Nouveaux AntiCoagulants par voie Orale (NACO) ou Anticoagulant Oraux Directs (AOD) : Prévention et traitement curatif de la MTEV

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Nabeul; TUNISIE

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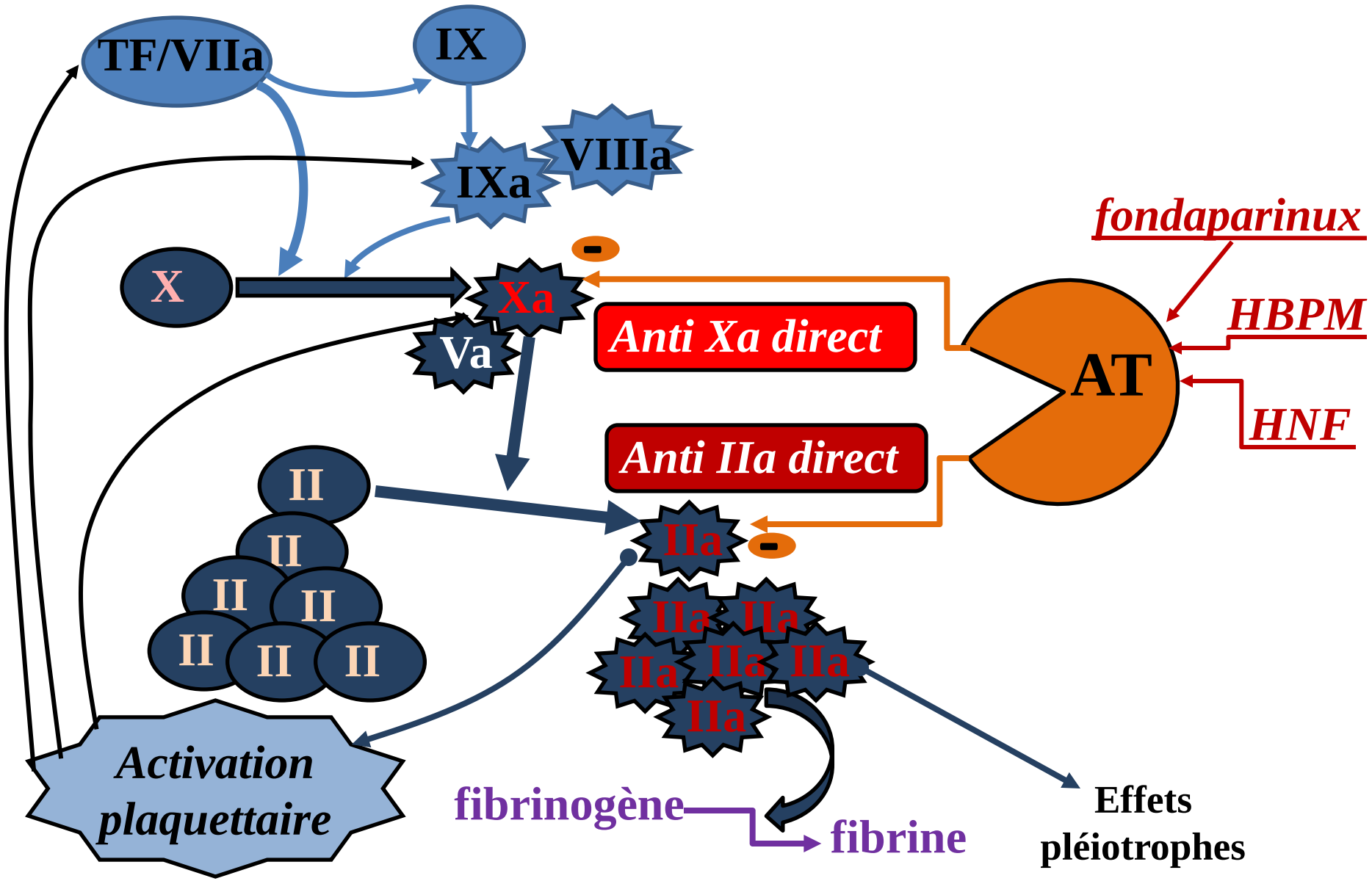
Hammamet 28 mai 2016

Hémostase - Anticoagulants



Anticoagulants Oraux Directs (AOD)

Anti IIa direct

Gatrans

- ximelagatran
- Dabigatrans (PRADAXA)®

Anti Xa direct

Xabans

- **Rivaroxaban** (XARELTO)®
- **Apixaban** (ELIQUIST)®
- Edoxaban (SAVAYSA)®

Anticoagulants Oraux Directs (AOD)

Anti IIa direct	*Anti Xa direct*	
Dabigatrans (PRADAXA)®	**Rivaroxaban** (XARELTO)®	**Apixaban** (ELIQUIST)®
Petites molécules (faible masse moléculaire)		
628 Da (471)	**436 Da**	**460 Da**
➤SYNTHESE CHIMIQUE: facile, reproductible et peu cher ➤ Passage placentaire et dans le lait maternel +++ CI femme enceinte et allaitante ➤ Action sur les facteurs activés (IIa ou Xa) libres et fixés		
Inhibe directement le facteur IIa libre et lié à la fibrine	Inhibe directement le facteur Xa libre et lié au complexe prothrombinase	
Prodrogue : dabigatran Etexilate		
Délais d'action: rapide, dépendant de l'absorption		

Pharmacocinétique des AOD

❶ Absorption - Distribution

	Anti IIa direct	***Anti Xa direct***	
	Dabigatrans (PRADAXA)®	**Rivaroxaban** (XARELTO)®	**Apixaban** (ELIQUIST)®
biodisponibilité	***4 - 7 %***	***80 %***	***60 %***
délai d'action	2 h	2 à 4 h	2 h
fixation protéique	***35%***	***95%***	***90%***
transporteur	P-glycoprotéine (P-gp)	P-glycoprotéine (P-gp)	P-glycoprotéine (P-gp)

Inducteurs de la P-gp

Rifampicine
Millepertuis
Carbamazépine

Inhibiteurs de la P-gp

Quinidine
Amiodarone
Vérapamil
Ritonavir
Clarithromicyne

Substrats de la P-gp

Kétoconazole

Pharmacocinétique des AOD

❷ Élimination

	Anti IIa direct	*Anti Xa direct*	
	Dabigatrans (PRADAXA)®	**Rivaroxaban** (XARELTO)®	**Apixaban** (ELIQUIST)®
Elimination rénale	***80 %***	***33 %***	***25 %***
↘ dose	30< Cl creat <50	15< Cl creat <50	15< Cl creat <50
CI	Cl creat < 30	Cl creat < 15	Cl creat < 15
transporteur	(P-gp)	(P-gp)	(P-gp)
Elimination hépatique		++ ***(CYP 3A4)***	++ ***(CYP 3A4)***

Inducteurs du CYP 3A4

Rifampicine
Carbamazépine

Inhibiteurs du CYP 3A4

Ketoconazole
Ritonavir
Clarithromicyne

Pharmacocinétique des AOD

❸ Demi-vie ($T_{1/2}$)

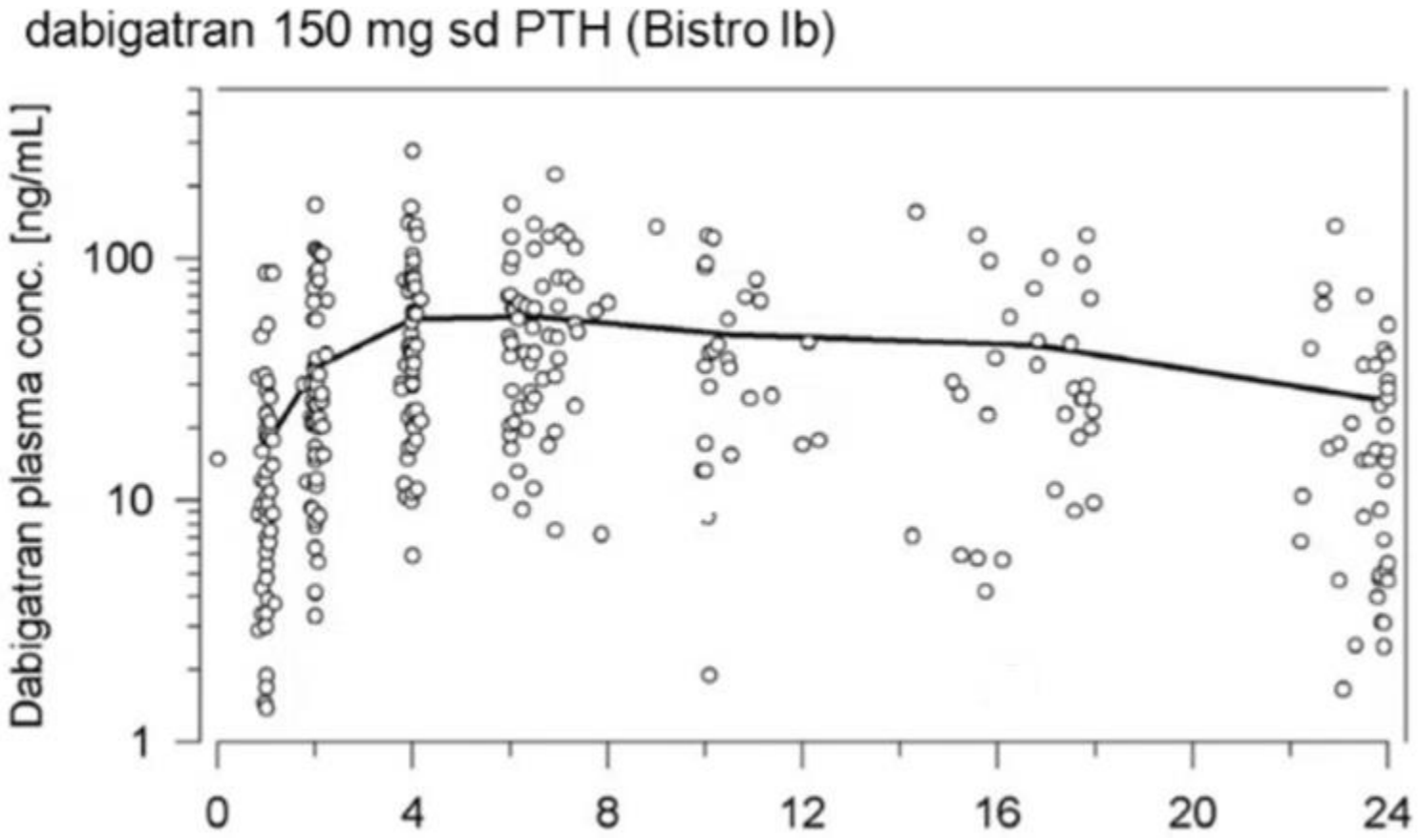
	Anti IIa direct	*Anti Xa direct*	
	Dabigatrans (PRADAXA)®	**Rivaroxaban** (XARELTO)®	**Apixaban** (ELIQUIST)®
T1/2	***12 – 17 h***	***9 – 13 h***	***9 – 14 h***
administration	***2 prises / j***	***1 prises / j***	***2 prises / j***
Elimination	***•2 T1/2 : 75 % • 3.5 T1/2: >90 % • 5 T1/2: > 95 %***		

- Variabilité intra et inter individuelle +
- Coefficient de variabilité (CV) : 30 à 50 %

  Âge; IR

  Interaction médicamenteuse

Variabilité de la Pharmacocinétique des AOD



Stangier 2005

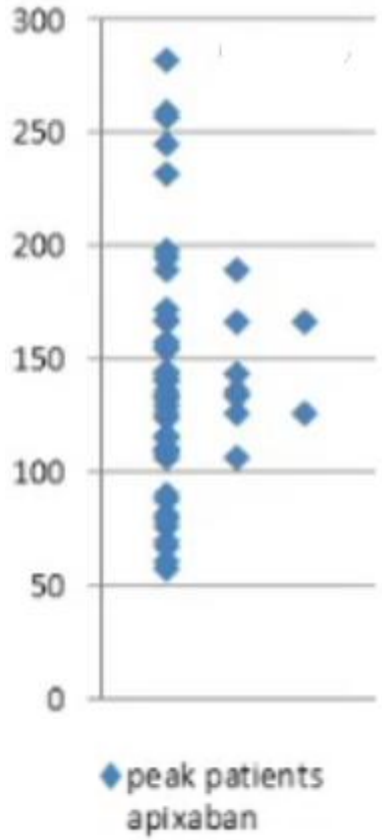
CV (%) de la concentration plasmatique de dabigatran, 12 h après 150 mg:
PETRO-EX: 91 %, RELY: 81 % , BISTRO II: 87 %

Variabilité de la Pharmacocinétique des AOD

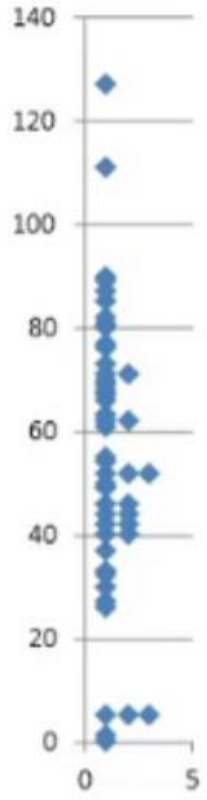
Apixaban treated patients
Total Hip Replacement
TGT and anti-Xa levels

Unpublished data

MM SAMAMA



Peak



Anti-Xa activity

Variabilité de la Pharmacocinétique des AOD

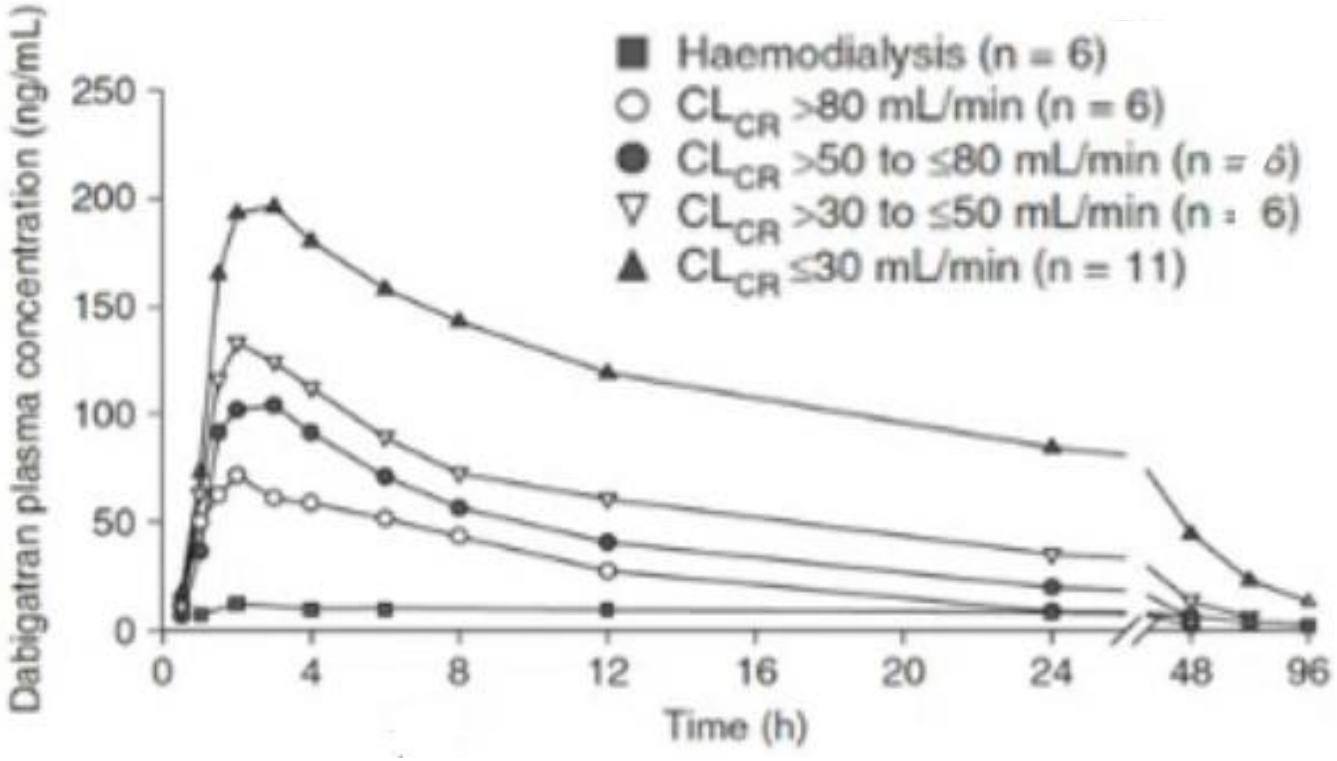
Clin Pharmacokinet 2010; 49 (4): 259-268

Influence of Renal Impairment on the Pharmacokinetics and Pharmacodynamics of Oral Dabigatran Etexilate

An Open-Label, Parallel-Group, Single-Centre Study

Joachim Stangier,[1] *Karin Rathgen,*[1] *Hildegard Stähle*[1] and *Dago Mazur*[2]

Dabigatran
150 mg x1 PO

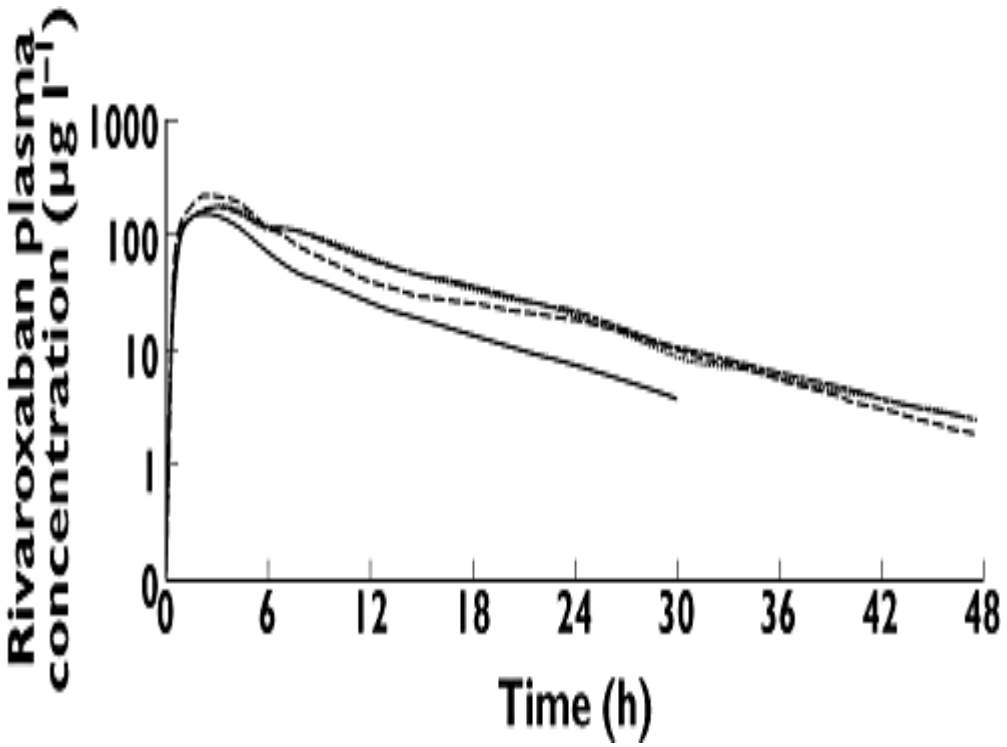


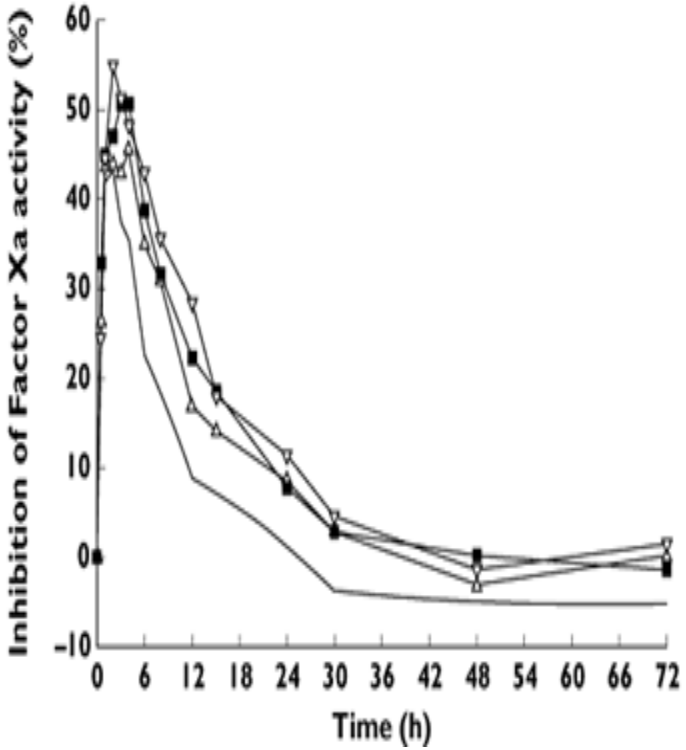
Variabilité de la Pharmacocinétique des AOD

BJCP British Journal of Clinical Pharmacology

Volume 70, Issue 5, pages 703–712, November 2010

Effects of renal impairment on the pharmacokinetics, pharmacodynamics and safety of rivaroxaban, an oral, direct Factor Xa inhibitor





Développement des AOD

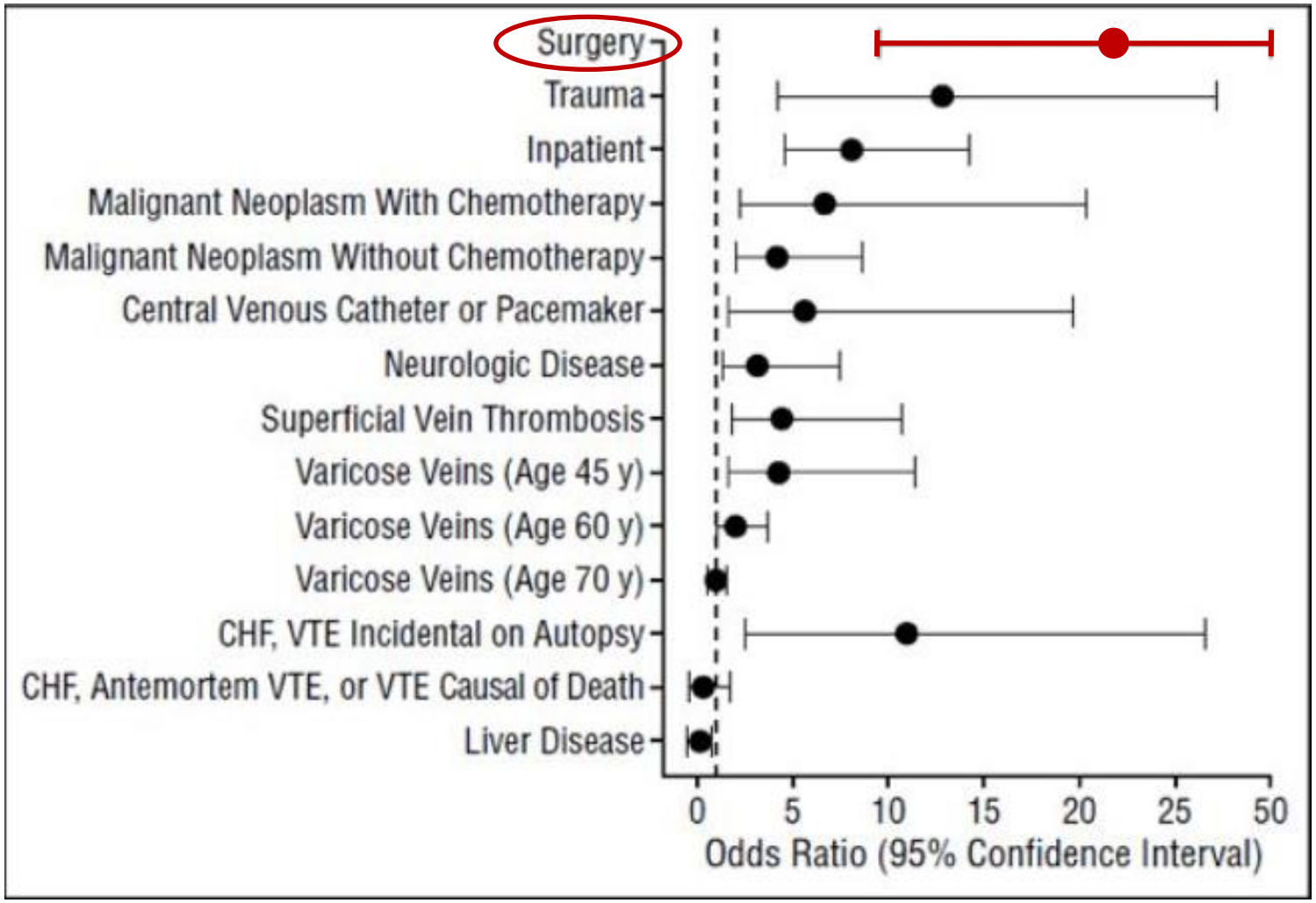
☝ **Traitement préventif**

- En milieux chirurgical (PTH, PTG)
- En milieux médical

✌ Traitement curatif

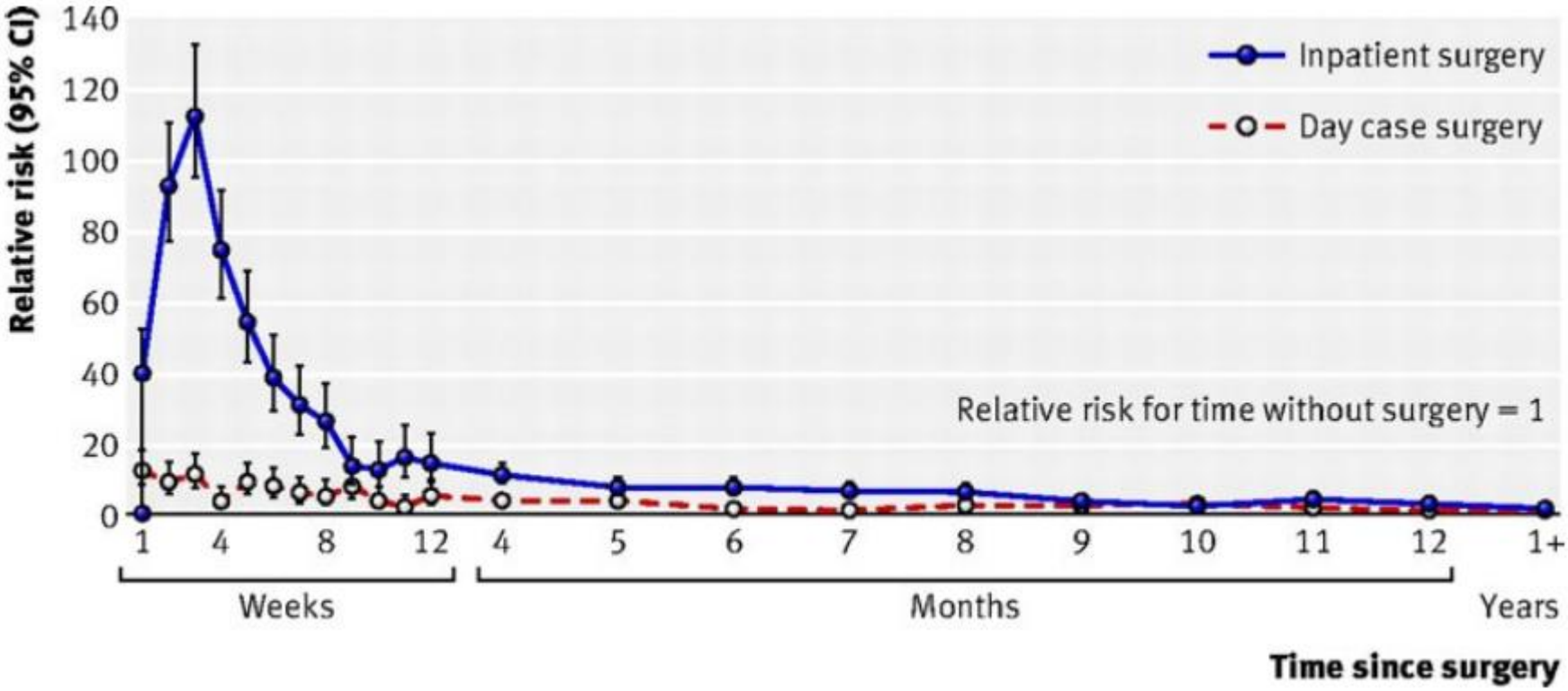
- MTEV (TVP et EP)
- FA (non valvulaire)
- Σd coronarien aiguë

Maladie Thromboembolique
Réalités



John A. Heeit,; rch Intern Med. 2000, 160 : 809-15

Maladie Thromboembolique
Réalités



Sweethland S. B.M.J. 2009, 339 : b4583

Maladie Thromboembolique
Réalités

PTH ; PTG

Risque Thrombotique +++ → EFFICACITÉ des anticoagulants

Risque Hémorragique +++ → SÉCURITÉ des anticoagulants

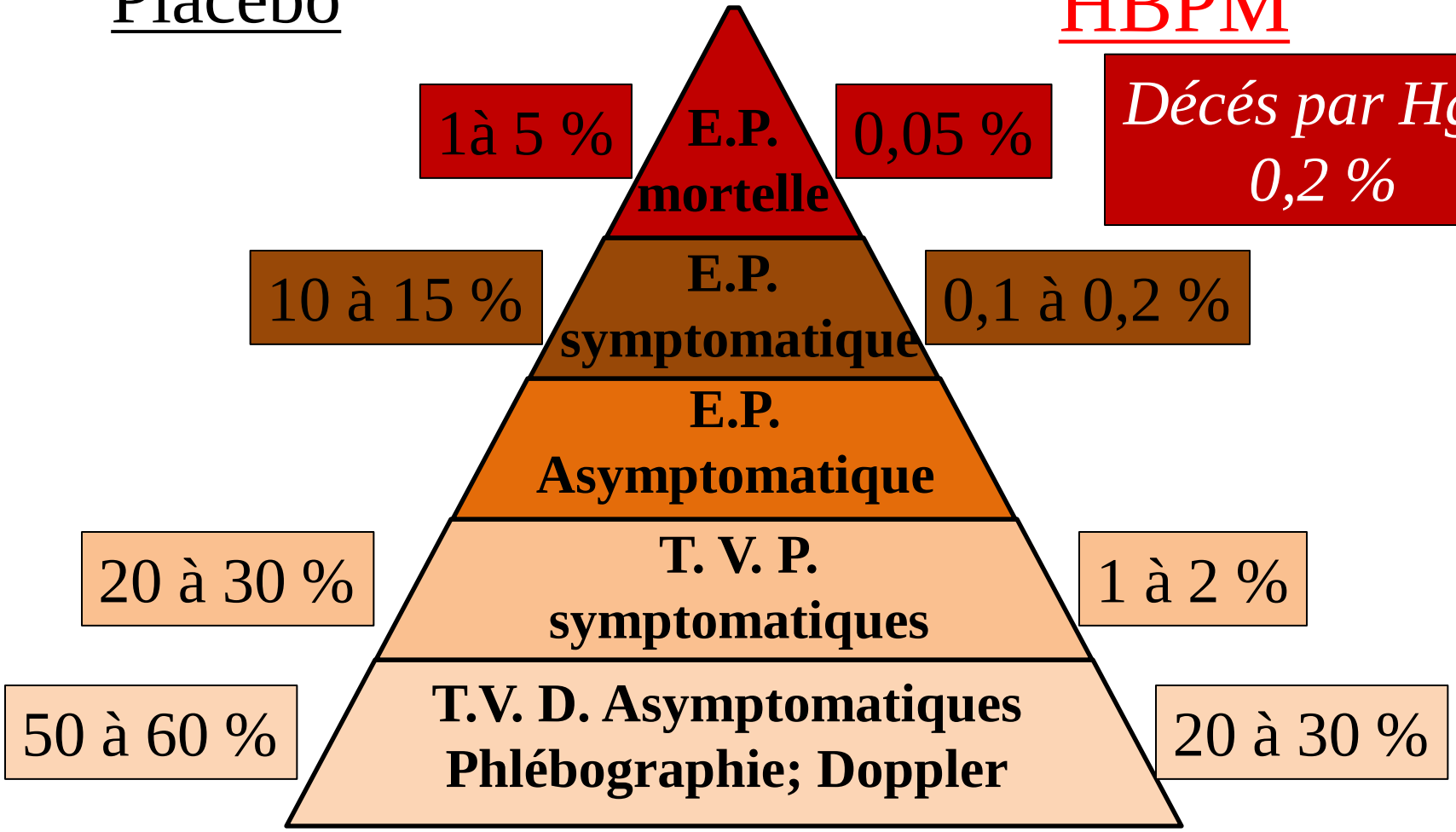
Terrain
- Age (> 65 ans)
- Obésité
- Thrombolphilie, ATCDS de MTE
- Kc et son traitement
- Immobilité et alitement
- compression veineuse

Maladie Thromboembolique
Réalités (PTH ; PTG)

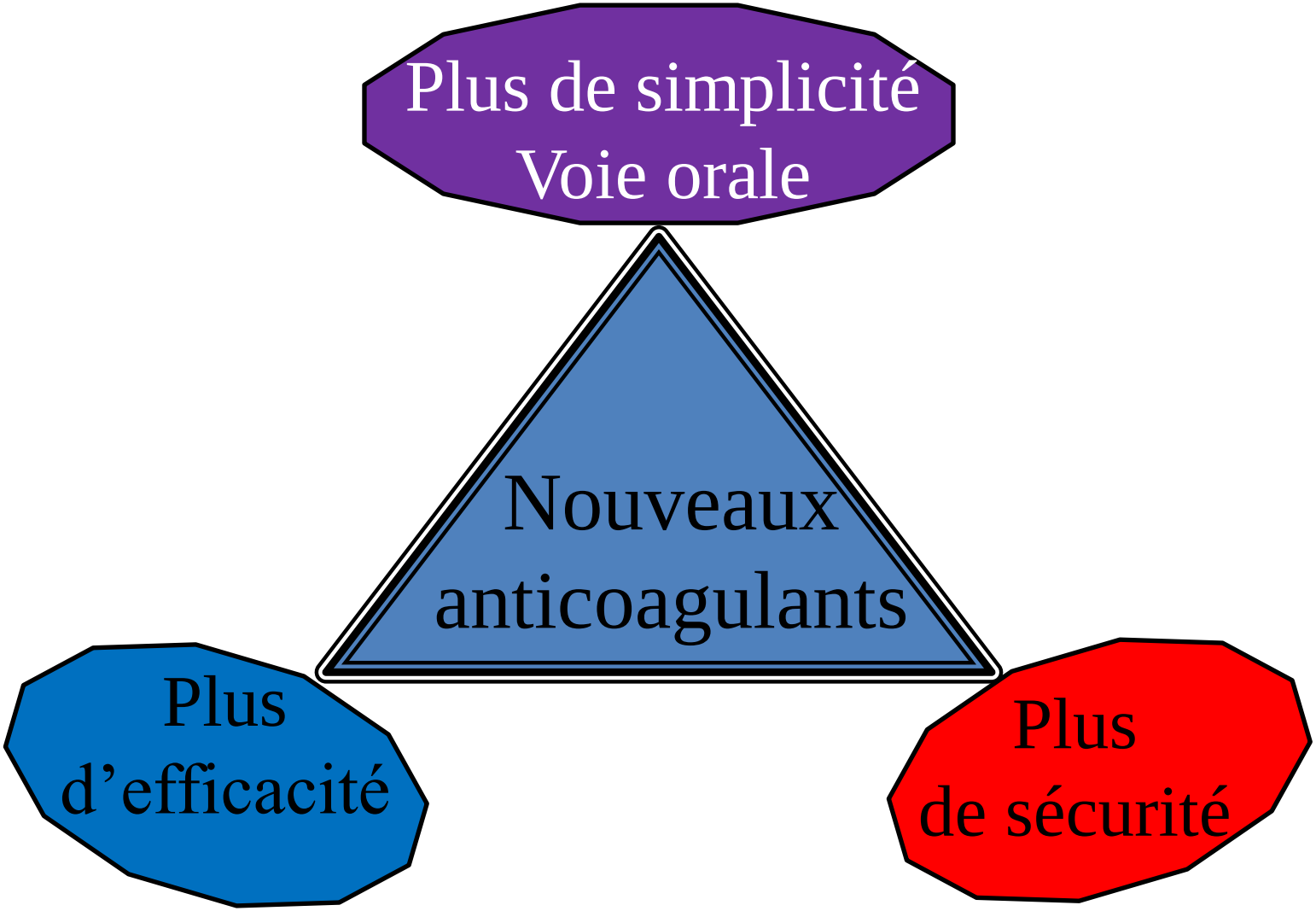
Placébo

HBPM

Décés par Hgie
0,2 %



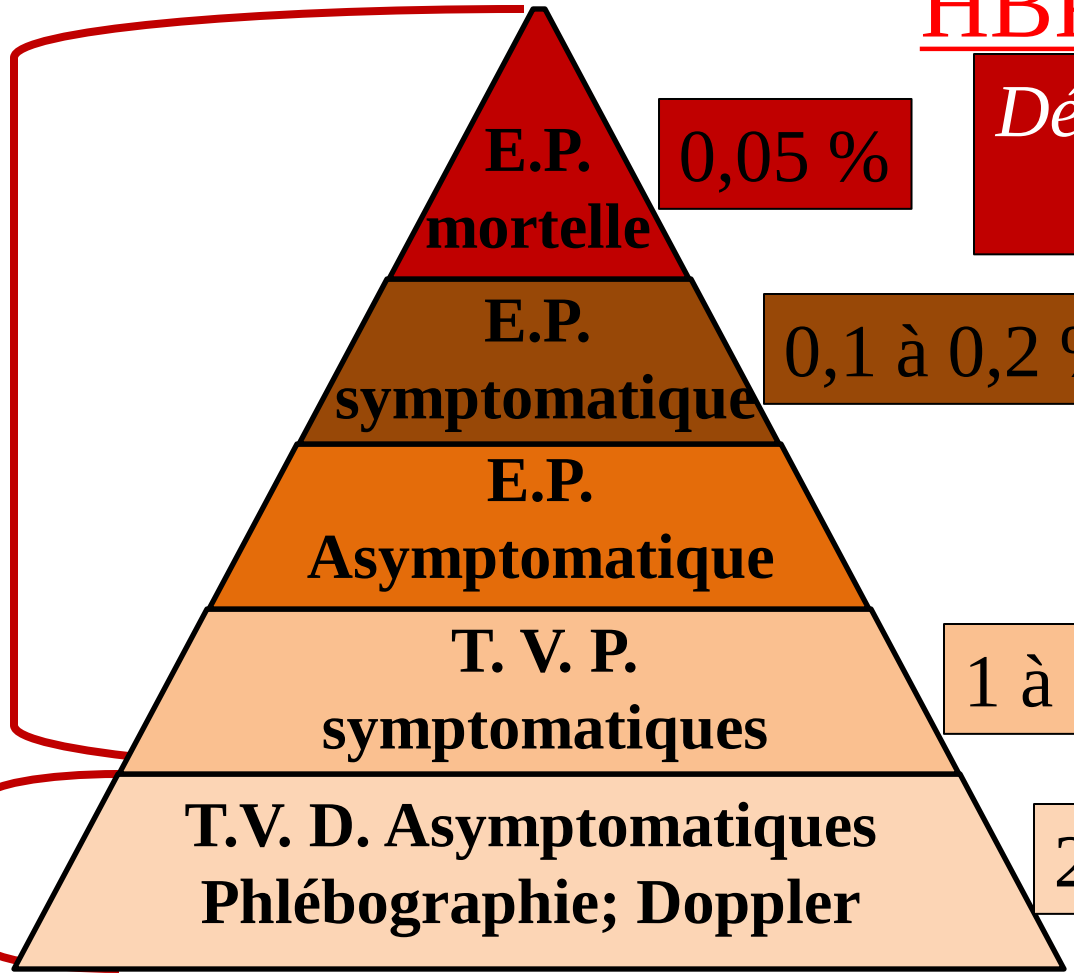
Maladie Thromboembolique
Perspectives (PTH ; PTG)



Maladie Thromboembolique
Perspectives (PTH ; PTG)

HBPM

Décés par Hgie
0,2 %



Essais Ψ 3

Essais Ψ 2

journal of thrombosis and haemostasis™

J Thromb Haemost 2007; 5: 1438–43.

Association between asymptomatic deep vein thrombosis detected by venography and symptomatic venous thromboembolism in patients undergoing elective hip or knee surgery

D. J. QUINLAN,* J. W. EIKELBOOM,† O. E. DAHL,‡ B. I. ERIKSSON,§ P. S. SIDHU* and J. HIRSH†

*Department of Radiology, King's College Hospital, London, UK; †Thrombosis Service, McMaster University, ON, Canada; ‡International Surgical Thrombosis Forum, Thrombosis Research Institute, London, UK; and §Department of Orthopaedic Surgery, Sahlgrenska University Hospital/Östra, Göteborg, Sweden

Exploration between **asymptomatic DVT and symptomatic venous thromboembolism** (VTE) in patients undergoing total hip replacement (THR) or TKR treated with standart doses of enoxaparine (30 mg bid or 40 mg od) by comparing the incidence of asymptomatic DVT in venographic studies with the incidence of symptomatic VTE in studies where venography was not performed.

Association between asymptomatic deep vein thrombosis detected by venography and symptomatic venous thromboembolism in patients undergoing elective hip or knee surgery

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J Thromb Haemost 2007; 5: 1438–43.

1 - Influence of the adjudication center

Table 2 Comparison of asymptomatic deep vein thrombosis (DVT) rates according to venogram reading committees

	Total hip replacement			Total knee replacement		
Reading committee	Total DVT % (95% CI)	Proximal DVT % (95% CI)	Distal DVT % (95% CI)	Total DVT % (95% CI)	Proximal DVT % (95% CI)	Distal DVT % (95% CI)
All	13.2 (12.2–14.2)	3.0 (2.5–3.5)	10.0 (9.2–10.9)	38.1 (35.5–40.8)	5.7 (4.4–7.0)	32.2 (29.7–34.8)
McMaster	8.7 (7.4–10.0)	1.7 (1.1–2.3)	7.1 (5.9–8.2)	27.2 (22.6–31.7)	5.4 (3.1–7.7)	21.3 (17.1–25.5)
Gothenburg	19.5 (18.0–21.0)*	5.8 (5.0–6.7)	13.9 (12.6–15.2)	42.7 (39.4–46.0)	5.6 (4.0–7.1)	37.9 (34.7–41.1)
Absolute difference (%)†	10.9	4.1	6.8	15.6	0.2	16.6
Relative difference (%)†	125‡	239§	97	57‡	3	78

*P for heterogeneity 0.0004; †between the two reading committees; ‡P for heterogeneity < 0.0001; §P for heterogeneity 0.0012. CI, confidence interval.

Asymptomatic DVT

	PTH	PTG
Mc Master center	8.7 %	27.2 %
Gothenburg center	19.5 %	42.7 %

Association between asymptomatic deep vein thrombosis detected by venography and symptomatic venous thromboembolism in patients undergoing elective hip or knee surgery

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J Thromb Haemost 2007; 5: 1438–43.

2 – No parallel between asymptomatic DVT and symptomatic VTE

Asymptomatic DVT 10 veinographic studies 5796 patients	Symptomatic VTE no veinography; 2 studies 3500 patients
PTH : 13.2 %	**PTH : 2.7 %**
PTG : 38.1 %	PTG : 1.8 %

Prévention de la maladie Thromboembolique
Dabigatran après PTH; PTG

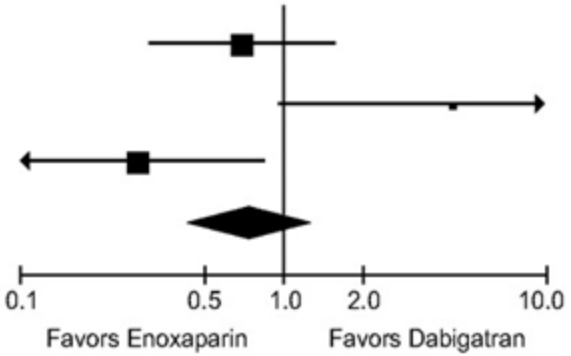
Étude (indication; N)	Compa-rateur	efficacité		Saignement Majeurs	
RE-NOVATE (PTH; 3463)	Enoxa 40 mg	Dabid.150mg : 8.6%	**6.7 %**	Dabid.150mg : 1.3%	**1.6 %**
		Dabid.220mg : 6%		Dabid.220mg : 2%	
RE-MODEL (PTG; 2076)	Enoxa 40 mg	Dabid.150mg : 40.5%	**37.7 %**	Dabid.150mg : 1.3%	**1.3 %**
		Dabid.220mg : 36.4%		Dabid.220mg : 1.5%	
RE-MOBILIZE (PTG; 2596)	Enoxa 30 mg ×2	Dabid.150mg : 33.7%	**25.3 %**	Dabid.150mg : 0.6 %	**1.4 %**
		Dabid.220mg : 31.3%		Dabid.220mg : 0.6 %	

Caprini JA; ISTH in Genova Switzerland, Abstract #O-W-050
Friedman RJ : Thromb. Res. 2010; 126: 175-82
RE-NOVATE : The Lancet 2007; 370: 949
RE-MODEL : journal of thrombosis and haemostasis 2007; 5: 2178-85

Prévention de la maladie Thromboembolique
Dabigatran après PTH; PTG

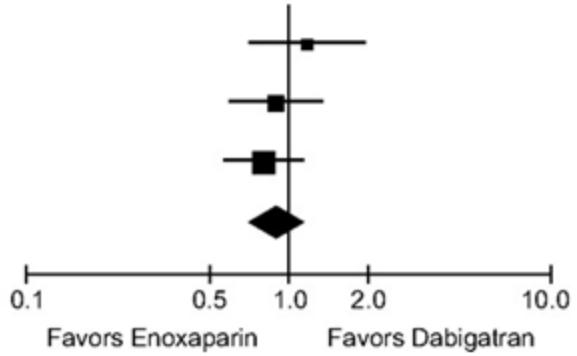
Trial	n/N (%) Enoxaparin	Dabigatran	OR (95% CI)
RE-MOBILIZE	10/868 (1.2)	14/857 (1.6)	0.70 (0.31 - 1.59)
RE-MODEL	9/685 (1.3)	2/675 (0.3)	4·48 (0.96 - 20.81)
RE-NOVATE	4/1142 (0·4)	14/1137 (1.2)	0.28 (0.09 - 0.86)
Total	**23/2695 (0.9)**	**30/2669 (1.1)**	**0.76 (0.44 - 1.31)**

Test for heterogeneity: $I^2 = 76\%$, $P = .02$
Test for overall effect: $P = .32$



Trial	n/N (%) Enoxaparin	Dabigatran	OR (95% CI)
RE-MOBILIZE	33/868 (3.8)	28/857 (3.3)	1.17 (0.70 - 1.95)
RE-MODEL	46/694 (6.6)	50/679 (7.4)	0.89 (0.59 - 1.35)
RE-NOVATE	58/1154 (5.0)	71/1146 (6.2)	0.80 (0.56 - 1.14)
Total	**137/2716 (5.0)**	**149/2682 (5.6)**	**0.90 (0.71 - 1.15)**

Test for heterogeneity: $I^2 = 0\%$, $P = .49$
Test for overall effect: $P = .40$



RE-NOVATE : The Lancet 2007; 370: 949
RE-MODEL : journal of thrombosis and haemostasis 2007; 5: 2178-85
Menno V. Huissman: Circ Cardiovasc Qual Outcomes 2011; 3: 652-60

Prévention de la maladie Thromboembolique **Rivaroxaban** après PTH; PTG

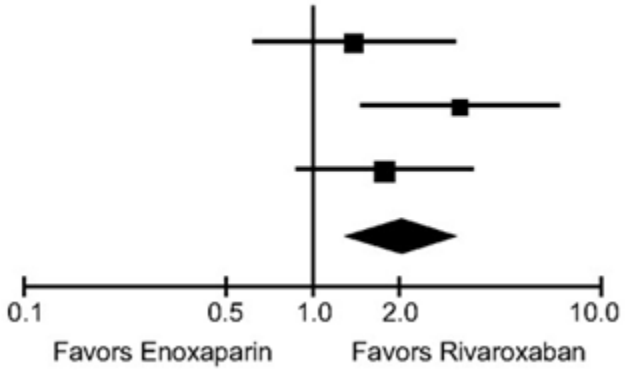
Étude (indication; N)	Compa-rateur	Efficacité Enoxa vs **Rivaroxaban 10 mg**	Saignement majeur Enoxa vs **Rivaroxaban 10 mg**
RECORD 1 (PTH; 2076)	Enoxa 40 mg	**3.7 vs 1.1 %**	**0.1 vs 0.3 %**
RECORD 2 (PTH; 2596)	Enoxa 40 mg	**9.3 vs 2.0 %**	**< 0.1 %**
RECORD 3 (PTG; 3463)	Enoxa 40 mg	**18.9 vs 9.6 %**	**0.5 vs 0.6 %**
RECORD 4 (PTG; 2055)	Enoxa 30mg ×2	**10.1 vs 6.9 %**	**0.3 vs 0.7 %**

RECORD 1 à 4 : Drugs 2009; 69: 1829-51
RECORD 1 : N Engl J Med 2008; 358: 2765-75
RECORD 3 : N Engl J Med 2008; 358: 2776-86

Prévention de la maladie Thromboembolique **Rivaroxaban** après PTH; PTG

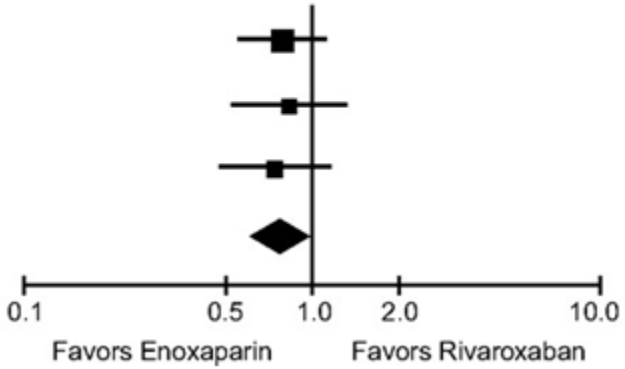
Trial	n/N (%) Enoxaparin	Rivaroxaban	OR (95% CI)
RECORD1	14/2206 (0.6)	10/2193 (0.5)	1.39 (0.62 - 3.15)
RECORD3	26/1217 (2.1)	8/1201 (0.7)	3.26 (1.47 - 7.22)
RECORD4	21/1508 (1.4)	12/1526 (0.8)	1.78 (0.87 - 3.63)
Total	**61/4931 (1.2)**	**30/4920 (0.6)**	**2.04 (1.32 - 3.17)**

Test for heterogeneity: $I^2 = 13\%$, $P = .32$
Test for overall effect: $P = .001$



Trial	n/N (%) Enoxaparin	Rivaroxaban	OR (95% CI)
RECORD1	56/2224 (2.5)	70/2209 (3.2)	0.79 (0.55 - 1.13)
RECORD3	34/1239 (2.7)	40/1220 (3.3)	0.83 (0.52 - 1.32)
RECORD4	34/1508 (2.3)	46/1526 (3.0)	0.74 (0.47 - 1.16)
Total	**124/4971 (2.5)**	**156/4955 (3.1)**	**0.79 (0.62 - 0.99)**

Test for heterogeneity: $I^2 = 0\%$, $P = .94$
Test for overall effect: $P = .049$



RECORD 1 : N Engl J Med 2008; 358: 2765-75; RECORD 3 : N Engl J Med 2008; 358: 2776-86
RECORD 1 à 4 : Drugs 2009; 69: 1829-51
Menno V. Huissman: Circ Cardiovasc Qual Outcomes 2011; 3: 652-60

Prévention de la maladie Thromboembolique **Apixaban** après PTH; PTG

Étude (indication; N)	Compa-rateur	Efficacité Enoxa vs Apixaban 2,5 mg×2	Saignement majeur Enox vs Apixaban 2,5 mg×2
ADVANCE 1 (PTG; 2287)	Enoxa 30mg × 2	**8.8 vs 9%**	
ADVANCE 2 (PTG; 1973)	Enoxa 40 mg	**24.3 vs 15.06 %**	**4.8 vs 3.5 %**
ADVANCE 3 (PTH; 3866)	Enoxa 40 mg	**3.9 vs 1.4 %**	**4.5 vs 4.1%**

ADVANCE 1 : N Engl J Med 2009; 361: 594-60
ADVANCE 2 :The Lancet 2010; 375: 807-15
ADVANCE 3 N Engl J Med 2010; 363: 2487-98

Prévention de la maladie Thromboembolique ADO (PTH; PTG)

Molécule	Prévention Orthopédie (PTH , PTG)		
	Dose	Efficacité	Risque Hémor.
Dabigatran PRADAXA®	**220 mg**	=	=
Rivaroxaban XARELTO®	**10 mg**	↗	=
Apixaban ELIQUIST®	**2,5 mg × 2**	↗	↘

Développement des AOD

☝ **Traitement préventif**

- En milieux chirurgical (PTH, PTG)
- En milieux médical

✌ Traitement curatif

- TVP et EP
- FA (non valvulaire)
- Σd coronarien aiguë

Prévention de la maladie Thromboembolique
AOD en milieux médical, soins intensifs

Molécule	Prévention en milieux médical		
	Dose	Efficacité	Risque Hémor.
Rivaroxaban XARELTO®	**10 mg** ***MAGELLAN***	=	↗
Apixaban ELIQUIST®	**2,5 mg × 2** ***ADOPT***	=	↗

MAGELLAN : N Engl J Med 2013; 368: 513-23

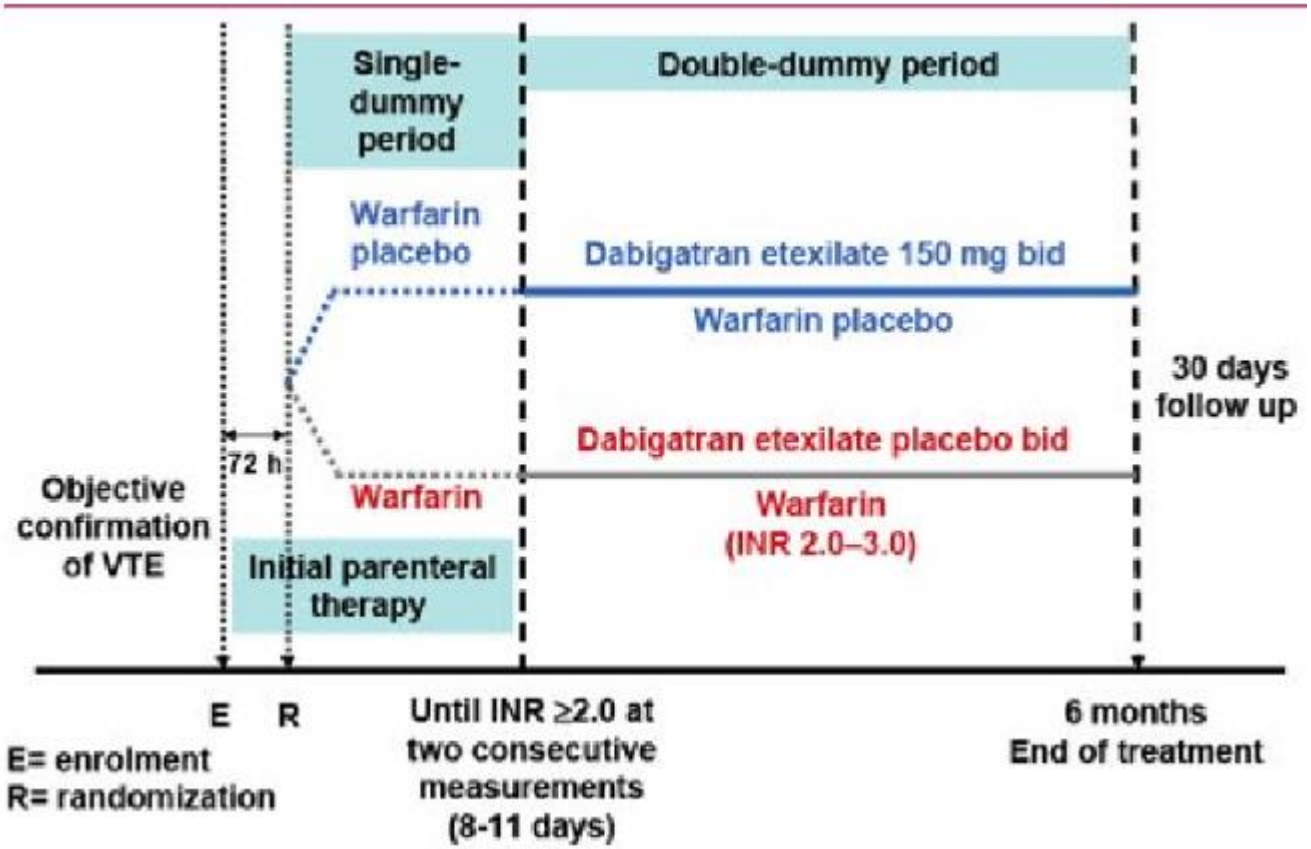
ADOPT : N Engl J Med 2011; 365: 2167-77

Développement des AOD

- Traitement préventif
  - En milieux chirurgical (PTH, PTG)
  - En milieux médical
- **Traitement curatif**
  - **TVP et EP**
  - FA (non valvulaire)
  - Σd coronarien aiguë

Traitement de la maladie Thromboembolique
Dabigatran après TVP; EP

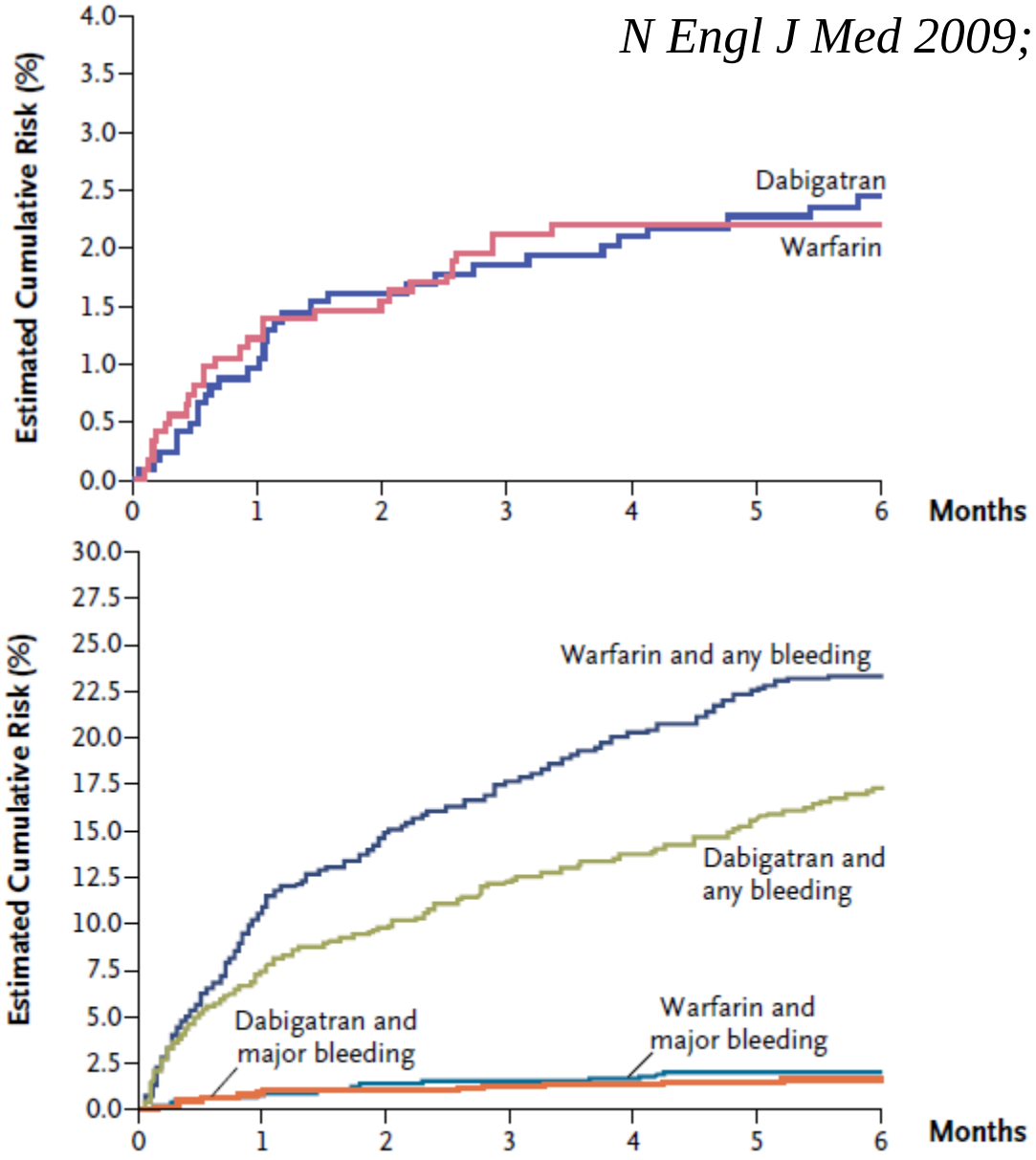
RE-COVER study



RE-COVER: N Engl J Med 2009; 361: 2342-52

Dabigatran après TVP; EP **(RE-COVER study)**

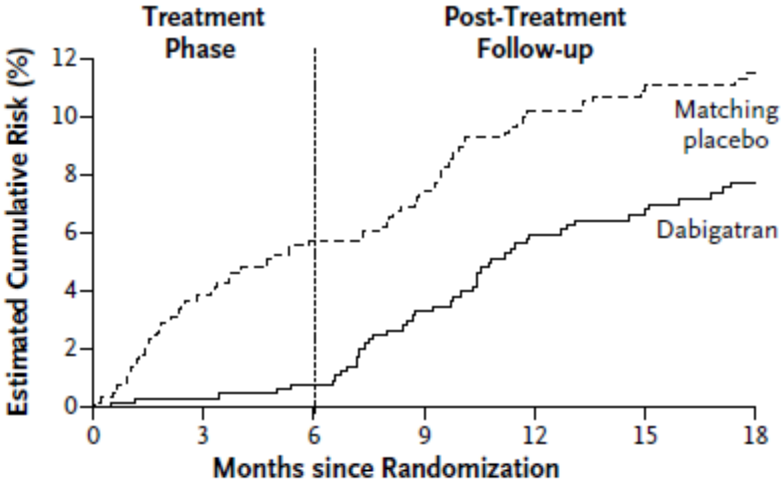
N Engl J Med 2009; 361: 2342-52

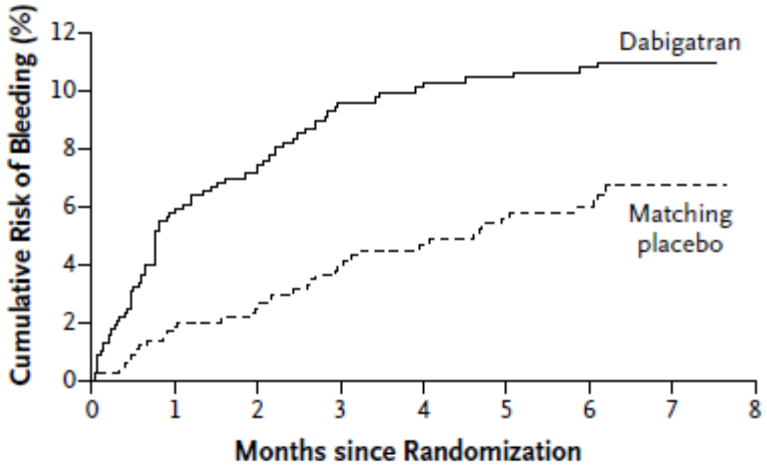


Dabigatran après TVP; EP **(extended treatment)**

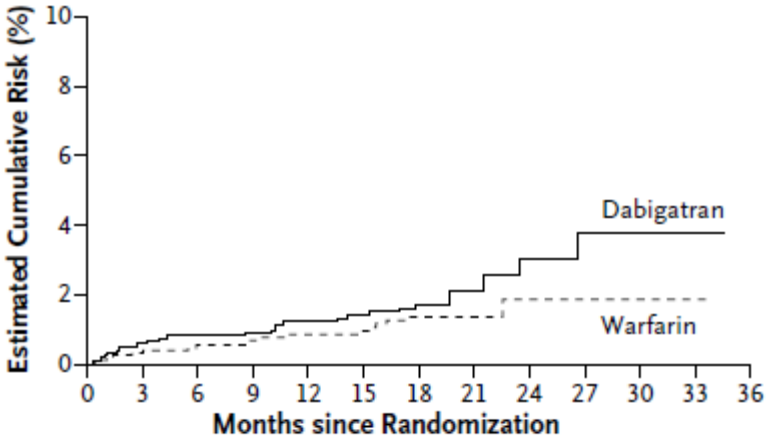
N Engl J Med 2013; 368: 709-18

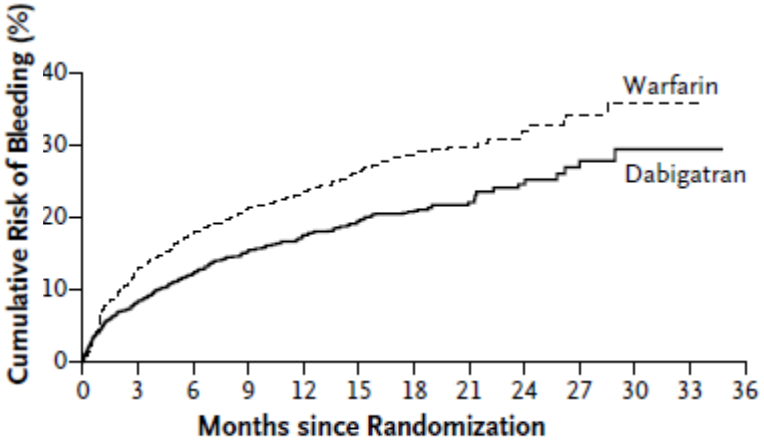
Placebo-Control Study





Active-Control Study



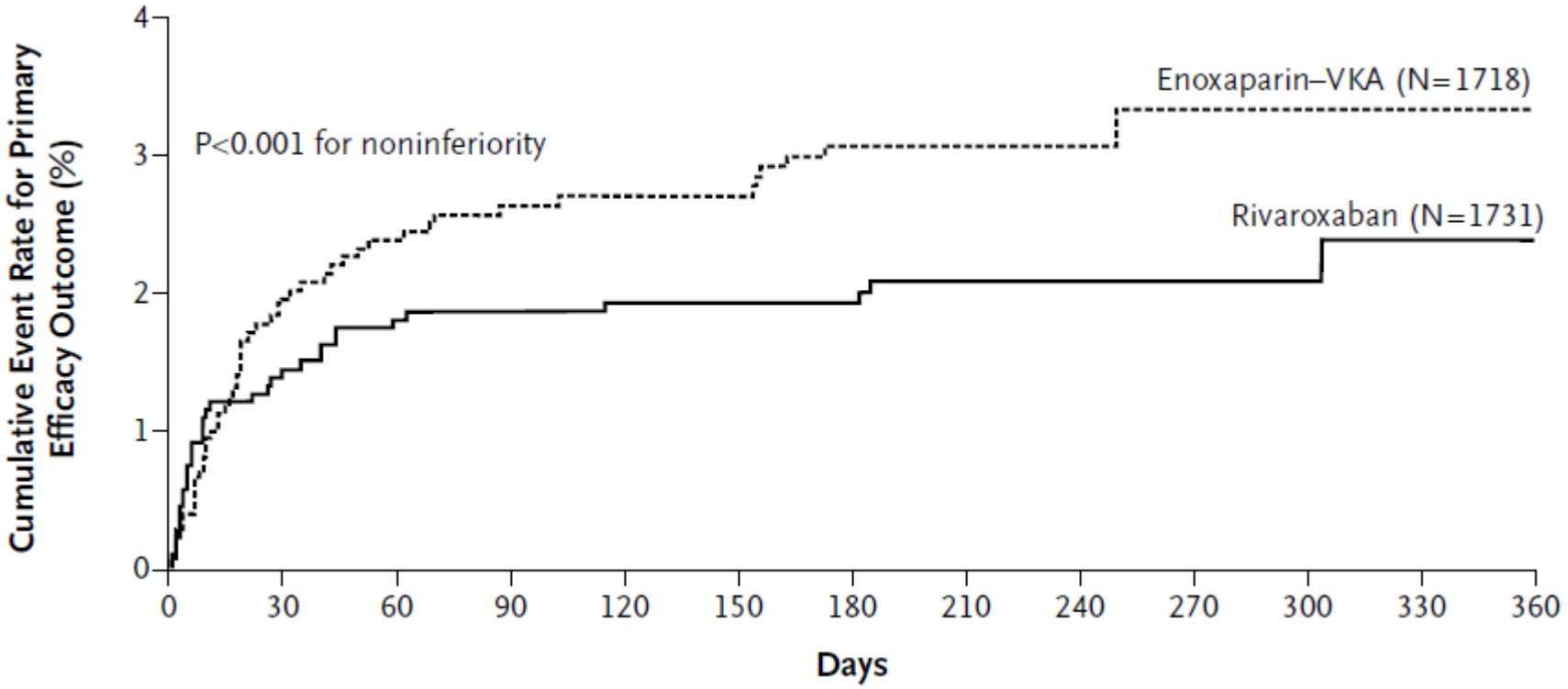


Traitement de la maladie Thromboembolique
Rivaroxaban après TVP; EP

Programme EINSTEIN

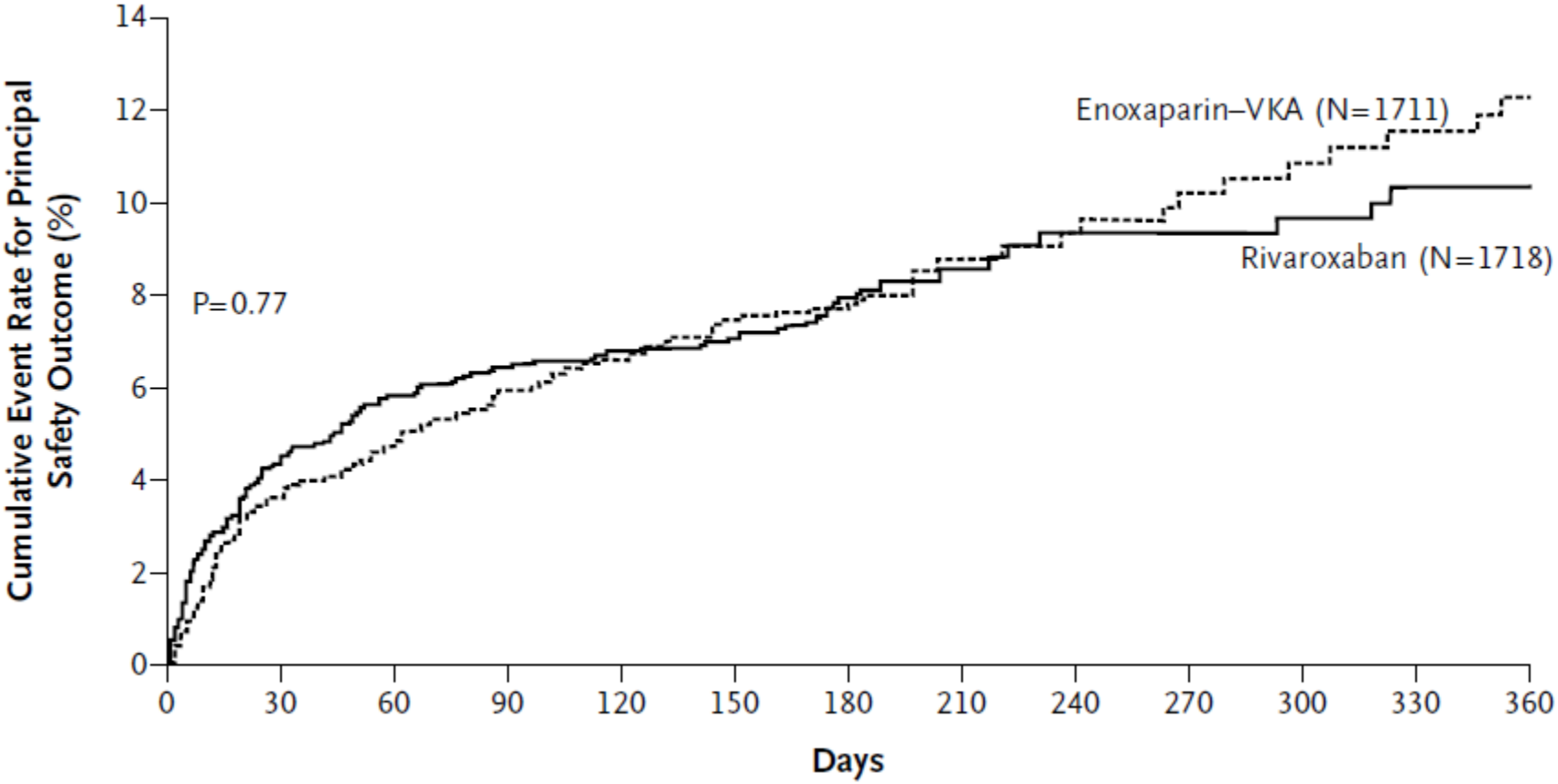
- Administration d'emblé du Rivaroxaban
- Traitement d'attaque (3 sem) : 15 mg × 2 /j
- Traitement d'entretien (6-12 mois) : 20 mg /j
- 3 études :
  - EINSTEIN-DVT
  - EINSTEIN-EP
  - EINSTEIN-EXT

Traitement de la maladie Thromboembolique
Rivaroxaban après TVP (Efficacité)



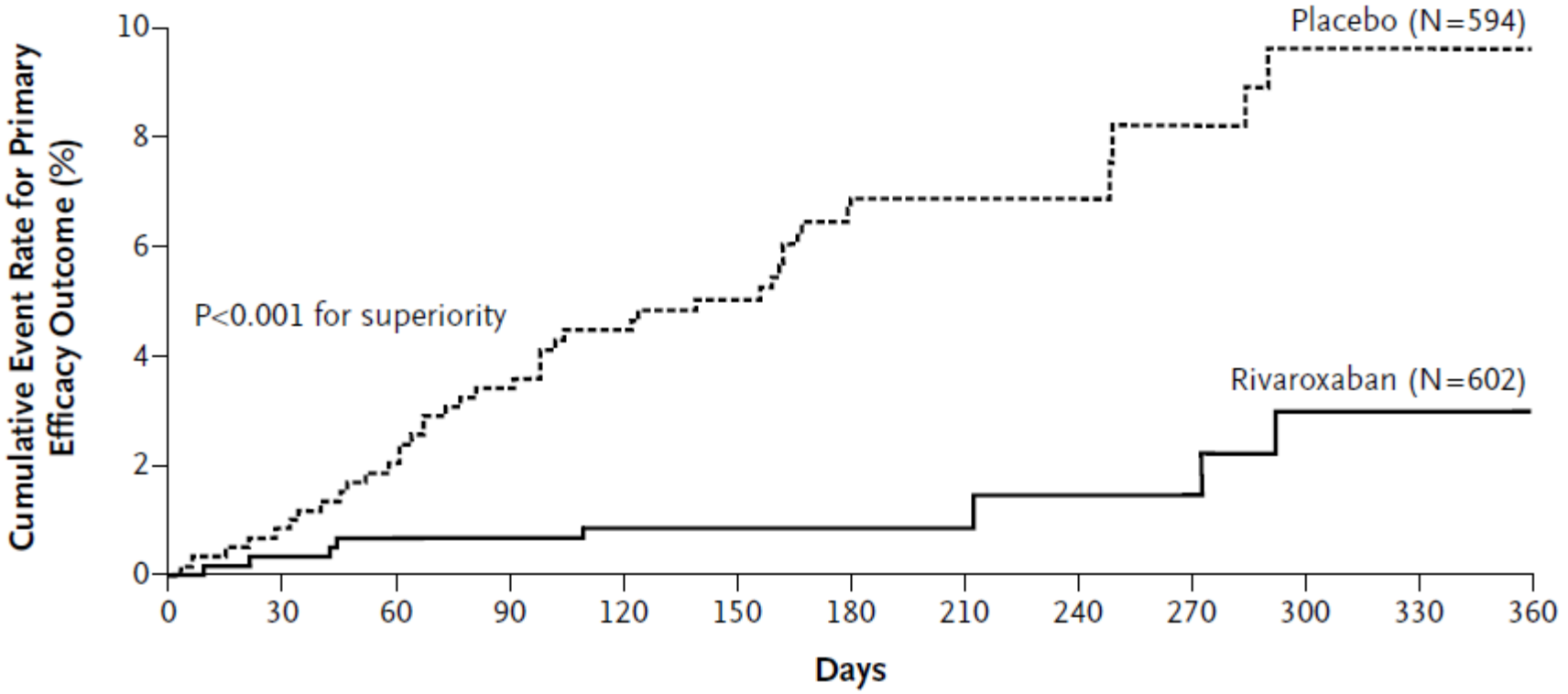
EINSTEIN-DVT: N Engl J Med 2010; 363: 2499-510

Traitement de la maladie Thromboembolique
Rivaroxaban après TVP (Saignement)



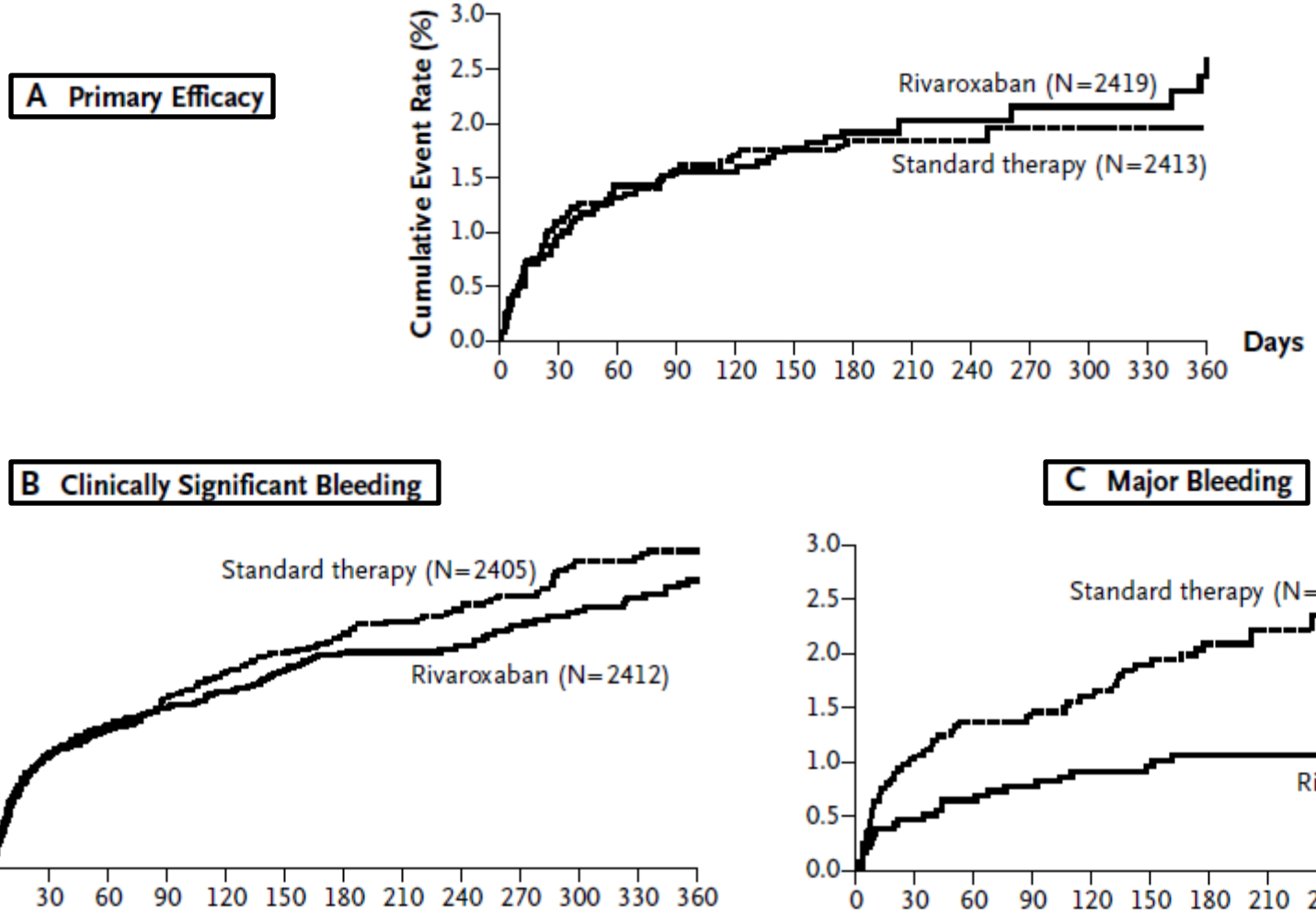
EINSTEIN-DVT: N Engl J Med 2010; 363: 2499-510

Traitement de la maladie Thromboembolique **Rivaroxaban** après TVP (Efficacité au long court)



EINSTEIN-DVT: N Engl J Med 2010; 363: 2499-510

Traitement de la maladie Thromboembolique
Rivaroxaban après EP (Efficacité)



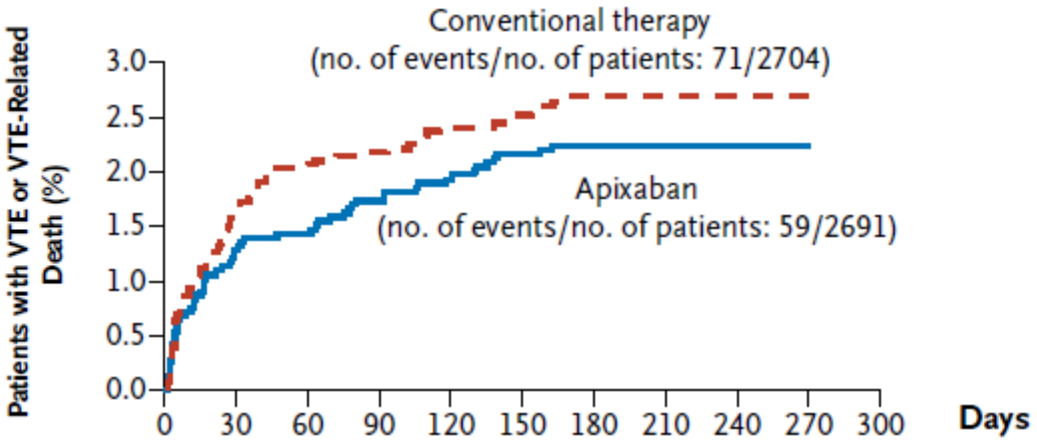
EINSTEIN-EP: N Engl J Med 2012; 366: 1287-97

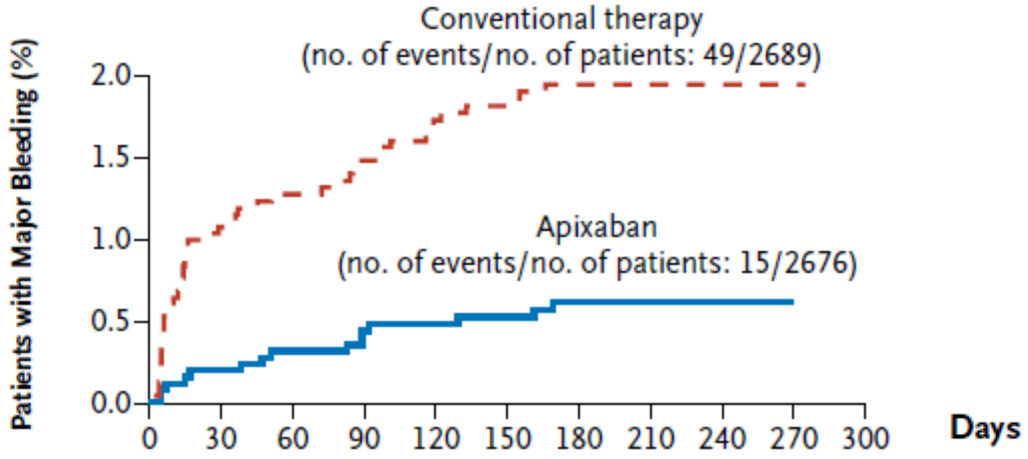
Traitement de la maladie Thromboembolique
Apixaban après TVP; EP

Programme AMPLIFY

- Administration d'emblé de l'Apixaban
- Traitement d'attaque (7 jours) : 10 mg × 2 /j
- Traitement d'entretien (6 mois) : 5 mg × 2 /j
- 2 études :
  - AMPLIFY
  - AMPLIFY-EXT

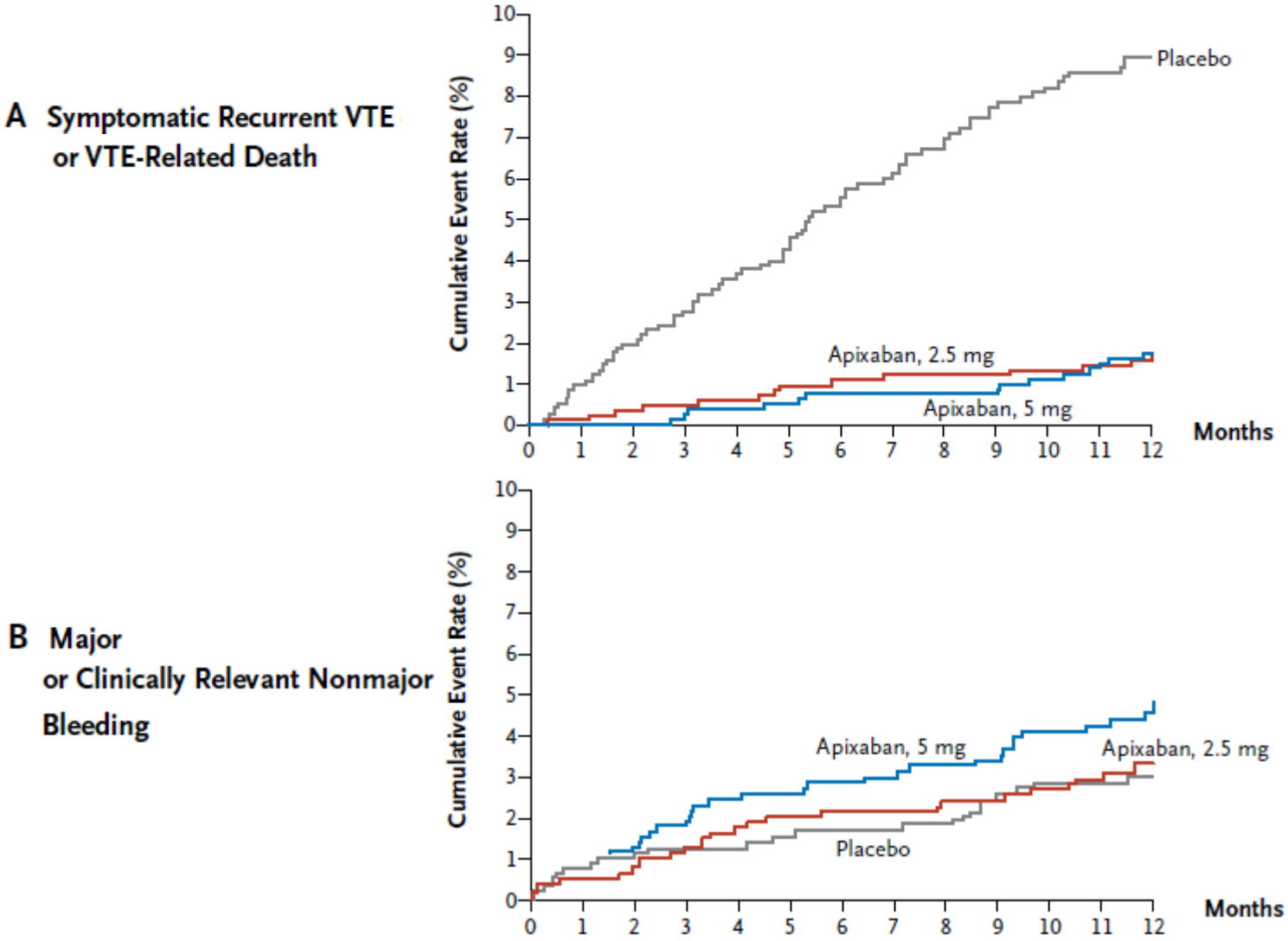
Traitement de la maladie Thromboembolique **Apixaban** après TVP; EP (AMPLIFY)





AMPLIFY: N Engl J Med 2013; 369: 799-808

Traitement de la maladie Thromboembolique **Apixaban** après TVP; EP (AMPLIFY-EXT)



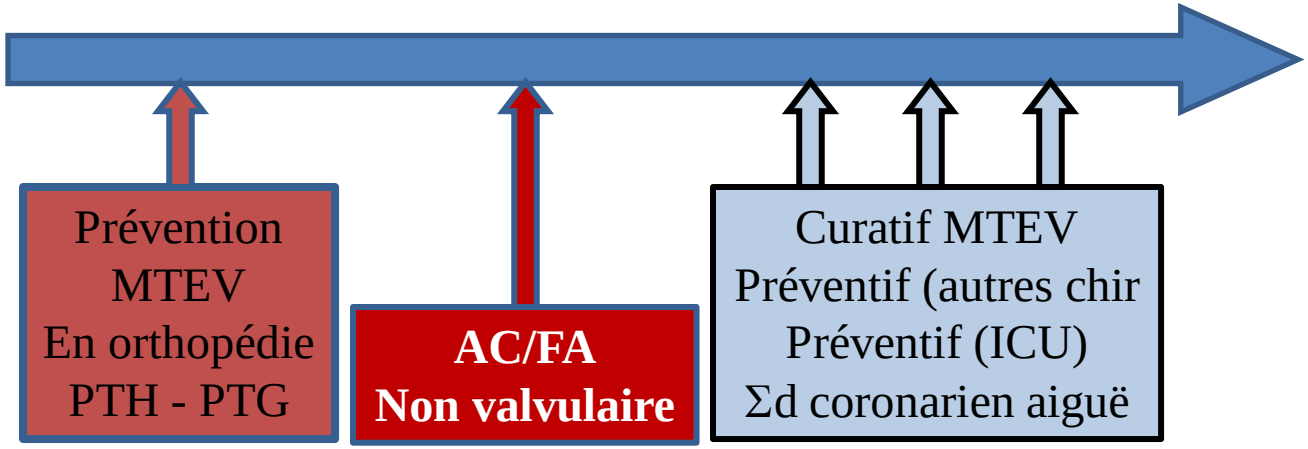
AMPLIFY-EXT : N Engl J Med 2013; 368: 699-708

Traitement de la maladie Thromboembolique
AOD (TVP; EP)

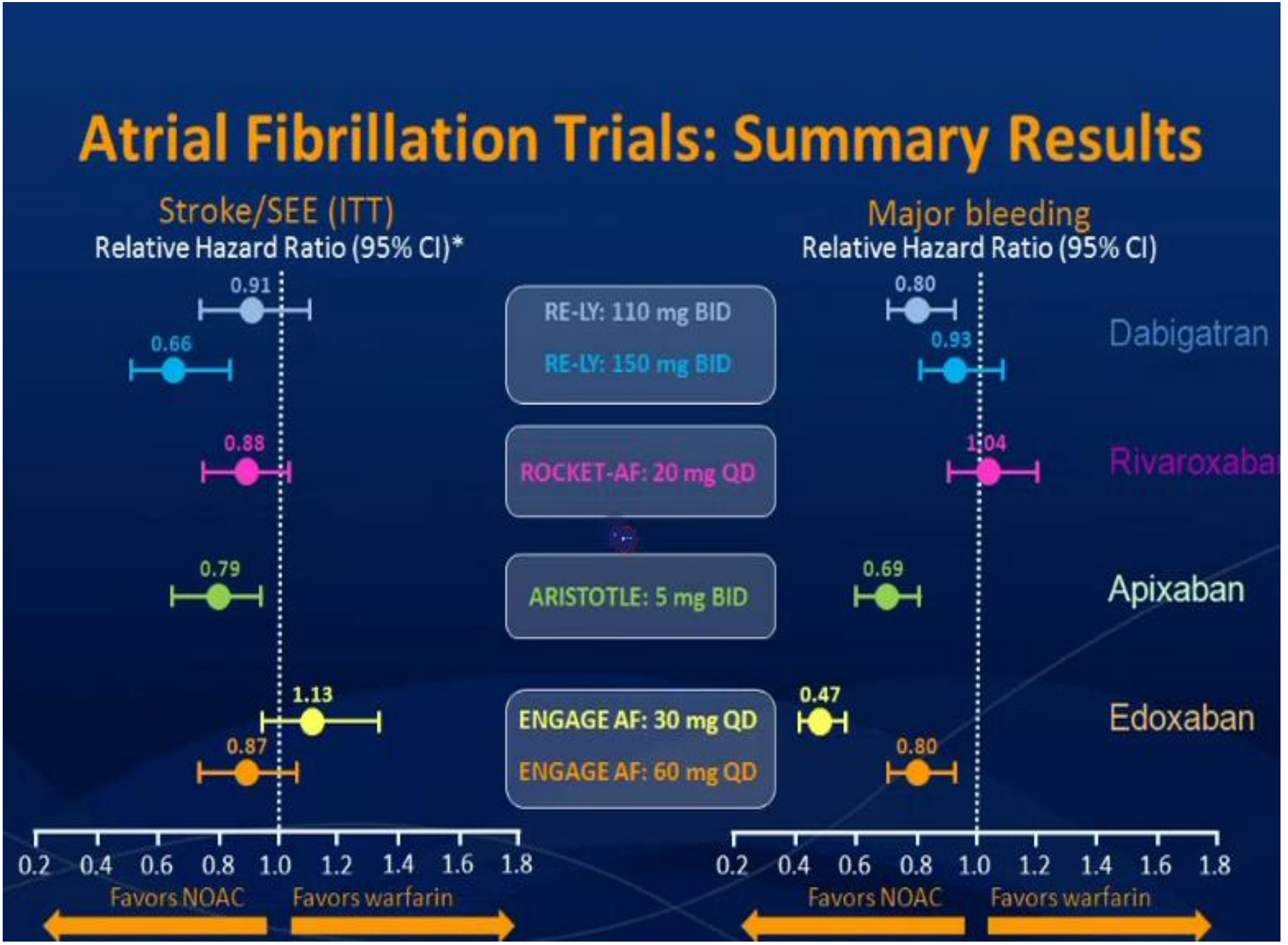
Molécule	Dose	Efficacité	Risque Hémor
Dabigatran PRADAXA®	***-HBPM (1sem)*** ***-puis 150 mg×2/j***	=	= ; ↘
Rivaroxaban XARELTO®	***- 15 mg×2/j (3sem)*** ***- Puis 20 mg/j***	=	= ; ↘
Apixaban ELIQUIST®	***- 10 mg×2/j (7J)*** ***- Puis 5mg×2/j***	=	↘

Développement des AOD

- Traitement préventif
  - En milieux chirurgical (PTH, PTG)
  - En milieux médical
- **Traitement curatif**
  - TVP et EP
  - **FA (non valvulaire)**
  - Σd coronarien aiguë



Atrial Fibrillation Trials: Summary Results



ESC AF Guidelines 2012: Recommendations for Anticoagulation in Patients with Nonvalvular AF

Recommendation	Class	Level
In patients with CHA_2DS_2-VASc score ≥ 2, OAC therapy with: • A dose-adjusted VKA (INR 2-3); or • A direct thrombin inhibitor (dabigatran); or • An oral factor Xa inhibitor (eg, rivaroxaban, apixaban*) ... is recommended unless contraindicated	I	A
In patients with CHA_2DS_2-VASc score of 1, OAC therapy with: • A dose-adjusted VKA (INR 2-3); or • A direct thrombin inhibitor (dabigatran); or • An oral factor Xa inhibitor (eg, rivaroxaban, apixaban*) ... should be considered, based upon an assessment of the risk for bleeding complications and patient preferences	IIa	A

*Pending approval

ESC = European Society of Cardiology; INR = international normalized ratio;
OAC = oral anticoagulation

Adapted from Camm AJ, et al. *Eur Heart J.* 2012;33(21):2719-2747.

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EHRA PRACTICAL GUIDE

Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation

Hein Heidbuchel[1]*, Peter Verhamme[2], Marco Alings[3], Matthias Antz[4], Hans-Christoph Diener[5], Werner Hacke[6], Jonas Oldgren[7], Peter Sinnaeve[2], A. John Camm[8], and Paulus Kirchhof[9,10]

European guidelines have expressed a **preference for NOACs over VKA** in stroke prevention for AF patients, based on their over-all clinical benefit

CONCLUSION

	Anti IIa direct	***Anti Xa direct***		
AOD	Dabigatrans (PRADAXA)®	**Rivaroxaban** (XARELTO)®	**Apixaban** (ELIQUIST)®	Edoxaban (SAVAYSA)®

MTEV

Préventif — PTH ; PTG
- *Orthopédie (Fx col fémur) ?*
- *Autre chirurgie ?*

Curatif — Phlébite ; EP
- *Durée du Ttt ?*
- *Ambulatoire?*
- *Mdes cancéreux ?*