LA TERAPIA DEL TEV: QUALI FARMACI, QUALI DOSAGGI, QUALI PROBLEMI

SE E QUALI DIFFERENZE PRATICHE TRA I NAO SINGOLO FARMACO E QUELLI DOPO TERAPIA PARENTERALE

DAVIDE IMBERTI

DIPARTIMENTO DI MEDICINA INTERNA

CENTRO EMOSTASI E TROMBOSI
OSPEDALE GUGLIELMO DA SALICETO
PIACENZA

Il *sottoscritto Imberti Davide*

dichiara

di aver avuto negli ultimi due anni rapporti di consulenza con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- *ALFA WASSERMANN*
- *ASPEN*
- *BAYER*
- *BMS-PFIZER*
- *BOHERINGER INGELHEIM*
- *COVIDIEN*
- *DAIICHI-SANKYO*
- *IL*
- *ITALFARMACO*
- *KEDRION*
- *SANOFI AVENTIS*

AGENDA

- Introduzione
- Le evidenze della letteratura
- Conclusioni

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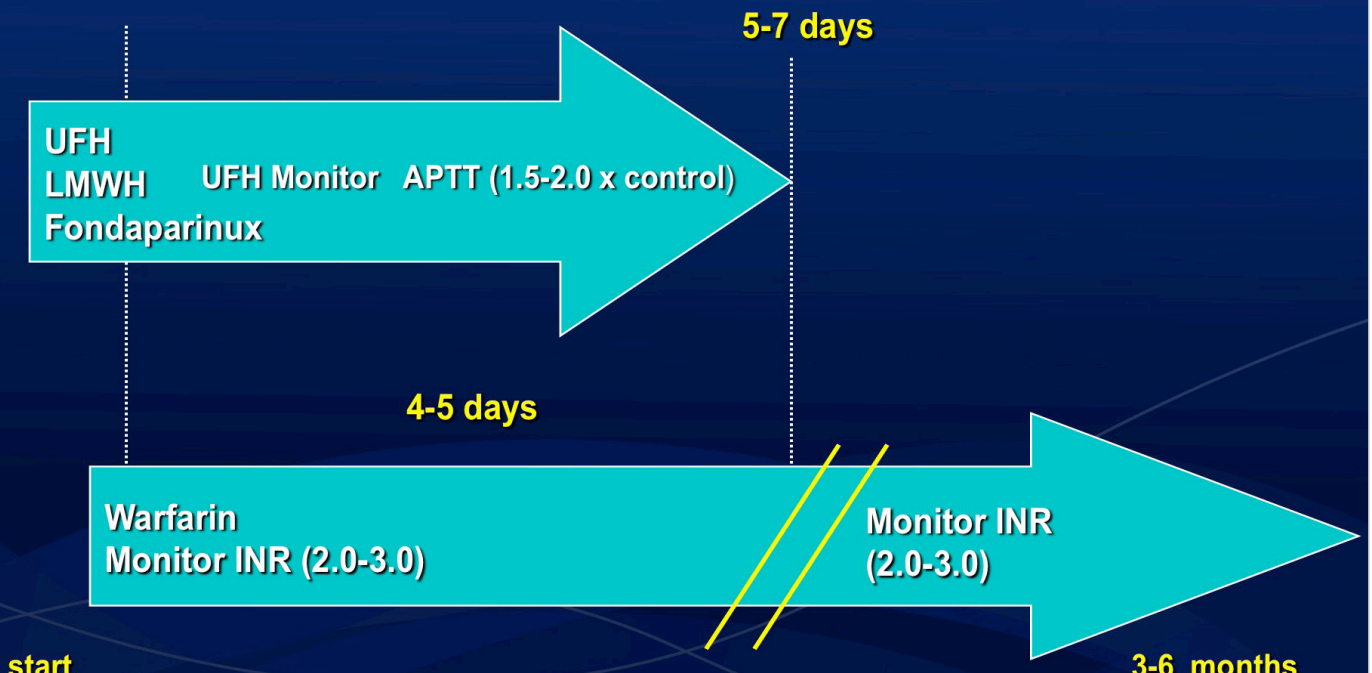
A.T.H.O.S. STUDY
Results

	Acenocoumarol (N=60)	Hep + Acenocoumarol (N=60)
Symptomatic VTE	20%	6.7%
Asympt DVT extens	39.6%	8.2%
Major bleeding	5.0%	3.0%

Brandjes, N Engl J Med, 1992

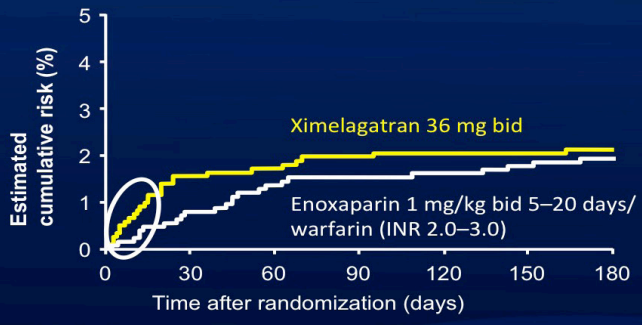
Initial and long term treatment of VTE



Kearon, Chest, 2008

Rationale for intensified initial treatment in phase III VTE treatment studies

Evidence of early recurrent VTE in THRIVE study with ximelagatran[1]



Evidence of early recurrent VTE in the van Gogh PE study with idraparinux[2]

- Early separation of the curves indicates the need for intensified anticoagulant treatment in the acute phase

*Heparin followed by an adjusted-dose VKA for either 3 or 6 months

1. Fiessinger J-N *et al. JAMA* 2005
2. The van Gogh Investigators. *N Engl J Med* 2007

Treatment of acute VTE with new anticoagulants: possible options

- Start with standard parenteral drugs (i.e. LMWHs) for the initial therapy before the new compound
- Start therapy with an intensive regimen of the new compound for the first weeks ("single drug approach")

NOAC VTE: study designs

	RE-COVER I[1] RE-COVER II[2]	EINSTEIN-DVT[3] EINSTEIN-PE[4]	AMPLIFY[5]	Hokusai-VTE[6]
Study drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Study design*	Double-blind	Open-label	Double-blind	Double-blind
Pre-randomization heparin	NR	<48 hrs	<36 hrs	<48 hrs
Heparin lead-in	At least 5 days	None	None	At least 5 days
Dose	150 mg BID	15 mg BID x 3 wk then 20 mg QD	10 mg BID x 7 d then 5 mg BID	60 mg QD 30 mg QD†
Dose reduction	NONE	NONE	NONE	18%
Randomized population	2,564[1] 2,568[2]	3,449[3] 4,833[4]	5,400	8,292
Treatment duration	6 months	Pre-specified 3, 6, 12 months	6 months	Flexible 3 to 12 months

*Comparator was warfarin in each case
†Dose was halved to 30 mg in patients perceived to be at higher risk for bleeding by predefined criteria
NR=not reported

1. Schulman et al. N Engl J Med 2009;361:2342–2352; 2. Schulman et al. Blood 2011;118:Abstract 205
3. EINSTEIN Investigators. N Engl J Med 2010;363:2499–2510; 4. EINSTEIN–PE Investigators. N Engl J Med 2012;366:1287–1297
5. Agnelli et al. N Engl J Med 2013;369:799–808; 6. The Hokusai-VTE Investigators. N Engl J Med 2013; e-pub ahead of print

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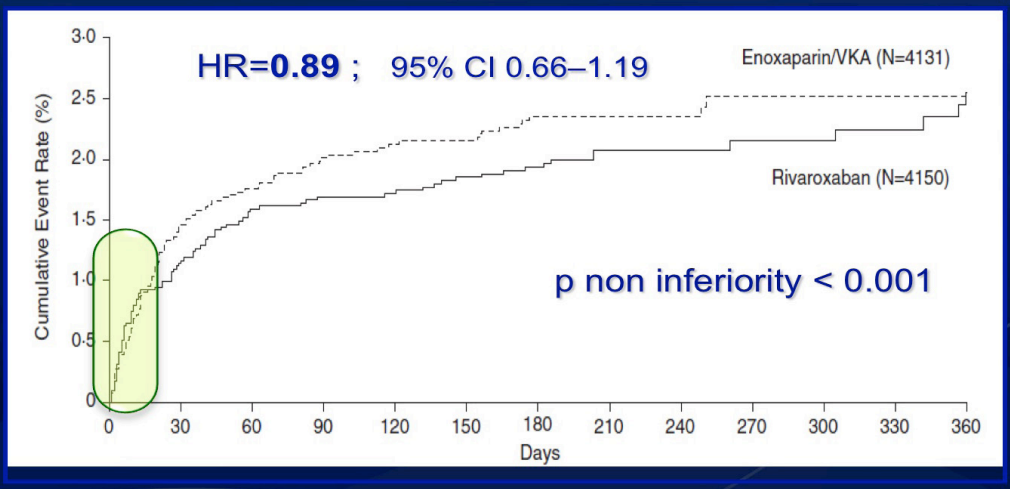
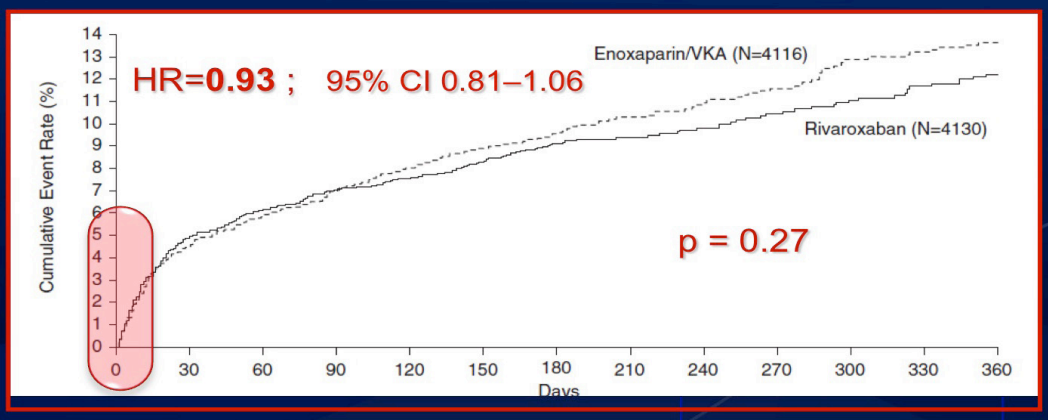
Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies



Primary efficacy outcome

Prins, Thrombosis Journal, 2013

Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies

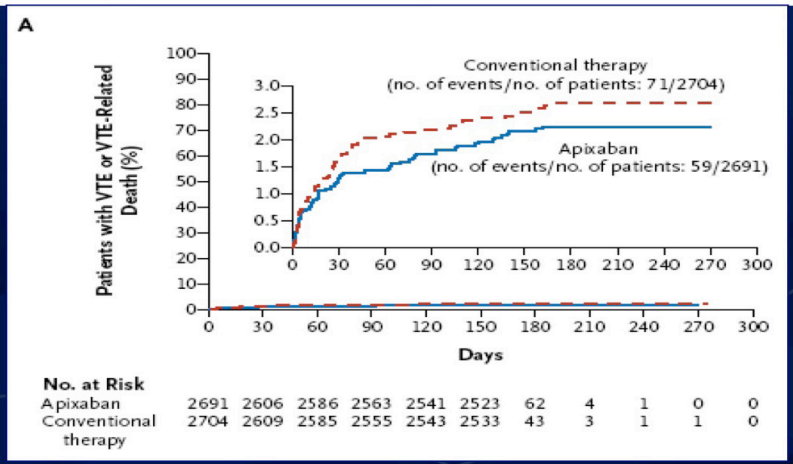


Major bleeding or CRNMB

Prins, Thrombosis Journal, 2013

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 AUGUST 29, 2013 VOL. 369 NO. 9

Oral Apixaban for the Treatment of Acute Venous Thromboembolism



Agnelli, NEJM, 2013

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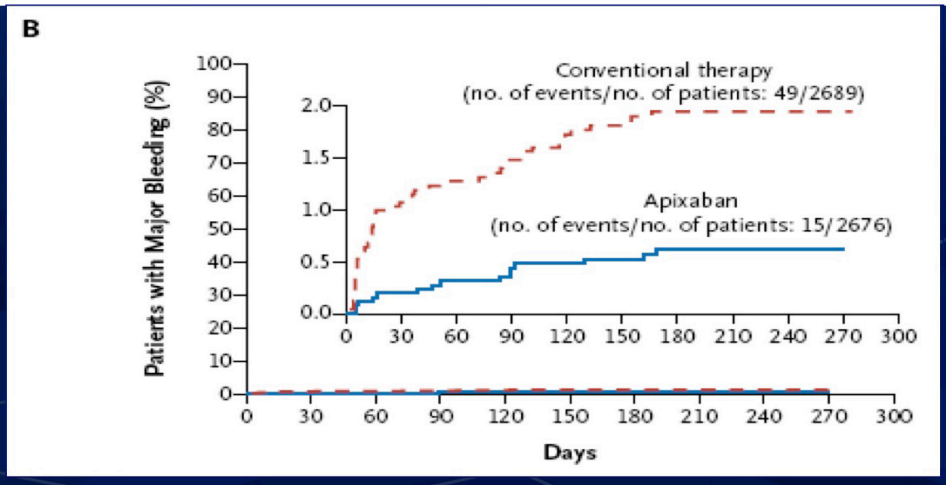


Agnelli, NEJM, 2013

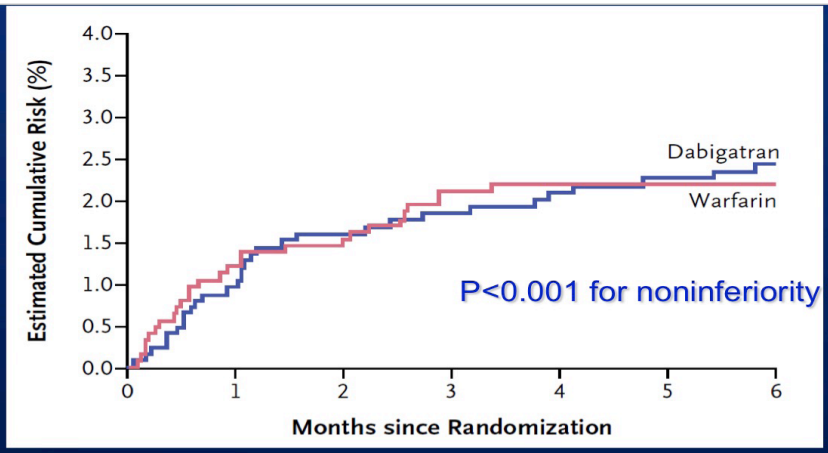
Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism

RECOVER

Efficacy outcome
Recurrent VTE

HR= 1.10 (95% CI= 0.65-1.84)

NEJM 2009; 361: 2342-52



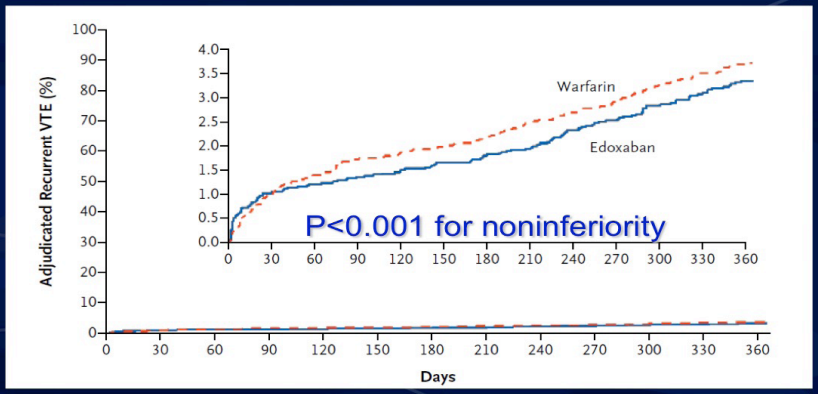
Edoxaban versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism

HOKUSAY

Efficacy outcome
Recurrent VTE

HR= 0.89 (95% CI= 0.7-1.13)

NEJM 2013; 369: 1406-15



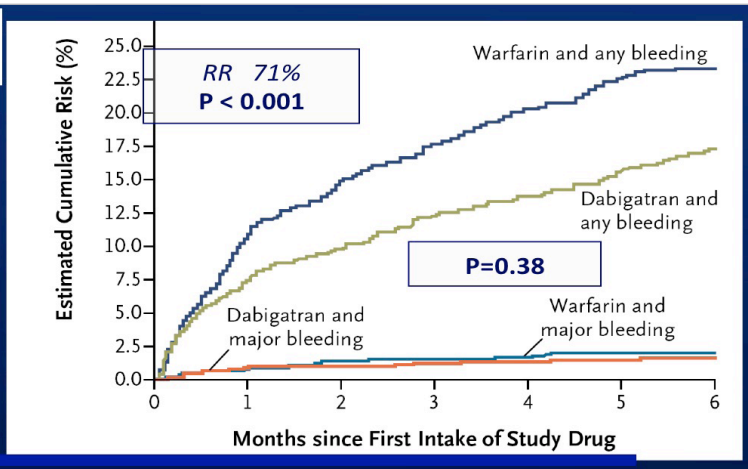
Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism

RECOVER

Safety outcome

Major bleeding / any bleeding

NEJM 2009; 361: 2342-52



Edoxaban versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism

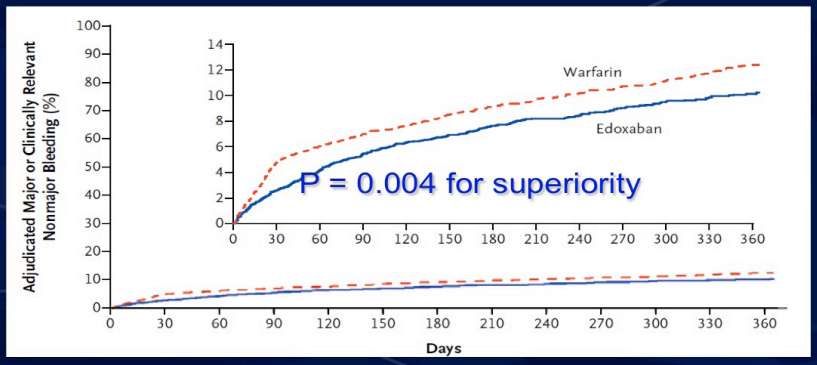
HOKUSAY

Safety outcome

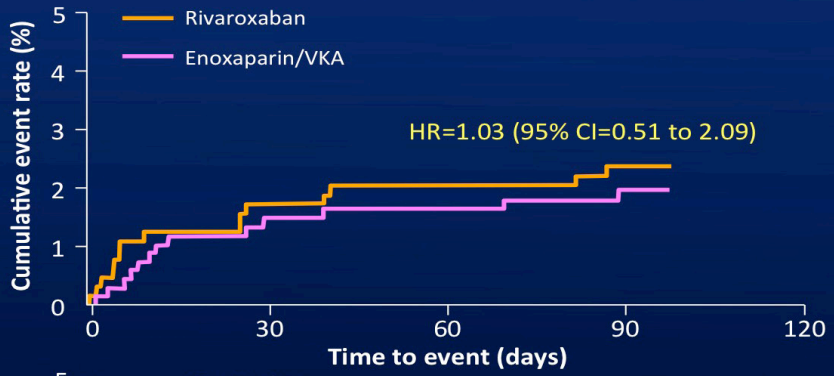
Major + Clinically Relevant non Major Bleeding

HR= 0.81 (95% CI= 0.71-0.94)

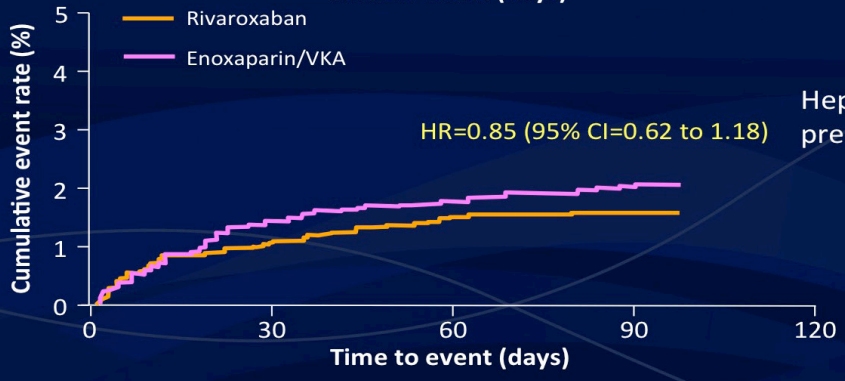
NEJM 2013; 369: 1406-15



Use of Prestudy Heparin Does Not Affect Outcomes



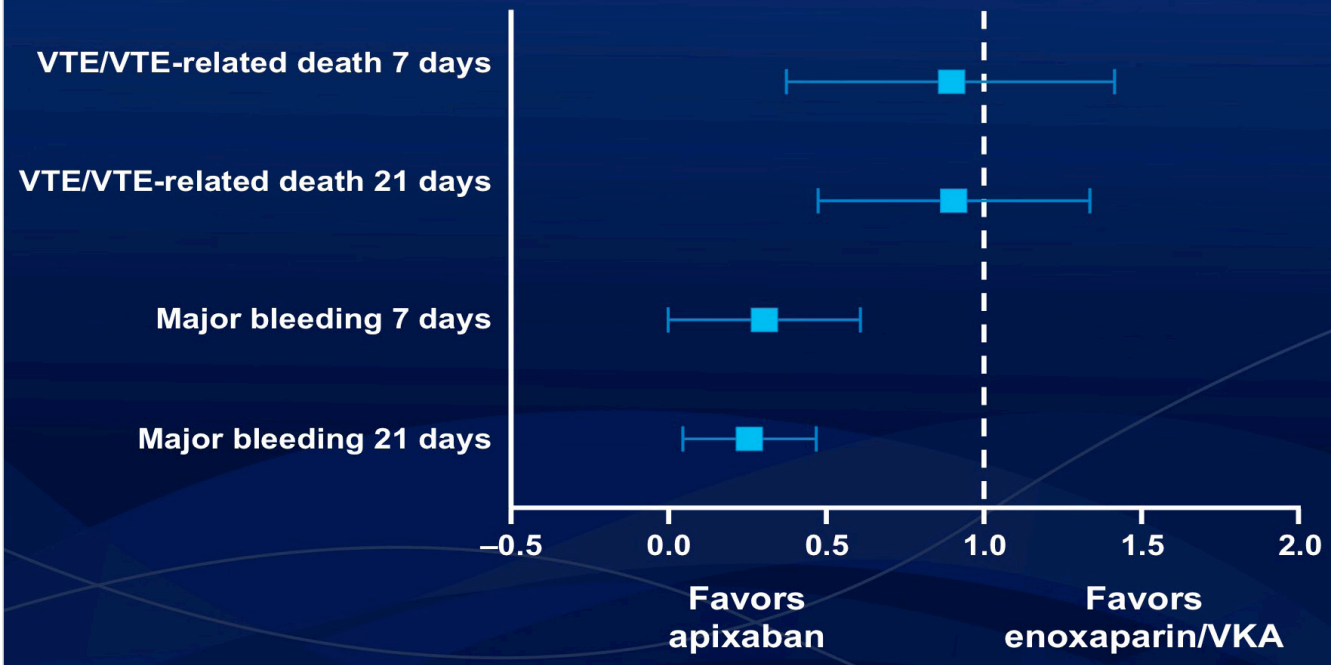
No heparin prerandomization (n=1344)



Heparin prerandomization (n=6937)

Prandoni, Acad Emerg Med, 2015

AMPLIFY- Adjudicated VTE/VTE-Related Death and Major Bleeding During the First 7 and 21 Days



Raskob, Thromb Haemost, 2016

RE-COVER/RE-COVER II: bleeding outcomes by treatment period

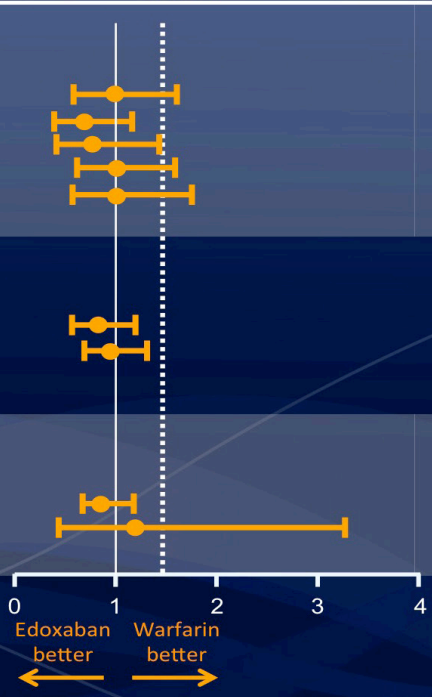
Profile of less bleeding with dabigatran than with warfarin

	Dabigatran	Warfarin	HR (95% CI)
Major bleeding			
1: Any study drug	**37 (1.4)**	**51 (2.0)**	**0.73 (0.48–1.11)**
2. Oral drug only	24 (1.0)	40 (1.6)	**0.60 (0.36–0.99)**
Major and clinically-relevant non-major bleeding			
1: Any study drug	**136 (5.3)**	**217 (8.5)**	**0.62 (0.50–0.76)**
2. Oral drug only	109 (4.4)	189 (7.7)	0.56 (0.45–0.71)
Any bleeding			
1: Any study drug	**411 (16.1)**	**567 (22.2)**	**0.70 (0.61–0.79)**
2. Oral drug only	354 (14.4)	503 (20.4)	0.67 (0.59–0.77)

Schulman, Circulation, 2013

Subgroup analysis for efficacy

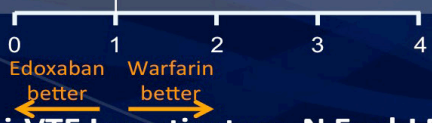
Subgroup	Edoxaban N	Edoxaban n	Edoxaban (%)	Warfarin N	Warfarin n	Warfarin (%)	Hazard Ratio 95% CI	P-value for Interaction
Initial Heparin Treatment Duration On or After Randomization								0.4984
0-5 days	870	34	(3.9)	583	24	(4.1)		
6 days	922	23	(2.5)	717	27	(3.8)		
7 days	726	18	(2.5)	749	25	(3.3)		
8-9 days	885	34	(3.8)	1011	40	(4.0)		
≥10 days	715	21	(2.9)	1062	30	(2.8)		
Initial Heparin Treatment Duration On or After Randomization								
<Median (7 days)	1792	57	(3.2)	1300	51	(3.9)		
≥Median (7 days)	2326	73	(3.1)	2822	95	(3.4)		
Initial Type of Heparin Treatment Received								
Enoxaparin	3958	122	(3.1)	3956	138	(3.5)		
UFH	148	8	(5.4)	151	7	(4.6)		



The Hokusai-VTE Investigators. N Engl J Med 2013

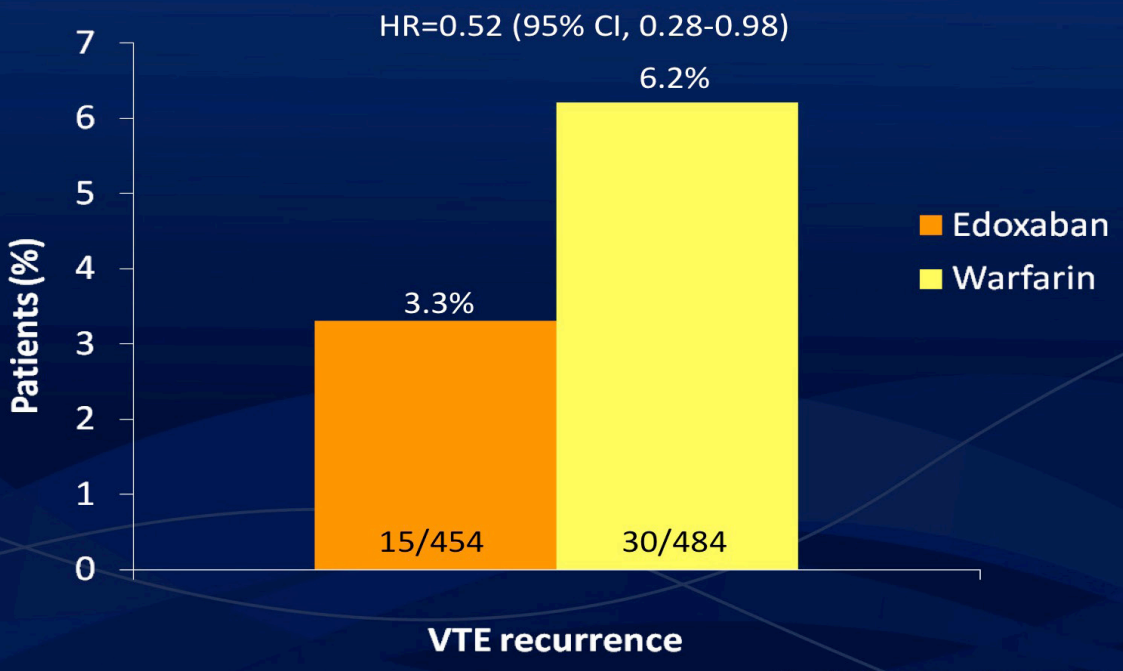
Subgroup analysis for safety

Subgroup	Edoxaban N	Edoxaban n	Edoxaban (%)	Warfarin N	Warfarin n	Warfarin (%)	Hazard Ratio 95% CI	P-value for Interaction
Initial Heparin Treatment Duration On or After Randomization								0.6078
0-5 days	870	82	(9.4)	583	63	(10.8)		
6 days	922	65	(7.0)	717	77	(10.7)		
7 days	726	56	(7.7)	749	84	(11.2)		
8-9 days	885	77	(8.7)	1011	91	(9.0)		
≥10 days	715	69	(9.7)	1062	108	(10.2)		
Initial Heparin Treatment Duration On or After Randomization								
<Median (7 days)	1792	147	(8.2)	1300	140	(10.8)		
≥Median (7 days)	2326	202	(8.7)	2822	283	(10.0)		
Initial Type of Heparin Treatment Received								
Enoxaparin	3958	333	(8.4)	3956	403	(10.2)		
UFH	148	16	(10.8)	151	18	(11.9)		



The Hokusai-VTE Investigators. N Engl J Med 2013

Subgroup analysis in PE patients with NT-proBNP ≥500 pg/mL



Brekelmans, Lancet Hamatol, 2016

Reduction in the lenght of stay with rivaroxaban as a single-dose regimen for the treatment of DVT and PE

	EINSTEIN DVT			EINSTEIN PE		
	RIVA	ENOXA/ AVK	P	RIVA	ENOXA/ AVK	P
Hospitalized	872 (50.6%)	909 (53.1%)	0.144	2163 (89.7%)	2165 (89.9%)	0.828
Not hospitalized	851 (49.4%)	802 (46.6%)		249 (10.3%)	244 (10.1%)	
Lenght of stay/days (mean)	6.2	7.9	0.0001	6.6	7.5	0.0001

Van Bellen, Curr Med Res Opin, 2014

XALIA STUDY
Length of hospital stay

Analysis	Length of stay (LS mean, days)		Ratio (95% CI)*
	Rivaroxaban	Standard anticoagulation	
Before propensity score adjustment	4.8	7.5	
Propensity score-adjusted	5.0	7.7	

* Mean length of stay calculated from hospitalised patients only; ratio based on ANOVA of log-transformed LS data.

ANOVA = analysis of variance; LS = least-squares; VTE = venous thromboembolism.

Ageno, Lancet Haematol, 2016

Hospitalizations and Length of Hospital Stay by Treatment Group

	Apixaban (n=2676)	Enoxaparin/warfarin (n=2689)	HR (95% CI)	*P* value	NNT
Number of all-cause hospitalizations*	182	218			
Number of subjects with ≥1 hospitalization* (%)	153 (5.72)	190 (7.07)	0.804 (0.650–0.995)	0.045	74
Number of subjects with ≥1 hospitalization in the first 30 days* (%)	61 (2.28)	90 (3.35)	0.676 (0.488–0.935)	**0.018**	93
Total length of stay in hospitalization, days	1535	2197	–	–	–
Mean ± SD length of hospital stay per hospitalized subject, days	10.2 ± 13.7	11.7 ± 28.2	–	0.5002	–
Average estimated length of hospital stay per subject, days	0.57	1.01	–	**<0.0001**	–

*After the index event. A Cox proportional hazards regression model was used to examine the effects of treatment with apixaban versus enoxaparin/warfarin. A zero-inflated Poisson regression was used to estimate the mean length of stay because many subjects were not readmitted. CI, confidence interval; HR, hazard ratio; NNT, number needed to treat; SD, standard deviation.

Liu, J Am Heart Assoc, 2015

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Antithrombotic therapy for VTE disease: CHEST guidelines 2016

Summary of recommendations in non cancer patients

- **In patients with DVT of the leg or PE and no cancer, as long-term (first 3 months) anticoagulant therapy, we suggest dabigatran, rivaroxaban, apixaban or edoxaban over VKA therapy** (all Grade 2B). **For patients with DVT of the leg or PE and no cancer who are not treated with dabigatran, rivaroxaban, apixaban or edoxaban, we suggest VKA therapy over LMWH** (Grade 2C).

Kearon, Chest, 2016

CONCLUSIONI
«SINGLE DRUG THERAPY»

- Terapia domiciliare
- Riduzione tempi degenza
- Semplificazione protocollo terapeutico
- Nessun rischio di HIT
- Pazienti non complianti/rifiuto terapia iniettiva

CONCLUSIONI
«LEAD INIZIALE CON EPARINA»

- Pazienti con EP potenzialmente instabile
- Pazienti con TEV idiopatico in fase di studio (es. paraneoplastica ?)
- Difficoltà logistico-organizzative per l'accesso alla prescrizione del PT
- Pazienti già in trattamento con dosi terapeutiche di eparina (da più di 48 h ?)