Scuola di Specializzazione in Malattie dell'Apparato Cardiovascolare
Direttore Prof. Massimo Volpe
Facoltà di Medicina e Psicologia, Università di Roma Sapienza
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Dr.ssa Roberta Coluccia

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Progetto Formazione Avanzata in Cardiologia nel Web 2014
Scuola di Specializzazione in Malattie dell'Apparato Cardiovascolare

Direttore: Prof. Massimo Volpe
E-mail: massimo.volpe@uniroma1.it

Coordinatore: Dr. Giuliano Tocci
E-mail: giuliano.tocci@uniroma1.it

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Edoxaban versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Edoxaban versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism

The Hokusai-VTE Investigators*

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INTRODUCTION

- Venous thromboembolism (VTE) is the 3rd most common cardiovascular disease after MI and stroke.

- The standard treatment consists of (LMW) heparin/ vitamin K antagonist (VKA).

- New oral anticoagulants with and without heparin are effective and safe in the treatment of VTE.

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EDOXABAN

- Oral direct factor Xa inhibitor with a rapid onset of action and relatively long half-life (about 10-14 hours).
- Dose of 60 mg once daily was selected based on phase II data
- Dose of 30 mg once daily should be used in case of
  - moderate renal impairment (CrCl 30-50 ml/min)
  - low body weight (< 60 Kg)
  - concomitant use of P-gp inhibitors

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Hokusai-VTE study

- Randomized, double blind, event driven, non-inferiority study.

- Designed to broaden applicability to real world practice, by encouraging physicians to enroll all VTE patients
    - Starting with standard parenteral heparin
    - At least 3 months treatment, duration flexible
    - All patients followed for 12 months
    - Halving the dose for patients perceived to be at risk for bleeding

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AIM OF THE STUDY

- LMW heparin followed by EDOXABAN vs LMW heparin followed by WARFARIN in the treatment of acute symptomatic deep-vein thrombosis (involving the popliteal, femoral or iliac veins or acute) and/or symptomatic pulmonary embolism.

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EXCLUSION CRITERIA

- Controindications to heparin or warfarin
- Previuos treatment with heparin (> 48 hours) or VKA
- Cancer
- Treatment with aspirin (>100 mg daily) or dual antiplatelet therapy
- Renal Disease (CrCl < 30 ml/min)

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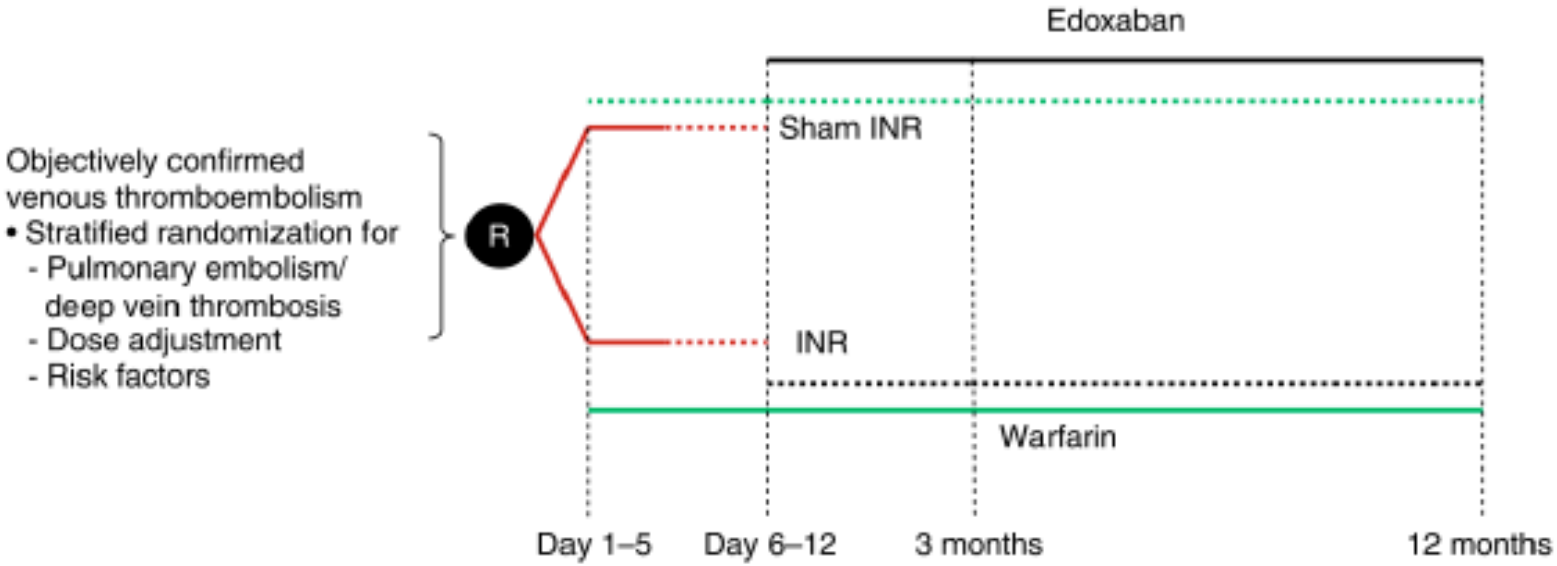
STUDY DESIGN



All patients receive initial heparin treatment for at least 5 days after randomization.

- Edoxaban
- Placebo edoxaban
- Warfarin
- Placebo warfarin
- Low-molecular-weight heparin

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STUDY OUTCOMES

Efficacy Outcome

- The incidence of symptomatic recurrent VTE (the composite of DVT, non-fatal PE or fatal PE in the overall study period)

Safety Outcome

- The composite of major or clinically relevant non-major bleeding in the on-treatment period

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General Characteristics of Study Population

Characteristic	All Patients		Patients with Deep-Vein Thrombosis Only		Patients with Pulmonary Embolism	
	Edoxaban (N=4118)	Warfarin (N=4122)	Edoxaban (N=2468)	Warfarin (N=2453)	Edoxaban (N=1650)	Warfarin (N=1669)
Age						
Mean — yr	55.7±16.3	55.9±16.2	54.7±16.0	54.9±15.9	57.1±16.6	57.4±16.5
≥75 yr — no. (%)	560 (13.6)	544 (13.2)	282 (11.4)	273 (11.1)	278 (16.8)	271 (16.2)
Male sex — no. (%)	2360 (57.3)	2356 (57.2)	1497 (60.7)	1481 (60.4)	863 (52.3)	875 (52.4)
Weight — no. (%)						
≤60 kg†	524 (12.7)	519 (12.6)	320 (13.0)	304 (12.4)	204 (12.4)	215 (12.9)
>100 kg	611 (14.8)	654 (15.9)	360 (14.6)	379 (15.5)	251 (15.2)	275 (16.5)
Creatinine clearance ≥30 to ≤50 ml/min — no. (%)†	268 (6.5)	273 (6.6)	152 (6.2)	153 (6.2)	116 (7.0)	120 (7.2)
Patients receiving 30 mg of edoxaban at randomization — no. (%)†	733 (17.8)	719 (17.4)	425 (17.2)	411 (16.8)	308 (18.7)	308 (18.5)
Anatomical extent of qualifying event — no. (%)‡						
Limited	—	—	603 (24.4)	596 (24.3)	128 (7.8)	123 (7.4)
Intermediate	—	—	795 (32.2)	773 (31.5)	679 (41.2)	682 (40.9)
Extensive	—	—	1035 (41.9)	1049 (42.8)	743 (45.0)	778 (46.6)
Not assessable	—	—	35 (1.4)	35 (1.4)	100 (6.1)	86 (5.2)
Concomitant DVT — no. (%)	—	—	—	—	410 (24.8)	404 (24.2)
Baseline NT-proBNP — no. (%)						
Patients with measurement	—	—	—	—	1484 (89.9)	1505 (90.2)
Patients with level ≥500 pg/ml	—	—	—	—	454 (27.5)	484 (29.0)
Right ventricular dysfunction — no./total no. (%)§	—	—	—	—	172/498 (34.5)	179/504 (35.5)
Causes of DVT or PE — no. (%)¶						
Unprovoked	2713 (65.9)	2697 (65.4)	1666 (67.5)	1655 (67.5)	1047 (63.5)	1042 (62.4)
Temporary risk factor	1132 (27.5)	1140 (27.7)	655 (26.5)	655 (26.7)	477 (28.9)	485 (29.1)
Cancer	378 (9.2)	393 (9.5)	209 (8.5)	205 (8.4)	169 (10.2)	188 (11.3)
Previous VTE	784 (19.0)	736 (17.9)	416 (16.9)	414 (16.9)	368 (22.3)	322 (19.3)

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TREATMENT

- 40% of patients were treated for 12 months.
- Adherence to edoxaban treatment was 80% or more.
- Among patients receiving warfarin, the INR was in the therapeutic range for 63.5% of the time.

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RESULTS

Outcome	Edoxaban (N=4118)	Warfarin (N=4122)	Hazard Ratio with Edoxaban (95% CI)	P Value
Primary efficacy outcome: first recurrent VTE or VTE-related death — no./total no. (%)				
All patients				
Event during overall study period	130/4118 (3.2)	146/4122 (3.5)	0.89 (0.70–1.13)	<0.001 (for noninferiority)
Fatal PE	4/4118 (0.1)	3/4122 (0.1)		
Death, with PE not ruled out	20/4118 (0.5)	21/4122 (0.5)		
Nonfatal PE with or without DVT	49/4118 (1.2)	59/4122 (1.4)		
DVT alone	57/4118 (1.4)	63/4122 (1.5)		
Event during on-treatment period	66/4118 (1.6)	80/4122 (1.9)	0.82 (0.60–1.14)	<0.001 (for noninferiority)
Patients with index DVT	2468/4188 (59.9)	2453/4122 (59.5)		
Event during overall study period	83/2468 (3.4)	81/2453 (3.3)	1.02 (0.75–1.38)	
Event during on-treatment period	48/2468 (1.9)	50/2453 (2.0)	0.96 (0.64–1.42)	
Patients with index PE	1650/4118 (40.1)	1669/4122 (40.5)		
Event during overall study period	47/1650 (2.8)	65/1669 (3.9)	0.73 (0.50–1.06)	
Event during on-treatment period	18/1650 (1.1)	30/1669 (1.8)	0.60 (0.34–1.08)	
Safety outcome during on-treatment period — no. (%)				
Primary safety outcome: first major or clinically relevant nonmajor bleeding	349 (8.5)	423 (10.3)	0.81 (0.71–0.94)	0.004 (for superiority)
Major bleeding	56 (1.4)	66 (1.6)	0.84 (0.59–1.21)	0.35 (for superiority)
Fatal	2 (<0.1)	10 (0.2)		
Intracranial	0	6 (0.1)		
Gastrointestinal	1 (<0.1)	2 (<0.1)		
Retroperitoneal	0	1 (<0.1)		
Other	1 (<0.1)	1 (<0.1)		
Nonfatal in critical site	13 (0.3)	25 (0.6)		
Intracranial	5 (0.1)	12 (0.3)		
Retroperitoneal	0	3 (0.1)		
Other	8 (0.2)	10 (0.2)		
Nonfatal in noncritical site	41 (1.0)	33 (0.8)		
Clinically relevant nonmajor bleeding	298 (7.2)	368 (8.9)	0.80 (0.68–0.93)	0.004 (for superiority)
Any bleeding	895 (21.7)	1056 (25.6)	0.82 (0.75–0.90)	<0.001 (for superiority)
Other adverse event — no. (%)				
Any adverse event occurring during on-treatment period	2821 (68.5)	2928 (71.0)		
Any serious adverse event	503 (12.2)	544 (13.2)		
Any serious adverse event leading to permanent discontinuation of the study drug	121 (2.9)	105 (2.5)		
Any drug-related adverse event leading to permanent discontinuation of the study drug	41 (1.0)	51 (1.2)		

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PULMONARY EMBOLISM + EVIDENCE OF RIGHT VENTRICULAR DISFUNCTION

EDOXABAN
VTE in 15 of 454 pt (3,3%)

EDOXABAN
VTE in 22 of 733 pt (3,0%)

WARFARIN
VTE in 30 of 484 pt (6,2%)

WARFARIN
VTE in 30 of 719 pt (4,2%)

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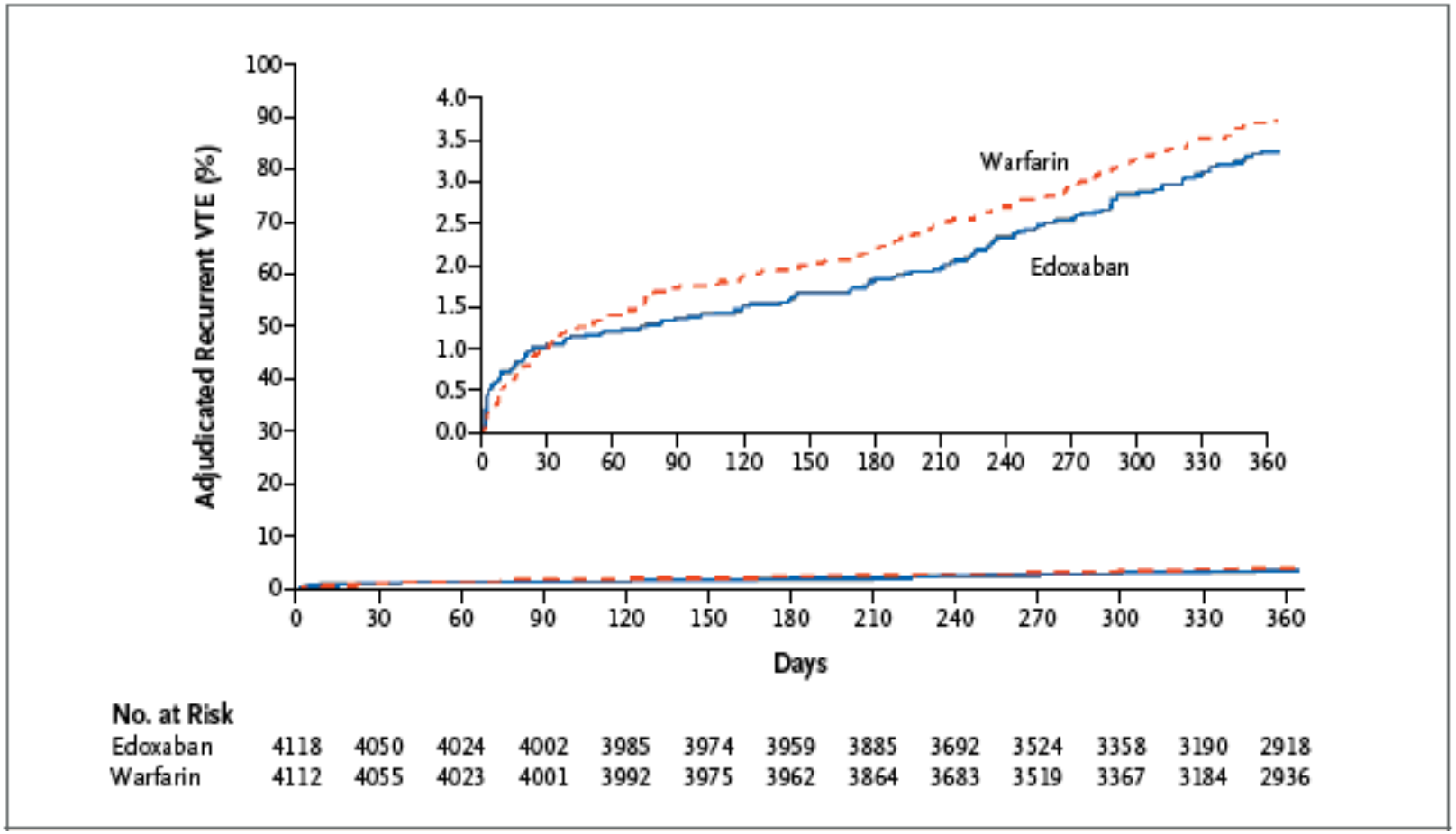
Kaplan-Meier curves for the Incidence of the Primary Endpoint



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CONCLUSIONS

(LMW) heparin/edoxaban regimen was:

- non-inferior to standard therapy for preventing recurrent VTE
- consistent efficacy in patient with DVT and PE
- clinically significant reduction in recurrent VTE in right ventricular dysfunction subgroup
- less clinically relevant bleeding
- dose adaptation (30 mg) effective and safe

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Grazie per la Vostra Attenzione!

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