Oral rivaroxaban alone for the treatment of symptomatic pulmonary embolism: the EINSTEIN PE study

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on behalf of the EINSTEIN Investigators

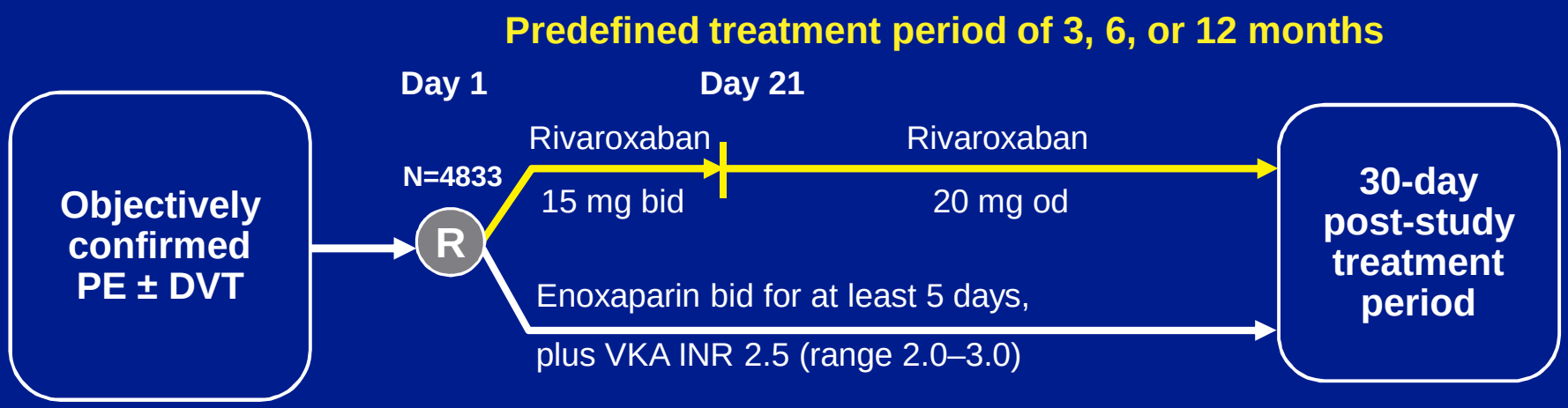
Disclosures for Harry R Büller

Research Support/P.I.	Sanofi-aventis, Bayer HealthCare, Bristol-Myers Squibb, Daiichi-Sankyo, GlaxoSmithKline, Pfizer, Roche, Isis, Thrombogenics
Employee	No relevant conflicts of interest to declare
Consultant	Sanofi-aventis, Bayer HealthCare, Bristol-Myers Squibb, Daiichi-Sankyo, GlaxoSmithKline, Pfizer, Roche, Isis, Thrombogenics
Major Stockholder	No relevant conflicts of interest to declare
Speakers Bureau	No relevant conflicts of interest to declare
Scientific Advisory Board	Sanofi-aventis, Bayer HealthCare, Bristol-Myers Squibb, Daiichi-Sankyo, GlaxoSmithKline, Pfizer, Roche, Isis, Thrombogenics

EINSTEIN PE: study design

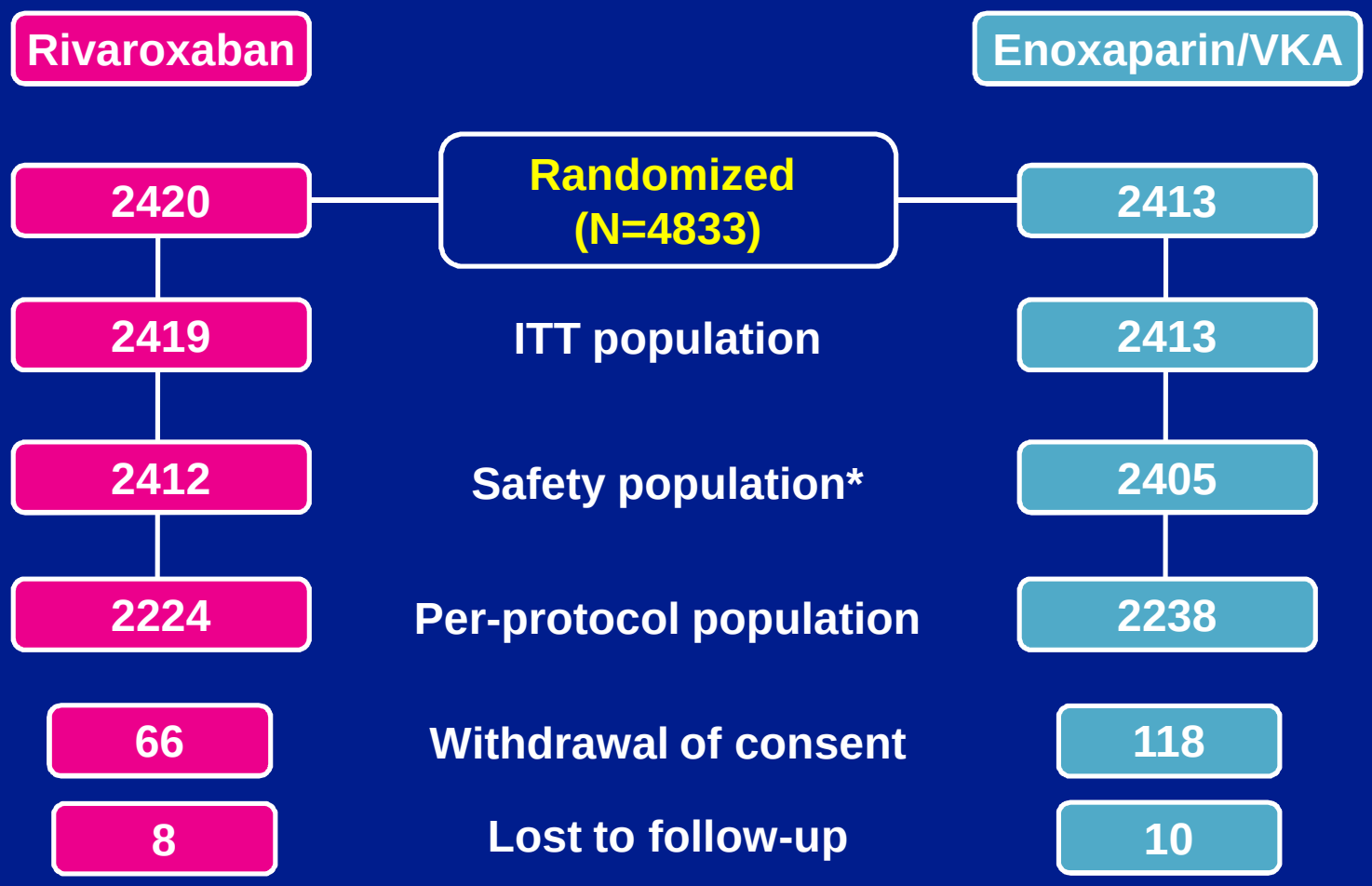
Randomized, open-label, event-driven, non-inferiority study

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



- Primary efficacy outcome: first recurrent VTE
- Principal safety outcome: first major or non-major clinically relevant bleeding

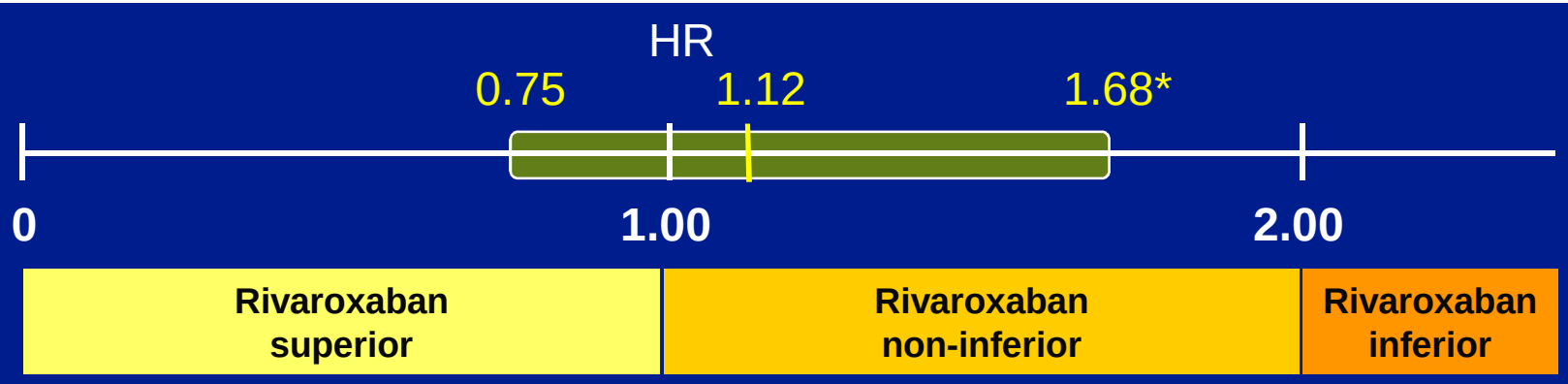
Patient flow



*As treated

EINSTEIN PE: 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)

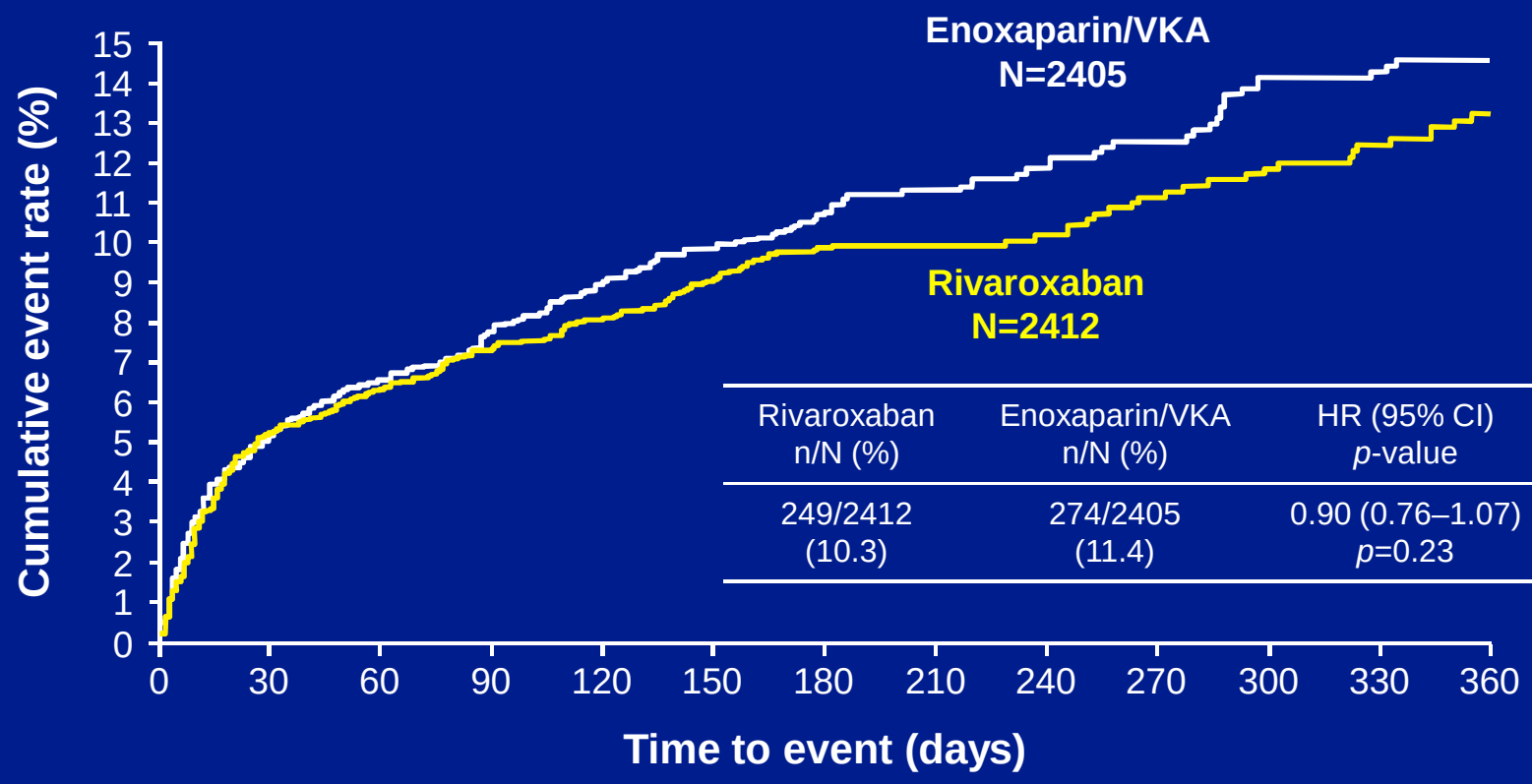


p=0.57 for superiority (two-sided)

P=0.0026 for non-inferiority (one-sided)

*Potential relative risk increase <68.4%; absolute risk difference 0.24% (–0.5 to 1.02)

EINSTEIN PE: principal safety outcome – major or non-major clinically relevant bleeding



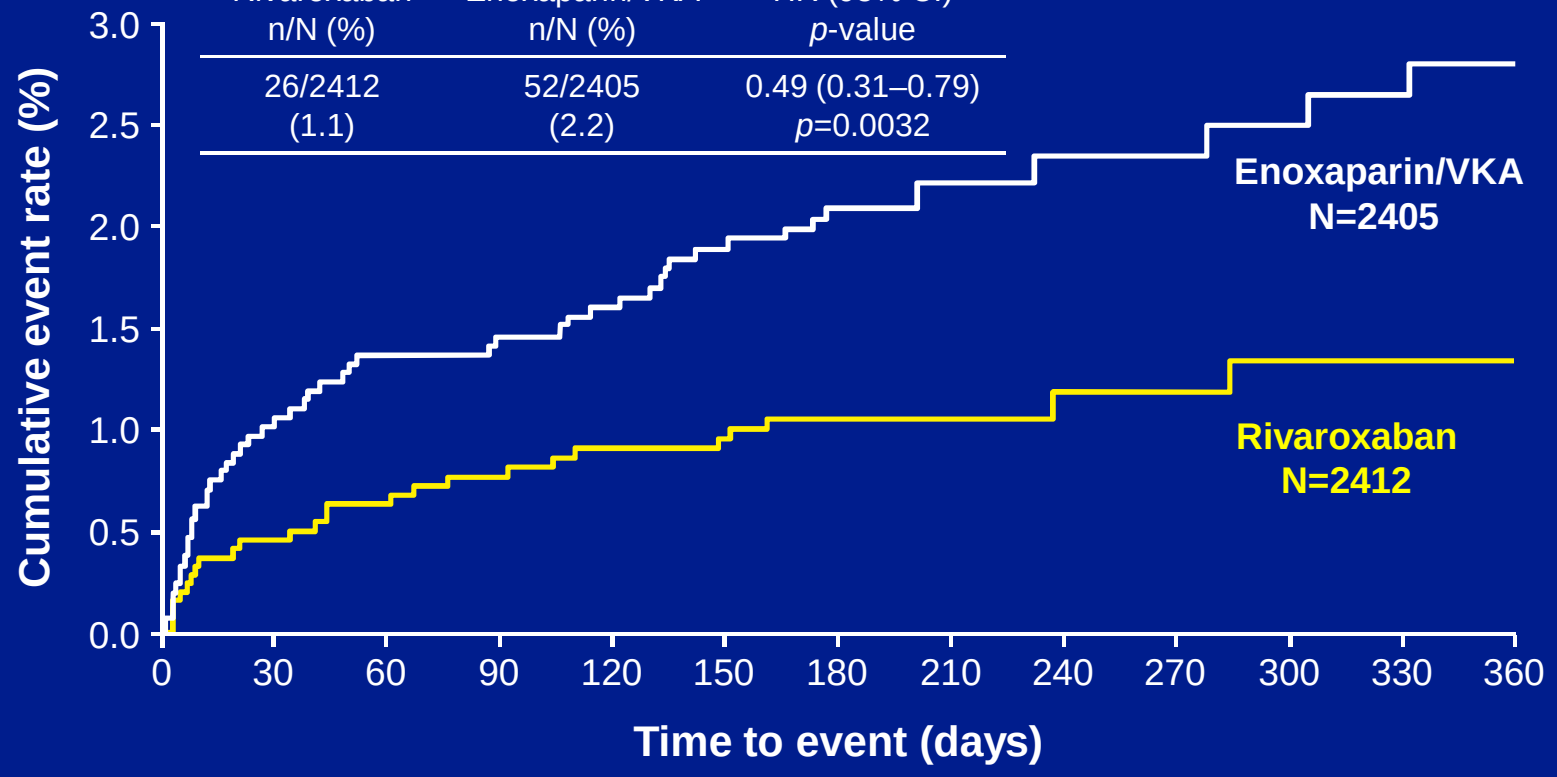
Rivaroxaban n/N (%)	Enoxaparin/VKA n/N (%)	HR (95% CI) *p*-value
249/2412 (10.3)	274/2405 (11.4)	0.90 (0.76–1.07) *p*=0.23

Number of patients 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

EINSTEIN PE: major bleeding

Rivaroxaban n/N (%)	Enoxaparin/VKA n/N (%)	HR (95% CI) *p*-value
26/2412 (1.1)	52/2405 (2.2)	0.49 (0.31–0.79) *p*=0.0032



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

EINSTEIN PE: conclusions

- In patients with acute symptomatic PE with or without DVT, rivaroxaban showed:
  - Non-inferiority to LMWH/VKA for efficacy: HR=1.12 (0.75–1.69); $p_{\text{non-inferiority}}$ =0.0026 for non-inferiority margin of 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

EINSTEIN PE