Edoxaban in VTE:

- New insights from the Hokusai-VTE study -

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Disclosures for Harry R Büller

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VTE treatment studies - new oral anticoagulants

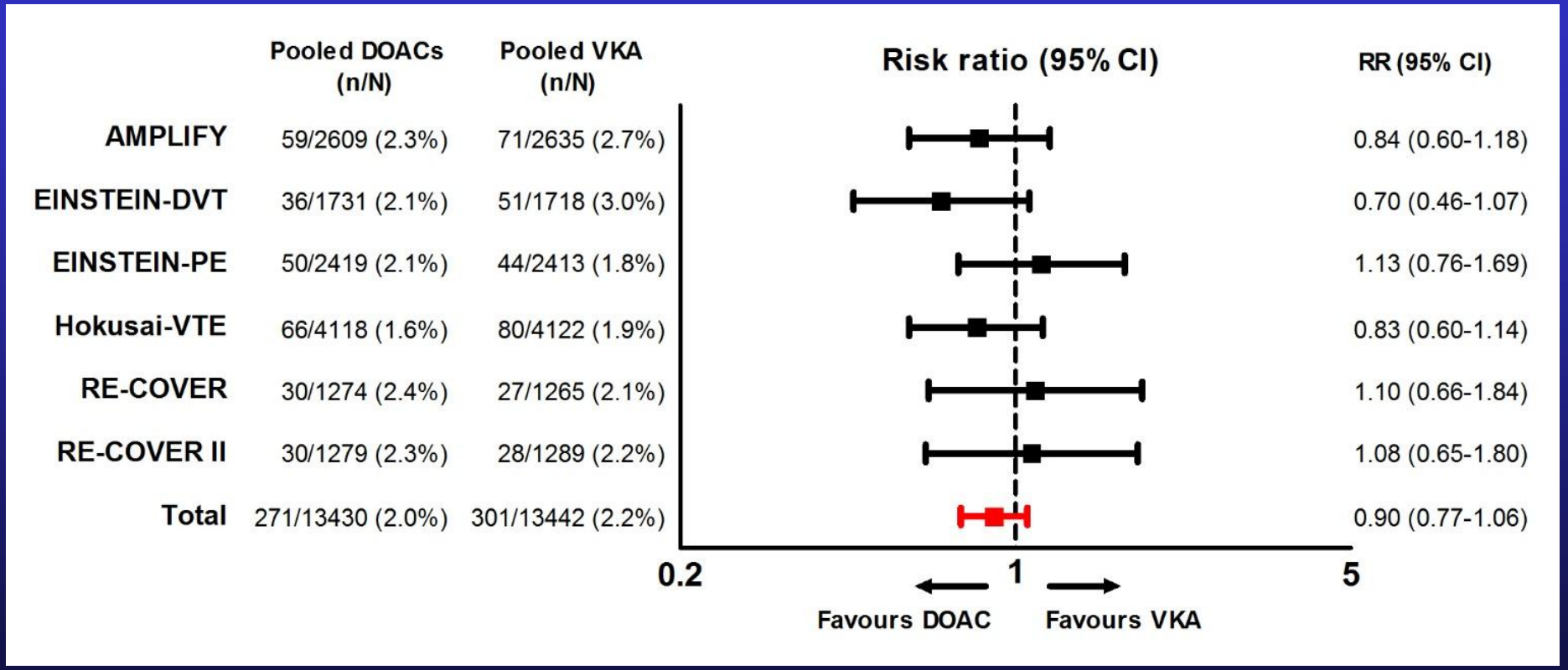
	Hokusai-VTE	EINSTEIN-DVT EINSTEIN-PE	AMPLIFY	RE-COVER I RE-COVER II
Drug	Edoxaban	Rivaroxaban	Apixaban	Dabigatran
Study design	Double-blind	Open-label	Double-blind	Double-blind
Heparin lead-in	At least 5 days	None	None	At least 5 days
Dose	60 mg qd 30 mg qd (CrCl, bw, P-gp)	15 mg bid x 3 wk then 20 mg qd	10 mg bid x 7 days then 5 mg bid	150 mg bid
Non-inferiority margin	1.5	2.0	1.8	2.75
Sample size	8,292	**EINSTEIN-DVT** 3,449 **EINSTEIN-PE** 4,832	5,400	**RE-COVER I** 2,564 **RE-COVER II** 2,568
Treatment duration	Flexible 3 to 12 months	Pre-specified 3, 6, or 12 months	6 months	6 months

Adapted from Raskob et al. J Thromb Haemost 2013. doi:10.1111/jth.12230

Differences and similarities

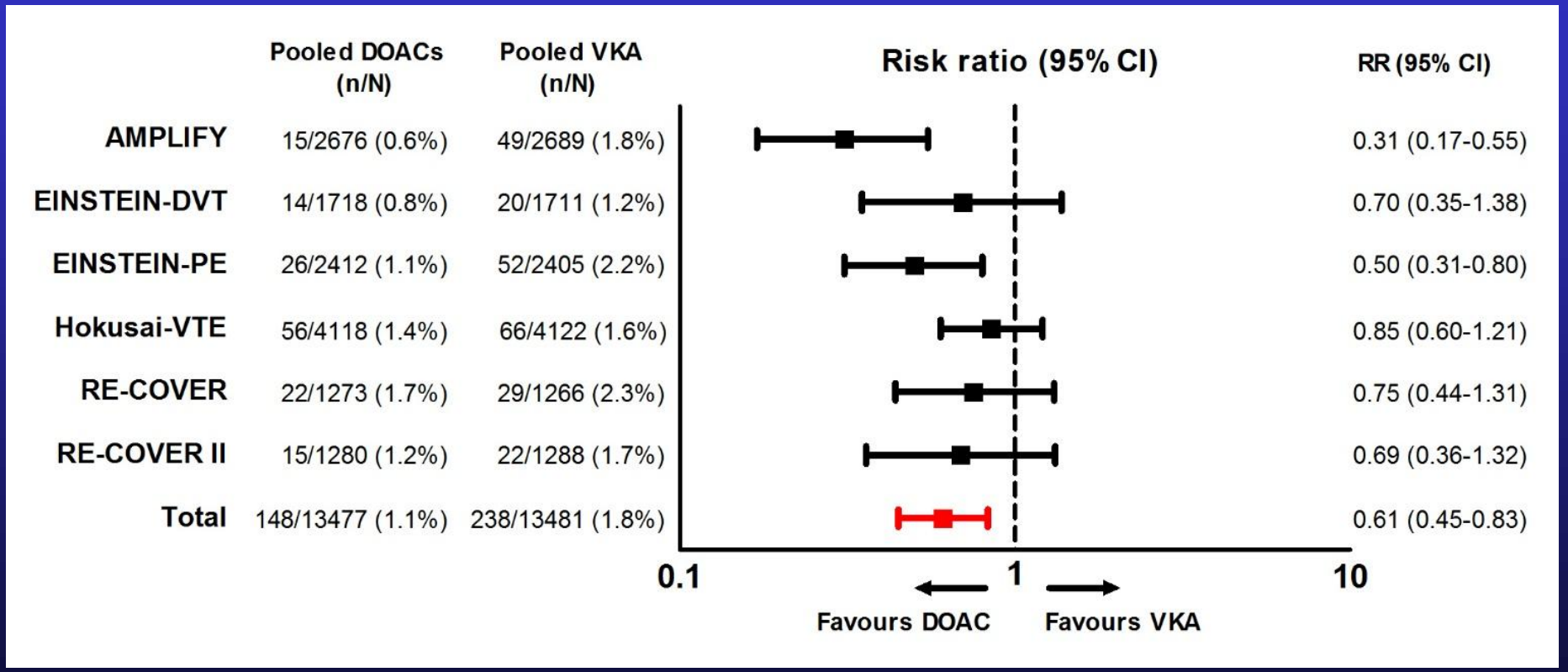
- Hokusai / Recover I/II used initial heparin
- Mostly DVT and PE combined
- Duration of treatment / follow-up variable
- Comparable definition of efficacy and safety outcomes
- The same adjudication committee

Overall efficacy



Van Es et al. Blood 2014

Overall major bleeding



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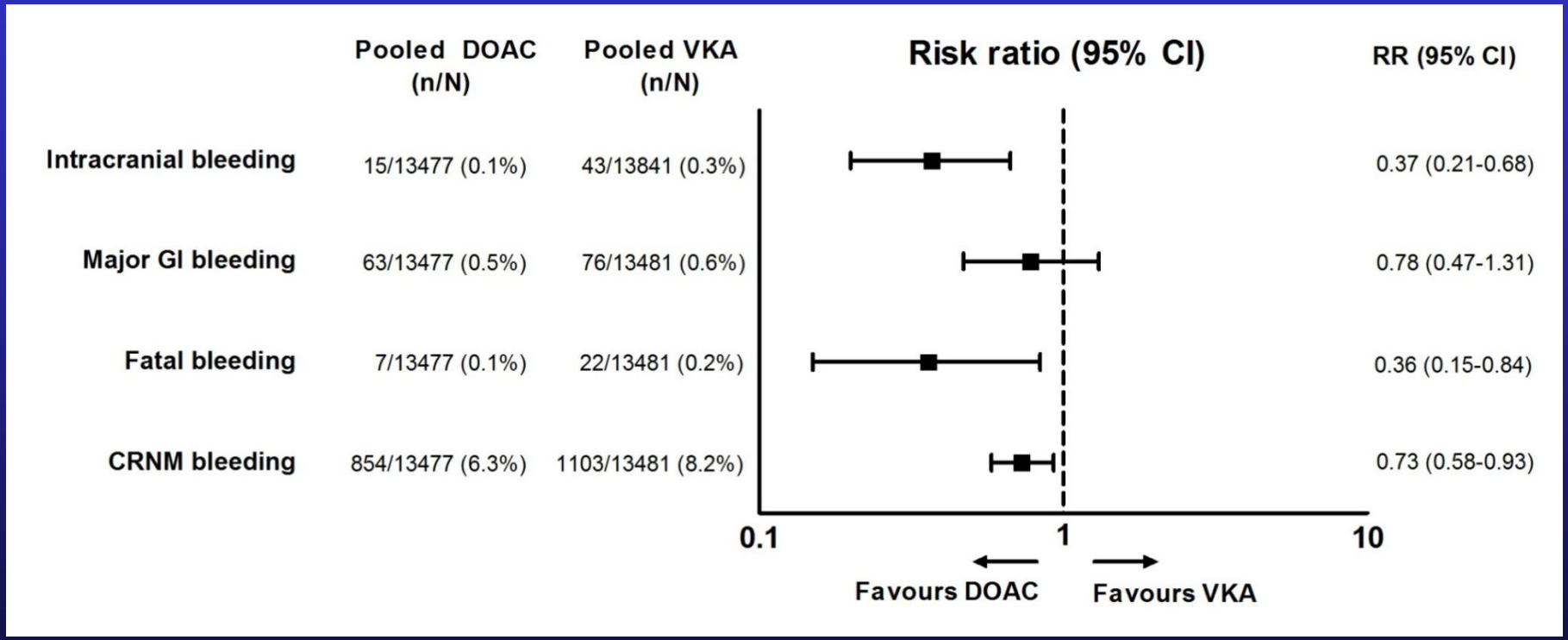
Bleeding components



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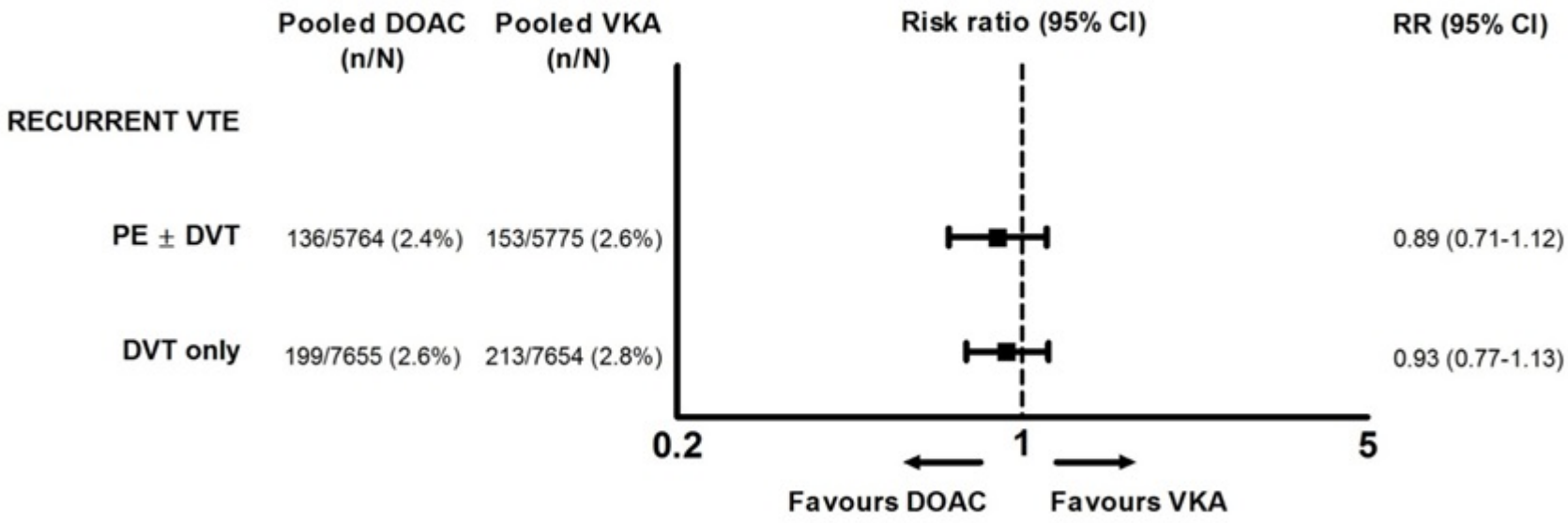
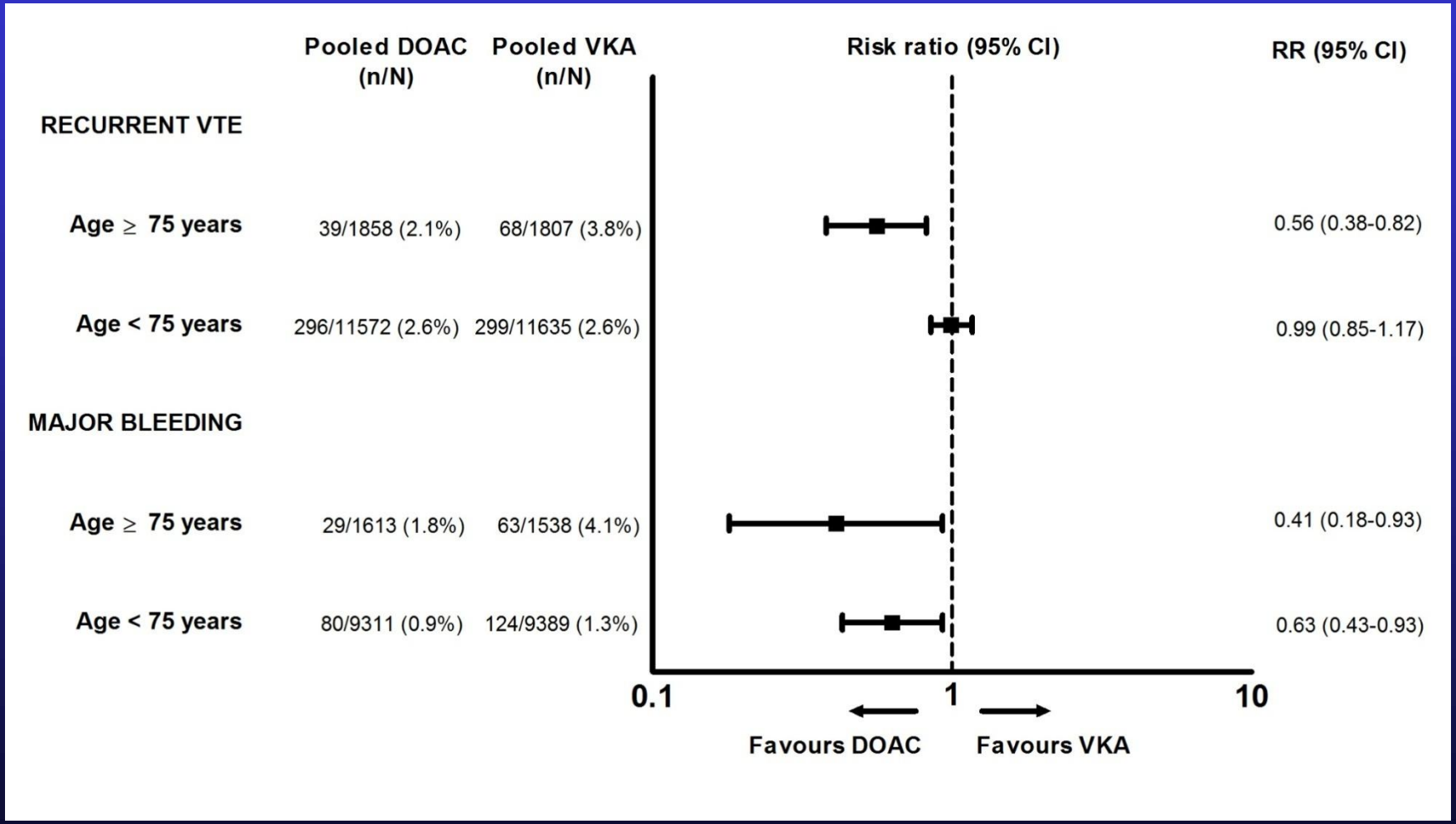
PE / DVT

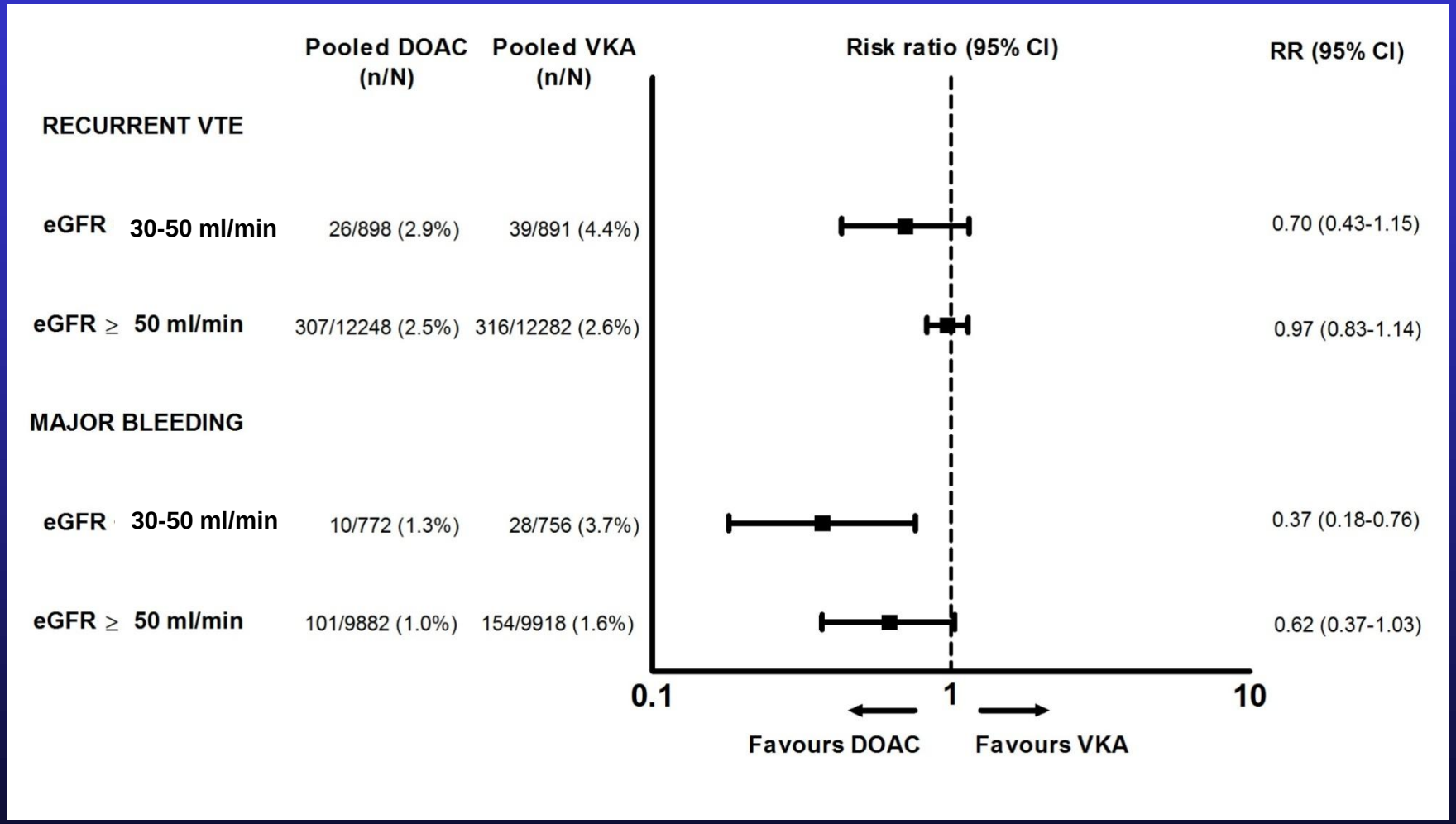

Pooled DOAC (n/N)
Pooled VKA (n/N)
Risk ratio (95% CI)
RR (95% CI)
RECURRENT VTE
PE ± DVT
136/5764 (2.4%)
153/5775 (2.6%)
0.89 (0.71-1.12)
DVT only
199/7655 (2.6%)
213/7654 (2.8%)
0.93 (0.77-1.13)
0.2
1
5
Favours DOAC
Favours VKA

Elderly



Van Es et al. Blood 2014

Renal function



Van Es et al. Blood 2014

Conclusions

- DOAC's are effective, but safer, both in DVT and PE
- Also in important subgroups; elderly, clearance 30-50, and obese
- Unresolved is whether to give initial heparin

Hokusai - VTE study

- Major Findings and Key Additional Analyses -

Hokusai-VTE Study

- Unique design
  - All patients followed for 12 months
  - Initial parenteral heparin in all
  - Treatment at least 3 months
  - Halving the dose for patients perceived to be at higher risk of bleeding (Cr.Cl 30-50; BW <60Kg; P-gp)
  - Stratified randomisation (DVT/PE; dose edoxaban; risk factors)

Edoxaban for the Treatment of Acute Symptomatic Venous Thromboembolism the HOKUSAI-VTE study

On behalf of the HOKUSAI -VTE Investigators

Baseline characteristics

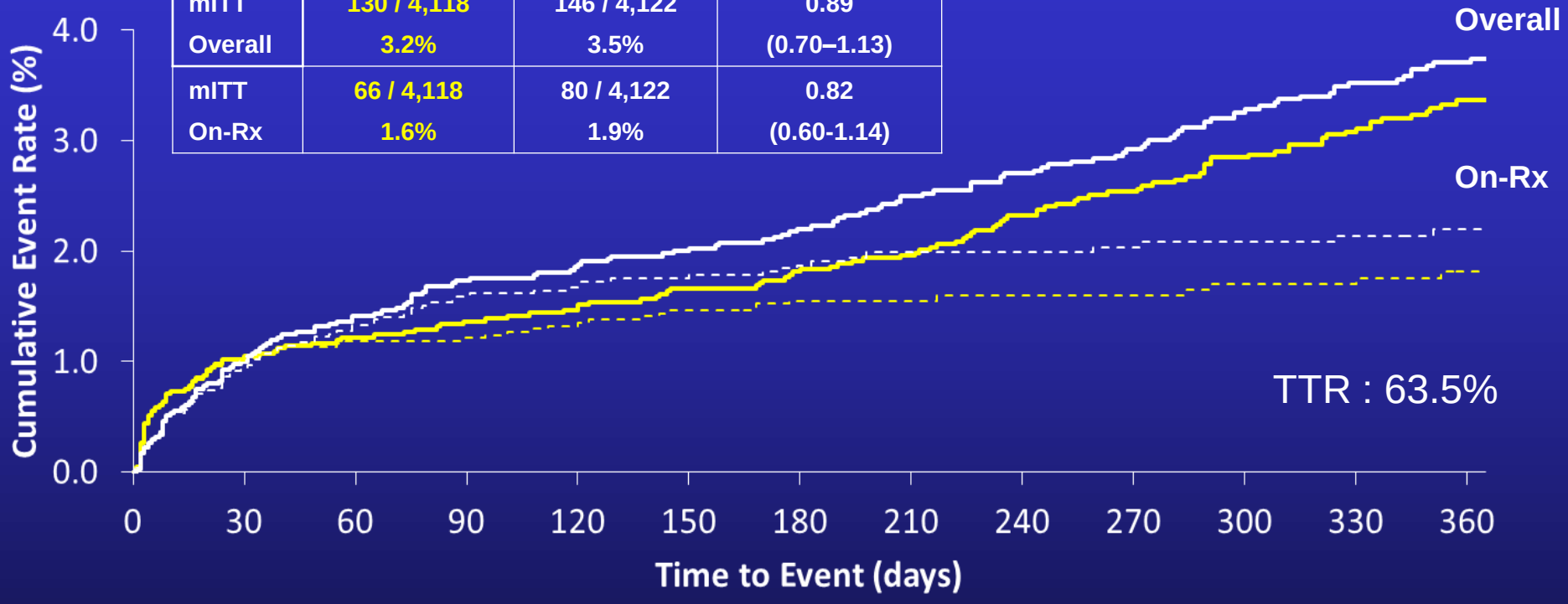
	Edoxaban (N=4118)	Warfarin (N=4122)
Mean age, years (SD)	56 (16)	56 (16)
Male gender, n (%)	2360 (57)	2356 (57)
Qualifying diagnosis, n (%)		
DVT	2468 (60)	2453 (60)
PE	1650 (40)	1669 (40)
Clinical presentation and risk factors, n (%)		
Unprovoked	2713 (66)	2697 (65)
Cancer	378 (9)	393 (10)
Previous VTE	784 (19)	736 (18)
Dose of 30 mg (e.g ≤ 60 kg, CrCl≥30 ≤50 ml/min), n (%)	733 (18)	719 (17)

Severity index event

	Edoxaban (N=4118)	Warfarin (N=4122)
DVT – no. (%)	2468 (60)	2453 (60)
Most proximal site – no. (%)		
Popliteal Vein	603 (24)	596 (24)
Superficial Femoral Vein	795 (32)	773 (32)
Femoral or Iliac Vein	1035 (42)	1049 (43)
PE – no. (%)	1650 (40)	1669 (40)
Anatomical extent – no. (%)		
Limited	128 (8)	123 (7)
Intermediate	679 (41)	682 (41)
Extensive	743 (45)	778 (47)
Concomitant DVT – no. (%)	410 (25)	404 (24)
NT pro-BNP ≥500 pg/ml – n/N (%)	465/1565 (30)	507/1599 (32)
Right Ventricular Dysfunction – n/N (%)	414/937 (44)	427/946 (45)

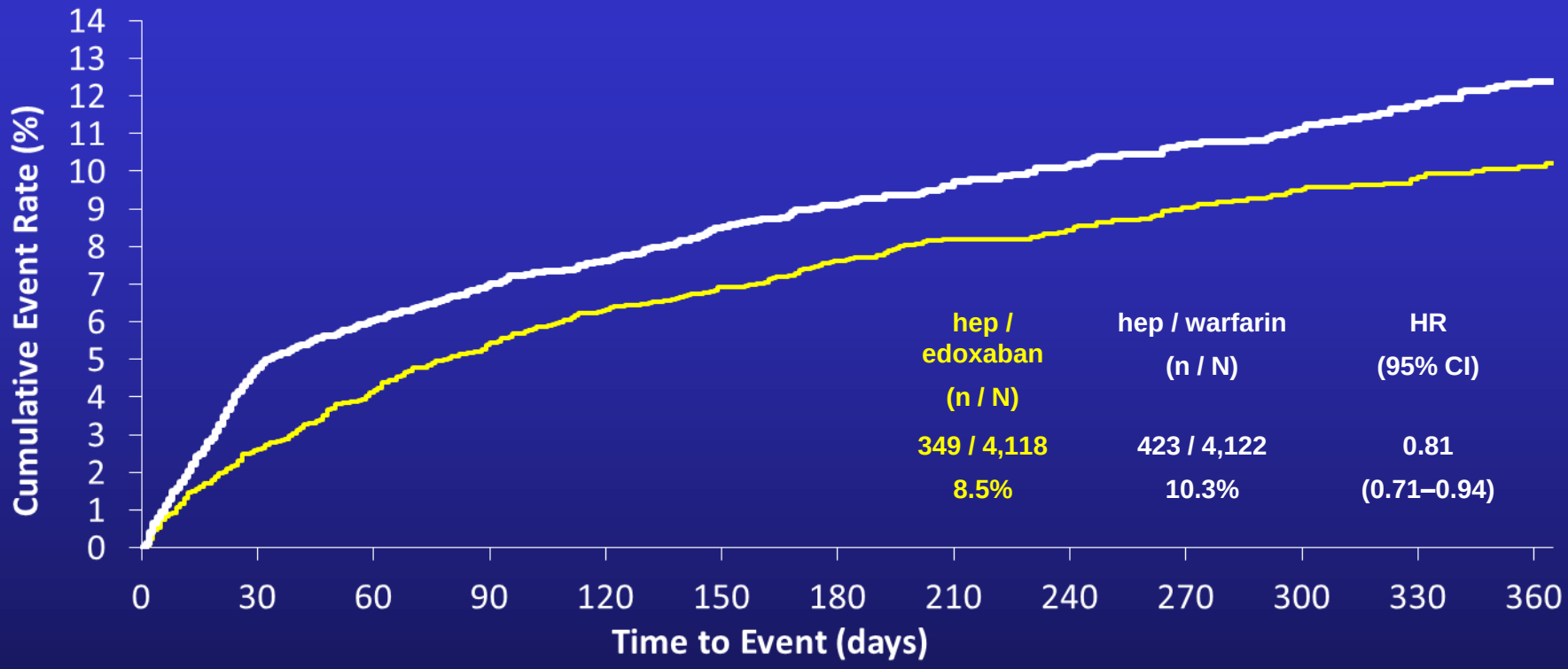
Primary Efficacy Outcome

	hep / edoxaban (n / N)	hep / warfarin (n / N)	HR (95% CI)
mITT Overall	130 / 4,118 3.2%	146 / 4,122 3.5%	0.89 (0.70–1.13)
mITT On-Rx	66 / 4,118 1.6%	80 / 4,122 1.9%	0.82 (0.60-1.14)



***Edoxaban* superior** | ***Edoxaban* non-inferior**

Principal Safety Outcome



Number of patients at risk

warfarin	4122	3757	3627	3522	3313	3218	2979	2165	2007	1883	1754	1613	1212
edoxaban	4118	3840	3695	3587	3382	3308	3038	2192	2043	1904	1767	1650	1241

Conclusions

LMW heparin / edoxaban regimen

- As effective as standard therapy
- Less clinically relevant bleeding
- Once daily after initial heparin

Hokusai-VTE Study

- Unique a-priori defined sub studies
  - Asian patients
  - Right ventricular dysfunction
  - Dose reduction group
  - Extended duration of treatment
  - Cancer patients

Right ventricular dysfunction

- N-terminal pro-brain natriuretic peptide (NT-proBNP)
  - All PE-patients at baseline
  - Morning sample
  - Core laboratory
  - 500 pg per ml or above

- Ventricular dimensions
  - In random sample of 1002 PE patients
  - Spiral CT, 4 chamber view
  - Independent blinded review
  - Ration right to left ventricular diameter 0.9 or above

Anatomical extent of PE at baseline

	Einstein PE %		Hokusai PE group %		Amplify PE group * %	
	Rivaroxaban	Standard	Edoxaban	Standard	Apixaban	Standard
Limited	13	12	8	7	9	10
Intermediate	58	59	41	41	42	44
Extensive	25	24	45	47	38	36

* Different method was used to define extensive PE

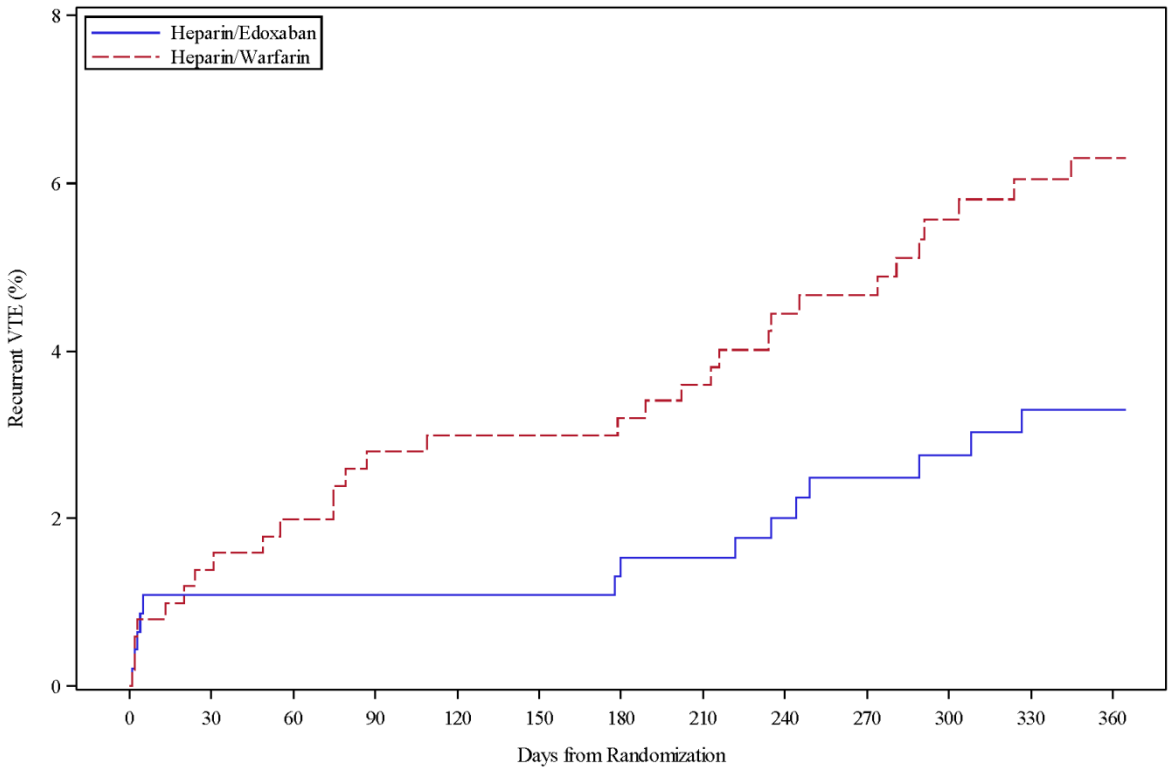
NT-proBNP and recurrent VTE

	Edoxaban	Warfarin
NT-proBNP ≥ 500 pg/mL – n	465	507
*** Recurrent VTE – n (%)**	14 (3.0)	30 (5.9)
- Fatal PE – n	4	13
- Non-fatal PE – n	8	13
- DVT only – n	2	4
NT proBNP < 500 pg/mL – n	1100	1092
*** Recurrent VTE – n (%)**	30 (2.7)	33 (3.0)
- Fatal PE – n	4	2
- Non-fatal PE – n	16	16
- DVT only – n	10	15

HR 0.50;
95% CI 0.27-0.95;
p = 0.03

HR 0.89;
95% CI 0.54-1.46;
p = 0.65

Kaplan-Meier cumulative rates of recurrent VTE in PE patients with NT-proBNP levels ≥ 500 pg/mL



Baseline characteristics (1)

Characteristic*	Edoxaban 60 mg (n=3385)	Edoxaban 30 mg (n=733)
Criteria for dose reduction at randomization		
Body weight ≤60kg		442 (60.3)
CrCl 30–50 ml/min		184 (25.1)
P-glycoprotein use		22 (3.0)
Two or more criteria		85† (11.6)
Other characteristics		
Mean age, years ± SD	54.7 ± 15.4	59.9 ± 19.2
Age ≥75 years	352 (10.4)	208 (28.4)
Male sex	2115 (62.5)	245 (33.4)
History diabetes	339 (10.0)	83 (11.3)
History cardiovascular disease	413 (12.2)	133 (18.1)
History cerebrovascular disease	134 (4.0)	44 (6.0)

*Unless otherwise indicated, data are expressed as number (percentage) of patients.
†81 patients met both renal and body weight criteria, 4 patients who used P-glycoprotein inhibitor, 3 patients met renal criterion and one had low body weight.
CrCl, creatinine clearance.

Relative efficacy/ safety in 30 mg dose group

	Edoxaban N = 733 (%)	Warfarin N = 719 (%)	Hazard ratio (95 % CI)
First recurrent VTE	22 (3.0)	30 (4.2)	0.73 (0.42-1.26)
Clinically relevant non major or major bleeding	58 (7.9)	92 (12.8)	0.62 (0.44-0.86)
Major bleeding	11 (1.5)	22 (3.1)	0.50 (0.24-1.03)

Extended treatment

- To evaluate the risks and benefits of extended treatment with edoxaban compared with warfarin in Hokusai-VTE patients who continued therapy beyond 3 months

- To compare the outcomes among patients treated for different durations (>3 to ≤ 6 months, > 6 to <12 months, and 12 months)

VTE = venous thromboembolism

Raskob G et al. [Published online 22 March 2016.] *Lancet Haematol.* 2016.

Comparable Baseline Characteristics and VTE Risk Factors Across Extended

Characteristics	3 to ≤6 months		>6 to <12 months		12 months	
	Edoxaban (n=1076)	Warfarin (n=1084)	Edoxaban (n=896)	Warfarin (n=851)	Edoxaban (n=1661)	Warfarin (n=1659)
Age, median ≥75 years old	56.0 14%	56.0 13%	57.0 11%	56.0 12%	57.0 12%	56.0 12%
Male	55%	55%	60%	58%	61%	59%
Creatinine clearance >50 mL/min ≥30 to ≤50 mL/min	 94% 6%	 95% 5%	 95% 5%	 93% 7%	 94% 6%	 94% 6%
Dose reduction criteria met[a]	17%	16%	15%	17%	16%	17%
Extent of VTE Limited Extensive	 28% 38%	 30% 37%	 26% 42%	 24% 44.5%	 21% 43%	 20% 45%
DVT only PE ± DVT	56% 44%	56% 44%	57% 43%	58% 42%	63% 37%	63% 37%
Causes of VTE Unprovoked Temporary risk factor History of cancer	 58% 36% 9%	 58% 35% 10%	 66% 26% 11%	 66% 27% 9%	 74% 20% 8%	 74% 20% 8%
Previous VTE	13%	12%	18%	18%	25%	24%
Known thrombophilia	2%	4%	5%	4%	5%	5%

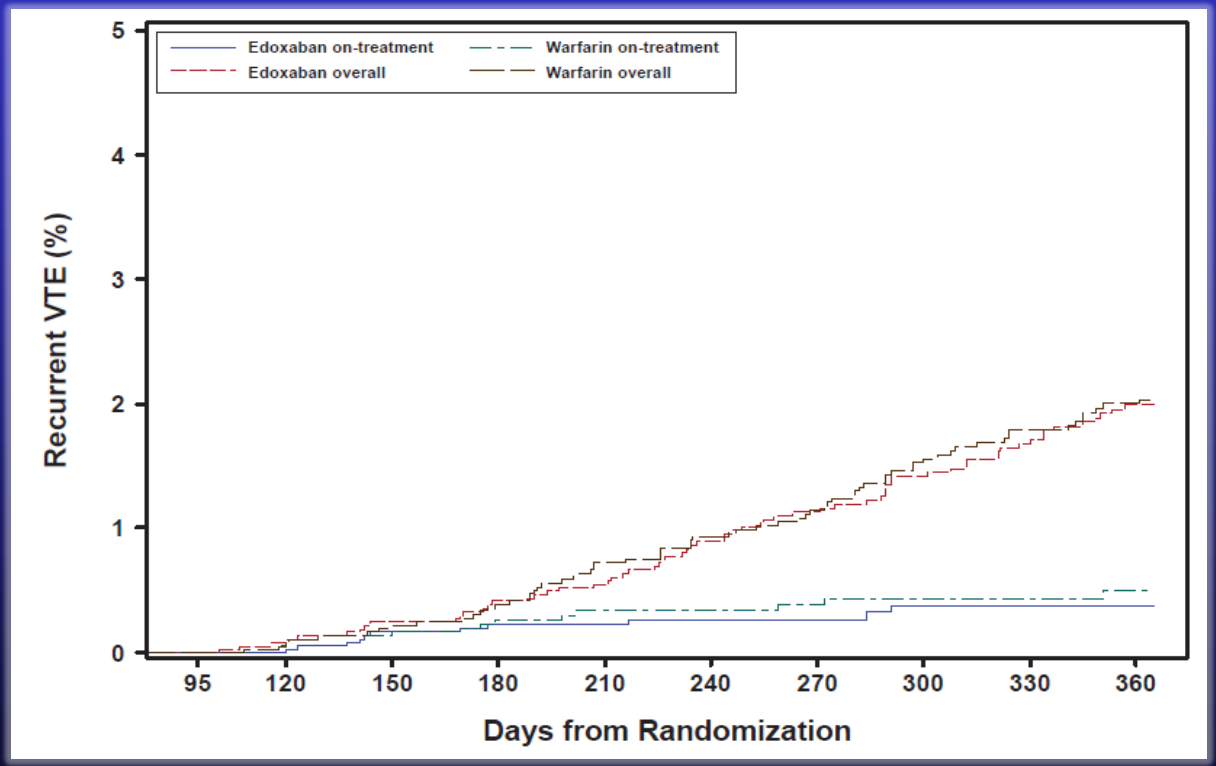
[a]At randomization.

VTE = venous thromboembolism; DVT= deep venous thrombosis; PE = pulmonary embolism.

Raskob G et al. [Published online 22 March 2016.] *Lancet Haematol.* 2016.

Cumulative Incidence of Recurrent VTE Over Extended Treatment Period (>3 – 12 Months)

- Cumulative incidence of recurrent VTE was similar for edoxaban and warfarin for both on-treatment and overall analyses



Warfarin overall
Edoxaban overall

HR 0.97
(95% CI, 0.69-1.37)

Warfarin on-treatment
Edoxaban on-treatment

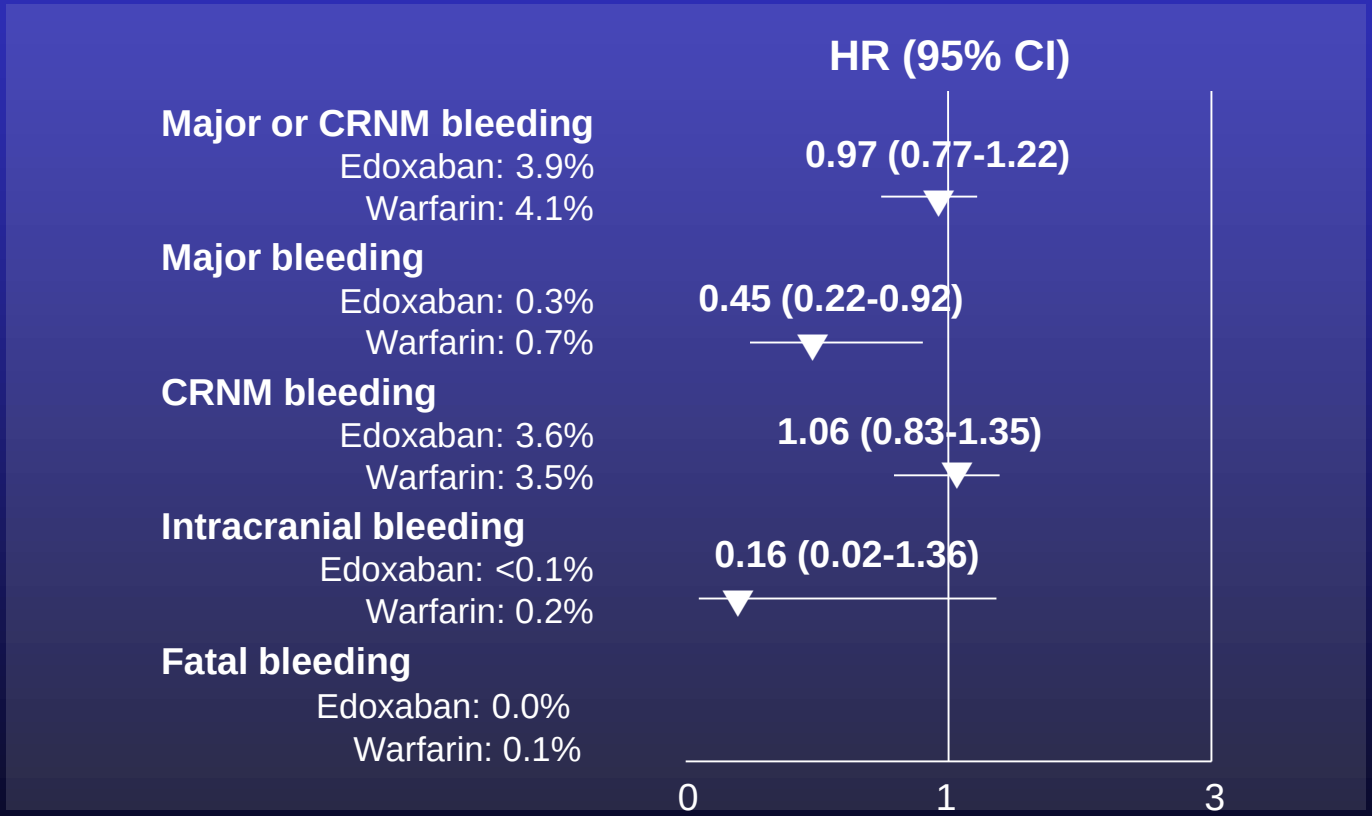
HR 0.78
(95% CI, 0.36-1.72)

VTE = venous thromboembolism; HR = hazard ratio; CI = confidence interval.

Raskob G et al. [Published online 22 March 2016.] *Lancet Haematol.* 2016.

Major Bleeding During Extended Treatment Period (>3 -12 Months)

- Significantly lower incidences of major bleeding were observed with edoxaban vs warfarin during the extended treatment period in the on-treatment analysis



HR = hazard ratio; CI = confidence interval; CRNM = clinically relevant non-major.

Raskob G et al. [Published online 22 March 2016.] *Lancet Haematol.* 2016.

Baseline characteristics - total population

	Edoxaban (N=4118)	Warfarin (N=4122)
Mean age, years (SD)	56 (16)	56 (16)
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N Engl J Med 2013; 369: 1406 - 15

Baseline characteristics - cancer patients

	Edoxaban (N=378)	Warfarin (N= 393)
Mean age, years (SD)	66 (13)	67 (12)
Male gender, n (%)	181 (48)	206 (52)
Qualifying diagnosis, n (%)		
DVT	209 (55)	205 (52)
PE	169 (45)	188 (48)
Cancer status, n		
History of cancer	378	393
Active cancer	109	99
Dose of 30 mg, n (%) (e.g ≤ 60 kg, CrCl≥30 ≤50 ml/min)	97 (26%)	91 (23%)
Duration of treatment, days median (IQ range)	213 (176, 358)	208 (154, 359)

Relative Efficacy by cancer subgroup

	Edoxaban	Warfarin	HR (95% CI)
History of cancer	378	393	
First Recurrent VTE , n (%)	14 (3.7)	28 (7.1)	0.53 (0.28 - 1.00)
Active cancer	109	99	
First Recurrent VTE , n (%)	4 (3.7)	7 (7.1)	0.55 (0.16 -1.85)
No cancer at entry , cancer diagnosed during follow-up	78	97	
First Recurrent VTE , n (%)	13 (16.7)	19 (19.6%)	0.73 (0.36, 1.49)
No cancer at entry or during follow-up	3,658	3,629	
First Recurrent VTE , n (%)	103 (2.8)	99 (2.7)	1.03 (0.78 -1.36)

Safety outcomes – history of cancer

	Edoxaban (N= 378)	Warfarin (N=393)	Hazard ratio (95% CI)	P Value
Bleeding†: First major or clinically relevant non major – no. (%)	**47 (12.4)**	**74 (18.8)**	0.64 (0.45 -0.92)	0.0165
Major bleeding – no. (%)	**10 (2.6)**	**13 (3.3)**		
Fatal	0	2 (0.5)		
Intracranial	0	2 (0.5)		
Non-Fatal	**10 (2.6)**	**11 (2.8)**		
Intracranial	**0**	**5 (1.3)**		
Clinically Relevant Non-Major, no. (%)	**39 (10.3)**	**64 (16.3)**		
Death (all causes)	**40 (10.6%)**	**40 (10.2%)**		

† some patients have more than 1 bleeding

Conclusions
- Subgroups -

- **Right ventricular dysfunction**
  - With indicators of RVD (BNP/CT) heparin/edox. more effective than heparin VKA
- **Dose reduction**
  - Efficacy maintained
  - Less bleeding
- **Extended treatment**
  - Efficacy as warfarin
  - Less major bleeding
- **Cancer-VTE**
  - if VKA is used, edoxaban as effective, but safer