CLINICA DELLA EMBOLIA POLMONARE
NUOVI ANTICOAGULANTI ORALI:
UNA RIVOLUZIONE COPERNICANA ?

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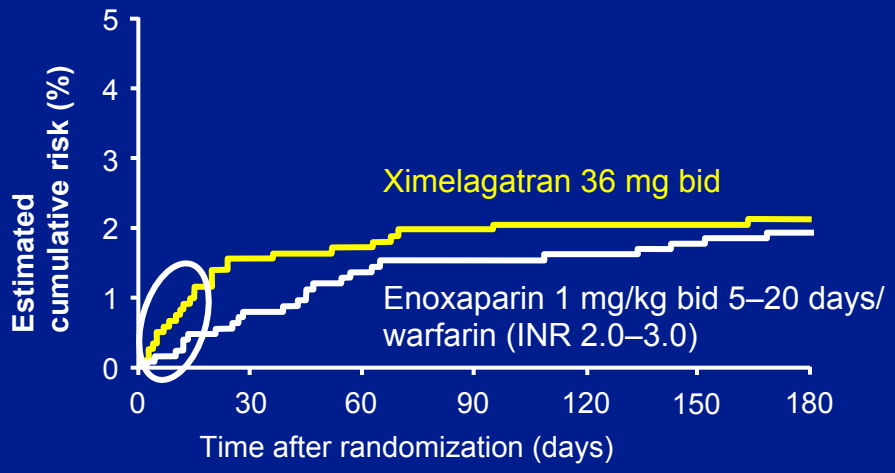
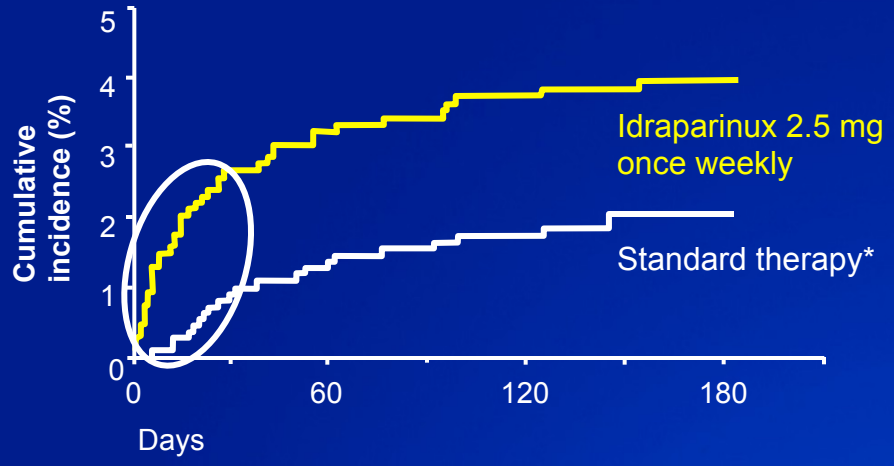
NAC in VTE patients

Evidence of early recurrent VTE in THRIVE study with ximelagatran[1]



Evidence of early recurrent VTE in the van Gogh PE study with idraparinux[2]



- Early separation of the curves indicates the need for intensified anticoagulant treatment in the acute phase

*Heparin followed by an adjusted-dose VKA for either 3 or 6 months

1. Fiessinger J-N et *al. JAMA* 2005;293:681–689;
2. The van Gogh Investigators. *N Engl J Med* 2007;357:1094–1104

NAC in PE patients

Only PE patients enrolled

- *Einstein PE – rivaroxaban*
- *Cassiopea – idrabiotaparinux*

Both DVT and PE patients enrolled

- *Hokusai – edoxaban*
- Amplify – apixaban
- Recover - dabigatran

Single-drug approach

- Amplify – apixaban
- *Einstein(s)- rivaroxaban*

Multiple-drug approach

- Recover – dabigatran
- *Hokusai – edoxaban*
- *Cassiopea - idrobiotaparinux*

PE as index event in NOAC VTE trials

	% patients (n/N)			
	RE-COVER™ I +II[1,2]	**Hokusai-VTE[3]**	**EINSTEIN DVT +PE[4,5]**	**AMPLIFY[6]**
PE as index event NOAC arm Warfarin arm	 31.4% 32.2%	 40.0% 40.5%	 58.6% 58.7%	 34.6% 33.5%
Primary efficacy results; PE as index event NOAC arm Warfarin arm	 2.9% (23/795) 3.1% (25/807)	 2.8% (47/1650) 3.9% (65/1669)	 2.1% (50/2419) 1.8% (44/2413)	 2.3% (21/900) 2.6% (23/886)

NOAC = novel oral anticoagulant

1. Schulman S et al. N Engl J Med 2009;361:2342–52; **2.** Schulman S et al. Circulation 2014;129:764–72;
3. Hokusai VTE investigators. N Engl J Med 2013;369:1406–15; **4.** EINSTEIN investigators. N Engl J Med 2010;363:2499–510;
5. EINSTEIN investigators. N Engl J Med 2012;366:1287–97; **6.** Agnelli G et al. N Engl J Med 2013;369:799–808

Joint symposium with SIAPAV: New anticoagulants (NAC)

NAC and Pulmonary Embolism

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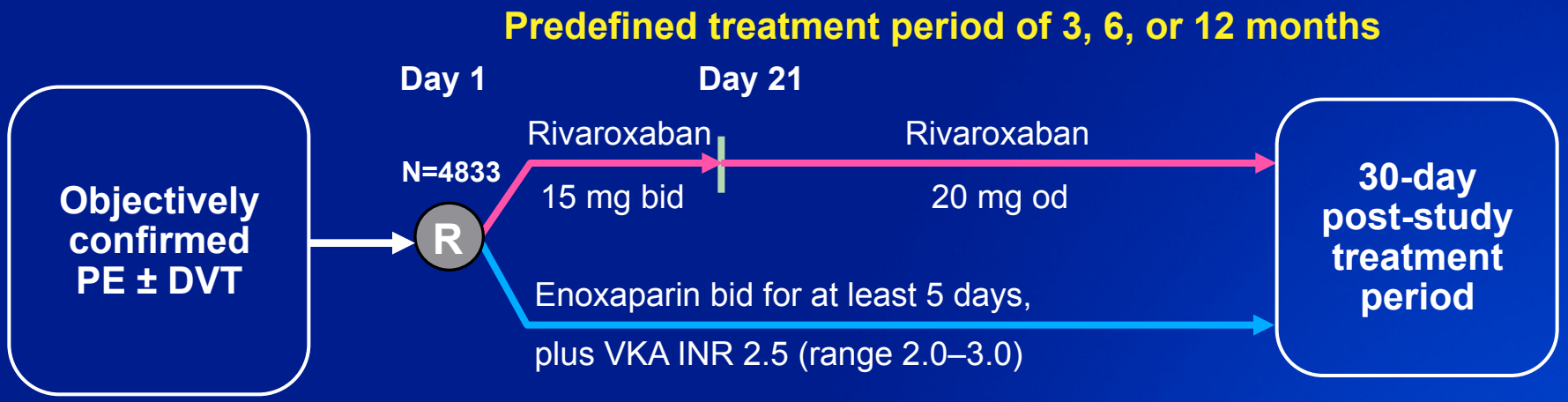
A CRITICAL "GOAL" TO BE ACHIEVED WITH ANY NEW TREATMENT OF PE

- To reach both the best short-term and long-term efficacy according to the:
  - *Extension of pulmonary thromboemboli*
  - *The risk stratification of early PE-related mortality (ESC - PESI)*

EINSTEIN PE: study design

Randomized, open-label, event-driven, non-inferiority study

- Up to 48 hours' heparins/fondaparinux treatment permitted before study entry
- 88 primary efficacy outcomes needed
- Non-inferiority margin: 2.0

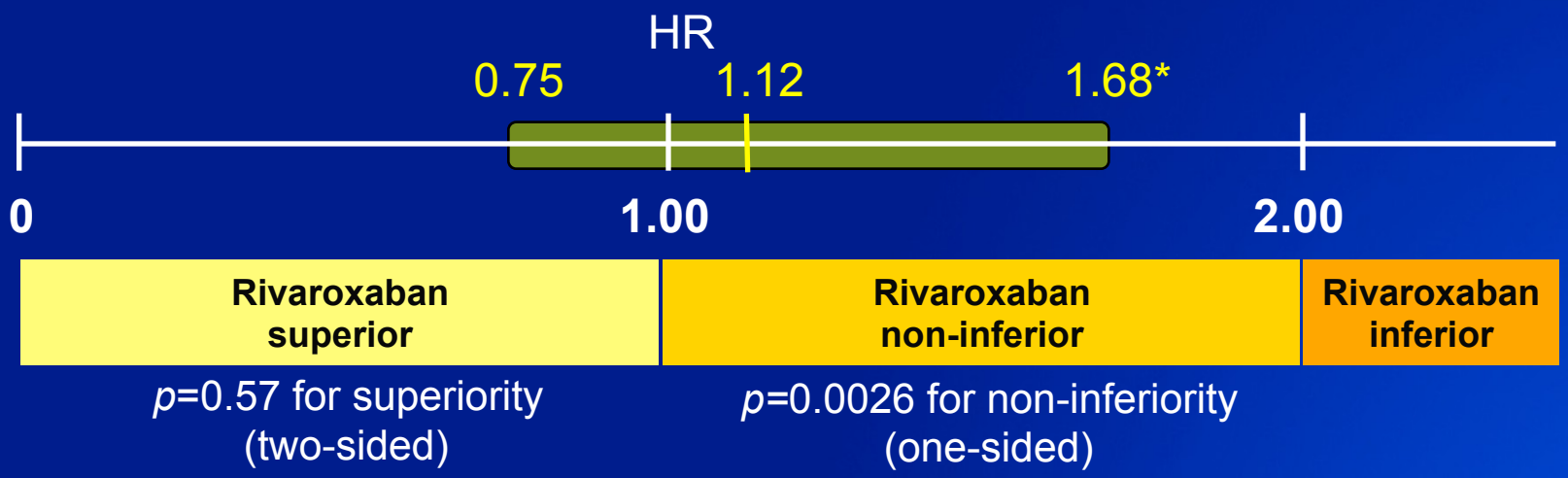


- Primary efficacy outcome: first recurrent VTE
- Principal safety outcome: first major or non-major clinically relevant bleeding

The EINSTEIN–PE Investigators. *N Engl J Med* 2012; DOI: 10.1056/NEJMoa1113572

EINSTEIN PE: primary efficacy outcome analysis

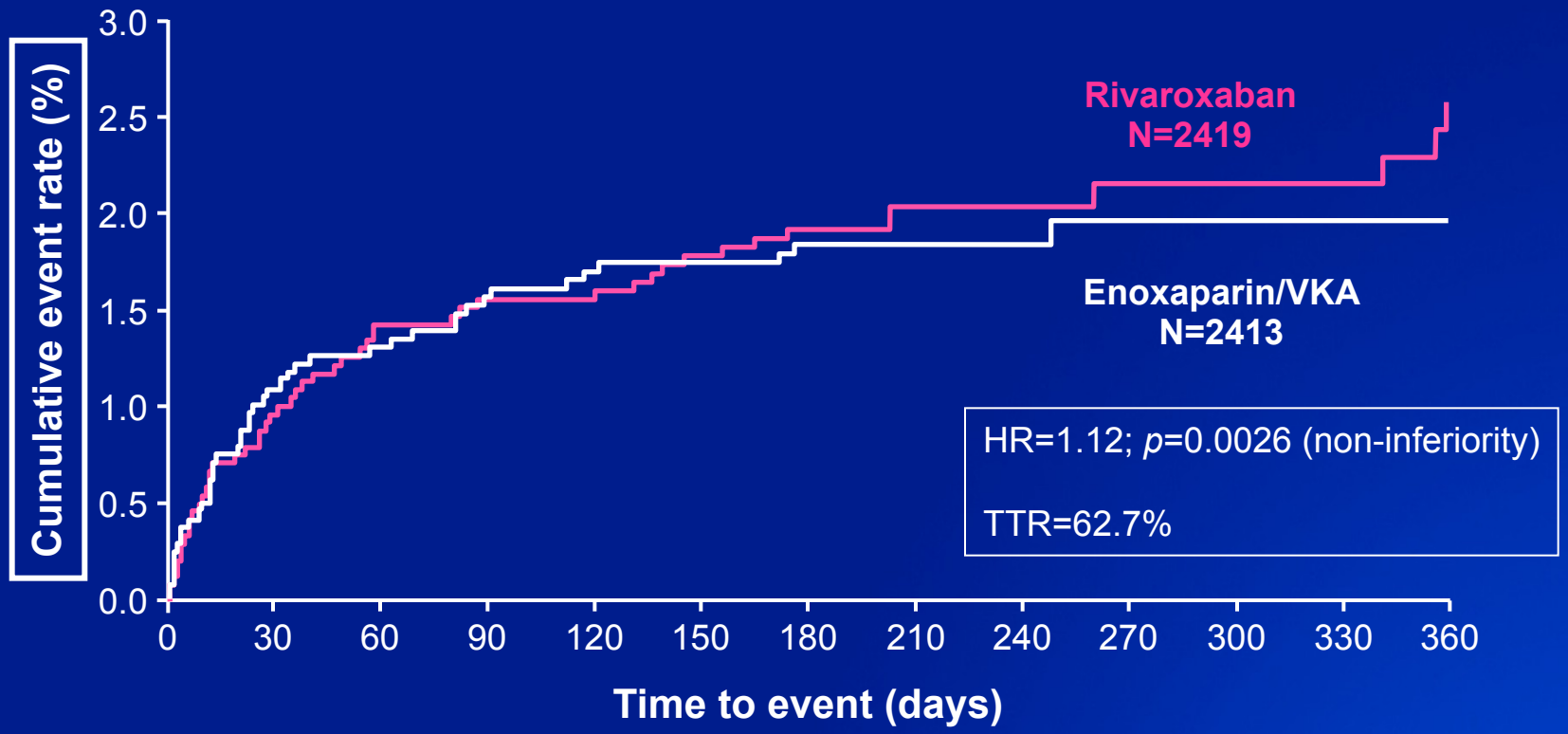
	Rivaroxaban (N=2419)		Enoxaparin/VKA (N=2413)	
	n	(%)	n	(%)
First symptomatic recurrent VTE	**50**	**(2.1)**	**44**	**(1.8)**
Recurrent DVT	18	(0.7)	17	(0.7)
Recurrent DVT + PE	0		2	(<0.1)
Non-fatal PE	22	(0.9)	19	(0.8)
Fatal PE/unexplained death where PE cannot be ruled out	10	(0.4)	6	(0.2)



*Potential relative risk increase <68.4%; absolute risk difference 0.24% (–0.5 to –1.02)

The EINSTEIN–PE Investigators. *N Engl J Med* 2012; DOI: 10.1056/NEJMoa1113572

EINSTEIN PE: primary efficacy outcome: time to first event

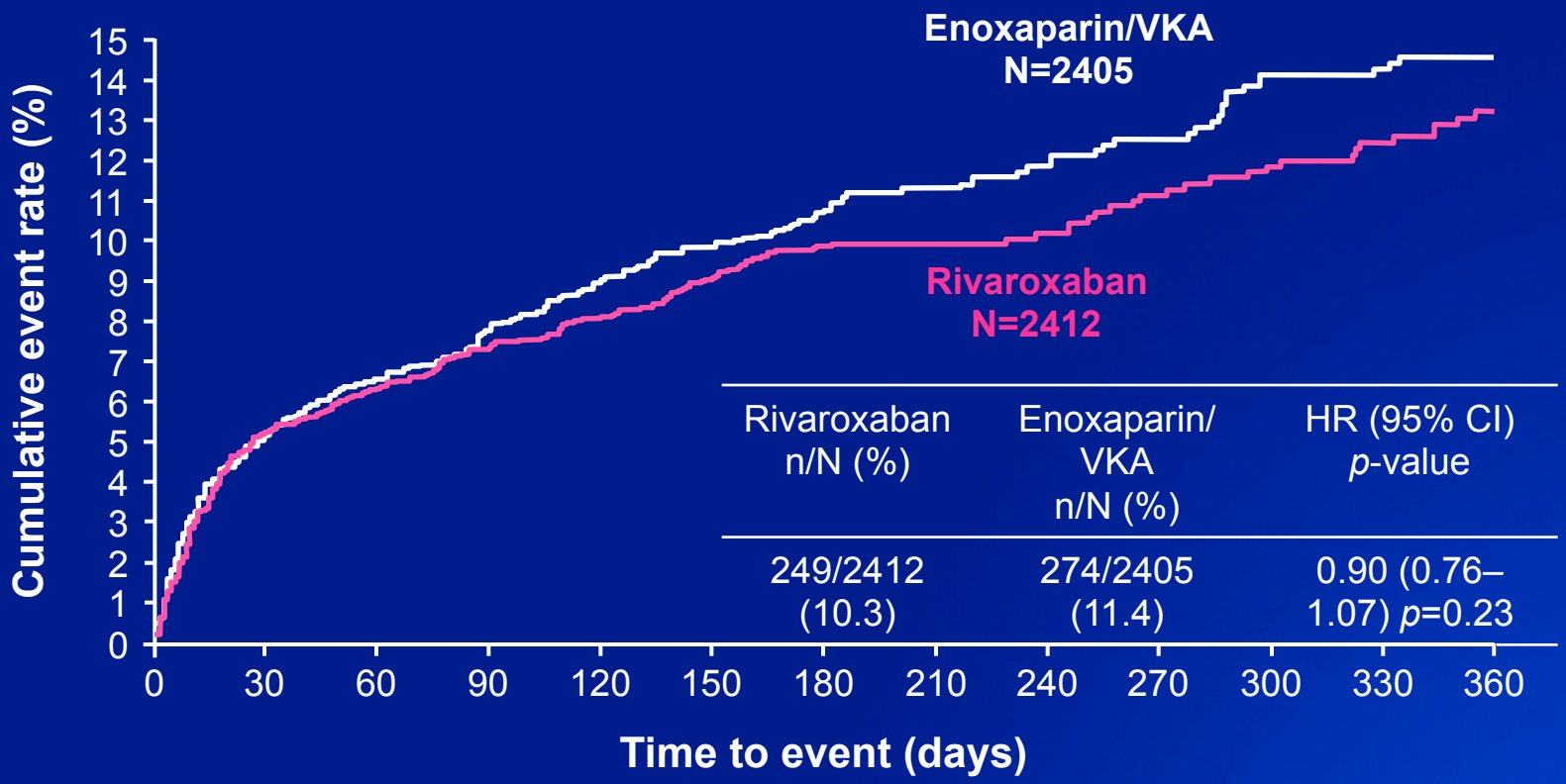


Number of patients at risk													
Rivaroxaban	2419	2350	2321	2303	2180	2167	2063	837	794	785	757	725	672
Enoxaparin/VKA	2413	2316	2295	2274	2155	2146	2050	835	787	772	746	722	675

ITT population

The EINSTEIN–PE Investigators. *N Engl J Med* 2012; DOI: 10.1056/NEJMoa1113572

EINSTEIN PE: principal safety outcome – major or non-major clinically relevant bleeding



Rivaroxaban n/N (%)	Enoxaparin/ VKA n/N (%)	HR (95% CI) *p*-value
249/2412 (10.3)	274/2405 (11.4)	0.90 (0.76–1.07) *p*=0.23

Number of patients at risk

Rivaroxaban	2412	2183	2133	2024	1953	1913	1211	696	671	632	600	588	313
Enoxaparin/VKA	2405	2184	2115	1990	1923	1887	1092	687	660	620	589	574	251

Safety population

EINSTEIN PE: major bleeding

	Rivaroxaban (n=2412)		Enoxaparin/VKA (n=2405)		HR (95% CI) *p*-value
	n	(%)	n	(%)	
Major bleeding*	**26**	**(1.1)**	**52**	**(2.2)**	0.49 (0.31–0.80) *p*=0.0032
Fatal	**2**	**(<0.1)**	**3**	**(0.1)**	
Retroperitoneal	0		1	(<0.1)	
Intracranial	2	(<0.1)	2	(<0.1)	
In a critical site	**7**	**(0.2)**	**26**	**(1.1)**	
Intracranial	1	(<0.1)	10	(0.4)	
Retroperitoneal	1	(<0.1)	7	(0.3)	
Intraocular	2	(<0.1)	2	(<0.1)	
Pericardial	0		2	(<0.1)	
Intra-articular	0		3	(0.1)	
Adrenal gland	1	(<0.1)	0		
Hemothorax	1	(<0.1)	1	(<0.1)	
Abdominal	1		2	(<0.1)	
↓ hb ≥2 g/dl, ≥2 units red cells	**17**	**(0.7)**	**26**	**(1.1)**	

*Some patients had >1 event. Safety population

The EINSTEIN–PE Investigators. *N Engl J Med* 2012; DOI: 10.1056/NEJMoa1113572

Anatomical extent of PE at baseline and recurrent VTE

	Rivaroxaban		Enoxaparin/VKA	
	n/N	(%)	n/N	(%)
Limited (≤25 % of vasculature of a single lobe)	5/309	(1.6)	4/299	(1.3)
Intermediate	35/1392	(2.5)	31/1424	(2.2)
Extensive (multiple lobes and >25% of entire pulmonary vasculature)	10/597	(1.7)	8/576	(1.4)

The EINSTEIN–PE Investigators. *N Engl J Med* 2012; DOI: 10.1056/NEJMoa1113572

Treatment of acute pulmonary embolism with dabigatran or warfarin: a pooled analysis of data from RE-COVER™ and RE-COVER™ II

S Schulman et al.

Presented at the European Society of Cardiology Congress

30 August–3 September 2014

Barcelona, Spain

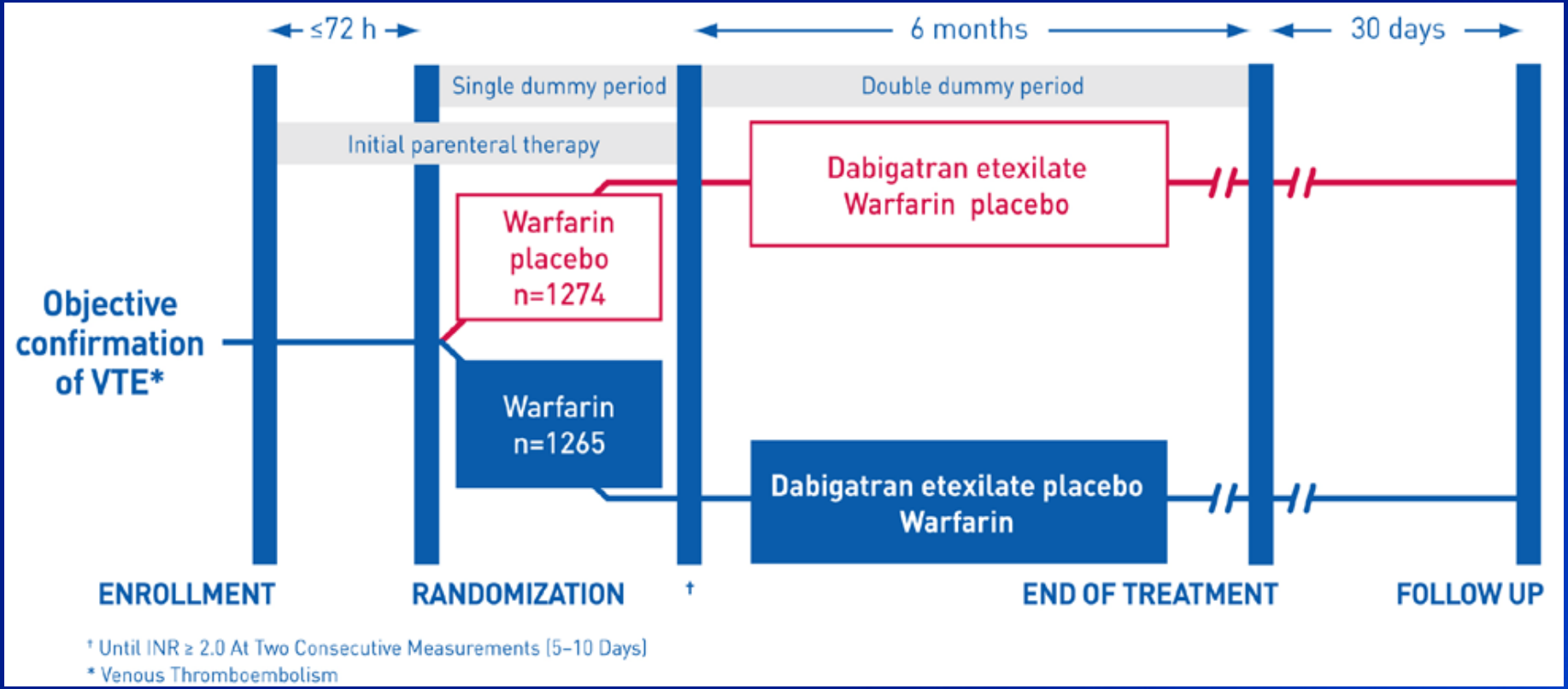
Background

- PE and DVT are distinct, but overlapping, manifestations of VTE[1,2]
- Dabigatran etexilate (dabigatran), an oral direct thrombin inhibitor, was as effective as warfarin for the prevention of VTE recurrence and related deaths, with a lower risk of bleeding, in two Phase III trials (RE-COVER™[3] and RE-COVER™ II[4])
- Prespecified subgroup analysis of pooled data from RE-COVER™[3] and RE-COVER™ II[4] investigated the efficacy and safety of dabigatran versus warfarin according to index event (symptomatic PE with or without DVT, or DVT alone)[5]

DVT = deep vein thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism

1. Murin S et al. Thromb Haemost 2002;88:407–14; **2.** White RH. Circulation 2003;107:14–8;
3. Schulman S et al. N Engl J Med 2009;361:2342–52; **4.** Schulman S et al. Circulation 2014;129:764–72;
5. Schulman S et al. ESC 2014; abstract 5509

RE-COVER
Trial Design



Schulman, N Engl J Med, 2009

RE-COVER™/RE-COVER™ II study design

- Patients:
  - ≥18 years of age
  - Acute, symptomatic, objectively verified proximal DVT of the legs and/or PE
    - Testing for initial symptomatic DVT/PE was performed locally
    - If a patient had more than one event, the last event prior to randomization was classified as the qualifying event
  - Considered appropriate for 6 months of anticoagulant therapy
- Randomized to warfarin or warfarin–placebo plus parenteral anticoagulation for ≥5 days until INR was ≥2.0 at two consecutive measurements
- Parenteral therapy then discontinued and patients continued warfarin (INR 2.0–3.0) or received dabigatran 150 mg BID for 6 months (double-dummy, oral-only treatment period)

BID = twice daily; INR = international normalized ratio

Schulman S et al. ESC 2014; abstract 5509

Study outcomes

- Primary efficacy outcome
  - Recurrent, symptomatic, objectively confirmed VTE or VTE-related death
  - From randomization (i.e. start of parenteral therapy plus warfarin/warfarin–placebo) to the end of the prespecified post-treatment follow-up (i.e. 6 months + 30 days)

- Safety outcomes
  - Major bleeding events (ISTH criteria)
  - Major or clinically relevant non-major bleeding events
  - Any bleeding events
  - All counted from start of double-dummy, oral-only period (treatment with oral dabigatran or warfarin alone) to end of 6-month treatment period
  - All outcomes centrally adjudicated

ISTH = International Society on Thrombosis and Haemostasis

Schulman S et al. ESC 2014; abstract 5509

Statistical analysis

- Hazard ratios and 95% confidence intervals for within-subgroup treatment comparisons and interaction P-values for subgroup and treatment x subgroup interaction were based on the Cox regression analysis model, stratified by study and with treatment as a factor

Schulman S et al. ESC 2014; abstract 5509

Index VTE events

- 31.4% of patients had symptomatic PE as their index event
  - 71% of these had symptomatic PE alone

Qualifying event	Dabigatran (n=2553)	Warfarin (n=2554)	Total (n=5107)
No symptomatic PE, n (%) Symptomatic DVT only Neither symptomatic PE nor symptomatic DVT	1758 (68.9) 1755 (68.7) 3 (0.1)	1747 (68.4) 1744 (68.3) 3 (0.1)	3505 (68.6) 3499 (68.5) 6 (0.1)
Symptomatic PE, n (%) Symptomatic PE and symptomatic DVT Symptomatic PE only	795 (31.1) 226 (8.9) 569 (22.3)	807 (31.6) 240 (9.4) 567 (2.2)	1602 (31.4) 466 (9.1) 1136 (22.2)

Schulman S et al. ESC 2014; abstract 5509

Baseline characteristics (I)

- Generally similar across patients with PE and DVT alone as index event and across treatment groups

	Index event: symptomatic DVT alone		Index event: symptomatic PE	
	Dabigatran (n=1758)	**Warfarin (n=1747)**	**Dabigatran (n=795)**	**Warfarin (n=807)**
Mean age, years (±SD)	54.5 (±15.8)	54.3 (±16.2)	55.6 (±16.3)	55.6 (±16.2)
Male, n (%)	1100 (62.6)	1090 (62.4)	420 (52.8)	431 (53.4)
Race, n (%) White Black Asian	1536 (87.4) 30 (1.7) 192 (10.9)	1504 (86.1) 32 (1.8) 211 (12.1)	670 (84.3) 24 (3.0) 100 (12.6)	689 (85.4) 19 (2.4) 99 (12.3)
Mean weight, kg (±SD)	83.7 (±18.9)	83.1 (±18.8)	85.8 (±20.5)	84.7 (±19.4)
Mean BMI, kg/m^2 (±SD)	28.4 (±5.4)	28.2 (±5.4)	29.1 (±6.2)	28.8 (±6.1)
Mean creatinine clearance, mL/min (±SD)	106.8 (±41.9)	105.6 (±38.8)	107.5 (±43.0)	106.2 (±44.0)

BMI = body mass index; SD = standard deviation

Schulman S et al. ESC 2014; abstract 5509

Baseline characteristics (II)

	Index event: symptomatic DVT alone		Index event: symptomatic PE	
	Dabigatran (n=1758)	Warfarin (n=1747)	Dabigatran (n=795)	Warfarin (n=807)
Concomitant therapy, n (%)				
CV medication	907 (51.6)	891 (51.0)	433 (54.5)	447 (55.4)
≥1 antithrombotic, anticoagulant, or NSAID*	532 (30.3)	484 (27.7)	239 (30.1)	213 (26.4)
Risk factors for VTE recurrence at baseline, n (%)				
Active cancer at baseline or during study	121 (6.9)	119 (6.8)	52 (6.5)	43 (5.3)
Previous VTE	392 (22.3)	351 (20.1)	183 (23.0)	173 (21.4)
Thrombophilia†	125 (7.1)	124 (7.1)	84 (10.6)	75 (9.3)
Recent prolonged immobilization	231 (13.1)	254 (14.5)	135 (17.0)	127 (15.7)
Current smoker	409 (23.3)	409 (23.4)	140 (17.6)	144 (17.8)

*Included NSAIDs, acetylsalicylic acid, platelet inhibitors other than acetylsalicylic acid, and other antithrombotic agents

†More than half of patients were not tested for thrombophilia: no index PE, dabigatran 1221 (69.5%), warfarin 1198 (68.6%); with index PE, dabigatran 455 (57.2%), warfarin 487 (60.3%)

CV = cardiovascular; NSAID = non-steroidal anti-inflammatory

Schulman S et al. ESC 2014; abstract 5509

Efficacy outcomes

- No significant interactions, indicating similar treatment effects of dabigatran vs warfarin regardless of index event

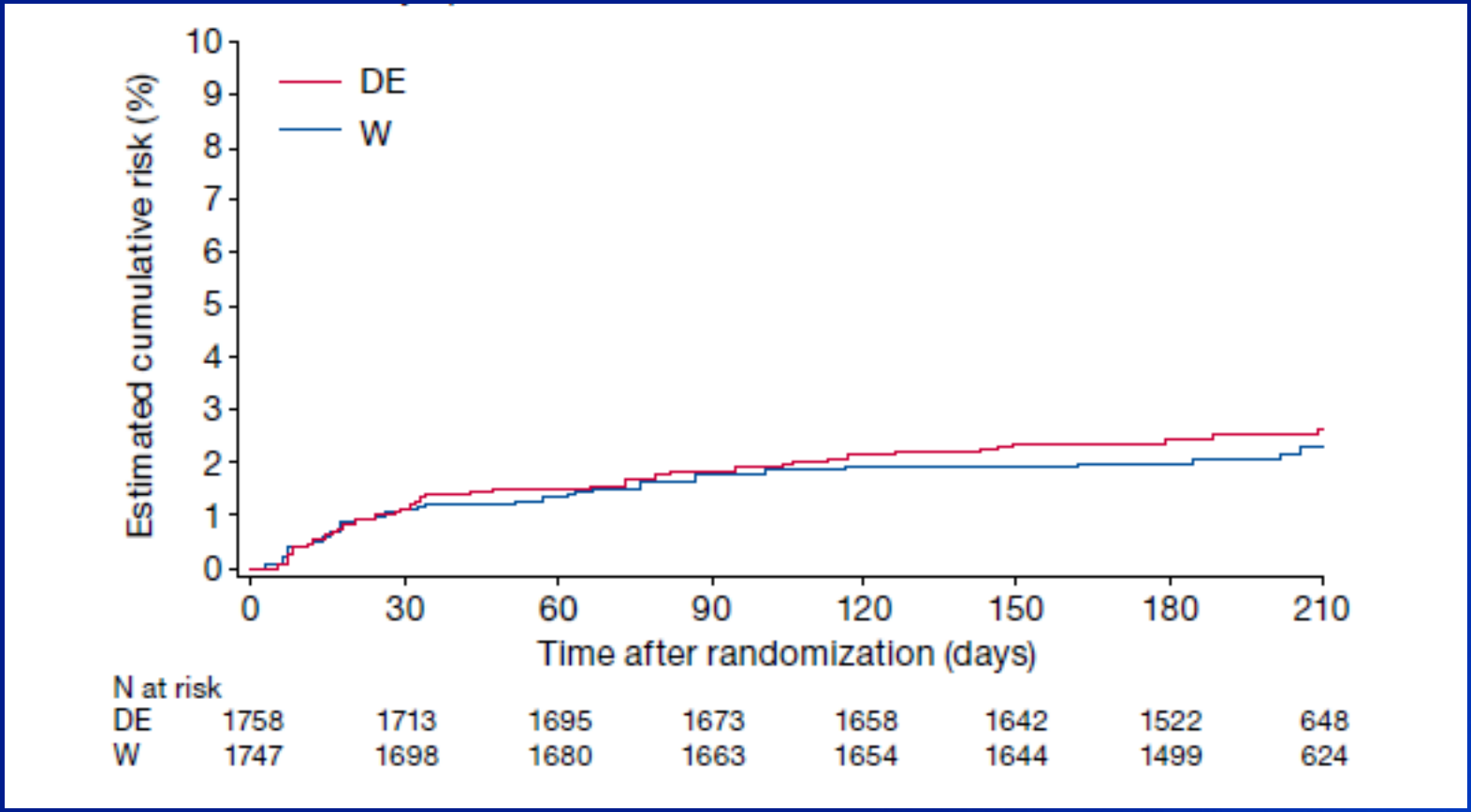
	PE as index event	Events, % (n/N)		HR (95% CI)	P-value (interaction)
		Dabigatran	Warfarin		
VTE/VTE-related death	No Yes	2.6 (45/1758) 2.9 (23/795)	2.1 (37/1747) 3.1 (25/807)	1.20 (0.78–1.86) 0.93 (0.53–1.64)	0.48
VTE-related death	No Yes	0 (0/1758) 0.3 (2/795)	0 (0/1747) 0.4 (3/807)	– 0.67 (0.11–4.03)	0.99
Non-fatal PE	No Yes	0.5 (9/1758) 1.8 (14/795)	0.5 (8/1747) 1.6 (13/807)	1.10 (0.42–2.85) 1.09 (0.51–2.32)	0.98
DVT	No Yes	2.0 (36/1758) 0.9 (7/795)	1.7 (29/1747) 1.1 (9/807)	1.23 (0.75–2.01) 0.79 (0.29–2.11)	0.43

Until the end of the post-treatment period; First occurrence of primary efficacy endpoint

CI = confidence interval; HR = hazard ratio

Schulman S et al. ESC 2014; abstract 5509

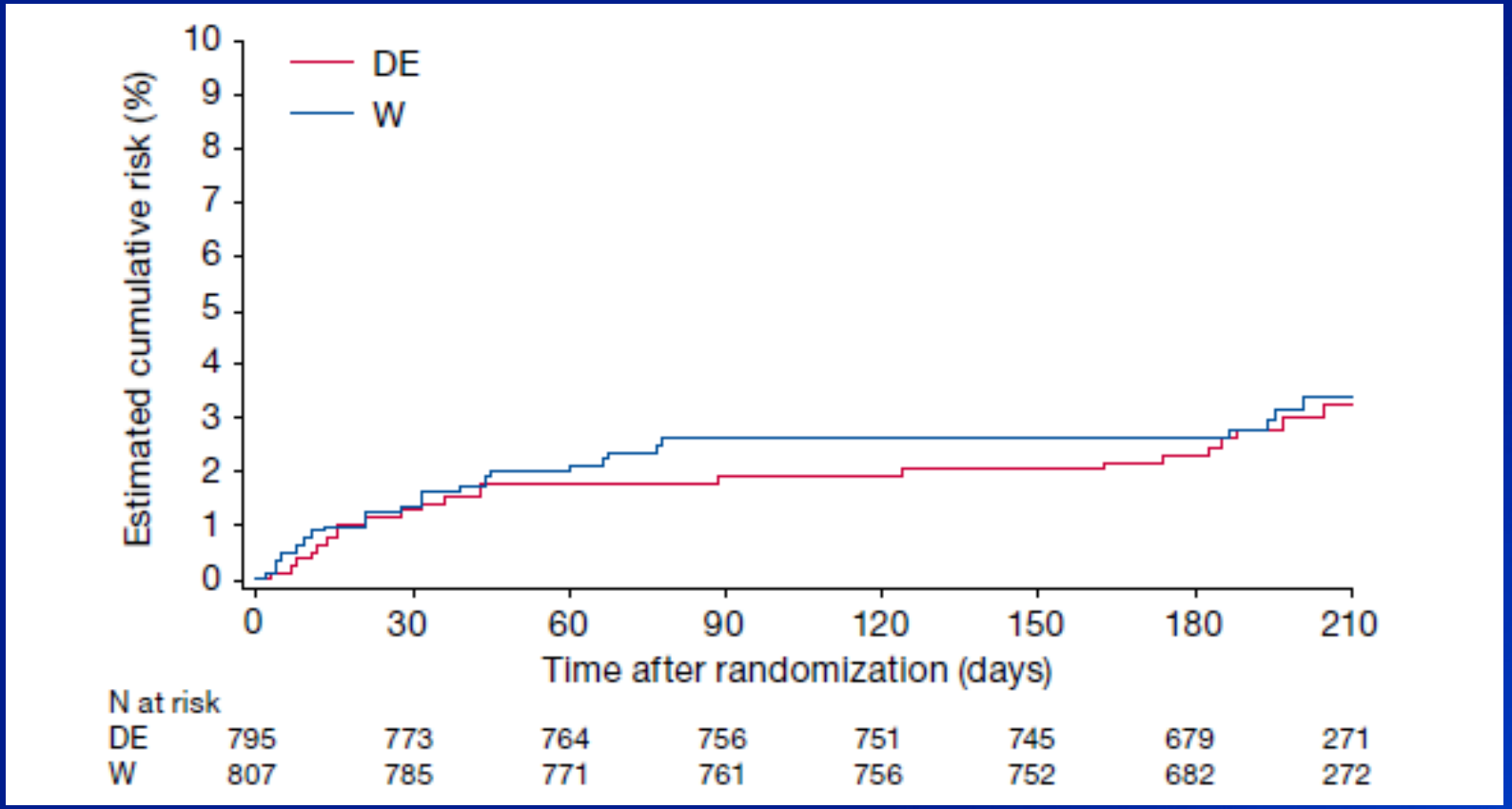
Cumulative event rates for VTE and VTE-related deaths with dabigatran and warfarin: symptomatic DVT alone at baseline



DE = dabigatran etexilate; W = warfarin

Schulman S et al. ESC 2014; abstract 5509

Cumulative event rates for VTE and VTE-related deaths with dabigatran and warfarin: symptomatic PE at baseline



Schulman S et al. ESC 2014; abstract 5509

Safety outcomes

- No significant interactions, indicating similar treatment effects of dabigatran vs warfarin regardless of index event
- Fewer major bleeds with dabigatran vs warfarin (non-significant)
- Significantly fewer major/clinically relevant non-major bleeds and any bleeds with dabigatran vs warfarin

	PE as index event	Events, % (n/N)		HR (95% CI)	P-value (interaction)
		Dabigatran	Warfarin		
Major bleeding events	No Yes	1.2 (20/1697) 0.5 (4/759)	1.9 (32/1694) 1.0 (8/768)	0.62 (0.35–1.08) 0.50 (0.15–1.67)	0.76
Major or clinically relevant non-major bleeding events	No Yes	4.3 (73/1697) 4.7 (36/759)	7.9 (134/1694) 7.2 (55/768)	0.53 (0.40–0.70) 0.65 (0.43–0.99)	0.42
Any bleeding events	No Yes	13.6 (230/1697) 16.3 (124/759)	19.4 (328/1694) 22.8 (175/768)	0.67 (0.57–0.80) 0.68 (0.54–0.85)	0.96

During the double-dummy period

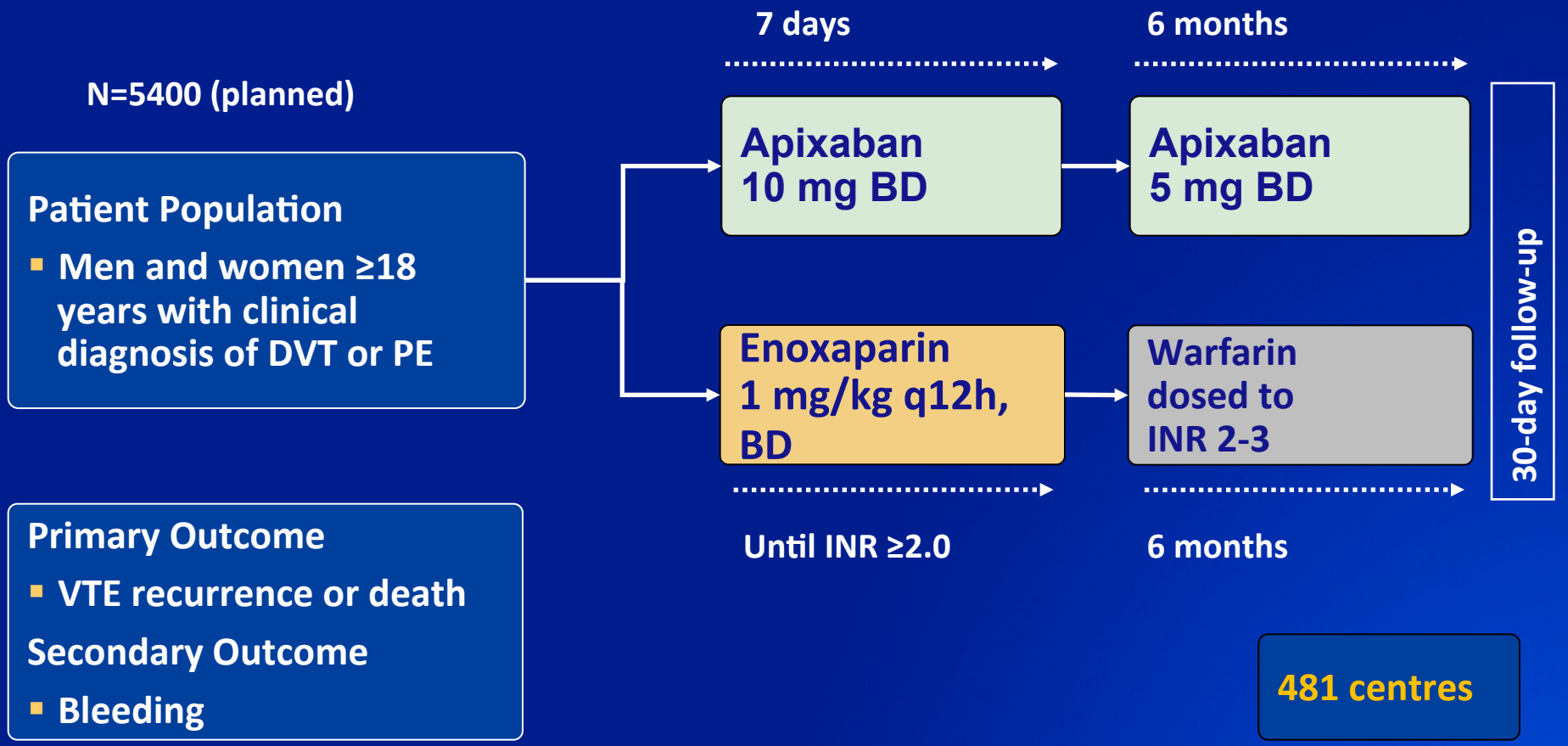
Schulman S et al. ESC 2014; abstract 5509

Conclusions

- Data support the use of dabigatran as a fixed-dose oral treatment for PE, as well as for DVT, following initial parenteral anticoagulation
- Incidence of recurrent PE was greater in patients with PE than in those with proximal DVT alone as their index event, irrespective of treatment allocation
- However, dabigatran was as effective as warfarin at preventing recurrent PE or DVT, with a lower risk of bleeding, regardless of whether patients initially presented with PE or with DVT alone

Schulman S et al. ESC 2014; abstract 5509

AMPLIFY: Efficacy and safety of apixaban for the treatment of DVT or PE

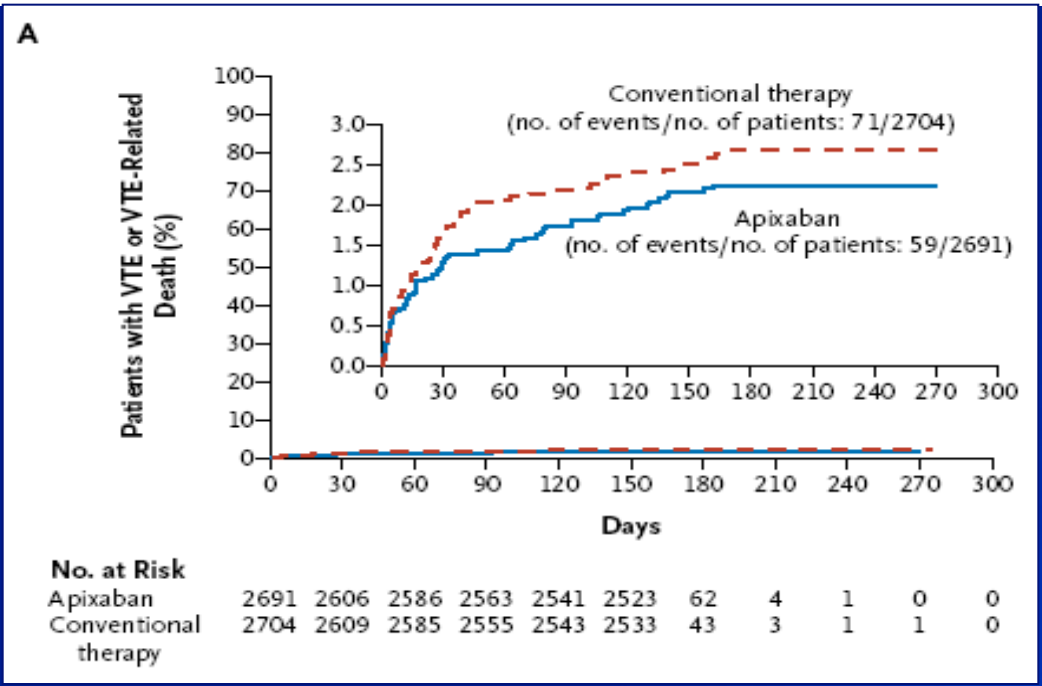


Agnelli, *NEJM*, 2013

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 29, 2013 VOL. 369 NO. 9

Oral Apixaban for the Treatment of Acute Venous Thromboembolism



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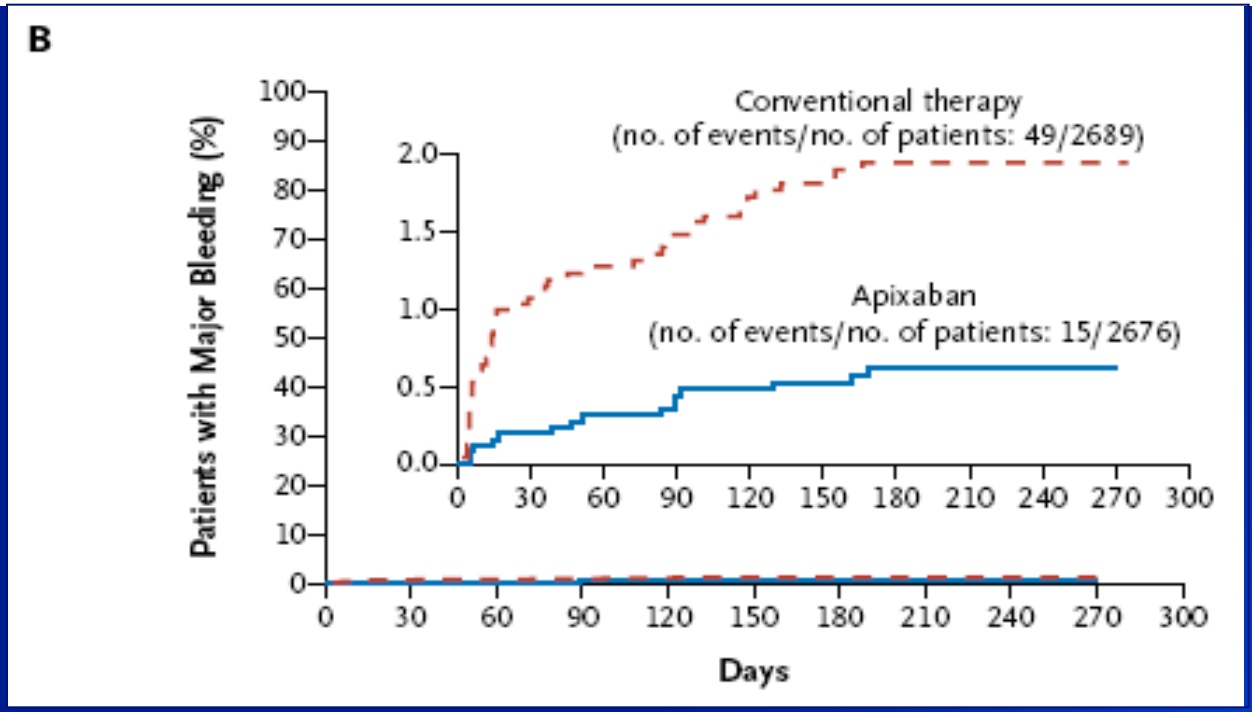


Agnelli, *NEJM*, 2013

Hokusai-VTE: study design

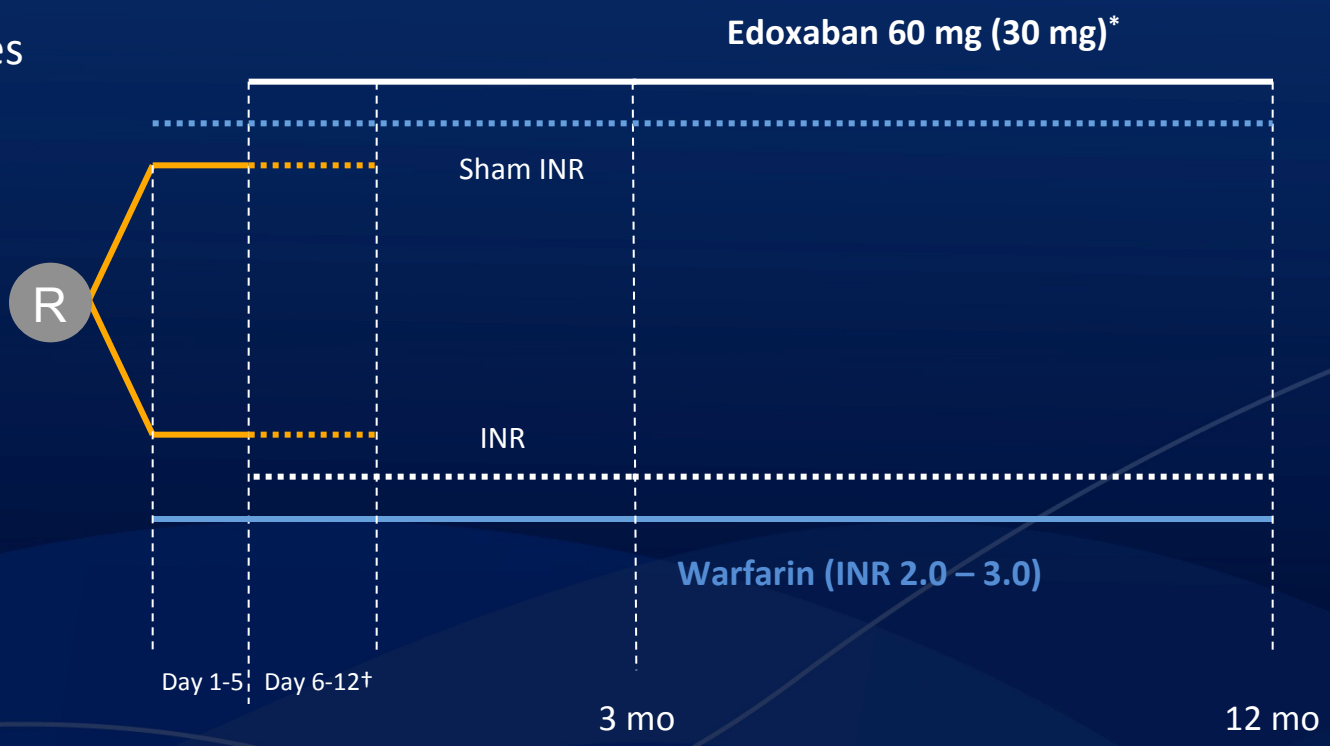
Randomized, double-blind, event-driven study

N=8,292
439 sites in 37 countries

Objectively confirmed VTE

Stratified randomization:
- DVT / PE
- Dose of edoxaban
- Risk factors

All patients followed for 12-months regardless of treatment duration



Edoxaban
Placebo Edoxaban
Warfarin
Placebo Warfarin
Low-molecular-weight heparin / UFH

*Dose was halved to 30 mg in patients perceived to be at higher risk for bleeding due to potential overanticoagulation by predefined criteria

†During days 6-12 edoxaban or placebo edoxaban was started once heparin was stopped

Raskob et al. J Thromb Haemost 2013;11:1287–1294
The Hokusai-VTE Investigators. N Engl J Med 2013

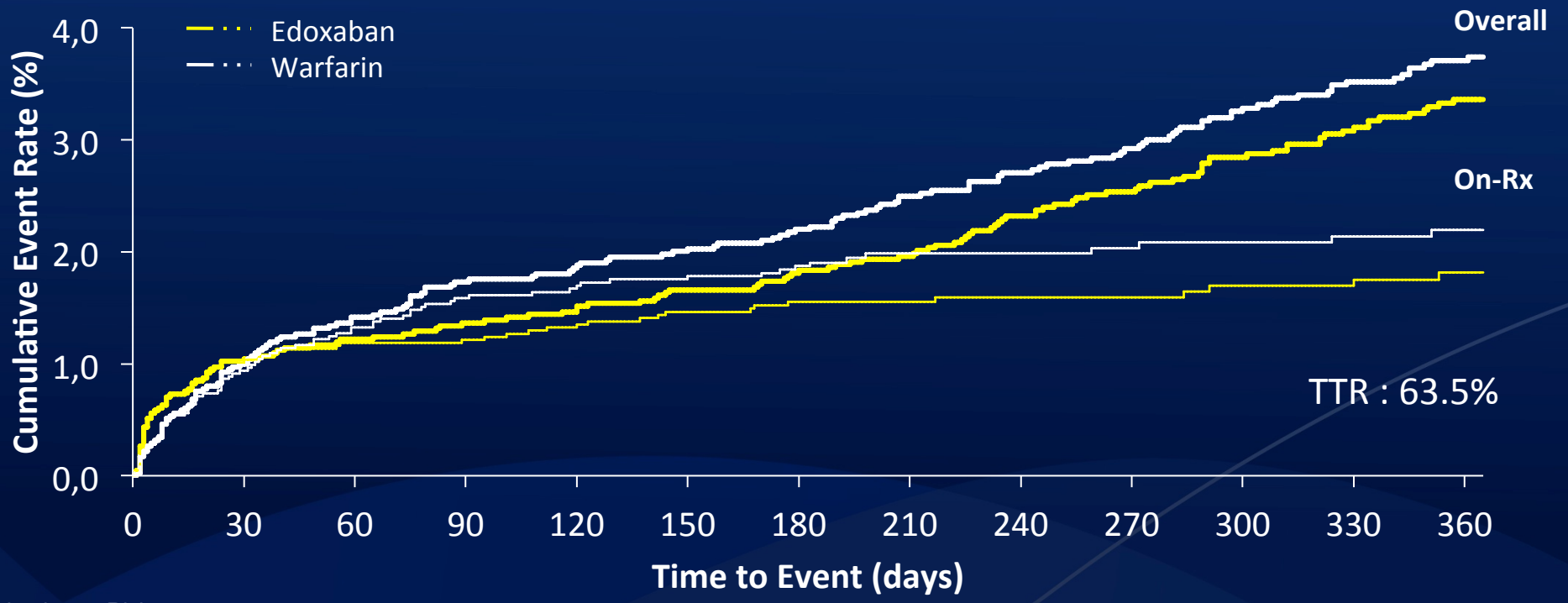
Primary efficacy outcome (recurrent VTE)

Outcome	Edoxaban (N=4118)	Warfarin (N=4122)	Relative risk (95% CI)
All patients, n (%)			
Overall study period	130 (3.2)	146 (3.5)	0.89 (0.70–1.13)*
On-treatment period	66 (1.6)	80 (1.9)	0.82 (0.60–1.14)*
Patients with index DVT, n (%)	2468 (59.9)	2453 (59.5)	
Overall study period	83 (3.4)	81 (3.3)	1.02 (0.75–1.38)
On-treatment period	48 (2.0)	50 (2.0)	0.96 (0.64–1.42)
Patients with index PE, n (%)	1650 (40.1)	1669 (40.5)	
Overall study period	47 (2.8)	65 (3.9)	0.73 (0.50–1.06)
On-treatment period	18 (1.1)	30 (1.8)	0.60 (0.34–1.08)

*P<0.001 for non-inferiority

The Hokusai-VTE Investigators. N Engl J Med 2013

Kaplan-Meier curves of efficacy outcomes – overall analysis



Number at Risk:

Edoxaban Overall	4118	4050	4024	4002	3985	3974	3959	3885	3692	3524	3358
3190	2918										
Warfarin Overall	4122	4055	4023	4001	3992	3975	3962	3864	3683	3519	3367
3184	2936										
Edoxaban On-tx	4118	3892	3793	3724	3539	3478	3200	2320	2169	2029	1890
1769	1308										
Warfarin On-tx	4122	3893	3791	3703	3499	3423	3170	2305	2140	2015	1880
1740	1306										

The Hokusai-VTE Investigators, N Engl J Med, 2013

Efficacy outcomes
Subgroup analysis: 30 mg[#]

Characteristic	Edoxaban (N=733)	Warfarin (N=719)	Relative risk (95% CI)
Efficacy			
Recurrent VTE	22 (3.0)	30 (4.2)	0.73 (0.42–1.26)

[#]At randomization and for overall (12-month) treatment period regardless of treatment duration

The Hokusai-VTE Investigators. N Engl J Med 2013

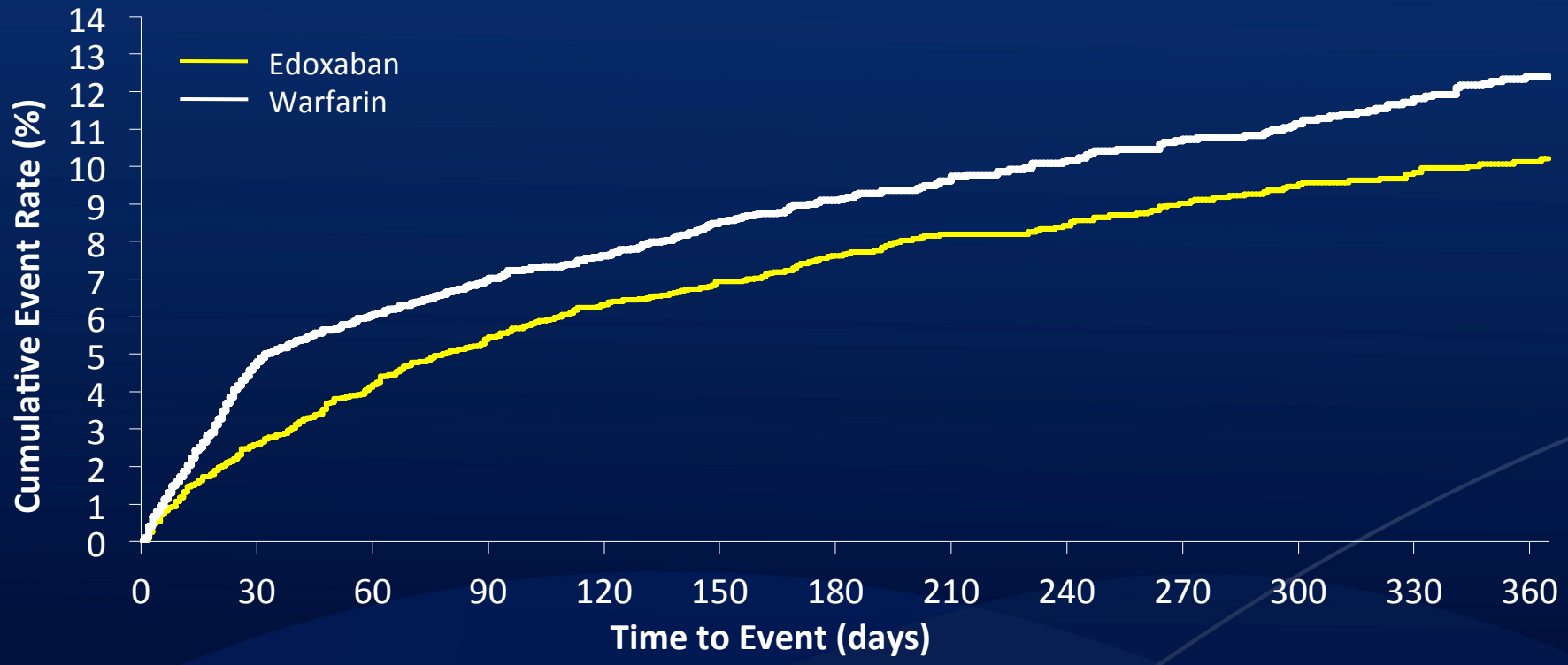
Principal safety outcomes

Outcome	Edoxaban (N=4118)	Warfarin (N=4122)	Relative risk (95% CI)
First major or clinically relevant non-major bleeding, n (%)	349 (8.5)	423 (10.3)	0.81 (0.71–0.94)*
Major bleeding, n (%)	56 (1.4)	66 (1.6)	0.84 (0.59–1.21)#
Fatal	2 (<0.1)	10 (0.2)	
Non-fatal in critical sites	13 (0.3)	25 (0.6)	
Non-fatal in non-critical sites	41 (1.0)	33 (0.8)	
Clinically relevant non-major bleeding, n (%)	298 (7.2)	368 (8.9)	0.80 (0.68–0.93)*
Any bleeding, n (%)	895 (21.7)	1056 (25.6)	0.82 (0.75–0.90)†

*P=0.004, #P=0.35, †P<0.001 for superiority

The Hokusai-VTE Investigators. N Engl J Med 2013

Kaplan-Meier curves of principal safety outcome



Number of patients at risk													
warfarin	4122	3757	3627	3522	3313	3218	2979	2165	2007	1883	1754	1613	1212
edoxaban	4118	3840	3695	3587	3382	3308	3038	2192	2043	1904	1767	1650	1241

The Hokusai-VTE Investigators. N Engl J Med 2013

Safety outcomes
Subgroup analysis: 30 mg

Characteristic	Edoxaban (N=733)	Warfarin (N=719)	Relative risk (95% CI)
Safety			
Primary: First major or clinically relevant non-major bleeding, n (%)	58 (7.9)	92 (12.8)	0.62 (0.44–0.86)
Major bleeding, n (%)	11 (1.5)	22 (3.1)	0.50 (0.24–1.03)
Clinically relevant non-major bleeding, n (%)	47 (6.4)	70 (9.7)	

The Hokusai-VTE Investigators. N Engl J Med 2013

Subgroup of patients with pulmonary embolism

Subgroup analysis in Hokusai-VTE

- Approximately 90% of PE patients had a baseline NT-proBNP level measured
- In PE patients with NT-proBNP levels ≥500 pg/mL recurrent VTE occurred in 15 of 454 patients (3.3%) who received edoxaban and in 30 of 484 patients (6.2%) given warfarin (HR 0.52 [0.28-0.98])

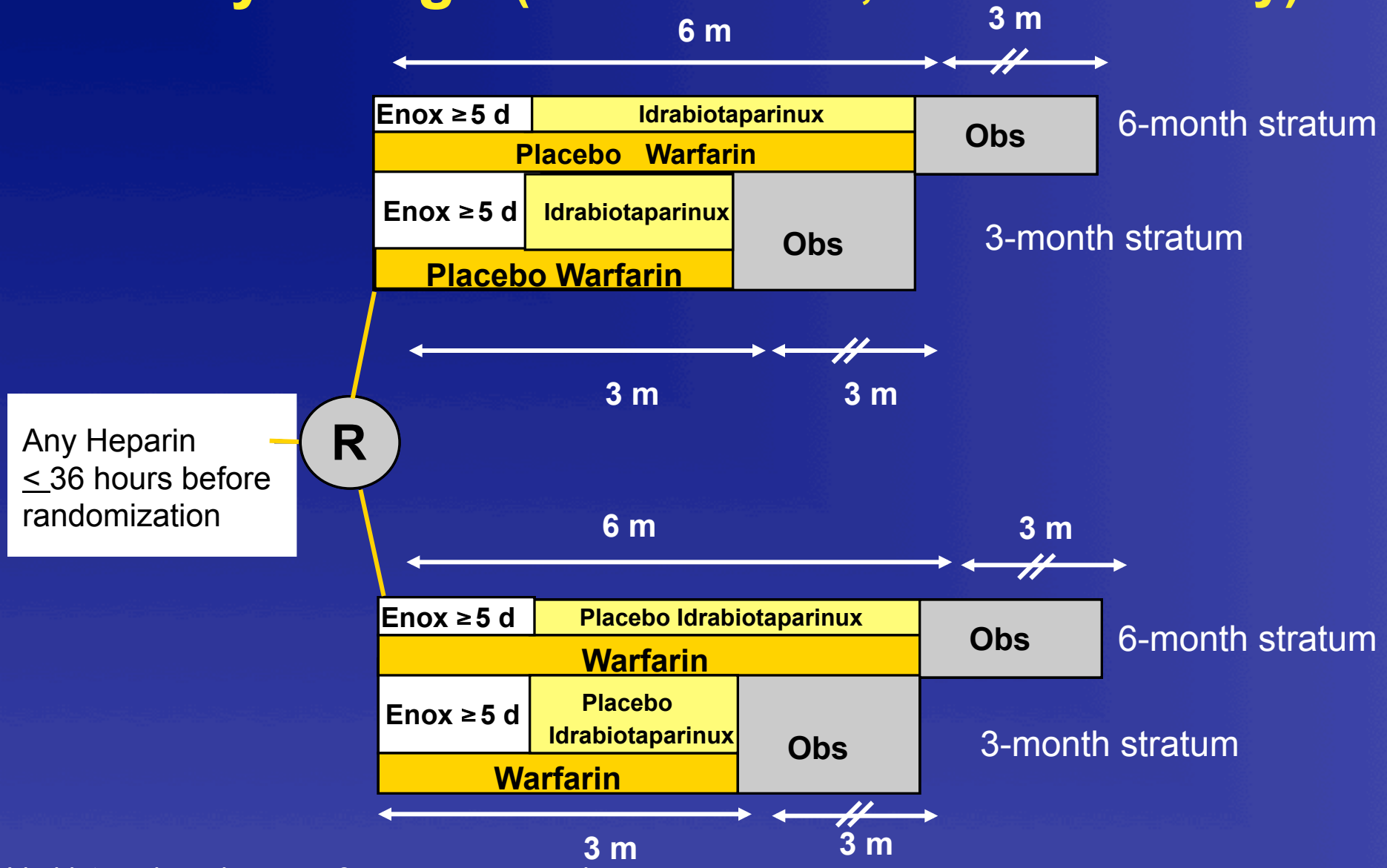
- Of the 1002 random sample of patients measured by CT, approximately 35% had RV dysfunction
- Similar results were observed in patients with RV dysfunction on CT as in those with NT-proBNP levels ≥500 pg/mL (HR 0.42 [0.15-1.20])

The Hokusai-VTE Investigators. N Engl J Med 2013

Clinical study Assessing SSR126517E Injections Once-weekly in Pulmonary Embolism therapeutic Approach

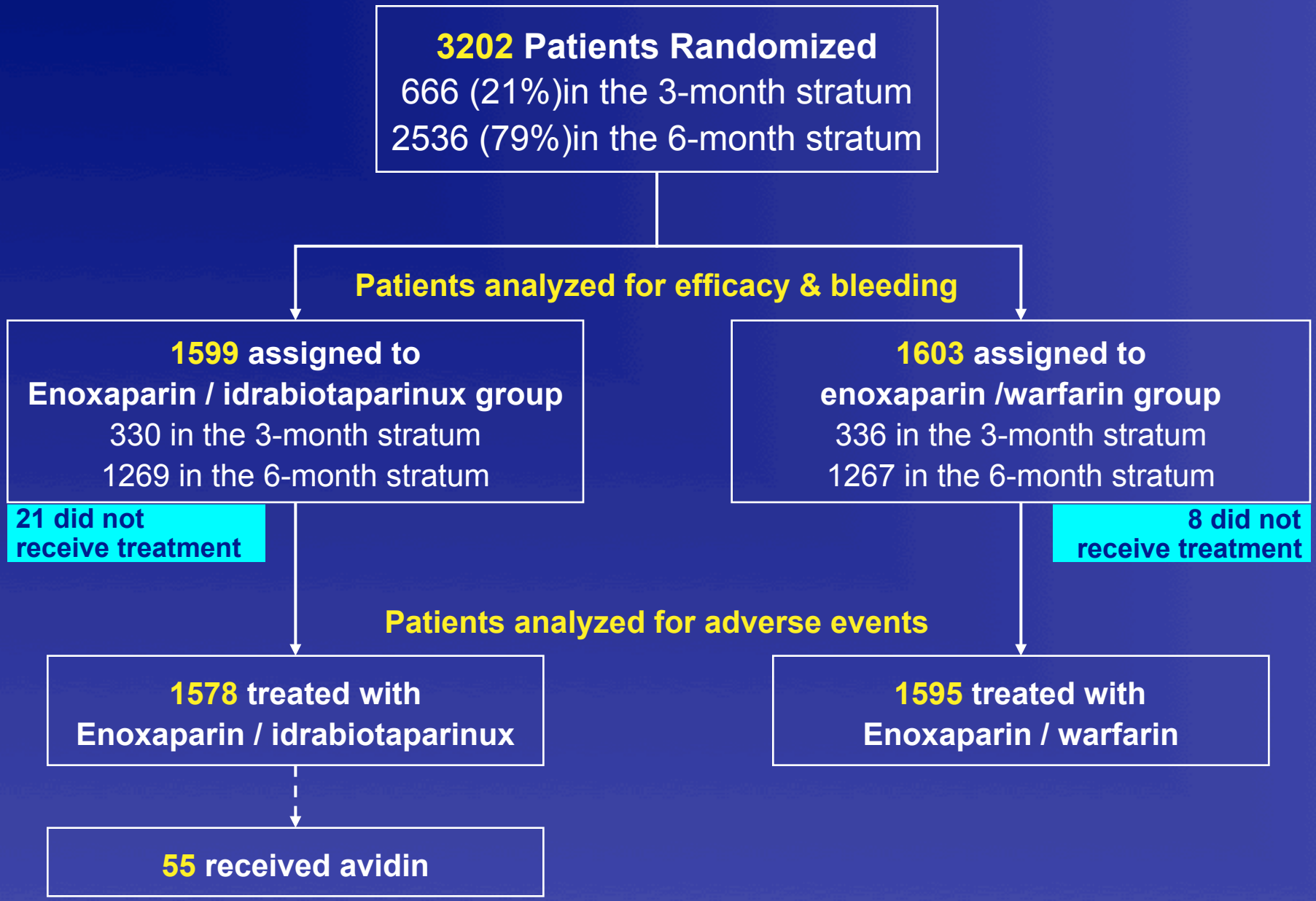
On behalf of the CASSIOPEA Investigators

Study Design (double blind, double dummy)



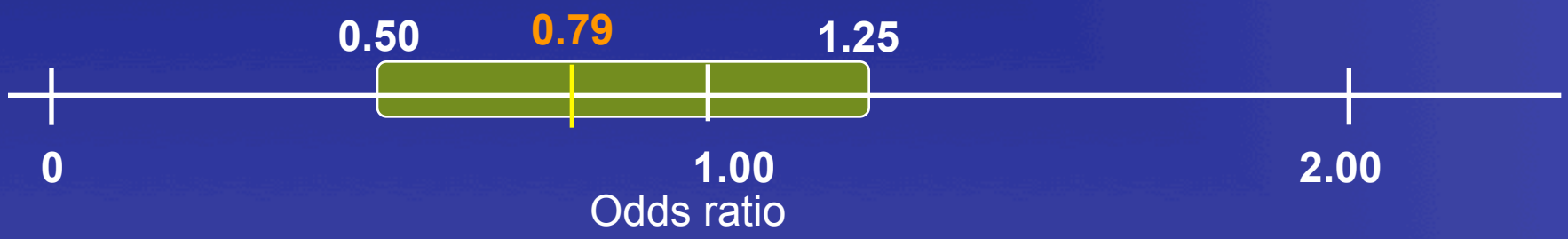
Idrabiotaparinux dose was 3 mg sc once a week
Patients with severe renal insufficiency : one dose of 3 mg and then 1.8 mg sc once a week

Patient flow



Primary efficacy outcome analysis
Randomized population (3 months – both strata)

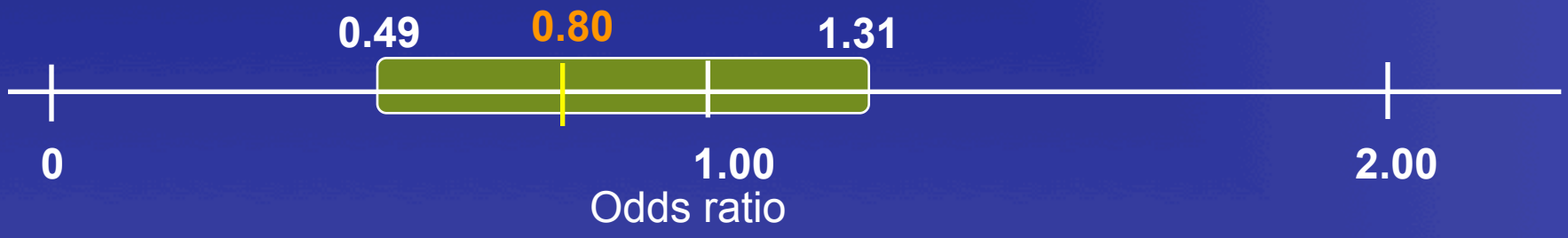
	Idrabiotaparinux (n=1,599)		Warfarin (n=1,603)	
	n	(%)	n	(%)
First symptomatic recurrent VTE	34	(2.1)	43	(2.7)
Recurrent DVT	5	(0.3)	18	(1.1)
Non-fatal PE	13	(0.8)	9	(0.6)
Fatal PE/unexplained death where PE cannot be ruled out	16	(1.0)	16	(1.0)



p<0.0001 for non-inferiority

Secondary efficacy outcome analysis
Randomized population (6 months stratum)

	Idrabiotaparinux (n=1,269)		Warfarin (n=1,267)	
	n	(%)	n	(%)
First symptomatic recurrent VTE	29	(2.3)	36	(2.8)
Recurrent DVT	7	(0.6)	17	(1.3)
Non-fatal PE	9	(0.7)	10	(0.8)
Fatal PE/unexplained death where PE cannot be ruled out	13	(1.0)	9	(0.7)

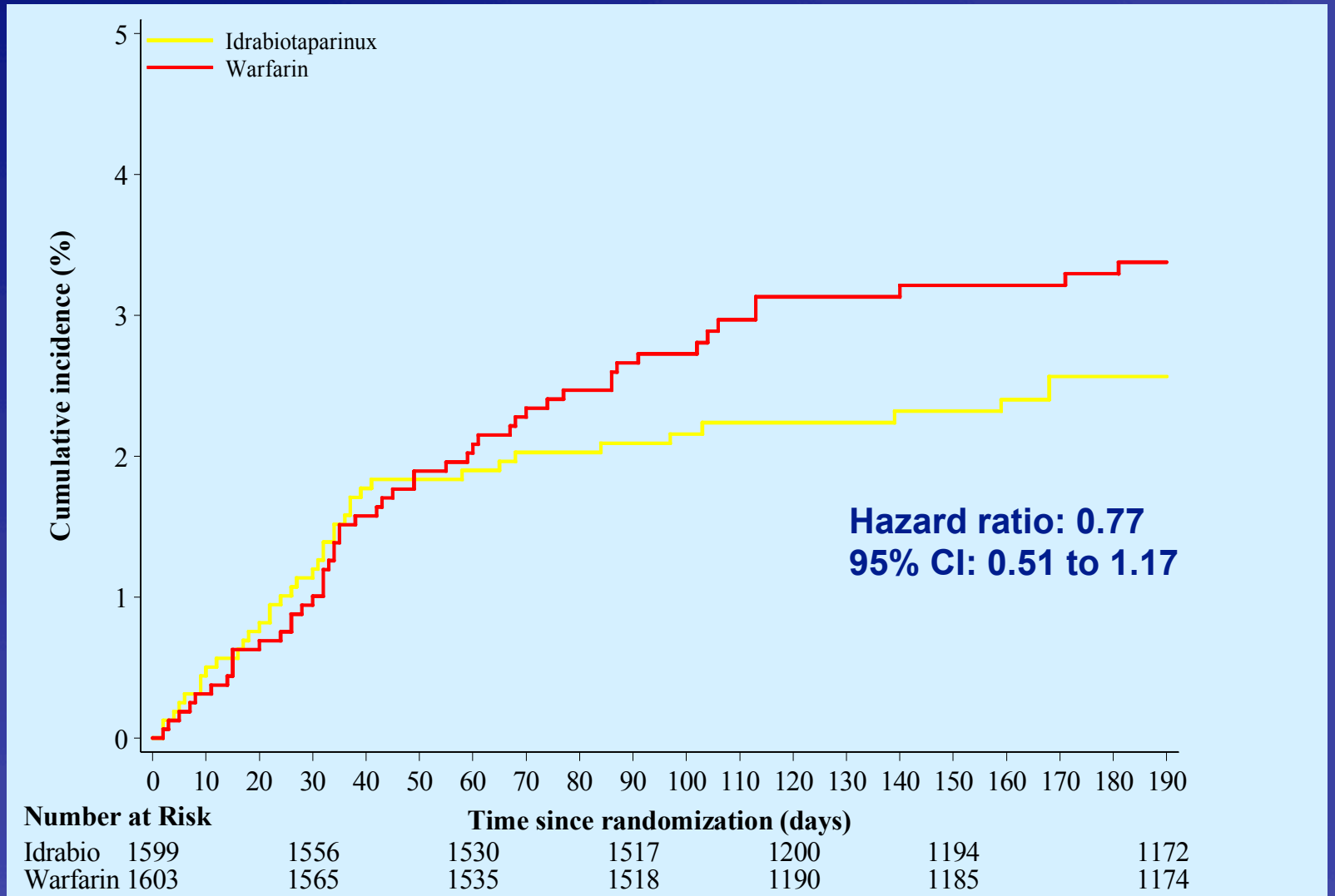


Idrabiotaparinux superior	Idrabiotaparinux non-inferior	Idrabiotaparinux inferior

p<0.0001 for non-inferiority

Efficacy results

Kaplan-Meier cumulative incidence of PE/DVT (fatal or not) in the combined 3-month and 6-month period - Randomized population



Primary safety outcome analysis
Randomized population (3 months – both strata)

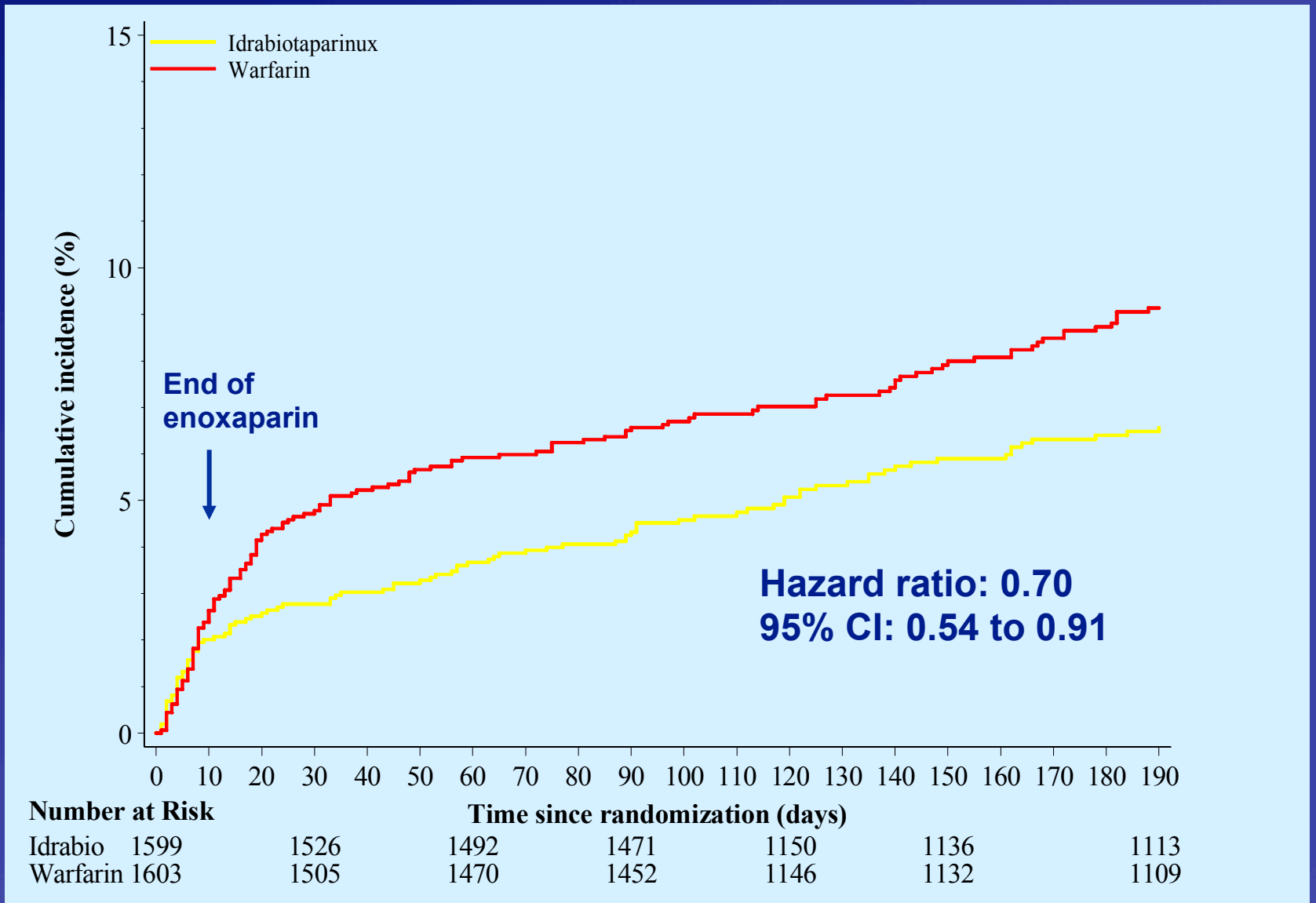
	Idrabiotaparinux (n=1,599)		Warfarin (n=1,603)	
	n	(%)	n	(%)
Clinically relevant bleedings				
Patients with event	72	(4.5)	106	(6.6)

Idrabiotaparinux superior	Idrabiotaparinux inferior

P=0.0098 for superiority (two-sided)

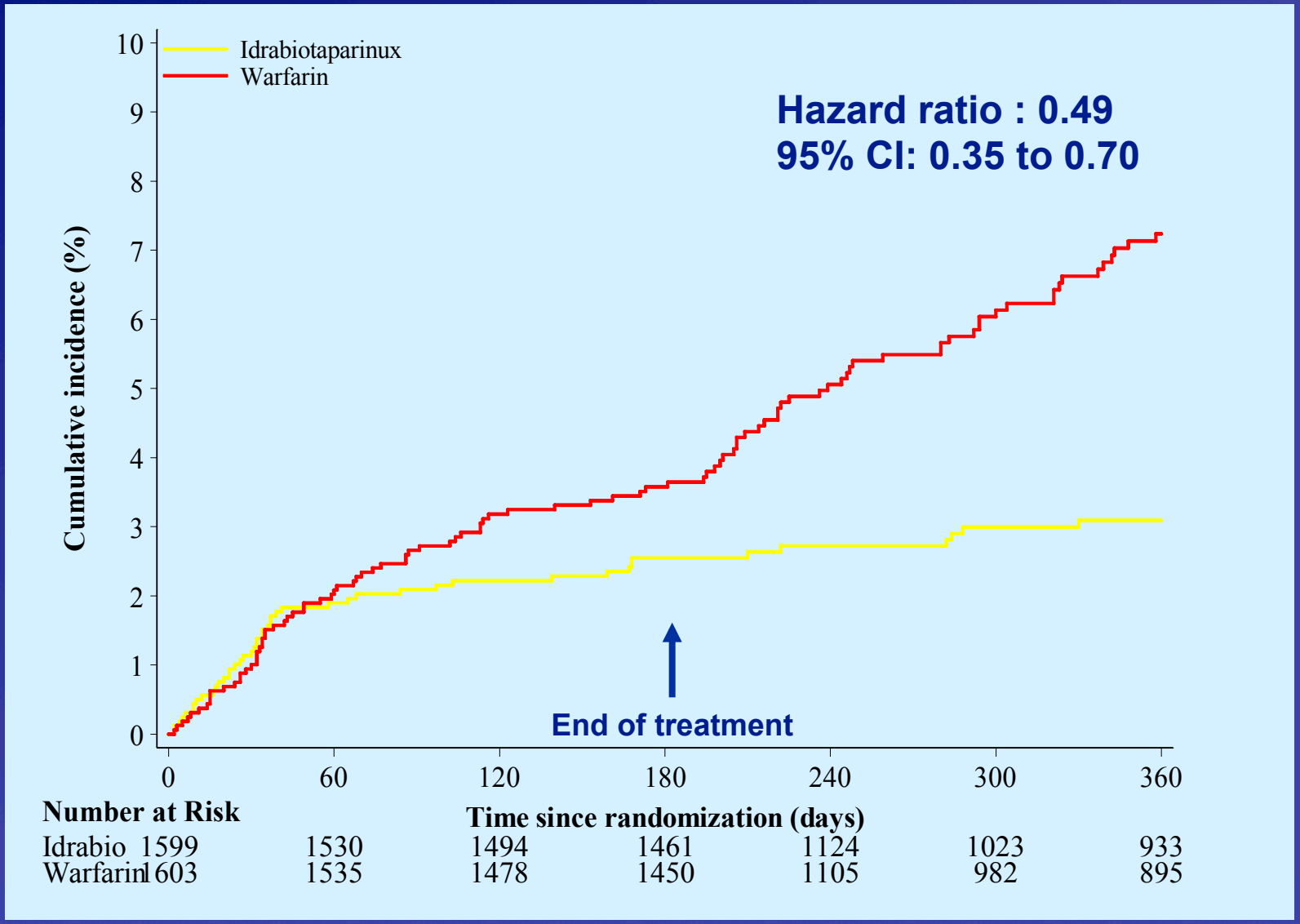
Bleeding results

Kaplan-Meier cumulative incidence of clinically relevant bleeding in the combined 3-month and 6-month period - Randomized population



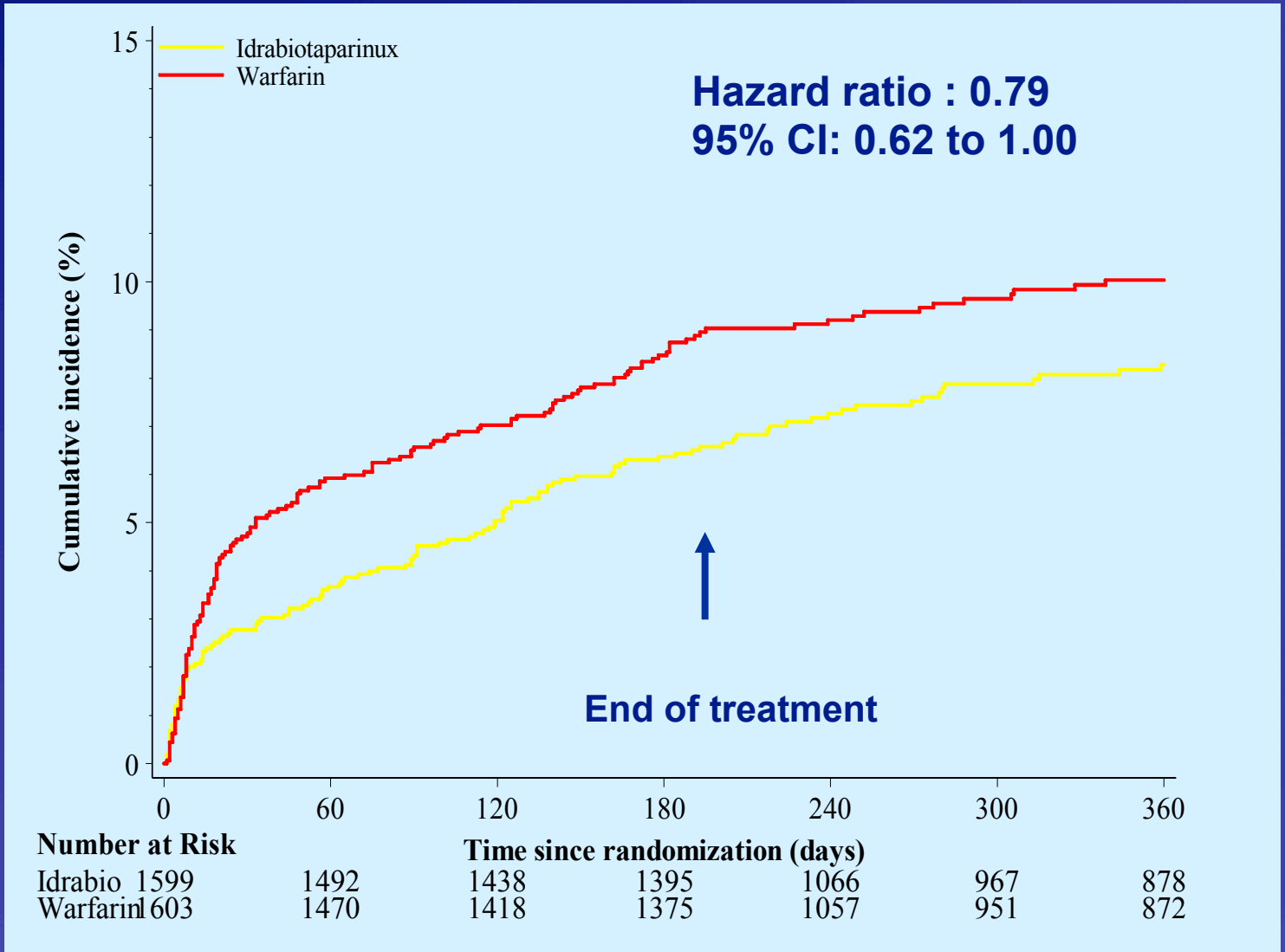
Efficacy results

Kaplan-Meier cumulative incidence of PE/DVT (fatal or not) up to the end of study - Randomized population



Bleeding results

Kaplan-Meier cumulative incidence of clinically relevant bleeding up to the end of study - Randomized population



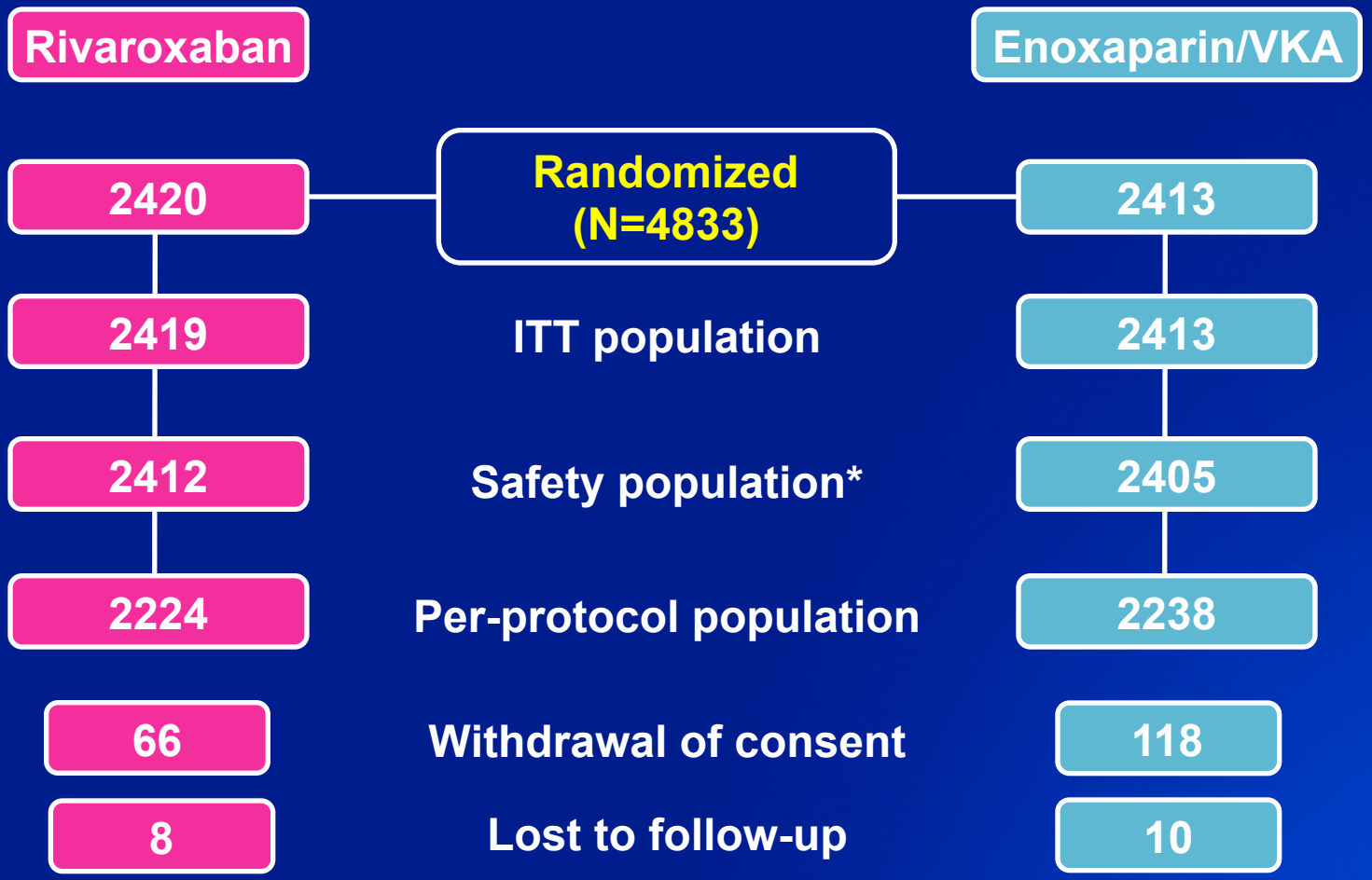
EINSTEIN PE: key secondary and other outcomes

Outcome	Rivaroxaban		Enoxaparin/VKA		HR (95% CI)
	n/N	(%)	n/N	(%)	
Net clinical benefit*	83/2419	(3.4)	96/2413	(4.0)	0.85 (0.63–1.14)
Total mortality	58/2419	(2.4)	50/2413	(2.1)	1.13 (0.77–1.65)
On-treatment					
Cerebrovascular events	12/2412	(0.5)	13/2405	(0.5)	
ACS	15/2412	(0.6)	21/2405	(0.9)	
Off-treatment (+ 30 days)					
Cerebrovascular events	2/2206	(<0.1)	1/2197	(<0.1)	
ACS	3/2206	(0.1)	2/2197	(<0.1)	
ALT>3×ULN + bilirubin>2× ULN	5/2355	(0.2)	4/2327	(0.2)	

*Primary efficacy outcome plus major bleeding

The EINSTEIN–PE Investigators. *N Engl J Med* 2012; DOI: 10.1056/NEJMoa1113572

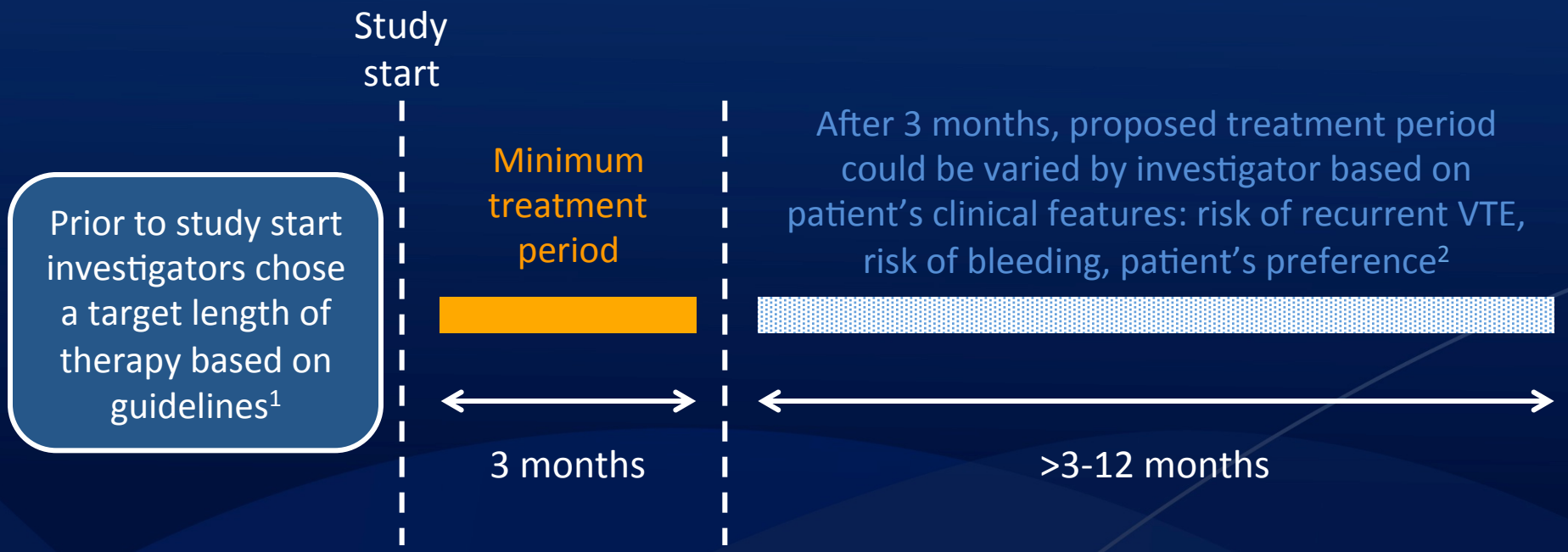
Einstein PE - Patient flow



*As treated

The EINSTEIN–PE Investigators. *N Engl J Med* 2012; DOI: 10.1056/NEJMoa1113572

Flexible treatment duration



1. Hokusai-VTE clinical study protocol. Version 5.0, 16 April 2012. Daiichi Sankyo Inc
2. Raskob et al. J Thromb Haemost 2013;11:1287–1294

ESC GUIDELINES
Recomendations for acute phase treatment: intermediate or low-risk patients

Recommendations for acute phase treatment

Recommendations	Class[a]	Level[b]	Ref[c]
PE without shock or hypotension (intermediate-or low-risk)[d]			
Anticoagulation: combination of parenteral treatment with VKA			
Initiation of parenteral anticoagulation is recommended without delay in patients with high or intermediate clinical probability of PE while diagnostic work-up is in progress.	I	C	352
LMWH or fondaparinux is the recommended form of acute phase parenteral anticoagulation for most patients.	I	A	273, 274, 281, 353
In parallel to parenteral anticoagulation, treatment with a VKA is recommended, targeting an INR of 2.5 (range 2.0–3.0).	I	B	352, 354
Anticoagulation: new oral anticoagulants			
As an alternative to the combination of parenteral anticoagulation with a VKA, anticoagulation with rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) is recommended.	I	B	296
As an alternative to the combination of parenteral anticoagulation with a VKA, anticoagulation with apixaban (10 mg twice daily for 7 days, followed by 5 mg twice daily) is recommended.	I	B	297
As an alternative to VKA treatment, administration of dabigatran (150 mg twice daily, or 110 mg twice daily for patients ≥80 years of age or those under concomitant verapamil treatment) is recommended following acute-phase parenteral anticoagulation.	I	B[e]	293, 294
As an alternative to VKA treatment, administration of edoxaban* is recommended following acute-phase parenteral anticoagulation.	I	B	298
New oral anticoagulants (rivaroxaban, apixaban, dabigatran, edoxaban) are not recommended in patients with severe renal impairment.[f]	III	A	293, 295–298

Conclusions

- The treatment of PE with NAC is effective and safer than with the std anticoagulant treatment
- The efficacy of both rivaroxaban and edoxaban has been proved also in severe PE
- Patients with PE could be treated with a single-drug approach (rivaroxaban, apixaban), irrespective of the extention of PE
- The administration of a short course of LMWH followed by a NAC (dabigatran, edoxaban) is effective in patients at moderate risk of early mortality
- Remember that these conclusions could not be applied in some specific clinical settings (older pts, renal disease, cancer)

RELEVANT ISSUES RELATED TO THE NAC PHASE III STUDIES ON PTS WITH PE

- All Patients at HIGH risk (ESC or similar) were excluded in studies using NAC
- Some studies did not predefine the recording of the risk class or PE Extension of the enrolled patients
- In all studies patients with older age, moderate renal disease and above all cancer were under-represented