Rimini, 19 ottobre 2012

Un nuovo approccio per il trattamento del TEV:

il "single drug approach"

I. Iori

1^ Medicina Interna – Centro Emostasi e Trombosi

Azienda Ospedaliera – I.R.C.C.S. – A.S.M.N. Reggio Emilia

Treatment for venous thromboembolism

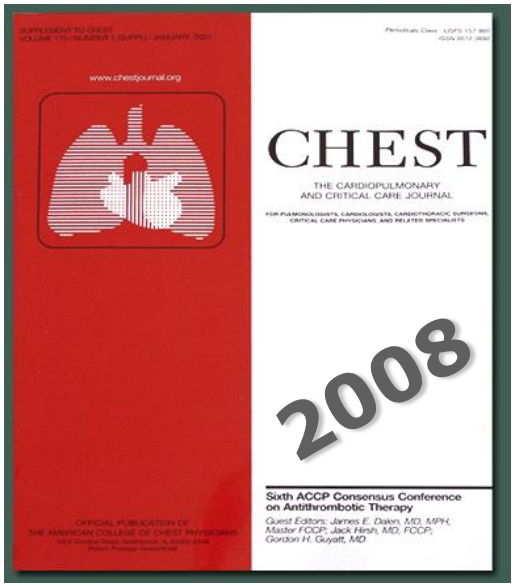
iv Heparin: 1A

sc Heparin: 1A

sc LMWH: 1A

Fondaparinux: 1A

Trombolysis: 1B



Clive Kearon
Susan R. Kahn
Giancarlo Agnelli
Samuel Goldhaber
Gary E. Raskob
Antony J. Comerota

vitamin K antagonists

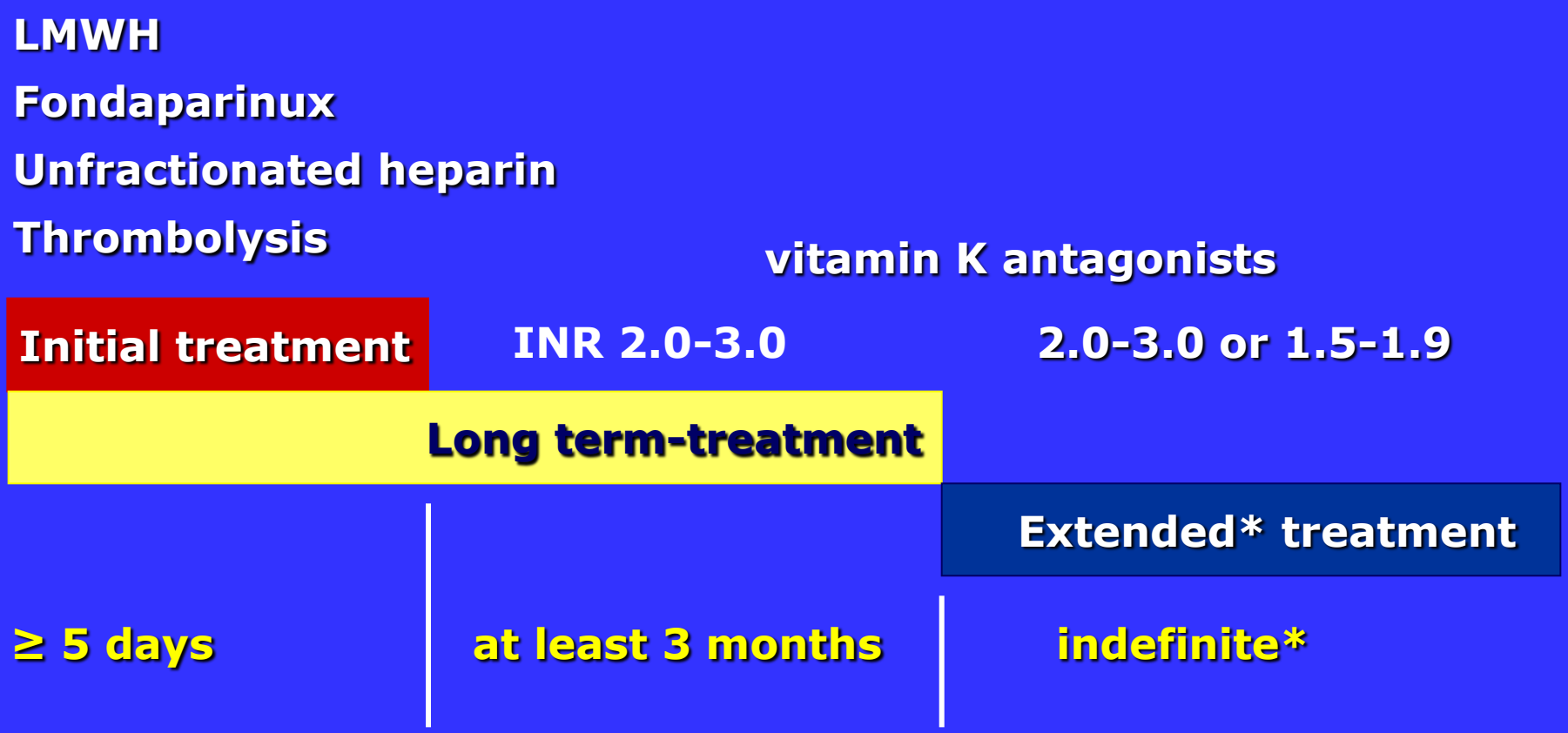
INR 2.0-3.0: 1A

≥ 5 days

3 months – long term: 1A

Kearon C Chest 2008; 133: 454S

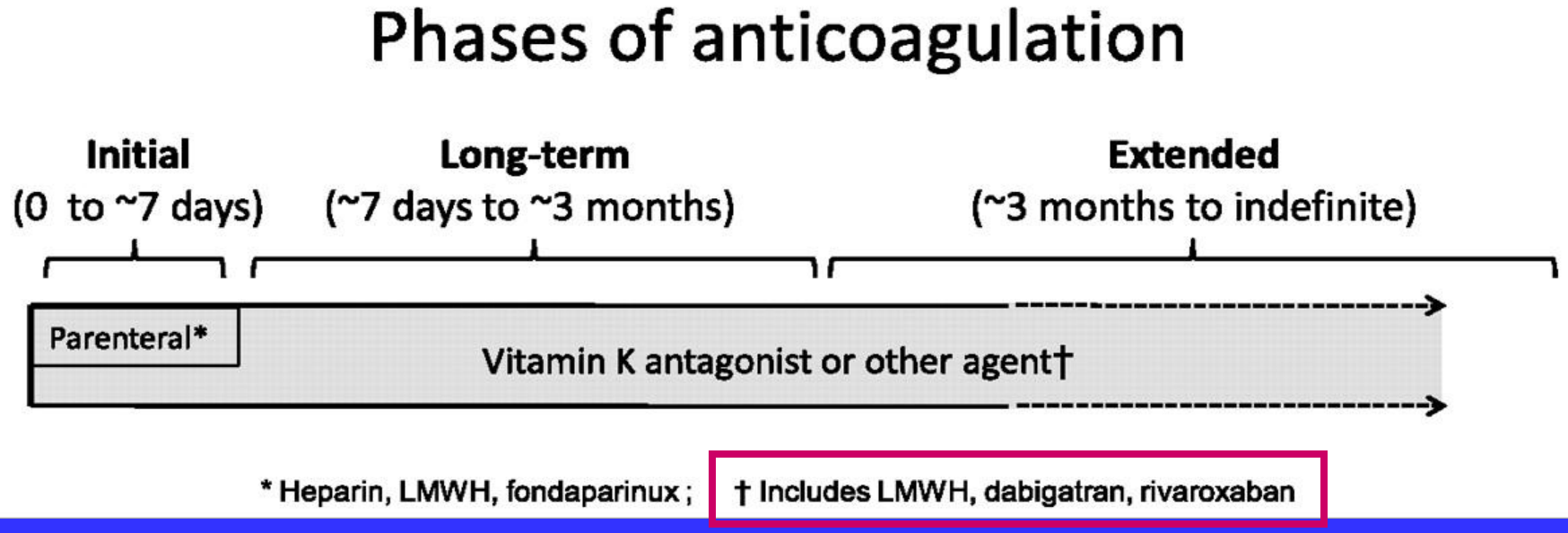
Treatment of VTE: current practice



* With re-assessment of the individual risk-benefit at periodic intervals

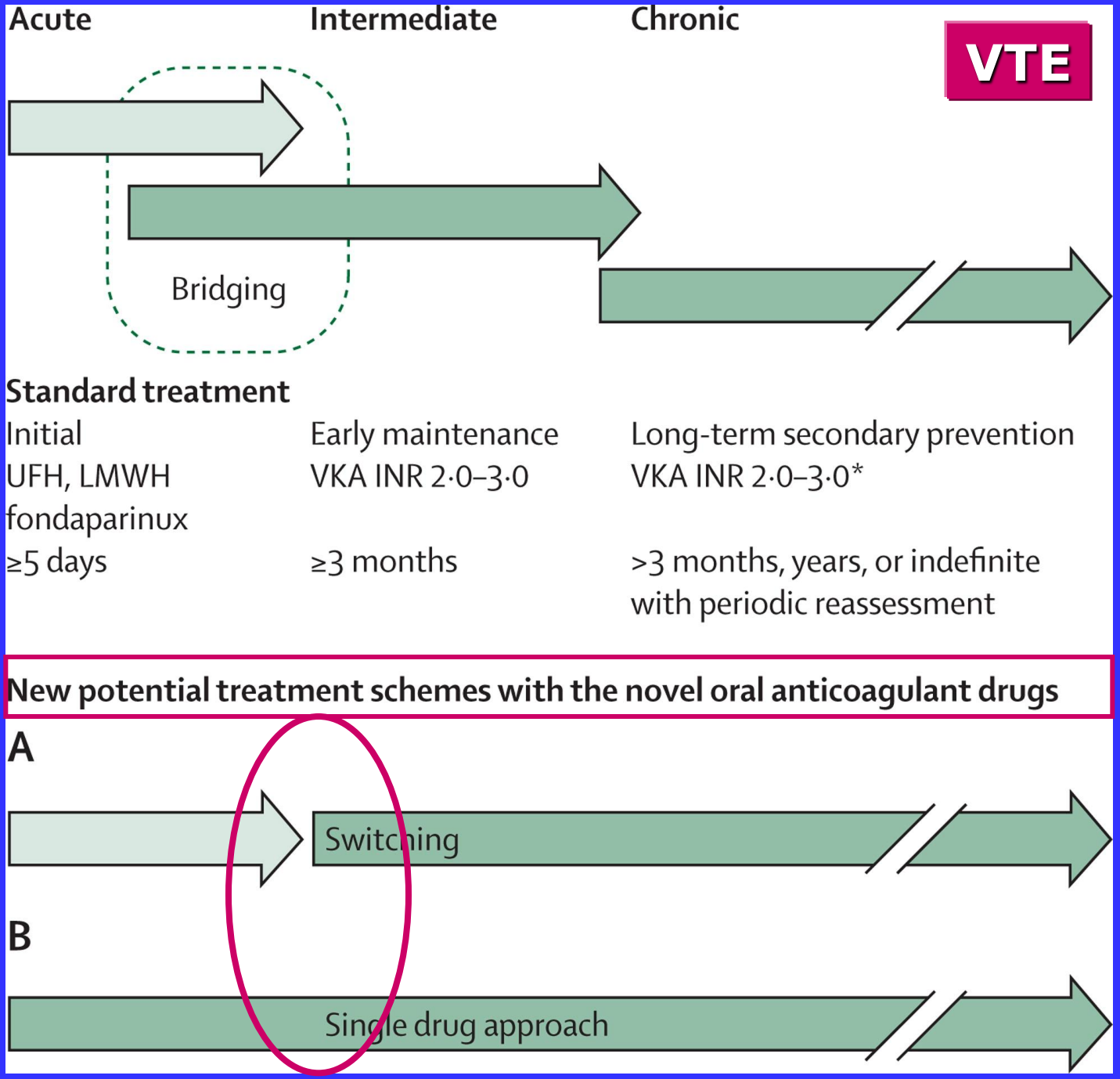
Agnelli G N Engl J Med 2010; 363: 266

VTE disease - phases of anticoagulation



Kearon C Chest 2012; 141: e419S

Three phases of the disease with the corresponding standard treatment



Goldhaber SZ Lancet Published online April 10, 2012

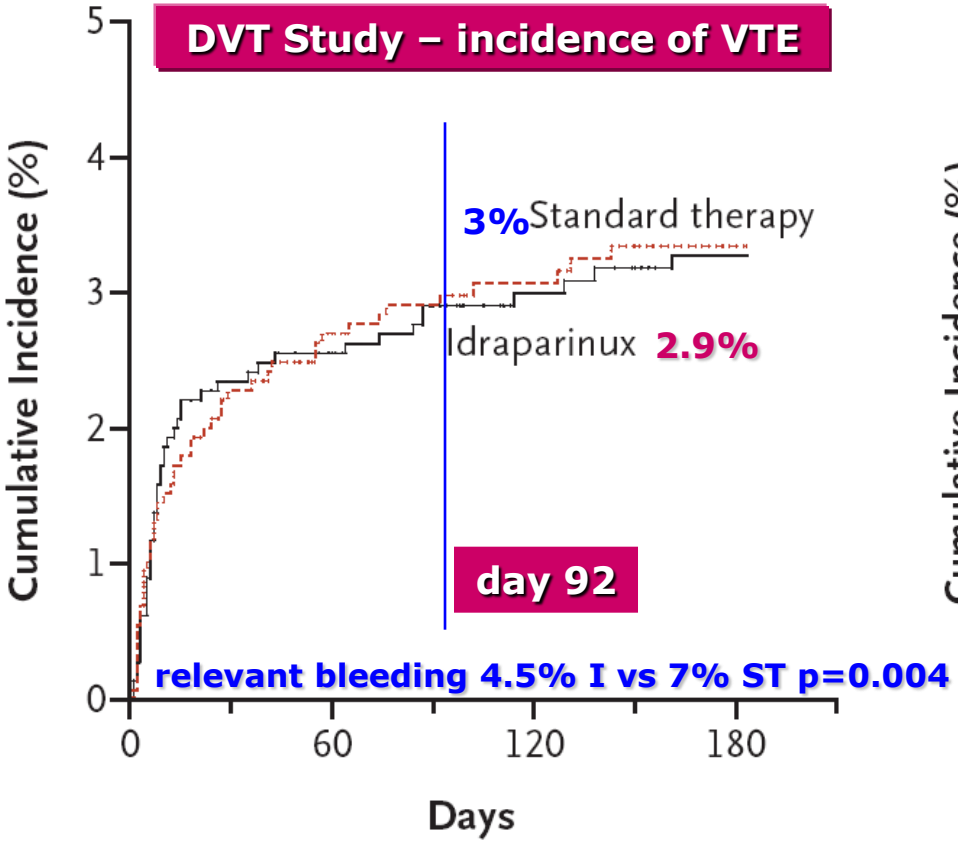
Clinical trials on the treatment of venous thromboembolism with new oral agents

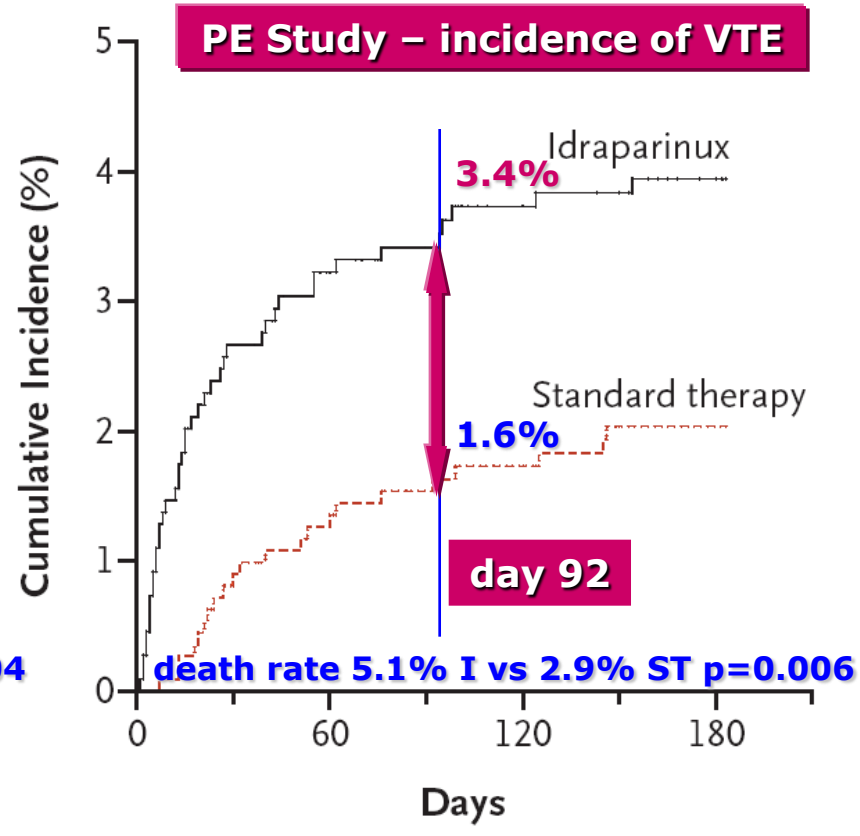
<table>
<tr><th>ACUTE</th><th>LONG TERM</th><th>EXTENDED</th></tr>
<tr><td></td><td>Dabigatran (RECOVER)
Edoxaban (HOKUSAI)</td><td rowspan="2">Dabigatran (REMEDY)
Dabigatran (RESONATE)
Rivaroxaban (EINSTEIN Extension)
Apixaban (AMPLIFY Extension)</td></tr>
<tr><td colspan="2">Rivaroxaban (EINSTEIN DVT)
Rivaroxaban (EINSTEIN PE)
Apixaban (AMPLIFY)</td></tr>
</table>

C. Becattini Thromb Res 2012; 129: 392

Idraparinux versus standard therapy for VTE disease

noninferiority trials 2904 DVT and 2215 PE to compare the efficacy and safety of subcutaneous idraparinux 2.5 mg once weekly versus heparin followed by an adjusted-dose VKA for 3 or 6 months





The van Gogh Investigators N Engl J Med 2007; 357: 1094

Clinical trials on the treatment of venous thromboembolism

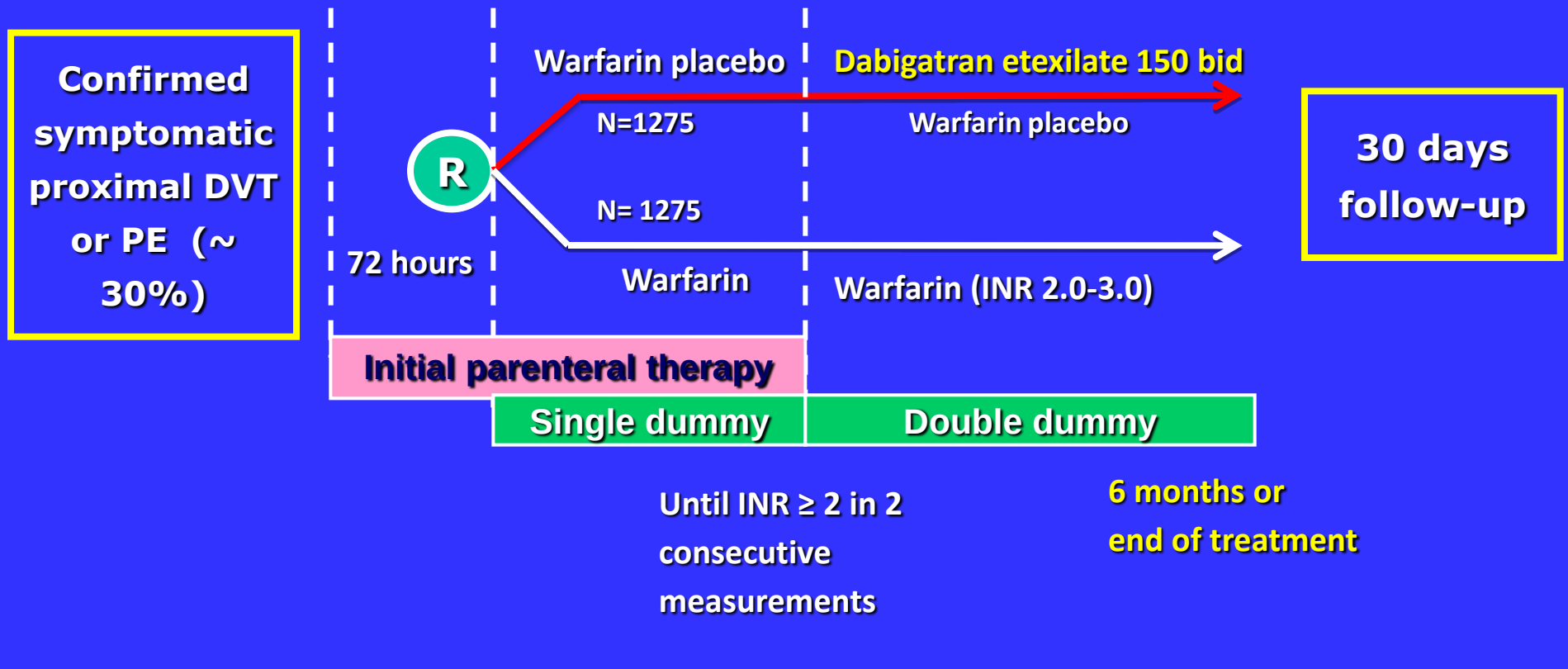
Trial	Design / Time	Drug	Comparator	Patients	Primary Outcome (Recurrent VTE)	Major Bleeding
					Drug vs comparator (%), p-value	
RECOVER	Double blind 6 months	LMWH/Dabigatran 150 mg t.d.	Warfarin	2539 acute VTE	2.4 vs 2.1 P<0.001 (non inferiority)	1.6 vs 1.9
EINSTEIN DVT	Open label 3, 6, or 12 months	Rivaroxaban 15 mg t.d. for 3 weeks, followed by 20 mg o.d.	VKA	3449 acute DVT	2.1 vs 3.0 P<0.001	8.1 vs 8.1 p=0.77
EINSTEIN PE	Open label 3, 6, or 12 months	Rivaroxaban 15 mg t.d. for 3 weeks, followed by 20 mg o.d.	VKA	ongoing acute PE	ongoing	ongoing
AMPLIFY	Double blind 6 months	Apixaban 10 mg t.d. for 7 days followed by 5 mg t.d. for 6 months	VKA	acute VTE	ongoing	ongoing
HOKUSAI	Double blind <12 months	LMWH/Edoxaban 60 mg o.d.	Warfarin	ongoing acute VTE	ongoing	ongoing
REMEDY	Double blind up to 36 months	Dabigatran 150 mg t.d.	Warfarin	2856	1.8 vs 1.3 p=0.03 (non inferiority)	0.9 vs 1.8 p=0.058
RE-SONATE	Double blind 6 months	Dabigatran 150 mg t.d.	Placebo	1343 (pre-treatment 6–18 months)	0.4 vs 5.6 p<0.0001	0.3 vs 0 p=0.996
EINSTEIN Extension	Double blind 6–12 months	Rivaroxaban 20 mg o.d.	Placebo	1196 pre-treatment <12 months	1.3 vs 7.1 p<0.001	0.7 vs 0 P=0.11
AMPLIFY Extension	Double blind 12 months	Apixaban 2.5 mg t.d or Apixaban 5 mg t.d.	Placebo	pre-treatment 6–12 months	ongoing	ongoing

C. Becattini Thromb Res 2012; 129: 392

RE-COVER Study

Dabigatran versus Warfarin in the tratment of Acute VTE

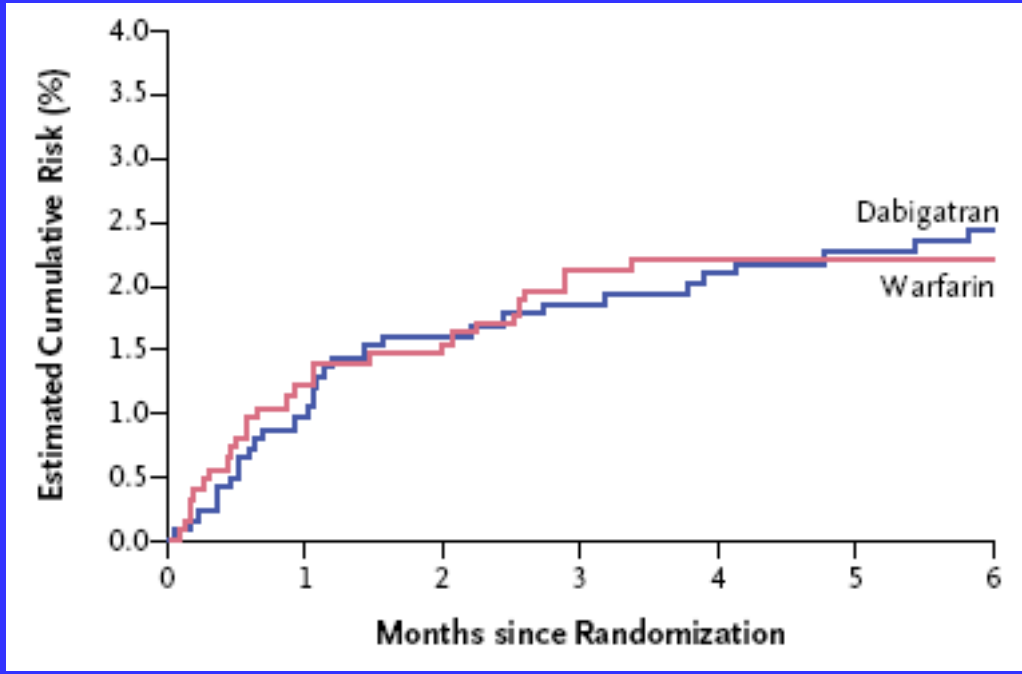
Randomized, double-blind, non inferiority trial

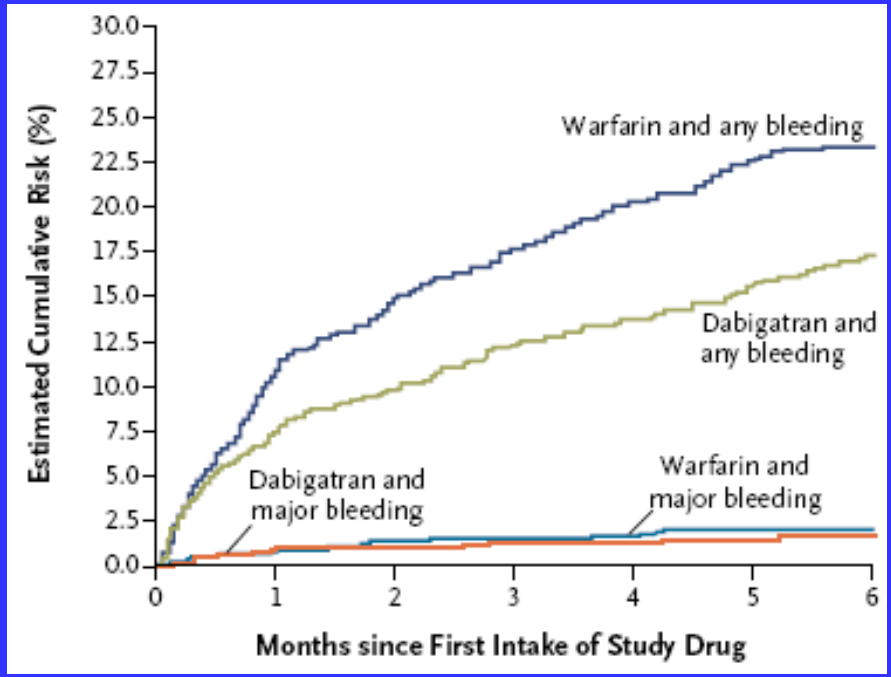


Schulman S N Engl J Med 2009; 361: 2342

RE-COVER Study

Dabigatran is effective as Warfarin, with similar safety profile





Recurrent VTE or death

2.4% dabigatran 2.1% Warfarin

HR 1.1, 95% CI 0.65-1.34

p< 0.001 for non-inferiority criteria

Bleeding

1.6% dabigatran 1.9% Warfarin

HR 0.82, 95% CI 0.45-1.48

Schulman S N Engl J Med 2009; 361: 2342

Secondary prevention of VTE: the RE-MEDY and RE-SONATE studies

RE-MEDY – duble blind, noninferiority study

2856 VTE patients received 3-12 months of anticoagulant therapy after were randomly assigned to dabigatran 150 mg b.i.d or warfarin for additional 6-36 months

recurrent symptomatic VTE in 1.8% with dabigatran and 1.3% warfarin

major bleeding in 0.9% with dabigatran and 1.8% warfarin

any bleeding in 19% patients with dabigatran and in 26% warfarin

dabigatran was effective as warfarin for extended treatment of VTE with a reduced risk of bleeding

RE-SONATE – double blind study

1343 VTE patients after 6-18 months of anticoagulant therapy were randomly assigned to dabigatran 150 mg b.i.d. or placebo for 6 m.

recurrent VTE was observed in 0.4% treated with dabigatran and 5.6% with placebo ($p < 0.001$); two major bleeding with dabigatran

relevant nonmajor bleeding in 5.3% treated with dabigatran and 1.8% with placebo ($p=0.001$)

Tripodi A J Intern Med 2012 Mar 24 Epub

EINSTEIN-DVT

Oral Rivaroxaban for Symptomatic VTE

EINSTEIN DVT: study outcomes

Primary efficacy outcome*

- Symptomatic recurrent VTE: composite of recurrent DVT, non-fatal PE or fatal PE

Principal safety outcome*

- Combination of major and clinically relevant non-major bleeding

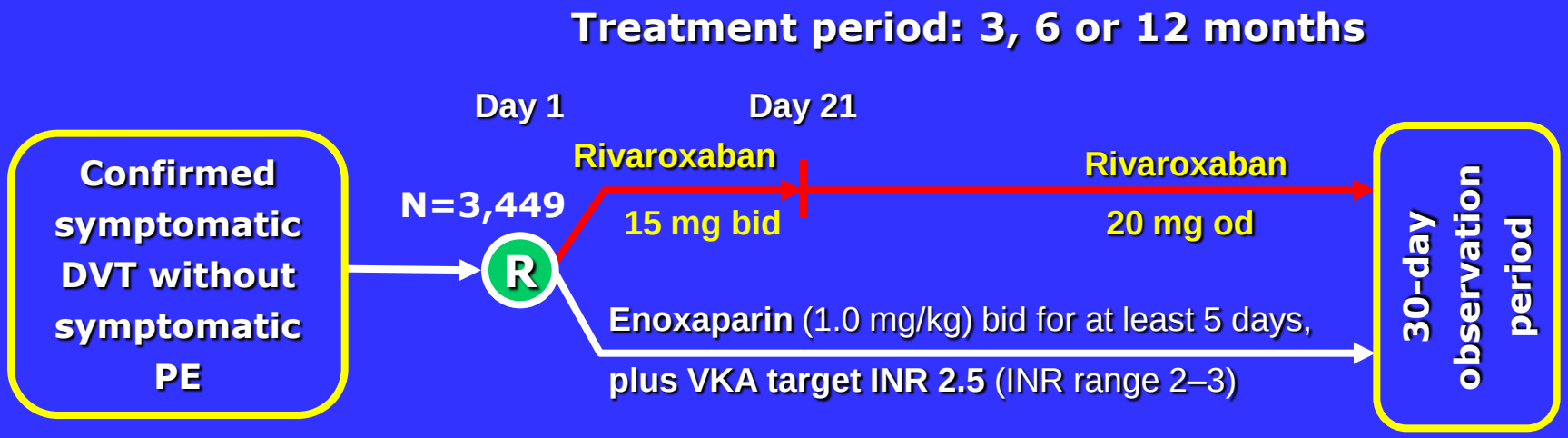
*Adjudicated by the central independent and blinded adjudication committee

EINSTEIN Investigators N Engl J Med 2010; 363: 2499 - 510

EINSTEIN DVT: study design

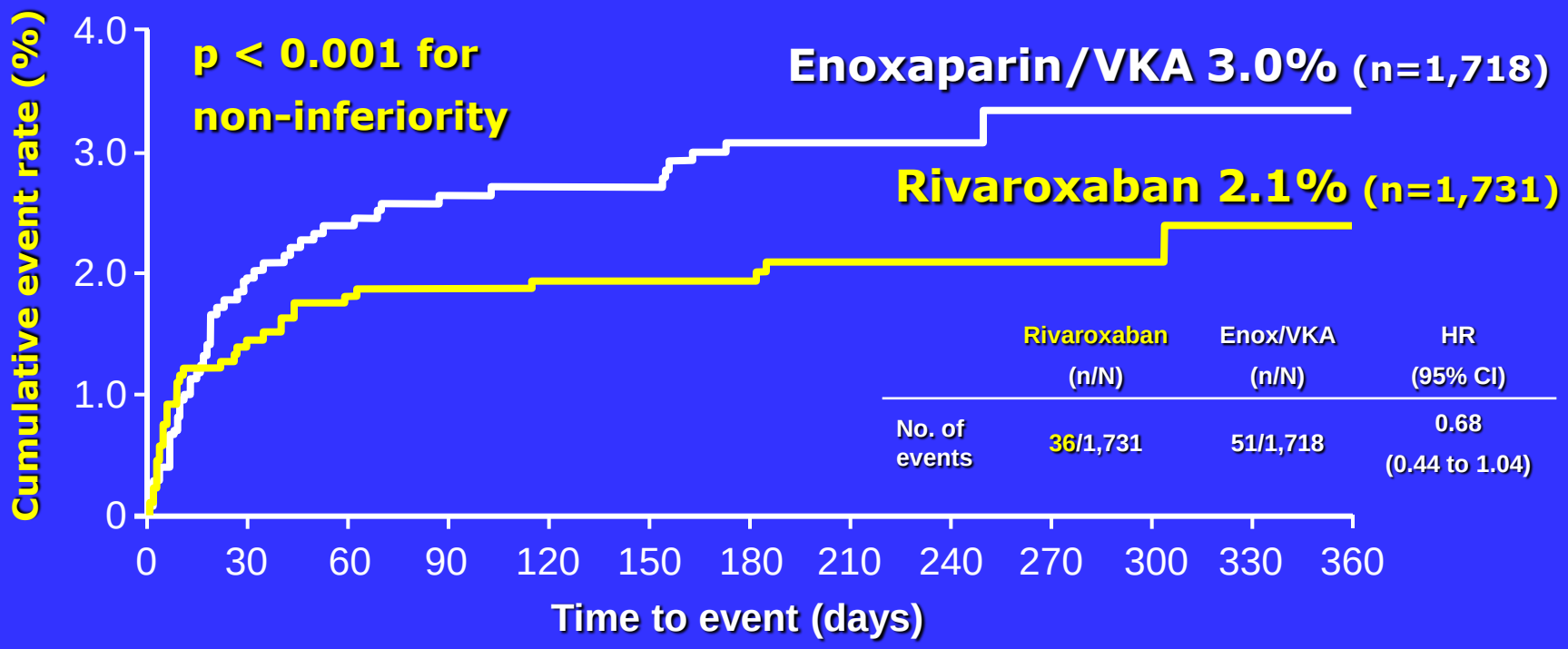
Randomized, open-label, event-driven, non-inferiority study

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



EINSTEIN Investigators N Engl J Med 2010; 363: 2499 - 510

Primary efficacy outcome: time to first event



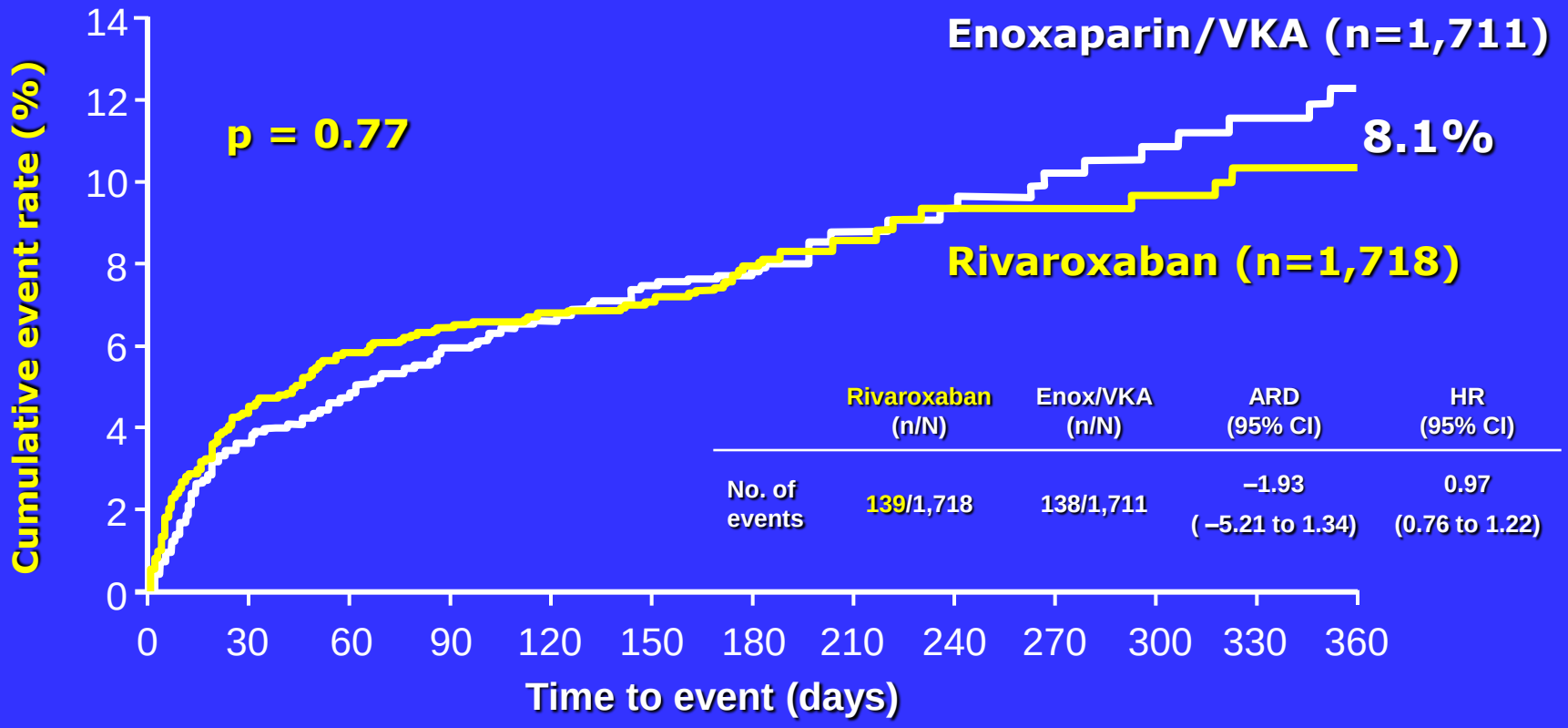
Number of subjects at risk

Rivaroxaban	1,731	1,668	1,648	1,621	1,424	1,412	1,220	400	369	363	345	309	266
Enox/VKA	1,718	1,616	1,581	1,553	1,368	1,358	1,186	380	362	337	325	297	264

EINSTEIN Investigators. N Engl J Med 2010

Principal safety outcome: time to first event

major or clinically relevant bleeding



	Rivaroxaban (n/N)	Enox/VKA (n/N)	ARD (95% CI)	HR (95% CI)
No. of events	139/1,718	138/1,711	–1.93 (–5.21 to 1.34)	0.97 (0.76 to 1.22)

Number of subjects at risk

Rivaroxaban	1,718	1,585	1,538	1,382	1,317	1,297	715	355	338	304	278	265	140
Enox/VKA	1,711	1,554	1,503	1,340	1,263	1,238	619	338	321	287	268	249	118

EINSTEIN Investigators. N Engl J Med 2010

EINSTEIN DVT: conclusions

- In patients who had acute symptomatic proximal DVT, without symptomatic PE, rivaroxaban showed:
  - Non-inferiority to LMWH/VKA for efficacy: HR=0.68 (95% CI 0.44–1.04); $p<0.001$ for non-inferiority
  - Similar findings for principal safety outcome: HR=0.97 (95% CI 0.76–1.22); $p=0.77$
  - Consistent efficacy and safety results irrespective of age, body weight, gender, creatinine clearance and cancer
  - No evidence for liver toxicity
- Oral rivaroxaban 15 mg bid for 3 weeks followed by rivaroxaban 20 mg od, could provide clinicians and patients with a simple approach for the acute and continued treatment of DVT that potentially improves the benefit–risk profile of anticoagulation

EINSTEIN Investigators. N Engl J Med 2010

Rivaroxaban

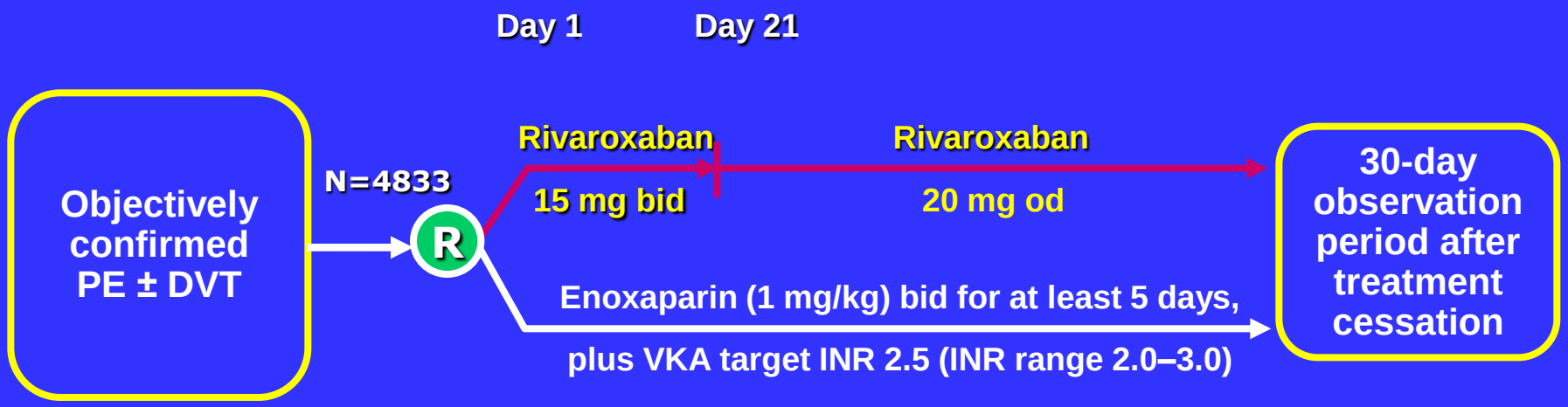
EINSTEIN PE

EINSTEIN PE: study design

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

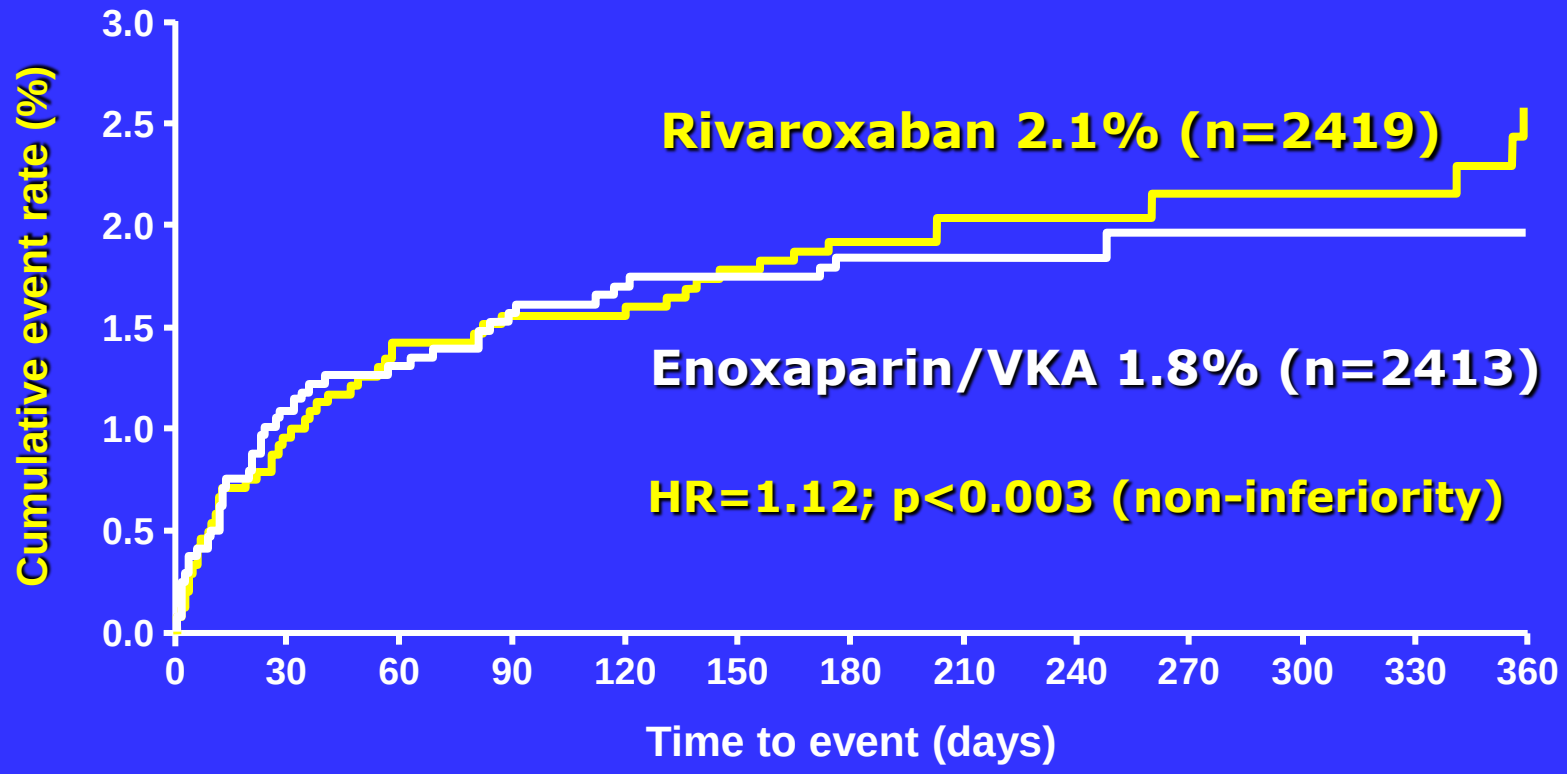
- Up to 48 hours' heparins/fondaparinux treatment permitted before study entry
- 88 primary efficacy outcomes needed
- Non-inferiority margin: 2.0

Predefined treatment period of 3, 6 or 12 months



The EINSTEIN–PE Investigators N Engl J Med 2012

Primary efficacy outcome: time to first event



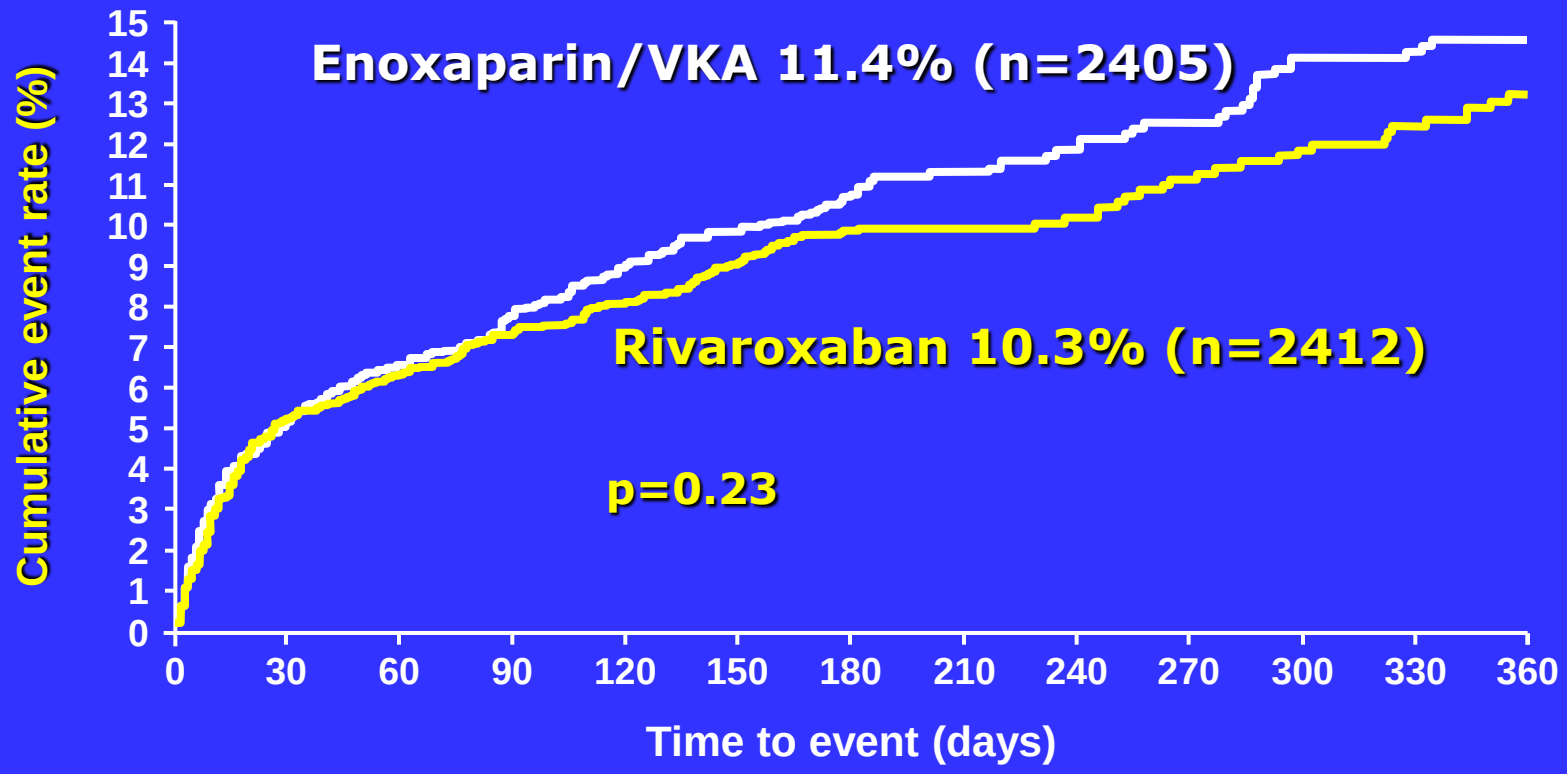
Number of patients at risk

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: major or non-major clinically relevant bleeding



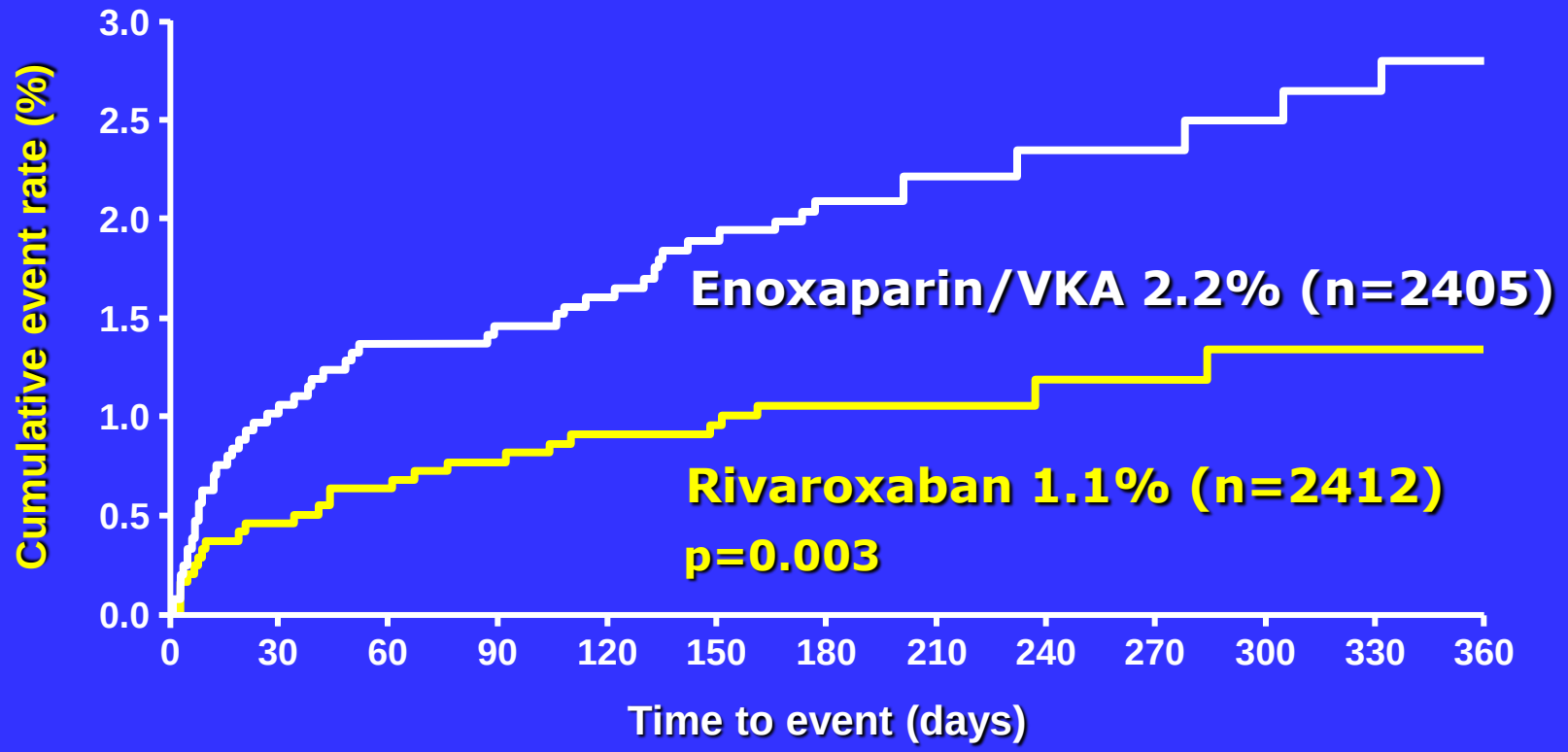
Number of patients at risk

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

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

Conclusions

- **In patients with acute symptomatic PE ± DVT rivaroxaban showed:**
  - Non-inferiority to LMWH/VKA for efficacy: HR=1.12 (0.75–1.69); $p_{\text{non-inferiority}}$=0.0026 for (margin: 2.0)
  - Similar findings for principal safety outcome: HR=0.90 (0.76–1.07); p=0.23
  - Superiority for major bleeding: HR=0.49 (0.31–0.79) p=0.0032
  - Consistent efficacy and safety results irrespective of age, body weight, gender, kidney function and cancer
  - No evidence for liver toxicity
- **Oral rivaroxaban, 15 mg twice daily for 3 weeks followed by 20 mg once daily, could provide clinicians and patients with a simple, single-drug approach for the acute and continued treatment of PE that potentially improves the benefit–risk profile of anticoagulation**

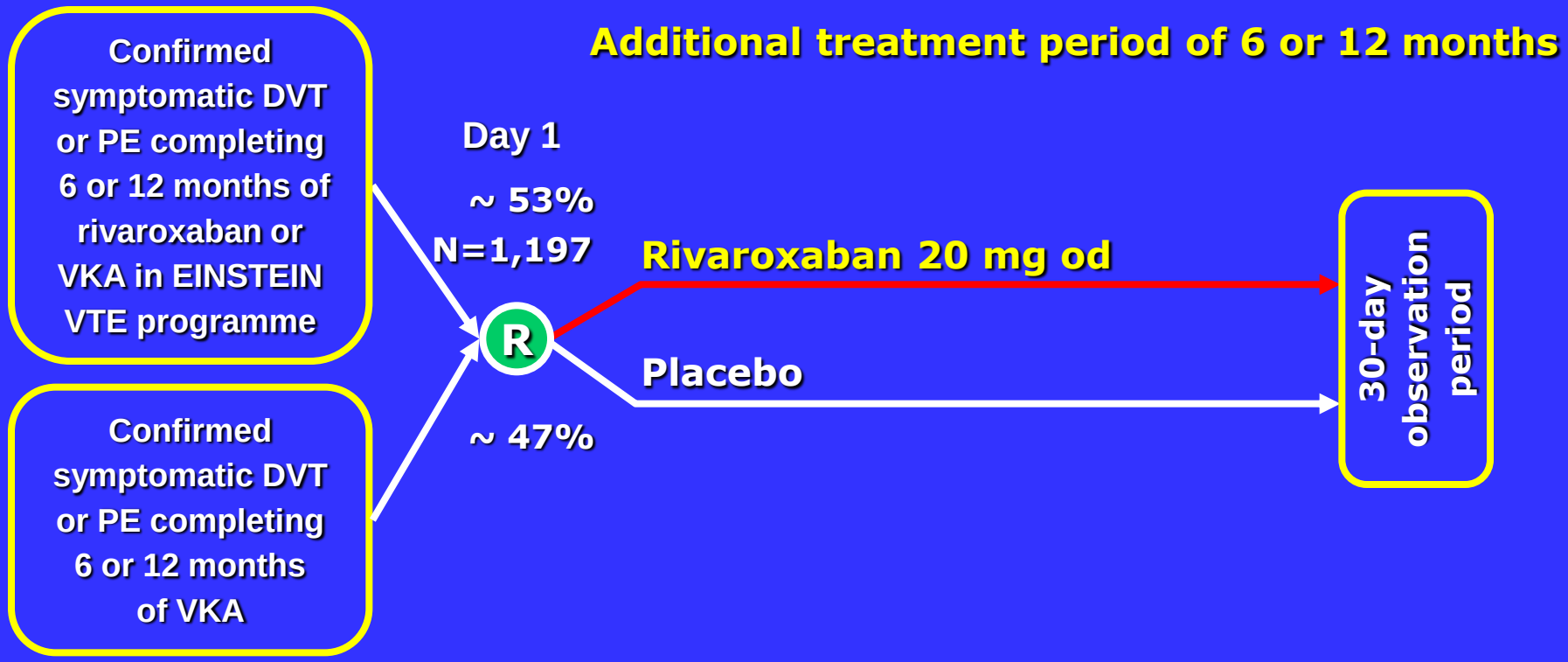
The EINSTEIN–PE Investigators N Engl J Med 2012

Rivaroxaban

EINSTEIN Extension

EINSTEIN Extension: Study design

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



EINSTEIN Investigators N Engl J Med 2010

EINSTEIN Extension: Major outcomes

- **Primary efficacy outcome***
  - Symptomatic recurrent VTE , i.e. composite of recurrent DVT, non-fatal PE or fatal PE, or unexplained death where PE cannot be excluded
- **Principal safety outcome***
  - Major bleeding, defined as overt bleeding associated with:
    - A fall in hemoglobin of 2 g/dL or more, *or*
    - A transfusion of 2 or more units of packed red blood cells or whole blood, *or*
    - Occurrence at a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, *or*
    - Death

*Adjudicated by the Central Independent Adjudication Committee

EINSTEIN Investigators N Engl J Med 2010

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	122 (21%)	134 (22%)
≥80	373 (63%)	373 (62%)
Index event*		
DVT	349 (59%)	376 (63%)
PE with or without DVT	234 (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

EINSTEIN Investigators N Engl J Med 2010

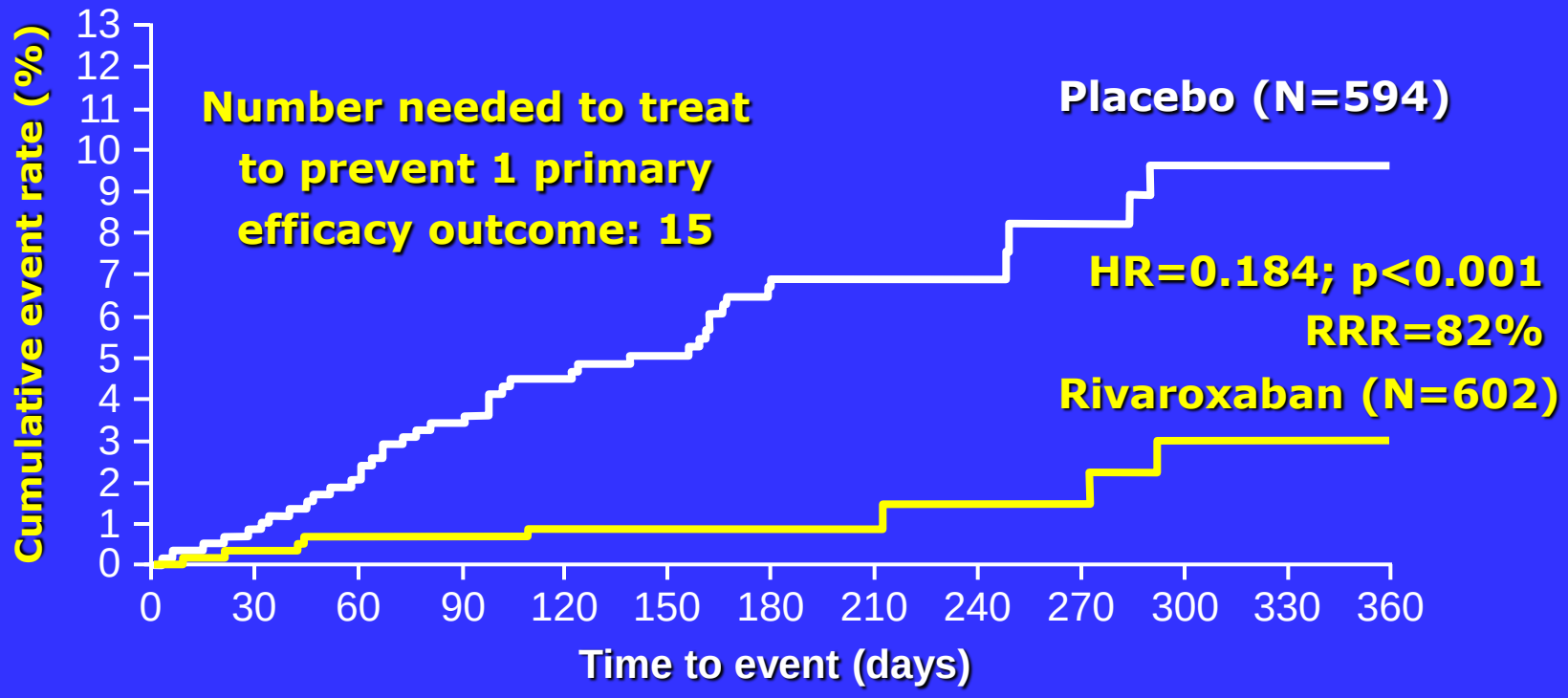
Primary efficacy outcome

	Placebo (n=594) n (%)		Rivaroxaban (n=602) n (%)	
Symptomatic recurrent VTE*	**42**	**(7.1%)**	**8**	**(1.3%)**
Recurrent DVT	31	(5.2)	5	(0.8)
Non-fatal PE	13	(2.2)	2	(0.3)
Fatal PE	1	(0.2)	0	
Unexplained death (where PE cannot be excluded)	0		1	(0.2)

ITT population; *Some patients experienced more than one event

EINSTEIN Investigators N Engl J Med 2010

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	555	522	468	444	164	138	133	110	93	85

EINSTEIN Investigators N Engl J Med 2010

Major bleeding

	Placebo (n=590) n (%)	Rivaroxaban (n=598) n (%)
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 of ≥2 units	0	4
Gastrointestinal bleeding	0	3 (0.5)
Menorrhagia	0	1 (0.2)

***p=0.11**

- Number needed to harm: approximately 139

Safety population

EINSTEIN Investigators N Engl J Med 2010

EINSTEIN Extension: conclusions

- In patients who had completed 6 or 12 months of anticoagulation, rivaroxaban showed:
  - An 82% relative risk reduction in the recurrence of VTE (HR=0.184; *p*<0.001)
  - Absolute risk reduction 5.8% hence 15 patients need to be treated to prevent one recurrent VTE event
  - Low incidence of major bleeding (0.7%; p=0.11; NNH approximately 139)
  - Efficacy and safety results were consistent irrespective of bodyweight and creatinine clearance
  - Modest increase in clinically relevant non-major bleeding (5.4% vs 1.2%; *p*<0.01)
  - No signal for liver toxicity
- **Oral rivaroxaban 20 mg od, could provide clinicians and patients with a simple and effective option for continued anticoagulant treatment**

EINSTEIN Investigators N Engl J Med 2010

Patient characteristics

	Rivaroxaban (n=1,731)	Enoxaparin/VKA (n=1,718)
Males (%)	57	56
Age, mean (years)	56	56
Body mass index, mean (kg/m^2)	28	28
Creatinine clearance (%)		
<50 ml/min	7	7
50–<80 ml/min	23	23
≥80 ml/min	69	68
Patients with secondary DVT (%)	39	37
Patients with active cancer (%)	7	5
Intended treatment duration (%)		
3 months	12	12
6 months	63	63
12 months	25	25
Pre-treatment for maximum 48 hours with LMWH, heparin/fondaparinux (%)	73	71

ITT population

EINSTEIN Investigators N Engl J Med 2010

Patient characteristics

	Rivaroxaban (N=2419)	Enoxaparin/VKA (N=2413)
Males (%)	54.1	51.7
Age, mean (years)	57.9	57.5
Body mass index, mean (kg/m^2)	28.3	28.4
Creatinine clearance (%)		
<30 ml/min	0.2	<0.1
30–49 ml/min	8.6	7.9
50–79 ml/min	26.3	24.6
≥80 ml/min	64.3	67.0
Previous VTE (%)	18.8	20.3
Patients with active cancer (%)	4.7	4.5
Intended treatment duration (%)		
3 months	5.3	5.1
6 months	57.3	57.5
12 months	37.4	37.5
Pretreatment for maximum of 48 hours with LMWH, heparin/fondaparinux (%)	92.5	92.1
Concomitant DVT (%)	24.9	24.3

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

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	**6**	**(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		
Rectal/pulmonary/abdominal	1	(<0.1)	2	(<0.1)	
Fall in haemoglobin ≥2 g/dl and/or transfusion of ≥2 units	**18**	**(0.7)**	**26**	**(1.1)**	

***Some patients had >1 event**
Safety population

The EINSTEIN–PE Investigators N Engl J Med 2012

Non-major clinically relevant and trivial bleeding

	Rivaroxaban (N=2412)		Enoxaparin/VKA (N=2405)	
	n	(%)	n	(%)
Non-major clinically relevant bleeding*	228	(9.5)	235	(9.8)
Urogenital/uterus	90	(3.7)	84	(3.5)
Nasal	47	(1.9)	41	(1.7)
Rectal	27	(1.1)	24	(1.0)
Skin/injection site	24	(1.0)	46	(1.9)
Gastrointestinal	37	(1.6)	17	(0.7)
Miscellaneous	22	(0.9)	40	(1.7)
Trivial bleeding*	606	(25.1)	612	(25.4)

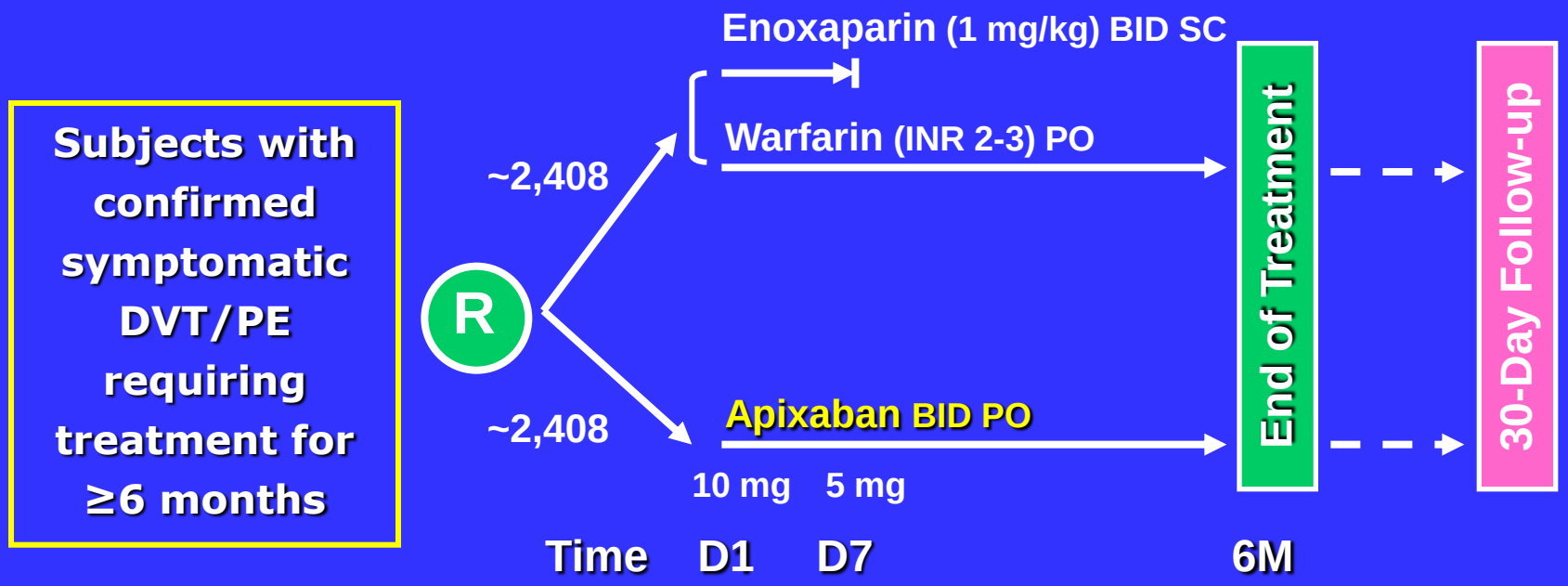
***Some patients had >1 event**
Safety population

	Warfarin	Dabigatran	Rivaroxaban	Apixaban
Target	VKOR and factors II,VII,IX,X	Factor IIa (thrombin)	Factor Xa	Factor Xa
Time to peak concentration	72–96 h	1.5–3 h	2–4 h	1–3 h
Vol. of dist.		60–70 l	50 l	Reported as low
Half-life	40 h	12–14 h	9–13 h	9–14 h
Metabolism	Liver-CYP2C9	Conjugation	Liver-CYP3A4 and CYP2J2	Partially through CYP3A4
Elimination	Bile and urine	80% renal, 20% faecal	66% faecal, 33% renal	75% faecal, 25% renal
Administration	Once daily	Once or twice daily	Once daily	Twice daily
Monitoring	INR	Not needed	Not needed	Not needed
Antidote or potential therapy for bleeding	Vitamin K, FFP, PCC or rFVIIa	FFP, PCC or rFVIIa	FFP, PCC or rFVIIa	FFP, PCC or rFVIIa
Assay	PT/INR	Experimental	Experimental	Experimental
Drug interactions	CYP 2C9	PPIs decrease absorption and potent P-gp inhibitors	Potent CYP 3A4 inhibitors and P-gp inhibitors	Potent CYP 3A4 inhibitors

Phillips KW Thromb Haemost 2010; 103: 34

Amplify

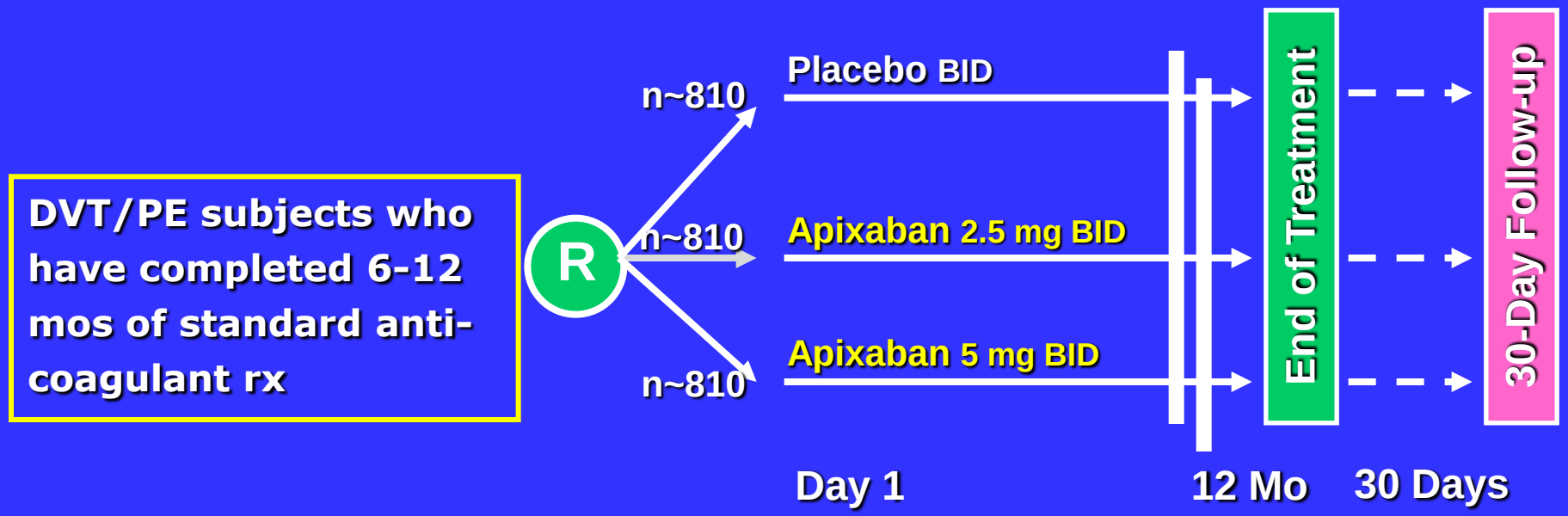
6-Month Double-Blind Active-Controlled Non-Inferiority Study



- N planned = 4,816
- Based upon non-inferiority margin 1.8, power 90%, and a 1-sided 97.5% CI

Amplify- Extension

12-Month Double-Blind Placebo-Controlled Extended Treatment Study



- N based on power 90% to detect superiority of apixaban to placebo (~60% RRR) using two-sided alpha=0.025 for comparing each apixaban arm to placebo.
- Study ends after all subjects have completed 12 months of treatment.