vs non-Asians, from the randomised trials. In general, the absolute risk reductions were numerically greater in Asians than in non-Asians. A. Major bleeding; B. Intra-cranial haemorrhage; C. Gastrointestinal bleeding; D. All (major plus minor) bleeding episodes.

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

Summary

	Stoke/SEE	Ischaemic stroke	Haemorrhagic stroke	Myocardial infarction	All-casue death	Major bleeding	Intra-cranial Haemorrhage	GI bleeding	All bleeding
Dabigatran 150mg	V	V	V			V	V		V
Dabigatran 110mg			V			V	V		V
Rivaroxaban							V		
Apixaban			V			V	V		V
Edoxaban 60mg			V		V	V	V		V

[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.

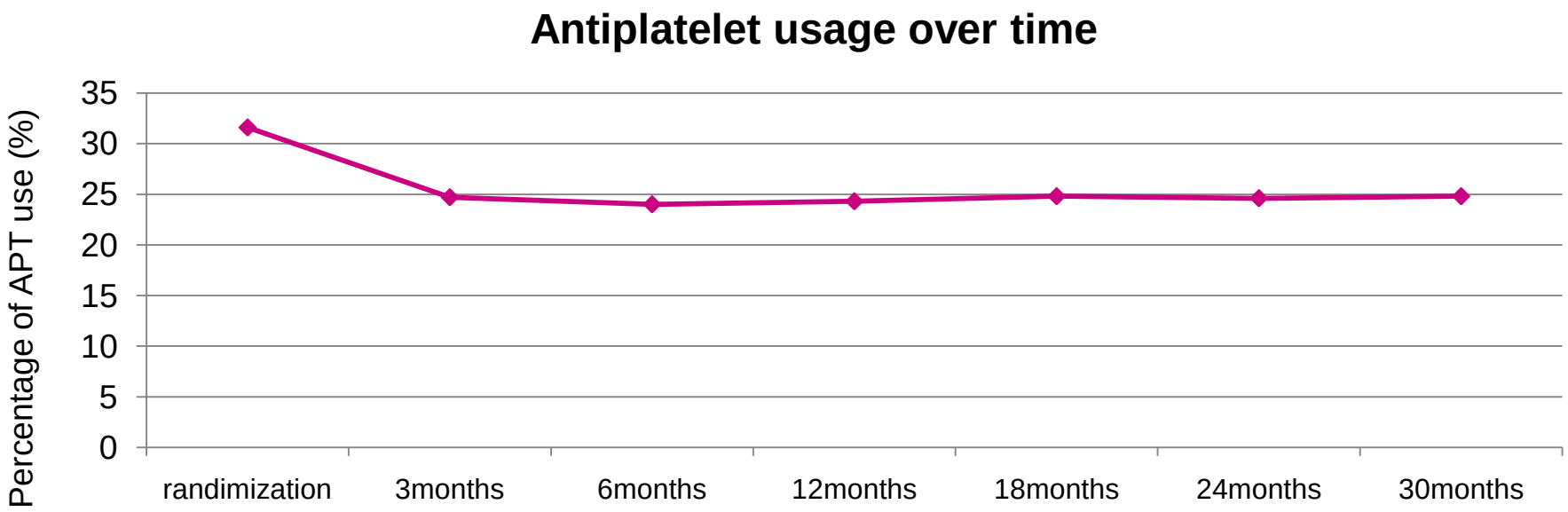
Int J Cardiol. **2015;180:246-54.**

Concomitant use of antiplatelet therapy with edoxaban or warfarin : A Subgroup Analysis of the ENGAGE AF-TIMI 48 Trial

J Am Heart Assoc. 2016;5: e002587 doi: 10.1161/JAHA.115.002587

Concomitant Antiplatelet Use

. Use of antiplatelet medication was administered at the discretion of the treating physician
. Dual antiplatelet therapy was prohibited
. 92% of antiplatelet was aspirin



Ref) J Am Heart Assoc. 2016;5: e002587 doi: 10.1161/JAHA.115.002587

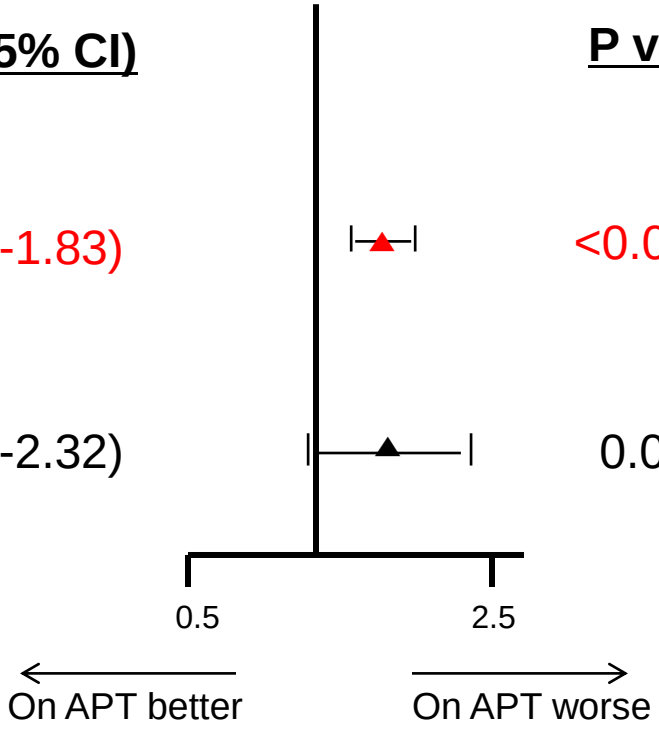
Baseline Characteristics

Variables	Not on antiplatelet therapy (n=14,997)	on antiplatelet therapy (n=4,912)	P value
Age, yr, median (IQR)	72 (64,77)	72 (64,78)	0.52
Female	40%	32%	<0.001
CHADS2 score ≥4	22%	24%	<0.001
HAS-BLED score≥3	35%	79%	<0.001
diabetes	35%	41%	<0.001
Prior MI	9%	18%	<0.001
Prior coronary revascularization	8%	26%	<0.001
Peripheral arterial disease	3%	6%	<0.001
Carotid artery disease	5%	9%	<0.001
Prior stroke or TIA	28%	28%	0.87
Prior non-ICH bleeding history	9%	12%	<0.001
Dose reduced at randomization	26%	25%	0.07

Ref) J Am Heart Assoc. 2016;5: e002587 doi: 10.1161/JAHA.115.002587

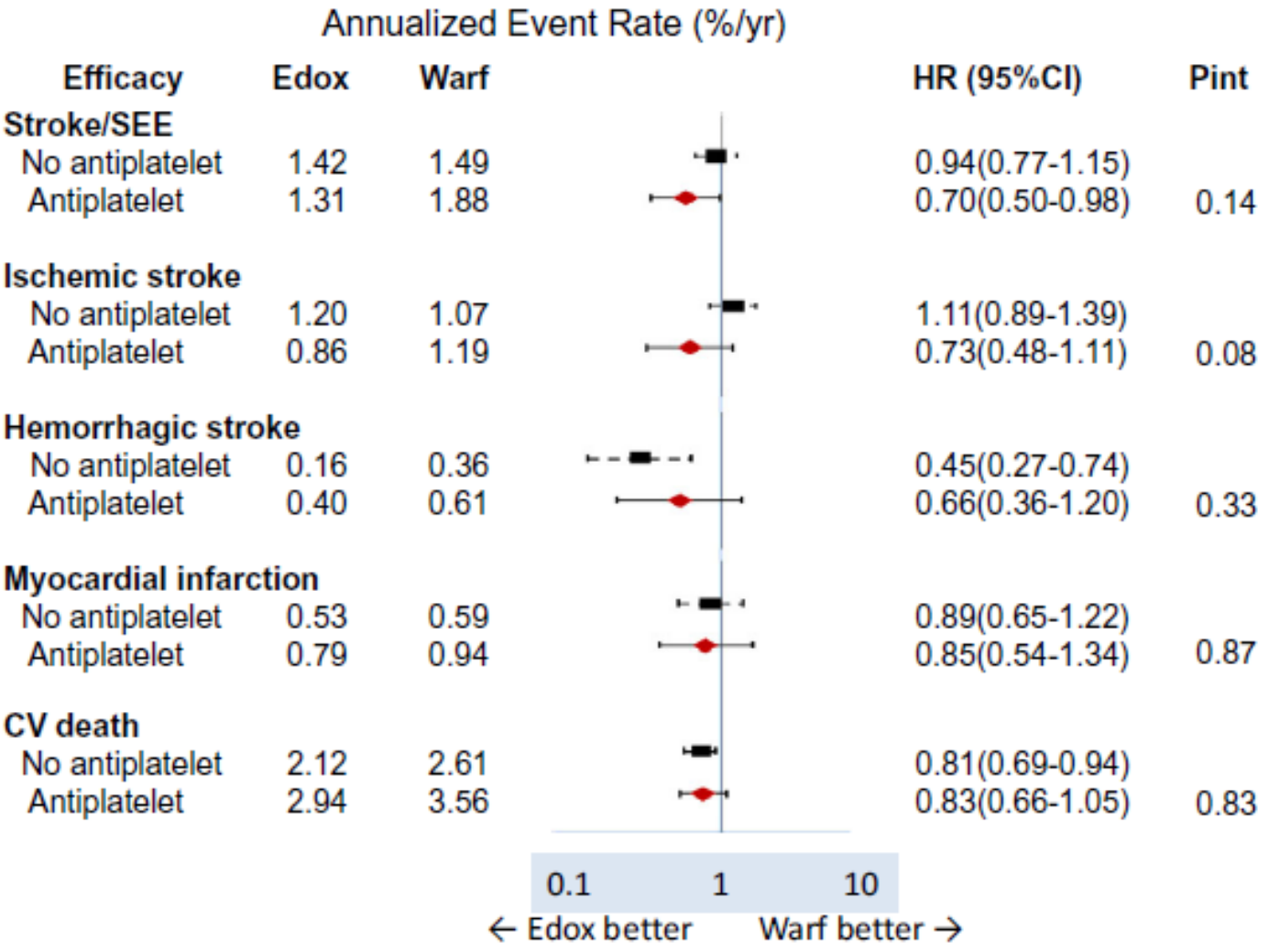
Bleeding in patients with vs without APT at 3 months (overall population)

Events	Adj HR (95% CI)	P value
Major Bleeding	1.61 (1.41-1.83)	<0.001
Fatal Bleeding	1.51 (0.98-2.32)	0.060



Ref) J Am Heart Assoc. 2016;5: e002587 doi: 10.1161/JAHA.115.002587

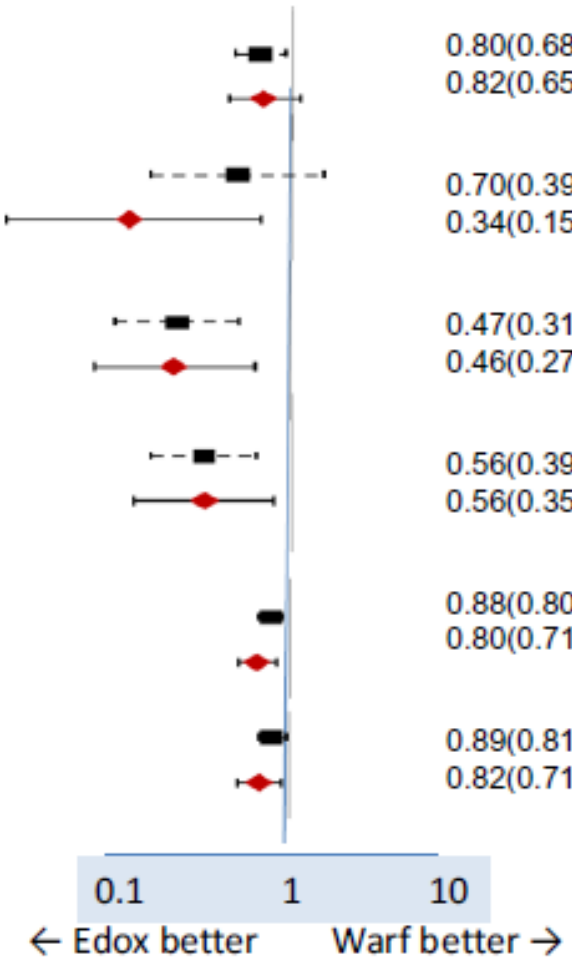
Efficacy of edoxaban vs. warfarin stratified by antiplatelet therapy



Ref) J Am Heart Assoc. 2016;5: e002587 doi: 10.1161/JAHA.115.002587

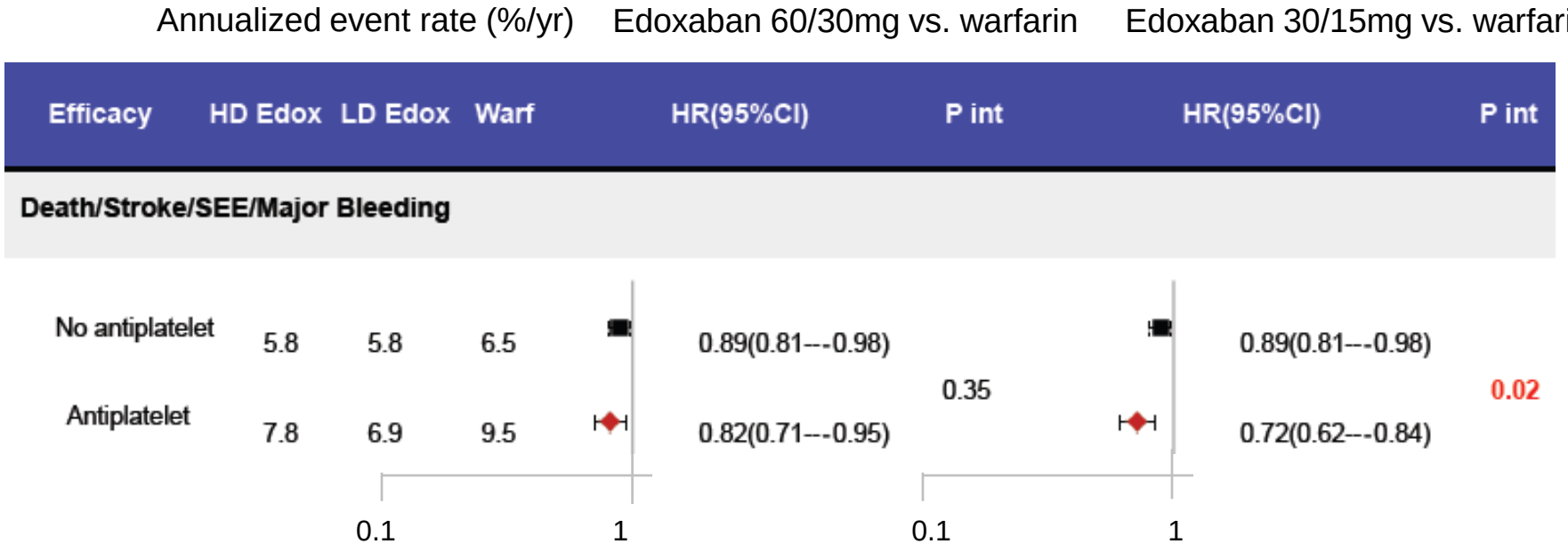
Safety of Edoxaban vs. warfarin stratified by antiplatelet therapy

Efficacy	Edox	Warf	HR (95%CI)	Pint
	Annualized Event Rate (%/yr)			
Major bleeding				
No antiplatelet	2.04	2.54	0.80(0.68-0.95)	
Antiplatelet	3.55	4.38	0.82(0.65-1.04)	0.91
Fatal bleeding				
No antiplatelet	0.17	0.24	0.70(0.39-1.23)	
Antiplatelet	0.19	0.56	0.34(0.15-0.81)	0.17
Intracranial bleeding				
No antiplatelet	0.27	0.57	0.47(0.31-0.71)	
Antiplatelet	0.54	1.18	0.46(0.27-0.79)	0.98
Life-threatening bleeding				
No antiplatelet	0.36	0.64	0.56(0.39-0.79)	
Antiplatelet	0.63	1.14	0.56(0.35-0.88)	1.00
Any bleeding				
No antiplatelet	9.72	11.07	0.88(0.80-0.95)	
Antiplatelet	14.93	18.66	0.80(0.71-0.91)	0.25
Net: Death/Stroke/SEE/Major bleeding				
No antiplatelet	5.84	6.50	0.89(0.81-0.98)	
Antiplatelet	7.75	9.47	0.82(0.71-0.95)	0.35

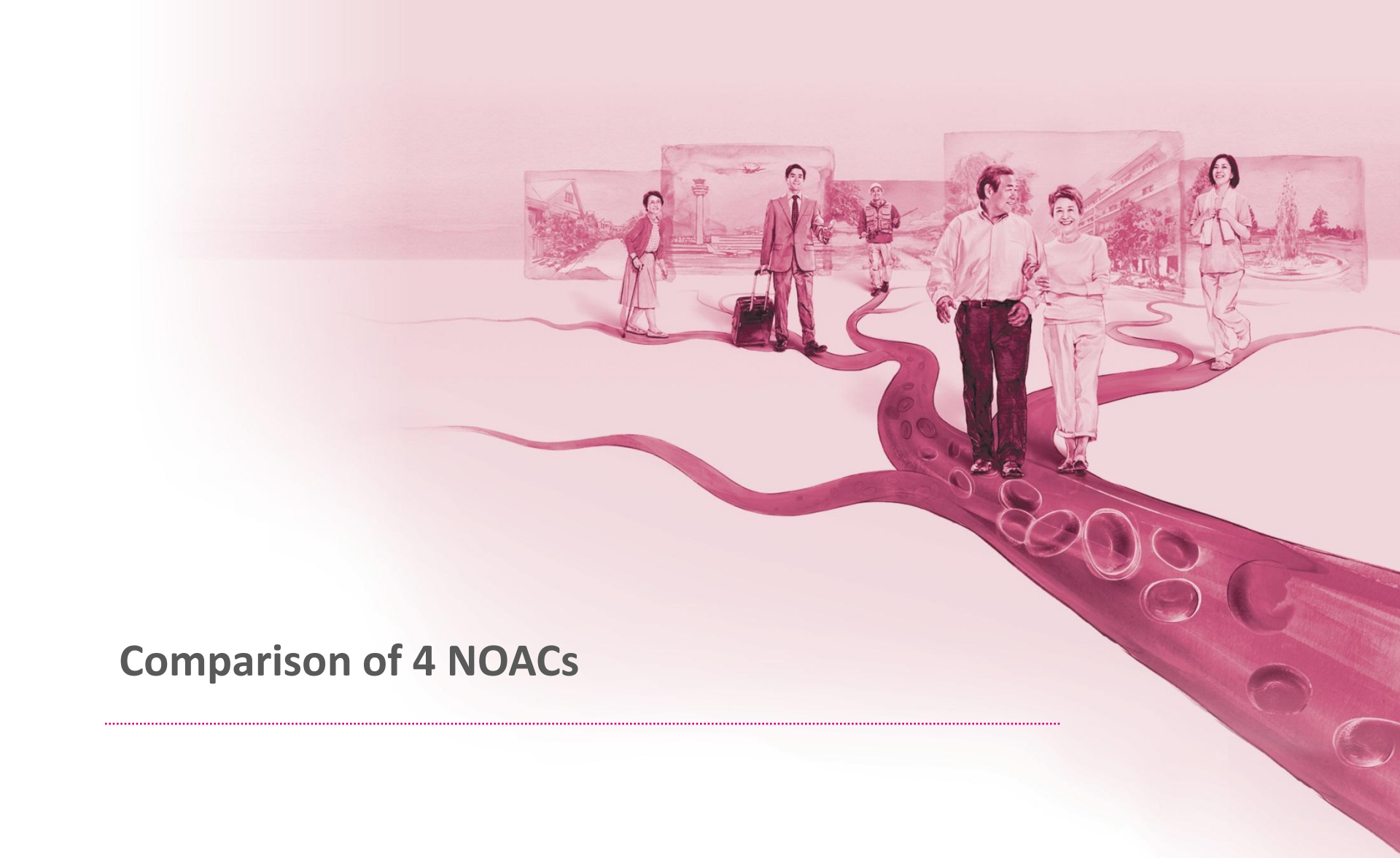


Ref) J Am Heart Assoc. 2016;5: e002587 doi: 10.1161/JAHA.115.002587

Net clinical outcome of edoxaban vs. warfarin stratified by antiplatelet therapy



Ref) J Am Heart Assoc. 2016;5: e002587 doi: 10.1161/JAHA.115.002587



Comparison of 4 NOACs

Comparison of 4 NOACs' profiles

	Xarelto rivaroxaban tablets	Pradaxa dabigatran etexilate	Eliquis (apixaban) tablets	Lixiana edoxaban tablets
administration	QD With food	bid	bid	**QD**
formulation	tablet	capsule	tablet	**tablet**
CYP metabolism	extensive	None	extensive	**<4%**
Renal elimination	35%	80%	25%	**50%**
Protein binding	92~95%	35%	87%	**40~59%**
Half life	9~13 hrs	14~17 hrs	8~15 hrs	**9~10 hrs**
Tmax	2.5~4 hrs	2~3 hrs	3~4 hrs	**1~2 hrs**
bioavailability	60~100 %	6~7 %	50~60 %	**62%**
transporter	P-gp/BCRP	P-gp	P-gp/BCRP	**P-gp**
GI tolerability	No problem	Dyspepsia 5~10%	No problem	**No problem**
Switch from warfarin	INR 3.00이하	INR 2.00이하	INR 2.00이하	**INR 2.50이하**

Comparison of 4 NOACs' phase 3 trials

Study characteristics	RE-LY (Dabigatran)	ROCKET-AF (Rivaroxaban)	ARISTOTLE (Apixaban)	ENGAGE-AF (Edoxaban)
Study design	Randomised open label	Multi-centre randomised double- blind, double-dummy	Randomised control double-blind parallel arm	Three-group, randomised, double-blind, double-dummy
Number of patients	18,113	14,264	18,201	21,105
Follow up period, months	24	40	40	34
Randomised groups	Dose adjusted warfarin vs blinded doses of dabigatran (150 mg bid, 110 mg bid)	Dose adjusted warfarin vs rivaroxaban 20 mg OD	Dose adjusted warfarin vs apixaban 5 mg bid	Dose adjusted warfarin vs high-dose or low-dose edoxaban strategy
Age, years#	71.5 ± 8.7	73 [65–78]	70 [63–76]	72 [64–78]
Female, %	36.4	39.7	35.2	38
$CHADS_2$, (mean)	2.2	3.5	2.1	2.8
$CHADS_2$ 3–6, %	32.5	87.0	30.2	n/a 54%
Paroxysmal AF, %	32.8	17.6	15.3	25.4
Prior stroke, TIA or SE, %	20.0	54.8	19.4	28.3
Heart failure, %	32.0	62.5	35.4	57.4
Prior myocardial Infarction, %	16.6	17.3	14.2	n/a 12%
Diabetes, %	23.3	40.0	25.0	36.1
Hypertension, %	78.9	90.5	87.5	93.6

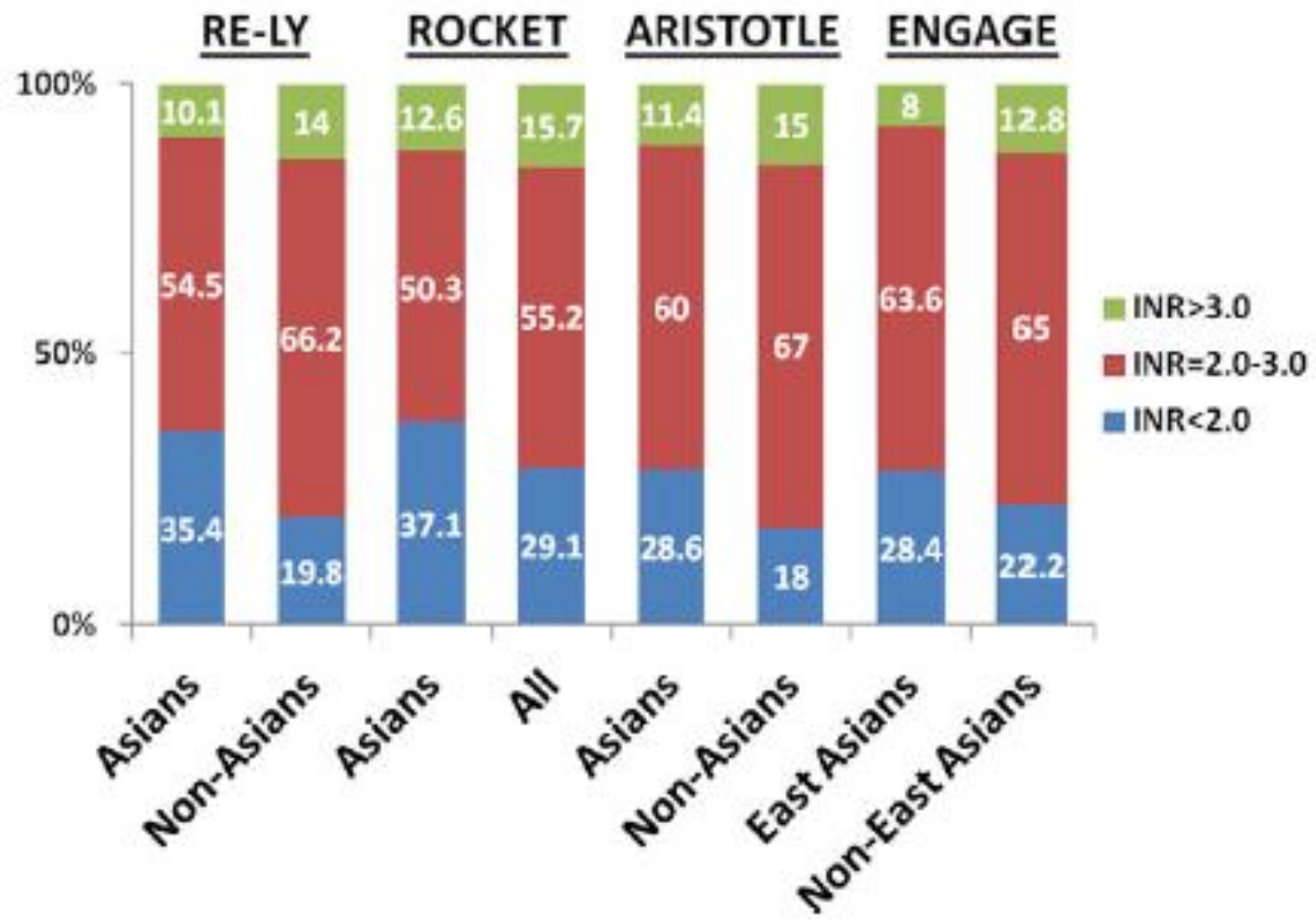
Thrombosis and Haemostasis 111.5/2014

Comparison of 4 NOACs' phase 3 trials

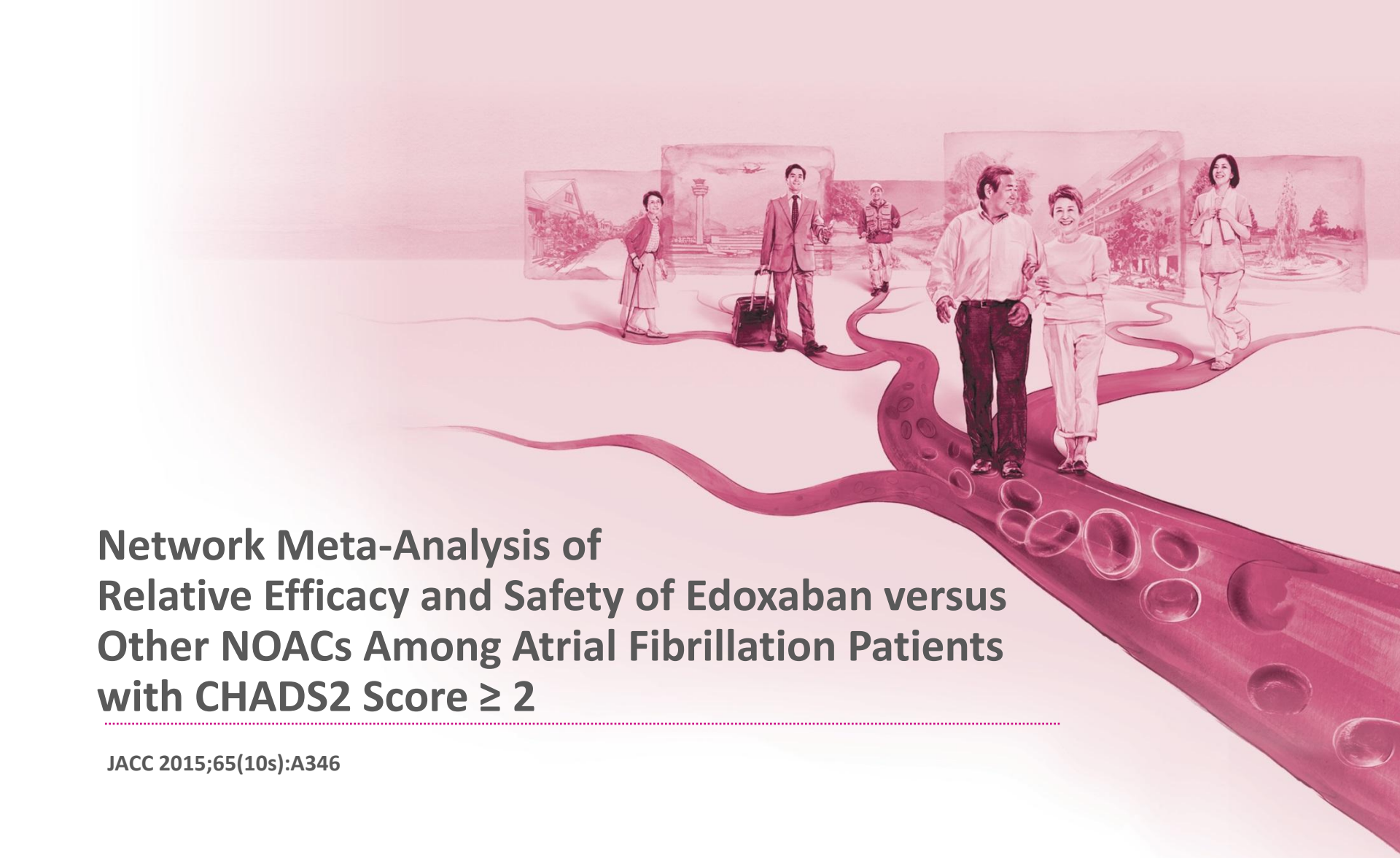
Study characteristics	RE-LY (Dabigatran)	ROCKET-AF (Rivaroxaban)	ARISTOTLE (Apixaban)	ENGAGE-AF (Edoxaban)
Medication				
Aspirin, %	39.8	36.5	30.9	29.3
Vitamin K antagonist, %	49.6	62.4	57.2	58.9
TTR, % (obtained in warfarin arm)	64	55	62	68
Endpoint crude event rates (%/yr)(obtained in warfarin arm)				
Stroke or SE	1.7	2.4	1.6	1.8
Death from any cause	4.3	2.2*	3.9	4.4
Myocardial infarction	0.5	1.1*	0.6	0.8
ISTH major bleeding	3.4*	3.4*	3.1*	3.4*

Thrombosis and Haemostasis 111.5/2014

Comparison of 4 NOACs' TTR



International Journal of Cardiology 180(2015) 246-254



Network Meta-Analysis of Relative Efficacy and Safety of Edoxaban versus Other NOACs Among Atrial Fibrillation Patients with CHADS2 Score ≥ 2

JACC 2015;65(10s):A346

Overview

- **Objective :** To compare the efficacy and safety of edoxaban versus other NOACs after adjustment of baseline patient characteristics

- **Methods:** Network meta-analysis using data from ENGAGE-AF TIMI-48, RE-LY, ROCKET-AF and ARISTOTLE with warfarin as a common comparator

- **Patients:** Atrial fibrillation patients with CHADS2 Score ≥ 2

	RELY	ROCKET-AF	ARISTOTLE	ENGAGE-AF TIMI-48
Total patients in phase 3 trial	18,113	14,264	18,201	21,105
Years of follow-up(median)	2.0	1.9	1.8	2.8
Patients with CHADS2 score ≥ 2	68%	100%	66%	100%
Patients with previos stroke or transent ischemic attack	20%	55%	19%	28%
Patients with hear failure	32%	62%	35%	57%

JACC 2015;65(10s):A346

Risk ratio of edoxaban vs. other NOACs

- **Composite endpoint of stroke and systemic embolism**

- Similar for edoxaban compared to other NOACs

- **Major bleeding risk**

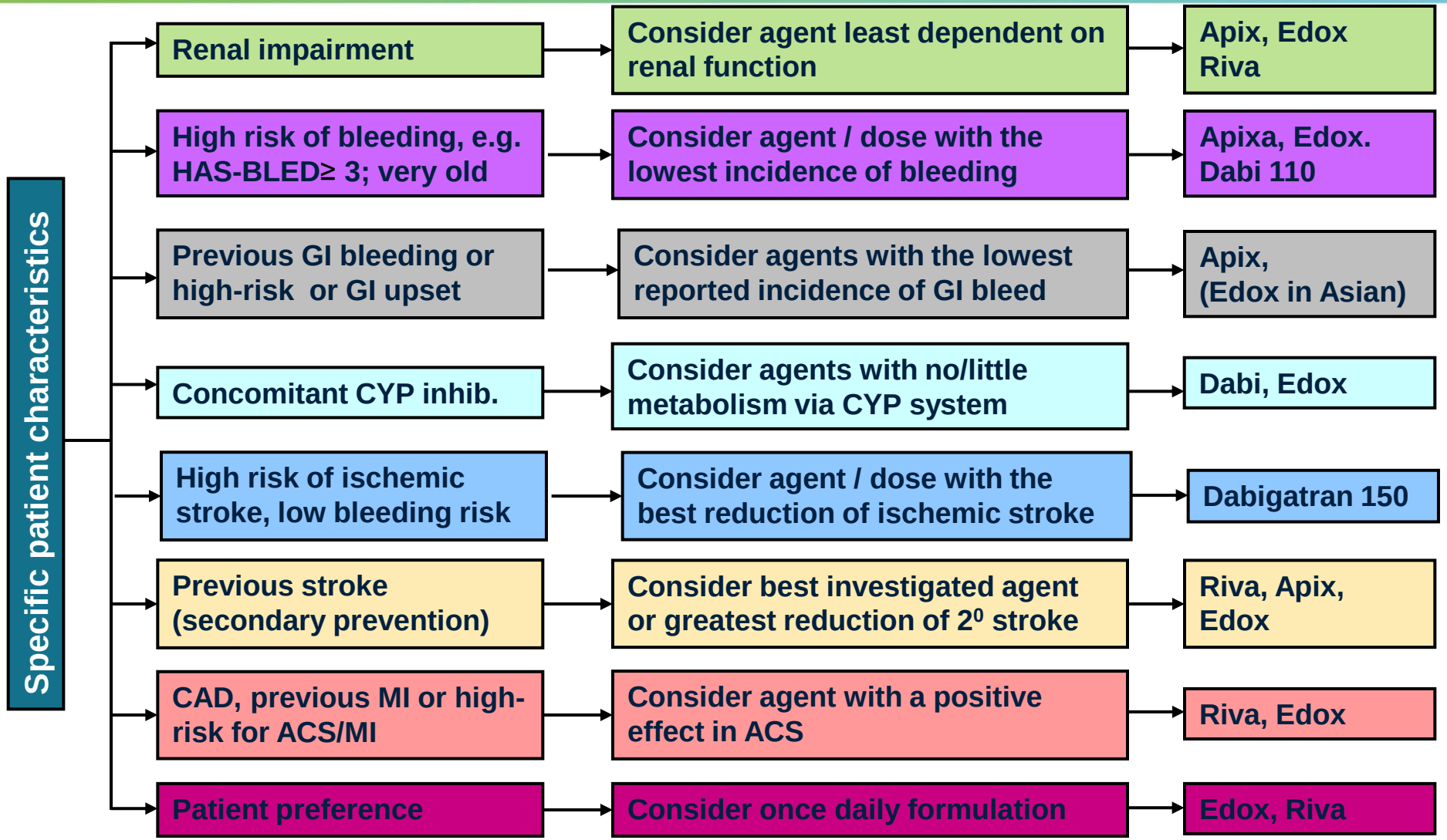
- Significant reductions by 24%, 28%, and 17% compared to rivaroxaban QD, and dabigatran 150 mg BID, and dabigatran 110 mg BID
- similar between edoxaban QD and apixaban BID

	Dabigatran 150mg twice daily(BID)	Dabigatran 110mg twice daily(BID)	Rivaroxaban(20mg/15mg) once daily(QD)	Apixaban(5mg/2.5mg) twice daily(BID)
Composite of stroke and systemic embolism(SEE)				
Edoxaban (60mg/30mg*) QD	1.26(0.97, 1.64)	0.95(0.74, 1.22)	0.90(0.70, 1.16)	1.08(0.86, 1.37)
Major bleeding				
Edoxaban (60mg/30mg*) QD	0.72(061, 0.84)	0.83(0.71, 0.98)	0.76(0.66, 0.89)	1.08(0.91, 1.28)

*In the ENGAGE AF–TIMI 38, if patients randomized to edoxaban groups have an anticipated increased drug exposure (any one or multiple of the following: creatinine clearance [CrCl] 30-50 mL/min, body weight ≤60 kg, or concomitant administration of verapamil or quinidine [strong P-gp inhibitors]), they receive a 50% dose reduction (60 mg reduced to 30 mg).

JACC 2015;65(10s):A346

summary & conclusion



Savelieva I and Camm AJ. Clinical Cardiology 2013 Gonzalez-Quesada CJ and Giugliano RP. JTT 2014 (in press)

Thanks for your attention !!