La thrombose veineuse profonde : nouveautés dans le traitement

Laurence Camoin-Jau,

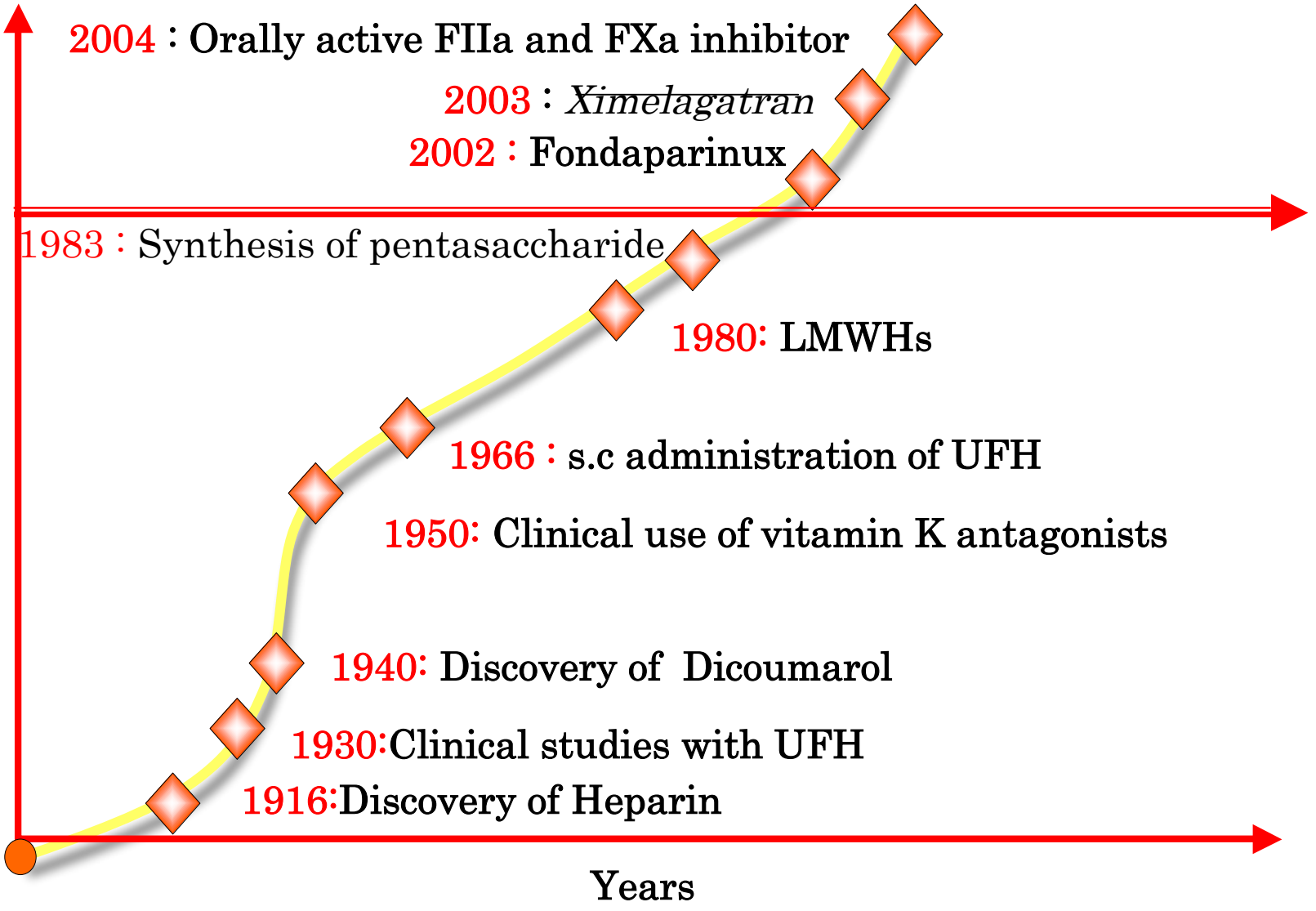
Laboratoire d'Hématologie, UMR-S 6O8

Hôpital La Conception – AP-HM

Marseille, France

JAT, Mars 2010
Nice

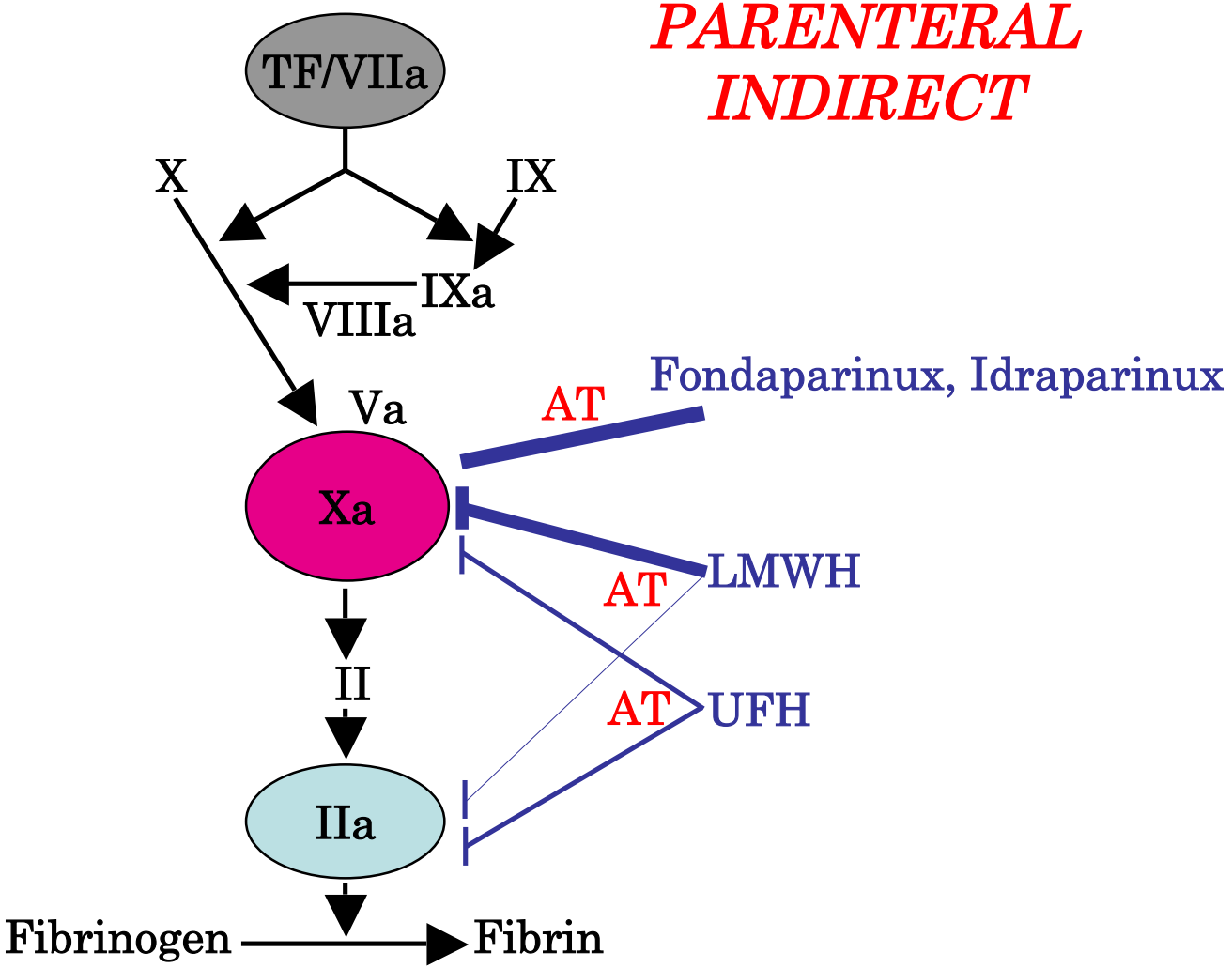
History of antithrombotic agents



Inhibitors of FXa

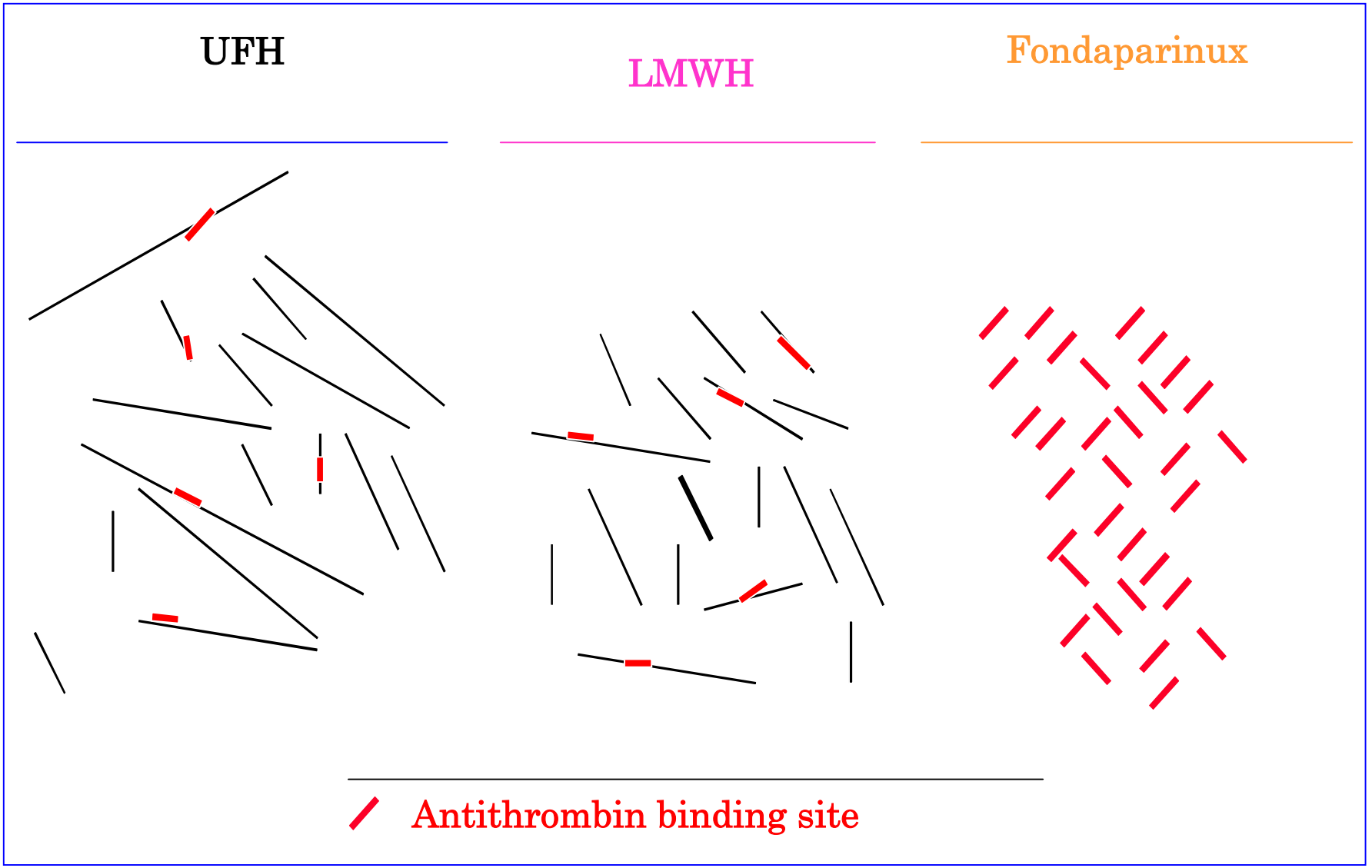
ORAL
DIRECT

PARENTERAL
INDIRECT



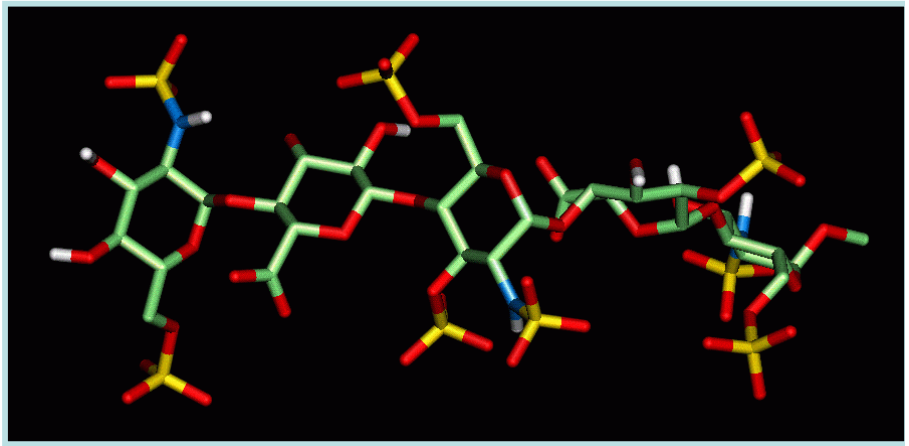
AT, antithrombin; adapted from Weitz *et al.*, *J Thromb Haemost* 2005

Heparin and its derivates



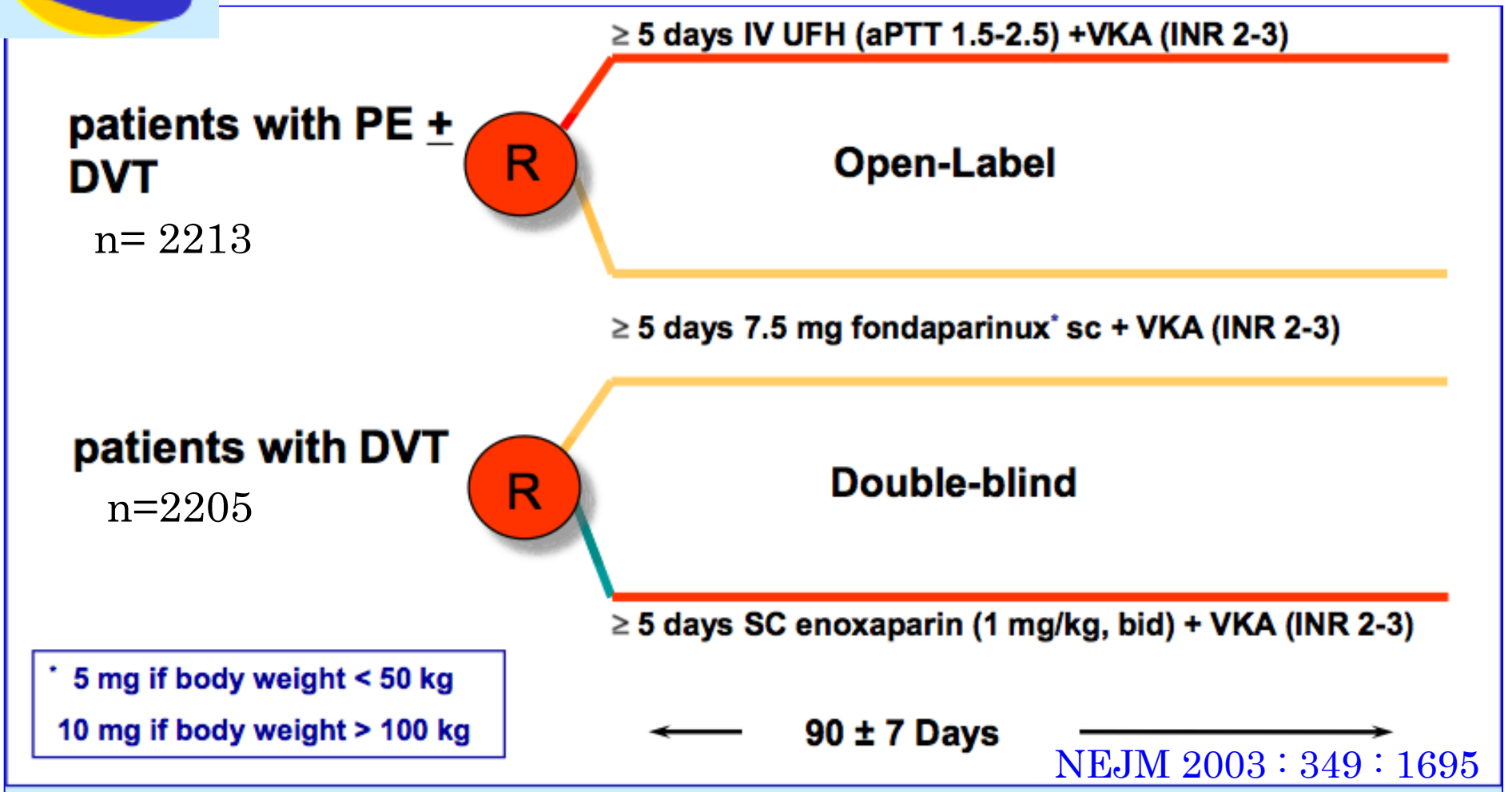
Fondaparinux: First in New Class of Synthetic Inhibitors of Factor Xa

- Synthetic pentasaccharide
- Specificity for anti-Xa inhibition
  - Binds to AT and accelerates Xa inhibition by 300f
  - Unable to inactivate thrombin
- Absorbed by subcutaneous injection
- Peak concentration 2-3 hours
- Half life= 17-21 hours
- Renal excretion



Herbert JM et al. *Cardiovasc Drug Rev.* 1997;15:1.
van Boeckel CAA et al. *Angew Chem, Int Ed Engl.* 1993;32:1671.

Matisse study design



NEJM 2003 : 349 : 1695

Primary Efficacy Outcome (3 months)

- Fatal PE / unexplained death
- Recurrent symptomatic non-fatal PE or DVT

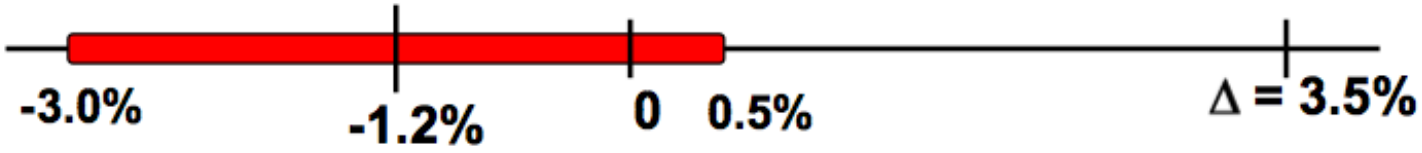
Principal Safety Outcome (initial treatment)

- Major bleed
- Clinically relevant non-major bleed

Primary efficacy outcome

Matisse PE

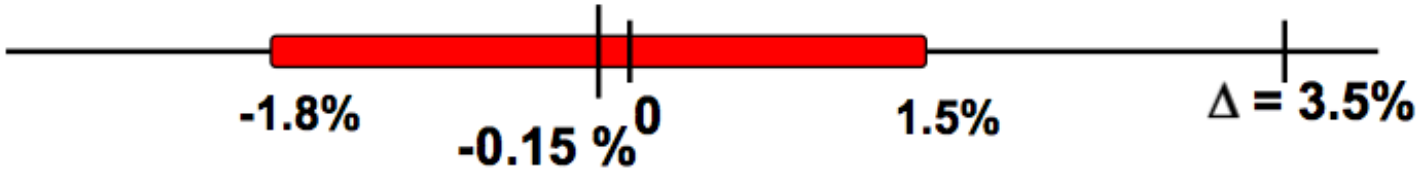
	Fondaparinux (N=1103)	UFH (N=1110)
Fatal PE	16 (1.5 %)	15 (1.4 %)
Non-fatal PE or DVT	26 (2.4 %)	41 (3.6 %)
Total symptomatic recurrent VTE	42 (3.8 %)	56 (5.0 %)



Fondaparinux - UFH (95% CI)

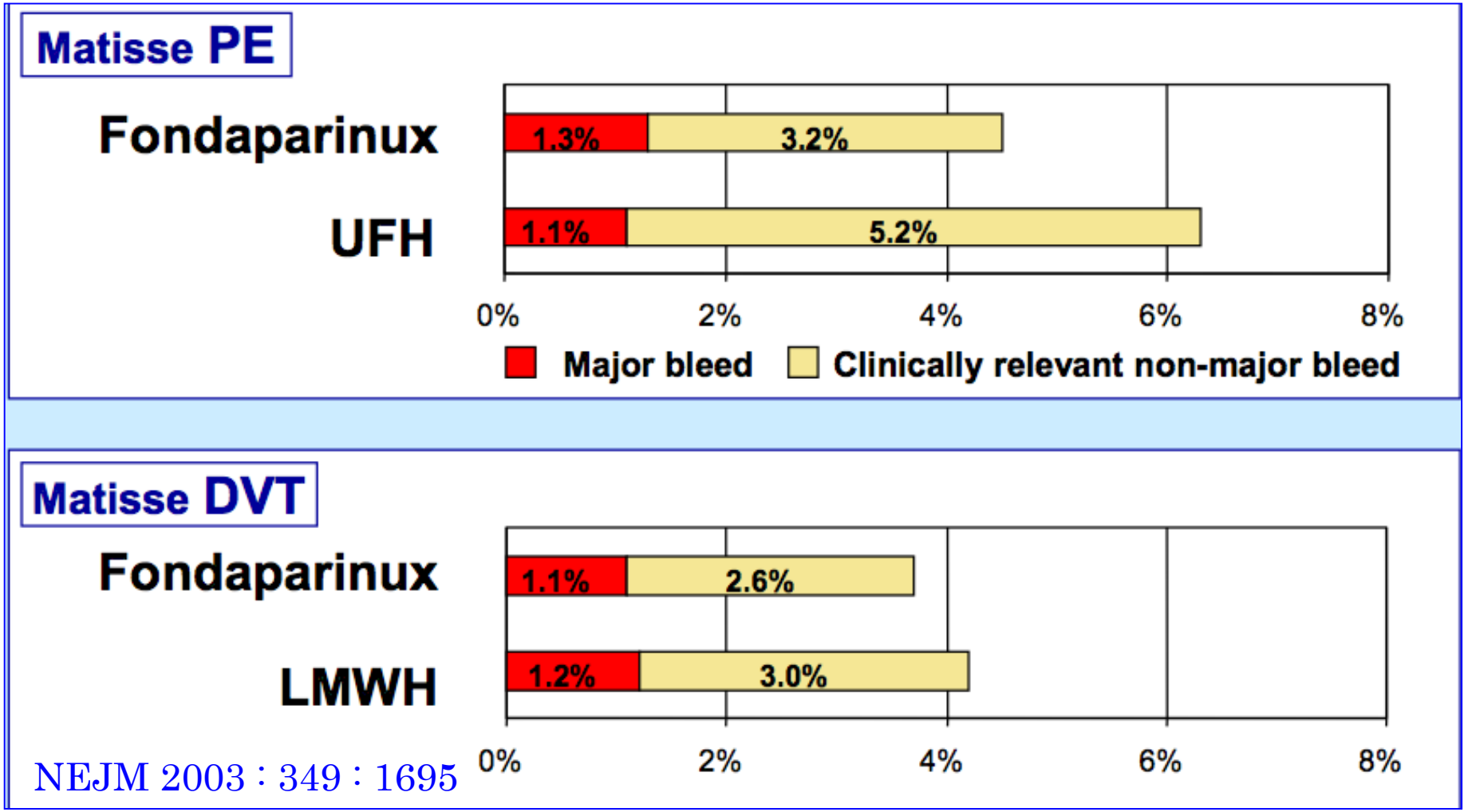
Matisse DVT

	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 %)



NEJM 2003 : 349 : 1695 Fondaparinux - LMWH (95% CI)

Principal safety outcome



NEJM 2003 : 349 : 1695

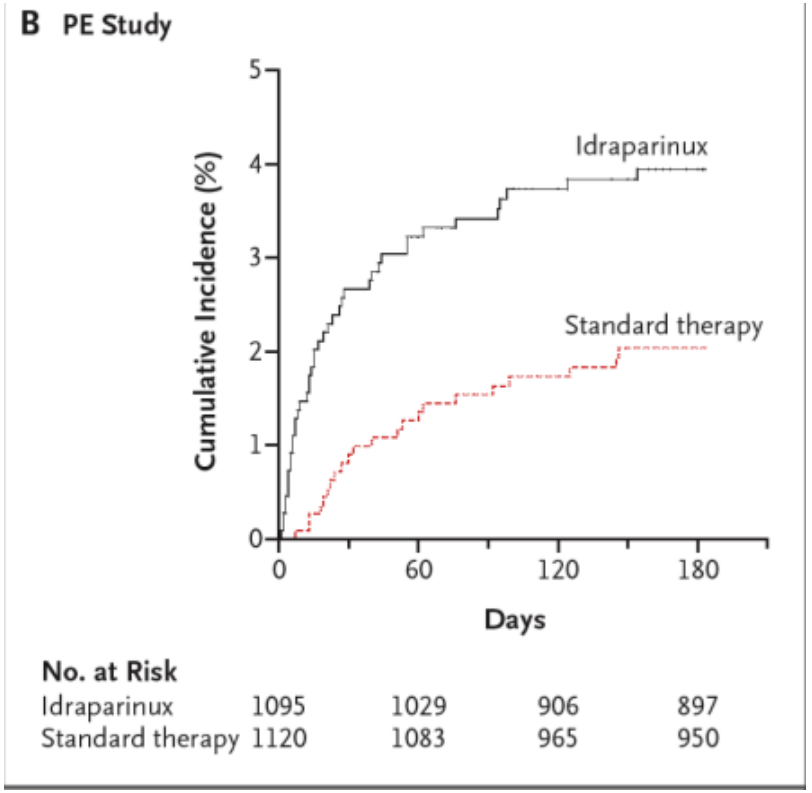
Idraparinux

- Hypermethylated form of fondaparinux = tighter binding to antithrombin
- Status： phase III clinical trials
- 80-120 hr half-life = subcutaneous injection once weekly
- Renal elimination
- No antidote

Idraparinux versus Standard Therapy for Venous Thromboembolic Disease

The van Gogh Investigators*

- Randomised open label, non inferiority trials
- DVT n = 2904
- PE : n= 2215
- SC idraparinux (2.5 mg once weekly) or a heparin followed by an adjusted-dose oral vitamin K antagonist for either 3 or 6 months
- Primary efficay outcome : 3 months for symptomatic recurrent VTE
- In patients with DVT : efficacy similar



N Engl J Med 2007;357:1094-104

Extended Prophylaxis of Venous Thromboembolism with Idraparinux

The van Gogh Investigators*

N Engl J Med 2007;357:1105-12.

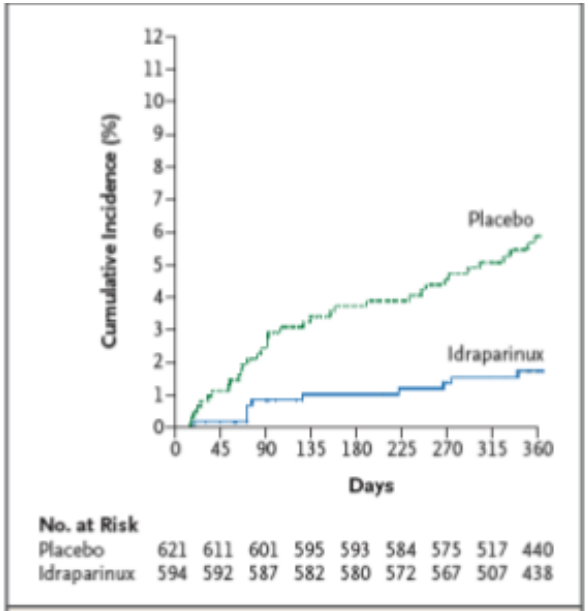


Figure 2. Kaplan–Meier Cumulative Incidence of First Confirmed Symptomatic Recurrent Venous Thromboembolism, According to Study Group.

RESULTS

Of 1215 patients, 6 of 594 (1.0%) in the idraparinux group and 23 of 621 (3.7%) in the placebo group had recurrent venous thromboembolism (P=0.002). Major bleeding occurred in 11 patients (1.9%) in the idraparinux group and in none in the placebo group (P<0.001). Of these 11 episodes, 3 were fatal intracranial hemorrhages. As compared with patients whose initial treatment was a vitamin K antagonist, patients whose initial treatment was idraparinux who were assigned to 6 months in the placebo group had a lower incidence of recurrent thromboembolism (0.7% vs. 5.9%); patients who received 6 additional months of idraparinux therapy had a higher incidence of major bleeding (3.1% vs. 0.9%).

Comparison of idraparinux with vitamin K antagonists for prevention of thromboembolism in patients with atrial fibrillation : a randomised, open-label, non inferiority trial

- Trial stopped after randomisation of 4576 patients (2283 idraparinux, 2293 vitamin K antagonists)
- Mean follow-up period : 10.7 ± 5.4 months
- Excess of clinical relevant bleeding with idraparinux (346 cases / 226 cases , 19.7 vs 11.3 per 100 patients-years)
- 21 instances of intracranial bleeding with idraparinux and 9 with vitamin K antagonists (1.1 vs 0.4per 100 patient-years , p=0.014)

Lancet 2008; 371 : 315-21

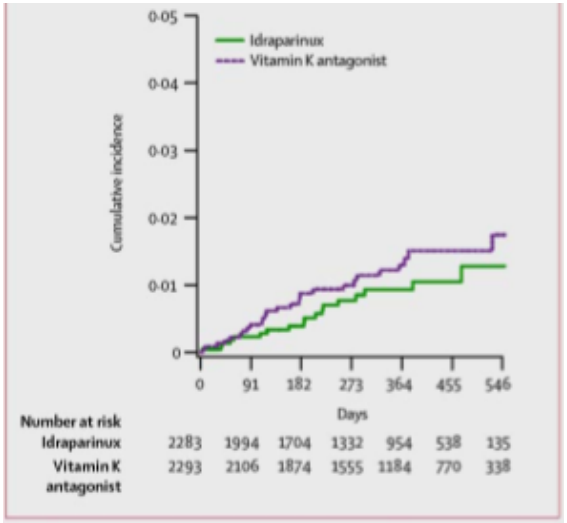


Figure 2: Kaplan-Meier cumulative incidence curves of first confirmed symptomatic recurrent stroke or non-CNS systemic embolism

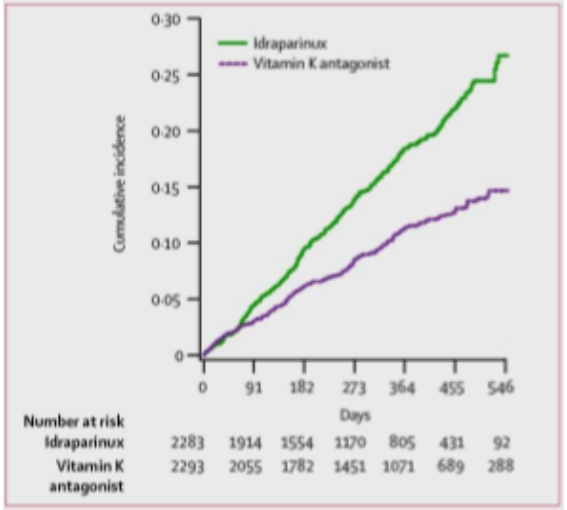
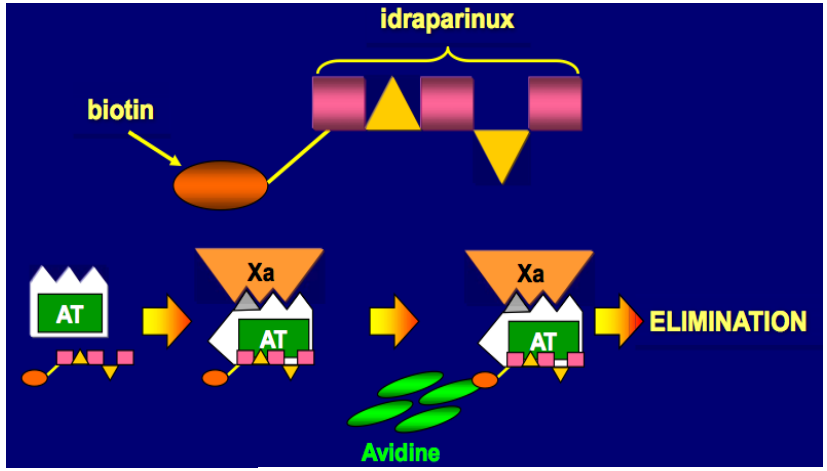


Figure 3: Kaplan-Meier cumulative incidence curves of first clinically relevant bleeding during the randomised treatment period

Concept of biotinylated long-acting pentasaccharide as a neutralizable anticoagulant drug :idrabiotaparinux



	Fondaparinux	Idraparinux	Idrabiotaparinux
Target	factor Xa	factor Xa	factor Xa
Route of administration	sc	sc	sc
Therapeutic dose	7.5 (5–10) mg	2.5 mg	3.0 mg
Bioavailability, %	100	100	100
Half-life	17 hours	60 days	60 days
s.c. dosing interval	once daily	once weekly	once weekly
Renal elimination	yes	yes	yes
Antidote	no	no	avidin

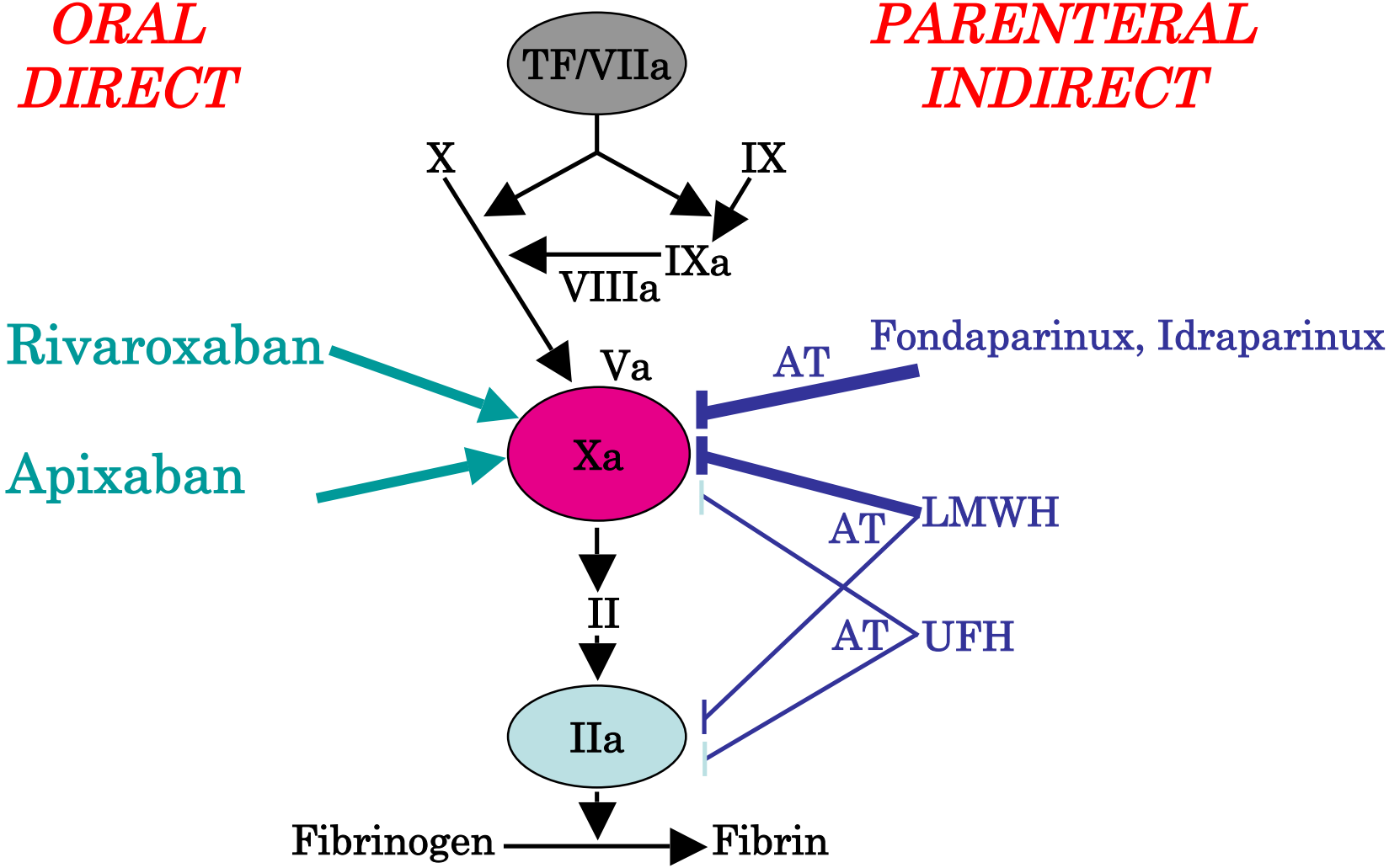
Harenberg J. Thromb Haemost 2009

Development of idrabiotaparinux
Equinox Study

- Patients with symptomatic and confirmed DVT
  - Idrabiotaparinux (3 mg, n=385)
  - Idraparinux (2.5 mg, n=370)
- In a substudy (n=52) : reversal of anti- coagulant effect and safety by 100 mg i.v. avidin infused over 30 min were assessed using avidin
- Clinically relevant bleedings occurred less frequently with idrabiotaparinux (5.2% versus 7.3%) compared to idraparinux as well as major bleedings (0.8% versus 3.8%), respectively
- Rates of recurrent VTE were similar with idrabiotaparinux and idraparinux (2.3% versus 3.2%)

Buller et al, Blood 2008 : 112 :abstract

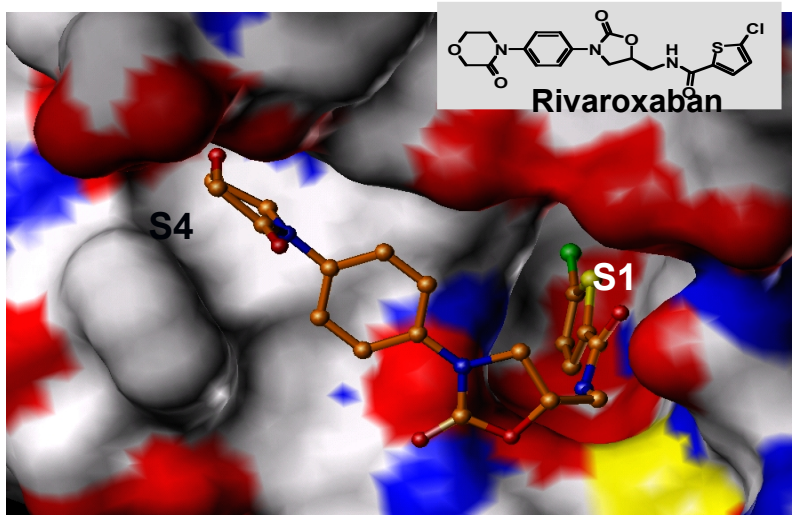
Inhibitors of FX

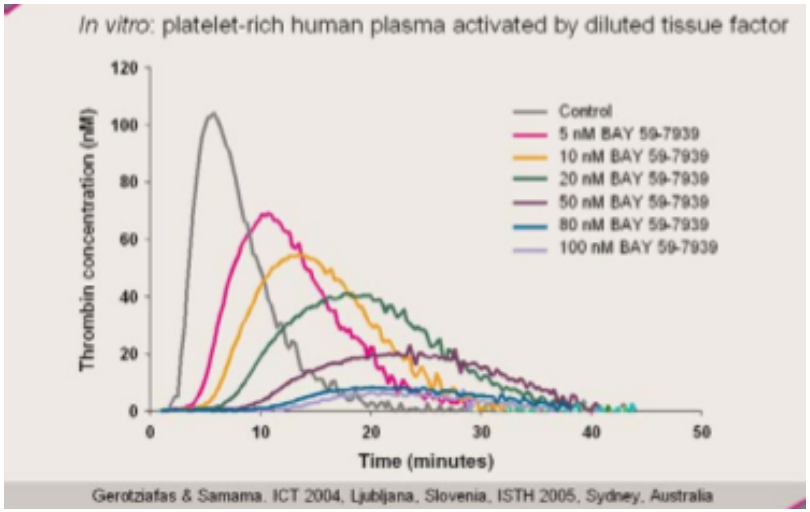


AT, antithrombin; adapted from Weitz *et al.*, *J Thromb Haemost* 2005

Rivaroxaban (Xarelto®)

- Specific, competitive, direct FXa inhibitor
- Inhibits free and clot-associated FXa activity, and prothrombinase activity
- Inhibits thrombin generation via inhibition of FXa activity
  - Prolongs time to thrombin generation
  - Inhibits peak thrombin generation
  - Reduces the total amount of thrombin generated
- Does not require a cofactor





Roehrig *et al., J Med Chem* 2005;

Perzborn *et al., J Thromb Haemost* 2005

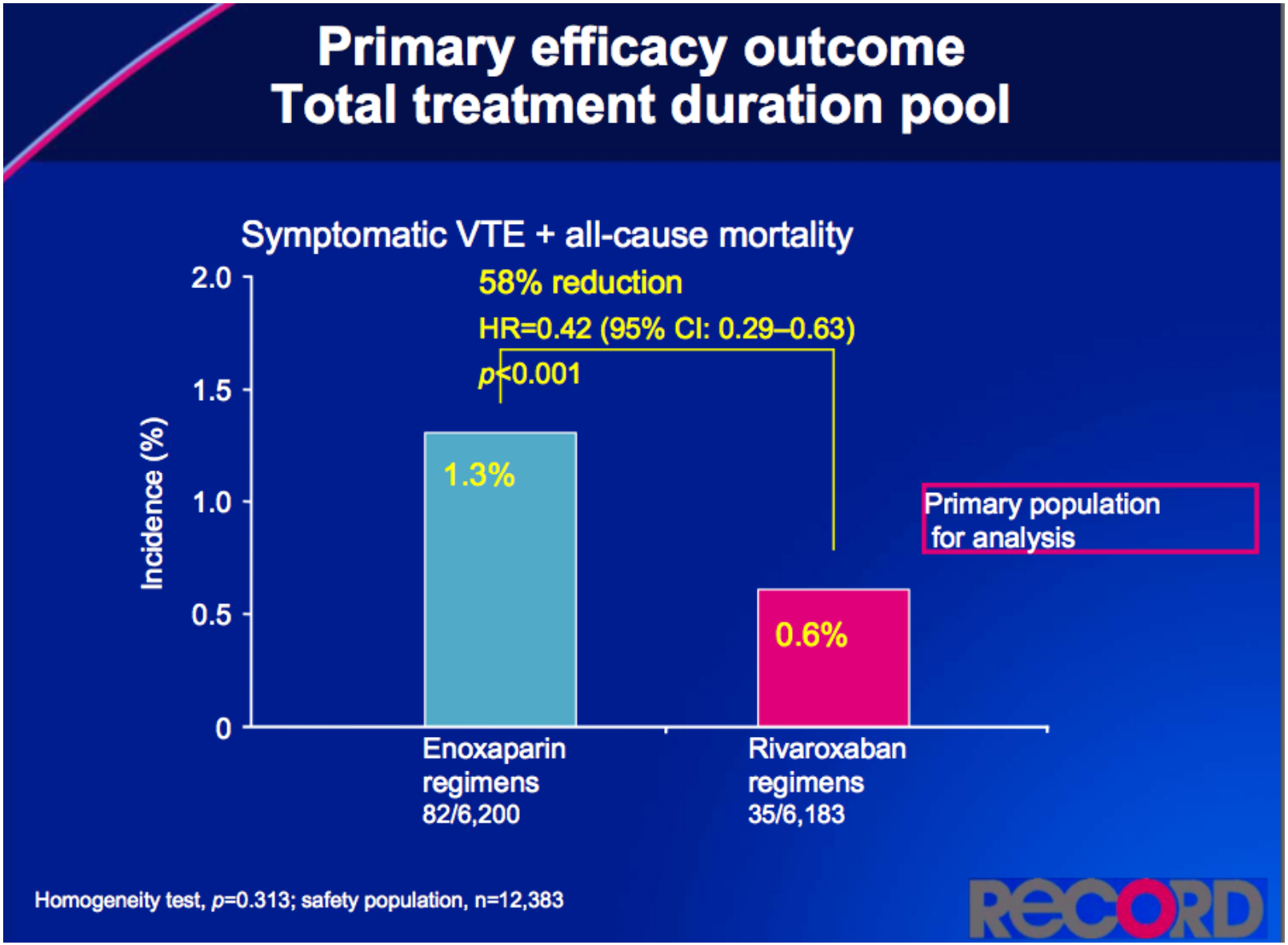
Rivaroxaban has predictable pharmacokinetics

- High oral bioavailability
- Rapid onset of action – no substantial accumulation after multiple doses
- Low intra-individual variability/moderate inter-individual variability
- Terminal half-life from 7 to 11h
- A dual mode of elimination:
  - 1/3 of drug excreted unchanged by the kidneys
  - 2/3 of drug metabolized by the liver
  - No major or active circulating metabolites
- Food restrictions are not necessary
- No coagulation monitoring required

Kubitza *et al.*, *Eur J Clin Pharmacol* 2005; *Clin Pharmacol Ther* 2005; *Blood* 2006;
Weinz *et al.*, *ISSX* 2004

A pooled analysis of the RECORD1, 2, 3, and 4 studies

Primary efficacy outcome
Total treatment duration pool

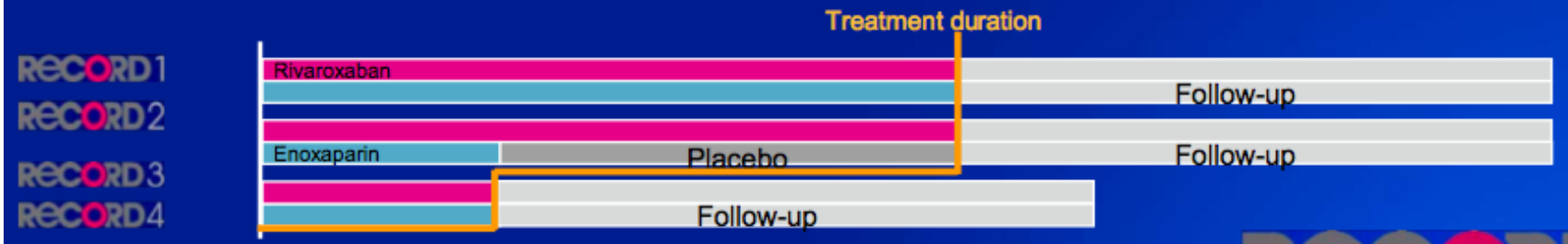


Homogeneity test, p=0.313; safety population, n=12,383

RECORD

Treatment-emergent bleeding
Total treatment duration pool

n (%)	Enoxaparin regimens (n=6,200)		Rivaroxaban regimens (n=6,183)		*p*-value#
Major bleeding	13	(0.21)	24	(0.39)	0.076
Major bleeding including surgical site	85	(1.37)	111	(1.80)	0.063
Any clinically relevant non-major bleeding	145	(2.34)	177	(2.86)	0.076
Major + clinically relevant non-major bleeding	158	(2.55)	197†	(3.19)	0.039
Any bleeding	401	(6.47)	434	(7.02)	0.255



#Analyzed using a Cox regression model

†Patients may have had more than one type of event; safety population, n=12,383

Rivaroxaban-Clinical Studies

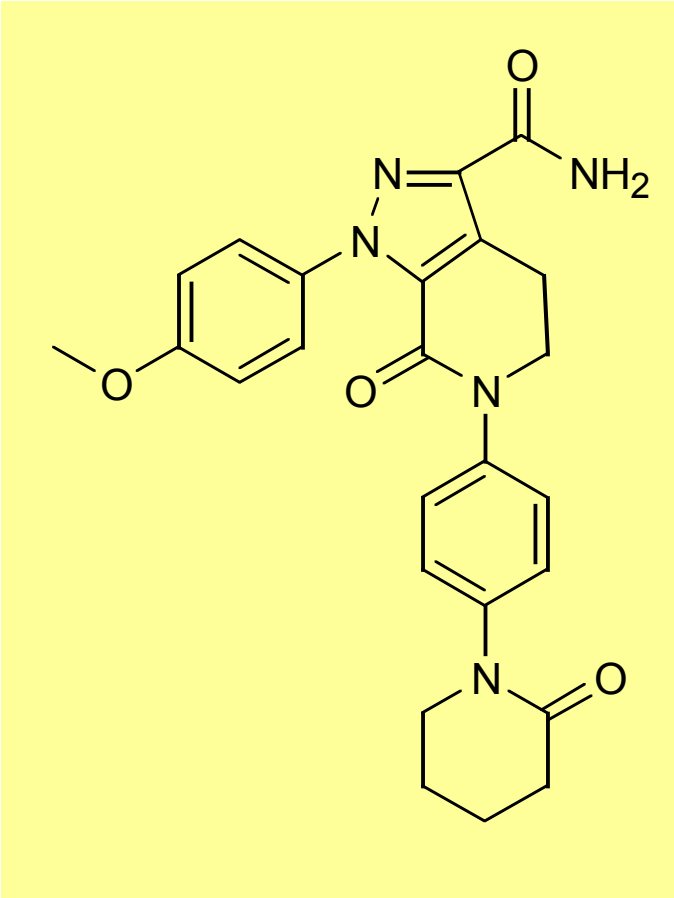
- VTE Treatment

- Atrial Fibrillation

ACS treatment

Apixaban

- Oral, direct, selective factor Xa inhibitor
- Produces concentration-dependent anticoagulation
- No formation of reactive intermediates
- No organ toxicity or LFT abnormalities in chronic toxicology studies
- Low likelihood of drug interactions or QTc prolongation
- Good oral bioavailability
- No food effect
- Balanced elimination (~25% renal)
- Half-life ~12 hrs



ADVANCE-1

Schéma de l'étude

Patients opérés d'une PTG n = 3195

→ **R**

Apixaban 2,5mg 1 cp x 2 /j (1) n = 1599

Enoxaparine 30 mg x 2/j SC (2) n = 1596

Critères de jugement

- Principal : critère composite : toute TVP, EP non fatale, décès toutes causes
- Hémorragie majeure

Durée totale de suivi : 60 jours

(1) 1ère prise 12-24h après la chirurgie pour l'énoxaparine et 6-8h pour le placebo oral
(2) 1ère prise 6-8h après la chirurgie pour le rivaroxaban et 12-24h pour le placebo sous cutané

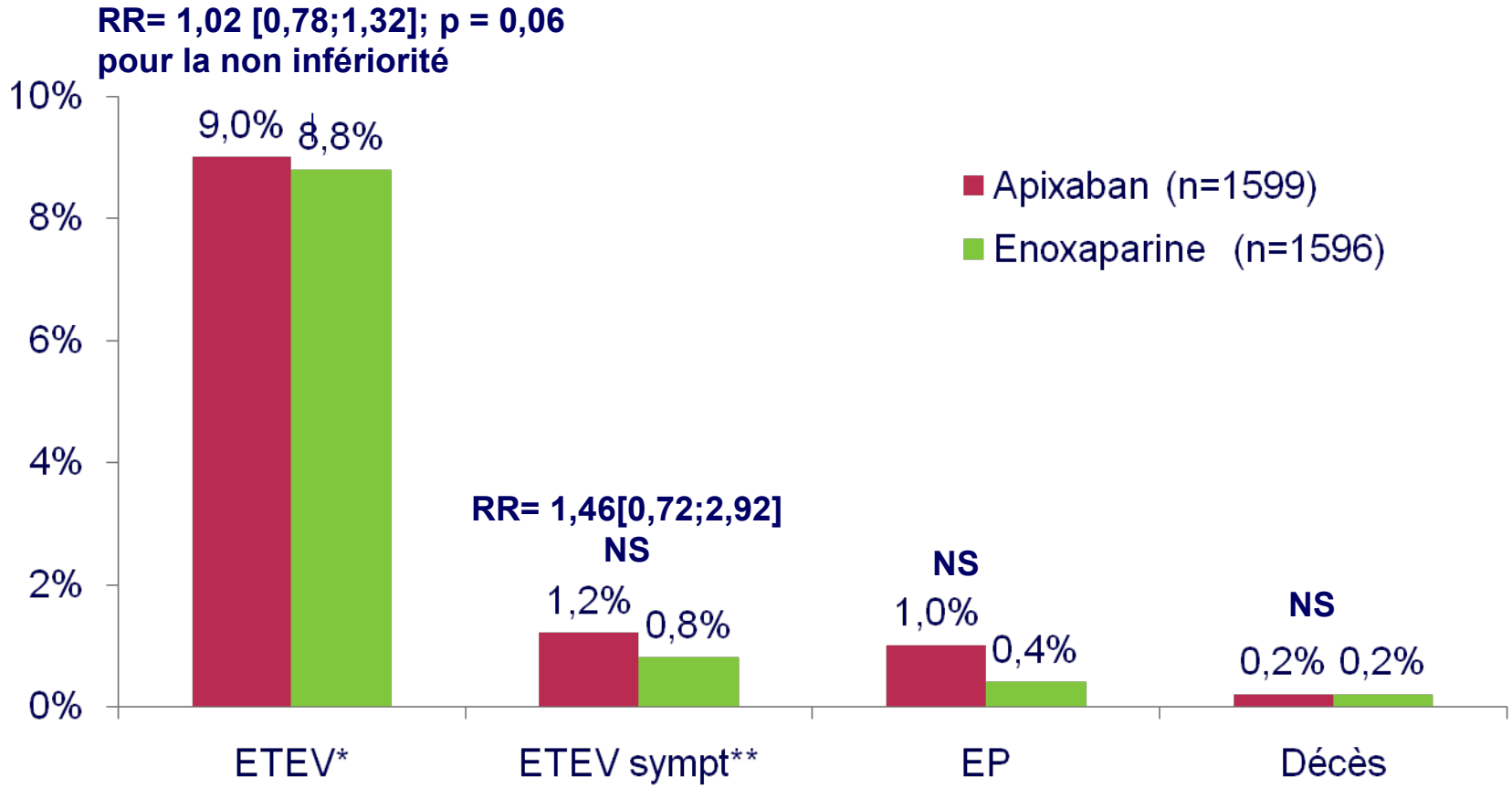
TVP : thrombose veineuse profonde ; EP : embolie pulmonaire

Lassen MR et al.
N Engl J Med 2009;361:594-604 .

Résultats

Efficacité

ADVANCE-1



L'apixaban 2,5 mg x 2/j n'a pas montré sa non-infériorité par rapport à l'enoxaparine 30 mgx2/j

* Evénements thromboemboliques veineux définis en ITT sur la population avec phlébographie interprétable (n=1157 dans le groupe apixaban et n= 1130 dans le groupe enoxaparine)

** ETEV symptomatiques définis par une thrombose veineuse proximale ou distale symptomatique, et embolie pulmonaire (EP)

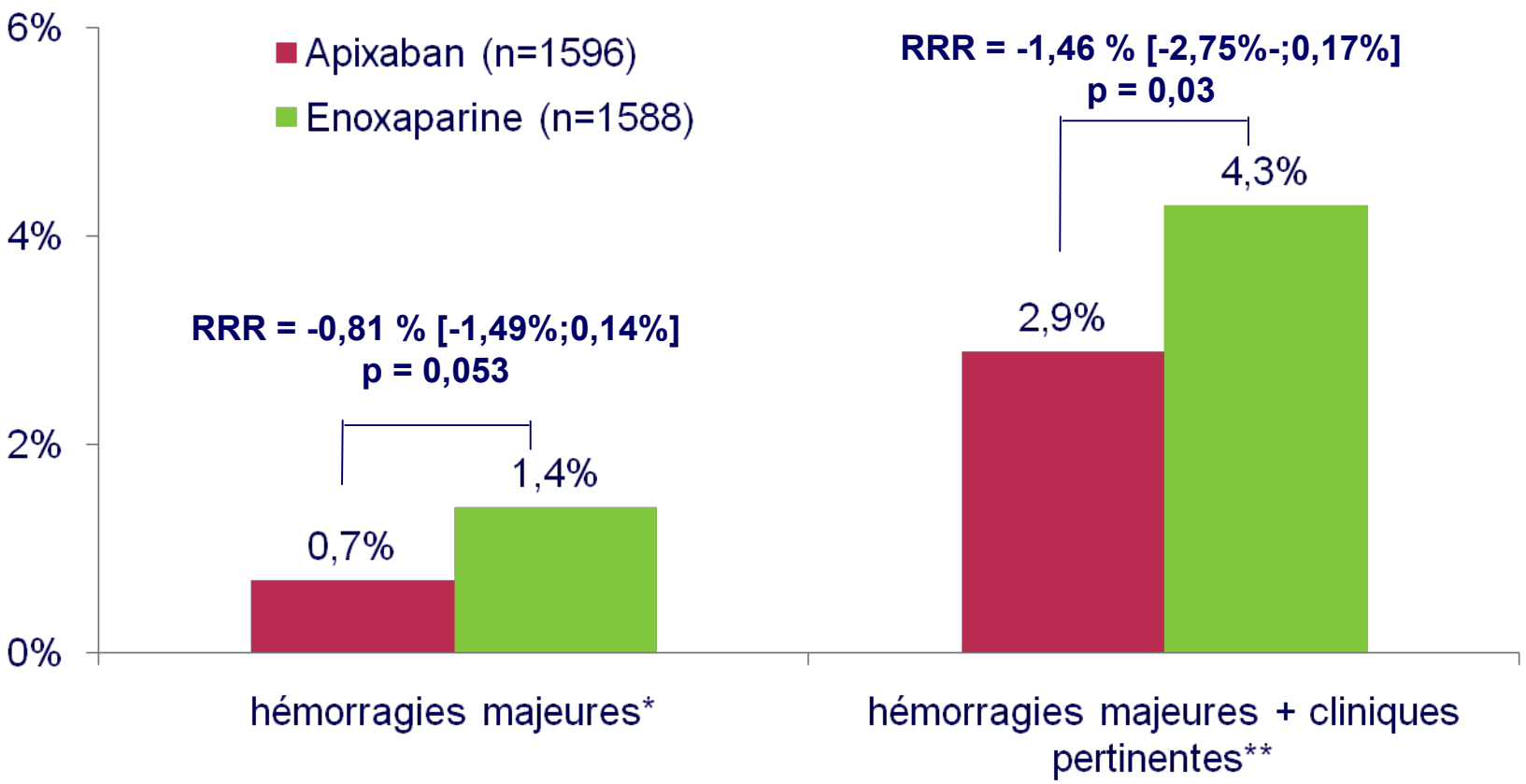
RR : risque relatif ; ITT : intention de traiter

Lassen MR et al.
N Engl J Med 2009;361:594-604 .

ADVANCE-1

Résultats

Tolérance



* définies par un saignement survenant dans un organe critique (ex retropéritoine) nécessitant une chirurgie ou situé en dehors du site opératoire et associé à une chute de l'hémoglobine de 2 g/dL en 24 heures ou la transfusion de 2 CG.

** définies par un hématome > 25 cm^2, un hématome ou hémorragie du site opératoire important, épistaxis, gingivorragies, hématurie macroscopique, rectorragie, hémoptysie, vomissement sanglant.

Lassen MR et al. N Engl J Med 2009;361:594-604 .

Overview of completed/ongoing phase 3 clinical trials involving apixaban

	Comparator	No. of patients (approximate)	Results expected/published	Acronym
AF	VKA	15 000	2011	ARISTOTLE
VTE, primary prophylaxis				
Orthopedic	LMWH	6 200	2009,[7] 2010	ADVANCE-1,2
Orthopedic	LMWH	5 400	2010	ADVANCE-3
Medical	LMWH	6 500	Early 2010	ADOPT
VTE acute treatment	LMWH + VKA	2 900	2012	AMPLIFY
VTE secondary prevention	Placebo (before randomization, all patients have received 6-12 months of anticoagulation)	2 400	2012	AMPLIFY extension study
Post–acute coronary syndrome	Placebo (all patients will receive standard treatment, such as aspirin, β-blocker)	11 000	2012	APPRAISE-2

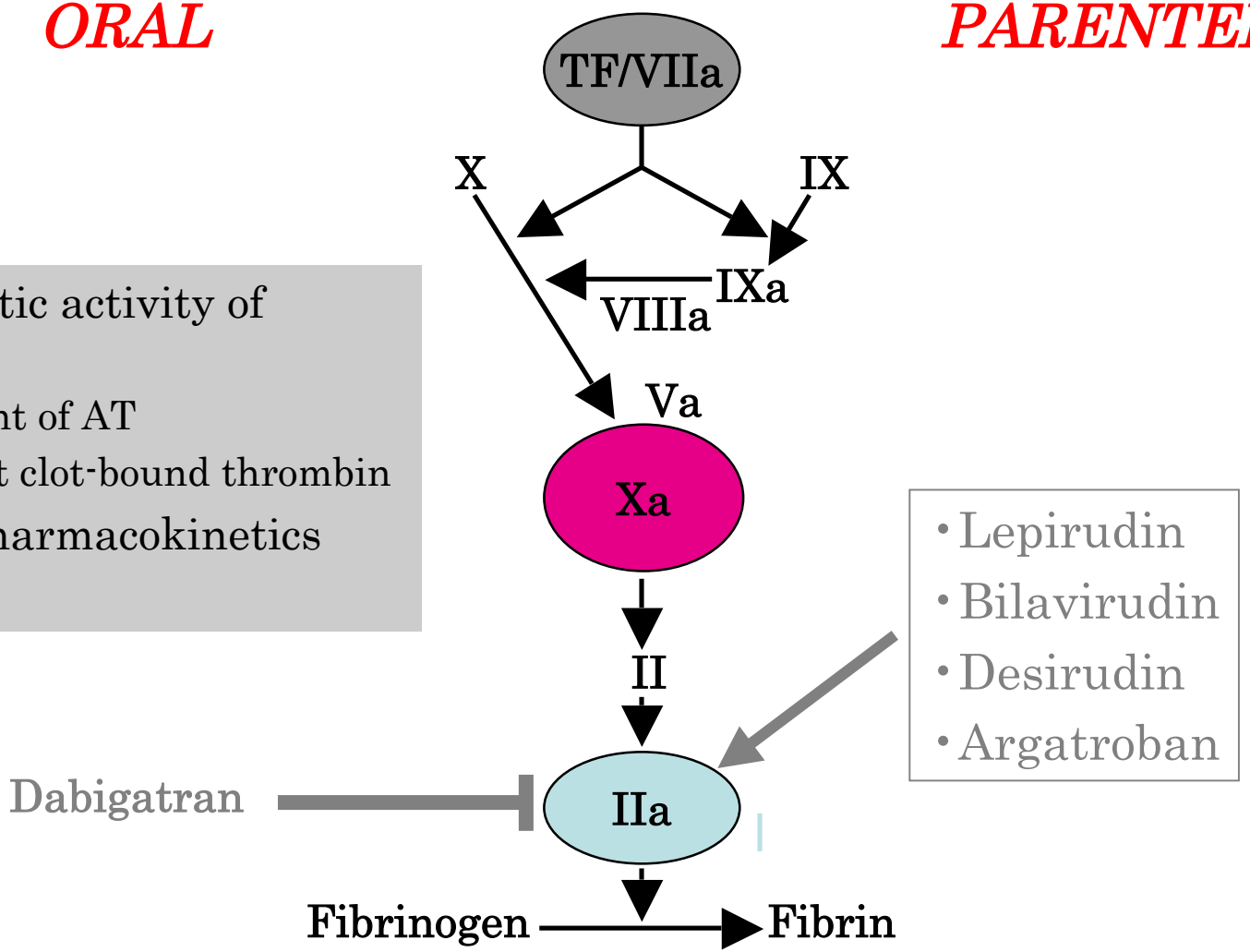
Garcia et al, Blood 2010 : 115 : 15

Direct Thrombin Inhibitors

ORAL

PARENTERAL

- Block enzymatic activity of thrombin
  - –Independent of AT
  - –Also inhibit clot-bound thrombin
- Predictable pharmacokinetics
- Short half life



AT, antithrombin; adapted from Weitz *et al.*, *J Thromb Haemost* 2005

Direct Thrombin Inhibitors

Lepirudin (Refludan®)

- Renal clearance
- ½ life=1-3 hours
- IV bolus and drip
- Monitored by PTT
- Bleeding potential
- Induces antibodies (40%)
- Prolonged anticoagulant action
- No antidote

Argatroban

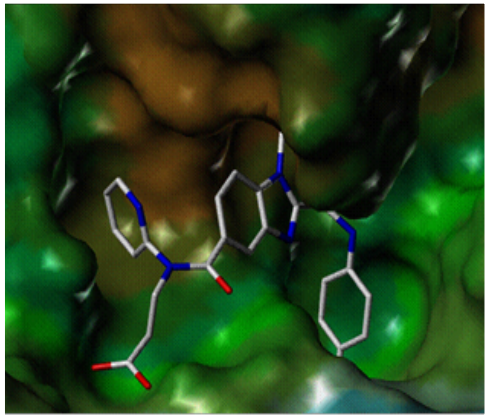
- Hepatic metabolism
- ½ life=45 minutes
- IV drip
- Monitored by PTT
- Bleeding potential
- No antibody formation
- Rapidly cleared
- No antidote

Main indication:

HEPARIN-INDUCED THROMBOCYTOPENIA AND THROMBOSIS

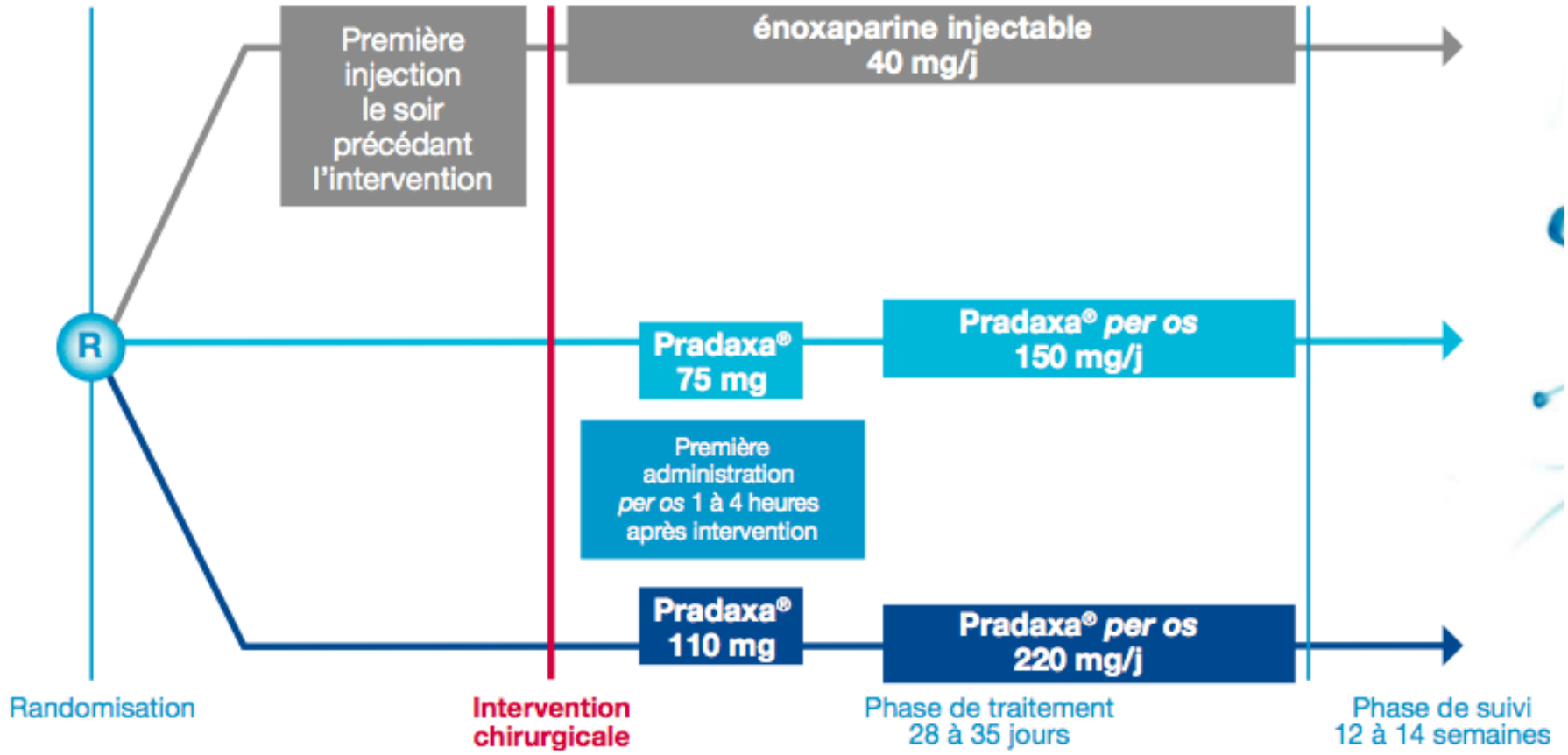
Dabigatran etexilate (Pradaxa®)
Oral direct thrombin inhibitor

- Dabigatran etexilate is an oral prodrug, converted to dabigatran, a potent reversible DTI
- Dabigatran
  - Binds clot-bound and free thrombin with high affinity and specificity
  - Bioavailability: 6.5%
  - Renal excretion: 80%
  - Half-life: 12–17 hours
  - No interaction with food
  - No participation with CYP450
  - Predictable anticoagulant effect
  - Fixed dose
  - No need for coagulation or platelet monitoring
  - No liver toxicity based on available clinical data



Eriksson et al, J Thromb Haemost 2005 ; 3: 103, Stangeir et al , Thromb Haemost 2001 ; 86

Design de l'étude ÉTUDE RE-NOVATE[12]



Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial

Bengt I Eriksson, Ola E Dahl, Nadia Rosencher, Andreas A Kurth, C Niek van Dijk, Simon P Frostick, Martin H Prins, Rohan Hettiarachchi,
Stefan Hantel, Janet Schnee, Harry R Büller, for the RE-NOVATE Study Group

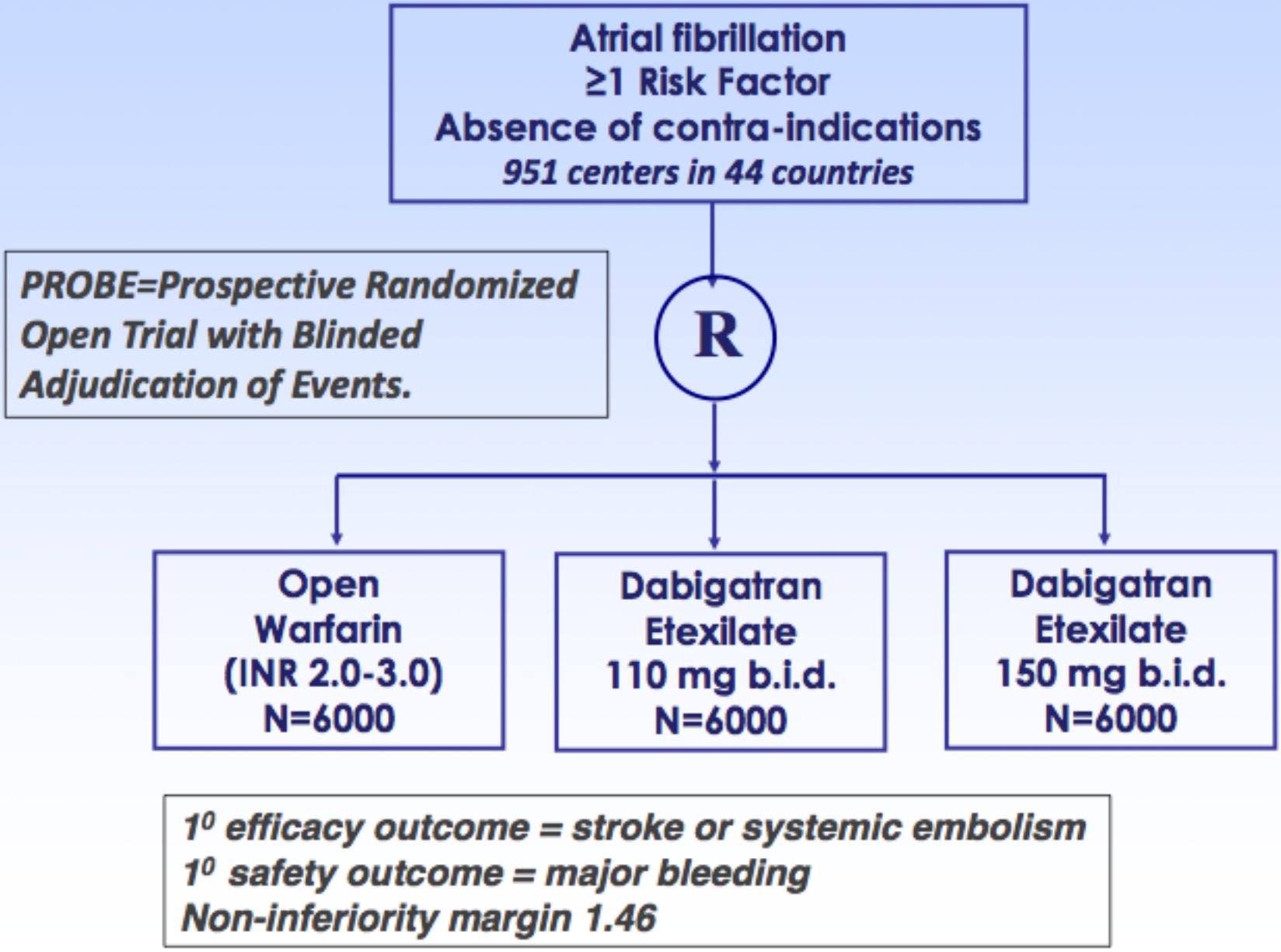
Lancet 2007; 370: 949-56

	Dabigatran etexilate		Enoxaparin
	220 mg	150 mg	
Primary efficacy outcome*	53/880 (6·0%, 4·5 to 7·6%)	75/874 (8·6%, 6·7 to 10·4%)	60/897 (6·7%, 5·1 to 8·3%)
Absolute difference vs enoxaparin	–0·7% (–2·9 to 1·6%)	1·9% (–0·6 to 4·4%)	..
p value for non-inferiority vs enoxaparin†	<0·0001	<0·0001	..
Total asymptomatic deep-vein thrombosis‡	40/874 (4·6%)	63/871 (7·2%)	56/894 (6·3%)
Proximal	18/905 (2·0%)	28/885 (3·2%)	32/914 (3·5%)
Distal only	22/874 (2·5%)	35/871 (4·0%)	24/894 (2·7%)
Symptomatic deep-vein thrombosis‡	6/1137 (0·5%)	9/1156 (0·8%)	1/1142 (0·1%)
Symptomatic pulmonary embolism‡	5/1137 (0·4%)	1/1156 (0·1%)§	3/1142 (0·3%)
Death¶	3/1137 (0·3%)	3/1156 (0·3%)§	0/1142 (0%)
Major venous thromboembolism|| and venous thromboembolism-related mortality**	28/909 (3·1%, 2·0 to 4·2%)	38/888 (4·3%, 2·9 to 5·6%)	36/917 (3·9%, 2·7 to 5·2%)

No significant difference in major bleeding rates with either dose of dabigatran compared with enoxaparine
No increase in liver enzyme concentrations

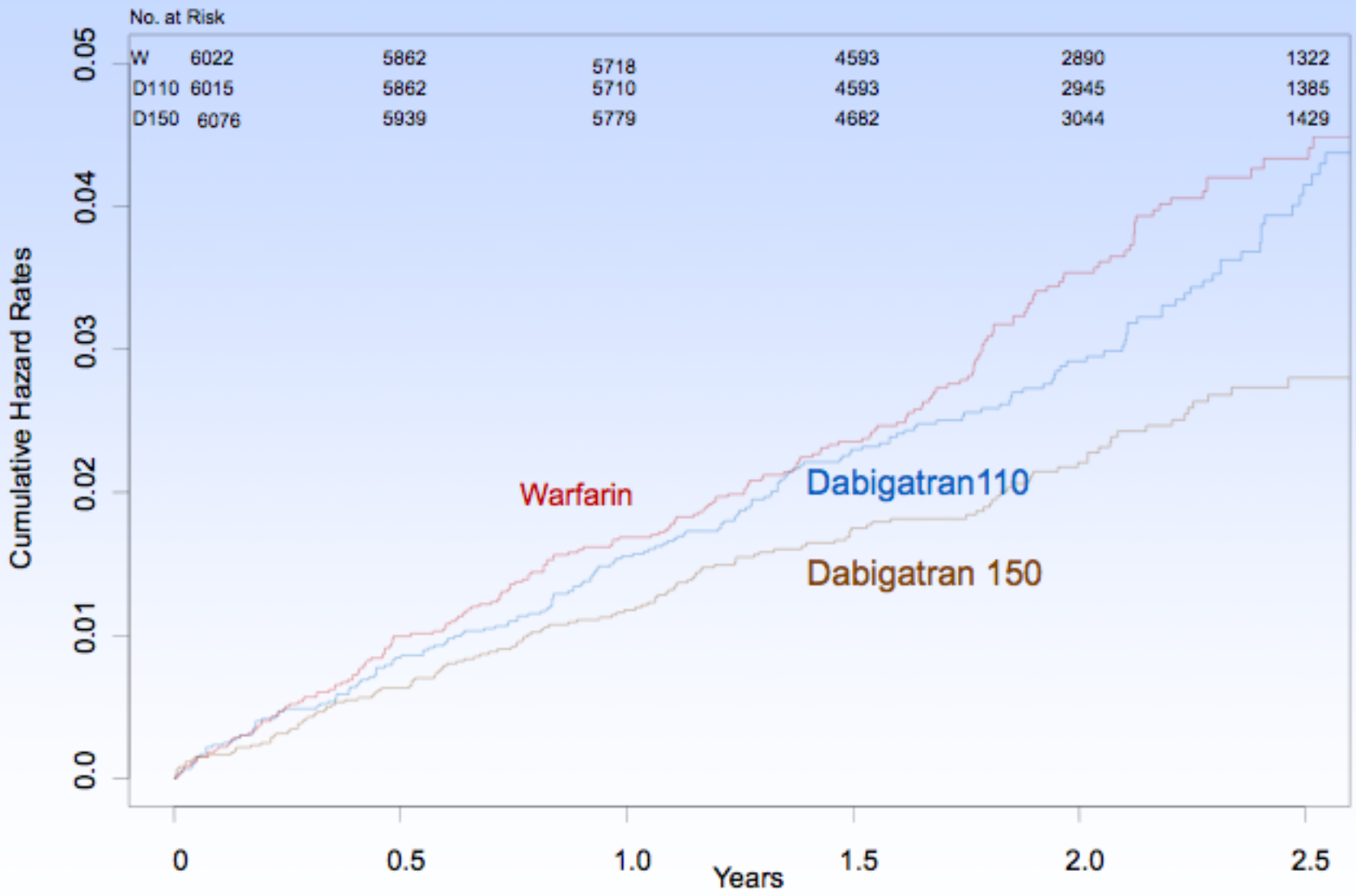
Design of RE-LY

RELY®
Study of stroke prevention in atrial fibrillation



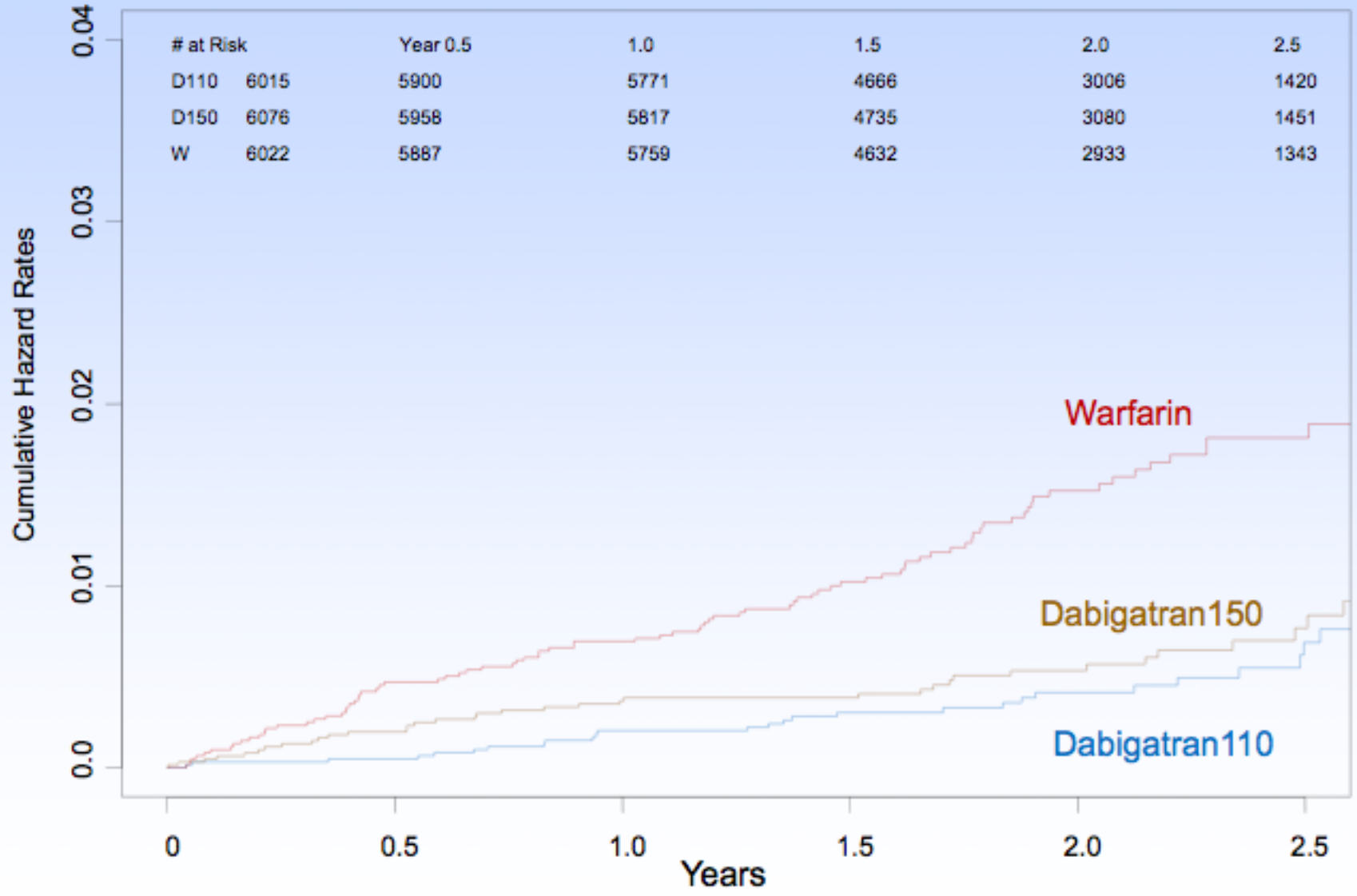
Stroke or Systemic Embolism

RELY®
Study of stroke prevention in atrial fibrillation



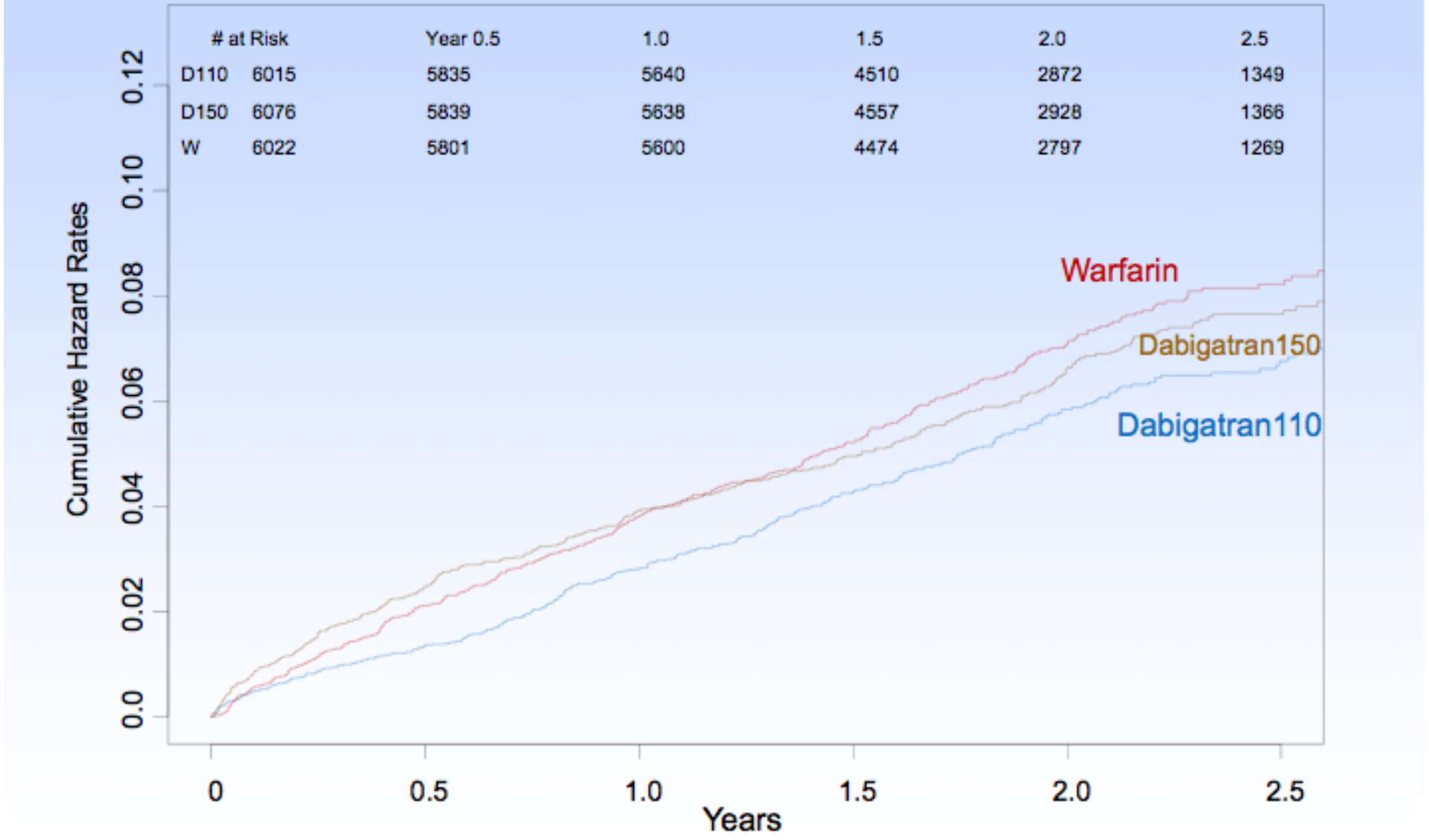
All Intracranial Bleeding

RELY®
Study of stroke prevention in atrial fibrillation



Major Bleeding

RELY®
Study of stroke prevention in atrial fibrillation



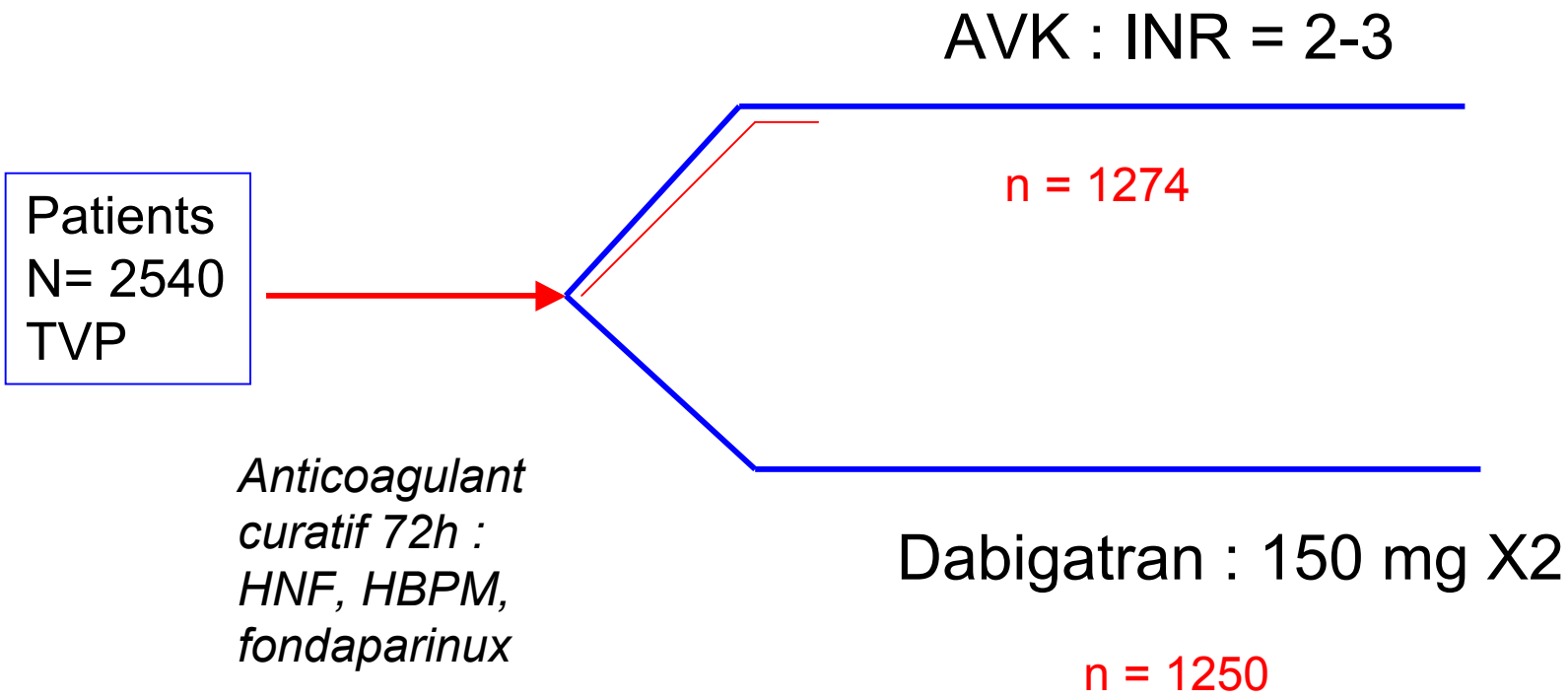
Conclusions

RELY®
Study of stroke preventi
in atrial fibrillation

- Dabigatran 110 mg had a similar rate of stroke as warfarin with significantly reduced major bleeding
- Dabigatran 150 mg significantly reduced stoke compared to warfarin with similar risk of major bleeding
- Both doses markedly reduced intra-cranial hemorrhage
- Both doses are free of liver and other major toxicity, although they increase dyspepsia and GI bleeding

Intérêt du dabigatran dans la MTEV : RECOVER

228 centres, 29 pays



Schulman S et coll. Dabigatran exilate versus warfarine in the treatment of venous thromboembolism. Session plénière, ASH, 6 décembre 2009.

RECOVER : efficacité et décès

	Dabigatran (n = 1274)	Warfarine (1265)	RR
TVP symptomatique	16 (1,3 %)	18 (1,4 %)	0,87 (0,44-1,71)
TVP non fatale	13 (1 %)	7 (0,6 %)	1,85 (0,74-4,64)
Décès liés à une TVP	1 (0,1 %)	3 (0,2 %)	0,33(0,03-3,15)
Décès totaux	21 (1,7 %)	21 (1,7 %)	0,98 (0,53-1,79)

Schulman S et coll. Dabigatran exilate versus warfarine in the treatment of venous thromboembolism. Session plénière, ASH, 6 décembre 2009.

RECOVER : complications hémorragiques

	Dabigatran (n = 1274)	Warfarine (n = 1265)	RR
Hémorragies majeures	20 (1,6 %)	24 (1,9 %)	0,82 (0,45-1,48)
Hémorragies fatales	1	1	
Hémorragies sur organe critique (intracrânienne/hémarthrose/hémo-ptysie)	1 (0/1/0)	9 (3/5/1)	
Chute d'Hb ≥ 2 g/dL ou transfusion ≥ 2 culots	20	18	
Hémorragies majeures ou non majeures mais impactant la clinique	71 (5,6 %)	111 (8,8 %)	0,63 (0,47-0,84)
Ensemble des complications hémorragiques majeures et mineures	205 (16,1 %)	277 (21,9 %)	0,71 (0,59-0,85)

Schulman S et coll. Dabigatran exilate versus warfarine in the treatment of venous thromboembolism. Session plénière, ASH, 6 décembre 2009.

Requirements of new prophylactic agents

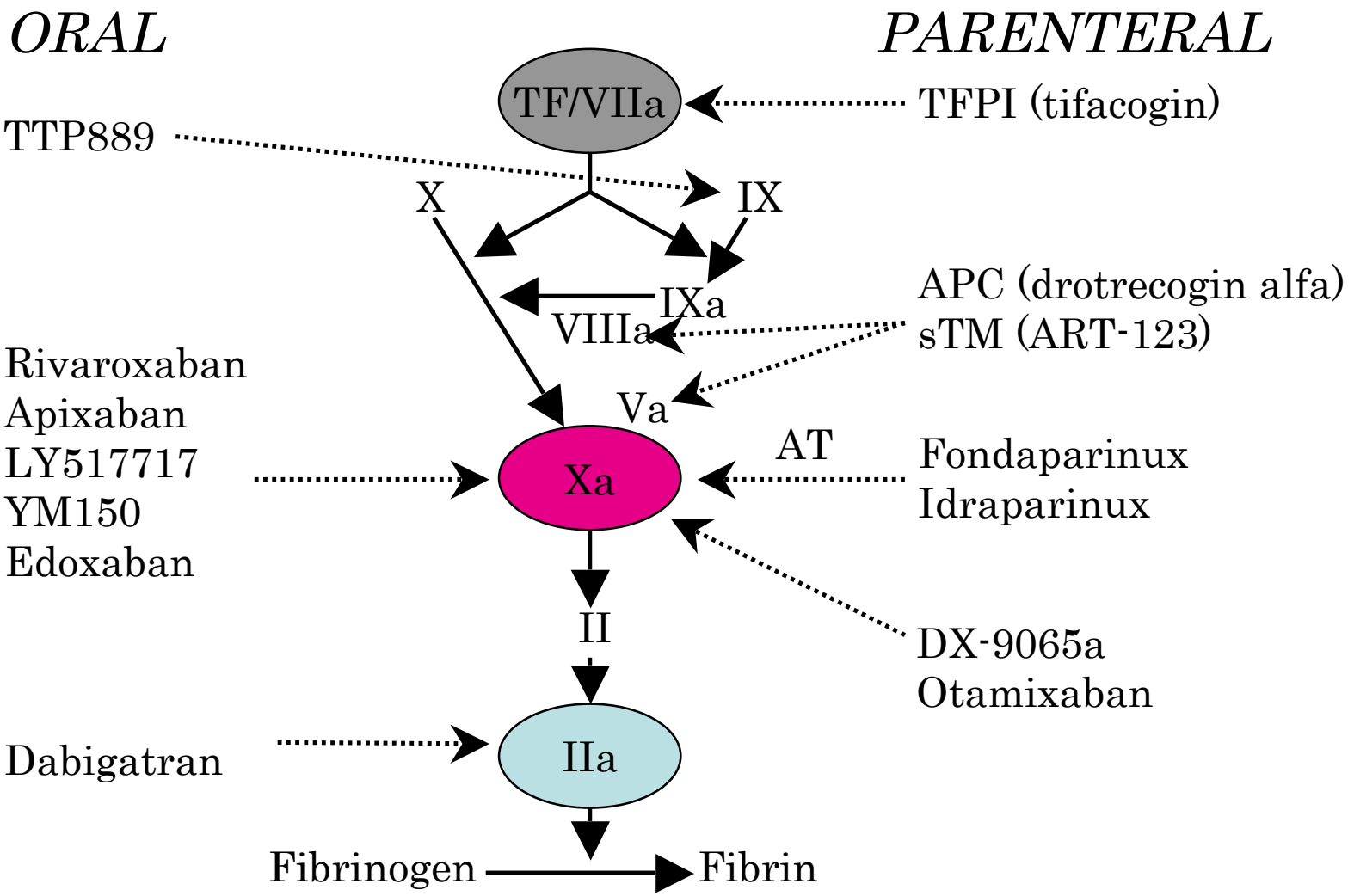
- At least as efficacious as current standard therapy
- At least as safe as current standard therapy
- Available for oral administration
- Require no monitoring
- No relevant interactions with food and common drugs
- Cost-effective

… in order to aid treatment compliance and avoid the serious consequences of thrombosis and bleeding

Comparison of three upcoming novel specific oral anticoagulants

Drug Class	Company	Half-life	Bioavailability	Elimination
Apixaban Anti-Xa	BMS/Pfizer	8-15	50-85 %	25 % renal 75 % liver
Rivaroxaban Anti-Xa	Bayer/J & J	7-13	> 80 %	33 % renal (unchanged) 33% renal (inactive metabolites) 33 % biliary
Dabigatran Direct thrombin inhibitor	B-I	14-17	6-8 %	80 % renal 20 % biliary

New anticoagulants



Adapted from Weitz & Bates, *J Thromb Haemost* 2005