NOACs in VTE treatment

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University Hospital of Padova
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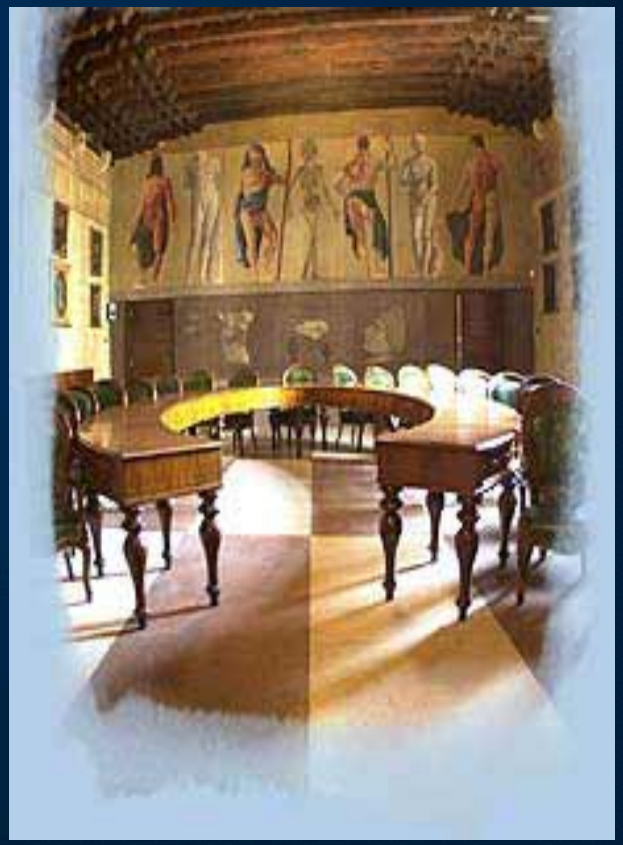


Palazzo del Bo, Università di Padova

FINANCIAL DISCLOSURES

Il sottoscritto

ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

DICHIARA

che negli ultimi due anni ha avuto scientifici (advisory board, progetti di ricerca, consulenze) con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

BAYER HEALTHCARE

DAIICHI-SANKYO

ALFA WASSERMANN

MEDIOLANUM

GSK - ASPEN

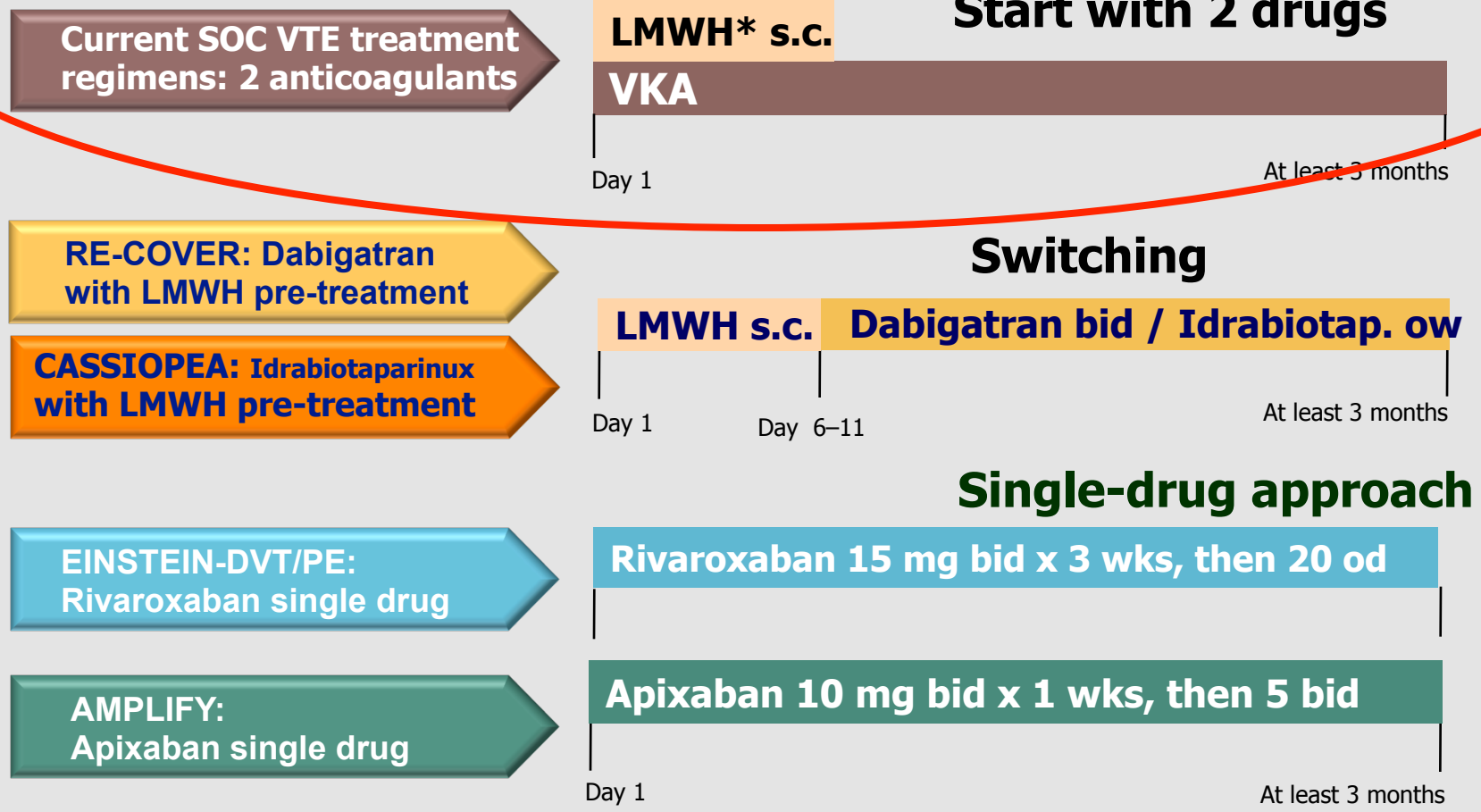
Single Drug Approach in the past

- Before 90's ⟶ Warfarin
- 2000-2005 ⟶ Ximelagatran (THRIVE Study)
- 2007-2011 ⟶ Idraparinux & Idrabiotaparinux

VAN GOGH DVT & PE, CASSIOPEA

- 2012-future: NOACs

Single drug approach vs switching in VTE treatment



*Or UFH or fondaparinux

Current approach to PE treatment

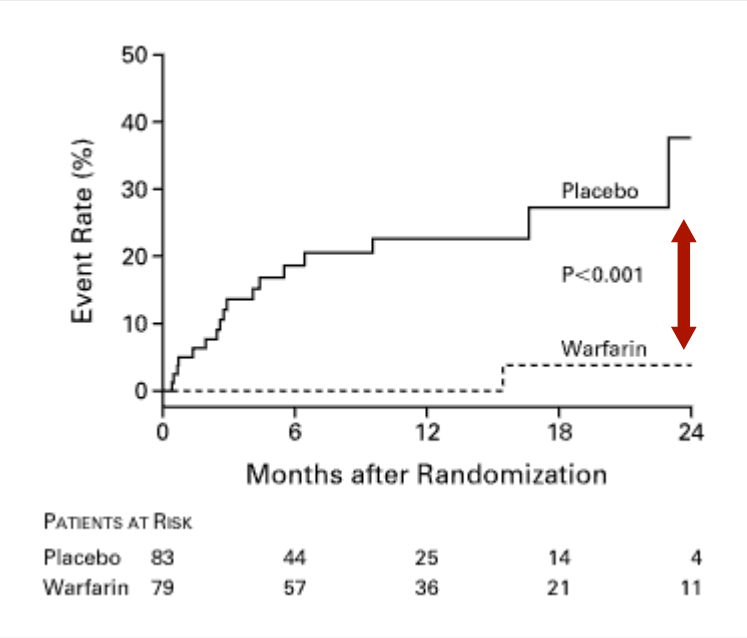
Current SOC VTE treatment regimens: 2 anticoagulants

*Or UFH or fondaparinux

Why only 3 months?

Long-term secondary prophylaxis

Highly effective, BUT…



Recurrence reduced by 90%

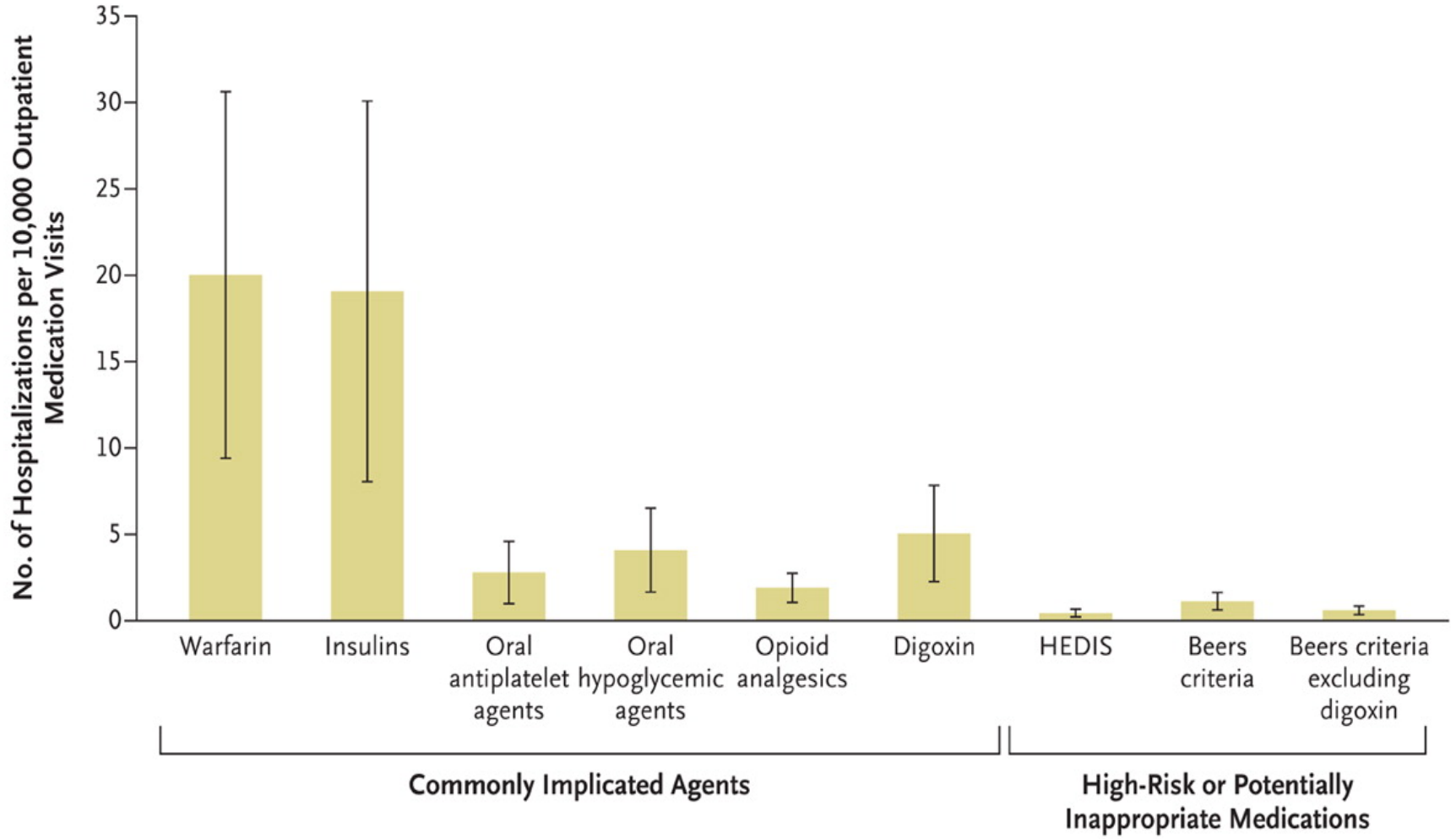
***Major bleeding*:**

3,8% / year

Study discontinued after 2 years

C Kearon. N Engl J Med 1999;340:910-907

VKA: emergency admissions due to undesired effects



Limitations of VKA therapy

VKA therapy has several limitations leading to underuse and leaving patients at risk of VTE or bleeding

- Narrow therapeutic window (INR range 2-3)
- Unpredictable response
- Numerous drug-drug interactions
- Numerous food-drug interactions
- Warfarin resistance
- Slow onset/offset of action
- Routine coagulation monitoring
- Frequent dose adjustments

1. Ansell J, et al. *Chest* 2008;133;160S-198S; 2. Umer Ushman MH, et al. *J Interv Card Electrophysiol* 2008; 22:129-137;
2. Nutescu EA, et al. *Cardiol Clin* 2008; 26:169-187.

Even With Close Monitoring in a Clinical Trial, Patients Frequently Out of Therapeutic Range

Clinical Trials

Only 58% of INR Values in Therapeutic Range

(INR = 2.0–2.85)

Real World Practice

As low as 37% of Time Spent Within Therapeutic Range

(INR = 2.0–2.85)

INR=international normalized ratio

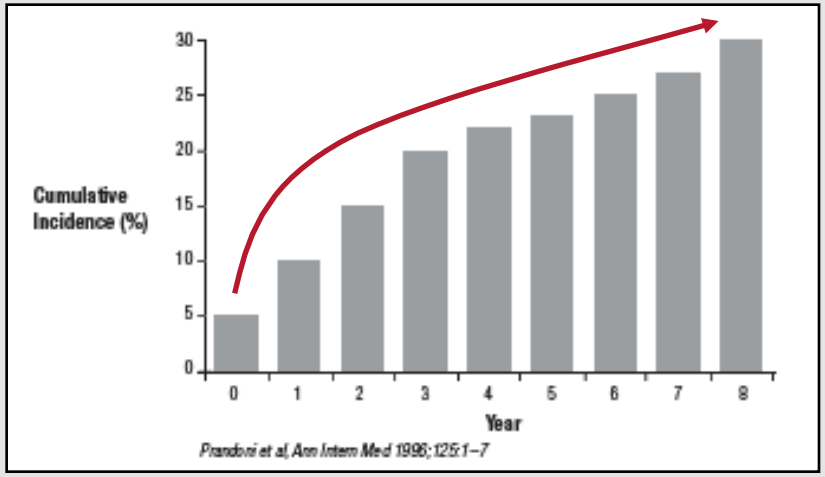
Schulman S; and Duration of Anticoagulation (DURAC) Trial Study Group. *J Intern Med* 1994;236:143-152.

Willey et al. Clin Ther 2004;26:1149-1159

9

Rationale for long-term secondary prophylaxis

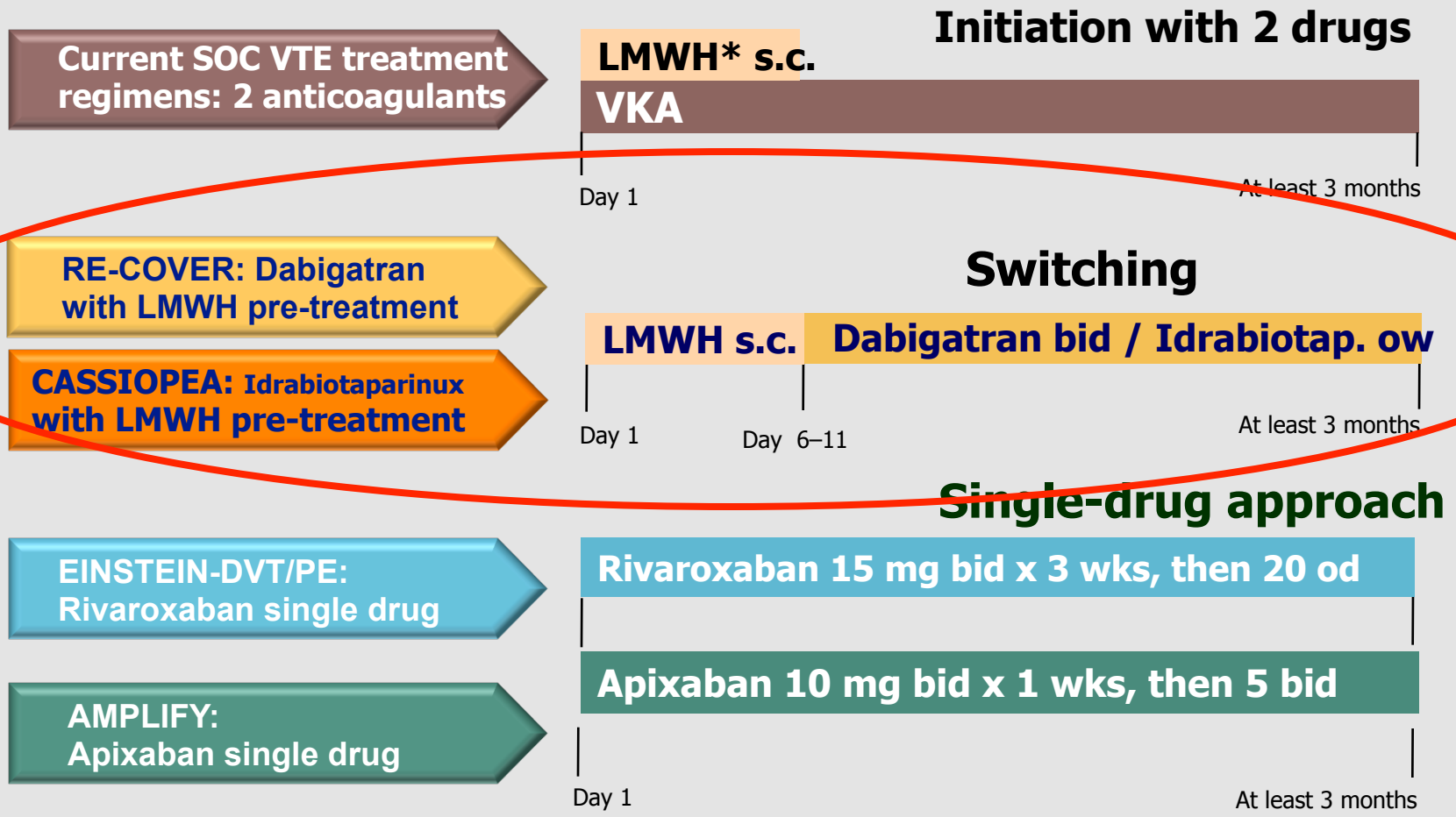
	Cumulative Incidence		Survival rate
	Recurrent DVT	Post thrombotic syndrome	
2 years	17%	25%	80%
5 years	24%	30%	74%
8 years	30%	30%	69%



Prandoni P, et al. Ann Intern Med 1996;125:1-7

Prandoni P, et al. Haematologica 1997; 82: 423-428

Single drug approach vs switching in VTE treatment



*Or UFH or fondaparinux

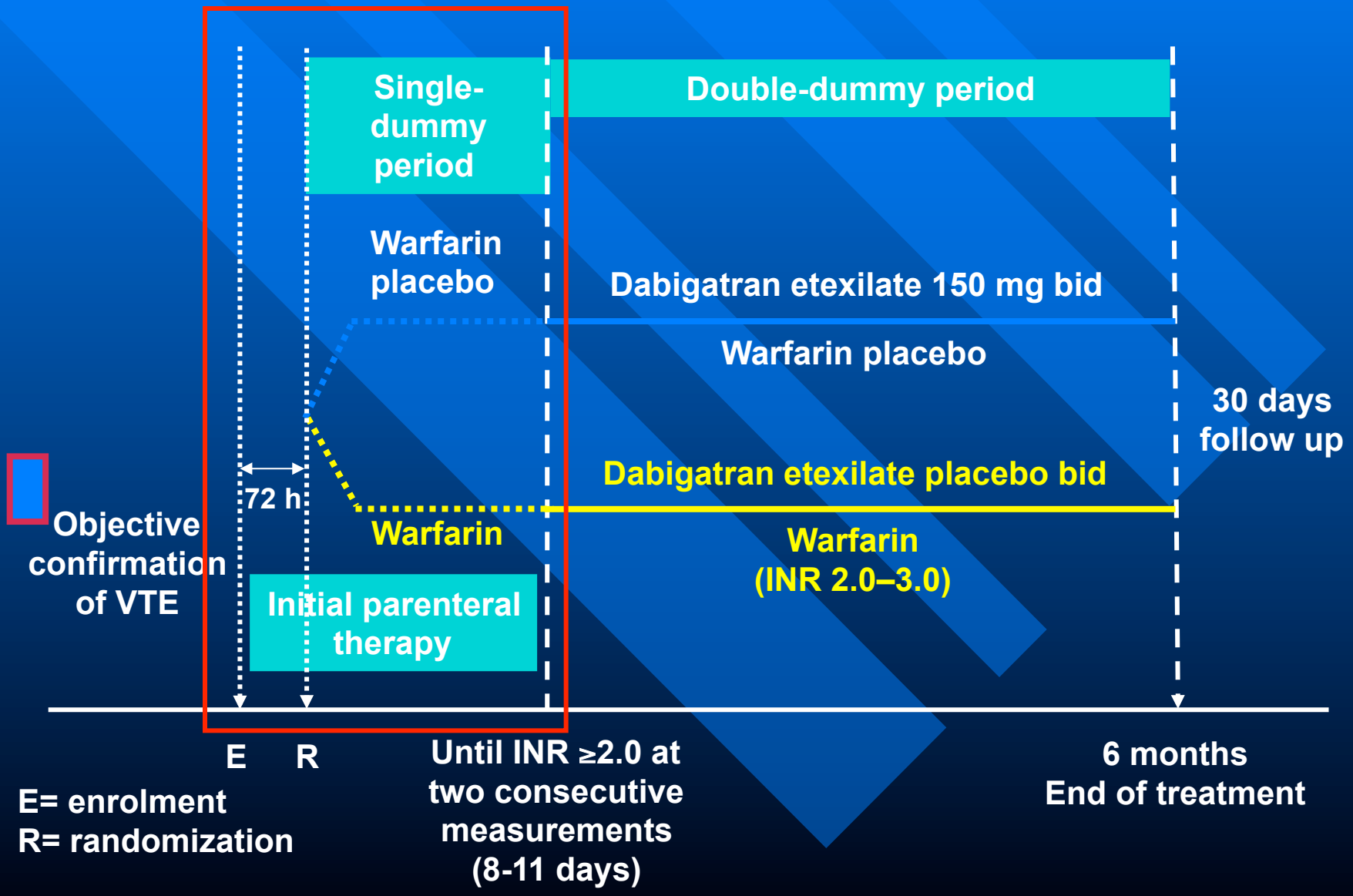
Schulman S, Kearon C, Kakkar AK,
Mismetti P, Schellong S, Eriksson H,
Baanstra D, Schnee J, Goldhaber SZ

The RE-COVER Study Group

Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism

N Engl J Med 2009

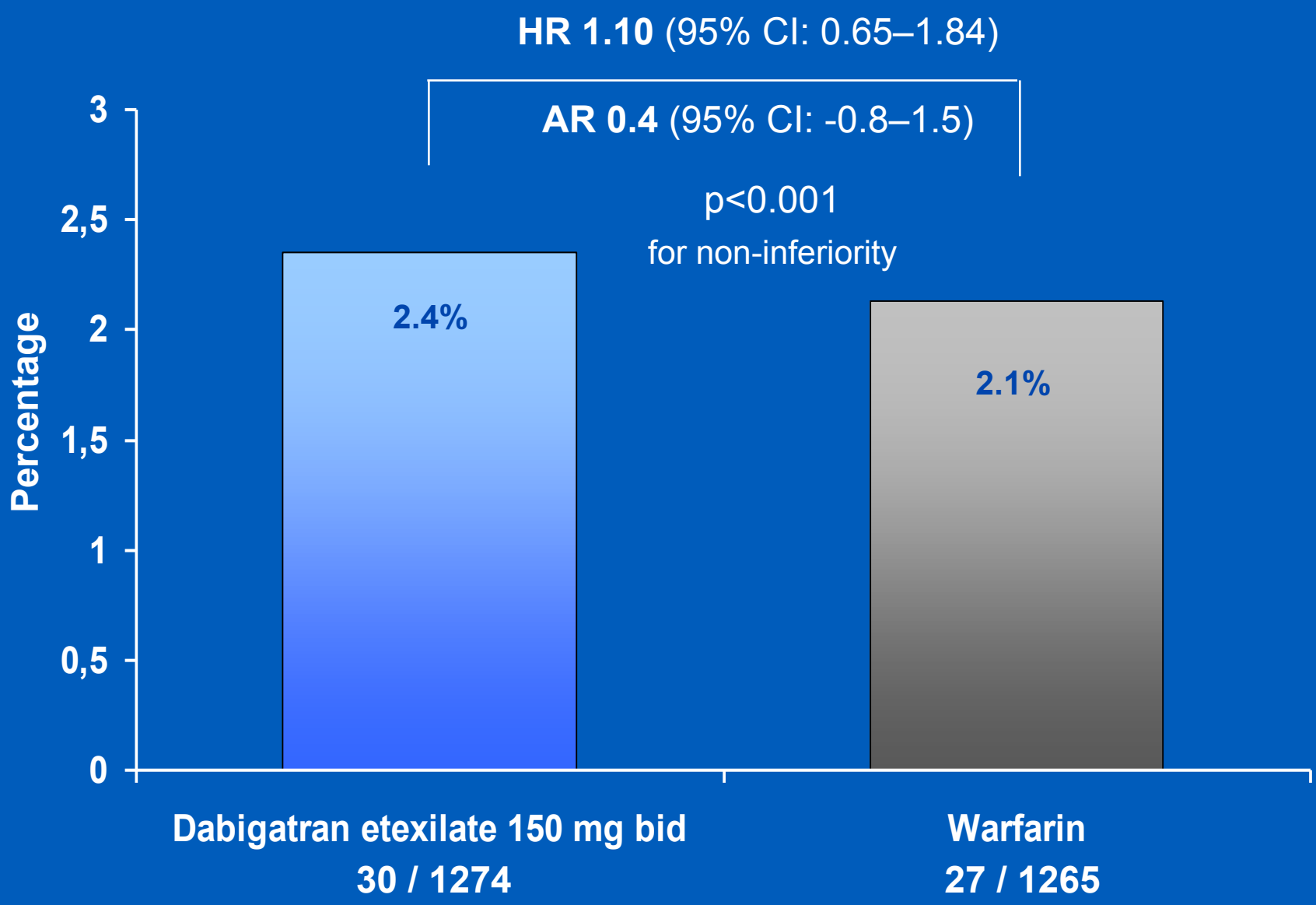
RE-COVER™ Trial Design



E= enrolment
R= randomization

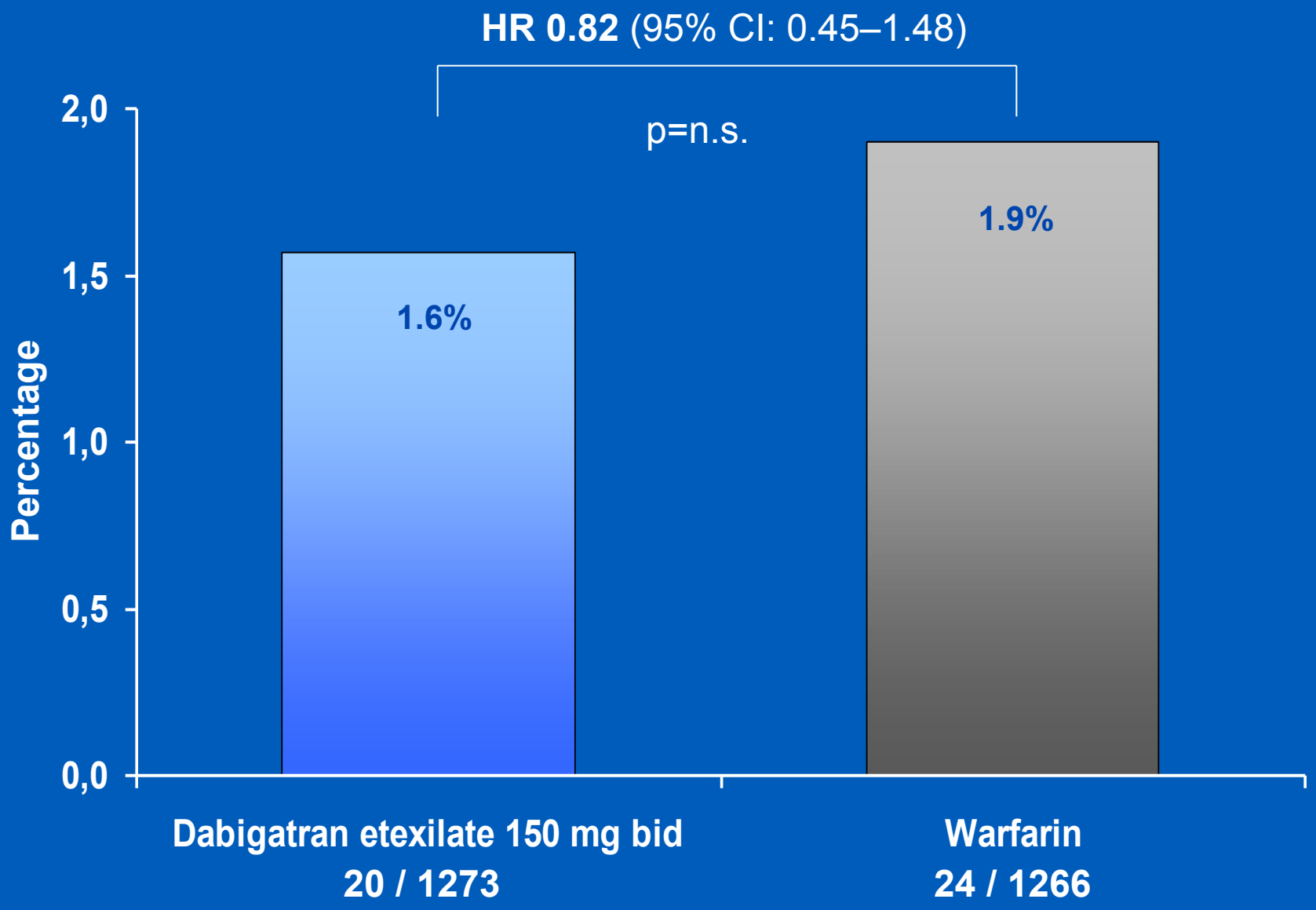
Non-inferior in VTE or related death

RECOVER™
Study of treatment of venous thromboembolism



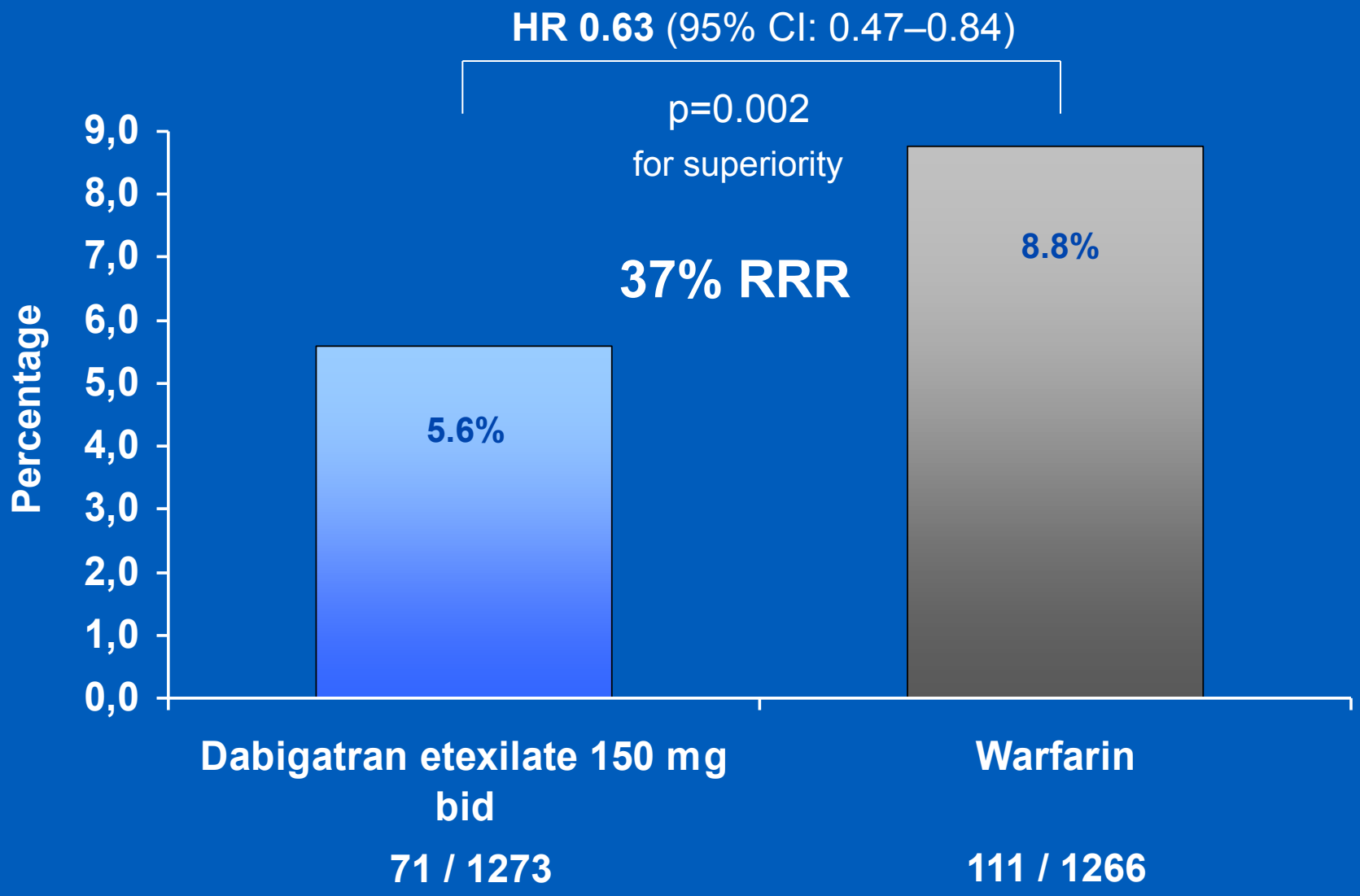
Comparable on major bleeds

RECOVER™
Study of treatment of venous thromboembolism



Significant reduction in major / clinically relevant bleeds

RECOVER™
Study of treatment of venous thromboembolism



Dabigatran ISMP surveillance programme

1. Available at: http://www.ismp.org/QuarterWatch/pdfs/2011Q4.pdf. Accessed June 2012.
2. Available at: http://www.ismp.org/QuarterWatch/pdfs/2011Q1.pdf. Accessed June 2012.

- Overall in 2011[1]
  - 3,781 serious adverse events (AEs) were linked to dabigatran
    - 542 deaths
    - warfarin associated with 1,106 serious AEs and 72 deaths
  - 2,367 cases involved haemorrhage
    - warfarin ranked second with 731 cases of haemorrhage
  - 644 cases of stroke
  - 291 cases of acute renal failure
  - 15 cases of liver failure
- In Q1 2011 it was noted[2]
  - haemorrhage cases were occurring in oldest patients with a median age of 80 years
  - raised question whether older patients were receiving too high a dose

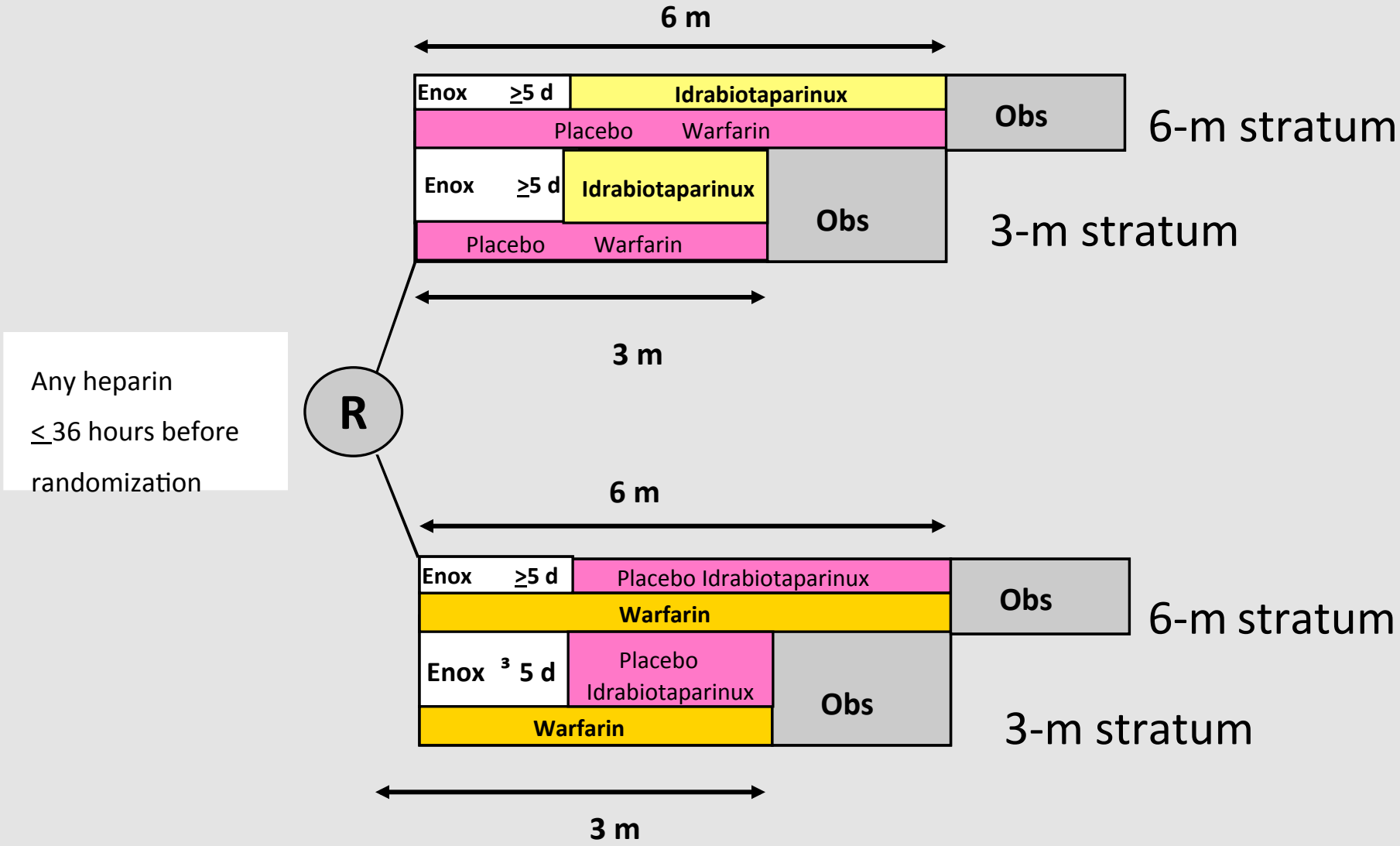
*US indication.

ISMP = The Institute for Safe Medication Practices

M. Donati, M. Melis – Focus Farmacovigilanza, 2015 genn-febb

Future (?) Treatment of VTE: Idrabiotaparinux

Study Design (double-blind, double-dummy)



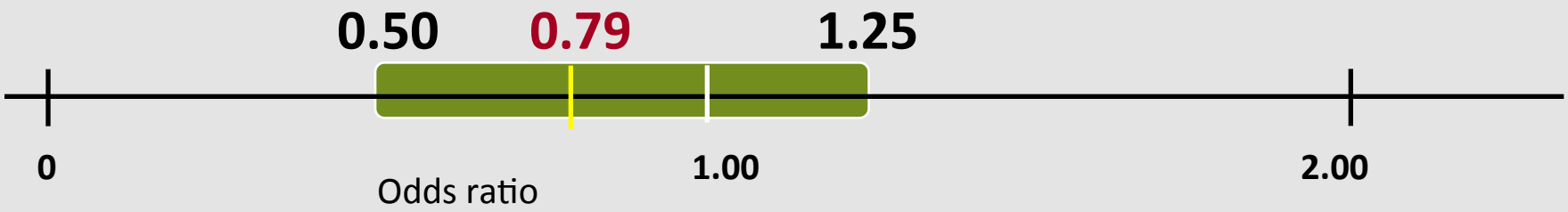
Idrabiotaparinux dose: 3 mg sc once a week

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

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)



Idrabiotaparinux superior | **Idrabiotaparinux non-inferior** | **Idrabiotaparinux inferior**

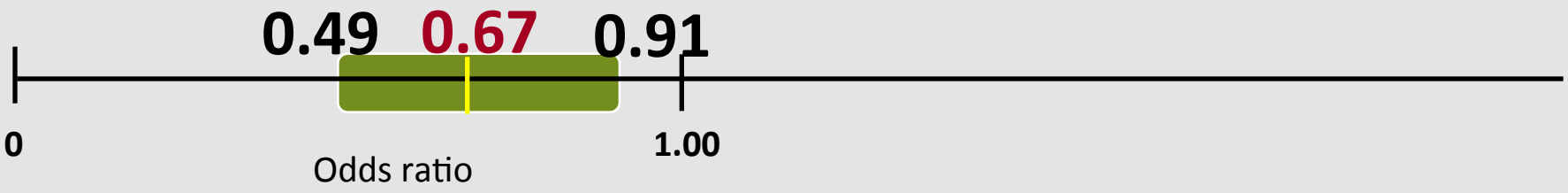
p<0.0001 for non-inferiority

HR Büller for the CASSIOPEA Investigators. Lancet 2012;379:123-129

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)



P=0.0098 for superiority

(two-sided)

HR Büller. Lancet 2012;379:123-129

The "Single Drug Approach" of the new (current) ERA

Edoxaban

Rivaroxaban

Apixaban

Design of the studies with the new oral anticoagulants in established VTE

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	Thrombin	Factor Xa	Factor Xa	Factor Xa
Study acronym	RE-COVER	EINSTEIN	AMPLIFY	HOKUSAI
Study design	DB, R, NI	O, R, NI	DB, R, NI	DB, R, NI
Dosage	150 mg bid	15 mg bid (21d) then 20 mg od	10 mg bid (7d) then 5 mg bid	60 mg od
Initial UFH/ LMWH	Mandatory (≥ 5d)	**Optional (max. 36h)**	**Optional (max. 36h)**	Mandatory (5-12d)

R: randomized, DB: double blind, O: open label, NI: non-inferiority

* All vs. warfarin (monitored with target INR 2-3)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Rivaroxaban for Symptomatic Venous Thromboembolism

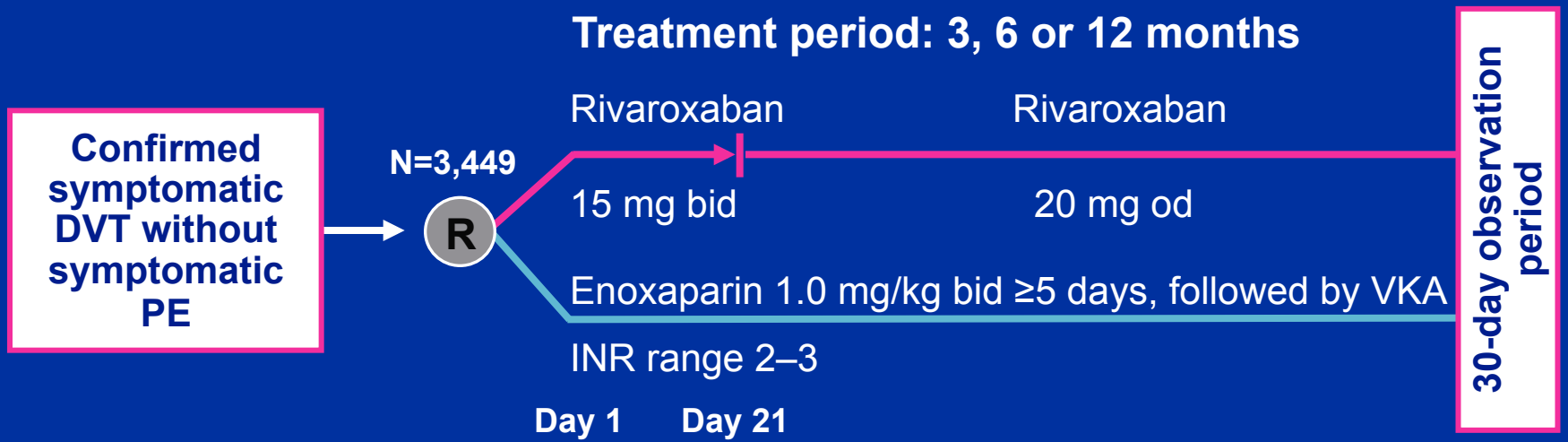
The EINSTEIN Investigators*

Harry R Büller
on behalf of the EINSTEIN Investigators
Academic Medical Center, Amsterdam, The Netherlands

EINSTEIN DVT: study design

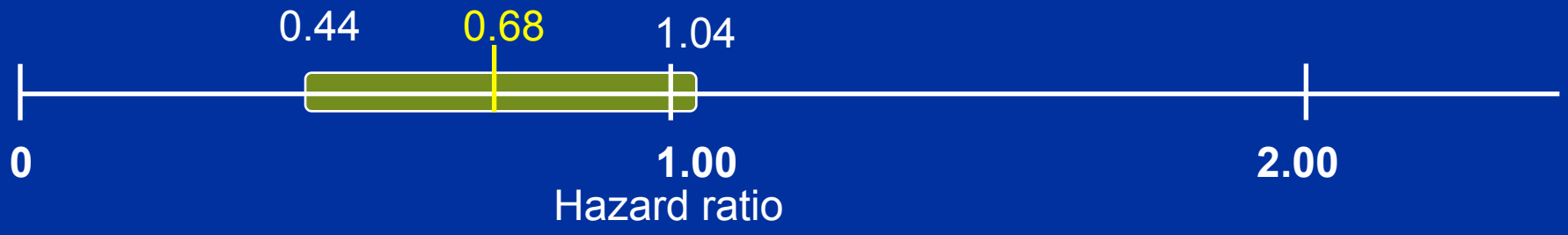
Randomized, open-label, event-driven, non-inferiority study

- Up to 48 hours' heparins/fondaparinux treatment permitted before study entry
- 88 primary efficacy outcomes needed



Primary efficacy outcome analysis

	Rivaroxaban (n=1,731)		Enoxaparin/VKA (n=1,718)	
	n	(%)	n	(%)
First symptomatic recurrent VTE	**36**	**(2.1)**	**51**	**(3.0)**
Recurrent DVT	14	**(0.8)**	28	**(1.6)**
Recurrent DVT + PE	1	**(<0.1)**	0	**(0)**
Non-fatal PE	20	**(1.2)**	18	**(1.0)**
Fatal PE/unexplained death where PE cannot be ruled out	4	**(0.2)**	6	**(0.3)**



Rivaroxaban superior	Rivaroxaban non-inferior	Rivaroxaban inferior

p=0.076 for superiority (two-sided)

p<0.0001 for non-inferiority (one-sided)

ITT population

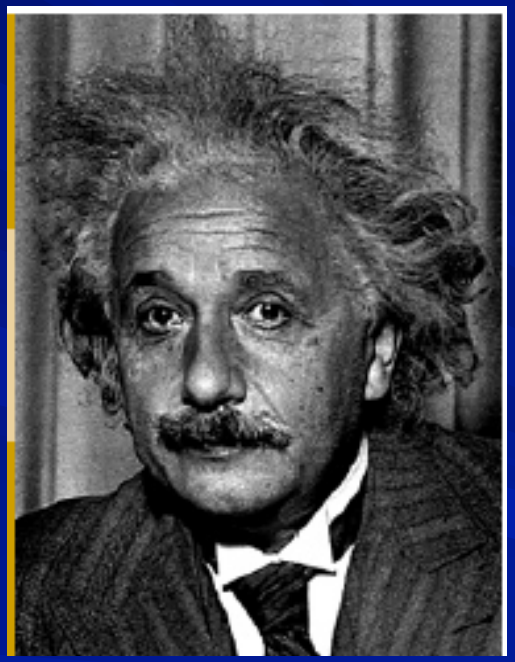
Principal safety outcome analysis

	Rivaroxaban (n=1,718)		Enox/VKA (n=1,711)		HR (95% CI)
	n	(%)	n	(%)	*p* value
First major or clinically relevant non-major bleeding	**139**	**(8.1)**	**138**	**(8.1)**	**0.97 (0.76–1.22) *p*=0.77**
Major bleeding	**14**	**(0.8)**	**20**	**(1.2)**	
Contributing to death	1	(<0.1)	5	(0.3)	
In a critical site	3	(0.2)	3	(0.2)	
Associated with fall in Hb ≥2 g/dl and/ or transfusion of ≥2 units	10	(0.6)	12	(0.7)	
Clinically relevant non-major bleeding	**126**	**(7.3)**	**119**	**(7.0)**	

Safety population

RIVAROXABAN FOR THE TREATMENT OF PE

EINSTEIN PE STUDY

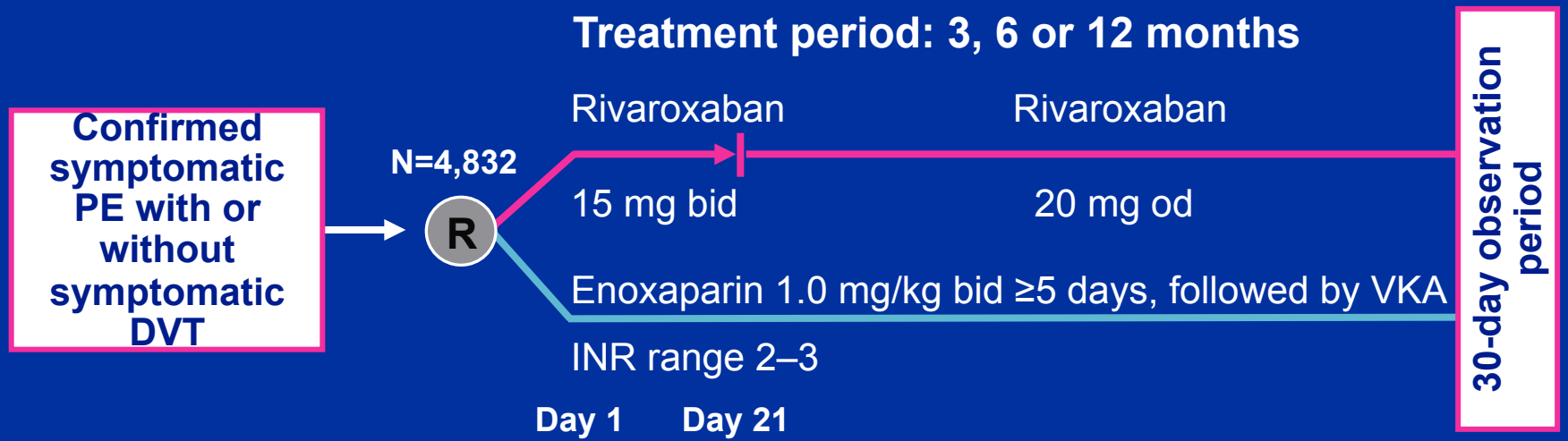


RIVAROXABAN VS ENOXAPARIN + WARFARIN

EINSTEIN PE: study design

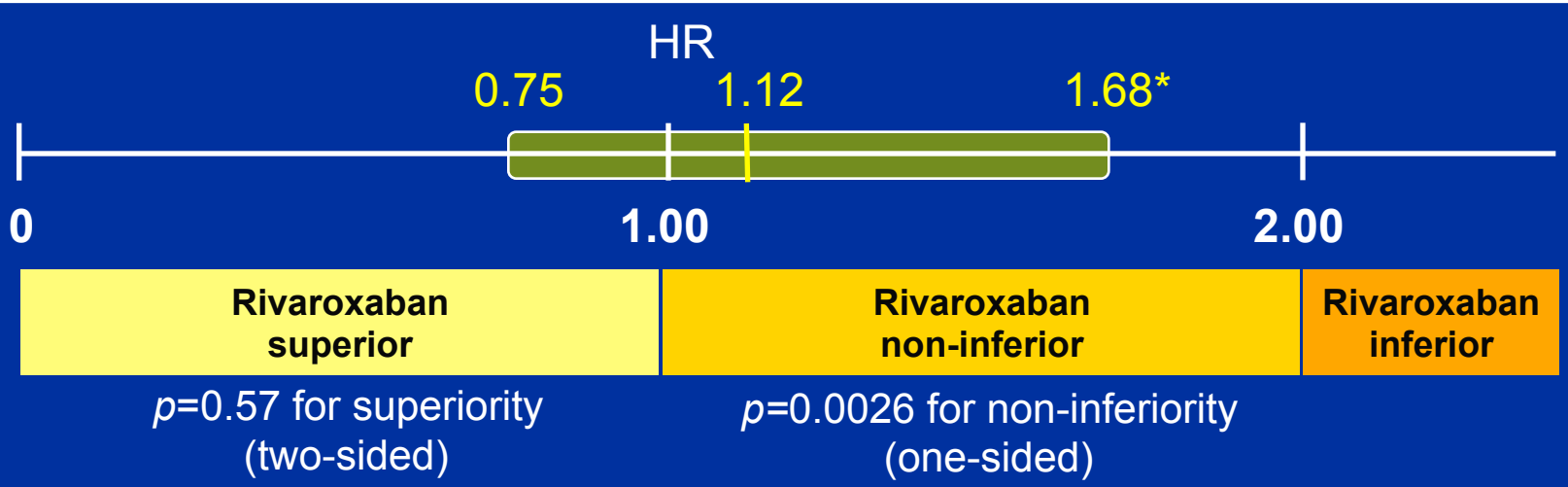
Randomized, open-label, event-driven, non-inferiority study

- Up to 48 hours' heparins/fondaparinux treatment permitted before study entry
- 88 primary efficacy outcomes needed



EINSTEIN PE: primary efficacy outcome analysis

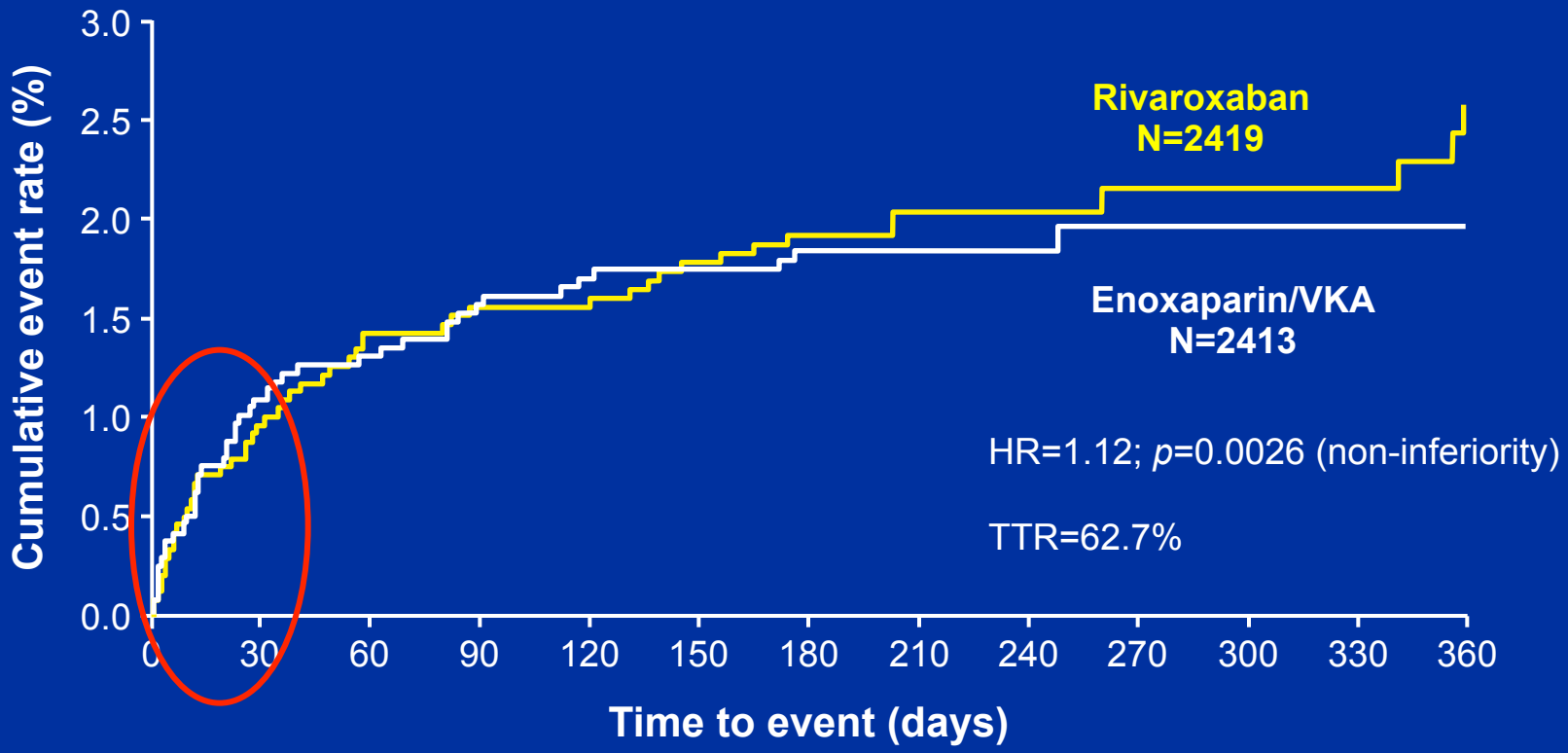
	Rivaroxaban (N=2419)		Enoxaparin/VKA (N=2413)	
	n	(%)	n	(%)
First symptomatic recurrent VTE	**50**	**(2.1)**	**44**	**(1.8)**
Recurrent DVT	18	(0.7)	17	(0.7)
Recurrent DVT + PE	0		2	(<0.1)
Non-fatal PE	22	(0.9)	19	(0.8)
Fatal PE/unexplained death where PE cannot be ruled out	10	(0.4)	6	(0.2)



*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
Büller HR *et al. N Engl J Med* 2012. DOI: 10.1056/NEJMoa1113572

EINSTEIN PE: primary efficacy outcome: time to first event



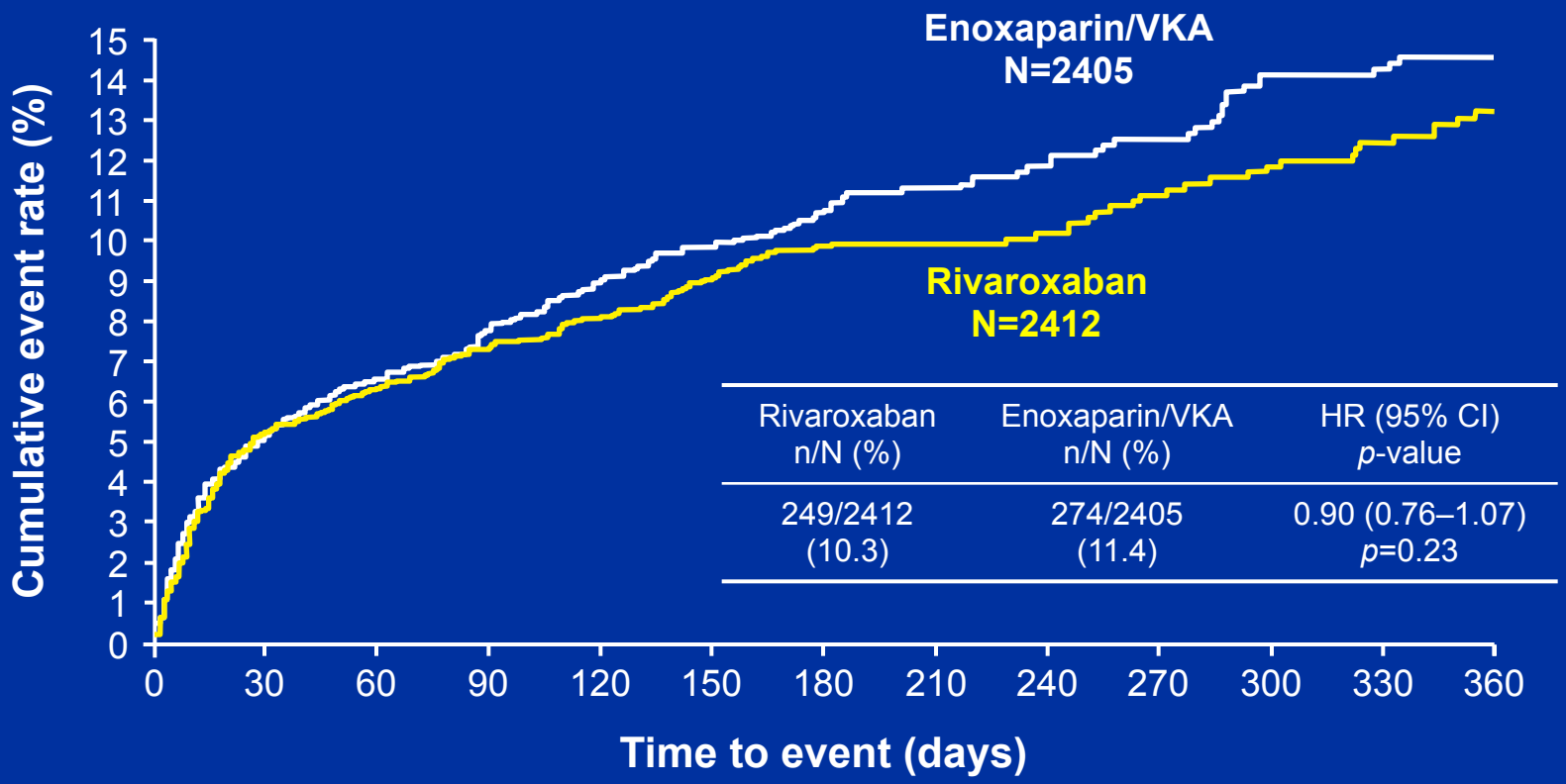
Number of patients at risk													
Rivaroxaban	2419	2350	2321	2303	2180	2167	2063	837	794	785	757	725	672
Enoxaparin/VKA	2413	2316	2295	2274	2155	2146	2050	835	787	772	746	722	675

ITT population

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

Buller HR *et al. 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

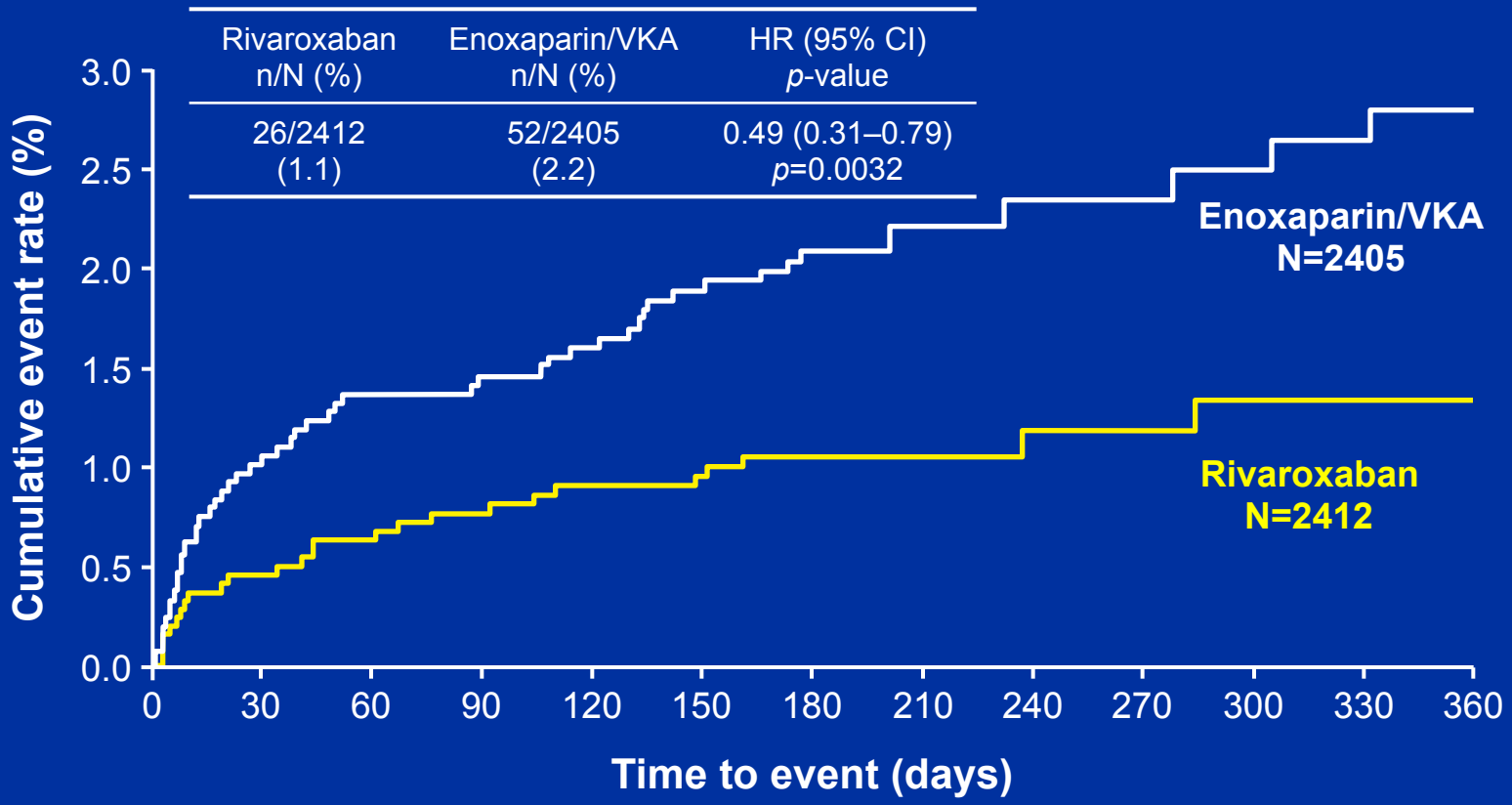
Number of patients at risk													
Rivaroxaban	2412	2183	2133	2024	1953	1913	1211	696	671	632	600	588	313
Enoxaparin/VKA	2405	2184	2115	1990	1923	1887	1092	687	660	620	589	574	251

Safety population

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

Buller HR *et al. N Engl J Med* 2012. DOI: 10.1056/NEJMoa1113572

EINSTEIN PE: major bleeding



Number of patients at risk													
Rivaroxaban	2412	2281	2248	2156	2091	2063	1317	761	735	700	669	659	350
Enoxaparin/VKA	2405	2270	2224	2116	2063	2036	1176	746	719	680	658	642	278

Safety population

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

Buller HR *et al. N Engl J Med* 2012. DOI: 10.1056/NEJMoa1113572

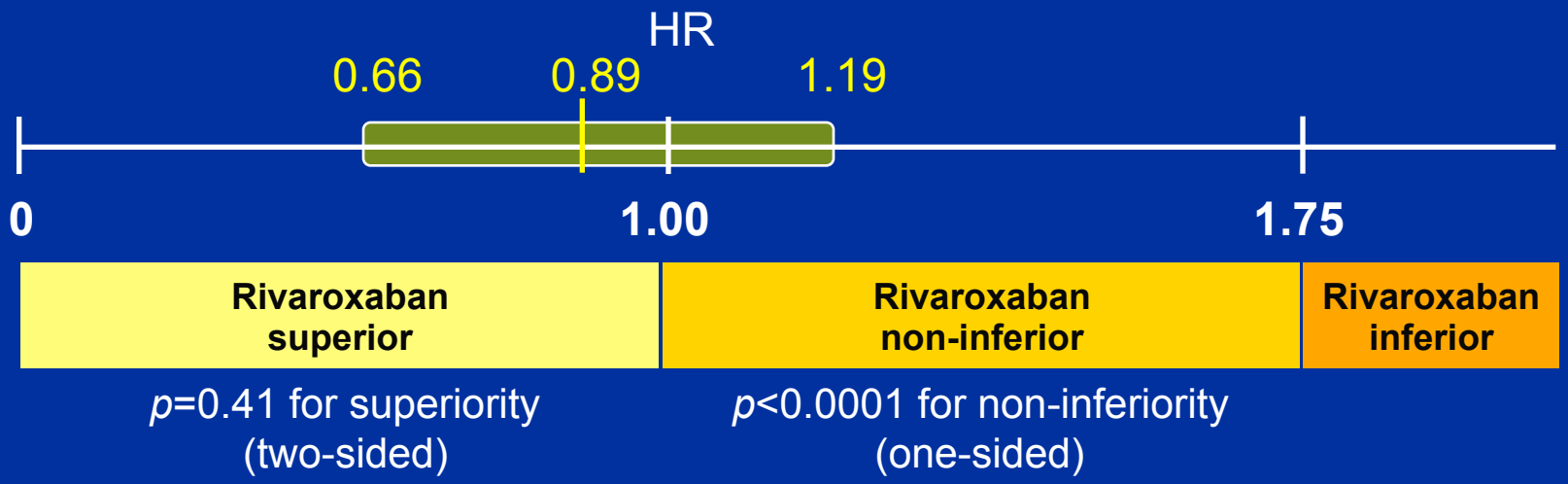
RIVAROXABAN FOR THE TREATMENT OF VTE

EINSTEIN DVT + PE
Pooled analysis

RIVAROXABAN VS ENOXAPARIN + WARFARIN

EINSTEIN DVT and PE pooled analysis: primary efficacy outcome analysis

	Rivaroxaban (N=4150)		Enoxaparin/VKA (N=4131)	
	n	(%)	n	(%)
First symptomatic recurrent VTE	**86**	**(2.1)**	**95**	**(2.3)**
Recurrent DVT	32	(0.8)	45	(1.1)
Recurrent DVT + PE	1	(<0.1)	2	(<0.1)
Non-fatal PE	43	(1.0)	38	(0.9)
Fatal PE/unexplained death where PE cannot be ruled out	15	(0.4)	13	(0.3)

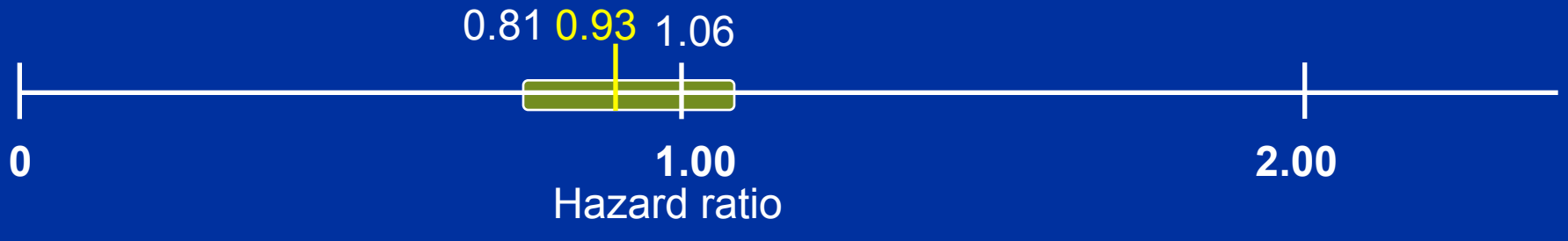


ITT population

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

EINSTEIN DVT and PE pooled bleeding analysis

First major or non-major clinically relevant bleeding



Rivaroxaban superior	Rivaroxaban non-inferior	Rivaroxaban inferior

p=0.27 for superiority (two-sided)

p<0.0001 for non-inferiority (one-sided)

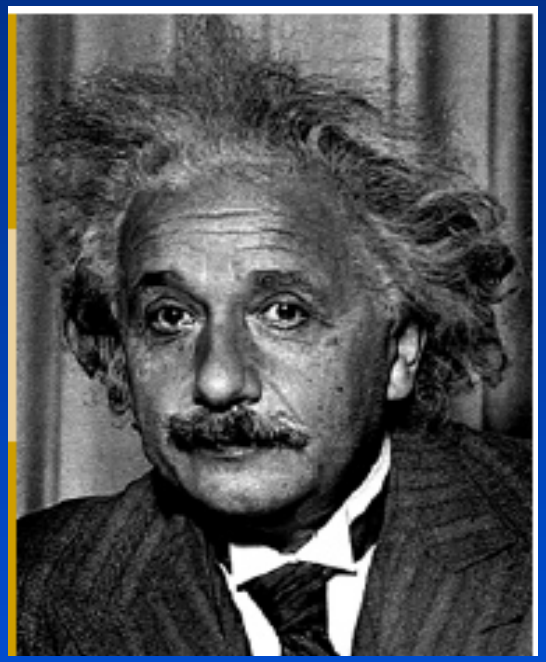
Major bleeding

Rivaroxaban superior	Rivaroxaban non-inferior	Rivaroxaban inferior

p=0.0018 for superiority (two-sided)

RIVAROXABAN IN THE SECONDARY PREVENTION OF VTE

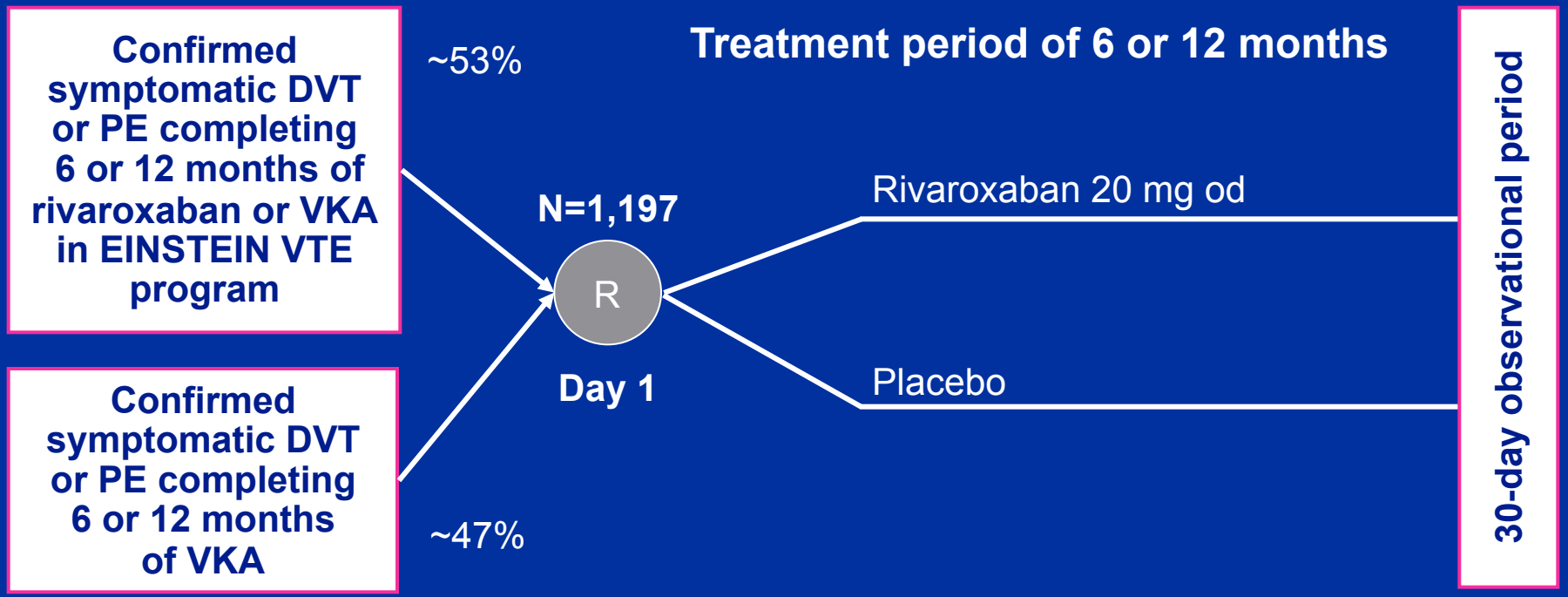
EINSTEIN EXTENSION



RIVAROXABAN VS PLACEBO AFTER 6 MONTHS OF CONVENTIONAL TREATMENT

Study design

Randomized, double-blind, placebo-controlled, event-driven (n=30), superiority study



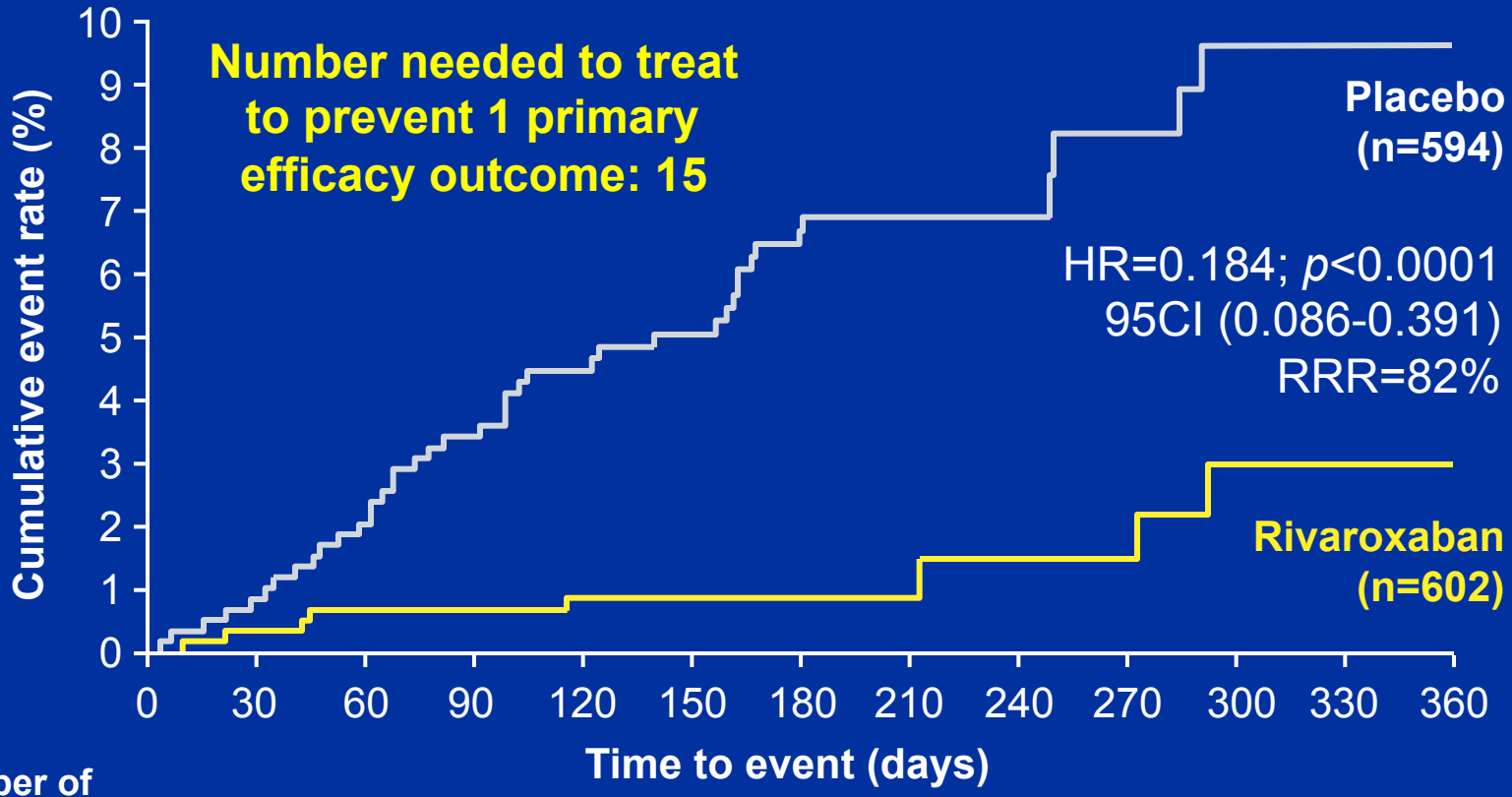
EINSTEIN Extension Trial ID: NCT00439725

Patient characteristics

	Placebo (n=594)	Rivaroxaban (n=602)
Males (%)	57	59
Age, mean (years)	58	58
Body mass index, mean (kg/m^2)	28	28
Creatinine clearance (mL/min)		
<50	49 (8%)	37 (6%)
50–<80	121 (20%)	134 (22%)
≥80	373 (63%)	371 (62%)
Index event*		
DVT	350 (59%)	376 (63%)
PE with or without DVT	233 (39%)	213 (35%)
Risk factors		
Patients with idiopathic DVT/PE	358 (60%)	344 (57%)
Patients with risk factors	236 (40%)	258 (43%)

ITT population; *index event not confirmed in all patients.

Primary efficacy outcome analysis (time to first event)



Number of subjects at risk													
Rivaroxaban	602	590	583	573	552	503	482	171	138	132	114	92	81
Placebo	594	582	570	554	521	467	444	164	138	133	110	93	85

ITT population

Principal safety outcome: major bleeding

	Placebo (n=590)	Rivaroxaban (n=598)
Major bleeding	**0**	**4 (0.7%)***
Bleeding contributing to death	0	0
Bleeding in a critical site	0	0
Associated with fall in hemoglobin ≥2 g/dL and/or transfusion		
Gastrointestinal bleeding	0	3 (0.5%)
Menorrhagia	0	1 (0.2%)

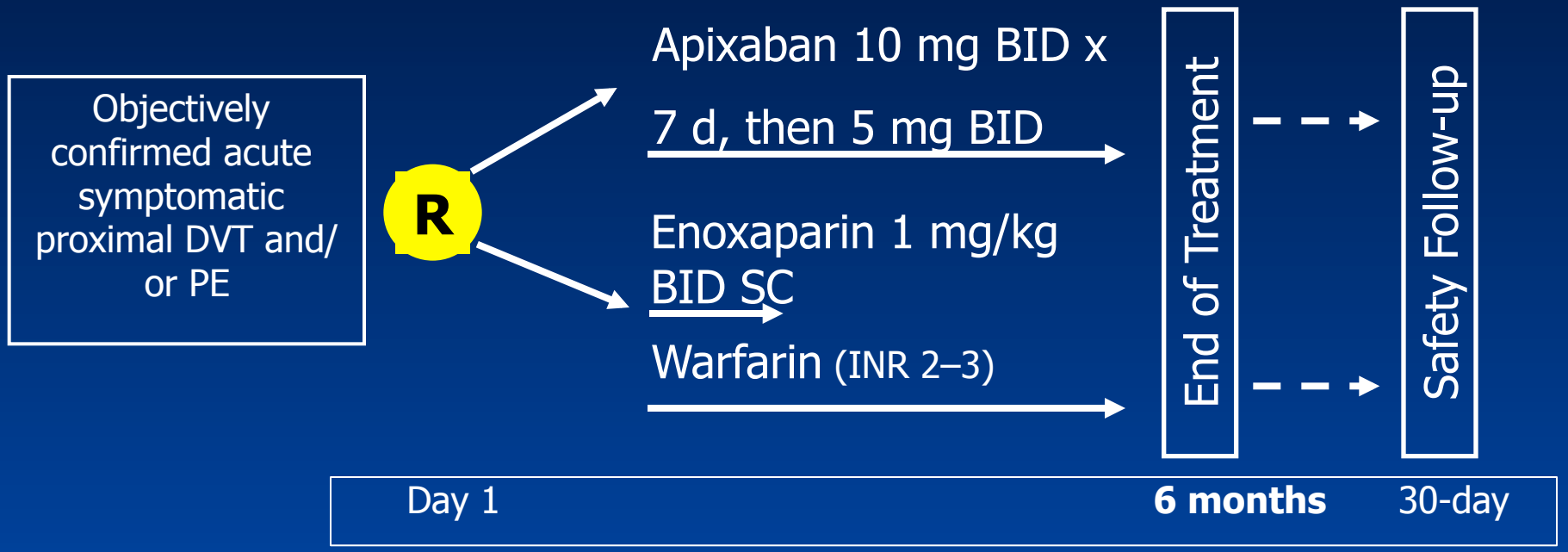
**p*=0.11

- Number needed to harm: approximately 139

Safety population

The AMPLIFY Study

- **Aim:** To compare the efficacy and safety of apixaban alone with conventional anticoagulant therapy (enoxaparin/warfarin) for **6 months** in patients with acute symptomatic DVT and/or PE
- **Design:** Randomised, double-blind, noninferiority study



Agnelli G et al. N Engl J Med 2013; 369:799-808

Clinical Characteristics at Baseline

	Apixaban n=2691	Enoxaparin/Warfarin n=2704
Location of qualifying DVT, n (%)		
Popliteal vein	426 (24)	441 (25)
Femoral vein	570 (33)	585 (33)
Common femoral or iliac vein	753 (43)	754 (42)
Anatomic extent of qualifying PE, n (%)		
Limited: ≤25% of vasculature of a single lobe	79 (9)	89 (10)
Intermediate	392 (42)	395 (44)
Extensive: ≥2 lobes with ≥50% of vasculature for each lobe	357 (38)	326 (36)
Not assessable	102 (11)	96 (11)
Risk factors for recurrent VTE, n (%)		
Previous VTE	463 (17)	409 (15)
Known thrombophilia	74 (3)	59 (2)
Active cancer	66 (3)	77 (3)

Agnelli G et al. N Engl J Med 2013; 369:799-808

Efficacy Outcomes

	Apixaban n=2609	Enoxaparin/ Warfarin n=2635	Relative Risk (95% CI)	*P* Value
First recurrent VTE or VTE-related death, n (%)	59 (2.3)	71 (2.7)	0.84 (0.60–1.18)	<0.0001 non-inferiority
Index event: DVT	38/1698 (2.2)	47/1736 (2.7)	0.83 (0.54–1.26)	
Index event: PE ± DVT	21/900 (2.3)	23/886 (2.6)	0.90 (0.50–1.61)	
VTE or CV-related death, n (%)	61 (2.3)	77 (2.9)	0.80 (0.57–1.11)	
VTE or all-cause death, n (%)	84 (3.2)	104 (4.0)	0.82 (0.61–1.08)	

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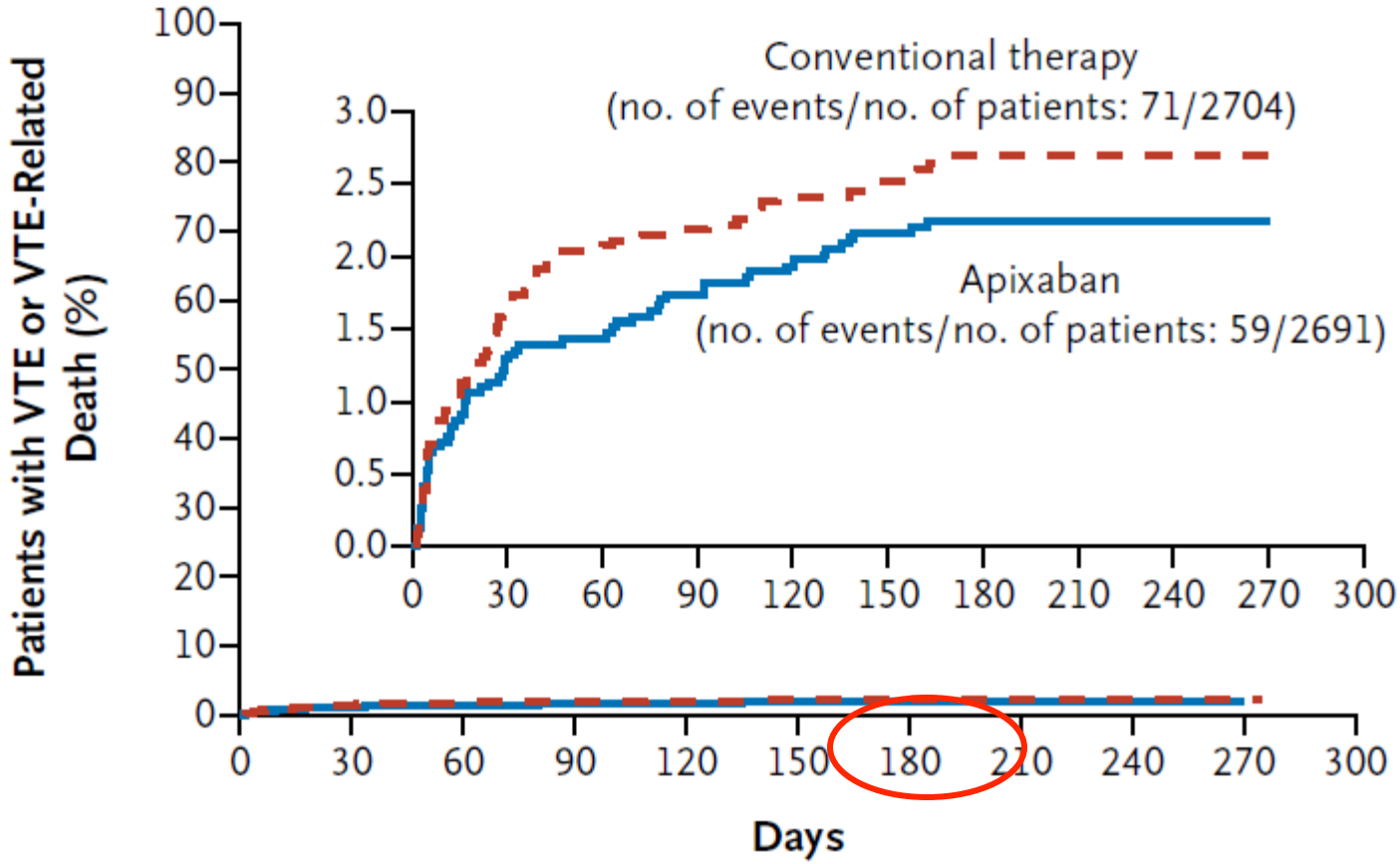
First Recurrent VTE/VTE-related Death



No. at Risk

Apixaban	2691	2606	2586	2563	2541	2523	62	4	1	0	0
Conventional therapy	2704	2609	2585	2555	2543	2533	43	3	1	1	0

Agnelli G et al. N Engl J Med 2013; 369:799-808

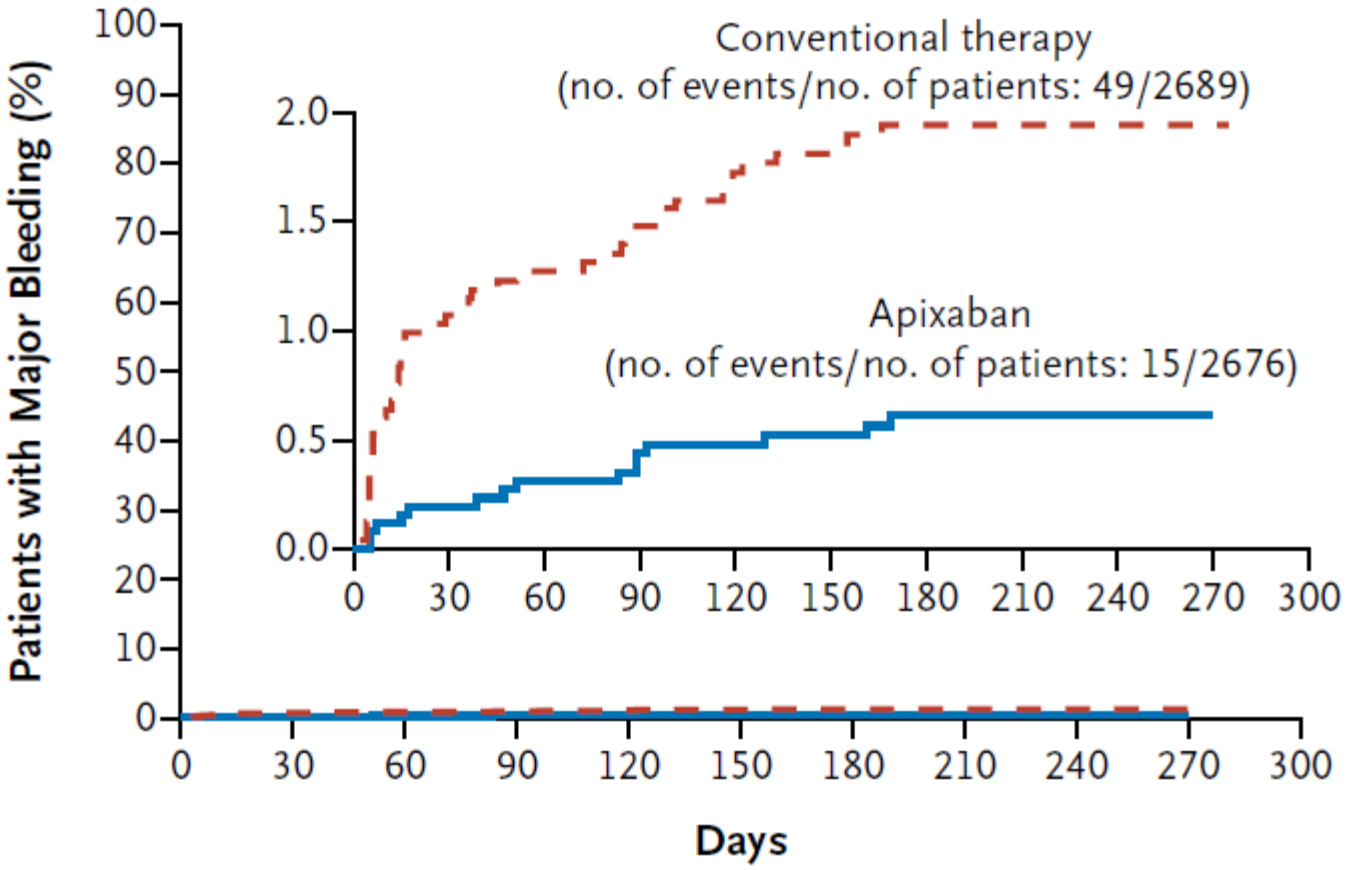
Bleeding Outcomes*

Event	Apixaban n=2676	Enoxaparin/ Warfarin n=2689	Relative Risk (95% CI)	*P* Value
Major bleeding, n (%)	15 (0.6)	49 (1.8)	0.31 (0.17–0.55)	<0.0001 Superiority
CRNM bleeding, n (%)	103 (3.9)	215 (8.0)	0.48 (0.38–0.60)	
Major or CRNM bleeding, n (%)	115 (4.3)	261 (9.7)	0.44 (0.36–0.55)	

* For patients who had >1 event, only the first event was counted.

Agnelli G et al. N Engl J Med 2013; 369:799-808

Major Bleeding



No. at Risk

Apixaban	2676	2519	2460	2409	2373	2339	61	4	1	0	0
Conventional therapy	2689	2488	2426	2383	2339	2310	43	3	1	1	0

Agnelli G et al. N Engl J Med 2013; 369:799-808

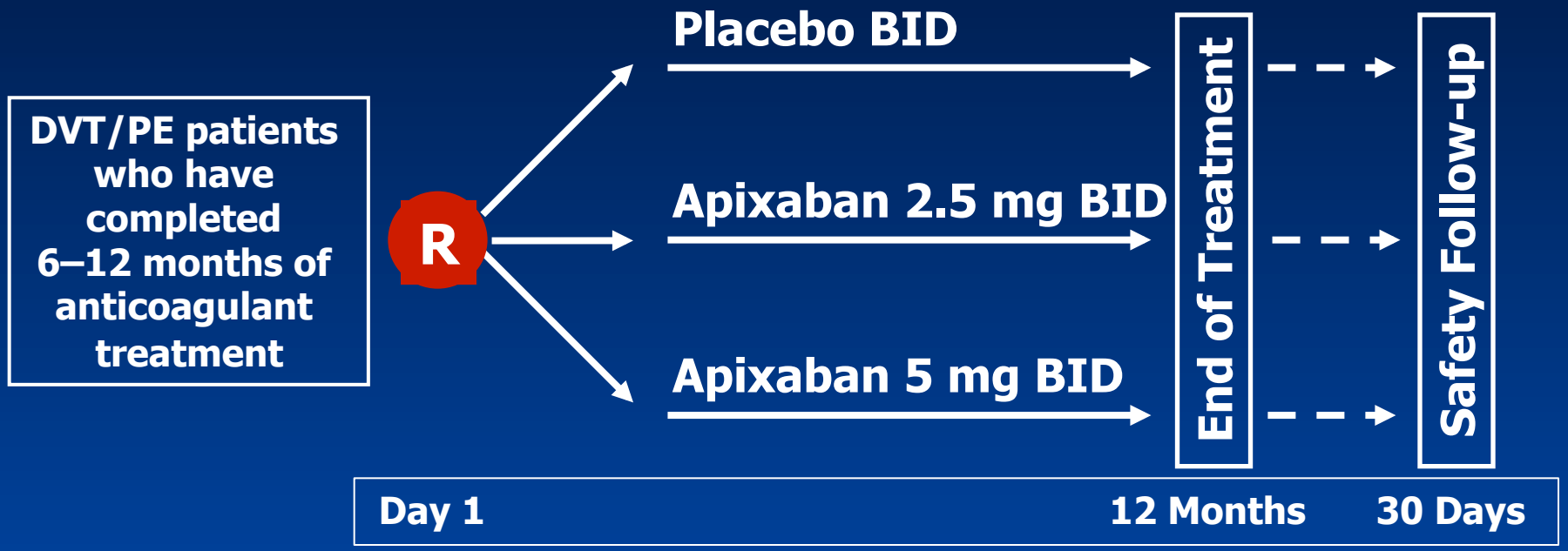
Apixaban for Extended Treatment of Venous Thromboembolism (VTE)

The AMPLIFY-EXTENSION Study

Agnelli G.A, et al. N Engl J Med 2013; 368:699-708

Aim and Design

- **Aim:** To compare the efficacy and safety of two doses of apixaban with placebo for the extended treatment of patients with VTE
- **Design:** Randomized, double blind, placebo-controlled, superiority study



BID, twice daily; DVT, deep vein thrombosis; PE, pulmonary embolism; R, randomization

Agnelli G.A, et al. N Engl J Med 2013; 368:699-708

Efficacy Outcomes

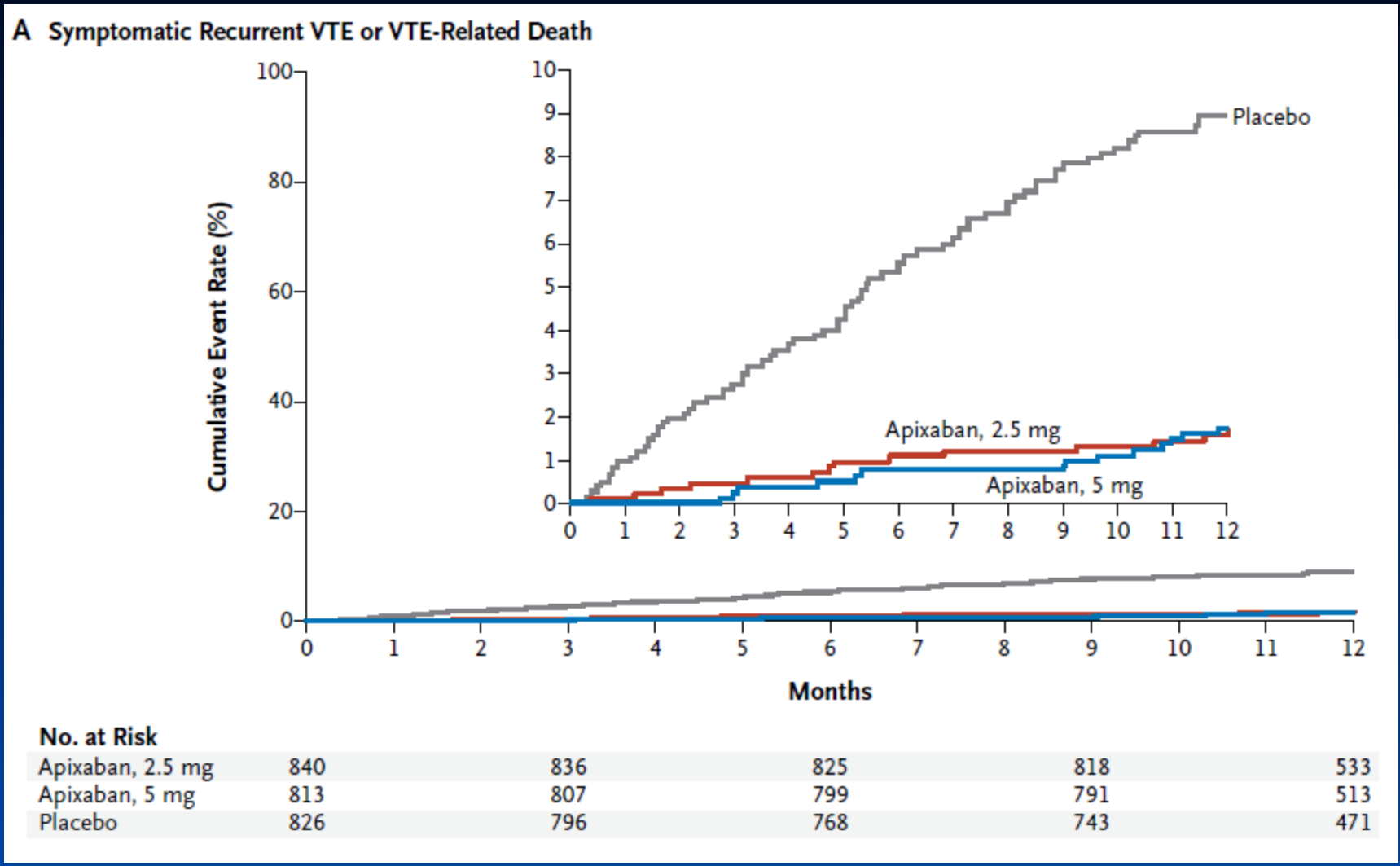
Event	Apixaban 2.5 mg N=840	Apixaban 5 mg N=813	Placebo N=829	Apixaban 2.5 mg vs placebo RR (95% CI)	Apixaban 5 mg vs placebo RR (95% CI)	Apixaban 2.5 mg vs 5 mg RR (95% CI)
Recurrent VTE or VTE-related death	14 (1.7)	14 (1.7)	73 (8.8)	0.19 (0.11, 0.33)	0.20 (0.11, 0.34)	0.97 (0.46, 2.02)
Recurrent VTE, VTE-related death, MI, stroke, or CV-related death	18 (2.1)	19 (2.3)	83 (10.0)	0.21 (0.13, 0.35)	0.23 (0.14, 0.38)	0.92 (0.48, 1.74)
Recurrent VTE or all-cause death*	32 (3.8)	34 (4.2)	96 (11.6)	0.33 (0.22, 0.48)	0.36 (0.25, 0.53)	–

CI, confidence interval; CV, cardiovascular; ITT, intent-to-treat; MI, myocardial infarction; RR, relative risk; VTE, venous thromboembolism

* Includes 13, 20, and 19 subjects lost to follow-up and counted as an outcome event in the 2.5 mg, 5 mg, and placebo groups, respectively

Agnelli G.A, et al. N Engl J Med 2013; 368:699-708

Efficacy Outcomes



Agnelli G.A, et al. N Engl J Med 2013; 368:699-708

Safety Outcomes

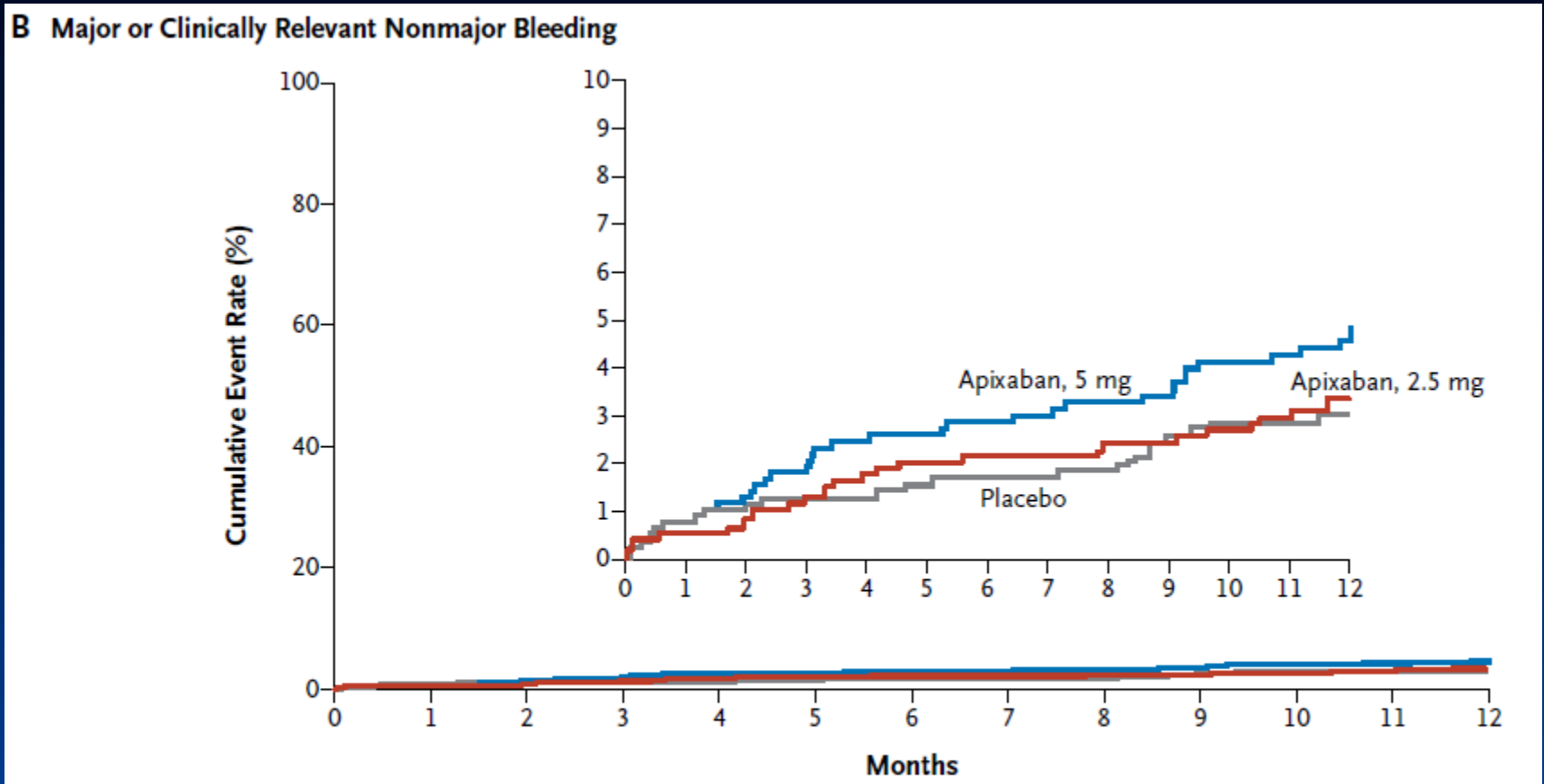
Event	Apixaban 2.5 mg N=840	Apixaban 5 mg N=811	Placebo N=826	Apixaban 2.5 mg vs placebo RR (95% CI)	Apixaban 5 mg vs placebo RR (95% CI)	Apixaban 2.5 mg vs 5 mg RR (95% CI)
Major bleed	2 (0.2)	1 (0.1)	4 (0.5)	0.49 (0.09, 2.64)	0.25 (0.03, 2.24)	1.93 (0.18, 21.25)
Clinically relevant non-major bleed	25 (3.0)	34 (4.2)	19 (2.3)	1.29 (0.72, 2.33)	1.82 (1.05, 3.18)	0.71 (0.43, 1.18)
Major or clinically relevant non-major bleeding	27 (3.2)	35 (4.3)	22 (2.7)	1.20 (0.69, 2.10)	1.62 (0.96, 2.73)	0.74 (0.46, 1.22)

Major Bleeds

- 2.5 mg: 2 events, both Intraocular
- 5.0 mg: 1 event, Gastrointestinal
- Placebo: 4 events, Intraocular, Stroke, Urogenital, Gastrointestinal

Agnelli G.A, et al. N Engl J Med 2013; 368:699-708

Safety Outcomes



No. at Risk					
Apixaban, 2.5 mg	840	786	759	737	354
Apixaban, 5 mg	811	751	716	689	331
Placebo	823	749	687	651	298

Agnelli G.A, et al. N Engl J Med 2013; 368:699-708

HOKUSAI VTE

Great Wave at Kanagawa. ***Katsushika Hokusai*** *1760-1831 (25.4 x 37.1 cm) color woodblock print from Hokusai's series Thirty-six Views of Mount Fuji, which are the high point of Japanese prints.*

The Hokusai-VTE Investigators. N Engl J Med 2013

Hokusai-VTE clinical study protocol, Version 5.0, 16 April 2012, Daiichi Sankyo

The NEW ENGLAND JOURNAL of MEDICINE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Edoxaban versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism

The Hokusai-VTE Investigators*

ABSTRACT

BACKGROUND

Whether the oral factor Xa inhibitor edoxaban can be an alternative to warfarin in patients with venous thromboembolism is unclear.

METHODS

In a randomized, double-blind, noninferiority study, we randomly assigned patients with acute venous thromboembolism, who had initially received heparin, to receive edoxaban at a dose of 60 mg once daily, or 30 mg once daily (e.g., in the case of patients with creatinine clearance of 30 to 50 ml per minute or a body weight below 60 kg), or to receive warfarin. Patients received the study drug for 3 to 12 months. The primary efficacy outcome was recurrent symptomatic venous thromboembolism. The principal safety outcome was major or clinically relevant nonmajor bleeding.

RESULTS

A total of 4921 patients presented with deep-vein thrombosis, and 3319 with a pulmonary embolism. Among patients receiving warfarin, the time in the therapeutic range was 63.5%. Edoxaban was noninferior to warfarin with respect to the primary efficacy outcome, which occurred in 130 patients in the edoxaban group (3.2%) and 146 patients in the warfarin group (3.5%) (hazard ratio, 0.89; 95% confidence interval [CI], 0.70 to 1.13; P<0.001 for noninferiority). The safety outcome occurred in 349 patients (8.5%) in the edoxaban group and 423 patients (10.3%) in the warfarin group (hazard ratio, 0.81; 95% CI, 0.71 to 0.94; P=0.004 for superiority).

The members of the writing committee (Harry R. Büller, M.D., Hervé Décousus, M.D., Michael A. Grosso, M.D., Michele Mercuri, M.D., Saskia Middeldorp, M.D., Martin H. Prins, M.D., Gary E. Raskob, Ph.D., Sebastian M. Schellong, M.D., Lee Schwocho, Ph.D., Annelise Segers, M.D., Minggao Shi, Ph.D., Peter Verhamme, M.D., and Phil Wells, M.D.) assume responsibility for the content and integrity of the article. Address reprint requests to Dr. Büller at the Department of Vascular Medicine, Academic Medical Center, F4-275, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands, or at h.r.buller@amc.uva.nl.

*The affiliations of the authors (members of the writing committee) are listed in the Appendix. The investigators participating in the Hokusai-VTE study and the study committees are listed in the Supplementary Appendix, available at NEJM.org.

This article was published on September 1, 2013, at NEJM.org.

N Engl J Med 2013.
DOI: 10.1056/NEJMoa1306638

Hokusai-VTE: study design

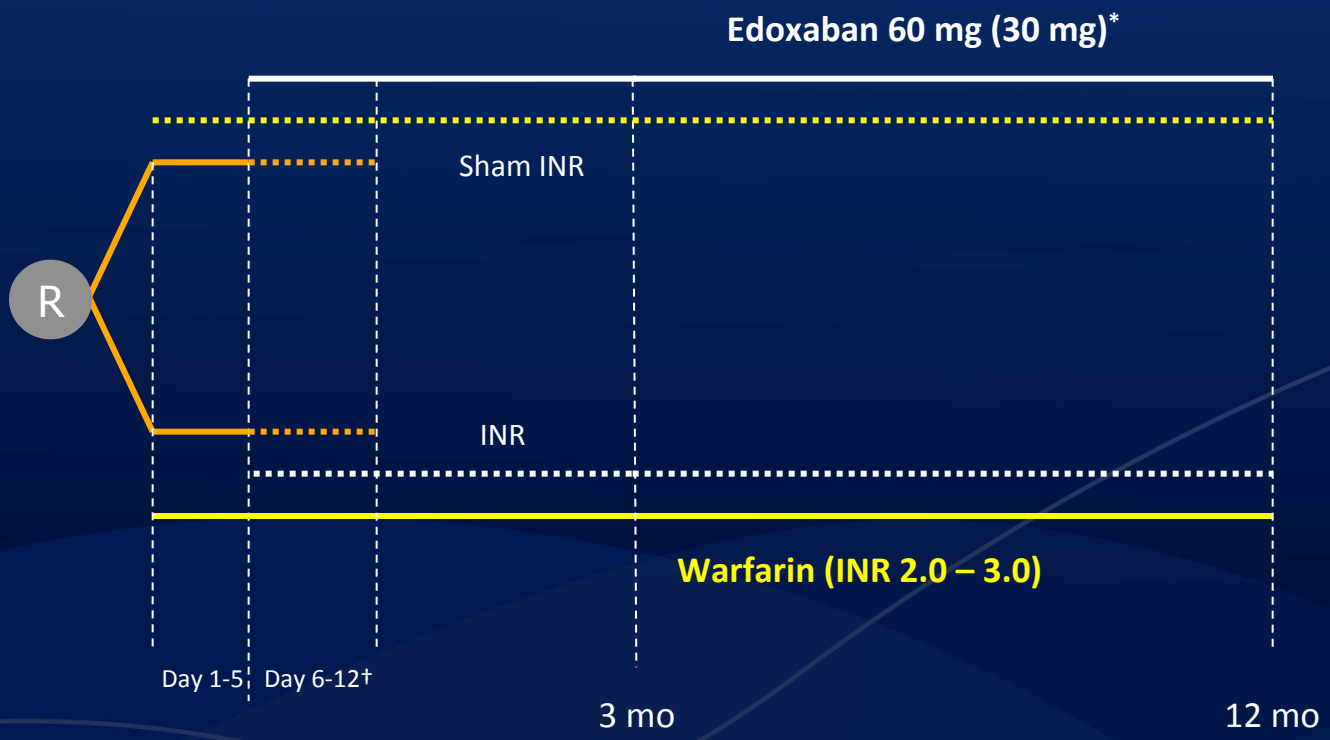
Randomized, double-blind, event-driven study

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

Dosing regimens in Hokusai-VTE

Edoxaban dose was 60 mg once daily with or without food

Edoxaban dose was halved to 30 mg once daily with or without food

- At randomization:
  - Permanent: CrCl 30–50 mL/min
    Body weight ≤60 kg
  - Temporary: Concomitant potent P-gp inhibitor use, only while on these medications: quinidine, verapamil
- During study:
  - Permanent: CrCl 30-50 mL/min and >20% drop from baseline
    Body weight ≤60 kg and >10% drop from baseline
  - Temporary: Concomitant potent P-gp inhibitor use , only while on these medications: quinidine, verapamil, erythromycin, clarithromycin, ketoconazole, azithromycin, itraconazole

The Hokusai-VTE Investigators. N Engl J Med 2013

Hokusai-VTE clinical study protocol, Version 5.0, 16 April 2012, Daiichi Sankyo

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

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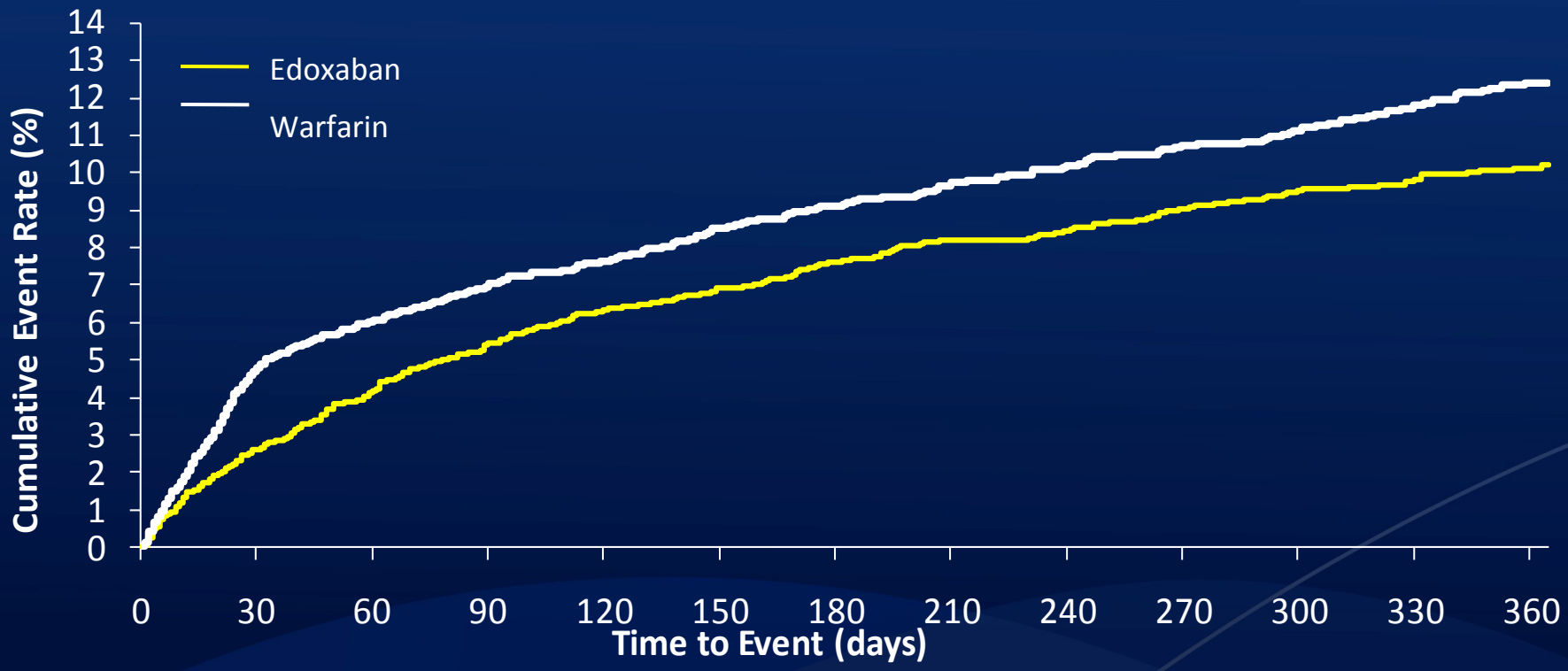
Efficacy outcomes
Subgroup analysis: 30 mg[#]

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

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

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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

Major bleeding

Outcome	Edoxaban (N=4118)	Warfarin (N=4122)
Fatal, n (%)	2 (<0.1)	10 (0.2)
Intracranial	0	6 (0.1)
Gastrointestinal	1 (<0.1)	2 (<0.1)
Retroperitoneal	0	1 (<0.1)
Other	1 (<0.1)	1 (<0.1)
Non-fatal in critical sites, n (%)	13 (0.3)	25 (0.6)
Intracranial	5 (0.1)	12 (0.3)
Retroperitoneal	0	3 (<0.1)
Other	8 (0.2)	10 (0.2)
Non-fatal in non-critical sites, n (%)	41 (1.0)	33 (0.8)

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)	

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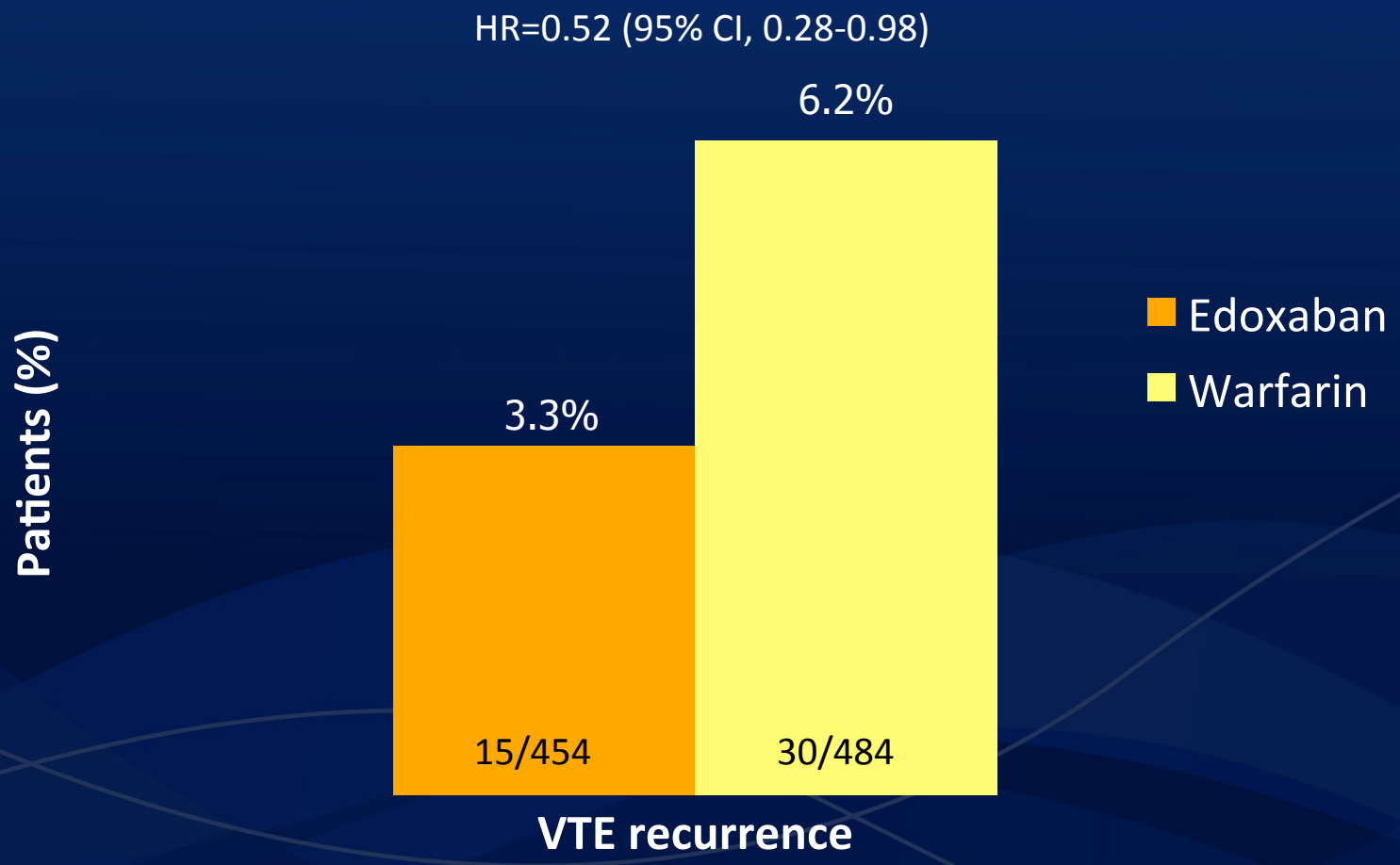
Subgroup analysis in Hokusai-VTE

- 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

Subgroup analysis in PE patients with NT-proBNP ≥500 pg/mL



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NOACs head-to-head

	Dose	Major Bleedings	% PE patients	Duration of treatment	% CRF Patients (ClCr<50%)	Cancer patients
EINSTEIN DVT	15 mg bid for 21 d+ 20 mg od	HR 0.30 (0.8%/1.2%) p=0.77	/	3,6,12 months	14%	12%
EINSTEIN PE	15 mg bid for 21 d +20 mg od	HR 0.49 (0.31-0.79)	4532	3,6,12 months	16.8%	9.2%
EINSTEIN-EXT	20 mg od	0%/0.7% (p= 0.11)	/	6-12 months	14%	----
AMPLIFY	10 mg bid 7 gg + 5mg bid	RR 0.31 (0.17-0.55) P<0.0001	1786 (34%)	6 months	14%	6%
AMPLIFY - EXT	2.5 mg bid 5.0 mg bid	RR 0.49 RR 0.25	/	12 months	16.9%	5.2%
HOKUSAI	60 mg (30 mg)	RR 0.81 (0.71-0.94) p<0.001	3319 (40%)	3-12 months	13%	5%

NOACs head-to-head

	Dose	Major Bleedings	% CRF Patients (ClCr<50%)
ROCKET AF	20 mg od	HR 1.03 (0.96-1.11) p=0.77 HR 0.50 for ICH P<0.001	40%
ARISTOTLE	5 mg bid	HR 0.69 (0.60-0.80) P<0.001	33%

Conclusion

- New oral direct F Xa inhibitors are as safe as effective for VTE treatment
- Rivaroxaban is currently the only orally available drug in the market conceived as a single drug approach
- We need more data for the use of these drugs in selected patients, such as: elder patients, patients with severe renal insufficiency or with cancer
- Antidote (ongoing studies PRT)??? Do we really need it??


LOONEY TUNES
"That's all Folks!"