Trattamento e prevenzione delle recidive nei pazienti con trombosi venosa profonda: i nuovi anticoagulanti orali

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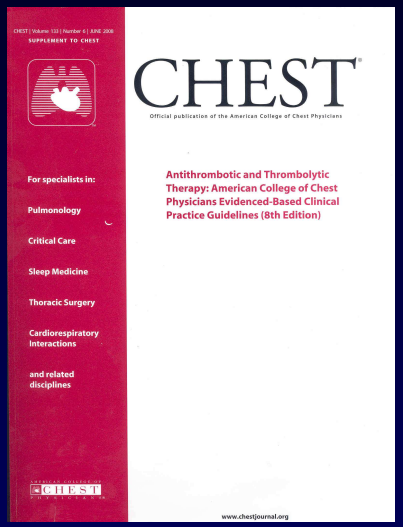
Cona, Ferrara 29.09.12

ACCP 2008 Treatment of Venous Thromboembolism

UFH (iv, sc, sc fixed doses)
LMWH
Fondaparinux
Thrombolysis

(Grade 1B)



Initial treatment

VKAs INR 2-3

VKAs INR 2-3 or 1.5-2.5

Long-term treatment (Early Phase)

Extended treatment (Late Phase)

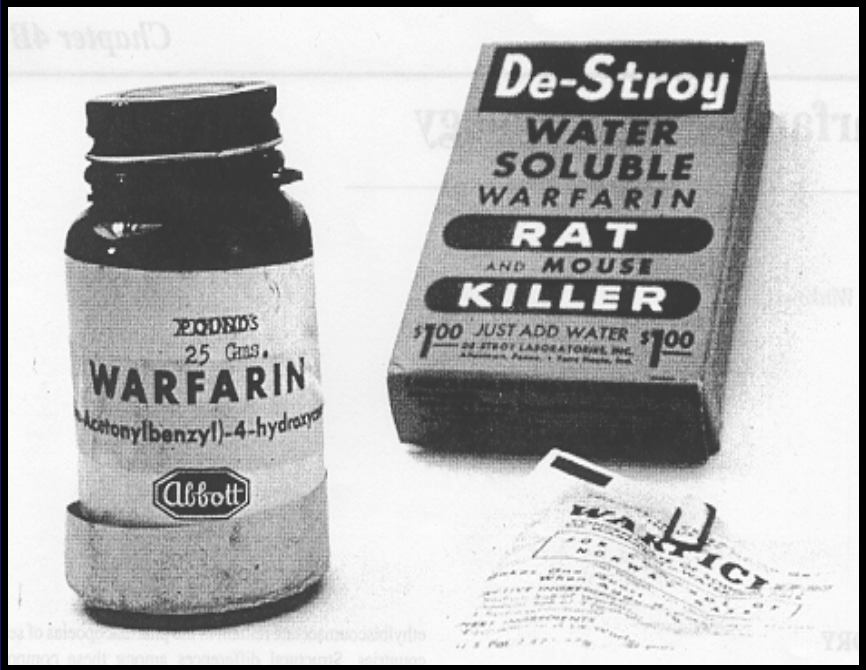
≥ 5 days

3-mo

Indefinite

With re-assessment of the individual risk-benefit at periodic intervals

Warfarin

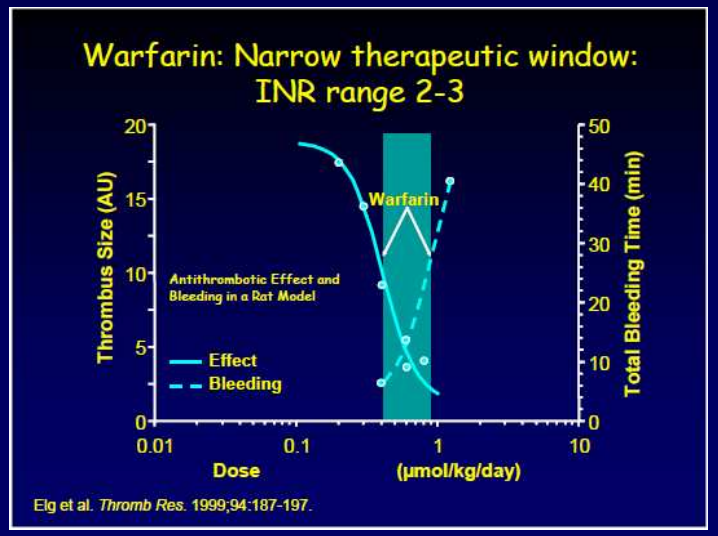


- 1940s: Sintesi Warfarin
- 1948: Uso come Rodenticida
- 1953: Primo studio Clinica

Interferenza con la sintesi epatica dei fattori II, VII, IX, X "vitamina K" dipendenti.

Effetto…

- differente da persona a persona
- Variabile nel tempo nella stessa persona
- Non correlato a "DOSE FISSA"



Even With Close Monitoring in a Clinical Trial Patients Frequently out of Therapeutic Range

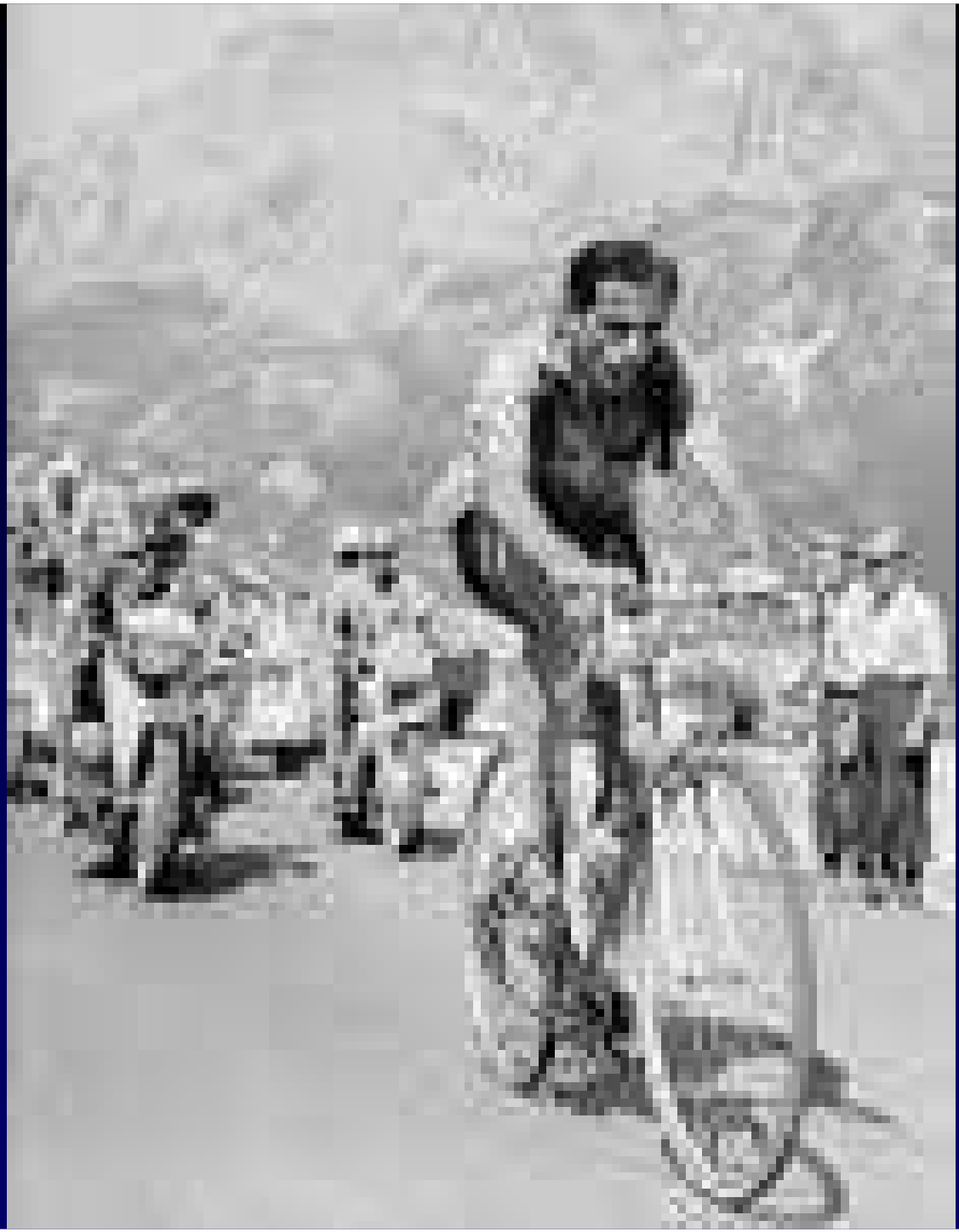
Clinical Trials	Real world Practice
Only 58% of INR Values in Therapeutic Range	As low as 37% Values in Therapeutic Range
• Difficulties in predicting the anticoagulant effect • Monitoring assays difficult to standardize • Frequent dose adjustment	• Overlap with parenteral anticoagulant • Slow onset/Offset action • Food and drug interactions = Frequent monitoring when introducing new drugs

Drawbacks of VKAs

- Efficacy excellent (4-5% recurrences al 3-mo)
- … but safety requires improvement (2% major bleeding/yearly – 0.2% fatal bleeding) = a high adverse event profile

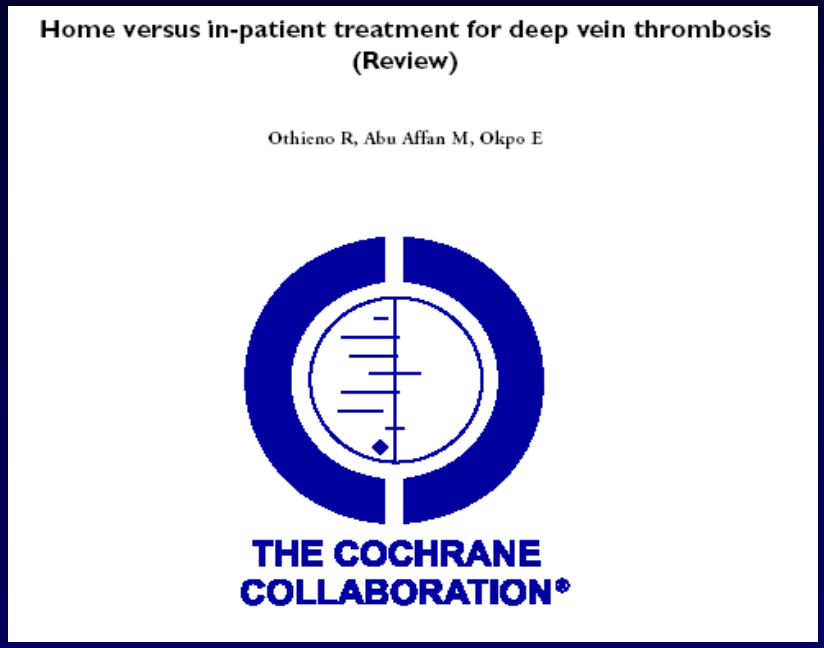
- Warfarin was the first cause of deaths for drugs causing adverse effects in therapeutic use
- Warfarin caused 8% of the 702.000 ADEs treated in ED/year: 17% required hospitalization

J Thromb Thrombolysis 2008



Vantaggi delle LMWH

1. Facilità di gestione della terapia
2. Riduzione dei tempi di ospedalizzazione rispetto al periodo di trattamento con eparina standard
3. Ottima maneggevolezza e sicurezza
4. Buona farmacocinetica. Dosaggio fisso pro-kg senza monitoraggio di laboratorio
5. Compatibile con i trattamenti a lungo termine.
6. Può essere usata in gravidanza



LMWHs – Major Drawbacks -

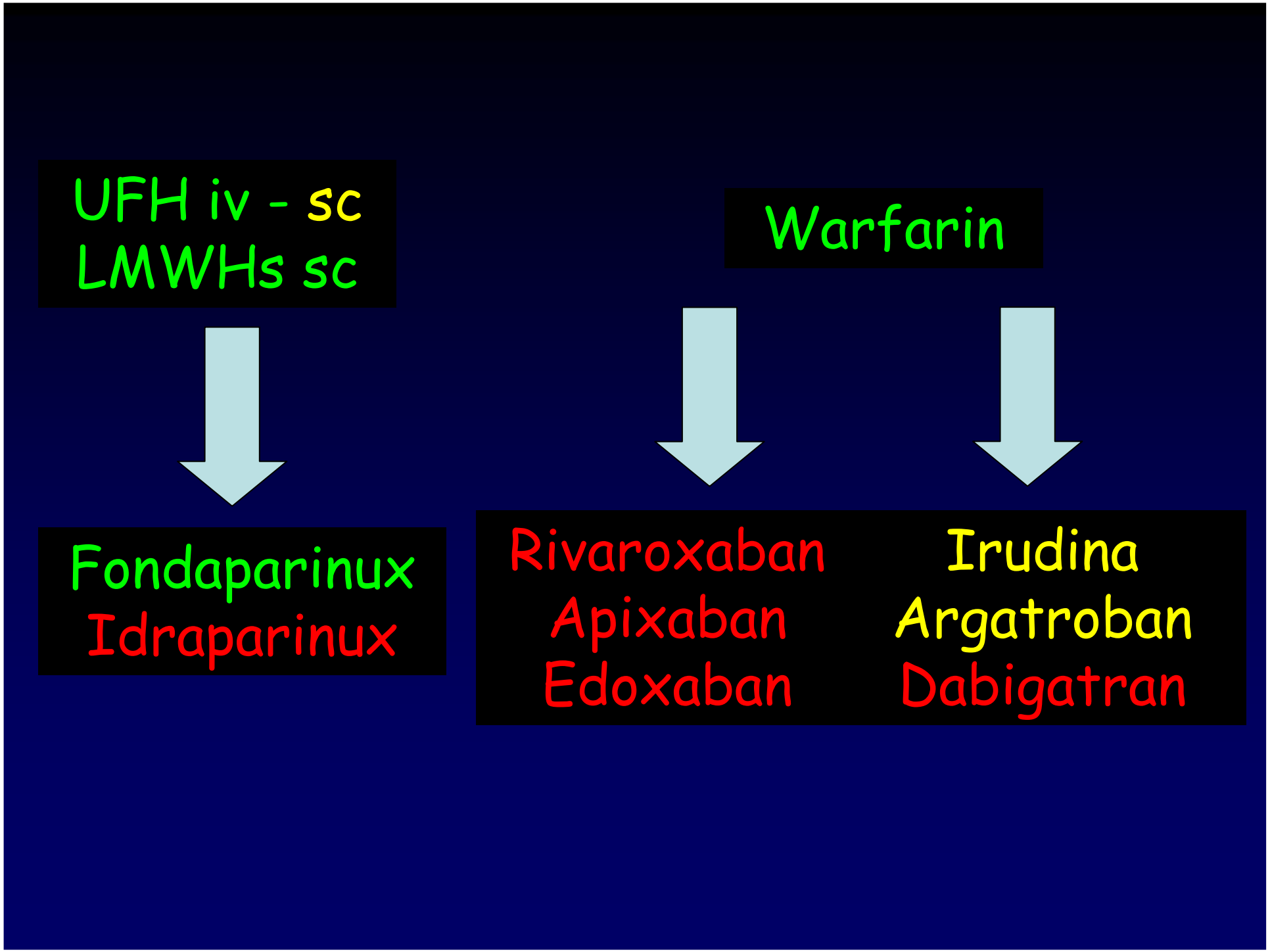
The Baxter Affair- 2008

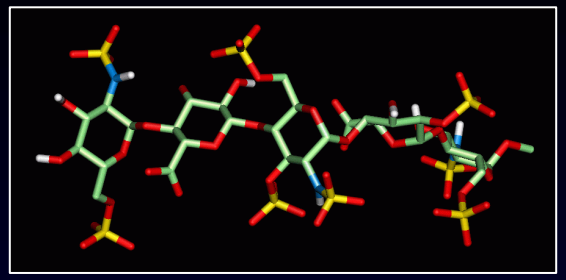
The drawbacks of UFH are reduced with LMWH, but:

- injections
- residual risk of HIT
- renal excretion
- dosage in special populations
- osteoporosis
- Animal extraction
- Allergies not so rare
- Risk of chemical/biological contamination of batches

This family-owned workshop in Xinwangzhuang, a village in Juangsu Province, China, processes pig intestines. Mucous membranes from the intestines are used to make heparin (**The New York Times, March 30, 2008**)

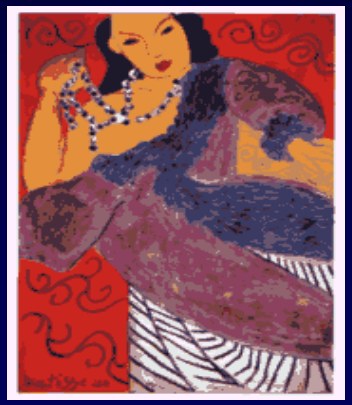
Contaminant : chondroitine hypersulfate (OSCS): 5 - 20%
Several severe Hypotension – anaphilactoid reactions


UFH iv - sc
LMWHs sc
Warfarin
Fondaparinux
Idraparinux
Rivaroxaban
Apixaban
Edoxaban
Irudina
Argatroban
Dabigatran



Fondaparinux

- Studio Rembrandt = Studio Fase II in TVP prox



PS VS ENOXAPARIN

- Studio Matisse DVT = Studio Fase III in TVP prox vs enoxaparina

PS VS UFH

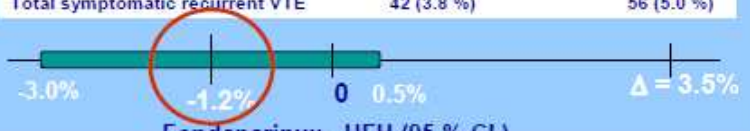
- Studio Matisse PE = Studio Fase III in PE vs UFH

Fondaparinux: Studio Matisse

Primary efficacy outcome – 3 months -

Matisse PE

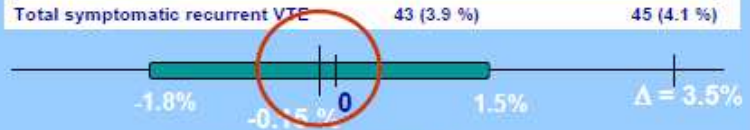
	Fondaparinux (N=1103)	UFH (N=1110)
Fatal PE	16 (1.5 %)	15 (1.4 %)
Non-fatal PE or DVT	26 (2.4 %)	41 (3.6 %)
Total symptomatic recurrent VTE	42 (3.8 %)	56 (5.0 %)



Fondaparinux - UFH (95 % CI)

Matisse DVT

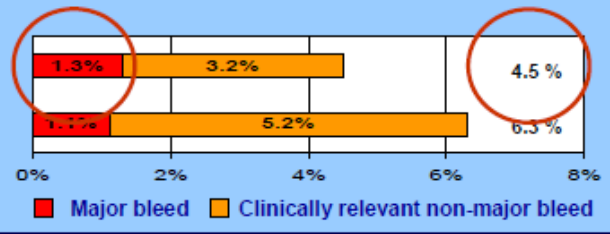
	Fondaparinux (N=1098)	LMWH (N=1107)
Fatal PE	5 (0.5 %)	5 (0.5 %)
Non-fatal PE or DVT	38 (3.5 %)	40 (3.6 %)
Total symptomatic recurrent VTE	43 (3.9 %)	45 (4.1 %)



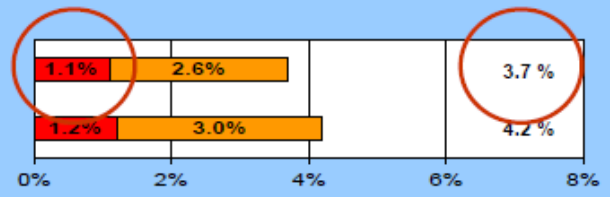
Fondaparinux - LMWH (95 % CI)

Principal Safety Outcome - initial treatment -

Matisse PE



Matisse DVT



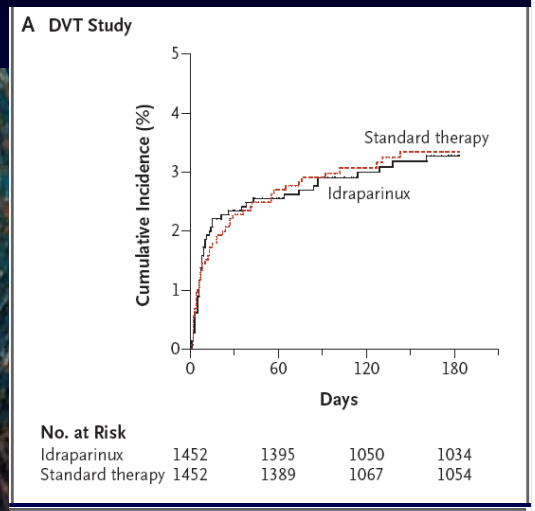
Potenziali Vantaggi Fondaparinux

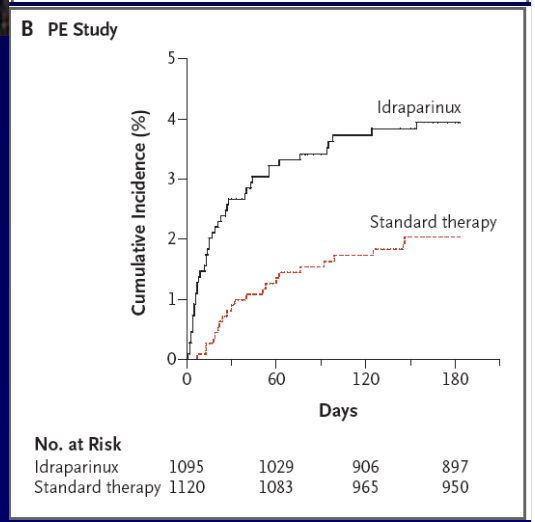
- Prodotto di origine sintetica
- Azione selettiva su Xa
- Azione Rapida
- Nessuna necessità di controlli laboratorio
- No HIT
- Monosomministrazione giornaliera
- 5 mg (< 50 Kg), 7.5 mg (50-100 Kg), 10 mg (> 100 Kg).
-

** Fondaparinux da non usare se clearance creat < 30 ml/Min

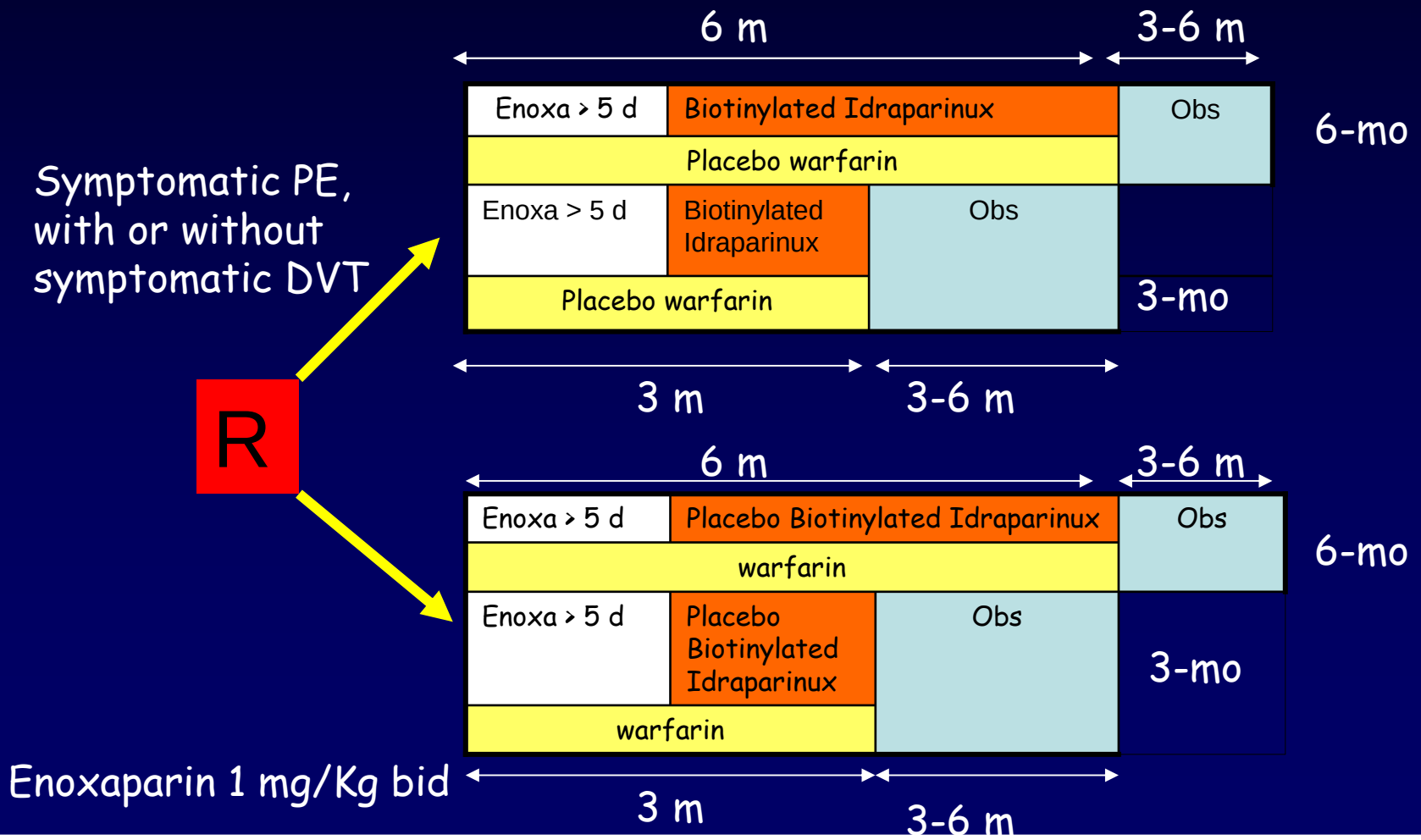
Idraparinux e Idraparinux biotinilato

- Studio Persist = Studio Fase II in TVP prox
- Studio Van Gogh DVT = Studio Fase III in TVP prox
- Studio Van Gogh PE = Studio Fase III in PE
- Studio Van Gogh Extension = Studio Fase III su durata ottimale terapia
- Cassiopea

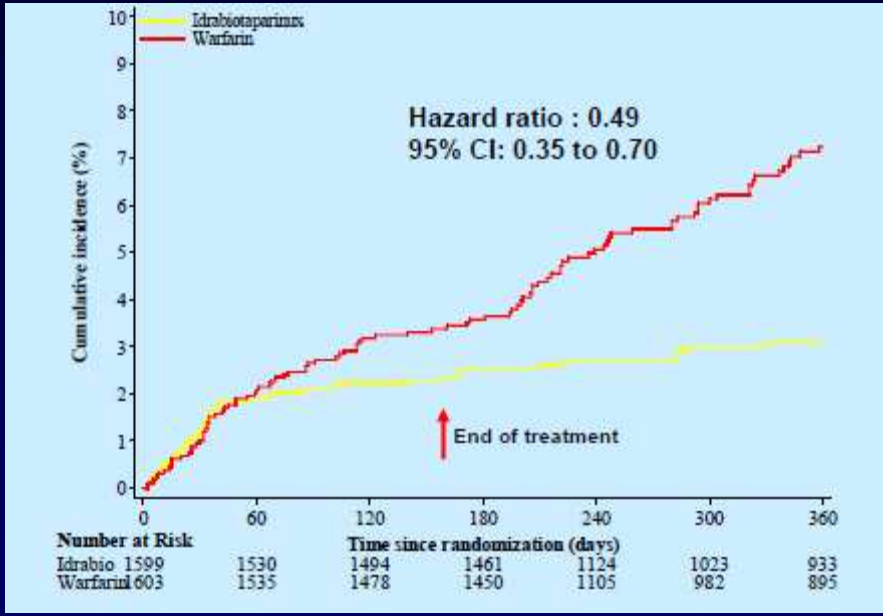




CASSIOPEA study design
3,200 patients with PE

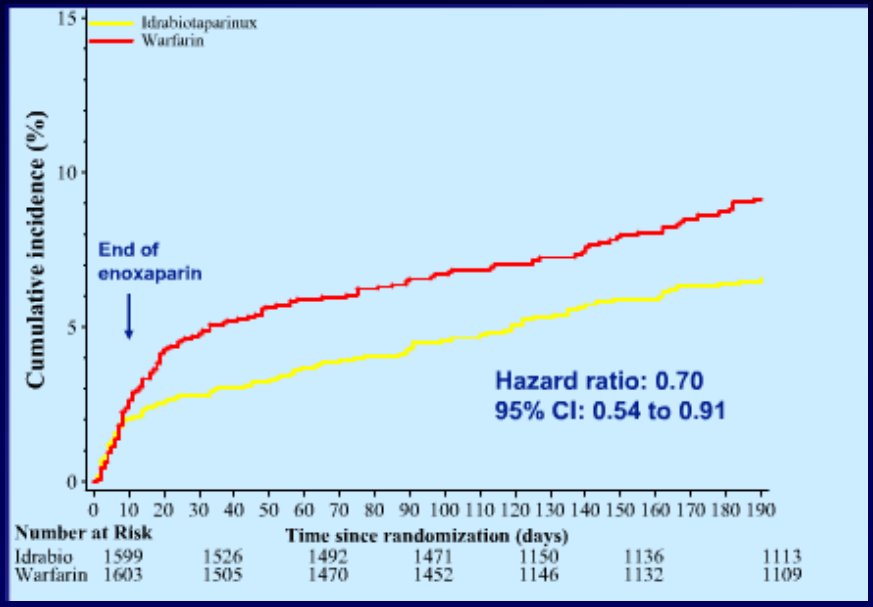


Efficacy



Kaplan-Meier cumulative incidence of PE/DVT (fatal or not) up to the end of study - Randomized population

Bleeding



Kaplan-Meier cumulative incidence of Clinically Relevant Bleedings up to the end of study - Randomized population

CONCLUSION

- Idrabiotaparinux, weekly administration, after initial treatment with enoxaparin, is:
  - As effective as adjusted daily dose of warfarin for long term treatment and prevention of venous thromboembolism in patients with PE with or without DVT.
  - Associated with less bleeding.

- Protective effect of idrabiotaparinux sustained along 6 additional months after treatment cessation without impact on bleeding risk.

- These results confirm idrabiotaparinux weekly administration as efficient and safe alternative to the daily oral anticoagulants in PE treatment.

The 'ideal' oral anticoagulant

- Oral, preferably once daily
- Rapid onset and offset of action
- Predictable PK and PD
- Low propensity for food and drug interactions
- Fixed doses
- Wide therapeutic window
- Few side effects
- $\Rightarrow$ Easy to use with no need for monitoring

FX functions

- FX occupies a critical juncture in the coagulation cascade - principal mediator of thrombin generation from prothrombin via the prothrombinase complex.
- Limited other functions
  - Weak proinflammatory and proliferative activities
  - No direct effect on platelet activation

Why target FXa ?

- Inhibition earlier in the cascade = Activation of one molecule of FX results in the generation of 1000 molecules of FIIa (concept of amplification) = FXa is more thrombogenic than thrombin.
- Response curve of Xa suggests a wider therapeutic window than anti-IIa
- Restricted activity to FXa

FII functions

Procoagulant
- Fibrin formation
- Platelet activation
- Feedback activation
- TAFI activation

Anticoagulant
- Protein C activation
- Prostacyclin formation

Inflammation
- P-selectin expression
- Cell adhesion
- Chemotaxis

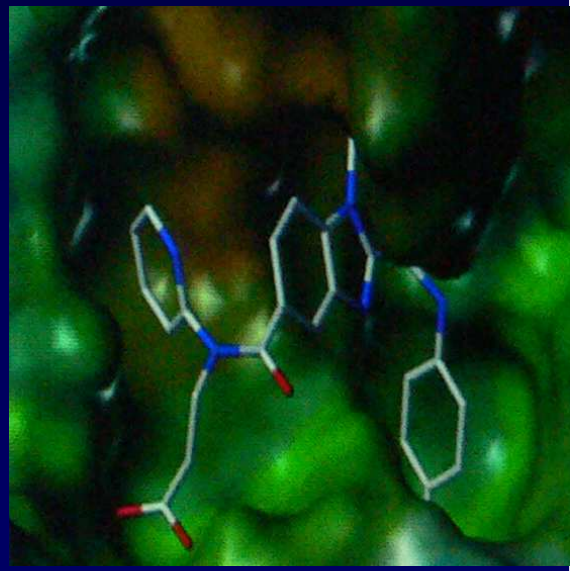
Cellular Proliferation
- Tissue repair
- Grow factor secretion
- Angiogenesis

Why target FII ?

- Inhibition of thrombin and clotting factors activation by thrombin (F V, F VIII, F XIII, PC, TAFI). Thrombin amplifies its own generation by activating FV e FVIII key factors for intrinsic tenase and prothrombinase (feed back activation).
- Inhibition of already formed thrombin

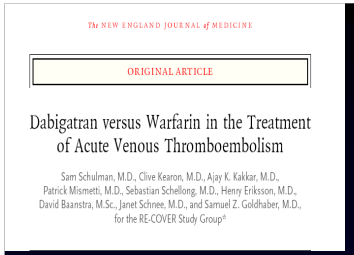
Dabigatran Etexilate - Pradaxa

- Inbitore diretto della trombina sia libera che legata al trombo, specifico e reversibile
- Di sintesi, Profarmaco
- Biodisponibilità relativamente bassa = 5-7%
- Picco plasmatico in 2-6 ore, Emivita 12-17 ore.
- PK/PD prevedibile e non influenzata da alimenti = dosi fisse e nessuna necessità monitoraggio coagulazione
- Escrezione renale = 80%
- Assenza di metabolizzazione da parte del CYP450
- Non emersa tossicità epatica



Dabigatran etexilate Program

Prevention VTE in elective hip/knee (Renovate I e II; Remodel, Remobilize)	Phase III
Treatment of VTE (Recover I e II; Remedy, Resonate)	Phase III
ACS (Redeem)	
Atrial fibrillation (Rely)	Phase III



RE-COVER™ Trial Design

Single-dummy period

Double-dummy period

Warfarin placebo

Dabigatran etexilate 150 mg bid

Warfarin placebo

30 days follow up

Objective confirmation of VTE

72 h

Warfarin

Initial parenteral therapy

Dabigatran etexilate placebo bid

Warfarin (INR 2.0–3.0)

E

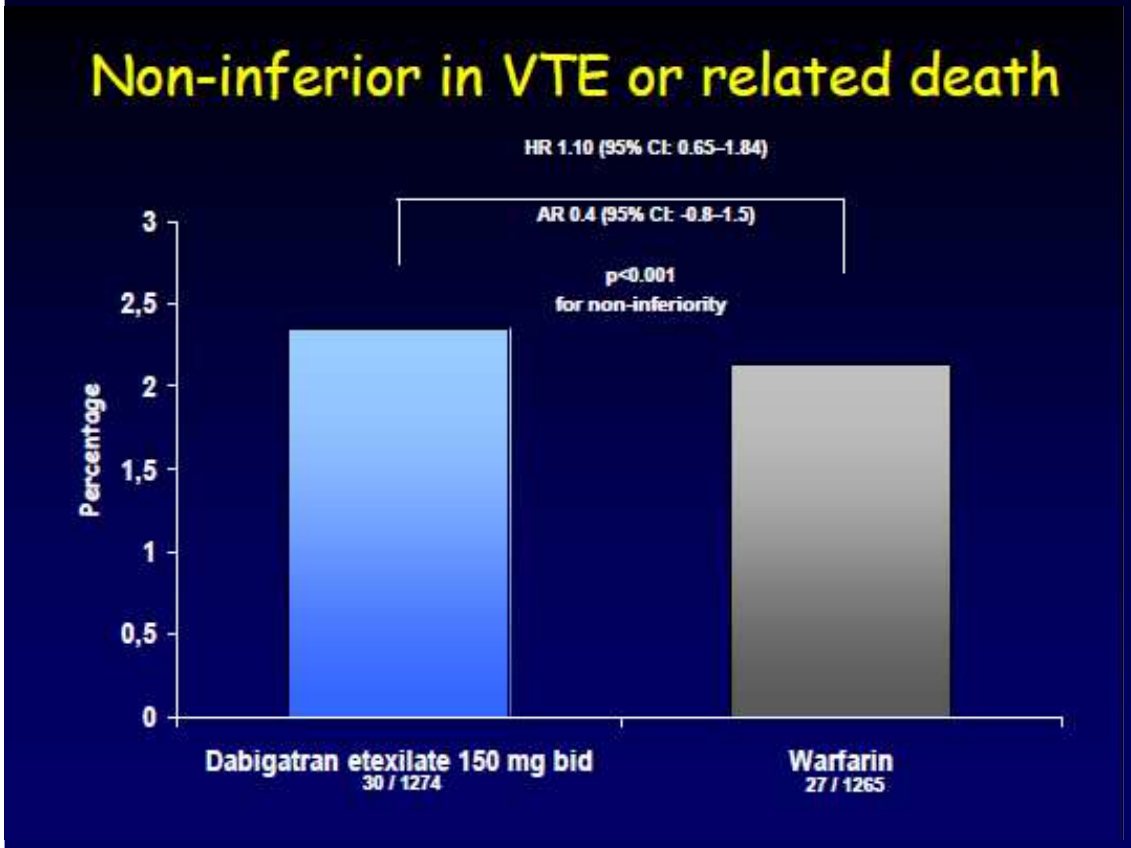
R

Until INR ≥2.0 at two consecutive measurements (8-11 days)

6 months End of treatment

E= enrolment
R= randomization

RE-COVER™ Trial Design



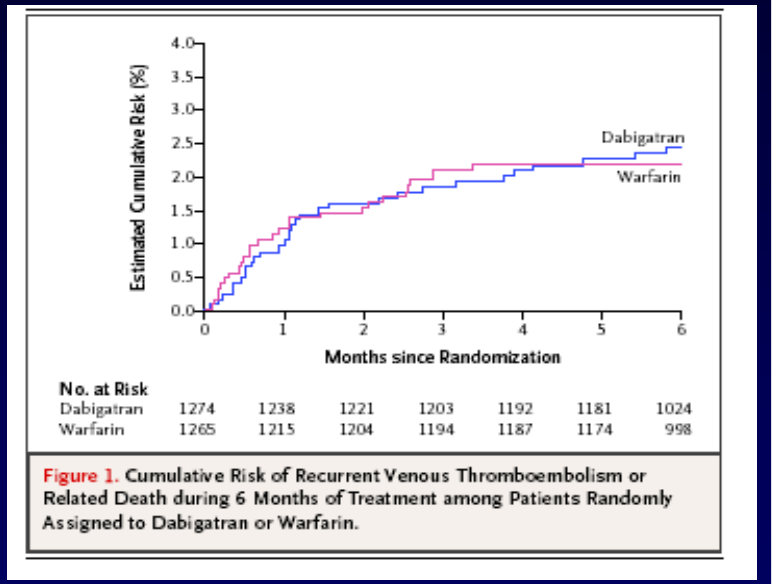
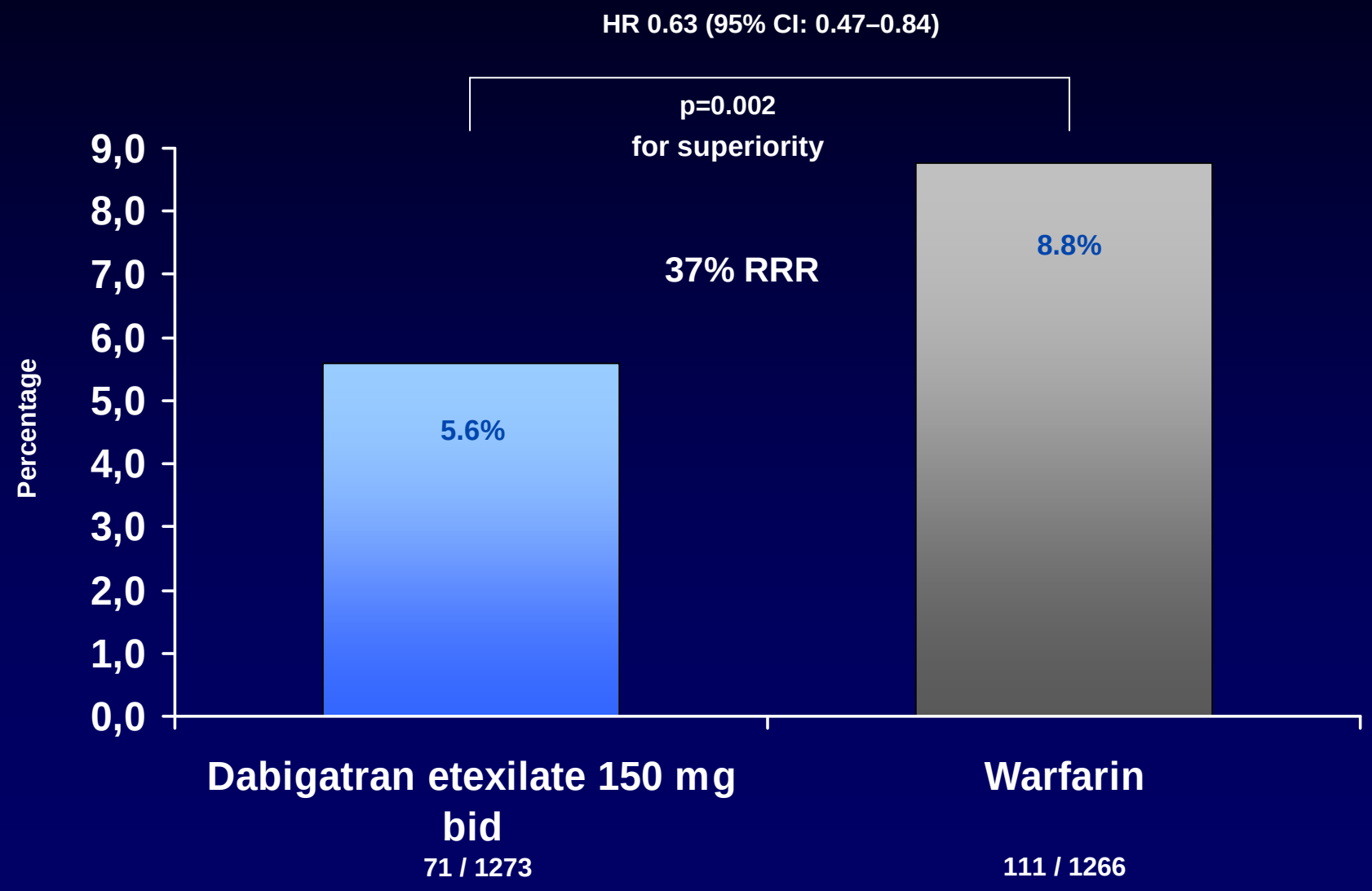
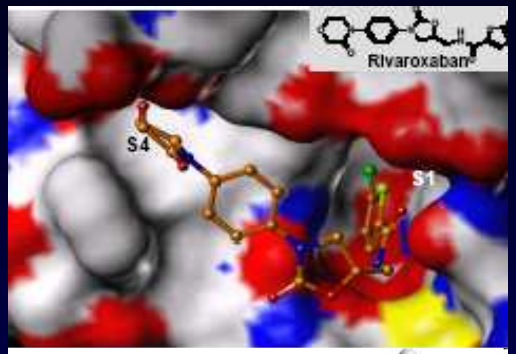


Figure 1. Cumulative Risk of Recurrent Venous Thromboembolism or Related Death during 6 Months of Treatment among Patients Randomly Assigned to Dabigatran or Warfarin.

Significant reduction in major / clinically relevant bleeds



Rivaroxaban Xarelto ®



Oral, direct Factor Xa inhibitor, with high selectivity for Factor Xa(k1 0.4±0.02 nM).

Reversibly inhibits free and clot-bound Factor Xa activity, prothrombinase activity and thrombin generation.

Oxazolidone derivative with more than 80% bioavailability after oral administration.

- Rapid onset of action
- Half-life: 7–11 hours
- Dual mode of elimination:
  - 1/3 of drug excreted unchanged by the kidneys
  - 2/3 of drug metabolized by the liver: half excreted renally; half excreted by the fecal route
- No dietary restrictions

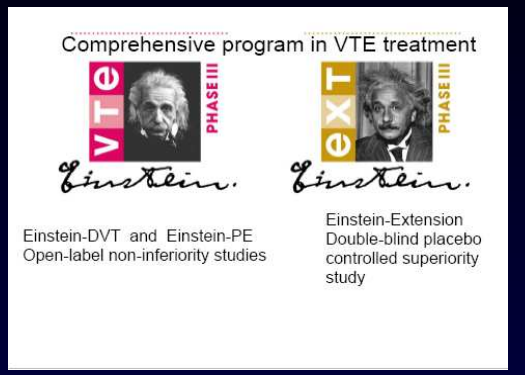
Perzborn et al, J Thromb Haemost 2005

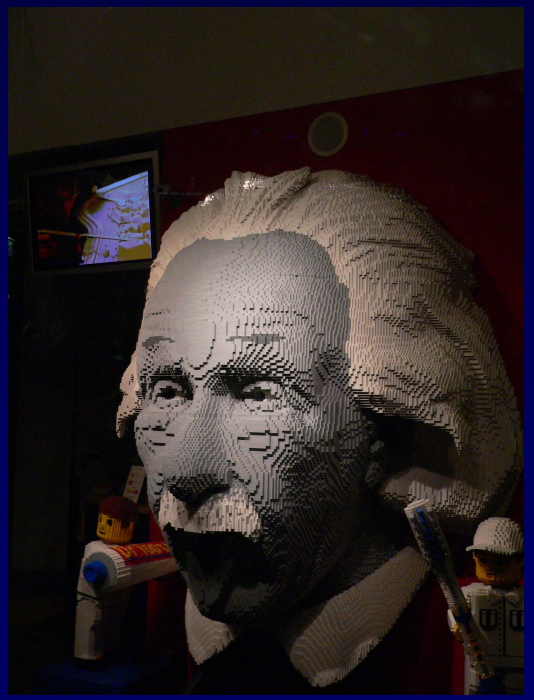
Rivaroxaban Xarelto ® : Clinical program overview: 50,000 patients to be enrolled

	Phase II	Phase III
VTE prevention	ODIXa-HIP1 ODIXa-HIP2 ODIXa-KNEE ODIXa-OD-HIP	RECORD RECORD1 RECORD2 RECORD3 RECORD4
VTE prevention in hospitalized medically ill patients		MAGELLAN
VTE treatment	ODIXa-DVT **EINSTEIN-DVT**	 **EINSTEIN-DVT** **EINSTEIN-PE** EINSTEIN-EXT
Stroke prevention in atrial fibrillation		ROCKET AF Japanese Phase III Study
Secondary prevention of acute coronary syndrome	ATLAS	

Rivaroxaban

- Odixa – DVT = fase II in TVP prossimale
- Einstein Study II = fase II in TVP prossimale
- Einstein III – DVT = fase III in TVP prossimale
- Einstein III – PE = fase III in PE
- Einstein Extension

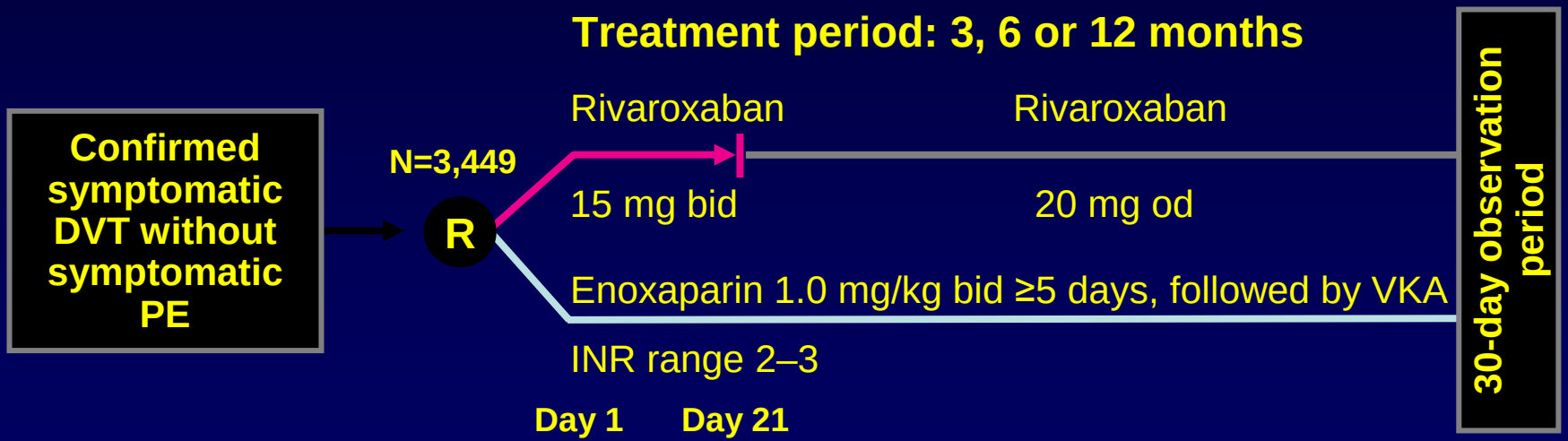




EINSTEIN DVT: study design

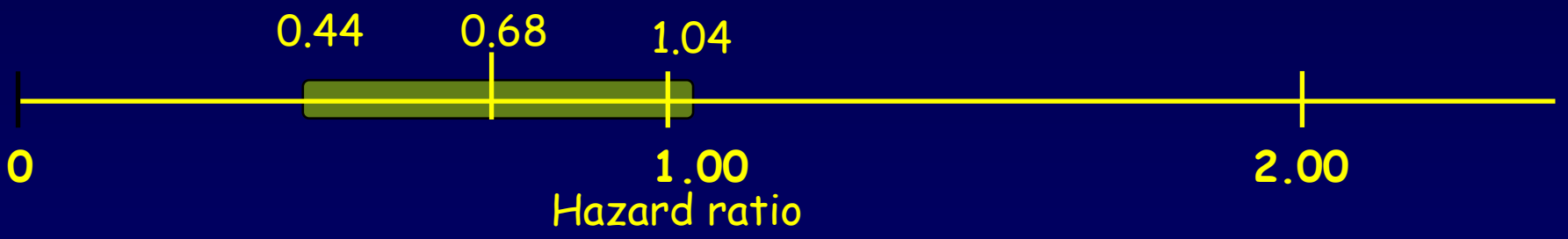
Randomized, open-label, event-driven, non-inferiority study

- Up to 48 hours' heparins/fondaparinux treatment permitted before study entry
- 88 primary efficacy outcomes needed



Primary efficacy outcome analysis

	Rivaroxaban (n=1,731)		Enoxaparin/VKA (n=1,718)	
	n	(%)	n	(%)
First symptomatic recurrent VTE	**36**	**(2.1)**	**51**	**(3.0)**
Recurrent DVT	14	(0.8)	28	(1.6)
Recurrent DVT + PE	1	(<0.1)	0	(0)
Non-fatal PE	20	(1.2)	18	(1.0)
Fatal PE/unexplained death where PE cannot be ruled out	4	(0.2)	6	(0.3)



Rivaroxaban superior | Rivaroxaban non-inferior | Rivaroxaban inferior

p=0.076 for superiority (two-sided)

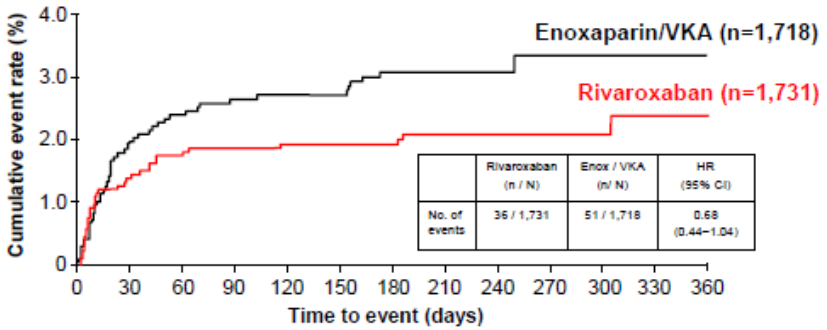
p<0.0001 for non-inferiority (one-sided)

ITT population

EINSTEIN DVT trial

EINSTEIN DVT

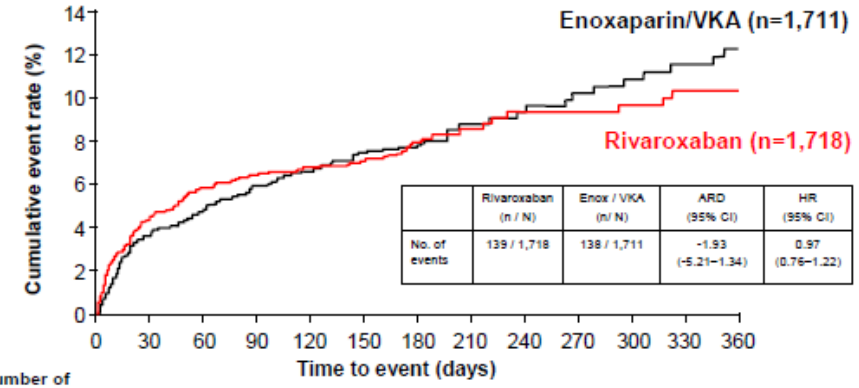
Primary efficacy outcome: time to first event



Number of subjects at risk													
Rivaroxaban	1,731	1,668	1,648	1,621	1,424	1,412	1,220	400	369	363	345	309	266
Enox/VKA	1,718	1,616	1,581	1,553	1,368	1,358	1,186	380	362	337	325	297	264

EINSTEIN DVT trial [34]

Principal safety outcome: time to first event



Number of subjects at risk													
Rivaroxaban	1,718	1,585	1,538	1,382	1,317	1,297	715	355	338	304	278	265	140
Enox/VKA	1,711	1,554	1,503	1,340	1,263	1,238	619	338	321	287	268	249	118

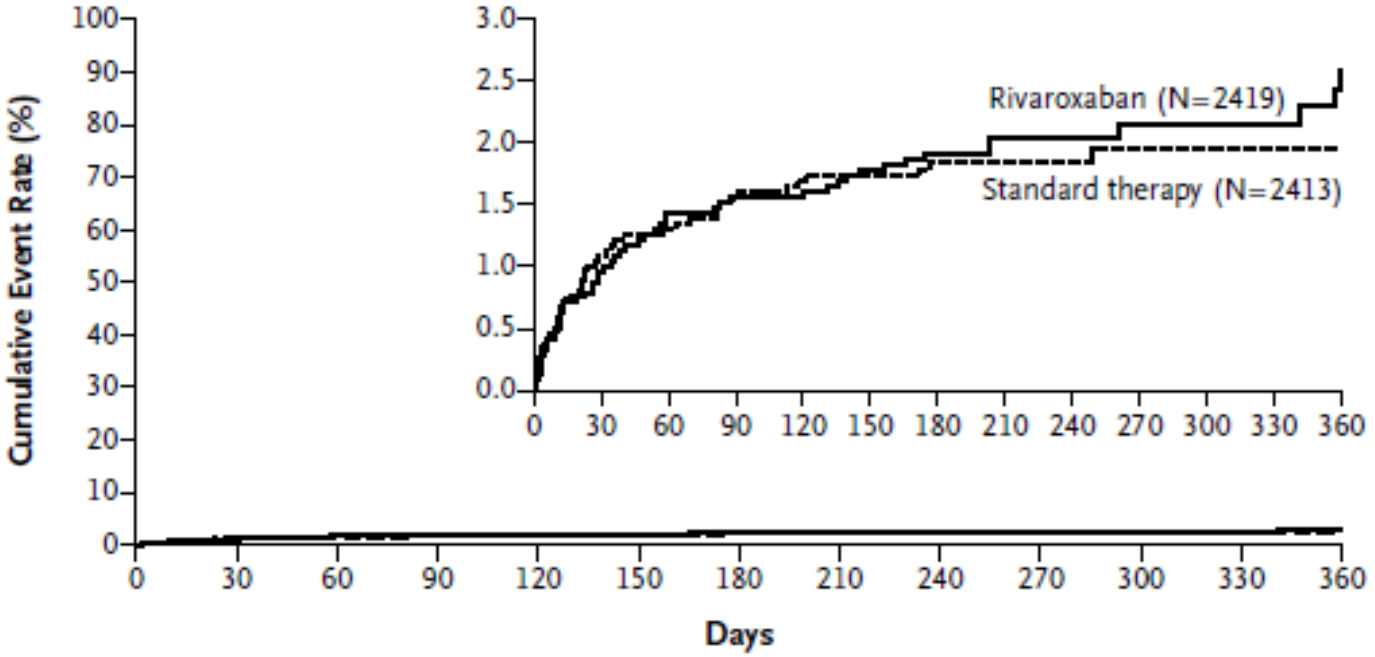
EINSTEIN DVT trial [35]

Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism

The EINSTEIN–PE Investigators*

N Engl J Med 2012;366:1287-97.

A Primary Efficacy



No. at Risk

Rivaroxaban	2419	2350	2321	2303	2180	2167	2063	837	794	785	757	725	672
Standard therapy	2413	2316	2295	2273	2155	2146	2050	835	787	772	746	722	675

Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism

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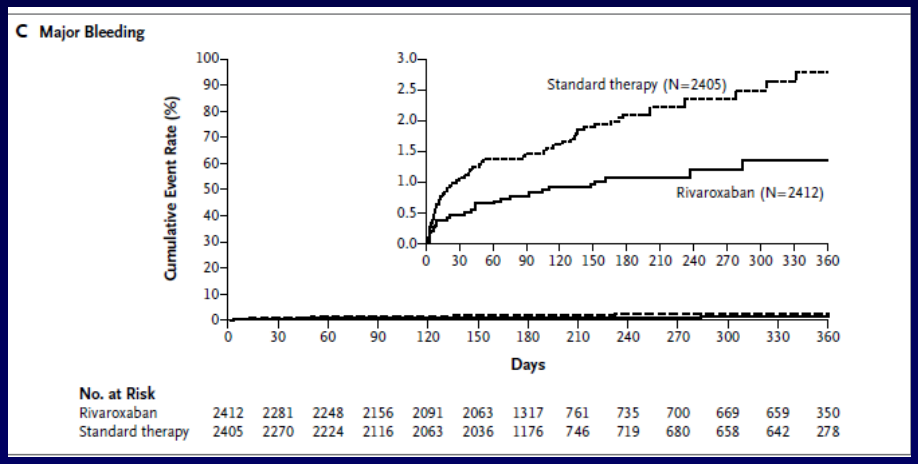
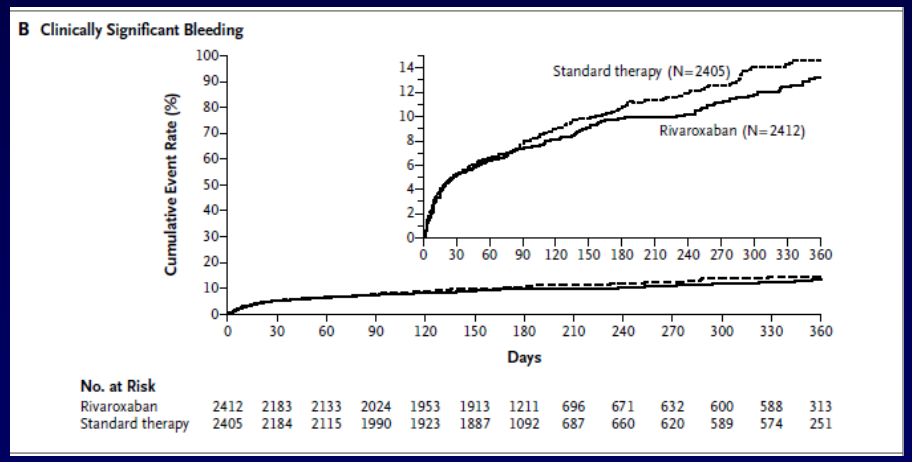




Apixaban and DVT-PE Treatment

- DVT Treatment Botticelli Study = Studio Fase II in TVP prossimale
- Amplify Study = studio fase III in TVP prossimale ed PE (4800 pts)

Journal of Thrombosis and Haemostasis, 6: 1313–1318 DOI: 10.1111/j.1538-7836.2008.03054.x

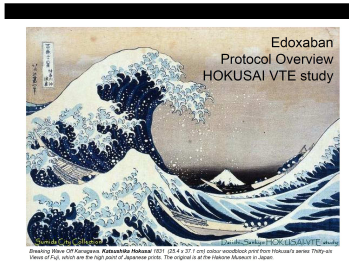
ORIGINAL ARTICLE

Efficacy and safety of the oral direct factor Xa inhibitor apixaban for symptomatic deep vein thrombosis. The Botticelli DVT dose-ranging study

ON BEHALF OF THE BOTTICELLI INVESTIGATORS,[1] THE WRITING COMMITTEE, H. BULLER,* D. DEITCHMAN,† M. PRINS‡ and A. SEGERS*§

Bleeding Events

	Apixaban 5 mg bid (n=128)	Apixaban 10 mg bid (n=133)	Apixaban 20 mg od (n=124)	LMWH = VKA (n=126)
Major or clinically relevant non-major bleeding	11	6	9	10
Event rate (%)	8.5	4.5	7.3	7.9
95% CI	4.4, 14.9	1.7, 9.6	3.4, 13.3	3.9. 14.1
Major bleeding	1	0	1	0
Event rate (%)	0.8	0	0.8	0
95% CI	0, 4.3	0, 2.7	0, 4.4	0, 2.9

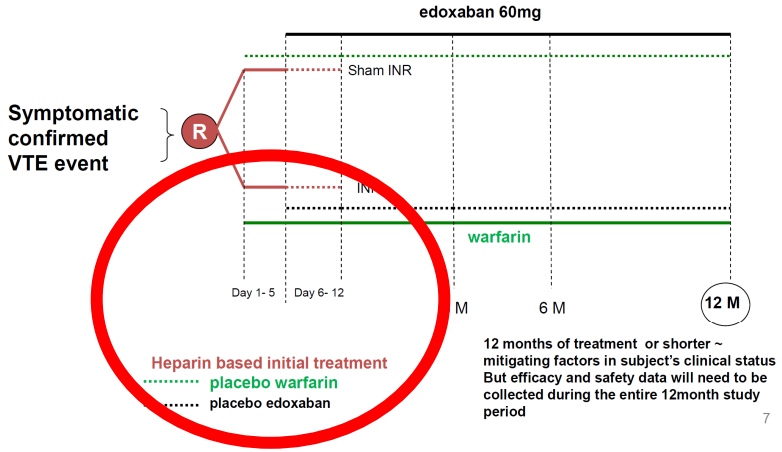


Hokusai VTE

Design

Hokusai VTE

Randomized double blind study with clinical outcomes



Double blind treatment Edoxaban-Warfarin

Hokusai VTE

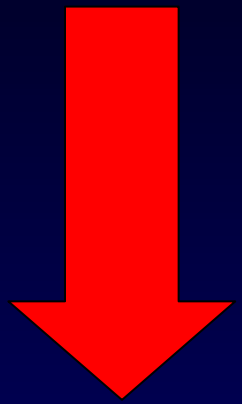
Edoxaban group

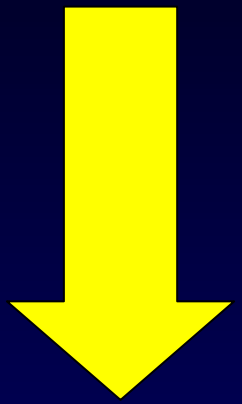
- Edoxaban
  - 60 mg od
  - 30 mg od in patients wit
    - Body weight ≤ 60 Kg
    - Calculated CrCl 0 – 50 mL/min
    - Concomitant use of strong PgP inhibitors : verapamil, quinidine
- Warfarin placebo

Warfarin group

- warfarin, INR 2-3 (target 2.5)
- Edoxaban placebo

LA RECIDIVA DI TVP

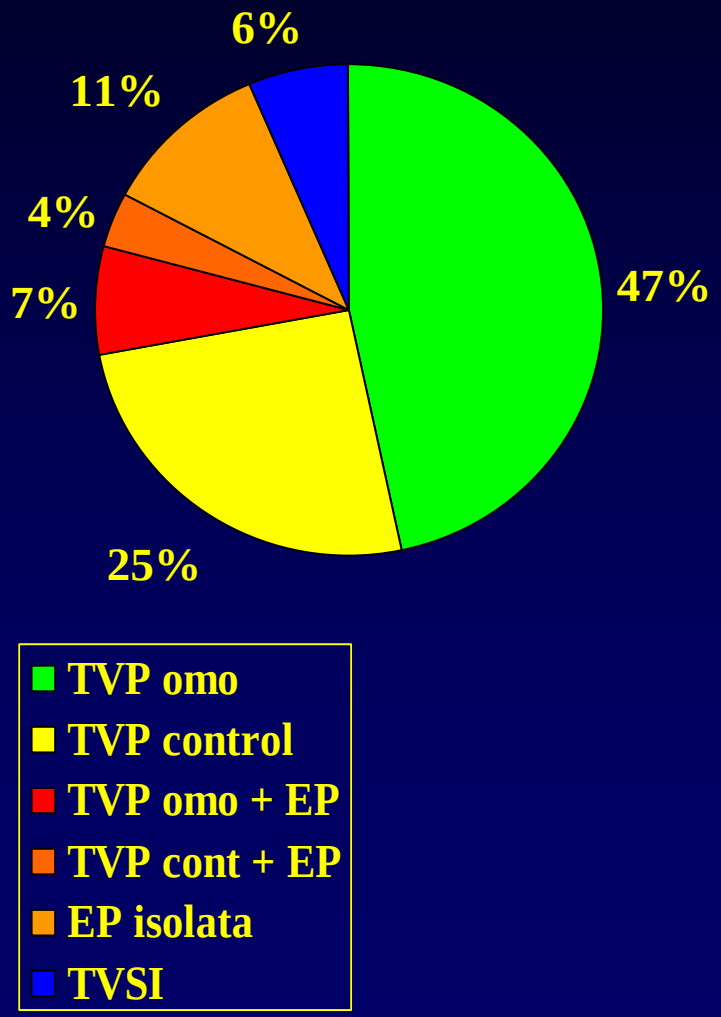




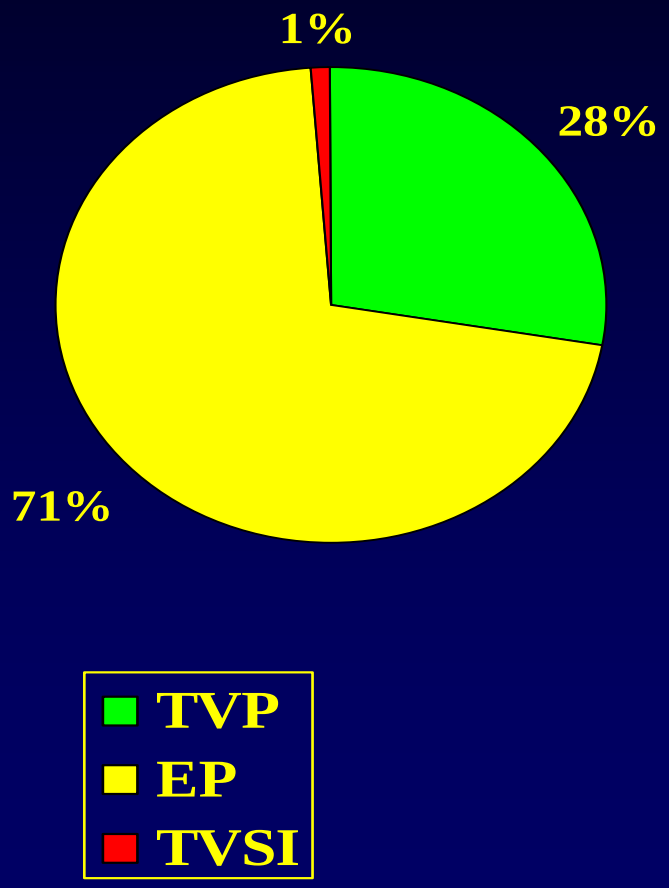
In Corso di Terapia

Dopo Sospensione della Terapia

Recidive di MTV con 1^ evento TVP prossimale



Recidive di MTV con 1^ evento EP



LA RECIDIVA DI TVP/EP DOPO SOSPENSIONE TERAPIA

TVP non provocata o con fattori di rischio permanenti →
- A 1 anno = 7-14%
- A 5 anni = 15-30%

5-15%

TVP provocata da fattori di rischio removibili →
- A 1 anno = 3%
- A 5 anni = 5%

La frequenza non cambia in base al tipo di durata della terapia anticogulante (3-24 mesi)

(Prandoni, Ann Intern Med 1996; Zurich Study, Circulation 1996; Hansson P-O, Arch Int Med 2000; Heit, Arch Int Med 2000).

ARTICLE | Annals of Internal Medicine

The Risk for Fatal Pulmonary Embolism after Discontinuing Anticoagulant Therapy for Venous Thromboembolism

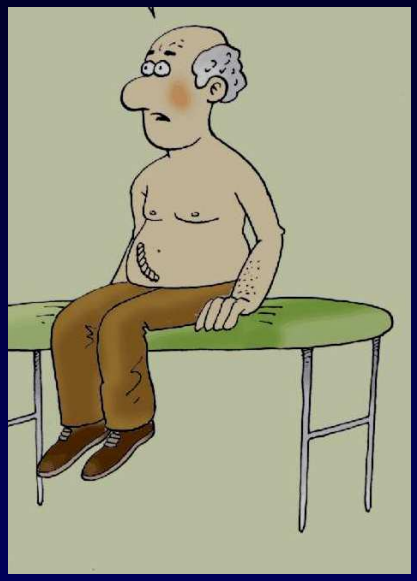
James D. Douketis, MD; Chu Shu Gu, MSc; Sam Schulman, MD, PhD; Angelo Ghirarduzzi, MD; Vittorio Pengo, MD; and Paolo Prandoni, MD, PhD

- Il rischio di decesso per EP fatale = 0.19-0.49 / 100 persone / anno
- 1^ anno = incidenza 0.35-0.81%
- anni successivi = 0.15-0.40 / 100 persone / anno

- Il case-fatality rate della recidiva di PE = 3.8-9%

- Età (HR 2.12 CI, 1.58-2.81)
- TEV non provocata (HR 2.42 CI, 1.20-4.90)
- PE vs TVP n.s.
  - DVT = 3.8-8.5%
  - PE = 5.7-12.3%
  - PE+DVT =2.7-8.9%

Durata Ottimale Terapia Antitrombotica



1000 sospensioni terapia per TEV

- 100 recidive a 1 anno; 200 a 5 anni
- 7-8 decessi a 1 anno; 10 decessi a 5 anni

1000 prosecuzioni di terapia per TEV

- 10 Emorragie Maggiori a 1 anno; 20 a 5 anni
- 50 Emorragie Clinicamente rilevanti a 1 anno e 150 a 5 anni
- 1 decesso a 1 anno e 5 decessi a 5 anni

Options after the initial VKA treatment

Withdraw Rx with low risk of recurrence

Extend VKA in moderate-High risk of recurrence

Withdraw Rx with High clinical burden (bleeding) = select patients with not acceptable management burden (bleeding) = <u>intermediate duration of treatment or low-intensity of anticoagulant effect</u>

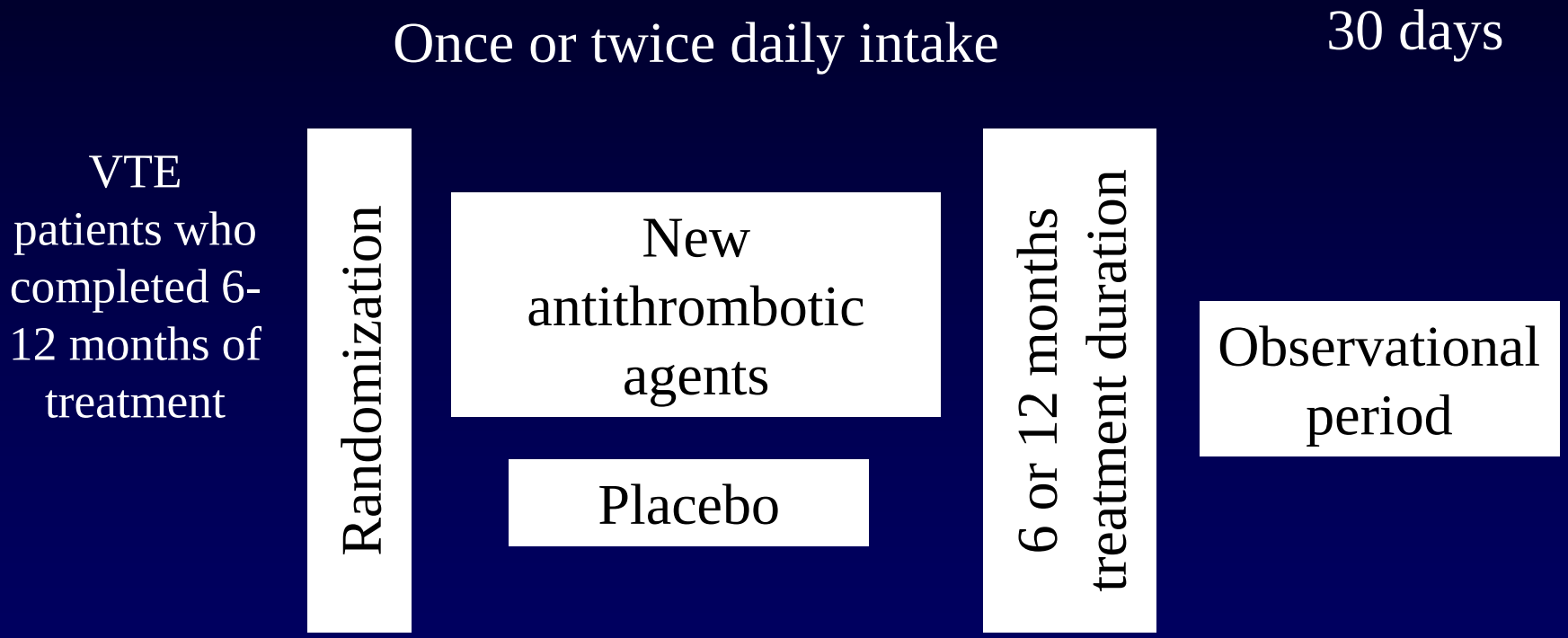
Indefinite duration of Anticoagulant treatment

New Strategies

- Modulate intensity of Anticoagulant effect
- Other Drugs ASA, Statins
- New antithrombotics with better profile

Patient's preference

Extension studies (Secondary Prophylaxis)



Dabigatran etexilate: Remedy Study 1160.47

Objectives	Efficacy and safety od Dabigatran Etexilate 150 mg bid vs warfarin for long-term treatment and secondary prevention of symptomatic VTE
Study Design	Randomized, double-blind, parallel, active,controlled trial
Patient Population	Male and female patients with confirmed symptomatic DVT or PE that have been treated with approved anticoagulant or study drug (in Trial 1160.53)
Treatment	18 months
Endpoints	Primary: recurrent symptomatic VTE and deaths related to VTE. Secondary: DVT, PE, all deaths 18 months
Treatment Groups	Dabigatran Etexilate 150 mg bid vs Warfarin INR 2-3
Endpoints Number of Subjects (Total)	Target enrolment of 1000 patients per treatment group

Dabigatran etexilate: Remedy Study 1160.47

Outcome	Dabigatran (n=1430), n (%)	Warfarin (n=1426), n (%)	HR	p
Recurrent VTE	26 (1.8)	18 (1.3)	1.44	0.03[a]
Deaths	17	19	0.90	NS
Major bleeds	13 (0.9)	25 (1.8)	0.52	0.058
Any bleeding	277 (19)	373 (26)	0.71	<0.0001
ACS	13 (0.9)	3 (0.2)	__[b]	0.02

a. p for noninferiority

b. HR for ACS was not a planned analysis

Dabigatran etexilate: Resonate

- Patients with VTE, with 6-18 months anticoagulants, randomized to placebo or dabigatran 150mg bd for 6 months
- Efficacy (VTE recurrence)
  - Dabigatran 3/681 (0.4%)
  - Placebo 37/662 (5.6%)

    H.R. 0.08 (0.02-0.25)

- Patients with VTE, with 6-18 months anticoagulants, randomized to placebo or dabigatran 150mg bd for 6 months
- Efficacy (VTE recurrence)
  - Dabigatran 3/681 (0.4%)
  - Placebo 37/662 (5.6%)

    H.R. 0.08 (0.02-0.25)

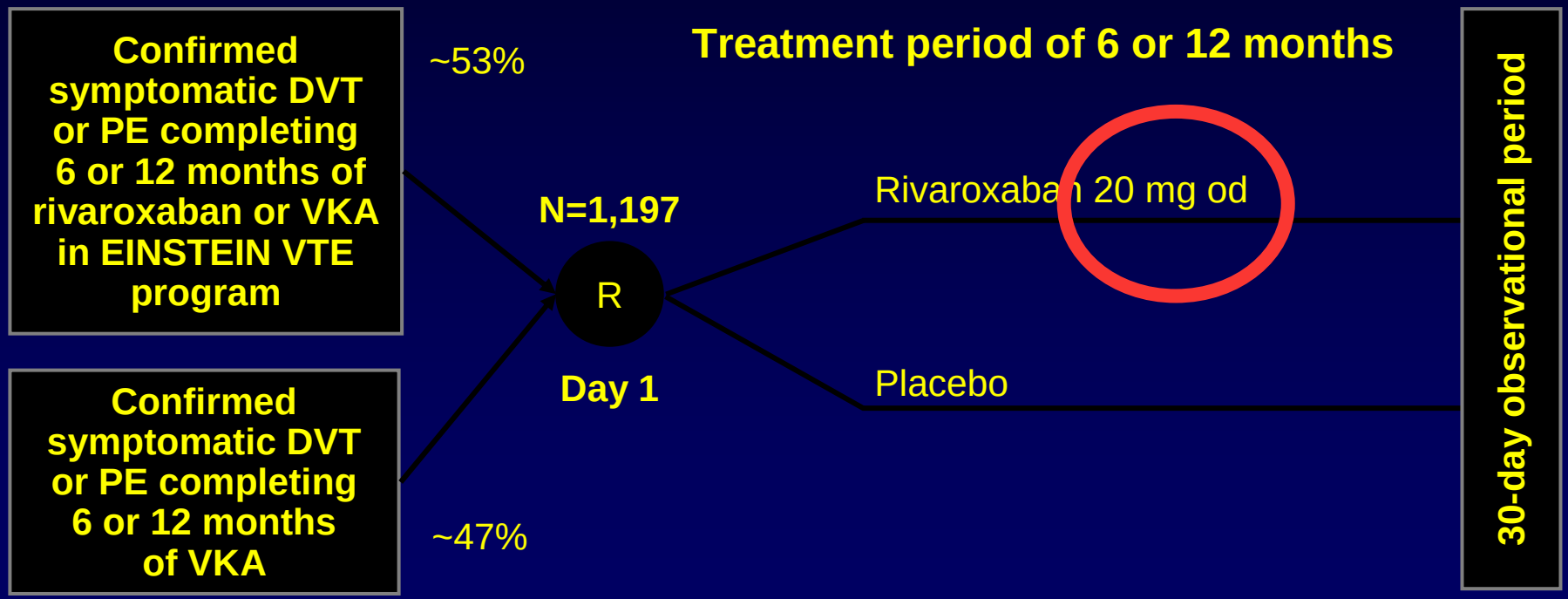
- Safety (Major bleeding)
  - Dabigatran 2/681 (0.4%)
  - Placebo 0/662
- Safety (Clinically relevant bleeding)
  - Dabigatran 36/681 (5.3%)
  - Placebo 12/662 (1.8%)

    H.R. 2.9 (1.5-5.6)

RIVAROXABAN IN THE SECONDARY PREVENTION OF VTE: EINSTEIN EXTENSION STUDY DESIGN

Einstein-Extension
Double-blind placebo controlled superiority study

Randomized, double-blind, placebo-controlled, event-driven (n=30), superiority study

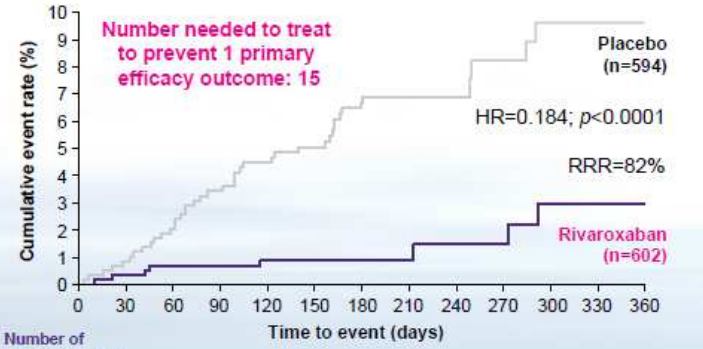


EINSTEIN Extension Trial ID: NCT00439725

RIVAROXABAN IN THE SECONDARY PREVENTION OF VTE: EINSTEIN EXTENSION STUDY DESIGN

Einstein-Extension
Double-blind placebo controlled superiority study

Primary efficacy outcome analysis (time to first event)



Number of subjects at risk													
Rivaroxaban	602	590	583	573	552	503	482	171	138	132	114	92	81
Placebo	594	582	570	554	521	467	444	164	138	133	110	93	85

ITT population

Primary efficacy outcome and individual components

	Placebo (n=594)		Rivaroxaban (n=602)	
Symptomatic recurrent VTE*	42	7.1%	8	1.3%
Recurrent DVT	31	5.2%	5	0.8%
Non-fatal PE	13	2.2%	2	0.3%
Fatal PE	1	0.2%	0	
Unexplained death (where PE cannot be excluded)	0		1	0.2%

Xarelto® rivaroxaban

ITT population; *some patients experienced more than one event

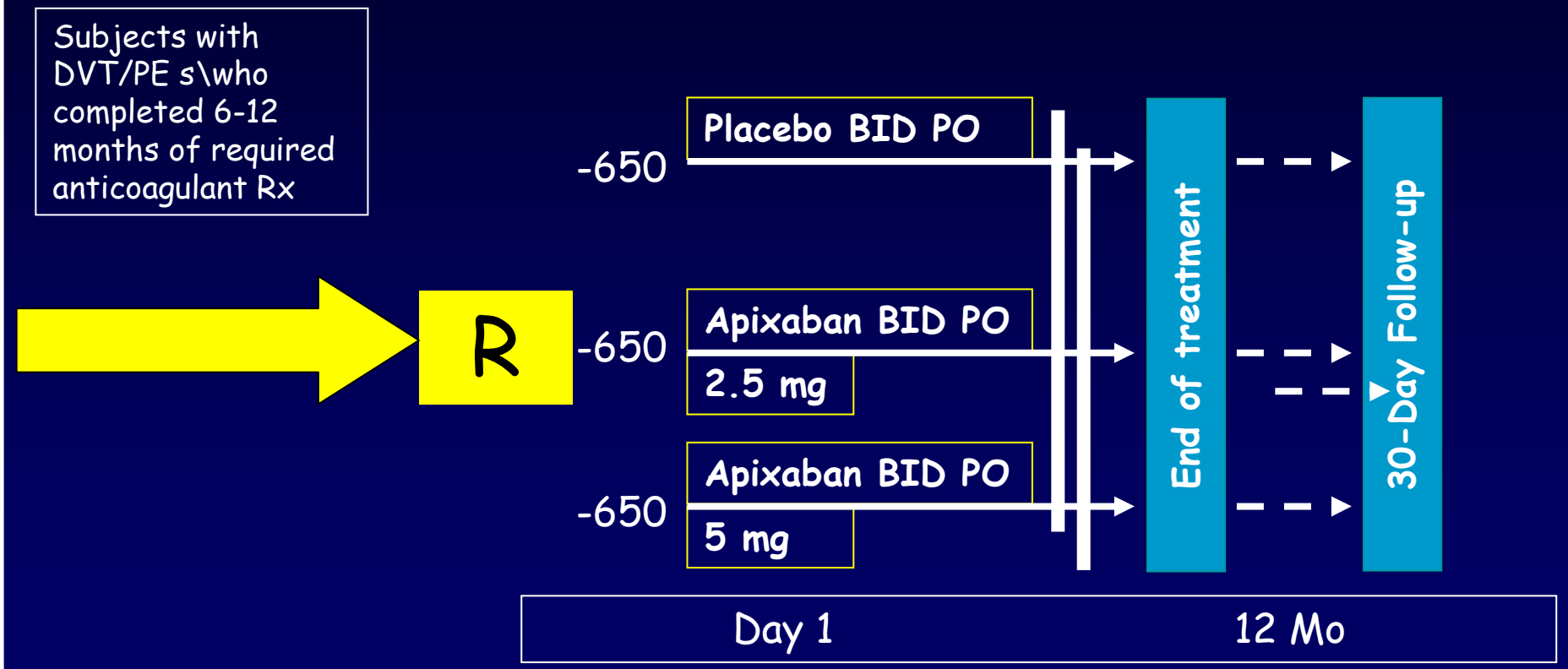
Conclusions

- In patients who had completed 6 or 12 months of anticoagulation, rivaroxaban showed:
  - An 82% relative risk reduction in the recurrence of VTE (HR=0.184; $p<0.0001$)
  - Absolute risk reduction 5.8% hence 15 patients need to be treated to prevent one recurrent VTE event
  - Low incidence of major bleeding (0.7%; $p=0.11$; NNH approximately 139)
  - Efficacy and safety results were consistent irrespective of bodyweight and creatinine clearance
  - Modest increase in clinically relevant non-major bleeding (5.4% vs 1.2%; $p<0.01$)
  - No signal for liver toxicity
- Oral rivaroxaban, 20 mg once-daily, provides clinicians and patients with a simple and effective option for continued anticoagulant treatment

EINSTEIN ext

Xarelto® rivaroxaban

Amplify - Extension



Enrollment ends after 78 adjudicated efficacy events occur and the last active subjects completes 12 months of study treatment / or after 120 adjudicated events

….non solo luci…
…problemi con i nuovi farmaci…

- Mancanza di antidoto (realmente abbiamo bisogno di un antidoto per farmaci con breve durata d'azione?)
- Necessità di un test di laboratorio per misurare la compliance (in caso di emorragia o trombosi)
- Necessità di un test di laboratorio per misurare l'effetto (chirurgia)
- Stesso farmaco per tutti i pazienti ? (metabolismo epatico o renale, durata d'azione, rischio trombotico, etc.)
- Farmaci diversi per diverse patologie? (TEV, FA, protesi valvolari cardiache)

Potential VTE Management Landscape

Name	Rivaroxaban	Apixaban	Dabigatran	Edoxaban
Company	Bayer/JNJ	BMS/Pfizer	Boehringer	Daiichi Sankyo
Time to Cmax	2-3 hr	3 hr	2 hr	2 hr
Bioavailability	> 40%	Good*	4-5%	> 45%
Disposition/ Metabolism	CYP3A/P-gp	CYP3A/P-gp	P-gp	P-gp
Protein binding	97%	87%	~50%	54%
Half life	5-9 hr	9-14 hr	14-17 hr	8-10 hr
Clearance	Renal: 66% Hepatic: ≤ 34%	Renal: 25% Hepatic: ≤ 75%	Renal: 80% Hepatic: ≤20%	Renal: 35% Hepatic: ≤ 65%
Linear PK	no	yes	unknown	yes

Potential VTE Management Landscape

	Rivaroxaban	Apixaban	Dabigatran	Edoxaban
Dose	20 mg	5 mg X 2	150 mg X 2	60 mg
Cl creat 30-50 ml/min	YES 15 mg ?	YES 2.5 mg X 2	YES 75mg 2cp/od	30 mg
Cl creat < 30 ml/min	NO < 15 ml/min	NO	NO	NO

Inibitori e Induttori del CYP3A

Inibitori moderati

Amprenavir
Ciprofloxacina
Diltiazem
Eritromicina
Fluconazolo
Fluvoxamina
Norfloxacina
Verapamil

Succo di pompelmo
Alcool in acuto
Noce moscata
Olio di sesamo

Inibitori potenti

Amiodarone
Atazanavir
Cisapride
Claritromicina
Indinavir
Itraconazolo
Ketoconazolo
Nefazodone
Nelfinavir
Ritonavir
Telitromicina
Troleandomicina
Voriconazolo

Induttori

Carbamazepina
Efavirenz
Nevirapina
Fenitoina
Fenobarbital
Rifabutina
Rifapentina
Rifampicina

Erba di San Giovanni
Alcool in cronico
Eucaliptolo

The Medical Letter, XXXIV, 17, 2005

Inibitori della P-glicoproteina

Strutture ad anello triciclico	**Alcaloidi**	**Neurolettici**
Fenotiazina, Acridina "Orange", Acido carboxilico	Colchicina, Reserpina	Fenotiazina, Tioxanteni
Antifungini	**Antimalarici**	**Antiaritmici**
ketoconazolo	Primaquina Cloroquina	Chinidina
Ca-antagonisti	**Immunosoppressori**	**???**
verapamil	ciclosporina	

Induttori della P-glicoproteina

desametasone
iperico
rifampicina

Brinkmann U, Eichelbaum M. The Pharmacogenomics journal : 2001, VOL. 1, P: 59-64.


Cosa ci aspetta il futuro ?

Grazie per
l'attenzione !!!