Prevention and therapy of **V**enous **T**hrombo**E**mbolism

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ESO EUROPEAN STROKE ORGANISATION

HSO Hellenic Stroke Organization

Disclosures

- Scholarships: European Stroke Organization; Hellenic Society of Atherosclerosis.
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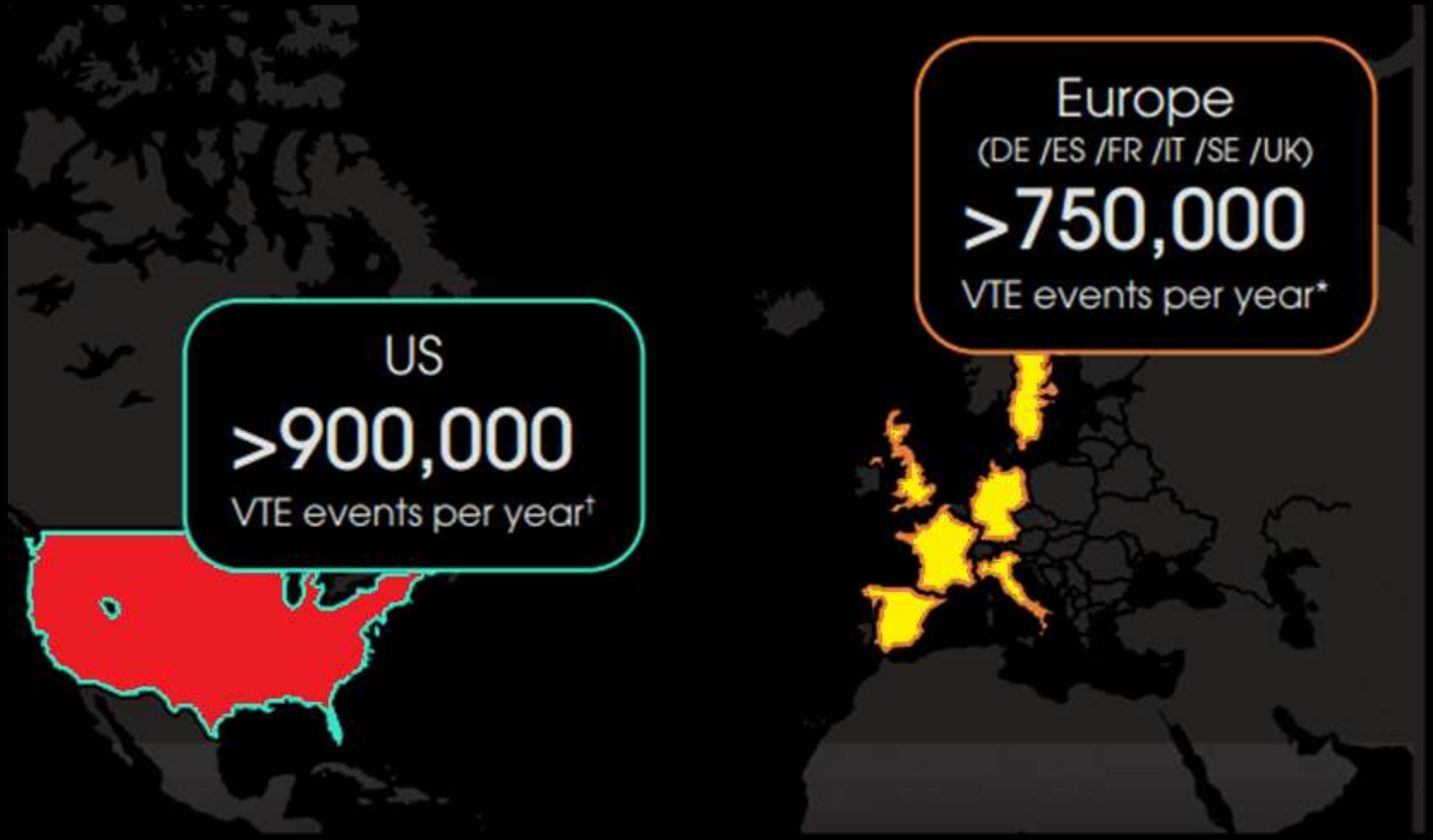
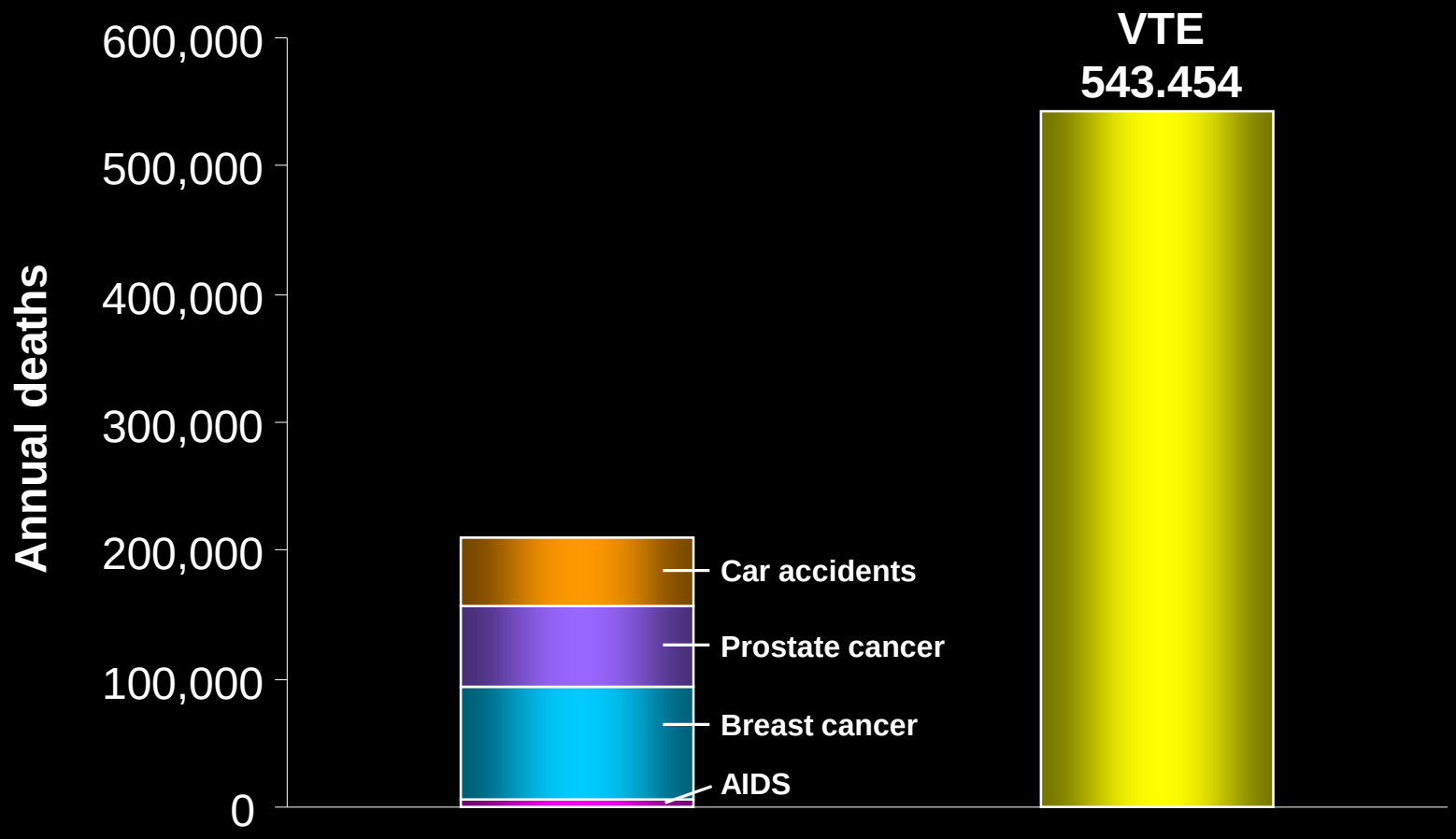
- Participation in trials:
  - ENOS / National coordinator (Greece).
  - NAVIGATE-ESUS / National coordinator (Greece)
  - PRECIOUS / National coordinator (Greece).
  - BIOSIGNAL / Principal Investigator (Larissa).
  - EBBINGHAUS / Principal Investigator (Larissa).
  - FOURIER / Principal investigator (Larissa).
  - PREVISE / Principal investigator (Larissa).
  - GLORIA-AF / Sub-investigator (Larissa).

Venous **T**hrombo**E**mbolism

VTE is a major cause of morbidity

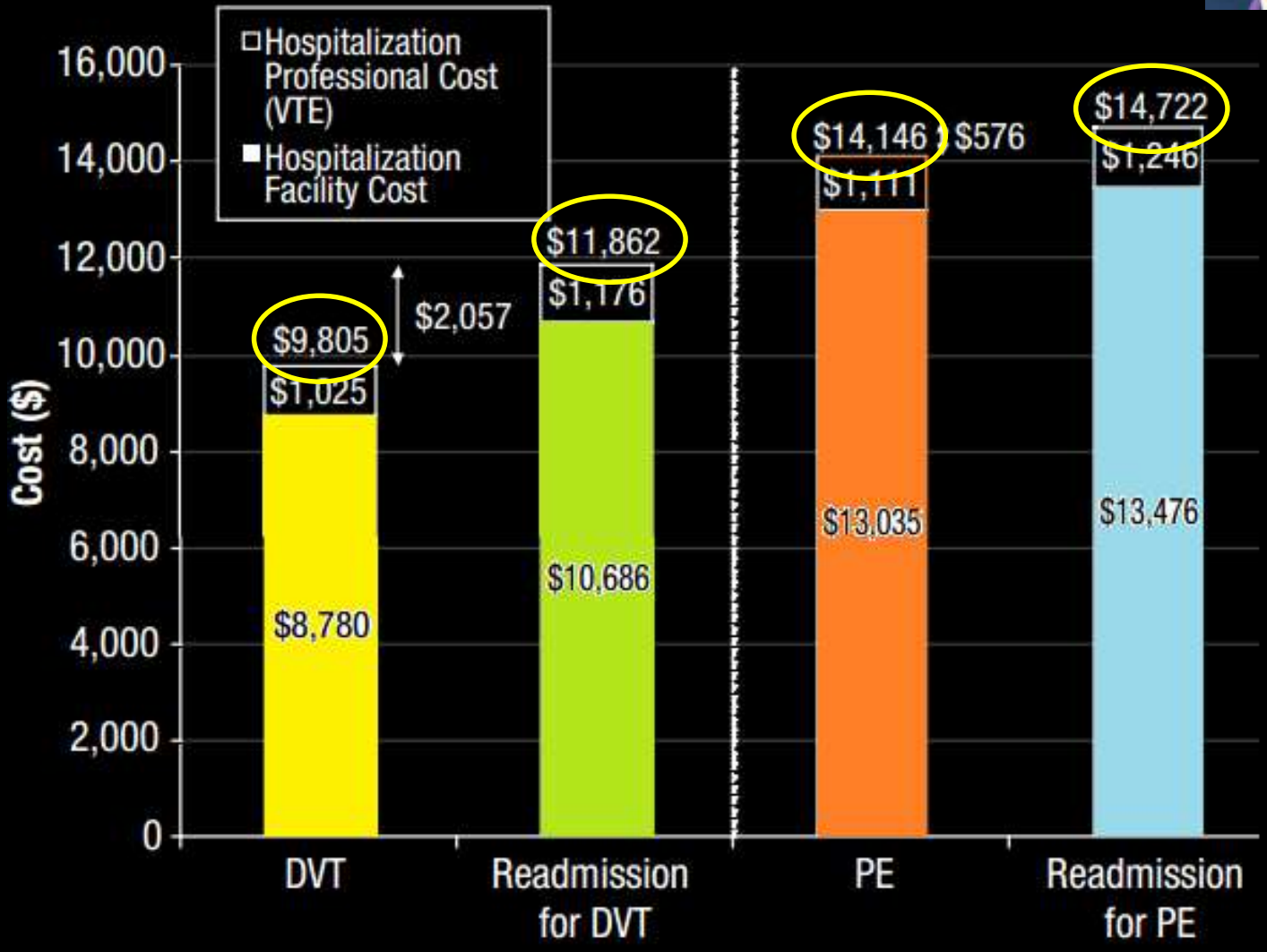


VTE is a major cause of mortality



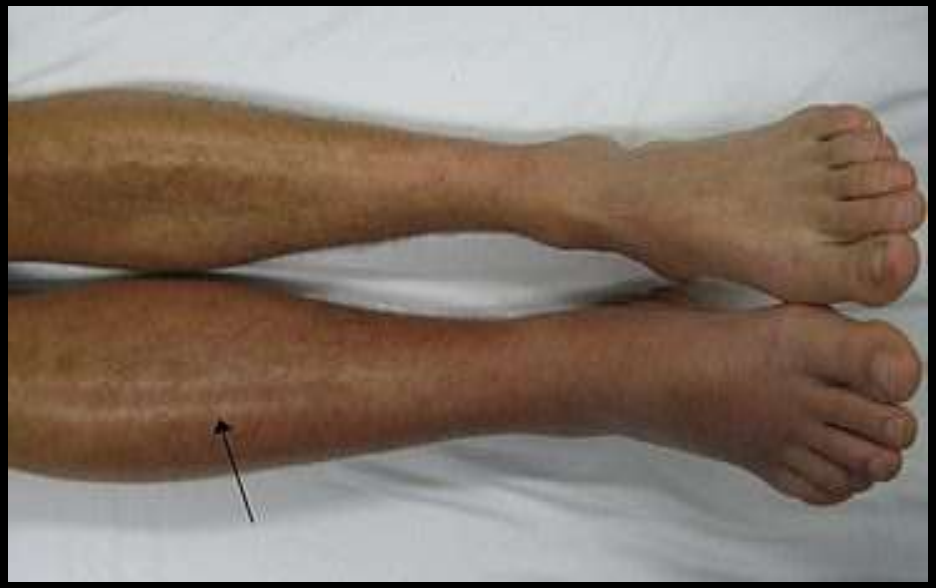
Cohen. Thromb Haemost 2007;98:756–764

VTE is a major financial burden



Clinical scenario

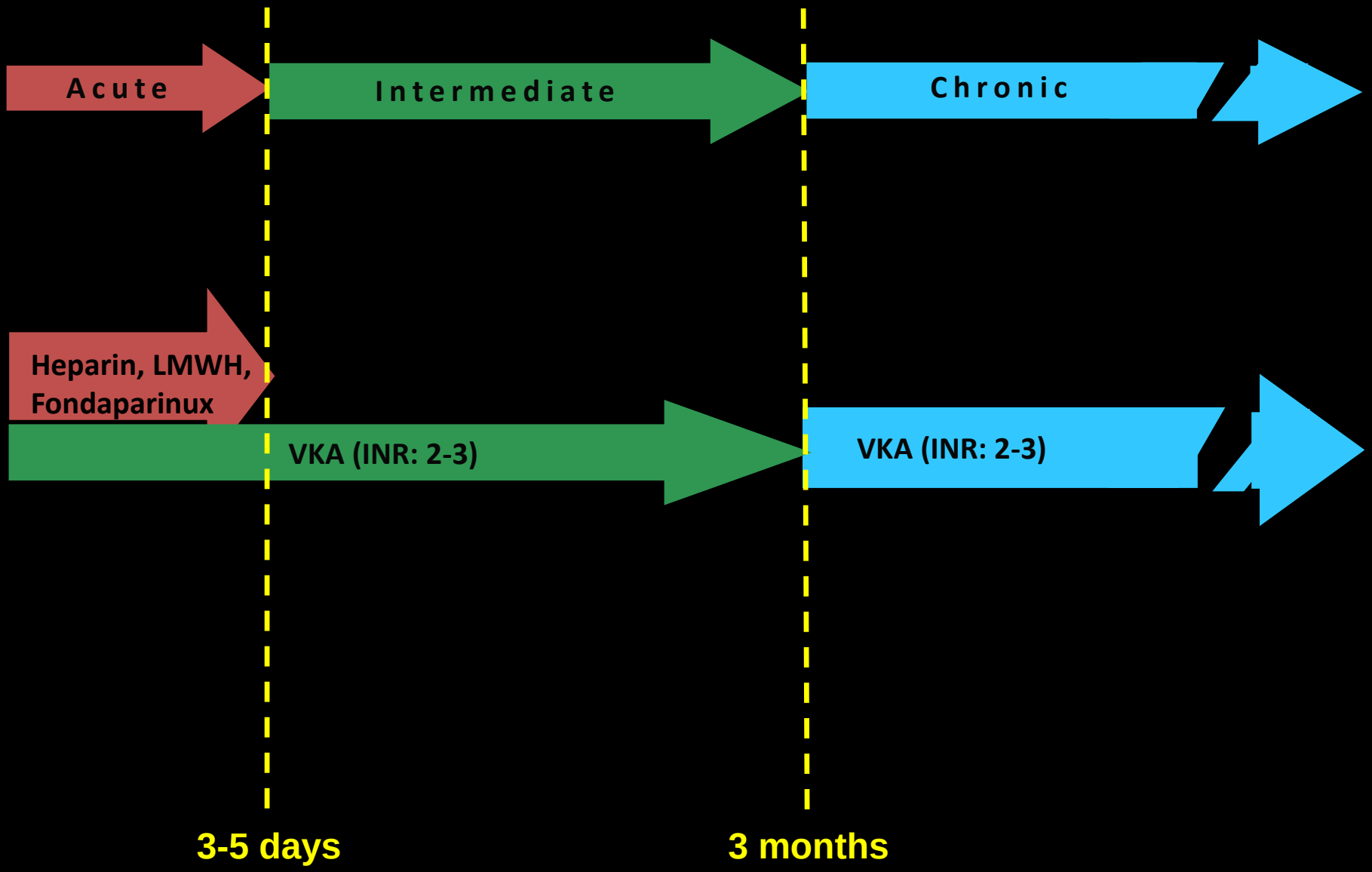
- ✓ ♂, 74yrs
- ✓ Arterial hypertension on valsartan/HCTZ 1x1 and amlodipine 1x1
- ✓ Diabetes Mellitus on metformin 1x2 and glimepiride
- ✓ Depression on escitalopram 1x1
- ✓ Benign prostate hyperplasia on alfuzocin 1x1



Question

1. Start LMWH for 3 months.
2. Start Acenocoumarol for 3 months.
3. Start LMWH for 5 days and continue with Acenocoumarol for 3 months.
4. Start Rivaroxaban for 3 months.
5. Start LMWH for 5 days and continue with Rivaroxaban for 3 months.
6. Start Dabigatran for 3 months.
7. Start LMWH for 5 days and continue with Dabigatran for 3 months.
8. Start Apixaban for 3 months.
9. Start LMWH for 5 days and continue with Apixaban for 3 months.

VTE: Treatment strategy (*until recently…*)

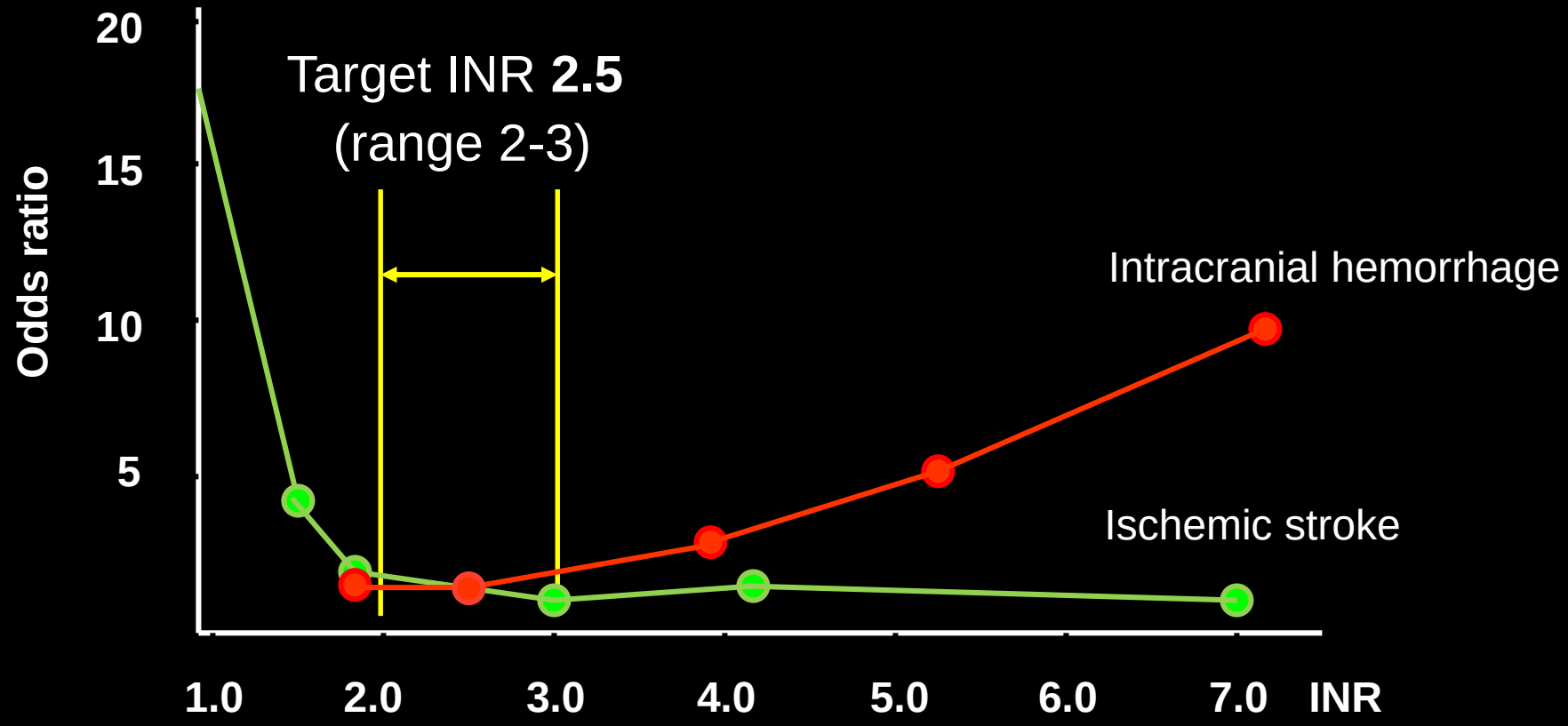


VitK-antagonists: far from perfect

VitK-antagonists: far from perfect

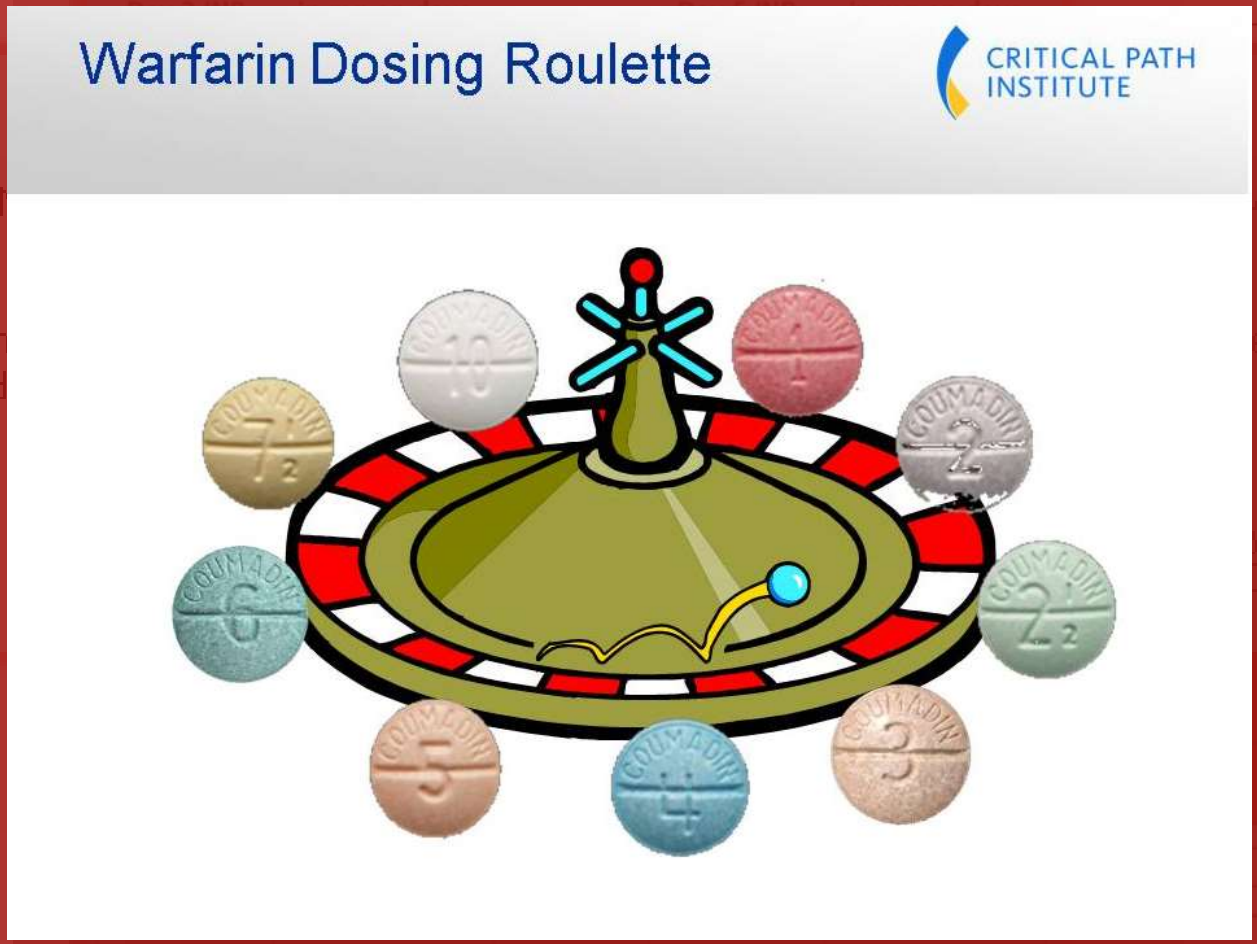
Don't forget my INR !

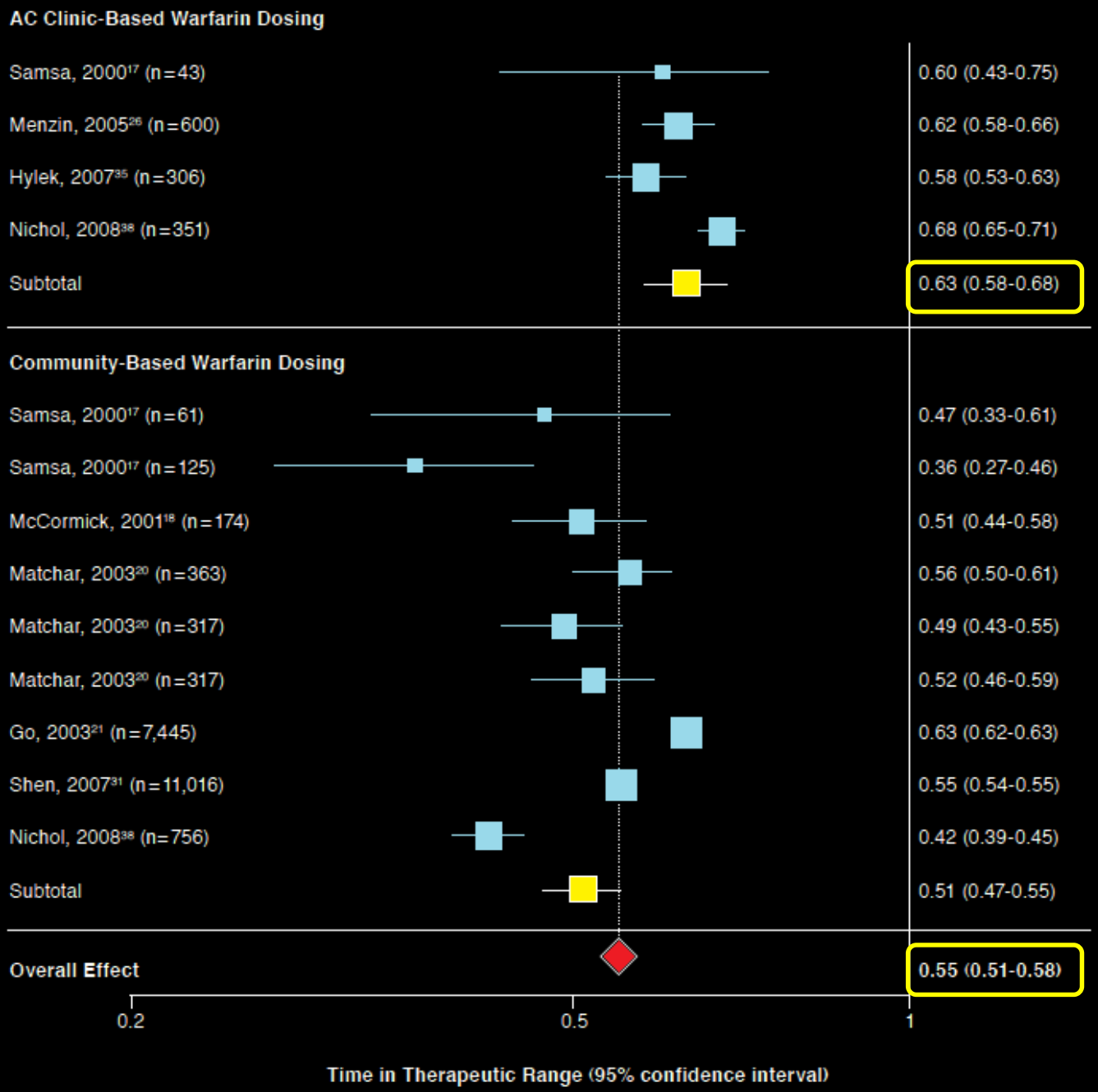
VitK-antagonists: far from perfect



Courtesy of Patrik Michel, adapted from Hylek et al. NEJM 1996; 335:540-6

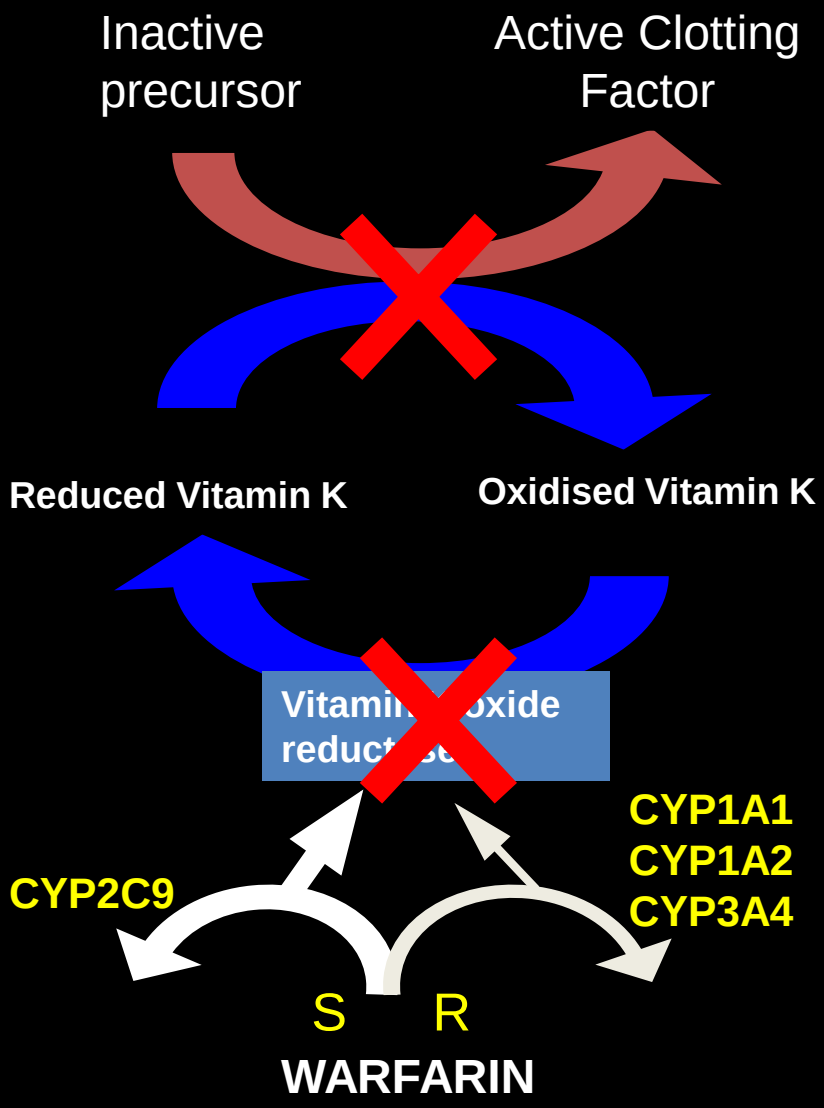
VitK-antagonists: far from perfect





Baker. J Manag Care Pharm 2009;15:244-52

Why is it so difficult ?



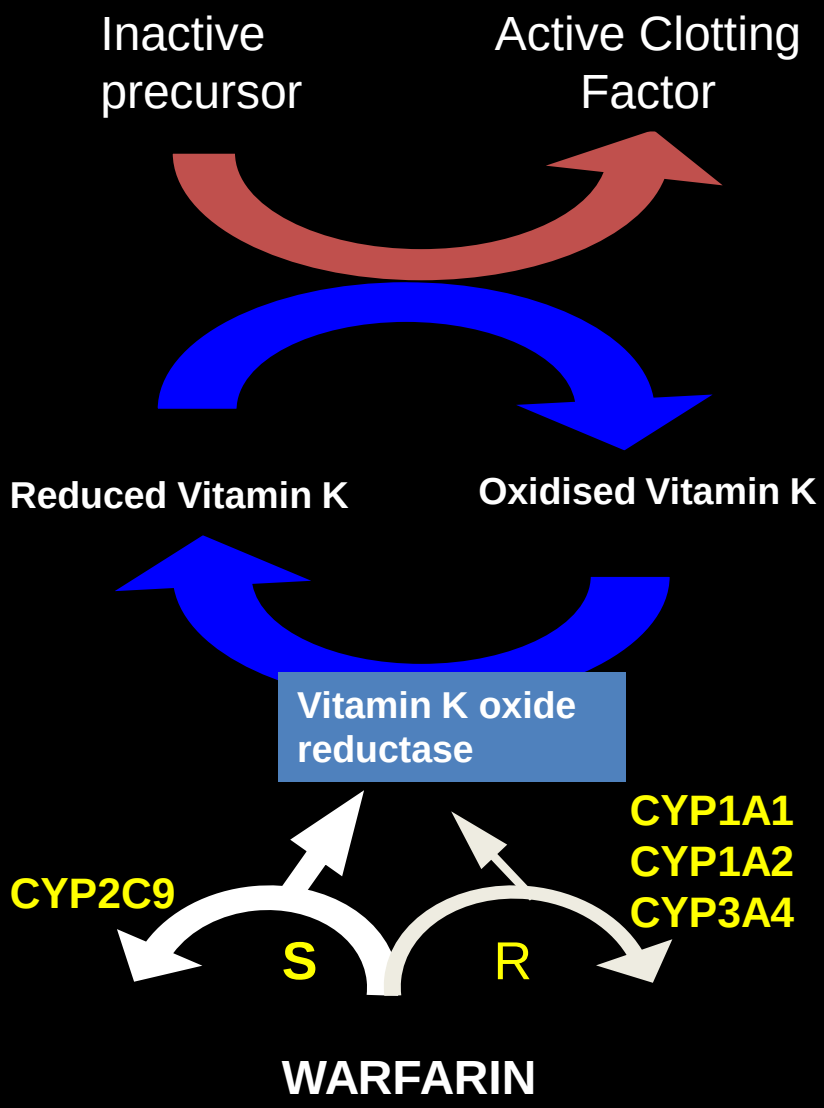
- Diet

VitK-antagonists: far from perfect

Moderately High Vitamin K Content of Foods (25-100 mcg) *Limit to 3 servings/day:*	
½ c Asparagus	38 mcg
½ c frozen Asparagus	72 mcg
½ c raw Broccoli	45 mcg
½ c cooked Cabbage	37 mcg
½ c green Cabbage	82 mcg
1 c cooked Celery	57 mcg
½ Black-eyed dried peas	32 mcg
½ c Kiwi	31 mcg
½ c Spinach Noodles	81 mcg
½ c frozen Okra	44 mcg
½ c dried Prunes	25 mcg
1 c stewed Prunes	65 mcg
1 c Blueberries/ Blackberries	28 mcg
1 c Green Leaf Lettuce	97 mcg
1 c Romaine Lettuce	57 mcg
1 c Raw Watercress	85 mcg

High Vitamin K Content of Foods (100-550 mcg) *Limit to 1 serving/day:*	
½ c Beet greens	350 mcg
½ c cooked Broccoli	110 mcg
½ c Brussels Sprouts	150 mcg
½ c cooked Collards	530 mcg
½ c raw Kale	274 mcg
½ c cooked Kale	550 mcg
½ c Mustard Greens	210 mcg
½ c Green or Scallion Onions	105 mcg
½ c cooked Spinach	444 mcg
1 c raw Spinach	130 mcg
½ c Swiss Chard	287 mcg
½ c Turnip Greens	265 mcg
½ c frozen Turnip Greens	425 mcg
1 c raw Endive	116 mcg
1 c raw Parsley (10 Sprigs)	165 mcg

VitK-antagonists: far from perfect

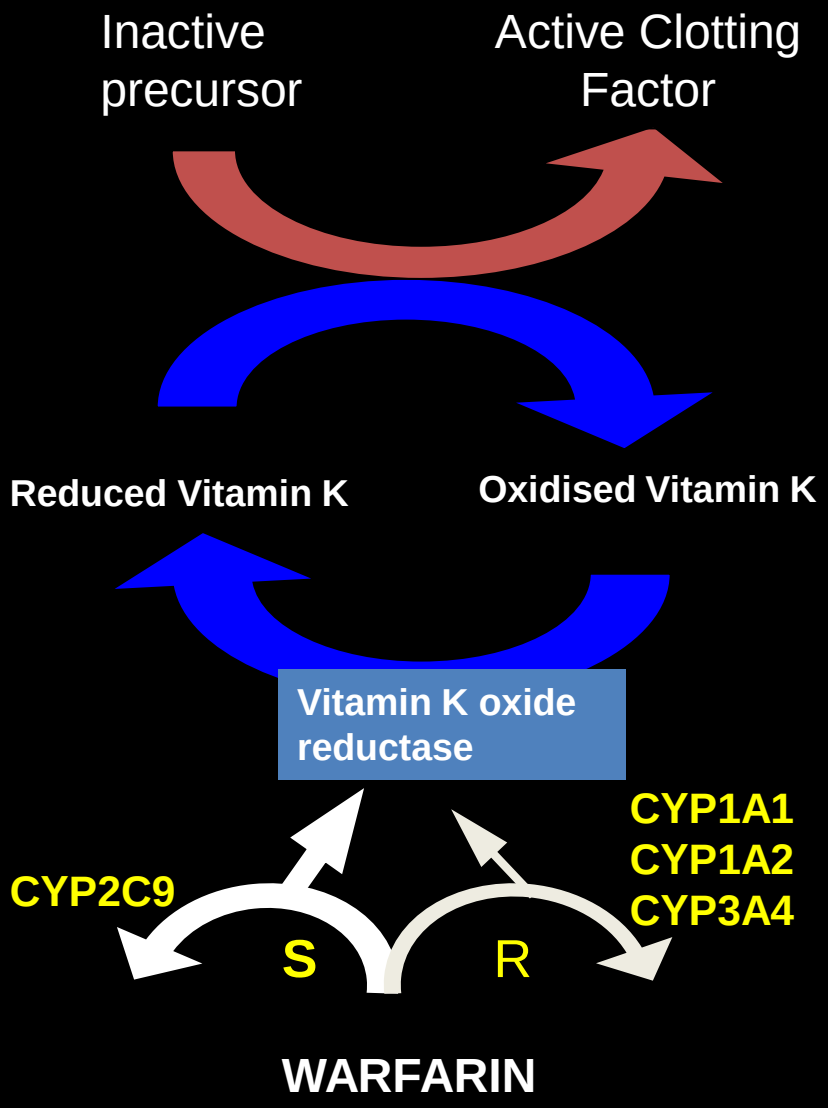


- **Diet**
- **Drugs**

VitK-antagonists: far from perfect

Abciximab
Acetaminophen
Alcohol
(acute and chronic)
Allopurinol
Aminodarone
Aminoglutethimide
Amobarbital
Anabolic steroids
Aspirin
Azathioprine
Butabarbital
Butalbital
Carbamazepine
Cefoperazone
Cefotetan
Cefoxitin
Ceftriaxone
Chenodiol
Chloral hydrate
Chloramphenicol
Chlorpropamide
Chlorthalidone
Cholestyramine
Cimetidine
Ciprofloxacin
Clarithromycin
Clofibrate

VitK-antagonists: far from perfect



- **Diet**
- **Drugs**
- **Polymorphisms**

VitK-antagonists: far from perfect

Estimated warfarin daily dose (mg) based on patient age and genotype

Age (years)	CYP2C9*1	CYP2C9*2	CYP2C9*3
20	6.5 (2.9, 10.2)	5.8 (1.9, 9.8)	5.5 (1.3, 9.8)
25	6.3 (2.7, 9.9)	5.6 (1.8, 9.4)	5.3 (1.2, 9.4)
30	6.0 (2.5, 9.6)	5.3 (1.6, 9.0)	5.0 (1.1, 9.0)
35	5.8 (2.2, 9.3)	5.1 (1.5, 8.7)	4.8 (1.0, 8.6)
40	5.5 (2.0, 9.0)	4.8 (1.3, 8.3)	4.5 (0.8, 8.3)
45	5.3 (1.8, 8.8)	4.6 (1.1, 8.0)	4.3 (0.7, 7.9)
50	5.0 (16, 8.5)	4.3 (1.0, 7.7)	4.0 (0.5, 7.5)
55	4.8 (1.3, 8.2)	4.1 (0.8, 7.4)	3.8 (0.3, 7.2)
60	4.5 (1.1, 7.9)	3.8 (0.5, 7.1)	3.5 (0.1, 6.9)
65	4.3 (0.9, 7.7)	3.5 (0.3, 6.8)	3.3 (-0.1, 6.6)
70	4.0 (0.6, 7.4)	3.3 (0.1, 6.5)	3.0 (-0.3, 6.4)
75	3.8 (0.4, 7.2)	3.0 (-0.2, 6.3)	2.8 (-0.6, 6.1)
80	3.5 (0.9, 6.9)	2.8 (-0.5, 6.0)	2.5 (-0.8, 5.9)
85	3.3 (-0.2, 6.7)	2.5 (-0.8, 5.8)	2.3 (-1.1, 5.7)
90	3.0 (-0.5, 6.5)	2.3 (-1.1, 5.6)	2.0 (-1.5, 5.5)

VitK-antagonists: far from perfect

"… lower initiation doses should be considered for patients with certain genetic variations in CYP2C9 and VKORC1 enzymes …"

FDA 2007

VitK-antagonists: far from perfect

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Emergency Hospitalizations for Adverse Drug Events in Older Americans

Daniel S. Budnitz, M.D., M.P.H., Maribeth C. Lovegrove, M.P.H.,
Nadine Shehab, Pharm.D., M.P.H., and Chesley L. Richards, M.D., M.P.H.

VitK-antagonists: far from perfect

Table 4. National Estimates of Medications Commonly Implicated in Emergency Hospitalizations for Adverse Drug Events in Older U.S. Adults, 2007–2009.*

Medication	Annual National Estimate of Hospitalizations (N=99,628)		Proportion of Emergency Department Visits Resulting in Hospitalization
	no.	*% (95% CI)*	*%*
Most commonly implicated medications†			
Warfarin	33,171	33.3 (28.0–38.5)	46.2
Insulins	13,854	13.9 (9.8–18.0)	40.6
Oral antiplatelet agents	13,263‡	13.3 (7.5–19.1)	41.5
Oral hypoglycemic agents	10,656	10.7 (8.1–13.3)	51.8
Opioid analgesics	4,778	4.8 (3.5–6.1)	32.4
Antibiotics	4,205	4.2 (2.9–5.5)	18.3
Digoxin	3,465	3.5 (1.9–5.0)	80.5
Antineoplastic agents	3,329‡	3.3 (0.9–5.8)‡	51.5
Antiadrenergic agents	2,899	2.9 (2.1–3.7)	35.7
Renin–angiotensin inhibitors	2,870	2.9 (1.7–4.1)	32.6
Sedative or hypnotic agents	2,469	2.5 (1.6–3.3)	35.2
Anticonvulsants	1,653	1.7 (0.9–2.4)	40.0
Diuretics	1,071‡	1.1 (0.4–1.8)‡	42.4

VitK-antagonists: far from perfect

- Narrow therapeutic window
- Frequent INR monitoring
- Frequent dose adjustments
- Unpredictable dose response
- Drug and food interactions
- Slow onset/offset of action

VitK-antagonists: far from perfect

NCBI Resources How To

PubMed.gov
US National Library of Medicine
National Institutes of Health

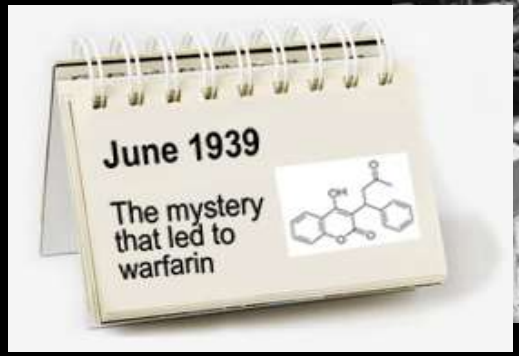
PubMed Search

Bull Chic Med Soc.

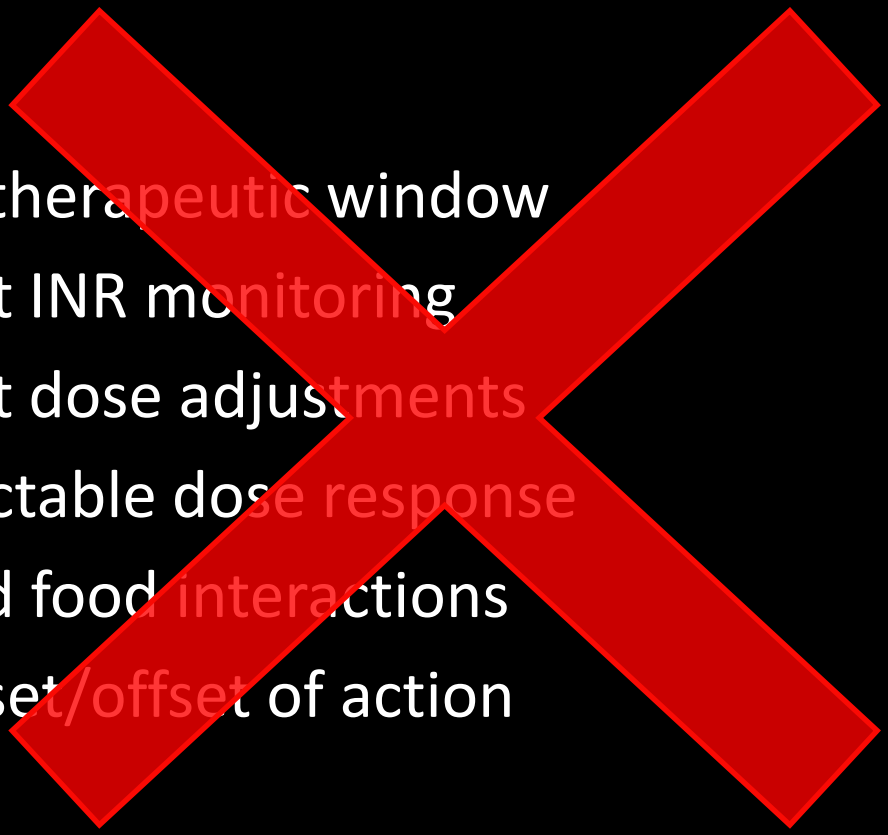
Can we look forward to better anticoagulant

LINK KP

PMID: 18124964 [PubMed - indexed for MEDLINE]



Anti-VKAs' limitations



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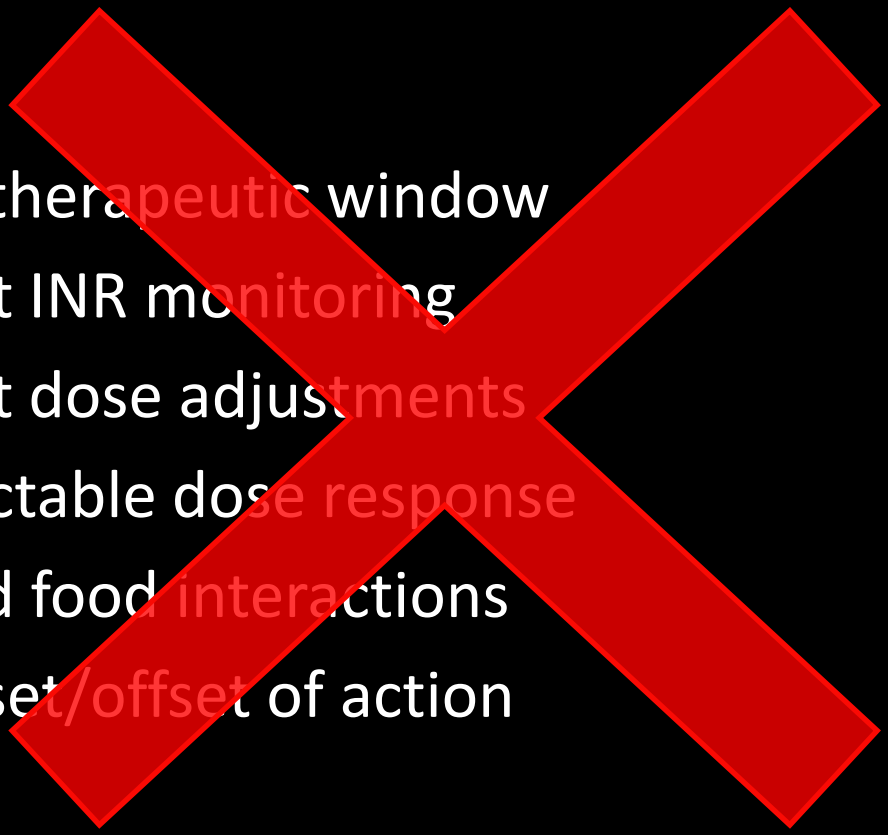

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NOACs


BAYER
Xarelto 20 mg
film-coated tablets
Rivaroxaban
For oral use
28 film-coated tablets


For oral use
ELIQUIS 2.5 mg film-coated tablets
apixaban
10 film-coated tablets


Pradaxa
150 mg
60 Kapseln
Boehringer Ingelheim

EINSTEIN - DVT

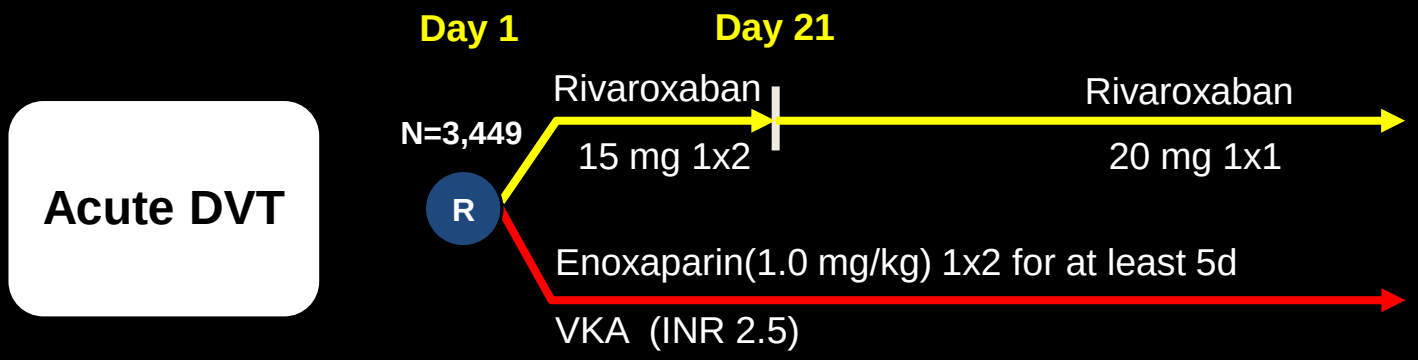
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Rivaroxaban for Symptomatic Venous Thromboembolism

The EINSTEIN Investigators*

EINSTEIN – DVT (a non-inferiority trial)



EINSTEIN - DVT

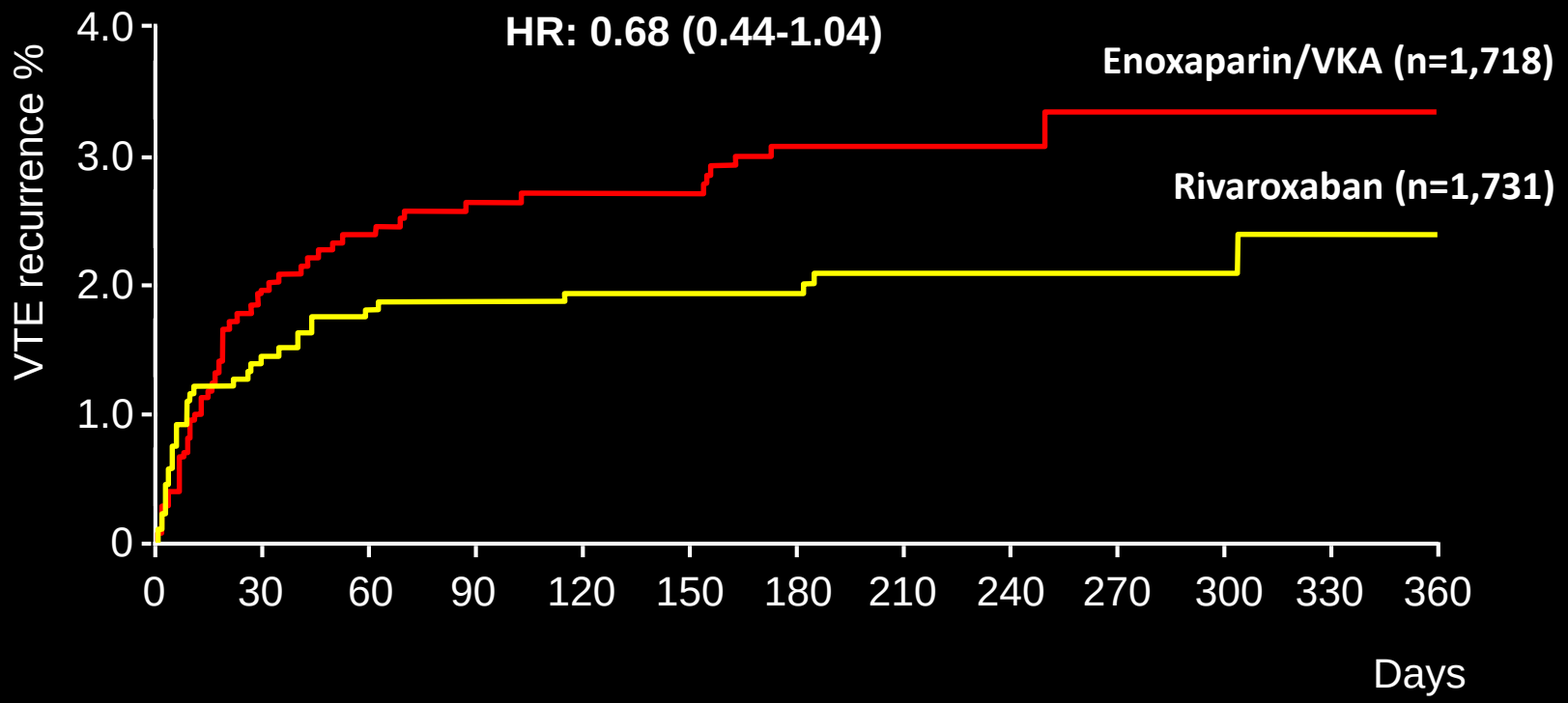
Table 1. Demographic and Clinical Characteristics of Patients with Deep-Vein Thrombosis, According to the Study and the Assigned Group.*

Characteristic	Acute DVT Study		Continued Treatment Study	
	Rivaroxaban (N=1731)	Standard Therapy† (N=1718)	Rivaroxaban (N=602)	Placebo (N=594)
Age — yr	55.8±16.4	56.4±16.3	58.2±15.6	58.4±16
Male sex — no. (%)	993 (57.4)	967 (56.3)	354 (58.8)	339 (57.1)
Weight — no. (%)				
≤50 kg	37 (2.1)	49 (2.9)	10 (1.7)	5 (0.8)
>50–100 kg	1443 (83.4)‡	1422 (82.8)‡	491 (81.6)‡	488 (82.2)‡
>100 kg	245 (14.2)‡	246 (14.3)‡	85 (14.1)‡	87 (14.6)‡
Missing data	6 (0.3)	1 (<0.1)	16 (2.7)	14 (2.4)
Creatinine clearance — no. (%)				
<30 ml/min	6 (0.3)	9 (0.5)	0	5 (0.8)
30–49 ml/min	115 (6.6)	120 (7.0)	37 (6.1)	44 (7.4)
50–79 ml/min	393 (22.7)	399 (23.2)	134 (22.3)	122 (20.5)
≥80 ml/min	1193 (68.9)	1170 (68.1)	373 (62.0)	373 (62.8)
Missing data	24 (1.4)	20 (1.2)	58 (9.6)	50 (8.4)
Initial diagnosis — no.				
DVT	1708	1697 (only 1 distal)	386	356
PE	12	11	216	238
Time from onset of symptoms to randomization — days				
Median	5	5	204	206
Interquartile range	3–10	3–10	188–302	189–307
Cause of DVT or PE — no. (%)				
Unprovoked	1055 (60.9)	1083 (63.0)	440 (73.1)	441(74.2)
Recent surgery or trauma	338 (19.5)	335 (19.5)	21 (3.5)	28 (4.7)
Immobilization	265 (15.3)	260 (15.1)	89 (14.8)	77 (13.0)
Estrogen therapy	140 (8.1)	115 (6.7)	23 (3.8)	22 (3.7)
Active cancer	118 (6.8)	89 (5.2)	28 (4.7)	26 (4.4)
Puerperium	6 (0.3)	11 (0.6)	1 (0.2)	0
Known thrombophilic condition — no. (%)	107 (6.2)	116 (6.8)	49 (8.1)	48 (8.1)
Previous VTE — no. (%)	336 (19.4)	330 (19.2)	108 (17.9)	84 (14.1)

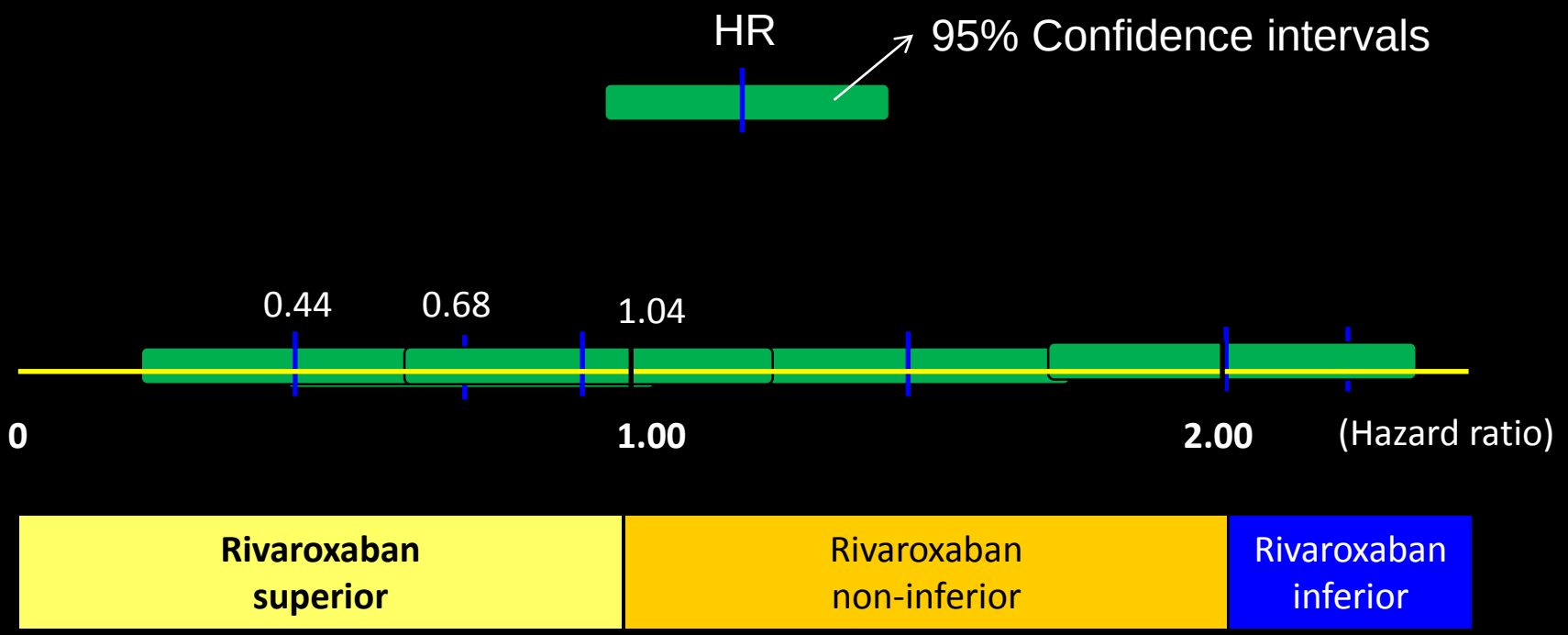
EINSTEIN - DVT

Outcome	Rivaroxaban	Enoxaparin–VKA	Hazard Ratio (95% CI)	P Value
	no. (%)			
Efficacy				
Intention-to-treat population	1731	1718		
Recurrent VTE	36 (2.1)	51 (3.0)	0.68 (0.44–1.04)	<0.001†
Type of recurrent VTE				
Fatal PE	1	0		
PE could not be ruled out	3	6		
Nonfatal PE	20	18		
Recurrent DVT plus PE	1	0		
Recurrent DVT	14	28		
Net clinical benefit in terms of VTE plus major bleeding	51 (2.9)	73 (4.2)	0.67 (0.47–0.95)	0.03

EINSTEIN – DVT: efficacy results



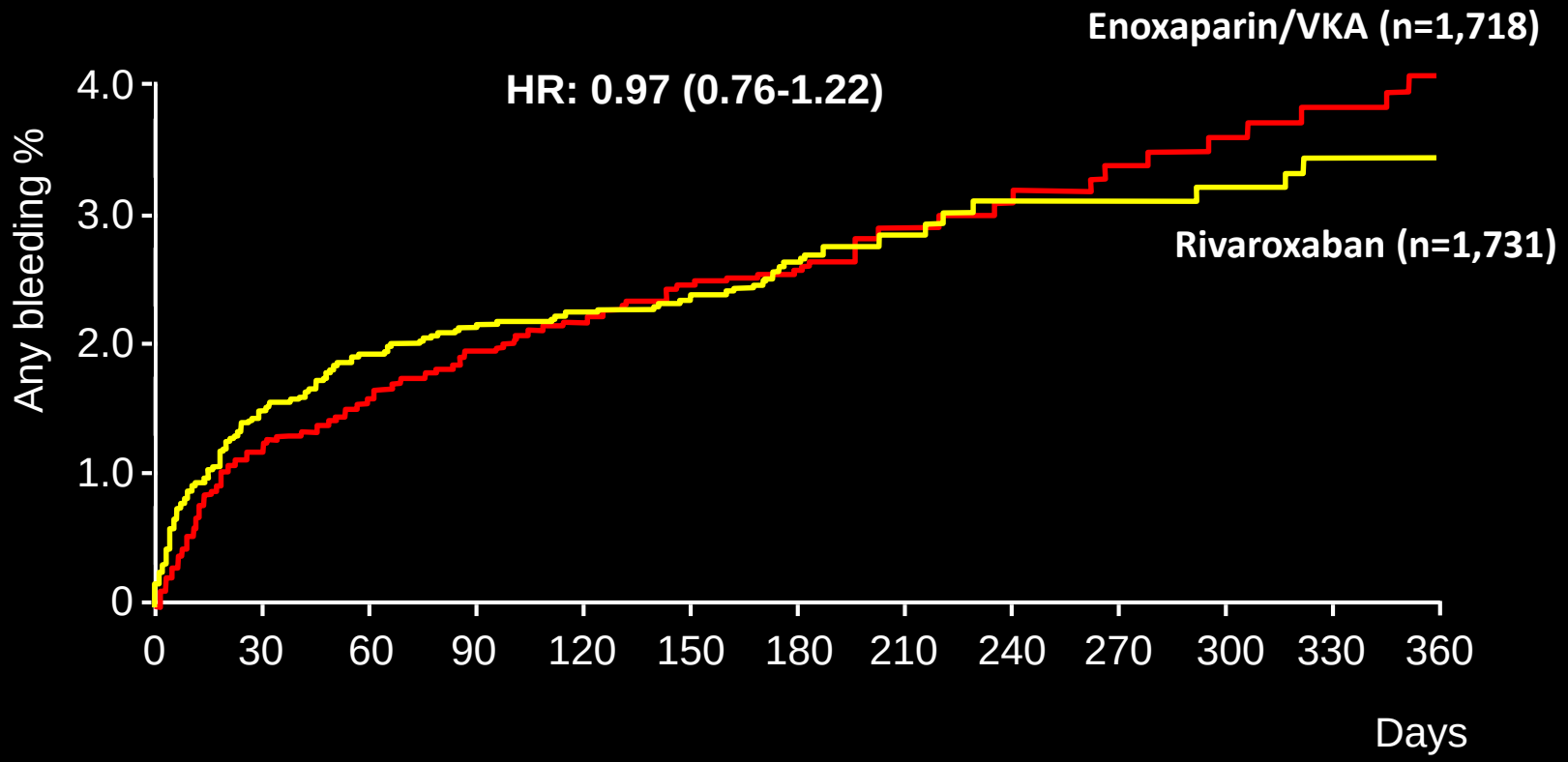
EINSTEIN – DVT: efficacy results



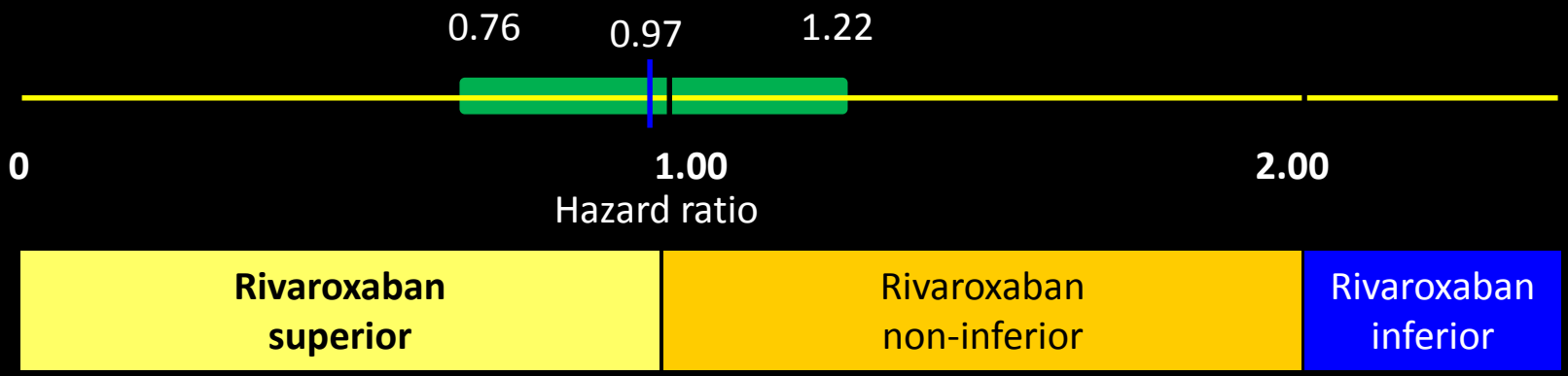
EINSTEIN – DVT: safety results

Outcome	Rivaroxaban	Enoxaparin–VKA	Hazard Ratio (95% CI)	P Value
	no. (%)			
Safety				
Safety population	1718	1711		
First major or clinically relevant nonmajor bleeding occurring during treatment	139 (8.1)	138 (8.1)	0.97 (0.76–1.22)	0.77
Major bleeding	14 (0.8)	20 (1.2)	0.65 (0.33–1.30)	0.21
Contributing to death	1 (<0.1)	5 (0.3)		
In a critical site	3 (0.2)	3 (0.2)		
Associated with a fall in hemoglobin of ≥2 g per deciliter, transfusion of ≥2 units, or both	10 (0.6)	12 (0.7)		
Clinically relevant nonmajor bleeding	126 (7.3)	119 (7.0)		
Total deaths through end of intended treatment period	38 (2.2)	49 (2.9)	0.67 (0.44–1.02)	0.06
Cause of death				
PE, or PE not ruled out	4	6		
Bleeding	2‡	5		
Cancer	25	20		
Cardiovascular disease	2	4		
Other	6	14		
Adverse events				
Any event emerging during treatment	1078 (62.7)	1080 (63.1)		
Any serious event emerging during treatment	201 (12.0)	233 (13.6)		
Any event resulting in permanent discontinuation of study drug	85 (4.9)	81 (4.7)		

EINSTEIN – DVT: safety results



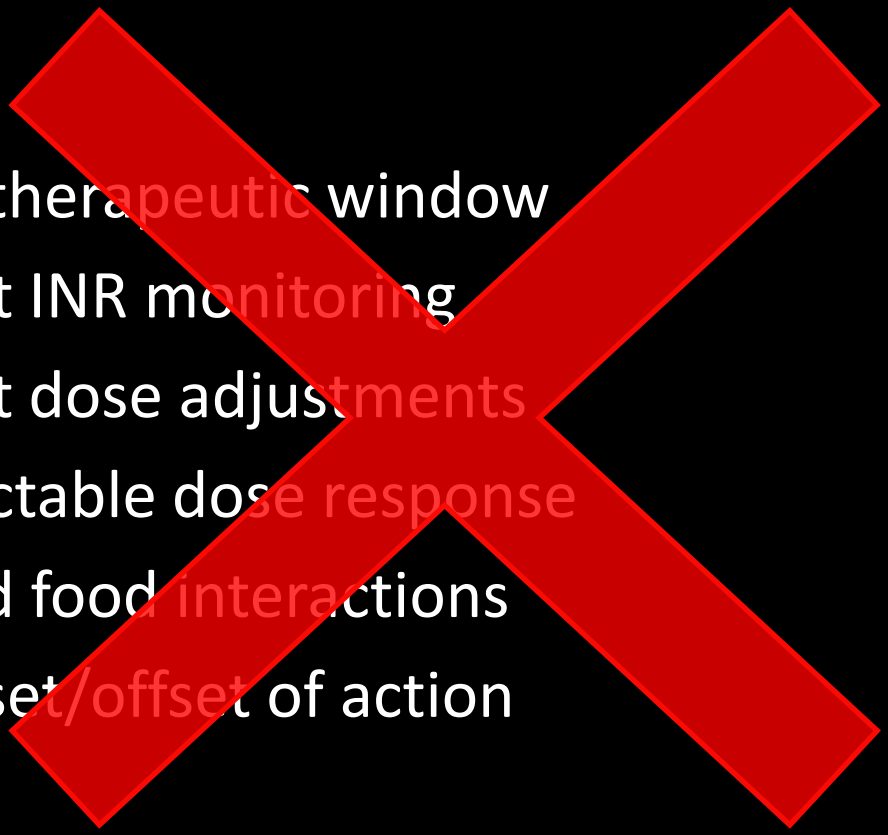
EINSTEIN – DVT: safety results



EINSTEIN – DVT: summary

- ✓ Rivaroxaban is non-inferior to enoxaparin/VKA (efficacy/safety)

Anti-VKAs' limitations



- Narrow therapeutic window
- Frequent INR monitoring
- Frequent dose adjustments
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Rivaroxaban in VTE: cost-effectiveness

Cost-effectiveness of rivaroxaban versus warfarin anticoagulation for the prevention of recurrent venous thromboembolism: A U.S. perspective

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ABSTRACT

Introduction: Rivaroxaban is an oral direct factor Xa inhibitor that is noninferior to warfarin in the prevention of recurrent venous thromboembolism (VTE). Whether rivaroxaban is cost-effective in the prevention of recurrent VTE, however, is not known.

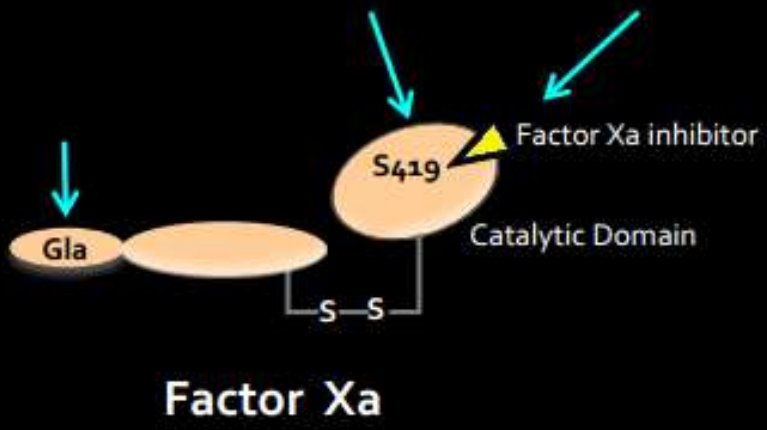
Material and Methods: To assess the cost effectiveness of rivaroxaban compared with warfarin in the prevention of recurrent VTE, we built a Markov state-transition model over a 10-year time horizon. The base case analysis consisted of a hypothetical cohort of 60-year-old patients with an initial VTE who received secondary prophylaxis with either rivaroxaban or warfarin for 3 to 12 months. Cost estimates were derived from the Healthcare and Utilization Project and other sources. Probabilities were based on literature values. Outcomes included costs in 2011 United States dollars, quality-adjusted life-years (QALYs), and incremental cost effectiveness ratios (ICERs) over 10 years from a societal perspective.

Results: Compared with warfarin, the rivaroxaban strategy cost less ($3,195 vs. $6,188) and was more effective (9.29 QALYs vs 9.14 QALYs). Our results were highly robust in sensitivity analyses. Warfarin was no longer dominated by rivaroxaban when the risk of major bleeding with rivaroxaban exceeds 3.8% (base case estimate: 0.96%).

Conclusion: In summary, prophylactic anticoagulation with rivaroxaban appears to be a cost effective, and perhaps cost saving, alternative to warfarin for the prevention of recurrent VTE.

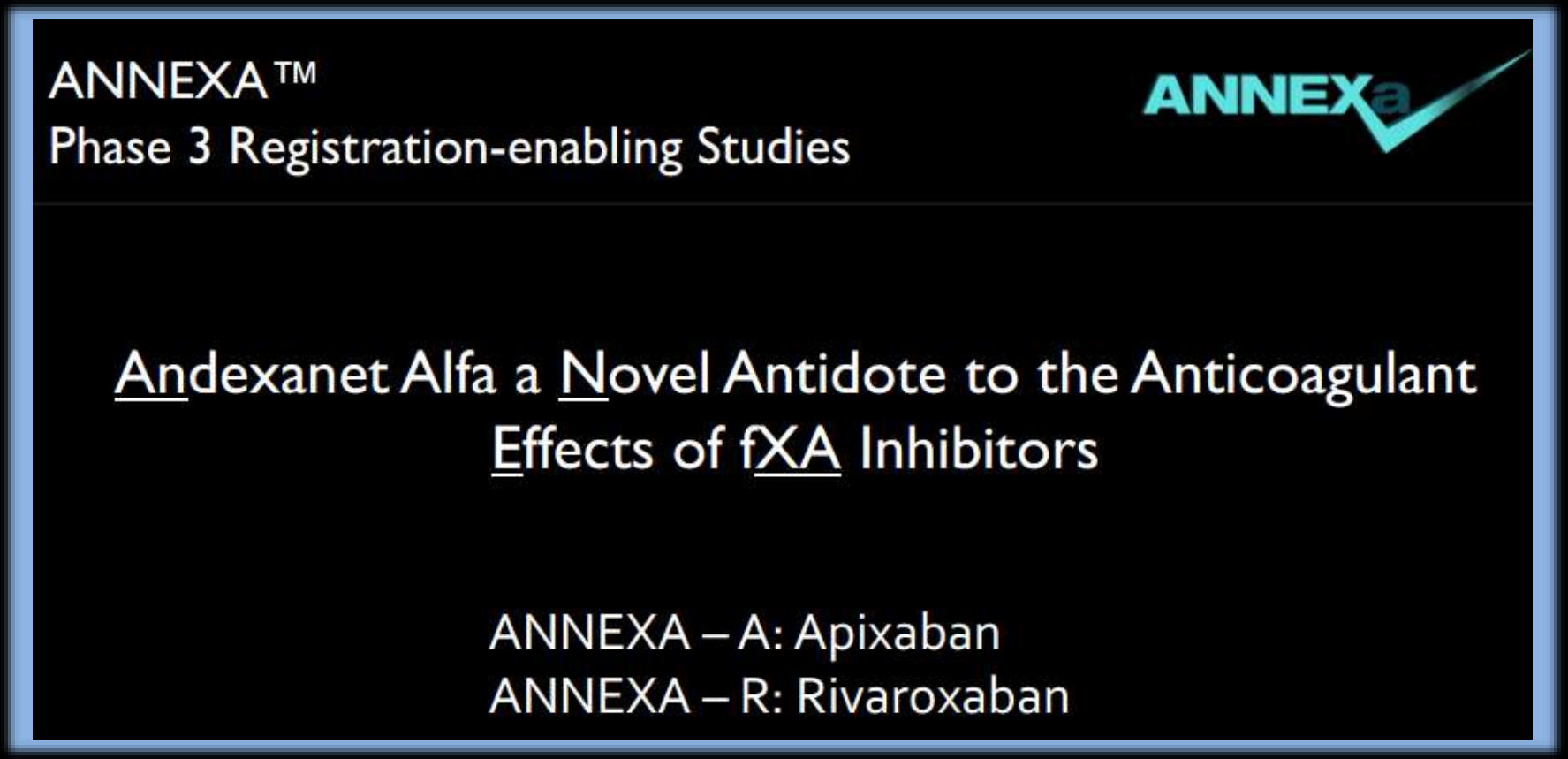
Rivaroxaban: no antidote ?????

Andexanet: an antidote for Xa inhibitors



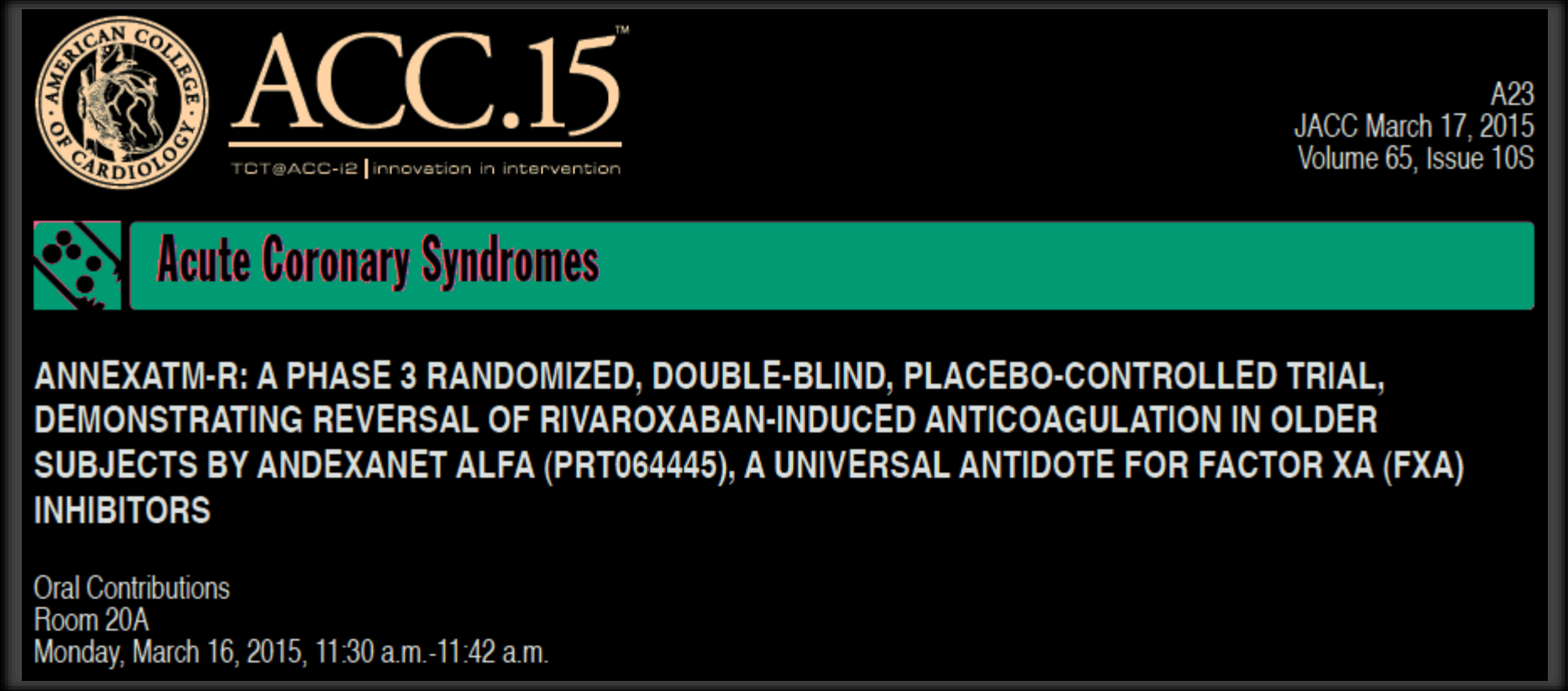
Crowther. AHA Scientific sessions 2014

Andexanet: an antidote for Xa inhibitors



Crowther. AHA Scientific sessions 2014

Andexanet: an antidote for Xa inhibitors



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A23
JACC March 17, 2015
Volume 65, Issue 10S

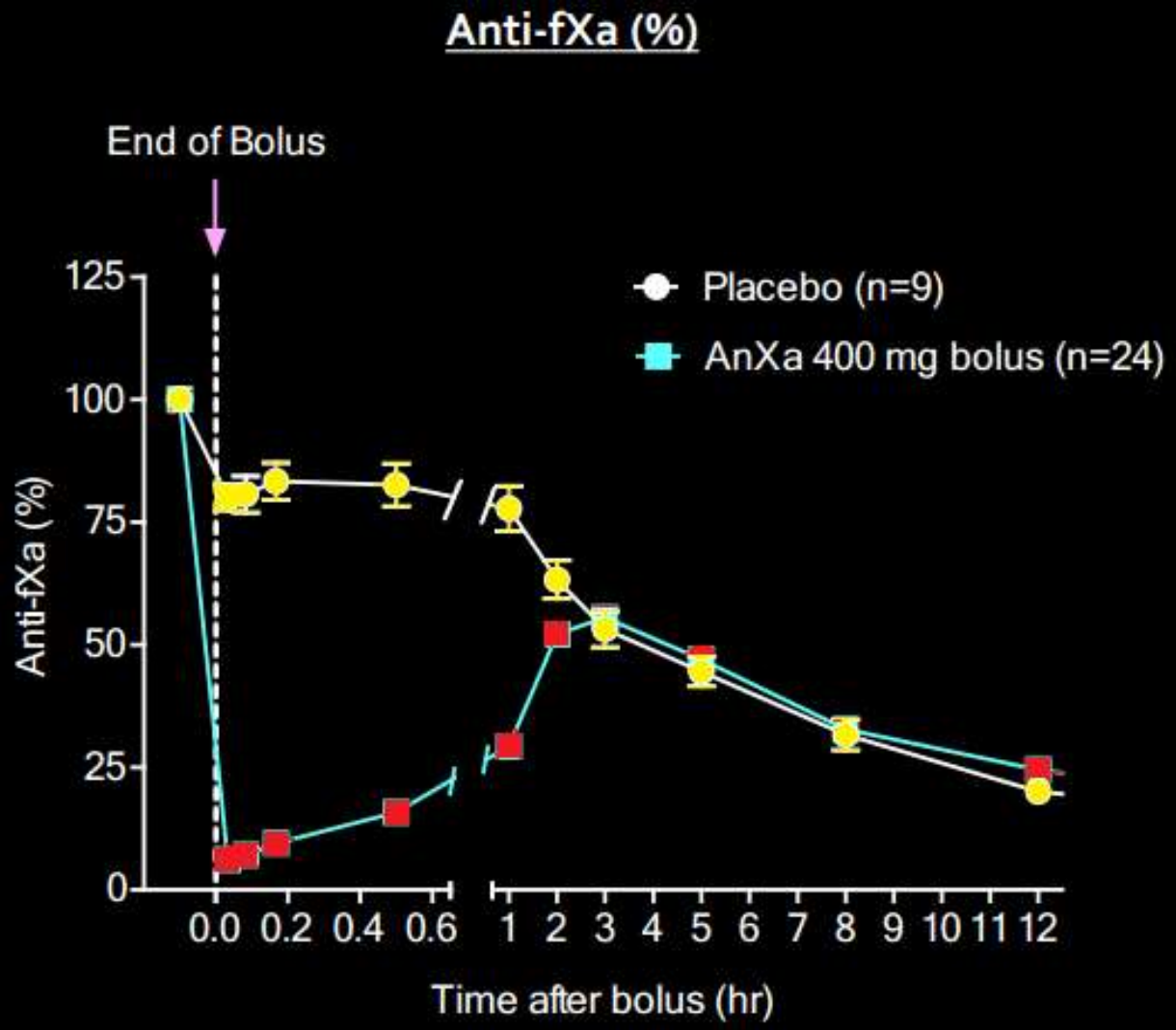
Acute Coronary Syndromes

ANNEXATM-R: A PHASE 3 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL, DEMONSTRATING REVERSAL OF RIVAROXABAN-INDUCED ANTICOAGULATION IN OLDER SUBJECTS BY ANDEXANET ALFA (PRT064445), A UNIVERSAL ANTIDOTE FOR FACTOR XA (FXA) INHIBITORS

Oral Contributions
Room 20A
Monday, March 16, 2015, 11:30 a.m.-11:42 a.m.

Gold. JACC, 4 days ago

Andexanet: an antidote for Xa inhibitors



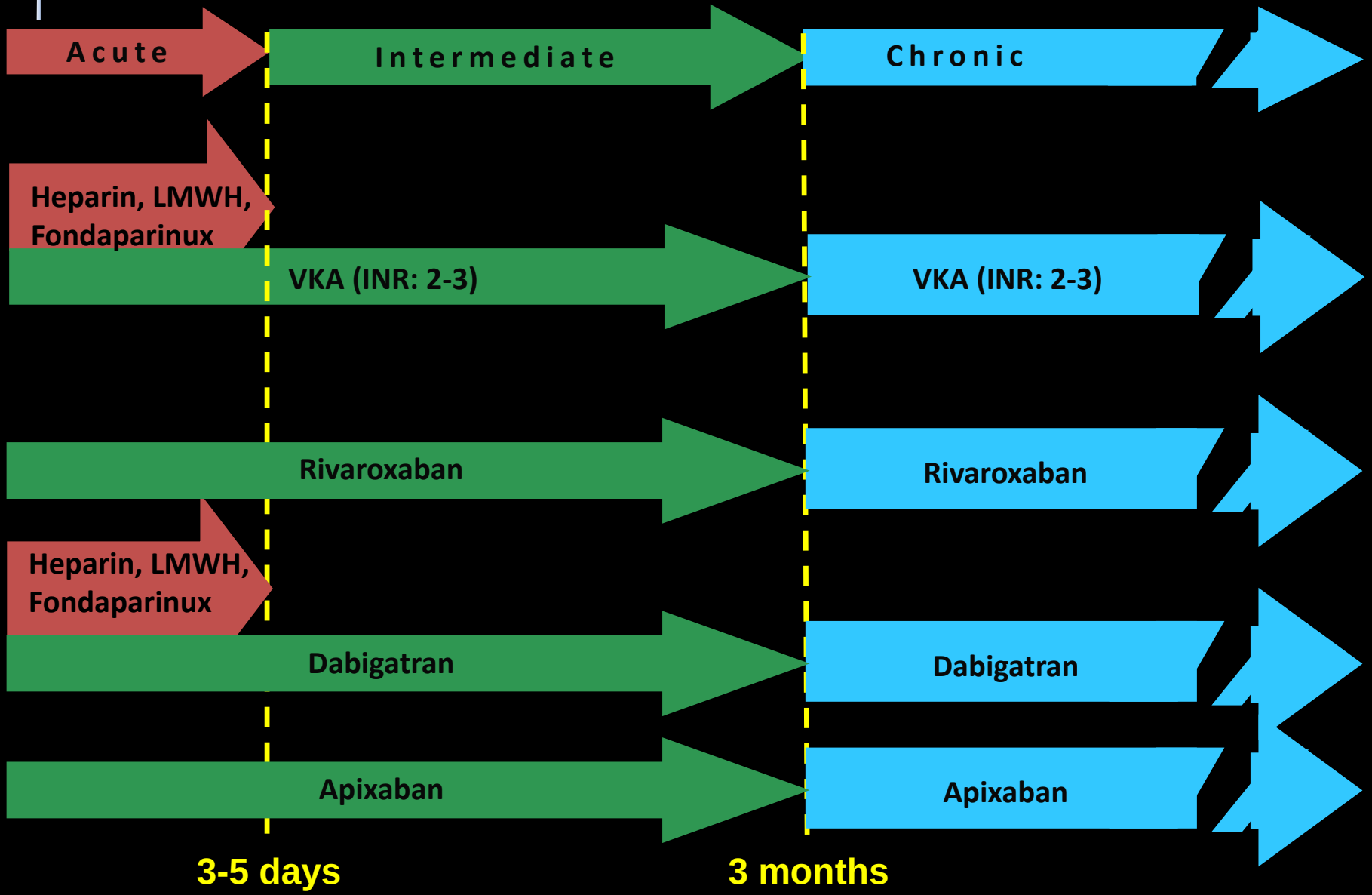
NOACs


BAYER
Xarelto 20 mg
film-coated tablets
Rivaroxaban
For oral use
28 film-coated tablets


For oral use
ELIQUIS 2.5 mg film-coated tablets
apixaban
10 film-coated tablets


Pradaxa
150 mg
60 Kapseln
Boehringer Ingelheim

VTE: Treatment strategy (*until recently…*)



Compliance

Europace
doi:10.1093/europace/euu319

Drug persistence with rivaroxaban therapy in atrial fibrillation patients—results from the Dresden non-interventional oral anticoagulation registry

Jan Beyer-Westendorf[1]*, Kati Förster[1], Franziska Ebertz[1], Vera Gelbricht[1], Thomas Schreier[1], Maria Göbelt[1], Franziska Michalski[1], Heike Endig[1], Kurtulus Sahin[2], Luise Tittl[1], and Norbert Weiss[1]

[1]Center for Vascular Medicine and Department of Medicine III, Division of Angiology, University Hospital 'Carl Gustav Carus' Dresden, Technical University Dresden, Fetscherstrasse 74, Dresden D-01307, Germany; and [2]ClinStat GmbH, Institute for Clinical Research and Statistics, Max-Planck-Str. 22a, Cologne D-50858, Germany

Received 18 September 2014; accepted after revision 14 October 2014

Compliance

Aims

Worldwide, rivaroxaban is increasingly used for stroke prevention in atrial fibrillation (SPAF) but little is known about the rates of or reasons for rivaroxaban discontinuations in daily care. Using data from a prospective, non-interventional oral anticoagulation (NOAC) registry, we analysed rivaroxaban treatment persistence.

Methods and results

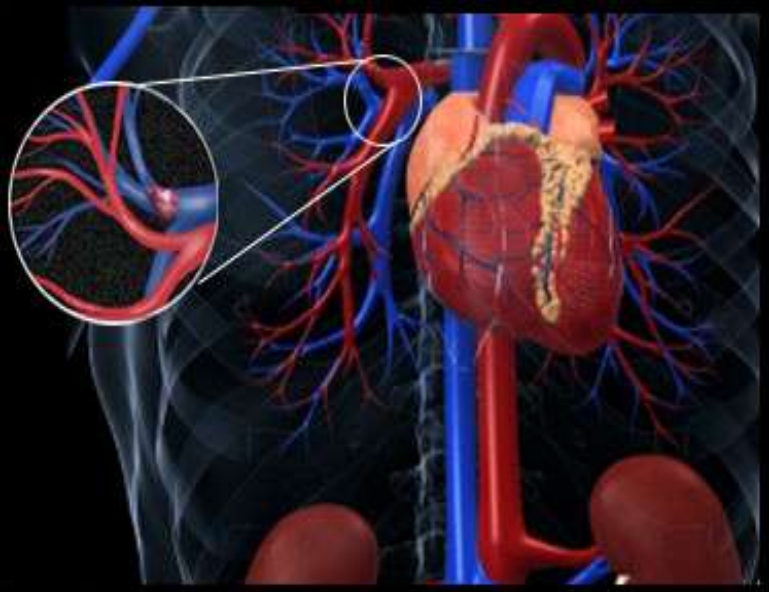
Persistence with rivaroxaban in SPAF was assessed in an ongoing, prospective, non-interventional registry of >2600 NOAC patients from daily care using the Kaplan–Meier time-to-first-event analysis. Reasons for and management of rivaroxaban discontinuation were assessed. Potential baseline risk factors for treatment discontinuation were evaluated using Cox regression analysis. Between October 2011 and April 2014, 1204 rivaroxaban SPAF patients were enrolled [39.3% switched from vitamin K antagonists (VKAs) and 60.7% newly treated patients]. Of these, 223 patients (18.5%) stopped rivaroxaban during follow-up (median 544 days), which translates into a discontinuation rate of 13.6 (95% CI 11.8–15.4) per 100 patient-years. Most common reasons for treatment discontinuations were bleeding complications (30% of all discontinuations), followed by other side-effects (24.2%) and diagnosis of stable sinus rhythm (9.9%). A history of chronic heart failure (HR 1.43; 95% CI 1.09–1.87; $P = 0.009$) or diabetes (HR 1.39; 95% CI 1.06–1.82; $P = 0.018$) were the only statistically significant baseline risk factors for rivaroxaban discontinuation. After discontinuation of rivaroxaban, patients received antiplatelet therapy (31.8%), VKA (24.2%), another NOAC (18.4%), heparin (9.9%), or nothing (15.7%).

Conclusion

Our data indicate that overall persistence with rivaroxaban therapy is high, with a discontinuation rate of ~15% in the first year of treatment and few additional discontinuations thereafter.

Clinical scenario 2

- ✓ ♂, 74yrs
- ✓ Arterial hypertension on valsartan/HCTZ 1x1 and amlodipine 1x1
- ✓ Diabetes Mellitus on metformin 1x2 and glimepiride
- ✓ Depression on escitalopram 1x1
- ✓ Benign prostate hyperplasia on alfuzocin 1x1



EINSTEIN – PE

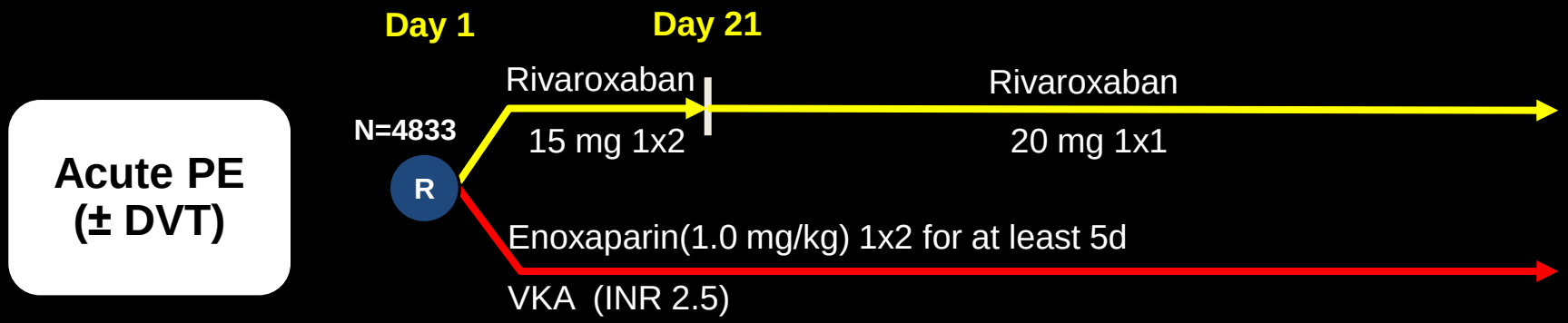
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism

The EINSTEIN–PE Investigators*

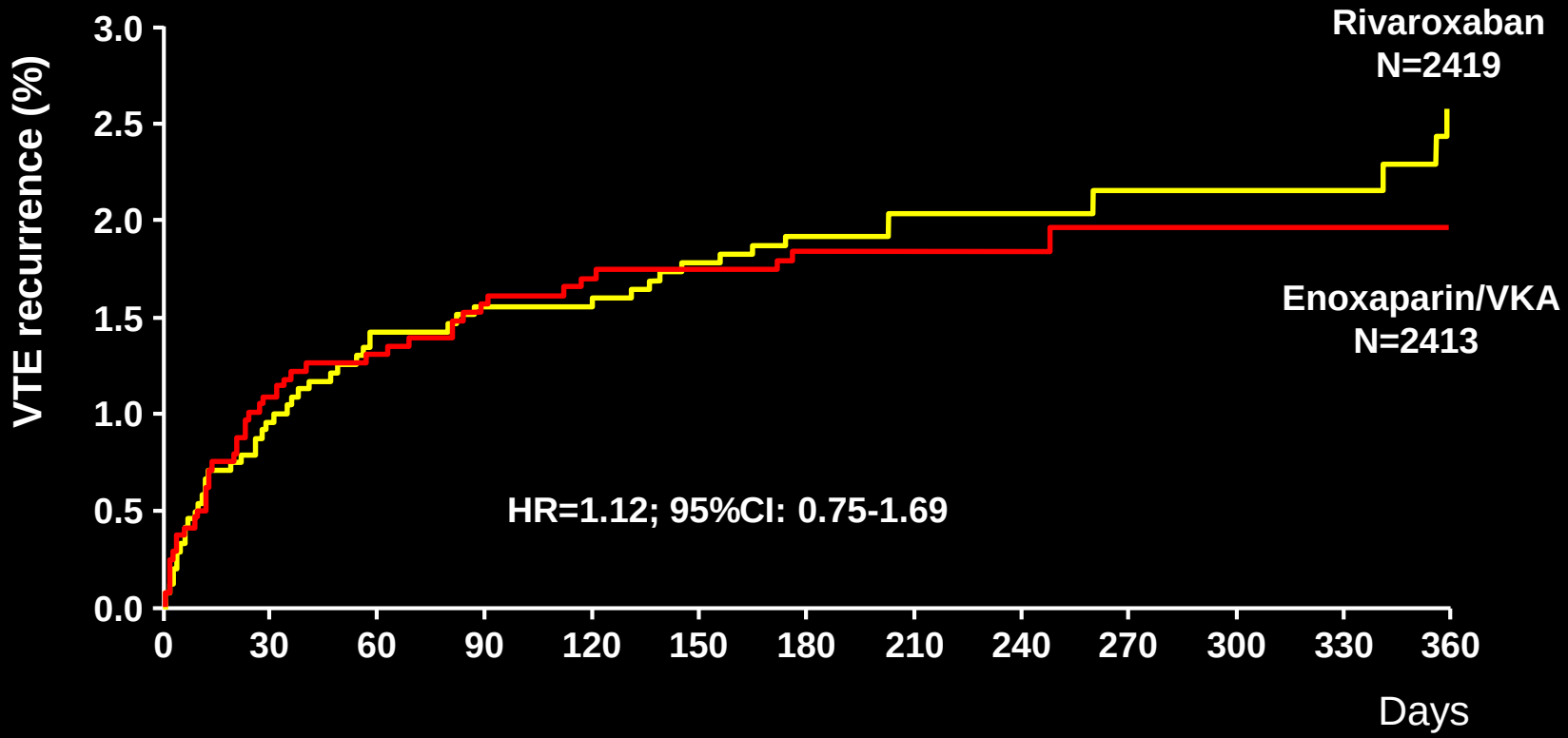
EINSTEIN - PE


Acute PE
(± DVT)
Day 1
Day 21
N=4833
R
Rivaroxaban
15 mg 1x2
Rivaroxaban
20 mg 1x1
Enoxaparin(1.0 mg/kg) 1x2 for at least 5d
VKA (INR 2.5)

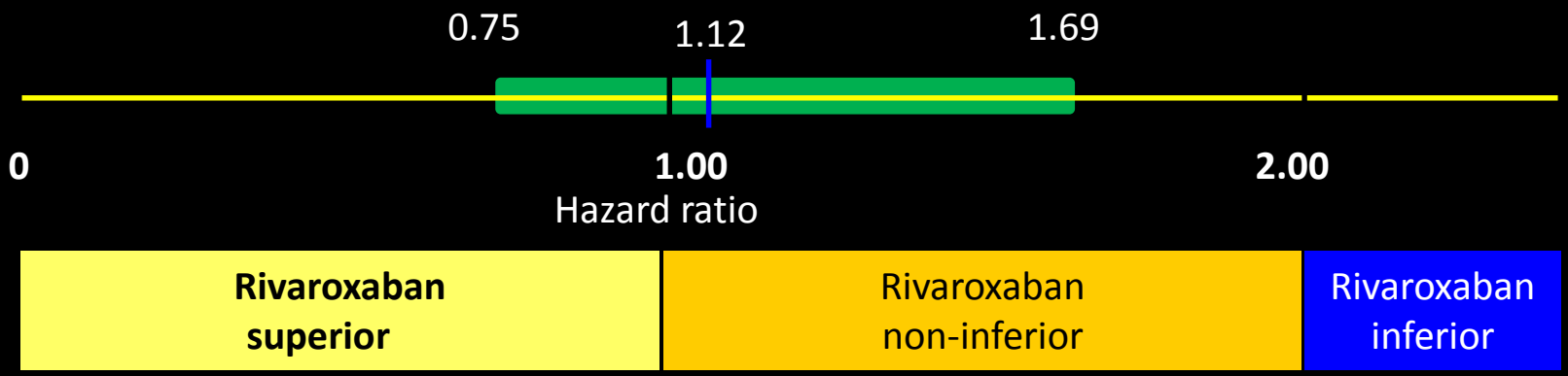
EINSTEIN – PE: efficacy results

Outcome	Rivaroxaban	Standard Therapy	Hazard Ratio (95% CI)*	P Value
Efficacy				
Intention-to-treat population — no. of patients	2419	2413		
Recurrent venous thromboembolism — no. (%)	50 (2.1)	44 (1.8)	1.12 (0.75–1.68)	0.003†
Type of first recurrent venous thromboembolism — no.				
Fatal pulmonary embolism	2	1		
Death in which pulmonary embolism could not be ruled out	8	5		
Nonfatal pulmonary embolism	22	19		
Recurrent deep-vein thrombosis plus pulmonary embolism	0	2		
Recurrent deep-vein thrombosis	18	17		
Net clinical benefit: venous thromboembolism plus major bleeding — no. (%)‡	83 (3.4)	96 (4.0)	0.85 (0.63–1.14)	0.28

EINSTEIN – PE: efficacy results



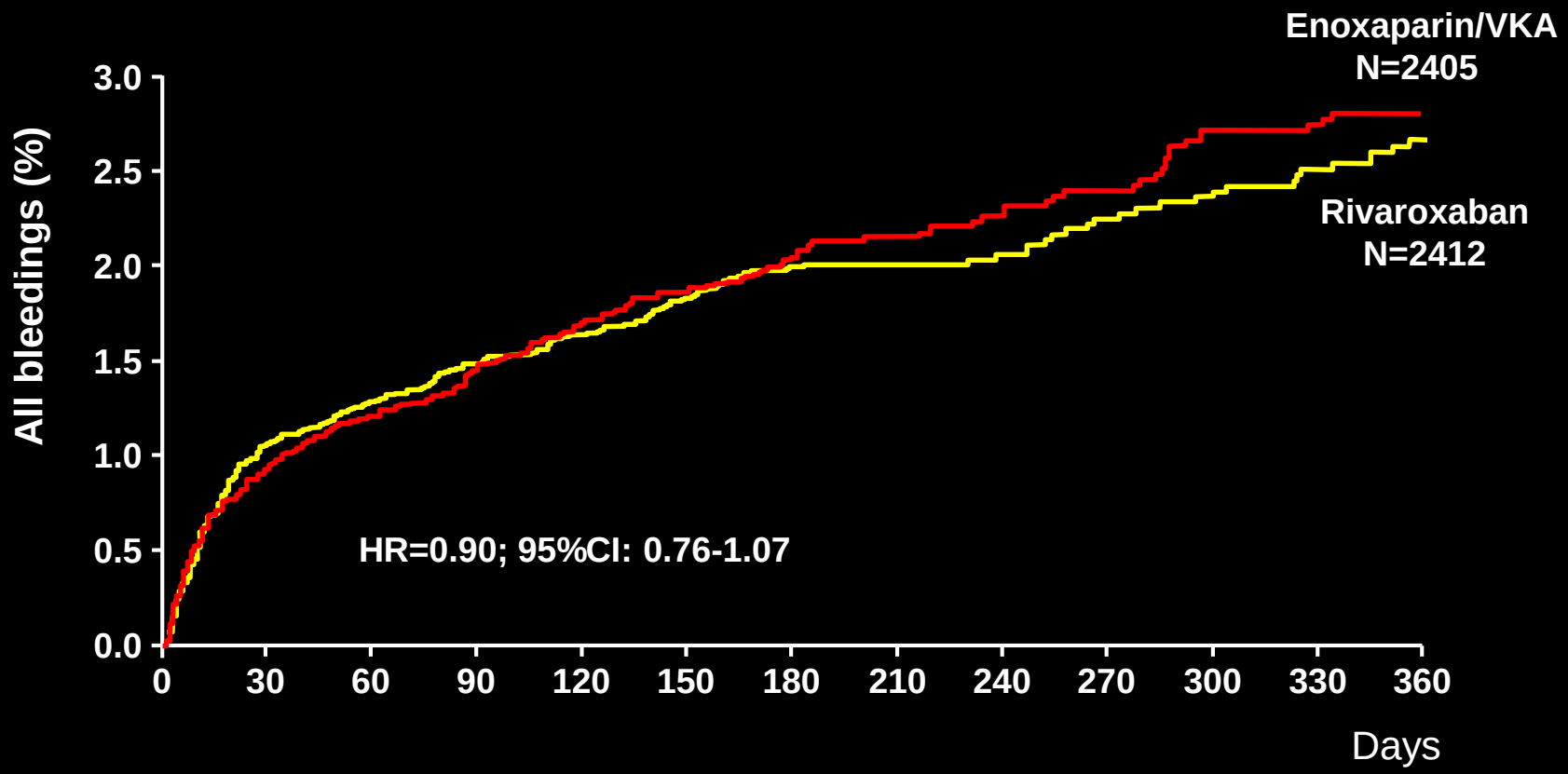
EINSTEIN – PE: efficacy results



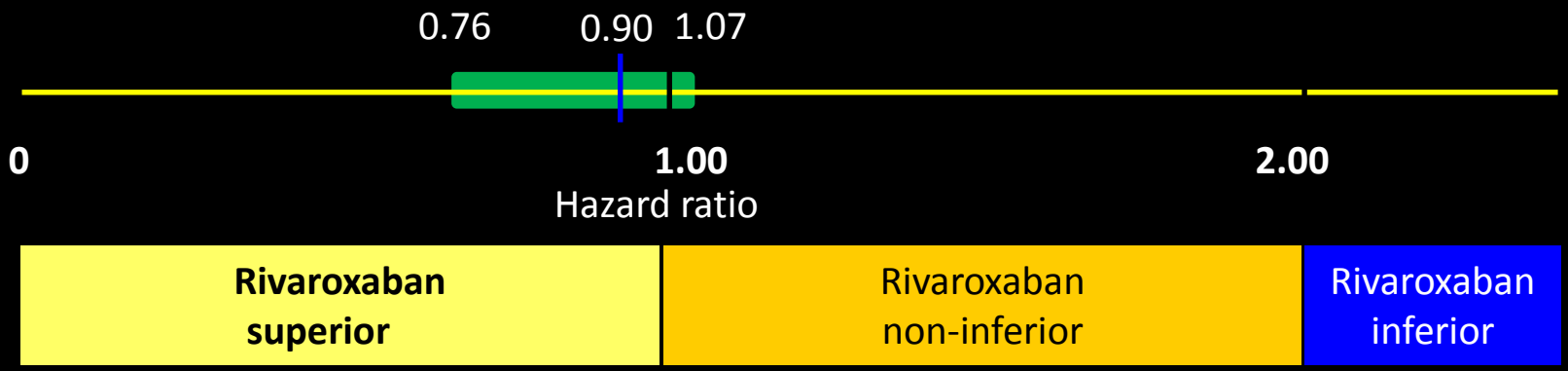
EINSTEIN – PE: safety results (all bleedings)

Outcome	Rivaroxaban	Standard Therapy	Hazard Ratio (95% CI)*	P Value
Safety				
No. of patients	2412	2405		
First episode of major or clinically relevant nonmajor bleeding during treatment — no. (%)	249 (10.3)	274 (11.4)	0.90 (0.76–1.07)	0.23
Major bleeding episode — no. (%)				
Any	26 (1.1)	52 (2.2)	0.49 (0.31–0.79)	0.003
Fatal	2 (<0.1)	3 (0.1)		
Retroperitoneal	0	1 (<0.1)		
Intracranial	2 (<0.1)	2 (<0.1)		
Other nonfatal episode in a critical site§	7 (0.3)	26 (1.1)		
Intracranial	1 (<0.1)	10 (0.4)		
Retroperitoneal	1 (<0.1)	7 (0.3)		
Intraocular	2 (<0.1)	2 (<0.1)		
Pericardial	0	2 (<0.1)		
Intraarticular	0	3 (0.1)		
Adrenal gland	1 (<0.1)	0		
Hemothorax	1 (<0.1)	1 (<0.1)		
Intraabdominal with hemodynamic instability	1 (<0.1)	2 (<0.1)		

EINSTEIN – PE: safety results (all bleedings)



EINSTEIN – PE: safety results (all bleedings)



EINSTEIN – PE: safety results (major bleeding)

Outcome	Rivaroxaban	Standard Therapy	Hazard Ratio (95% CI)*	P Value
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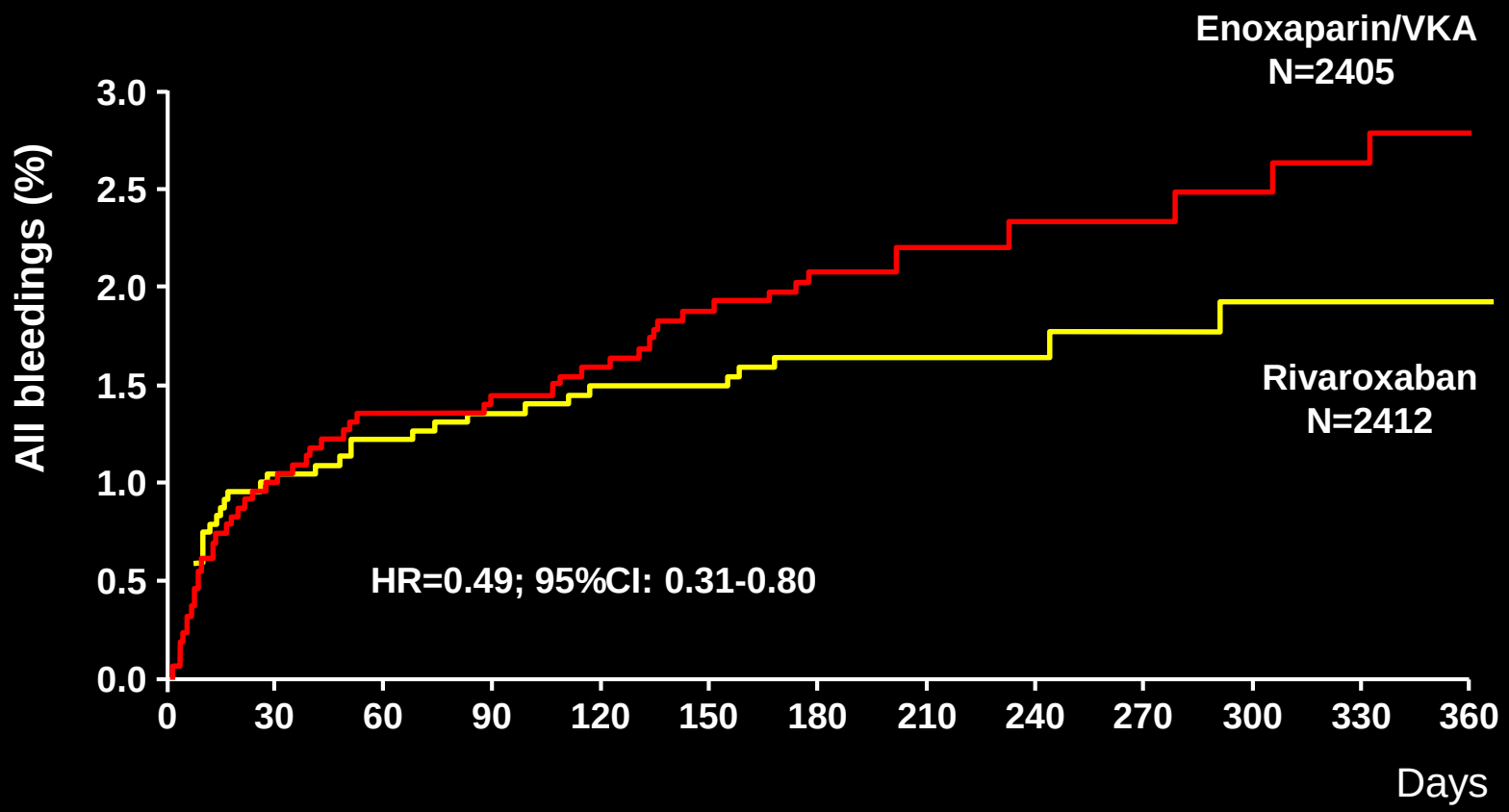
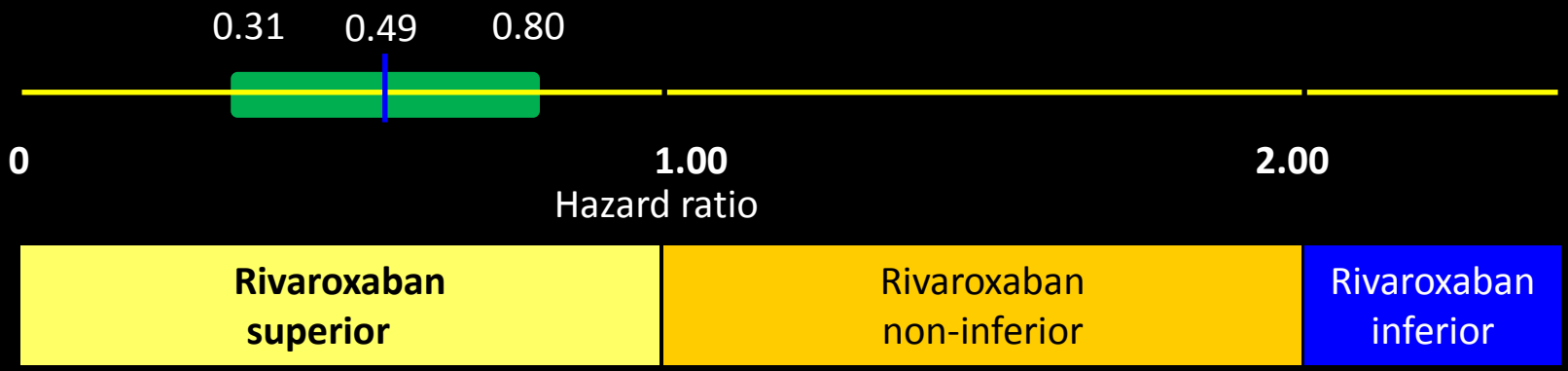
Adrenal gland	1 (<0.1)	0		
Hemothorax	1 (<0.1)	1 (<0.1)		
Intraabdominal with hemodynamic instability	1 (<0.1)	2 (<0.1)		

EINSTEIN – PE: safety results (major bleeding)



EINSTEIN – PE: safety results (major bleeding)



EINSTEIN – PE: summary

Rivaroxaban vs. enoxaparin/VKA:

- Non-inferior efficacy
- Non-inferior safety (any bleeding)
- Superior safety (major bleeding)

EINSTEIN – DVT/PE meta-analysis

Prins *et al. Thrombosis Journal* 2013, **11**:21
http://www.thrombosisjournal.com/content/11/1/21

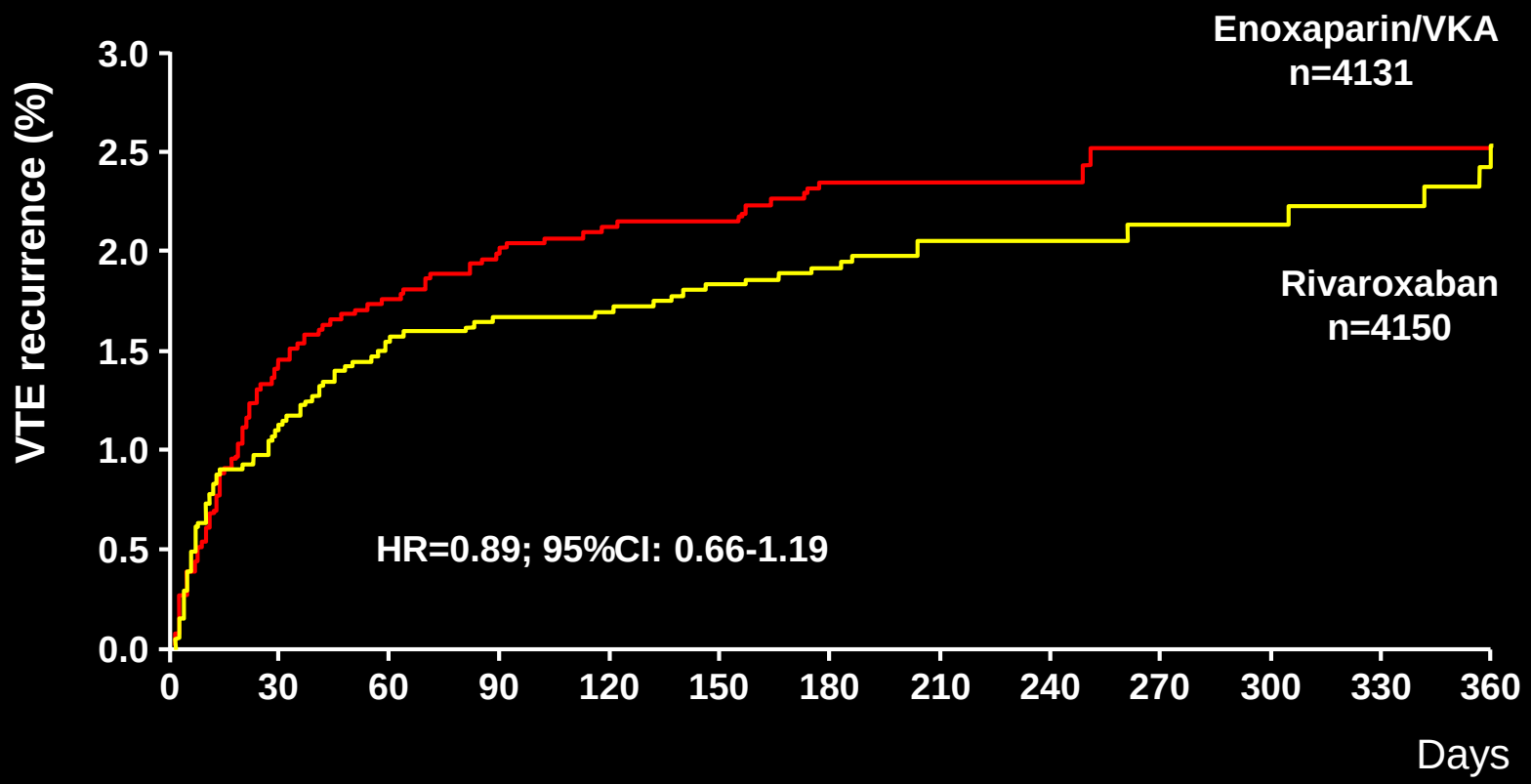
TJ THROMBOSIS JOURNAL

ORIGINAL CLINICAL INVESTIGATION Open Access

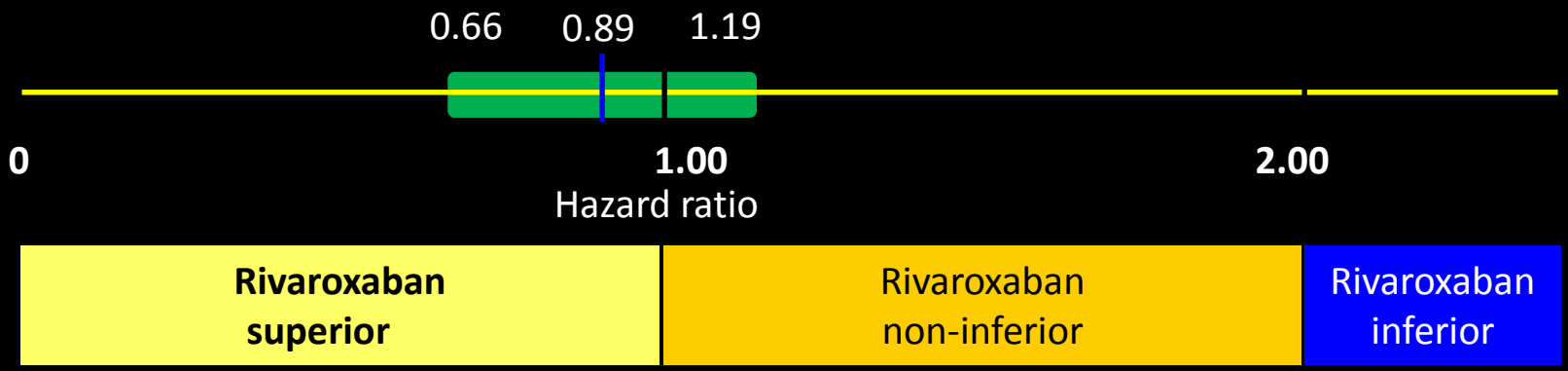
Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies

Martin H Prins[1*], Anthonie WA Lensing[2], Rupert Bauersachs[3], Bonno van Bellen[4], Henri Bounameaux[5], Timothy A Brighton[6], Alexander T Cohen[7], Bruce L Davidson[8], Hervé Decousus[9], Gary E Raskob[10], Scott D Berkowitz[11], Philip S Wells[12], on behalf of the EINSTEIN Investigators

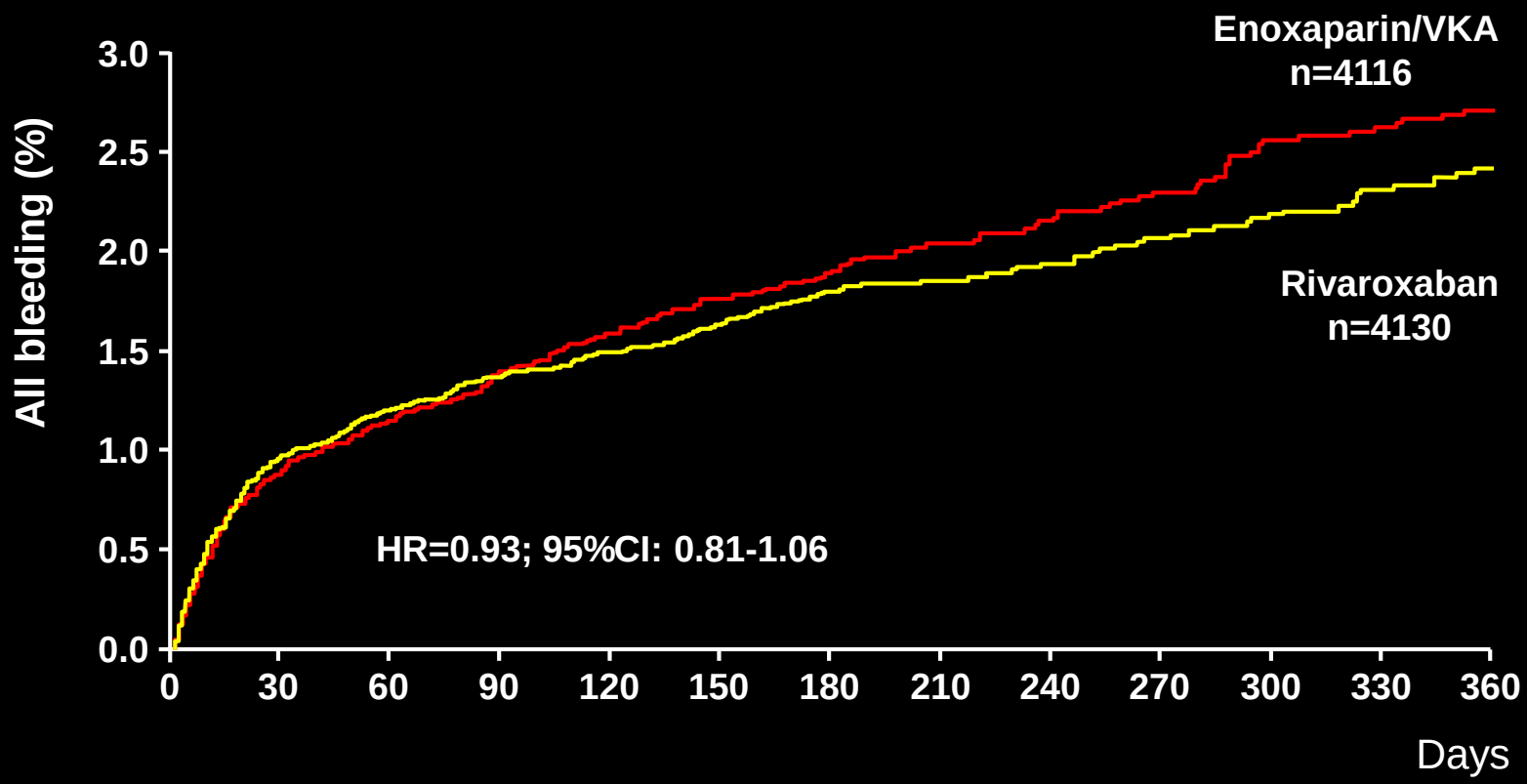
EINSTEIN – DVT/PE: efficacy results



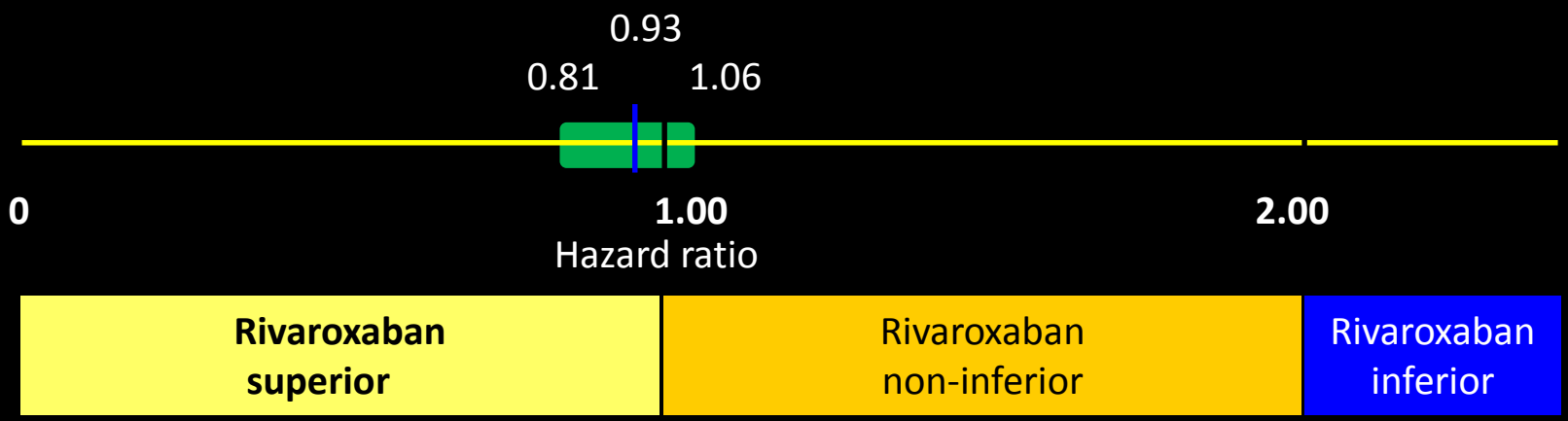
EINSTEIN – DVT/PE: efficacy results



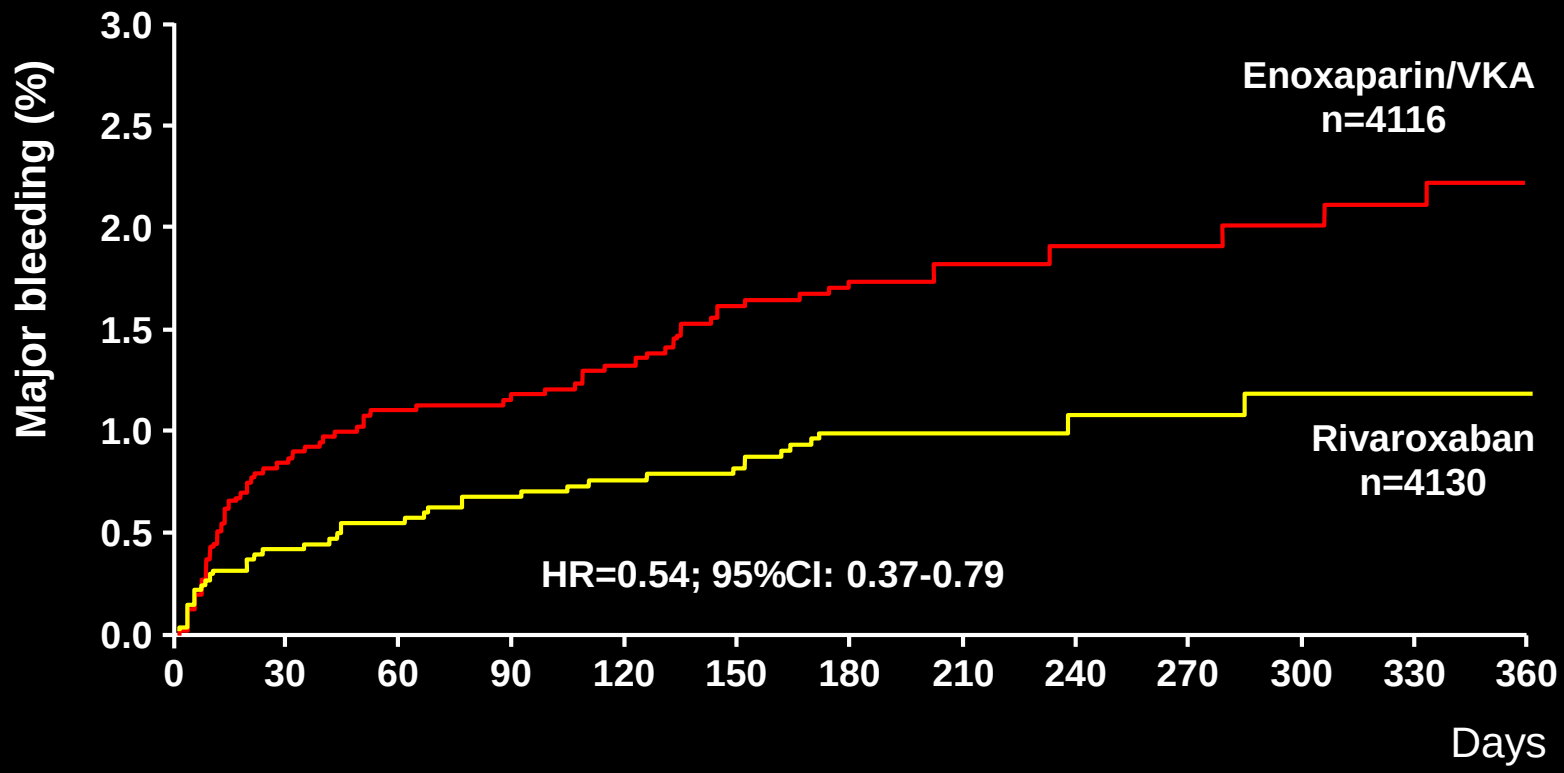
EINSTEIN – DVT/PE: safety results (all bleeding)



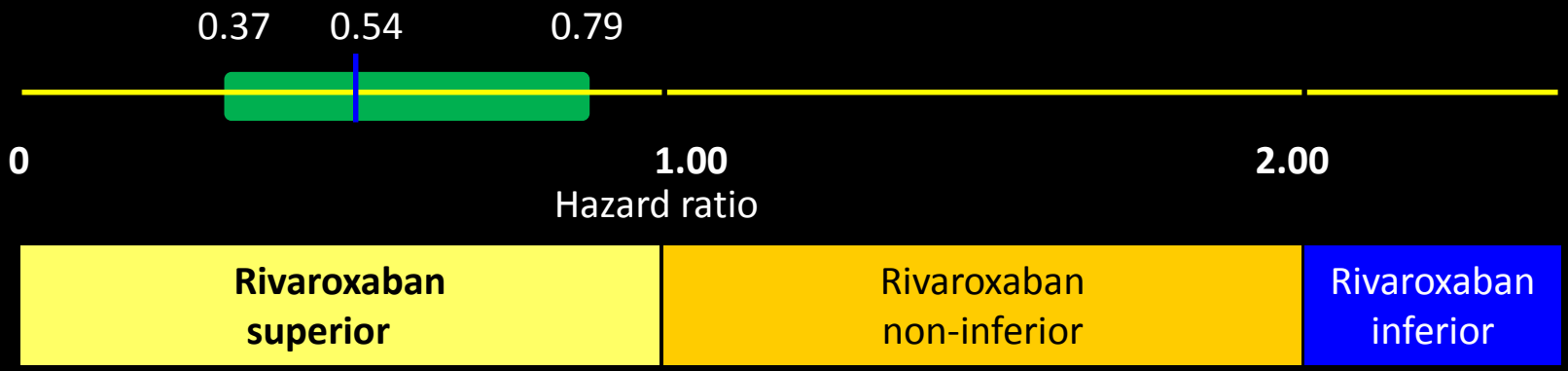
EINSTEIN – DVT/PE: safety results (all bleeding)



EINSTEIN – DVT/PE: safety results (major bleeding)



EINSTEIN – DVT/PE: safety results (major bleeding)



2014 ESC Guidelines

Recommendations	Class[a]	Level[b]
Anticoagulation: combination of parenteral treatment with VKA		
Initiation of parenteral anticoagulation is recommended without delay in patients with high or intermediate clinical probability of PE while diagnostic work-up is in progress.	I	C
LMWH or fondaparinux is the recommended form of acute phase parenteral anticoagulation for most patients.	I	A
In parallel to parenteral anticoagulation, treatment with a VKA is recommended, targeting an INR of 2.5 (range 2.0–3.0).	I	B

Recommendations	Class[a]	Level[b]
Anticoagulation: combination of parenteral treatment with VKA		
As an alternative to the combination of parenteral anticoagulation with a VKA, anticoagulation with rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) is recommended.	I	B
As an alternative to the combination of parenteral anticoagulation with a VKA, anticoagulation with apixaban (10 mg twice daily for 7 days, followed by 5 mg twice daily) is recommended.	I	B
As an alternative to VKA treatment, administration of dabigatran (150 mg twice daily, or 110 mg twice daily for patients ≥80 years of age or those under concomitant verapamil treatment) is recommended following acute-phase parenteral anticoagulation.	I	B[e]
As an alternative to VKA treatment, administration of edoxaban* is recommended following acute-phase parenteral anticoagulation.	I	B

2014 ESC Guidelines (for how long?)

Recommendations	Class[a]	Level[b]
For patients with PE secondary to a transient (reversible) risk factor, oral anticoagulation is recommended for 3 months.	I	B
For patients with unprovoked PE, oral anticoagulation is recommended for at least 3 months.	I	A
Extended oral anticoagulation should be considered for patients with a first episode of unprovoked PE and low bleeding risk .	IIa	B
Anticoagulation treatment of indefinite duration is recommended for patients with a second episode of unprovoked PE.	I	B

EINSTEIN – EXT

The NEW ENGLAND JOURNAL of MEDICINE

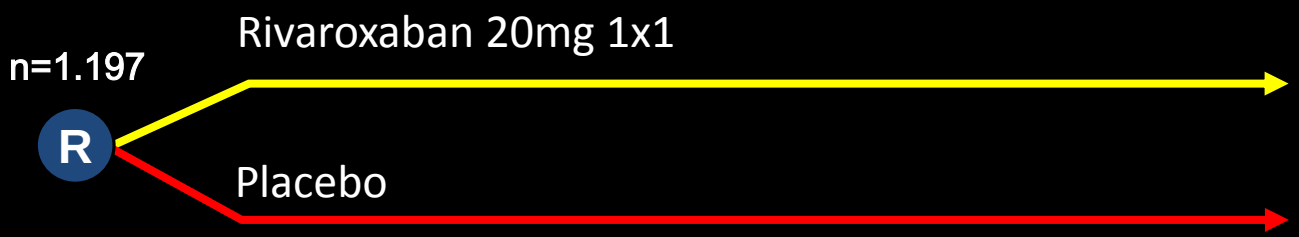
ORIGINAL ARTICLE

Oral Rivaroxaban for Symptomatic Venous Thromboembolism

The EINSTEIN Investigators*

EINSTEIN – EXT

VTE after 6-12 months of anticoagulation



EINSTEIN – EXT : efficacy results

Outcome	Rivaroxaban	Placebo	Hazard Ratio (95% CI)	P Value
	no. (%)			
Efficacy				
Intention-to-treat population	602	594		
Recurrent VTE	8 (1.3)	42 (7.1)†	0.18 (0.09–0.39)	<0.001
Type of recurrent VTE				
Fatal PE	0	1		
PE cannot be ruled out	1	0		
Nonfatal PE	2	13		
Recurrent DVT	5	31		

EINSTEIN – EXT: safety results

Outcome	Rivaroxaban	Placebo	Hazard Ratio (95% CI)	P Value
	no. (%)			
Safety				
Safety population	598	590		
First major or clinically relevant nonmajor bleeding	36 (6.0)	7 (1.2)	5.19 (2.3–11.7)	<0.001
Major bleeding†	4 (0.7)‡	0	NA	0.11
Contributing to death	0	0		
In a critical site	0	0		
Associated with a fall in hemoglobin of ≥2 g per deciliter, transfusion of ≥2 units, or both	4	0		
Clinically relevant nonmajor bleeding†	32 (5.4)‡	7 (1.2)		
Hematuria	9	0		
Epistaxis	8	1		
Rectal	7	2		
Skin	4	2		
Uterine	3	2		
Gastrointestinal	1	0		
Related to tooth extraction	1	0		
Ear	1	0		
Total deaths	1 (0.2)	2 (0.3)		

EINSTEIN – EXT: summary

- ✓ Rivaroxaban prevents VTE recurrence in the cost of an increase in minor bleeding

2014 ESC Guidelines

Recommendations	Class[a]	Level[b]
For patients with PE secondary to a transient (reversible) risk factor, oral anticoagulation is recommended for 3 months.	I	B
For patients with unprovoked PE, oral anticoagulation is recommended for at least 3 months.	I	A
Extended oral anticoagulation should be considered for patients with a first episode of unprovoked PE and low bleeding risk .	IIa	B
Anticoagulation treatment of indefinite duration is recommended for patients with a second episode of unprovoked PE	I	B
Rivaroxaban (20 mg once daily), dabigatran (150 mg twice daily, or 110 mg twice daily for patients ≥80 years of age or those under concomitant verapamil treatment) or apixaban (2.5 mg twice daily) should be considered as an alternative to VKA (except for patients with severe renal impairment) if extended anticoagulation treatment is necessary.[a]	IIa	B[e]

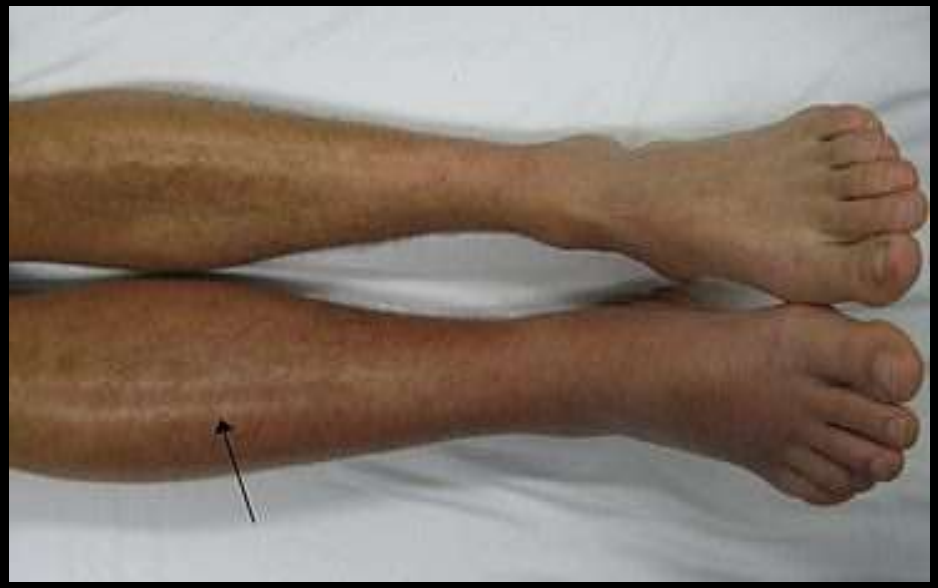
ESC 2014 Guidelines

Recommendations for duration of anticoagulation after pulmonary embolism

Recommendations	Class[a]	Level[b]
For patients with unprovoked PE, oral anticoagulation is recommended for at least 3 months.	I	A
Extended oral anticoagulation should be considered for patients with a first episode of unprovoked PE and low bleeding risk .	IIa	B
In patients who receive extended anticoagulation, the risk–benefit ratio of continuing such treatment should be reassessed at regular intervals.	I	C

Clinical scenario 3

- ✓ ♂, 74yrs
- ✓ Arterial hypertension on valsartan/HCTZ 1x1 and amlodipine 1x1
- ✓ Diabetes Mellitus on metformin 1x2 and glimepiride
- ✓ Depression on escitalopram 1x1
- ✓ Prostate cancer



NOACs in cancer patients

[Original Research **Pulmonary Vascular Disease**]

CHEST

Direct Oral Anticoagulants in Patients With VTE and Cancer

A Systematic Review and Meta-analysis

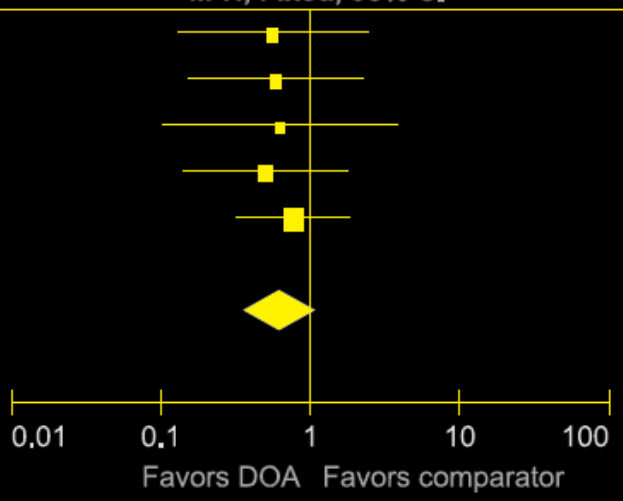
Maria Cristina Vedovati, MD; Federico Germini, MD; Giancarlo Agnelli, MD; and Cecilia Becattini, MD, PhD

NOACs in cancer patients – VTE recurrence

Study or Subgroup	DOA Events	DOA Total	Comparator Events	Comparator Total	Weight	Odds Ratio M-H, Fixed, 95% CI
AMPLIFY 2013	3	81	5	78	15.2%	0.56 [0.13, 2.43]
EINSTEIN-DVT 2010	4	118	5	89	17.1%	0.59 [0.15, 2.26]
EINSTEIN-PE 2012	2	114	3	109	9.4%	0.63 [0.10, 3.85]
HOKUSAI 2013	4	109	7	99	22.0%	0.50 [0.14, 1.77]
RECOVER I & II 2013	10	173	12	162	36.3%	0.77 [0.32, 1.83]
Total (95% CI)		**595**		**537**	**100.0%**	**0.63 [0.37, 1.10]**
Total events	23		32			

Heterogeneity: $Chi^2 = 0.36$, df = 4 (P = 0.99); $I^2 = 0\%$

Test for overall effect: Z = 1.62 (P = 0.10)

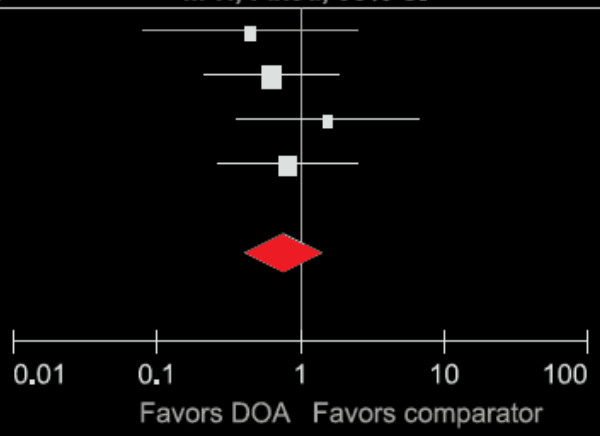


NOACs in cancer patients – major bleeding

Study or Subgroup	DOA Events	DOA Total	Comparator Events	Comparator Total	Weight	Odds Ratio M-H, Fixed, 95% CI
AMPLIFY 2013	2	87	4	80	18.2%	0.45 [0.08, 2.51]
EINSTEIN DVT & PE 2013	6	232	8	196	37.7%	0.62 [0.21, 1.83]
HOKUSAI 2013	5	109	3	99	13.4%	1.54 [0.36, 6.61]
RECOVER I & II 2013	6	159	7	152	30.7%	0.81 [0.27, 2.47]
Total (95% CI)		**587**		**527**	**100.0%**	**0.77 [0.41, 1.44]**
Total events	19		22			

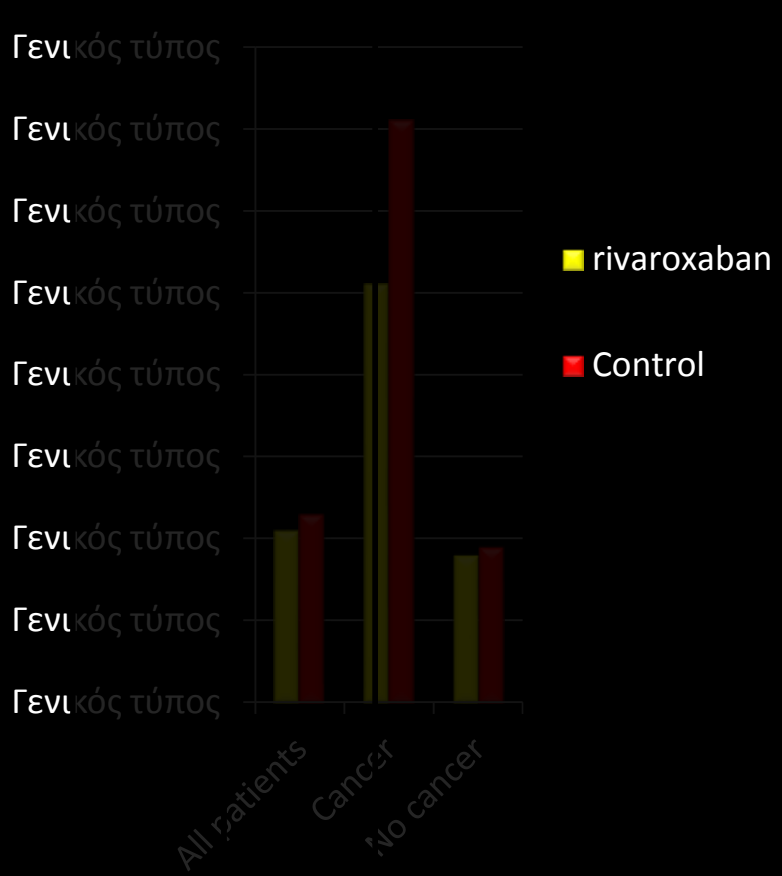
Heterogeneity: Chi² = 1.40, df = 3 (P = 0.70); I² = 0%

Test for overall effect: Z = 0.81 (P = 0.42)

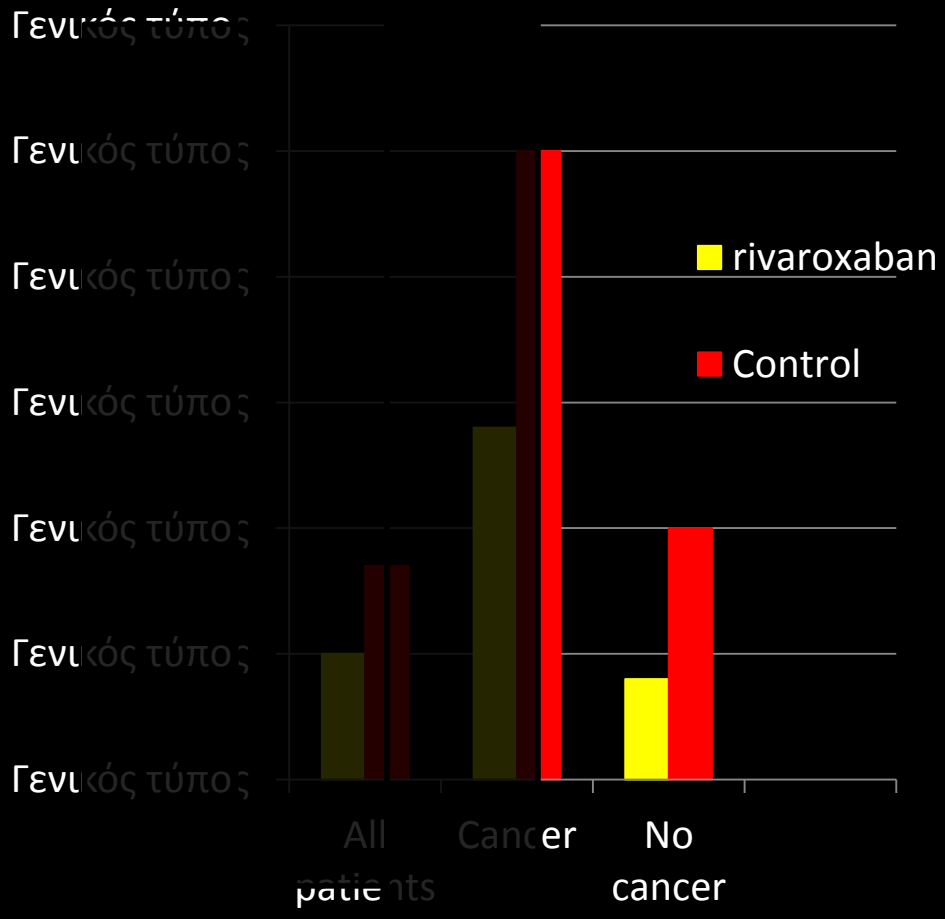


EINSTEIN – DVT/PE: cancer patients

VTE recurrence



Major bleeding



> 275,000 patients will be studied

Take-home messages

- Non-inferior to VKAs (efficacy).
- Non-inferior to VKAs (safety – all bleedings).
- Superior to VKAs (safety – major bleedings).

- Start directly with rivaroxaban - no need to start with LMWH
- Only once a day (compared to other NOACs).

- Cost-effective (compared to enoxaparin & VKA).
- Antidote is just around the corner.

- Good choice for cancer patients.

- Significant experience in millions of patients since 2008.
- Huge research program.