Krankenhaus
Dresden-Friedrichstadt
Städtisches Klinikum

20th Cardiology Update 2013

Single drug approach for anticoagulation of acute PE the EINSTEIN PE –Trial

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Medizinische Klinik 2
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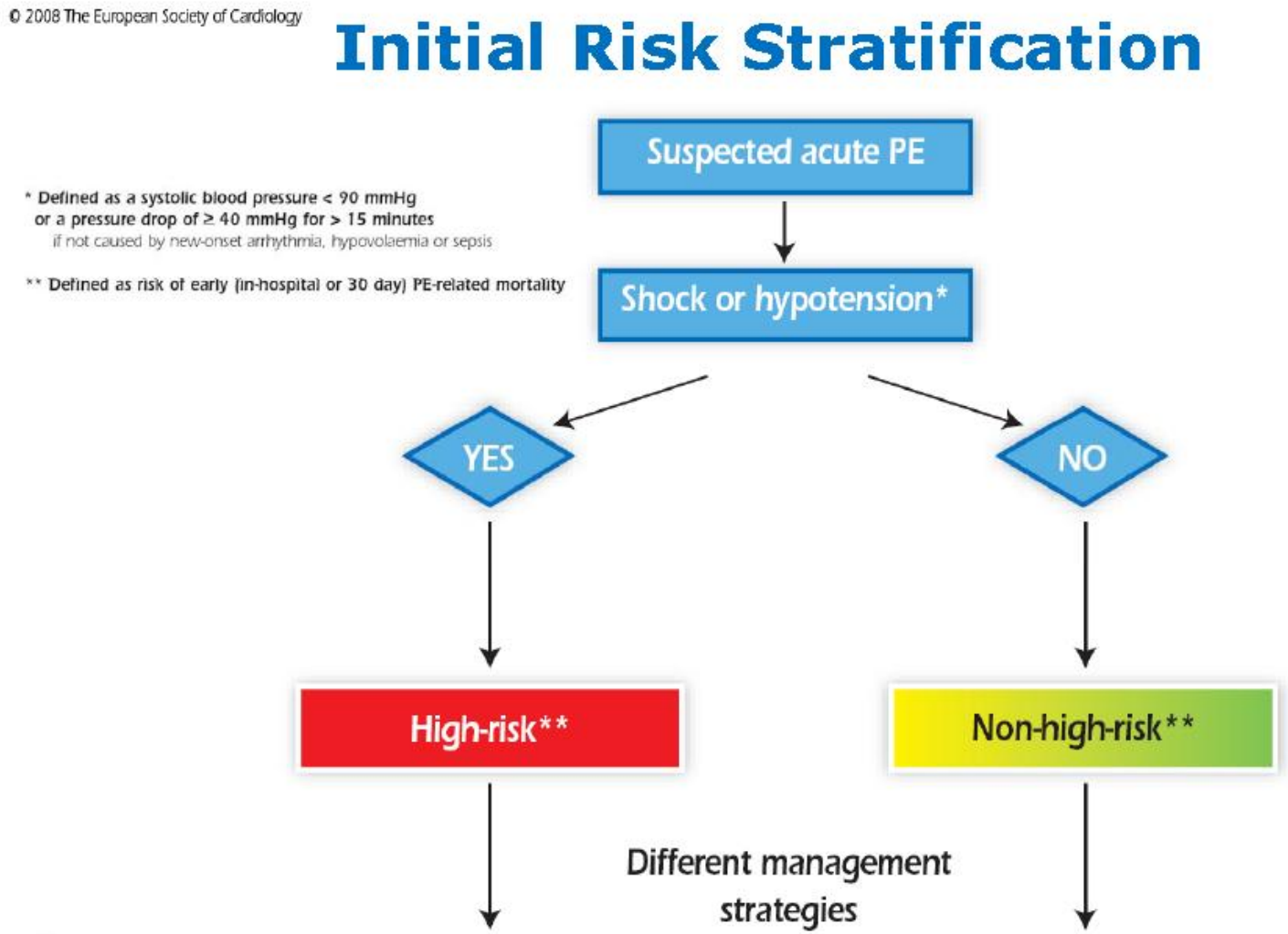
Risk categories

PE-related early MORTALITY RISK		RISK MARKERS		
		CLINICAL (Shock or hypotension)	RV Dysfunction	Myocardial injury
HIGH > 15%		+	(+)*	(+)*
NON HIGH	Inter mediate 3 - 15%	–	+	+
			+	–
			–	+
	Low <1%	–	–	–

ESC guidelines 2008

Krankenhaus Dresden-Friedrichstadt



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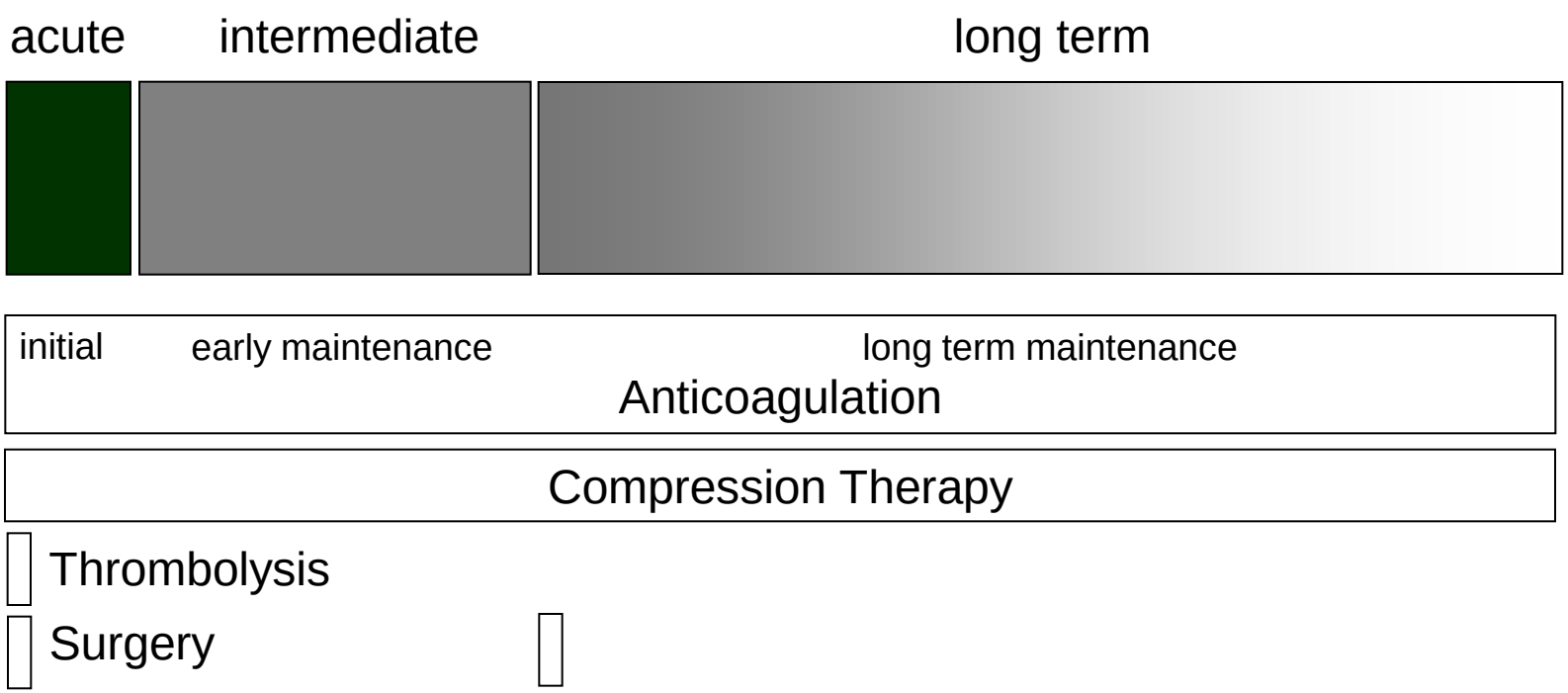
HIGH > 15%		+	(+)*	(+)*
NON HIGH	Inter mediate 3 - 15%	–	+	+
			+	–
			–	+
	Low <1%	–	–	–

Therapy of VTE



Anticoagulation in VTE

Initial therapy

- **NMH, Fondaparinux**
- **exceptions: high-risk PE, renal impairment**

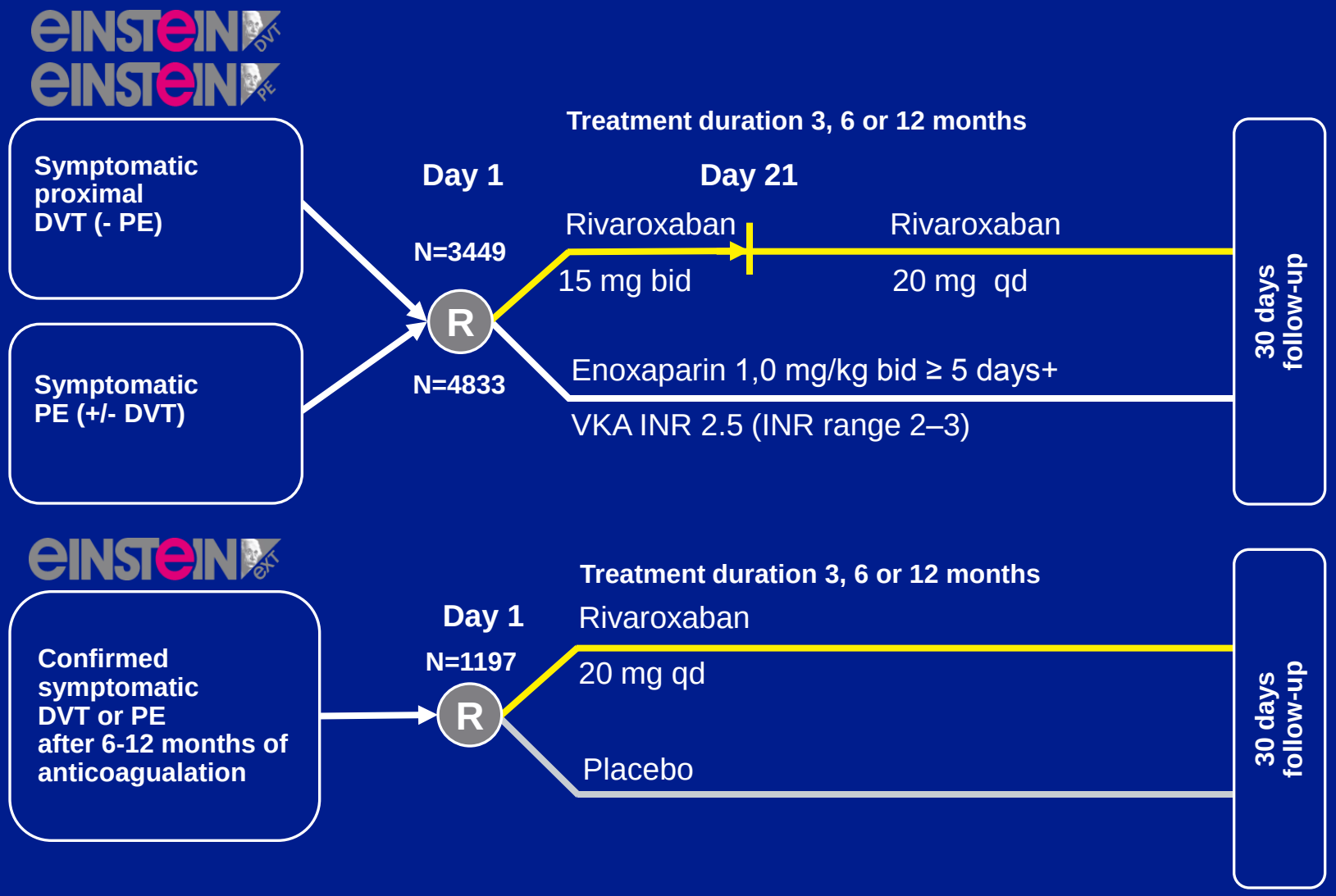
Early maintenance therapy

- **VKA**
- **exceptions: cancer, other comorbidities, planned procedures, very elderly, compliance issues...**

Prolonged maintenance therapy

- **VKA**
- **exceptions: rare cases**

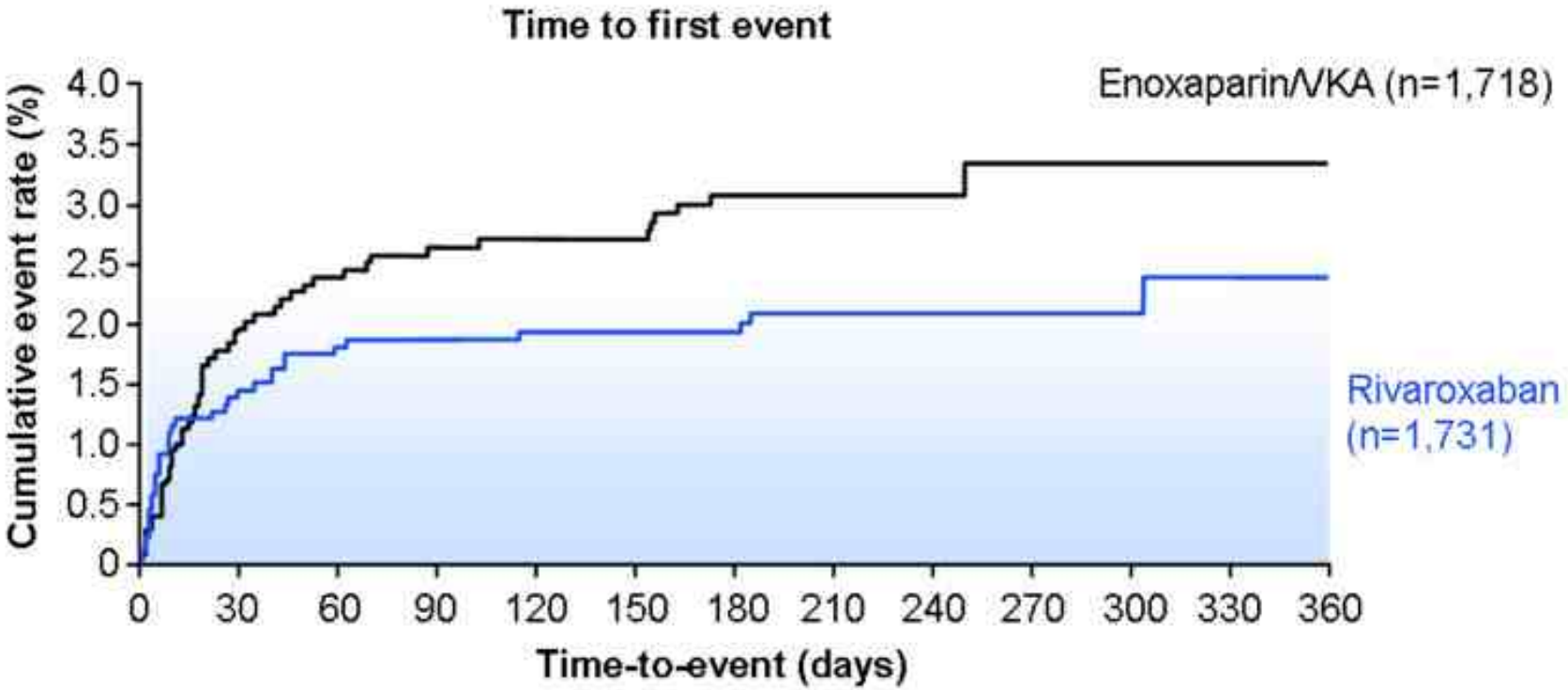
EINSTEIN clinical trial programme



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

2. The EINSTEIN–PE Investigators *N Engl J Med* 2012; 366:1287 - 1297

Einstein DVT primary outcome



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 DVT: bleeding

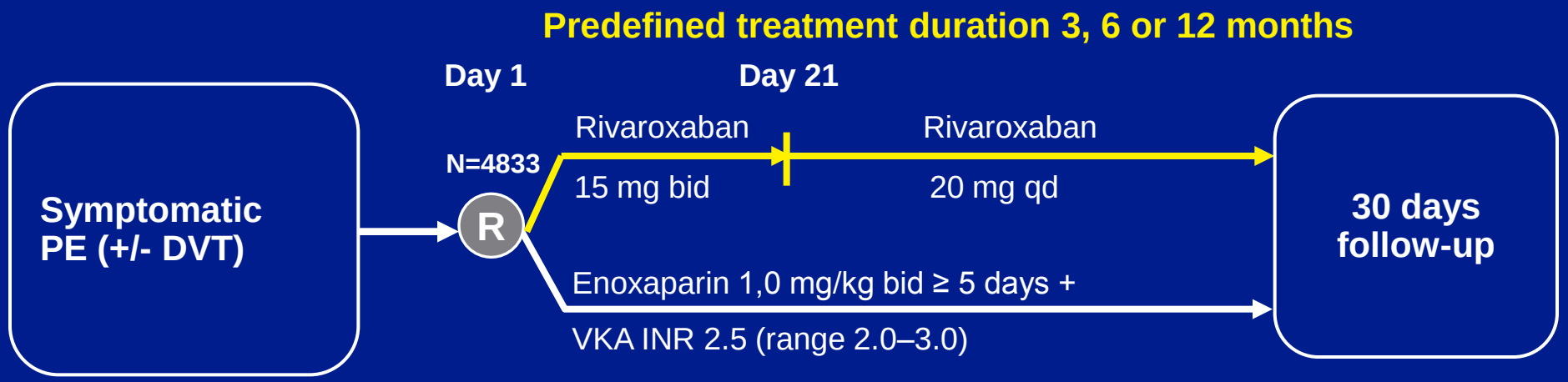
Krankenhaus Dresden-Friedrichstadt

	Rivaroxaban (n=1,718)		Enoxaparin/VKA (n=1,711)		HR (95% CI)
	n	(%)	n	(%)	*p* value
First major bleeding 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)	
Bleeding contributing to death	1	(< 0.1)	5	(0.3)	
Bleeding in a critical site	3	(0.2)	3	(0.2)	
Bleeding associated with fall in hemoglobin ≥ 2g/dL and/or transfusion of ≥ 2 units	10	(0.6)	12	(0.7)	
Clinically relevant non-major bleeding	129	(7.5)	122	(7.1)	

EINSTEIN PE: Study Design

Randomised, open, event driven non-inferiority trial

- Heparin/Fondaparinux treatment and/or 1 dose VKA allowed up to 48 hrs before randomisation
- Number of primary endpoint events: 88



The EINSTEIN–PE Investigators *N Engl J Med* 2012; 366:1287 - 1297

Endpoints

Primary efficacy endpoint:

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

Primary safety endpoint:

- Composite of major and non-major clinically relevant bleeds

Secondary endpoints

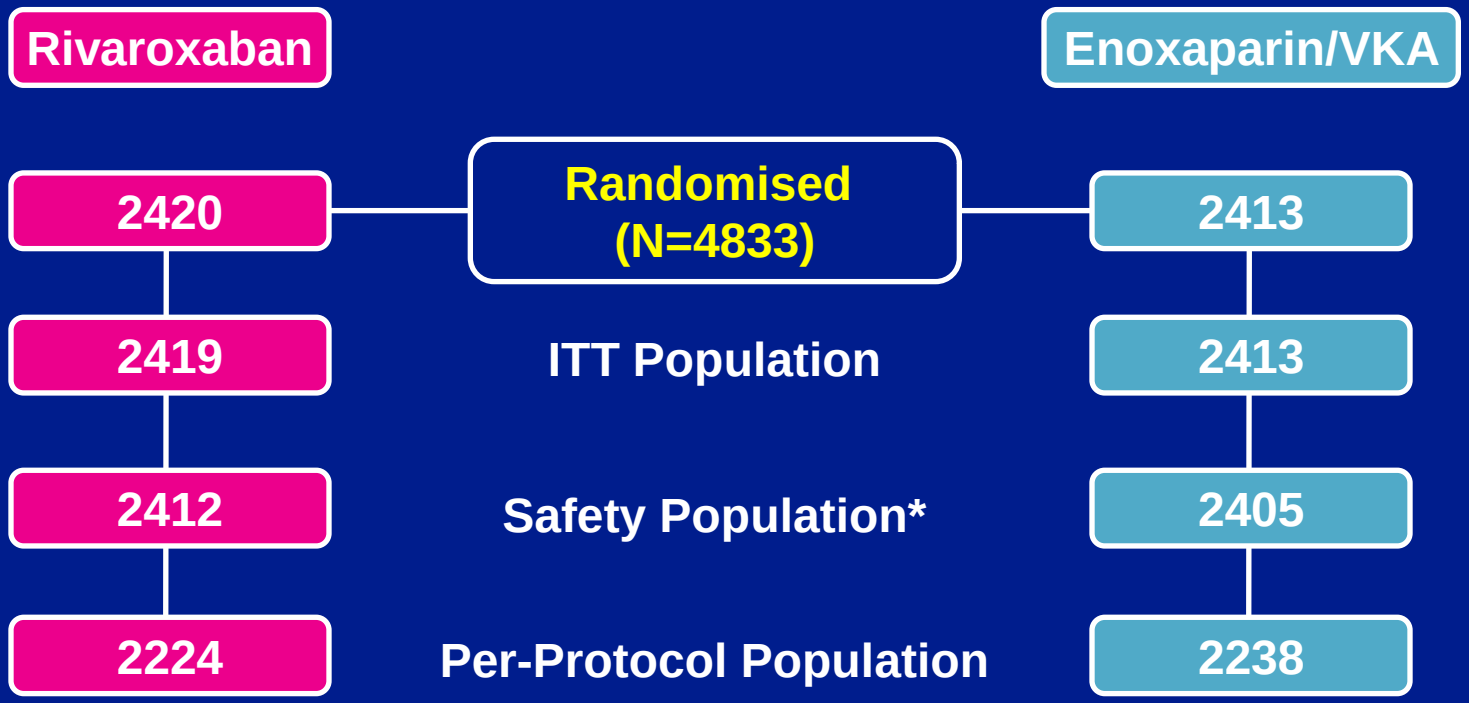
- Major bleeds
- Net clinical benefit: primary efficacy endpoint + major bleeds
- All cause mortality
- Vascular events

Central lab evaluation

- ALT and Bilirubin

The EINSTEIN–PE Investigators *N Engl J Med* 2012; 366:1287 - 1297

Patient flow diagram



*all ITT patients, having received ≥1 dose of study drug

The EINSTEIN–PE Investigators *N Engl J Med* 2012; 366:1287 - 1297

Demographic Data

	Rivaroxaban (n=2419)	Enoxaparin/VKA (n=2413)
Male (%)	54.1	51.7
Age (years, mean)	57.9	57.5
Body weight(%)		
≤50 kg	1.6	1.8
>50 – 100 kg	84.1	83.3
>100 kg	14.3	14.9
Creatinin clearance (%)		
<30 ml/min	0.2	<0.1
30 - < 50ml/min	8.6	7.9
50 – < 80 ml/min	26.3	24.6
≥80 ml/min	64.3	67.0
Known Thrombophilia	5.7	5.0
History of VTE (%)	18.8	20.3

The EINSTEIN–PE Investigators *N Engl J Med* 2012; 366:1287 - 1297

Clinical Characteristics

	Rivaroxaban (n=2419)	Enoxaparin/VKA (n=2413)
Concomitant symptomatic DVT (%)	25.1	24.5
Reason for PE(%)		
Idiopatic	64.7	64.3
Surgery of Trauma	17.2	16.5
Immobilisation	15.9	15.7
Estrogen Therapie	8.6	9.2
Active Cancer	4.7	4.5
Anatomic Extent of PE (%)		
Limited (≤ 25 % of vessels of one lobe)	12.8	12.4
Intermediate	57.5	59.0
Extensive (multiple lobes and > 25% of entire vasculature)	24.7	23.9

The EINSTEIN–PE Investigators *N Engl J Med* 2012; 366:1287 - 1297

Treatment Modalities

	Rivaroxaban (n=2419)	Enoxaparin/VKA (n=2413)
Pretreatment with Heparin or Fondaparinux (%)	92.5	92.1
Duration of treatment prior to randomisation (%)		
1 day	57.4	58.0
2 days	33.1	32.2
> 2 days	1.9	1.9
Intended treatment duration(%)		
3 months	5.3	5.1
6 months	57.3	57.5
12 months	37.4	37.5
Hospitalised Patients (%)	89.1	89.5
Patients at ICU	12.9	12.0

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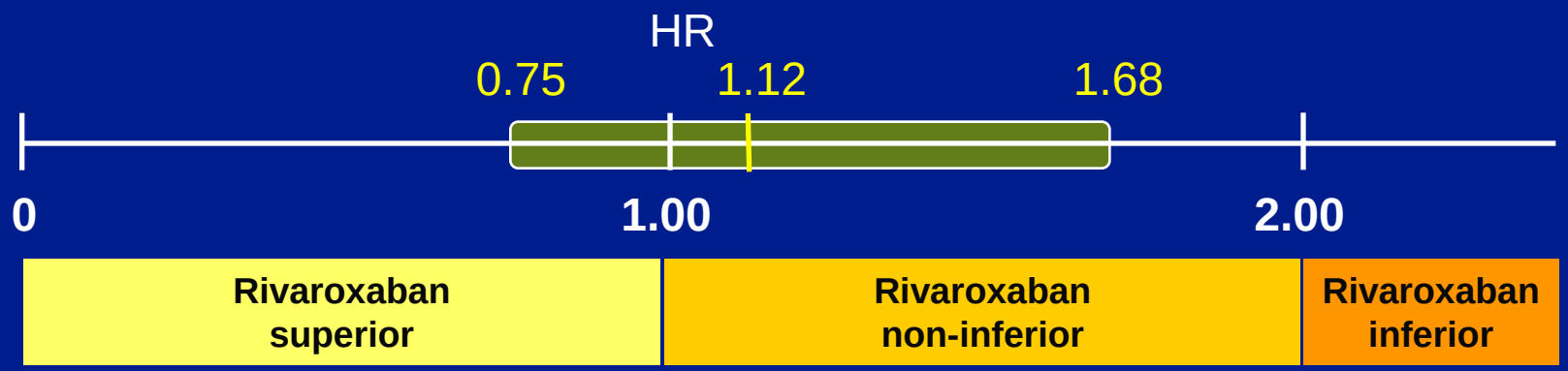
Primary Efficacy Endpoint: Recurrent Symptomatic VTE

	Rivaroxaban (N=2419)		Enoxaparin/VKA (N=2413)	
	n	(%)	n	(%)
First symptomatic recurrent VTE	**50**	**(2.1)**	**44**	**(1.8)**
Recurrent TVT	18	(0.7)	17	(0.7)
Recurrent TVT + LE	0		2	(<0.1)
Non-fatal PE	22	(0.9)	19	(0.8)
Fatal PE	2		1	
Death, PE not excluded	8		5	



p=0.57 for superiority (2 - sided)

p=0.0026 for non-inferiority (1 - sided)

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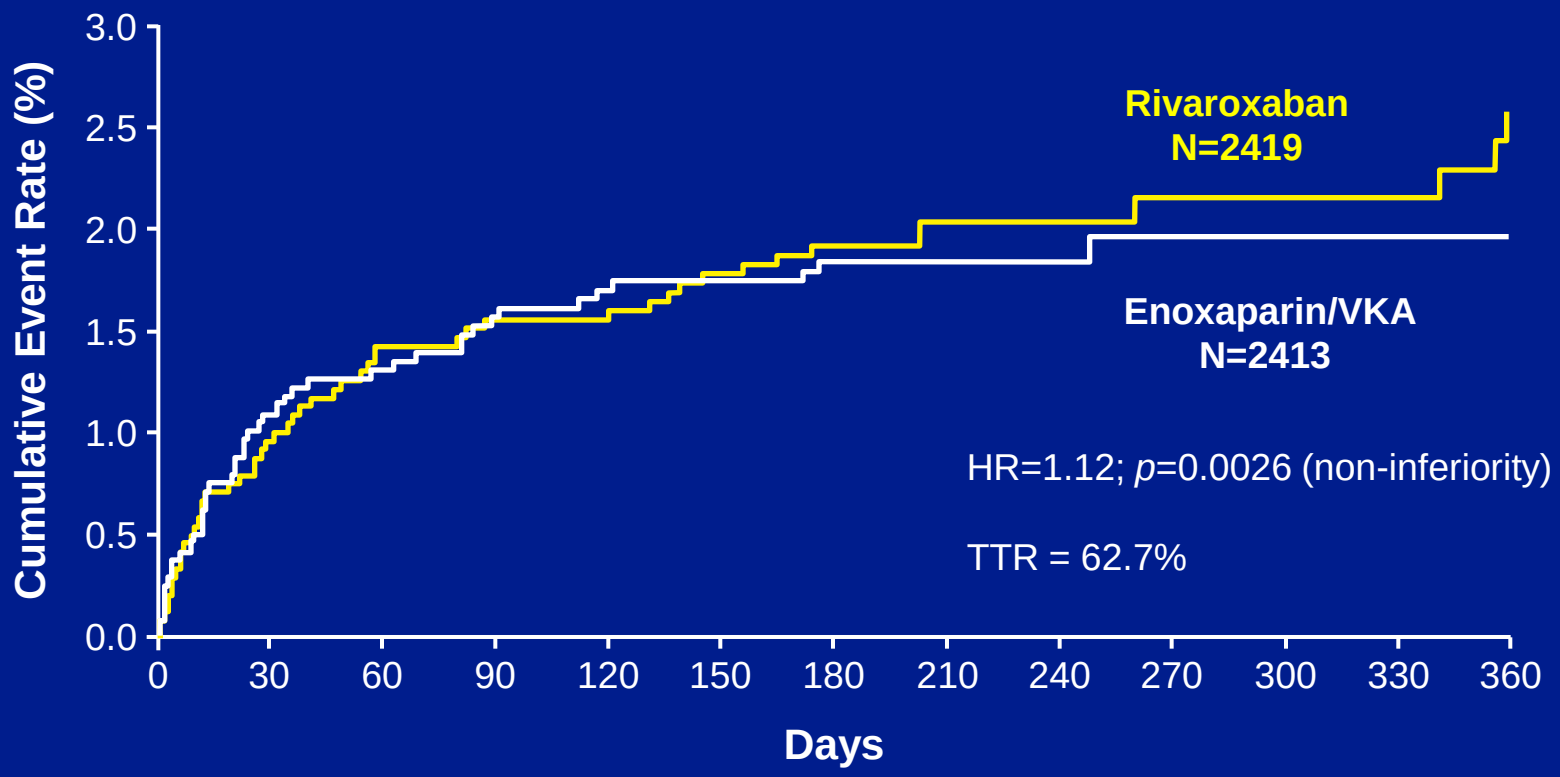
Recurrent Symptomatic VTE : Time-to-Event



Number of patients													
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

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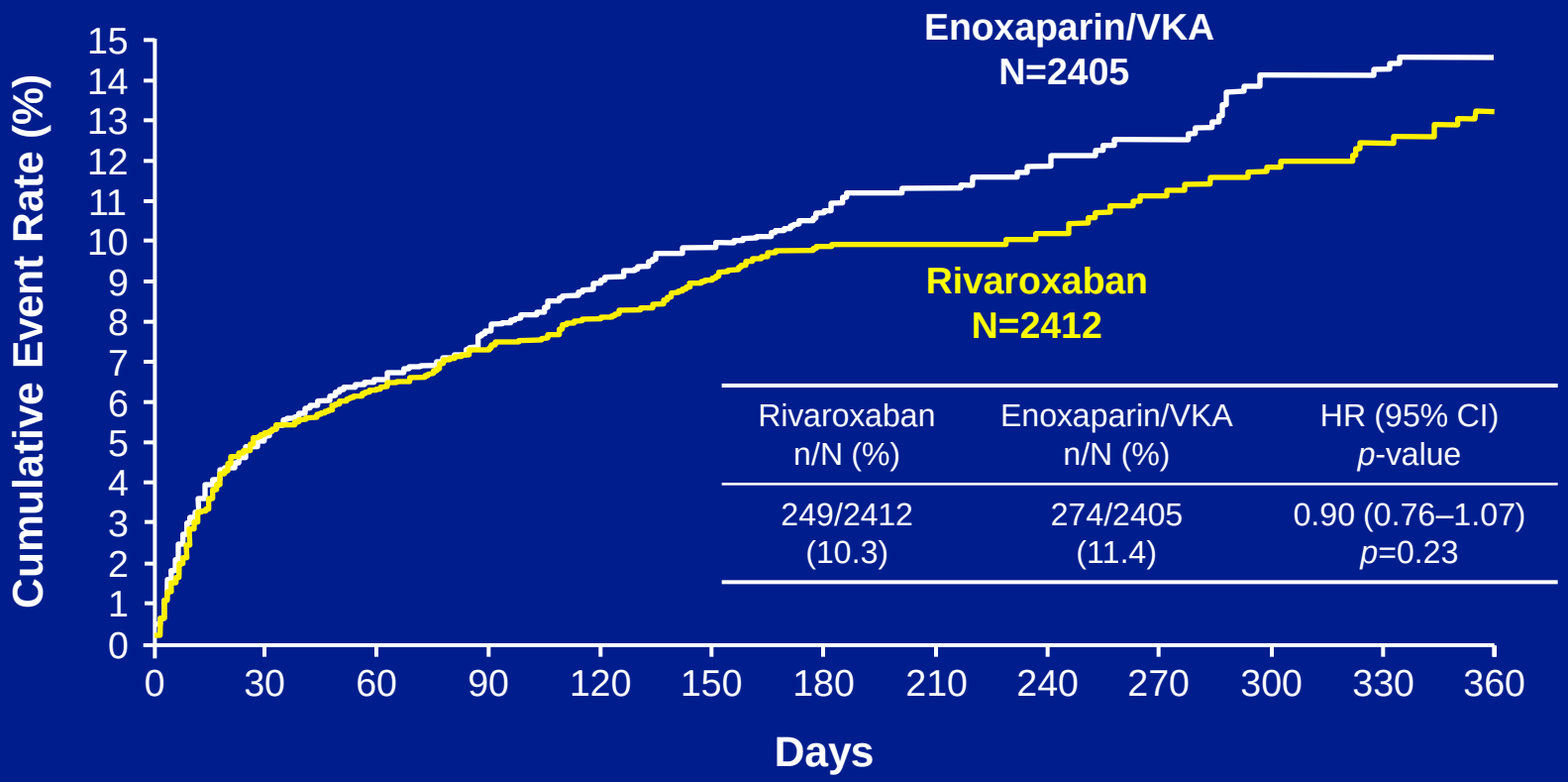
Primary safety endpoint: Major and non-major clinically relevant bleeds



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

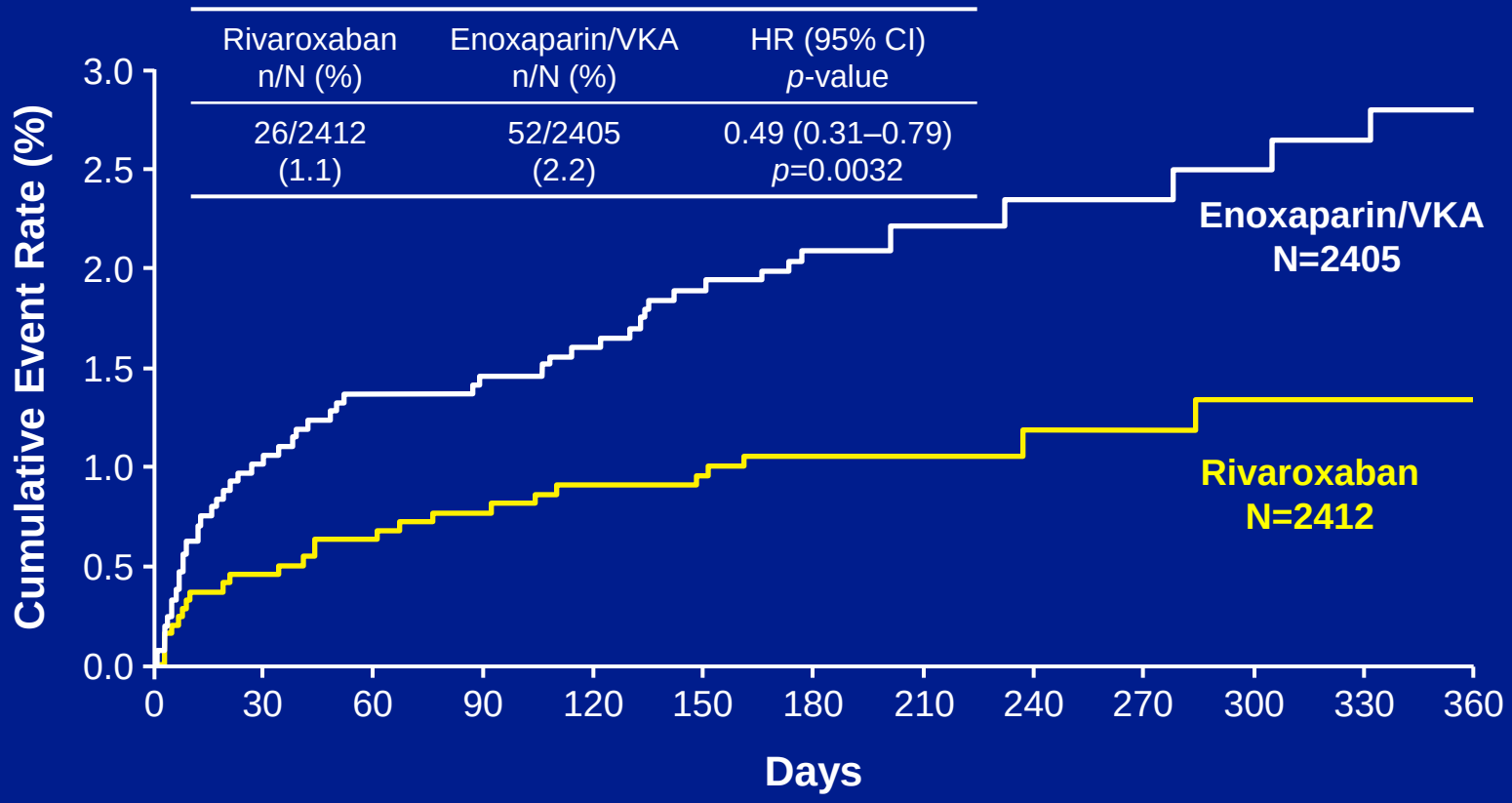
Number of patients

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; 366:1287 - 1297

Secondary Safety Endpoint: Major Bleeds



Number of patients													
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; 366:1287 - 1297

Analysis of Major Bleeds

	Rivaroxaban (n=2412)		Enoxaparin/VKA (n=2405)		HR (95% CI) *P*-value
	n	(%)	n	(%)	
Major bleeds*	**26**	**(1.1)**	**52**	**(2.2)**	**0.49 (0.31–0.79) *p*=0.003**
Fatal	**2**	**(<0.1)**	**3**	**(0.1)**	
Retroperitoneal	0		1	(<0.1)	
Intracranial	2	(<0.1)	2	(<0.1)	
Critical organ bleeds	**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)	
Perikardial	0		2	(<0.1)	
Intraarticular	0		3	(0.1)	
Adrenal gland	1	(<0.1)	0		
Hematothorax	1	(<0.1)	1	(<0.1)	
Intraabdominal (hemodyn instable)	1	(<0.1)	2	(<0.1)	
Hb↓ ≥2 g/dl, ≥2 Transfusionen	**17**	**(0.7)**	**26**	**(1.1)**	

*Some patients had >1 events. Safety population

The EINSTEIN–PE Investigators *N Engl J Med* 2012; 366:1287 - 1297

EINSTEIN PE: Secondary endpoints

Endpoint	Rivaroxaban		Enoxaparin/VKA		HR (95% CI)
	n/N	(%)	n/N	(%)	
Net clinical benefit	83/2419	(3.4)	96/2413	(4.0)	0.85 (0.63–1.14)
All cause mortality during treatment phase	58/2419	(2.4)	50/2413	(2.1)	1.13 (0.77–1.65)
Treatment phase					
Cerebrovascular events	12/2412	(0.5)	13/2405	(0.5)	
Acute coronary events	15/2412	(0.6)	21/2405	(0.9)	
Follow-up (30 days)					
Cerebrovascular events	2/2206	(<0.1)	1/2197	(<0.1)	
Acute coronary events	3/2206	(0.1)	2/2197	(<0.1)	
ALT>3×ULN + Bilirubin>2× ULN	5/2355	(0.2)	4/2327	(0.2)	

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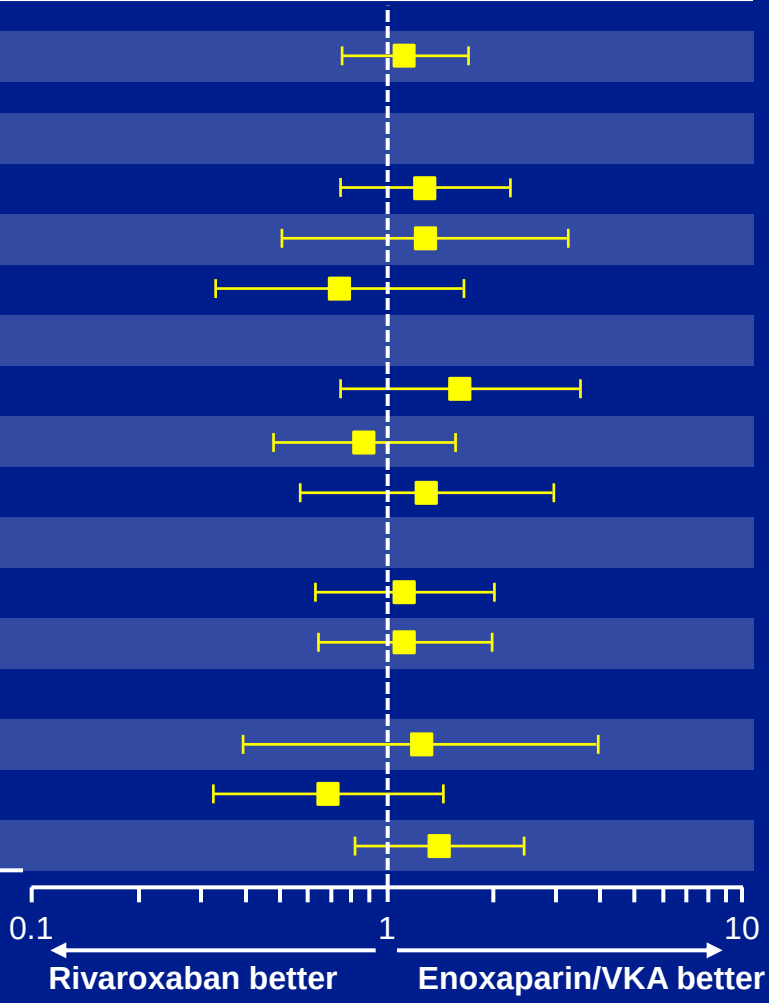
EINSTEIN PE: Primary efficacy endpoint
Subgroup analysis (1)

	Rivaroxaban		Enoxaparin/VKA		HR (95% CI)
	n/N	(%)	n/N	(%)	
Total population	50/2419	(2.1)	44/2413	(1.8)	
Age					
<65 years	29/1461	(2.0)	23/1479	(1.6)	
65–75 years	10/517	(1.9)	8/532	(1.5)	
>75 years	11/441	(2.5)	13/402	(3.2)	
Body weight					
≤70 kg	17/653	(2.6)	10/621	(1.6)	
>70–90 kg	20/1081	(1.9)	24/1119	(2.1)	
>90 kg	13/683	(1.9)	10/672	(1.5)	
Sex					
Male	25/1309	(1.9)	21/1247	(1.7)	
Female	25/1110	(2.3)	23/1166	(2.0)	
Creatinin Clearance					
<50 ml/min	7/211	(3.3)	5/193	(2.6)	
50–<80 ml/min	12/637	(1.9)	16/593	(2.7)	
≥80 ml/min	30/1555	(1.9)	22/1617	(1.4)	

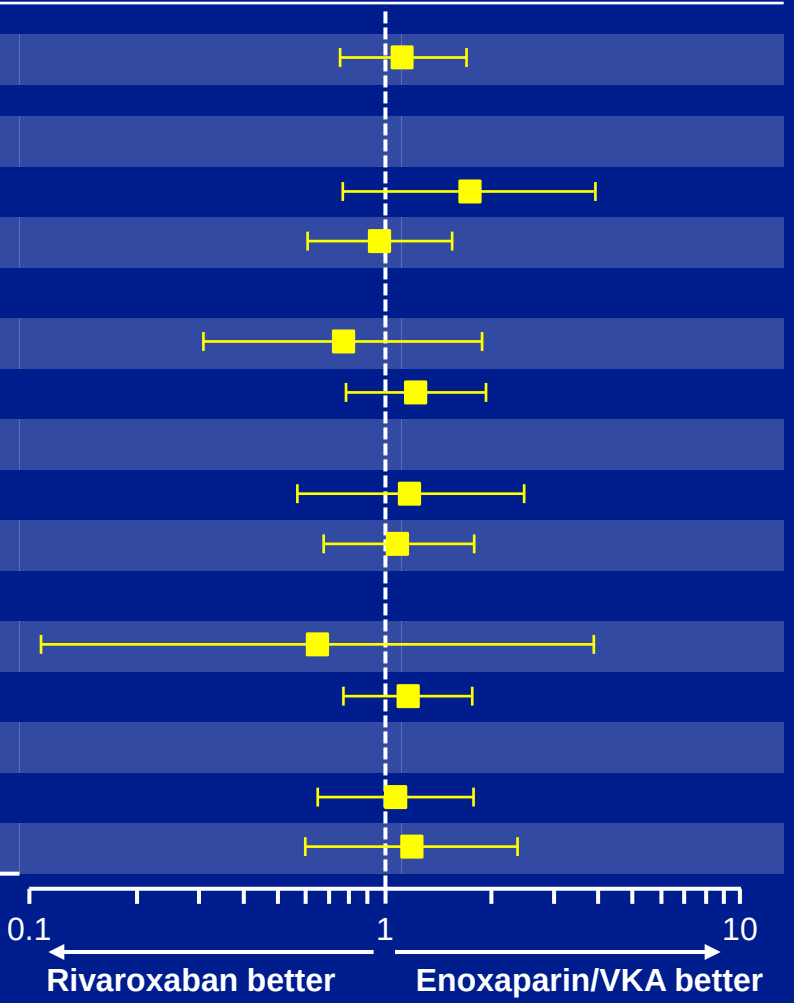


ITT Population

The EINSTEIN–PE Investigators *N Engl J Med* 2012; 366:1287 - 1297

EINSTEIN PE: Primary efficacy endpoint
Subgroup analysis (2)

	Rivaroxaban		Enoxaparin/VKA		HR (95% CI)
	n/N	(%)	n/N	(%)	
Total population	50/2419	(2.1)	44/2413	(1.8)	
Index PE					
With DVT	16/603	(2.7)	9/587	(1.5)	
Without DVT	34/1793	(1.9)	35/1803	(1.9)	
Heart disease					
Yes	9/428	(2.1)	10/374	(2.7)	
No	41/1991	(2.1)	34/2039	(1.7)	
Pulmonary disease					
Yes	16/627	(2.6)	13/608	(2.1)	
No	34/1792	(1.9)	31/1805	(1.7)	
Active cancer					
Yes	2/114	(1.8)	3/109	(2.8)	
No	48/2305	(2.1)	41/2304	(1.8)	
Idiopathic index PE					
Yes	32/1566	(2.0)	29/1551	(1.9)	
No	18/853	(2.1)	15/862	(1.7)	

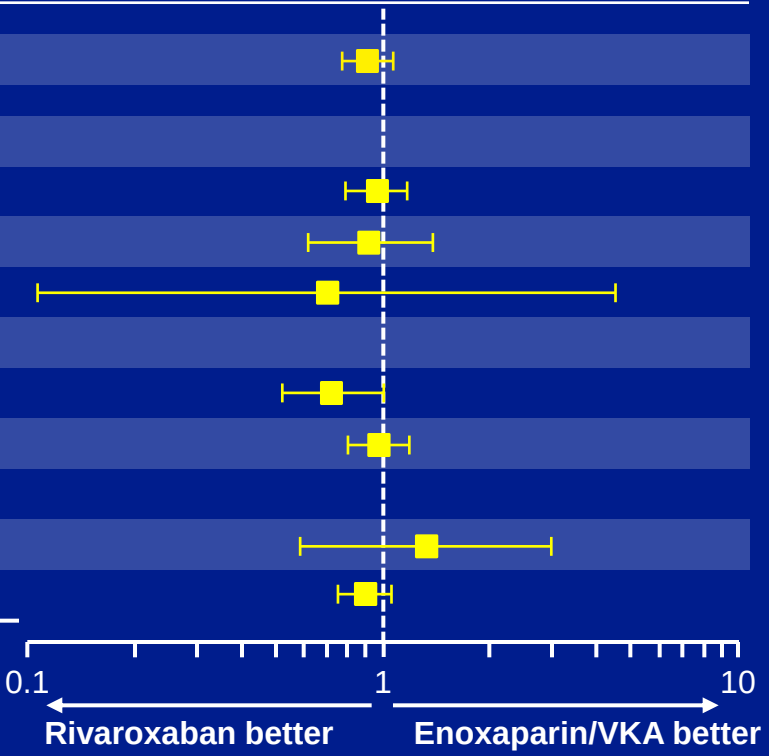


ITT Population

The EINSTEIN–PE Investigators *N Engl J Med* 2012; 366:1287 - 1297

EINSTEIN PE: Primary efficacy endpoint Subgroup analysis (3)

	Rivaroxaban		Enoxaparin/VKA		HR (95% CI)
	n/N	(%)	n/N	(%)	
Total population	249/2412	(10.3)	274/2405	(11.4)	
Pre-random. anticoagulation					
1 day	186/1749	(10.6)	195/1757	(11.1)	
2 days	45/460	(9.8)	47/441	(10.7)	
>2 days	3/23	(13.0)	2/19	(10.5)	
Fragile patients*					
Yes	64/508	(12.6)	80/476	(16.8)	
No	185/1904	(9.7)	194/1929	(10.1)	
Active cancer					
Yes	14/114	(12.3)	10/108	(9.3)	
No	235/2298	(10.2)	264/2297	(11.5)	



Safety population

*Fragile: Age > 75 Jahre and/or Body weight ≤50 kg and/or CrCL <50 ml/min

The EINSTEIN–PE Investigators *N Engl J Med* 2012; 366:1287 - 1297

Primary efficacy endpoint according to anatomic extent of PE

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

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Primary endpoints in fragile patients

	Rivaroxaban		Enoxaparin/VKA	
	n/N	(%)	n/N	(%)
Primary efficacy endpoint				
Yes	14/510	2.7	17/477	3.6
No	36/1909	1.9	27/1936	1.4

	Rivaroxaban		Enoxaparin/VKA	
	n/N	(%)	n/N	(%)
Primary safety endpoint				
Yes	64/508	12.6	80/476	16.8
No	185/1904	9.7	194/1929	10.1

The EINSTEIN–PE Investigators *N Engl J Med* 2012; 366:1287 - 1297

EINSTEIN PE: Summary

- Rivaroxaban in patients with acute symptomatic PE (with or without DVT) demonstrated:
  - Non-inferior efficacy as compared to Enoxaparin/VKA (HR=1.12 [0.75–1.68]; *p*=0.003)
  - Comparable safety as compared to Enoxaparin/VKA (HR=0.90 [0.76–1.07]; *p=0.23)*
  - Statistically significant reduction of major bleeds (HR=0.49 [0.31–0.79]; *p*=0.003)
  - Consistent efficacy and safety profiles independent of patient characteristics and concomitant diseases

Perspective:
Outpatient management of low risk PE

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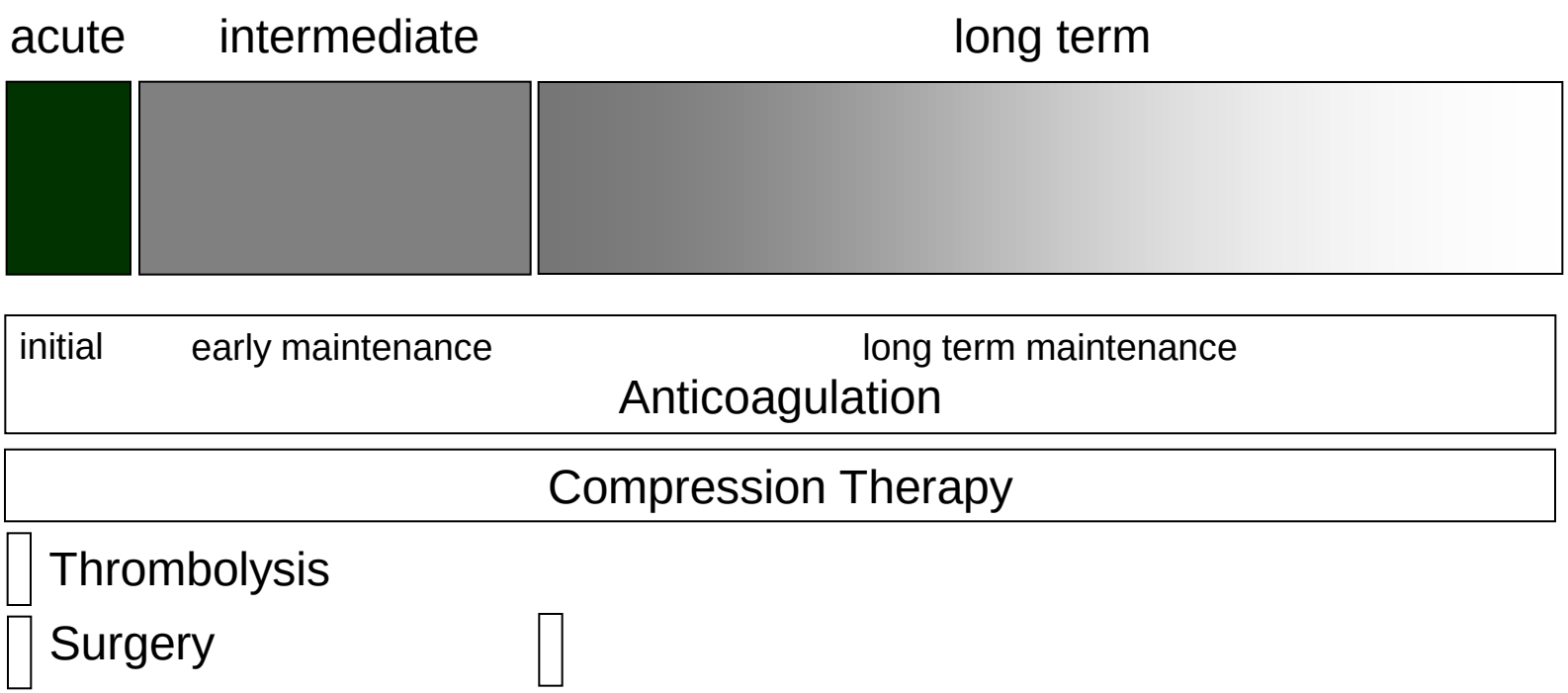
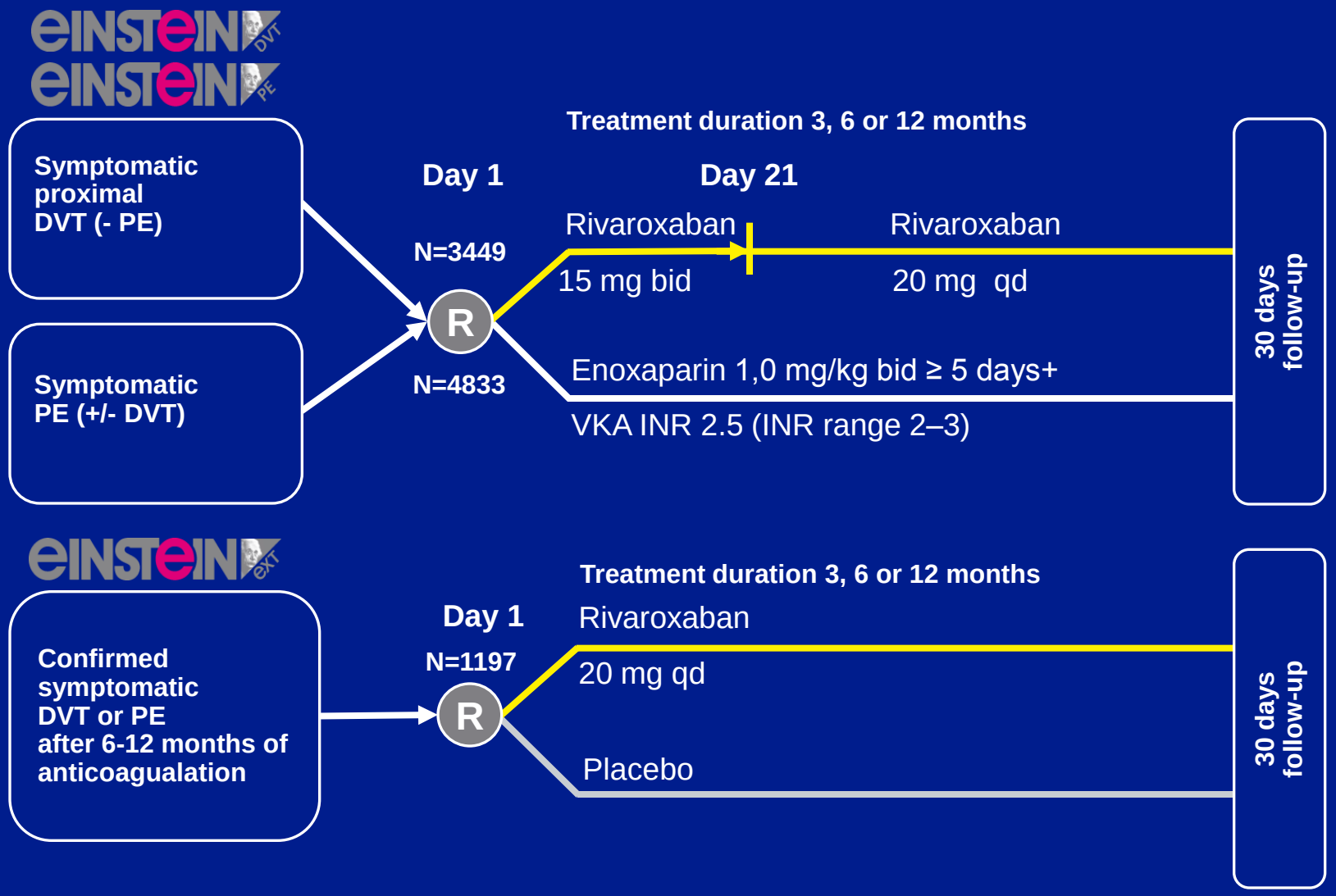
Städtisches Klinikum

- **Hemodynamically stabile**
- **No need for oxygen**
- **No major comorbidities (cancer ?)**
- **Outpatient surveillance provided**

Therapy of VTE



EINSTEIN clinical trial programme



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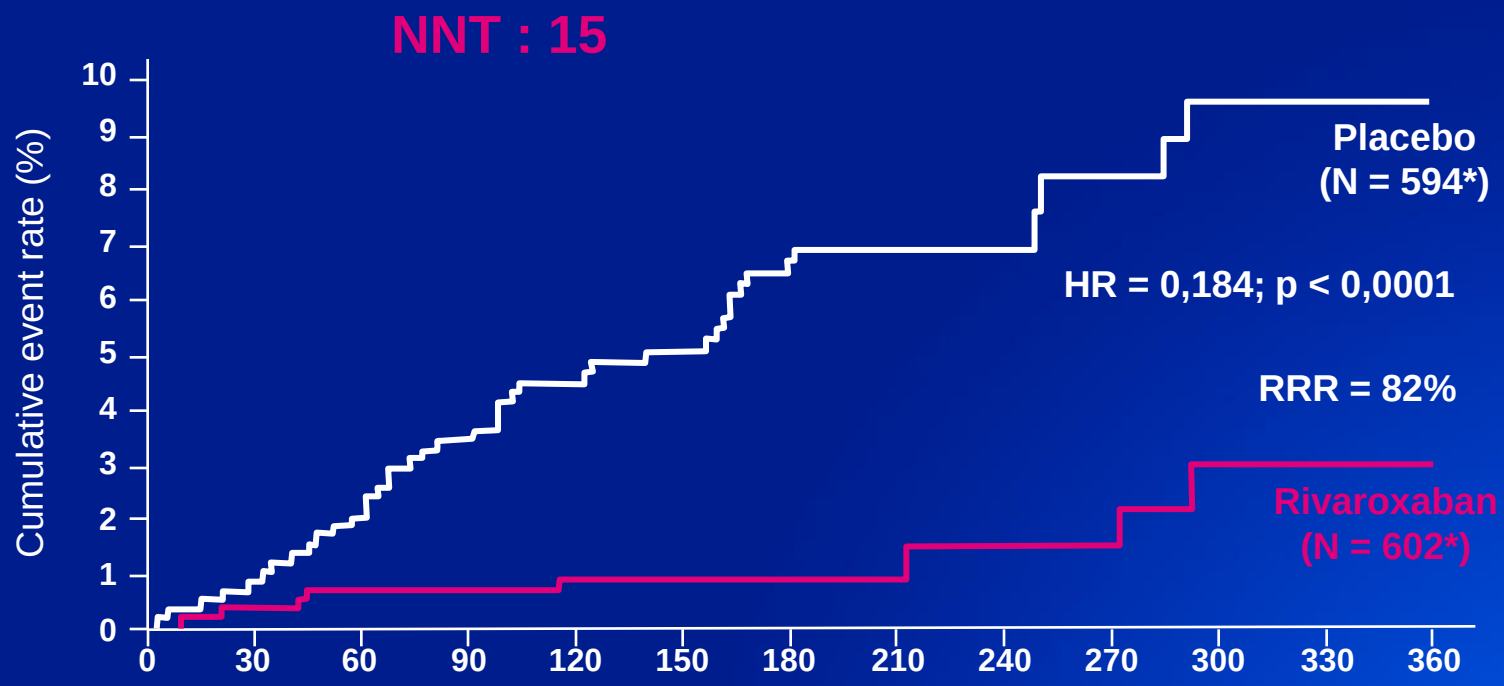
EINSTEIN EXT

Primary efficacy endpoint (time to event)



Number of patients													
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

VTE = Venöse Thromboembolie, * ITT-Population = Intention-to-Treat-Population für den primären Wirksamkeitsendpunkt, HR = Hazard Ratio; RRR = Relative Risikoreduktion, NNT = Number needed to Treat = Anzahl der behandelten Patienten, um 1 symptomatische VTE zu verhindern

Buller, HR et al. Abstract Iba-2; ASH 2009. Die Ergebnisse der EINSTEIN-Extension Studie wurden am 8.12.2009 während der ASH Tagung präsentiert.

EINSTEIN EXT

Primary safety endpoint

NNH ca. 139

	Placebo (n=590)	Rivaroxaban (n=598)
Major bleeds	**0**	**4 (0,7%)***
Fatal bleeds	0	0
Critical organ bleeds	0	0
Associated with Hb-drop of ≥ 2 g/dl and/or Transfusion of ≥ 2 units of red blood cells		
GI-bleeds	0	3 (0,5%)
Menorrhagic bleeds	0	1 (0,2%)

* p = 0,11

Sicherheitspopulation, EK = Erythrozyten-Konzentrat, NNH = Number Needed to Harm = Anzahl der behandelten Patienten, um eine schwere Blutung zu verursachen.
Buller, HR et al. Abstract Iba-2; ASH 2009. Die Ergebnisse der EINSTEIN-Extension Studie wurden am 8.12.2009 während der ASH Tagung präsentiert.

EINSTEIN EXT

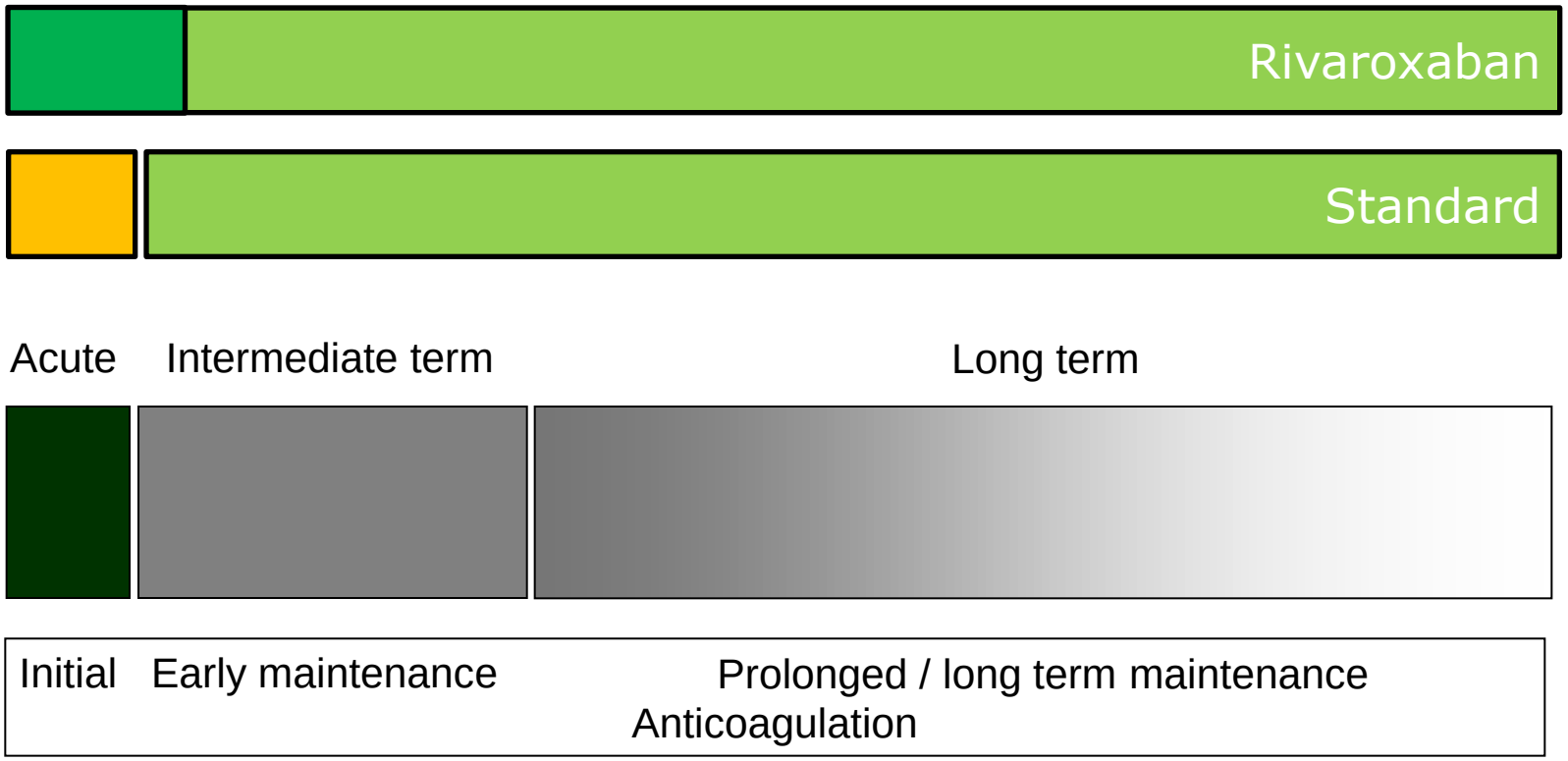
Additional Safety Endpoints

	Placebo (n=590)	Rivaroxaban (n=598)
Non-major clinically relevant bleeds	**7 (1,2%)**	**32 (5,4%)***
Urogenital/Uterus	2 (0,3%)	12 (2,0%)
Nasal	1 (0,2%)	8 (1,3%)
Rectal/anal	2 (0,3%)	6 (1,0%)
Dermal	2 (0,3%)	4 (0,7%)
Ear	0	1 (0,2%)
GI	0	1 (0,2%)
Surgical site	0	1 (0,2%)

* $p < 0,01$

#: Sicherheitspopulation; * einige Patienten hatten mehr als ein Ereignis
Buller, HR et al. Abstract Iba-2; ASH 2009. Die Ergebnisse der EINSTEIN-Extension Studie wurden am 8.12.2009 während der ASH Tagung präsentiert.

New oral treatment concept of PE with Rivaroxaban



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Thank you

for your attention