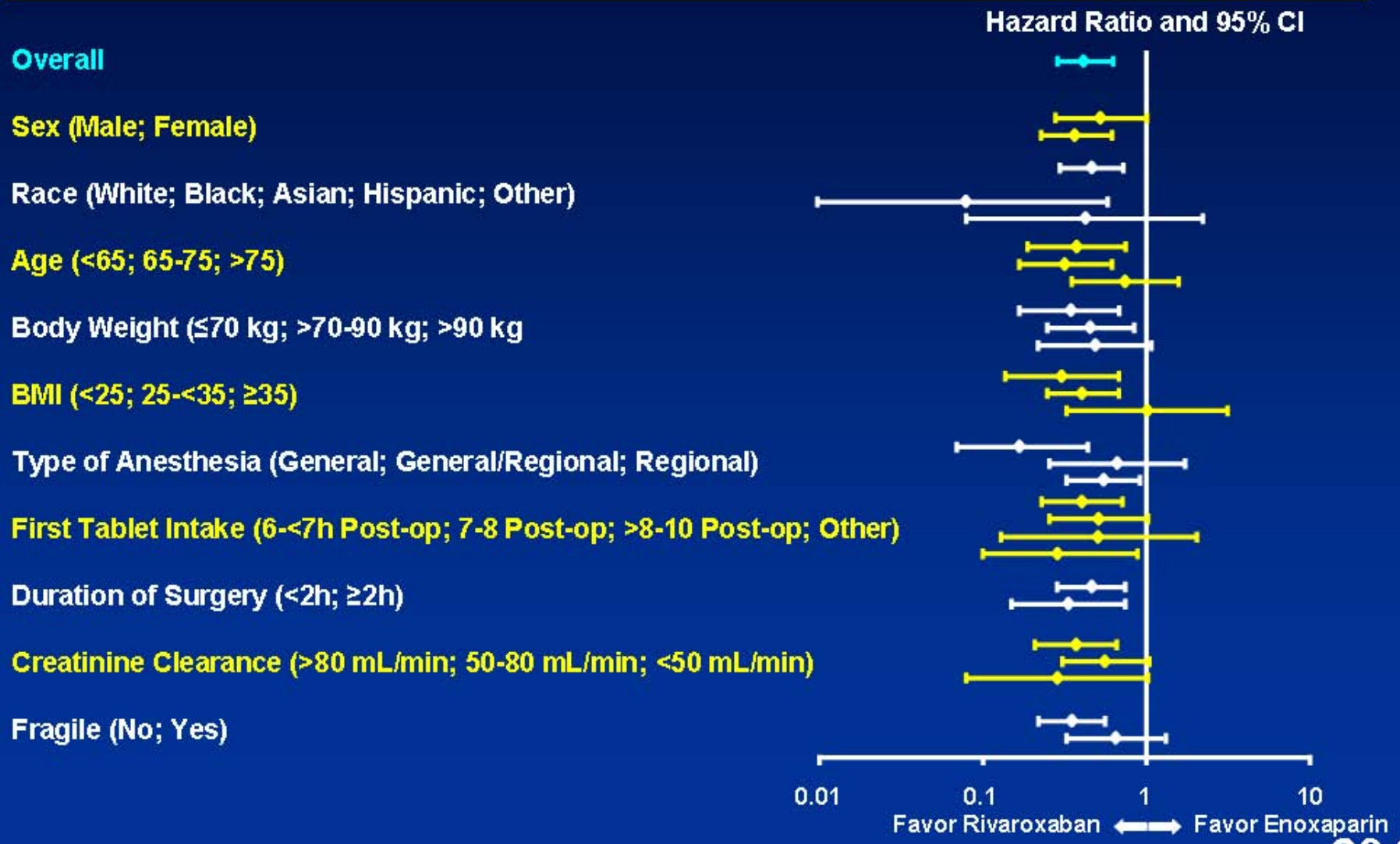
Symptomatic VTE or Death by Subgroup Pooled RECORD 1-4 Safety Population



GS-2

RECORD Studies: Exclusion Criteria

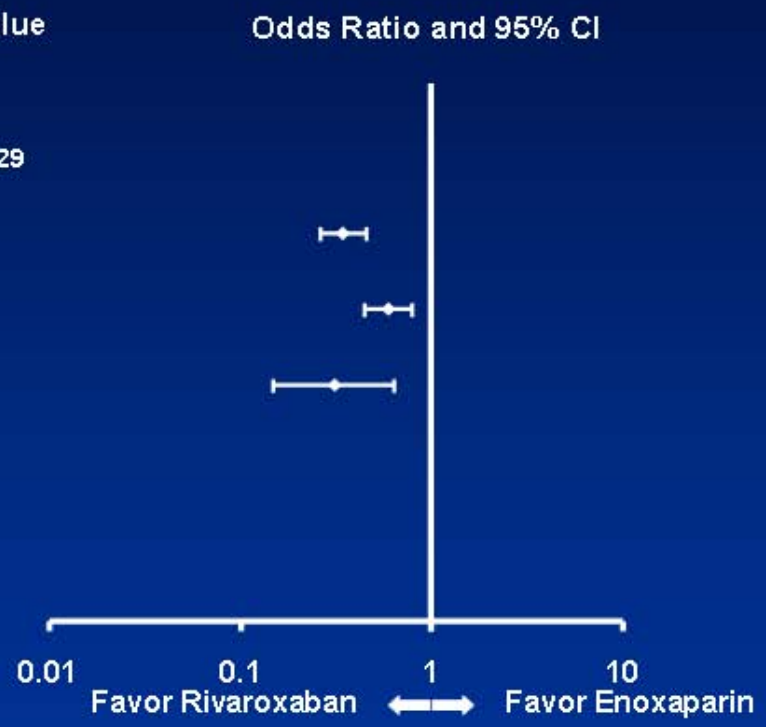
- Active bleeding or high risk of bleeding contraindicating treatment with LMWH
- Contraindication listed in the labeling or conditions precluding subject treatment with enoxaparin requiring dose adjustment (e.g., severe renal impairment)
- Significant liver disease (e.g., acute clinical hepatitis, chronic active hepatitis, cirrhosis)
- Conditions prohibiting bilateral venography (amputation of 1 leg, allergy to contrast media)
- Concomitant use of HIV-protease inhibitors
- Planned intermittent pneumatic compression
- Ongoing oral anticoagulant therapy
- Women who were pregnant, breast-feeding or had no adequate birth control

Analysis Populations RECORD 1-2 (THR)

Subject Population	Rivaroxaban N (%)	Enoxaparin N (%)	Total N (%)
Randomized			
Record 1	2266 (100)	2275 (100)	4541 (100)
Record 2	1252 (100)	1257 (100)	2509 (100)
Safety			
Record 1	2209 (98)	2224 (98)	4433 (98)
Record 2	1228 (98)	1229 (98)	2457 (98)
MITT Valid for Total VTE			
Record 1	1595 (70)	1558 (68)	3153 (69)
Record 2	864 (69)	869 (69)	1733 (69)
MITT Valid for Major VTE			
Record 1	1686 (74)	1678 (74)	3364 (74)
Record 2	961 (77)	962 (77)	1923 (77)
Per Protocol			
Record 1	1537 (68)	1492 (66)	3029 (67)
Record 2	812 (65)	803 (64)	1615 (64)

Total VTE by Creatinine Clearance Record 1-4 MITT Population

	Rivaroxaban n/N(%)	Enoxaparin n/N(%)	OR (95% CI)	p-value
CREATININE CLEARANCE				
RECORD 1-4				0.029
>80 mL/min	84/2532 (3.32)	224/2522 (8.88)	0.35 (0.27, 0.46)	
50-80 mL/min	83/1426 (5.82)	137/1454 (9.42)	0.6 (0.45, 0.81)	
30-<50 mL/min	13/245 (5.31)	34/248 (13.71)	0.32 (0.15, 0.65)	
<30 mL/min	1/15 (6.67)	2/12 (16.67)		



P-value for homogeneity based on LR-test for interaction between treatment group and subgroup in logistic regression.

Analysis Populations RECORD 3-4 (TKR)

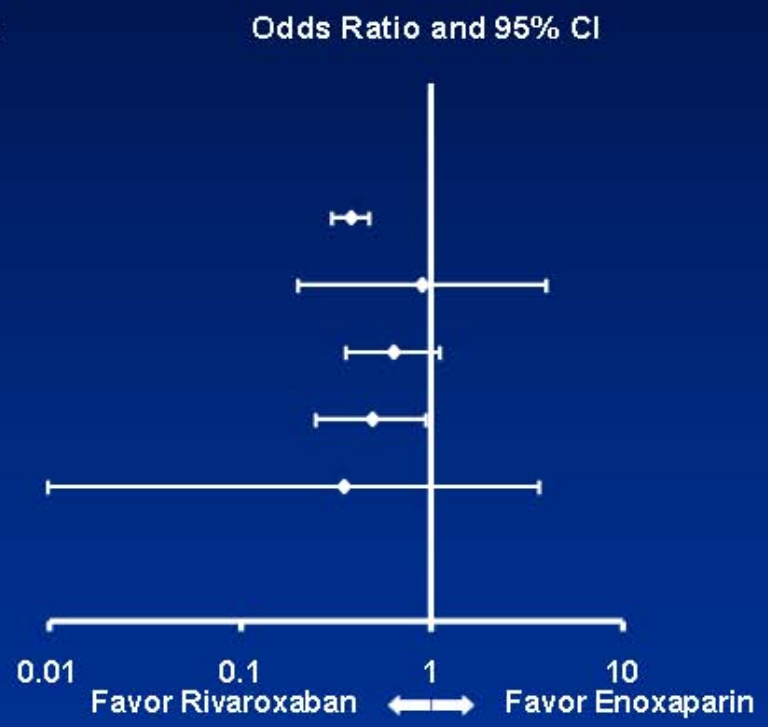
Population Study	Rivaroxaban n (%)	Enoxaparin n (%)	Total n (%)
Randomized			
RECORD 3	1254 (100)	1277 (100)	2531 (100)
RECORD 4	1584 (100)	1564 (100)	3148 (100)
Safety			
RECORD 3	1220 (97)	1239 (97)	2459 (97)
RECORD 4	1526 (96)	1508 (96)	3034 (96)
MITT Valid for Total VTE			
RECORD 3	824 (66)	878 (69)	1702 (67)
RECORD 4	965 (61)	959 (61)	1924 (61)
MITT Valid for Major VTE			
RECORD 3	908 (72)	925 (72)	1833 (72)
RECORD 4	1122 (71)	1112 (71)	2234 (71)
Per Protocol			
RECORD 3	793 (63)	838 (66)	1631 (64)
RECORD 4	864 (55)	878 (56)	1742 (55)

Subject Completion/Withdrawal Information by Treatment RECORD 1-4 Randomized Population

	Rivaroxaban N=6356 n(%)	Enoxaprin N=6373 n(%)	Total N=12729 n(%)
Completed Treatment	5679 (89.35)	5638 (88.47)	11371 (88.91)
Premature Termination	677 (10.65)	735 (11.53)	1412 (11.09)
Adverse Event	224 (3.52)	244 (3.03)	468 (3.68)
Clinical Endpoint Reached	23 (0.36)	59 (0.93)	82 (0.64)
Consent Withdrawn	289 (4.55)	273 (4.28)	562 (4.42)
Investigator Decision, Not Protocol Driven	10 (0.16)	15 (0.24)	25 (0.20)
Lost to Follow-Up	8 (0.13)	15 (0.24)	23 (0.18)
Non-compliant with Study Medication	40 (0.63)	28 (0.44)	68 (0.53)
Protocol Violation	78 (1.23)	91 (1.43)	169 (1.33)
Other	5 (0.07)	10 (0.14)	15 (0.10)

Total VTE by Race
Record 1-4 MITT Population

	Rivaroxaban n/N(%)	Enoxaparin n/N(%)	OR (95% CI)	p-value
RACE				
RECORD 1-4				0.191
White	127/3401 (3.73)	307/3366 (9.12)	0.38 (0.3, 0.47)	
Black	5/85 (5.88)	5/79 (6.33)	0.89 (0.2, 4)	
Asian	25/399 (6.27)	38/401 (9.48)	0.64 (0.36, 1.12)	
Hispanic	17/229 (7.42)	36/255 (14.12)	0.5 (0.25, 0.94)	
Other	1/18 (5.56)	5/40 (12.50)	0.35 (0.01, 3.67)	

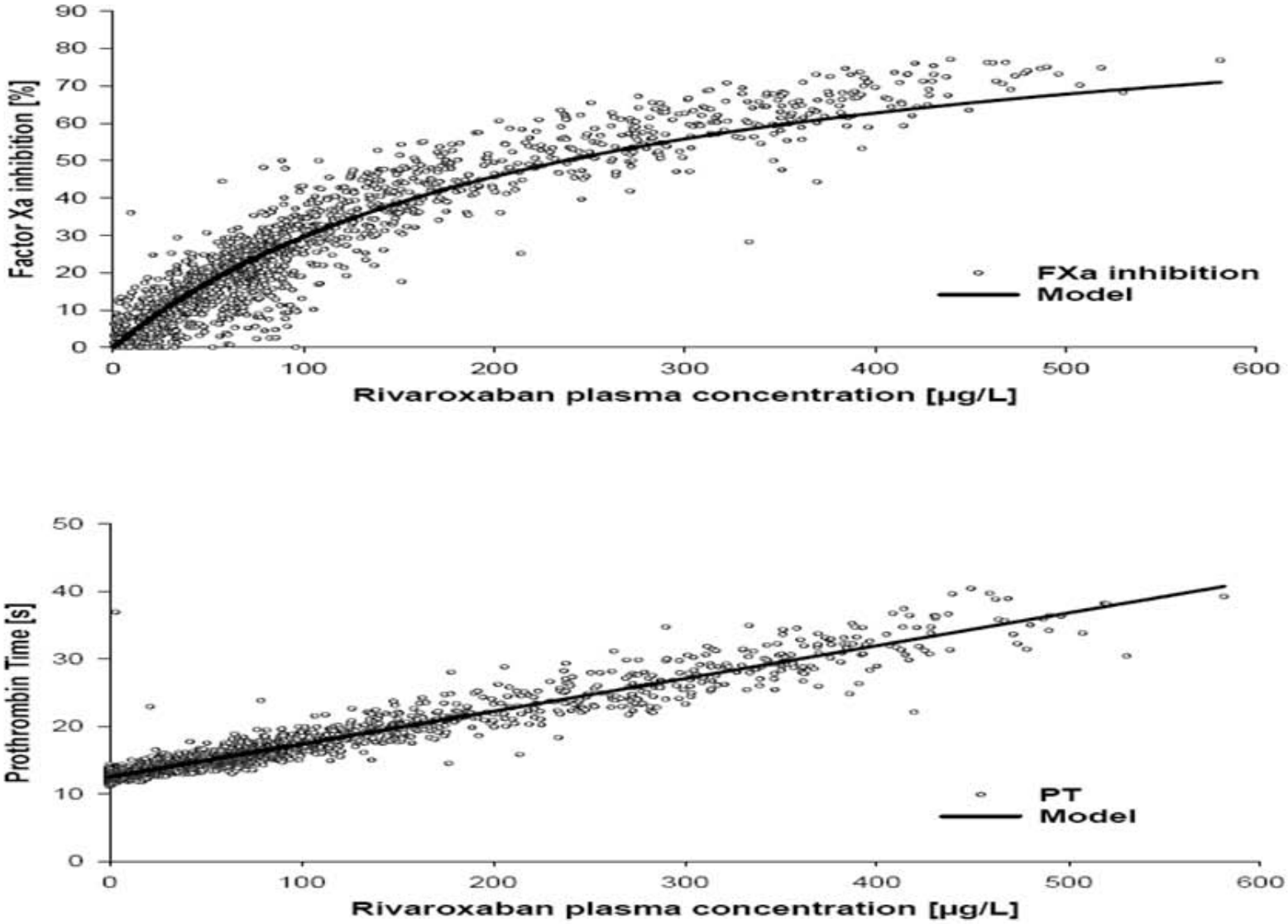


P-value for homogeneity based on LR-test for interaction between treatment group and subgroup in logistic regression.

Sensitivity Analyses for Total VTE

- Application of various scenarios for patients with inadequate assessment of thromboembolism (protocol-specified methods)
- Expansion of MITT population and inclusion of investigator reported assessments
- Assessment of treatment effect by center validity rates
- Analysis of a binary composite endpoint with missing data in components (Quan et al – Statistics in Medicine 2007; 26:4703-4718)
- Derivation of lowest Total VTE rate in rivaroxaban invalid population needed to negate superiority, for a range of rates in the enoxaparin invalid population

Figure 3-10: Correlation Between Rivaroxaban Plasma Concentrations and Factor Xa Inhibition (top) or PT (bottom) in Healthy Subjects Following Multiple Dosing (Phase 1)



r values of 0.97 for inhibition of Factor Xa activity, 0.98 for PT, when the Neoplastin® assay was used. The median steady-state peak plasma concentration of rivaroxaban in patients is estimated to be 125 µg/L (with maximum C_{max} of 196 µg/L).

Table 5-3: Incidence of Total VTE, Major VTE, Major Bleeding and Any Bleeding Events by Dose Group (Studies 10942, 10944, and 10945)

Outcome	RIVA 2.5 mg bid n/N (%)	RIVA 5 mg bid n/N (%)	RIVA 10 mg bid n/N (%)	RIVA 20 mg bid n/N (%)	RIVA 30 mg bid n/N (%)	ENOX 40 mg qd/ 30 mg bid n/N (%)
Total VTE (10944/10945) (PP population)	36/167 (21.6%)	38/166 (22.9%)	26/161 (16.1%)	38/156 (24.4%)	17/88 (19.3%)	49/176 (27.8%)
Total VTE (10942/10944/10945) (PP population)	50/230 (21.7%)	53/229 (23.1%)	37/216 (17.1%)	44/215 (20.5%)	25/134 (18.7%)	67/283 (23.7%)
Major VTE (10944/10945) (PP population)	5/167 (3.0%)	4/166 (2.4%)	5/161 (3.1%)	5/156 (3.2%)	1/88 (1.1%)	8/176 (4.5%)
Major VTE (10942/10944/10945) (PP population)	12/230 (5.2%)	9/229 (3.9%)	7/216 (3.2%)	5/215 (2.3%)	3/134 (2.2%)	13/283 (4.6%)
Postoperative Major bleeding event (10944/10945) (safety population)	2/232 (0.9%)	3/238 (1.3%)	5/236 (2.1%)	9/232 (3.9%)	10/143 (7.0%)	4/236 (1.7%)
Postoperative Major bleeding event (10942/10944/10945) (safety population)	2/308 (0.6%)	5/318 (1.6%)	7/304 (2.3%)	14/309 (4.5%)	18/217 (8.3%)	4/398 (1.0%)
Any postoperative bleeding event (10944/10945) (safety population)	15/232 (6.5%)	23/238 (9.7%)	23/236 (9.7%)	42/232 (18.1%)	27/143 (18.9%)	16/236 (6.8%)
Any postoperative bleeding event (10942/10944/10945) (safety population)	22/308 (7.1%)	30/318 (9.4%)	30/304 (9.9%)	56/309 (18.1%)	45/217 (20.7%)	27/398 (6.8%)

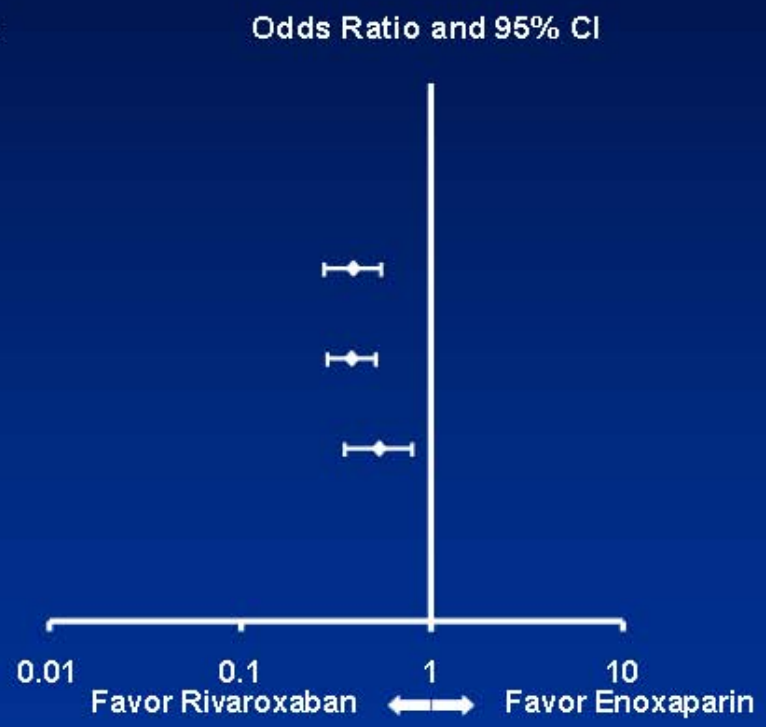
Key: bid= twice-daily; ENOX = enoxaparin; qd = once daily; RIVA = rivaroxaban

Total VTE Stratified by Validity Tercile Pooled RECORD 1-4 MITT Population

Validity Tercile Treatment	Study Pool	Incidence Total VTE (%)	Odds Ratio to Enoxaparin		Interaction p value
			Point Estimate	95% Confidence Interval	
Lower Tercile					
Rivaroxaban	RECORD 1-4	5.28	0.50	[0.37, 0.68]	0.196
Enoxaparin	RECORD 1-4	10.12			
Middle Tercile					
Rivaroxaban	RECORD 1-4	3.31	0.33	[0.23, 0.48]	
Enoxaparin	RECORD 1-4	9.19			
Upper Tercile					
Rivaroxaban	RECORD 1-4	4.20	0.44	[0.31, 0.61]	
Enoxaparin	RECORD 1-4	8.94			

Total VTE by Age
Record 1-4 MITT Population

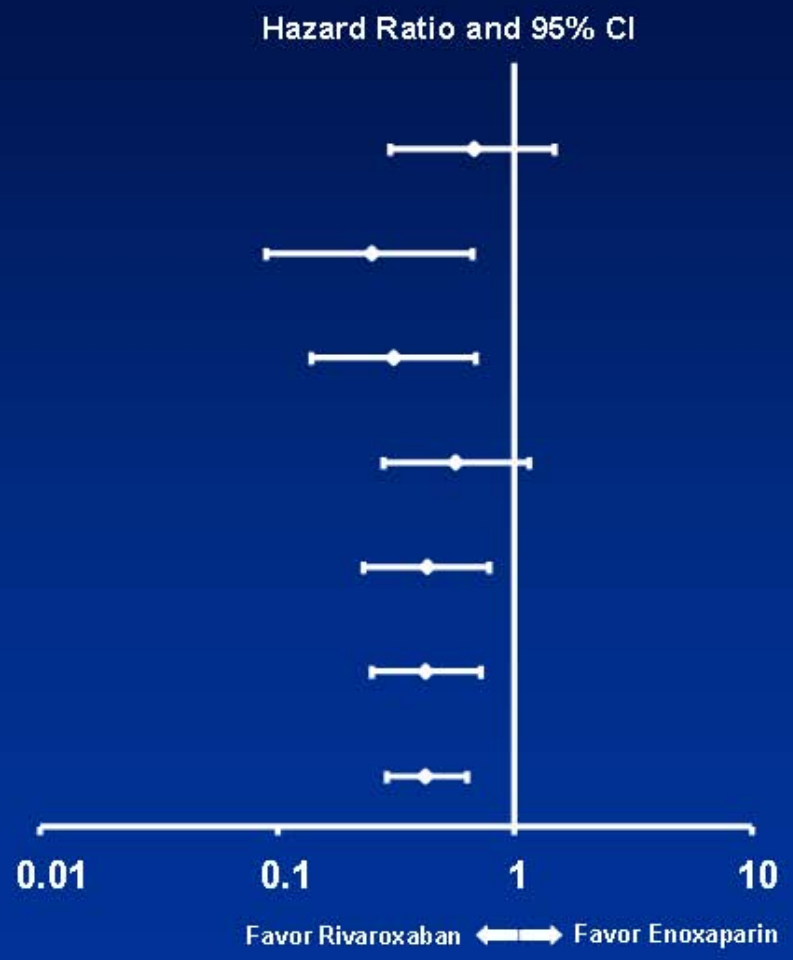
	Rivaroxaban n/N(%)	Enoxaparin n/N(%)	OR (95% CI)	p-value
AGE				
RECORD 1-4				0.462
<65	57/2081 (2.74)	136/2041 (6.66)	0.4 (0.28, 0.55)	
65-75	76/1584 (4.80)	188/1646 (11.42)	0.39 (0.29, 0.52)	
>75	48/583 (8.23)	78/577 (13.52)	0.54 (0.36, 0.81)	



P-value for homogeneity based on LR-test for interaction between treatment group and subgroup in logistic regression.

Symptomatic VTE or Death Treatment Phase By Study and Pooled Safety Population

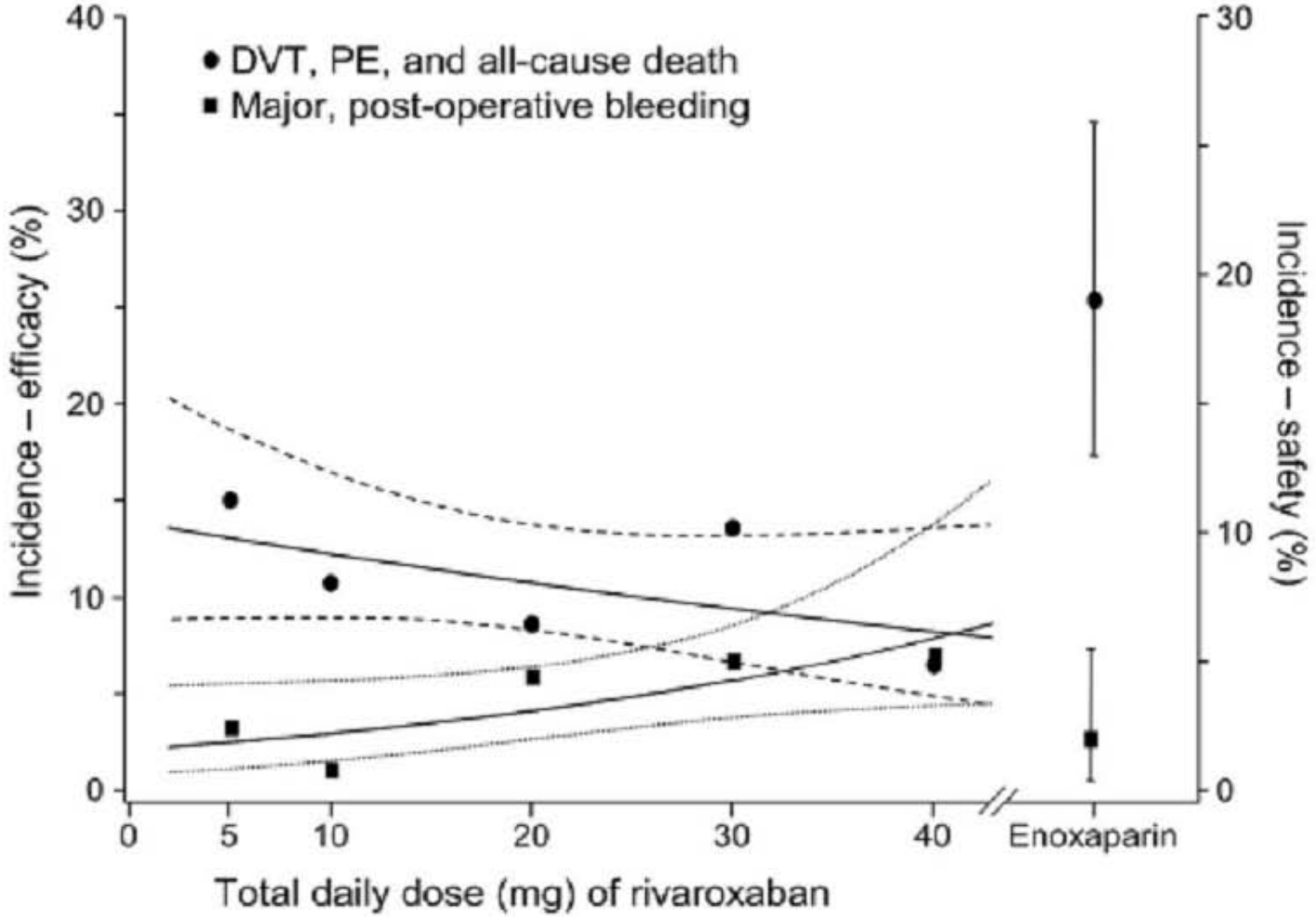
	Rivaroxaban n/N (%)	Enoxaparin n/N (%)	HR 95% CI
RECORD 1	10/2209 (0.45)	15/2224 (0.67)	0.67 (0.30, 1.48)
RECORD 2	5/1228 (0.41)	20/1229 (1.63)	0.25 (0.09, 0.66)
RECORD 3	8/1220 (0.66)	26/1239(2.1)	0.31 (0.14, 0.68)
RECORD 4	12/1526 (0.79)	21/1508 (1.39)	0.56 (0.28, 1.15)
Pooled R 1-2	15/3437 (0.44)	35/3453 (1.01)	0.43 (0.23, 0.78)
Pooled R 3-4	20/2746 (0.73)	47/2747 (1.71)	0.42 (0.25, 0.72)
Pooled R 1-4	35/6183 (0.57)	82/6200 (1.32)	0.42 (0.29, 0.63)



Wound Complication Adverse Events Treatment and Follow-up Pooled RECORD 1-4, Safety Population

Endpoint Studies	Rivaroxaban N =6183 n (%)	Enoxaparin N =6200 n (%)
Surgical Wound Complications (Any event)	379 (6.13)	321 (5.18)
Surgical wound complications, infectious	100 (1.62)	98 (1.58)
Surgical wound complications, non-infectious	303 (4.9)	234 (3.77)

Figure 5-5: Post-Operative Major Bleeding and Total VTE: Observed and Predicted Incidence With Once Daily Dosing (Study 11527) -Safety Population



Symptomatic VTE or Death Sensitivity Analyses Pooled RECORD 1-4 Safety Population

Duration Pool	Rivaroxaban N=6183 n (%)	Enoxaparin N=6200 n (%)	Hazard Ratio Pt Estimate	Hazard Ratio 95% CI	p value
Total Treatment duration (primary)	35 (0.57)	82 (1.32)	0.42	(0.29, 0.63)	<0.001
Treatment and follow up	50 (0.81)	101 (1.63)	0.49	(0.35, 0.69)	<0.001
Day 12 +/- 2	29 (0.47)	60 (0.97)	0.48	(0.31, 0.75)	0.001
Active Control	32 (0.52)	67 (1.08)	0.48	(0.31, 0.73)	<0.001

Literature Demographics Comparison

Parameter	THR		TKR	
	RECORD N=6890	GLORY N=6639	RECORD N=5493	GLORY N=8236
Median age (IQR)	64 (55, 72)	68 (57, 75)	67 (60, 73)	70 (63, 76)
Female (%)	55	59	66	66
Median BMI (IQR)	27 (24, 30)	27 (25, 31)	29.5 (26, 33)	30 (27, 35)
BMI >30 (%)	27	32	46	51

Regional Comparisons
THR and TKR – GLORY Registry

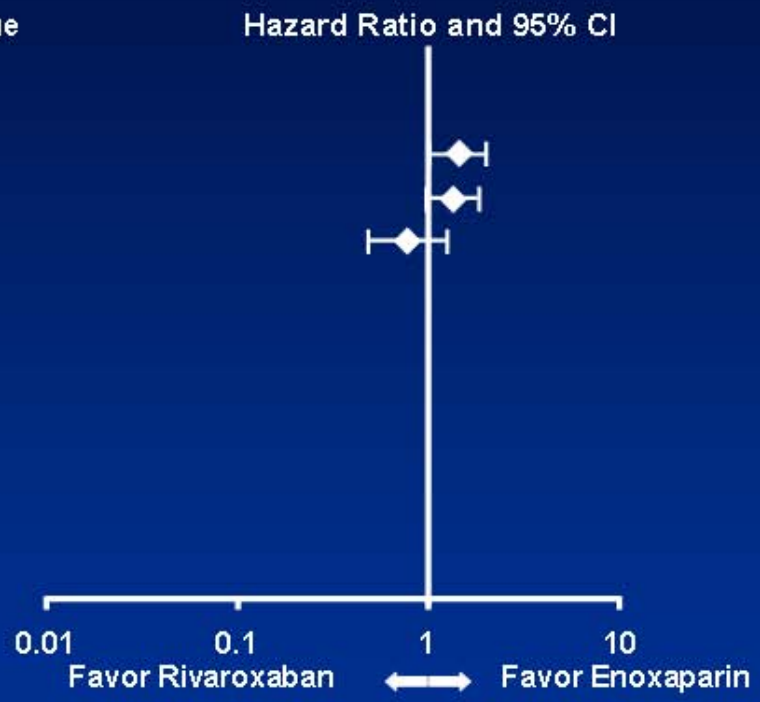
PARAMETER	THR		TKR	
	US N=1227	Other N=2723	US N=2065	Other N=2145
Median age, years (IQR)	68 (56, 76)	67 (56, 73)	69 (61, 76)	71 (65, 76)
Female, %	56	61	62	72
Median BMI (IQR)	28 (25, 33)	27 (24, 30)	31 (27, 36)	29 (26, 33)
Median length of hospital stay, days (IQR)	3 (3, 4)	10 (7, 15)	4 (3, 4)	10 (7, 14)
Type anesthesia, %				
General	64	34	37	28
Neuraxial only	33	60	57	61
Surgery < 2 hours, %	78	82	88	84

Efficacy Endpoints RECORD 1 and 4

	Riva n/N(%)	Enox n/N(%)	Odds/Hazard ratio (95%CI)
Total VTE			
	85/2560 (3.32)	155/2517(6.16)	0.52 (0.39, 0.69)
Major VTE			
	17/2808 (0.61)	55/2790 (1.97)	0.30 (0.16, 0.53)
Symptomatic VTE or death			
Treatment phase	22/3735(0.59%)	36/3732 (0.96%)	0.61 (0.36, 1.03)
Treatment and follow-up	31/3735(0.83%)	46/3732 (1.23%)	0.66 (0.42, 1.03)
Plus RECORD 2 active therapy phase	24/4963(0.48%)	41/4961 (0.83%)	0.58 (0.35, 0.96)

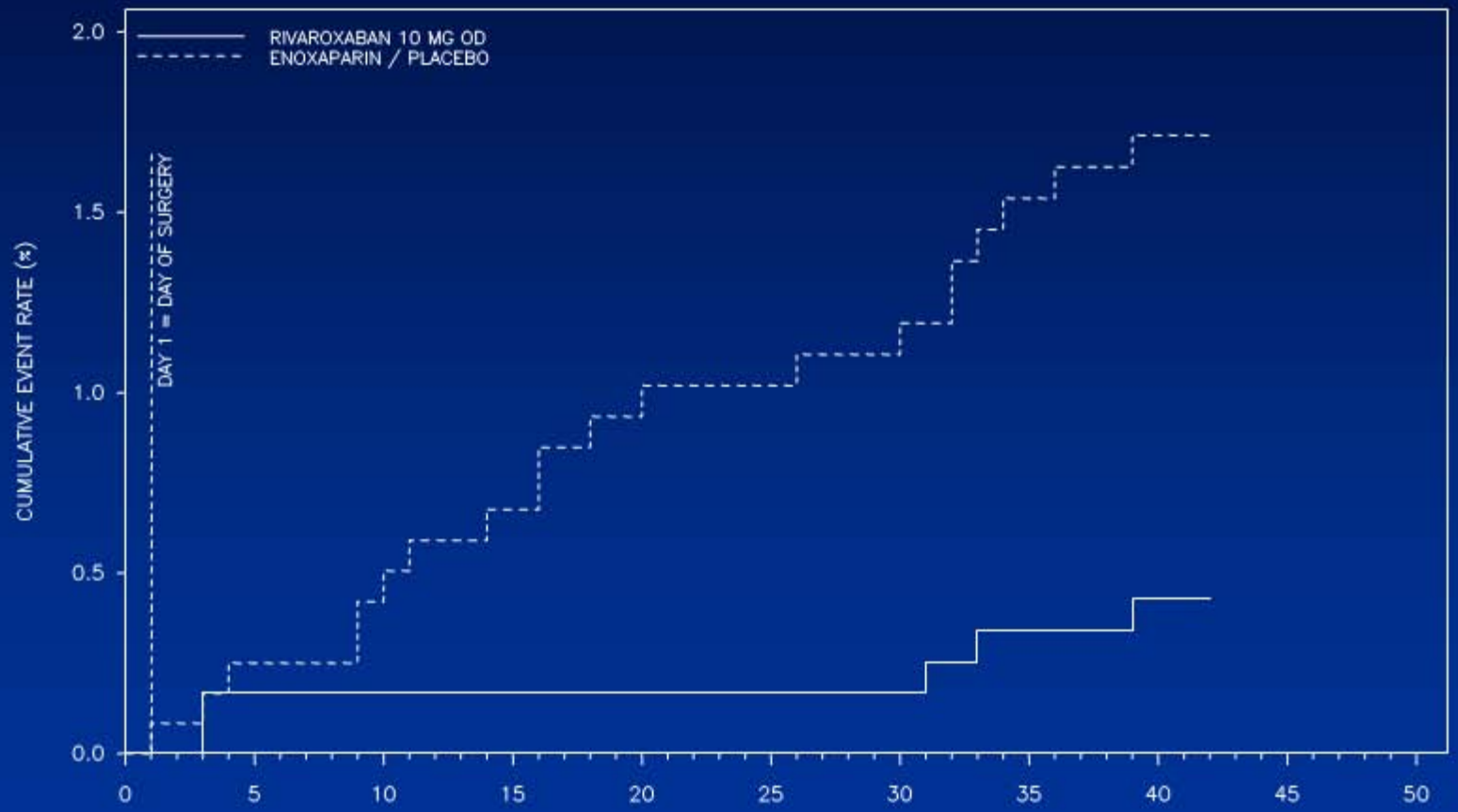
Major or Non-major Bleeding by Age
RECORD 1-4 Safety Population

	Rivaroxaban n/N (%)	Enoxaparin n/N (%)	HR (95% CI)	p-value
AGE				
RECORD 1-4				0.1
<65	78/2915 (2.68)	54/2905 (1.86)	1.44 (1.02, 2.04)	
65-75	89/2354 (3.78)	66/2381 (2.77)	1.35 (0.98, 1.86)	
>75	30/914 (3.28)	38/914 (4.16)	0.78 (0.48, 1.26)	



P-value for homogeneity based on LR-test for interaction between treatment group and subgroup in logistic regression.

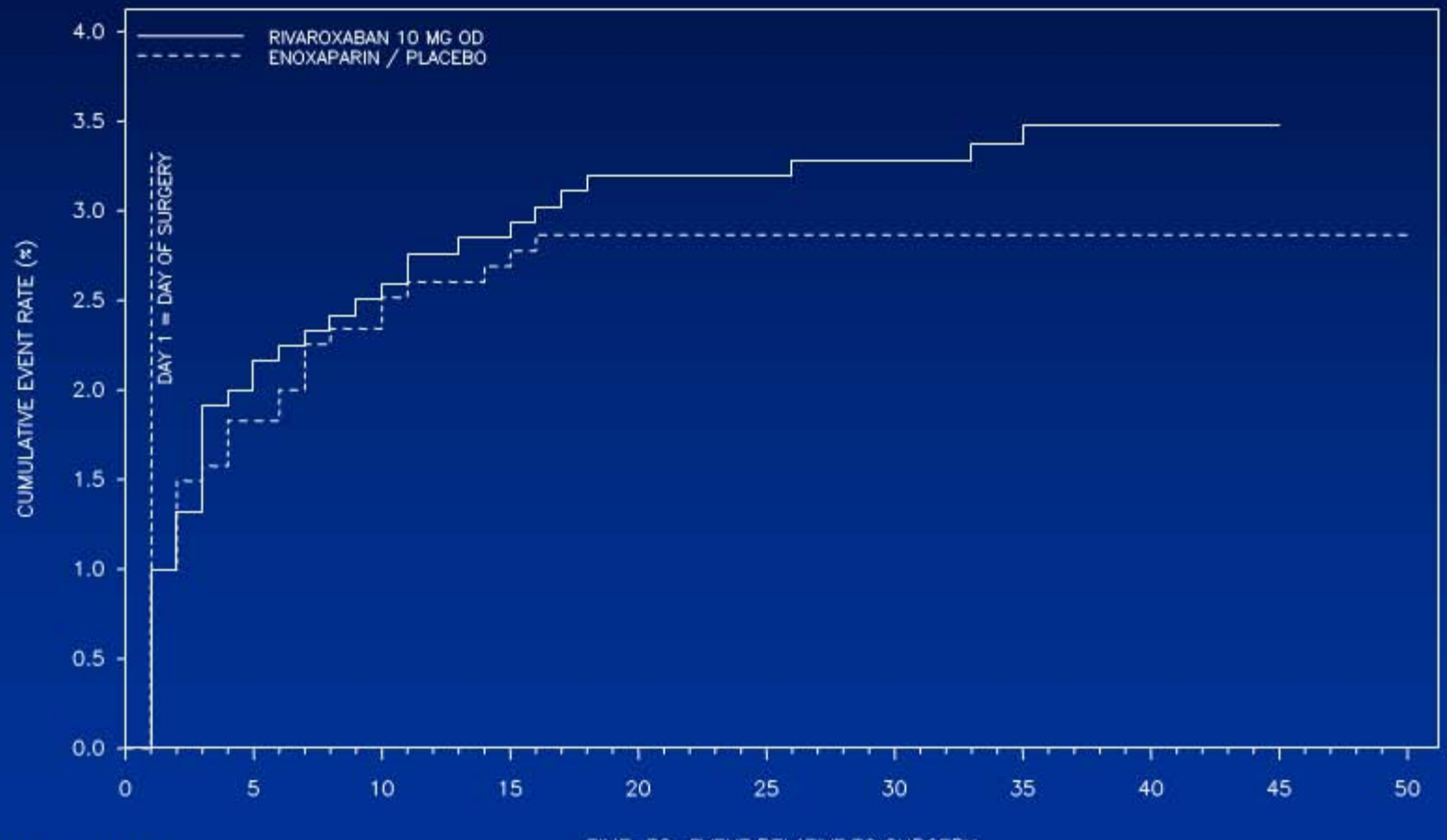
Symptomatic VTE or Death
RECORD 2 Safety Population



NUMBER OF SUBJECTS AT RISK

RIVAROXABAN	N=1228	N=1191	N=1180	N=1172	N=1166	N=1162	N=1160	N=1140	N=1116	N=0	N=0
ENOXAPARIN	N=1229	N=1184	N=1172	N=1158	N=1152	N=1147	N=1145	N=1133	N=1110	N=0	N=0

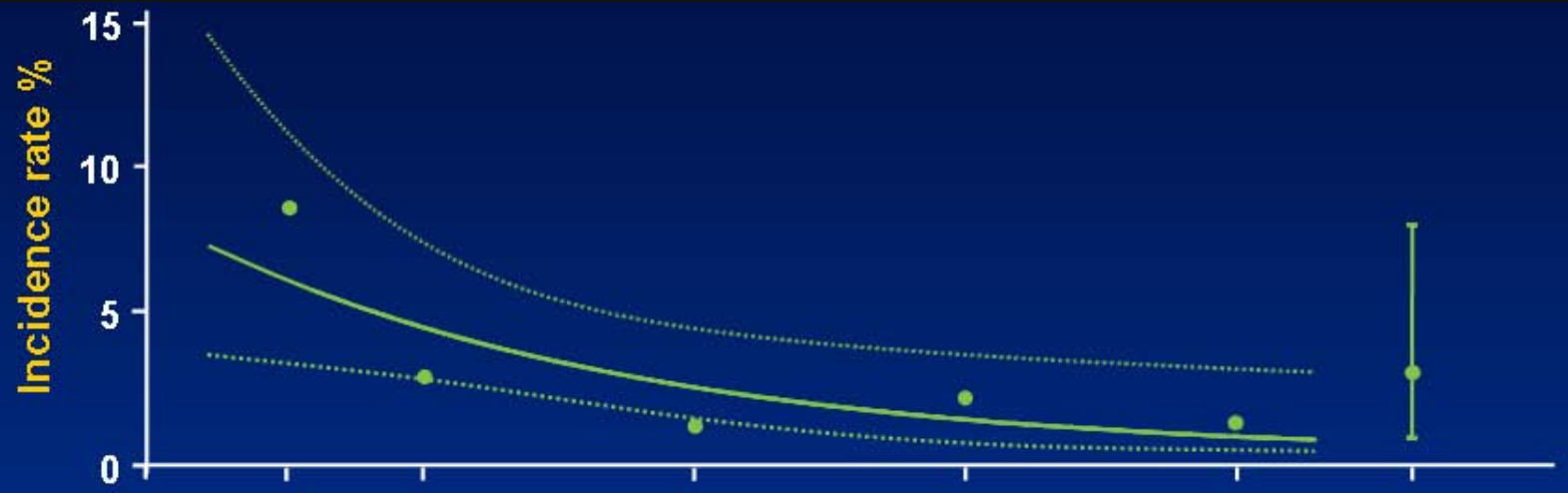
Treatment Emergent Major or Non-Major Clinically Relevant Bleeding RECORD 2 Safety Population



NUMBER OF SUBJECTS AT RISK

RIVAROXABAN	N=1228	N=1162	N=1134	N=1118	N=1104	N=1099	N=1092	N=963	N=149	N=1	N=0
ENOXAPARIN	N=1229	N=1156	N=1126	N=1111	N=1095	N=1083	N=1074	N=949	N=157	N=3	N=1

Phase 2 Study 11527- Once Daily Dosing Major VTE – Dose Related



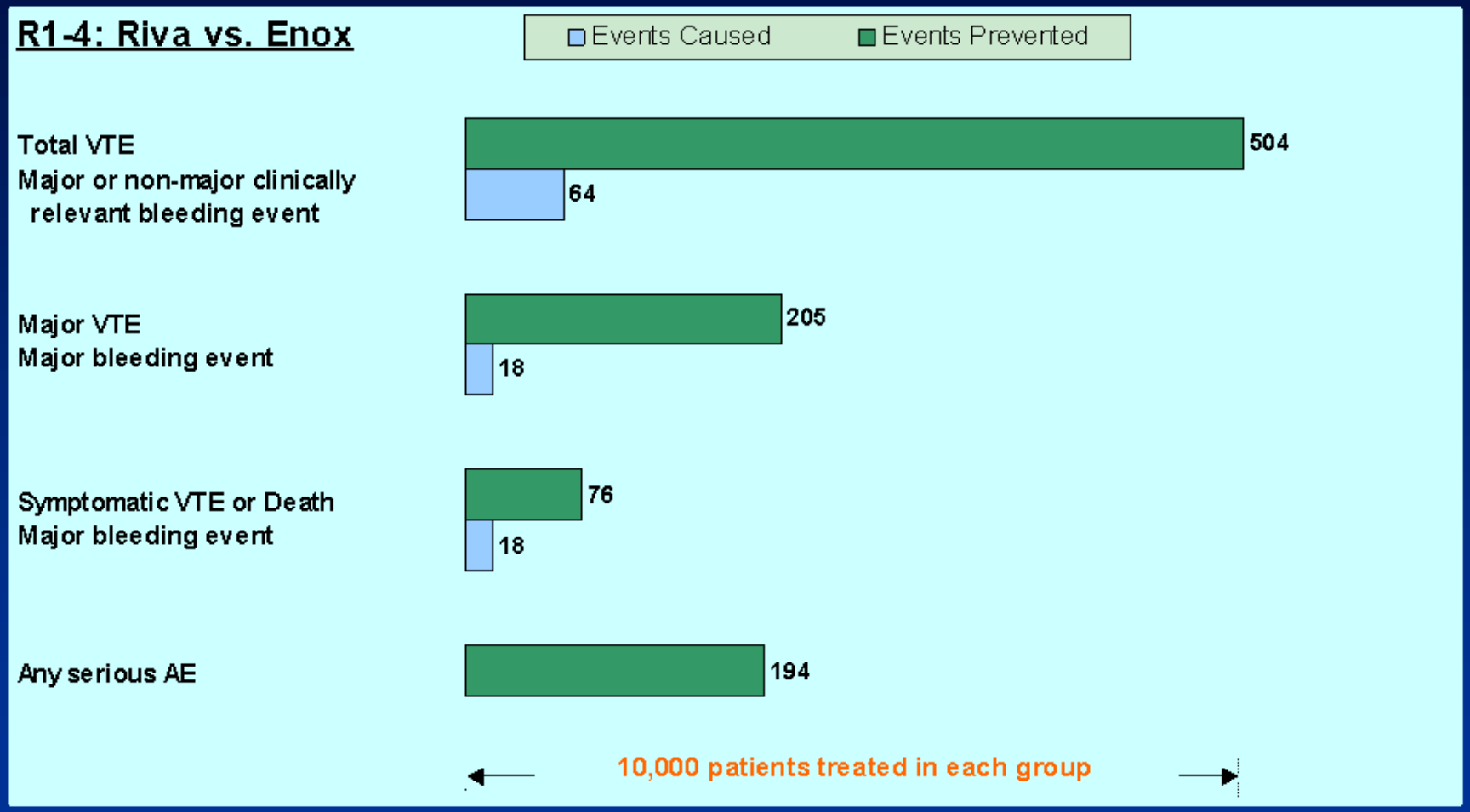
	Total daily dose of Rivaroxaban					Enox
	5 mg (n=94)	10 mg (n=113)	20 mg (n=106)	30 mg (n=104)	40 mg (n=94)	40 mg (n=107)
n	8	3	1	2	1	3
%	**8.5**	**2.7**	**0.9**	**1.9**	**1.1**	**2.8**
95% CI	3.7, 16.1	0.6, 7.6	0.0, 5.1	0.2, 6.8	0.0, 5.8	0.6, 8.0

Per-protocol population, n=618. p=0.0072 for dose trend

HIP od

RECORD 1 – 4: Excess Number of Events

Efficacy Endpoints and Treatment-Emergent AEs of Interest



All values are based on the safety population except Total and Major VTE, which are based on the MITT population.

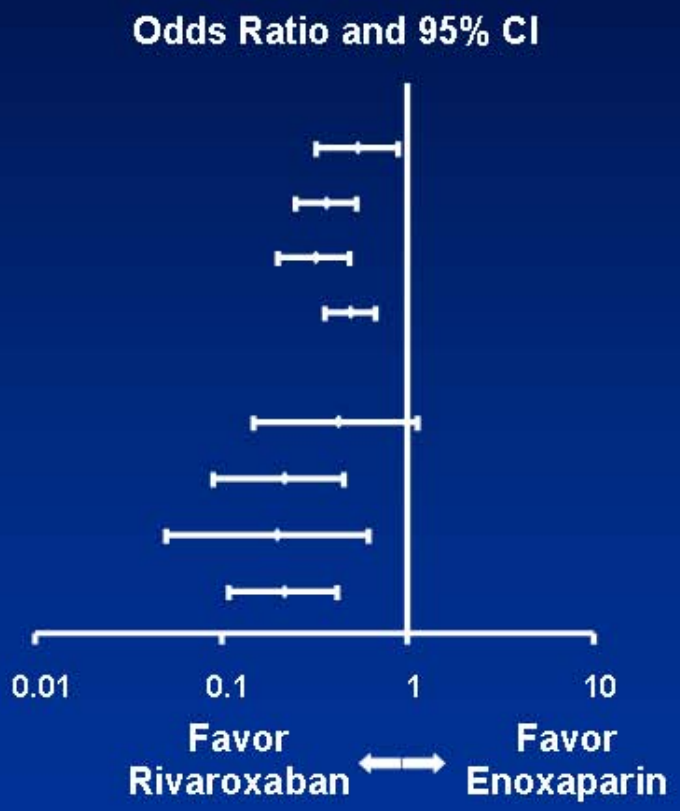
Investigator Reported Bleeding, DVT, and PE Adverse Events (Studies 10942, 10944, 10945, and 11527 Pooled, Safety Population)

Incidence of	RIVA 5 mg TDD (N=436)	RIVA 10 mg TDD (N=460)	RIVA 20 mg TDD (N=443)	RIVA 30 mg TDD (N=230)	RIVA 40 mg TDD (N=446)	RIVA 60 mg TDD (N=217)	RIVA Total (N=2232)	ENOX Total (N=555)
Any treatment-emergent bleeding event	44 (10.1%)	52 (11.3%)	56 (12.6%)	50 (21.7%)	101 (22.6%)	65 (30.0%)	368 (16.5%)	64 (11.5%)
Any treatment-emergent DVT or pulmonary embolism events	46 (10.6%)	36 (7.8%)	33 (7.4%)	9 (3.9%)	36 (8.1%)	17 (7.8%)	177 (7.9%)	66 (11.9%)

Key: DVT = deep vein thrombosis; ENOX = enoxaparin; RIVA = rivaroxaban; TDD = total daily dose

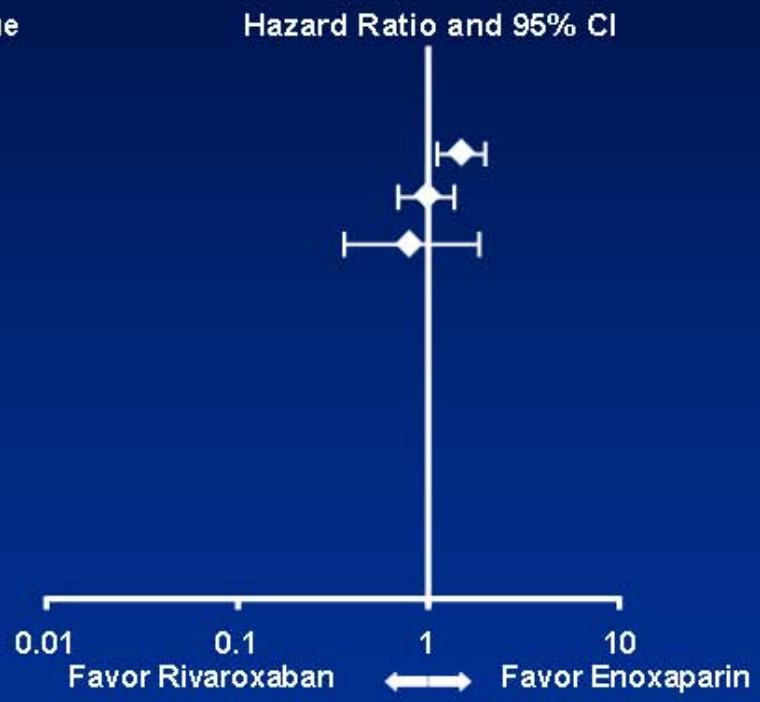
Efficacy and Corresponding Odds Ratio (95%CI) by 4 Regions - RECORD 1-4

	Rivaroxaban n/N(%)	Enoxaparin n/N(%)	OR (95% CI)
Total VTE			
US	27/565 (4.78)	49/572 (8.57)	0.54 (0.32, 0.89)
Western Europe	48/1498 (3.20)	122/1502 (8.12)	0.37 (0.25, 0.53)
Eastern Europe	34/954 (3.56)	88/927 (9.49)	0.32 (0.20, 0.49)
All Other Countries	72/1231 (5.85)	143/1263 (11.32)	0.50 (0.36, 0.68)
Major VTE			
US	7/620 (1.13)	16/617 (2.59)	0.43 (0.15, 1.12)
Western Europe	9/1591 (0.57)	40/1595 (2.51)	0.22 (0.09, 0.46)
Eastern Europe	4/1023 (0.39)	19/1000 (1.90)	0.20 (0.05, 0.62)
All Other Countries	12/1443 (0.83)	53/1465 (3.62)	0.22 (0.11, 0.42)



Major or Non-major Bleeding by Creatinine Clearance RECORD 1-4 Safety Population

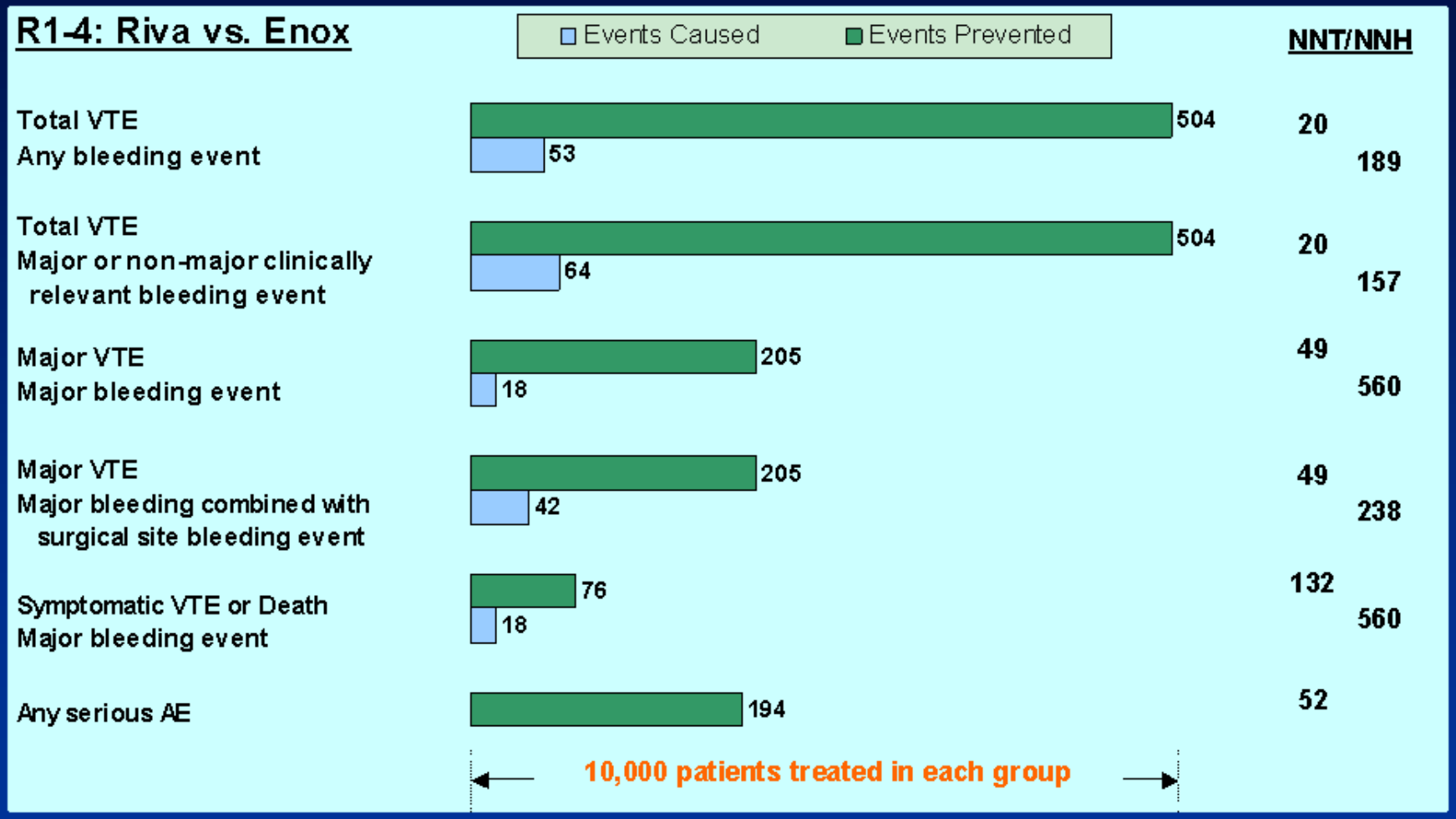
	Rivaroxaban n/N (%)	Enoxaparin n/N (%)	HR (95% CI)	p-value
CREATININE CLEARANCE				
RECORD 1-4				0.164
>80 mL/min	116/3617 (3.21)	77/3598 (2.14)	1.5 (1.12, 2)	
50-80 mL/min	66/2093 (3.15)	67/2114 (3.17)	0.99 (0.7, 1.39)	
30-50 mL/min	10/380 (2.63)	13/409 (3.18)	0.81 (0.36, 1.85)	
<30 mL/min	3/29 (10.34)	1/28 (3.57)		



P-value for homogeneity based on LR-test for interaction between treatment group and subgroup in logistic regression.

RECORD 1 – 4: Excess Number of Events, NNT/NNH

Efficacy Endpoints and Treatment-Emergent AEs of Interest



All values are based on the safety population except Total and Major VTE, which are based on the MITT population.

Modeled Impact of Combined Renal Impairment and Concomitant Use of CYP3A4 Inhibitor: AUC Fold Increase

	Normal renal function CRCL > 80 mL/min	Mild renal Impairment CRCL 50-79 mL/min	Moderate renal Impairment CRCL 30-49 mL/min	Severe renal Impairment CRCL < 30 mL/min
No CYP3A4 Inhibition	1.00	1.49	1.66	1.79
Weak (30%) CYP3A4 Inhibition	1.09	1.64	1.84	1.99
Moderate (50%) CYP3A4 Inhibition	1.15	1.75	1.98	2.15
Strong (90%) CYP3A4 Inhibition	1.32	2.04	2.35	2.57

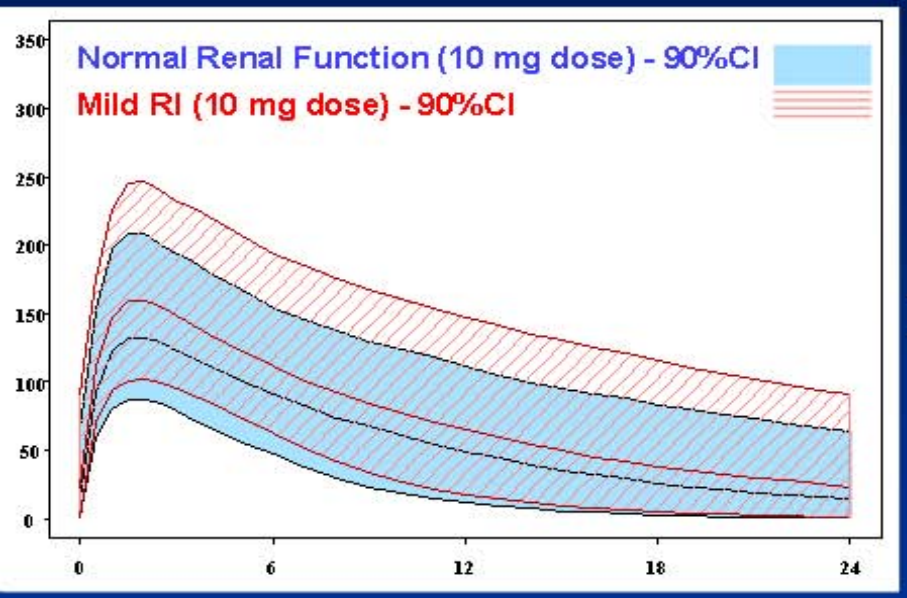
Frequency of Combined Renal Impairment and Concomitant Use of CYP3A4 Inhibitor Pooled RECORD 1-4 Safety Population

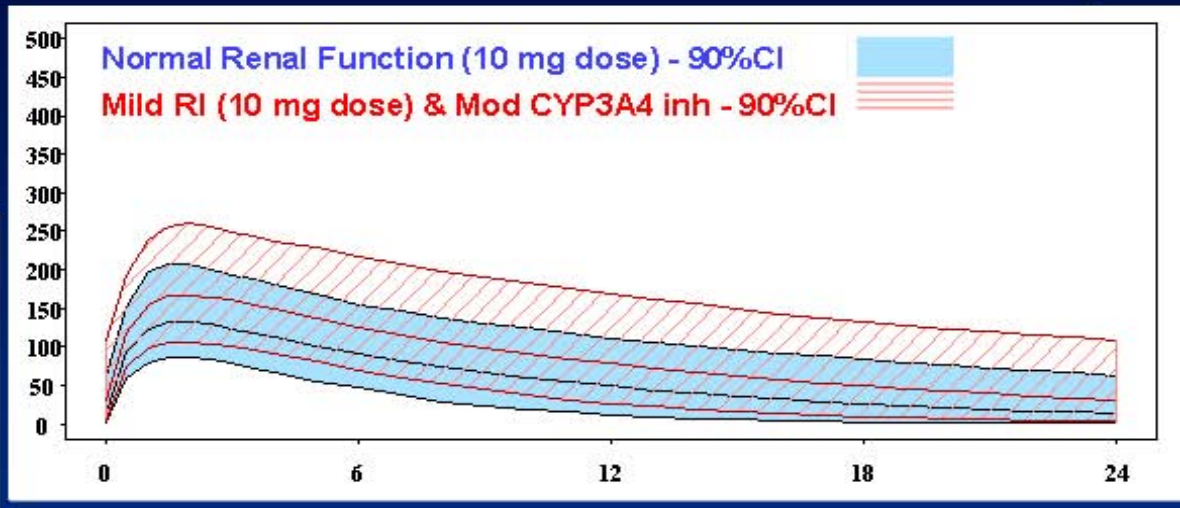
Total N=12268	Normal renal function CRCL > 80 mL/min	Mild renal Impairment CRCL 50-79 mL/min	Moderate renal Impairment CRCL 30-49 mL/min	Severe renal Impairment CRCL < 30 mL/min
No CYP3A4 Inhibition	54.9% (6739)	31.6% (3878)	5.8% (717)	0.4% (52)
Weak CYP3A4 Inhibition (30%)	1.7% (208)	0.9% (107)	0.2% (20)	<0.1% (1)
Moderate CYP3A4 Inhibition (50%)	2.0% (252)	1.7% (209)	0.4% (50)	<0.1% (4)
Strong CYP3A4 Inhibition (90%)	0.1% (16)	0.1% (13)	<0.1% (2)	<0.1% (0)

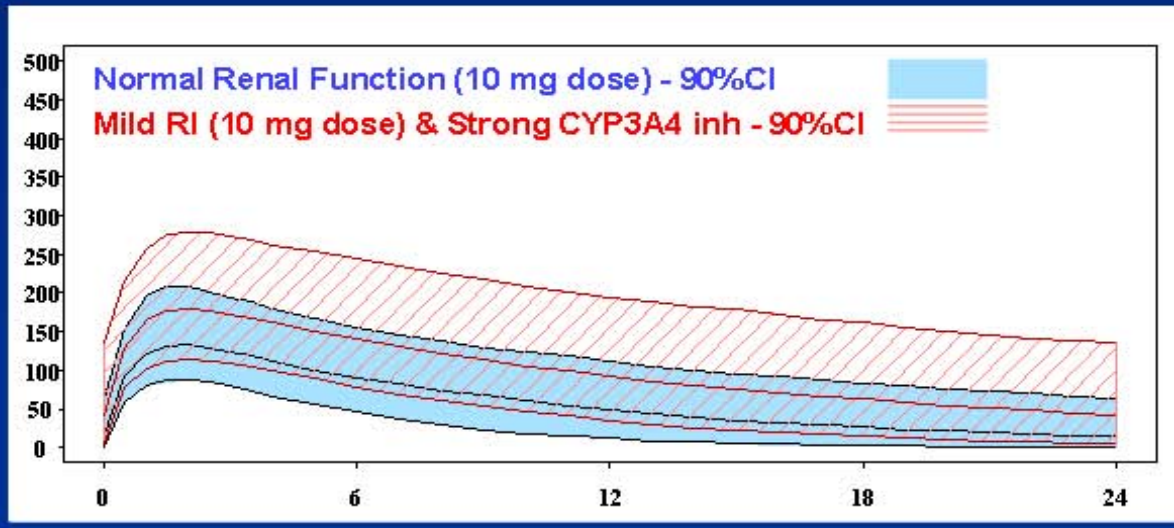
VTE Committee Death Components Summary Treatment and Follow up Phases RECORD 1-4 Safety Population

Endpoint	Rivaroxaban N = 6183 n / N (%)	Enoxaparin N = 6200 n / N (%)
Any death	13 (0.21)	25 (0.40)
VTE related	1 (0.02)	3 (0.05)
Not VTE related	7 (0.11)	11 (0.18)
Unexplained	5 (0.08)	11 (0.18)

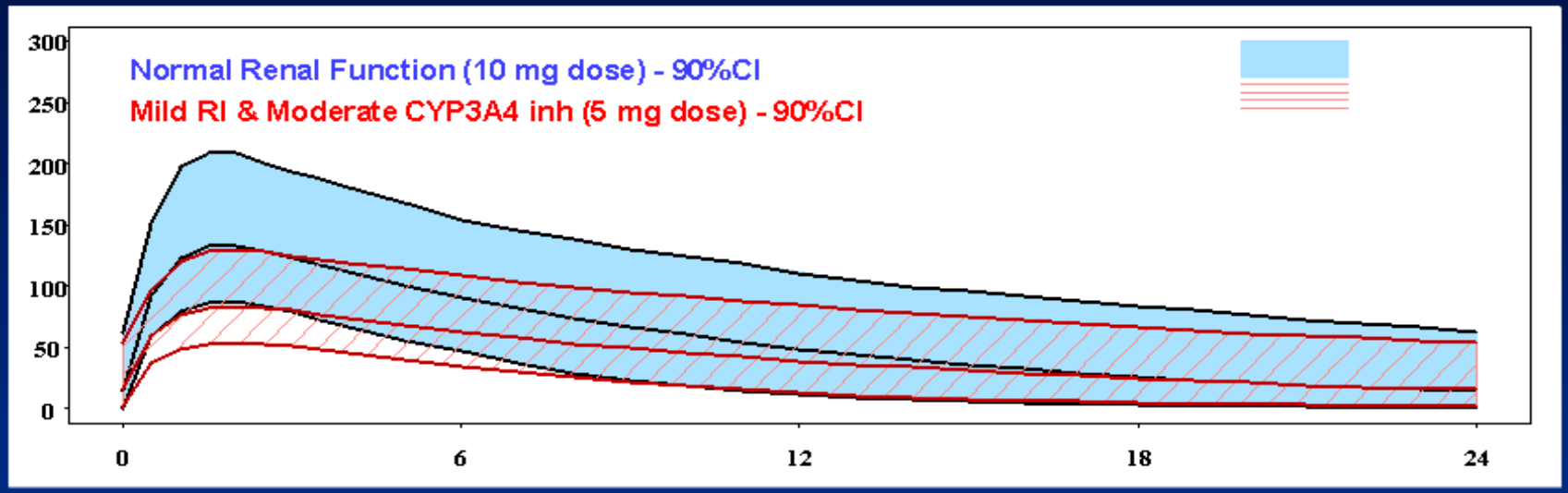
Predicted Steady State Plasma Concentration Window
10 mg qd in Phase 2 Target Population
CLCR 50-79 mL/min and Moderate or Strong CYP 3A4 Inhibition







Predicted Steady State Plasma Concentration Window
5 mg qd in Phase 2 Target Population
CLCR 50-79 mL/min and Moderate or Strong CYP 3A4 Inhibition



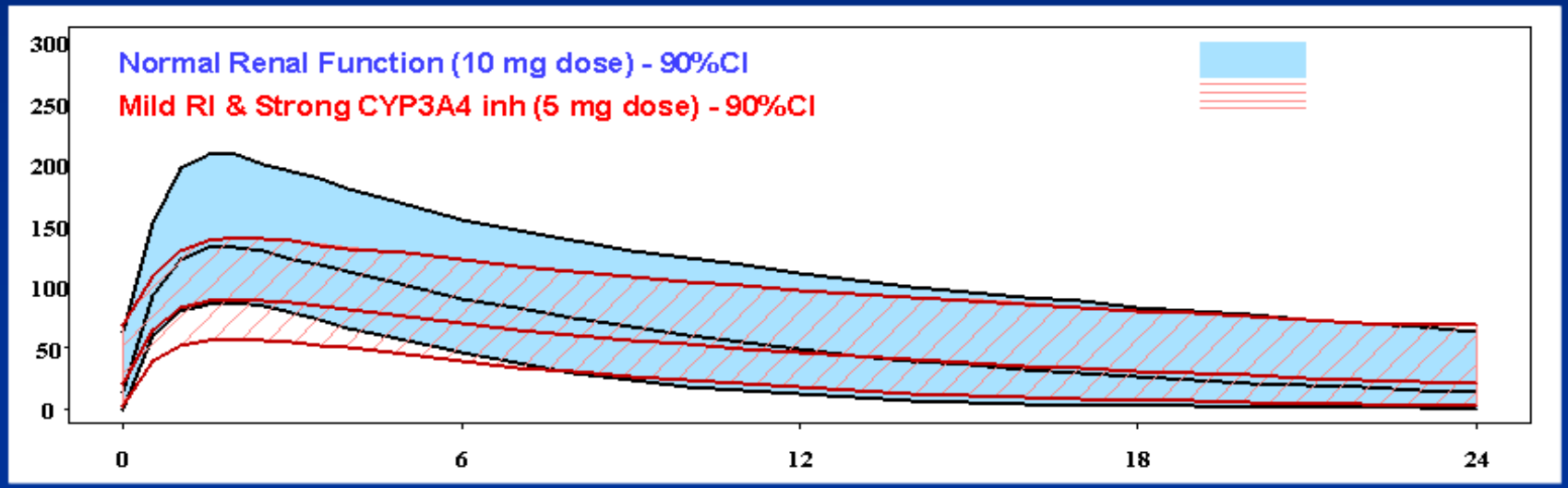


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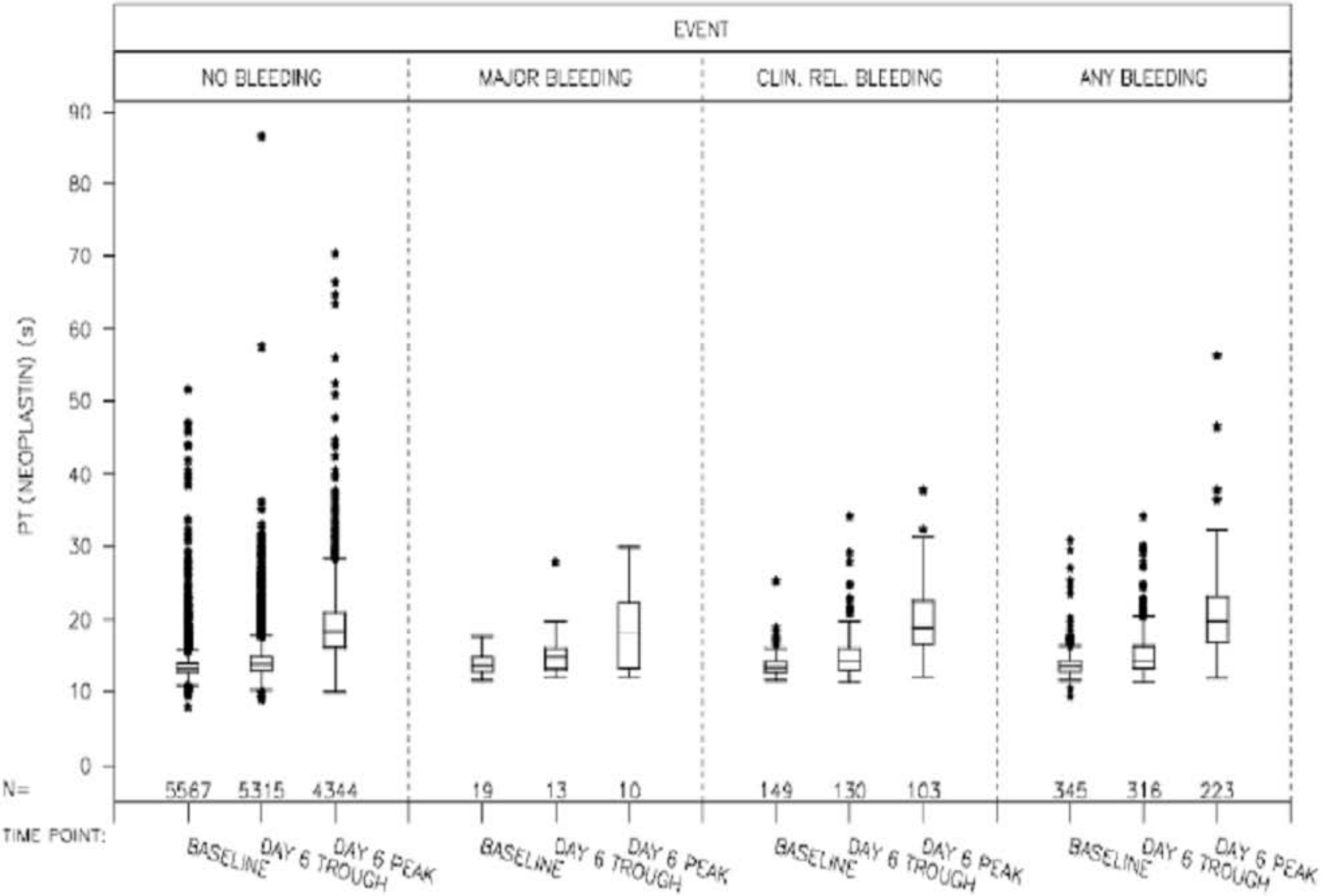
Figure 3-14: Distrubution of PT vs. Bleeding Events (Pooled Phase 3 RECORD Studies)



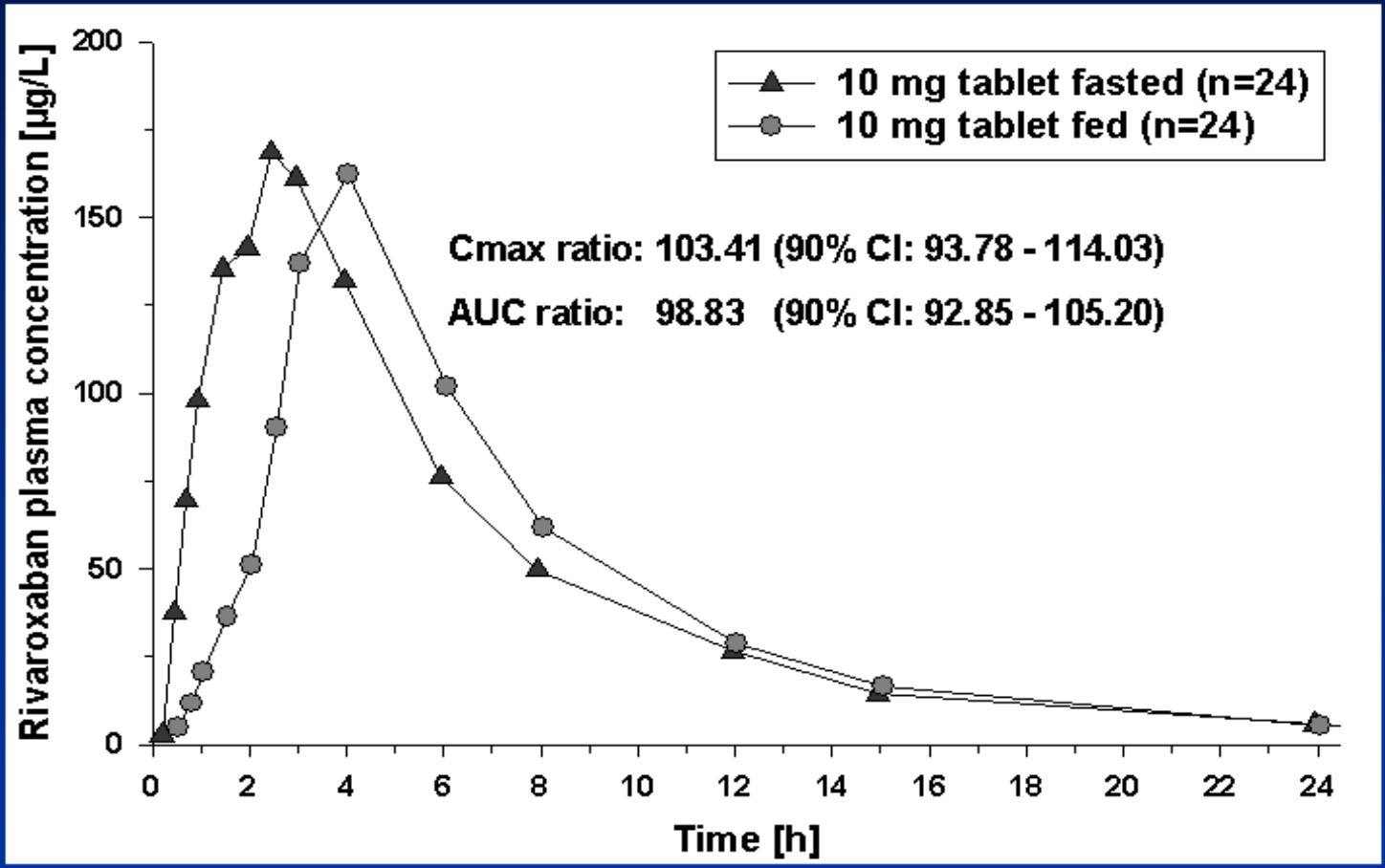
Non-Major Clinically Relevant Bleeding

- Overt bleeding events not meeting the criteria for major bleeding but associated with:
  - Medical intervention
  - Unscheduled contact (visit or telephone call) with a physician
  - (Temporary) cessation of study treatment, or
  - Associated with discomfort for the subject such as pain or impairment of activities of daily life

CRF Categories of Non-Major Clinically Relevant Bleeding

- Multiple source bleeding
- Spontaneous hematoma >25 cm2
- Excessive wound hematoma
- Spontaneous nose bleeding lasting for >5 minutes
- Gingival bleeding >5 minutes
- Macroscopic hematuria (spontaneous or lasting more than 24 hours, if associated with an intervention)
- Spontaneous rectal bleeding (more than a spot on toilet paper)
- Coughing blood
- Hematemesis
- Prolonged bleeding after venipuncture >5 minutes
- Other

Food Effect at 10 mg Dose Phase 1



Fondaparinux Orthopedic Surgery Phase 3 Program

- Four studies – all with fondaparinux 2.5 mg starting 4-8 hours after surgery
  - THR – EPHESUS (N=2309 – enoxaparin 40 mg)
  - THR – PENTATHLON (N=2275 - enoxaparin 60mg)
  - TKR – PENTAMAKS (N=1049 – enoxaparin 60 mg)
  - Hip Fx – PENTHIFRA (N=1711 – enoxaparin 40 mg)
- Bilateral venography between days 5-11
  - 75% evaluability rate
- Preplanned meta-analysis (Archives Internal Medicine 2002; 162:1833-1840)

Fondaparinux Efficacy Results

Parameter	Fondaparinux	Enoxaparin	Common odds reduction (95% CI)	P value
Total VTE	6.8%	13.7%	55.2% (45.8-63.1)	<0.001
Proximal DVT	1.3%	2.9%	57.4% (35.6-72.3)	<0.001
Symptomatic VTE	0.6%	0.4%	-	P=0.25
PE	0.3 %	0.3%	-	NS

Venographic and Clinical Endpoint Comparisons - Placebo

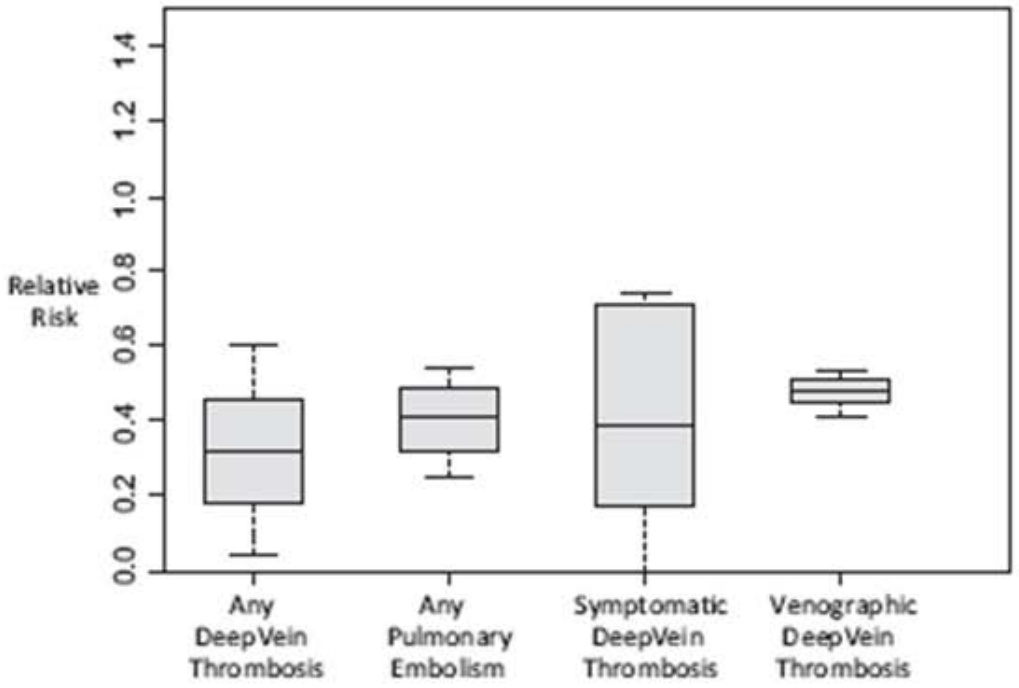
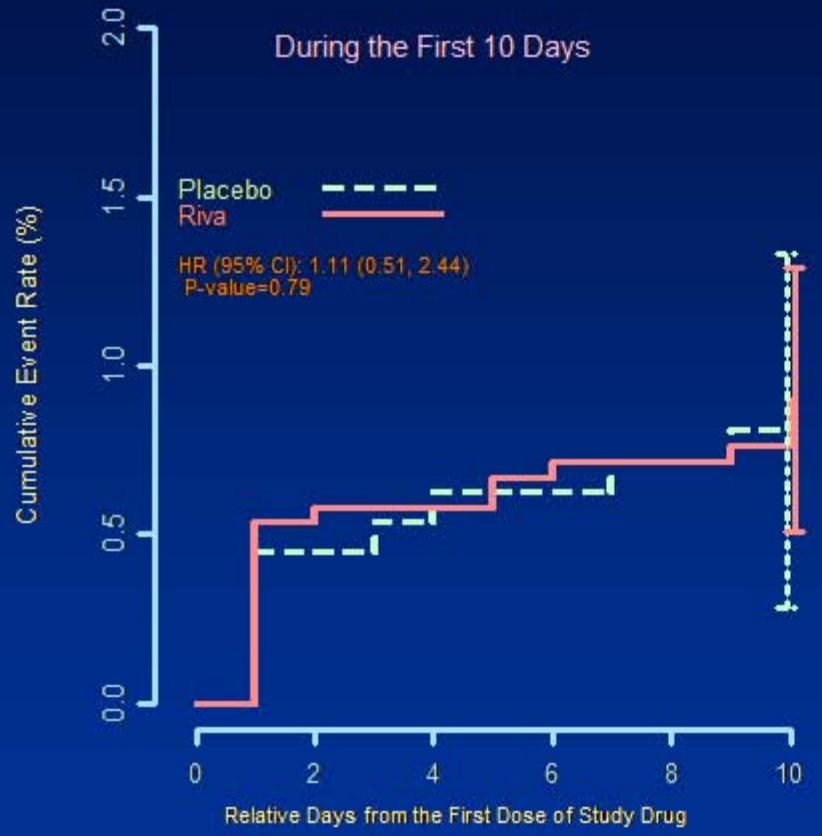


FIGURE 1. Summary of relative risks of venographic and symptomatic VTE from large (n ≥ 500) RCTs and metaanalyses of RCTs comparing pharmacologic thromboprophylaxis with placebo in surgical or medical patients. For a list of references of included studies, see text.

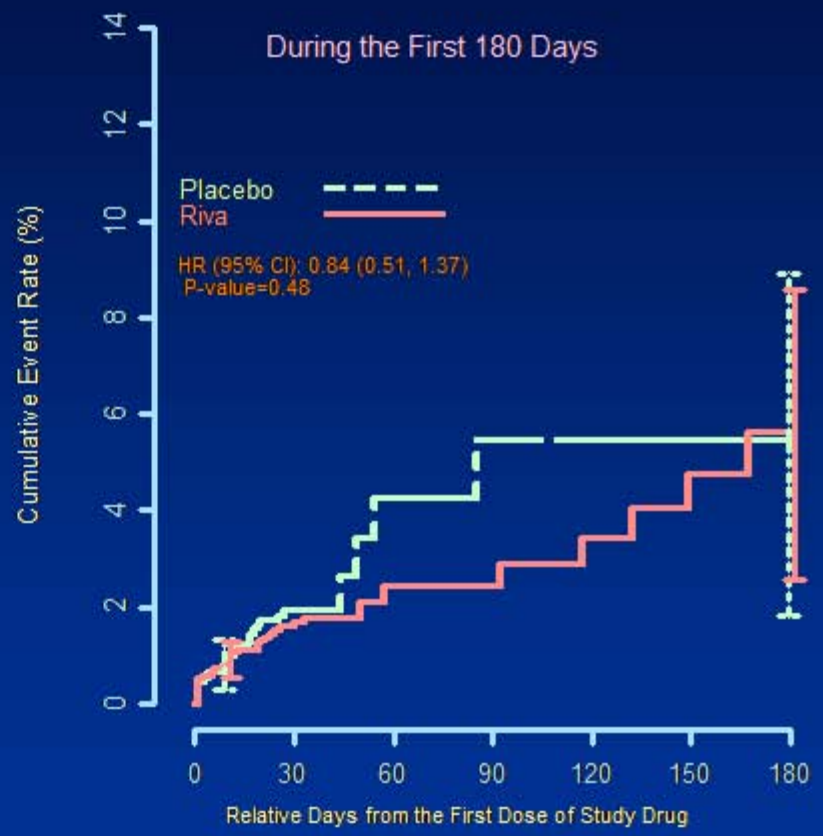
Eikelboom, et al, Chest, February 2009

Assessment of CV Rebound with Rivaroxaban in the ATLAS ACS TIMI 46 Study: D/MI/CVA



Number of Subjects at Risk:

Placebo	1121	1109	1104	1098	1096	1093
Riva	2246	2212	2204	2199	2185	2179



Number of Subjects at Risk:

Placebo	1121	608	102	79	58	46	24
Riva	2246	1313	276	222	177	130	84

Note: * Vertical bar shows 95% confidence interval at Day 10 and/or Day 180

D/MI/CVA/SRIR: Death, MI or Stroke

Breakdown of Components of the Clinical Composite Endpoint: ATLAS ACS TIMI 46 Study

10 days following D/C

	Rivaroxaban (n=2246)		Placebo (n=1121)	
D/MI/CVA/SRIR*	23	1%	9	0.8%
Death	11	0.5%	5	0.4%
MI	11	0.5%	4	0.4%
Stroke	2	0.1%	0	0%
Ischemic	1	<0.1%	0	0%
Hemorrhagic	1	<0.1%	0	0%
SRIR*	3	0.1%	0	0%

180 days following D/C

	Rivaroxaban (n=2246)		Placeb (n=1121)	
D/MI/CVA/SRIR*	49	2.2%	26	2.3%
Death	21	0.9%	14	1.2%
MI	28	1.2%	10	0.9%
Stroke	4	0.2%	3	0.3%
Ischemic	3	0.1%	3	0.3%
Hemorrhagic	1	<0.1%	0	0%
SRIR*	6	0.3%	1	0.1%

*D/MI/CVA/SRIR=Composite of death, MI, stroke or severe recurrent ischemia requiring revascularization

Deaths preceded by ALT >3x ULN concurrent with TB >2x ULN within 30 days – All Rivaroxaban Studies

Treatment group and Subject ID	Study (Randomization Ratio)	Key demographics	Causality assessment	Controversy
Rivaroxaban 220134004	EINSTEIN DVT/PE (1:1)	71 y/o Italian man with gastric cancer	Gastric cancer with liver metastases	none
Rivaroxaban 160183005	EINSTEIN DVT/PE (1:1)	63 y/o French woman with a history of hypertension, asthma and emphysema	Ischemic hepatitis	No documented hypotension
Rivaroxaban 11223-506006	Phase 2 VTE treatment (4:1)	72 y/o Czech woman with uterine cancer s/p chemo	Acute Hepatitis B infection	No inflammation on liver biopsy
Rivaroxaban 10944-84008	Phase 2 THR prophylaxis (4:1)	79 y/o German woman with hypertension and Parkinson's Disease	Cholestatic reaction, deteriorated after ERCP procedure	Contribution of liver failure to death
Placebo 200039	ATLAS ACS TIMI 46 (2:1)	44 y/o Australian woman	Sepsis, alcoholic hepatitis	
Enoxaparin 280130001	MAGELLAN (1:1)	72 y/o Belgian woman	Cardiac and renal failure	