TRATTAMENTO DEL TEV E DOACs: STRATIFICAZIONE DEL RISCHIO E PERSONALIZZAZIONE DELLA TERAPIA

DAVIDE IMBERTI

DIPARTIMENTO DI MEDICINA INTERNA

CENTRO EMOSTASI E TROMBOSI
OSPEDALE GUGLIELMO DA SALICETO
PIACENZA

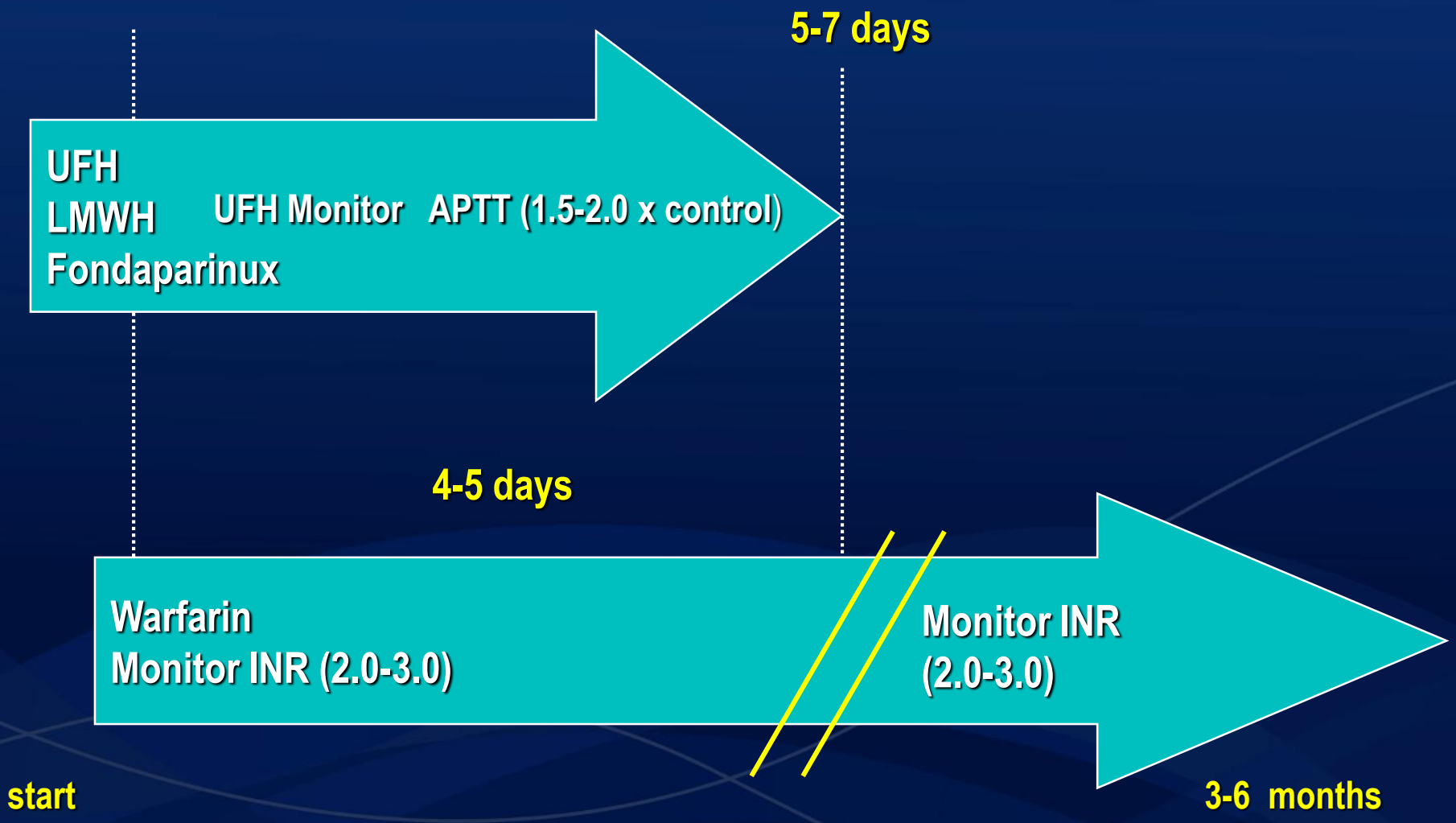
Il *sottoscritto Imberti Davide*

dichiara

di aver avuto negli ultimi due anni rapporti di consulenza con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- *ALFA WASSERMANN*
- *ASPEN*
- *BAYER*
- *BMS-PFIZER*
- *BOHERINGER INGELHEIM*
- *COVIDIEN*
- *DAIICHI-SANKYO*
- *IL*
- *ITALFARMACO*
- *KEDRION*
- *SANOFI AVENTIS*

Initial and long term treatment of VTE



Kearon, Chest, 2008

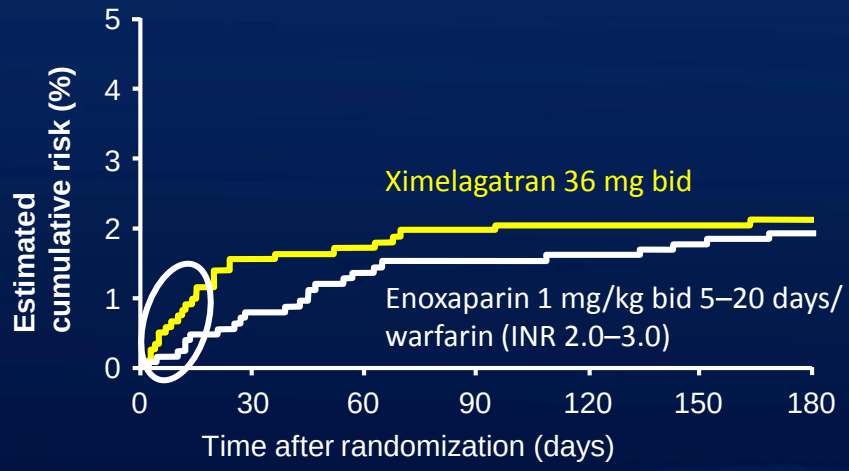
A.T.H.O.S. STUDY
Results

	Acenocoumarol (N=60)	Hep + Acenocoumarol (N=60)
Symptomatic VTE	20%	6.7%
Asympt DVT extens	39.6%	8.2%
Major bleeding	5.0%	3.0%

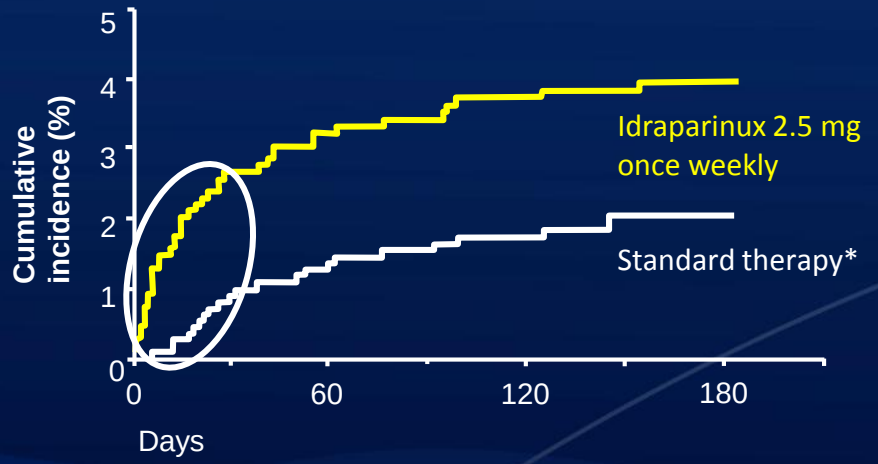
Brandjes, N Engl J Med, 1992

Rationale for intensified initial treatment in phase III VTE treatment studies

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
2. The van Gogh Investigators. *N Engl J Med* 2007

Treatment of acute VTE with new anticoagulants: possible options

- Start with standard parenteral drugs (i.e. LMWHs) for the initial therapy before the new compound

- Start therapy with an intensive regimen of the new compound for the first weeks (“single drug approach”)

NOAC VTE: study designs

	RE-COVER I[1] RE-COVER II[2]	EINSTEIN-DVT[3] EINSTEIN-PE[4]	AMPLIFY[5]	Hokusai-VTE[6]
Study drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Study design*	Double-blind	Open-label	Double-blind	Double-blind
Pre-randomization heparin	NR	<48 hrs	<36 hrs	<48 hrs
Heparin lead-in	At least 5 days	None	None	At least 5 days
Dose	150 mg BID	15 mg BID x 3 wk then 20 mg QD	10 mg BID x 7 d then 5 mg BID	60 mg QD 30 mg QD†
Dose reduction	NONE	NONE	NONE	18%
Randomized population	2,564[1] 2,568[2]	3,449[3] 4,833[4]	5,400	8,292
Treatment duration	6 months	Pre-specified 3, 6, 12 months	6 months	Flexible 3 to 12 months

*Comparator was warfarin in each case

†Dose was halved to 30 mg in patients perceived to be at higher risk for bleeding by predefined criteria

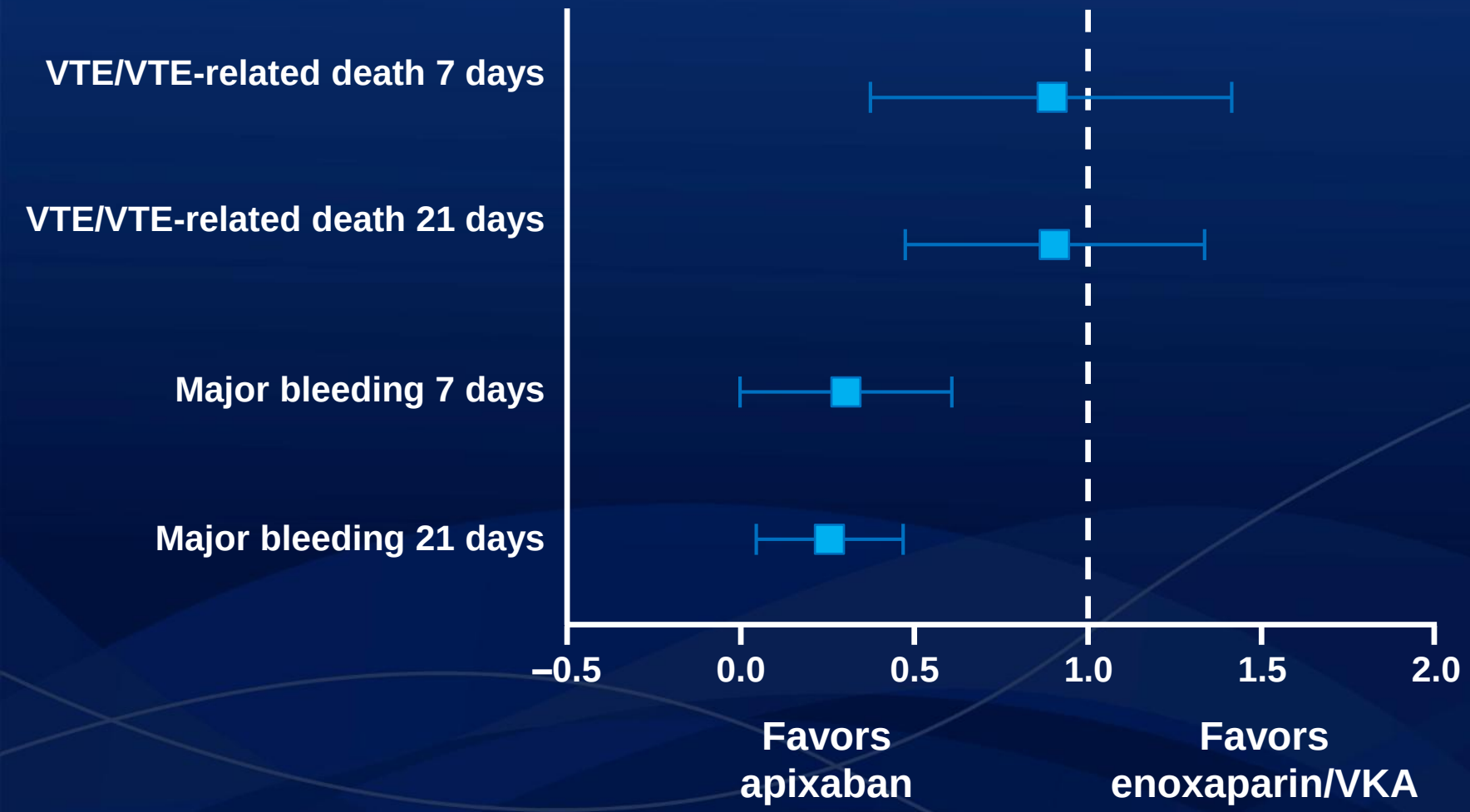
NR=not reported

1. Schulman et al. N Engl J Med 2009;361:2342–2352; 2. Schulman et al. Blood 2011;118:Abstract 205

3. EINSTEIN Investigators. N Engl J Med 2010;363:2499–2510; 4. EINSTEIN–PE Investigators. N Engl J Med 2012;366:1287–1297

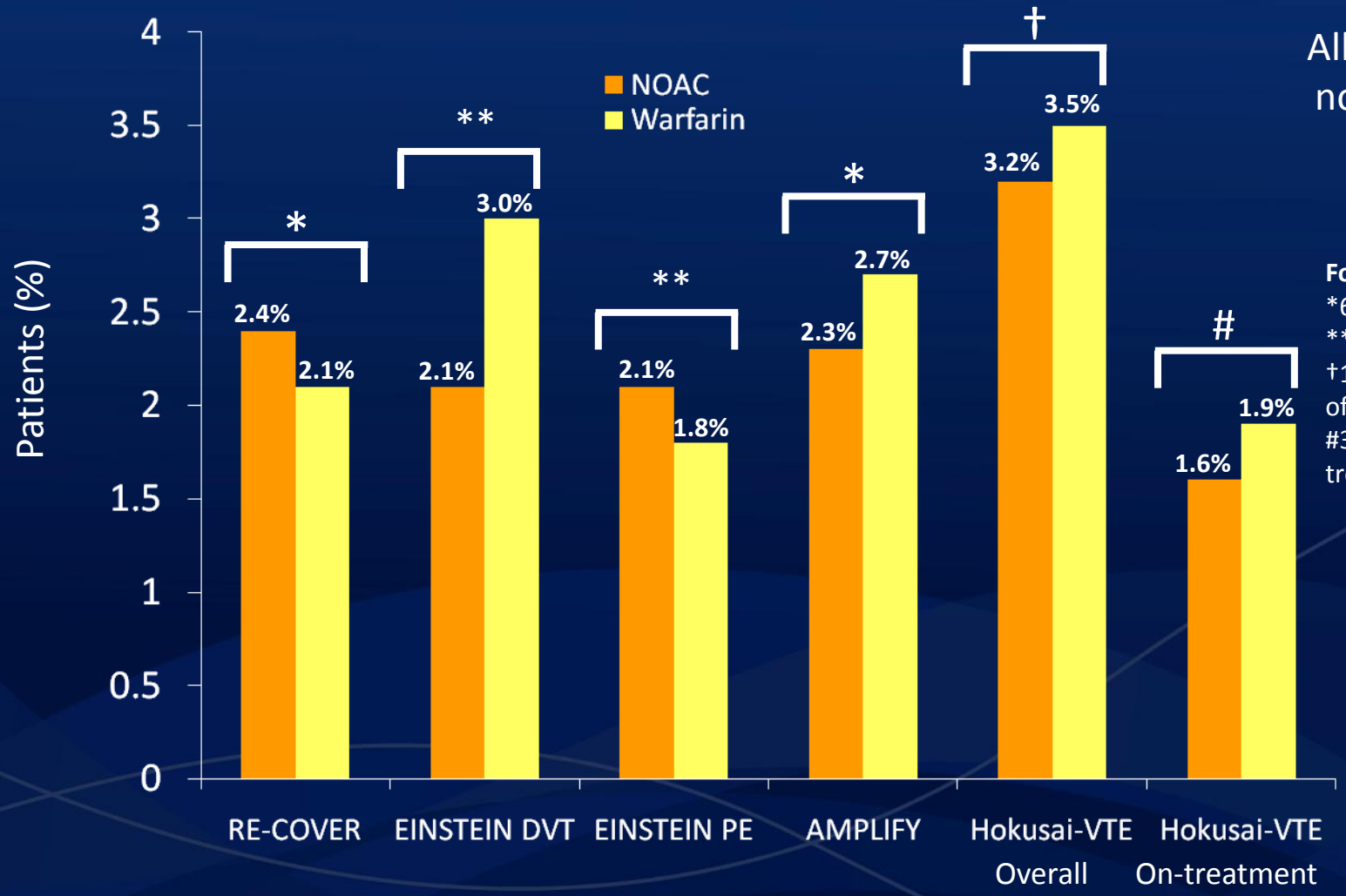
5. Agnelli et al. N Engl J Med 2013;369:799–808; 6. The Hokusai-VTE Investigators. N Engl J Med 2013; e-pub ahead of print

AMPLIFY- Adjudicated VTE/VTE-Related Death and Major Bleeding During the First 7 and 21 Days



Raskob, Thromb Haemost, 2016

Phase III VTE trials – recurrent VTE

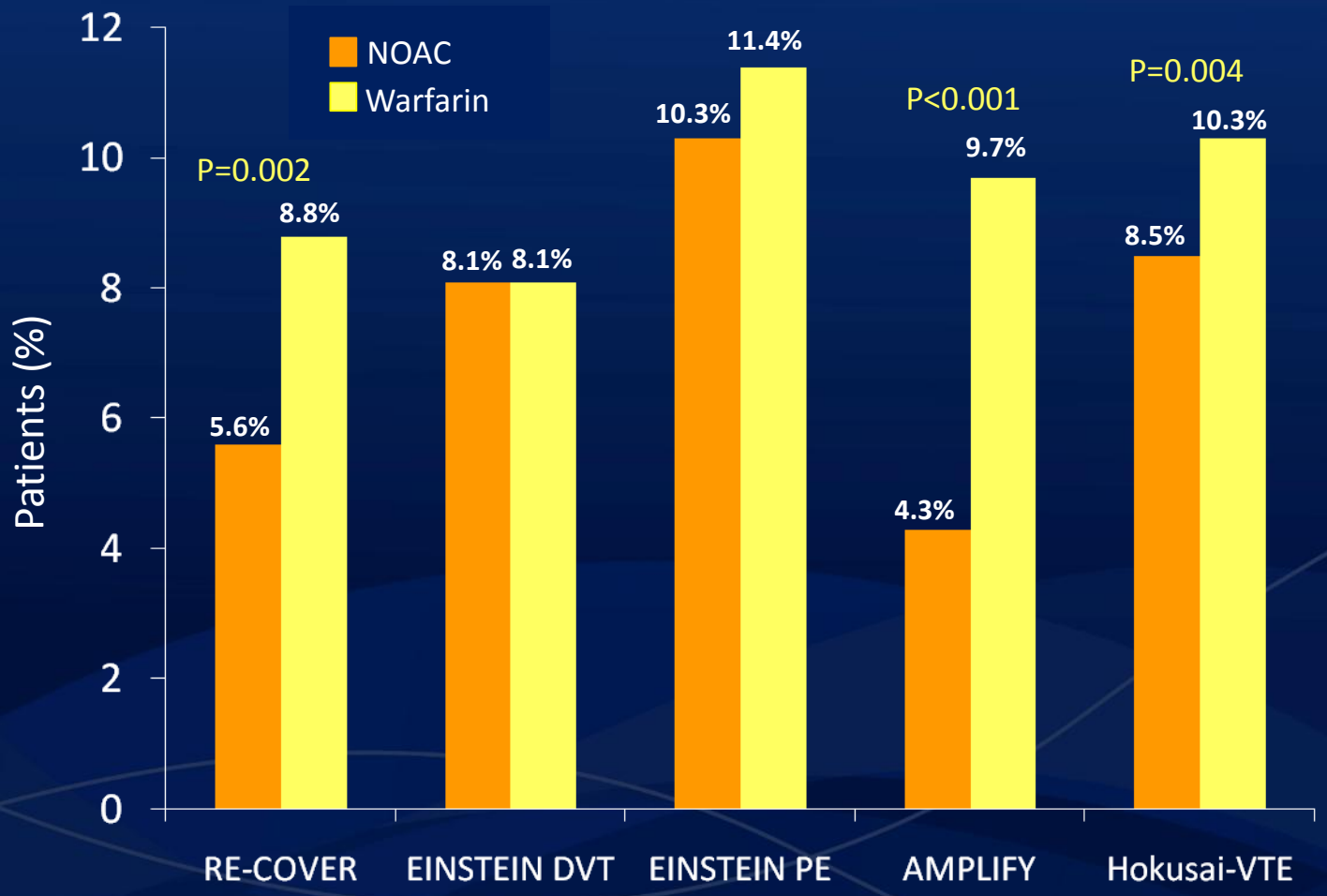


All NOACs were non-inferior to warfarin

Follow up period:
*6 months
**3, 6 or 12 months
†12 months regardless of treatment duration
#3 to 12 months (on-treatment analysis)

1. Schulman et al. N Engl J Med 2009;361:2342–2352
2. EINSTEIN Investigators. N Engl J Med 2010;363:2499–2510; 3. EINSTEIN–PE Investigators. N Engl J Med 2012;366:1287–1297
4. Agnelli et al. N Engl J Med 2013;369:799–808; 5. The Hokusai-VTE Investigators. N Engl J Med 2013; e-pub ahead of print

Phase III VTE trials – safety
Major or clinically relevant non-major bleeding



1. Schulman et al. N Engl J Med 2009;361:2342–2352
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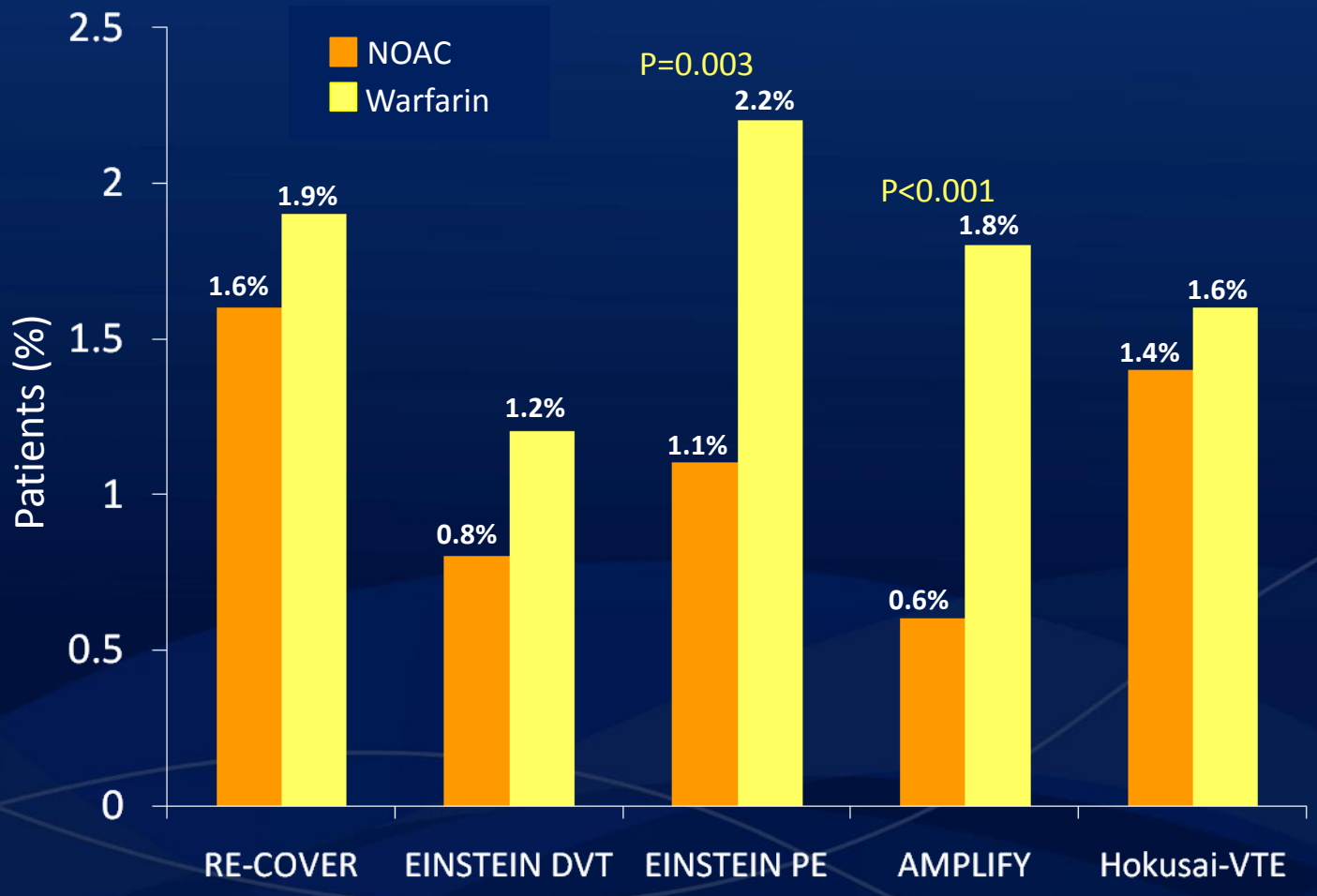
Phase III VTE trials – safety
Major bleeding



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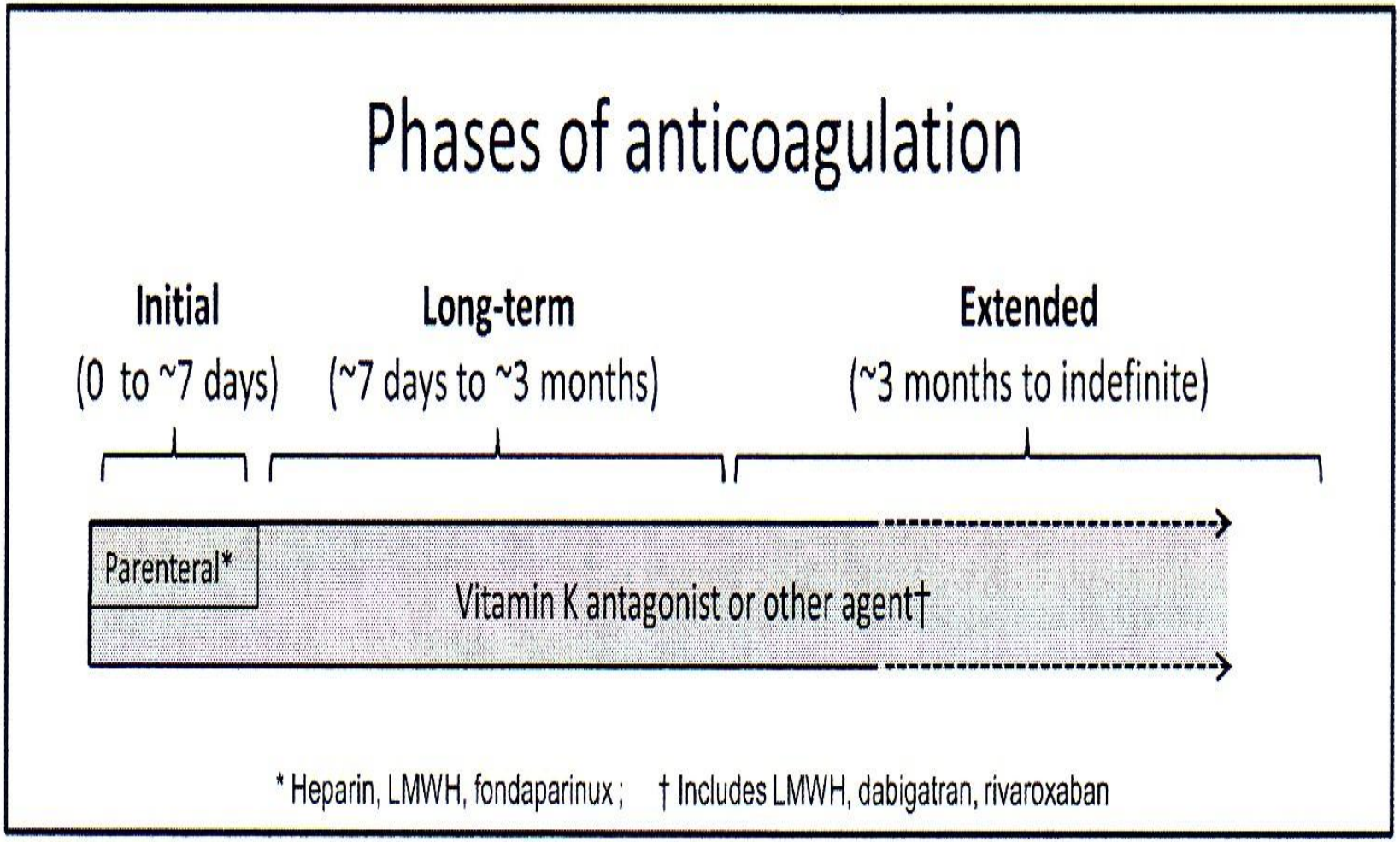
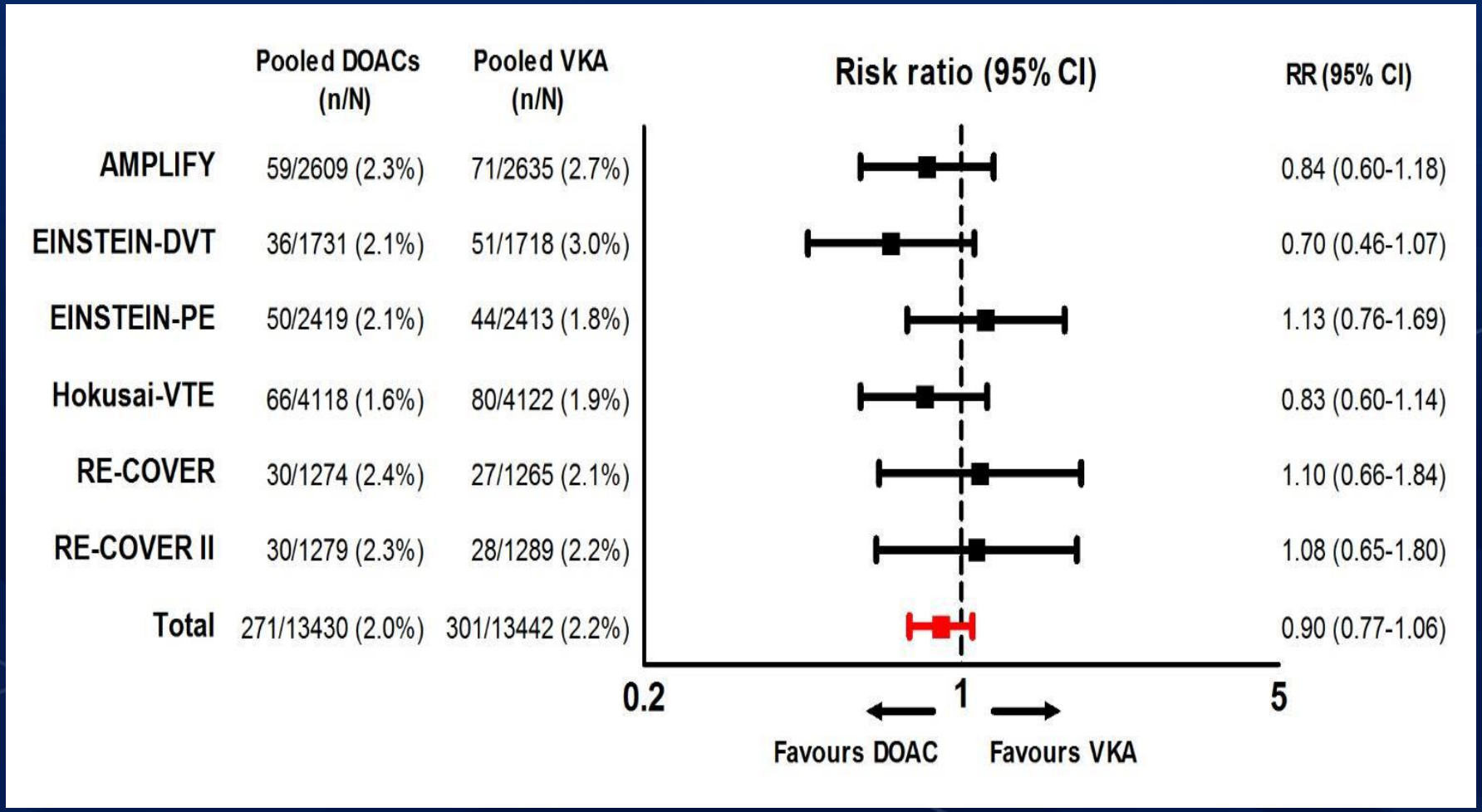
Initial and long term treatment of VTE



Kearon, Chest, 2012

Effectiveness and safety of NOACs as compared with VKAs in the treatment of acute symptomatic VTE: a systematic review and meta-analysis

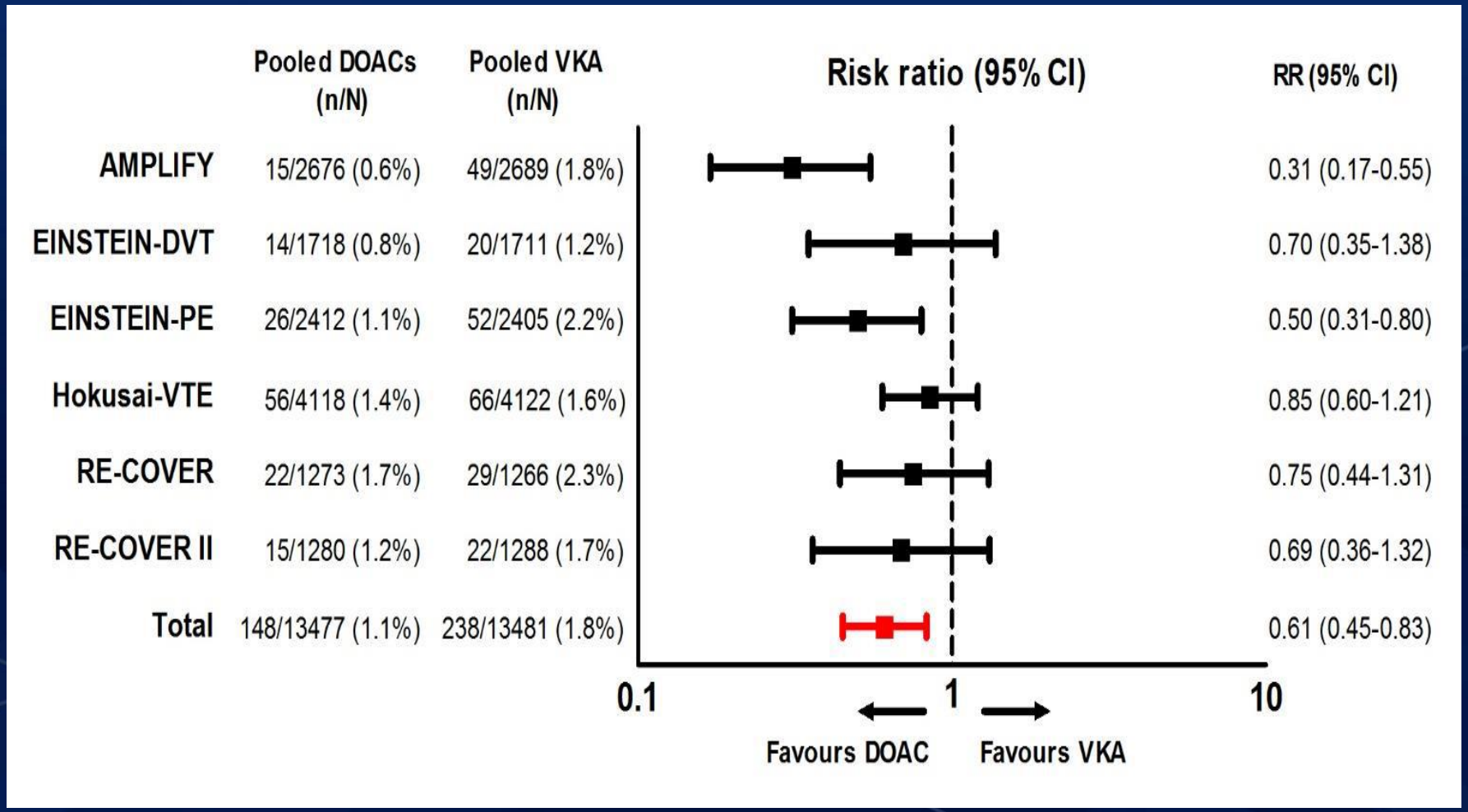
Overall efficacy



Van Es, Blood, 2014

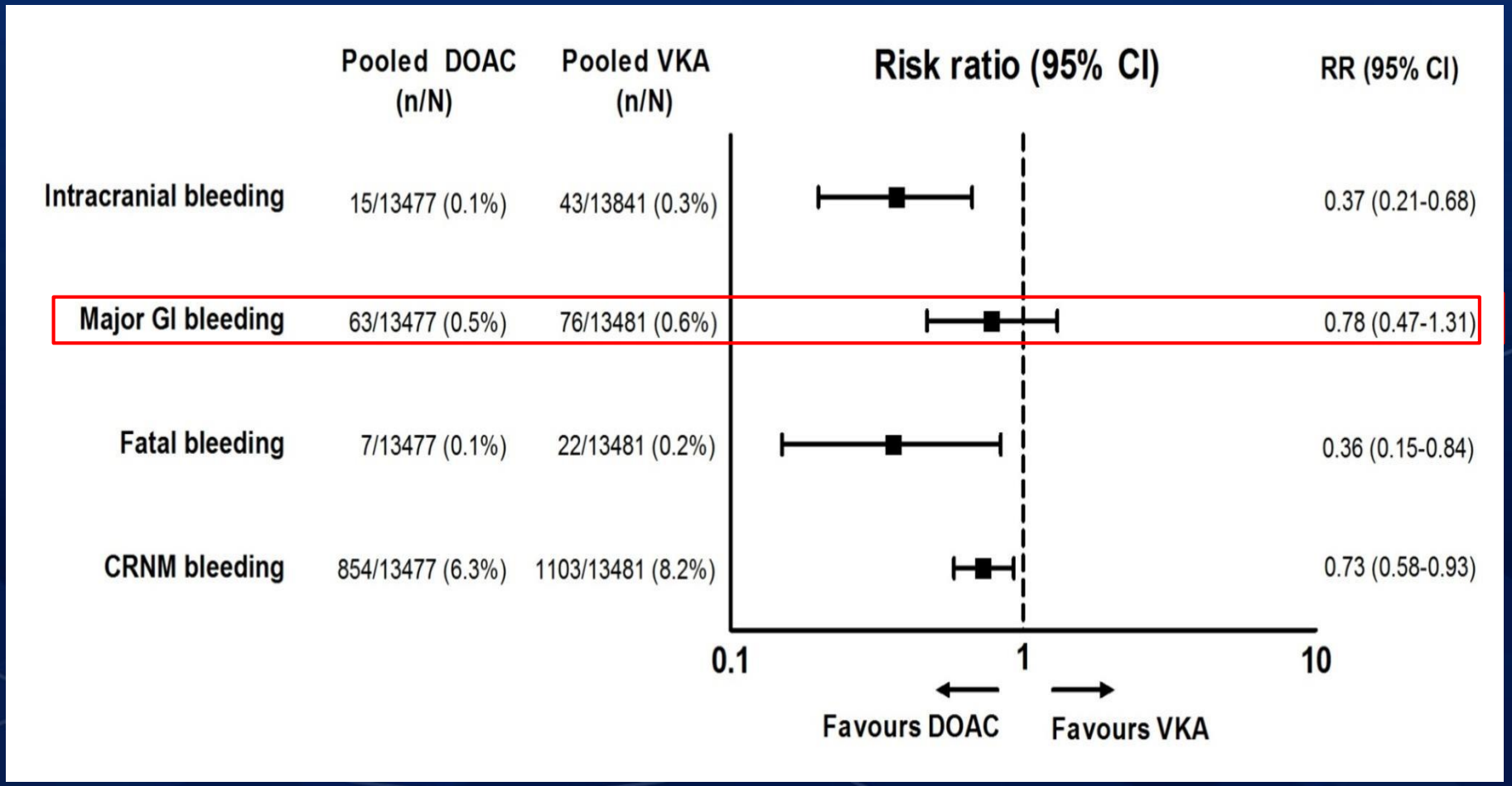
Effectiveness and safety of NOACs as compared with VKAs in the treatment of acute symptomatic VTE: a systematic review and meta-analysis

Overall major bleedings



Van Es, Blood, 2014

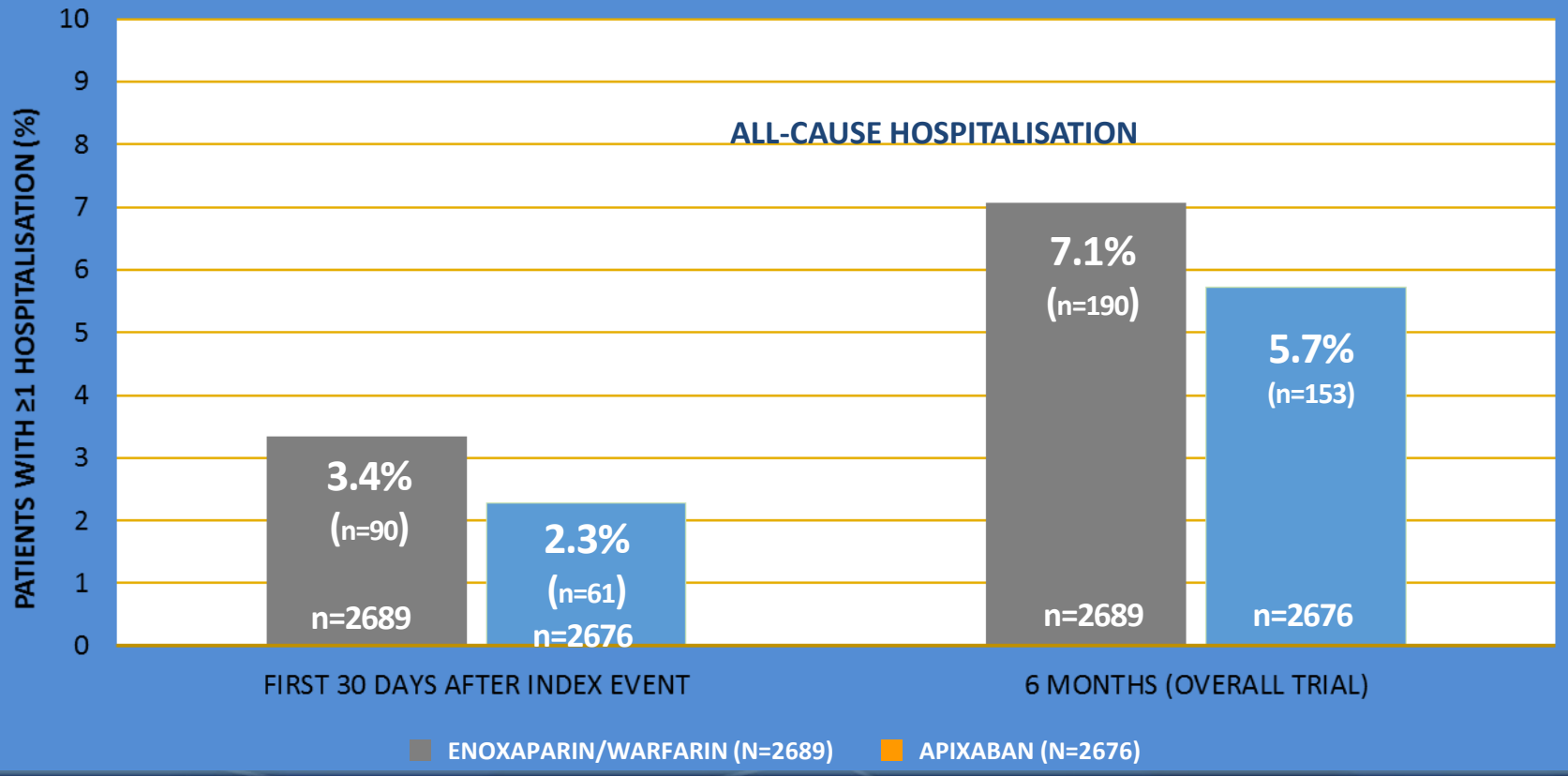
Bleeding components



Van Es, Blood, 2014

AMPLIFY sub-analysis: all-cause hospitalization rates

Apixaban demonstrated a lower all-cause hospitalization rate compared with enoxaparin/warfarin
The reduced number of hospitalisations in patients treated with apixaban was mainly due to fewer recurrent VTE and bleeding events vs patients treated with enoxaparin/warfarin



Liu, J Am Heart Assoc, 2015

AMPLIFY EXTENSION sub-analysis: all-cause hospitalization rates

Apixaban demonstrated a lower all-cause hospitalization rate compared with placebo
The reduced number of hospitalisations in patients treated with apixaban was mainly due to fewer recurrent VTE and bleeding events vs patients treated with placebo

Treatment	n	No of hospitalized subjects	Hospitalizations		*P* value*
			Event rate % (95% CI)	HR (95% CI)	
Placebo	829	62	7.48 (5.69–9.27)		
Apixaban 2.5 mg BID	840	42	5.00 (3.53–6.47)	0.64 (0.43–0.95)	0.026
Apixaban 5 mg BID	813	34	4.18 (2.81–5.56)	0.54 (0.36–0.82)	0.004
Apixaban 5 mg vs 2.5 mg BID				0.84 (0.54–1.32)	0.455

Liu, Thomb Haemost, 2016

Antithrombotic therapy for VTE disease: CHEST guidelines 2016

Summary of recommendations in non cancer patients

- **In patients with DVT of the leg or PE and no cancer, as long-term (first 3 months) anticoagulant therapy, we suggest dabigatran, rivaroxaban, apixaban or edoxaban over VKA therapy** (all Grade 2B). **For patients with DVT of the leg or PE and no cancer who are not treated with dabigatran, rivaroxaban, apixaban or edoxaban, we suggest VKA therapy over LMWH** (Grade 2C).

Kearon, Chest, 2016

A quali pazienti i NAO

- Fragili
- Pazienti con neoplasia
- EP
- Terapia “extended”

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EINSTEIN DVT and EINSTEIN PE pooled analysis: outcomes in fragile patients*

Outcome	Rivaroxaban		Enoxaparin/VKA		HR (95% CI)
	n/N	%	n/N	%	
Recurrent VTE					
Fragile	21/791	2.7	30/782	3.8	0.68 (0.39–1.18)
Non-fragile	65/3359	1.9	65/3349	1.9	0.98 (0.70–1.38)
Major bleeding					
Fragile	10/788	1.3	35/779	4.5	0.27 (0.13–0.54)
Non-fragile	30/3342	0.9	37/3337	1.1	0.80 (0.49–1.29)

*Age >75 years or CrCl <50 ml/min or body weight ≤50 kg

Prins, Thromb J, 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)	

* CrCl 30–50 mL/min, Body weight ≤60, Concomitant potent P-gp inhibitor use

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

Clinical presentation and course of bleeding events in patients with VTE, treated with apixaban or enoxaparin and warfarin. Results from the Amplify trial

Classification schemes: Major Bleeding

Category	Description
A. Clinical presentation	
1	Bleeding events presenting without any clinical emergency.
2	All bleeding events that could not be classified to any of the other three categories, as they presented with the need for some measures but without clear urgency.
3	Bleeding events presenting with great medical emergency; e.g. with hemodynamic instability, or cerebral major bleeding presenting with neurologic symptoms.
4	Bleeding events already fatal before or almost immediately upon entering the hospital.

Category	Description
B. Clinical course	
1	Bleeding events for which only measures were applied to treat discomfort, without transfusions of erythrocytes.
2	Bleeding events requiring only standard measures such as transfusions of erythrocytes, and straight forward measures.
3	Life threatening bleeding events requiring immediate and elaborate measures to avoid death. These bleedings could still be fatal after all interventions and could lead to persistent disability.
4	Bleeding events for which death was unavoidable, so that no lifesaving attempts were made.

Bleker, Thromb Haemost, 2016

Results of the classification of major bleeding events

	Apixaban	Enoxaparin/ warfarin
A.Clinical presentation		
Number of major bleeding events	14 **0.6 %**	49 **1.8%**
Category 1	2 (14.3%)	8 (16.3%)
Category 2	8 (57.1%)	19 (38.8%)
Category 3	3 (21.4%)	22 (44.9%)
Category 4	1 (7.1%)	0 (0%)
Number of major bleeding events	14	49
Category 1 or 2	10 (71.4%)	27 (55.1%)
Category 3 or 4	4 (28.5%)	22 (44.9%)

	Apixaban	Enoxaparin/ warfarin
B. Clinical course		
Number of major bleeding events	14	49
Category 1	1 (7.1%)	13 (26.5%)
Category 2	11 (78.6%)	30 (61.2%)
Category 3	2 (14.3%)	6 (12.2%)
Category 4	0 (0%)	0 (0%)
Number of major bleeding events	14	49
Category 1 or 2	12 (85.7%)	43 (87.7%)
Category 3 or 4	2 (14.3%)	6 (12.2%)

Bleker, Thromb Haemost, 2016

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VTE treatment in cancer patients: Phase III RCTs with new oral anticoagulants

Study	Randomized Intervention	Duration of treatment (months)	Total included patients N (%)	Randomized patients with active cancer* n (%)
RECOVER I-II [21,22]	• Dabigatran 150 mg BID • Enoxap. 1 mg/kg BID x 5 d + VKA daily	6	5.153	221 (4.3)
EINSTEIN DVT-PE [18,19]	• Riva. 15 mg BID x 3 weeks, 20 mg/die • Enoxap. 1 mg/kg BID x 5 d + VKA daily	3,6,12	8281	462 (5.6)
AMPLIFY [23]	• Apixaban 10 mg BID x 7 d, 5 mg/ die • Enoxap. 1 mg/kg BID x 5 d + VKA daily	6	5244	143 (2.7)
HOKUSAI-VTE [20]	• Edoxaban 30 or 60 mg/die • Enoxap. 1 mg/kg BID x 5 d + VKA daily	3-12	8240	208 (2.5)
Total			26.918	1.227 (4.6)

BID = twice daily; RCT = randomised clinical trials; VKA = vitamin K antagonist; VTE = venous thromboembolism.

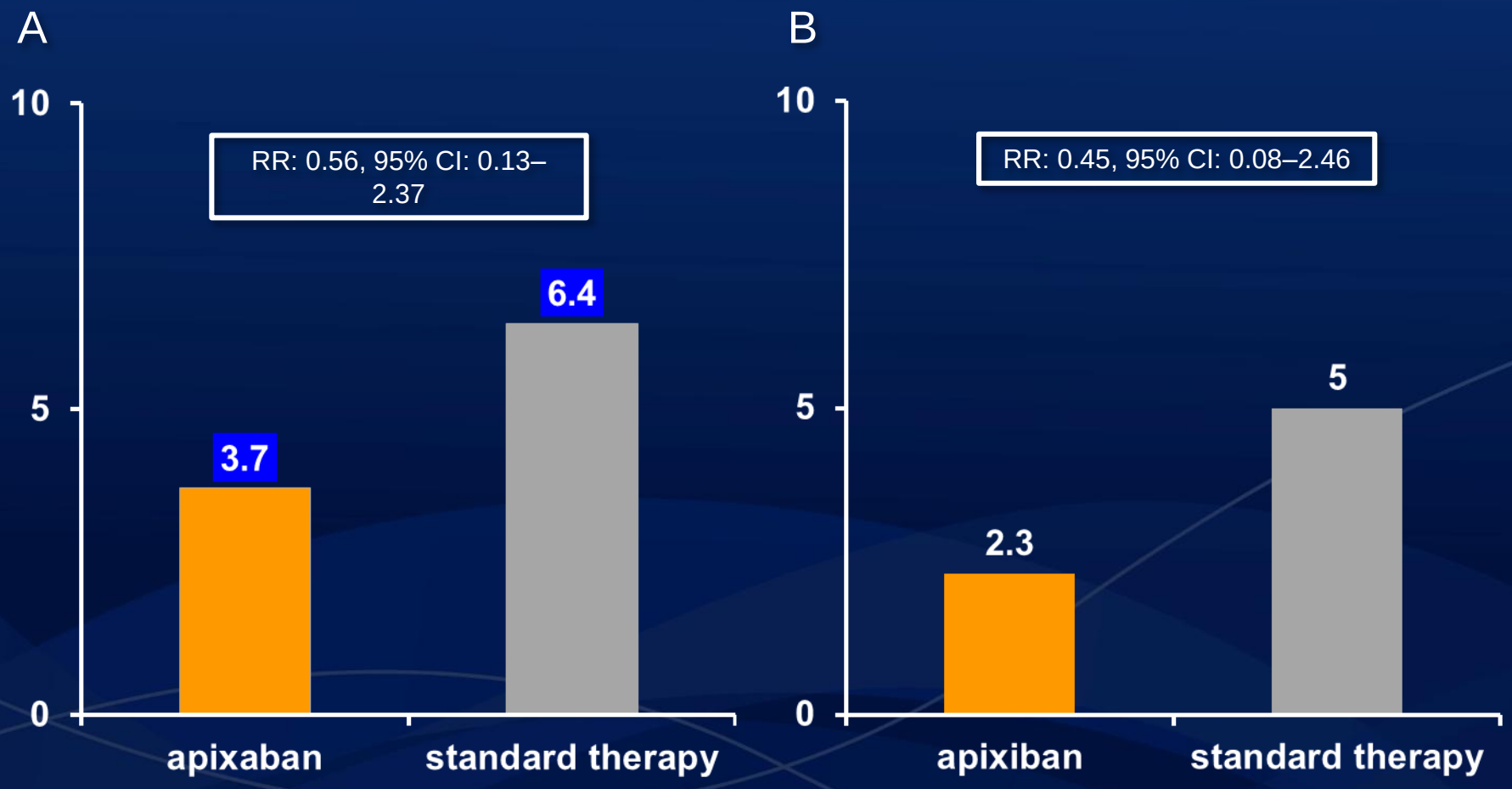
VTE treatment in cancer patients: Phase III RCTs with new oral anticoagulants

- Subgroup of patients with cancer treated with NOAC in RCT: *post hoc* analyses
  - Einstein trials
  - Hokusai-VTE trial
  - RECOVER I & II trials
  - Amplify trial

NOAC = new oral anticoagulant; RCT = randomised controlled trials; VTE = venous thromboembolism.

Schulman S, *et al. N Engl J Med* 2009; 361:2342–235;
Schulman S, *et al. Circulation* 2014; 129:764–772;
The EINSTEIN Investigators *N Engl J Med* 2010; 363:2499–2510;
The EINSTEIN Investigators *N Engl J Med* 2012; 366:1287–1297;
Agnelli G, *et al. N Engl J Med* 2013; 369:799–808;
The Hokusai-VTE Investigators *N Engl J Med* 2013; 369:1406–1415.

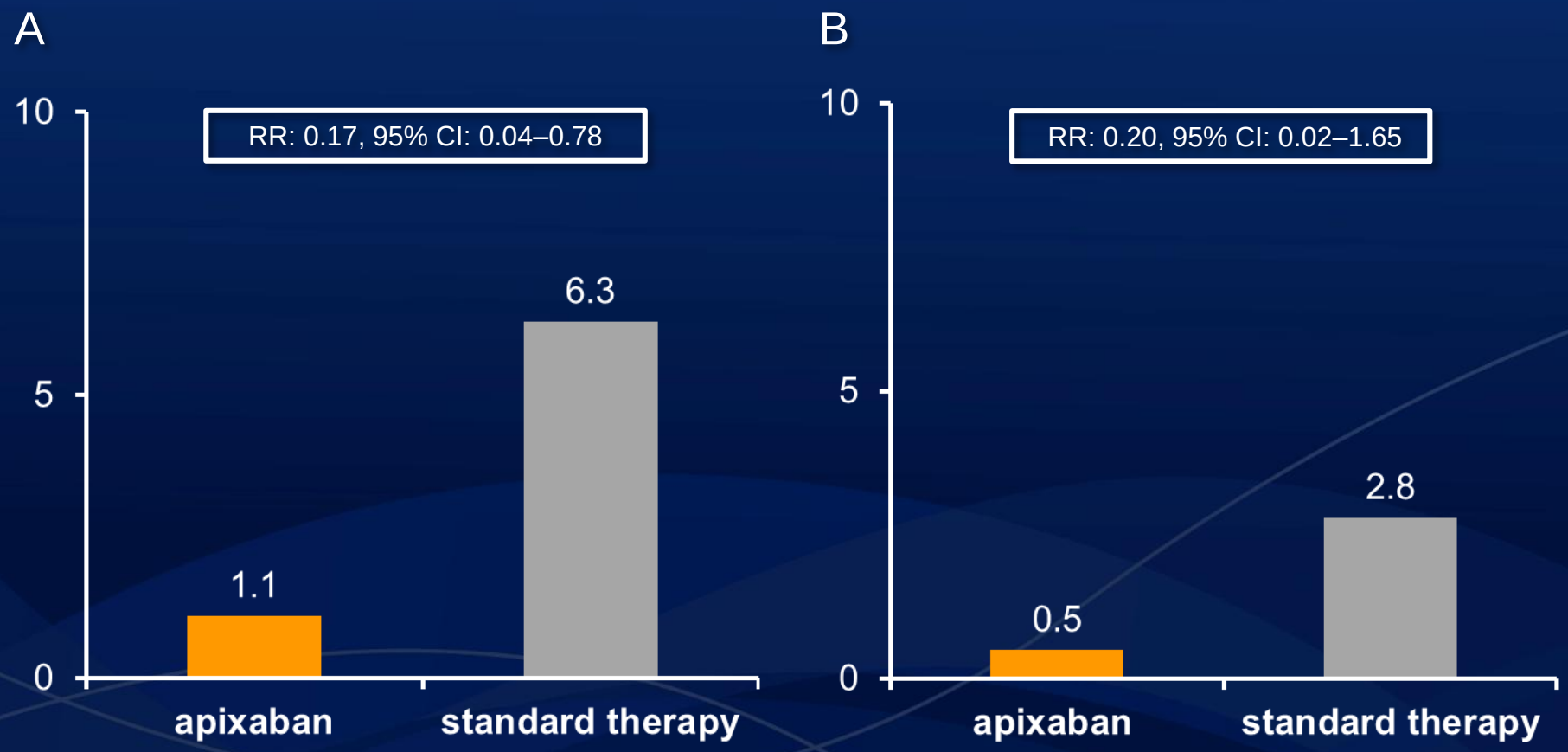
VTE recurrences (A) and major bleeding (B) in patients with active cancer



RR = relative risk; VTE = venous thromboembolism.

Agnelli , J Thromb Haemost , 2015

VTE recurrences (A) and major bleeding (B) in patients with history of cancer



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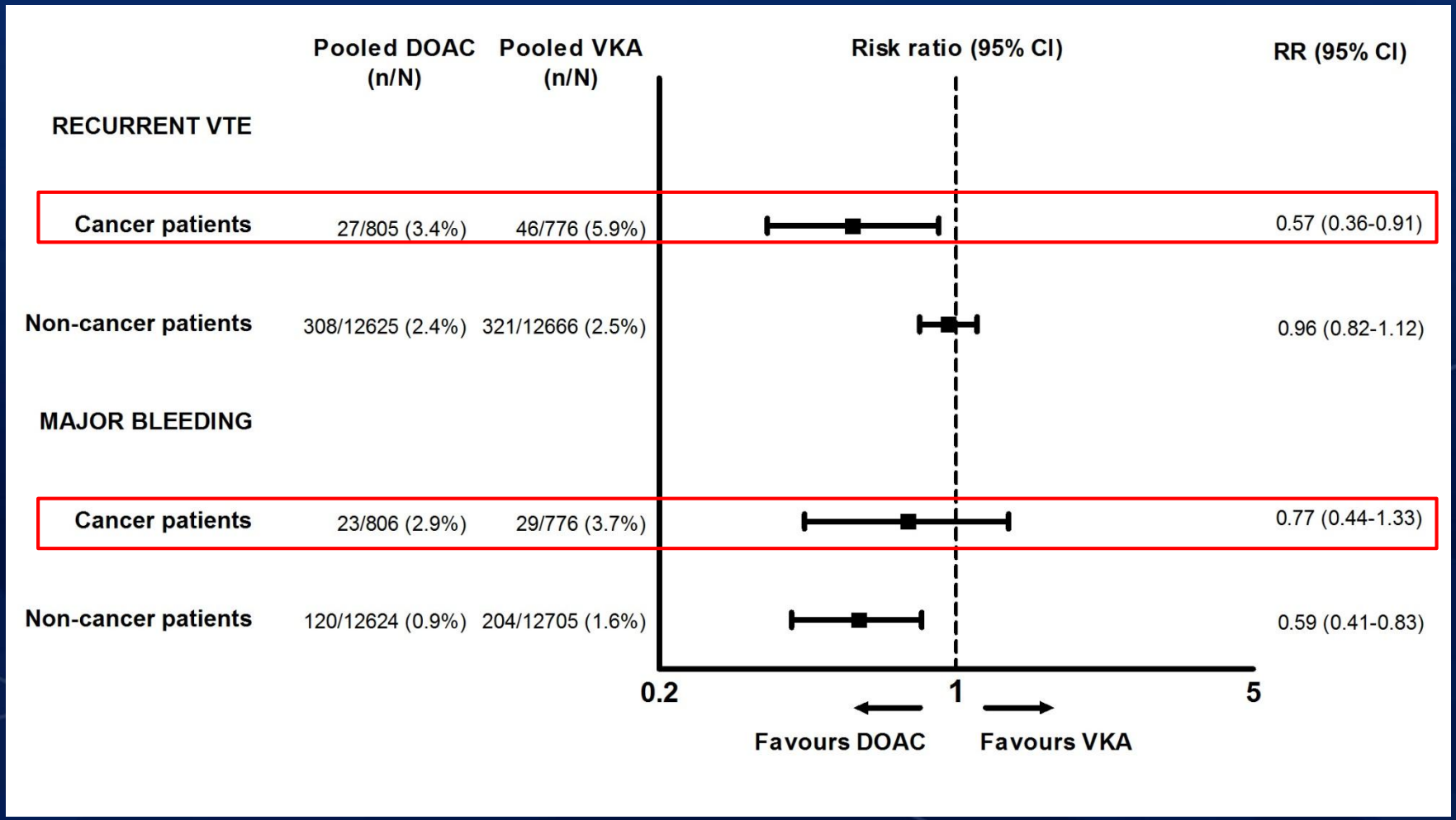
Agnelli , J Thromb Haemost , 2015

DOACs vs VKA for the treatment of VTE in cancer patients: results of a meta-analysis



Van Es , Blood, 2014

Antithrombotic therapy for VTE disease: CHEST guidelines 2016

Summary of recommendations in cancer patients

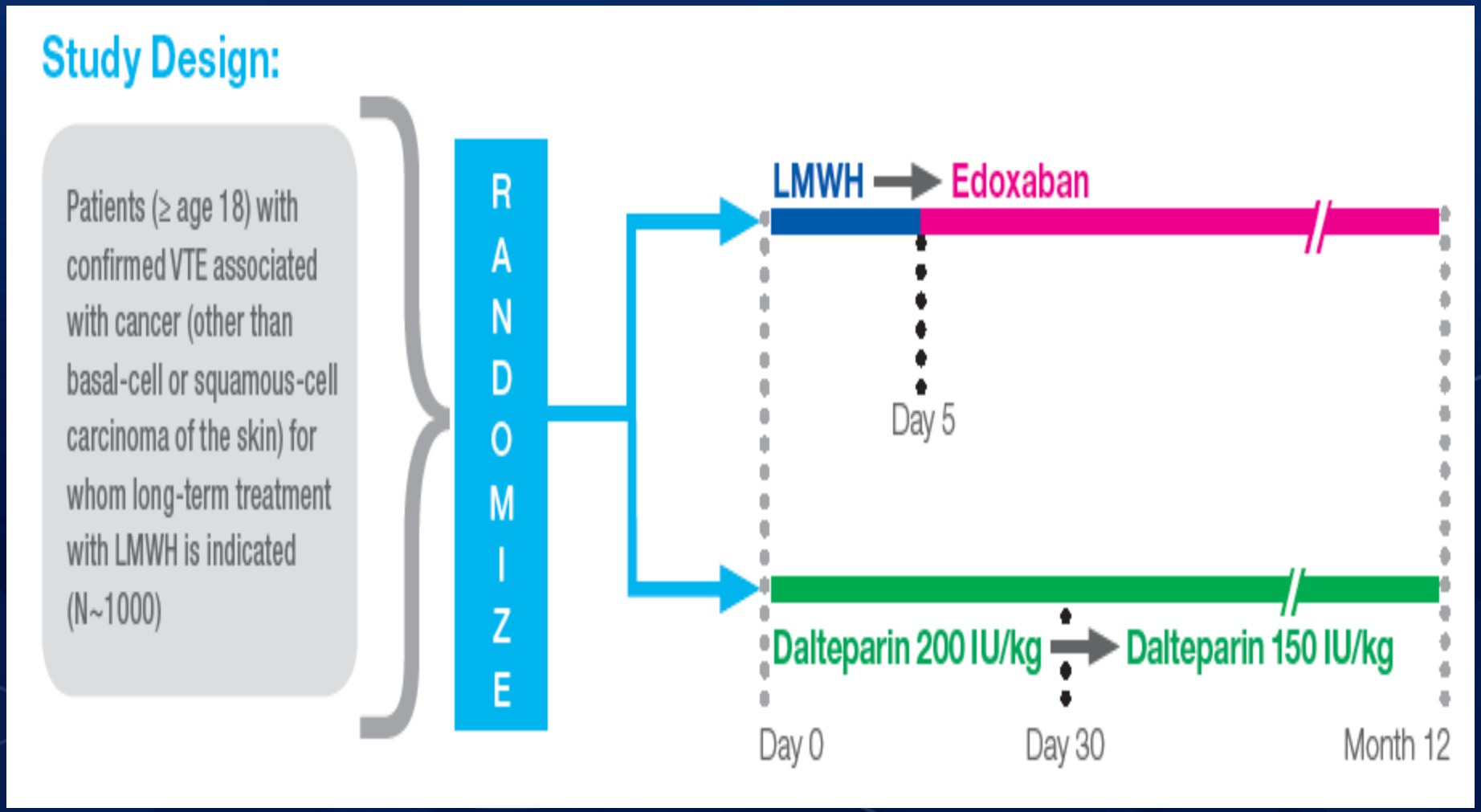
Choice of long-term (first 3 months) and extended (no scheduled stop date)

- *In patients **with DVT of the leg or PE and cancer** ("cancer-associated thrombosis"), as long-term (first 3 months) anticoagulant therapy, we **suggest** **LMWH over VKA therapy** (Grade 2C), **dabigatran** (Grade 2C), **rivaroxaban** (Grade 2C), **apixaban** (Grade 2C) or **edoxaban** (Grade 2C)*

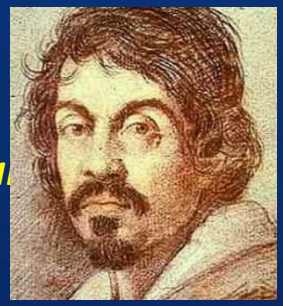
DVT = deep vein thrombosis, LMWH = low-molecular-weight heparin; PE = pulmonary embolism; VKA = vitamin K antagonist; VTE = venous thromboembolism.

Kearon, Chest, 2016

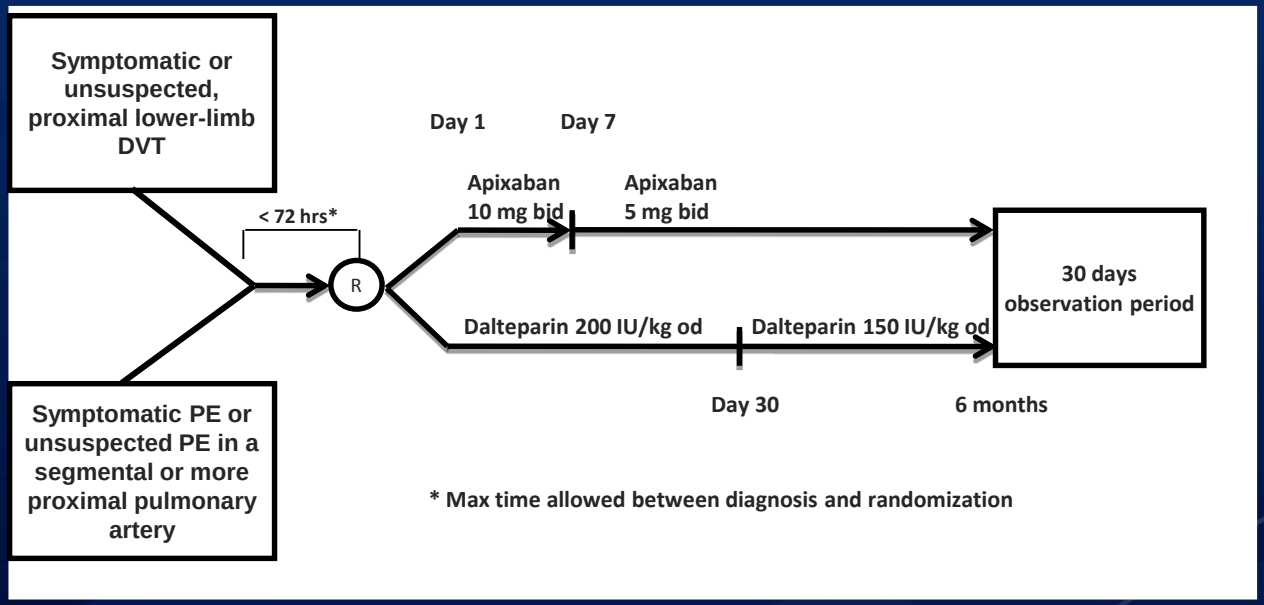
Hokusai cancer VTE trial
Study design



CARAVAGGIO



Apixaban for the treatment of venous thromboembolism in patients with ca
A prospective randomized open blinded-endpoint (PROBE) study



Principal Investigator	**Prof. Giancarlo Agnelli**
European Countries Involved	10
Centers Involved	≈ 120
Sample Size	≈ 1200 pts

Rivaroxaban in Cancer-Associated Thrombosis: CALLISTO Programme Overview

Name	Timeline
Ex-USA	
VTE treatment cancer registry (phase IV)	Starts end 2015
VTE treatment: phase I concept	Starts end 2015
VTE treatment: phase IV platelet	Starts early 2016
VTE treatment: vomiting, switching	Starts 2016
VTE treatment: SELECT-D (phase II)	*Ongoing, completion end 2016*
VTE treatment: CASTA-DIVA (phase II)	*Starts 2015*
USA	
VTE treatment: periprocedural management	Starts early 2015
VTE treatment cancer registry (phase IV)	Starts early 2015
VTE prophylaxis in high-risk patients (phase IIIb)	Planned
VTE treatment database	*Ongoing*

Studies in italics are investigator-initiated studies

CALLISTO

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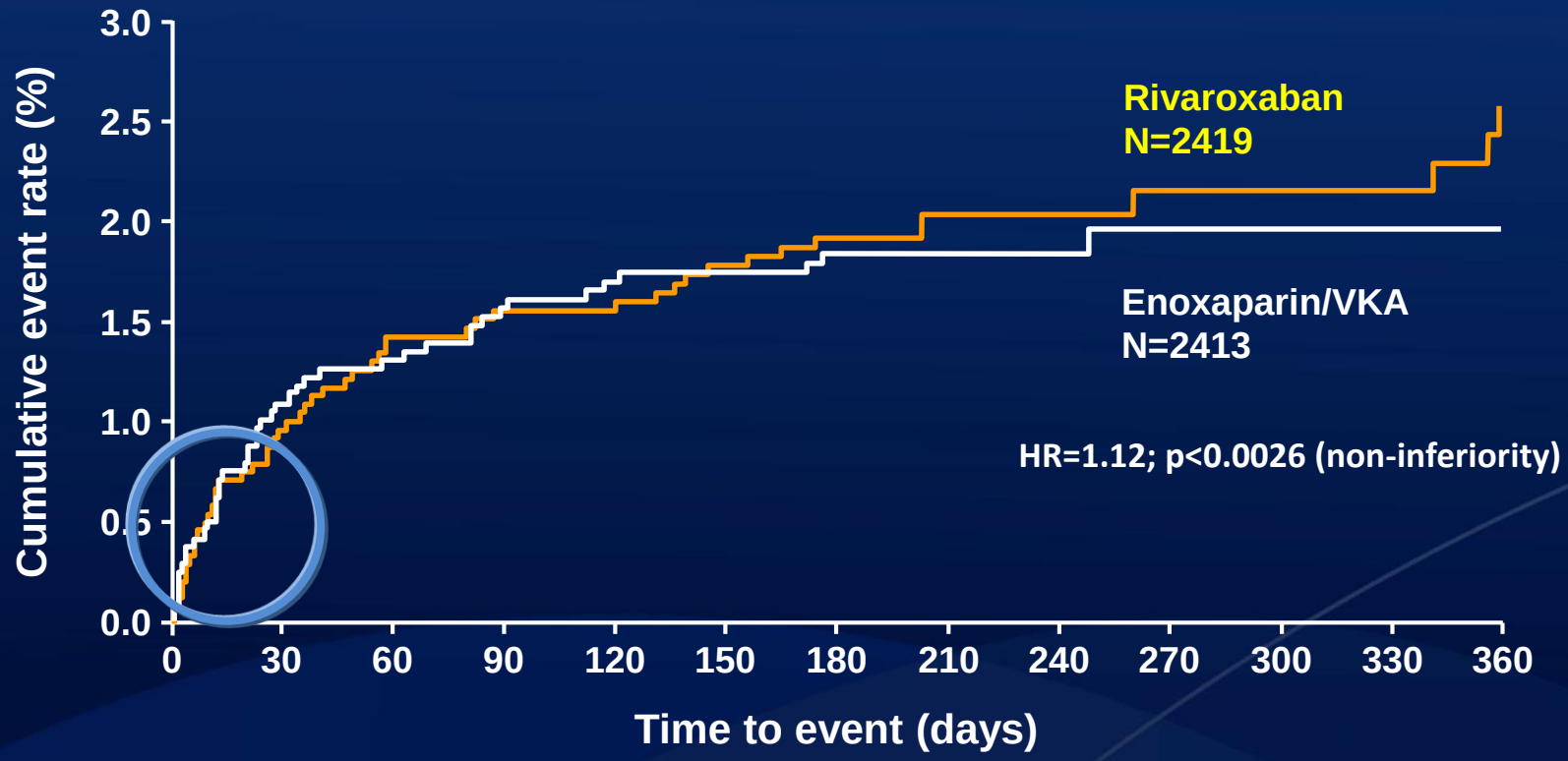
EINSTEIN PE
Primary efficacy outcome: time to first event



Number of patients at risk													
Rivaroxaban	2419	2350	2321	2303	2180	2167	2063	837	794	785	757	725	672
Enoxaparin/VKA	2413	2316	2296	2274	2157	2149	2053	837	789	774	748	724	677

ITT population

The EINSTEIN–PE Investigators, N Engl J Med, 2012

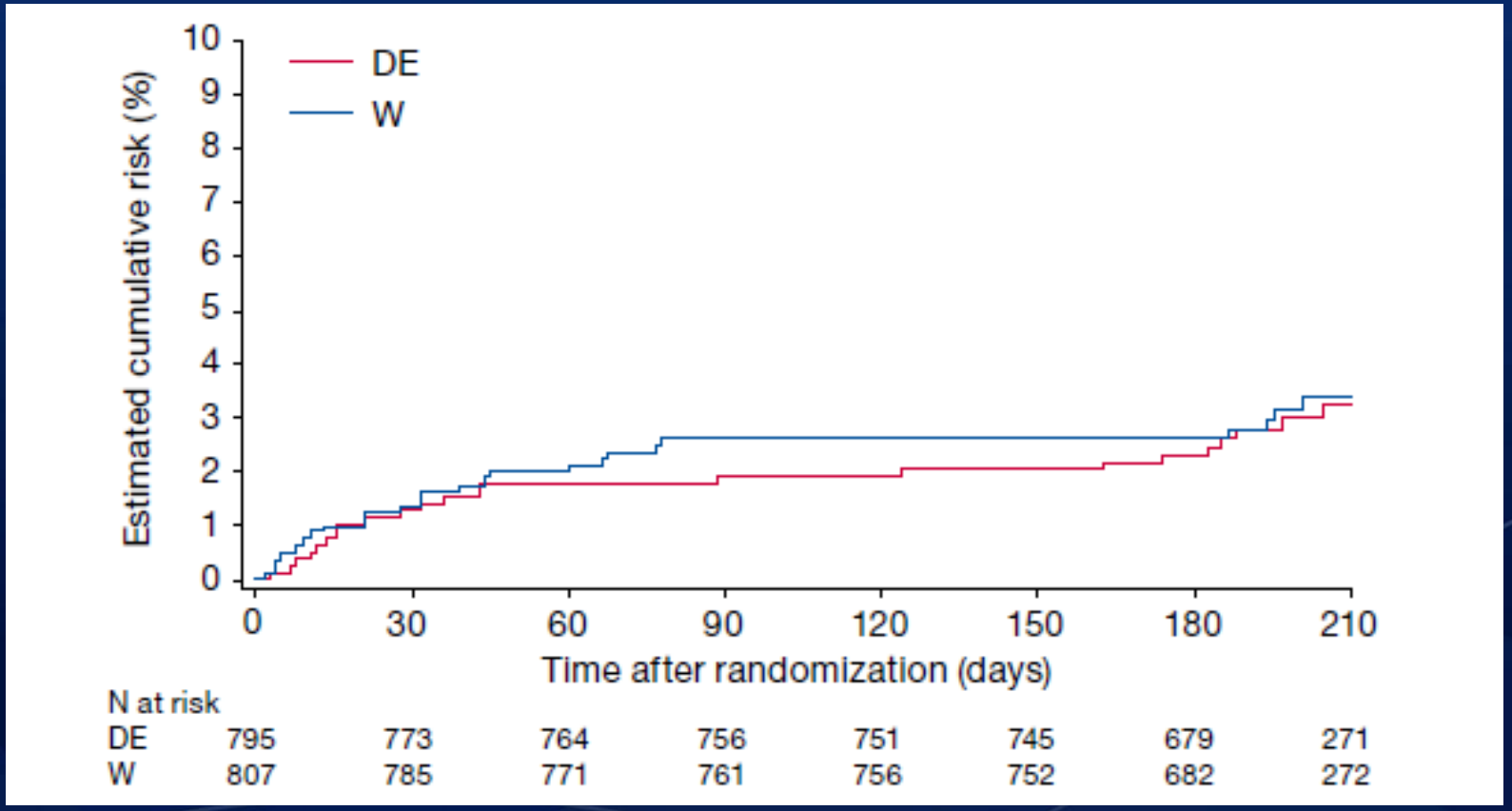
Principal safety outcome analysis: major or non-major clinically relevant bleeding

	Rivaroxaban (N=2412)		Enoxaparin/VKA (N=2405)		HR (95% CI) *p*-value
	n	(%)	n	(%)	
First major or non-major clinically relevant bleeding event	**249**	**(10.3)**	**274**	**(11.4)**	0.90 (0.76–1.07) *p*=0.23
Major bleeding	26	(1.1)	52	(2.2)	0.49 (0.31–0.80) *p*=0.0032
Contributing to death	2	(<0.1)	3	(0.1)	
In a critical site	6	(0.2)	27	(1.1)	
Associated with fall in haemoglobin ≥2 g/dl and/or transfusion of ≥2 units	18	(0.7)	26	(1.1)	
Non-major clinically relevant bleeding	228	(9.5)	235	(9.8)	

Safety population

The EINSTEIN–PE Investigators, N Engl J Med, 2012

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

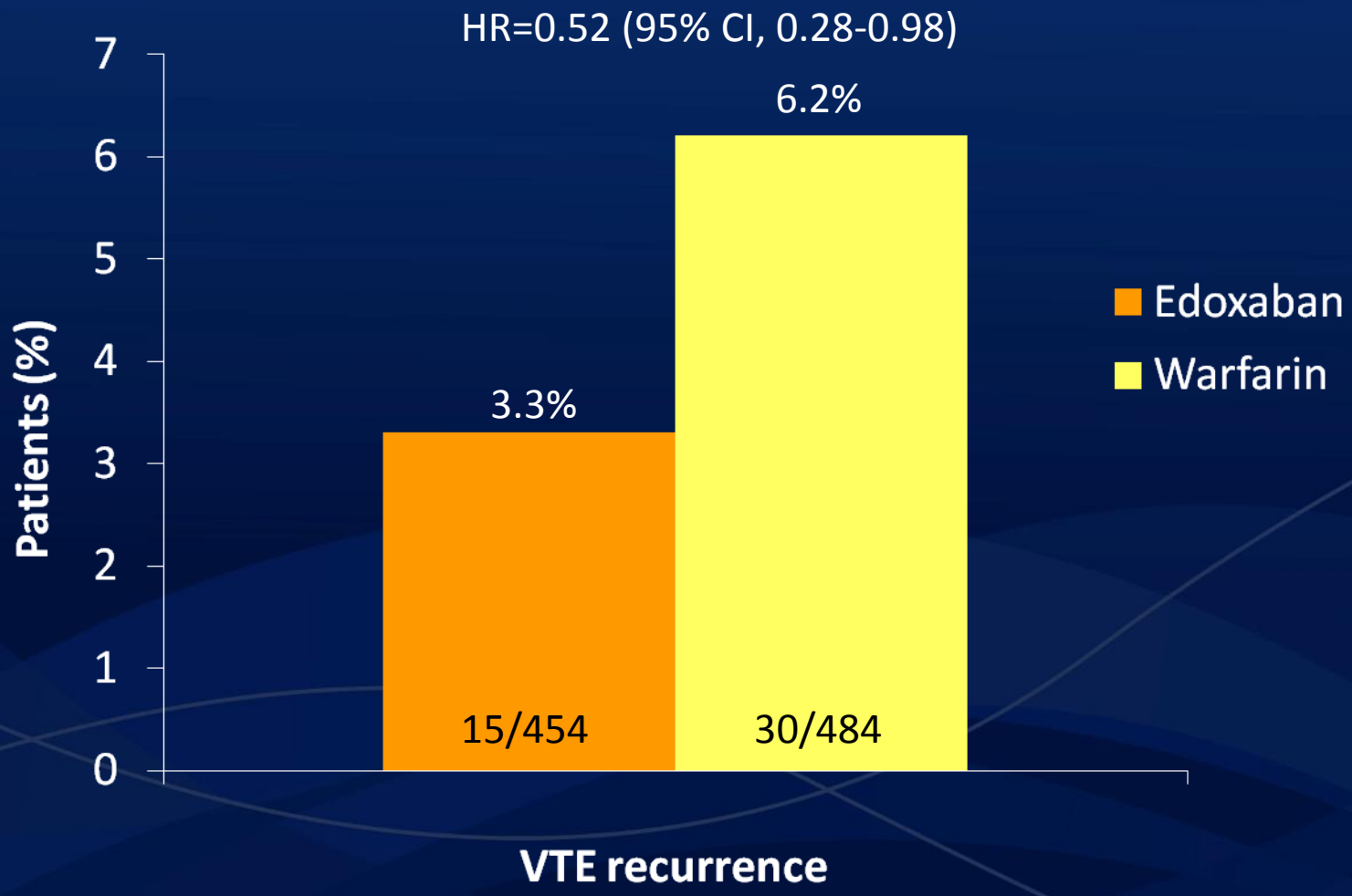
- No significant interactions, indicating similar treatment effects of dabigatran vs warfarin regardless of index event
- Fewer major bleeds with dabigatran vs warfarin (non-significant)
- Significantly fewer major/clinically relevant non-major bleeds and any bleeds with dabigatran vs warfarin

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

During the double-dummy period

Schulman S et al. ESC 2014; abstract 5509

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



Brekelmans, Lancet Hamatol, 2016

A quali pazienti i NAO

- Fragili
- Pazienti con neoplasia
- EP
- Terapia “extended”

Einstein, Amplify, Remedy, Resonate: EXTENSION

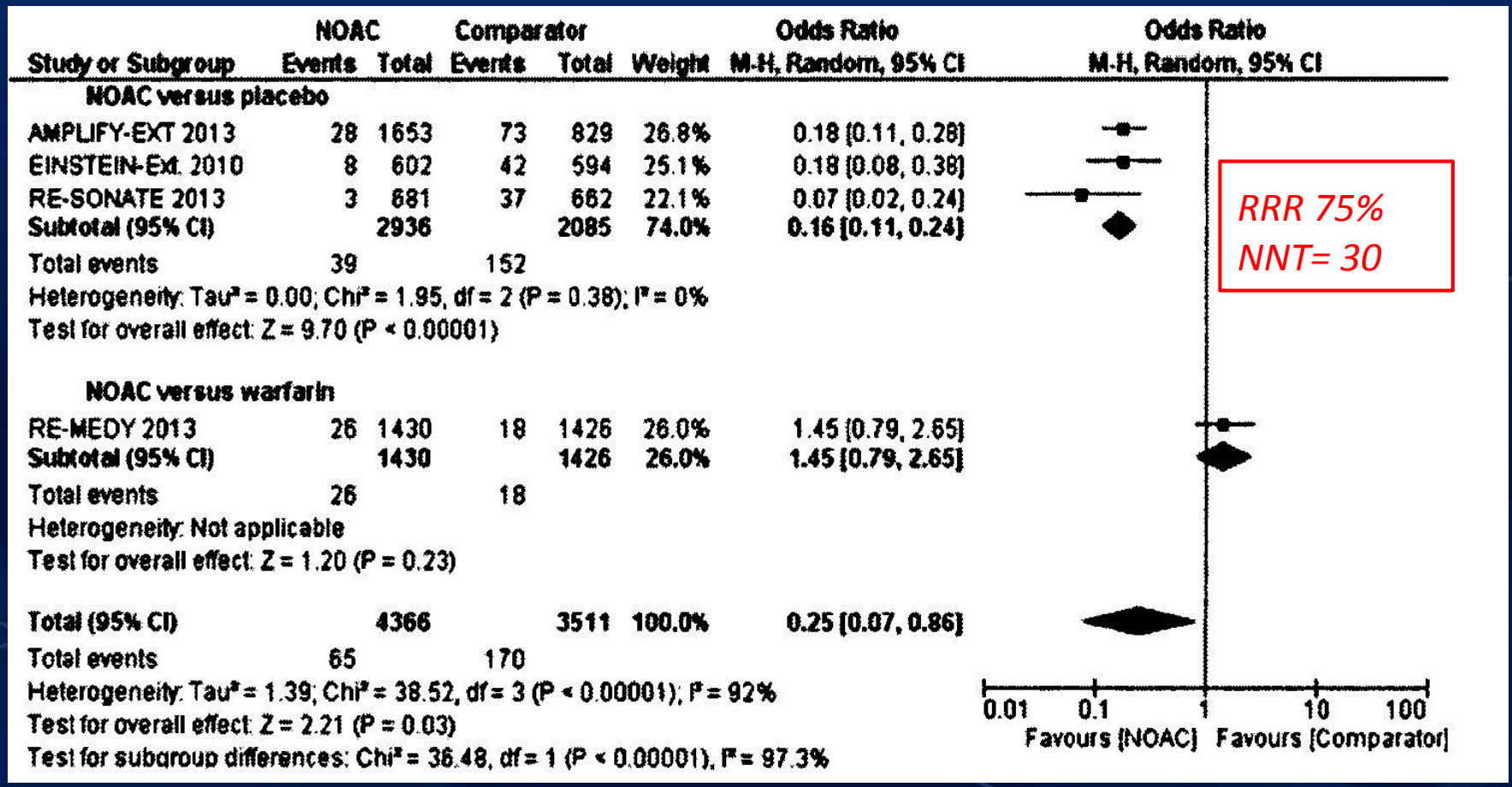
Study	Indication	Patients (n°)	Drug	Recurrent VTE#	Major bleeding#
EINSTEIN EXTENSION	Extension VTE	1196	Rivaroxaban 20 mg o.d. Vs placebo	1.3 vs 7.1 P<0.001**	0.7 vs 0 P=0.11*
AMPLIFY EXTENSION	Extension VTE	2486	Apixaban 2.5 mg b.d. or 5 mg b.d. Vs placebo	3.8 vs 4.2 vs 11.6 P<0.001	0.2 vs 0.1 vs 0.5
REMEDY	Extension VTE	2856	Dabigatran 150 mg b.d. Vs warfarin	1.8 vs 1.3 P=0.03*	0.9 vs 1.8 P=0.058* RRR -31%
RESONATE	Extension VTE	1343	Dabigatran 150 mg b.d. Vs placebo	0.4 vs 5.6 P<0.0001**	0.3 vs 0 P=0.996*

drugs vs comparator (%)
* for non inferiority, ** for superiority
≠ major and clinical relevant non major bleeding

Imberti, Clinical Appl Thromb, 2013

Efficacy and safety of NOACs for extended treatment of VTE: systematic review and meta-analyses of RCTs

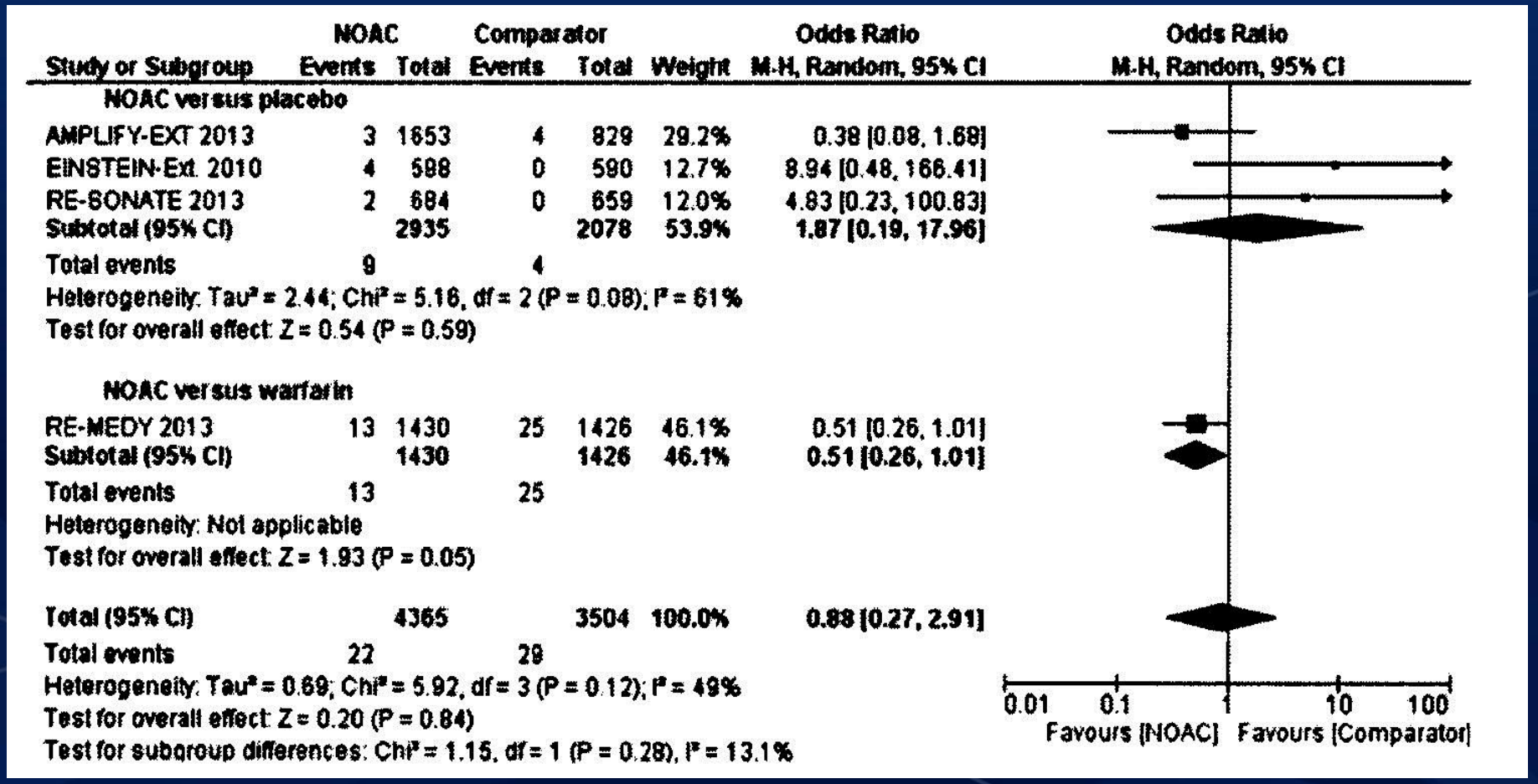
Recurrent VTE or VTE-related death



Sardar, Drugs, 2013

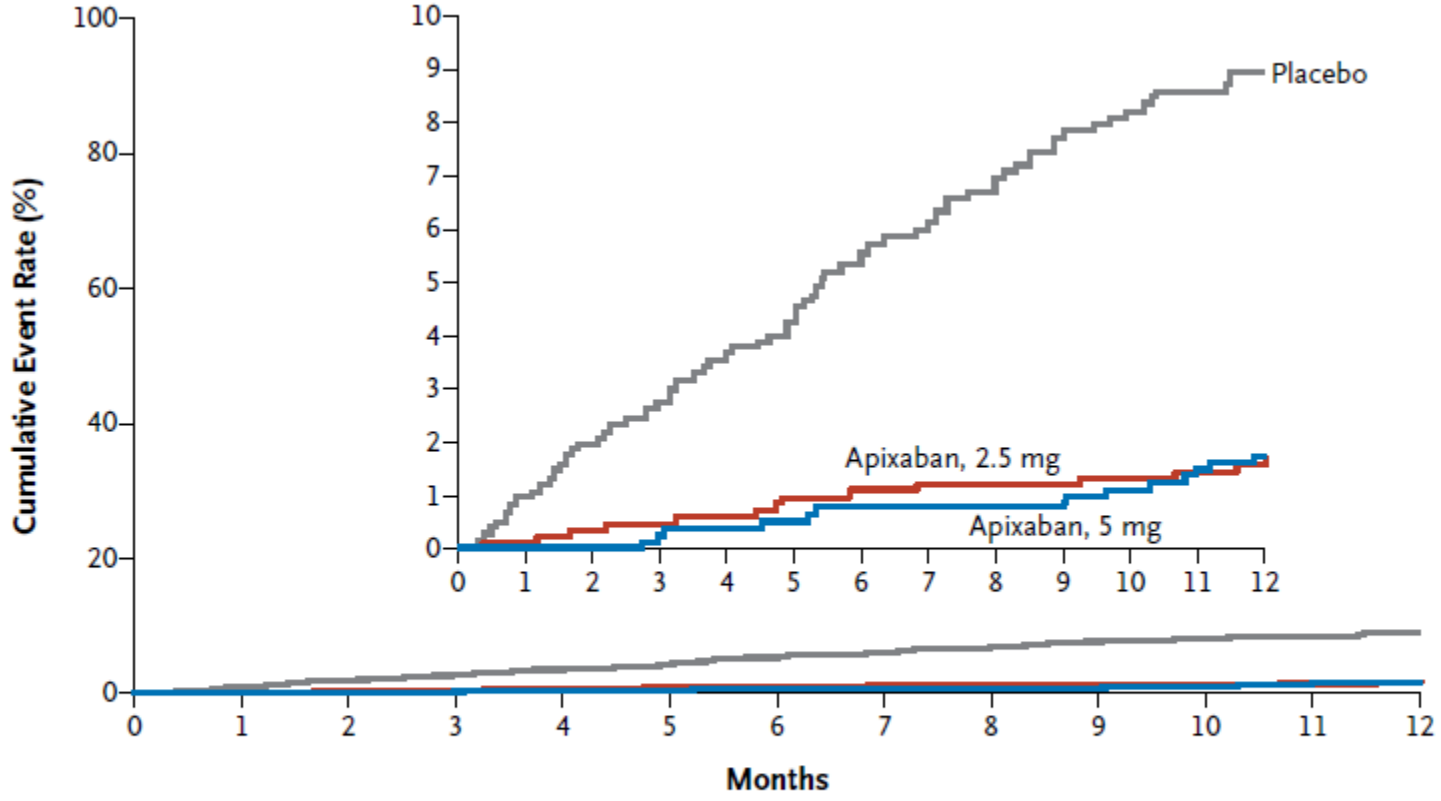
Efficacy and safety of NOACs for extended treatment of VTE: systematic review and meta-analyses of RCTs

Major bleeding



Sardar, Drugs, 2013

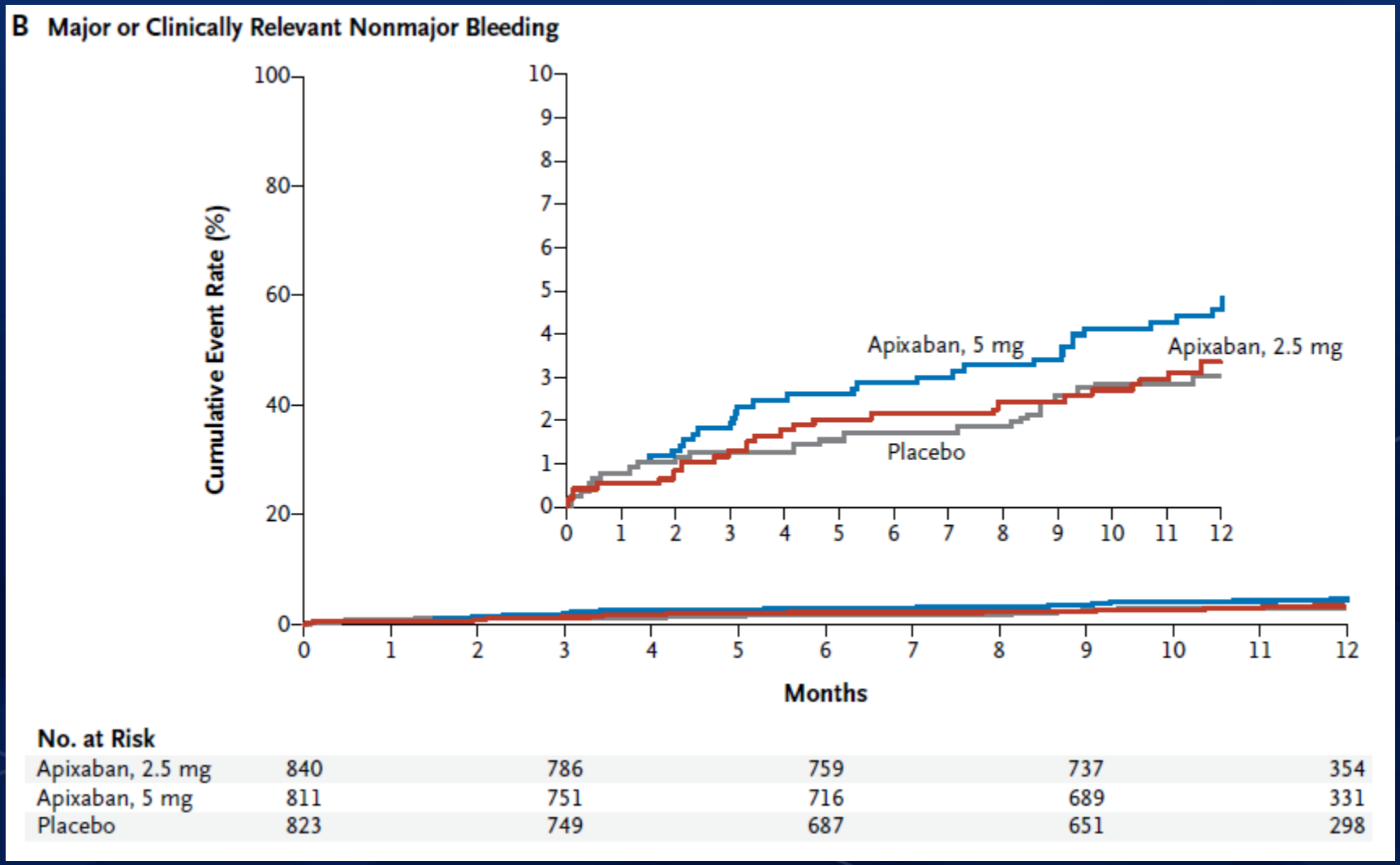
AMPLIFY EXTENSION
Efficacy Outcomes



No. at Risk					
Apixaban, 2.5 mg	840	836	825	818	533
Apixaban, 5 mg	813	807	799	791	513
Placebo	826	796	768	743	471

Agnelli, NEJM, 2012

Safety Outcomes

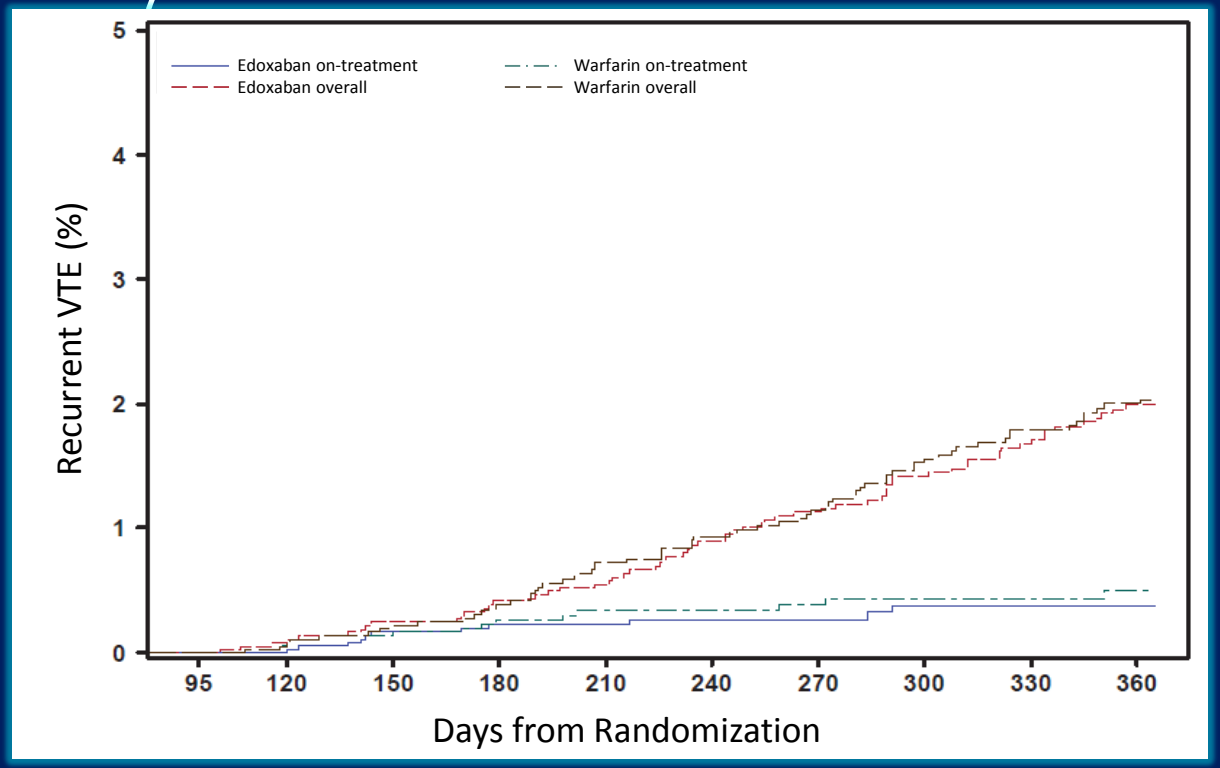


No. at Risk					
Apixaban, 2.5 mg	840	786	759	737	354
Apixaban, 5 mg	811	751	716	689	331
Placebo	823	749	687	651	298

Agnelli, NEJM, 2012

HOKUSAI: Extended Treatment Period (>3 – 12 Months)

- Cumulative incidence of recurrent VTE was similar between edoxaban and warfarin for both on-treatment and overall analyses



Warfarin overall
Edoxaban overall

HR 0.97
(95% CI 0.7-1.4)

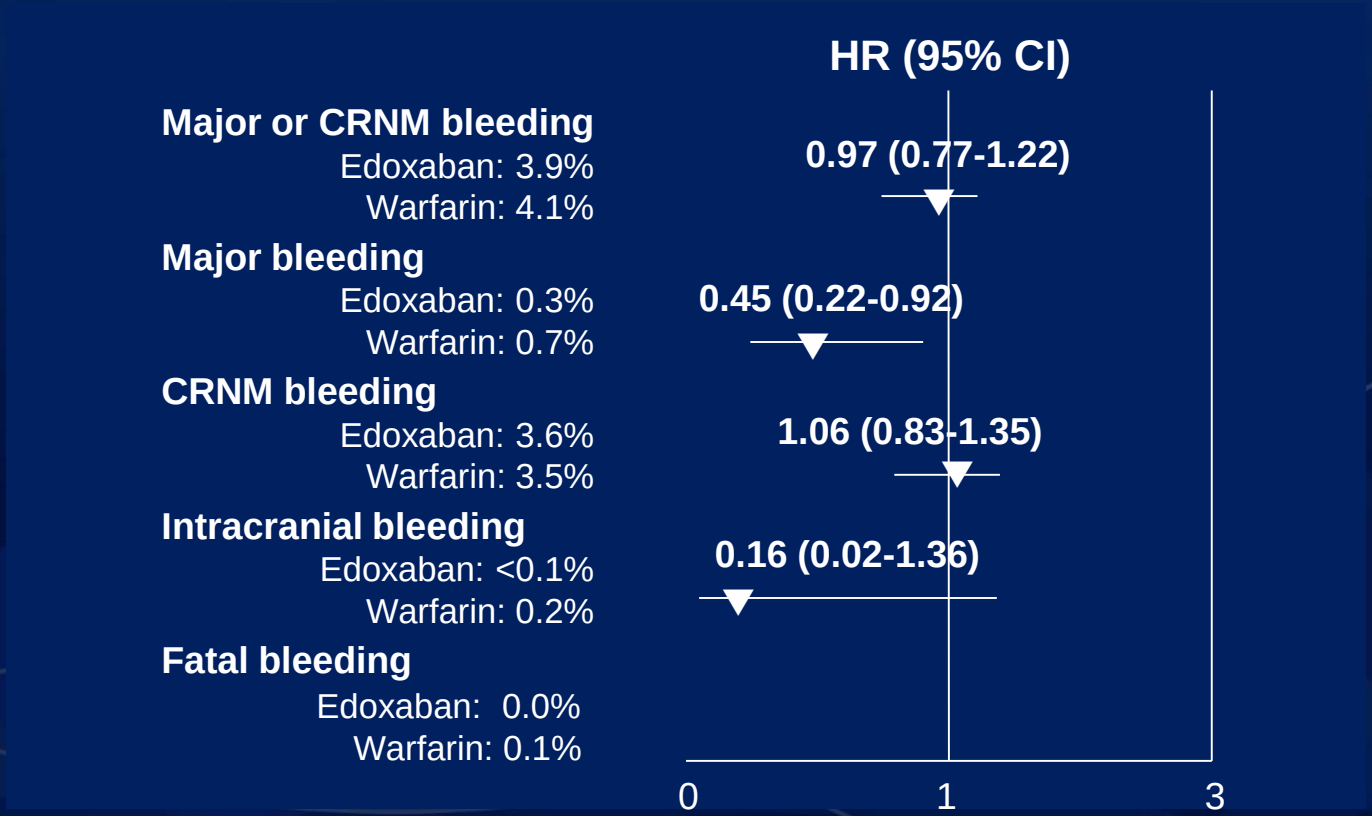
Warfarin
Edoxaban on-treatment

HR 0.78
(95% CI 0.36-1.72)

Raskob, Lancet Haematol, 2016

HOKUSAI: Extended Treatment Period (>3 – 12 Months)

- Significantly lower incidence of major bleeding was observed with edoxaban vs warfarin during the extended treatment period in the on-treatment analysis

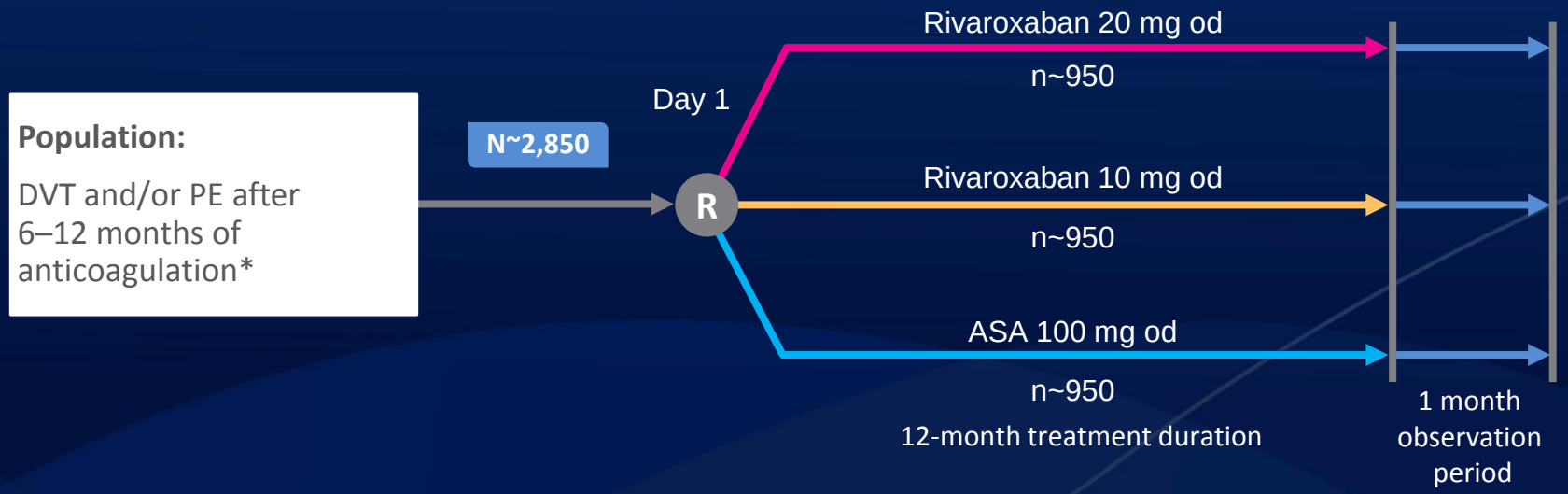


Raskob, Lancet Haematol, 2016

EINSTEIN CHOICE
Long-Term Secondary VTE Prevention Study

Official study title: Reduced-dosed Rivaroxaban and Standard-dosed Rivaroxaban Versus ASA in the Long-term Prevention of Recurrent Symptomatic Venous Thromboembolism in Patients With Symptomatic Deep-vein Thrombosis and/or Pulmonary Embolism

Objective: efficacy and safety of reduced-dosed rivaroxaban, standard-dosed rivaroxaban versus ASA for the long-term secondary prevention of recurrent symptomatic VTE in patients with symptomatic DVT and/or PE



Short design: Multicentre, randomized, double-blind, double-dummy, active-comparator, event-driven, superiority study

Indication: VTEx

FPFV: Q1-14
LPLV: Q4-16

*Completed 6–12 months (±1 month) with interruption of anticoagulation ≤1 week at randomization

www.clinicaltrials.gov/ct2/show/NCT02064439; Weitz JI *et al. Thromb Haemost* 2015