Gli anticoagulanti orali diretti: sicurezza nelle popolazioni fragili e altre informazioni dalla pratica clinica Tromboembolismo venoso

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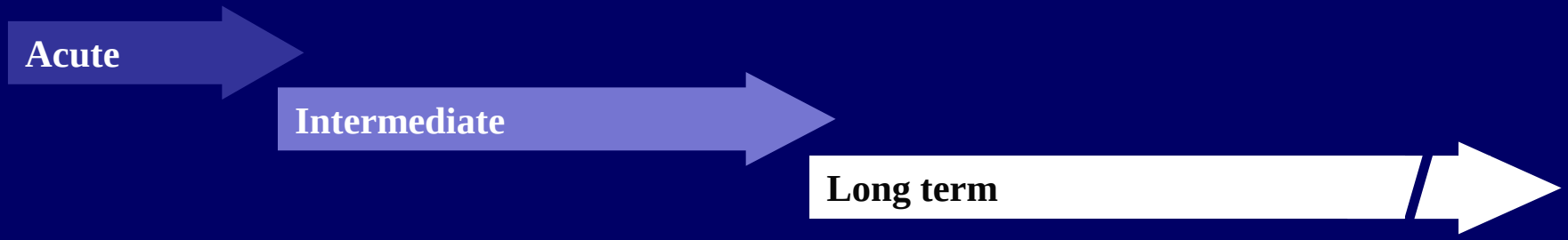
Conflitti di interesse

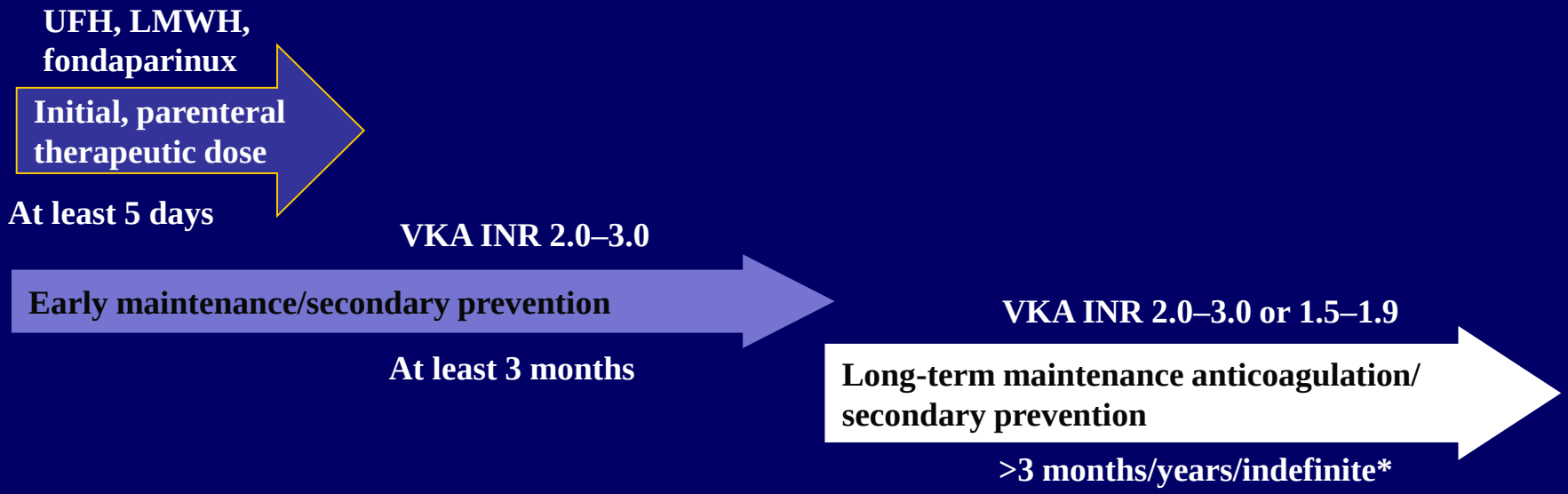
- **Supporto alla ricerca: Bayer Healthcare, Boehringer Ingelheim**
- **Advisory Boards: Bayer Healthcare, Boehringer Ingelheim, Daiichi Sankyo, BMS-Pfizer, Italfarmaco, ONO**
- **Fees per letture a congressi: Bayer Healthcare, Boehringer Ingelheim, Daiichi Sankyo, BMS-Pfizer, Stago**

VTE: disease phases and conventional anticoagulation treatment strategies

Phases of the disease

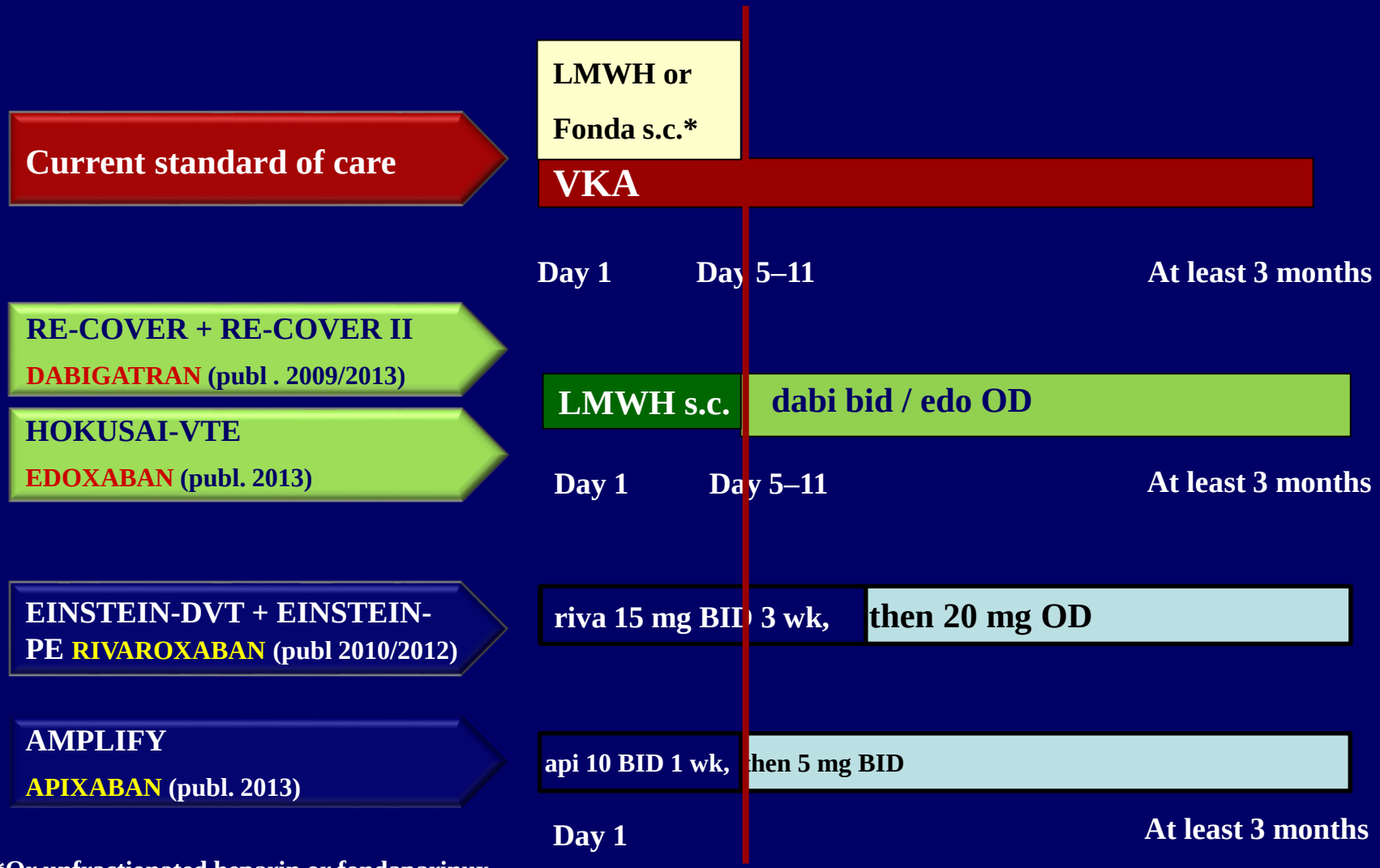


Types and intensity of conventional anticoagulation treatment



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

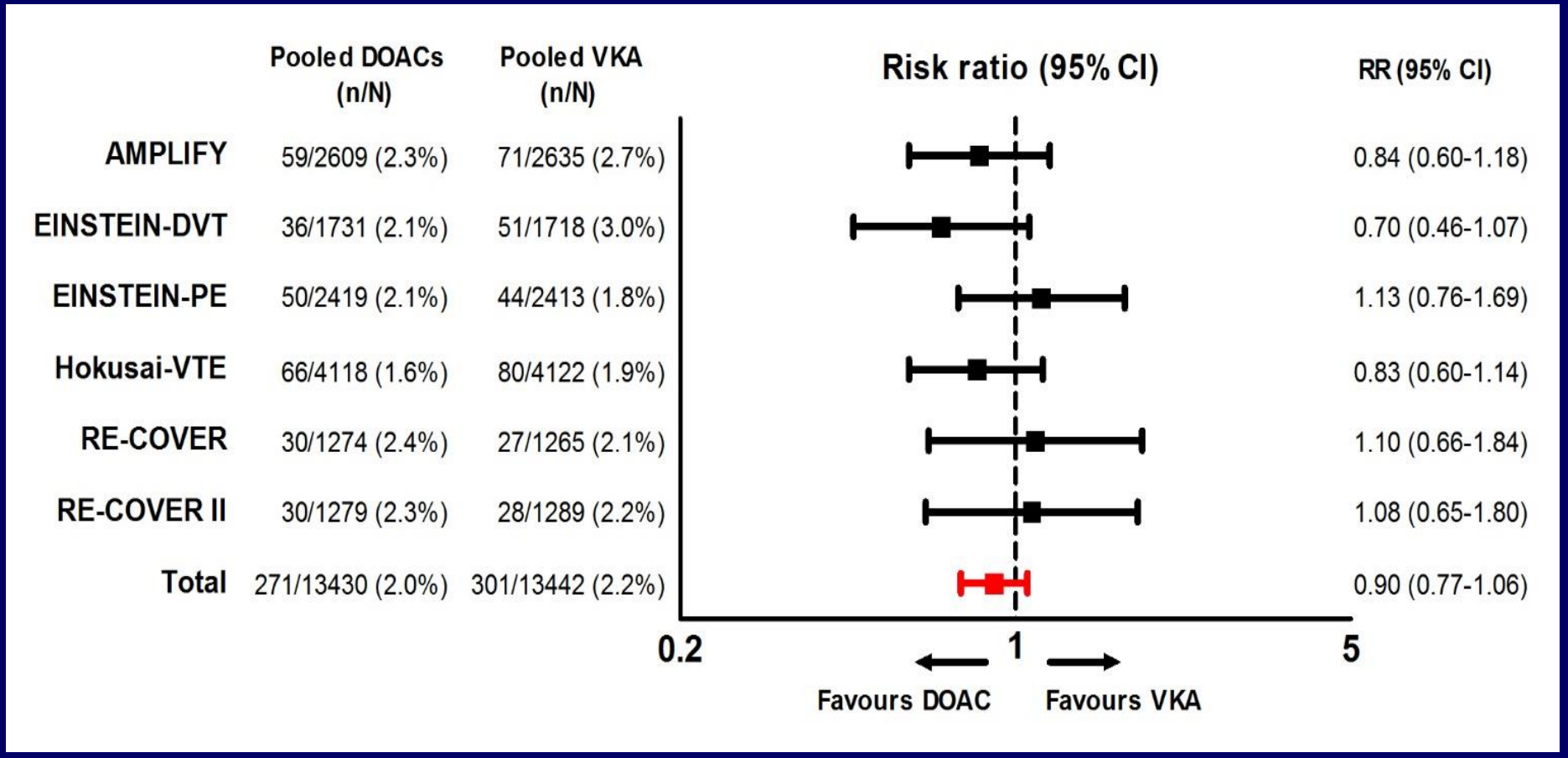
Venous thromboembolism: drugs and strategies



*Or unfractionated heparin or fondaparinux

BID = twice daily; LMWH = low molecular weight heparin; OD = once daily; s.c. = subcutaneous; VKA = vitamin K antagonist

DOAC Phase III VTE trials
Primary efficacy endpoint



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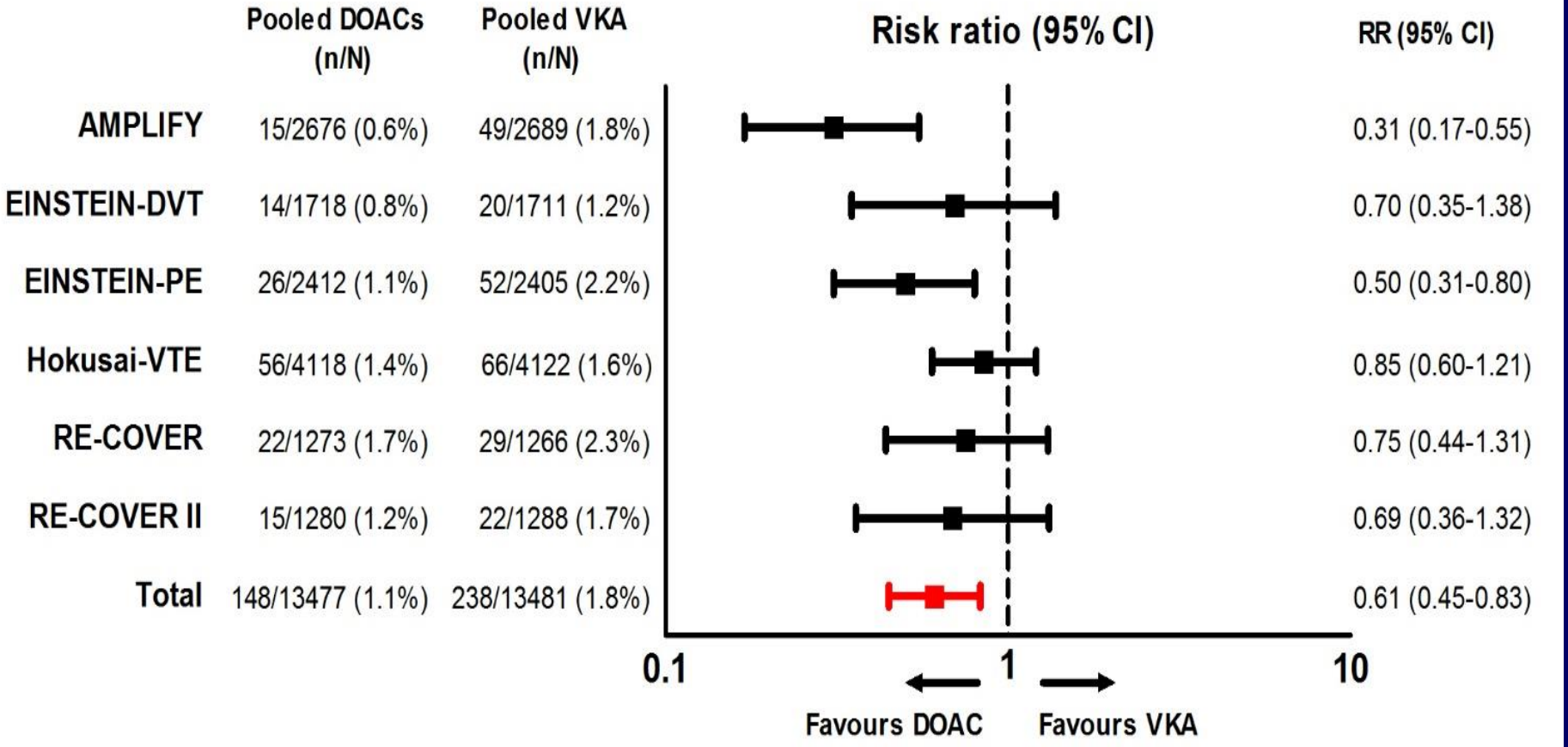
DOAC Phase III VTE trials
Major bleeding



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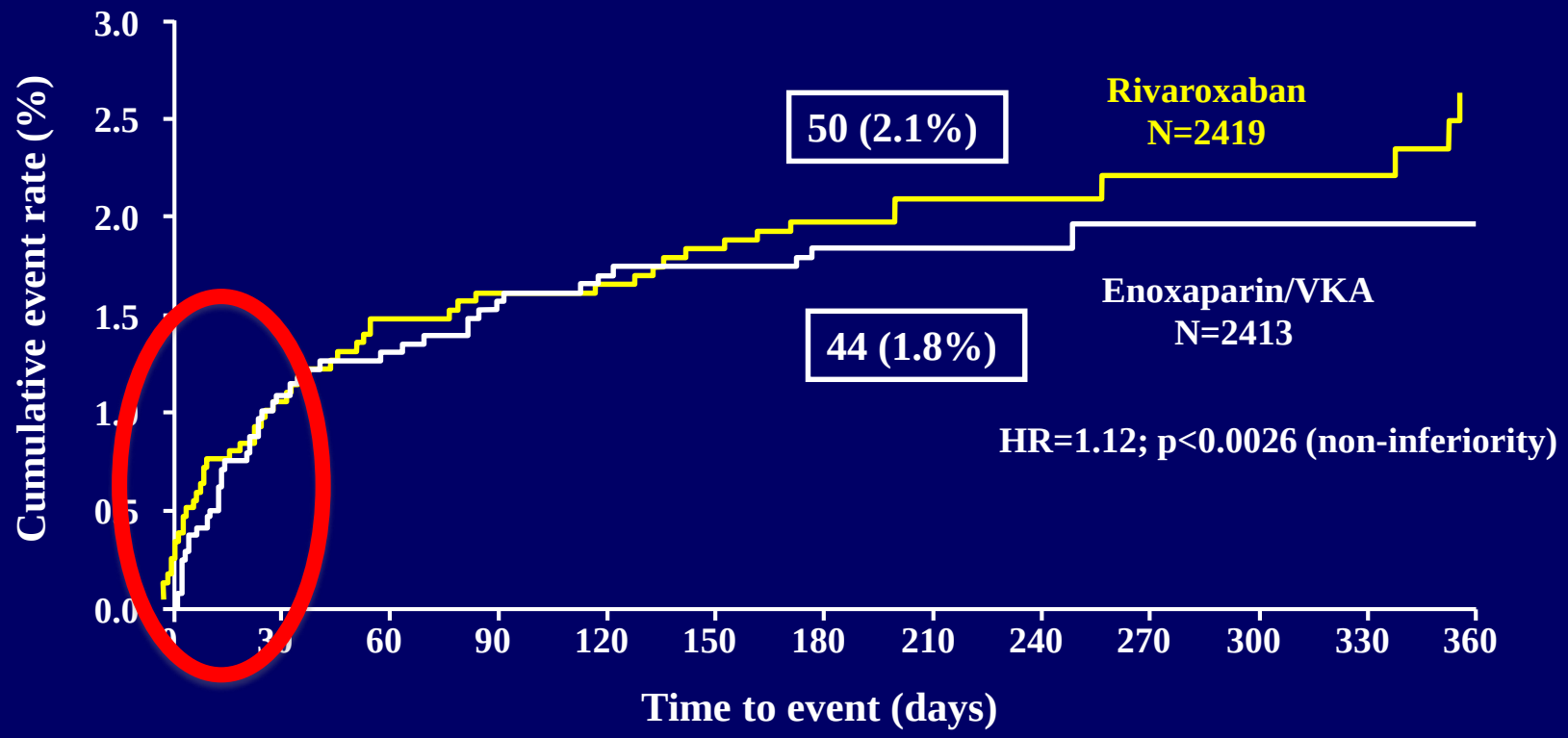
EINSTEIN PE Primary efficacy outcome: time to first event

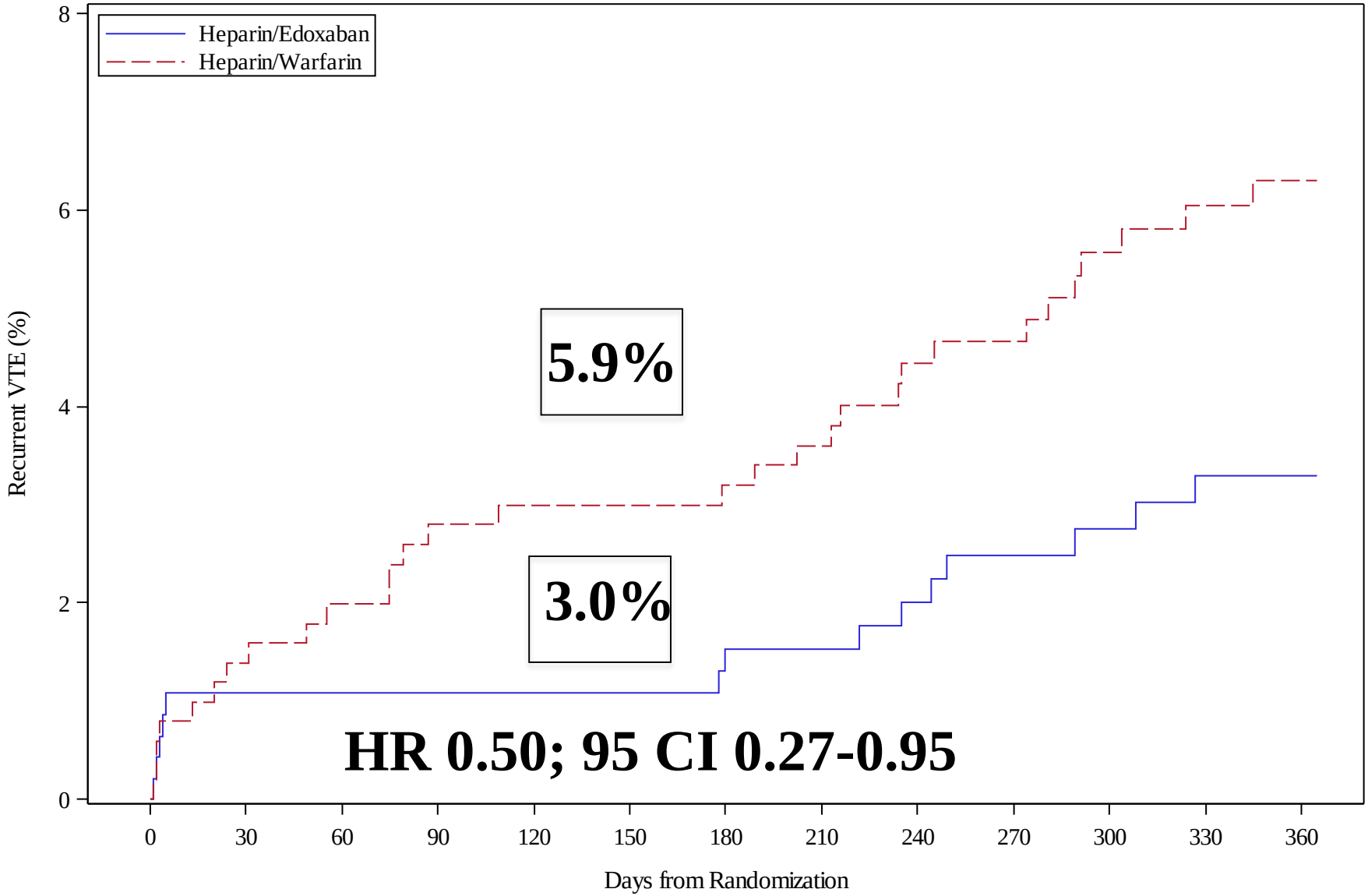


Number of patients at risk													
Rivaroxaban	2419	2350	2321	2303	2180	2167	2063	837	794	785	757	725	672
Enoxaparin/VKA	2413	2316	2296	2274	2157	2149	2053	837	789	774	748	724	677

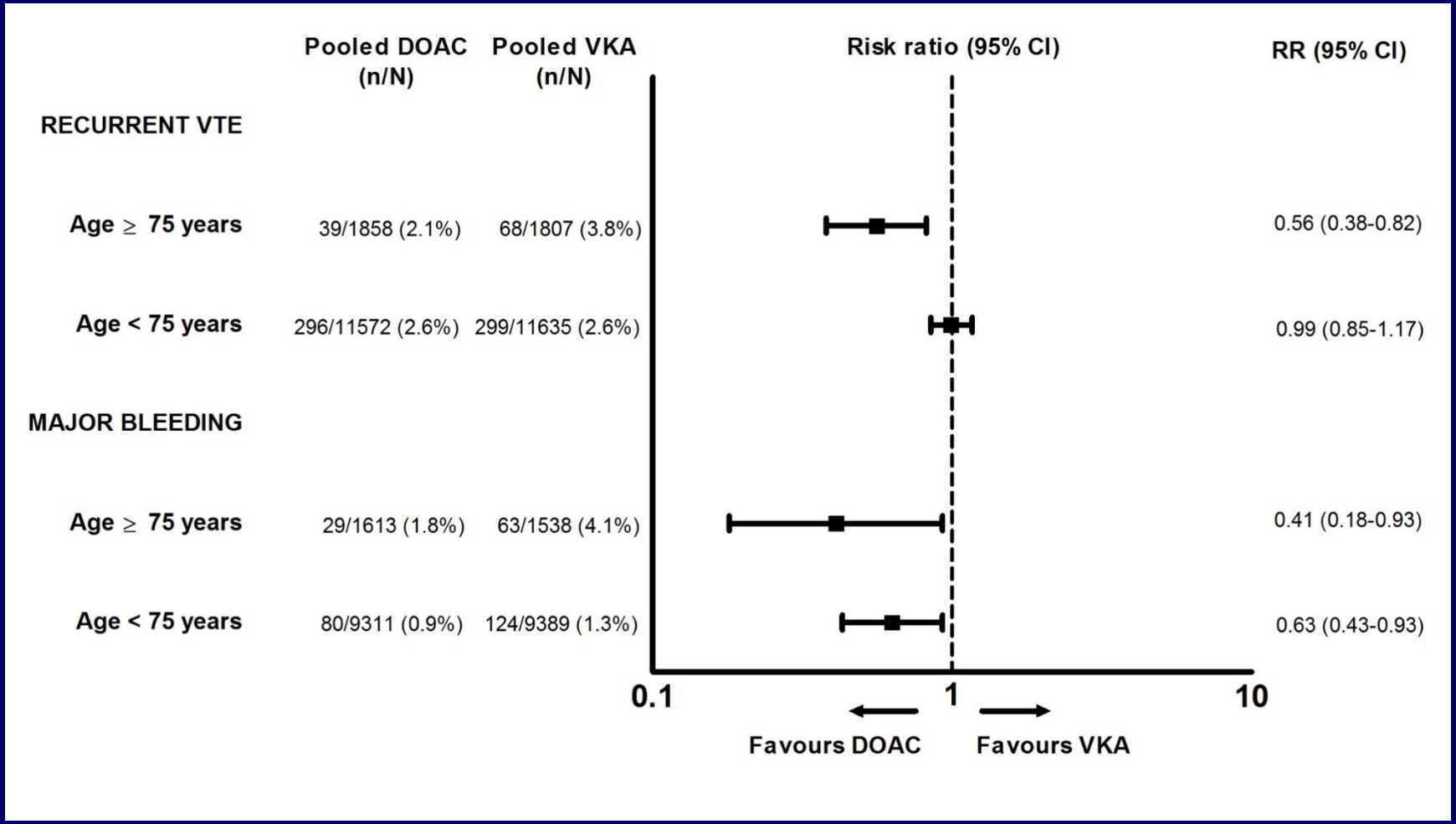
ITT population

The EINSTEIN Investigators. N Engl J Med 2012

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



Clinical outcomes in VTE trials in patients aged ≥ 75 years



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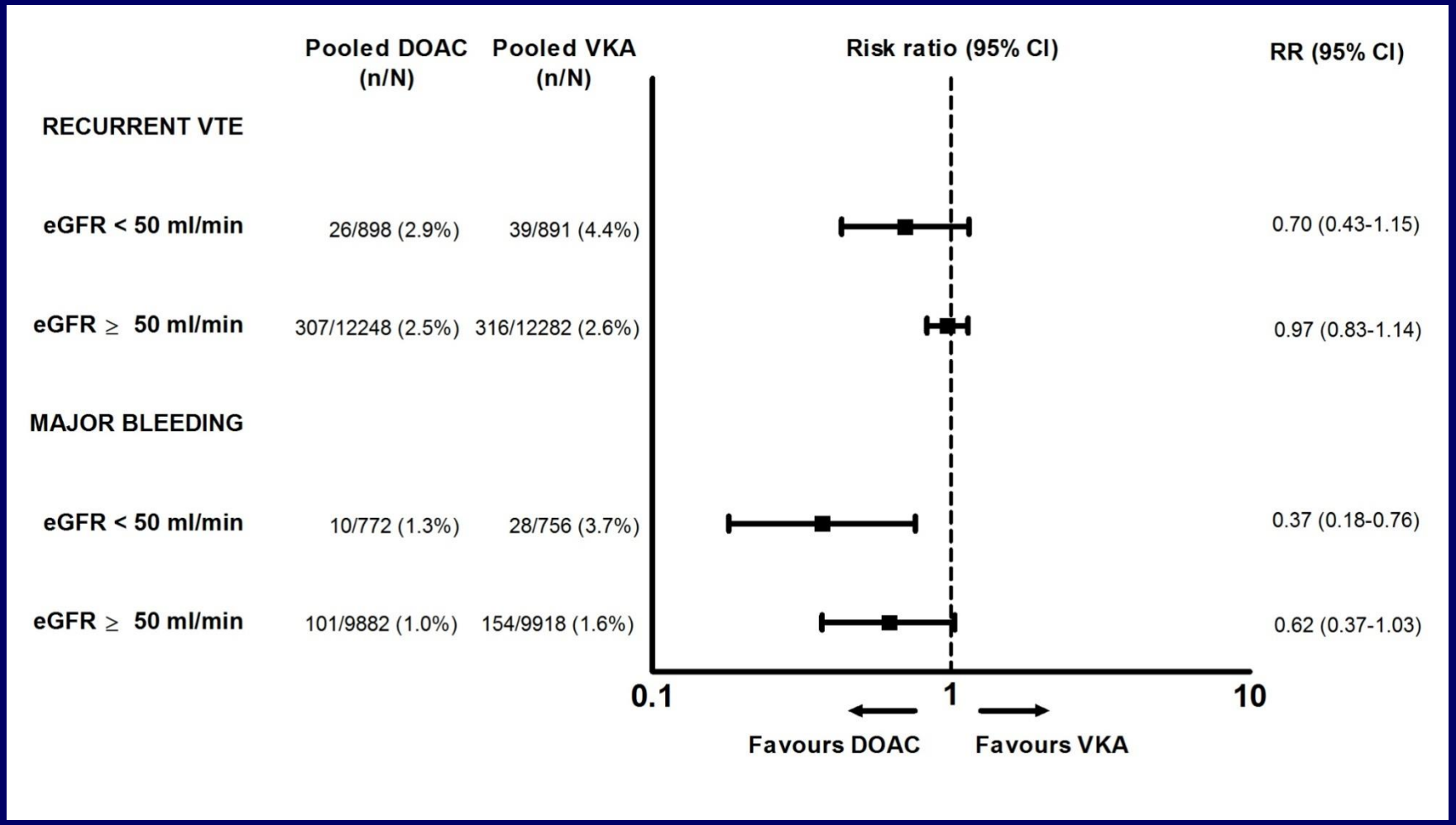
Clinical outcomes in VTE trials in patients with moderate renal failure



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Phase III Clinical Trials

- Registration trials
- Support marketing approval by the regulatory authorities
- Strict design to ensure well defined inclusion and exclusion criteria
- Strict protocol adherence, appropriate clinical endpoints and statistical validity

However...

- Event rates and patient characteristics may not fully reflect those observed in the patients seen in routine care
- Adherence, persistence and co-morbidities may vary between the strict environment of a clinical trial and that of ‘real-world’ therapy

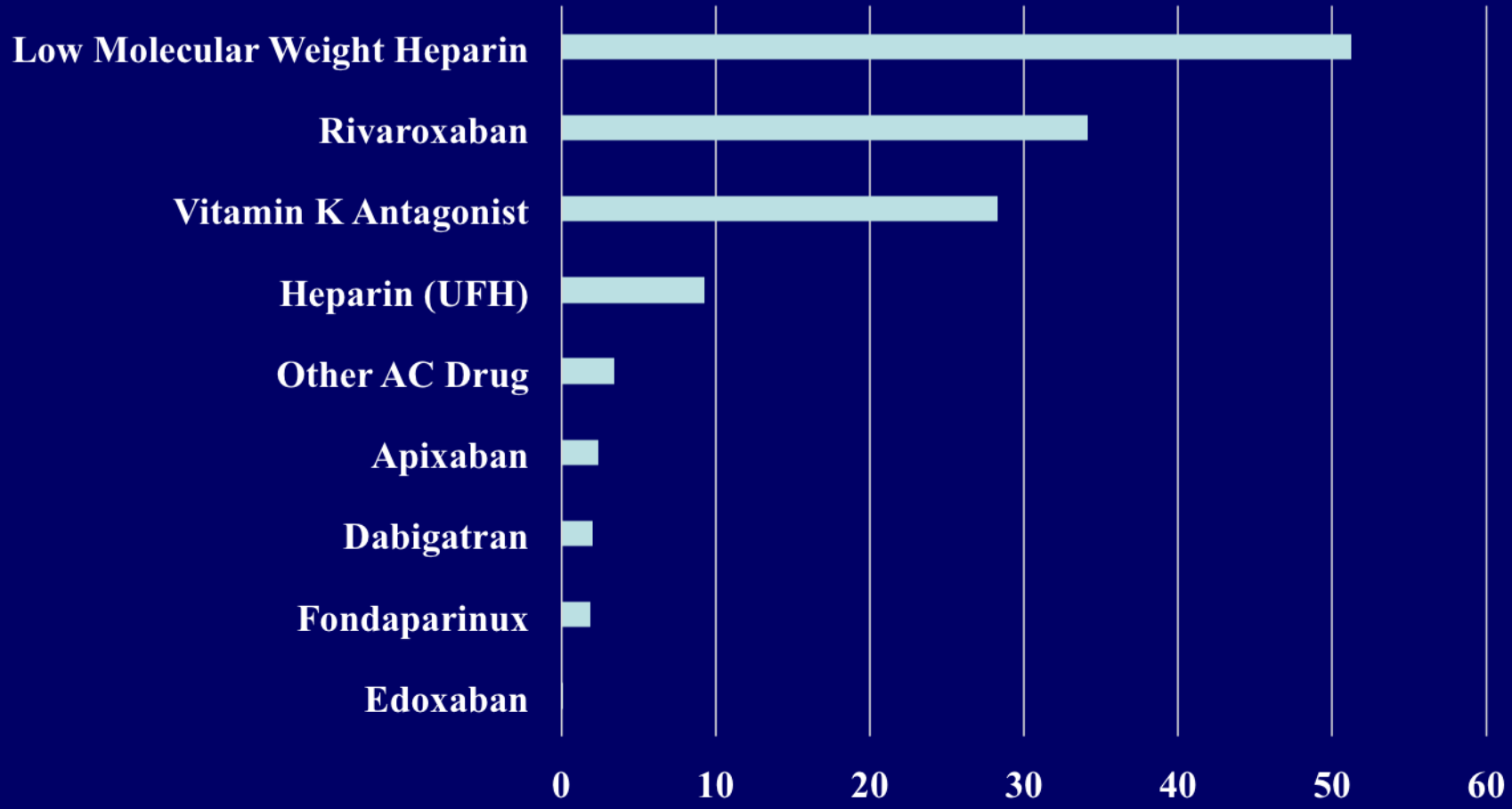
Post-authorization Studies

- Post-marketing surveillance studies (PMSS)
- Non-interventional studies
- Registries

International post-authorization studies including DOACs for the treatment of VTE

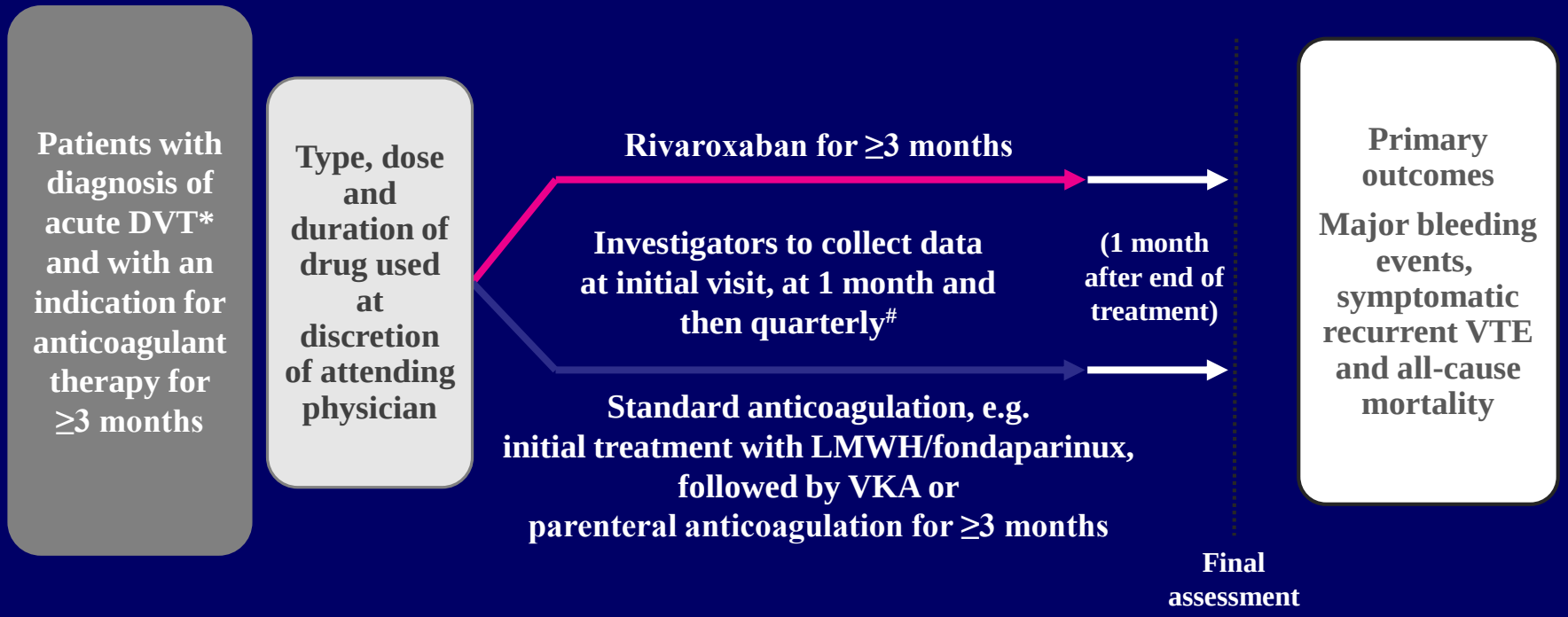
- **RIETE**
  - **All treatments, min. 3-month follow-up**
- **XALIA DVT (published)**
  - **Standard of care, rivaroxaban, 1 year follow-up**
- **GARFIELD VTE (ongoing)**
  - **All treatments, 3-year follow-up**
- **RE-COVERY (enrolment just started)**
  - **Standard of care, dabigatran, other DOACs, up to one-year follow-up**
- **ETNA (due to start soon upon approval of edoxaban)**

GARFIELD: Medication use at baseline: Low molecular weight heparin is most commonly used



XALIA:
A Prospective, Non-interventional Study

Objective: collect real-life data in patients with acute DVT treated with rivaroxaban or standard anticoagulation



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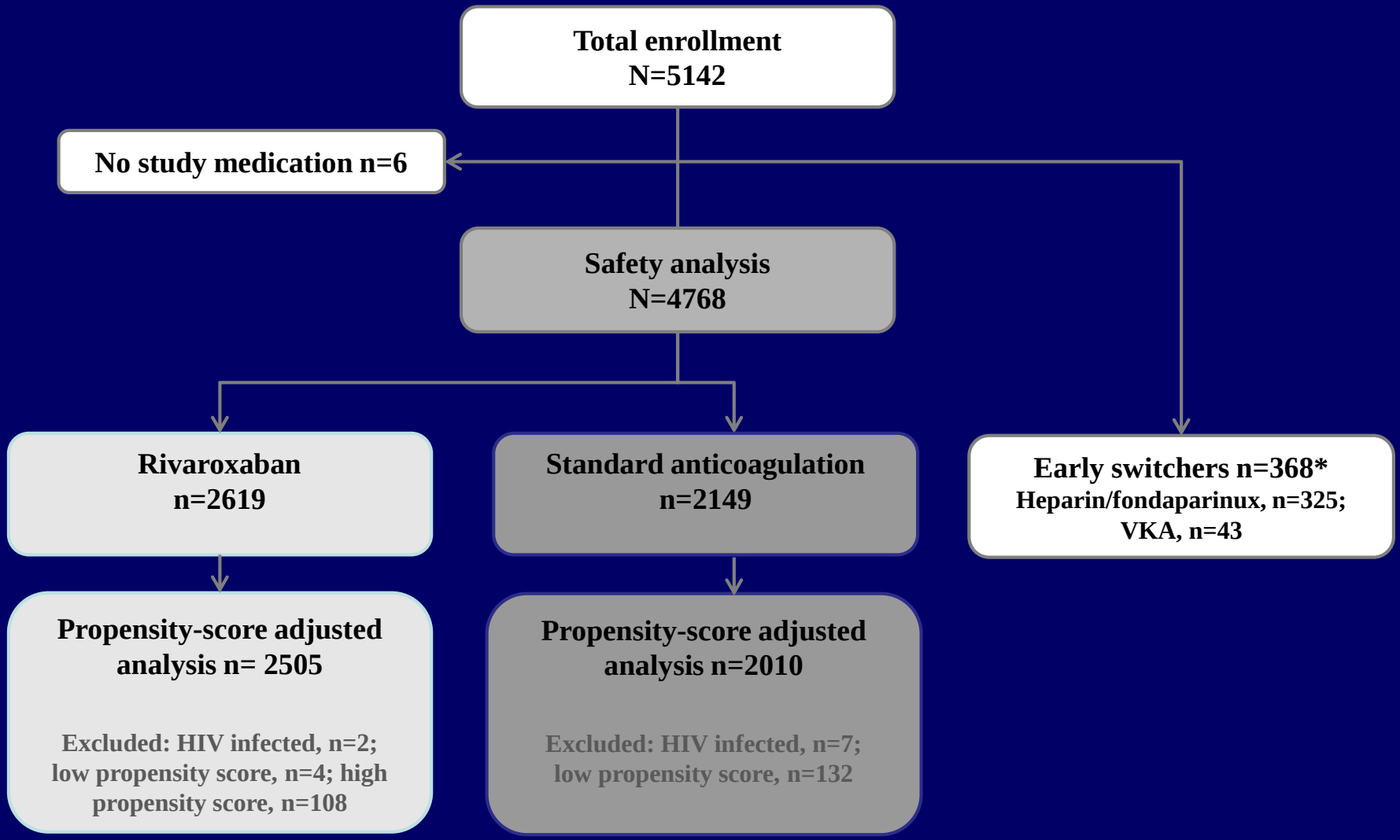
Patient Flow



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XALIA: Baseline Demographics and Clinical Characteristics (1)

	Rivaroxaban (n=2619)	Standard anticoagulation (n=2149)
Age, years, mean (SD)	57.3 (16.7)	63.0 (16.9)
<60 years, n (%)	1366 (52.2)	824 (38.8)
≥60 years, n (%)	1253 (47.8)	1325 (61.7)
Male sex, n (%)	1428 (54.5)	1116 (51.9)
Weight, kg, mean (SD)	82.4 (18.0)	80.6 (18.0)
BMI, kg/m^2, mean (SD)	28.0 (5.2)	28.4 (6.9)
Index diagnosis, n (%)		
DVT without PE	2399 (91.6)	1894 (88.1)
DVT with PE	220 (8.4)	255 (11.9)

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XALIA: Baseline Demographics and Clinical Characteristics (2)

	Rivaroxaban (n=2619)	Standard anticoagulation (n=2149)
First available CrCl, n (%)		
≥80 ml/min	1125 (43.0)	797 (37.1)
≥50–<80 ml/min	419 (16.0)	398 (18.5)
≥30–<50 ml/min	88 (3.4)	157 (7.3)
<30 ml/min	13 (0.5)	61 (2.8)
Not recorded	974 (37.2)	736 (34.2)
Previous VTE, n (%)	630 (24.1)	481 (22.4)
Previous major bleeding episode, n (%)	37 (1.4)	64 (3.0)
Active cancer, n (%)	146 (5.6)	411 (19.1)
Thrombophilia, n (%)	157 (6.0)	112 (5.2)

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Treatment-Emergent Major Bleeding Outcomes

	Rivaroxaban (n=2619) n (%)	Standard anticoagulation (n=2149) n (%)	Hazard ratio* (95% CI)
Major bleeding (adjudicated)	**19 (0.7)**	**48 (2.3)**	**0.41 (0.24–0.70)**
Fatal	**0 (0.0)**	**2 (0.1)**	
Non-fatal critical site	**8 (0.3)**	**12 (0.6)**	
Intracranial (subdural, subarachnoid or cerebral)	**6 (0.2)**	**5 (0.2)**	
Non-fatal, other, non-critical site	**11 (0.4)**	**34 (1.6)**	
Gastrointestinal	**3 (0.1)**	**18 (0.8)**	

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Treatment-Emergent Thromboembolic Events

	Rivaroxaban (n=2619) n (%)	Standard anticoagulation (n=2149) n (%)	Hazard ratio* (95% CI)
Recurrent VTE (adjudicated)	**37 (1.4)**	**55 (2.6)**	**0.67 (0.44–1.03)**
Fatal PE	1 (<0.1)	1 (<0·1)	
Death where PE not ruled out	4 (0.2)	4 (0.2)	
Nonfatal PE	17 (0.6)	17 (0.8)	
Recurrent DVT plus PE	1 (<0.1)	4 (0.2)	
Recurrent DVT	13 (0.5)	30 (1.4)	
Other	1 (<0.1)	0 (0.0)	

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Treatment-Emergent Clinical Outcomes (Propensity-Score Adjusted Comparison)

	Rivaroxaban (n=2505) n (%)	Standard anticoagulation (n=2010) n (%)	Hazard ratio (95% CI)	p-value
Major bleeding	19 (0.8)	43 (2.1)	0.77 (0.40–1.50)	0.44
Recurrent VTE	36 (1.4)	47 (2.3)	0.91 (0.54–1.54)	0.72
All-cause mortality	11 (0.4)	69 (3.4)	0.51 (0.24–1.07)	0.07

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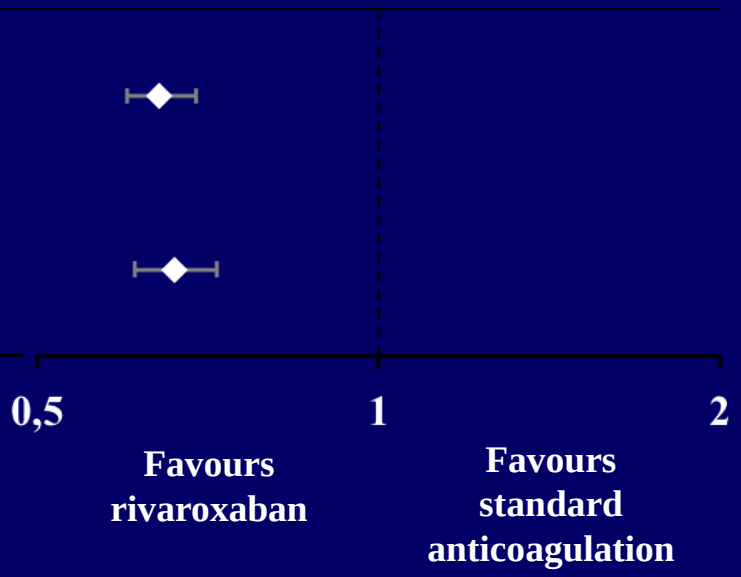
Length of Hospital Stay

Analysis	Length of stay (LS mean, days)		Ratio (95% CI)*
	Rivaroxaban	Standard anticoagulation	
Before propensity score adjustment	4.8	7.5	
Propensity score adjusted	5.0	7.7	



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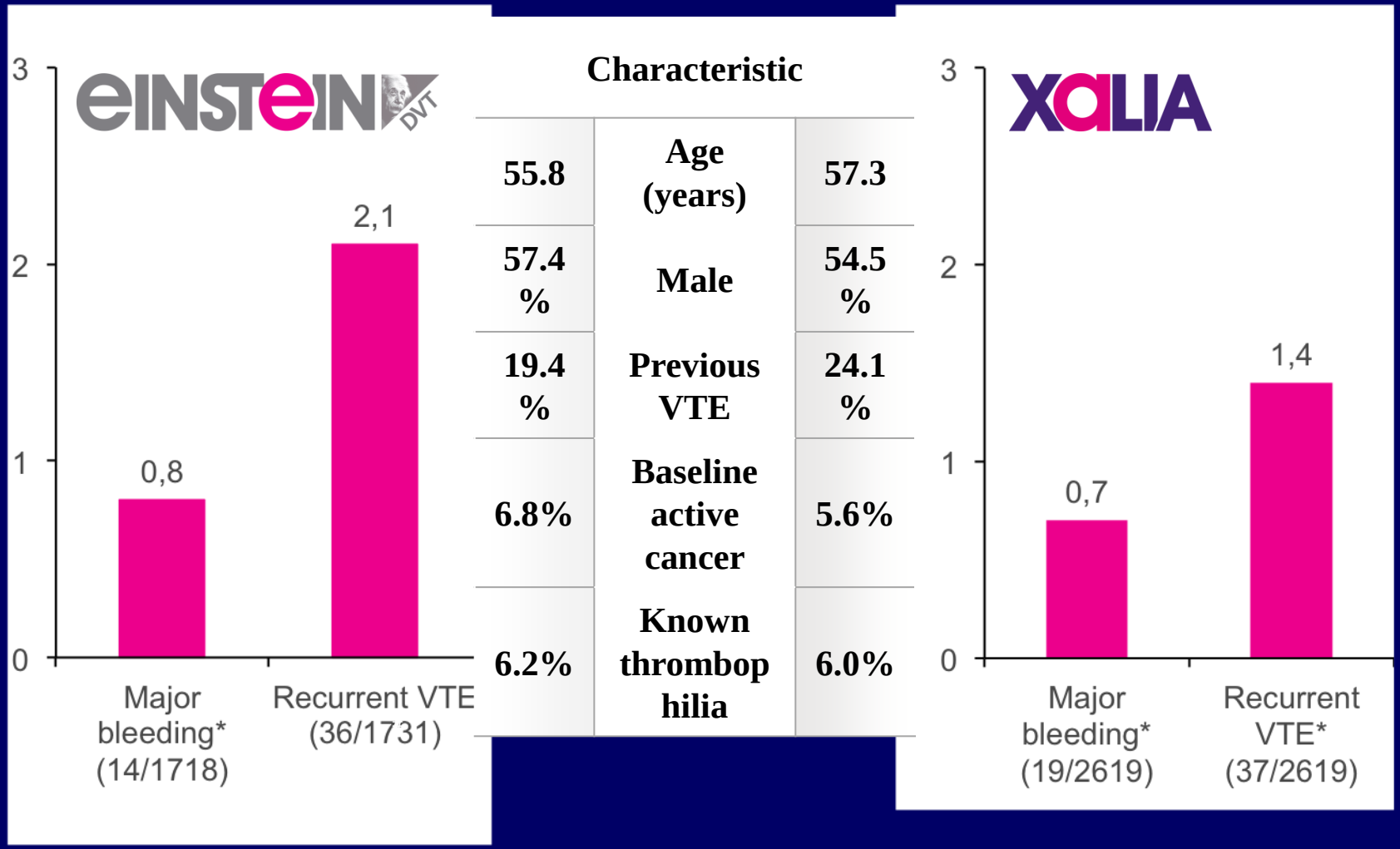
EINSTEIN DVT and XALIA: Rivaroxaban Outcomes



Characteristic		
55.8	Age (years)	57.3
57.4 %	Male	54.5 %
19.4 %	Previous VTE	24.1 %
6.8%	Baseline active cancer	5.6%
6.2%	Known thrombophilia	6.0%

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Conclusioni

Gli studi di fase III hanno evidenziato simile efficacia e maggior sicurezza dei farmaci anticoagulanti orali diretti rispetto alla terapia standard

Questi dati sono confermati in sottogruppi a maggior rischio inclusi negli studi (embolia polmonare, anziani, insufficienza renale)

L'approvazione di 4 nuove molecole constente una maggiore (e migliore) scelta per il trattamento del tromboembolismo venoso

Conclusioni

Nel primo studio di post-marketing:

I medici hanno usato rivaroxaban in pazienti più giovani e meno complessi

L'incidenza di eventi emorragici e recidive è stata bassa

L'analisi secondo il propensity score ha evidenziato simile efficacia e sicurezza rispetto alla terapia standard, senza segnali di inferiorità nelle popolazioni più fragili