Medically Ill Patient **A**ssessment of **R**ivaroxaban Versus Placebo **IN** Reducing Post-Discharge Venous Thrombo-**E**mbolism **R**isk (**MARINER**) Trial: Primary Results

Alex C. Spyropoulos, MD, FACP, FCCP, FRCPC
Professor of Medicine, The Donald and Barbara Zucker School of Medicine, Northwell Health at Lenox Hill Hospital, New York, NY

Cíle studie

Nemocní, kteří jsou hospitalizování pro závažné onemocnění a upoutání delší dobu na lůžku jsou ve vysokém riziku trombózy a embolie, proto se zvažuje tromboprofylaxe.

Cílem studie MARINER bylo zjistit, zda by nebylo vhodné podávání rivaroxabanu po dobu několika týdnů.

Vstupní kritéria

Věk 40 let
Hospitalizace 3 – 10 dnů
+ 1 z kritérií: srdeční selhání s EF < 45%
akutní respirační insuficience nebo exacerbace CHOPN
akutní CMP
akutní infekce

+ zvýšené riziko žilního trombembolismu, který byl posuzován podle modifikovaného International Medical Prevention on Venous Thromembolism (IMPROVE) skóre, které muselo být > 4, nebo 2-3 a současně minimálně dvojnásobné D dimery.

Vstupní charakteristika pacientů

Table 1. Characteristics of the Patients at Baseline.*

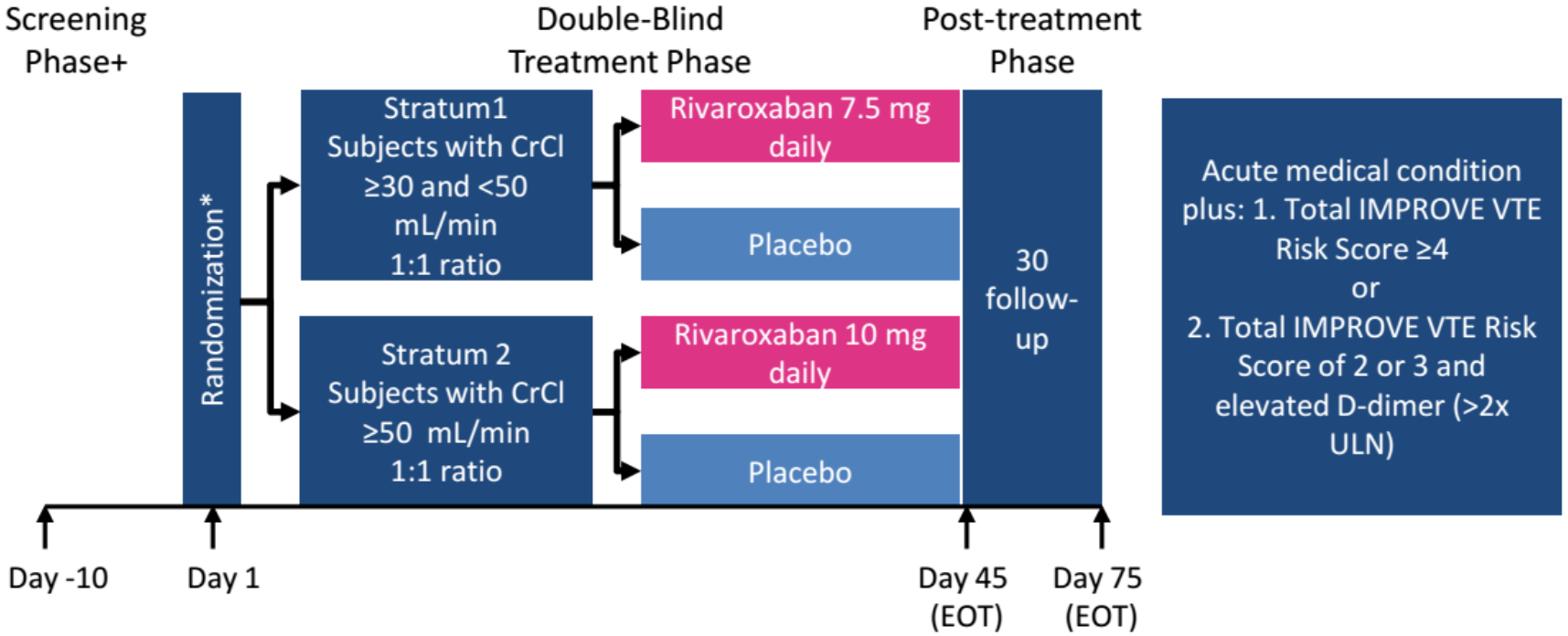
Characteristic	Rivaroxaban (N=6007)	Placebo (N=6012)
Mean age — yr	69.7	69.7
Age ≥75 yr — no. (%)	2154 (35.9)	2140 (35.6)
Male sex — no. (%)	3130 (52.1)	3154 (52.5)
White race — %†	5782 (96.3)	5808 (96.6)
Mean weight — kg	80.8	80.6
BMI‡	29.0	28.8
Creatinine clearance — no. (%)		
30 to <50 ml/min	1098 (18.3)	1099 (18.3)
≥50 ml/min	4909 (81.7)	4913 (81.7)
Reason for index hospitalization — no./total no. (%)		
Heart failure	2435/6003 (40.6)	2399/6011 (39.9)
Respiratory insufficiency or exacerbation of COPD	1575/6003 (26.2)	1611/6011 (26.8)
Ischemic stroke	860/6003 (14.3)	866/6011 (14.4)
Infectious disease	1048/6003 (17.5)	1045/6011 (17.4)
Inflammatory disease	85/6003 (1.4)	90/6011 (1.5)
Mean duration of index hospitalization — days	6.7	6.7
Mean duration of in-hospital thromboprophylaxis — days	6.2	6.2
History of VTE — no. (%)	765 (12.7)	748 (12.4)
History of cancer — no. (%)	488 (8.1)	533 (8.9)
ICU or CCU stay — no. (%)	3260 (54.3)	3240 (53.9)
Current lower-limb paralysis or paresis — no. (%)	1115 (18.6)	1122 (18.7)
Modified IMPROVE VTE risk score — no. (%)§		
2	2098 (34.9)	2151 (35.8)
3	1886 (31.4)	1779 (29.6)
≥4	2019 (33.6)	2075 (34.5)
D-Dimer level more than twice the upper limit of the normal range during index hospitalization — no. (%)¶	4226 (70.4)	4239 (70.5)
Aspirin use — no. (%)	3159 (52.6)	3046 (50.7)
Thienopyridine use — no. (%)	360 (6.0)	388 (6.5)

* CCU denotes cardiac care unit, COPD chronic obstructive pulmonary disease, ICU intensive care unit, and VTE venous thromboembolism.
† Race was reported by the patient.
‡ The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.
§ Modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) risk scores range from 0 to 10, with higher scores indicating a higher risk of venous thromboembolism (minimal clinically important difference, 2). Eleven patients had protocol violations: three patients in the rivaroxaban group and seven patients in the placebo group had a score of 1, and one patient in the rivaroxaban group had a score of 0.
¶ The normal range for D-dimer level was defined according to the local laboratory criteria.

The NEW ENGLAND JOURNAL of MEDICINE

MARINER Study Design

Randomized, double-blind, placebo controlled, event driven trial



Primary Efficacy Endpoint: Composite of symptomatic VTE or VTE-related death
Secondary Efficacy Endpoint: VTE-related death (hierarchical design)
Primary Safety Endpoint: Major Bleeding (ISTH Definition)

Estimated Sample Size – Event Driven Study

Sample size	Placebo	RRR	Events	Power for superiority	2 sided α
12,000	2.5%	40%	161	90%	5%

ress

Objectives

Primary Objective

- Prevention of symptomatic venous thromboembolism (VTE: lower extremity deep vein thrombosis [DVT] and non-fatal pulmonary embolism [PE])

  and

  VTE-related death (death due to PE or death in which PE cannot be ruled out as the cause)

Secondary Objectives

- VTE-related death
- Symptomatic VTE
- The composite of symptomatic VTE and all-cause mortality
- The composite of symptomatic VTE, myocardial infarction, non-hemorrhagic stroke and CV death
- All-cause mortality

Principal Safety Objective

- Major bleeding using International Society of Thrombosis and Haemostasis (ISTH) bleeding criteria

Secondary Safety Objective

- Non-major clinically relevant bleeding

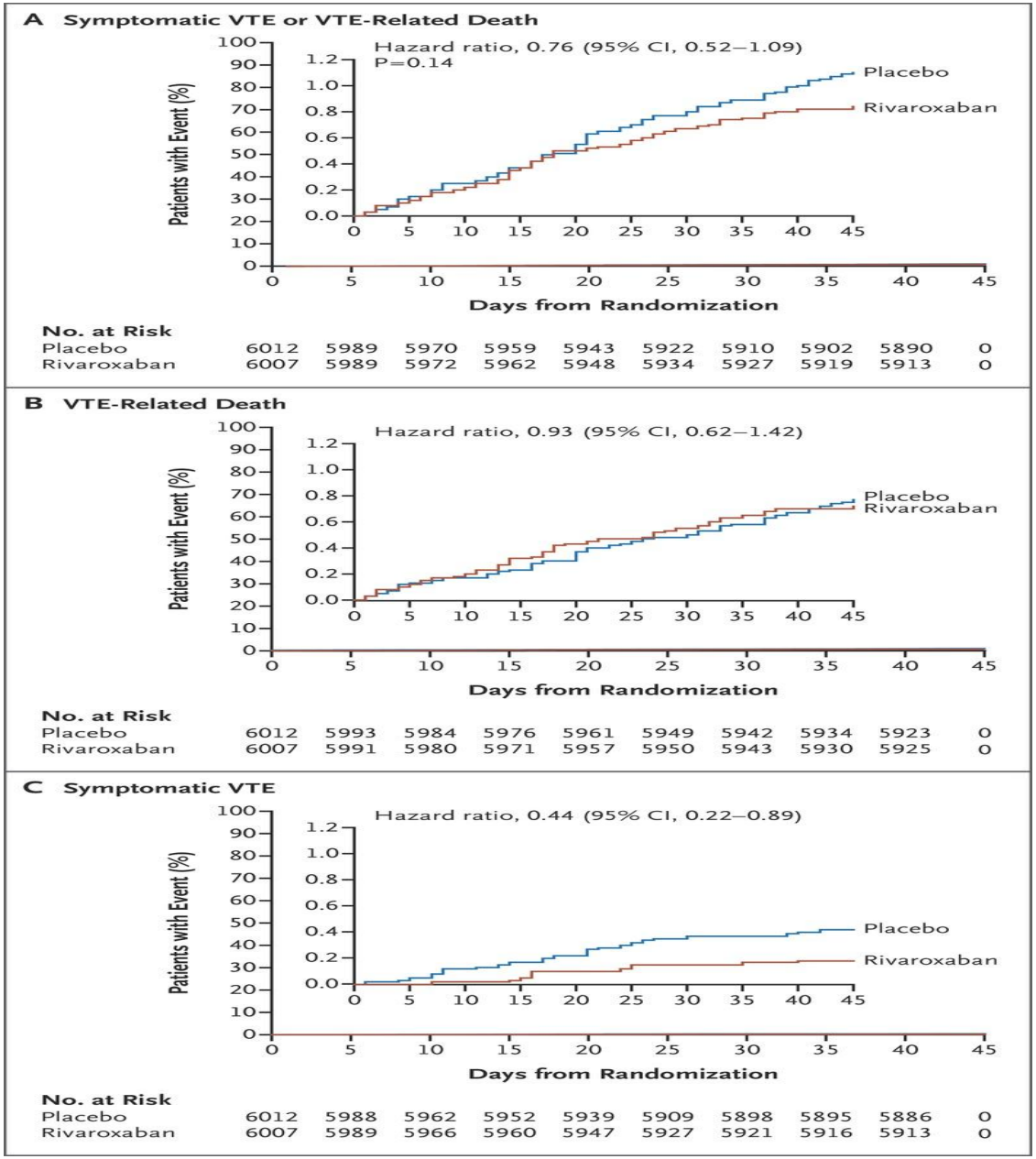
Components of the Primary Efficacy Outcome up to Day 45

	Rivaroxaban (N=6007)	Placebo (N=6012)	Rivaroxaban vs Placebo	
Outcomes	**n (%)**	**n (%)**	**Hazard Ratio (95% CI) [1]**	**p-value [2]**
Primary efficacy outcome (Sx VTE and VTE-related death)	**50 (0.83)**	**66 (1.10)**	**0.76 (0.52, 1.09)**	**0.136**
Symptomatic lower extremity DVT	4 (0.07)	13 (0.22)	0.31 (0.10, 0.94)	0.039
Symptomatic non-fatal PE	7 (0.12)	15 (0.25)	0.47 (0.19, 1.14)	0.096
VTE-related death	43 (0.72)	46 (0.77)	0.93 (0.62, 1.42)	0.751
Death (PE)	3 (0.05)	5 (0.08)	0.60 (0.14, 2.51)	0.485
Death (PE cannot be ruled out)	40 (0.67)	41 (0.68)	0.98 (0.63, 1.51)	0.912

[1] Hazard ratio (95% CI) and p-value are from the Cox proportional hazard model, stratified by baseline creatinine clearance (CrCl) (30-<50mL/min vs. >=50mL/min), with treatment as the only covariate.

[2] P-value (two-sided) for superiority of rivaroxaban versus placebo from the Cox proportional hazard model.

Kaplan–Meierovy kumulativní křivky pro primární cíl a jeho komponenty



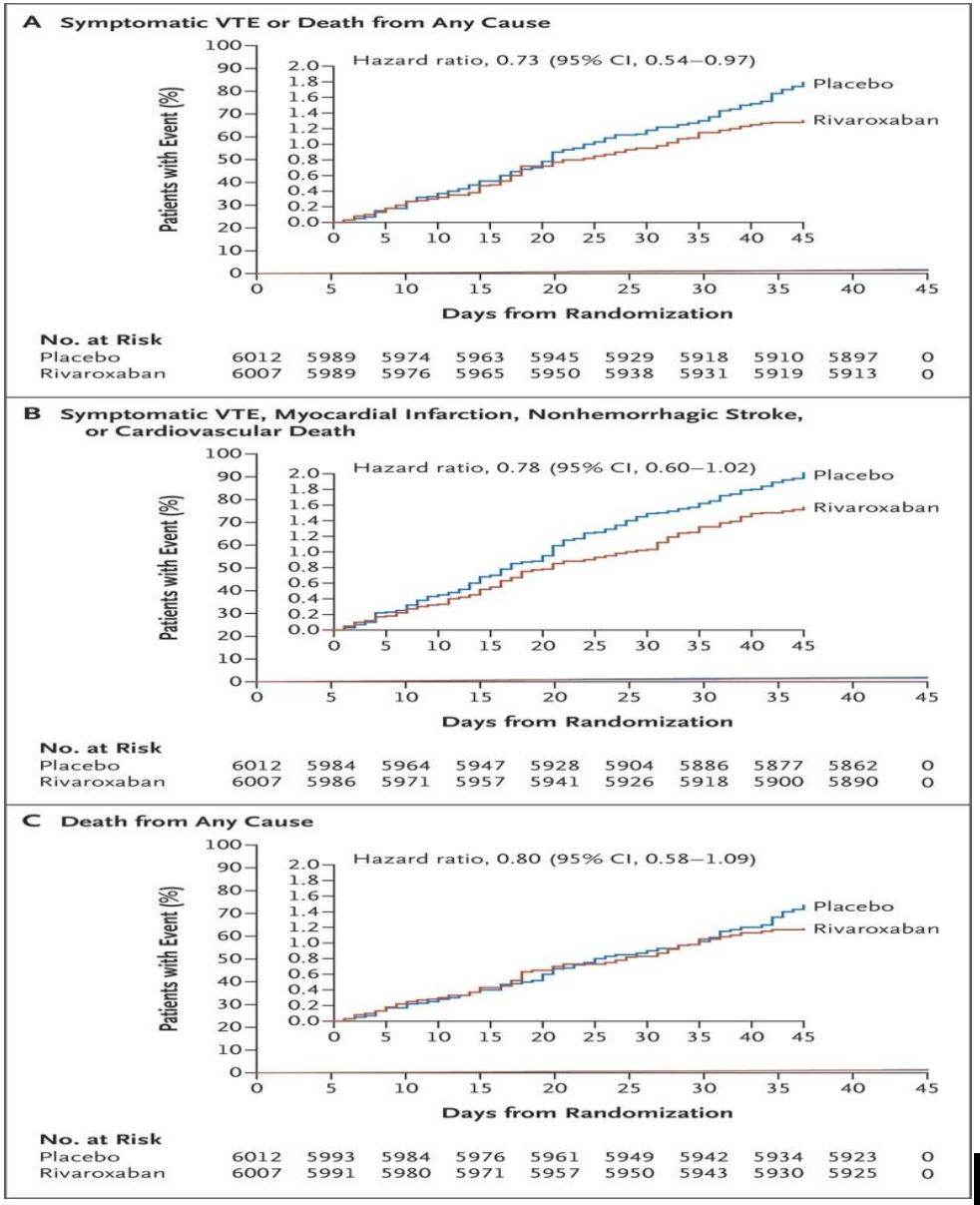
The NEW ENGLAND JOURNAL of MEDICINE

Secondary Efficacy Outcomes up to Day 45

	Rivaroxaban (N=6007)	Placebo (N=6012)	Rivaroxaban vs Placebo	
Secondary Efficacy Outcomes	**n (%)**	**n (%)**	**Hazard Ratio (95% CI) [1]**	**p-value [2]**
VTE-related death	43 (0.72)	46 (0.77)	0.93 (0.62, 1.42)	0.751
Symptomatic VTE (lower extremity DVT and non-fatal PE)	11 (0.18)	25 (0.42)	0.44 (0.22, 0.89)	0.023
Composite of symptomatic VTE and ACM	78 (1.30)	107 (1.78)	0.73 (0.54, 0.97)	0.033
Composite of symptomatic VTE, MI, Non-Hemorrhagic stroke and CV death [3]	94 (1.56)	120 (2.00)	0.78 (0.60, 1.02)	0.073
ACM	71 (1.18)	89 (1.48)	0.80 (0.58, 1.09)	0.156

[1] Hazard ratio (95% CI) and p-value are from the Cox proportional hazard model, stratified by baseline CrCl (30-<50 mL/min vs. >=50 mL/min), with treatment as the only covariate.
[2] P-value (two-sided) for superiority of rivaroxaban versus placebo from the Cox proportional hazard model.
[3] CV Death includes VTE-related death (PE and PE cannot be ruled out).

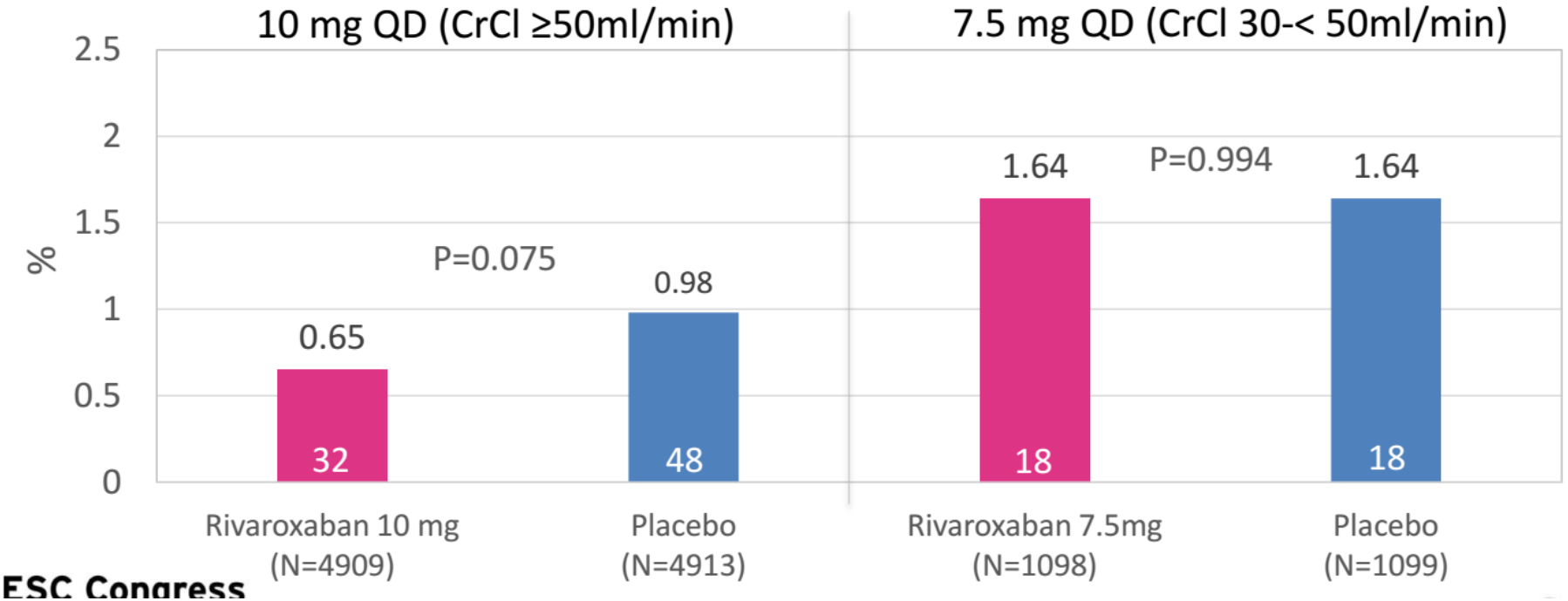
Kaplan–Meierovy křivky pro kompozitní sekundární cíle a příčiny úmrtí z jakékoliv příčiny



The NEW ENGLAND JOURNAL of MEDICINE

Primary Efficacy Outcome: By Dose Stratum/Baseline Renal Function

Symptomatic VTE and VTE-related Death up to Day 45



Bleeding Outcomes (On Treatment + 2 Days)

	Rivaroxaban (N=5982)	Placebo (N=5980)	Rivaroxaban vs Placebo	
	n (%)	n (%)	Hazard Ratio (95% CI) [1]	p-value [2]
Major bleeding	**17 (0.28)**	**9 (0.15)**	**1.88 (0.84, 4.23)**	**0.124**
A fall in hemoglobin of >=2g/dL	14 (0.23)	6 (0.10)	2.33 (0.89, 6.05)	0.084
A transfusion of >=2 units of packed RBC	11 (0.18)	3 (0.05)	3.66 (1.02, 13.10)	0.047
A critical site	3 (0.05)	2 (0.03)	1.50 (0.25, 8.97)	0.657
A fatal outcome	2 (0.03)	0 (0.0)	NA (NA, NA)	
Non-major clinically relevant bleeding	**85 (1.42)**	**51 (0.85)**	**1.66 (1.17, 2.35)**	**0.004**

Závěr

- rivaroxaban podávaný preventivně po dobu 45 dní nesnížil významně kompozitní cíl venozní fatální či nefatální trombembolie ve srovnání s placebem

- výskyt velkého krvácení v celé studii byl velmi nízký

- byl naznačen trend k prospěchu pro nemocné bez renální insuficience (CrCl > 50 ml/min), kteří užívali dávku 10mg rivaroxabanu.