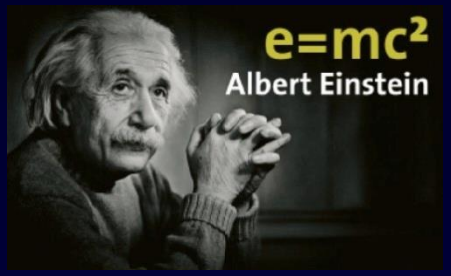
Evidence-Based Treatment of *Rivaroxaban* in DVT and PE : EINSTEIN-DVT & PE



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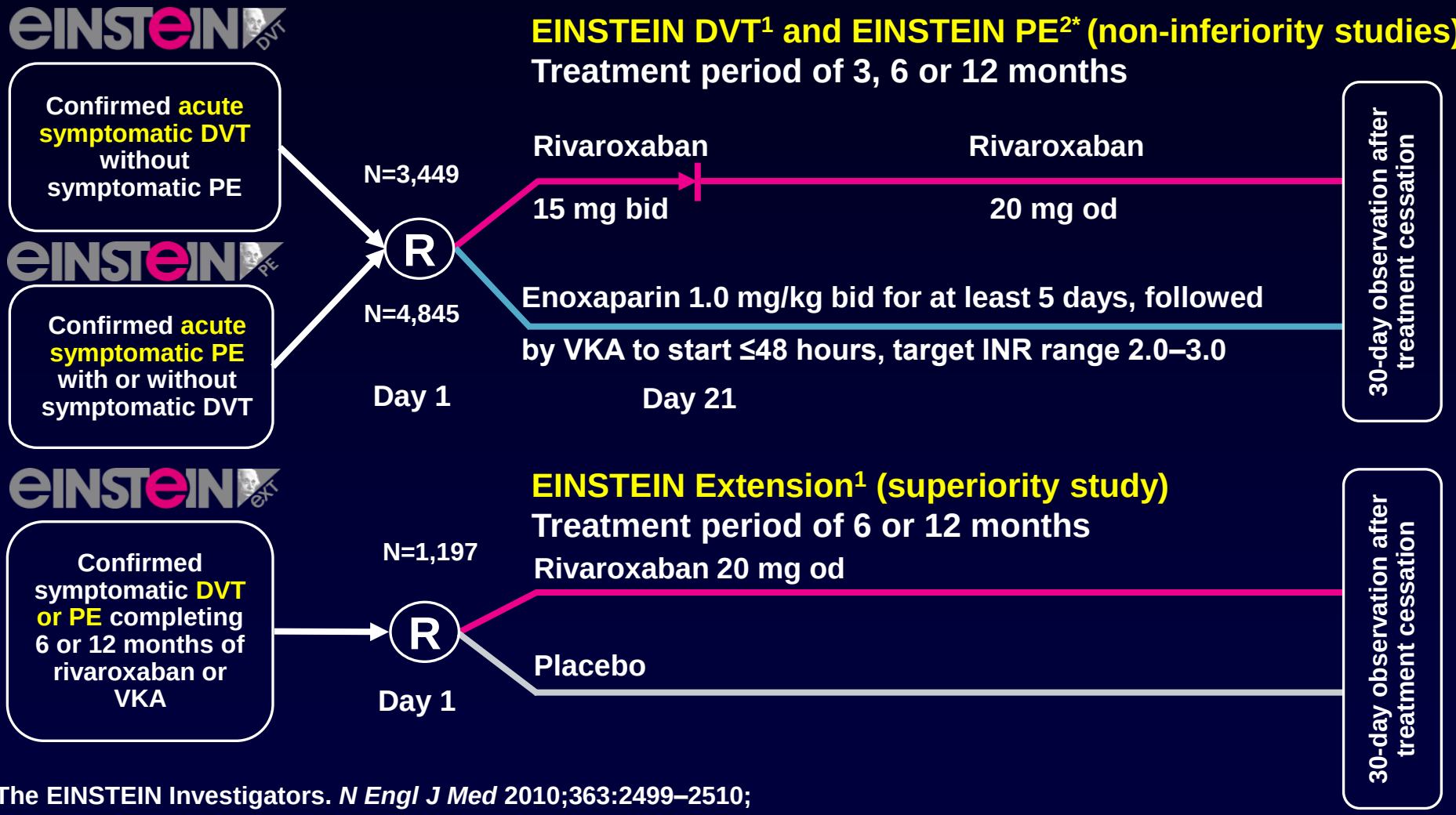
Rivaroxaban EINSTEIN phase III: study designs



1. The EINSTEIN Investigators. *N Engl J Med* 2010;363:2499–2510;
2. EINSTEIN PE. Available at: http://clinicaltrials.gov. Trial ID: NCT00439777. Accessed August 2011

EINSTEIN DVT and PE: study outcomes

Primary efficacy outcome*

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

Principal safety outcome*

- Combination of major and non-major clinically relevant bleeding

***Adjudicated by a central independent and blinded adjudication committee**

1. The EINSTEIN Investigators, *N Engl J Med* 2010;363:2499–2510; 2. EINSTEIN PE. Available at: http://clinicaltrials.gov. Trial ID: NCT00439777. Accessed August 2011

EINSTEIN DVT: patient characteristics

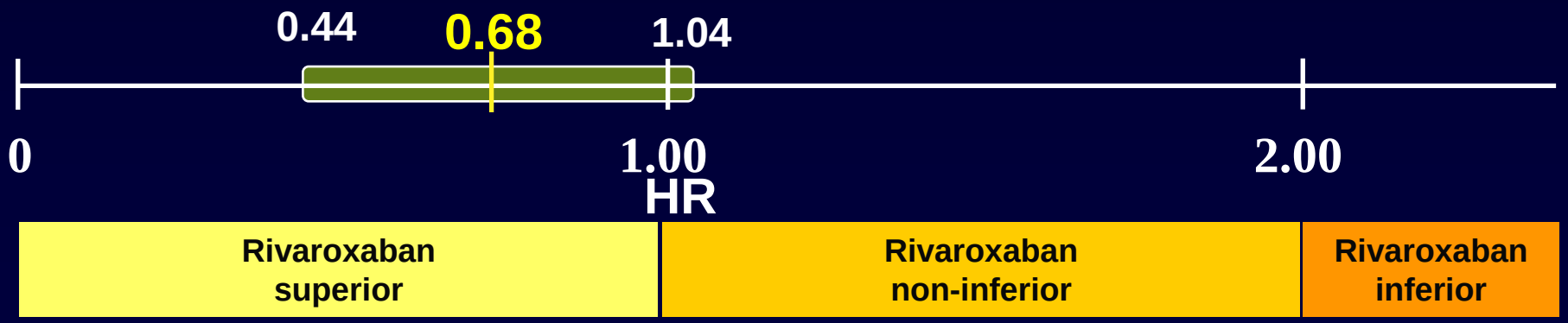
	Rivaroxaban (n=1,731)	Enoxaparin/VKA (n=1,718)
Males (%)	57.4	56.3
Age, mean (years)	55.8	56.4
Body mass index, mean (kg/m^2)	28	28
Creatinine clearance (%)		
<30 ml/min	0.3	0.5
30–49 ml/min	6.6	7.0
50–79 ml/min	22.7	23.2
≥80 ml/min	68.9	68.1
Previous VTE (%)	19.4	19.2
Patients with active cancer (%)	6.8	5.2
Intended treatment duration (%)		
3 months	12.0	11.8
6 months	62.6	63.0
12 months	25.4	25.1
Pretreatment for maximum 48 hours with LMWH, heparin/fondaparinux (%)	73.0	71.0

ITT population

The EINSTEIN Investigators. *N Engl J Med* 2010;363:2499–2510

EINSTEIN DVT : 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	(0.0)
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)



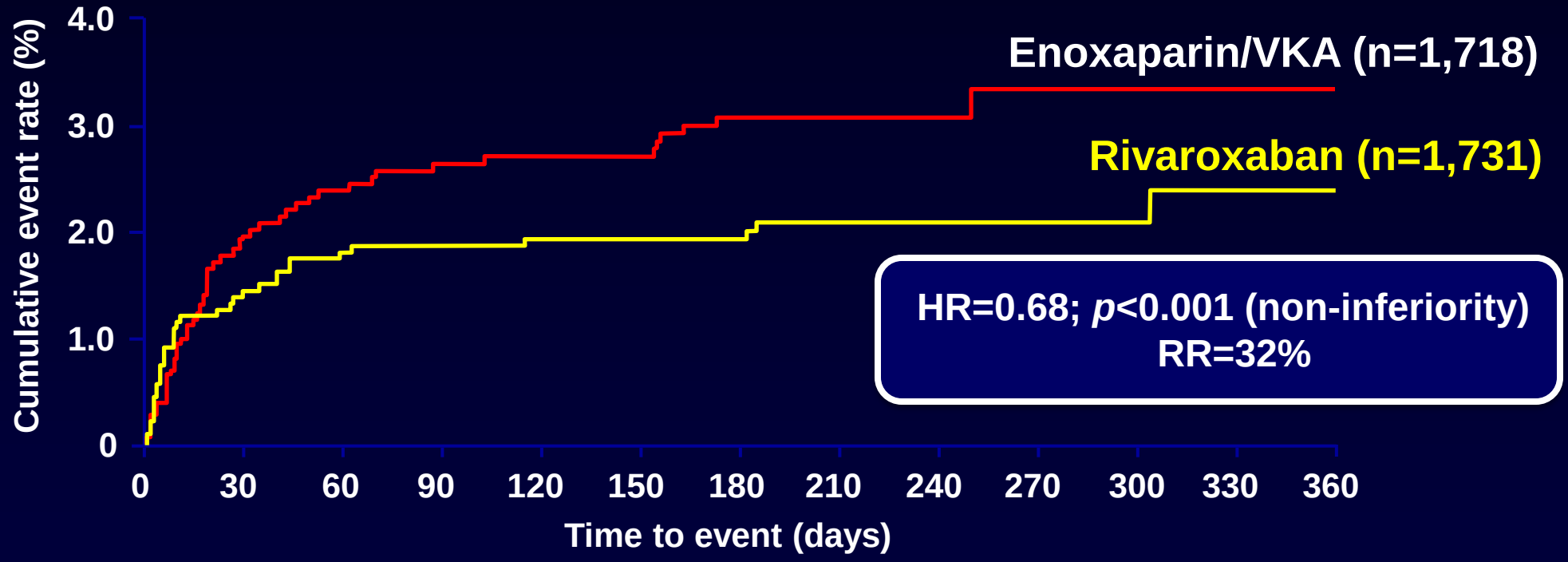
p=0.08 for superiority (two-sided)

p<0.001 for non-inferiority (one-sided)

ITT population

The EINSTEIN Investigators. *N Engl J Med* 2010;363:2499–2510

EINSTEIN DVT
: primary efficacy outcome – time to first symptomatic recurrent VTE



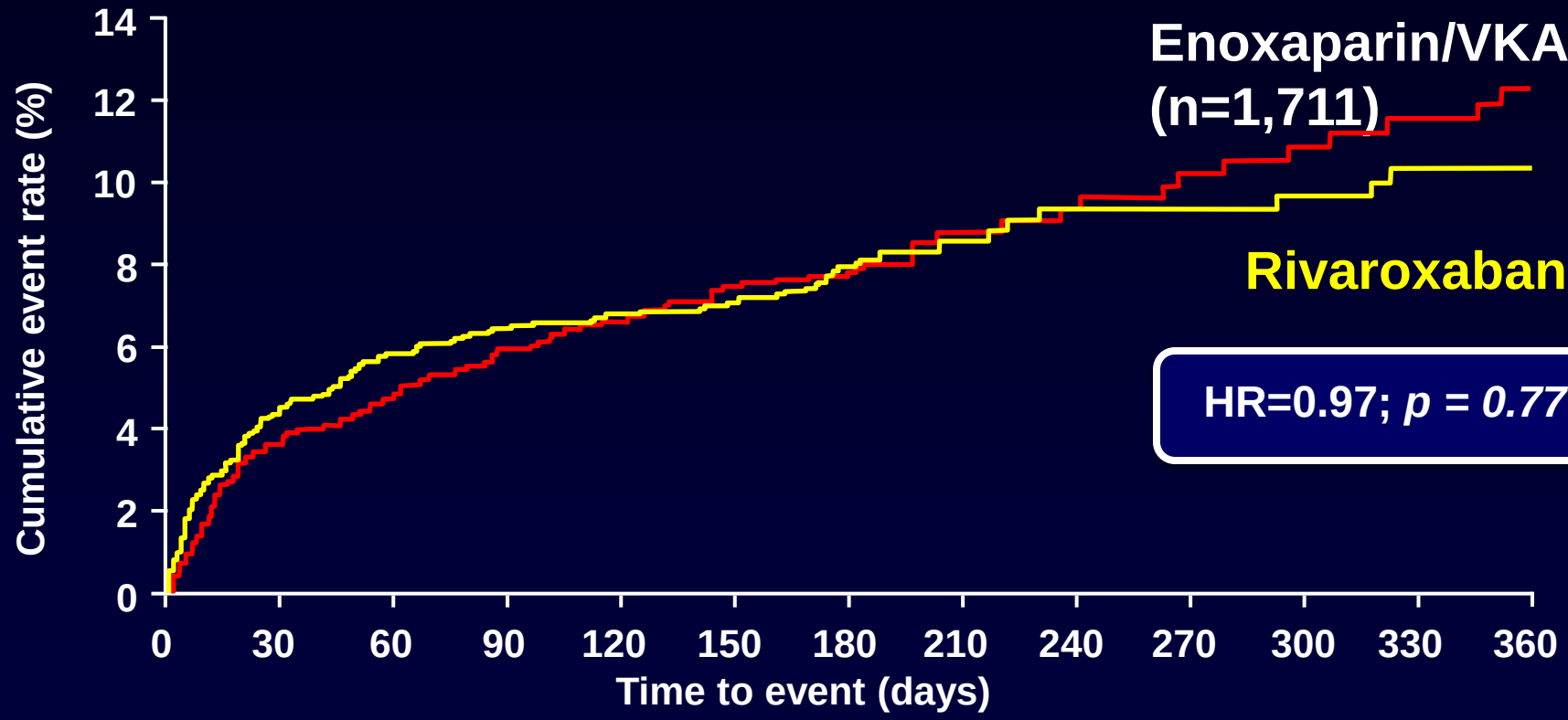
The EINSTEIN Investigators. *N Engl J Med* 2010;363:2499–2510

EINSTEIN DVT: principal safety outcome analysis

	Rivaroxaban (n=1,718)		Enoxaparin/VKA (n=1,711)		HR (95% CI)
	n	(%)	n	(%)	*p*-value
First major or non-major clinically relevant bleeding	**139**	**(8.1)**	**138**	**(8.1)**	**0.97 (0.76–1.22) *p*=0.77**
Major bleeding	14	(0.8)	20	(1.2)	0.65 (0.33–1.30) *p*=0.21
Contributing to death	1	(<0.1)	5	(0.3)	
In a critical site	3	(0.2)	3	(0.2)	
Associated with fall in haemoglobin ≥2 g/dl and/or transfusion of ≥2 units	10	(0.6)	12	(0.7)	
Non-major clinically relevant bleeding	126	(7.3)	119	(7.0)	

The EINSTEIN Investigators. *N Engl J Med* 2010;363:2499–2510

EINSTEIN DVT: principal safety outcome (composite of major or non-major clinically relevant bleeding)



The EINSTEIN Investigators. *N Engl J Med* 2010;363:2499–2510

EINSTEIN DVT: mean percentage of time in therapeutic range (TTR)

- INR values after discontinuation of initial enoxaparin, during temporary VKA interruptions and VKA restart were taken into account for the TTR calculation
- TTR during VKA treatment alone
  - INR <2.0 24.4%
  - INR 2.0–3.0 57.7%
  - INR >3.0 16.2%
  - Missing 1.7%
- Percentage of TTR varied from 54.1% during month 1 to 66.4% in month 10

The EINSTEIN Investigators. *N Engl J Med* 2010;363:2499–2510; EINSTEIN Integrated Protocol/Study number 11702/Version no 2.0/08Jun2009, incl. Amend 2, 3, 4

EINSTEIN DVT: key secondary and other outcomes

Outcome	Rivaroxaban n/N	Rivaroxaban (%)	Enoxaparin/VKA n/N	Enoxaparin/VKA (%)	HR (95% CI)
Net clinical benefit: (primary efficacy outcome plus major bleeding)	51/1,731	(2.9)	73/1,718	(4.2)	0.67 (0.47–0.95) *p*=0.03
Total mortality	38/1,731	(2.2)	49/1,718	(2.9)	0.67 (0.44–1.02)
Cardiovascular events	12/1,718	(0.7)	14/1,711	(0.8)	0.79 (0.36–1.71)

The EINSTEIN Investigators. *N Engl J Med* 2010;363:2499–2510 (Supplementary Appendix)

EINSTEIN DVT: conclusions

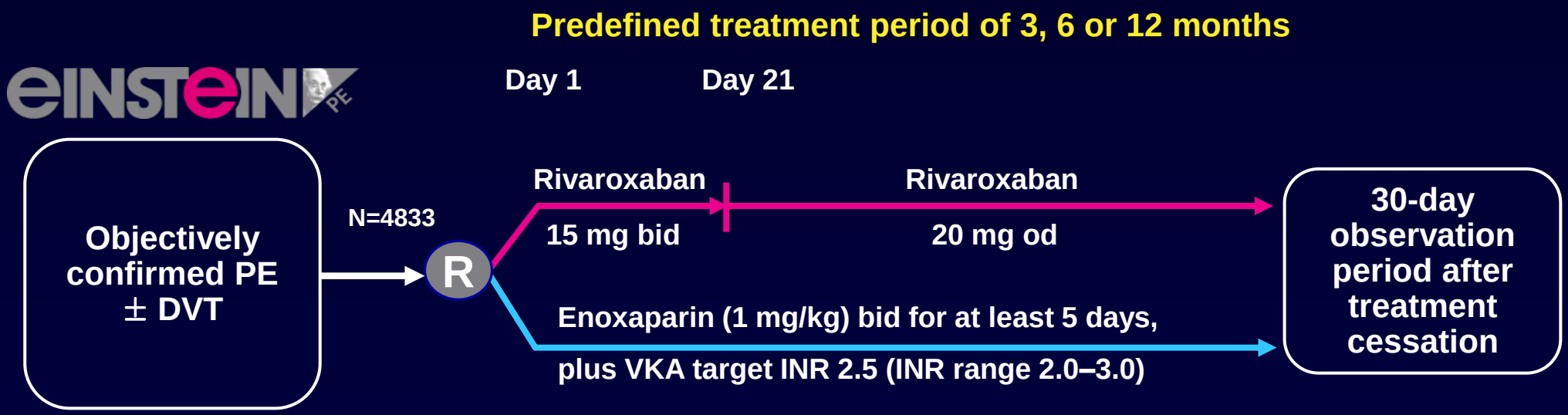
- In patients who had acute symptomatic proximal DVT, without symptomatic PE, rivaroxaban showed:
  - Non-inferiority to LMWH/VKA for efficacy (HR=0.68; 95% CI 0.44–1.04; $p<0.001$)
  - Similar findings for principal safety outcome between the two groups (HR=0.97; 95% CI 0.76–1.22; $p=0.77$)
  - Consistent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

The EINSTEIN Investigators. *N Engl J Med* 2010;363:2499–2510

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



The EINSTEIN–PE Investigators. *N Engl J Med* 2012

Patient characteristics

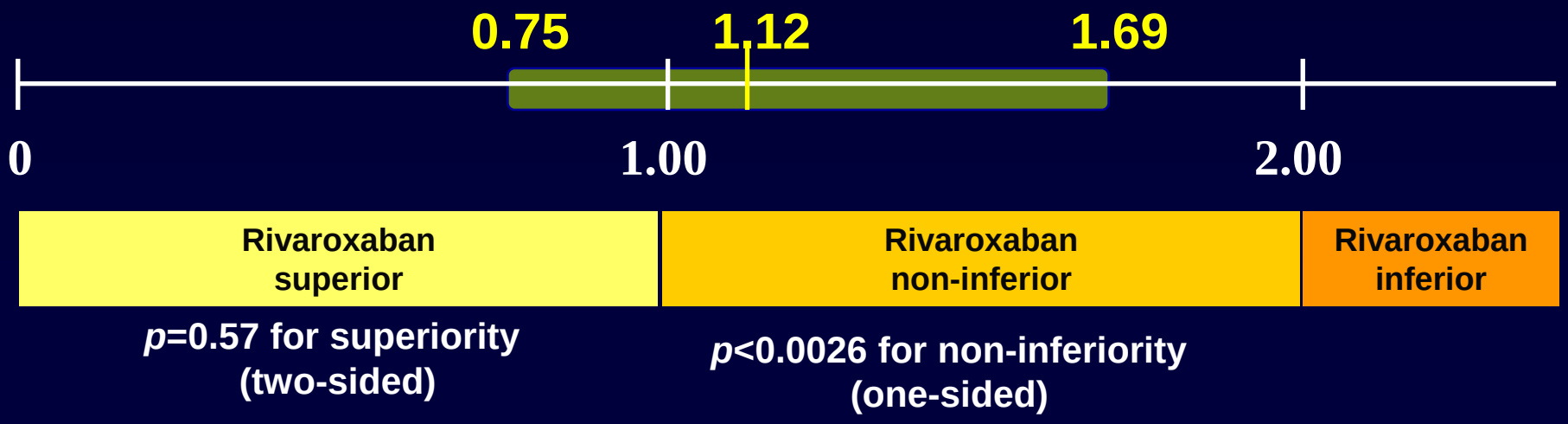
	Rivaroxaban (N=2419)		Enoxaparin/VKA (N=2413)	
Males (%)	54.1		51.7	
Age, mean (years)	57.9		57.5	
Body mass index, mean (kg/m^2)	28.3		28.4	
Creatinine clearance (%)				
<30 ml/min	0.2		<0.1	
30–49 ml/min	8.6		7.9	
50–79 ml/min	26.3		24.6	
≥80 ml/min	64.3		67.0	
Previous VTE (%)	18.8		20.3	
Patients 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	
Concommitant DVT (%)	24.9		24.3	

ITT population

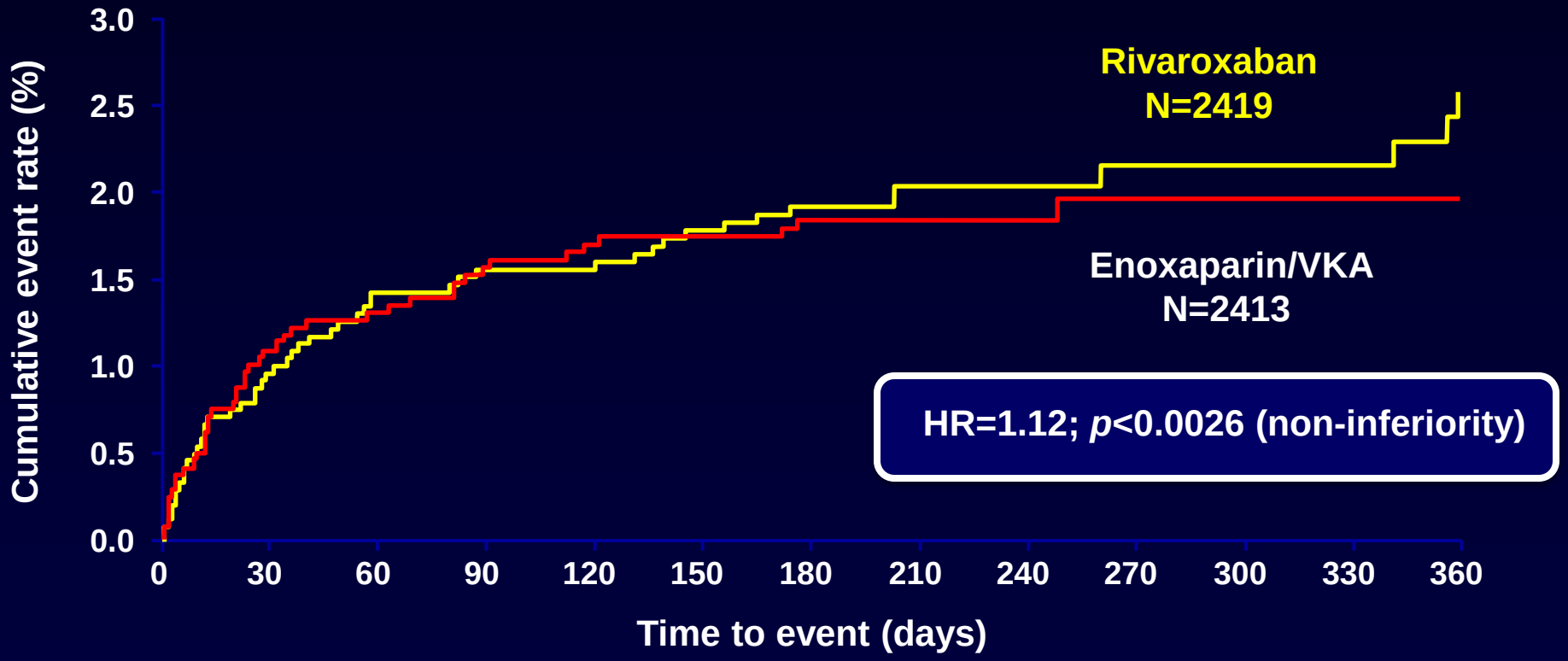
The EINSTEIN–PE Investigators. *N Engl J Med* 2012

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)



Primary efficacy outcome: time to first event

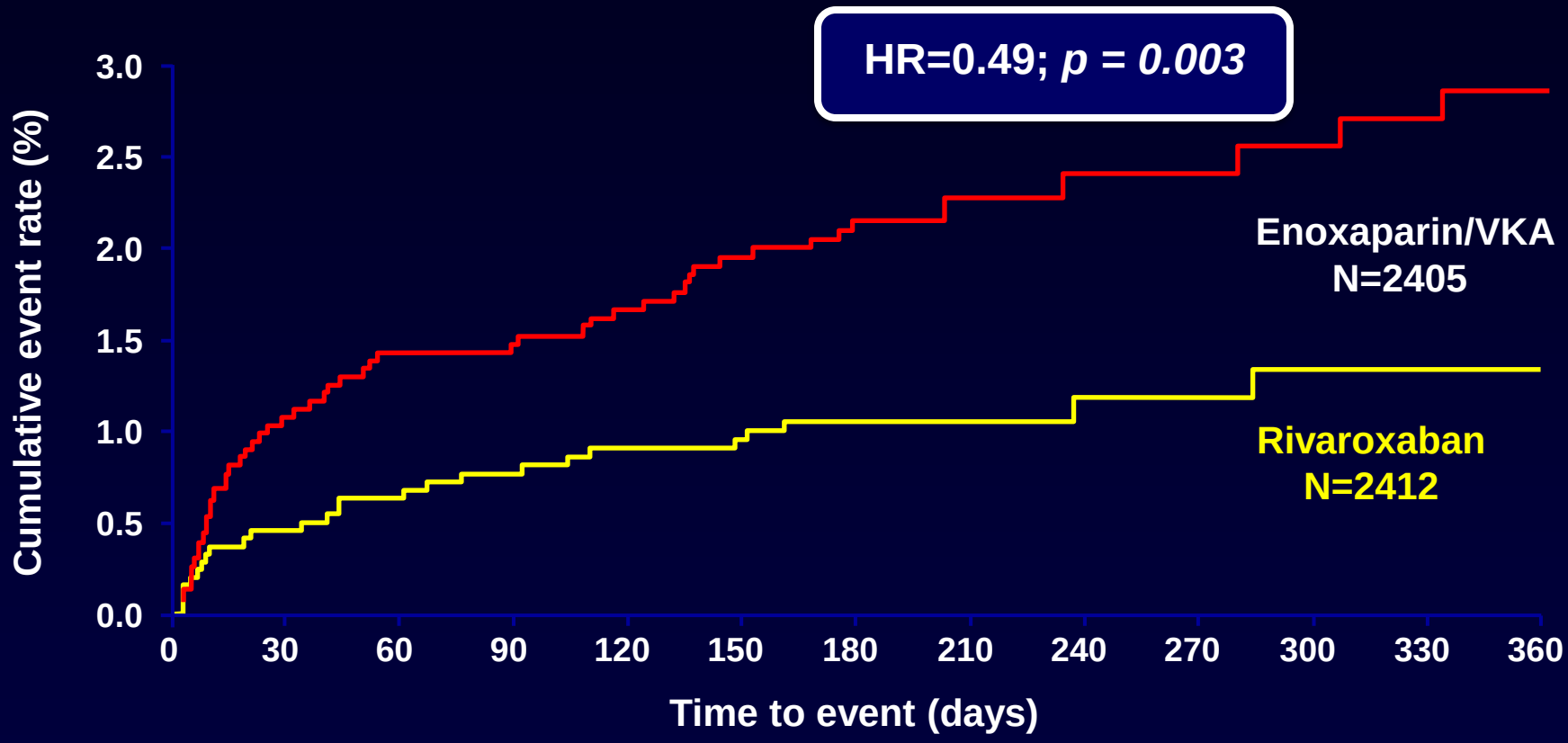


Major bleeding

	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*=0.003**
Fatal	**2**	**(<0.1)**	**3**	**(0.1)**	
Retroperitoneal	0		1	(<0.1)	
Intracranial	2	(<0.1)	2	(<0.1)	
In a critical site	**7**	**(0.3)**	**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	**17**	**(0.7)**	**26**	**(1.1)**	

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

Major bleeding

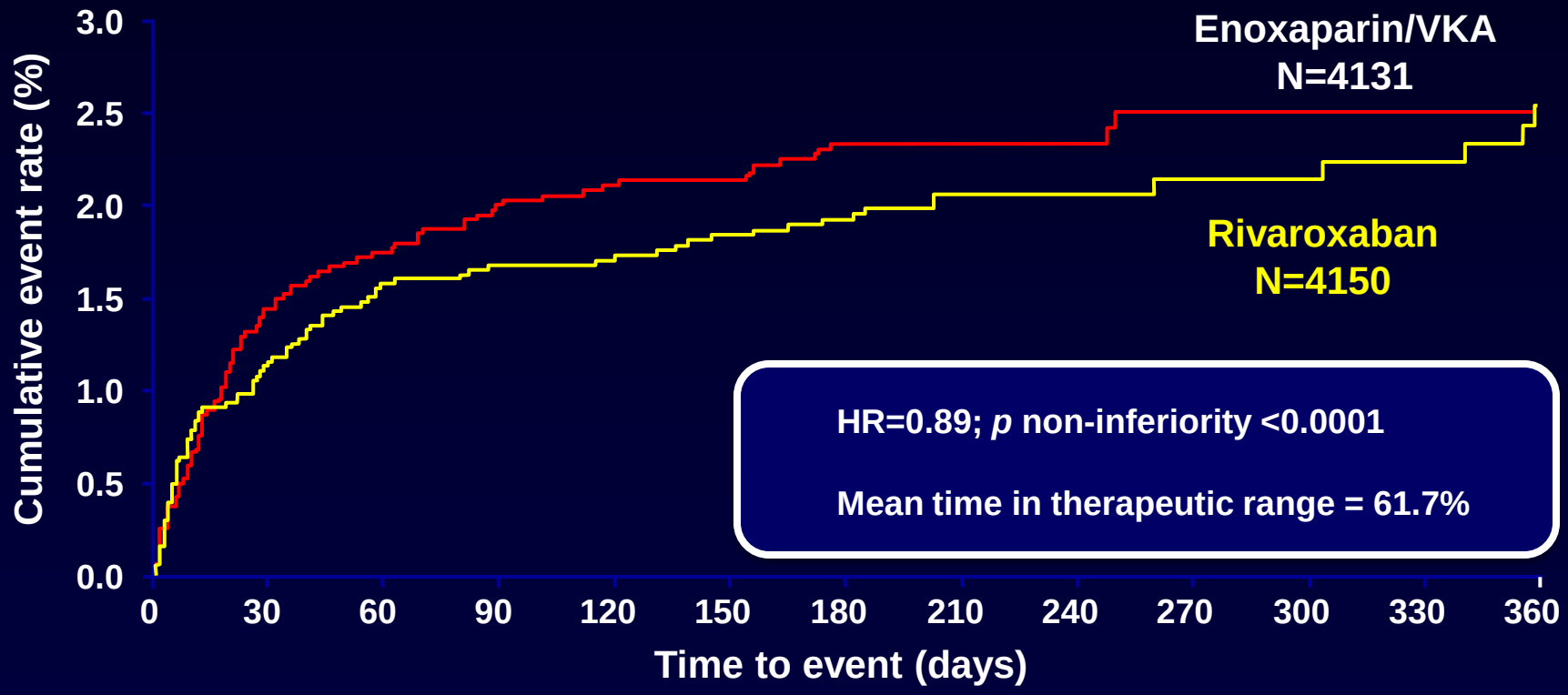


Conclusions

- In patients with acute symptomatic PE ± DVT rivaroxaban showed:
  - Non-inferiority to LMWH/VKA for efficacy: HR=1.12 (0.75–1.68); $p_{\text{non-inferiority}}$ =0.003 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=0.003
  - 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

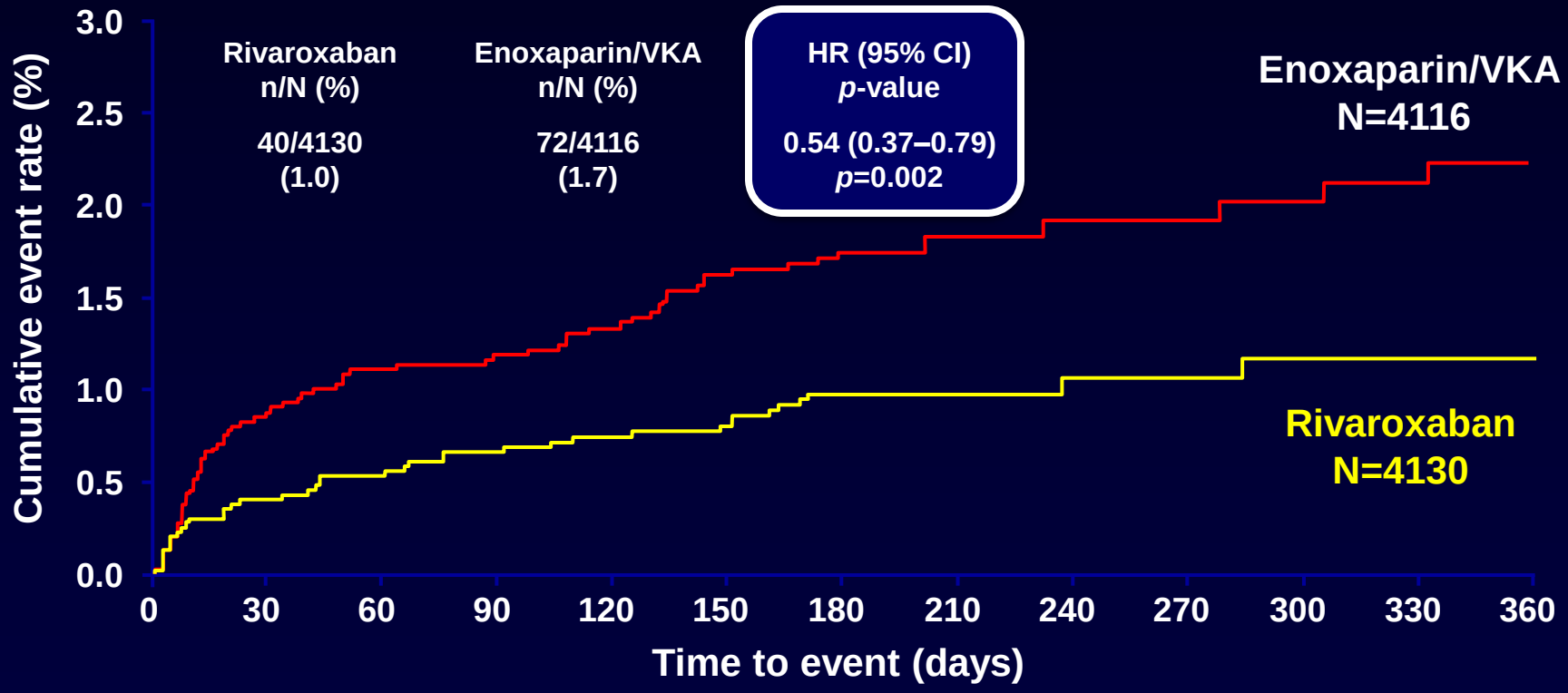
EINSTEIN DVT and PE : pooled analysis

EINSTEIN DVT and EINSTEIN PE pooled analysis: primary efficacy outcome



Buller HR, for the EINSTEIN Investigators. *ASH*, December 2012

EINSTEIN DVT and EINSTEIN PE pooled analysis: major bleeding

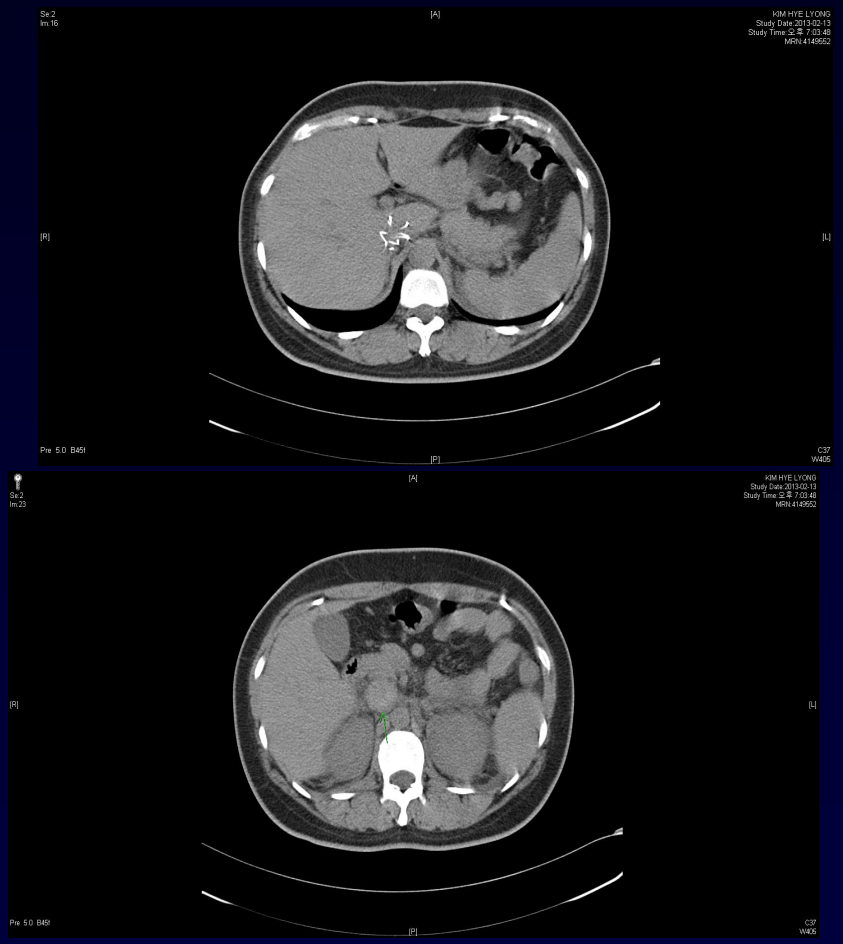


Buller HR, for the EINSTEIN Investigators. *ASH*, December 2012

EINSTEIN DVT and EINSTEIN PE pooled analysis: conclusions

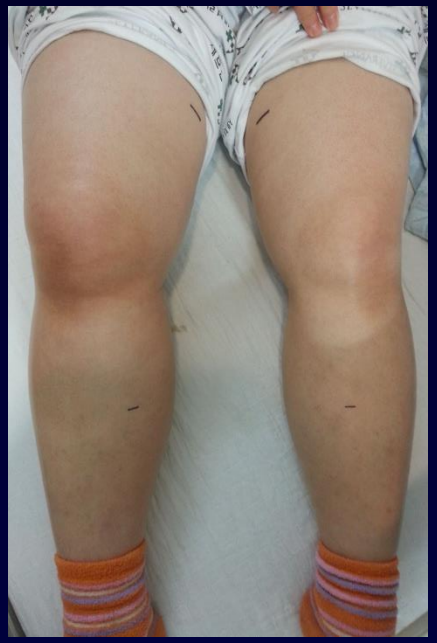
- In patients with acute symptomatic DVT and/or PE, rivaroxaban showed:
  - Non-inferiority versus enoxaparin/VKA for efficacy
  - Similar incidence rates to enoxaparin/VKA for the principal safety outcome
  - Superiority for major bleeding
  - Consistent efficacy and safety results irrespective of age, body weight, gender, renal function, cancer, and severity of DVT/PE
- Single-drug approach for treatment of acute DVT, PE and secondary prevention

F/39, PE w/ DVT s/p IVC filter thrombosis

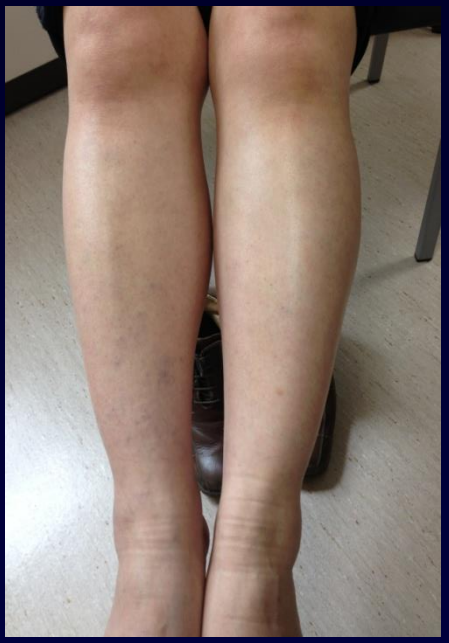


Rivaroxaban Treatment
(30 mg #2 for 3 wks ➔ 20 mg/d)

Before



After



Appreciate your attention ^^