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

Engage AF TIMI 48

Nuevos avances en el tratamiento anticoagulante de la FA
Estudio ENGAGE-TIMI 48

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Diseño del estudio: ENGAGE AF-TIMI 48

Aleatorizado, doble ciego, doble simulación, dirigido por eventos

PACIENTES
FA documentada en registros eléctricos en los últimos 12 meses
Anticoagulantes orales planeados
$CHADS_2$ ≥2

N=21.105

ALEATORIZACIÓN
La aleatorización 1:1:1 se estratifica por $CHADS_2$ puntuación 2–3 frente a 4–6 y la necesidad de una reducción de la dosis de edoxaban*

- Régimen Edoxaban 30 mg QD
- Régimen Edoxaban 60 mg QD
- Warfarina (INR 2,0–3,0)

Duración media del seguimiento de 2,8 años

*Dosis reducida al 50% si CrCl 30–50 ml/min, peso corporal ≤60 kg o el paciente recibe verapamilo, quinidina o dronedarona.
FA=fibrilación auricular; CrCl=aclaramiento de creatinina
INR=razón normalizada internacional

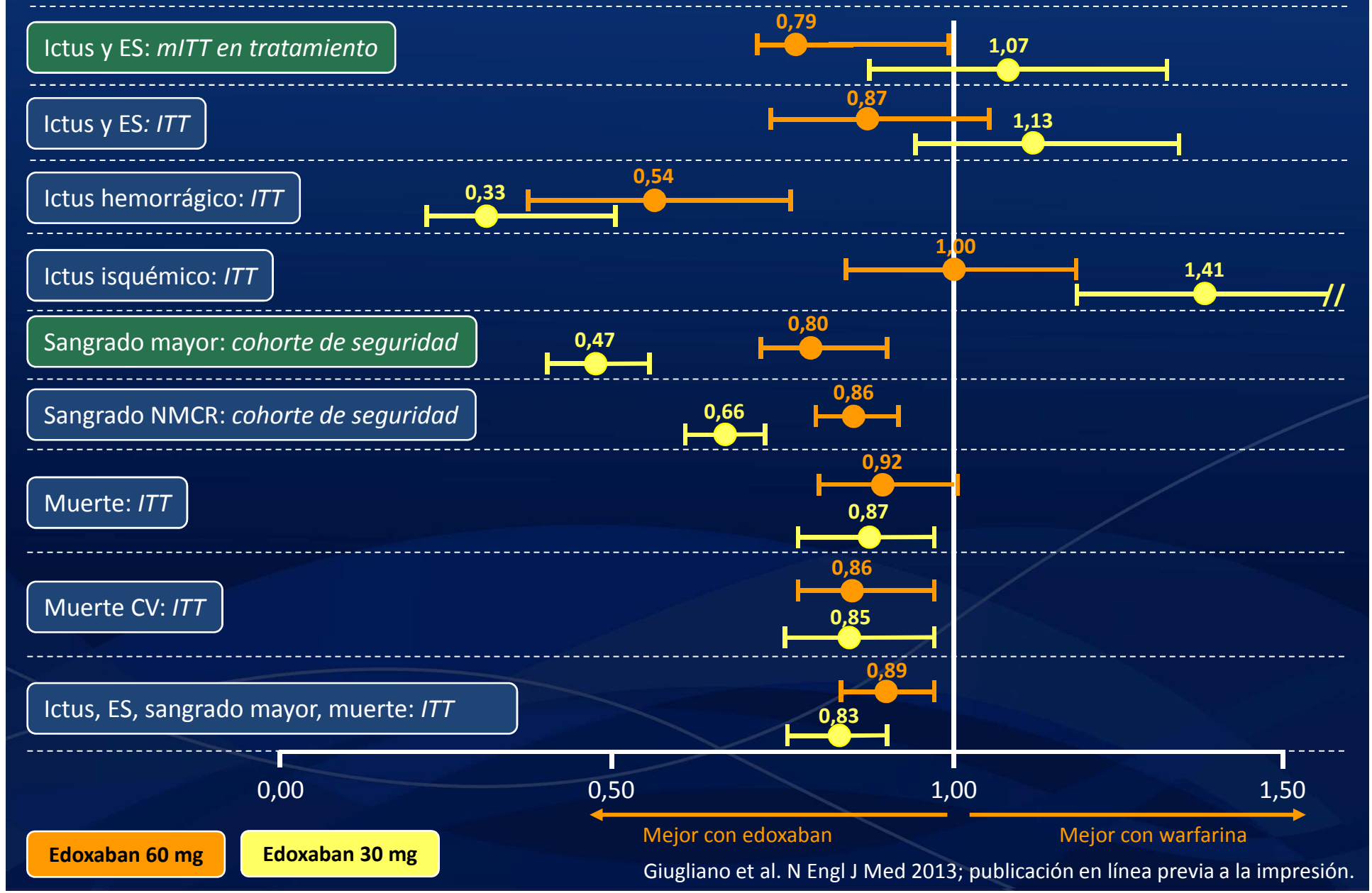
DU176b-C-U301 Protocol ver 8.0_07 Nov 2011. Daiichi Sankyo Inc
Giugliano et al. N Engl J Med 2013; publicación en línea previa a la impresión.

Características únicas del estudio

- Estudio aleatorizado y controlado con el mayor nº de pacientes (n=21.105) para la prevención del ictus en FA con un nuevo ACO
- Mayor tiempo de seguimiento (mediana de 2,8 años).
- Régimen de dosis una vez al día.
- Posibilidad de modificación de las dosis durante y después de la aleatorización, proporcionando datos sobre las tres dosis en los cuatro rangos de tratamiento.
- Pérdida mínima de datos.
- Terapia con warfarina con buen manejo, mediana de TRT del 68,4%.

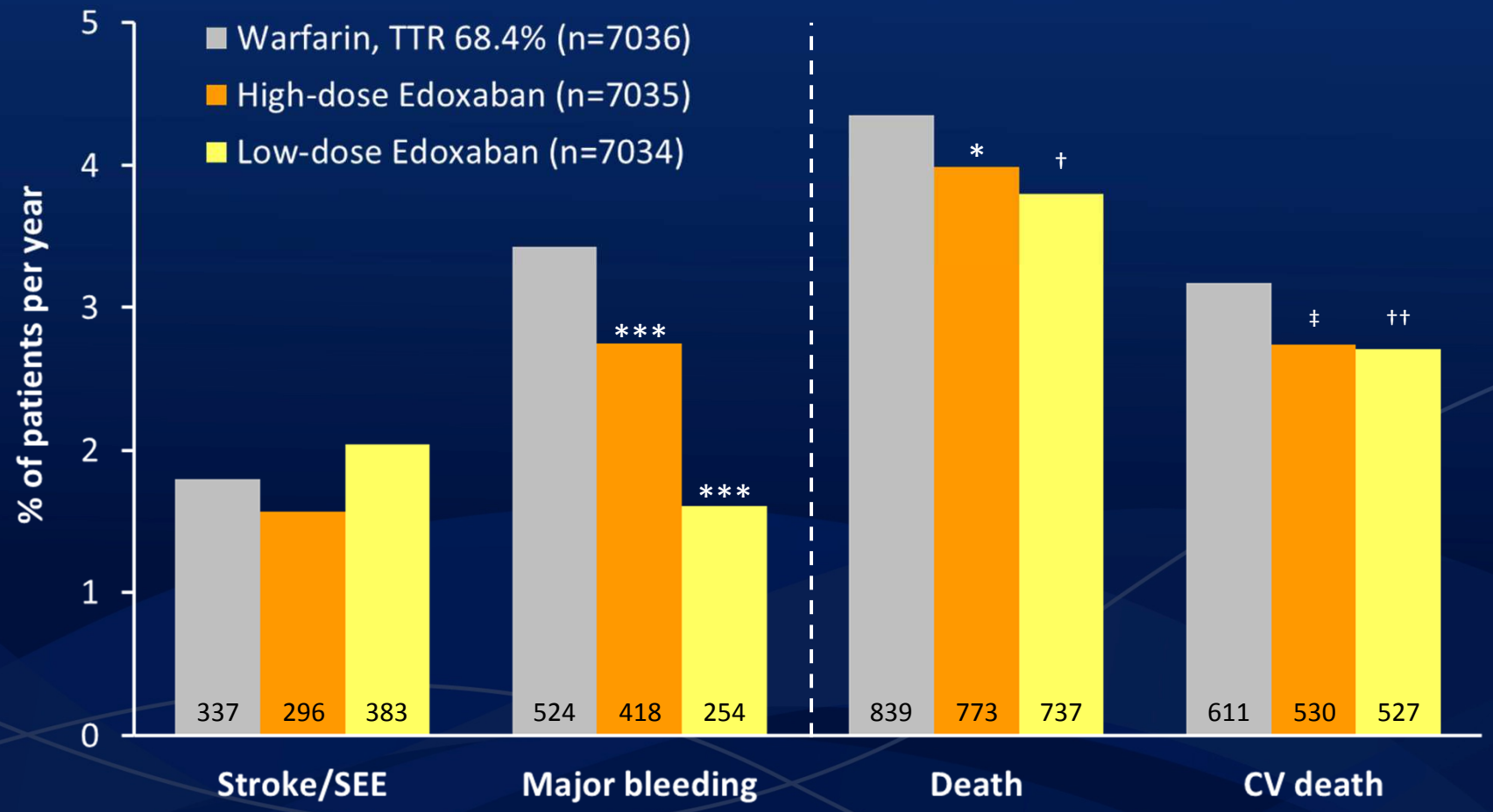
Giugliano et al. N Engl J Med 2013; publicación en línea previa a la impresión.

Resumen de los endpoints clave



Giugliano et al. N Engl J Med 2013; publicación en línea previa a la impresión.

ENGAGE AF: Primary and Mortality Endpoints



* P=0.08 vs warfarin; ** P=0.10 vs warfarin; *** P<0.001 vs warfarin; † P=0.006 vs warfarin; ‡ P=0.013 vs warfarin; †† P=0.008 vs warfarin

CV, cardiovascular; SEE, systemic embolic event; TTR, time in therapeutic range

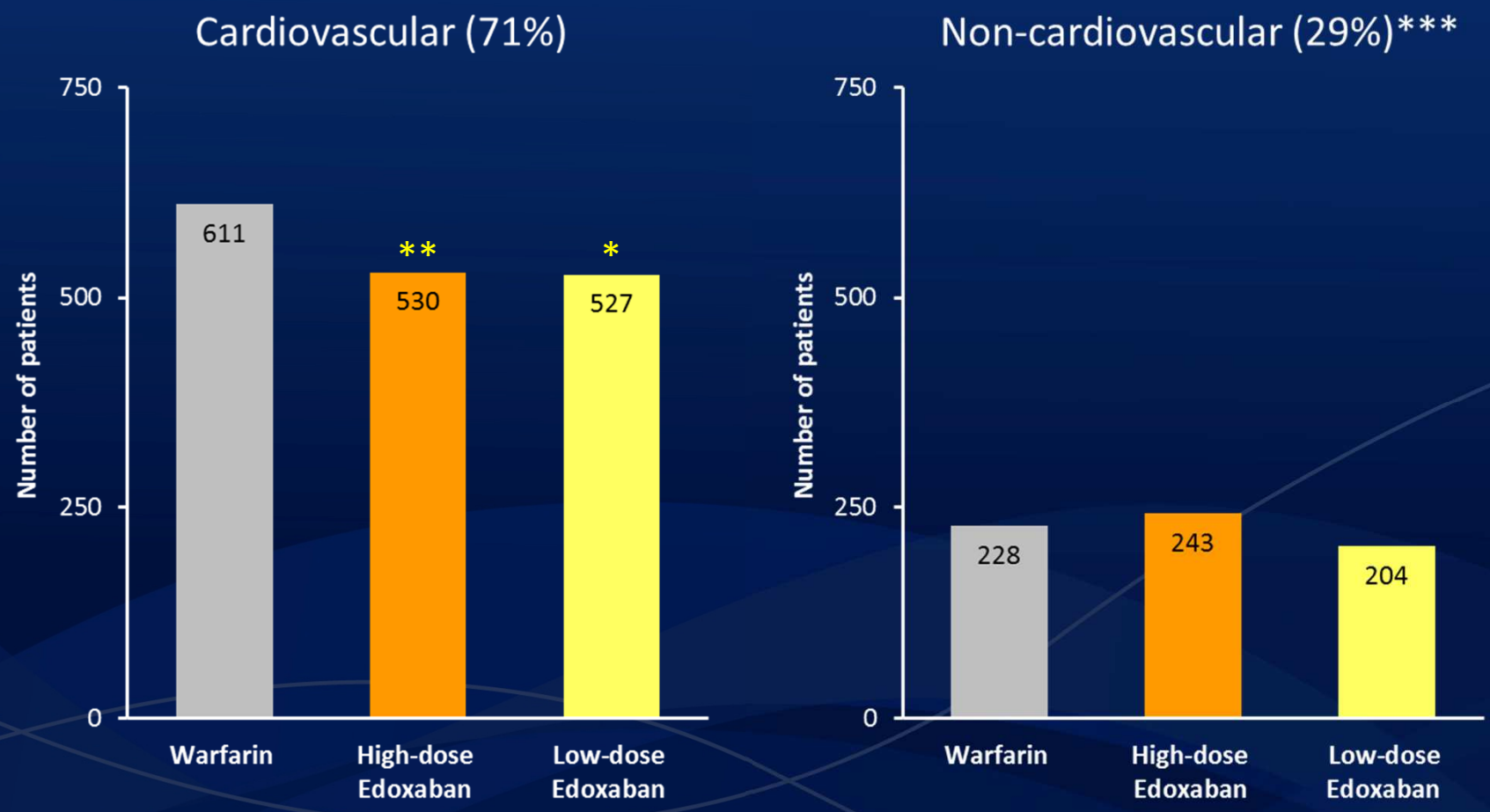
Giugliano RP et al. *NEJM* 2013;369:2093–104

ENGAGE AF: Methods

- All deaths, CV and bleeding events were adjudicated by an independent, blinded committee using prospective definitions:
  - Death: Cardiovascular (CV) vs Non-CV Subcategories of each
    NOTE: Bleeding deaths classified as CV
  - Bleeding: ISTH criteria
    - Fatal bleeds (directly caused death ≤7d)
    - Bleeding contributed to death (bleed on causal pathway to death within 30d)

CV, cardiovascular; ISTH, International Society on Thrombosis and Haemostasis

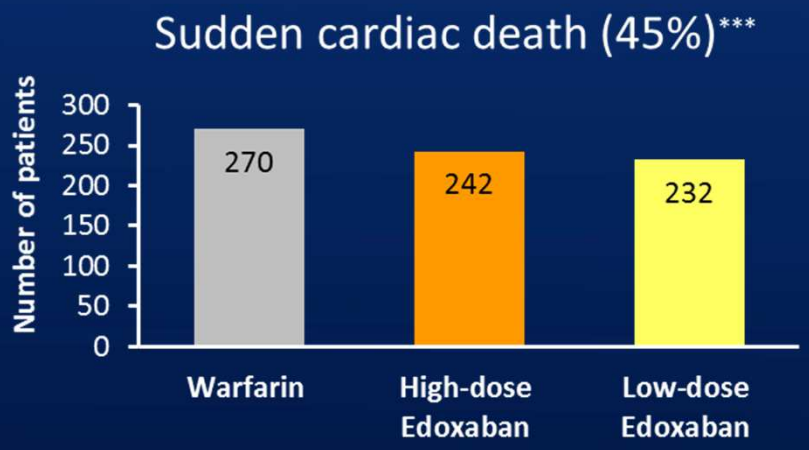
ENGAGE AF: Results - Causes of Death

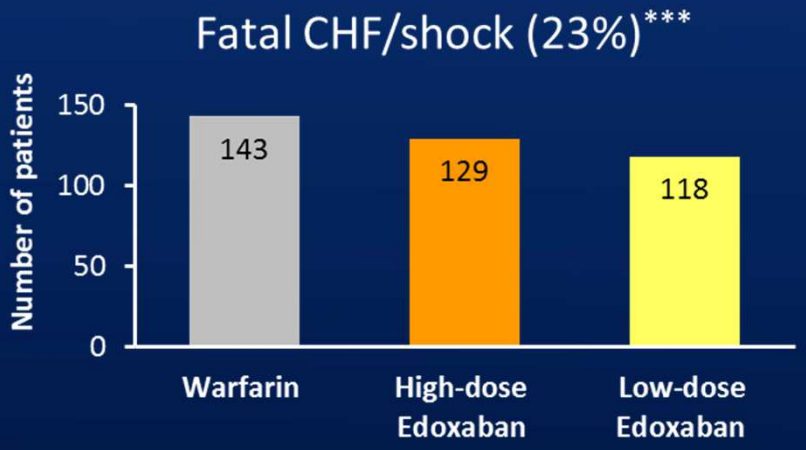


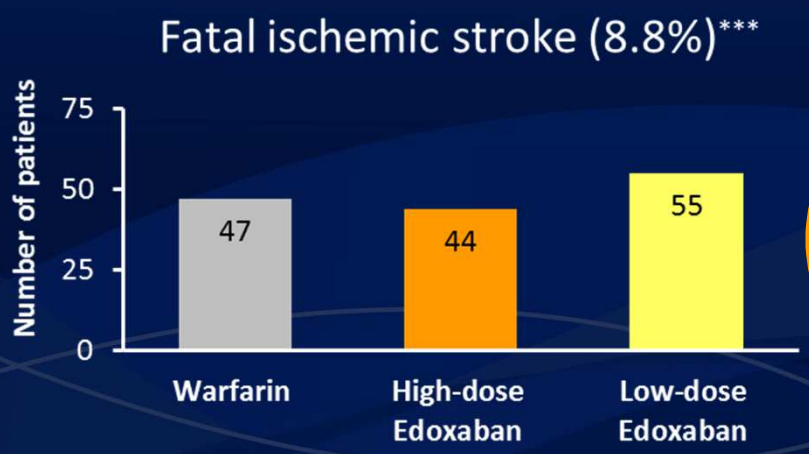
* P=0.008 vs warfarin; ** P=0.013 vs warfarin; *** P= NS for each pairwise comparisons

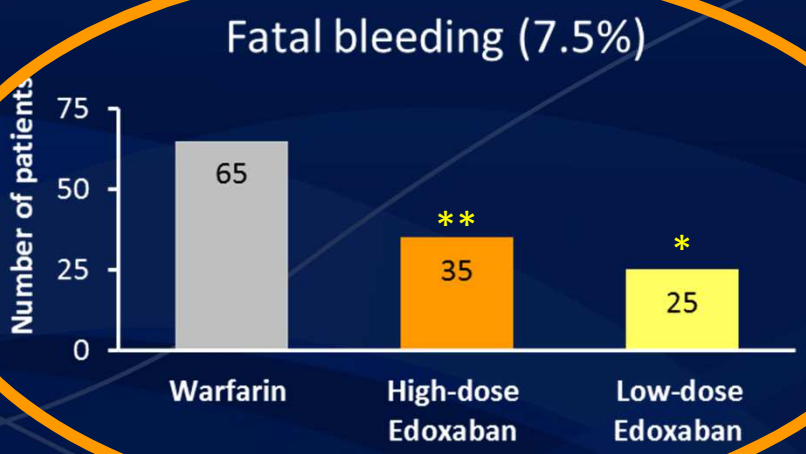
NS, non-significant

ENGAGE AF: Top 4 subclasses of CV death





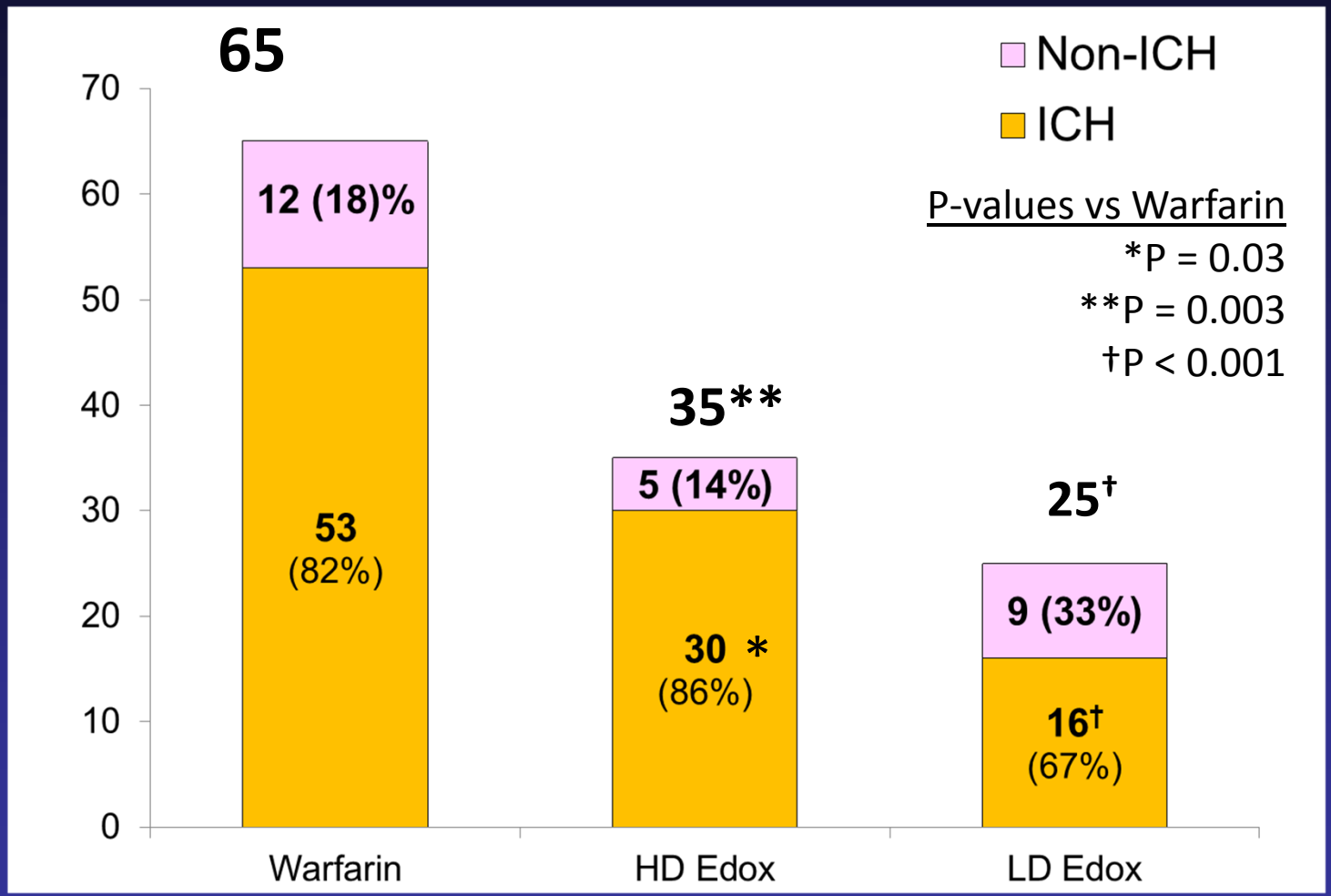




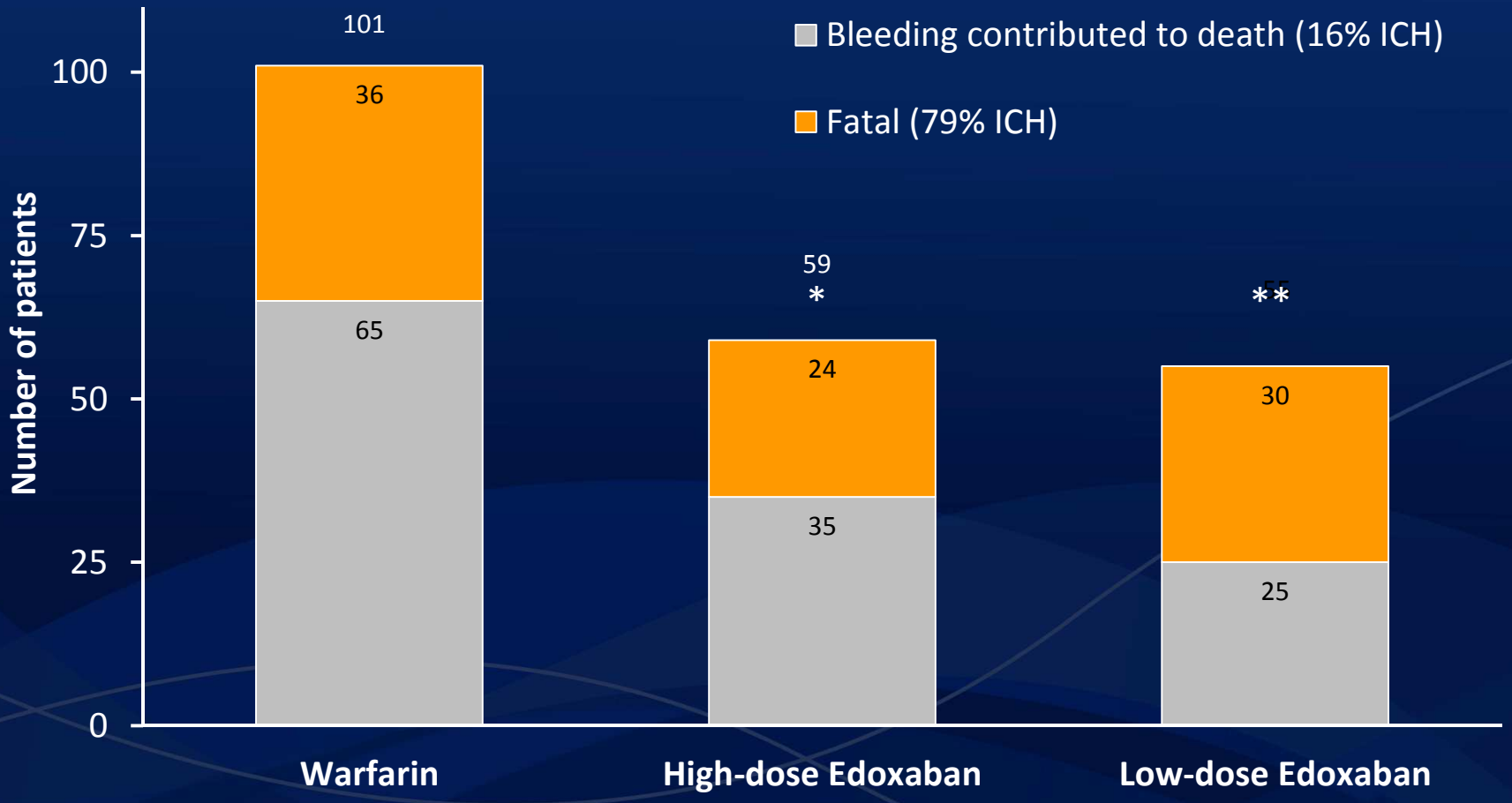
* P<0.001 vs warfarin; ** P=0.003 vs warfarin; *** P= NS for each pairwise comparisons

CHF, chronic heart failure; CV, cardiovascular

Fatal Bleeding by Location



ENGAGE AF: Bleeding related to death



* P=0.001 vs warfarin; ** P<0.001 vs warfarin

ICH, intracranial haemorrhage

ENGAGE AF prespecified stroke subanalysis: Background and rationale

- This prespecified stroke subanalysis of ENGAGE AF-TIMI 48 assessed the type, severity and timing of stroke observed in the warfarin and edoxaban groups
- This analysis also explored the modern definition of stroke, including ischaemic cerebrovascular events resolving completely within 24 hours and demonstrated evidence of infarction on brain imaging

INR, international randomised ratio; NVAF, non-valvular atrial fibrillation; SEE, systemic embolic event

Giugliano et al. Stroke 2014; [Epub ahead of print]

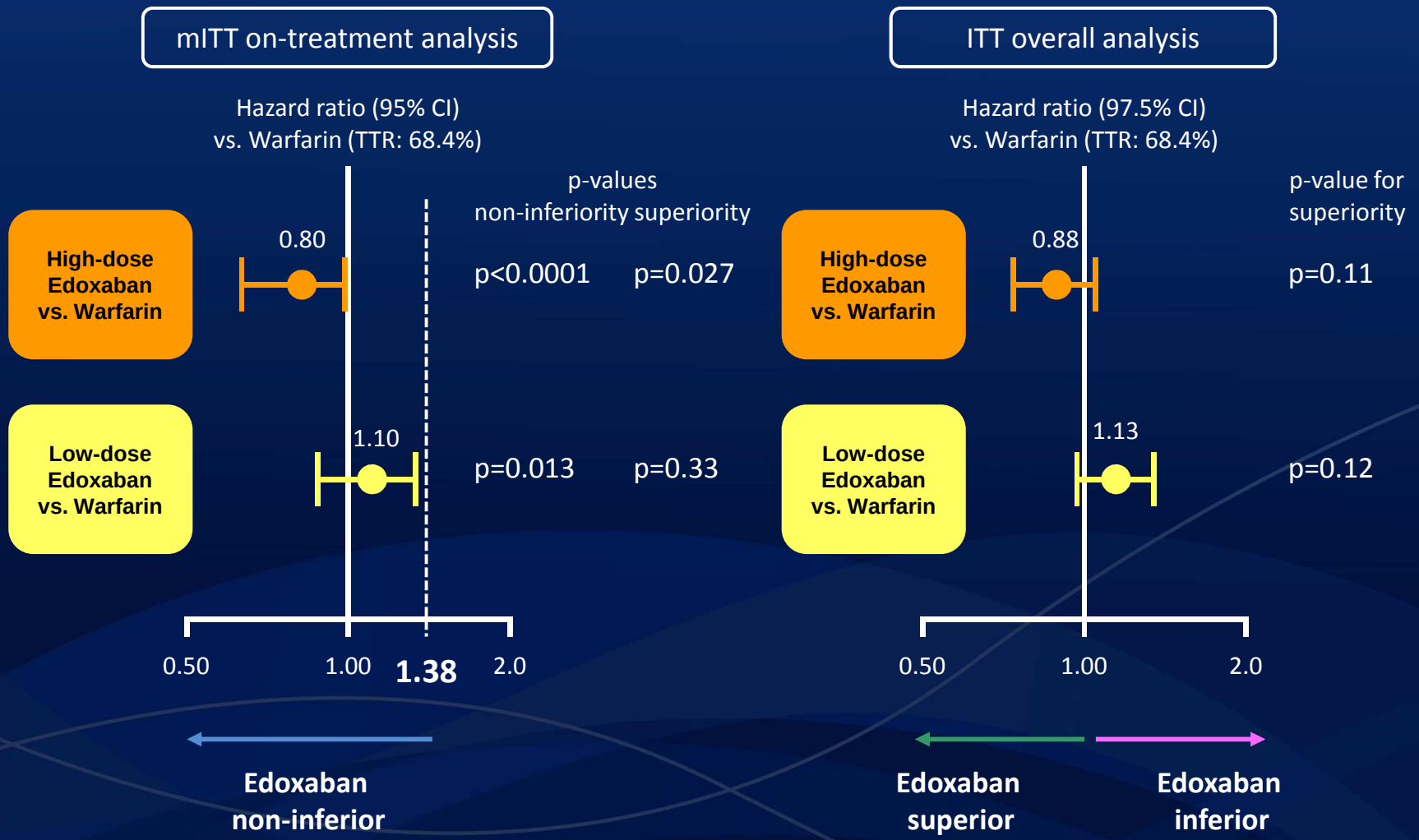
ENGAGE AF prespecified stroke subanalysis: Endpoint definitions

- Primary endpoint
  - First ischaemic or haemorrhagic stroke, defined as abrupt onset of focal neurological deficit due to infarction or bleeding lasting ≥24 hours or fatal in <24 hours. However, events meeting this criteria but completely resolved in <24 hours were classified as a TIA
  - Classified TIAs with a new infarction upon brain imaging and haemorrhagic transformation of an initial ischaemic stroke as an ischaemic stroke
- Secondary endpoints
  - Subtype of stroke: haemorrhagic stroke, haemorrhagic transformation of a primary ischemic stroke, subdural and epidural haematomas severity
  - Severity of stroke: modified Rankin Scale score 30–90 days after event

TIA, transient ischaemic attack

Giugliano et al. Stroke 2014; [Epub ahead of print]

Risk of all stroke



Giugliano et al. Stroke 2014; [Epub ahead of print]

Stroke events by treatment group

Events, %/y	Warfarin (n=7036)	High-dose Edoxaban (n=7035)	High-dose Edoxaban vs. Warfarin		Low-dose Edoxaban (n=7034)	Low-dose Edoxaban vs. Warfarin	
			Hazard ratio	p-value		Hazard ratio	p-value
All stroke	1.69	1.49	0.88	0.11	1.91	1.13	0.12
Haemorrhagic	0.47	0.26	0.54	**<0.001**	0.16	0.33	**<0.001**
Fatal	0.21	0.14	0.57	**0.002**	0.14	0.33	**<0.001**
Disabling, nonfatal*	0.07	0.03	0.36	0.081	0.02	0.36	0.079
Non-disabling†	0.19	0.09	0.35	**<0.001**	0.08	0.26	**<0.001**

New stroke definition reclassified 37 TIAs as ischaemic stroke (14 warfarin, 9 high-dose edoxaban, 14 low-dose edoxaban).
*Includes Rankin score 3–5.
†Rankin score 0 to 2 or alive with no score reported by the investigator (n=231).
‡Includes stroke with haemorrhagic transformation

Giugliano et al. Stroke 2014; [Epub ahead of print]

Intracranial events by treatment group

Events, %/y	Warfarin (n=7036)	High-dose Edoxaban (n=7035)	High-dose Edoxaban vs. Warfarin		Low-dose Edoxaban (n=7034)	Low-dose Edoxaban vs. Warfarin	
			Hazard ratio	p-value		Hazard ratio	p-value
All intracranial haemorrhages	0.85	0.39	0.47	<0.001	0.26	0.30	<0.001
Haemorrhagic stroke	0.47	0.26	0.54	<0.001	0.16	0.33	<0.001
Parenchymal	0.42	0.24	0.57	0.002	0.14	0.33	<0.001
Subarachnoid	0.06	0.02	0.36	**0.081**	0.02	0.36	**0.079**
Subdural or epidural	0.30	0.10	0.35	<0.001	0.08	0.26	<0.001
Fatal intracranial haemorrhages	0.27	0.15	0.58	0.031	0.08	0.28	<0.001
Fatal subdural or epidural bleed	0.07	0.01	0.15	0.013	0.01	0.15	0.013
Haemorrhagic transformation	n=8	n=12	1.49	**0.38**	n=20	2.48	0.03
Microhaemorrhage (without stroke)	n=2	n=3	-	-	n=0	-	-

Giugliano et al. Stroke 2014; [Epub ahead of print]

Net clinical outcome: Composite of death, stroke and ICH

Events, %/y	Warfarin (n=7036)	High-dose Edoxaban (n=7035)	High-dose Edoxaban vs. Warfarin		Low-dose Edoxaban (n=7034)	Low-dose Edoxaban vs. Warfarin	
			Hazard ratio	p-value		Hazard ratio	p-value
Death, nonfatal stroke, ICH*	5.74	5.04	0.88	**0.003**	5.20	0.90	**0.021**
Death or nonfatal stroke	5.49	4.94	0.90	**0.017**	5.15	0.93	0.13
Death or nonfatal ICH	4.88	4.27	0.87	**0.004**	4.03	0.82	**<0.001**
Death or nonfatal ischaemic stroke	5.27	4.85	0.92	0.064	5.06	0.96	0.35
Death or nonfatal haemorrhagic stroke	4.62	4.13	0.89	**0.019**	3.91	0.84	**<0.001**
Death or nonfatal disabling stroke†	4.61	4.24	0.92	0.078	4.15	0.90	**0.024**

*Excluding primary haemorrhagic stroke
†Includes Rankin score 3 to 5

Giugliano et al. Stroke 2014; [Epub ahead of print]

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

Christian T. Ruff, MD, MPH

On behalf of the Executive Committee and Investigators

TIMI Study Group
Brigham and Women's Hospital
Harvard Medical School
Boston, MA

Background

- **Initial appeal of NOACs**

  Fixed dosing without the need for routine monitoring

- **Emerging concern:**

  Optimizing risk / benefit of NOACs requires measuring drug concentration and / or antithrombotic activity

- **Pharmacokinetic modeling and simulation from Phase I/II studies of edoxaban*:**

  - Identified clinical features that significantly increased edoxaban exposure

  - Trough concentration closely correlated with bleeding

*Salazar DE, et al. J Thromb Haemost 2012; 107(5):925-936

Methods

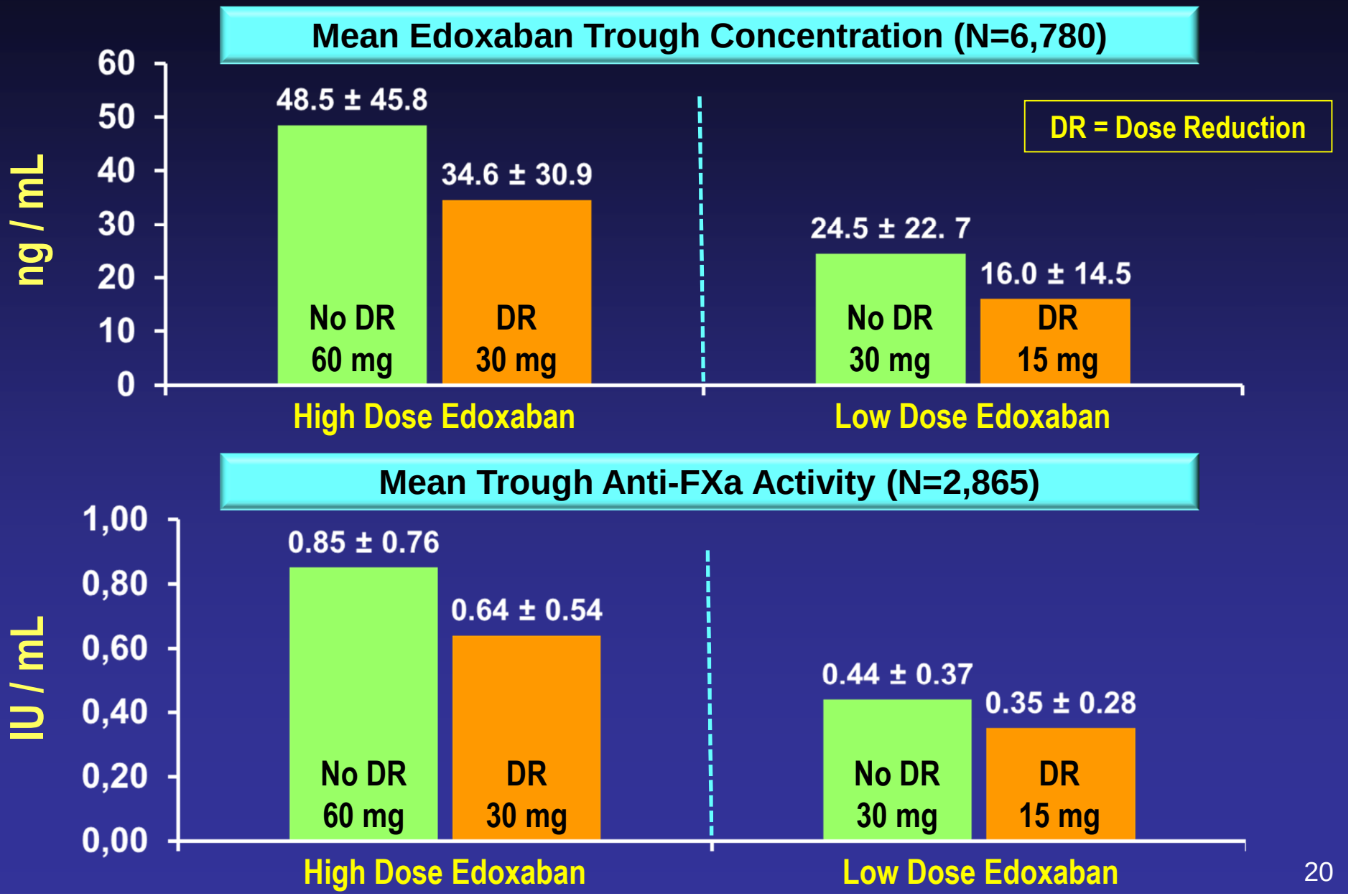
- Trough plasma samples 1-mo. post randomization*:

Edoxaban Concentration (N=6,780)	Anti-Fxa Activity (N=2,865, Substudy)
Quintiles Bioanalytical and ADME Labs	Rotachrome Heparin Assay Stago STAR Evolution Platform

- Correlated edoxaban dose, concentration, and anti-FXa activity.
- Compared efficacy and safety outcomes with warfarin stratified by dose reduction status.

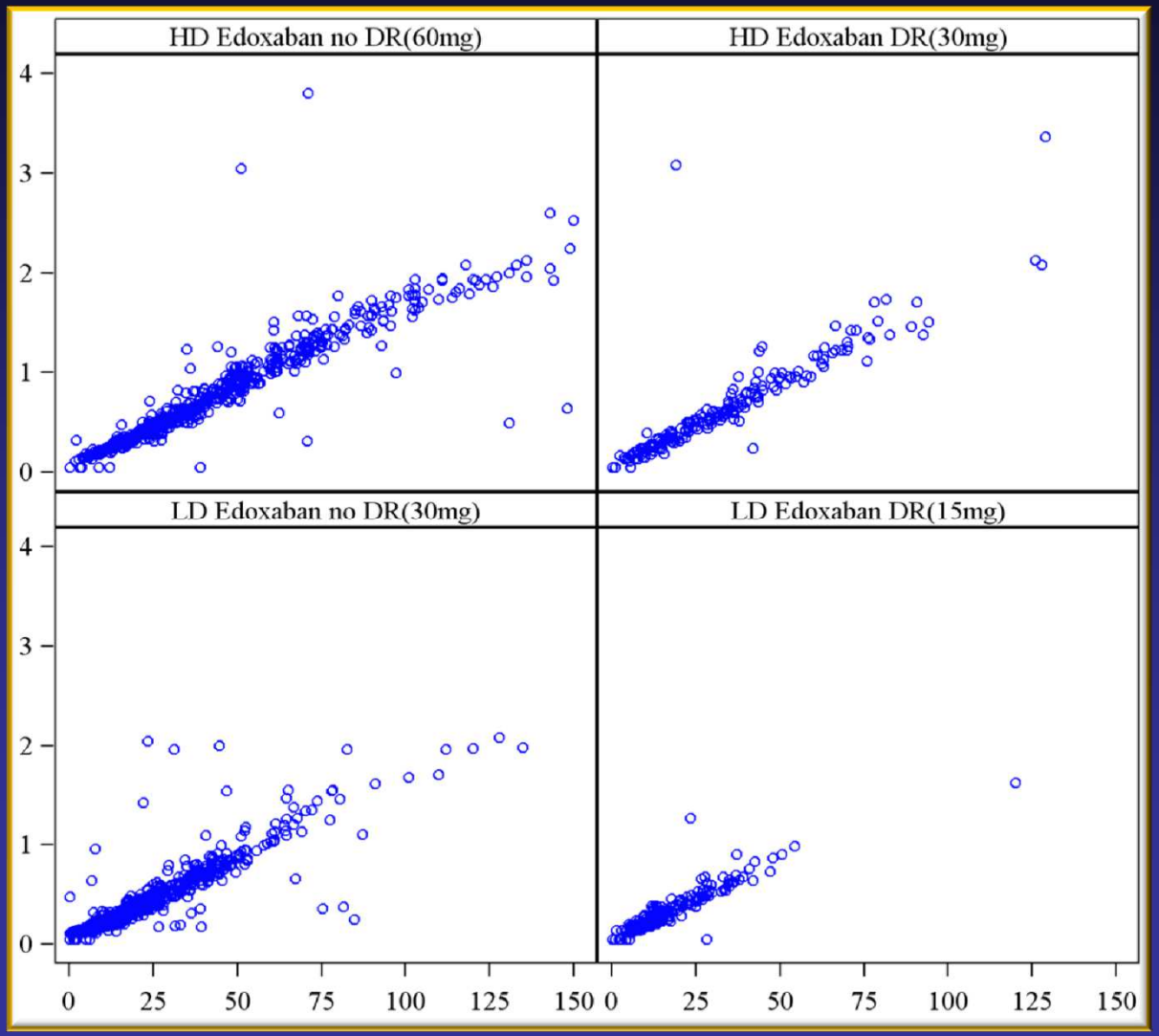
* Samples excluded if value < lower limit of detection, handling errors, drawn outside protocol time window, endpoint occurred before sample drawn

Edoxaban Concentration & Anti-FXa Activity

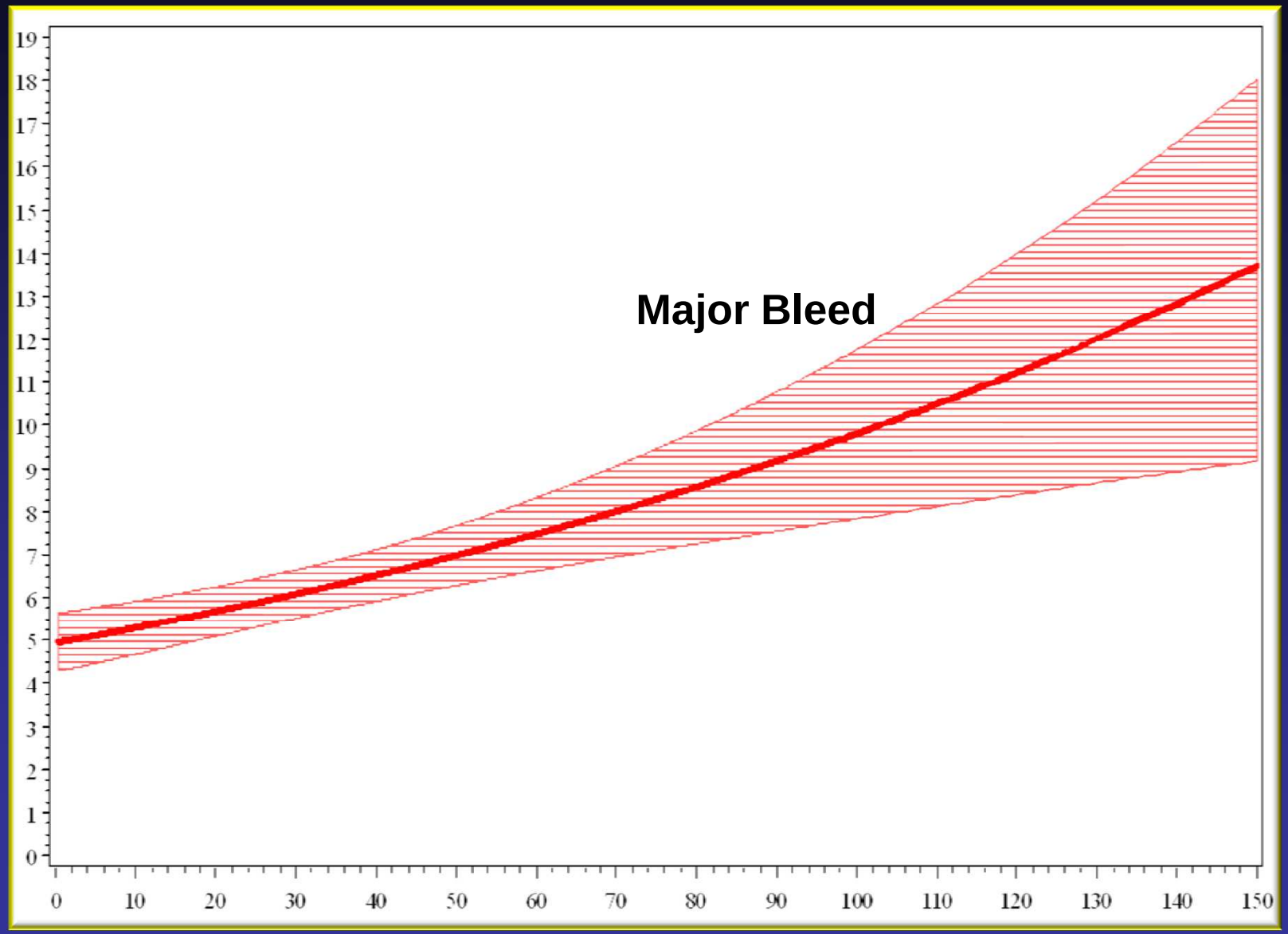


Correlation of Trough Edoxaban Concentration & Factor Xa Activity

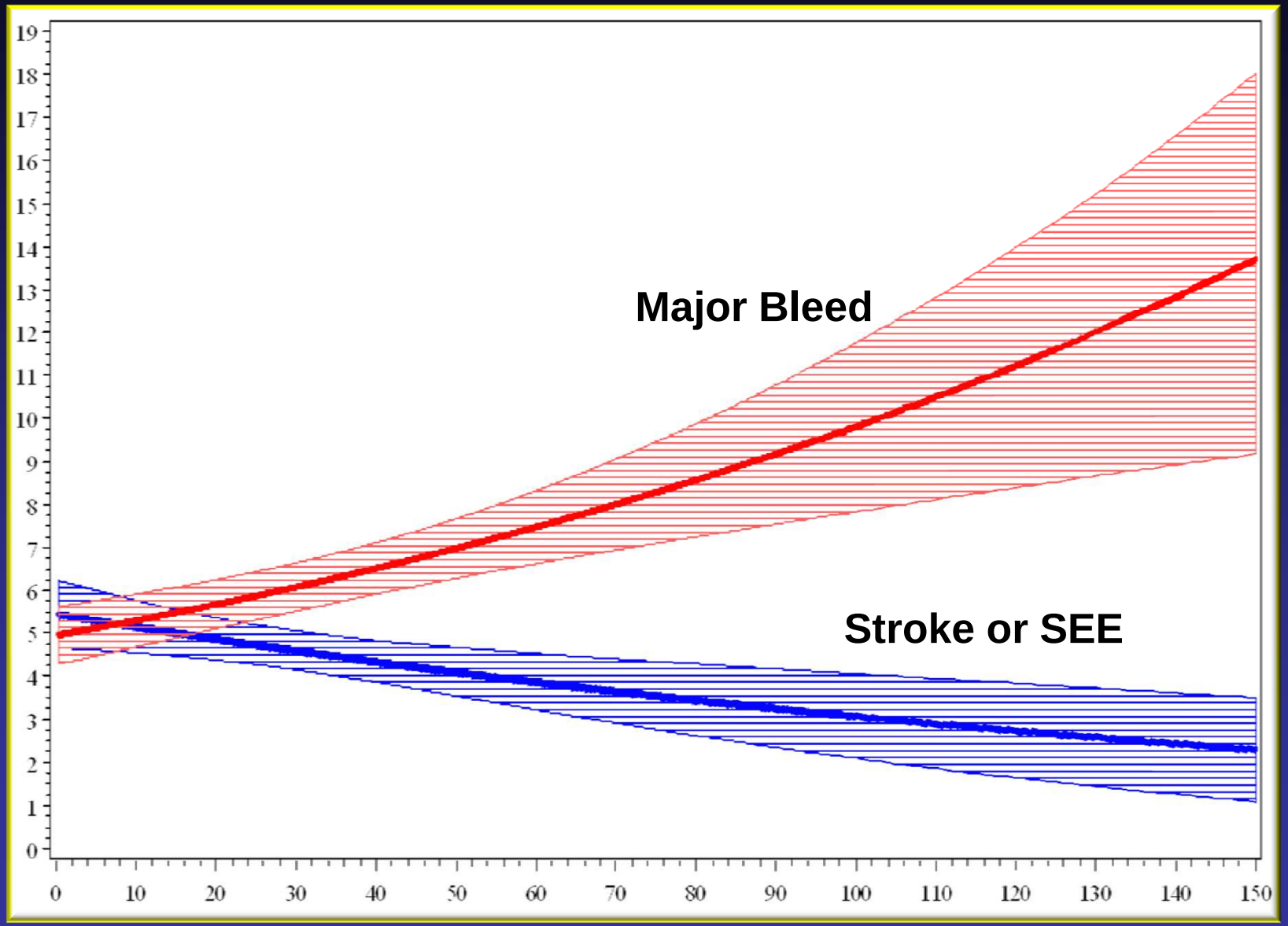
R = 0.96 P<0.0001



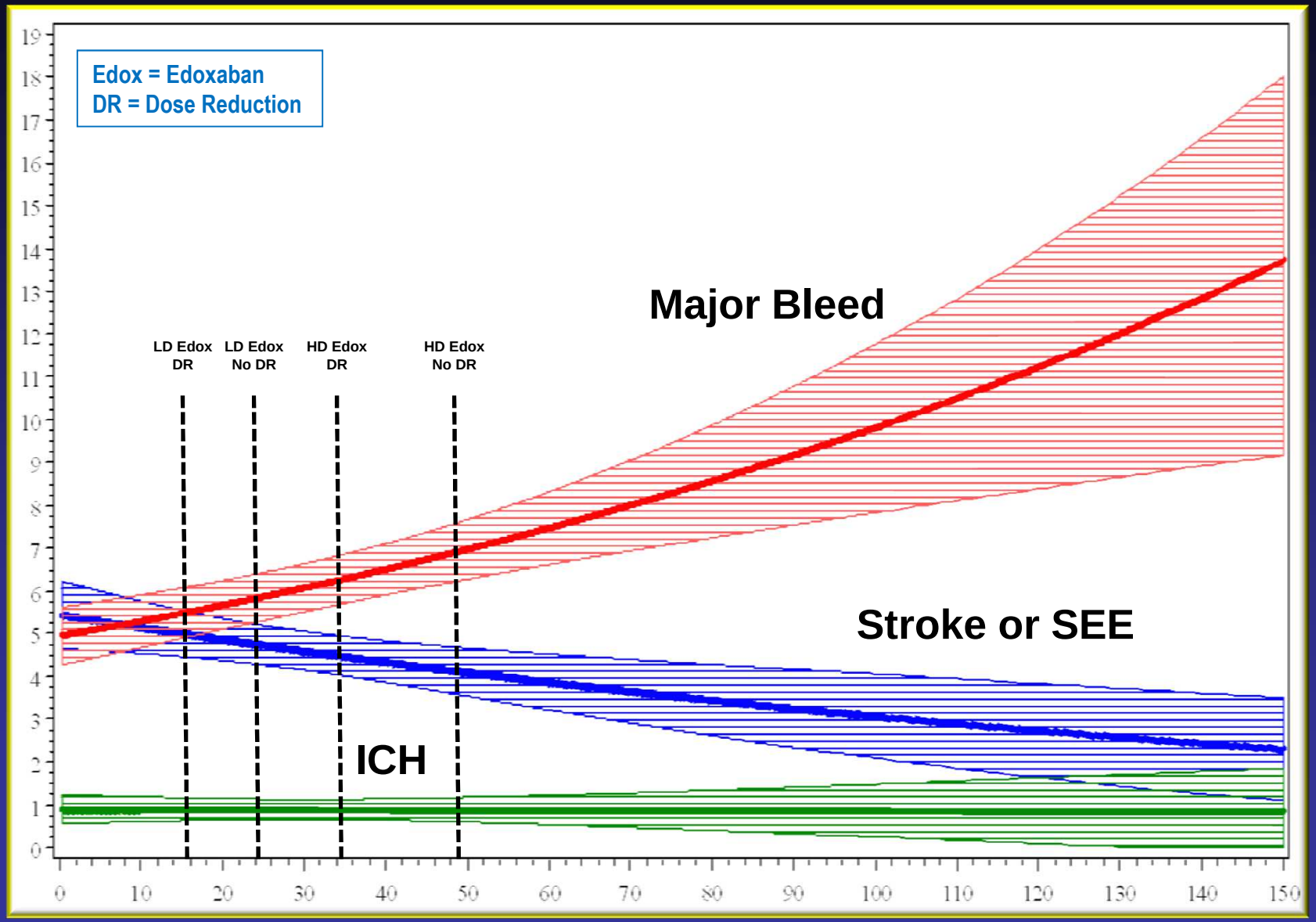
Edoxaban Trough Concentration & Outcomes



Edoxaban Trough Concentration & Outcomes



Edoxaban Trough Concentration & Outcomes



Engage AF
TIMI 48

BASELINE CHARACTERISTICS, OUTCOMES, AND COMPARISON OF EDOXABAN VS WARFARIN BY AF SUBTYPE IN 21,105 PATIENTS ENROLLED IN THE ENGAGE AF-TIMI 48 TRIAL

Methods: We categorized 21,105 patients enrolled in ENGAGE AF-TIMI 48 as having paroxysmal (<7 days duration), persistent (> 7 days but < 1 year), or permanent (> 1 year or failed cardioversion) AF based on the randomization ECG.

- Objetive: to evaluate clinical efficacy and safety outcomes during the 2.8 years median follow-up and compared results by AF subtype.

Engage AF TIMI 48

Baseline Characteristics, Efficacy and Safety Outcomes by AF Subtype

	Paroxysmal (N=5366)	Persistent (N=4868)	Permanent (N=10,865)	3-way P-value
Mean age	70.5 (9.5)	70.2 (9.7)	70.8 (9.2)	0.014
Women	45%	38%	35%	<0.001
VKA naive	52%	53%	31%	<0.001
CHADS2>3	20%	20%	25%	<0.001
Prior stroke	17%	16%	21%	<0.001
Prior CAD	36%	31%	33%	<0.001
Prior CHF	45%	60%	62%	<0.001
Diabetes	38%	36%	35%	0.030
CrCl < 50	20%	20%	19%	0.17
Mean SBP	131 (16)	129 (15)	130 (15)	<0.001
Aspirin	36%	31%	25%	<0.001
Amiodarone	19%	14%	7%	<0.001
Digoxin	13%	29%	39%	<0.001

Engage AF TIMI 48

Paroxística Permanente Persistente

Outcome	% per yr	% per yr	% per yr	Paroxysmal vs Perm	Persistent vs Perm
	-----	-----	-----	HR, P-value	HR, P NS
Efficacy	1.49	1.83	1.95	0.76,<0.001	0.94, 0.43
Stroke/SEE	1.18	1.44	1.54	0.77,0.003	0.94, 0.47
Isch stroke	0.29	0.33	0.29	1.00, 0.99	1.15, 0.45
Hem stroke	2.03	3.23	3.13	0.65,<0.001	1.03 ,0.59 1.00, 0.99
CV Death All Deaths	2.99	4.41	4.41	0.68 <0.001	
Bleeding	-----	-----	-----	HR, P-value	HR, P
Major	2.86	2.65	2.73	1.04, 0.52	0.96, 0.62 NS
Maj/CRNM	12.2	10.7	10.4	1.17, 0.001	1.03, 0.49
All	15.7	13.7	13.1	1.19,<0.001	1.05, 0.19
ICH	0.50	0.44	0.50	0.98, 0.91	0.87, 0.40
Fatal	0.17	0.25	0.26	0.65, 0.09	1.00. 0.99

Outcomes by Treatment and AF Subtype

Outcome / Subtype of AF	High-Dose Edox vs W		Low-Dose Edox vs W	
Stroke/SEE	HR		HR	
Paroxysmal AF	1.26	P-Inter.	1.31	P-Inter.
Persistent AF	0.82	0.05	0.97	0.42
Permanent AF	0.77		1.15	
Major Bleeding	HR		HR	
Paroxysmal AF	0.82	P-Inter.	0.42	P-Inter.
Persistent AF	0.74	0.80	0.57	0.31
Permanent AF	0.82		0.53	

Engage AF TIMI 48

Conclusion

Differences in baseline characteristics only partially explain why outcomes vary by AF subtype.

Therapies such as edoxaban that reduce bleeding compared to warfarin, while maintaining efficacy to prevent stroke (as were seen in ENGAGE AF-TIMI 48), may be especially attractive in patients with paroxysmal AF, as these patients appear to be at higher risk of non-major bleeding and lower risk of ischemic stroke and death.