Stroke Prevention in AF patients :Edoxaban

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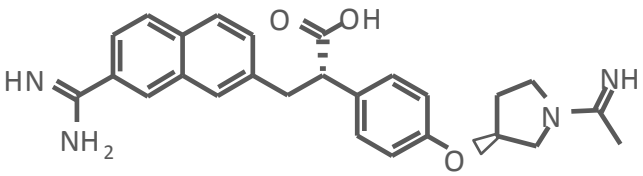
Engage AF
TIMI 48

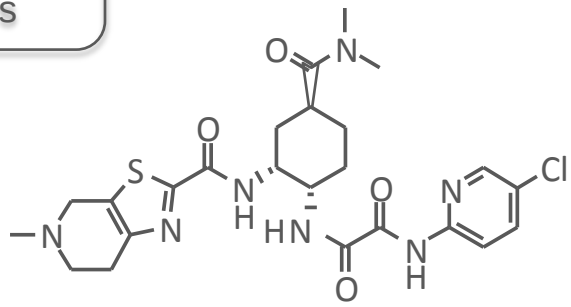
Development of edoxaban

DX-9065a

>10 years
>2500 compounds
>200 researchers

Edoxaban





FXa inhibitor program started in 1979

1979

DX-9065a discovered as the first small molecule direct FXa inhibitor in 1991

1991

Edoxaban developed from orally available FXa inhibitor DX-9065a

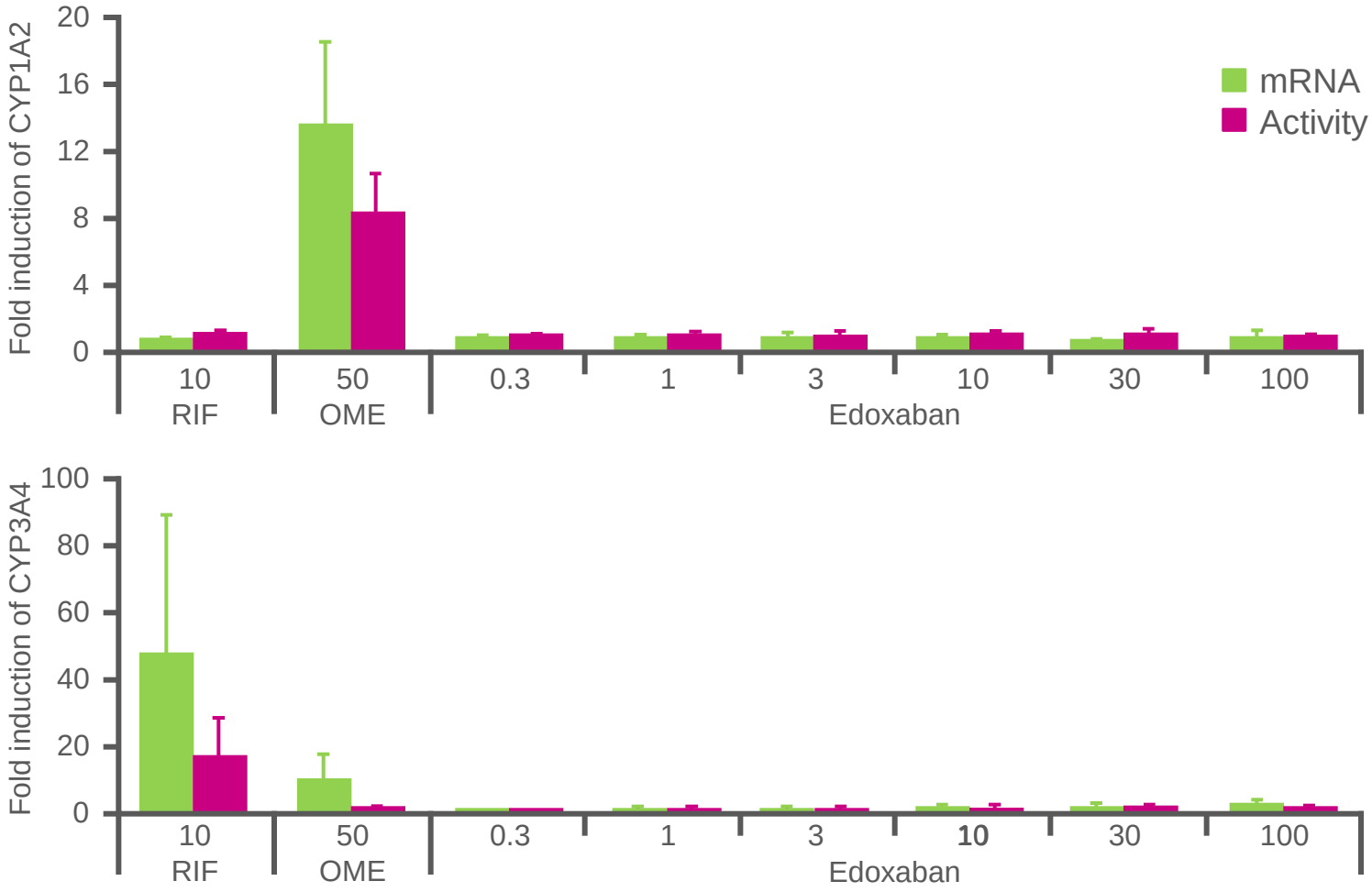
Early 2000s

Selective anti-FXa activity Ki*=41 nM (human)	→	Potent anti-FXa activity Ki=0.56 nM (human)
Poor oral bioavailability <10% (monkey)	→	Good oral bioavailability 51% (monkey)

* Ki, binding affinity of the inhibitor

Hara et al. Thromb Haemost 1994;71:314–319; Fujii et al. Drug Metab Pharmacokinet 2007;22:26–32
Raskob et al. J Thromb Haemost 2013;11:1287–1294; Ruff et al. Am Heart J 2010;160:635–641
Morishima et al. Blood 2004;104: Abstract 1862; Yokoyama et al. Circulation 1995;92:485–491
Furugohri et al. J Thromb Haemost 2008;6:1542–1549

Edoxaban does not induce CYP450 isozymes

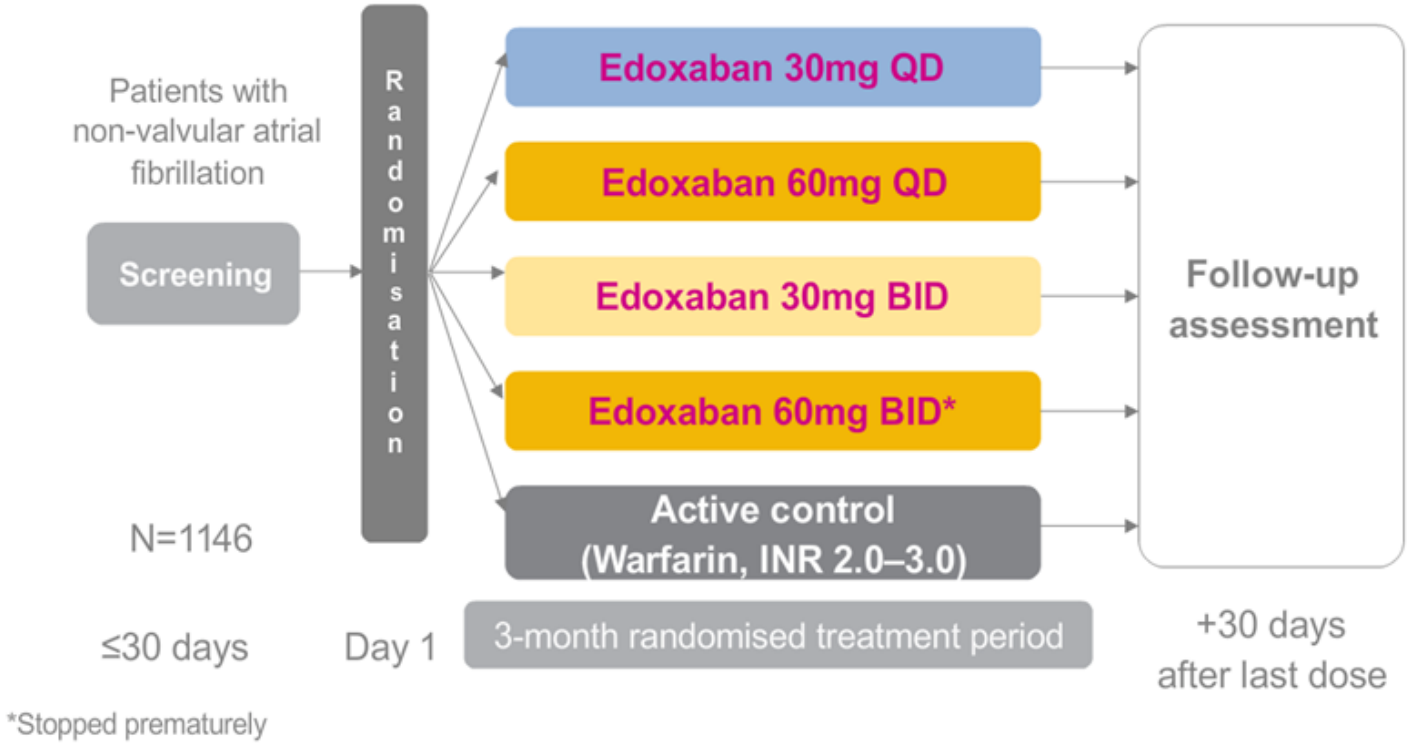


mRNA=messenger RNA RIF=rifampicin OME=omeprazole

Phase II study of Edoxaban (NVAF)

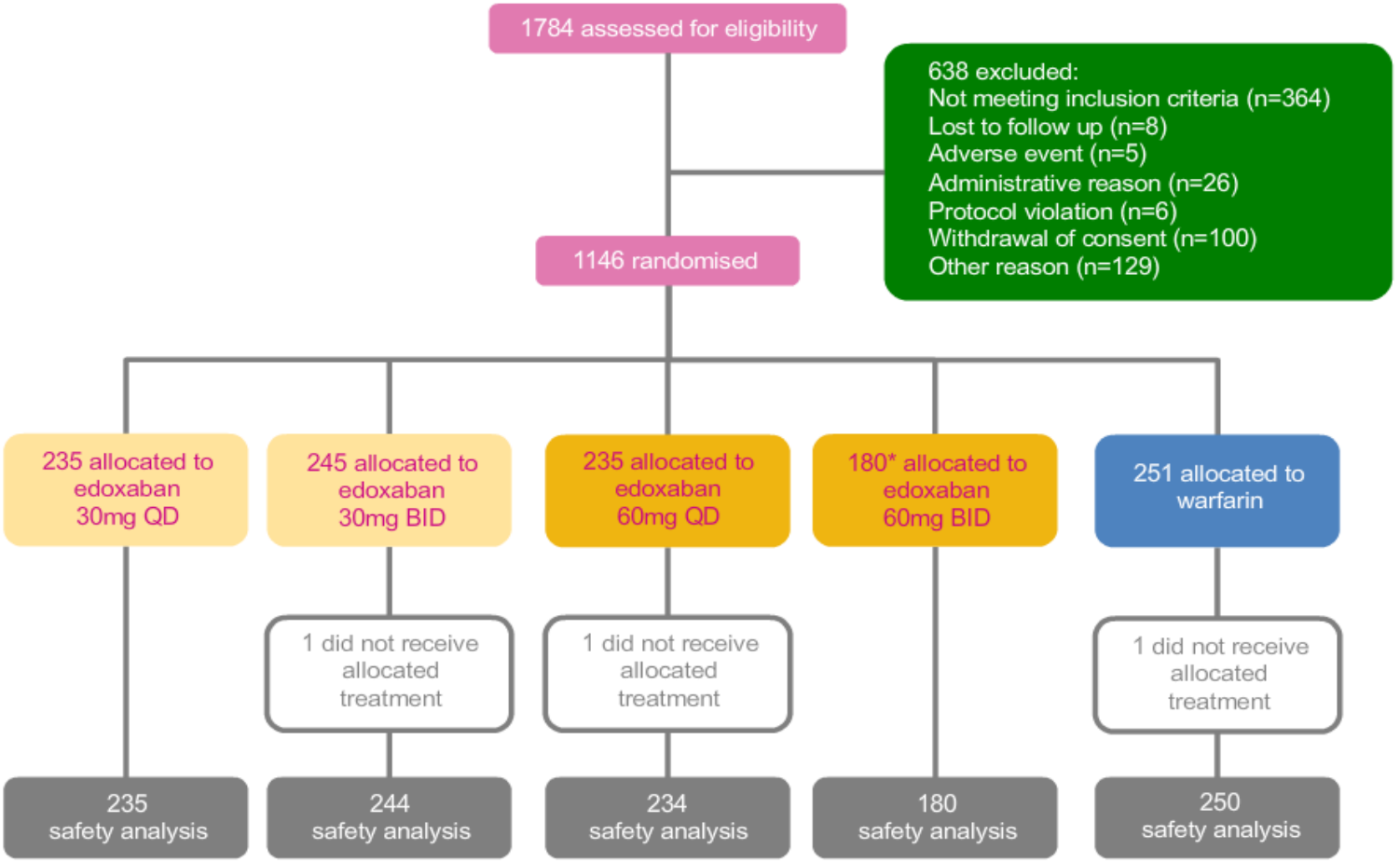
. **Study design**: Randomized, parallel group, multi-dose, active-controlled, double blind edoxaban, open-label warfarin

. Primary endpoint: occurrence of major and/or clinically relevant non-major bleeding, elevated hepatic and/or bilirubin



Thrombosis and Haemostasis 2010;104:633-641

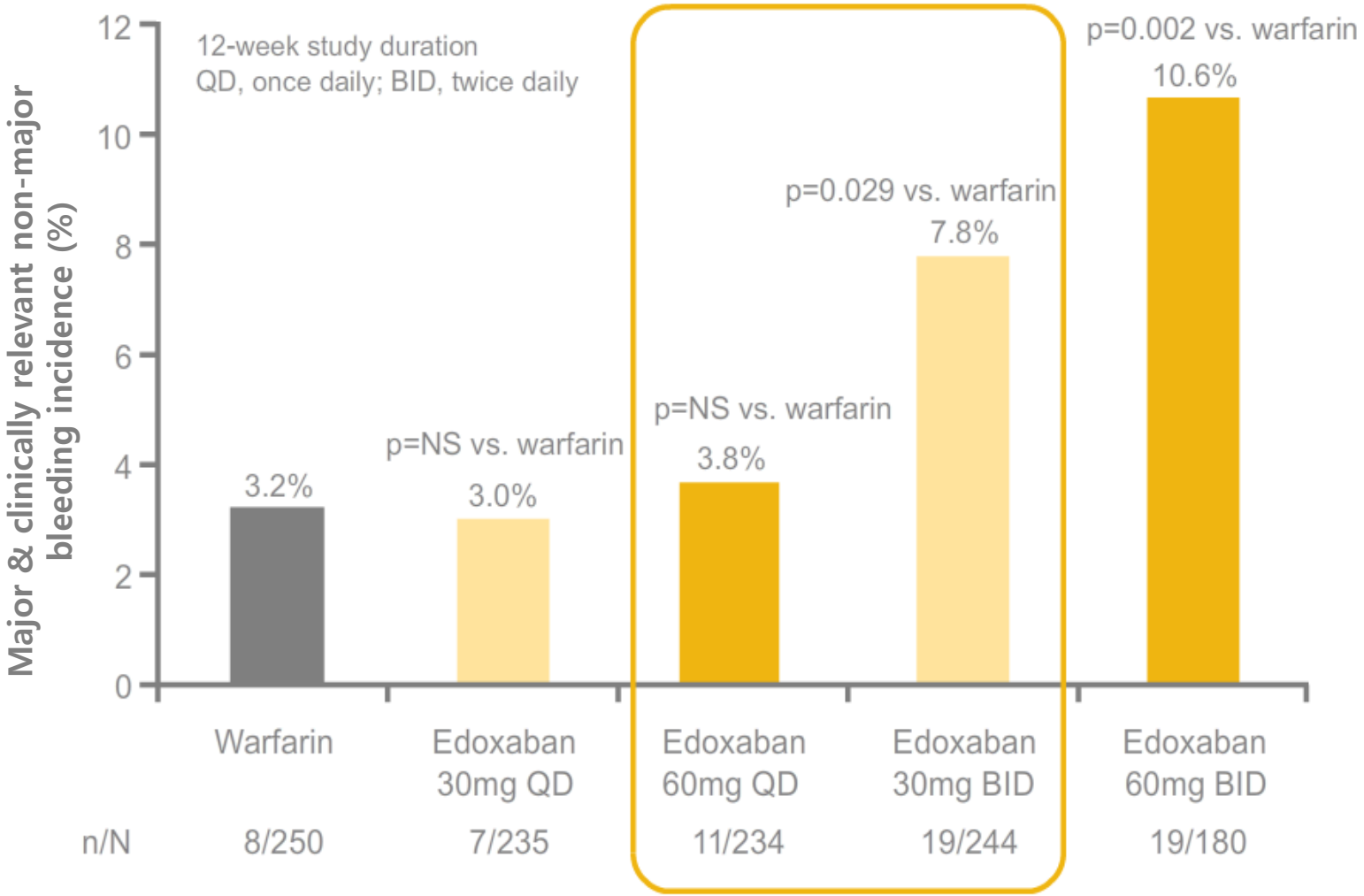
Phase II study of Edoxaban (NVAF)



*Treatment group discontinued early based on recommendation by data safety monitoring committee

Thrombosis and Haemostasis 2010;104:633-641

Phase II study of Edoxaban (NVAF)



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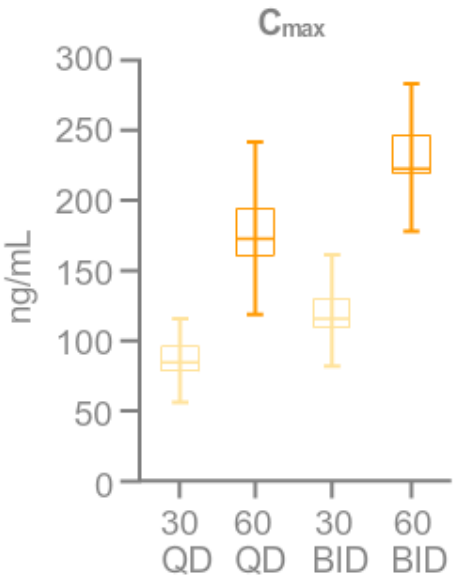
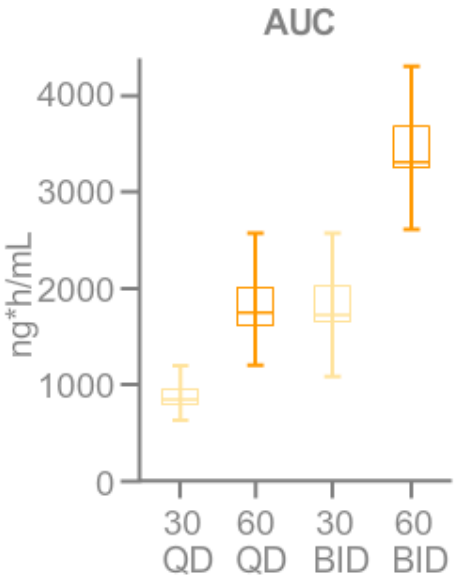
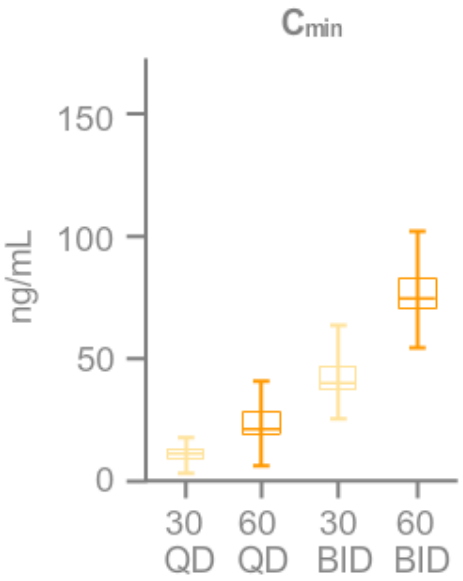
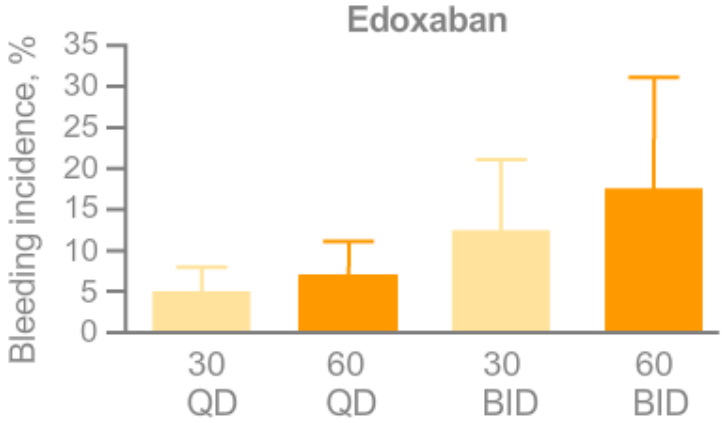
Phase II study of Edoxaban (NVAF)





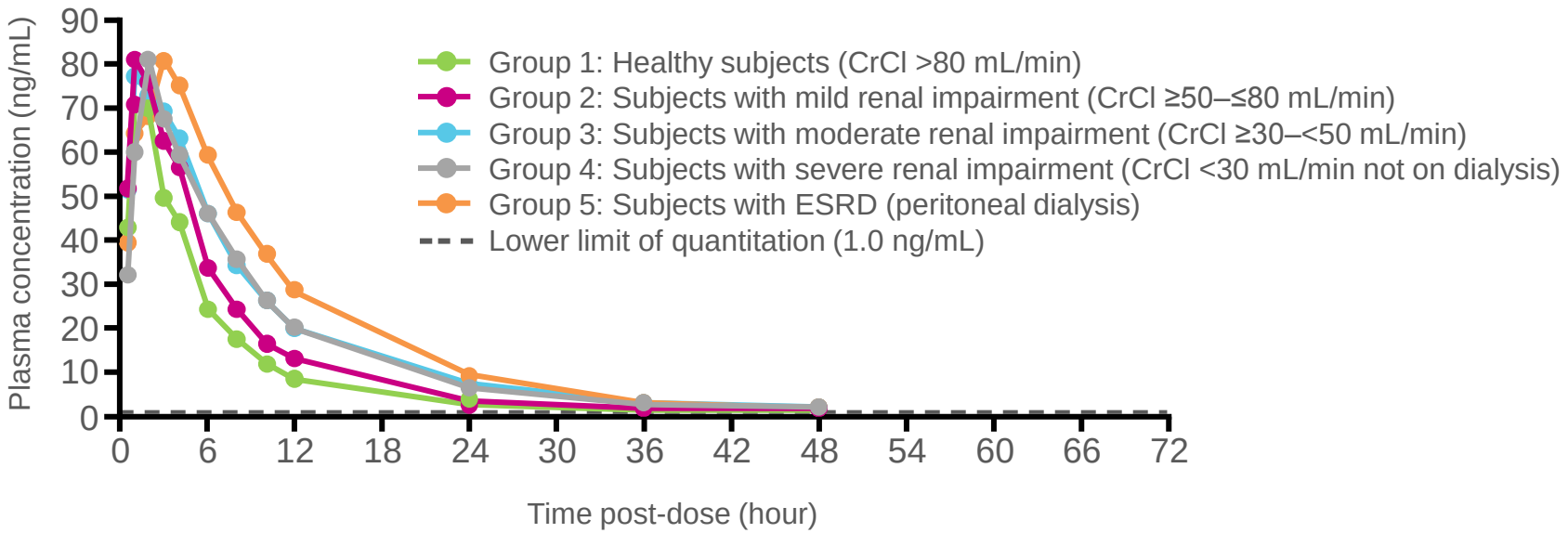


AUC, area under the plasma concentration-time curve from 0 to 24 hours at steady-state;
C_{max}, maximum steady-state plasma concentration;
C_{min}, minimum steady-state concentration;
QD, once daily; BID, twice daily



Thrombosis and Haemostasis 2010;104:633-641

Renal impairment increases exposure to edoxaban

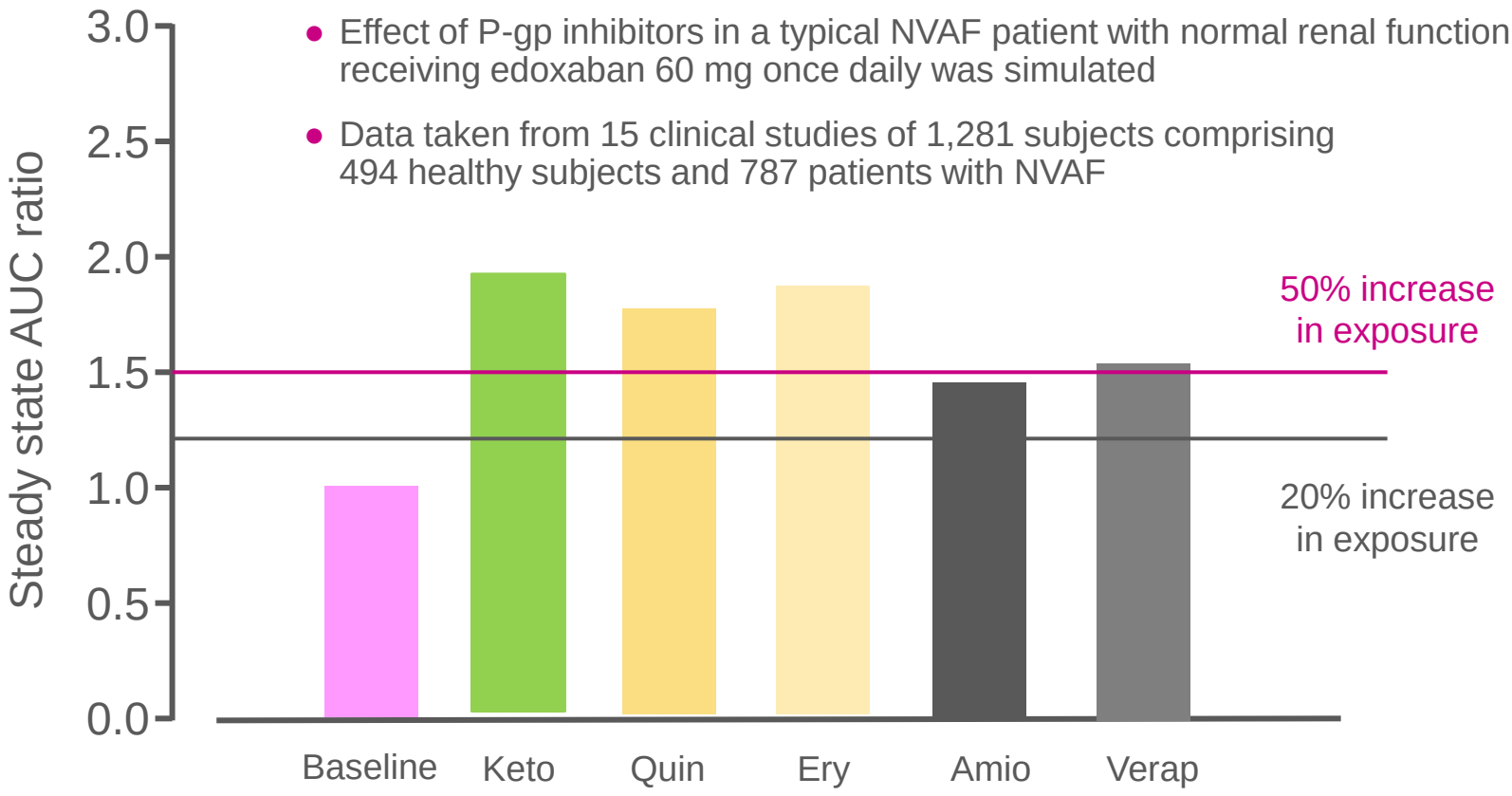


	Renal function group				
	Healthy (n=8)	**Mild renal impairment (n=8)**	**Moderate renal impairment (n=8)**	**Severe renal impairment (n=8)**	**Peritoneal dialysis (n=8)**
AUC_{0-24} (ng•h/mL)	419 (90.3)	581 (126)	720 (175)	700 (156)	879 (311)
AUC_{0-24} (norm)	5.86 (1.98)	7.56 (0.94)	9.85 (3.72)	10.1 (3.15)	13.5 (5.88)
$AUC_{0-\infty}$ (ng•h/mL)	453 (102)	636 (152)	816 (209)	857 (199)	1031 (377)
$AUC_{0-\infty}$ (norm)	6.35 (2.22)	8.24 (1.00)	11.2 (4.38)	12.3 (3.60)	157 (6.90)

All results are presented as the arithmetic mean (SD) except for T_{max}, which is presented as the median (range).
PK parameters normalized for body weight (kg) are indicated by (norm).

Ridout et al. Poster presented at Am Coll Clin Pharm/Eur Soc Clin Pharm 2009

Simulation of impact of P-gp inhibitors on edoxaban exposure

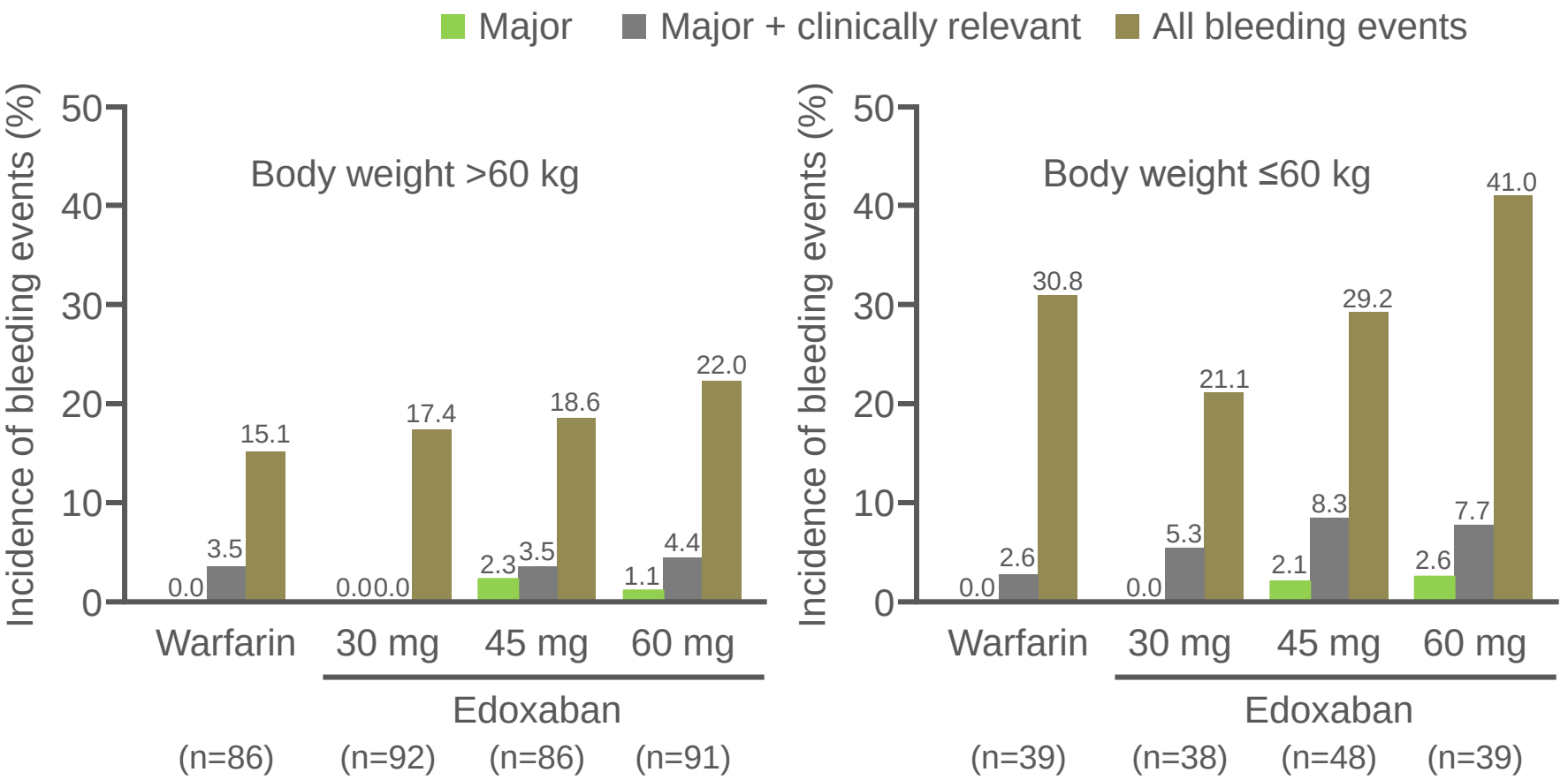


Keto=ketoconazole; Quin=quinidine ; Ery=erythromycin; Amio=amiodarone ; Verap=verapamil

Salazar et al. Thromb Haemost 2012;107:925–934

Impact of body weight on safety of edoxaban

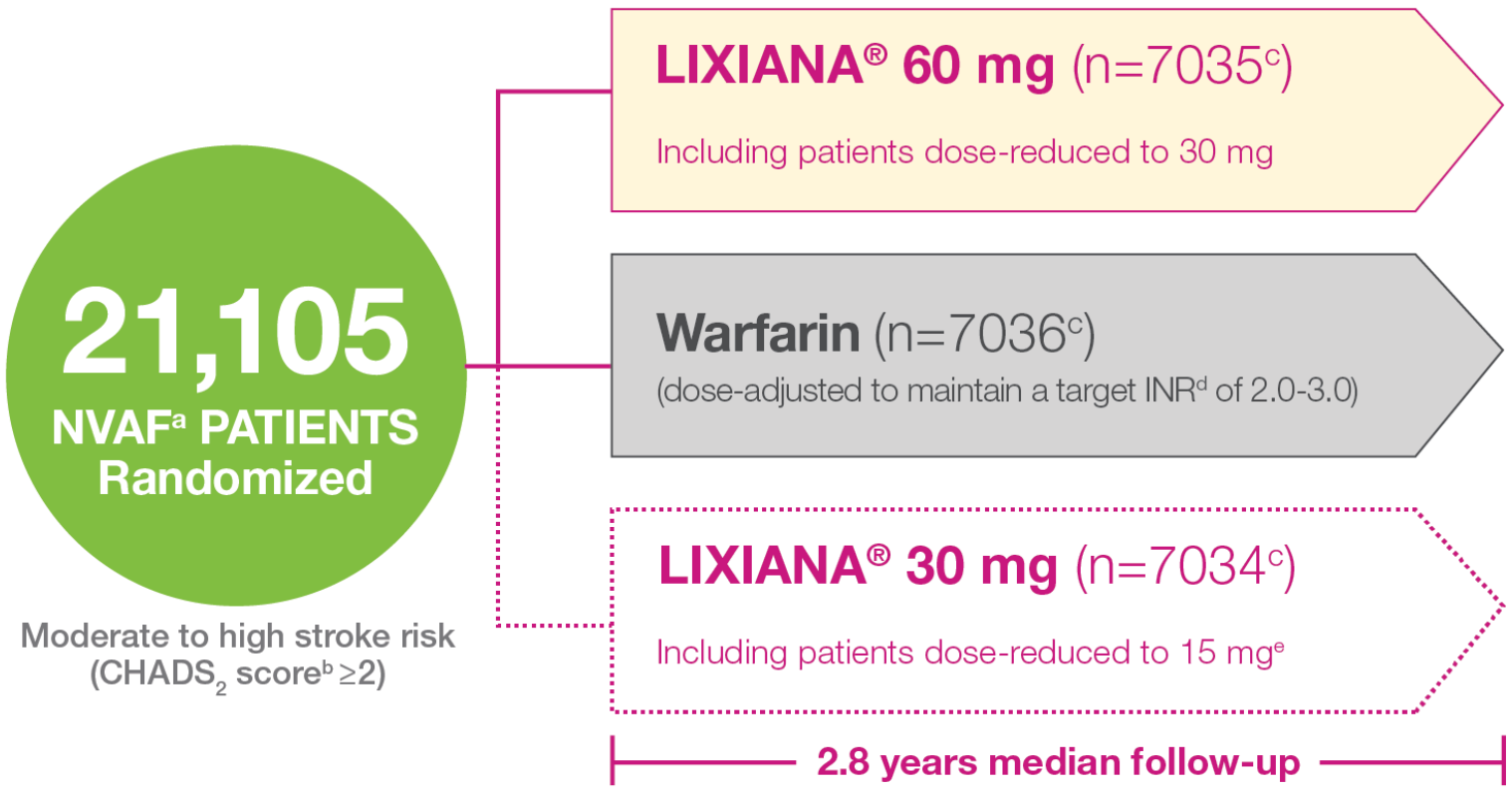
- Data taken from a safety study of edoxaban in 536 Japanese AF patients



Yamashita et al. Circ J 2012;76:1840–1847

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;369(22):2093-2104

Primary efficacy and safety outcome measures

- Primary efficacy
  - Time to first stroke (ischemic or hemorrhagic) 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 hemoglobin level of 2 g/dL 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;369(22):2093-2104

Inclusion Criteria

- Male or female patients, age ≥21 years
- Written informed consent provided
- History of AF documented by an electrical tracing within the prior12 months and for which anticoagulation is indicated and planned for the duration of the study
  - Including paroxysmal, persistent or permanent AF
  - Including subjects with or without previous VKA experience
- $CHADS_2$ risk score ≥2
  - Patients score 1 point for presence of congestive heart failure, hypertension (>140/90 or medically treated), age ≥75 years or diabetes mellitus
  - Patients score 2 points for having a prior stroke or transient ischemic attack

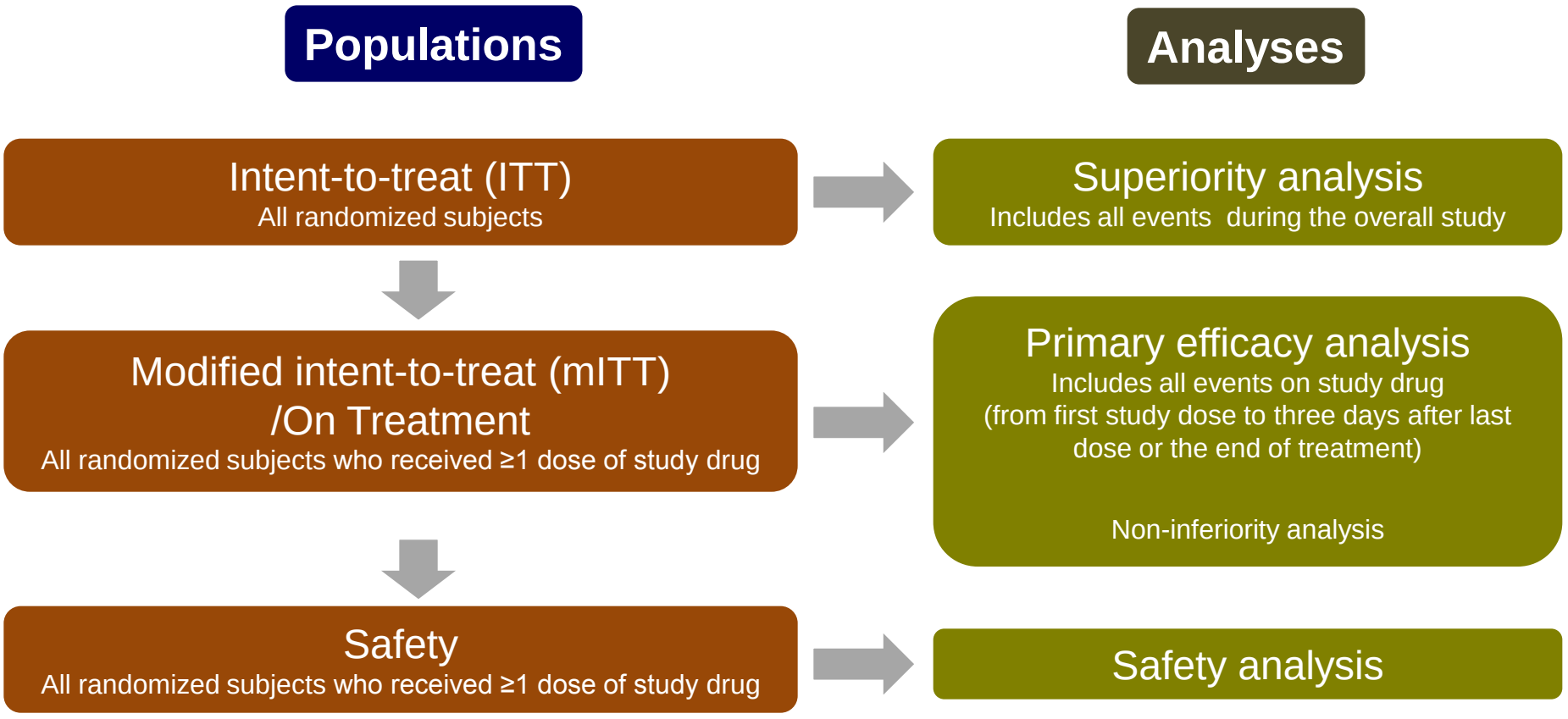
Giugliano et al. *N Engl J Med.* 2013;369(22):2093-2104

Key exclusion Criteria

- Transient AF secondary to other reversible disorders
- Severe renal insufficiency (calculated CrCl <30 mL/min)
- High risk of bleeding due to concomitant conditions e.g. history of intracranial, intraocular, spinal, retroperitoneal, or intra-articular bleeding; overt gastrointestinal bleeding or active ulcer within the previous year; recent severe trauma, major surgery, or deep organ biopsy within the previous 10 days
- Dual-antiplatelet therapy (e.g., aspirin plus thienopyridine) or anticipated need to receive such therapy
- Moderate or severe mitral stenosis, unresected atrial myxoma, or a mechanical heart valve
- Acute MI, stroke, acute coronary syndrome, or percutaneous coronary intervention within the previous 30 days
- Subjects who are unlikely to comply with the protocol

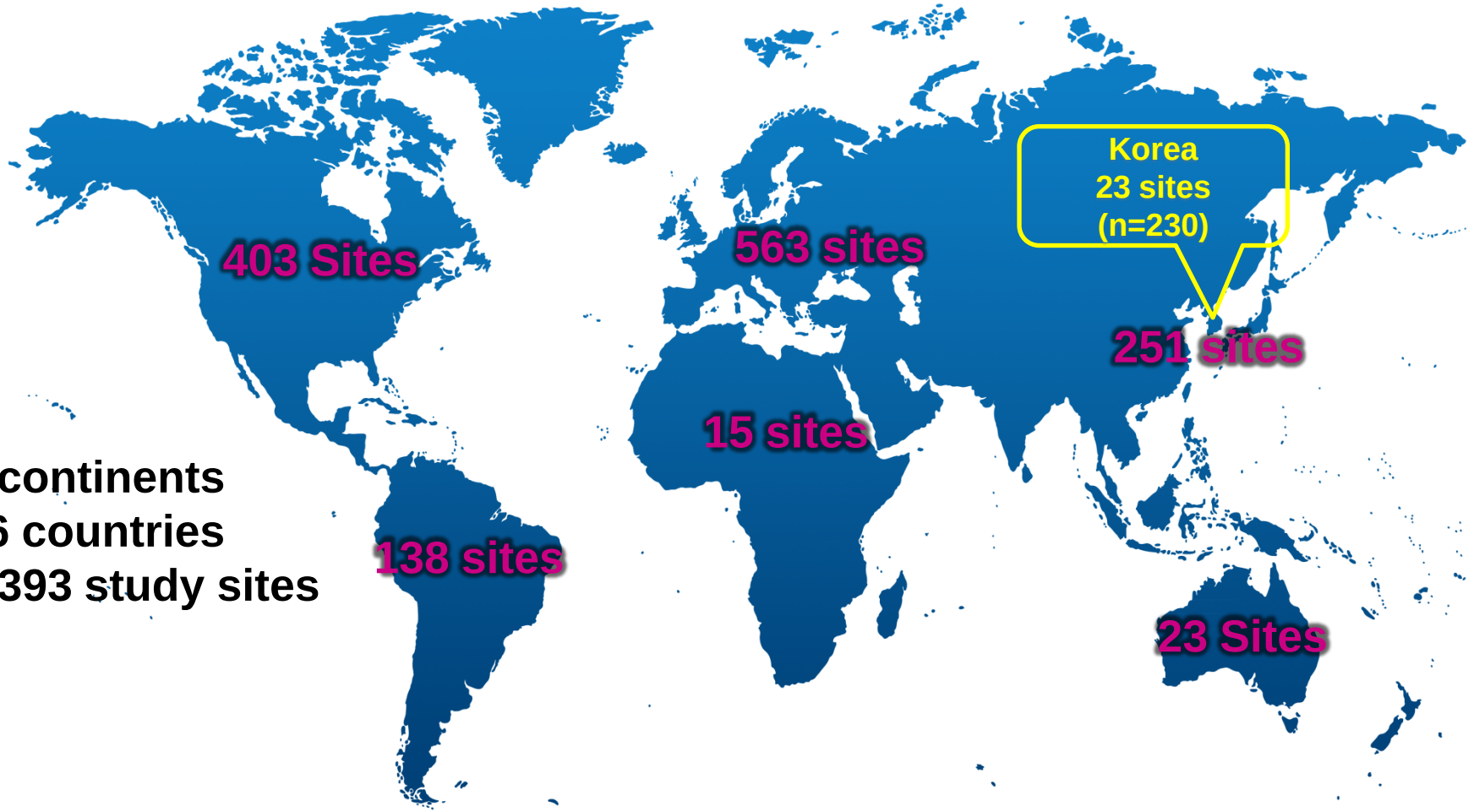
Giugliano et al. *N Engl J Med.* 2013;369(22):2093-2104

Populations/Analysis definition



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

Global participants



6 continents
46 countries
1,393 study sites

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

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;369(22):2093-2104

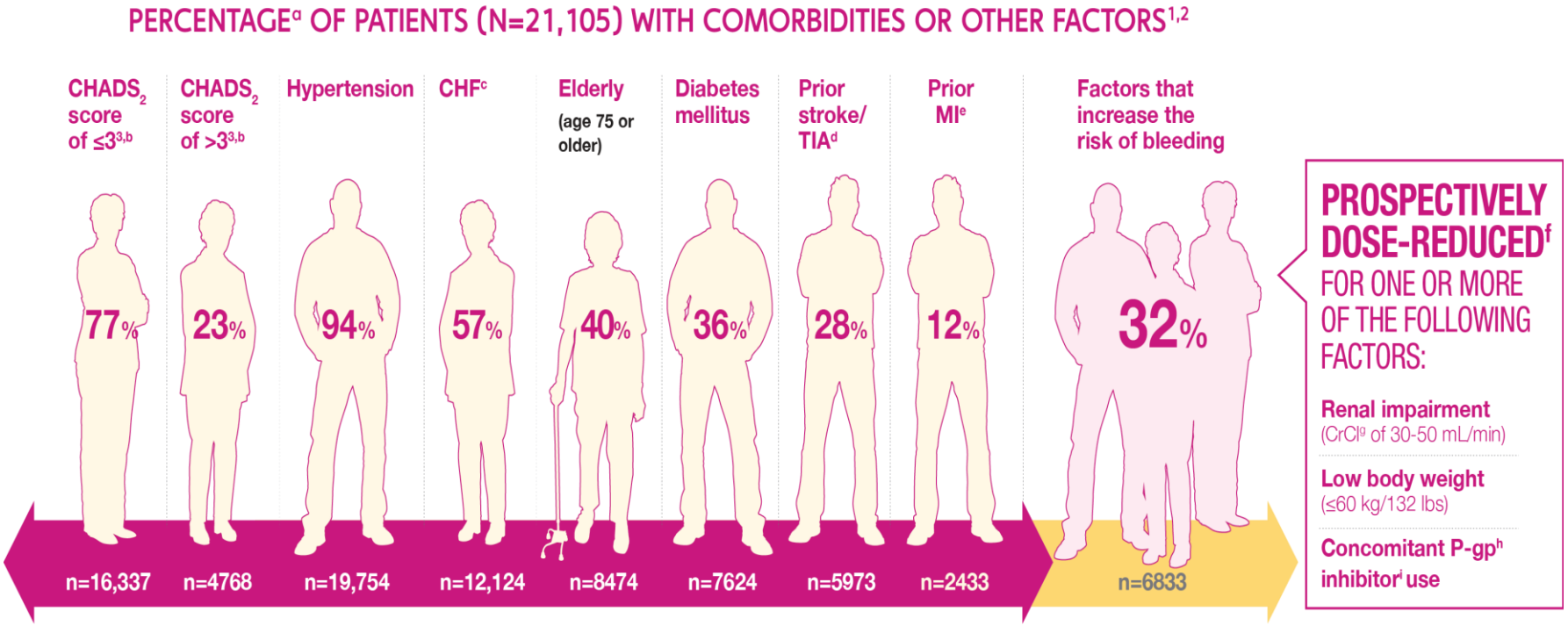
Patients Characteristics

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;369(22):2093-2104

ENGAGE AF-TIMI 48
Broad Range of Patients [1,2]



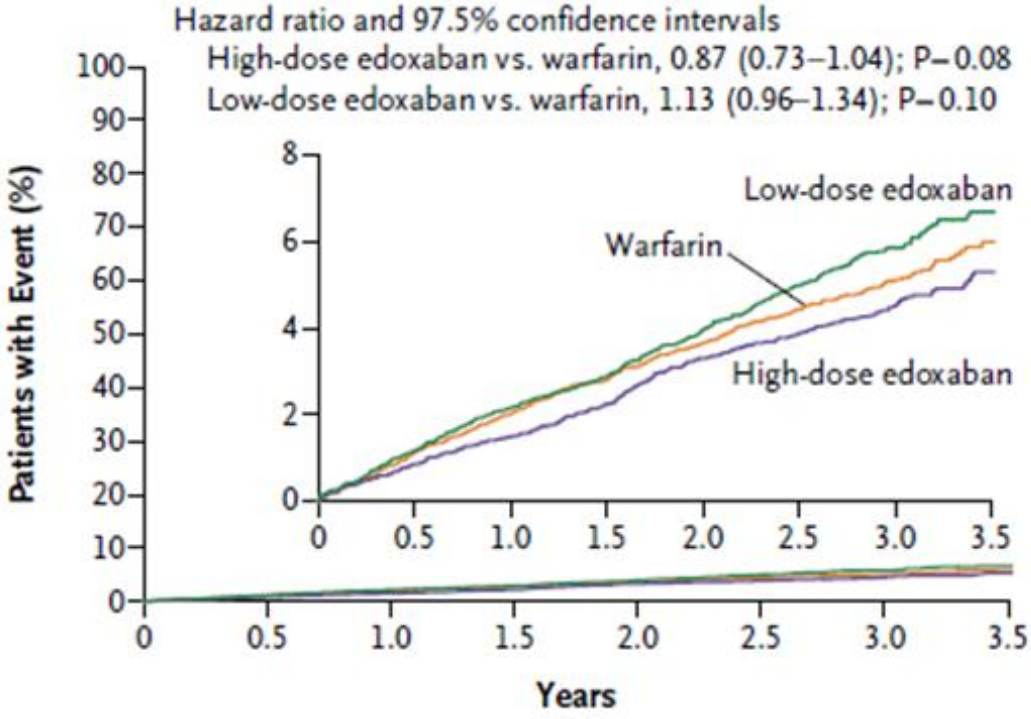
[a] Percentages are approximate. [b] Mean $CHADS_2$ score in the trial was 2.8. [c] Congestive heart failure. [d] Transient ischemic attack. [e] Myocardial infarction. [f] ~32% of patients (~25% [n=5356] at randomization, and an additional ~7% [n=1477] during the trial) received a dose reduction (half-dose).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

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*

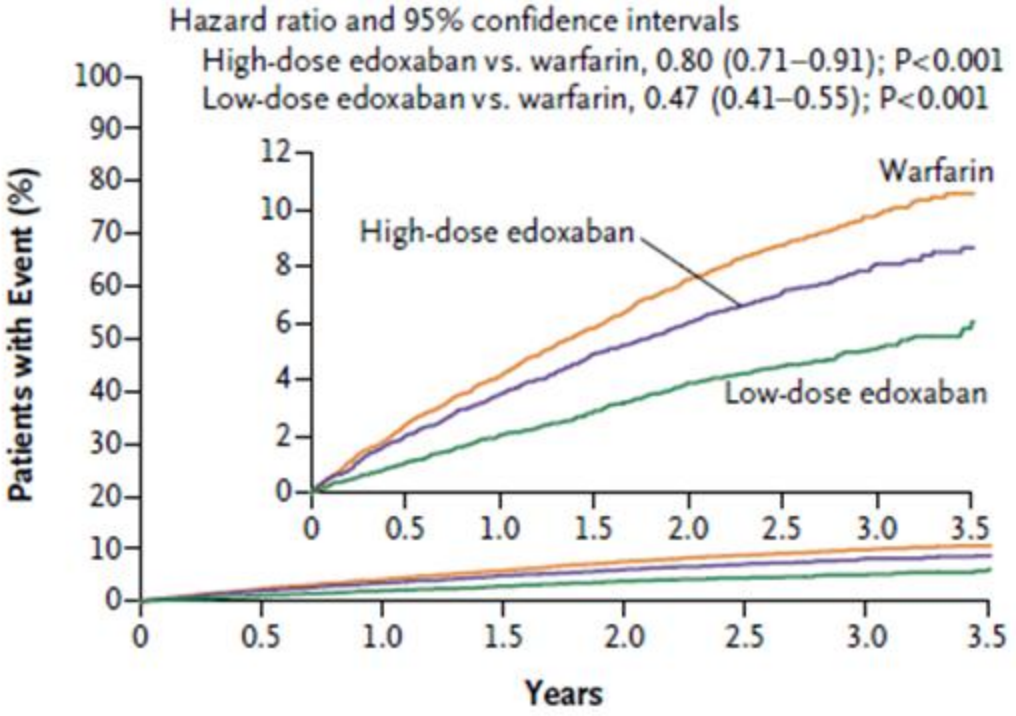
Primary Efficacy Endpoint
Stroke and Systemic Embolism



No. at Risk								
Warfarin	7036	6798	6615	6406	6225	4593	2333	536
High-dose edoxaban	7035	6816	6650	6480	6283	4659	2401	551
Low-dose edoxaban	7034	6815	6631	6461	6277	4608	2358	534

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

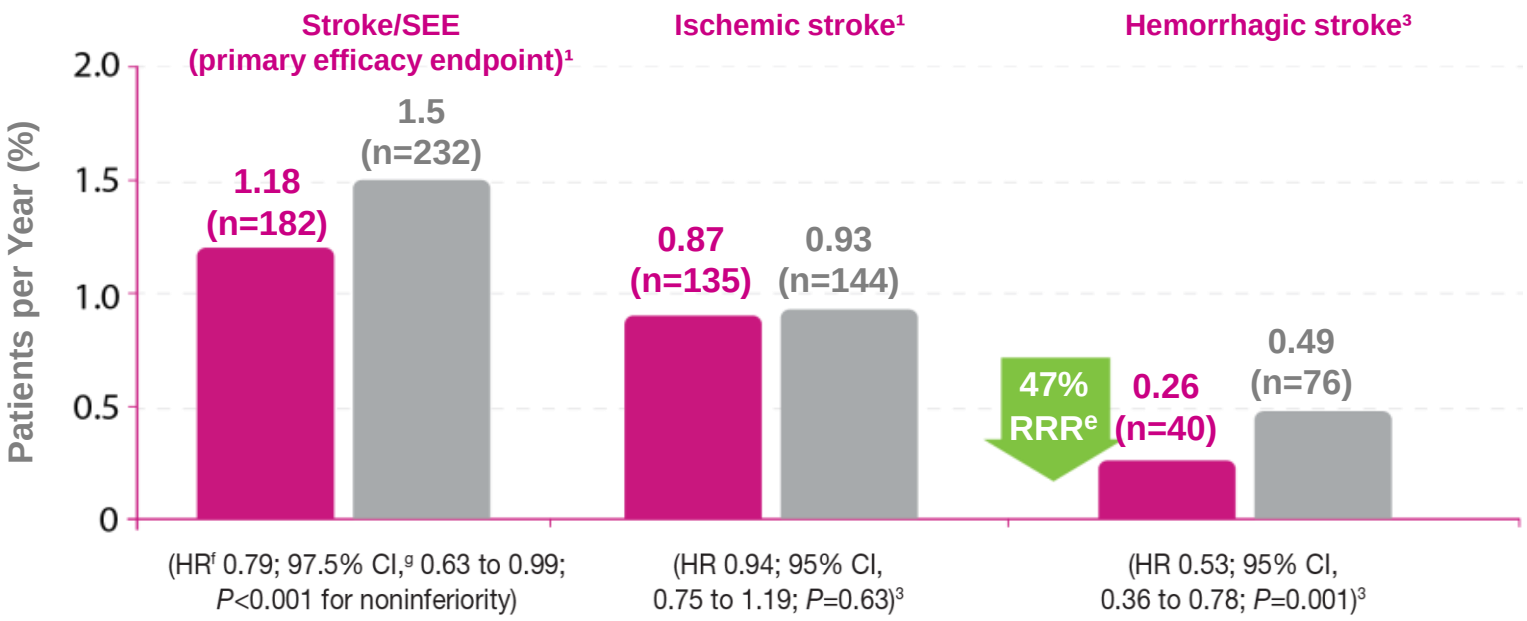
Primary Safety Endpoint
Major bleeding



No. at Risk								
Warfarin	7012	6116	5630	5278	4941	3446	1687	370
High-dose edoxaban	7012	6039	5594	5232	4910	3471	1706	345
Low-dose edoxaban	7002	6218	5791	5437	5110	3635	1793	386

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

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



ITT population for superiority test
0.87 (0.73–1.04) p=0.08
97.5% CI

Edoxaban 60/30mg®[b] (n=7012)

Warfarin (n=7012)

[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.

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

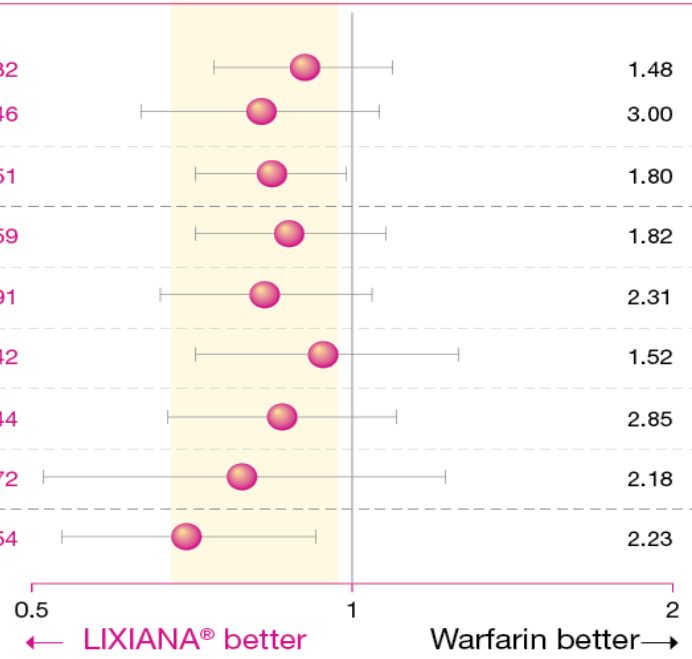
Once-daily Edoxaban Was Comparable to Warfarin in Reducing Stroke/SEE Risk[1]

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

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

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

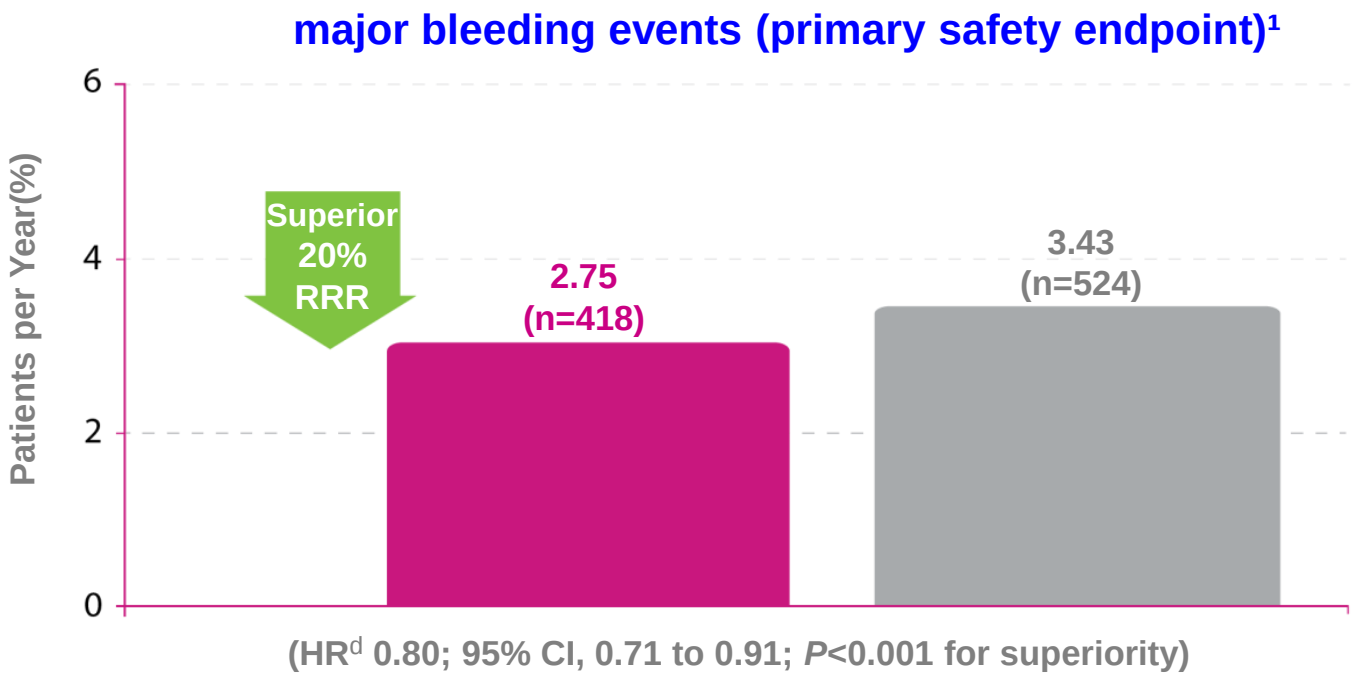
Subgroups	Patients (n)[b]	LIXIANA®[c] % of patients with event/yr	Warfarin % of patients with event/yr
$CHADS_2$ score[f]			
≤3	16,337	1.32	1.48
>3	4768	2.46	3.00
Hypertension	19,754	1.51	1.80
CHF	12,124	1.59	1.82
Elderly (≥75 yrs)	8474	1.91	2.31
Diabetes	7624	1.42	1.52
Prior stroke/TIA	5973	2.44	2.85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

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

Once-daily Edoxaban 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]

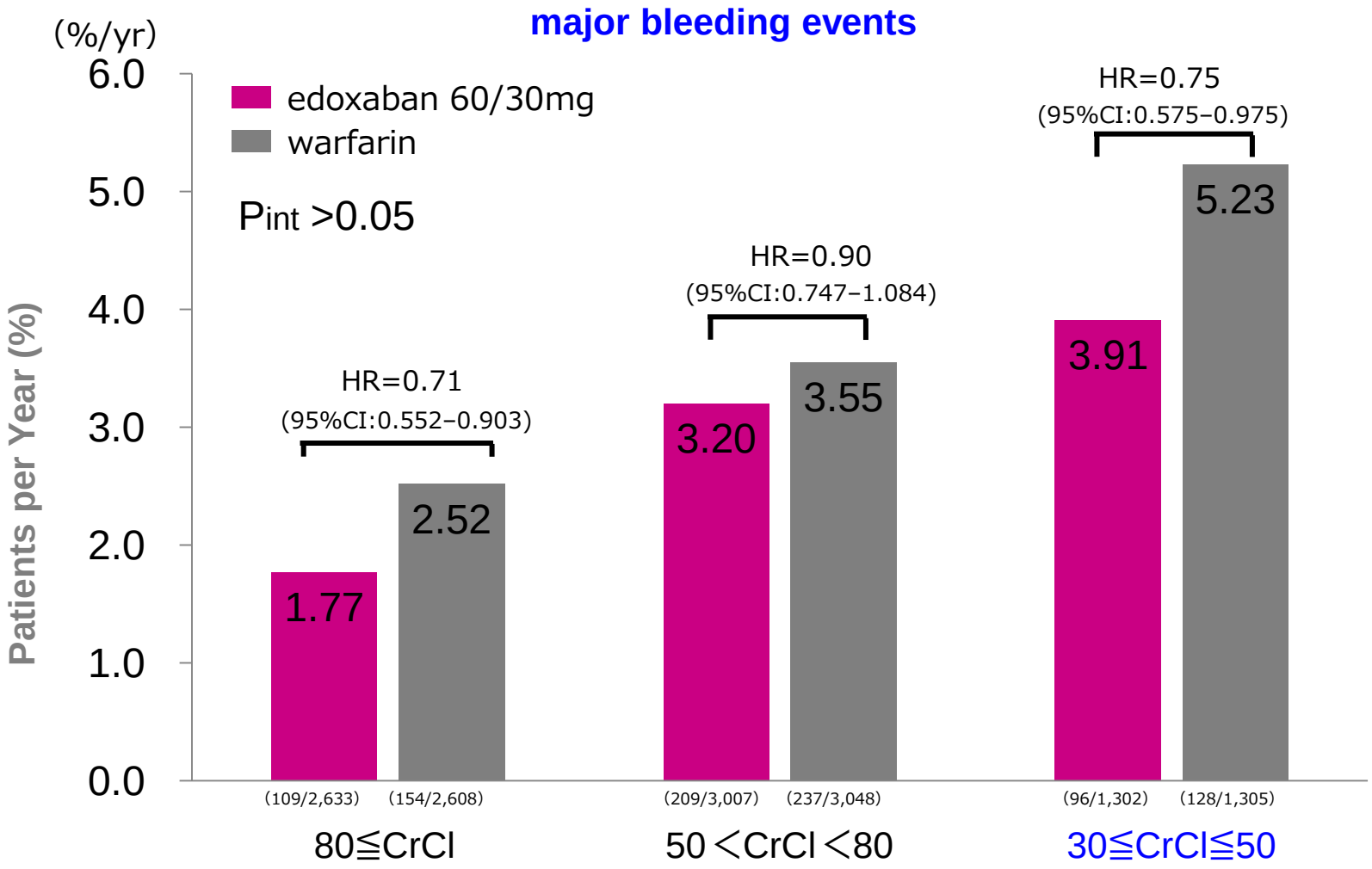
	LIXIANA®[b] (n=7012)	Warfarin (n=7012)	Relative Risk Reduction	HR[c] and 95% CI[d]
Intracranial bleeding	**0.39** (n=61)	0.85 (n=132)	53%	HR, 0.47; 95% CI, 0.34 to 0.63; *P*<0.001
Life-threatening bleeding	**0.40** (n=62)	0.78 (n=122)	49%	HR, 0.51; 95% CI, 0.38 to 0.70; *P*<0.001
Fatal bleeding	**0.21**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

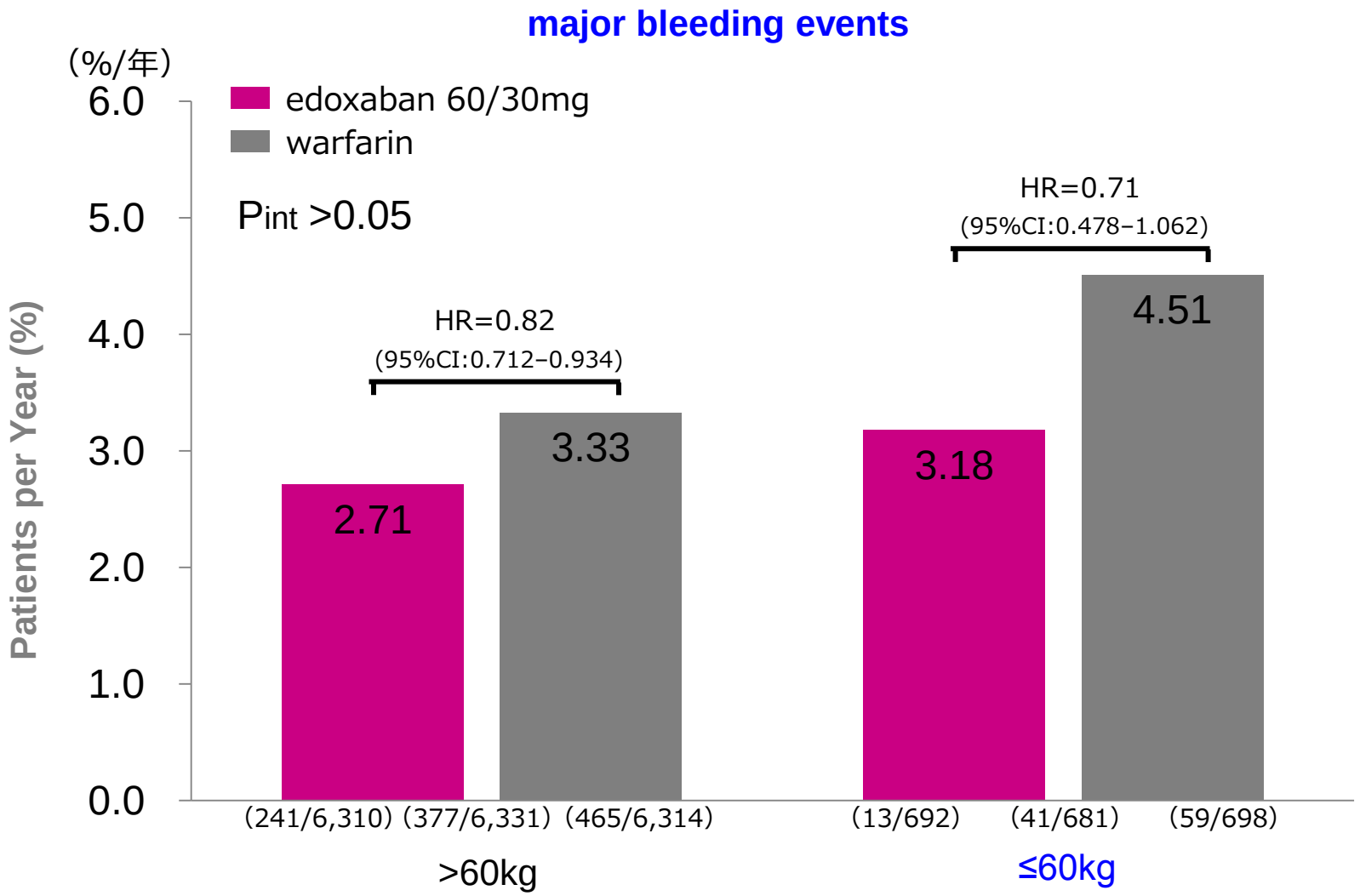
[a] Time from first dose of study drug to last does plus 3 days
[b] Includes patients talking LIXIANA 60 mg and those dose-reduced to 30mg
[c] Hazard ratio [d] Confidence interval

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

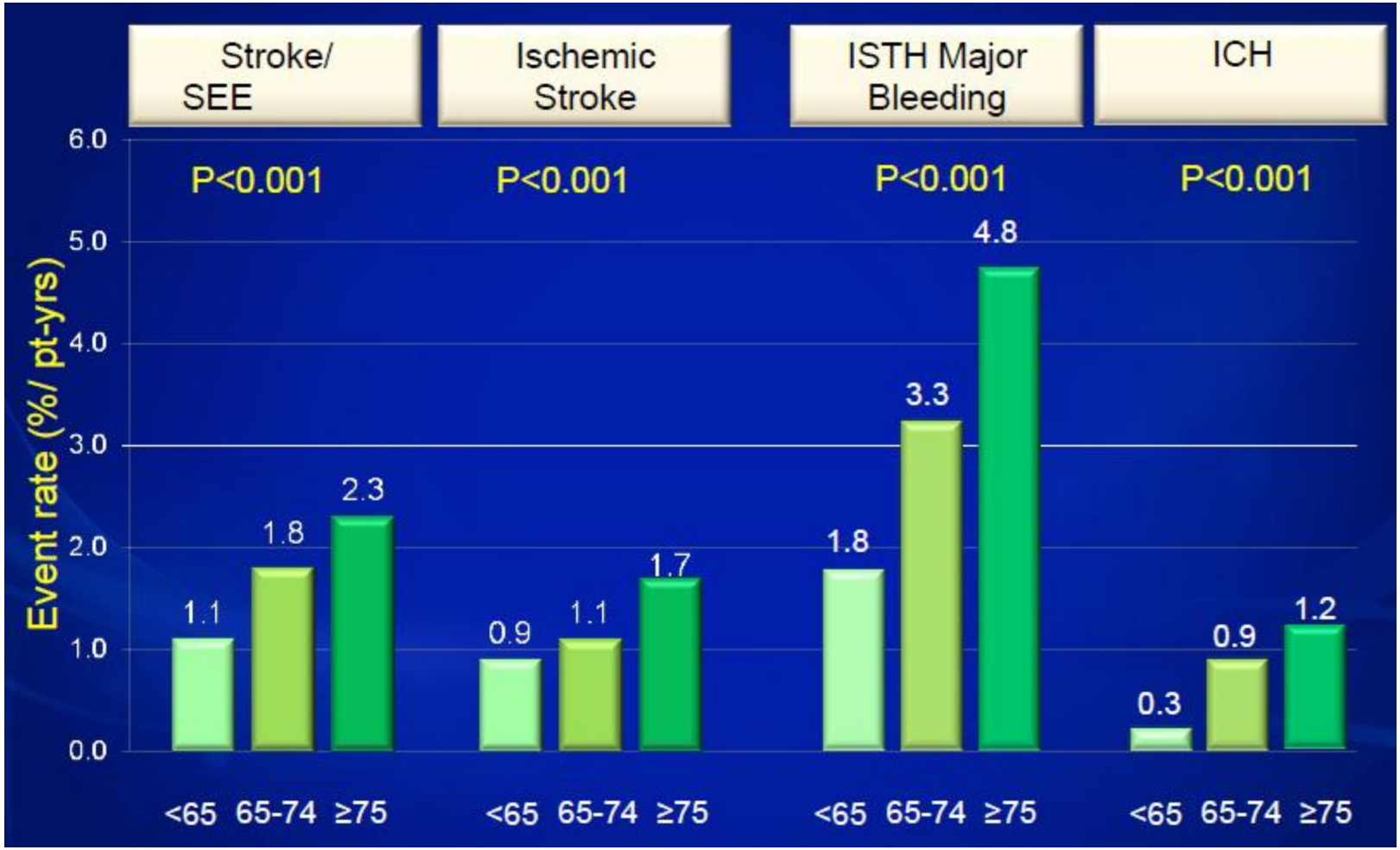
Once-daily Edoxaban Was Superior to Warfarin in Reducing the Risk of Major Bleeding in renal impairment pts.



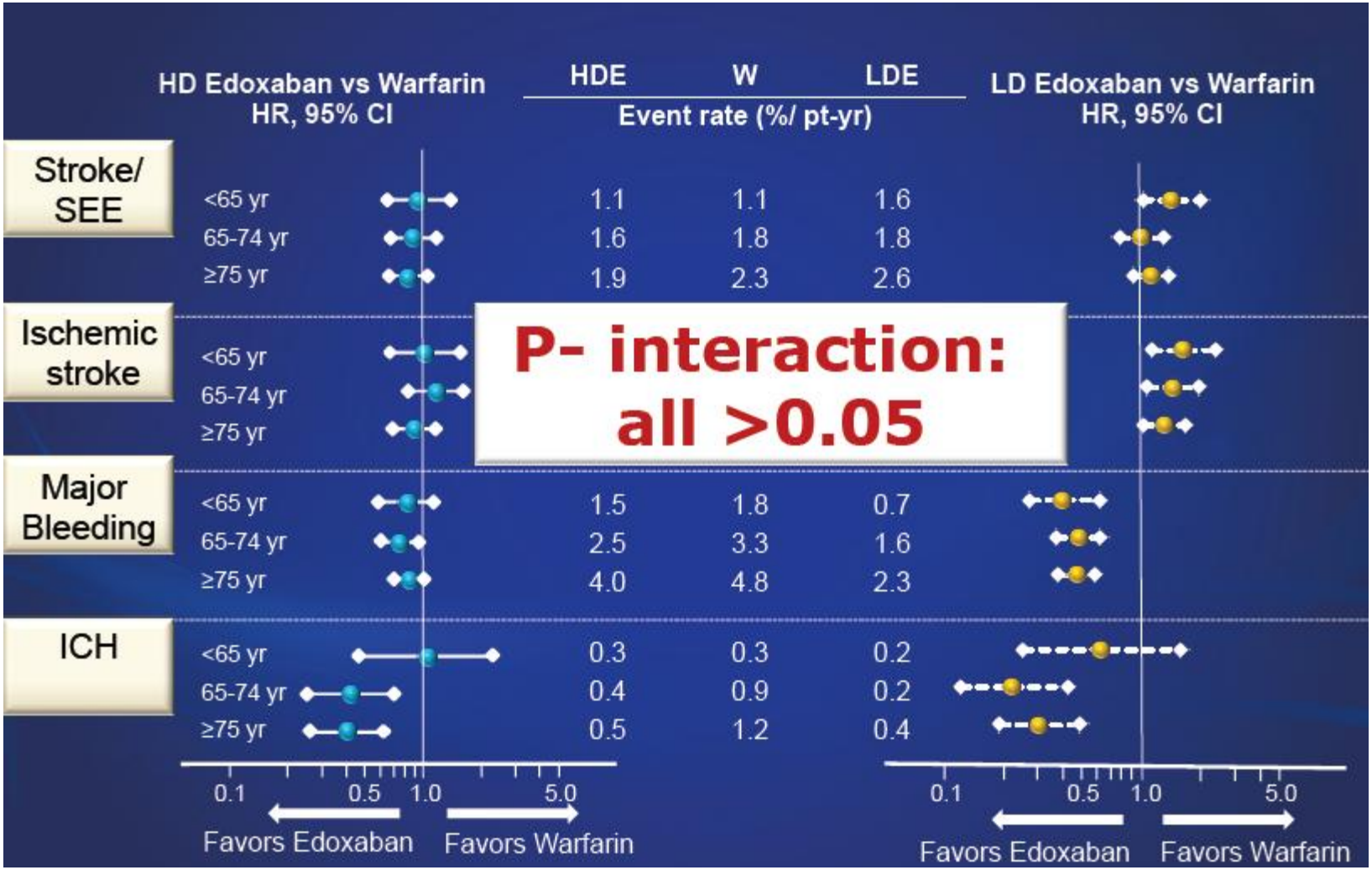
Once-daily Edoxaban Was Superior to Warfarin in Reducing the Risk of Major Bleeding in low body weight pts.



Event rate by age (Warfarin only)

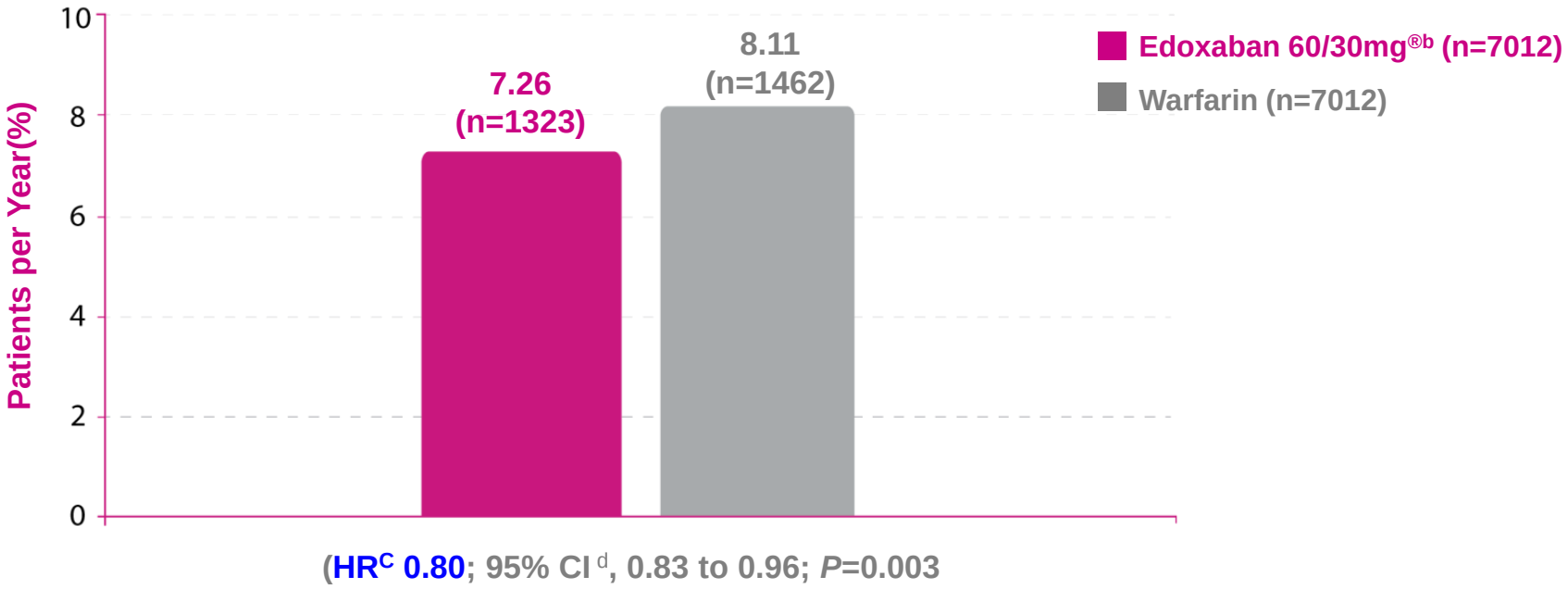


Event rate by age



The Primary Net Clinical Outcome[1]

Net Clinical Outcome (overall study period[a])[1]
Stroke/SE/Major bleeding/Death



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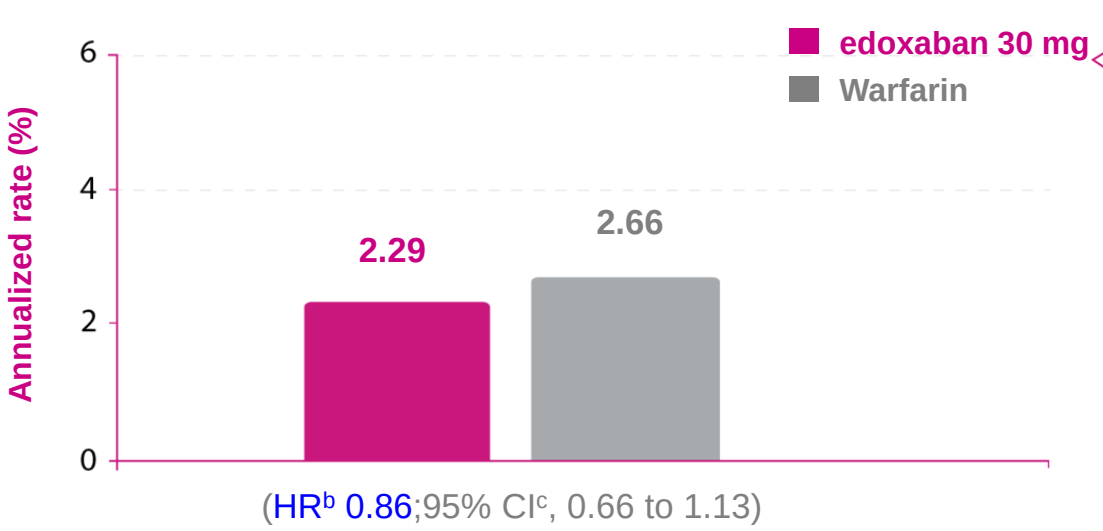
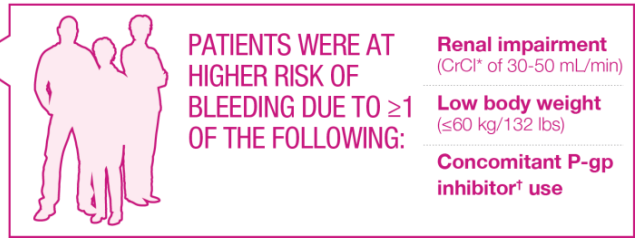
Giugliano et al. *N Engl J Med.* 2013;369(22):2093-2104

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

Stroke/SEE (overall study period)[1]



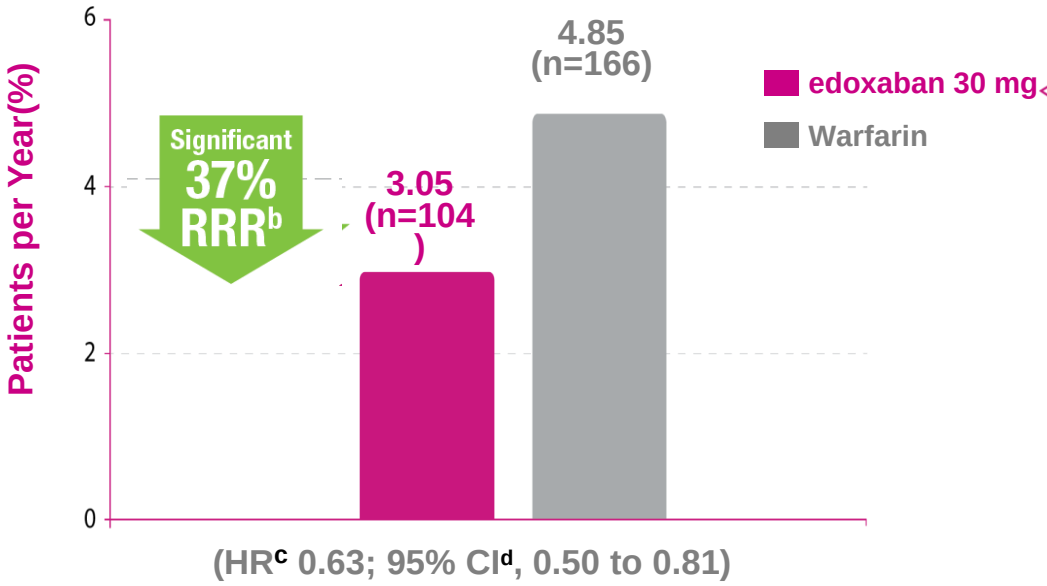


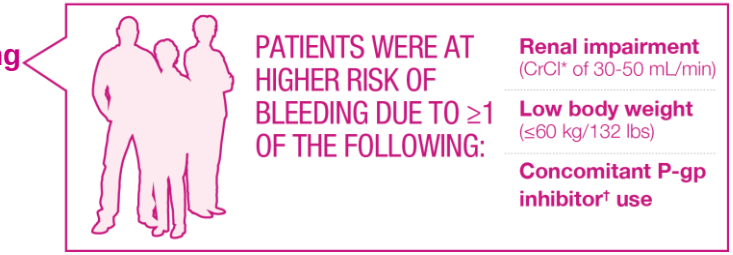
[a] All randomized subjects who received at least 1 dose of randomized drug and did not have any major protocol violations
[b] Hazard ratio [c] Confidence interval
[d] Creatinine clearance.
†Verapamil, dronedarone, or quinidine.

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

Major Bleeding Compared With Warfarin in Patients Who Were Dose-reduced to Edoxaban 30 mg[1]

Major bleeding (on-treatment period) [1]

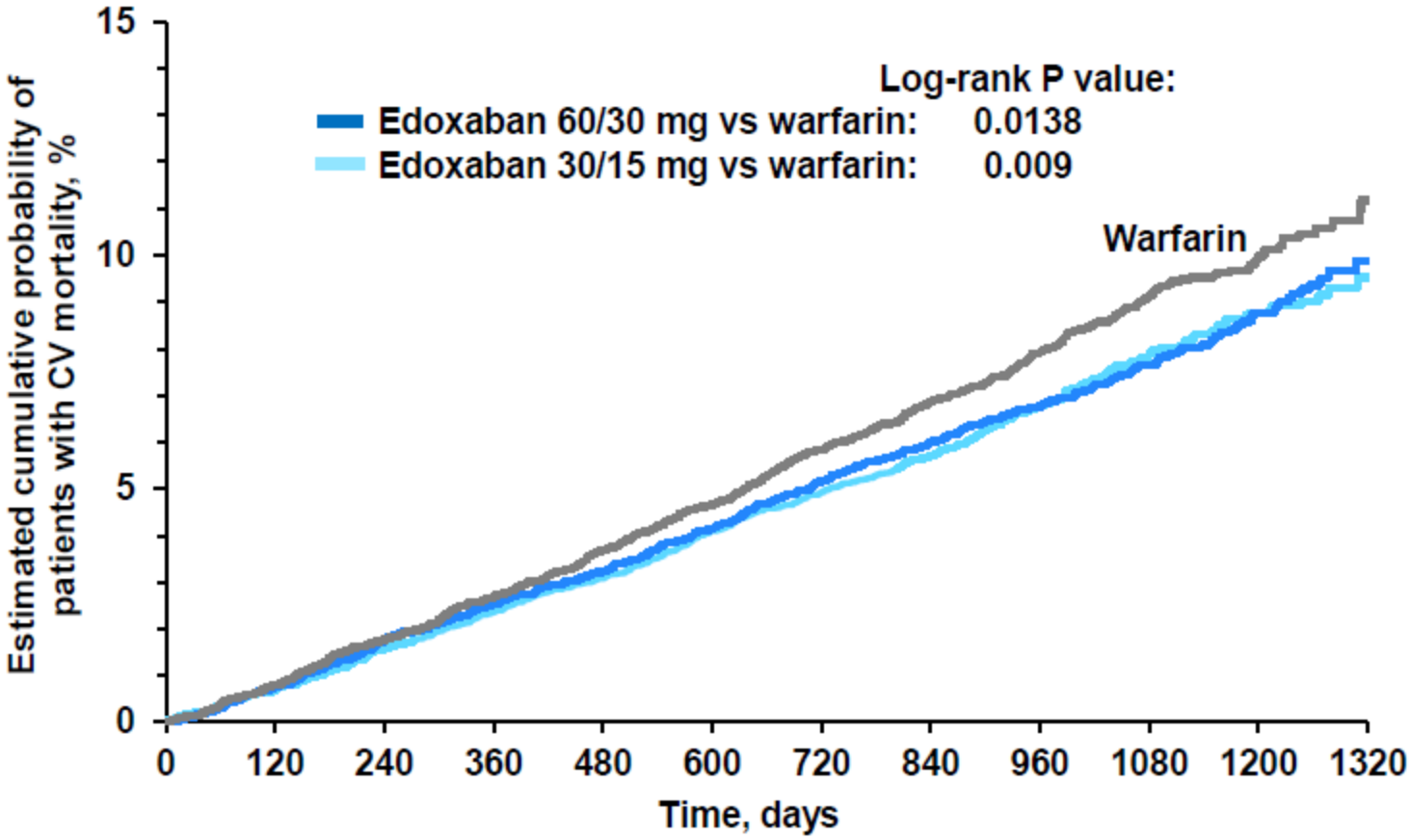




a Time from first dose of study drug to last dose plus 3 days. b Relative risk reduction. c Hazard ratio. d Confidence interval.
* Creatinine clearance. † Verapamil, dronedarone, or quinidine.

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

CV mortality (ITT Overall)



Giugliano RP. NEJM 2013; 369:2093-2104

Edoxaban 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

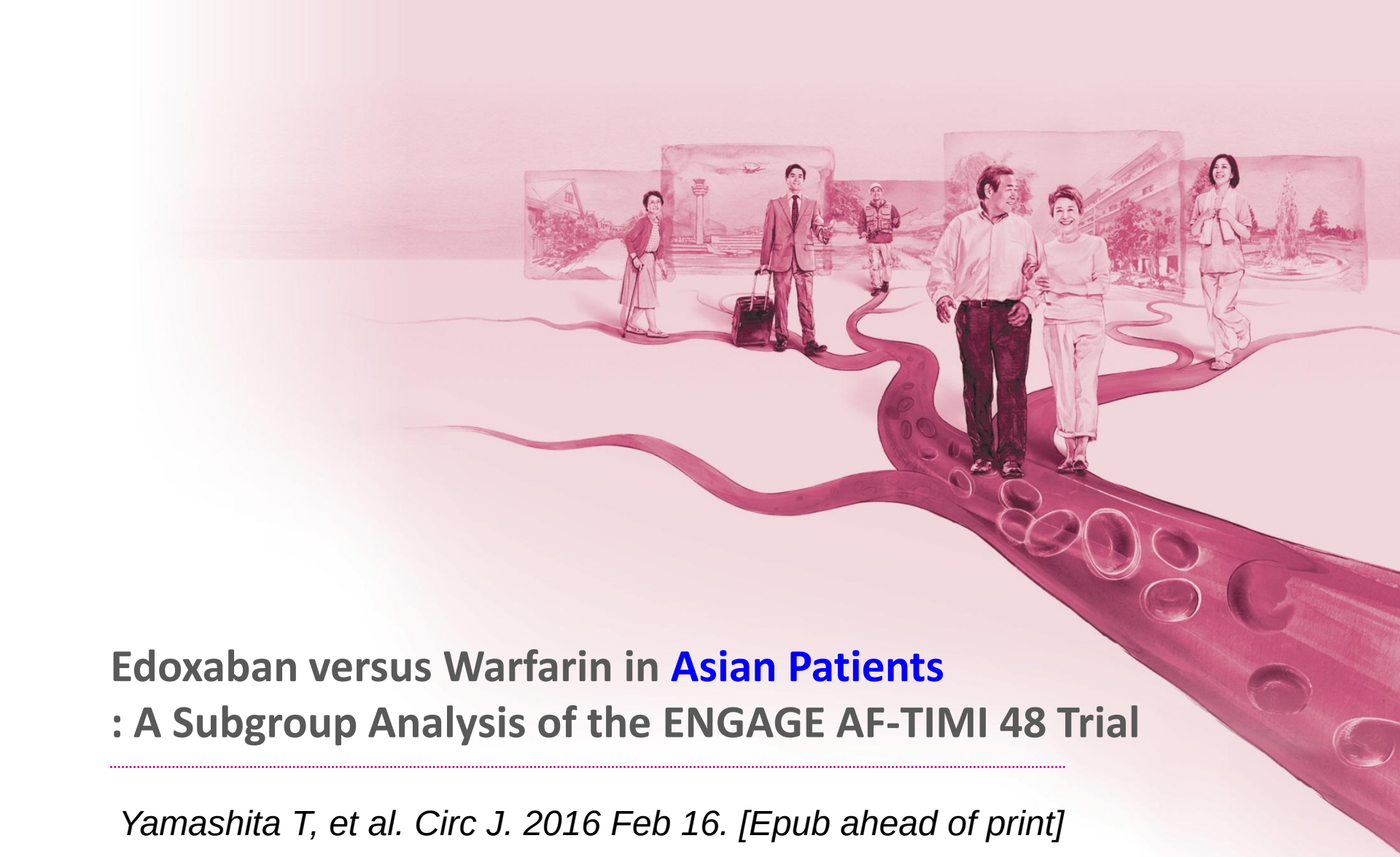
HD=higher dose. LD=low dose. HR=hazard ratio. SEE=systemic embolic event. ICH=intracranial haemorrhage. GI=gastrointestinal.

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

http://dx.doi.org/10.1016/ S0140-6736(14)61943-7

ENGAGE-AF

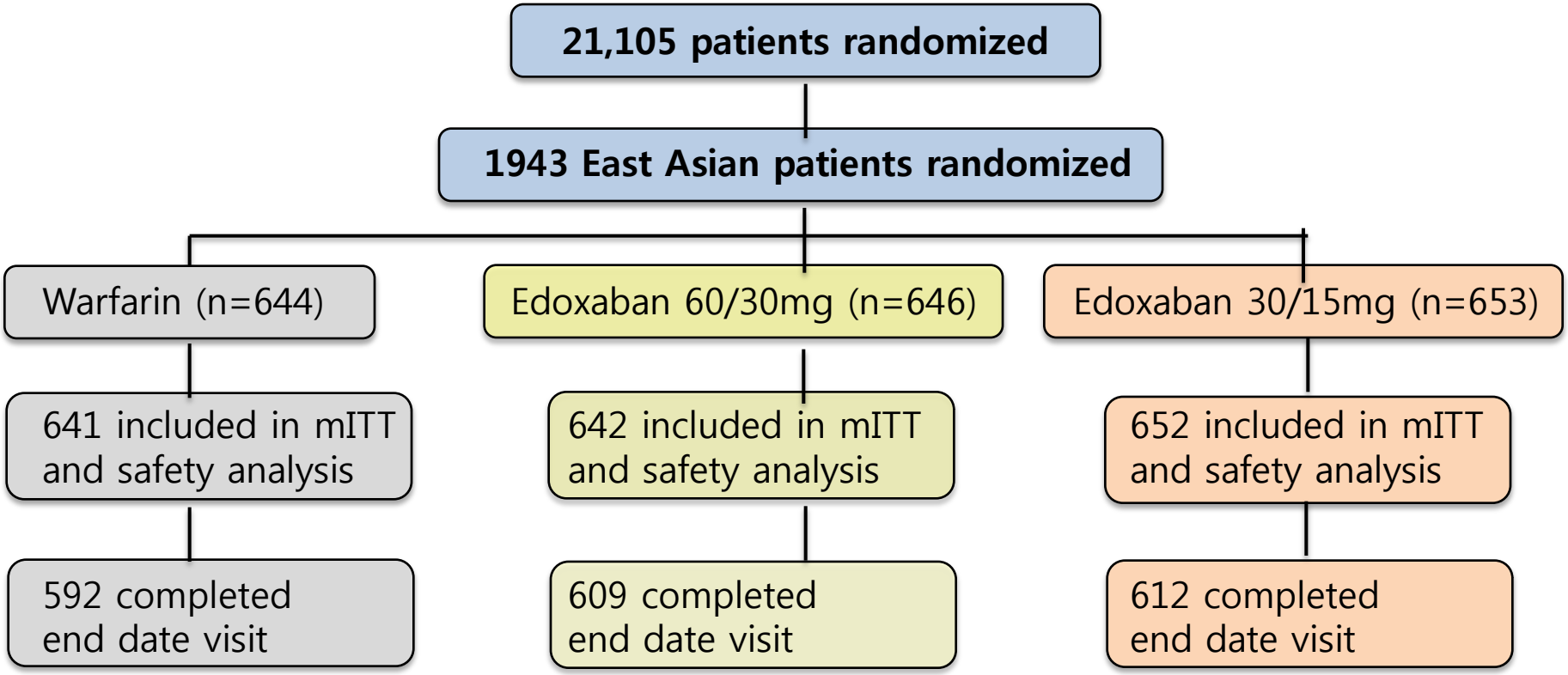
- Once-daily regimens of edoxaban (60/30 mg) were noninferior to warfarin with respect to the prevention of stroke or systemic embolism
- and were associated with significantly lower rates of bleeding and death from cardiovascular causes.



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

Yamashita T, et al. Circ J. 2016 Feb 16. [Epub ahead of print]

Patients disposition



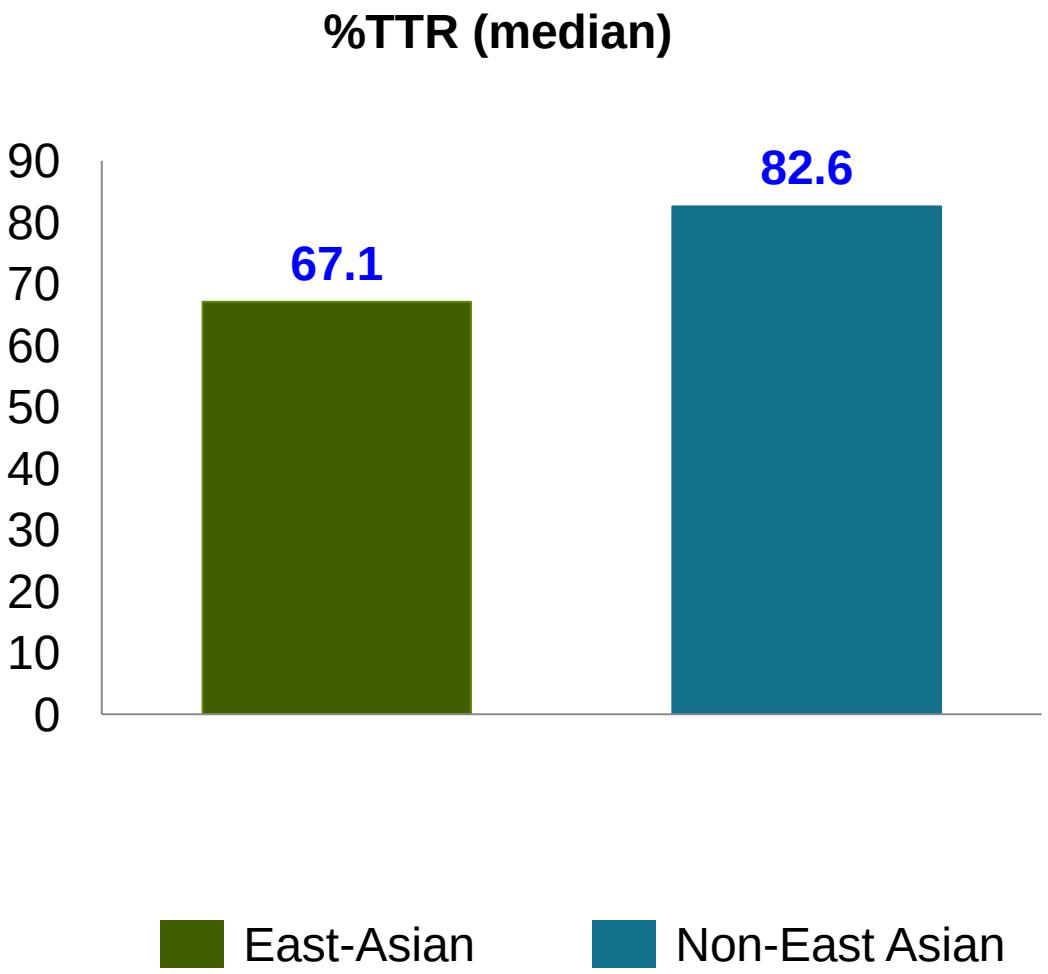
	Japan	China	Korea	Taiwan
Edoxaban 60/30mg	336	150	84	72
Edoxaban 30/15mg	337	152	78	85
warfarin	337	163	64	77

Yamashita T, et al. Circ J. 2016 Feb 16. [Epub ahead of print]

Baseline Demographics and Characteristics

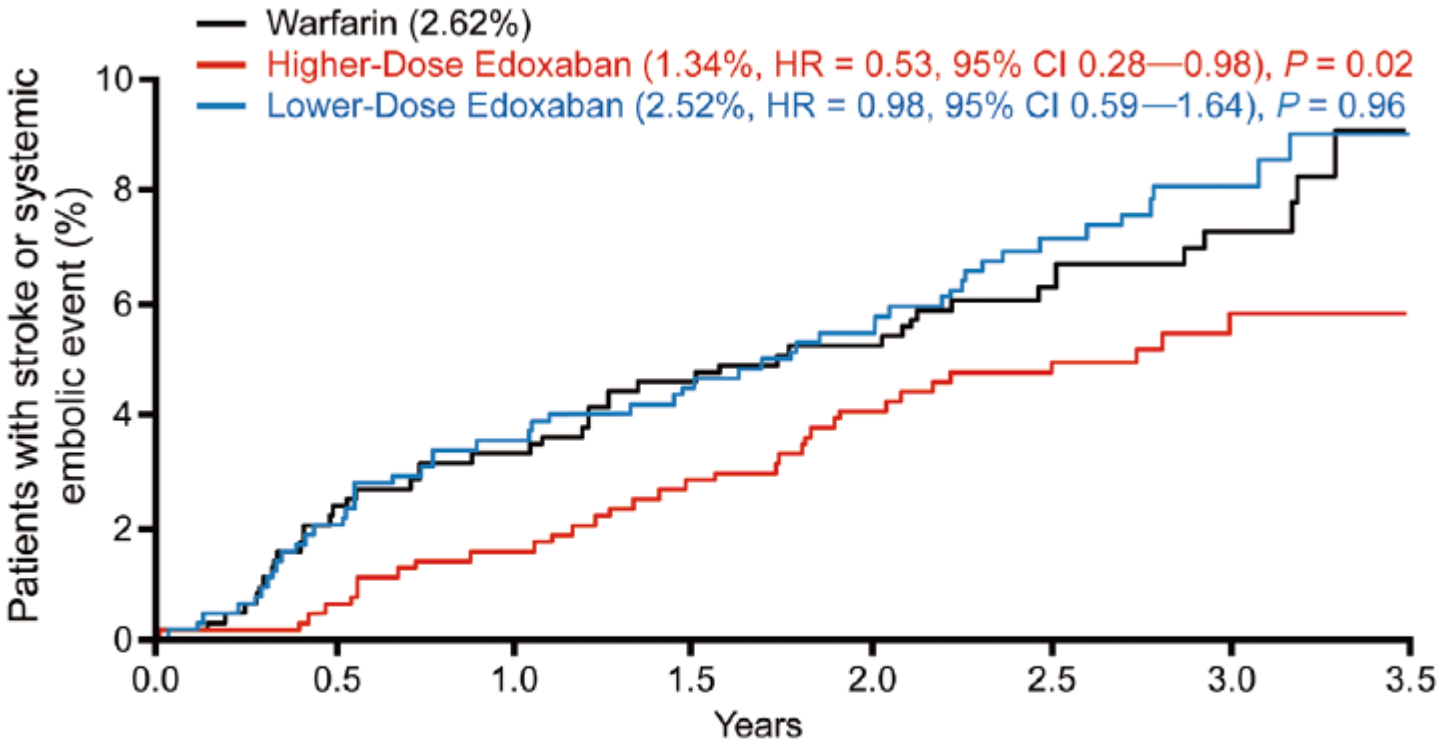
	East Asian (n=1,943)	Non-East Asian (n=19,162)
Age, y, median	71	72
Females, n (%)	545(28.0)	7495(39.1)
Weight, kg, mean	67.0	85.6
Paroxysmal AF, n (%)	373(19.2)	4993(26.1)
CHADS2 score, mean±SD	2.9±1.0	2.8±1.0
≤3, n (%)	1487(76.5)	14850(77.5)
4-6, n (%)	456(23.5)	4312(22.5)
Dose reduction at randomization, 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)

TTR for warfarin treated patients



Yamashita T, et al. Circ J. 2016 Feb 16. [Epub ahead of print]

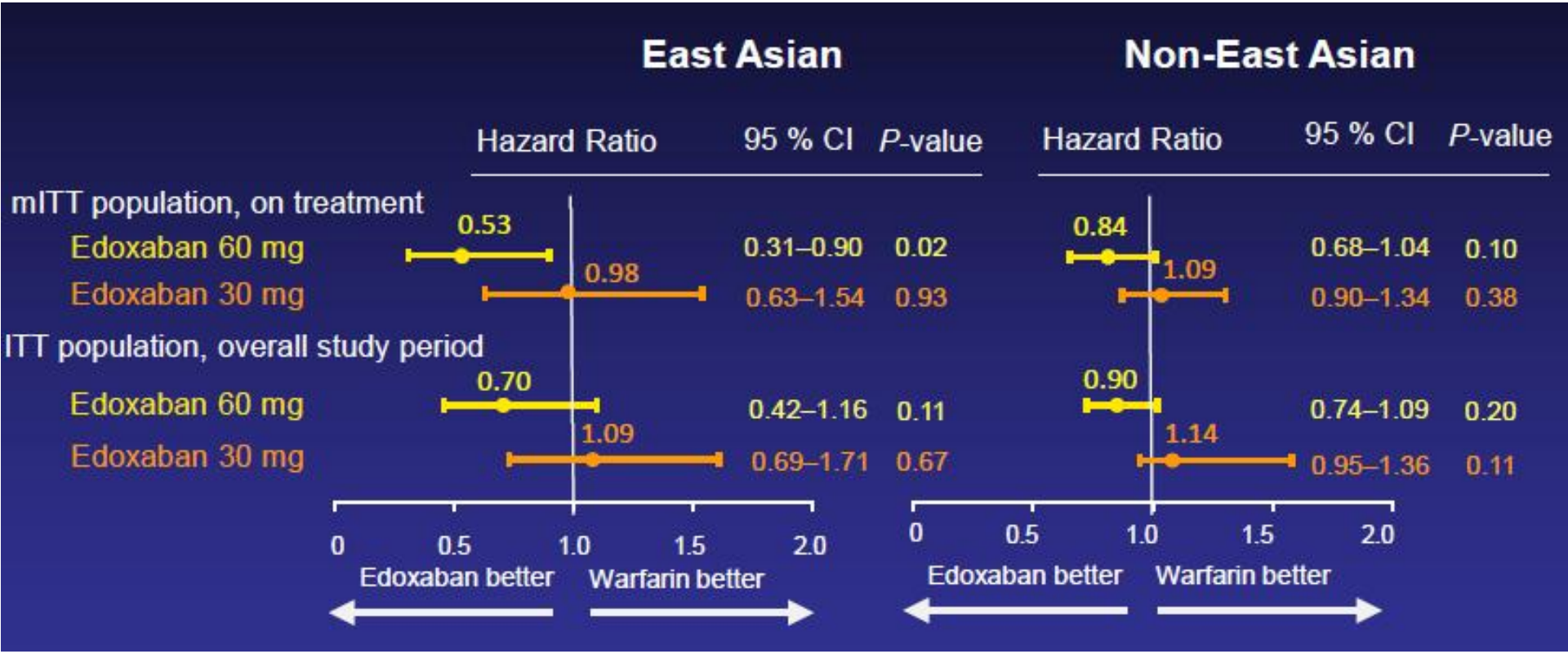
Primary Efficacy Endpoint (East Asian)



Warfarin	644	618	607	593	583	441	253	42
Edoxaban 60 mg	646	636	626	615	600	467	265	54
Edoxaban 30 mg	653	635	617	605	594	449	254	46

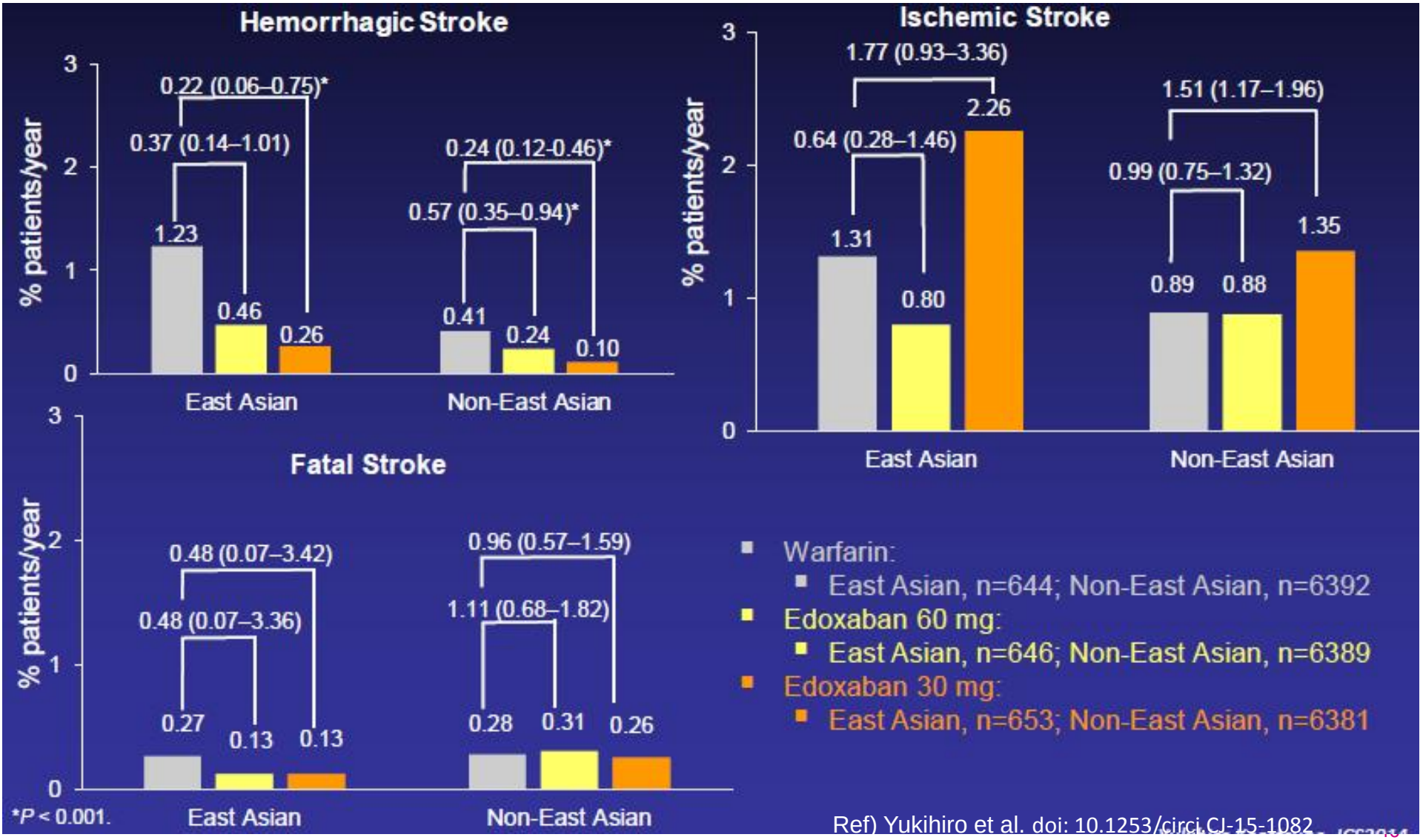
Yamashita T, et al. Circ J. 2016 Feb 16. [Epub ahead of print]

Primary Efficacy Endpoint (Stroke or SEE)



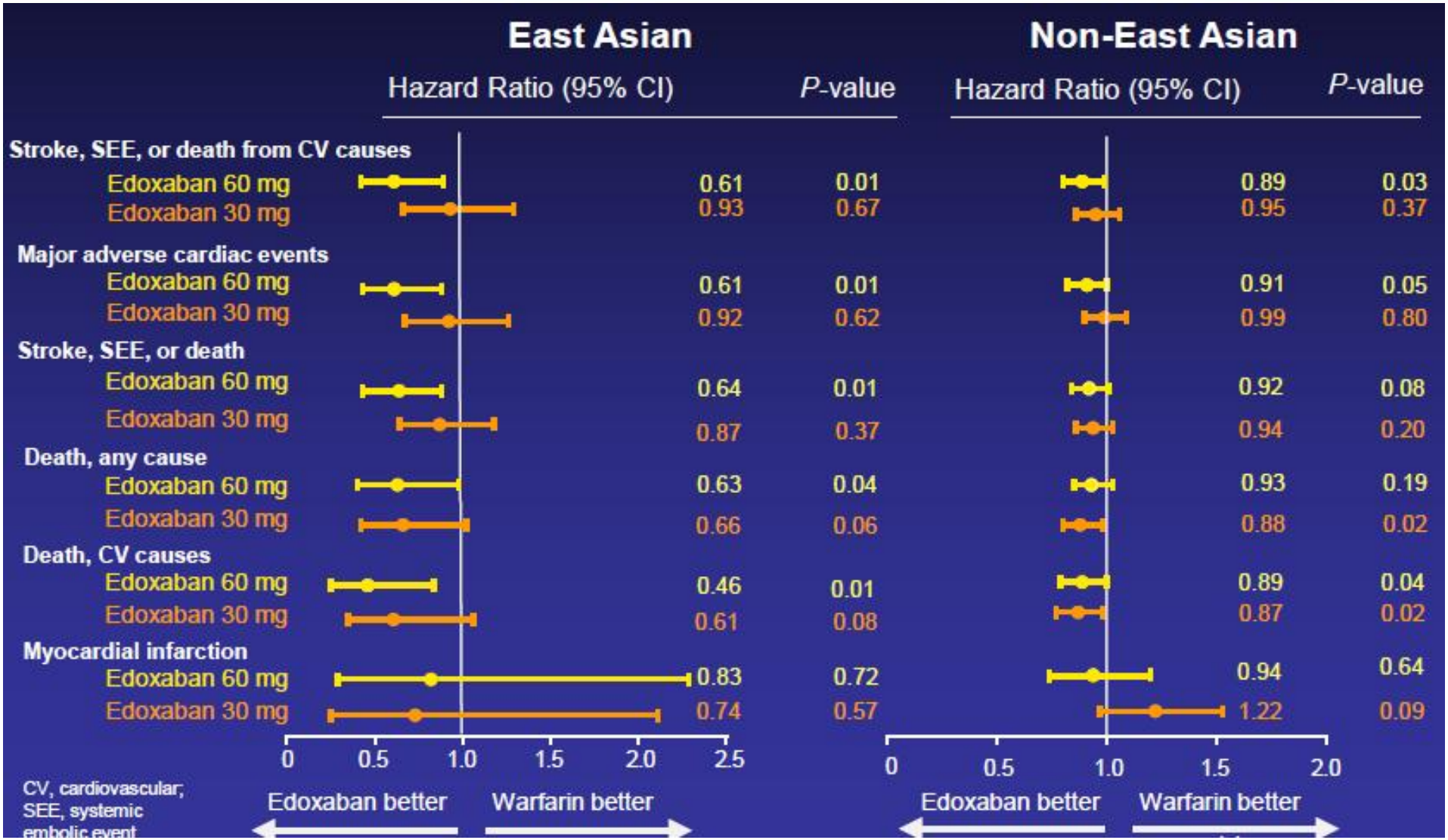
Yamashita T, et al. Circ J. 2016 Feb 16. [Epub ahead of print]

Stroke (East Asian)



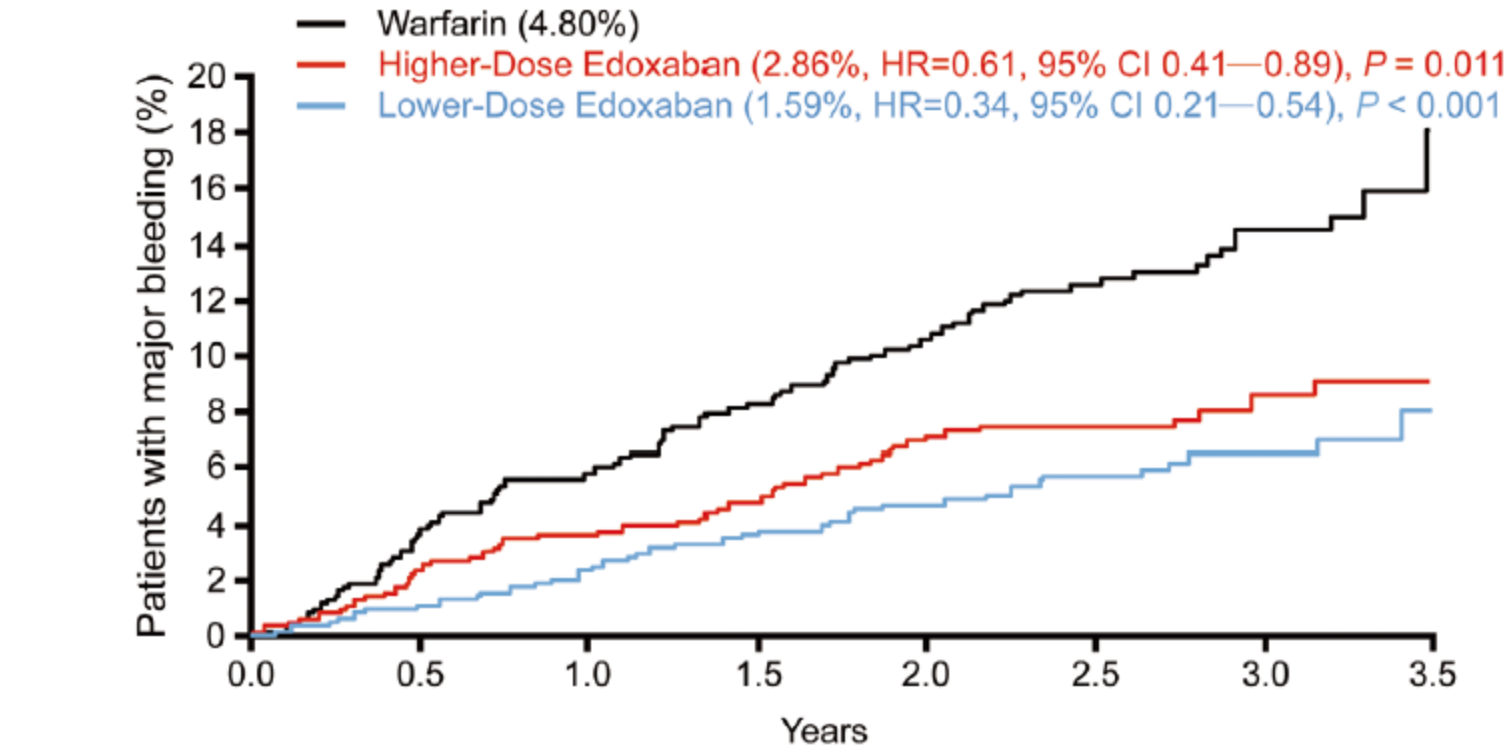
Ref) Yukihiro et al. doi: 10.1253/circj.CJ-15-1082

Secondary Efficacy Endpoint



Yamashita T, et al. Circ J. 2016 Feb 16. [Epub ahead of print]

Primary safety Endpoint (Major bleeding)



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

Yamashita T, et al. Circ J. 2016 Feb 16. [Epub ahead of print]

Summary

. In East Asian patients with AF, both doses of once-daily edoxaban:

- Reduce stroke and SEE similar to warfarin
- Reduce bleeding compared with warfarin
- Achieved results consistent with those outside East Asia

. Edoxaban 60/30mg regimen is effective and safe in the Asians.

Yamashita T, et al. Circ J. 2016 Feb 16. [Epub ahead of print]

Relationship Between Edoxaban Dose, Concentration, Anti-Factor Xa Activity and Outcomes in the ENGAGE AF-TIMI 48 Trial

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

Analysis of data from ENGAGE AF-TIMI 48 Trial: Overview

- **Objective**
  - To correlate edoxaban dose, plasma concentration, and anti-factor Xa activity
  - To compare efficacy and safety outcomes with warfarin stratified by dose reduction status

- **Procedures**
  - Trough blood samples were collected 1 month after randomization.

Edoxaban concentration (N=6,780)
measured by Quintiles Bio-analytical and ADME Laboratories

Anti-factor Xa activity (N=2,865, sub-study)
measured by the Rotachrome Heparin assay on the Stago STAR Evolution platform

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

Edoxaban concentration & Anti-factor Xa activity

- **Edoxaban concentration**

Dose reduction resulted in a decrease in mean exposure of 29%
in the edoxaban 60/30 mg* regimens.

- **Anti-factor Xa activity**

Dose reduction resulted in a decrease in mean anti-factor Xa activity by 25%
in the edoxaban 60/30 mg* regimens.

Figure 1: Mean trough edoxaban concentration

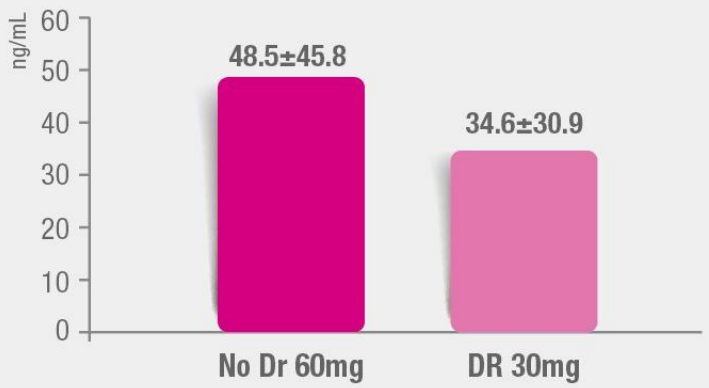
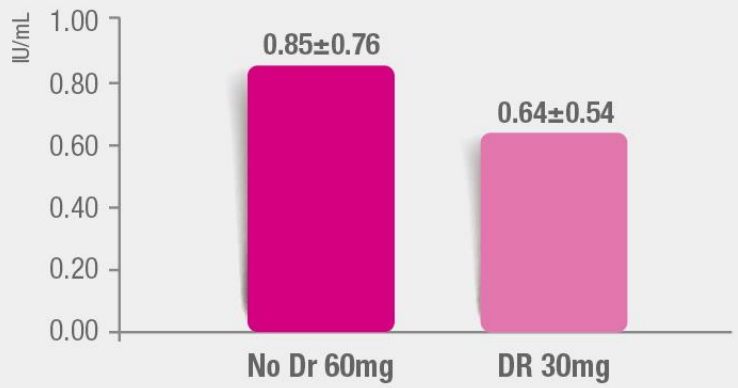


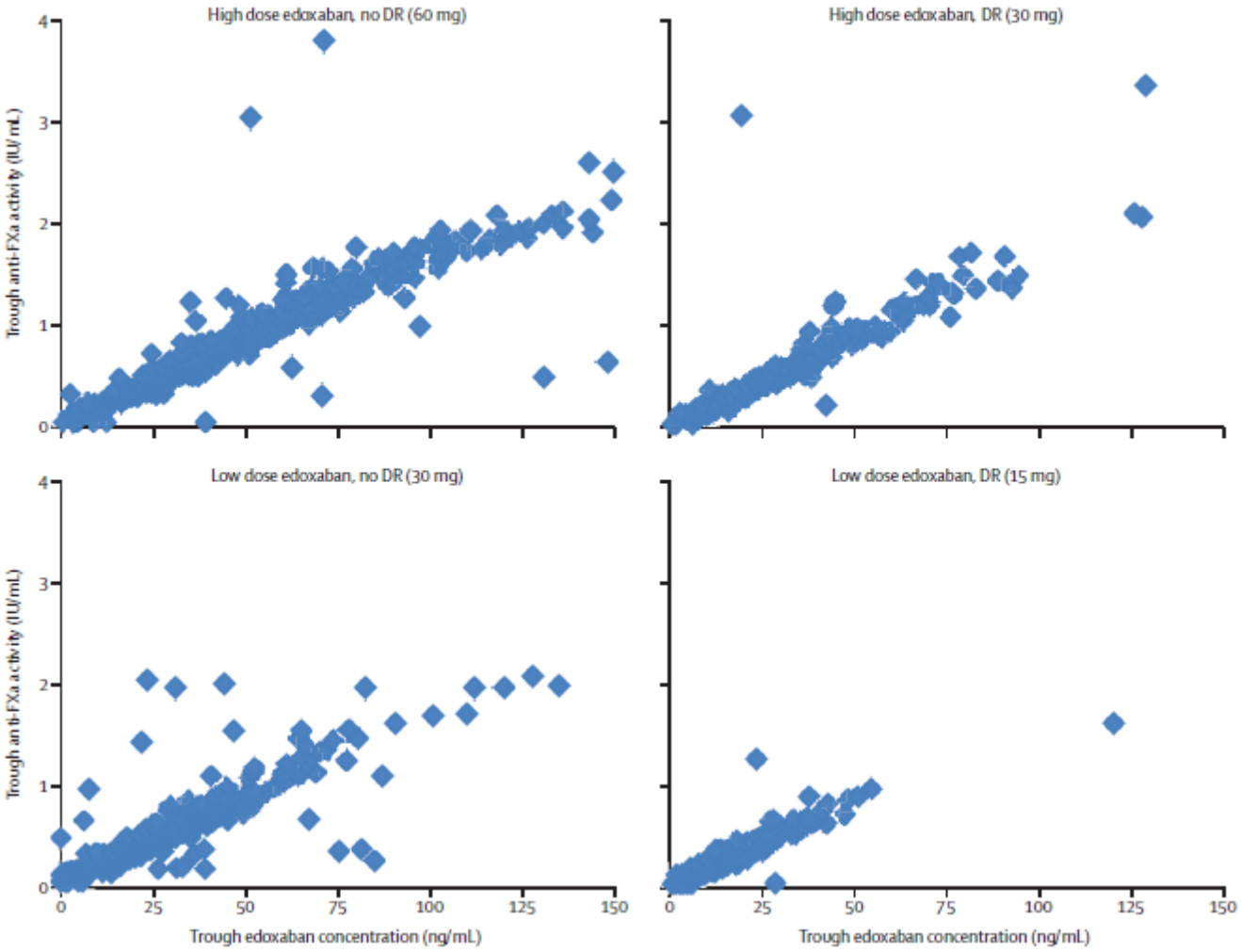
Figure 2: Mean trough anti-factor Xa activity



*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).

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

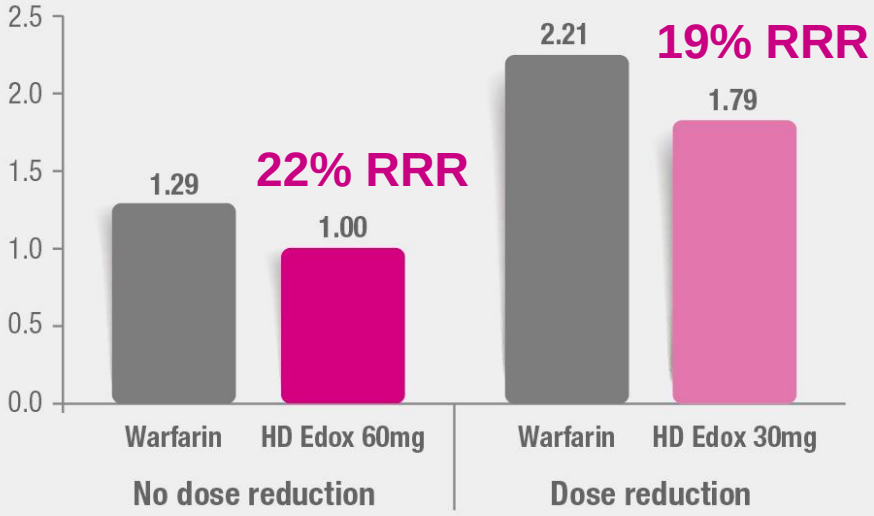
Edoxaban concentration & Anti-factor Xa activity



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

Stroke or SEE

<Stroke /SEE>



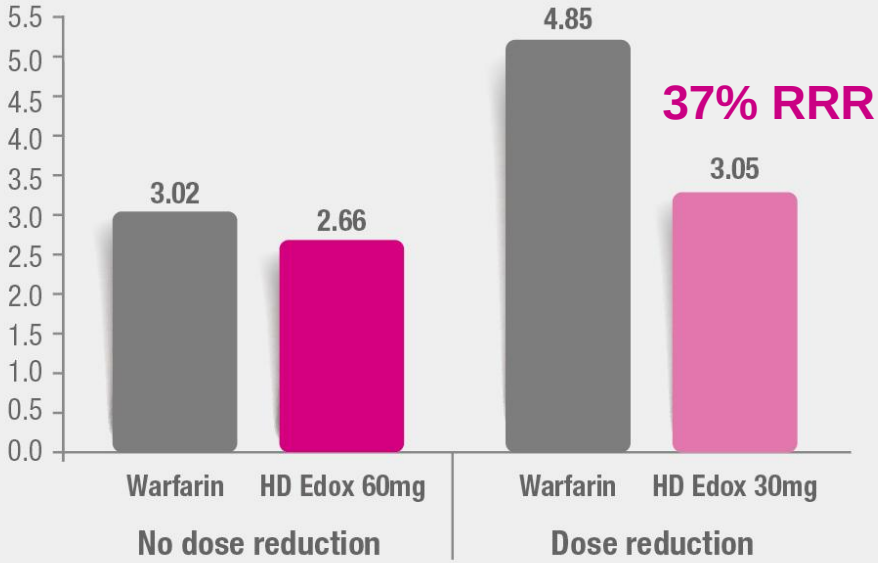
	Edoxaban 60/30 mg* vs warfarin		
	No dose reduction HR(95% CI)	Dose reduction HR(95% CI)	Pinteraction
Stroke or SEE	0.78 (0.61-0.99)	0.81 (0.58-1.13)	0.85

*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).

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

Major bleeding

<Major bleeding>



	Edoxaban 60/30 mg* vs warfarin		
	No dose reduction HR(95% CI)	Dose reduction HR(95% CI)	Pinteraction
Major bleed	0.88 (0.76-1.03)	0.63 (0.50-0.81)	0.023

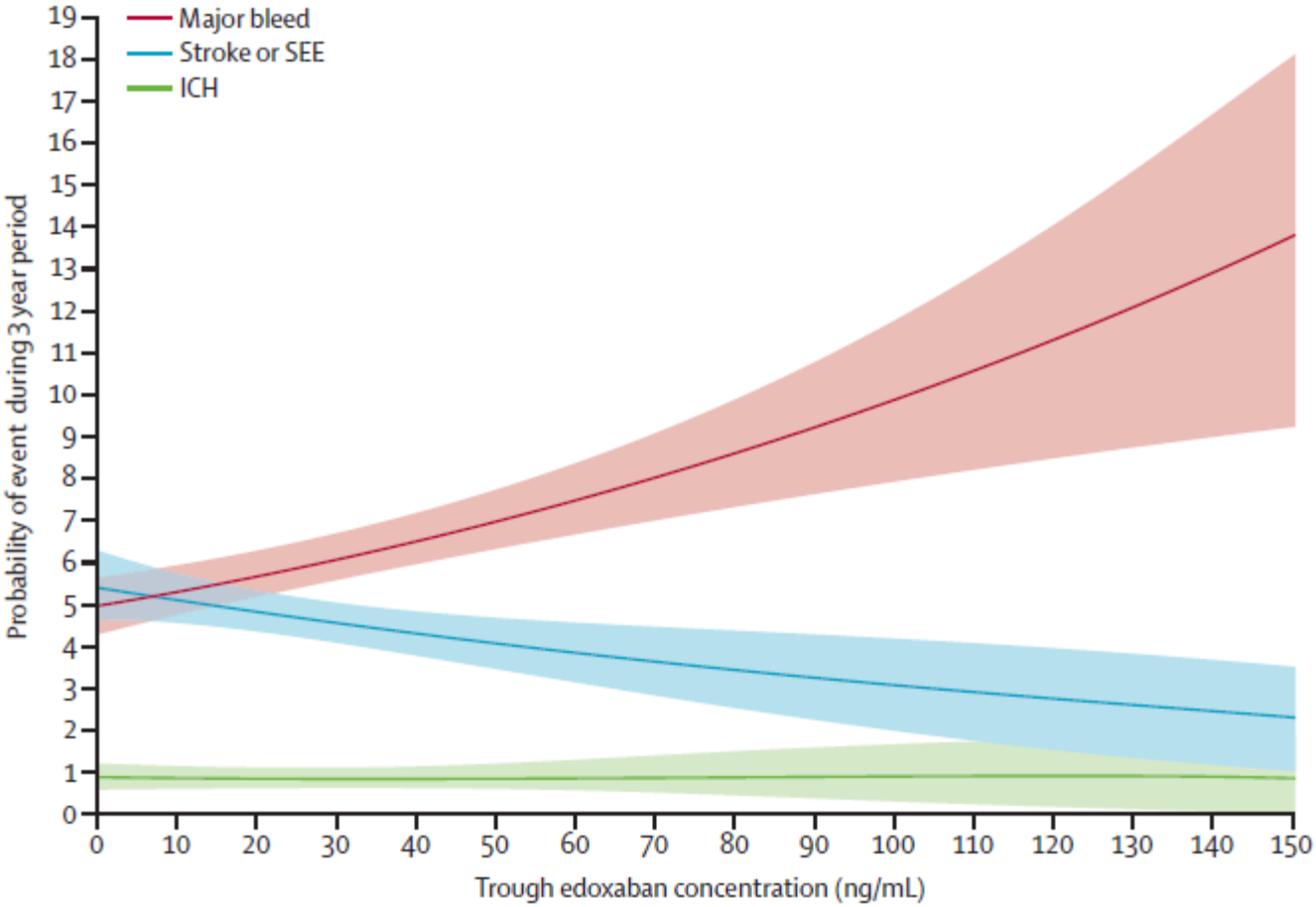
*In the ENGAGE AF–TIMI 38, if patients randomized to edoxaban groups have an anticipated increased drug exposure (any one or multiple of the following: creatinine clearance [CrCl] 30-50 mL/min, body weight ≤60 kg, or concomitant administration of verapamil or quinidine [strong P-gp inhibitors]), they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

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

Clinical outcomes & Edoxaban trough concentration

- **Therapeutic window of edoxaban**
  - Major bleed: narrower (steeper) / Stroke or SEE: wider (shallower)/ ICH: widest (nearly flat)

Probability of clinical outcomes versus edoxaban concentration



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

Summary

- Strategy of tailoring of the edoxaban dose on the basis of **clinical factors** achieved the dual goal of preventing excess drug concentrations and optimizing an individual patient's risk of ischemic and bleeding events.
- Therapeutic window for edoxaban is narrower for major bleeding than thromboembolism.
- Edoxaban 60/30mg regimen is effective and safe

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

Take Home Messages

- Once-daily regimens of edoxaban were noninferior to warfarin with respect to the prevention of stroke or systemic embolism
- and were associated with significantly lower rates of bleeding and death from cardiovascular causes.

- Edoxaban was effective and safe in the Asians.

- Strategy of tailoring of the edoxaban dose on the basis of **clinical factors** was effective and safe.

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