Le Rivaroxaban dans la TVP et l'EP: Deux études pour deux pronostics différents

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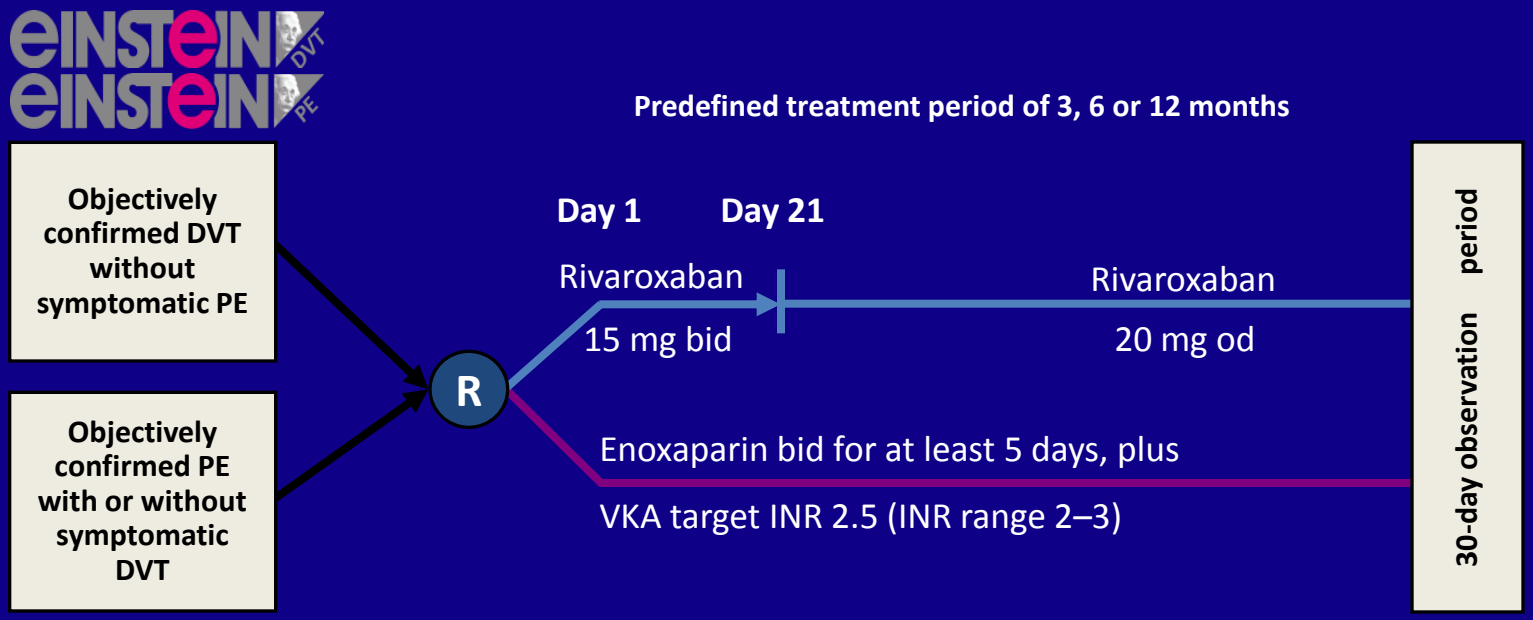
Liens d’intérêt

- BAYER
- LEO PHARMA
- GSK

EINSTEIN - DVT

Design ENSTEIN - DVT

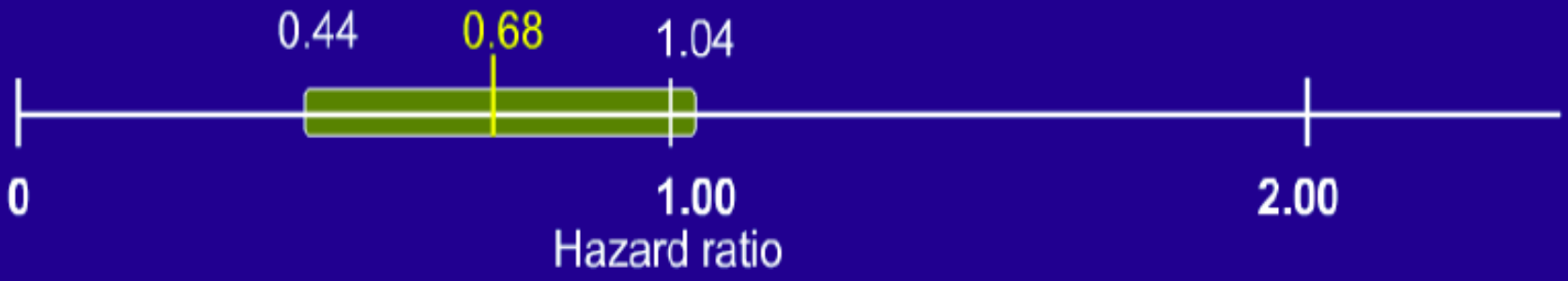


Données démographiques

	Rivaroxaban (n=1,731)	Enoxaparin/VKA (n=1,718)
Males (%)	57	56
Age, mean (years)	56	56
Body mass index, mean (kg/m²)	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/fondaparinux (%)	73	71

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)
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)



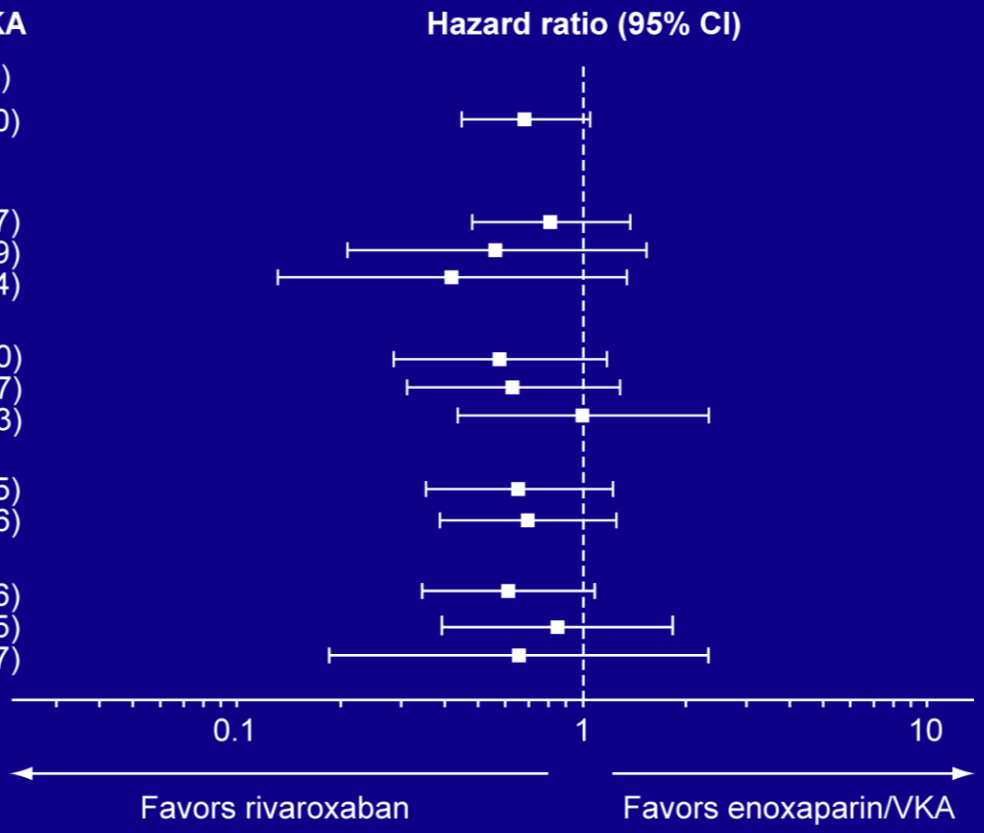
Rivaroxaban superior	Rivaroxaban non-inferior	Rivaroxaban inferior

p=0.076 for superiority (two-sided)

p<0.0001 for non-inferiority (one-sided)

Critère de jugement principal: récidives de thrombose veineuse profonde, embolie pulmonaire fatale ou non fatale

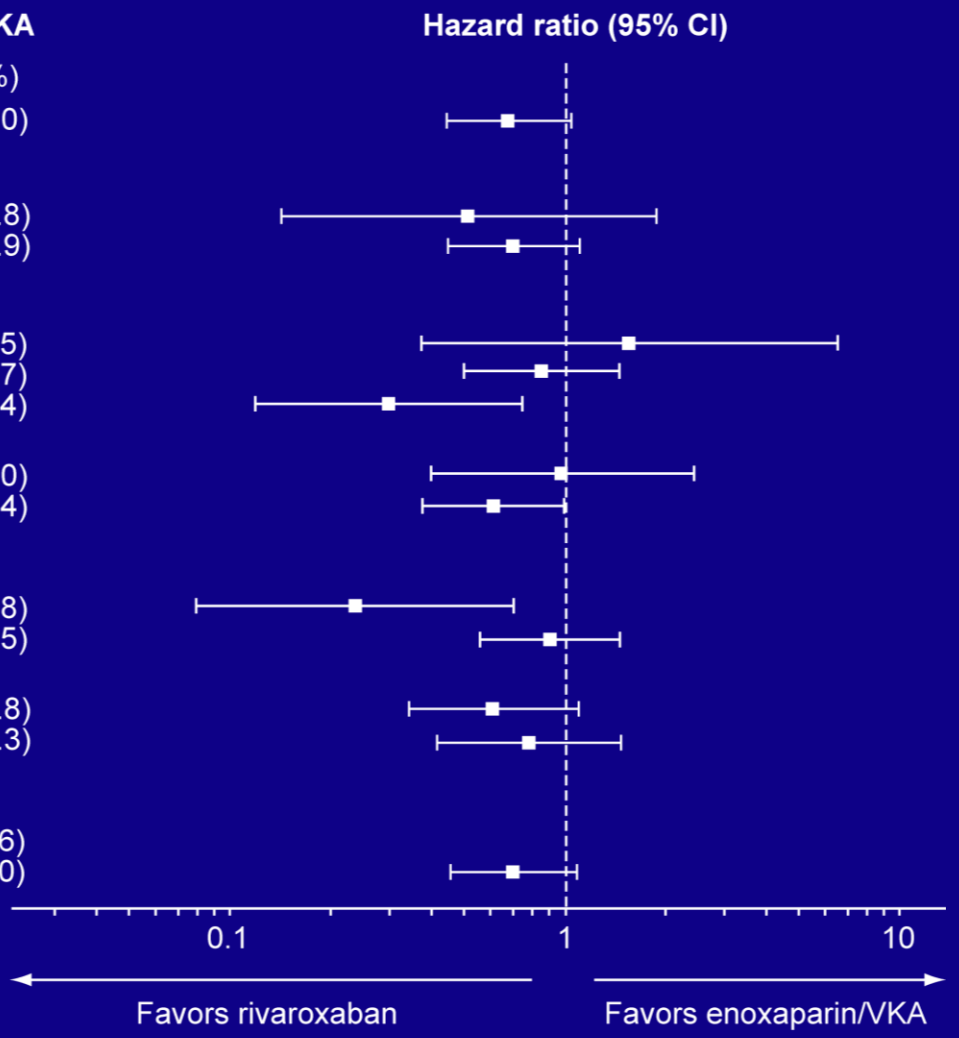
	Rivaroxaban		Enoxaparin/VKA	
	n/N	(%)	n/N	(%)
Overall	36/1731	(2.1)	51/1718	(3.0)
Age				
<65 years	26/1145	(2.3)	30/1111	(2.7)
65–75 years	6/371	(1.6)	11/382	(2.9)
>75 years	4/215	(1.9)	10/225	(4.4)
Weight				
≤70 kg	12/494	(2.4)	21/524	(4.0)
>70–90 kg	13/740	(1.8)	19/707	(2.7)
>90 kg	11/491	(2.2)	11/486	(2.3)
Gender				
Male	17/993	(1.7)	24/967	(2.5)
Female	19/738	(2.6)	27/751	(3.6)
Creatinine clearance				
≥80 ml/min	19/1193	(1.6)	30/1170	(2.6)
50–<80 ml/min	12/393	(3.1)	14/399	(3.5)
<50 ml/min	4/121	(3.3)	6/129	(4.7)



EINSTEIN DVT trial

Critère de jugement principal: récidives de thrombose veineuse profonde, embolie pulmonaire fatale ou non fatale

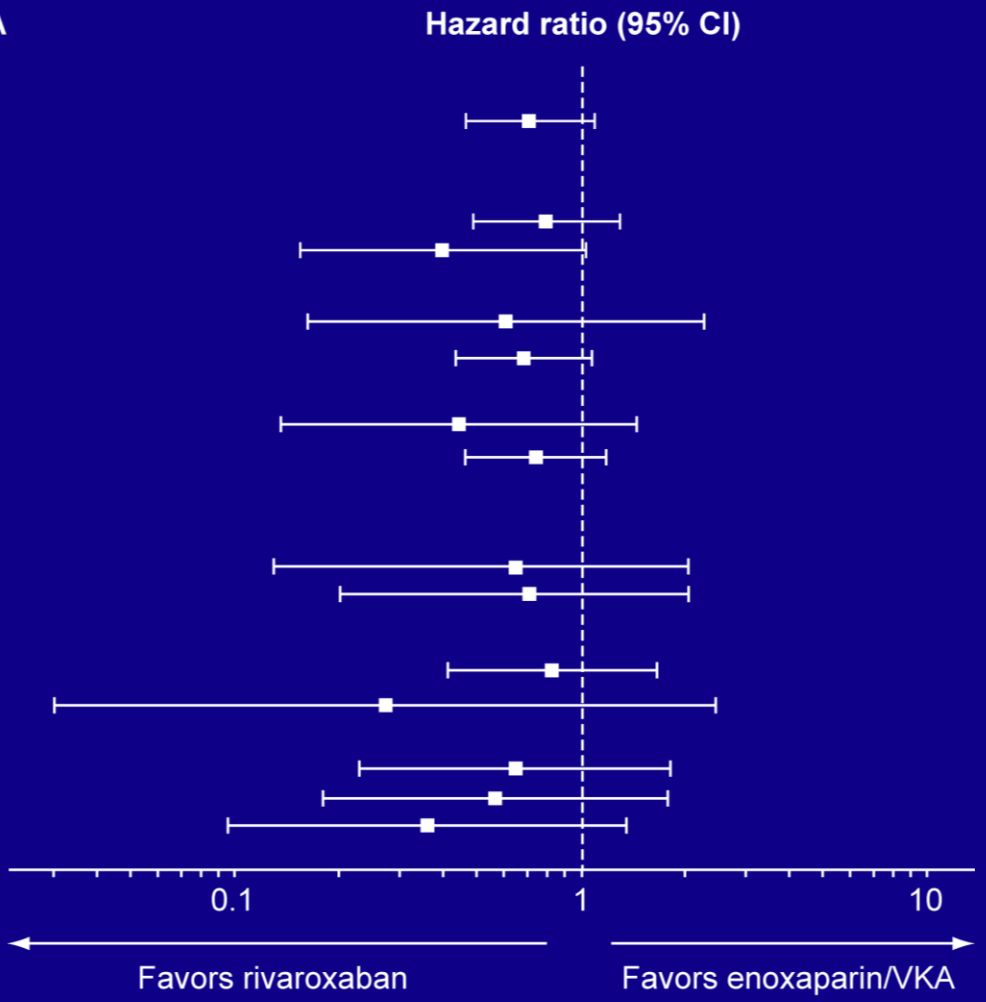
	Rivaroxaban		Enoxaparin/VKA	
	n/N	(%)	n/N	(%)
Overall	36/1731	(2.1)	51/1718	(3.0)
Cardiac disease				
Yes	4/178	(2.2)	6/159	(3.8)
No	32/1553	(2.1)	45/1559	(2.9)
Intended duration of anticoagulation				
3 months	5/208	(2.4)	3/203	(1.5)
6 months	25/1083	(2.3)	29/1083	(2.7)
12 months	6/440	(1.4)	19/432	(4.4)
Pre-randomization LMWH				
No	9/467	(1.9)	10/505	(2.0)
Yes	27/1264	(2.1)	41/1213	(3.4)
Previous episode(s) of DVT/PE				
Yes	4/336	(1.2)	16/330	(4.8)
No	32/1395	(2.3)	35/1388	(2.5)
Spontaneous index DVT				
Yes	18/1055	(1.7)	30/1083	(2.8)
No	18/676	(2.7)	21/635	(3.3)
Known thrombophilic condition				
Yes	1/107	(0.9)	3/116	(2.6)
No	35/1624	(2.2)	48/1602	(3.0)



EINSTEIN DVT trial

Critère de jugement principal: récidives de thrombose veineuse profonde, embolie pulmonaire fatale ou non fatale

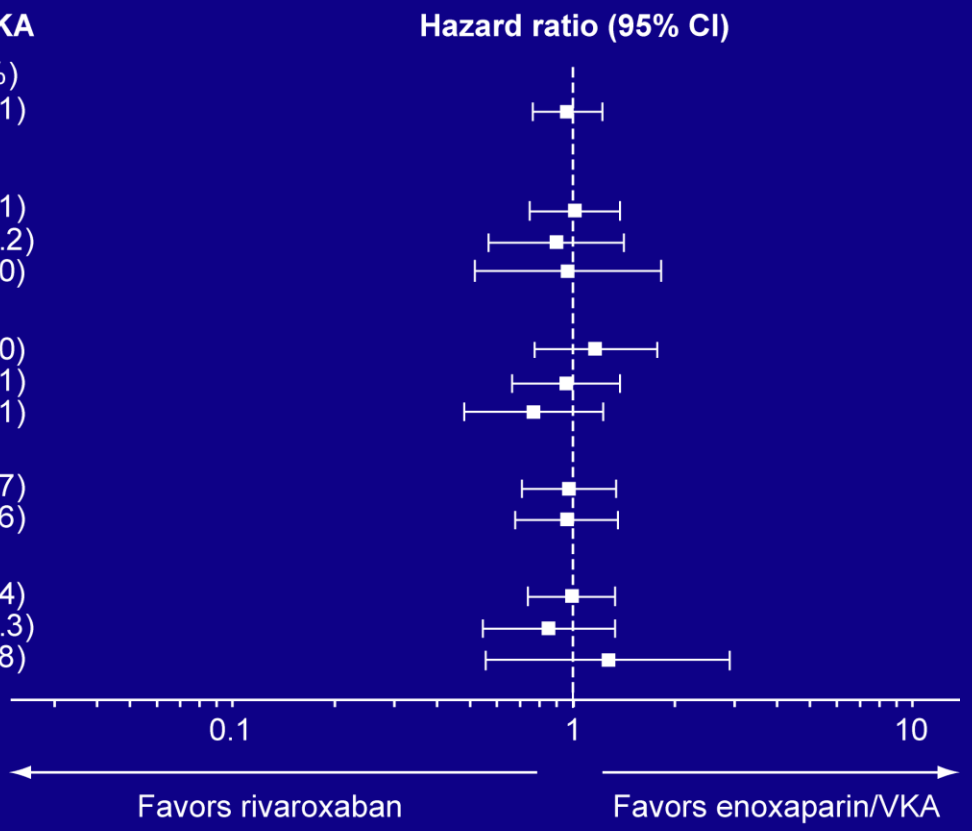
	Rivaroxaban		Enoxaparin/VKA	
	n/N	(%)	n/N	(%)
Overall	36/1731	(2.1)	51/1718	(3.0)
Location of index DVT				
Femoral or higher	30/1200	(2.5)	36/1165	(3.1)
Popliteal or lower	6/508	(1.2)	15/532	(2.8)
Active cancer				
Yes	4/118	(3.4)	5/89	(5.6)
No	32/1613	(2.0)	46/1629	(2.8)
Immobilization				
Yes	4/265	(1.5)	9/260	(3.5)
No	32/1466	(2.2)	42/1458	(2.9)
Vitamin K antagonist received				
Warfarin	28/1249	(2.2)	41/1256	(3.3)
Acenocoumarol	7/377	(1.9)	9/380	(2.4)
Region				
Western Europe	15/758	(2.0)	17/740	(2.3)
Eastern Europe	1/255	(0.4)	4/260	(1.5)
Australia and New Zealand	6/179	(3.4)	9/179	(5.0)
North America	5/163	(3.1)	8/163	(4.9)
Asia	3/211	(1.4)	8/211	(3.8)



EINSTEIN DVT trial

Hémorragies majeures ou cliniquement significatives

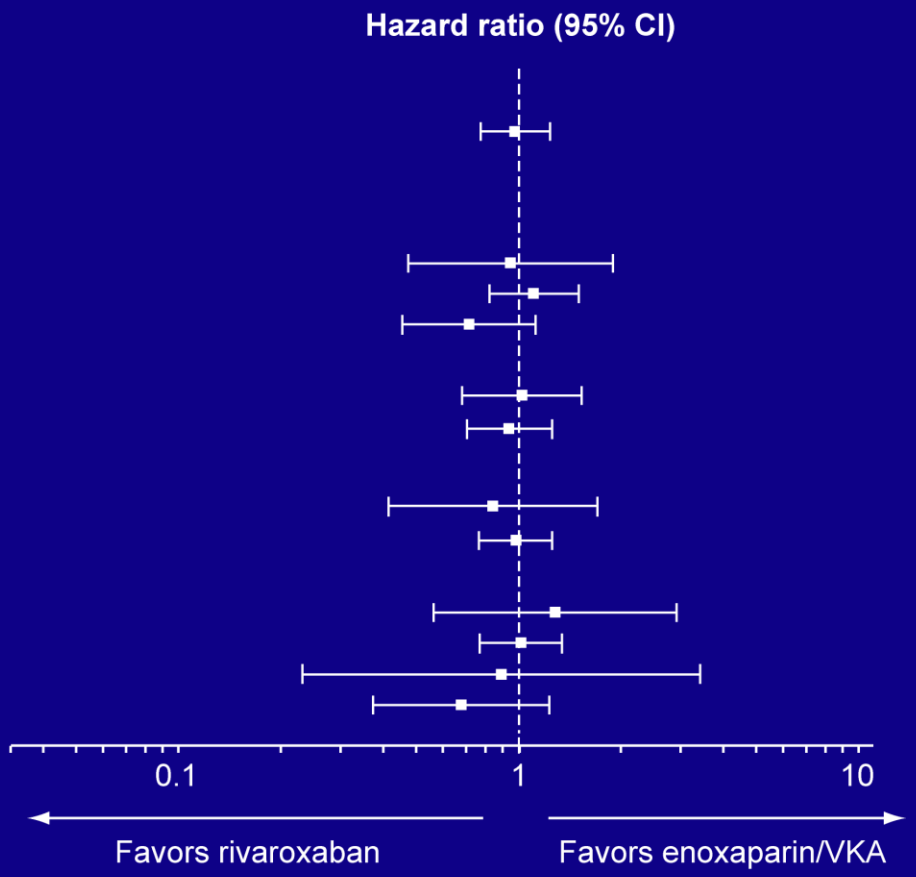
	Rivaroxaban		Enoxaparin/VKA	
	n/N	(%)	n/N	(%)
Overall	139/1718	(8.1)	138/1711	(8.1)
Age				
<65 years	86/1134	(7.6)	79/1107	(7.1)
65–75 years	34/369	(9.2)	39/381	(10.2)
>75 years	19/215	(8.8)	20/223	(9.0)
Weight				
≤70 kg	48/492	(9.8)	42/522	(8.0)
>70–90 kg	59/733	(8.0)	57/708	(8.1)
>90 kg	31/488	(6.4)	39/481	(8.1)
Gender				
Male	75/987	(7.6)	74/963	(7.7)
Female	64/731	(8.8)	64/748	(8.6)
Creatinine clearance				
≥80 ml/min	89/1186	(7.5)	86/1166	(7.4)
50–<80 ml/min	36/390	(9.2)	41/400	(10.3)
<50 ml/min	13/120	(10.8)	10/128	(7.8)



EINSTEIN DVT trial

Hémorragies majeures ou cliniquement significatives

	Rivaroxaban		Enoxaparin/VKA	
	n/N	(%)	n/N	(%)
Overall	139/1718	(8.1)	138/1711	(8.1)
Intended duration of anticoagulation				
3 months	16/207	(7.7)	16/201	(8.0)
6 months	90/1074	(8.4)	78/1079	(7.2)
12 months	33/437	(7.6)	44/431	(10.2)
Pre-randomization LMWH				
No	47/465	(10.1)	47/500	(9.4)
Yes	92/1253	(7.3)	91/1211	(7.5)
Active cancer				
Yes	17/118	(14.4)	14/88	(15.9)
No	122/1600	(7.6)	124/1623	(7.6)
Race				
Not available	13/122	(10.7)	10/123	(8.1)
White	101/1316	(7.7)	97/1315	(7.4)
Black	4/38	(10.5)	5/43	(11.6)
Asian	19/227	(8.4)	25/217	(11.5)



EINSTEIN DVT trial

Population fragile

Définition:

- age >75 ans
- poids ≤50 kg
- clairance à la créatinine <50 ml/min

Patients fragiles vs non-fragiles dans le groupe rivaroxaban:

- Récidives thromboemboliques HR 0.57 (0.23–1.44)
- Hémorragies majeures HR 0.27 (0.07–0.96)

EINSTEIN DVT trial

Effets secondaires

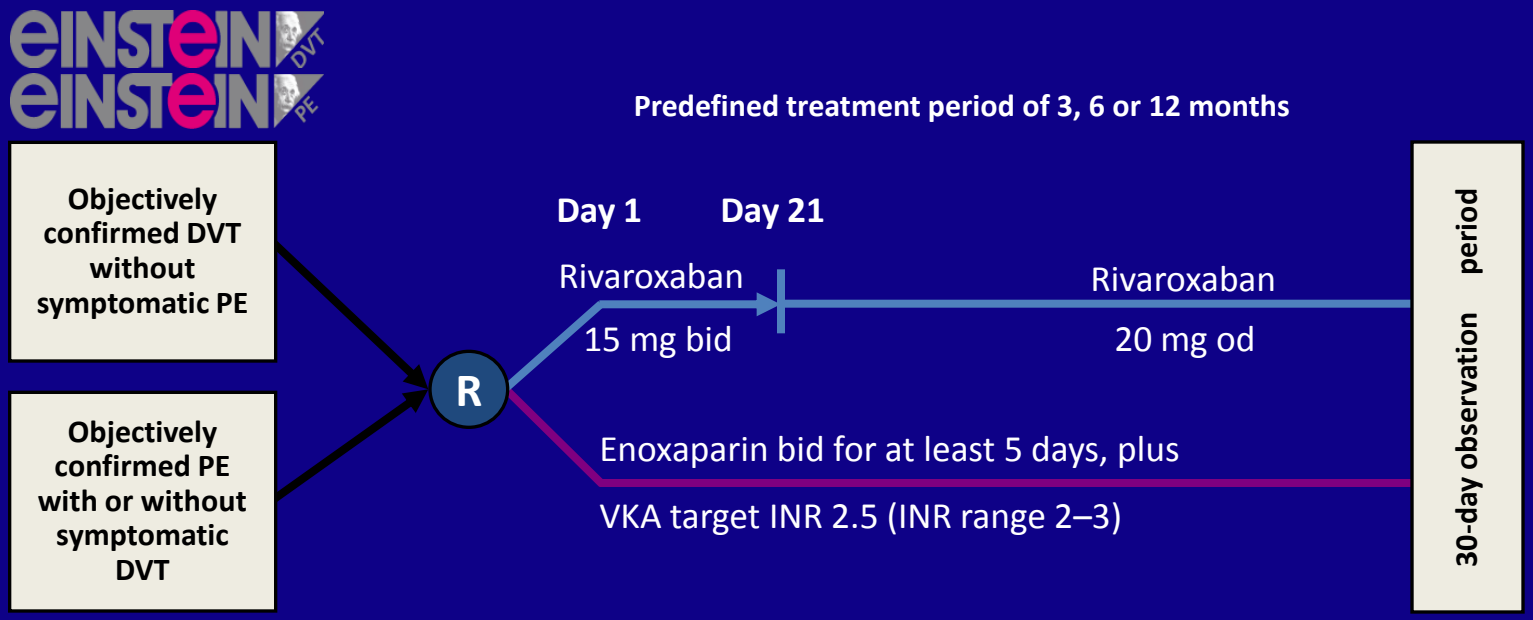
	Rivaroxaban (n=1,718)	Enox/VKA (n=1,711)	HR (95% CI)
	n (%)	N (%)	*p* value
First major or clinically relevant non-major bleeding	139 (8.1)	138 (8.1)	0.97 (0.76–1.22) *p*=0.77
Major bleeding	14 (0.8)	20 (1.2)	
Contributing to death	1 (<0.1)	5 (0.3)	
In a critical site	3 (0.2)	3 (0.2)	
Associated with fall in Hb ≥2 g/dl and/or transfusion of ≥2 units	10 (0.6)	12 (0.7)	
Clinically relevant non-major bleeding	129 (7.5)	122 (7.1)	

Objectifs secondaires

Outcome	Rivaroxaban n/N	(%)	Enoxaparin/VKA n/N	(%)	HR (95% CI)
Net clinical benefit: primary efficacy outcome + major bleeding	51/1,731	(2.9)	73/1,718	(4.2)	0.67 (0.47–0.95)
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)
ALT >3 x ULN + bilirubin >2 x ULN	2/1,682	(0.1)	4/1,648	(0.2)	
% time INR in range					
<2.0			24.4		
[2.0–3.0]			57.7		
>3.0			16.2		

EINSTEIN - PE

Design ENSTEIN - PE



Données démographiques

	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
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
Anatomical extent baseline PE, %		
Limited (single lobe, ≤25% of vasculature	12.8	12.4
Intermediate	57.5	59.0
Extensive (multiple lobes, >25% of entire vasculature)	24.7	23.9

ITT population

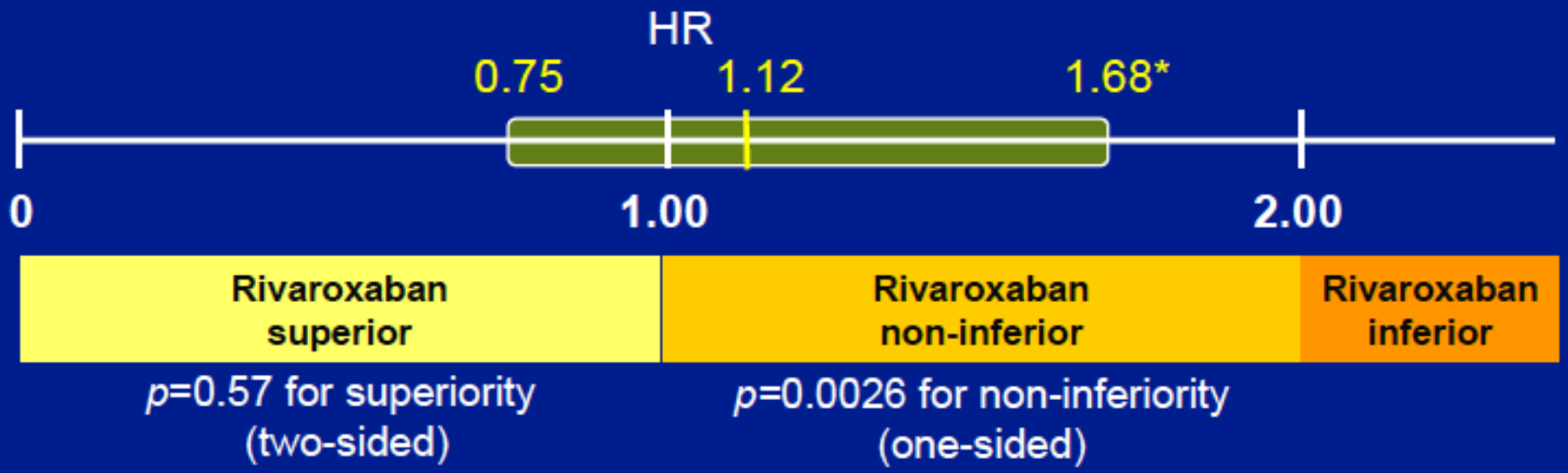
Données démographiques

	Rivaroxaban (n=2419)		Enoxaparin/VKA (n=2413)	
Prerandomization/initial treatment, n (%)	2237	(92.4)	2410	(99.9)
Median, days	1		8	
Mean study duration, days	263		268	
Mean treatment duration, days	216		214	
Compliance with study medication, n (%)				
<50%	31	(1.3)	64	(2.7)
≥50% to <80%	78	(3.2)	115	(4.8)
≥80%	2279	(94.2)	2226	(92.3)
Concomitant symptomatic DVT, %	25.1		24.5	
Hospitalization, % (median, days)	89.7	(6.0)	89.9	(7.0)
ICU	14.7	(4.0)	13.8	(4.0)

ITT population

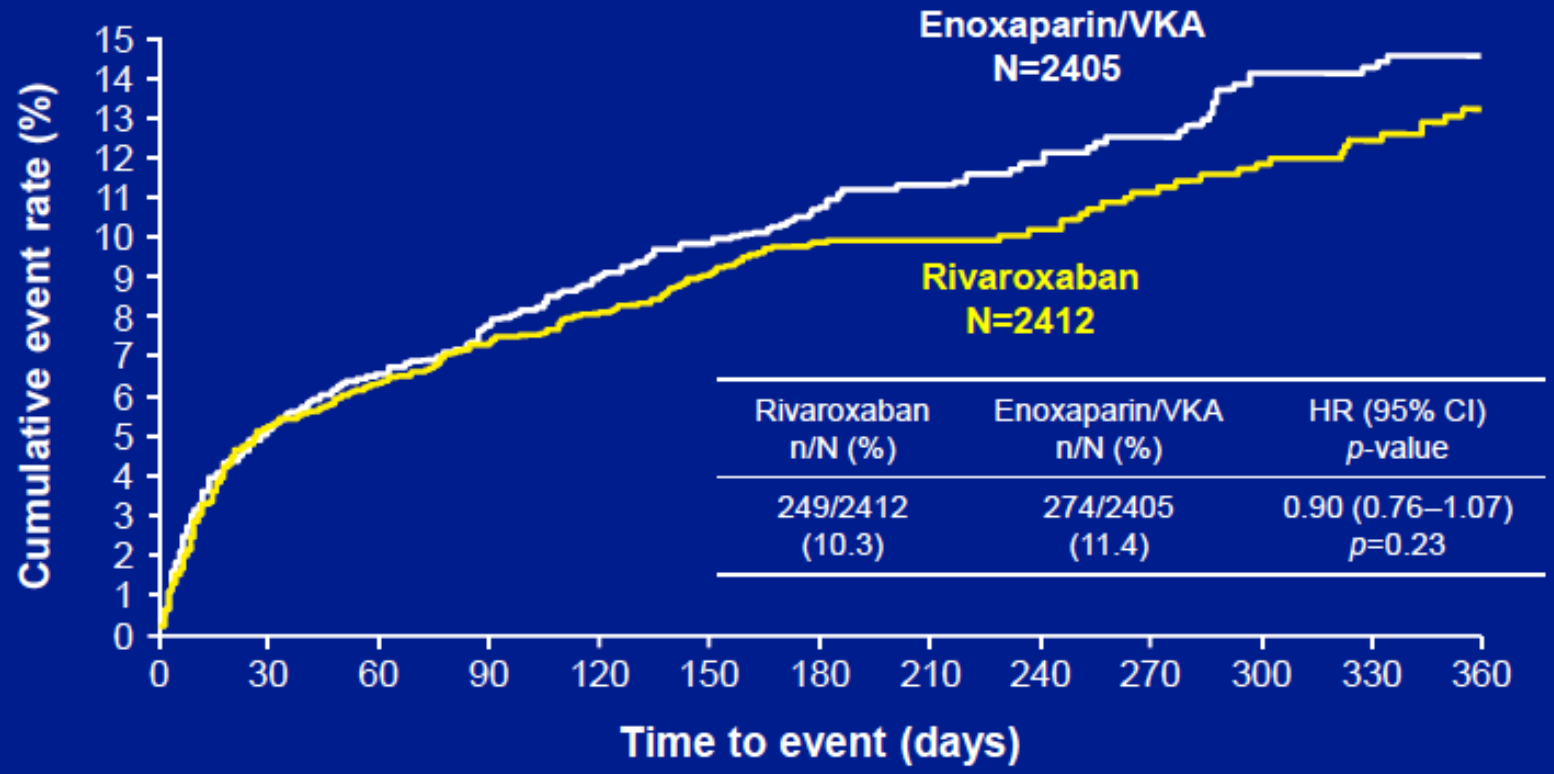
EINSTEIN PE: primary efficacy outcome analysis

	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)



*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

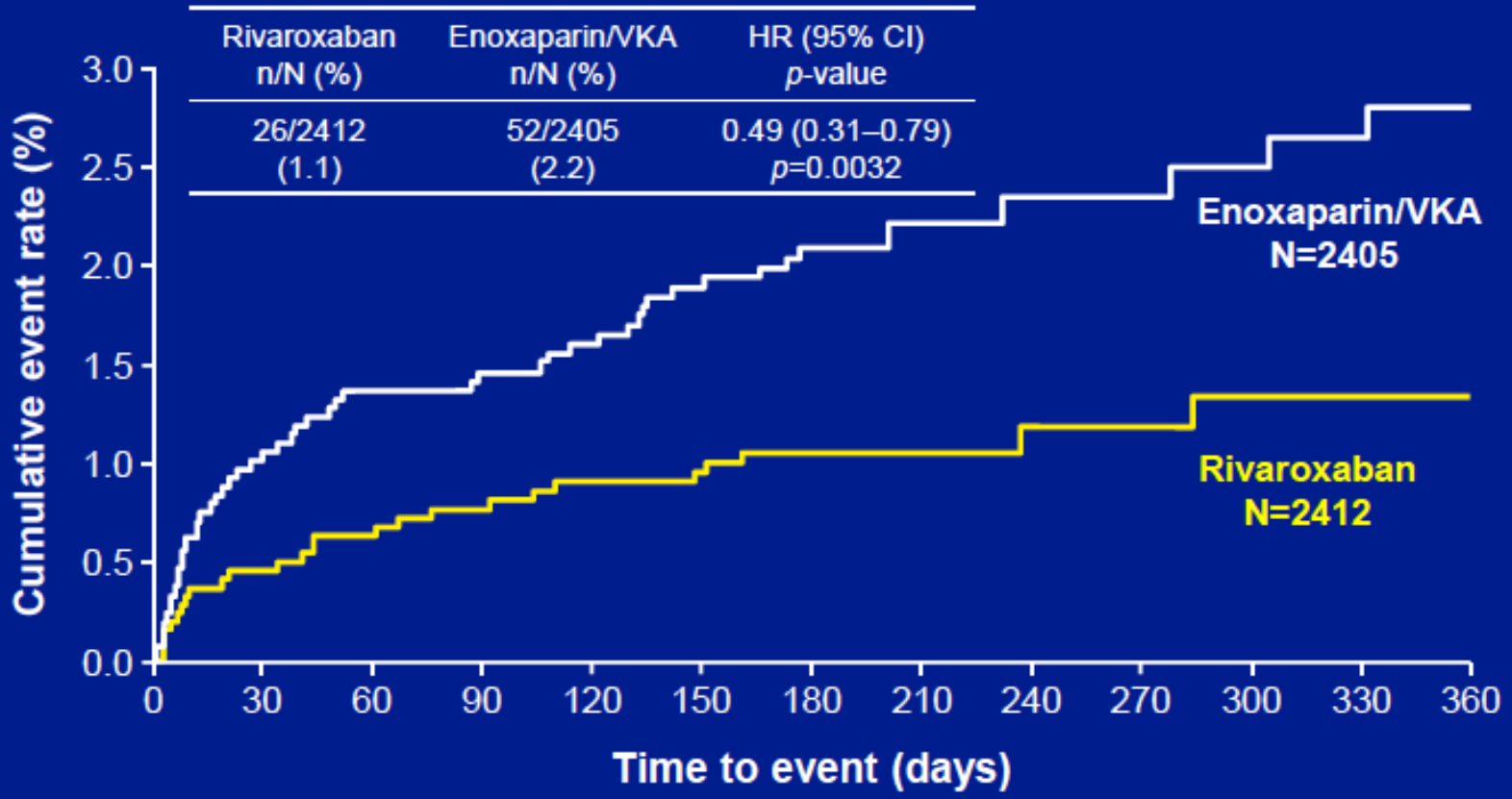


Rivaroxaban n/N (%)	Enoxaparin/VKA n/N (%)	HR (95% CI) *p*-value
249/2412 (10.3)	274/2405 (11.4)	0.90 (0.76–1.07) *p*=0.23

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

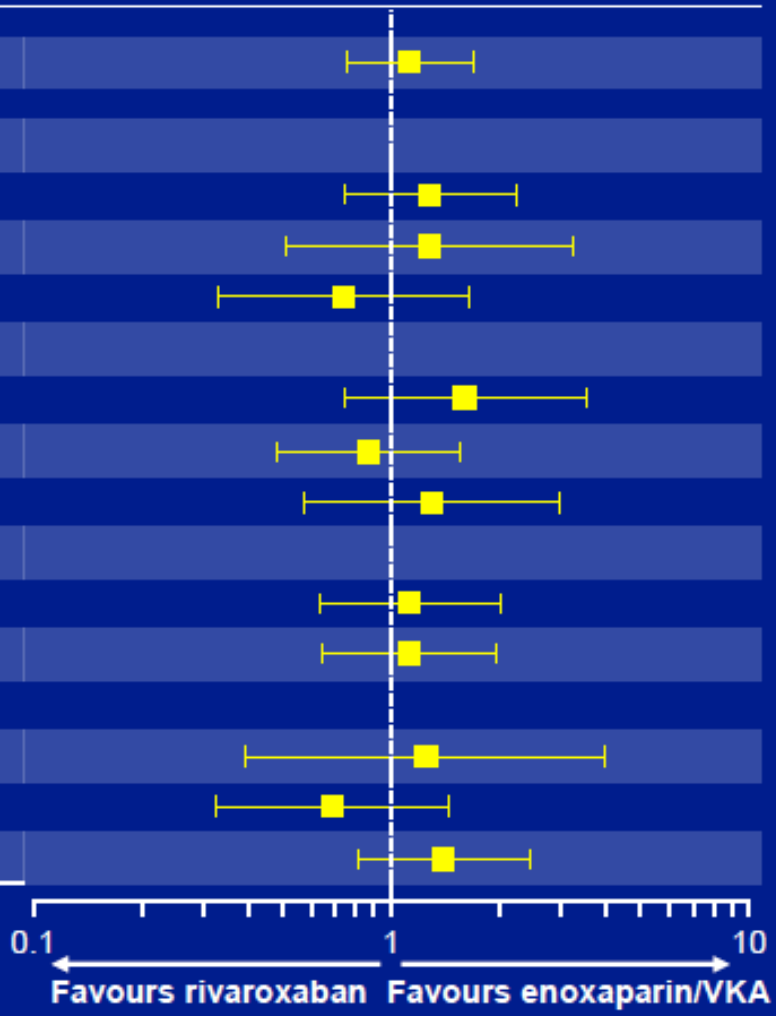


Number of patients at risk													
Rivaroxaban	2412	2281	2248	2156	2091	2063	1317	761	735	700	669	659	350
Enoxaparin/VKA	2405	2270	2224	2116	2063	2036	1176	746	719	680	658	642	278

Safety population

EINSTEIN PE: primary efficacy outcome by subgroup

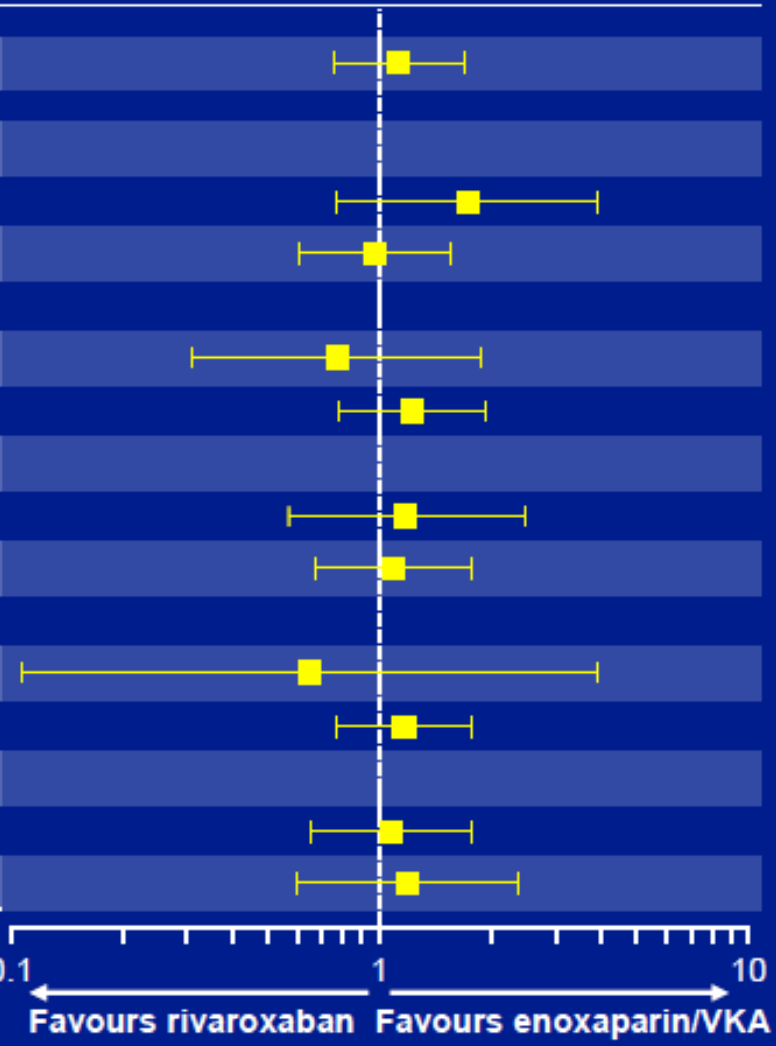
	Rivaroxaban		Enoxaparin/VKA	
	n/N	(%)	n/N	(%)
Overall	50/2419	(2.1)	44/2413	(1.8)
Age				
<65 years	29/1461	(2.0)	23/1479	(1.6)
65–75 years	10/517	(1.9)	8/532	(1.5)
>75 years	11/441	(2.5)	13/402	(3.2)
Body weight				
≤70 kg	17/653	(2.6)	10/621	(1.6)
>70–90 kg	20/1081	(1.9)	24/1119	(2.1)
>90 kg	13/683	(1.9)	10/672	(1.5)
Gender				
Male	25/1309	(1.9)	21/1247	(1.7)
Female	25/1110	(2.3)	23/1166	(2.0)
Creatinine 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

EINSTEIN PE: primary efficacy outcome by subgroup

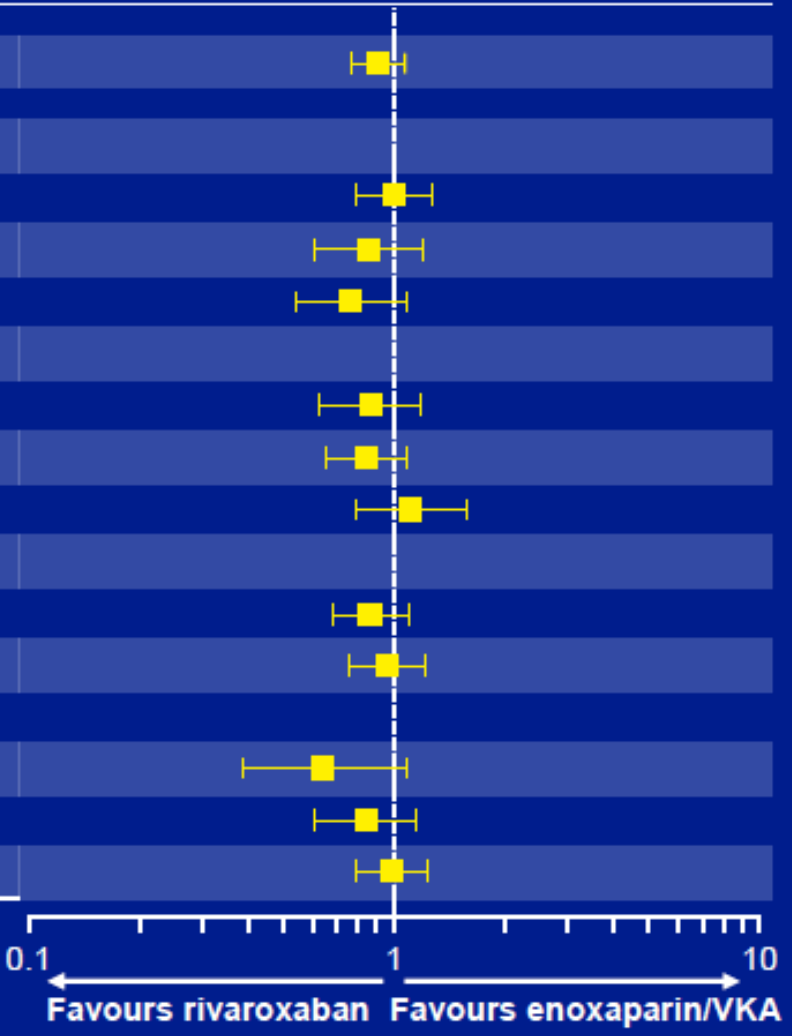
	Rivaroxaban		Enoxaparin/VKA		HR (95% CI)
	n/N	(%)	n/N	(%)	
Overall	50/2419	(2.1)	44/2413	(1.8)	
Index PE					
With DVT	16/603	(2.7)	9/587	(1.5)	
Without DVT	34/1793	(1.9)	35/1803	(1.9)	
Cardiac disease					
Yes	9/428	(2.1)	10/374	(2.7)	
No	41/1991	(2.1)	34/2039	(1.7)	
Pulmonary disease					
Yes	16/627	(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

EINSTEIN PE: principal safety outcome by subgroup

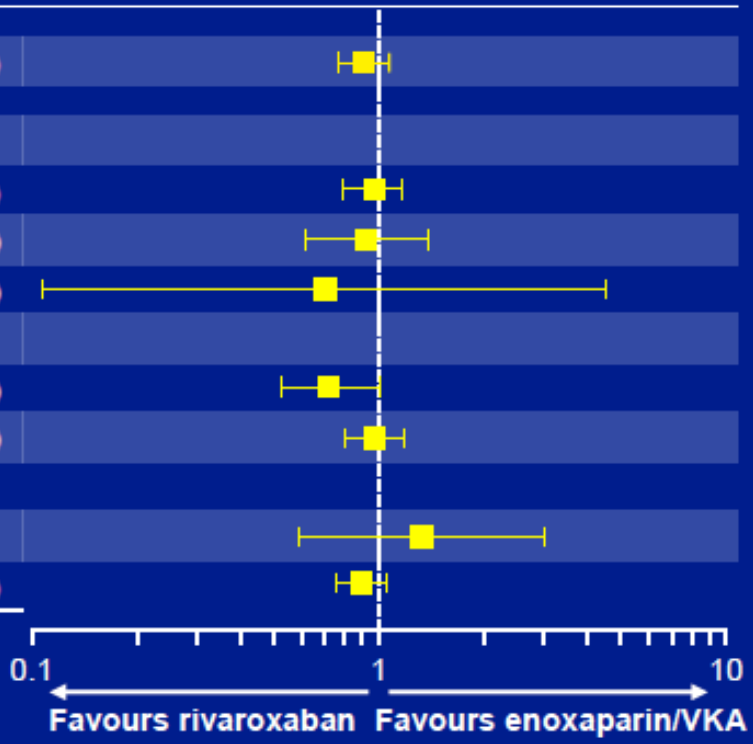
	Rivaroxaban		Enoxaparin/VKA		HR (95% CI)
	n/N	(%)	n/N	(%)	
Overall	249/2412	(10.3)	274/2405	(11.4)	
Age					
<65 years	132/1458	(9.1)	136/1472	(9.2)	
65–75 years	59/514	(11.5)	71/532	(13.3)	
>75 years	58/440	(13.2)	67/401	(16.7)	
Body weight					
≤70 kg	71/649	(10.9)	79/618	(12.8)	
>70–90 kg	110/1078	(10.2)	134/1116	(12.0)	
>90 kg	68/683	(10.0)	61/670	(9.1)	
Gender					
Male	117/1307	(9.0)	129/1243	(10.4)	
Female	132/1105	(11.9)	145/1162	(12.5)	
Creatinine clearance					
<50 ml/min	26/209	(12.4)	34/192	(17.7)	
50–<80 ml/min	73/634	(11.5)	81/593	(13.7)	
≥80 ml/min	149/1553	(9.6)	159/1610	(9.9)	



Safety population

EINSTEIN PE: principal safety outcome by subgroup

	Rivaroxaban		Enoxaparin/VKA	
	n/N	(%)	n/N	(%)
Overall	249/2412	(10.3)	274/2405	(11.4)
Prerandomization LMWH				
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)
Fragility				
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

Outcomes in fragile patients and its components

	Rivaroxaban		Enoxaparin/VKA		Hazard ratio	95% CI
	n/N	(%)	n/N	(%)		
CrCl <50 ml/min						
Major bleeding	2/209	(1.0)	6/192	(3.1)	0.29	(0.06–1.45)
Principal safety	26/209	(12.4)	34/192	(17.7)	0.64	(0.38–1.06)
Body weight <50 kg						
Major bleeding	0/22	(0)	1/28	(3.6)	N.D.	
Principal safety	1/ 22	(4.5)	6/28	(21.4)	0.18	(0.02–1.54)
Age >75 years						
Major bleeding	5/440	(1.1)	23/401	(5.7)	0.19	(0.07–0.50)
Principal safety	58/440	(13.2)	67/401	(16.7)	0.76	(0.53–1.07)

Deux facettes d'une même maladie

- Efficacité équivalente aux AVK
- Une tolérance
  - Équivalente dans la population TVP
  - Meilleure dans la population EP
- Quelle place en pratique ?