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XXIX Congreso de la Sociedad Andaluza de Medicina Interna (SADEMI)

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Nuevas evidencias en la prevención del ictus en FA

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Features of novel oral anticoagulants

	Dabigatran[1]	Rivaroxaban[1,2]	Apixaban[1,3]	Edoxaban[4-6]
Target	IIa (thrombin)	Xa	Xa	Xa
Hours to Cmax	1.25-3	2-4	3-4	1-2
CYP metabolism	None	32%	Yes	Minimal (<4%)
Bioavailability	6%	80%	60%	62%
Transporters	P-gp	P-gp/BCRP	P-gp/ BCRP	P-gp
Protein binding	35%	93%	87%	50%
Half-life	14-17 h	7-11 h	8-15 h	8-10 h
Renal elimination	80%	33%	25%	50%

BCRP, breast cancer resistance protein
CYP, cytochrome P450; P-gp, P-glycoprotein
NR, not reported

1. Eriksson et al. Clin Pharmacokinet 2009;48:1-22; 2. Xarelto [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2011; 3. ELIQUIS Summary of Product Characteristics. Bristol Myers Squibb/Pfizer EEIG, UK;
4. Ruff et al. Hot Topics in Cardiology 2009;18:1-32; 5. Matsushima et al. Am Assoc Pharm Sci 2011; abstract;
6. Ogata et al. J Clin Pharmacol 2010;50:743-53

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

Engage AF
TIMI 48

Study objectives

- To determine if two dose regimens (60 mg and 30 mg QD) of edoxaban were non-inferior to warfarin with respect to the composite primary efficacy endpoint of stroke (ischemic or hemorrhagic) and systemic embolic events (SEE) in patients with non-valvular atrial fibrillation

DU176b-C-U301 Protocol ver 8.0_07 Nov 2011. Daiichi Sankyo Inc
Giugliano et al. N Engl J Med 2013; e-pub ahead of print

Study design: ENGAGE AF-TIMI 48

Randomized, double-blind, double-dummy, event-driven study

PATIENTS
AF on electrical recording within last 12 months
Intended oral anticoagulant
$CHADS_2 \geq 2$

N=21,105

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

- Edoxaban 30 mg QD regimen
- Edoxaban 60 mg QD regimen
- Warfarin (INR 2.0–3.0)

Median duration of follow up 2.8 years

*Dose reduced by 50% if CrCl 30–50 mL/min, body weight ≤60 kg or patient receiving verapamil, quinidine or dronedarone
AF=atrial fibrillation; CrCl=creatinine clearance
INR=International Normalized Ratio; QD=once daily

DU176b-C-U301 Protocol ver 8.0_07 Nov 2011. Daiichi Sankyo Inc
Giugliano et al. N Engl J Med 2013; e-pub ahead of print

Primary efficacy and principal 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 (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells

SEE=systemic embolic event; ISTH=International Society on Thrombosis and Haemostasis

Giugliano et al. N Engl J Med 2013; e-pub ahead of print
Schulman & Kearon. J Thromb Haemost 2005;3:692–694

Key secondary composite efficacy outcomes

- Stroke, SEE and CV mortality (including bleeding)
- MACE: composite of non-fatal MI, non-fatal stroke, non-fatal SEE, and death due to CV cause or bleeding
- Stroke, SEE and all-cause mortality

CV=cardiovascular; MACE=major adverse cardiac events
MI=myocardial infarction; SEE, systemic embolic event

Giugliano et al. N Engl J Med 2013; e-pub ahead of print

Overall patient characteristics

Characteristic	Warfarin (n=7,036)	Edoxaban 60 mg (n=7,035)	Edoxaban 30 mg (n=7,034)
Median age [IQR], years	72 [64–78]	72 [64–78]	72 [64–78]
Female sex , n (%)	2,641 (37.5)	2,669 (37.9)	2,730 (38.8)
Region, n (%)			
North America	1,562 (22.2)	1,559 (22.2)	1,560 (22.2)
Latin America	888 (12.6)	886 (12.6)	887 (12.6)
Western Europe	1,078 (15.3)	1,079 (15.3)	1,079 (15.3)
Eastern Europe	2,381 (33.8)	2,383 (33.9)	2,380 (33.8)
Asia Pacific and South Africa	1,127 (16.0)	1,128 (16.0)	1,128 (16.0)
Paroxysmal atrial fibrillation, n (%)	1,778 (25.3)	1,753 (24.9)	1,835 (26.1)
Qualifying risk factors, n (%)			
Age ≥75 years	2,820 (40.1)	2,848 (40.5)	2,806 (39.9)
Prior stroke or transient ischemic attack	1,991 (28.3)	1,976 (28.1)	2,006 (28.5)
Chronic heart failure	4,048 (57.5)	4,097 (58.2)	3,979 (56.6)
Diabetes mellitus	2,521 (35.8)	2,559 (36.4)	2,544 (36.2)
Hypertension requiring treatment	6,588 (93.6)	6,591 (93.7)	6,575 (93.5)

IQR=interquartile range

Giugliano et al. N Engl J Med 2013; e-pub ahead of print

Overall patient characteristics

Characteristic	Warfarin (n=7,036)	Edoxaban 60 mg (n=7,035)	Edoxaban 30 mg (n=7,034)
$CHADS_2$, mean±SD, n (%)	2.8±1.0	2.8±1.0	2.8±1.0
≤3	5,445 (77.4)	5,422 (77.1)	5,470 (77.8)
4–6	1,591 (22.6)	1,613 (22.9)	1,564 (22.2)
Dose reduction at randomization*, n (%)	1,787 (25.4)	1,784 (25.4)	1,785 (25.4)
Creatinine clearance 30–50 mL/min	1,361 (19.3)	1,379 (19.6)	1,334 (19.0)
Weight ≤60 kg	701 (10.0)	684 (9.7)	698 (9.9)
Verapamil or quinidine	243 (3.5)	258 (3.7)	260 (3.7)
Previous vitamin K antagonist for ≥60 days, n (%)	4138 (58.8)	4140 (58.8)	4163 (59.2)
Medications at time of randomization, n (%)			
Aspirin	2,092 (29.7)	2,070 (29.4)	2,018 (28.7)
Thienopyridine	164 (2.3)	174 (2.5)	149 (2.1)
Amiodarone	827 (11.8)	866 (12.3)	799 (11.4)
Digoxin or digitalis preparations	2,176 (30.9)	2,078 (29.5)	2,073 (29.5)

Patients could appear in more than one category, therefore percentages may not total 100%

*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

SD=standard deviation

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Population/analysis definitions

Populations	Analyses
Intent-to-treat (ITT) All randomized subjects	Superiority analysis Includes all events during the overall study
Modified intent-to-treat (mITT) /On Treatment All randomized subjects who received ≥1 dose of study drug[1]	Primary efficacy analysis Includes all events on study drug (from first study dose to three days after last dose or the end of treatment) Non-inferiority analysis
Safety All randomized subjects who received ≥1 dose of study drug[2]	Safety analysis

1. Analyses based on randomized treatment even if incorrect drug or dosage is given, or dose is adjusted
2. Analyses based on randomized treatment if dose is adjusted. If incorrect drug or dosage is received for the entire study, analysis will be based on treatment actually received

DU176b-C-U301 Protocol ver 8.0_07 Nov 2011. Daiichi Sankyo Inc
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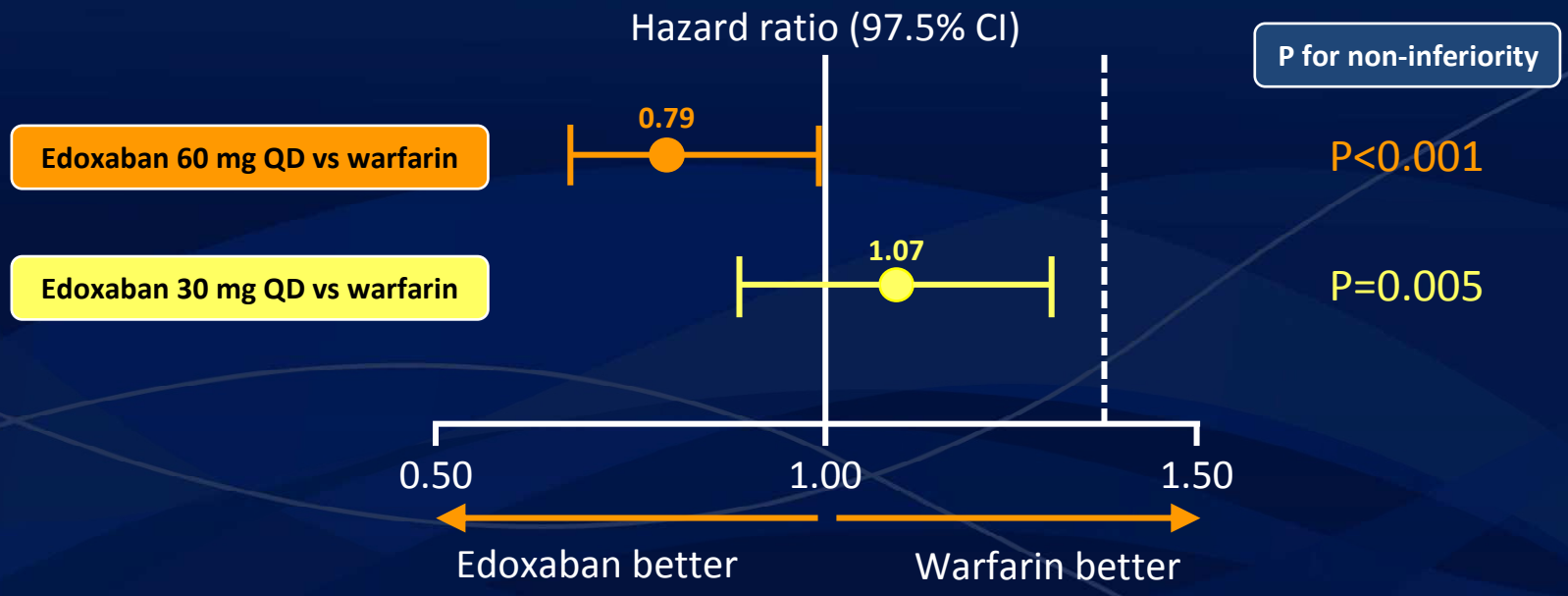
Primary efficacy endpoint: stroke or SEE mITT on-treatment analysis

				Edoxaban versus warfarin	
Treatment	**N**	**n**	**Incidence (%/yr)**	**HR (97.5% CI)**	**P for non-inferiority**
Warfarin (median TTR 68.4%)	7,012	232	1.50	-	-
Edoxaban 60 mg QD	7,012	182	1.18	0.79 (0.63–0.99)	P<0.001
Edoxaban 30 mg QD	7,002	253	1.61	1.07 (0.87–1.31)	0.005



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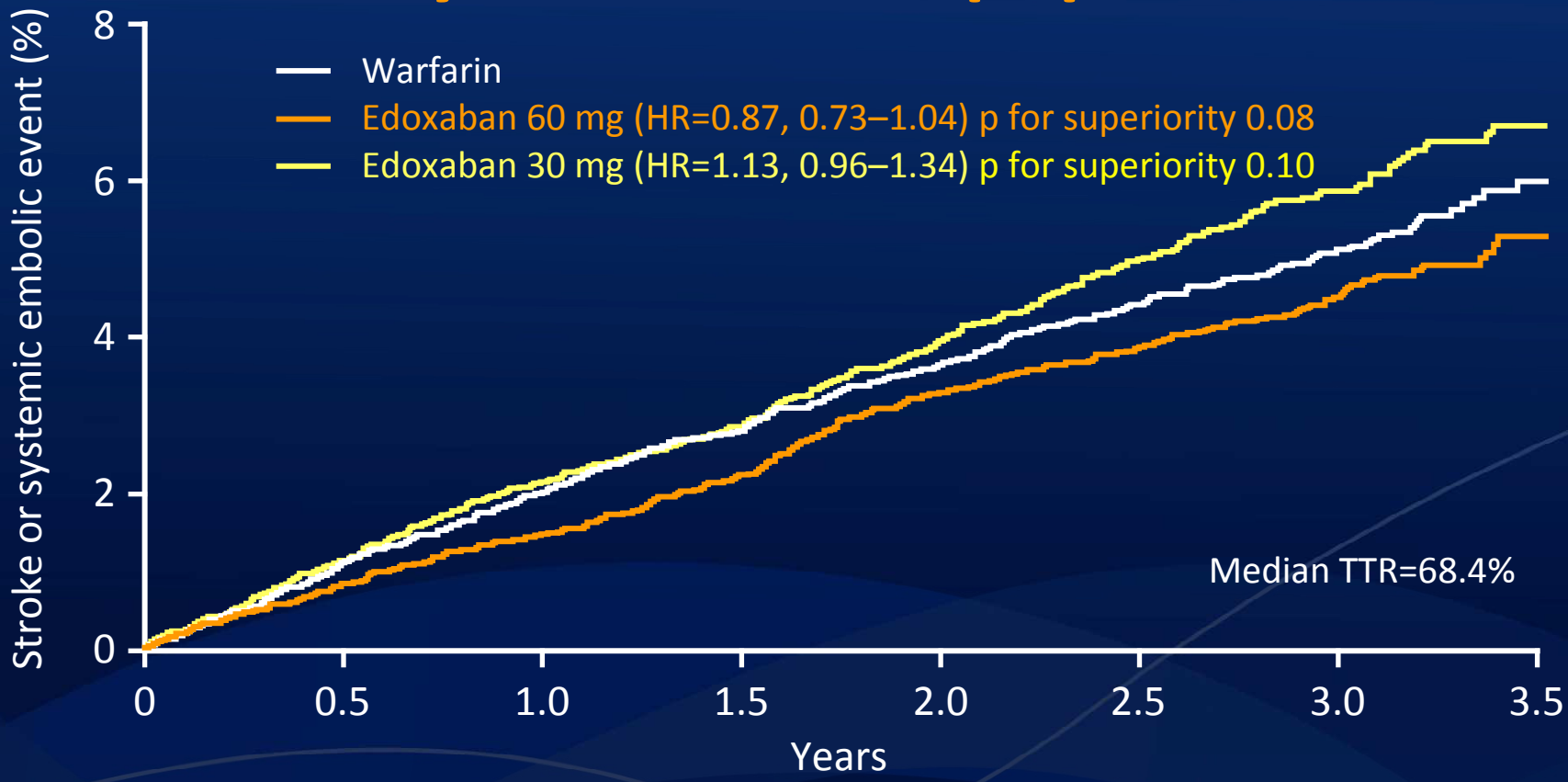
Kaplan-Meier of primary efficacy outcome ITT population



No.at risk								
Warfarin	7036	6798	6615	6406	6225	4593	2333	536
Edoxaban (60)	7035	6816	6650	6480	6283	4659	2401	551
Edoxaban (30)	7034	6815	6631	6461	6277	4608	2358	534

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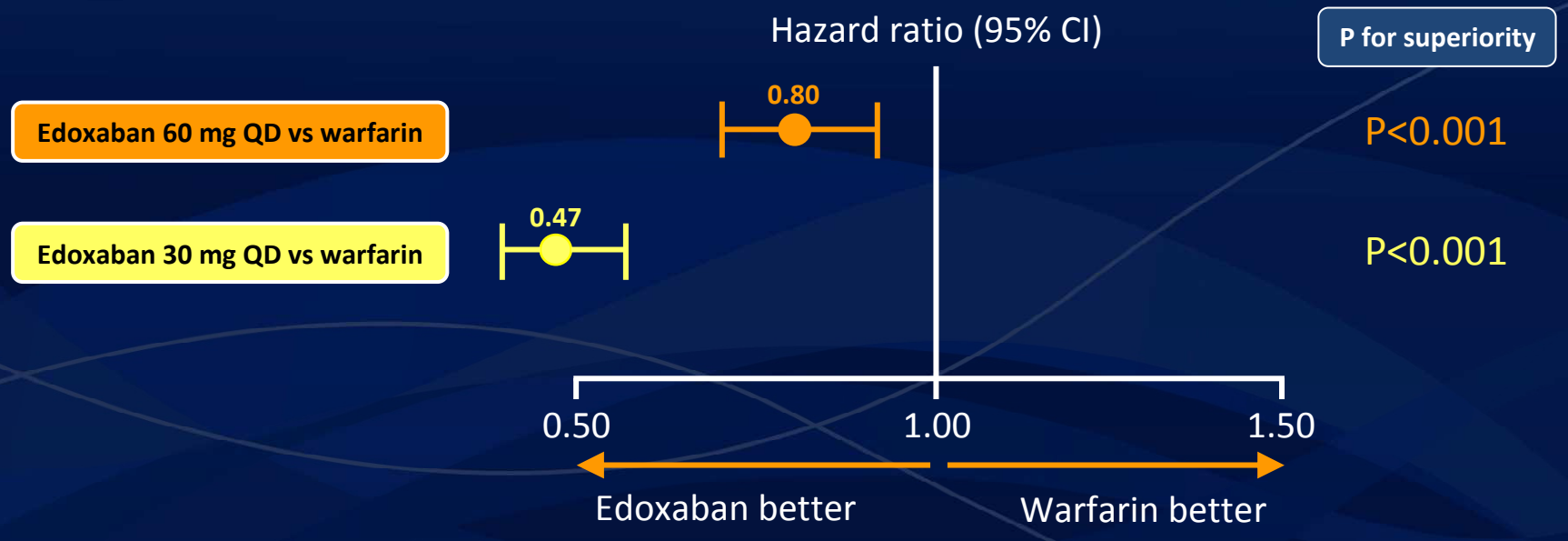
Major bleeding
Safety on-treatment analysis

				Edoxaban versus warfarin	
Treatment	**N**	**n**	**Incidence (%/yr)**	**HR (95% CI)**	**P value**
Warfarin	7,012	524	3.43	-	-
Edoxaban 60 mg QD	7,012	418	2.75	0.80 (0.71–0.91)	<0.001
Edoxaban 30 mg QD	7,002	254	1.61	0.47 (0.41–0.55)	<0.001



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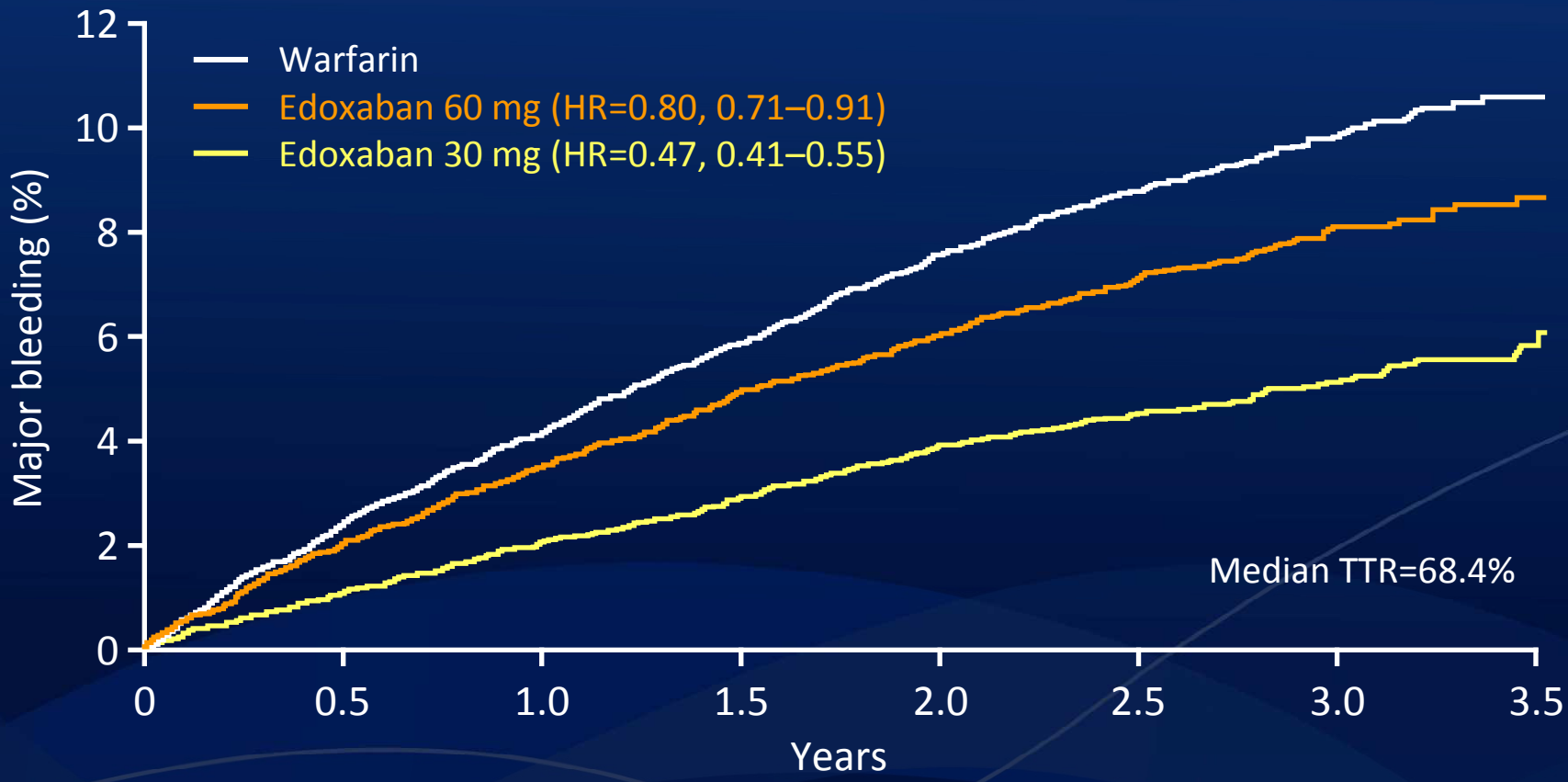
Kaplan-Meier of principal safety outcome



No.at risk								
Warfarin	7012	6166	5630	5278	4941	3446	1687	370
Edoxaban (60)	7012	6039	5594	5232	4910	3471	1706	345
Edoxaban (30)	7002	6218	5791	5437	5110	3635	1793	386

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Safety outcomes

Outcome	Warfarin (n=7,012)		Edoxaban 60 mg (n=7,012)		Edoxaban 60 mg versus warfarin		Edoxaban 30 mg (n=7,002)		Edoxaban 30 mg versus warfarin	
	n	%/yr	n	%/yr	HR (95% CI)	P	n	%/yr	HR (95% CI)	P
Major bleeding	524	3.43	418	2.75	0.80 (0.71–0.91)	<0.001	254	1.61	0.47 (0.41–0.55)	<0.001
Life-threatening bleeding	122	0.78	62	0.40	0.51 (0.38–0.70)	<0.001	40	0.25	0.32 (0.23–0.46)	<0.001
CRNM bleeding	1,396	10.15	1,214	8.67	0.86 (0.79–0.93)	<0.001	969	6.60	0.66 (0.60–0.71)	<0.001
Minor bleeding	714	4.89	604	4.12	0.84 (0.76–0.94)	0.002	533	3.52	0.72 (0.65–0.81)	<0.001
Major or CRNM bleeding	1,761	13.02	1,528	11.10	0.86 (0.80–0.92)	<0.001	1,161	7.97	0.62 (0.57–0.67)	<0.001
Any overt bleeding	2,114	16.40	1,865	14.15	0.87 (0.82–0.92)	<0.001	1,499	10.68	0.66 (0.62–0.71)	<0.001

Data are from the Safety cohort during the on-treatment period

CRNM=clinically relevant non-major

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Major bleeding

Outcome	Warfarin (n=7,012)		Edoxaban 60 mg (n=7,012)		Edoxaban 60 mg versus warfarin		Edoxaban 30 mg (n=7,002)		Edoxaban 30 mg versus warfarin	
	n	%/yr	n	%/yr	HR (95% CI)	P	n	%/yr	HR (95% CI)	P
Major bleeding	524	3.43	418	2.75	0.80 (0.71–0.91)	<0.001	254	1.61	0.47 (0.41–0.55)	<0.001
Fatal	59	0.38	32	0.21	0.55 (0.36–0.84)	0.006	21	0.13	0.35 (0.21–0.57)	<0.001
Critical organ/area	211	1.36	108	0.70	0.51 (0.41–0.65)	<0.001	69	0.44	0.32 (0.24–0.42)	<0.001
≥2 g/dL blood loss	327	2.13	317	2.08	0.98 (0.84–1.14)	0.78	187	1.19	0.56 (0.47–0.67)	<0.001
Intracranial	132	0.85	61	0.39	0.47 (0.34–0.63)	<0.001	41	0.26	0.30 (0.21–0.43)	<0.001
Fatal	42	0.27	24	0.15	0.58 (0.35–0.95)	0.03	12	0.08	0.28 (0.15–0.53)	<0.001
Gastrointestinal	190	1.23	232	1.51	1.23 (1.02–1.50)	0.03	129	0.82	0.67 (0.53–0.83)	<0.001
Upper	111	0.71	140	0.91	1.27 (0.99–1.63)	0.06	88	0.56	0.78 (0.59–1.03)	0.08
Lower	81	0.52	96	0.62	1.20 (0.89–1.61)	0.23	44	0.28	0.54 (0.37–0.77)	<0.001
Other location	211	1.37	131	0.85	0.62 (0.50–0.78)	<0.001	87	0.55	0.40 (0.31–0.52)	<0.001

Data are from the Safety cohort during the on-treatment period with interval censoring

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Net clinical outcomes

	Warfarin (n=7,012)		Edoxaban 60 mg (n=7,012)		Edoxaban 60 mg versus warfarin		Edoxaban 30 mg (n=7,002)		Edoxaban 30 mg versus warfarin	
	n	%/yr	n	%/yr	HR (95% CI)	P	n	%/yr	HR (95% CI)	P
Primary										
Composite of stroke, SEE, major bleeding, and all-cause mortality	1,462	8.11	1,323	7.26	0.89 (0.83–0.96)	0.003	1,248	6.79	0.83 (0.77–0.90)	<0.001
Secondary										
Composite of disabling stroke, life-threatening bleed, and all cause mortality	987	5.23	883	4.64	0.88 (0.81–0.97)	0.008	837	4.38	0.83 (0.76–0.91)	<0.001
Tertiary										
Exploratory composite of stroke, SEE, life-threatening bleed, and all-cause mortality	1,123	6.02	999	5.30	0.88 (0.81–0.96)	0.003	1,010	5.37	0.89 (0.82–0.97)	0.007

Data are from the overall treatment period

SEE=systemic embolic event

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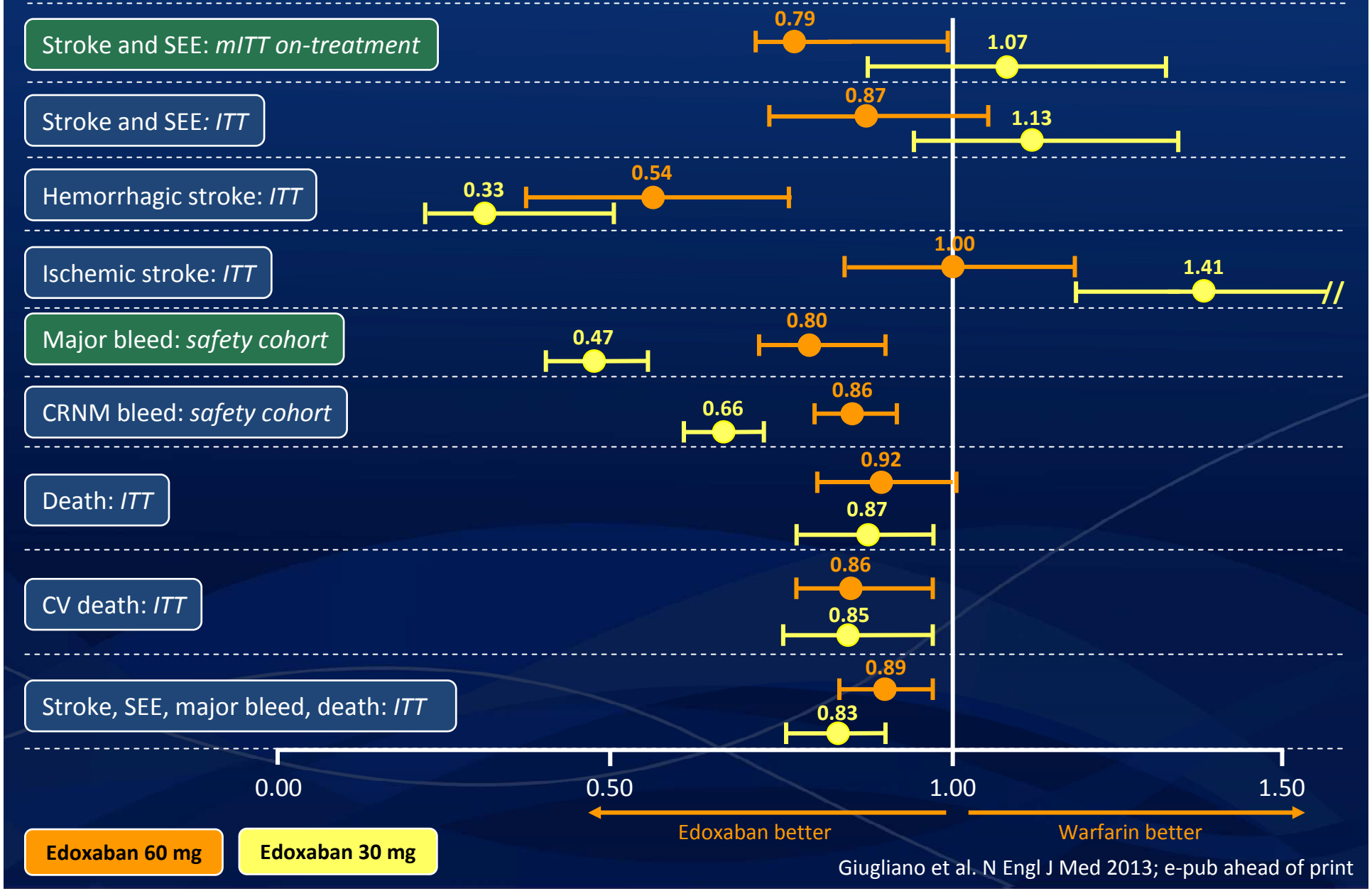
Summary of key outcomes



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Conclusion

- Both 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.

Giuglip for superiority 0.08

Unique study features

- Largest (n=21,105) RCT for stroke prevention in AF with a NOAC with the longest follow up (median 2.8 years)
- Dynamic dose modification at and after randomization providing data on three doses over a four-fold range
- Minimal missing data
- Well managed warfarin therapy, median TTR 68.4%

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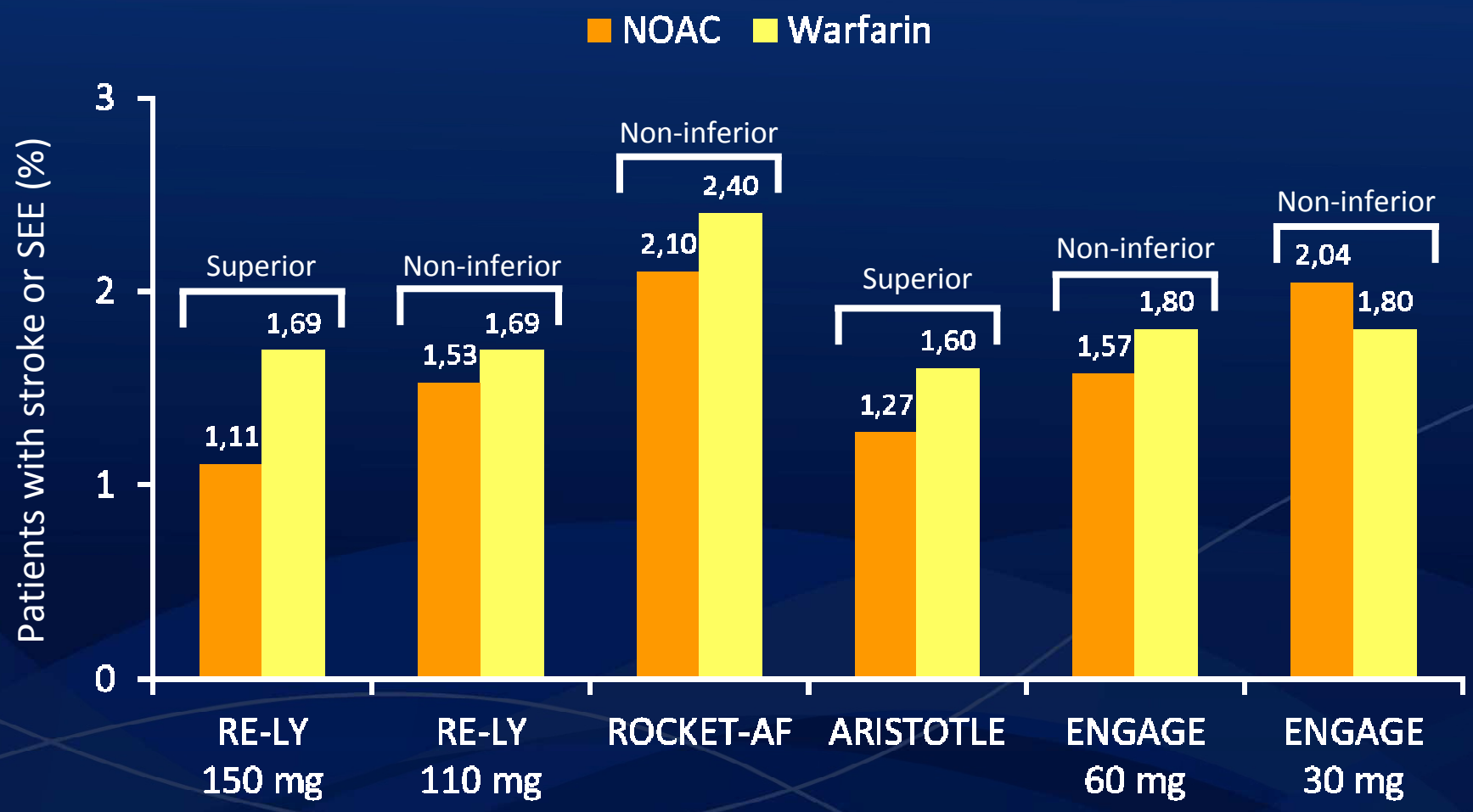
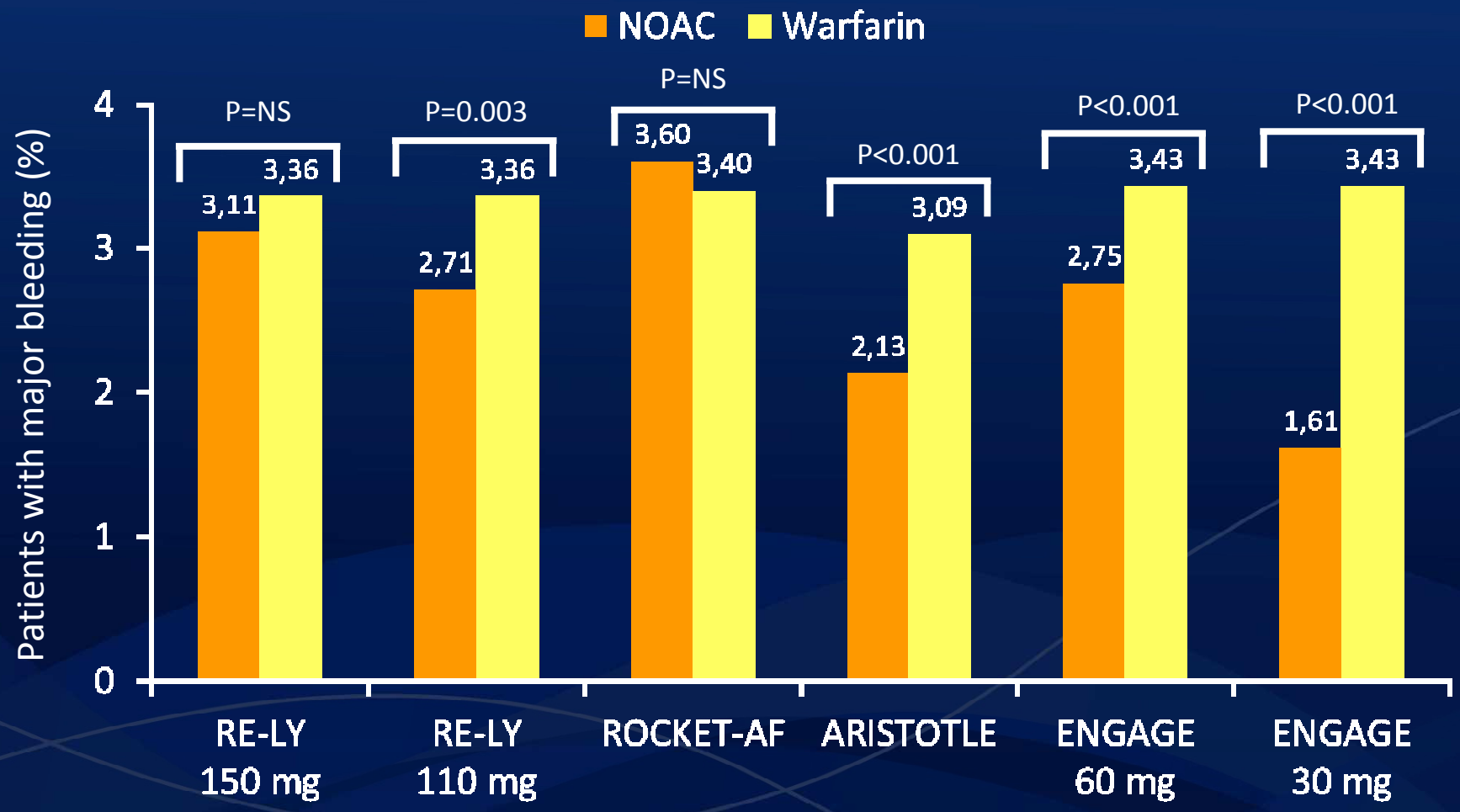
Phase III AF trials: ITT efficacy



1. Connolly et al. N Engl J Med 2009;361:1139–1151; 2. Patel et al. N Engl J Med 2011;365:883–891
3. Granger et al. N Engl J Med 2011;365:981–992; 4. Giugliano et al. N Engl J Med 2013; e-pub ahead of print

Phase III AF trials: major bleeding



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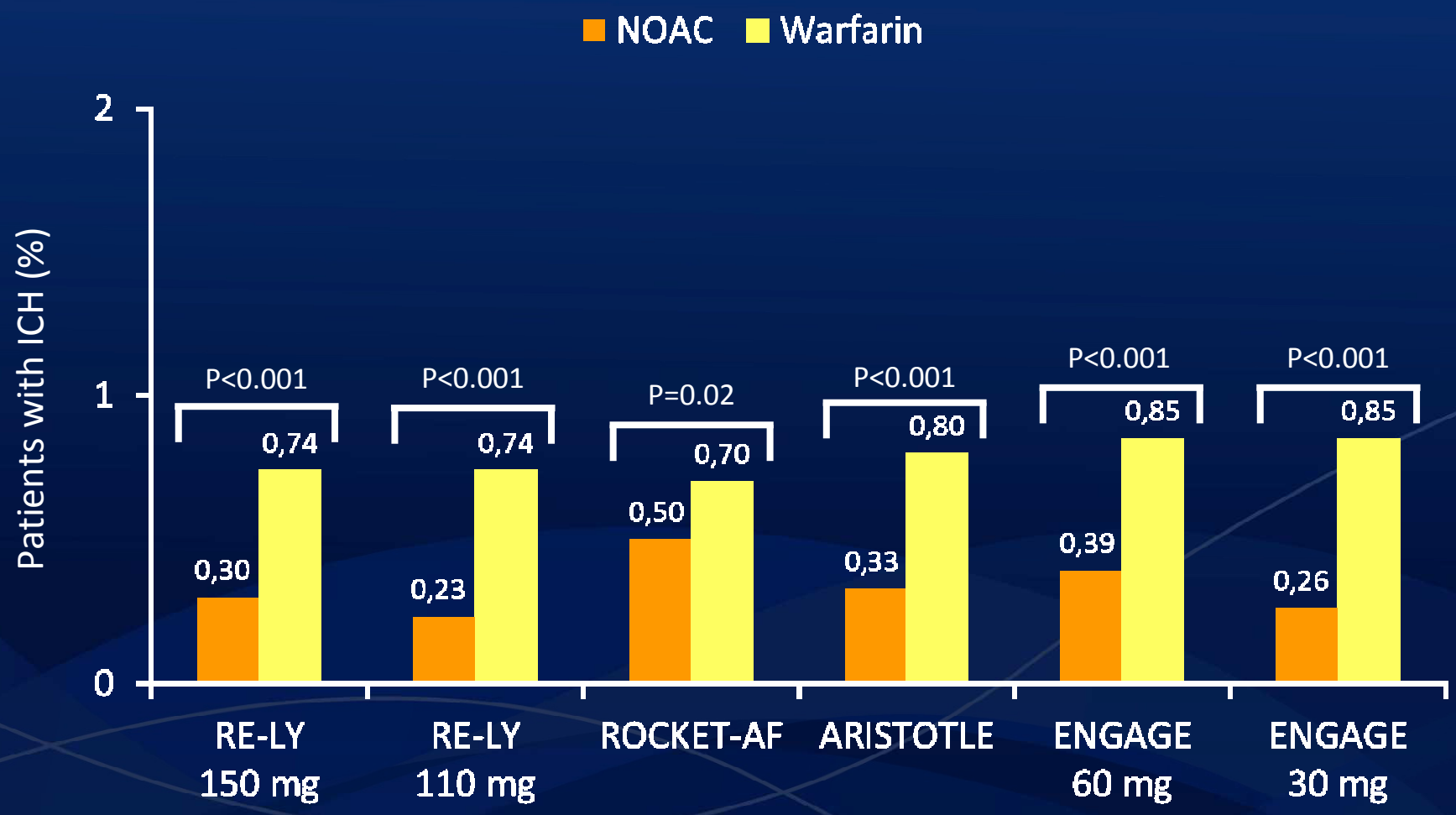
Phase III AF trials: intracranial hemorrhage



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Conclusiones Finales

- Los NACO han demostrado en ensayos de morbimortalidad en FANV una eficacia similar o mayor que los AVK, con una seguridad mayor .

- La reducción de la HIC es un dato constante y clínicamente muy relevante (Reducción cercana al 50%)

- Los cuatro ensayos clínicos realizados en pacientes con FANV, con dabigatrán, rivaroxabán, apixabán y edoxabán , muestran resultados favorables y consistentes entre ellos.