NOUVEAUX ANTICOAGULANTS ORAUX (NACO)

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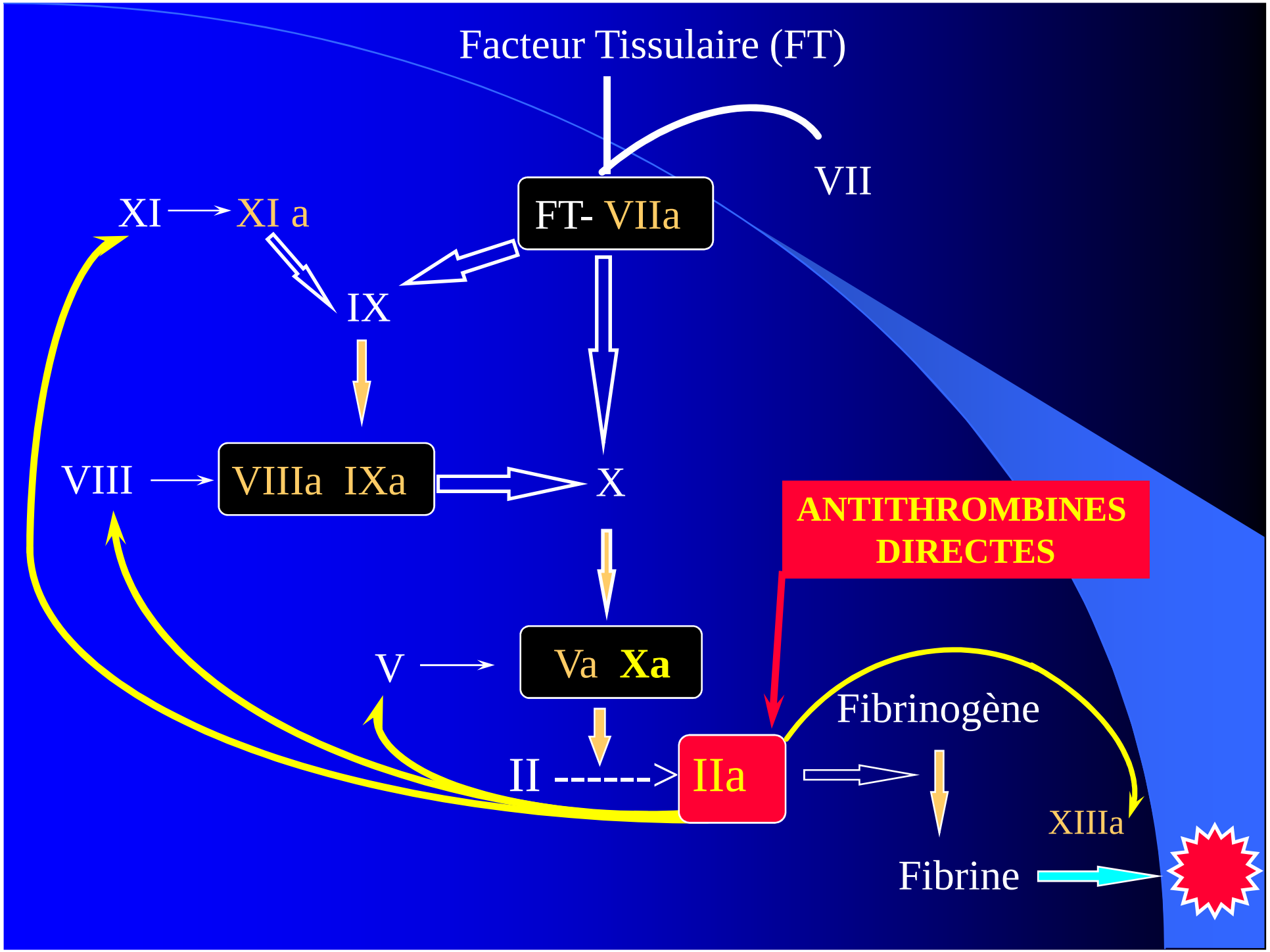
NACO

- Deux cibles principales
  - Thrombine (facteur IIa)
  - Facteur Xa

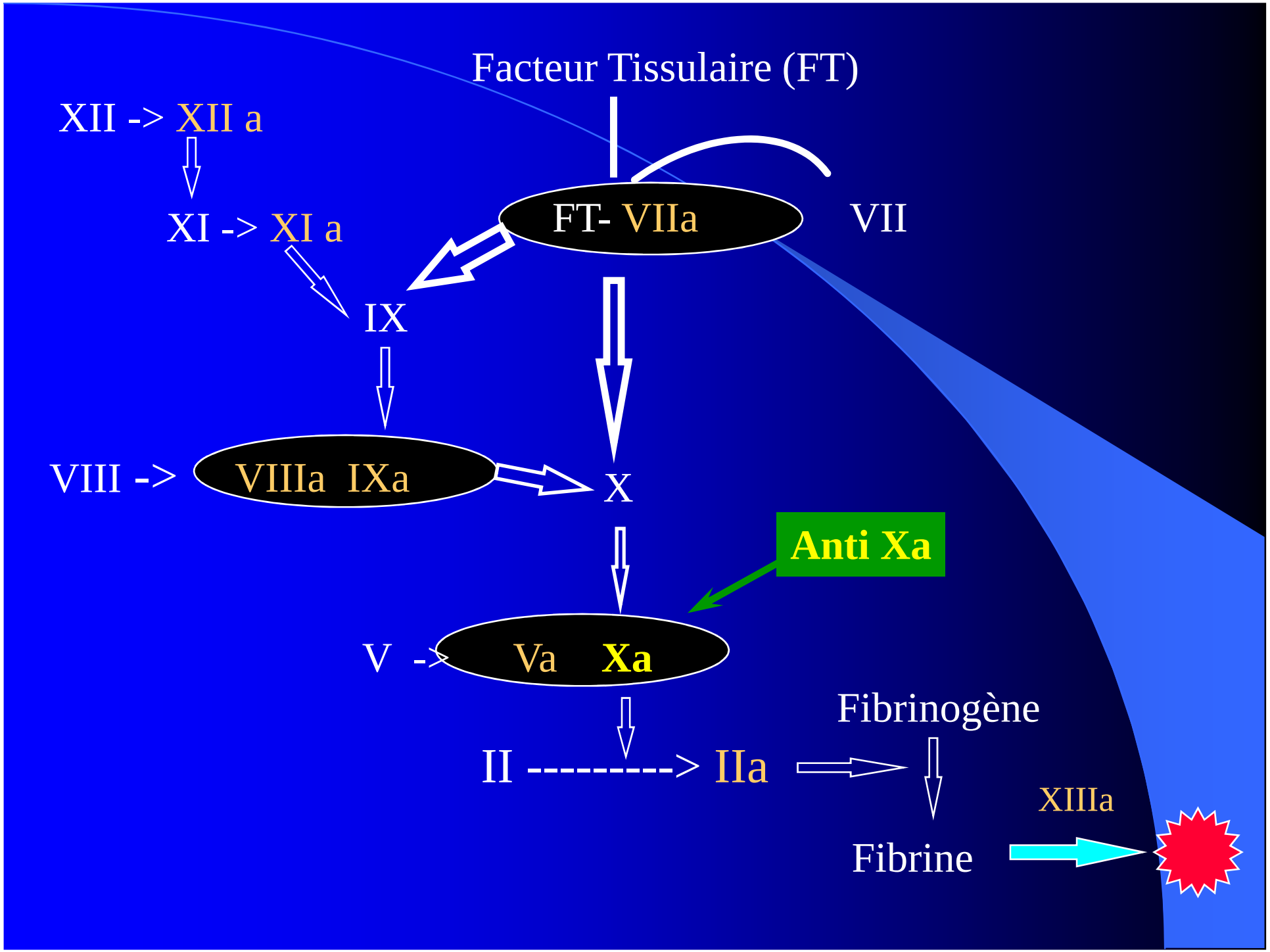

Facteur Tissulaire (FT)
VII
FT- VIIa
XI
XI a
IX
VIII
VIIIa IXa
X
ANTITHROMBINES DIRECTES
V
Va Xa
II
IIa
Fibrinogène
XIIIa
Fibrine

Dabigatran

- Antithrombine directe active par voie orale
- Tmax 2-4h et demi-vie 14-17h en ortho, donc 1 seule prise par jour
- Commercialisé sous le nom des **Pradaxa** [R]
  - Prévention de TVP après PTG-PTH
  - Fibrillation atriale

Dabigatran

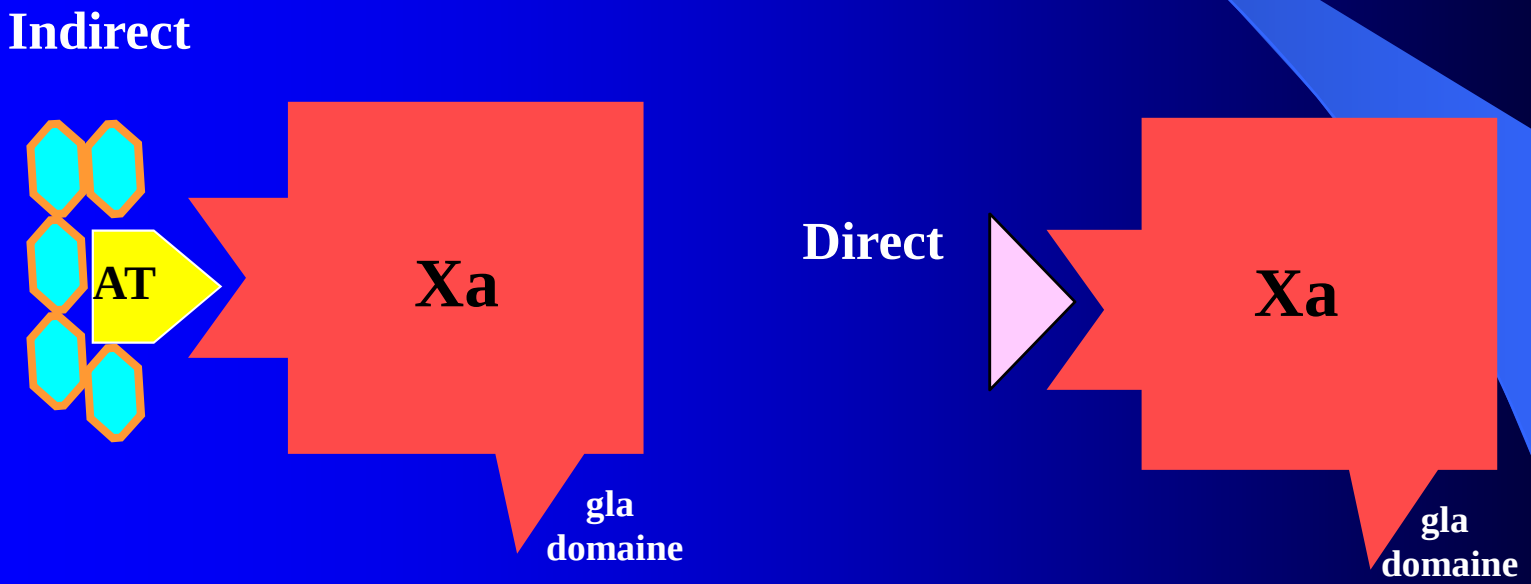
	75 mg	110 mg	150 mg
FA		220 mg en 2 prises/j 1 matin et soir Situation à risque	300 mg en 2 prises/j 1 matin et soir Sujet normal
PTH PTG	2cp soit 150 mg en 1 prise/j Situation à risque	2cp soit 220 mg en 1 prise/j Sujet normal	


Facteur Tissulaire (FT)
XII -> XII a
XI -> XI a
FT- VIIa
VII
IX
VIII ->
VIIIa IXa
X
Anti Xa
V ->
Va Xa
Fibrinogène
II ---------> IIa
XIIIa
Fibrine

ANTI Xa DIRECTS

- Rivaroxaban: Xarelto^{R}
- Apixaban: Eliquis^{R}
- Edoxaban

ANTI Xa SELECTIFS DIRECTS



Rivaroxaban

- Anti Xa direct
- Inhibition corrélée à la dose
- Demi-vie 9 heures
- Commercialisé sous le nom de **Xarelto** [R]
- **AMM:**
  - **Prévention de TVP après PTH ou PTG**
  - **Fibrillation atriale**
  - **Traitement de la TVP et prévention secondaire de la TVP et de l'embolie pulmonaire**

Rivaroxaban

	10 mg	15 mg	20 mg
FA		1prise/j Sujets à risque	1prise/j Poso habituelle
PTH PTG	1 prise/j		
Trt TVP PreventionEP		2 prise/j pdt 3 semaines	1 prise/j ensuite

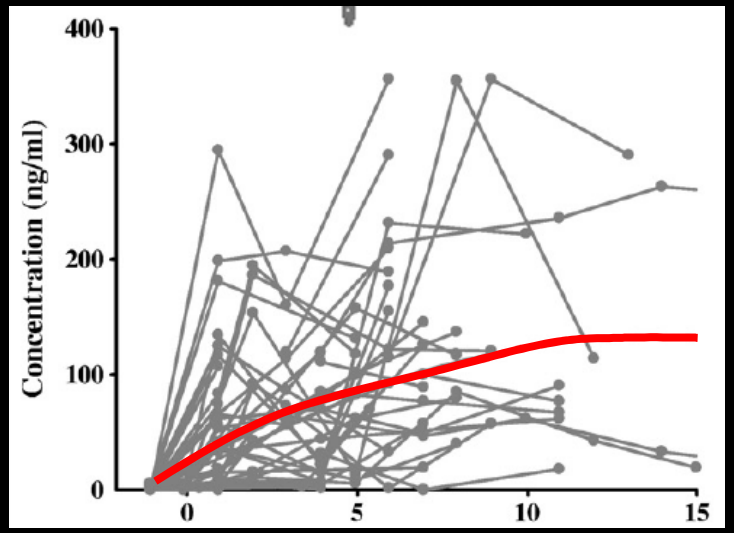
Apixaban

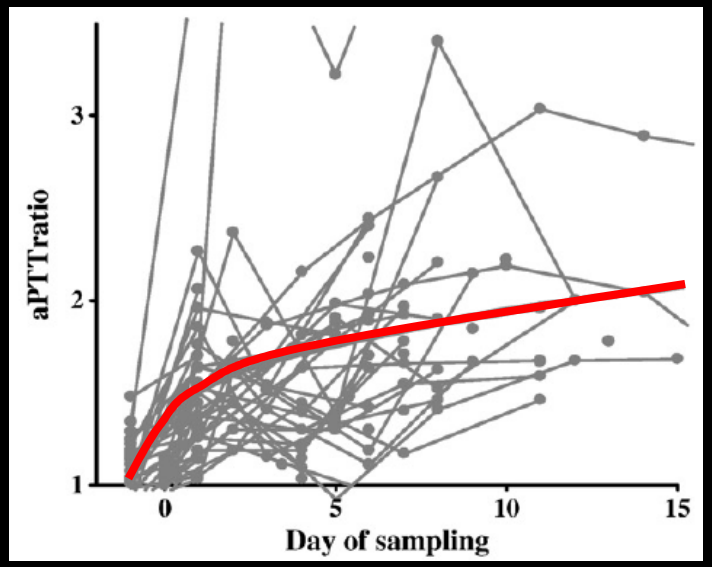
- Anti Xa réversible direct
- Biodisponibilité orale: 50%
- Demi-vie 10 à 15 heures
- Dose habituelle: 5 mg (cp à 2,5 mg, 2 fois/j)
- Commercialisé sous le nom de **Eliquis^{R}**
- Elimination:
  - renale à 25%, non renale à 75%
  - Métabolisme hepatique, excrétion biliaire et intestinale
- AMM: prévention de TVP après PTH ou PTG

NACO

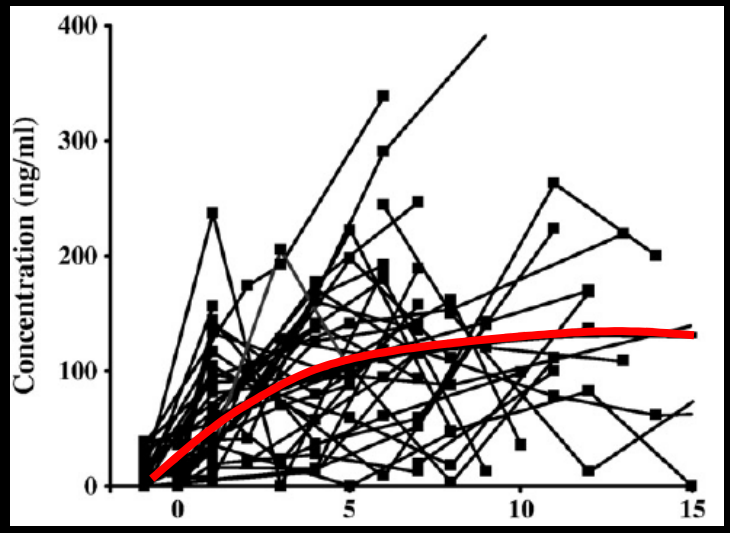
- **Avantages**
  - Actifs par voie orale
  - Action immédiate et demi-vie courte
  - Pas de surveillance biologique

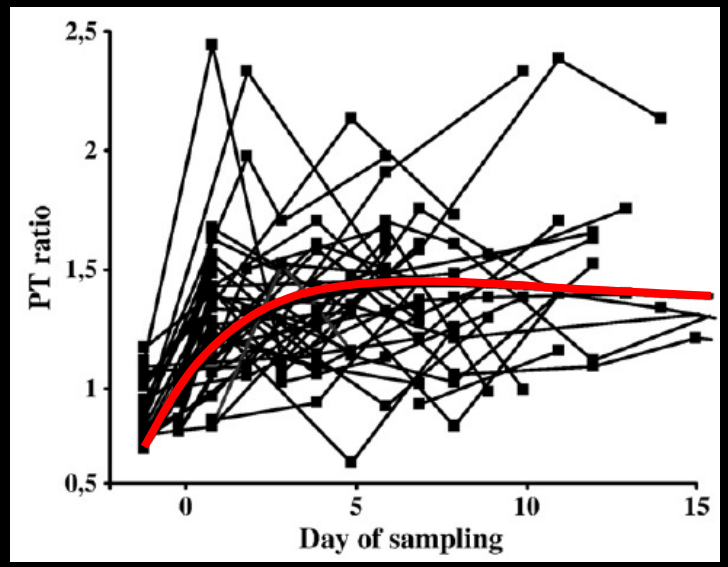
Dabigatran : PK - aPTT





Rivaroxaban : PK - PT

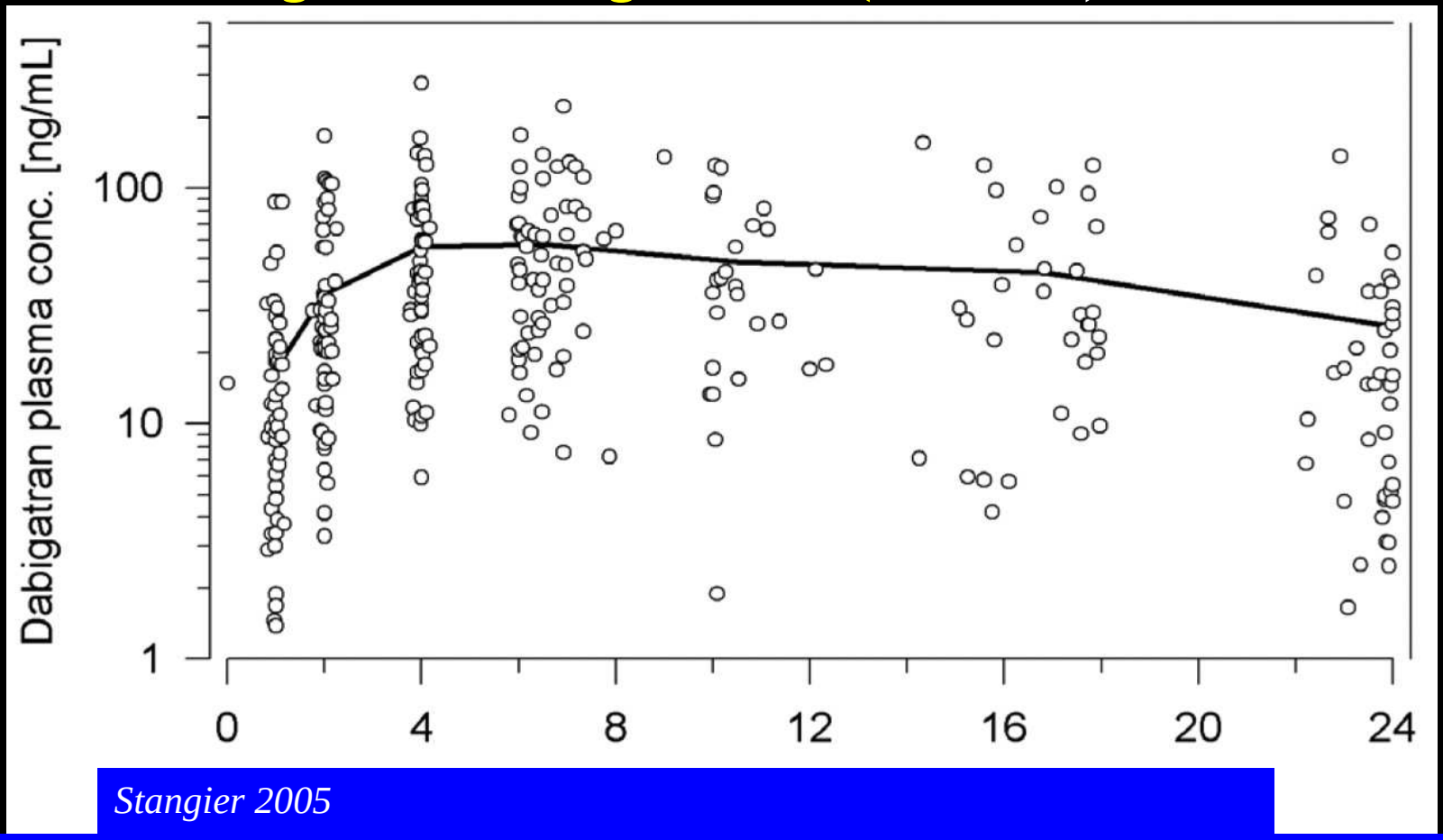




Freyburger et al. *Thromb Research* 2011.

Dabigatran: variabilité inter-individuelle

dabigatran 150 mg sd PTH (Bistro Ib)



Stangier 2005

CV (%) de la concentration plasmatique de dabigatran, 12 h après 150 mg:
PETRO-EX: 91 %, RELY: 81 % , BISTRO II: 87 %

Pourquoi cette variabilité?

ANTI IIa - ANTI Xa: Pharmacocinétique

	Bio-disponibilité	Elimination rénale	Tmax	Demi-vie (1)
Dabigatran	**7** %	**85** %	2 h	14h – 17h
Rivaroxaban	**80** %	**33** %	2 -4 h	7h – 13h
Apixaban	**66** %	**25** %	3 – 4 h	8h – 15h
Edoxaban	**50** %	**80** %	1 – 2 h	8h – 10h

(1) Sié P et al. Ann Fr Anesth Rea 2011

CYP3A4 inhibiteurs

Fort/ modéré:

ritonavir, indinavir, nelfinavir
Erythromycin, telithromycin, clarithromycin
Fluconazole, ketoconazole, itraconazole
nefazodone
bergamottin
quercetin
aprepitant
verapamil
chloramphenicol

Léger:

cimetidine
buprenorphine
cafestol

Inconnu:

amiodarone
ciprofloxacin
ciclosporin
diltiazem
imatinib
echinacea
enoxacin
saquinavir
fluoxetine/norfluoxetine, fluvoxamine

40 % de population cible >75 ans

→ au moins **1** P-gp ou CYP3A4 inhibiteur

Jungbauer et al. J Thromb Haemost 2010.

P-gp inhibiteurs

P-gp substrats

quinidine,propafénone, dronedarone
atorvastatine, simvastatine, lovastatin
diltiazem, verapamil, nicardipine, bepridil
celiprolol, talinolol, carvedilol
digoxine
amprenavir, saquinavir,
indinavir, nelfinavir, ritonavir
cyclosporine, tacrolimus
sirolimus, prednisolone, dexaméthasone
terfenadine,fexofenadine
cimétidine, ranitidine
erythromycine, rapamycine
levoxacine, sparfloxacine,
anthracyclines, taxanes….
loperamide, domperidone,phenytoine, morphine

P-gp inhibiteurs

Quinidine
Verapamil
Amiodarone
Erythromycine
Clarythromycine
ketoconazole
itraconazole
ritonavir

Drug–drug interactions for apixaban

Medication	Effect on CYP3A4	Effect on P-gp	Impact on apixaban C_{max}	Impact on apixaban AUC
Rifampin	+++	+++	↓ 42%	↓ 54%
Ketoconazole			↑ 1.6-fold	↑ 2-fold
Diltiazem			↑ 1.3-fold	↑ 1.4-fold
Naproxen	No effect		↑ 1.6-fold	↑ 1.5-fold

Caution with:

- **Strong inducers of both CYP3A4 and P-gp**, e.g. rifampin, phenytoin, carbamazepine, phenobarbital and St John's Wort
- **NSAIDS** including aspirin

Not recommended with:

- **Strong inhibitors of both CYP3A4 and P-gp** – azole-antimycotics (e.g., ketoconazole, itraconazole, voriconazole and posaconazole) and HIV protease inhibitors (e.g. ritonavir)

+++ = strong induction – – – = strong inhibition – – = moderate inhibition – = weak inhibition

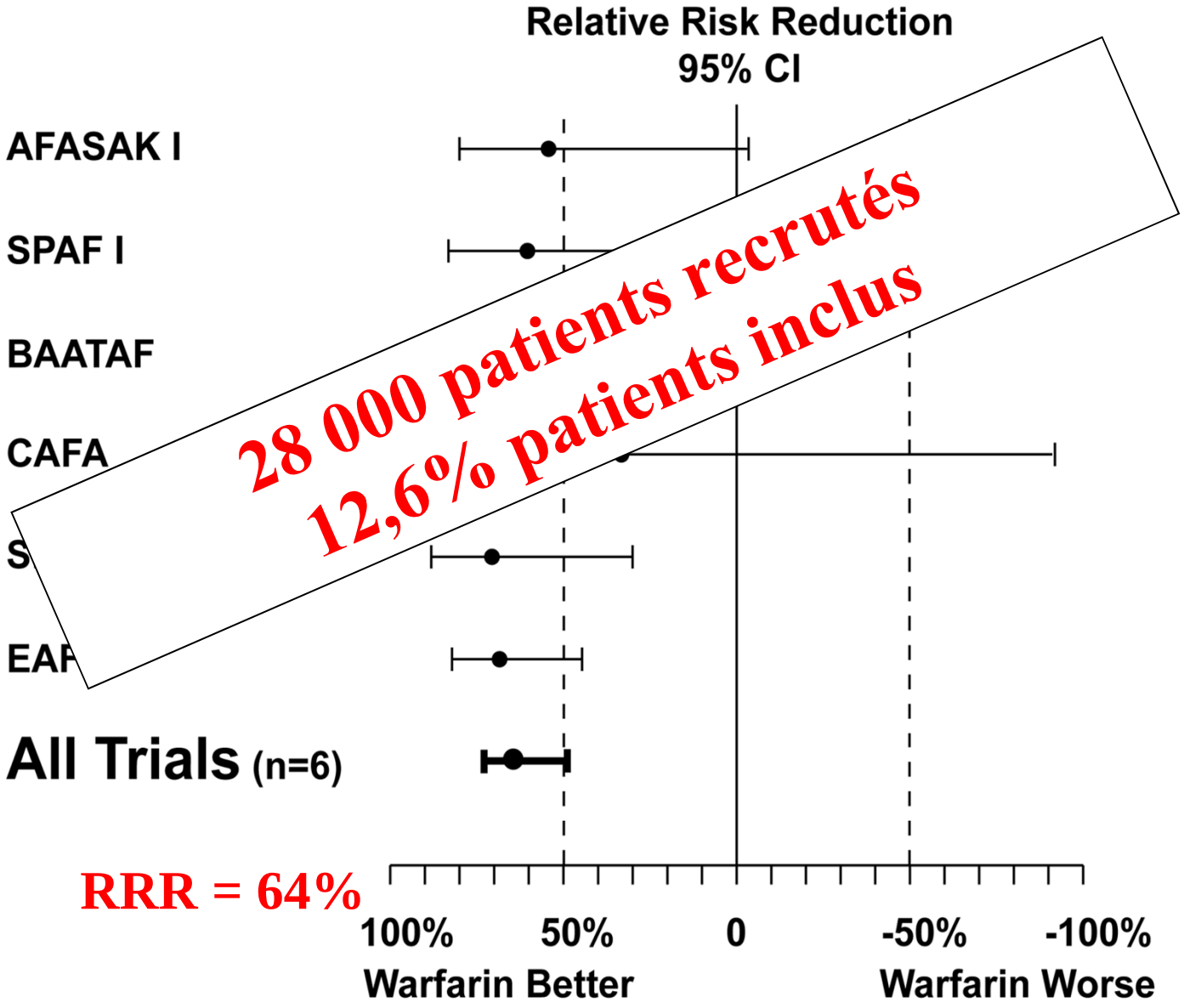
Eliquis™ SmPC 2011

Du côté des essais cliniques

Du côté des essais cliniques

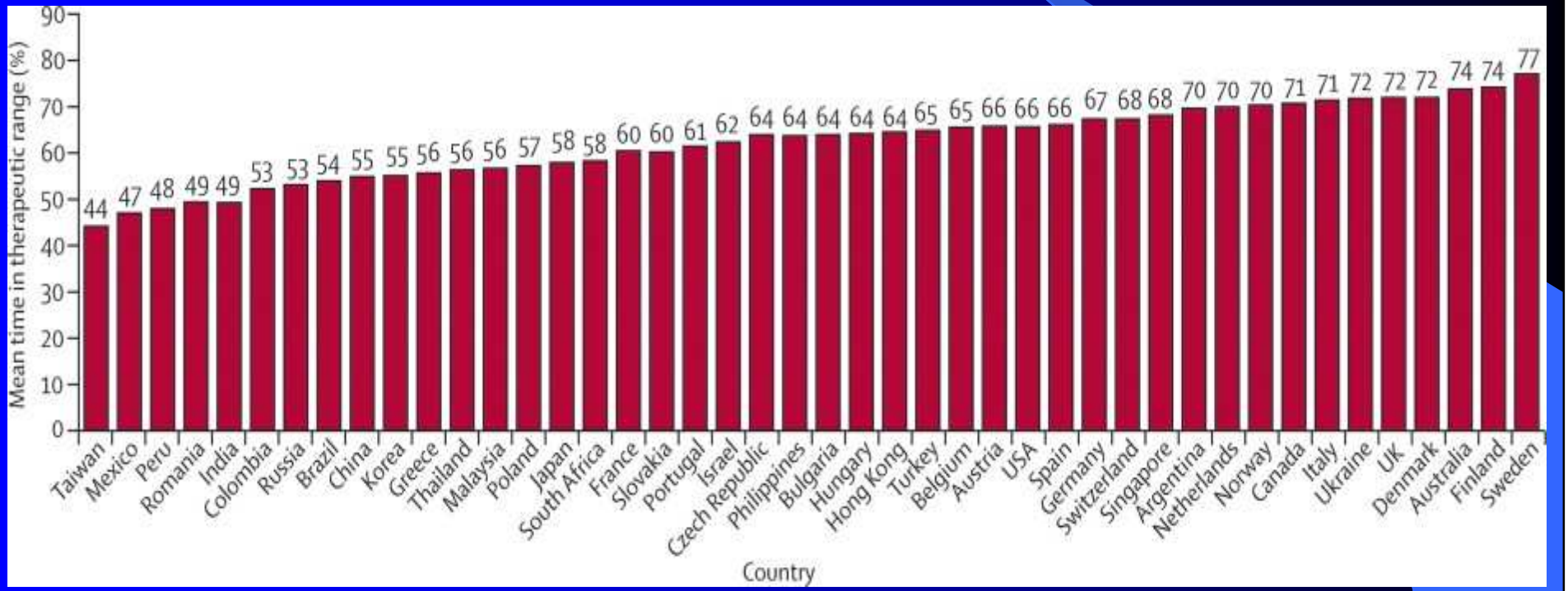
- Pour la FA, le comparateur est le traitement par antivitamines K (Coumadine^{R})
- Quelques rappels…

Adjusted-dose Warfarin Compared with Placebo/Control



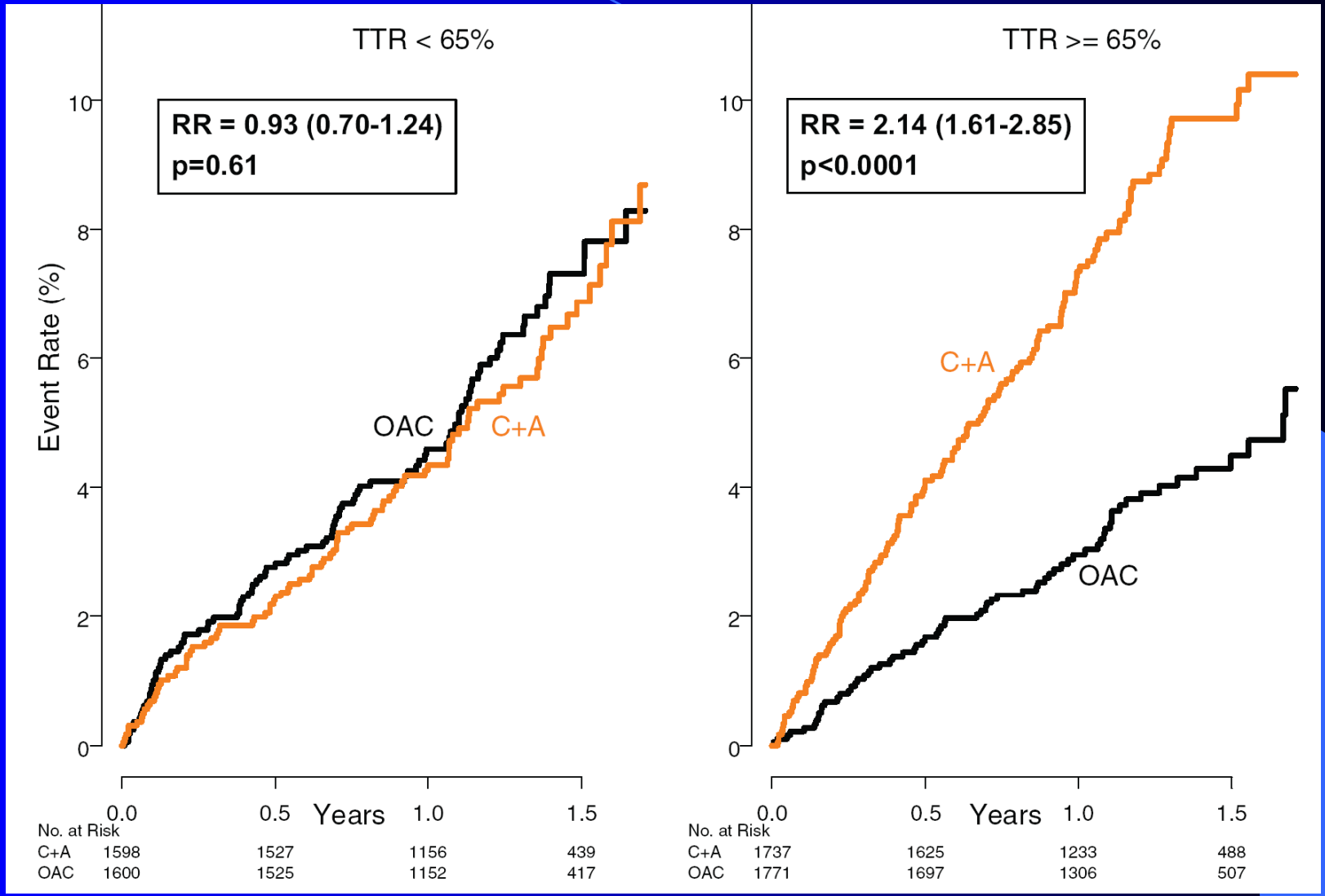
28 000 patients recrutés
12,6% patients inclus

ANTIVITAMINES K: Time in Therapeutic Range (TTR)



Wallentin et al. Lancet. 2010 Sep 18;376(9745):975-83

La limite : un TTR à 65 %



CONNOLLY S - Circulation. 2008;118:2029-2037

TTR: Quel impact?
% de temps avec INR 2-3

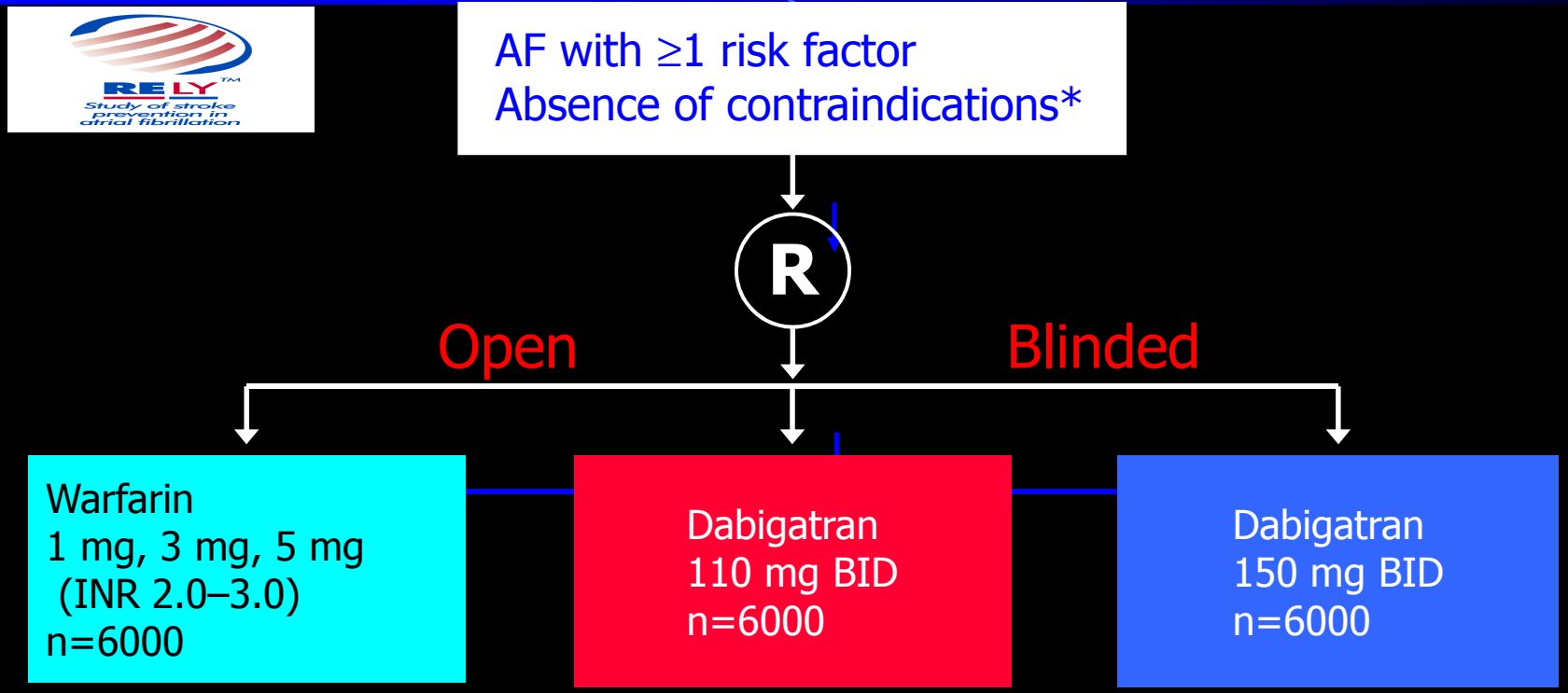
	Clopidogrel + ASA			OAC		
	n	Events, n	%/y	n	Events, n	%/y
Stroke, myocardial infarction, vascular death, or systemic embolism						
Quartile 1 (TTR <53.8%)	668	41	4.95	674	45	5.48
Quartile 2 (TTR 53.8%–65.0%)	930	49	4.20	926	51	4.46
Quartile 3 (TTR 65.1%–73.2%)	974	85	6.85	1004	39	3.04
Quartile 4 (TTR >73.3%)	763	59	6.24	767	31	3.25
Major hemorrhage						
Quartile 1 (TTR <53.8%)	668	12	1.45	674	24	2.92
Quartile 2 (TTR 53.8%–65.0%)	930	22	1.89	926	27	2.36
Quartile 3 (TTR 65.1%–73.2%)	974	42	3.38	1004	25	1.95
Quartile 4 (TTR >73.3%)	763	25	2.64	767	17	1.78

CONNOLLY S - Circulation. 2008;118:2029-2037

Du côté des essais cliniques

- Dabigatran dans la FA: essai RELY
- Rivaroxaban dans la FA: Essai Rocket
- Apixaban dans la FA: Essai Averroes
  EssaiAristotle

Phase III RE-LY®: dabigatran in AF

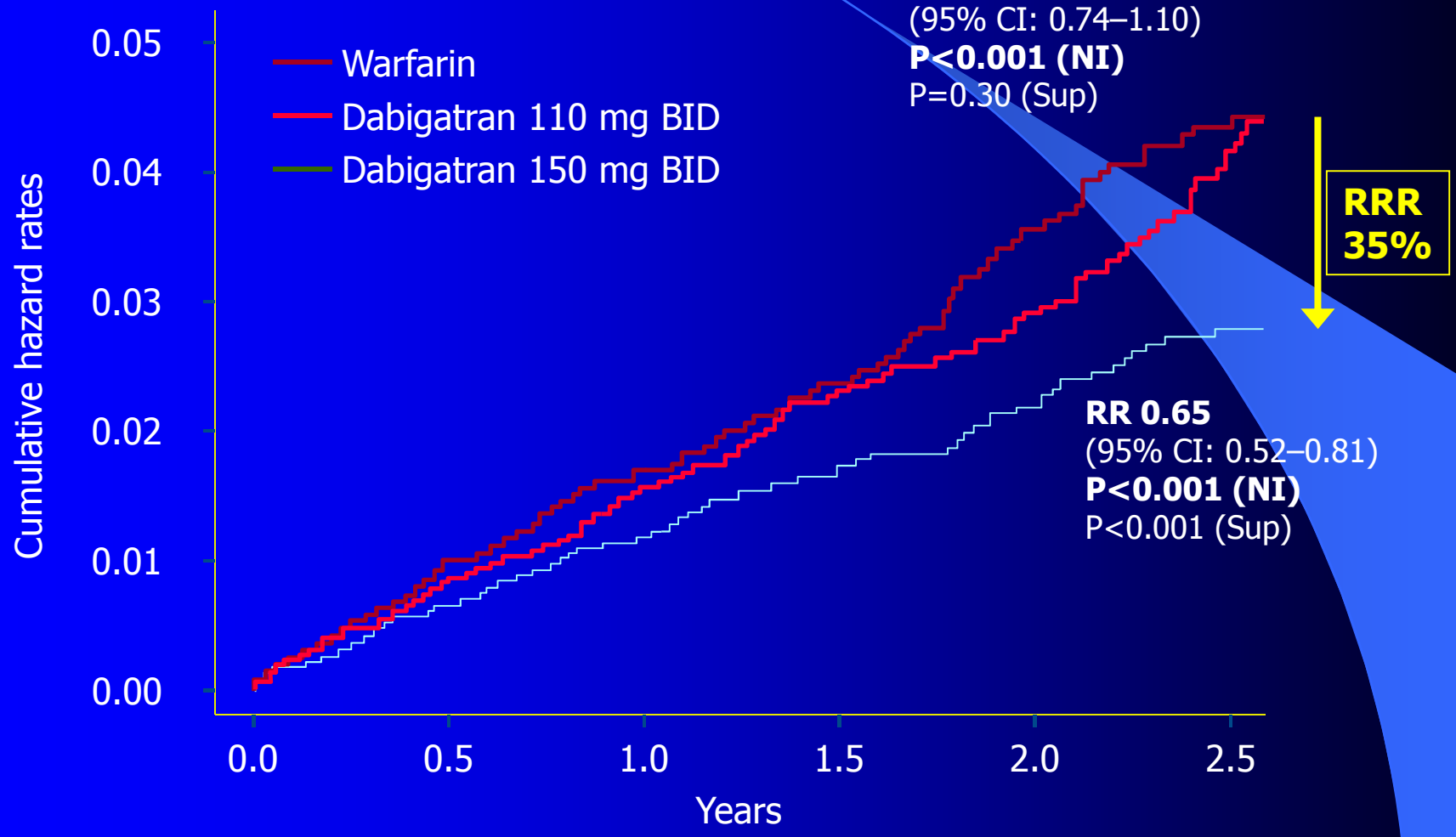


- Primary objective: to establish the non-inferiority of dabigatran to warfarin
- Minimum 1 year follow-up, maximum of 3 years and median of 2 years of follow-up

*Severe heart-valve disorder, stroke ≤14 days or severe stroke ≤6 months before screening, increased haemorrhage risk, creatinine clearance <30 mL/min, active liver disease, pregnancy; BID = twice daily; INR = international normalized ratio

Ezekowitz MD. Am Heart J 2009;157:805–10;
Connolly SJ. N Engl J Med 2009;361:1139–51

Phase III RE-LY®: time to first stroke or systemic embolism



BID = twice daily; NI = non-inferiority; RR = relative risk; RRR = relative risk reduction; Sup = superiority

Connolly SJ. N Engl J Med 2009;361:1139–51

Table 2. Efficacy Outcomes, According to Treatment Group.

Event	Dabigatran, 110 mg (N=6015)		Dabigatran, 150 mg (N=6076)		Warfarin (N=6022)		Dabigatran, 110 mg, vs. Warfarin		Dabigatran, 150 mg, vs. Warfarin		Dabigatran, 150 mg vs. 110 mg	
							Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
	no. of patients	*%/yr*	*no. of patients*	*%/yr*	*no. of patients*	*%/yr*						
Stroke or systemic embolism*	182	1.53	134	1.11	199	1.69	0.91 (0.74–1.11)	<0.001 for noninferiority, 0.34	0.66 (0.53–0.82)	<0.001 for noninferiority, <0.001	0.73 (0.58–0.91)	0.005
Stroke	171	1.44	122	1.01	185	1.57	0.92 (0.74–1.13)	0.41	0.64 (0.51–0.81)	<0.001	0.70 (0.56–0.89)	0.003
Hemorrhagic	14	0.12	12	0.10	45	0.38	0.31 (0.17–0.56)	<0.001	0.26 (0.14–0.49)	<0.001	0.85 (0.39–1.83)	0.67
Ischemic or unspecified	159	1.34	111	0.92	142	1.20	1.11 (0.89–1.40)	0.35	0.76 (0.60–0.98)	0.03	0.69 (0.54–0.88)	0.002
Nondisabling stroke	60	0.50	44	0.37	69	0.58	0.86 (0.61–1.22)	0.40	0.62 (0.43–0.91)	0.01	0.72 (0.49–1.07)	0.10
Disabling or fatal stroke	112	0.94	80	0.66	118	1.00	0.94 (0.73–1.22)	0.65	0.66 (0.50–0.88)	0.005	0.70 (0.53–0.94)	0.02
Myocardial infarction	86	0.72	89	0.74	63	0.53	1.35 (0.98–1.87)	0.07	1.38 (1.00–1.91)	0.048	1.02 (0.76–1.38)	0.88
Pulmonary embolism	14	0.12	18	0.15	11	0.09	1.26 (0.57–2.78)	0.56	1.61 (0.76–3.42)	0.21	1.27 (0.63–2.56)	0.50
Hospitalization	2311	19.4	2430	20.2	2458	20.8	0.92 (0.87–0.97)	0.003	0.97 (0.92–1.03)	0.34	1.06 (1.00–1.12)	0.04
Death from vascular causes	289	2.43	274	2.28	317	2.69	0.90 (0.77–1.06)	0.21	0.85 (0.72–0.99)	0.04	0.94 (0.79–1.11)	0.44
Death from any cause	446	3.75	438	3.64	487	4.13	0.91 (0.80–1.03)	0.13	0.88 (0.77–1.00)	0.051	0.97 (0.85–1.11)	0.66

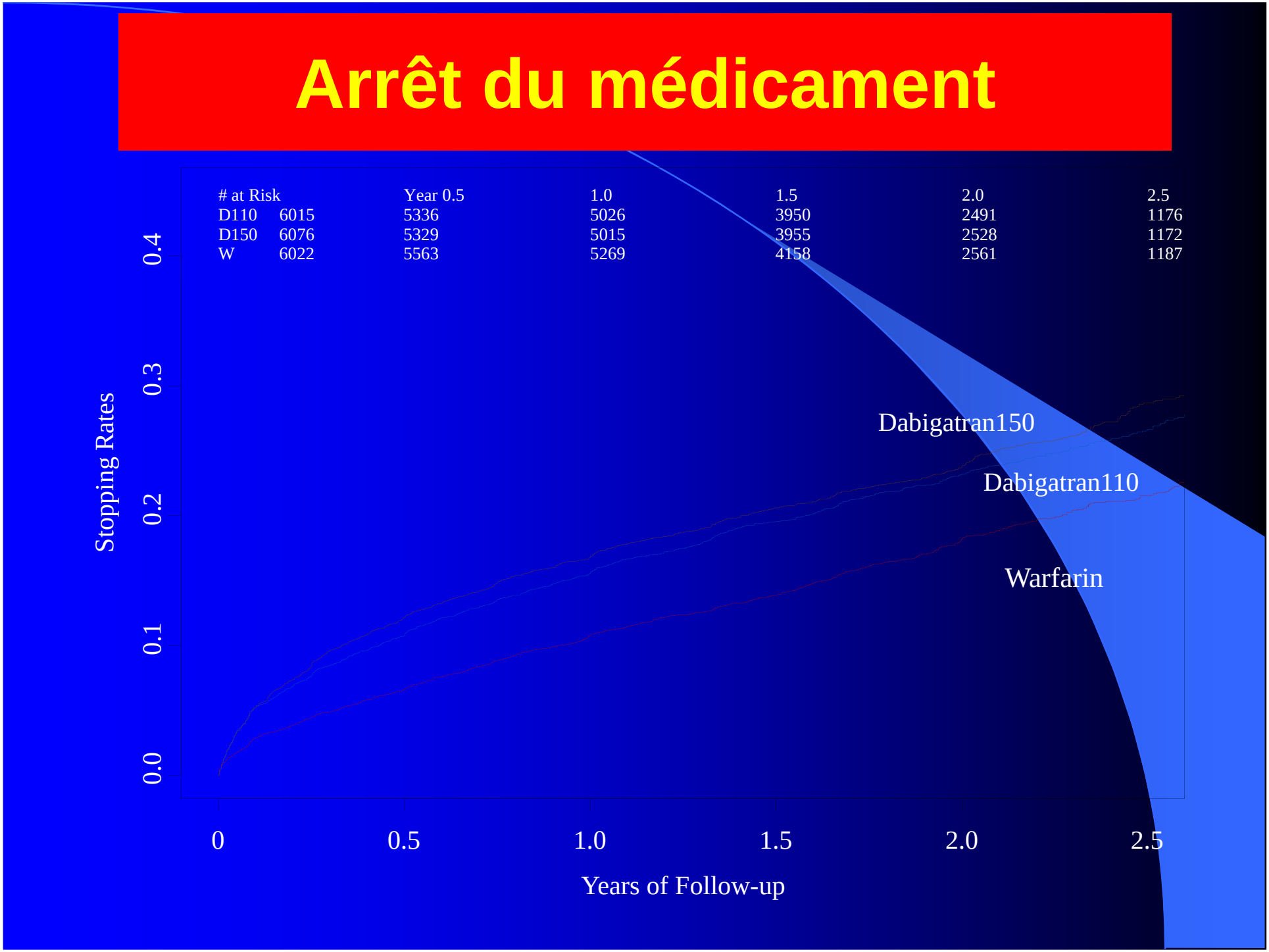
RELY: l'analyse de la FDA

- **1 Etude ouverte (pas de double aveugle)**

  *However, the comparison between warfarin and dabigatran was **not blinded** and thus all outcomes are subject to performance and ascertainment bias favouring dabigatran. This interpretation is reinforced by the FDA review, which found that lack of blinding of patients and clinicians led to 'differential treatment of patients during the study period' (performance bias) and that the presence of ascertainment and adjudication bias was sufficient to overturn the claim of a stroke benefit for dabigatran 150 mg BID as compared with warfarin*[2].

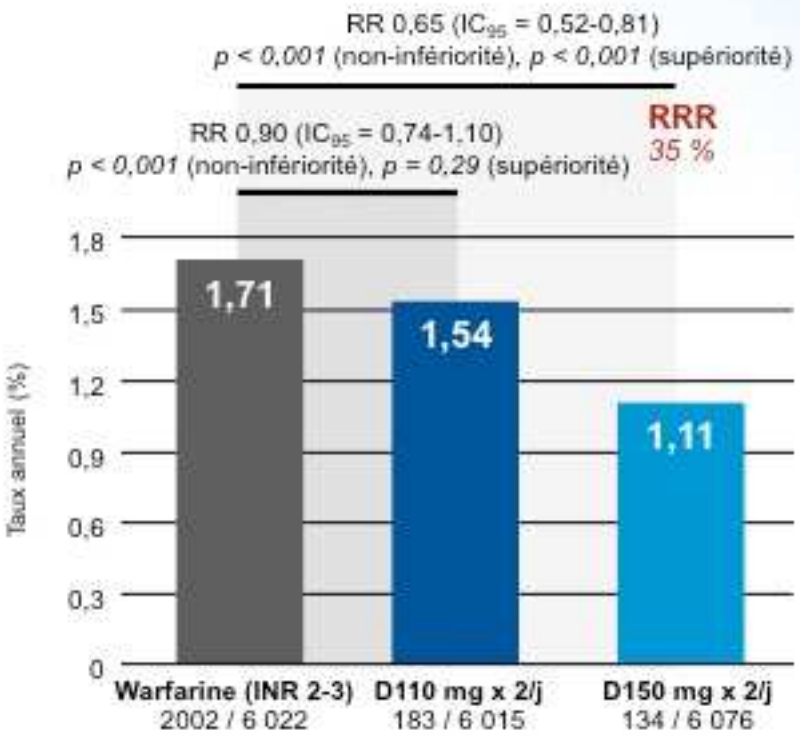
Cependant cette comparaison entre warfarine et dabigatran n'était pas faite en aveugle, et les conséquences sont l'objet de biais qui agissent en faveur du dabigatran,,,La présence de ces biais est suffisante pour contester l'affirmation d'une supériorité de dabigatran 150 mg, une fois par jour sur la warfarine,

Arrêt du médicament

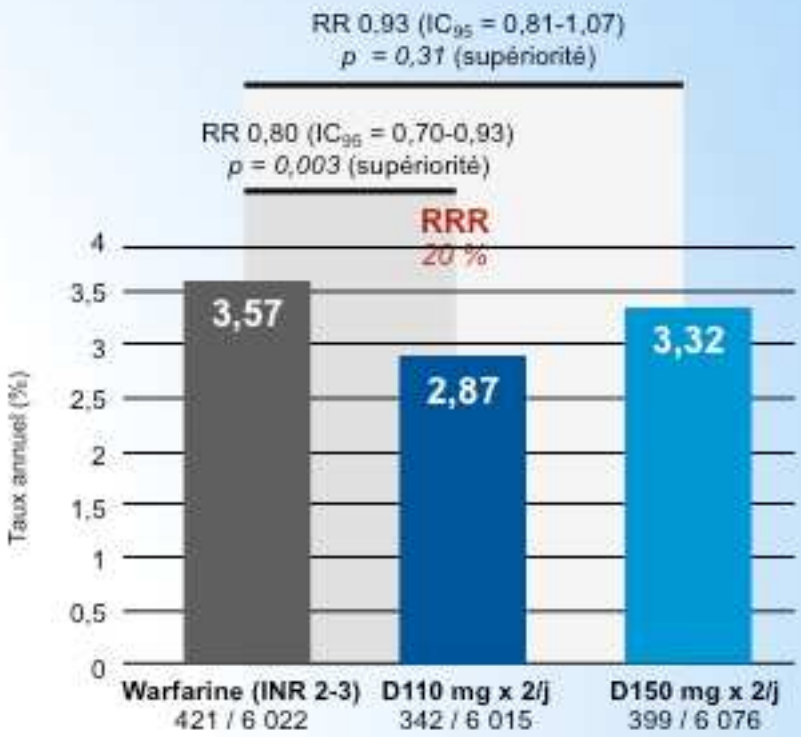


Critères principaux d'évaluation dans RE-LY®

Taux d'AVC et/ou d'embolie systémique
(Critère principal d'efficacité)

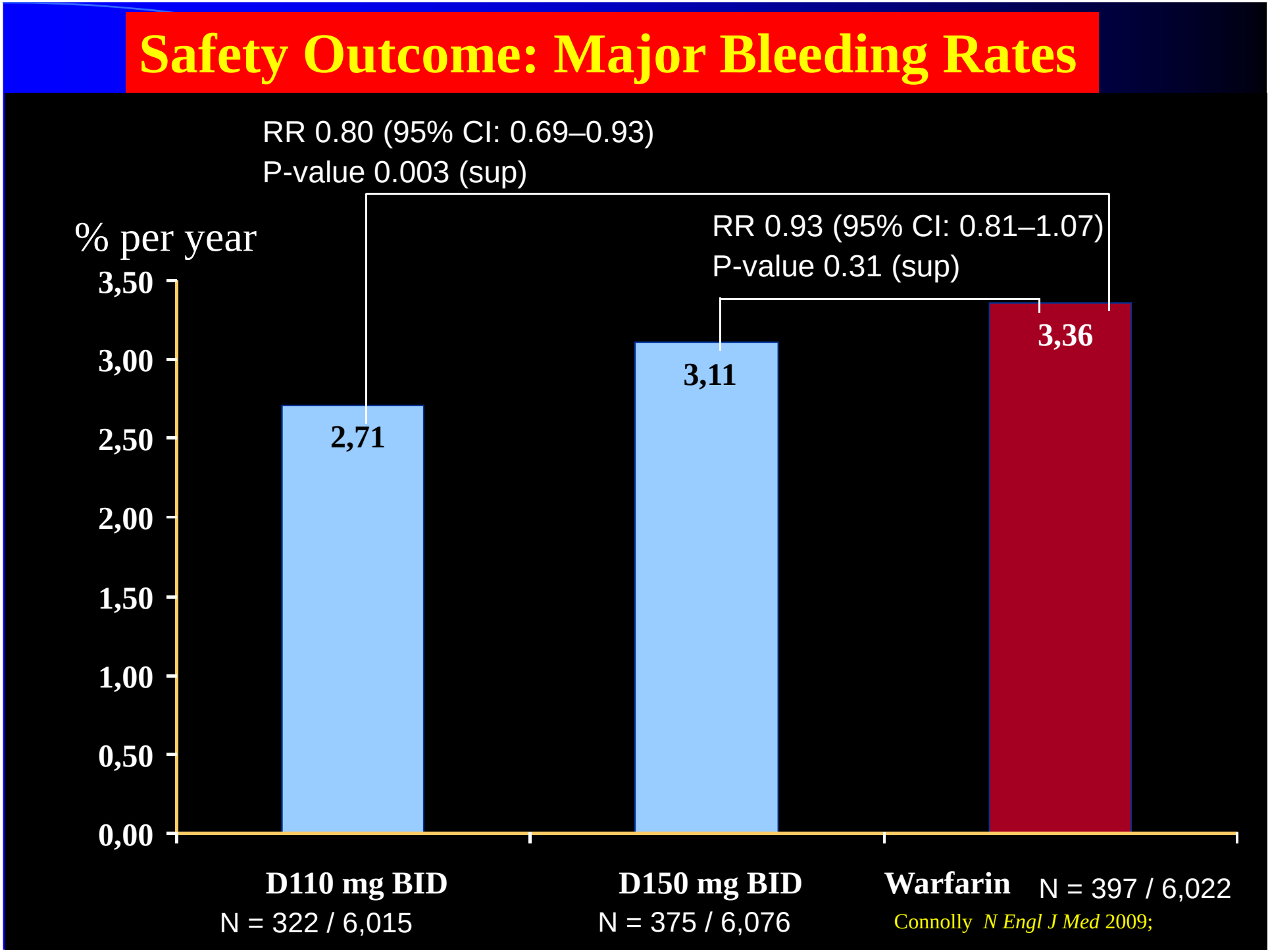


Taux d'hémorragies majeures
(Critère principal de tolérance)



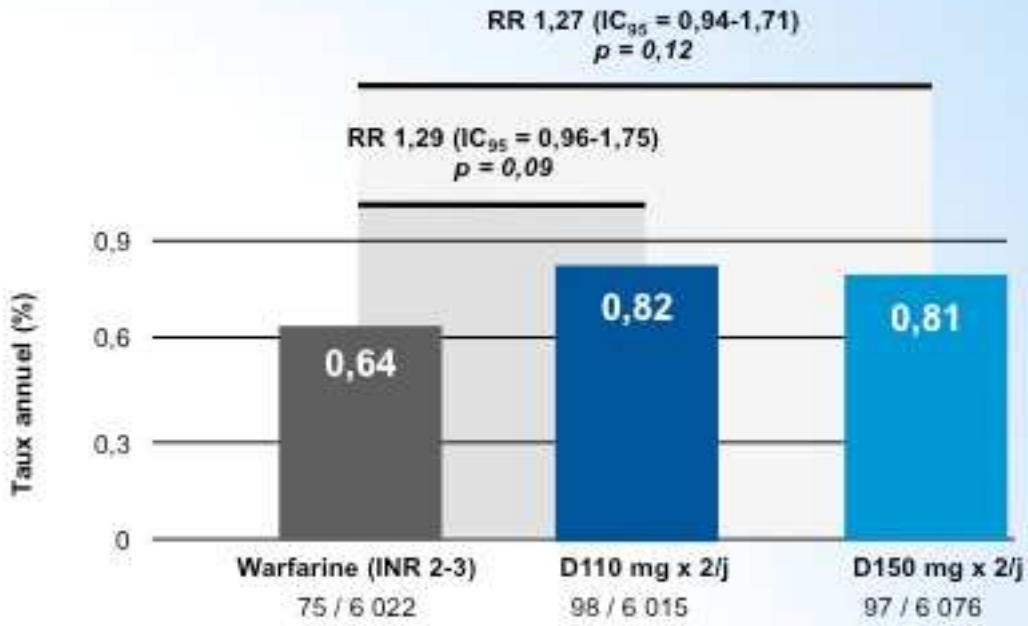
Connolly SJ *et al.* Dabigatran *versus* warfarine in patients with atrial fibrillation. N Engl J Med 2009;361:1139-51
Connoly SJ *et al.* New identified events in the RE-LY Trial. N Engl J Med 2010;363:1875-6. Supplementary appendix.
Résumé des caractéristiques du produit Pradaxa®.

Safety Outcome: Major Bleeding Rates



Connolly *N Engl J Med* 2009;

Infarctus du myocarde (IDM) (critère secondaire d'efficacité)



Le taux d'IDM a été légèrement augmenté avec le dabigatran etexilate 150 mg 2 fois par jour par rapport à la warfarine

RR = risque relatif ; D = dabigatran.

Connolly SJ *et al.* Dabigatran *versus* warfarine in patients with atrial fibrillation. N Engl J Med 2009;361:1139-51.
Connoly SJ *et al.* New identified events in the RE-LY Trial. N Engl J Med 2010;363:1875-6. Supplementary appendix.
Résumé des caractéristiques du produit Pradaxa®

Table 2: Key outcomes for dabigatran versus warfarin

Outcome	Dabigatran 110 and 150 mg BID	Warfarin once daily	RR [95% CI]	ARR ARI
Patients randomized	12091	6022		
Deaths (FDA)	890 7.4%	491 8.2%	0.90 [0.81, 1.00]	
Serious adverse events	Not reported	Not reported	?	?
Hospitalizations (NEJM)	4741 39.2%	2458 40.8%	0.96 [0.93, 1.00]	1.6%
Intracranial hemorrhage (FDA)	65 0.5%	90 1.5%	0.36 [0.26, 0.49]	1%
Adjudicated Ischemic stroke (FDA)	241 2%	118 2%	1.02 [0.82, 1.27]	
Bleeds leading to hospitalization minus intra-cranial hemorrhage (FDA)	589 4.9%	274 4.5%	1.07 [0.93, 1.23]	
MI (FDA)	176 1.5%	66 1.1%	1.33 [1.00, 1.76]	0.4%
Gastrointestinal bleeds (NEJM)	315 2.6%	120 2%	1.31 [1.06, 1.61]	0.6%
Withdrawal due to SAE (NEJM)	329 2.7%	105 1.7%	1.56 [1.26, 1.94]	1%
Withdrawal due to any adverse effect (FDA)	2381 19.7%	939 15.6%	1.26 [1.18, 1.35]	4.1%
Any adverse effect (FDA)	9449 78.1%	4551 75.6%	1.03 [1.02, 1.05]	2.5%
Dyspepsia (NEJM)	1395 11.5%	348 5.8%	2.00 [1.78, 2.24]	5.7%

Table 3. Safety Outcomes, According to Treatment Group.*

Event	Dabigatran, 110 mg		Dabigatran, 150 mg		Warfarin		Dabigatran, 110 mg, vs. Warfarin		Dabigatran, 150 mg, vs. Warfarin		Dabigatran, 150 mg vs. 110 mg	
	no. of patients	*%/yr*	*no. of patients*	*%/yr*	*no. of patients*	*%/yr*	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
Major bleeding	322	2.71	375	3.11	397	3.36	0.80 (0.69–0.93)	0.003	0.93 (0.81–1.07)	0.31	1.16 (1.00–1.34)	0.052
Life threatening	145	1.22	175	1.45	212	1.80	0.68 (0.55–0.83)	<0.001	0.81 (0.66–0.99)	0.04	1.19 (0.96–1.49)	0.11
Non–life threatening	198	1.66	226	1.88	208	1.76	0.94 (0.78–1.15)	0.56	1.07 (0.89–1.29)	0.47	1.14 (0.95–1.39)	0.17
Gastrointestinal†	133	1.12	182	1.51	120	1.02	1.10 (0.86–1.41)	0.43	1.50 (1.19–1.89)	<0.001	1.36 (1.09–1.70)	0.007
Minor bleeding	1566	13.16	1787	14.84	1931	16.37	0.79 (0.74–0.84)	<0.001	0.91 (0.85–0.97)	0.005	1.16 (1.08–1.24)	<0.001
Major or minor bleeding	1740	14.62	1977	16.42	2142	18.15	0.78 (0.74–0.83)	<0.001	0.91 (0.86–0.97)	0.002	1.16 (1.09–1.23)	<0.001
Intracranial bleeding	27	0.23	36	0.30	87	0.74	0.31 (0.20–0.47)	<0.001	0.40 (0.27–0.60)	<0.001	1.32 (0.80–2.17)	0.28
Extracranial bleeding	299	2.51	342	2.84	315	2.67	0.94 (0.80–1.10)	0.45	1.07 (0.92–1.25)	0.38	1.14 (0.97–1.33)	0.11
Net clinical benefit outcome‡	844	7.09	832	6.91	901	7.64	0.92 (0.84–1.02)	0.10	0.91 (0.82–1.00)	0.04	0.98 (0.89–1.08)	0.66

Etes vous SPORTIF?

ESSAI SPORTIF III, V

- Comparait dans la FA ximelagatran à Warfarine
  - Warfarine : AVC hémorragique
    - SPORTIF III (essai ouvert) = 0,53%/an
    - SPORTIF V (double aveugle) = 0,28%/an
    - Le risque relatif passait de 0,71 (en faveur de ximelagatran) dans l'essai ouvert (0,48-0,7) à 1,38 (0,91 – 2,10), non significatif, dans l'essai double aveugle

RELY: l'analyse de la FDA

2 Rôle de l'INR

Furthermore the FDA clinical reviewer found that the trend toward increased mortality with warfarin was entirely due to investigator sites where INR monitoring was inferior. At sites where INR was within therapeutic range ≥ 67% of the time, relative risk for mortality (RR 1.05) favoured warfarin over dabigatran

…l'augmentation de mortalité sous warfarine est entièrement due aux sites investigateurs ou le monitorage de l'INR était le moins bon. Dans les sites ouù l'INR était dans des zones thérapeutiques ≥ 67% du temps, ***le risque relatif pour la mortalité (RR 1.05) était en faveur de la warfarine sur le dabigatran***

RELY: l'analyse de la FDA

3 Aucun intérêt pour le 110 mg

Le 150 mg est le plus efficace (significativement supérieur au 110 mg). Le risque de séquelle d'un AVC ischémique est supérieur à celui d'un saignement

Chez les insuffisants rénaux (30-50ml/mn), concentration de dabi trois fois plus élevée que chez sujets normaux; les AVC ischémiques étaient de 1,3% patients-années par an avec 150 mg versus 2,4% patients années avec le 110 mg sans réduction du risque hémorragique (5,3 versus 5,7)

Du côté des essais cliniques

- Dabigatran dans la FA: essai RELY
- Rivaroxaban dans la FA: Essai Rocket
- Apixaban dans la FA: Essai Averroes
  Essai Aristotle

Du côté des essais cliniques

- Essai Rocket:
  - Conclusion: non infériorité mais pas de supériorité dans la population en ITT (intention de traiter)
  - TTR = 57,8% (le moins bon contrôle d'INR des trois études)

Incidence du critère primaire dans ROCKET-AF selon le mode d'analyse (intention de traiter ou per protocole)

	Rivaroxaban	Warfarine	RR	p
ITT (n = 14171)	2,12	2,42	0,88	0,117
PP (n = 14143)	1,70	2,15	0,79	0,015

Mahaffey K. Stroke prevention using the oral direct factor Xa inhibitor rivaroxaban compared with warfarine in patients with non-valvular atrial fibrillation (ROCKET-AF). Late-breaking clinical trail II. AHA 2010

Taux de saignements : résultats discordants

	Rivaroxaban	Warfarine	RR	P
Saignements intracrâniens	0,49	0,74	0,67	0,019
Hémorragies fatales	0,24	0,48	0,50	0,003
Transfusion	1,65	1,32	1,25	0,044
Chute $\geq$ 2 g/dL	2,77	2,26	1,22	0,019

Mahaffey K - Late-breaking clinical trials . AHA 2010

Du côté des essais cliniques

- Meta-analyse effectuée par la laboratoire:

  Supériorité de rivaroxaban sur dabigatran

- Avis de la commission de tranparence:
  - «Les comparaisons indirectes corrigées ne montrent pas de différence statistiquement significative ebn terme d'évènements thrombemboliques aussi bien entre rivaroxaban et dabigatran 110mg qu'entre rivaroxaban et dabigatran 150mg »

Du côté des essais cliniques

- Dabigatran dans la FA: essai RELY
- Rivaroxaban dans la FA: Essai Rocket
- Apixaban dans la FA: Essai Averroes
  Essai Aristotle

AVERROES :
apixaban versus aspirine dans la FA

	RR	IC à 95 %	p
AVC ou embolie systémique	0,46	0,33-0,64	< 0,001
AVC, embolies systémiques, infarctus ou décès vasculaire	0,66	0,53-0,83	< 0,001
Infarctus	0,85	0,48-1,50	0,57
Décès vasculaire	0,86	0,64-1,16	0,33
Hospitalisation CV	0,79	0,68-0,91	< 0,001
Décès totaux	0,79	0,62-1,02	0,07

Atrial Fibrillation with at Least One Additional Risk Factor for Stroke

Inclusion risk factors
- Age ≥ 75 years
- Prior stroke, TIA, or SE
- HF or LVEF ≤ 40%
- Diabetes mellitus
- Hypertension

Randomize
double blind, double dummy
(n = 18,201)

Major exclusion criteria
- Mechanical prosthetic valve
- Severe renal insufficiency
- Need for aspirin plus thienopyridine

Apixaban 5 mg oral twice daily
(2.5 mg BID in selected patients)

Warfarin
(target INR 2-3)

Warfarin/warfarin placebo adjusted by INR/sham INR based on encrypted point-of-care testing device

Primary outcome: stroke or systemic embolism

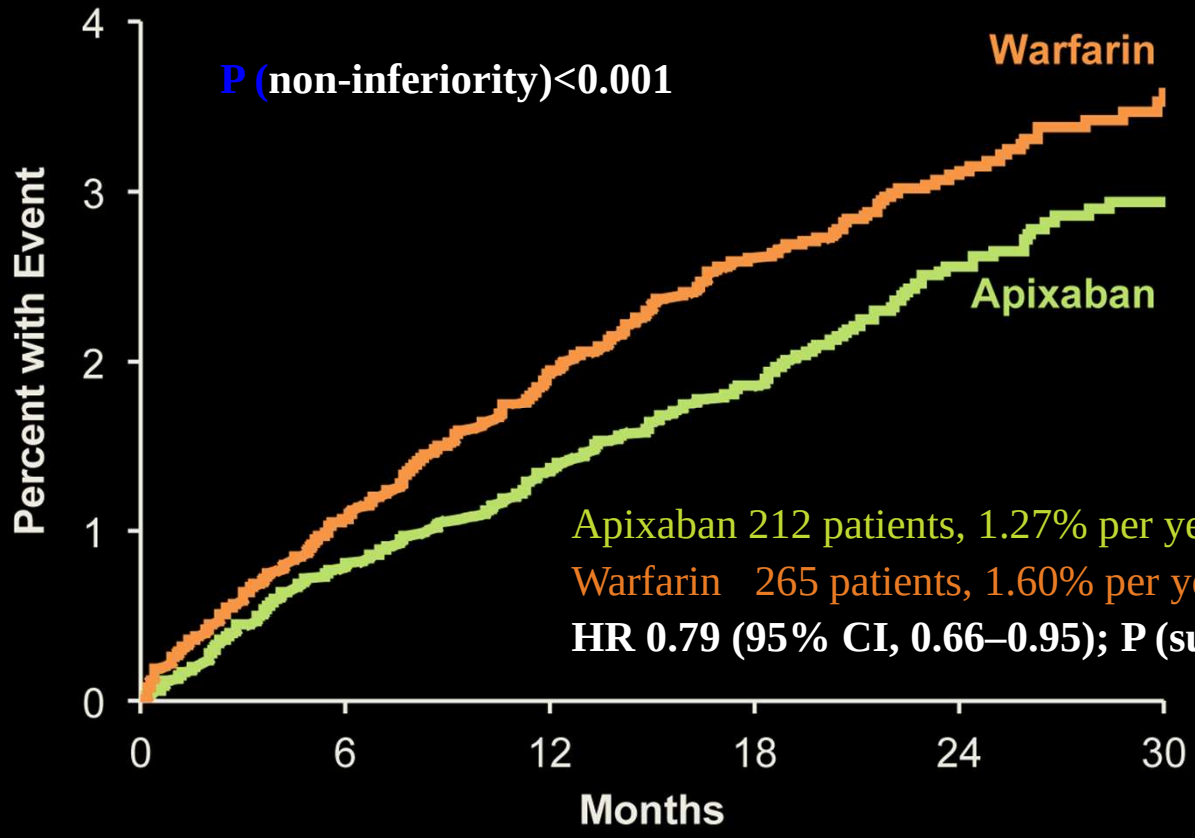
Hierarchical testing: non-inferiority for primary outcome, superiority for primary outcome, major bleeding, death

Conclusion
(Diapo Labo)

In patients with atrial fibrillation, apixaban is superior to warfarin at preventing stroke or systemic embolism, causes less bleeding, and results in lower mortality.

ARISTOTLE

Stroke (ischemic or hemorrhagic) or systemic embolism



21% RRR

Apixaban 212 patients, 1.27% per year

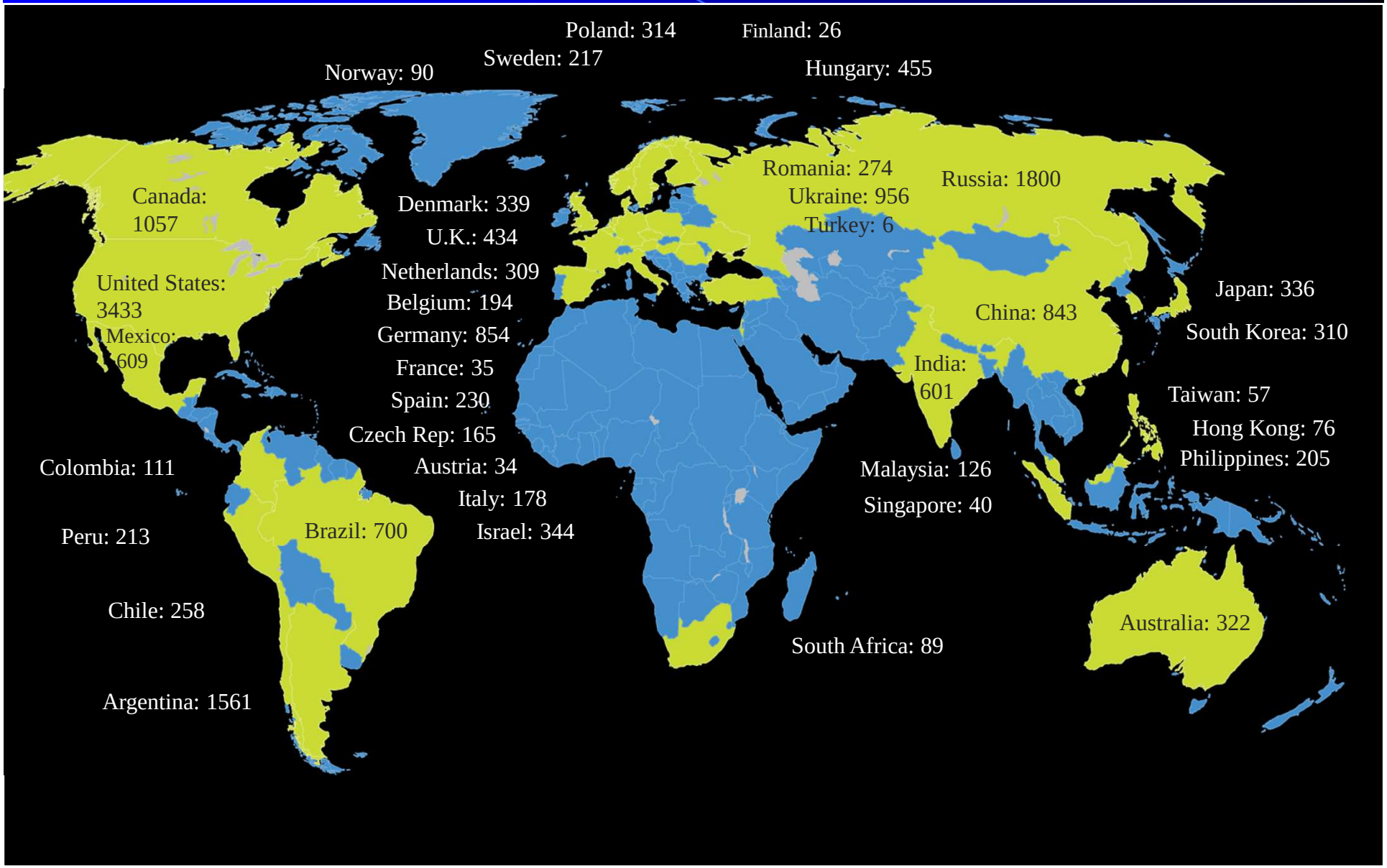
Warfarin 265 patients, 1.60% per year

HR 0.79 (95% CI, 0.66–0.95); P (superiority)=0.011

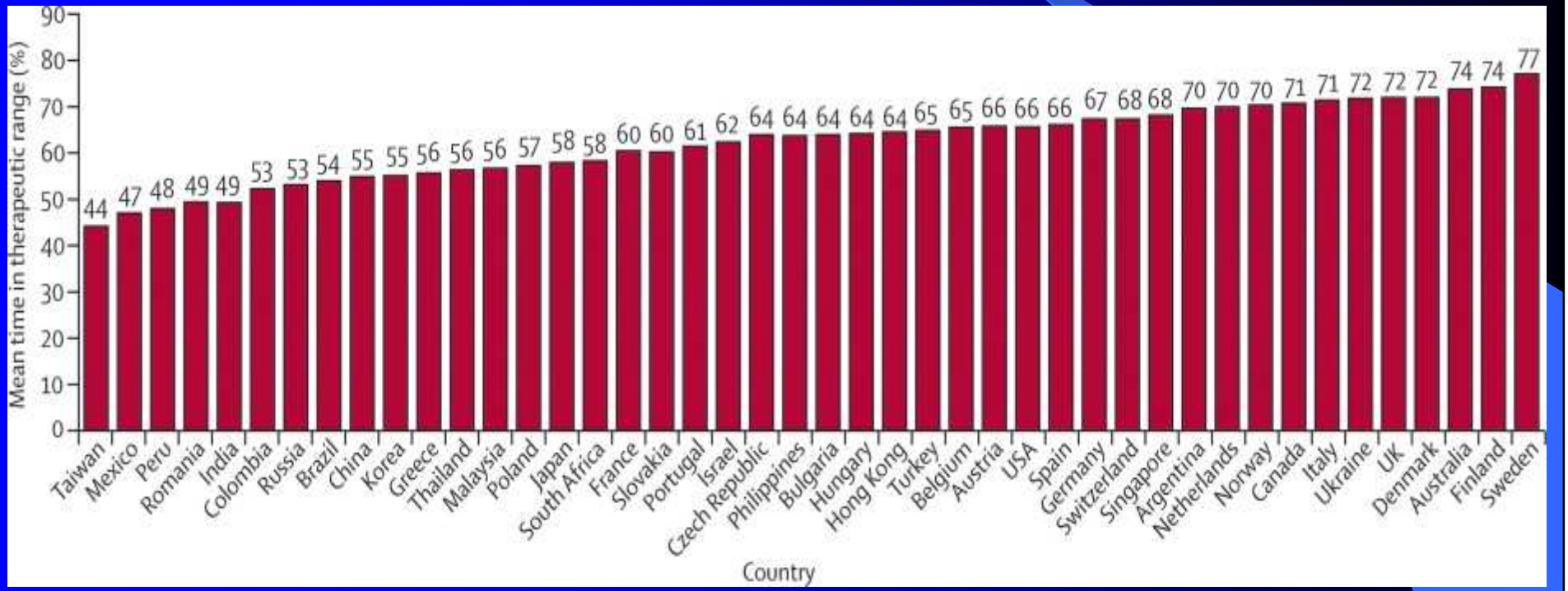
No. at Risk						
Apixaban	9120	8726	8440	6051	3464	1754
Warfarin	9081	8620	8301	5972	3405	1768

ARISTOTLE: Enrollment

18,201 patients, 1034 sites, 39 pays



ANTIVITAMINES K: Time in Therapeutic Range (TTR)

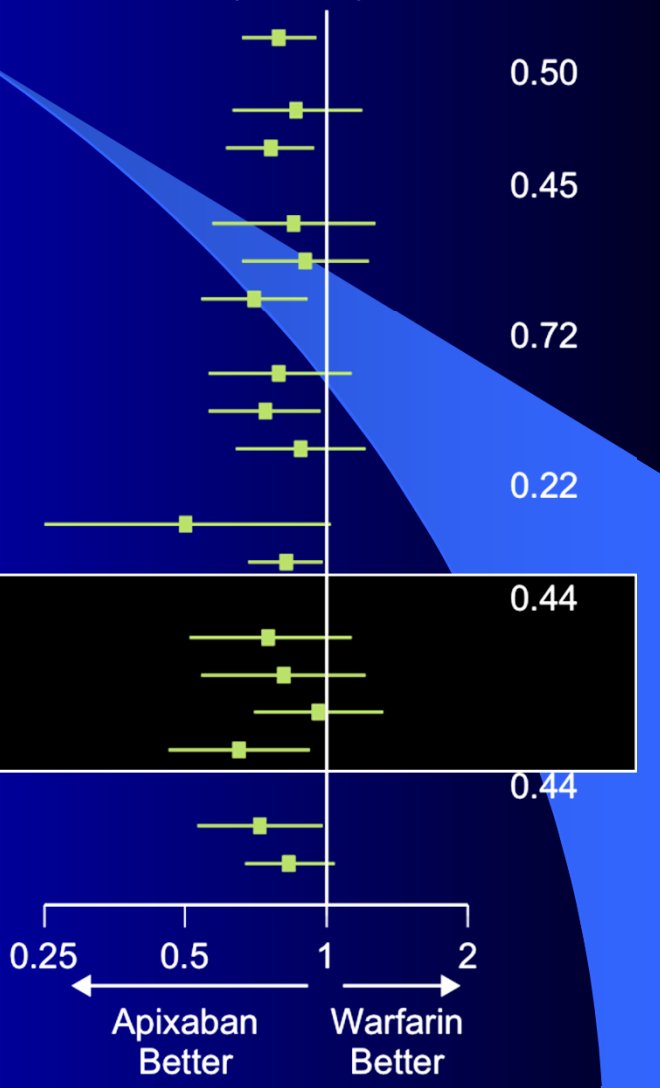


Wallentin et al. Lancet. 2010 Sep 18;376(9745):975-83

Subgroups for Stroke and Systemic Embolism

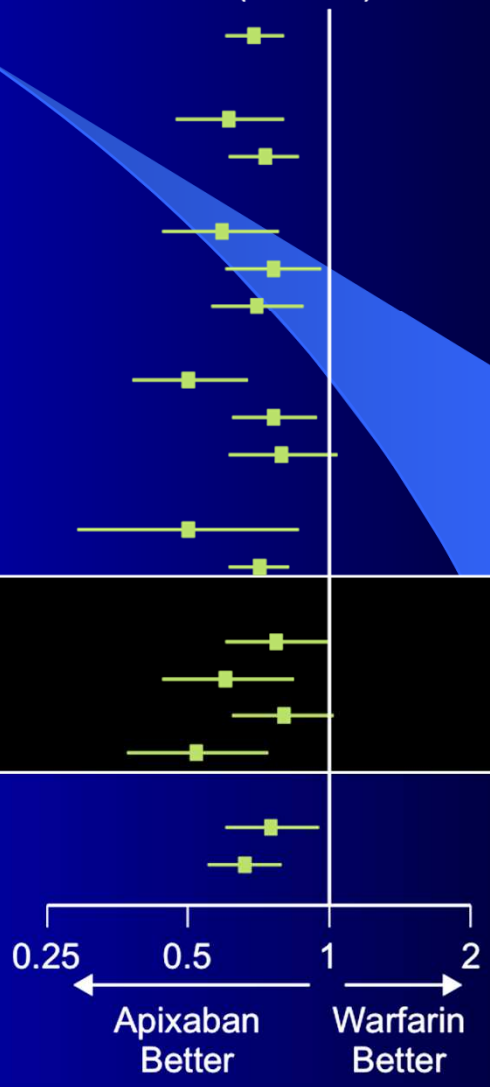
(2 of 2)

Characteristics	No. of Patients	Apixaban no. of events (%/yr)	Warfarin	P-value for Interaction
All Patients	18201	212 (1.27)	265 (1.60)	
Heart Failure				0.50
Yes	5541	70 (1.4)	79 (1.6)	
No	12660	142 (1.2)	186 (1.6)	
CHADs Score				0.45
≤ 1	6183	44 (0.7)	51 (0.9)	
=2	6516	74 (1.2)	82 (1.4)	
≥3	5502	94 (1.9)	132 (2.8)	
Level of Renal Impairment				0.72
Severe or Moderate	3017	54 (2.1)	69 (2.7)	
Mild	7587	87 (1.2)	116 (1.7)	
No impairment	7518	70 (1.0)	79 (1.1)	
Apixaban Dose				0.22
2.5 mg BID or placebo	831	12 (1.7)	22 (3.3)	
5 mg BID or placebo	17370	200 (1.3)	243 (1.5)	
Geographic Region				0.44
North America	4474	42 (1.0)	56 (1.3)	
Latin America	3468	43 (1.4)	52 (1.8)	
Europe	7343	75 (1.1)	77 (1.1)	
Asia/Pacific	2916	52 (2.0)	80 (3.1)	
Aspirin at Randomization				0.44
Yes	5632	70 (1.3)	94 (1.9)	
No	12569	142 (1.2)	171 (1.5)	



Subgroups for Major Bleeding
(2 of 2)

Characteristics	No. of Patients	Apixaban no. of events (%/yr)	Warfarin	P-value for Interaction
All Patients	18140	327 (2.13)	462 (3.09)	
Heart Failure				0.30
Yes	5527	87 (1.9)	137 (3.1)	
No	12613	240 (2.2)	325 (3.1)	
CHADs Score				0.40
≤ 1	6169	76 (1.4)	126 (2.3)	
=2	6492	125 (2.3)	163 (3.0)	
≥3	5479	126 (2.9)	173 (4.2)	
Level of Renal Impairment				0.03
Severe or Moderate	3005	73 (3.2)	142 (6.4)	
Mild	7565	157 (2.5)	199 (3.2)	
No impairment	7496	96 (1.5)	119 (1.8)	
Apixaban Dose				0.21
2.5 mg BID or placebo	826	20 (3.3)	37 (6.7)	
5 mg BID or placebo	17314	307 (2.1)	425 (3.0)	
Geographic Region				0.16
North America	4463	106 (2.8)	137 (3.6)	
Latin America	3460	60 (2.1)	94 (3.5)	
Europe	7313	110 (1.7)	135 (2.2)	
Asia/Pacific	2904	51 (2.1)	96 (4.1)	
Aspirin at Randomization				0.40
Yes	5608	129 (2.7)	164 (3.7)	
No	12532	198 (1.9)	298 (2.8)	



Methods

- The primary analyses were performed using Cox proportional hazards modeling with warfarin-naïve status and world region (North America, South America, Europe, Asia/Pacific) as strata.
- Efficacy analyses included all randomized patients (intention-to-treat) and included all events from randomization until the efficacy cutoff date (predefined as January 30, 2011).
- Bleeding analyses were **“on treatment”** including all randomized patients who received at least 1 dose of study drug and all events from initial receipt until 2 days after the last dose of study drug.

Du côté des essais cliniques

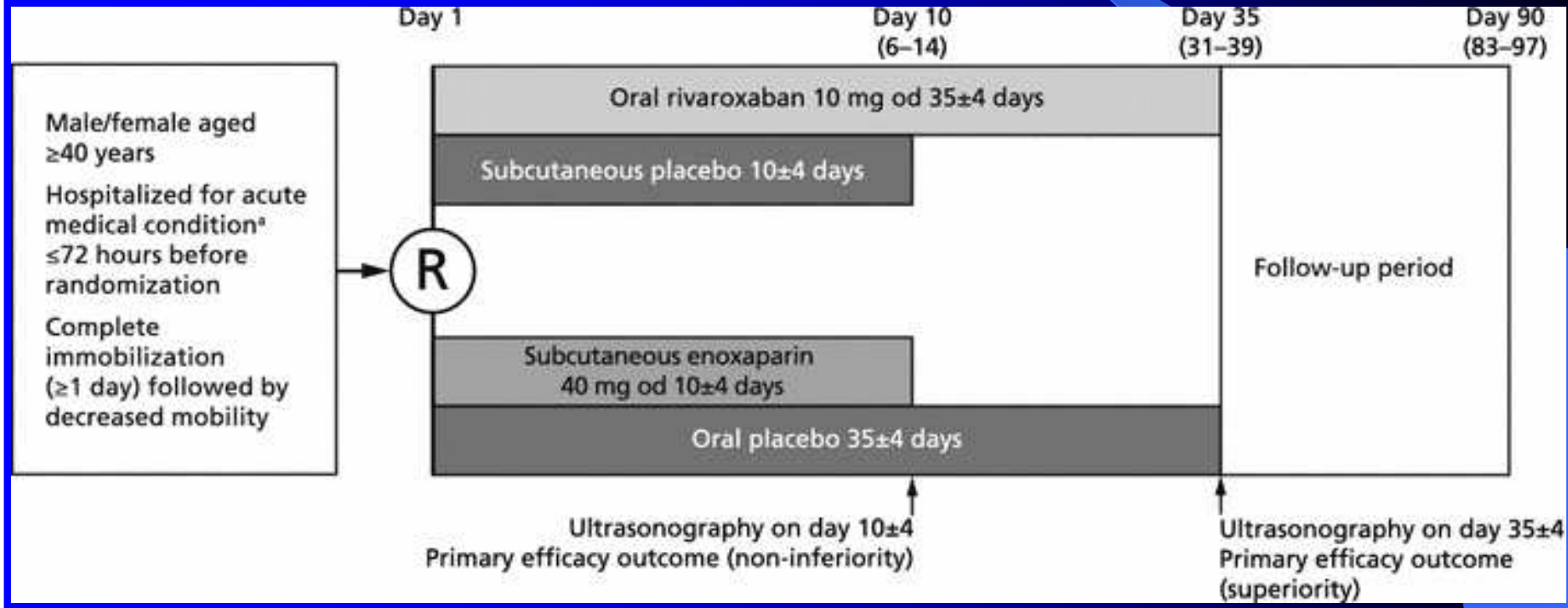
- Essai Aristotle:
  - Conclusion: non infériorité mais pas de supériorité dans la population en ITT (intention de traiter)
  - TTR = 62%

ARISTOTLE
Baseline Characteristics

Characteristic	Apixaban (n=9120)	Warfarin (n=9081)
Age, years, median (25th, 75th %ile)	70 (63, 76)	70 (63, 76)
Women, %	35	35
Region, %		
North America	25	25
Latin America	19	19
Europe	40	40
Asia/Pacific	16	16
Warfarin naïve, %	43	43
CHADS score, mean (+/- SD)	2.1 (+/- 1.1)	2.1 (+/- 1.1)
1, %	34	34
2, %	36	36
≥ 3, %	30	30

Où est passé MAGELLAN?

MAGELLAN


Day 1
Day 10 (6–14)
Day 35 (31–39)
Day 90 (83–97)
Male/female aged ≥40 years
Hospitalized for acute medical condition[a] ≤72 hours before randomization
Complete immobilization (≥1 day) followed by decreased mobility
R
Oral rivaroxaban 10 mg od 35±4 days
Subcutaneous placebo 10±4 days
Subcutaneous enoxaparin 40 mg od 10±4 days
Oral placebo 35±4 days
Follow-up period
Ultrasonography on day 10±4
Primary efficacy outcome (non-inferiority)
Ultrasonography on day 35±4
Primary efficacy outcome (superiority)

Où est passé MAGELLAN?

Mar Pollut Bull. 2012 Aug 19. pii: S0025-326X(12)00356-6. doi: 10.1016/j.marpolbul.2012.07.035. [Epub ahead of print]

Persistent organic pollutants in juvenile Magellan penguins (Spheniscus magellanicus) found on the northern shore of the state of São Paulo and southern shore of the state of Rio de Janeiro, Brazil.

Baldassin P, Taniguchi S, Gallo H, Silva RJ, Montone RC.

Source

Laboratório de Química Orgânica Marinha, IO-USP, Praça do Oceanográfico, 191, São Paulo, SP, CEP 05508-900, Brazil; Instituto Argonauta para a Conservação Costeira e Marinha, Rua Guarani, 835, Ubatuba, SP, CEP 11680-000, Brazil. Electronic address: pauletsbj@gmail.com.

Où est passé MAGELLAN?

Critère principal de jugement: TVP

- J10:
  - Rivaroxaban : 78 (2,7%)
  - Enoxaparine/Placebo: 82 (2,7%)
- J35:
  - Rivaroxaban 131 (4,4%)
  - Enox /Placebo: 175 (5,7%) p =0,02

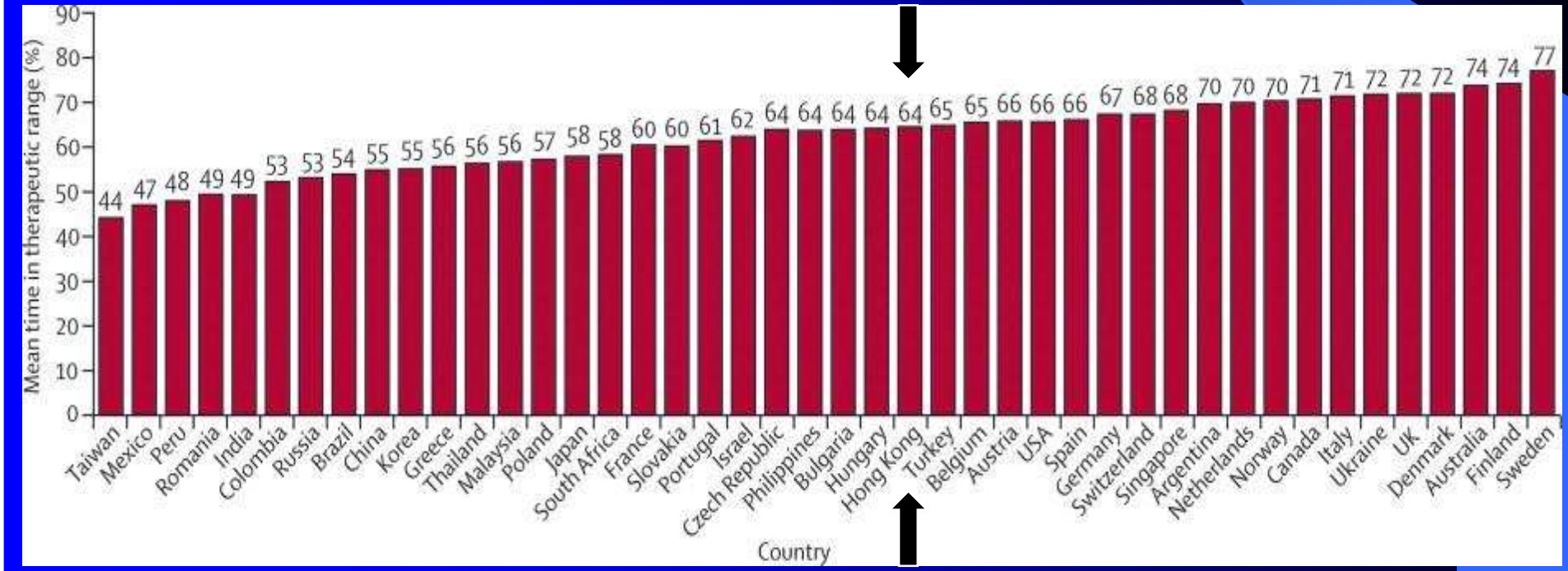
Où est passé MAGELLAN?

Hémorragies

- J10
  - Rivaroxaban: 111 (2,8%)
  - Enox/Placebo: 49 (1,2%) p<00001
- J35
  - Rivaroxaban ; 164 (4,1%)
  - Enox /Placebo: 67 (1,7%) p<0,0001

NACO:
Font-ils mieux que les AVK?

OUI → **NON**



Les NACO font-ils mieux que les AVK?

- Plus efficaces? NON
- Moins dangereux? NON
- Plus pratiques? OUI

Telles sont mes convictions, et si vous ne les aimez pas, j'en ai d'autres