New Oral Anticoagulants Prevention and Treatment of DVT and PE

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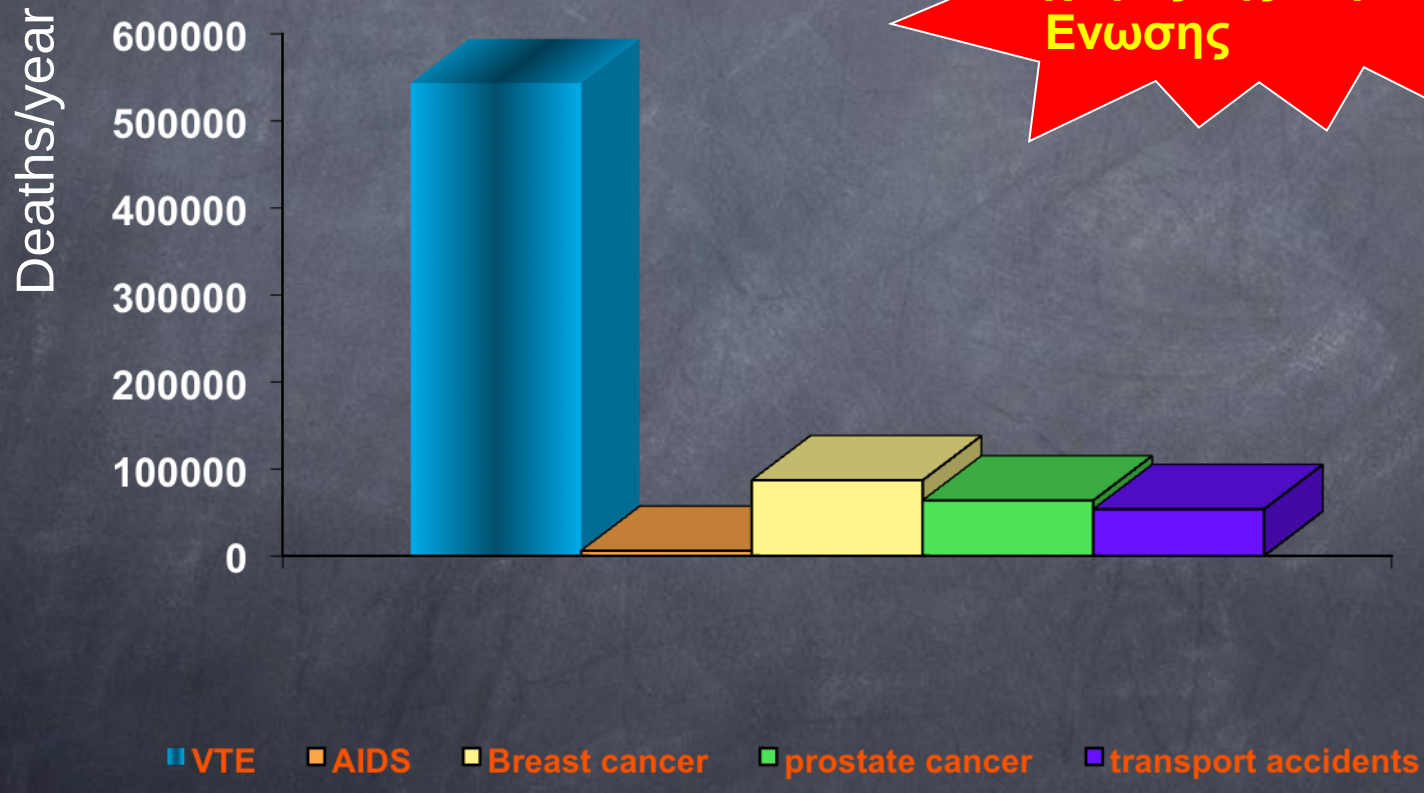
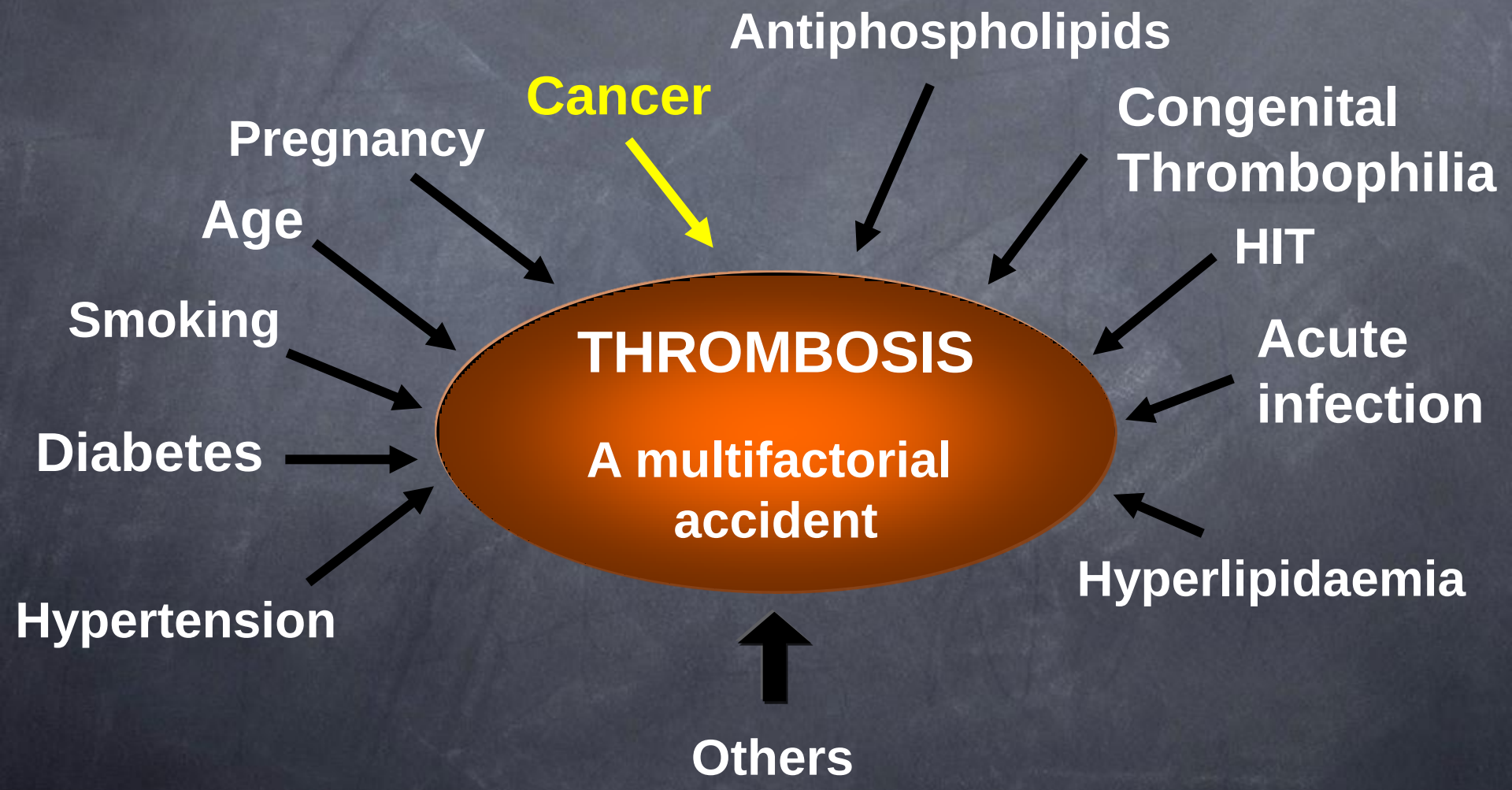
ΦΘΕ : Ένα μείζον πρόβλημα δημόσιας υγείας στην ΕΕ

12% των συνολικών θανάτων ετησίως στις χώρες της Ευρωπαικής Ενωσης

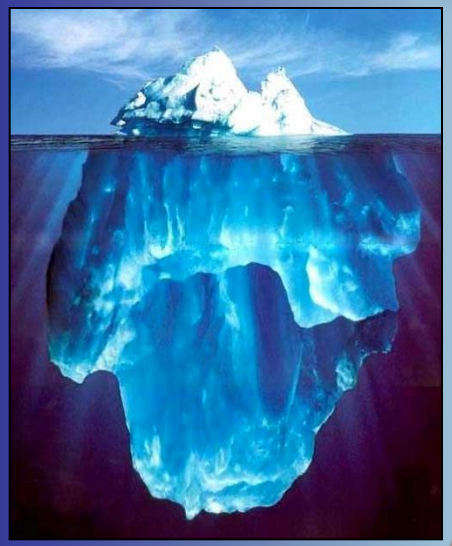


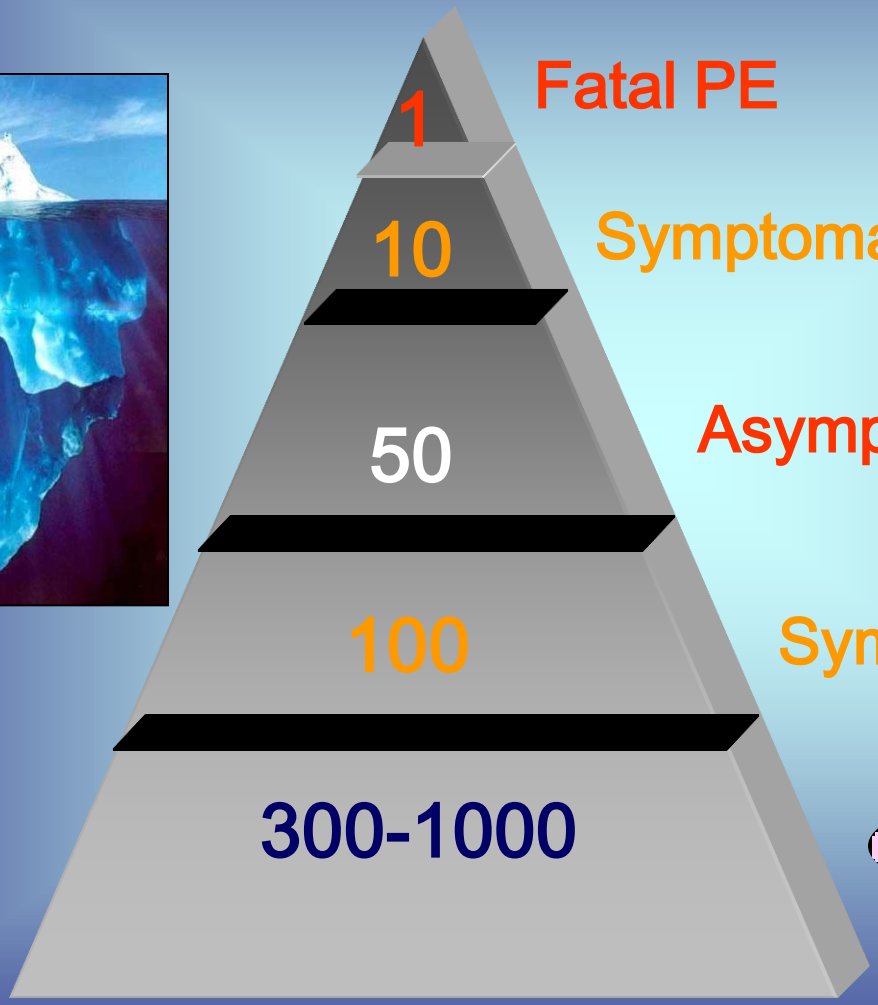
Cohen AT, et al (VITAE). Thromb Haemost 2007; 98: 756–764

VTE is a multifactorial and often silent disease



Venous thromboembolism
a multifactorial and silent disease



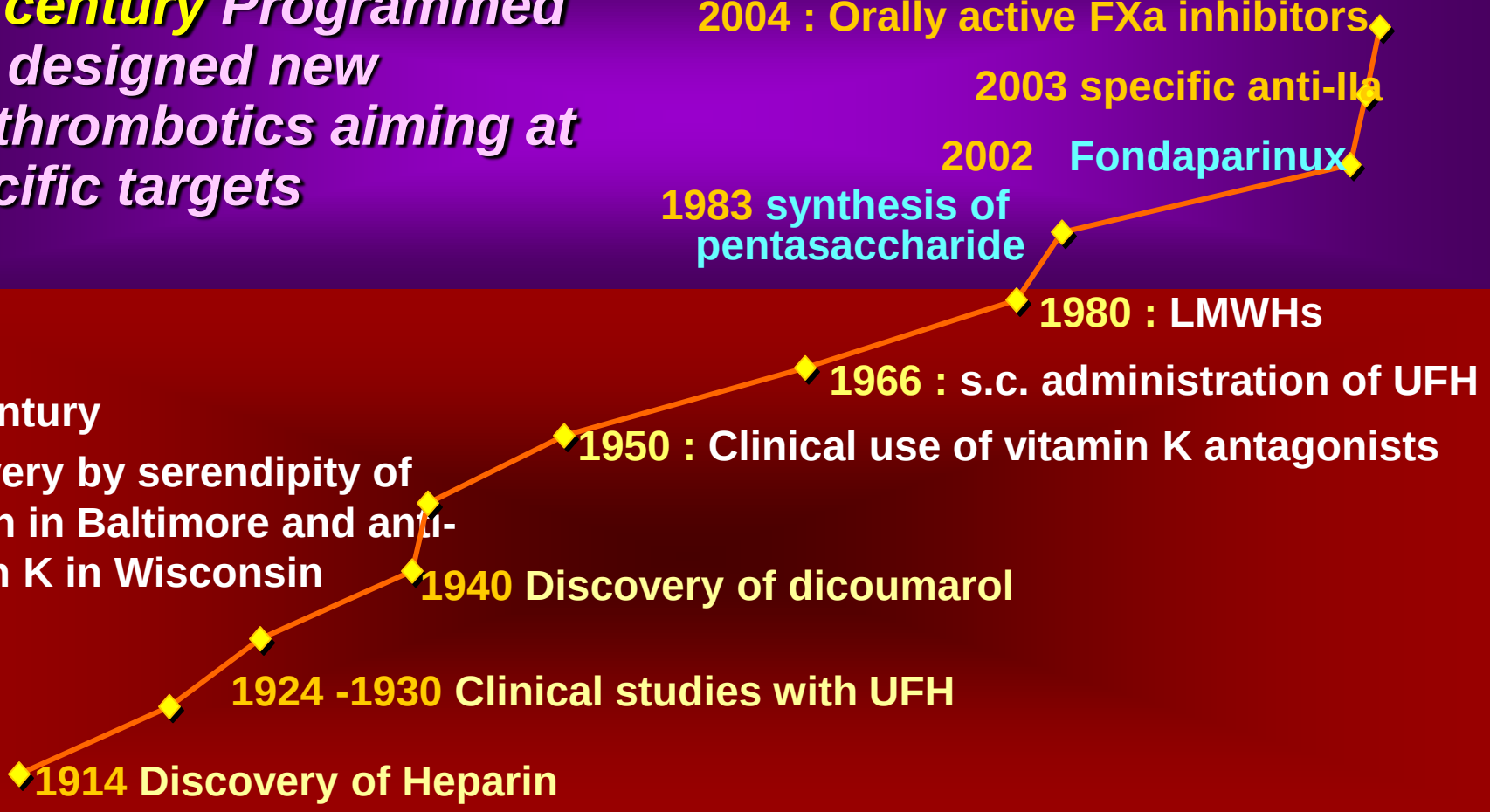


prophylaxis

Iceberg model

History of antithrombotic agents

21st century Programmed and designed new antithrombotics aiming at specific targets



Treatment with Vitamin K Antagonists

- 1,5 % of French population is treated with VKA
- 70% indication for arterial thrombosis (AF …)
- 30% indication for venous thromboembolism
- >760 kEuros : Annual cost for iatrogenic accidents due to VKA treatmen

Simple classification of anticoagulants

Factor Xa	Thrombin
AT-dependent inhibitors: Pentasaccharide, heparins, ULMWHs (semuloparin)	AT-dependent inhibitors: Heparins, danaparoid, ULMWHs (semuloparin)
	HCII-dependent inhibitors
Direct inhibitors: Rivaroxaban, apixaban, edoxaban …	Direct inhibitors: Dabigatran, lepirudin, bivalirudin…

Parenteral Oral

Gerotziafas GT, Samama MM. Current Pharmaceutical Design, 2005,

Thromboprophylaxis with NATA major abdominal surgery

RCT	Experimental design	n	primary efficacy end-point in total population
PEGASUS	fondaparinux 2.5 mg x 10 d versus dalteparin 2500 anti-Xa IU pre-op and 5000 anti-Xa IU post-op routine venography on d10	fondaparinux = 1027 dalteparin = 1021	fondaparinux =4.6% dalteparin = 6.1% 24.6% RRR (p=0.144)
Apollo	fondaparinux 2.5 mg x 10 days +mechanical prophylaxis versus placebo + mechanical prophylaxis routine venography on d10	fondaparinux = 635 placebo = 650	fondaparinux = 1.7% placebo = 5.3% 70% RRR

In both studies safety was similar in the two studied groups

Prophylaxis with NATA major abdominal surgery for cancer

RCT	Experimental design	n	subgroup of cancer patients	primary efficacy end-point in cancer subgroup	primary safety end-point in cancer
PEGASUS	fondaparinux 2.5 mg x 10 d versus dalteparin 2500 anti-Xa IU pre-op and 5000 anti-Xa IU post-operatively routine venography on day 10	Fondaparinux 1027 dalteparin = 1021	Fondaparinux 954 (66.6%) dalteparin = 987 (69.3%)	fondaparinux 4.7% Dalteparin 7.7% 38.6% RRR	fondaparinux 3.4% dalteparin 2.4%
Apollo	fondaparinux 2.5 mg x 10 d +mechanical prophylaxis versus placebo + mechanical prophylaxis routine venography on day 10	fondaparinux = 635 placebo = 650	fondaparinux = 246 placebo = 262	fondaparinux = 2.5% placebo = 6.7% 64% RRR	**in the cancer subgroup** safety was the same as in total population **in total population** fondaparinux = 1.6% placebo = 0.2%

Thromboprophylaxis with NATA in acutely ill medical patients

RCT	Experimental design	n	primary efficacy end-point in total population	primary safety end-point in total population
ARTEMIS	fondaparinux 2.5 mg x 10 d Versus placebo Routine venography on d10	Fondaparinux = 429 placebo = 420	fondaparinux =5.6% placebo = 10.5% 46.7% RRR	No significant difference between the two groups
MAGELLAN	rivaroxaban 10 mg x 35 d versus enoxaparin 4000 anti-Xa IU o.d. s.c. for 10 days followed by placebo until 35th day. Routine ultrasonography of the legs on d10 and d35	rivaroxaban = 3977 enox/placebo= 4001	in 10 days rivaroxaban = 2.7% enoxaparin = 2.7% p=0.0025 for non inferioriy In 35 days rivaroxaban = 4.4% enox/placebo= 5.7% p=0.02 for superiority 77% RRR	in 10 days rivaroxaban = 3.4% enoxaparin = 1.5% p<0.05 In 10-35 days rivaroxaban = 1.9% enox/placebo=0.6% p<0.05

Thromboprophylaxis with NATA in acutely ill medical patients with cancer

RCT	Experimental design	subgroup of cancer patients	primary efficacy end-point in cancer subgroup	primary safety end-point in cancer
ARTEMIS	fondaparinux 2.5 mg x 10 d Versus placebo routine venography on day 10	fondaparinux = 62 pts (14%) placebo = 69 pts (16.4%)	in subgroup of patients no difference is mentioned	major bleeding in one patient in each group
MAGELLAN	rivaroxaban 10 mg x 35 d versus enoxaparin 4000 anti-Xa IU o.d. s.c. for 10 days followed by placebo until 35th day. Routine ultrasonography of the legs on day 10 and day 35	rivaroxaban = 7% enox/placebo = 7%	**Rivaroxaban showed a non-significant trend to less efficacy than enoxaparin in patients with active cancer (RR 1.34; 95% CI 0.71-2.54)**	Descriptive values for the incidence of clinically relevant bleeding consistently favored enoxaparin over rivaroxaban across the covariates analyzed.

COMPASS : Frequency of thromboprophylaxis in acutelly ill and surgical patients in France and Greece

	n	Patients receiving thromboprophylaxis (n)	Patients receiving thromboprophylaxis (%)
All Compass Patients	806	594	73,7 %
Medical patients	414	256	61,84%
Surgical patients	392	338	86,22%

Prophylaxis administration and risk level according to ACCP and COMPASS RAM

	ACCP	Compass
High risk without prophylaxis	58 (14%)	88 (21,26%)
Moderate risk without prophylaxis	15 (3,62%)	22 (5,31%)
Low risk with prophylaxis	99 (23,91%)	43 (10,39%)

60% of medical patients received prophylaxis with LMWH

Type and dose of thromboprophylaxis in medical patients

- 32% of patients received the recommended type and dose of LMWH
- 55% of patients received LMWH at lower than the recommended dose of anti-Xa IU (<4000 IU/day)

LMWH	%
fondaparinux 2,5 mg	7
enoxaparin 40 mg o.d.	25
enoxaparin 60 mg o.d.	9
enoxaparin 20 mg o.d.	4
enoxaparin > 60 mg	1
nadroparin 0,3 ml	10
bemiparin 2500 IU	9
bemiparin 3500 IU	1
bemiparin 5000 IU	1
tinzaparin 0,35	31
tinzaparin 0,45	2

COMPASS Frequency of VTE and bleeding risk factors in hospitalised medical and surgical patients

Risk factors		Medical patients (n=414)	Surgical patients (n=392)
VTE risk factors	Personal history of cancer	32%	37%
	Pancreatic, gastro-intestinal, ovarian, prostate, lung or brain cancer	26%	29%
	Recent hospitalisation (within the last 3 months) for medical illness	30%*	16%
	Severe infection or sepsis	28%*	2%
	Total bed rest with bathroom privileges for > 3 days	28%*	2%
	Total bed rest without bathroom privileges for > 3 days	9%	6%
	Chemotherapy and/or and hormonotherapy	20%*	6%
	Metastatic disease	15%*	0
	Diabetes	18%	10,4%
	Chronic obstructive pulmonary disease	14%*	3,50%
	Varicose veins	13%	13%
	Heart failure NYHA class I or II	10%	7%
	Heart failure NYHA class III or IV	5%	0%
	Personal history of VTE	3%	1,5%
	Peripheral vascular disease	5,5%	5%
Bleeding risk factors	Recent haemorrhage	6%	5%
	Recent ischemic stroke with haemorrhagic transformation	1,5%*	0%
	Chronic renal insufficiency	10,5%*	5%
	Compensated cirrhosis	2,5%*	0,5%

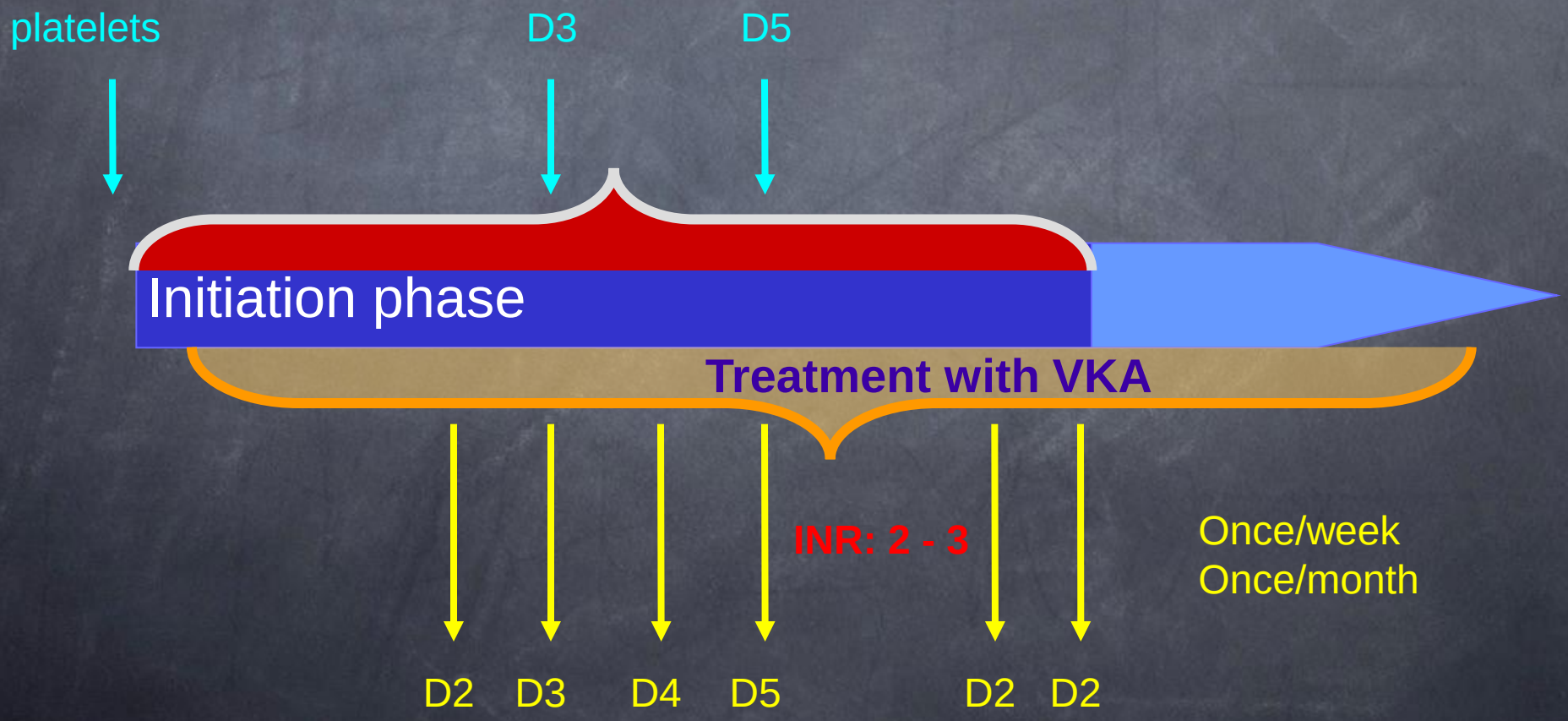
*p<0,05

Efficacy and safety of NATA in oncological patients

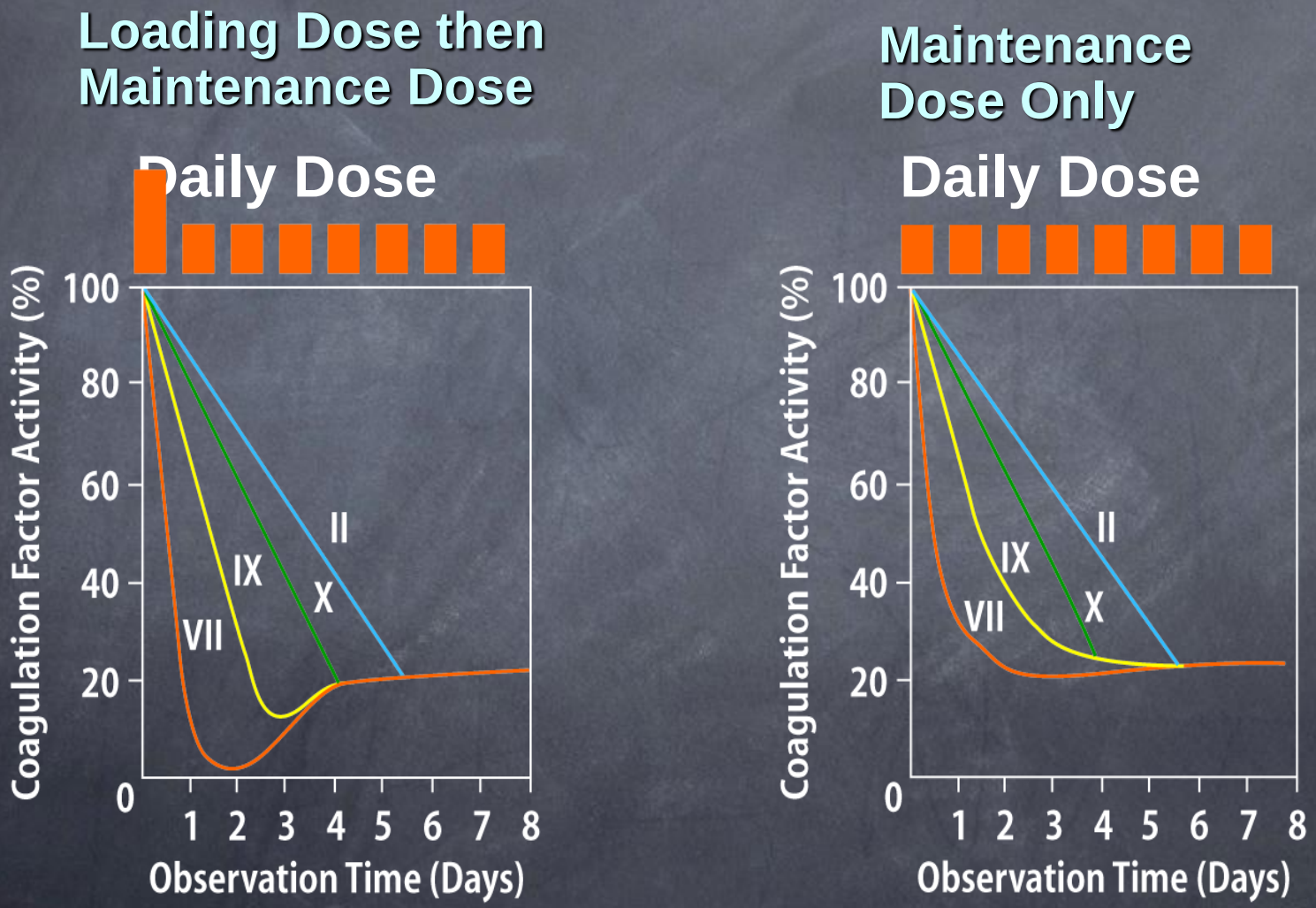
RCT	Experimental design	n	primary efficacy end-point	primary safety end-point
SAVE ONCO	patients with metastatic or locally advanced cancer initiating a new chemotherapy course treated with semuloparin, 20 mg subcutaneously once daily for 3.5 months or placebo	Semuloparin 1608 Placebo 1604	Semuloparin 1.2% Placebo 3.4% p<0.0001, RRR = 64%	Semuloparin 4% Placebo 3%

Basic principles for the management of VTE with parenteral anticoagulants and VKA

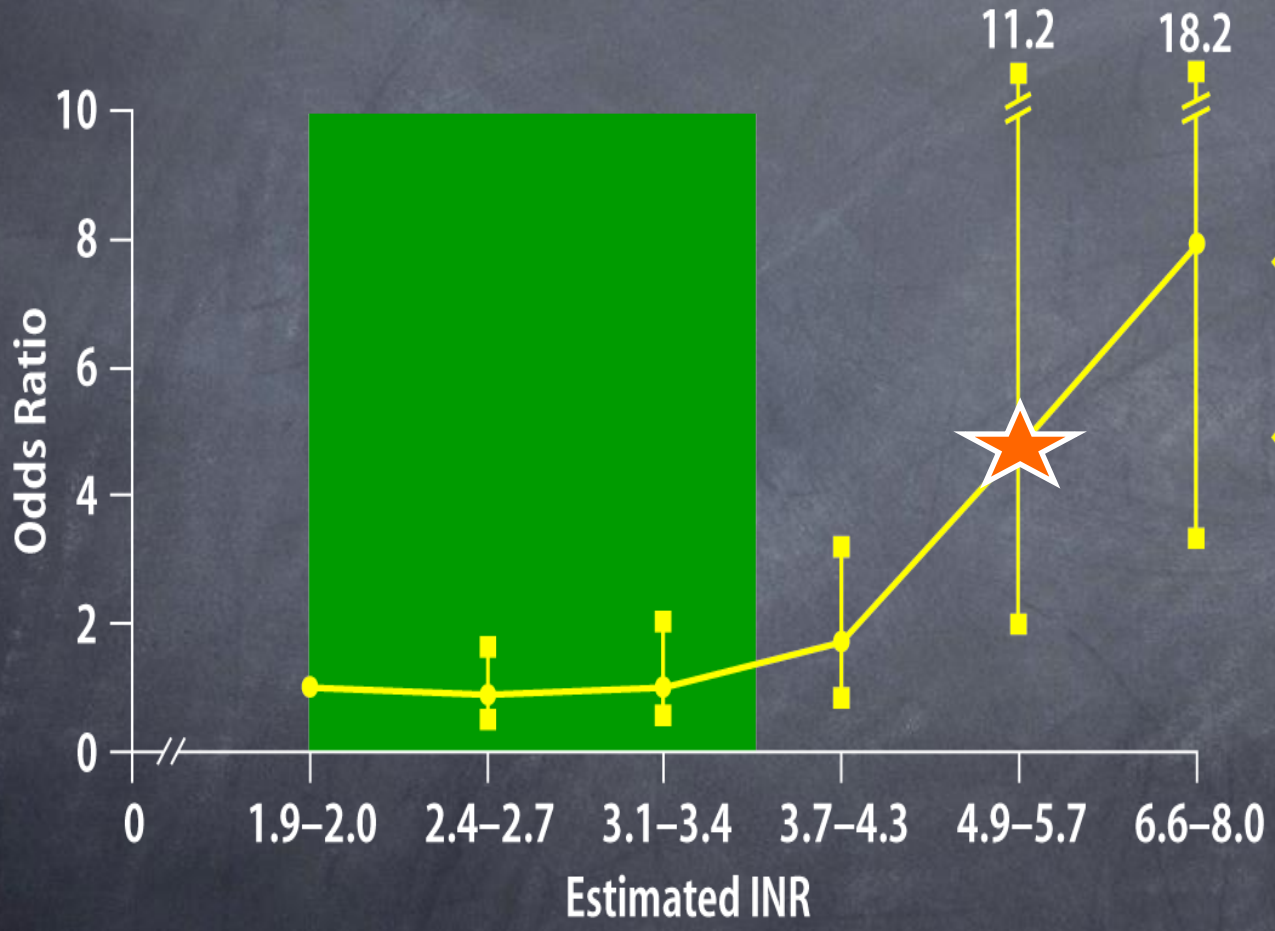
Treatment with LMWH at therapeutic doses (anti-Xa: 0,5 – 1 UI/ml)
or
UFH dose adjusted for aPTT ratio 2 – 3
or
Fondaparinux 7,5 mg 1 injection s.c. per day (Platelet monitoring is not recommended)



Effect of initial dose of warfarin (5 mg or 10 mg) on vitamin K dependent clotting factors



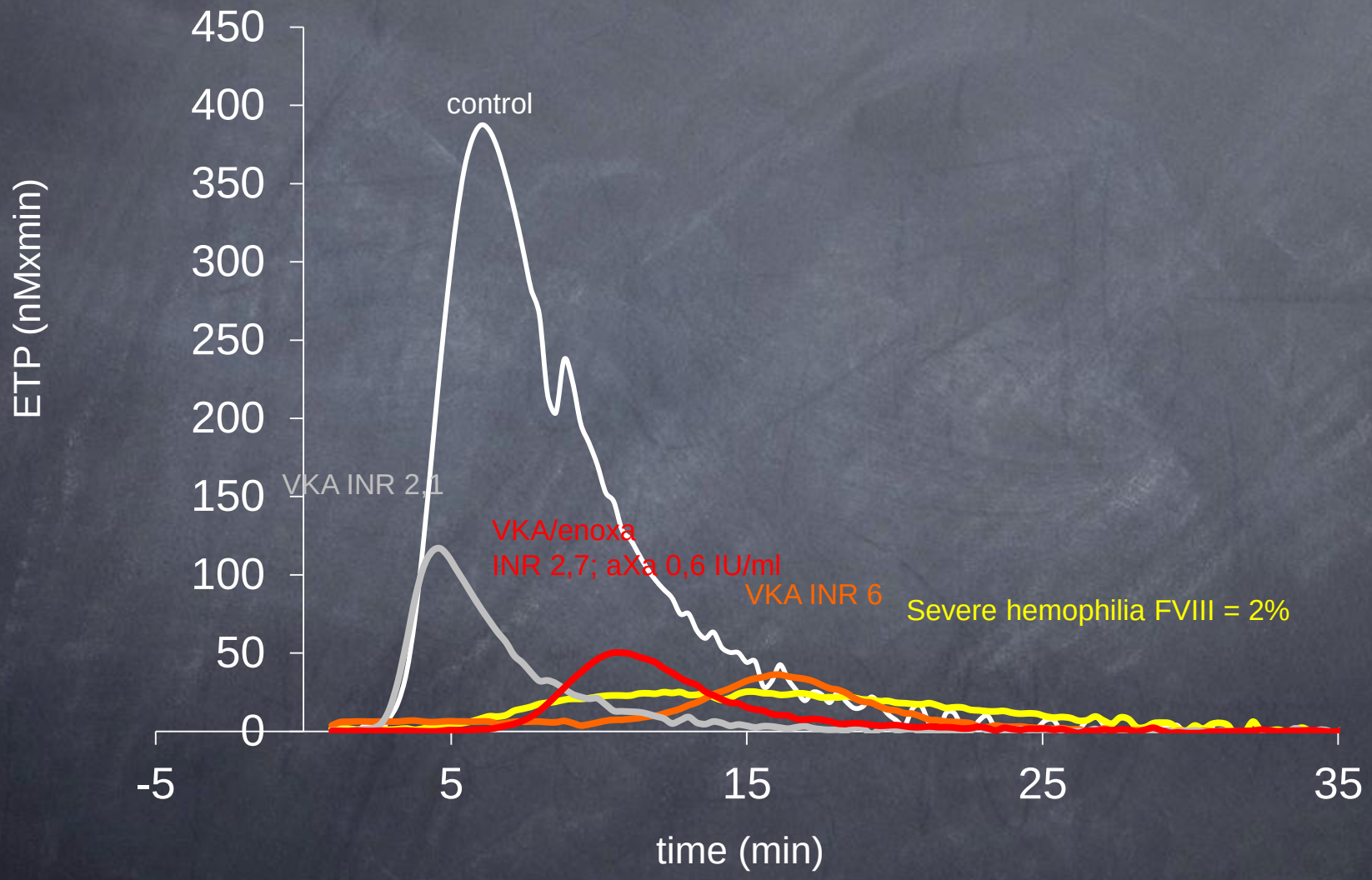
Risk of Intracranial Hemorrhage in Outpatients



- PTR above 2.0 (INR of 3.7 to 4.3) increases the risk of bleeding
- The estimated odds ratio of subdural hemorrhage increased 7.6 fold as the PTR increased from 2.0 to 2.5 (INR 3.7–4.3 to 5.7–6.8)

Adapted from: Hylek EM, Singer DE, Ann Int Med 1994;120:897-902

Thrombin generation in patients on VKA treatment



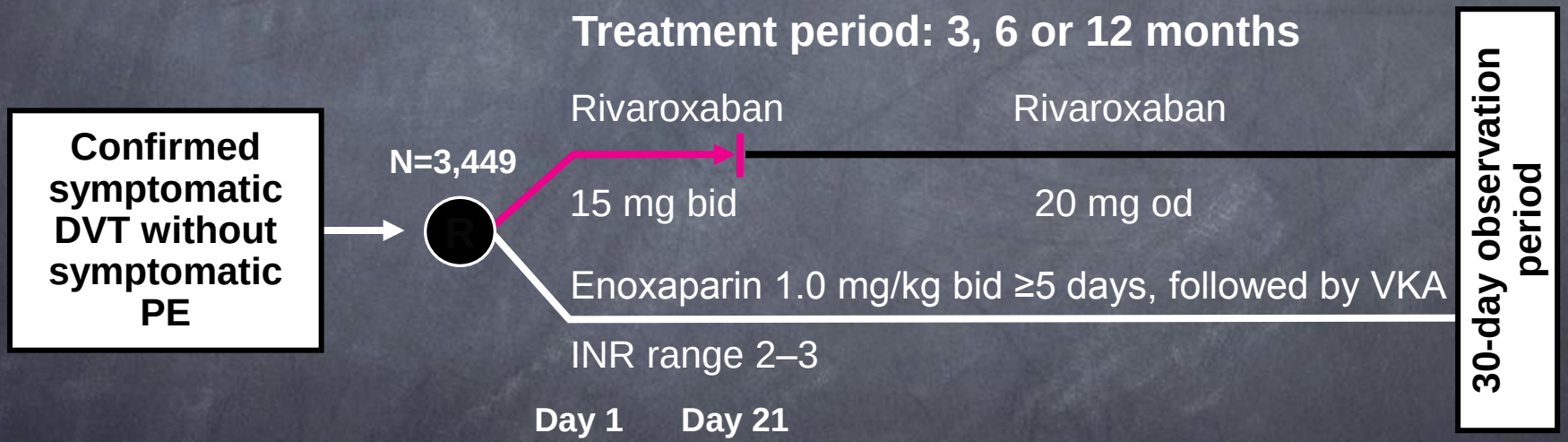
Gerotziafas et al Thromb Haemost. 2009;102:42-8.

Treatment of VTE with rivaroxaban

EINSTEIN DVT: study design

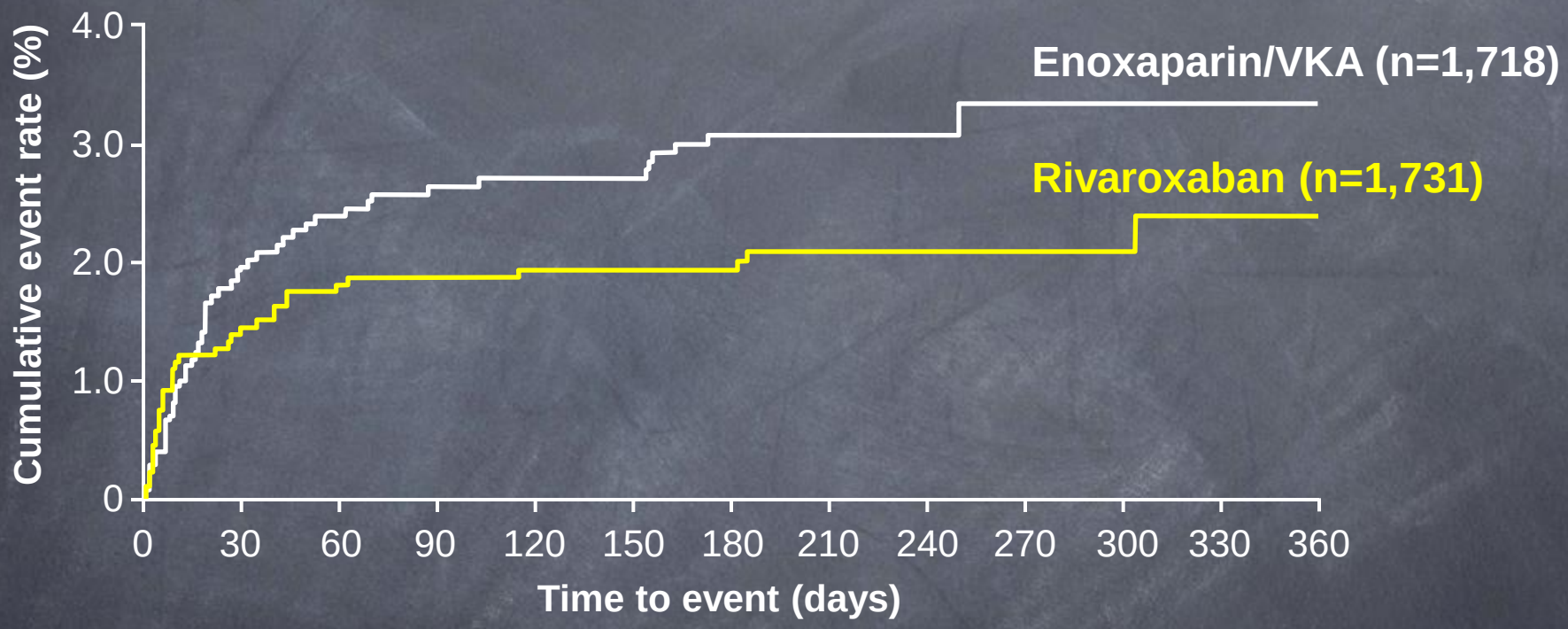
Randomized, open-label, event-driven, non-inferiority study

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



EINSTEIN DVT trial ID: NCT00440193

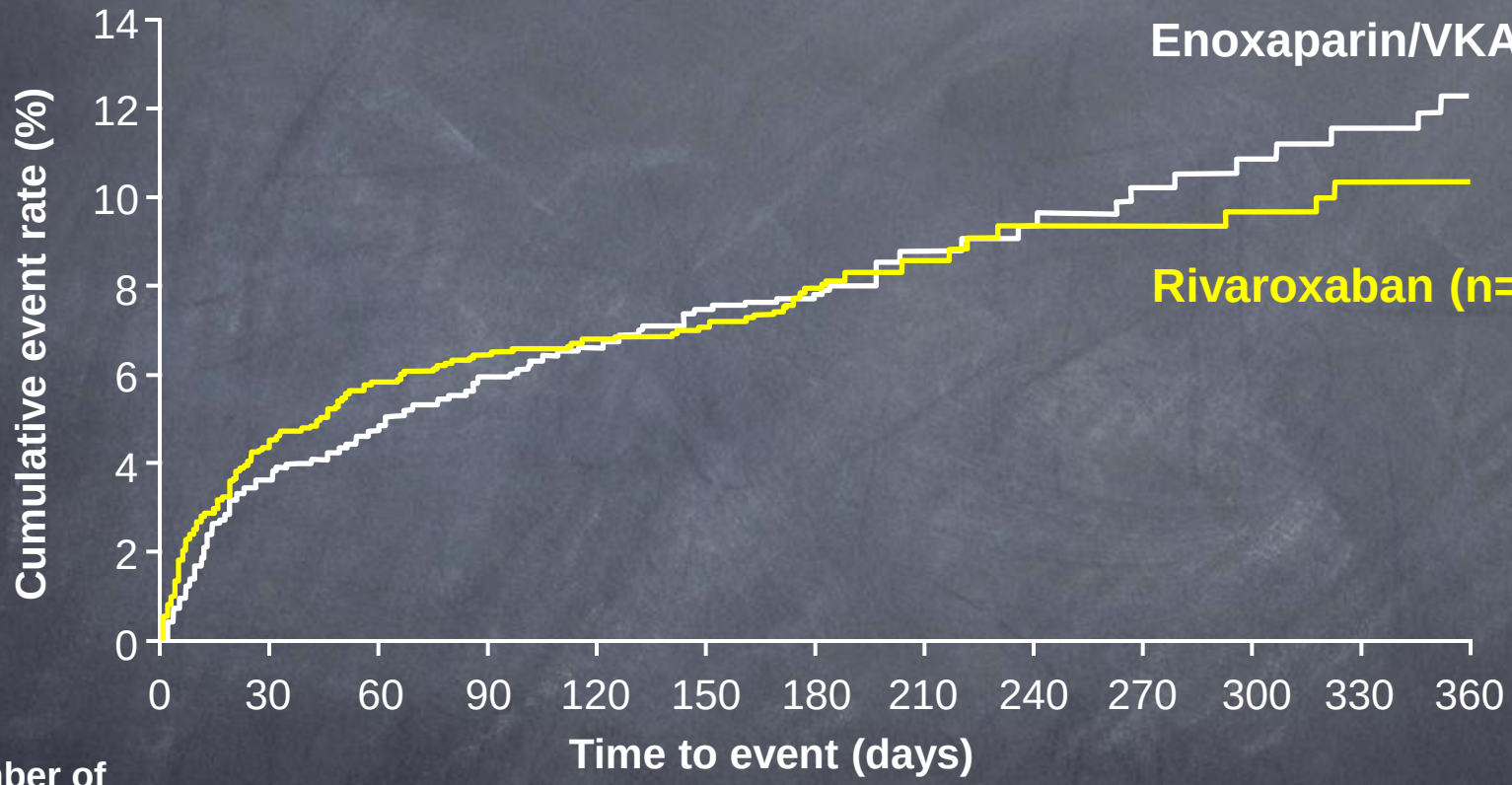
EINSTEIN DVT : Primary efficacy outcome: time to first event



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 : Principal safety outcome: time to first event

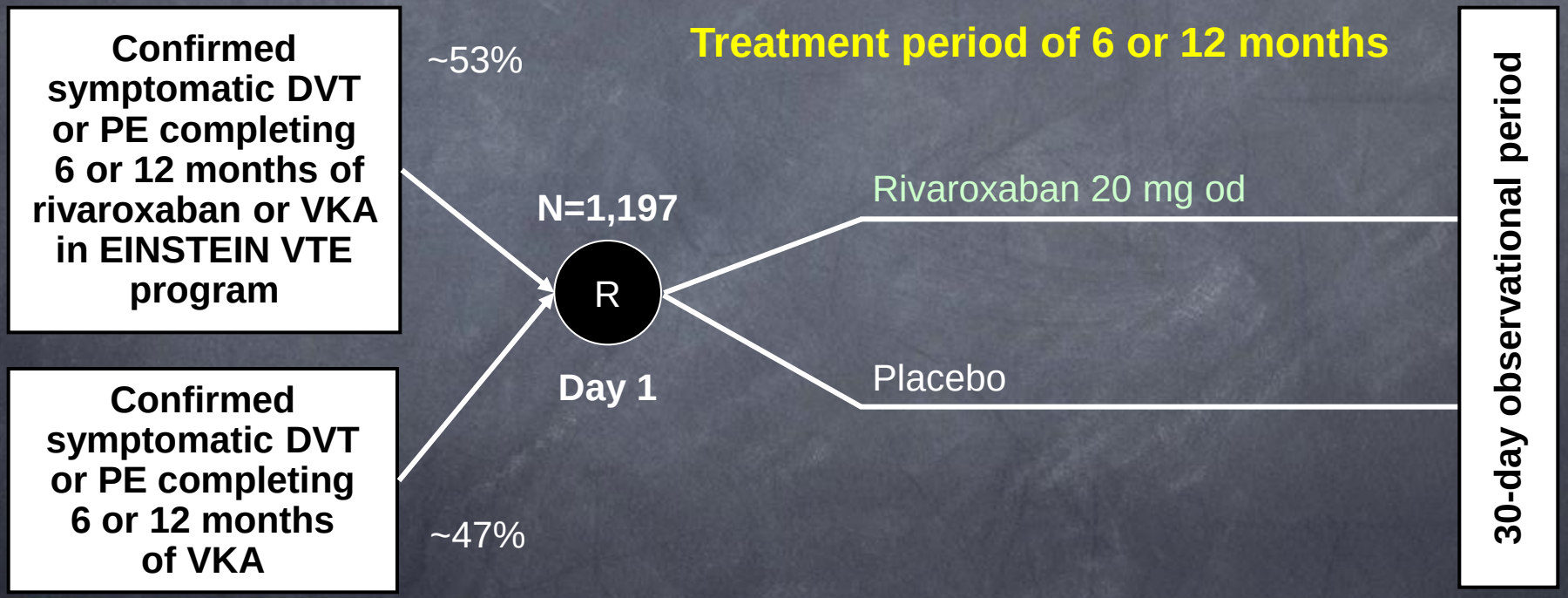


Number of subjects at risk

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 Extension study

Once-daily oral rivaroxaban versus placebo in the long-term prevention of recurrent symptomatic venous thromboembolism.



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

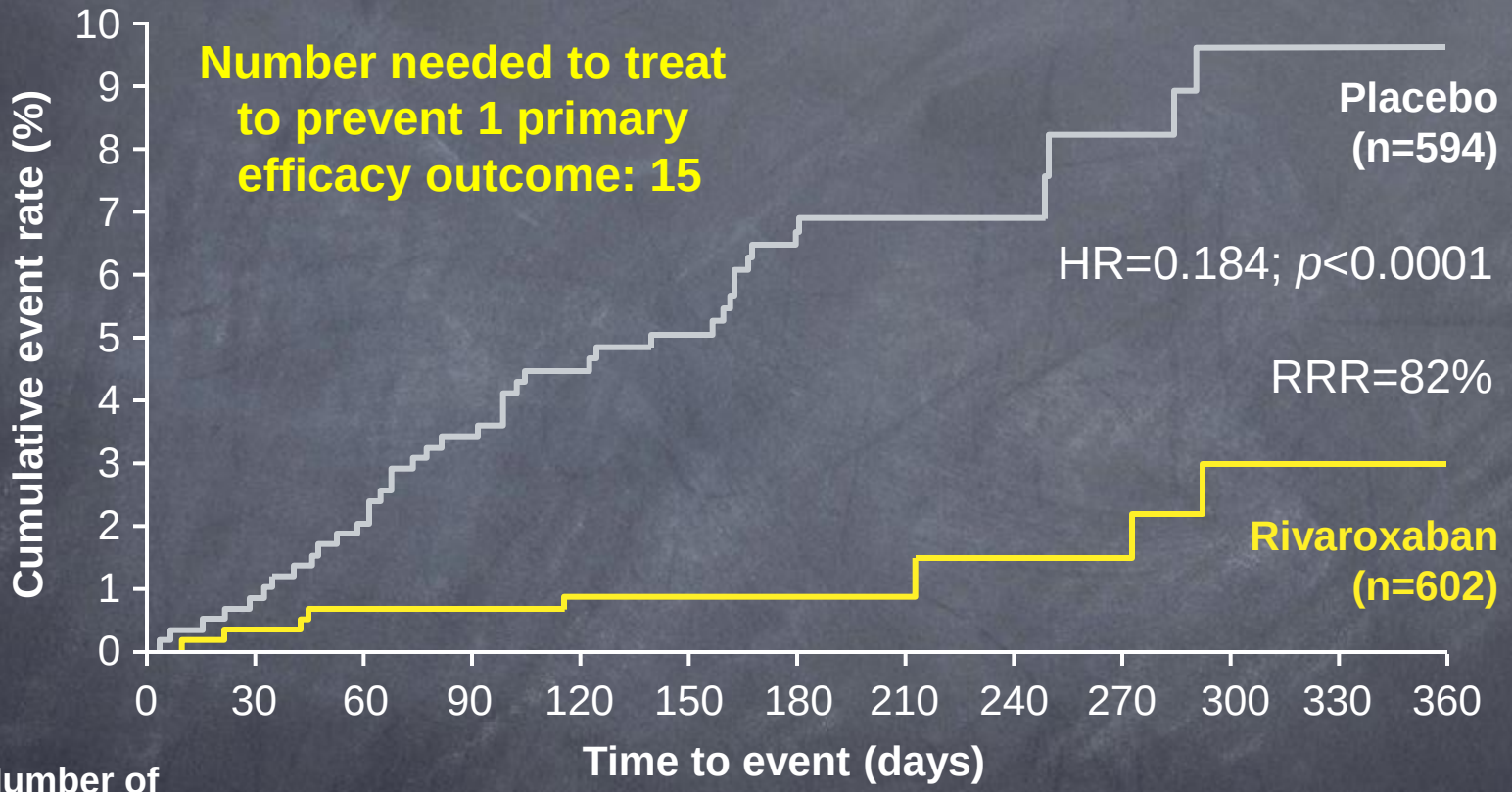
EINSTEIN DVT EXTENSION
Primary efficacy outcome and individual components

	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%**

no difference on efficacy out-come is mentioned for the subgroup of cancer patients as compared with the total population

ITT population; *some patients experienced more than one event

EINSTEIN DVT EXTENSION
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

EINSTEIN DVT EXTENSION Principal safety outcome: major bleeding

	Placebo (n=590)	Rivaroxaban (n=598)
Major bleeding	**0**	**4 (0.7%)***
Bleeding contributing to death	0	0
Bleeding in a critical site	0	0
Associated with fall in hemoglobin ≥2 g/dL and/or transfusion		
Gastrointestinal bleeding	0	3 (0.5%)
Menorrhagia	0	1 (0.2%)

**p*=0.11

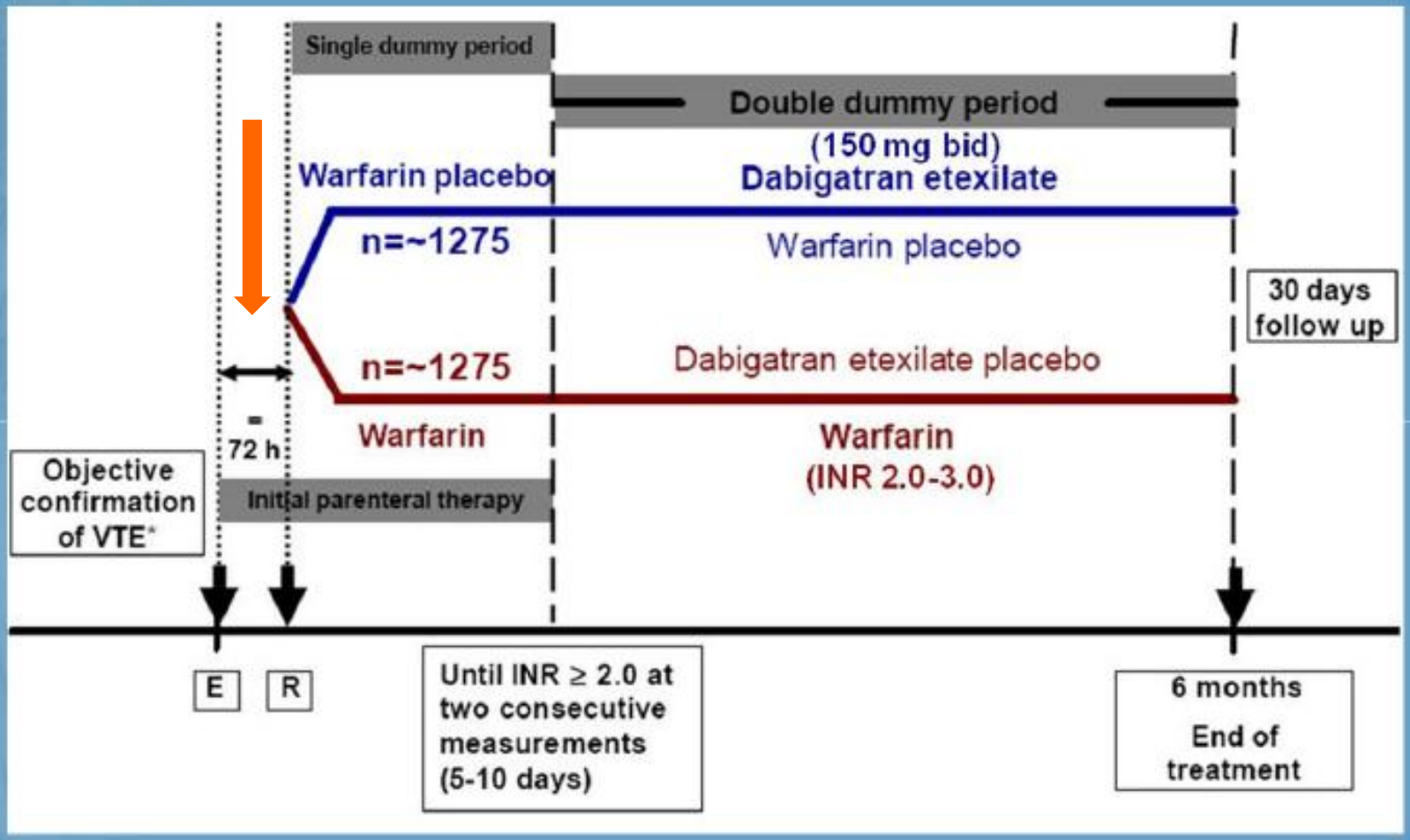
no difference on safety out-come is mentioned for the subgroup of cancer patients as compared with the total population

- Number needed to harm: approximately 139

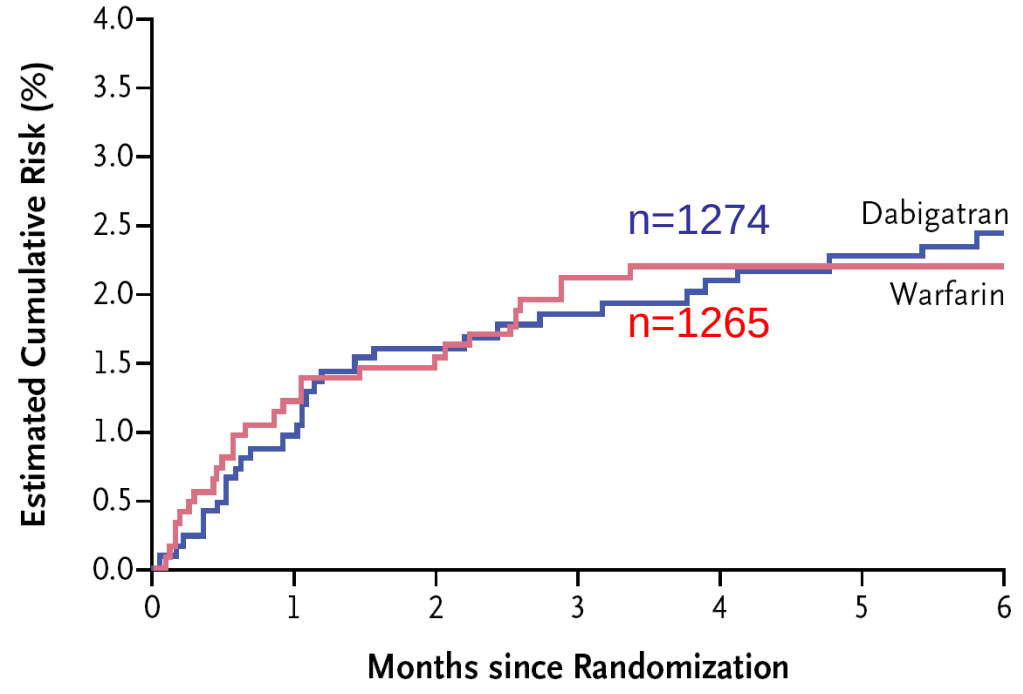
Safety population

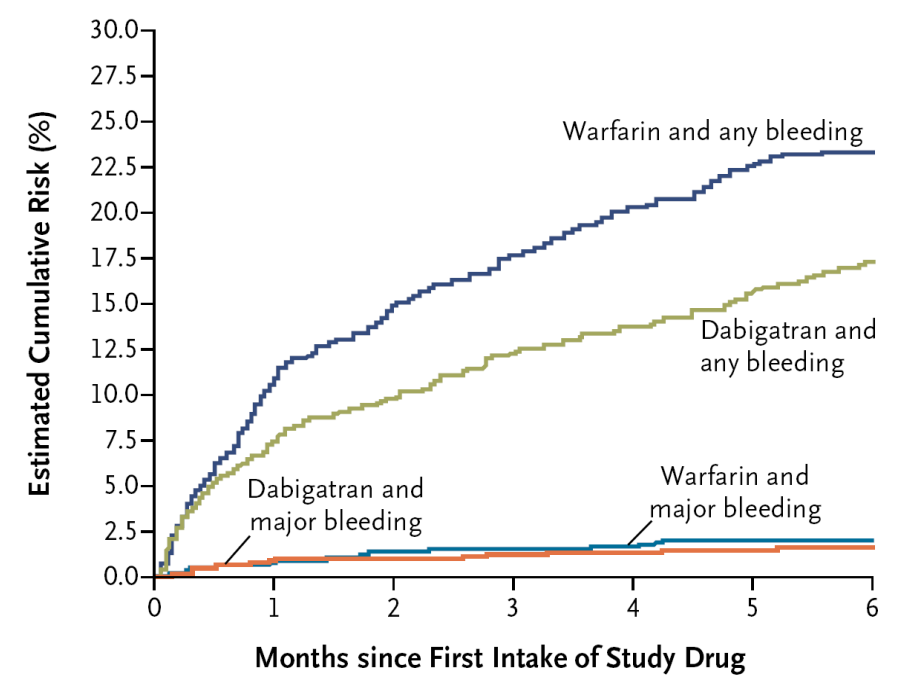
Dabigatran in the treatment of VTE

RE-COVER™ Trial Design



RE-COVER trial
Efficacy and safety outcomes during 6 Months of Treatment with Dabigatran or Warfarin in patients with acute VTE





Schulman et al NEJM 2009;361:2342-52

Apixaban : Phase III

Advance 1,2,3 – orthopaedic surgery

Adopt – medically ill

Aristotle -atrial fibrillation

Appraise 2 – ACS

Ampliy/Amplify extension – treatment of VTE

New oral antithrombotic agents in the prevention of VTE

Efficacy and safety	Fondaparinux 2.5 mg/d	Rivaroxaban 10 mg/d	Semuloparin
major abdominal surgery	Similar to LMWH	-	-
major abdominal surgery with cancer	Higher efficacy as compared to LMWH	-	-
Hospitalised acutelly ill medical patients	Similar to LMWH	Similar to the LMWH during the hospitalisation. Higher bleeding riskwhen prophyllaxis is extended	-
Hospitalised acutelly ill medical patients with cancer	Lower efficacy as compared to the LMWH	Lower efficacy as compared to LMWH	-
Cancer patients	-	-	Favorable benefit/risk ratio

Take home messages

- Specific FXa and FIIa inhibitors are effective in
  - ✓ Prevention of VTE
  - ✓ Treatment of VTE
- Have wide therapeutic window
- Are not devoyed of bleeding risk
- Fondaparinux, rivaroxaban and apixaban although they belong in the same pharmacological family they are heterogenous drugs
- In some groups of patients efficacy and safety profile of NATA could be improved if treatement could be tailored

New oral antithrombotic agents
New era in the treatment of DVT

- Specific FXa and FIIa inhibitors
  - Without routine laboratory monitoring and dose adjustment are as effective and safe as VKA
  - Have wide therapeutic window
  - Are not devoted of bleeding risk
  - Are not free from bleeding risk
  - In some groups of patients efficacy and safety profile of NATA could be improved if treatement could be tailored
  - Absence of antidote could be a potential limitation in urgent situations (i.e. accident, urgent surgery)
- Multiple choice of drugs may improve clinical outcome by individualization of the treatment in real life patients

New Direct Thrombin Inhibitors and Factor Xa Inhibitors for AF

Medication	Action	Phase III Trial	Comparator	Design	n
Dabigatran	DTI	**RE-LY**	Warfarin	Non-inferiority	18 113
Apixaban	Anti Xa	**AVERROES**	Aspirin	Superiority	5 600
		ARISTOLE	Warfarin	Non-inferiority	15 000
Rivaroxaban	Anti Xa	**ROCKET AF**	Warfarin	Non-inferiority	14 000
Edoxaban	Anti Xa	**ENGAGE**	Warfarin	Non-inferiority	16 500
Biotinylated Idraparinux	Anti Xa	**BOREALIS-AF**	Warfarin	Non-inferiority	9 600

Others include: LY 517717, YM 150