Quelles indications pour les anticoagulants oraux ?

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• Other Financial Benefit	• **NONE**

French alternate member to the CHMP (Committee for Medicinal Products for Human use) of the EMA (European Medicines Agency)

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Agence nationale de sécurité du médicament et des produits de santé

Extension

INITIATION
(5 – 21 days)

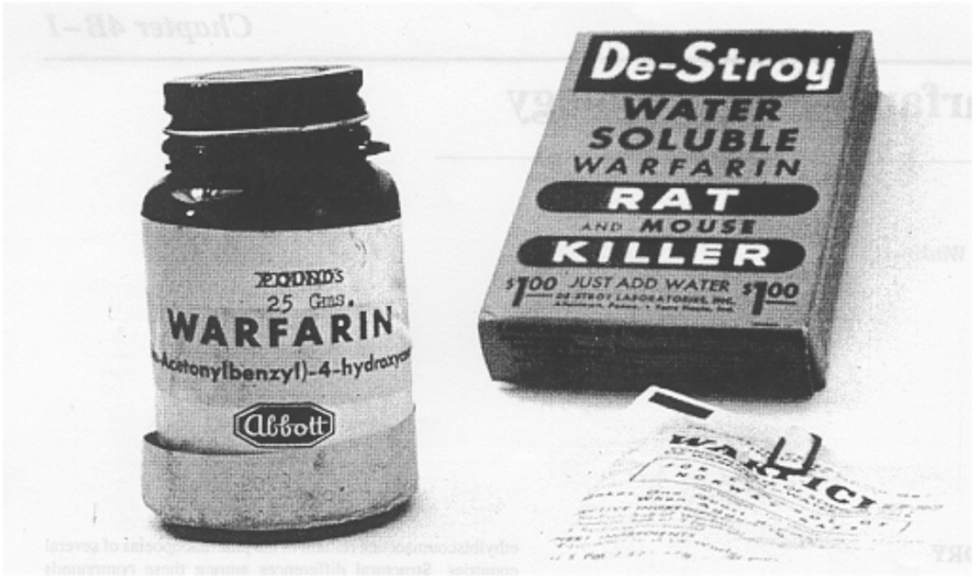
INITIAL TREATMENT
(3 – 6 months)

PREVENTION II
(up to indefinite)

- **UFH**
- **LMWH**
- **VKA** (initiation)

- **VKA**

- **VKA**



Extension

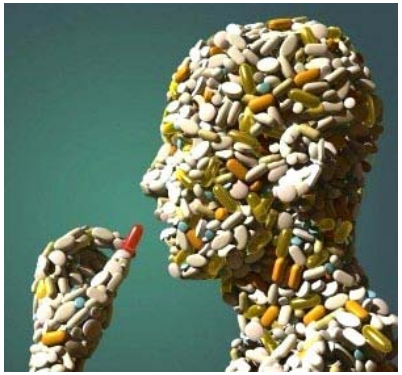
INITIATION
(5 – 21 days)

INITIAL TREATMENT
(3 months)

PREVENTION II
(up to indefinite)

- UFH
- LMWH
- Fondaparinux
- VKA (initiation)
- Rivaroxaban (15 mg bid)
- Apixaban (10 mg bid)

- VKA
- Rivaroxaban 20 mg oad
- Apixaban 5 mg bid
- Dabigatran 150 mg bid
- Edoxaban 60 mg oad



- VKA (INR 2.0-3.0)
- Rivaroxaban 20 mg oad
- Apixaban 2.5 mg bid
- Dabigatran 150 mg bid

- VKA (INR 1.5-2.0)
- Aspirin 100 mg oad
- Sulodexide 500 LSU bid
- Statins

Require confirmation or endorsement by GL

- Betrixaban

1. Données sur les indications sur les anticoagulants oraux dans la MTEV.

2. AOD et prévention secondaire de la MTEV

3. Données sur les indications des anticoagulants oraux dans la FA

4. AOD et prévention de la TV en chirurgie orthopédique

5. Ce qui n'est pas (encore) une indication des anticoagulants oraux directs

1. **Données sur les indications des anticoagulants oraux dans la MTEV.**

2. AOD et prévention secondaire de la MTEV

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ANTICOAGULANT DRUGS IN THE TREATMENT OF PULMONARY EMBOLISM
A CONTROLLED TRIAL

D. W. BARRITT
M.D. Lond., M.R.C.P.
S. C. JORDAN
M.B. Brist.
From the Departments of Medicine and Cardiology, United Bristol Hospitals

THE LANCET, JUNE 18, 1960

	N	Décès EP	Récidives non-fatales	Autres décès
Non traité	19	5	5	0
Héparine IV	16	0	0	1
+ AVK	54	0	1	2 (1 hémorragie)

Traitement de la MTEV

A la période initiale du traitement

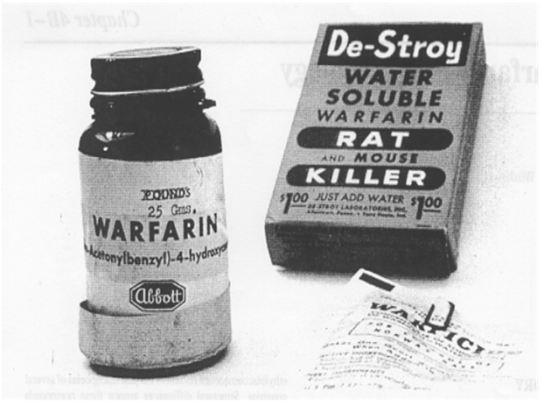
l'héparine doit être associée aux anticoagulants oraux

N Engl J Med 1992 ; 327 : 1485

Zones thérapeutiques du traitement anticoagulant

Indications	Zones thérapeutiques de l'INR
Prévention des TVP Traitement des TVP Traitement de l'EP Prévention des embolies - IDM - Fibrillation auriculaire - Pathologie valvulaire	2 – 3
Valves mécaniques	2,5 – 3,5

VKAs have a narrow therapeutic window



VKAs = vitamin K antagonists

PHOTO: BOEHRINGER INGELHEIM

Données sur le traitement de la MTEV depuis l'éclosion des AODs

- **DOACs developed to eliminate the need for TDM**
  - **In contrast to the requirement for INR monitoring associated with the long-established oral anticoagulant treatment with vitamin K antagonists**
- **All DOACs licensed without any requirement for TDM**
- **Doubts have been raised in the scientific community about not requiring TDM in the clinical use of DOACs**

Main characteristics

	Pradaxa	Xarelto	Eliquis	Lixiana
Mechanism of action	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Key sources of PK variability	Low oral BA, P-gp substrate, predominant renal elimination	P-gp and CYP3A4 substrate, some renal elimination	Moderate (~50%) oral BA, CYP3A4 substrate, some renal elimination	Moderate (~62%) oral BA, P-gp substrate, substantial (~50%) renal elimination
Measures of anticoagulant activity	dTT, ECT, aPTT	Calibrated quantitative anti-factor Xa assay	Calibrated quantitative anti-factor Xa assay	Calibrated quantitative anti-factor Xa assay
Antidote available	Praxbind	Andexanet (IndexXa)	Andexanet (IndexXa)	Andexanet (IndexXa)

Approved indications

	Pradaxa	Xarelto	Eliquis	Lixiana
Prevention of VTE in patient undergoing hip/knee replacement surgery	X	X	X	
Prevention of stroke and systemic embolism in non-valvular AF	X	X	X	X
Treatment of DVT and PE	X	X	X	X
Prevention of recurrent DVT and PE	X	X	X	X
Prevention of atherothrombotic events after ACS		X		

Posology

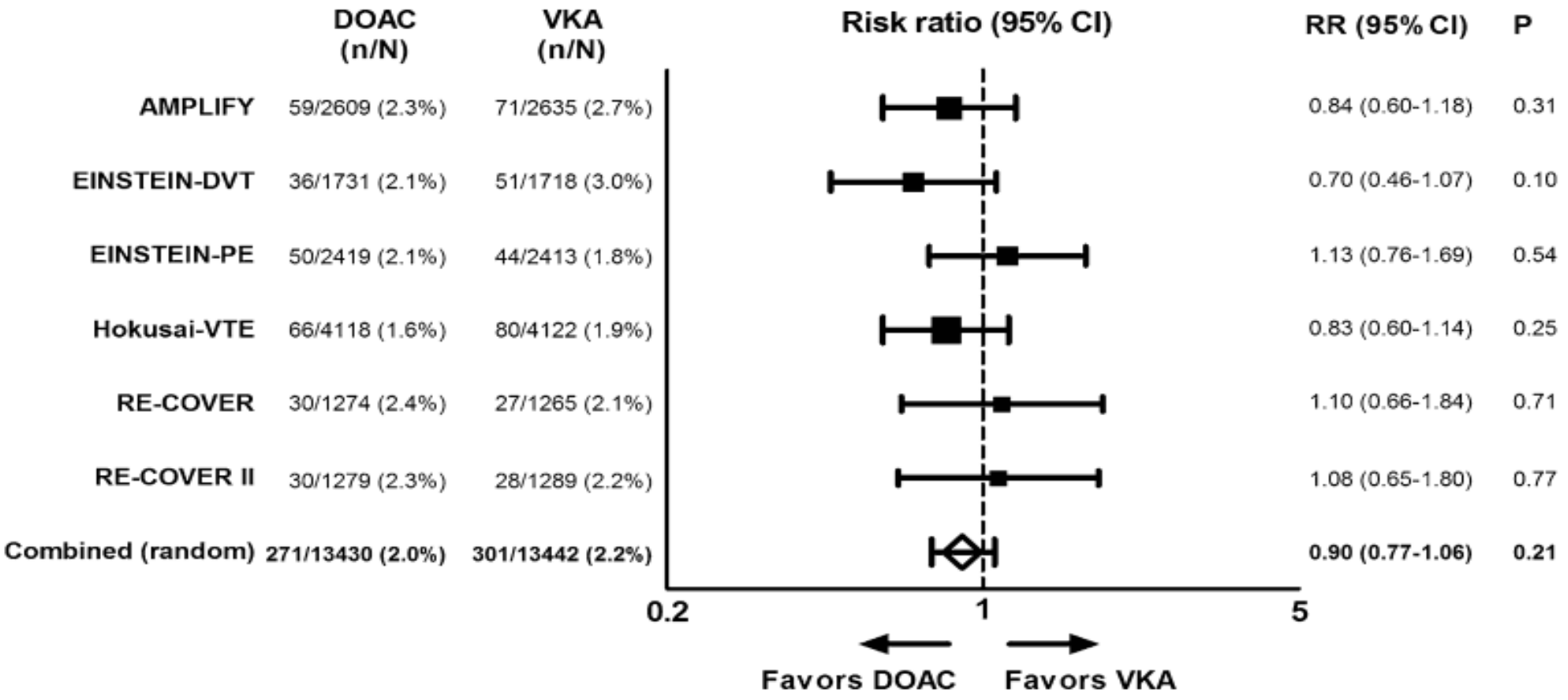
	Pradaxa	Xarelto	Eliquis	Lixiana
Prevention of VTE in patient undergoing hip/knee replacement surgery	220 mg OD or 150 mg OD	10 mg OD	2.5 mg BID	
Prevention of stroke and systemic embolism in non-valvular AF	150 mg BID or 110 mg BID	20 mg OD or 15 mg OD	5 mg BID or 2.5 mg BID	60 mg OD or 30 mg OD
Treatment of DVT and PE	150 mg BID or 110 mg BID	Day 1-21 15 mg BID Day 22- 20 mg OD or 15 mg OD	Day 1-7 10 mg BID Day 8- 5 mg BID	60 mg OD or 30 mg OD
Prevention of recurrent DVT and PE	150 mg BID or 110 mg BID	20 mg OD or 15 mg OD	2.5 mg BID	60 mg OD or 30 mg OD
Prevention of atherothrombotic events after ACS		2.5 mg BID		

Overview of phase III clinical trials with non-vitamin K-dependent new oral anticoagulants (NOACs) for theacute-phase treatment and standard duration of anticoagulation after VTE. ESC GL 2014

Drug	Trial	Design	Treatments and dosage	Duration	Patients	Efficacy outcome (results)	Safety outcome (results)
Dabigatran	RE-COVER[293]	Double-blind, double-dummy	Enoxaparin/dabigatran (150 mg b.i.d.)[a] vs. enoxaparin/warfarin	6 months	2539 patients with acute VTE	Recurrent VTE or fatal PE: 2.4% under dabigatran vs. 2.1% under warfarin	Major bleeding: 1.6% under dabigatran vs. 1.9% under warfarin
	RE-COVER II[294]	Double-blind, double-dummy	Enoxaparin/dabigatran (150 mg b.i.d.)[a] vs. enoxaparin/warfarin	6 months	2589 patients with acute VTE	Recurrent VTE or fatal PE: 2.3% under dabigatran vs. 2.2% under warfarin	Major bleeding: 15 patients under dabigatran vs. 22 patients under warfarin
Rivaroxaban	EINSTEIN-DVT[295]	Open-label	Rivaroxaban (15 mg b.i.d. for 3 weeks, then 20 mg o.d.) vs. enoxaparin/warfarin	3, 6, or 12 months	3449 patients with acute DVT	Recurrent VTE or fatal PE: 2.1% under rivaroxaban vs. 3.0% under warfarin	Major or CRNM bleeding 8.1% under rivaroxaban vs. 8.1% under warfarin
	EINSTEIN-PE[296]	Open-label	Rivaroxaban (15 mg b.i.d. for 3 weeks, then 20 mg o.d.) vs. enoxaparin/warfarin	3, 6, or 12 months	4832 patients with acute PE	Recurrent VTE or fatal PE: 2.1% under rivaroxaban vs. 1.8% under warfarin	Major or CRNM bleeding: 10.3% under rivaroxaban vs. 11.4% under warfarin
Apixaban	AMPLIFY[297]	Double-blind, double-dummy	Apixaban (10 mg b.i.d. for 7 days, then 5 mg b.i.d.) vs. enoxaparin/warfarin	6 months	5395 patients with acute DVT and/or PE	Recurrent VTE or fatal PE: 2.3% under apixaban vs. 2.7% under warfarin	Major bleeding: 0.6% under apixaban vs. 1.8% under warfarin
Edoxaban	Hokusai-VTE[298]	Double-blind, double-dummy	LMWH/edoxaban (60 mg o.d.; 30 mg o.d. if creatinine clearance 30–50 ml/min or body weight <60 kg) vs. UFH or LMWH/warfarin	Variable, 3–12 months	8240 patients with acute DVT and/or PE **(27044)**	Recurrent VTE or fatal PE: 3.2% under edoxaban vs. 3.5% under warfarin	Major or CRNM bleeding: 8.5% under edoxaban vs. 10.3% under warfarin

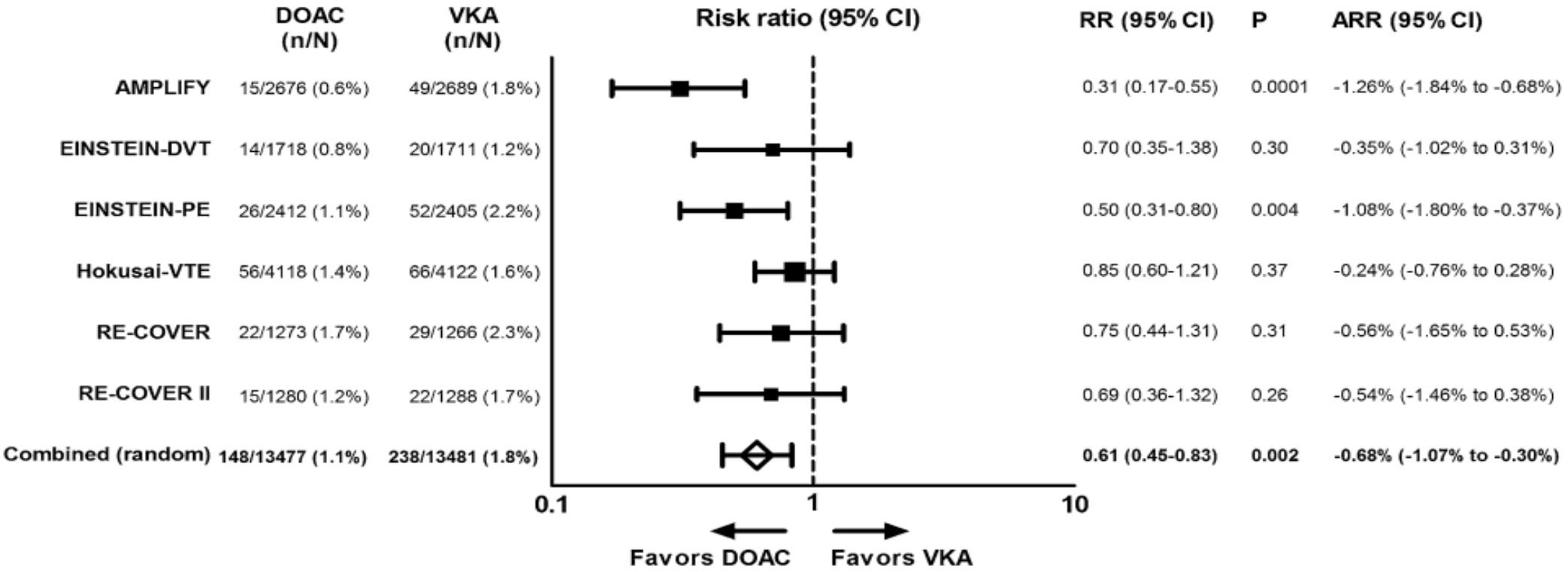
DOACs compared with VKA for acute VTE : evidence from phase 3 trials
Van Es N et al. Blood 2014;124:1968-75

First recurrent VTE or VTE-related death.



DOACs compared with VKA for acute VTE : evidence from phase 3 trials
Van Es N et al. Blood 2014;124:1968-75

Major bleeding.



DOACs compared with VKA for acute VTE : evidence from phase 3 trials
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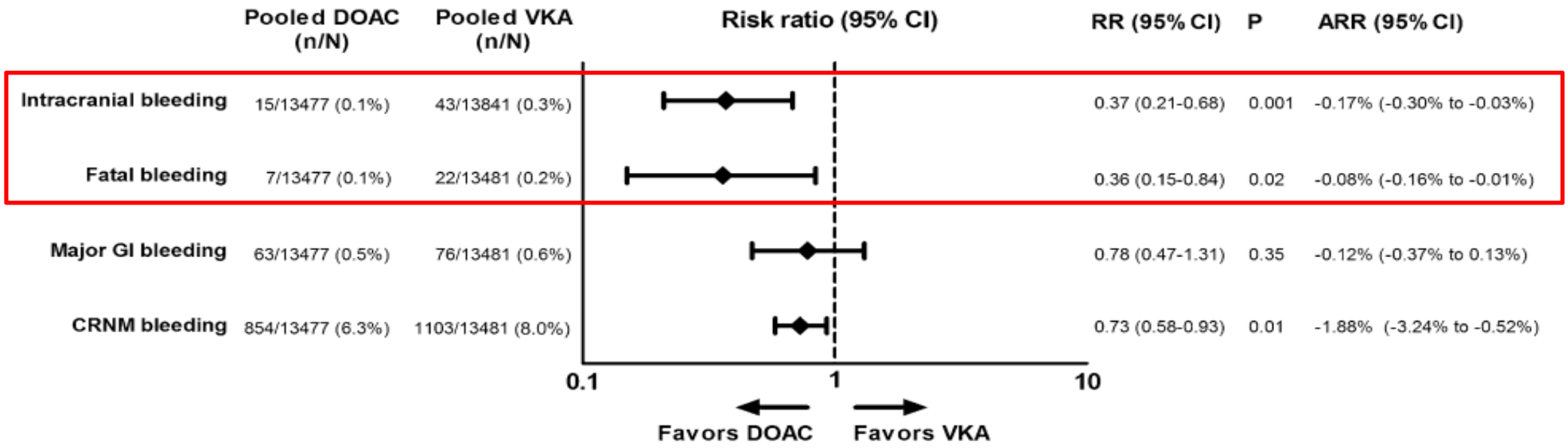
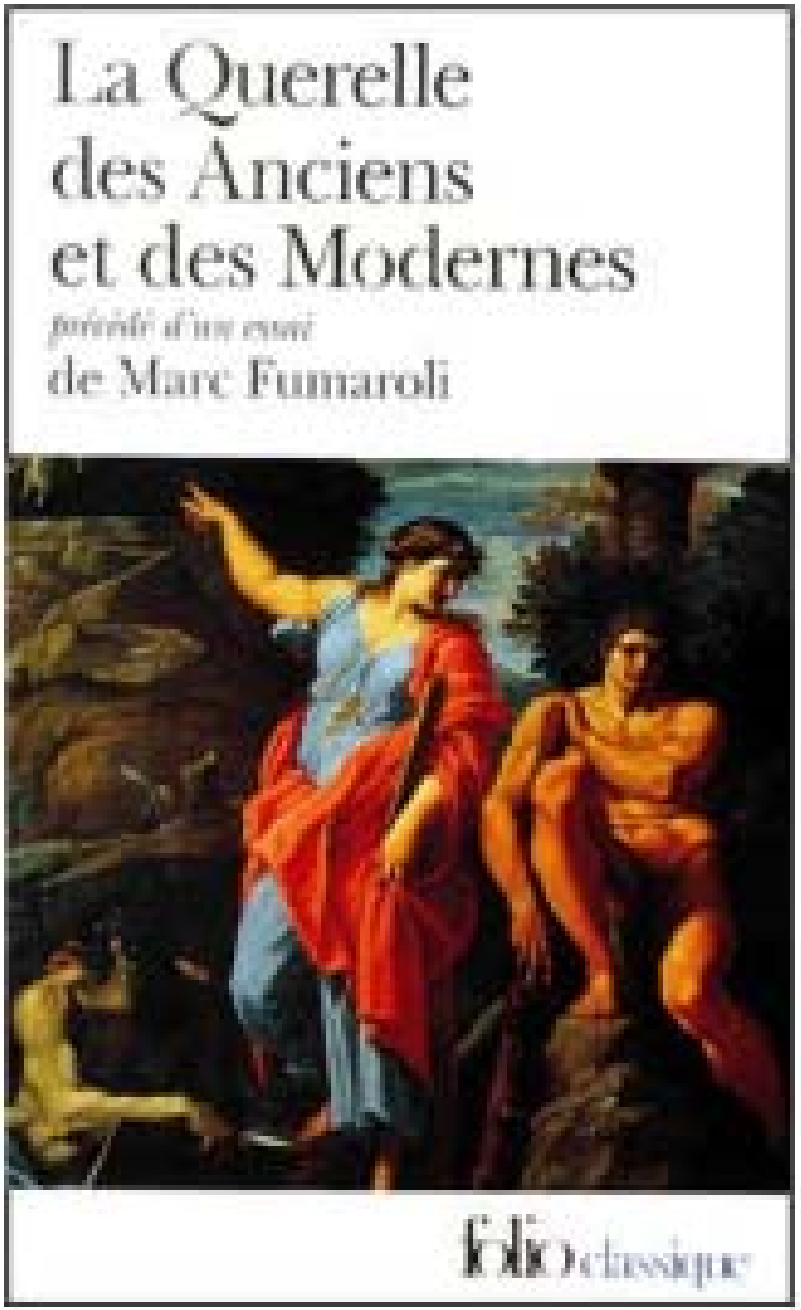
Intracranial, major gastrointestinal, fatal, and clinically relevant nonmajor bleeding.



Extrapolé en France sur le million de patients sous anticoagulants cela ferait théoriquement 2000 AVC hémorragique et 1000 saignements mortels évités.


thebmj
Fluid resuscitation for people with sepsis
Cardiovascular and non-cardiovascular effects of statins
Cholesterols: good, bad, and indifferent
UK legislation targeting "dangerous dogs"
DABIGATRAN
The analyses the regulators didn't see


La Querelle des Anciens et des Modernes
précédé d'un essai
de Marc Fumaroli

Comparison of the Short-Term Risk of Bleeding and Arterial Thromboembolic Events in Nonvalvular Atrial Fibrillation Patients Newly Treated With Dabigatran or Rivaroxaban Versus Vitamin K Antagonists

A French Nationwide Propensity-Matched Cohort Study

Géric Maura, PharmD*; Pierre-Olivier Blotière, MSc*; Kim Bouillon MD, PhD; Cécile Billionnet, MSc, PhD; Philippe Ricordeau, MD; François Alla, MD, PhD; Mahmoud Zureik, MD, PhD

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Agence nationale de sécurité du médicament et des produits de santé

SNIIRAM

32807 patients

respectively. After matching, no statistically significant difference in bleeding (hazard ratio, 0.88; 95% confidence interval, 0.64–1.21) or thromboembolic (hazard ratio, 1.10; 95% confidence interval, 0.72–1.69) risk was observed between dabigatran and VKA new users. Bleeding (hazard ratio, 0.98; 95% confidence interval, 0.64–1.51) and ischemic (hazard ratio, 0.93; 95% confidence interval, 0.47–1.85) risks were comparable between rivaroxaban and VKA new users.

***Conclusions*—**In this propensity-matched cohort study, our findings suggest that physicians should exercise caution when initiating either non-VKA oral anticoagulants or VKA in patients with nonvalvular atrial fibrillation.
(*Circulation*. 2015;132:1252-1260. DOI: 10.1161/CIRCULATIONAHA.115.015710.)

Major bleeding with vitamin K antagonists or direct oral anticoagulants in real-life

Cecilia Becattini, MD, PhD [a,*], Laura Franco, MD [a], Jan Beyer-Westendorf, MD [b], Luca Masotti, MD [c], Cinzia Nitti, MD [d], Simone Vanni, MD [e], Giorgia Manina, MD [f], Sergio Cattinelli, MD [g], Roberto Cappelli, MD [h], Rodolfo Sbrojavacca, MD [i], Fulvio Pomero, MD [j], Sandra Marten, MD [b], Giancarlo Agnelli, MD [a]

Conclusions: Admission for ICH is less frequent for DOAC patients compared with VKA patients. Admission for gastrointestinal MB is more frequent for DOAC as compared to VKA patients. Mortality seems lower in patients with MBs while on DOACs than VKAs but this finding varies across different types of MBs.

Internat Journal of Cardiol 2016

CHEST 2016 update Supplement
ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

Antithrombotic Therapy for VTE Disease

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

- **In patients with proximal DVT or PE, we recommend long-term (3 months) anticoagulant therapy over no such therapy (Grade 1B).**

- **In patients with DVT of the leg or PE and no cancer, as long-term (first 3 months) anticoagulant therapy, we suggest dabigatran, rivaroxaban, apixaban or edoxaban over VKA therapy (all Grade 2B).**

  For patients with DVT of the leg or PE and no cancer who are not treated with dabigatran, rivaroxaban, apixaban or edoxaban, we suggest VKA therapy over LMWH (Grade 2C).

- **In patients with DVT of the leg or PE and cancer, as long-term (first 3 months) anticoagulant therapy, we suggest LMWH over VKA therapy (Grade 2C), dabigatran (Grade 2C), rivaroxaban (Grade 2C), apixaban (Grade 2C) or edoxaban (Grade 2C).**

- **In patients with DVT of the leg or PE who receive extended therapy, we suggest that there is no need to change the choice of anticoagulant after the first 3 months (Grade 2C).**

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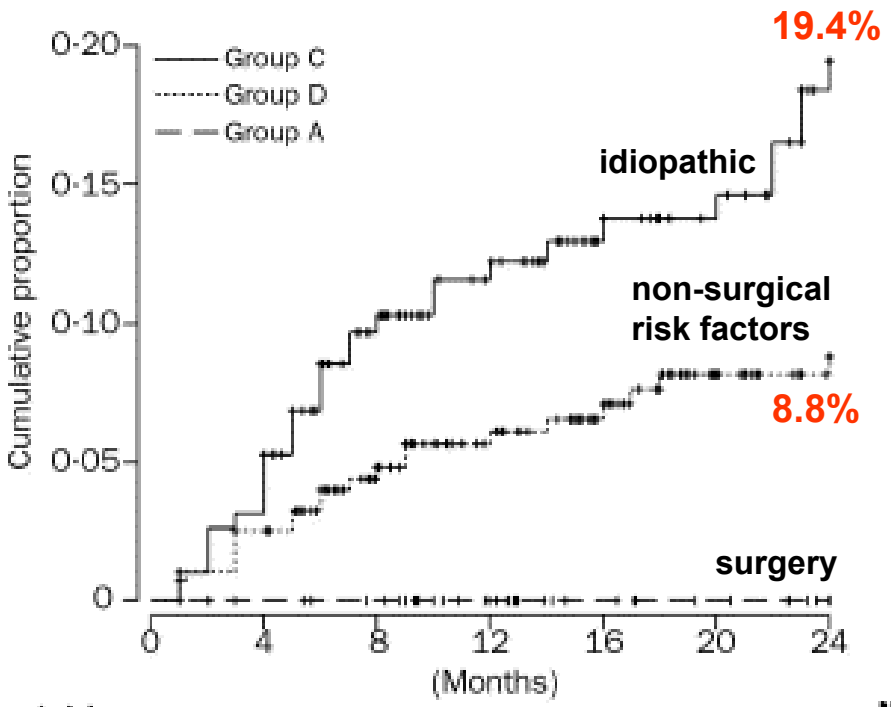
The risk of recurrent VTE, after stopping VKA therapy, is much lower if VTE has been provoked by a reversible risk factor* such as surgery, rather than if the episode is idiopathic.

- * Major : surgery, hospitalization, plaster cast, within 1 month.
- * Minor : the same 1 to 3 months before diagnosis ; estrogen, pregnancy, prolonged travel (>8h).
- The presence of thrombophilia is not used as a major guide for duration of t^t.

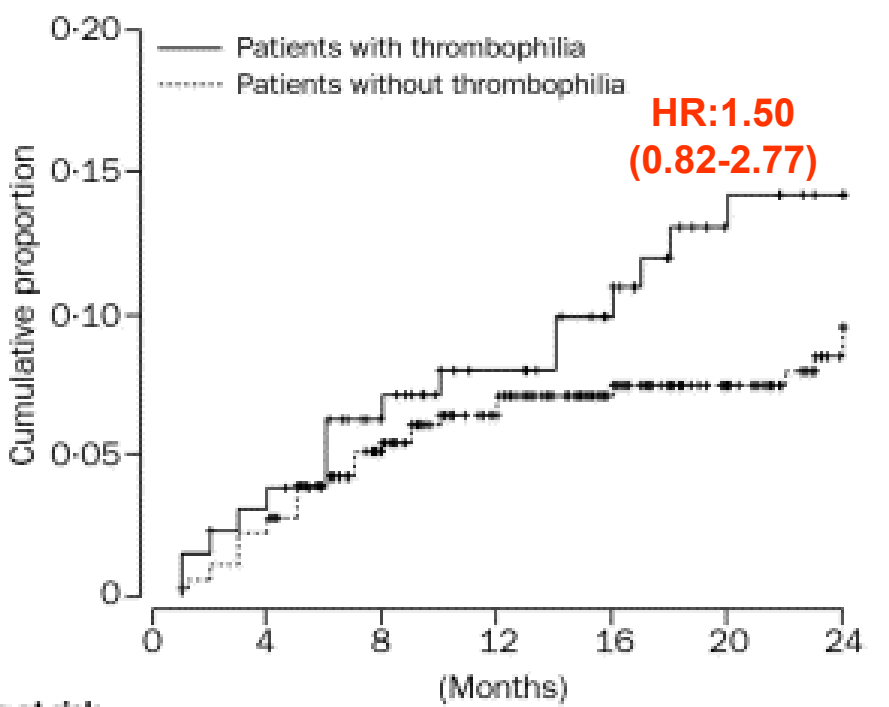
The greater the provoking risk factor, the lower the expected risk of recurrence after stopping anticoagulation.

Br Thorac Society. Lancet 1992;340:873-6
Levine MN et al. Thromb Haemost 1995;74:606-11
Pini M et al. Thromb Haemost 1994;72:191-7
Schulman S et al. N Engl J Med 1995;332:1661-5
Prandoni P et al. Ann Intern Med 1996;125:1-7
Baglin T. et al. Lancet 2003;362:523-26

Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic rik factors : pospective cohort study. Baglin T. et al. Lancet 2003;362:523-26



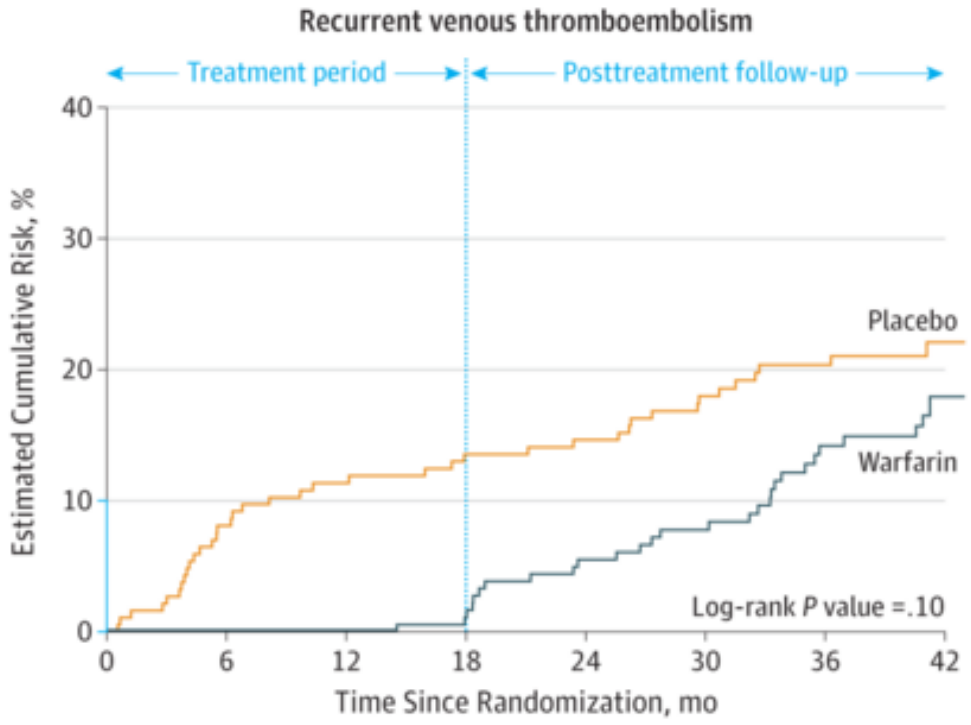
Number at risk							
Group C	193	184	153	133	110	98	81
Group D	279	269	235	209	185	155	139
Group A	86	82	79	71	61	58	53



Number at risk							
Patients with thrombophilia	130	125	111	100	90	76	71
Patients without thrombophilia	359	350	308	272	230	201	174

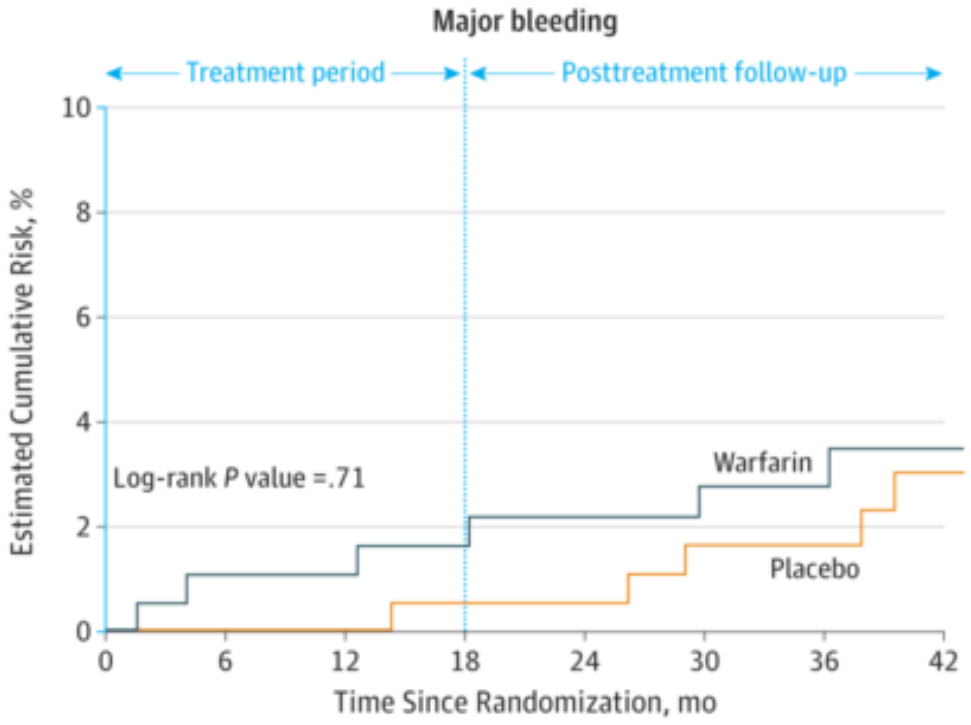
53 récidives à 2 ans sur 570 patients (dont 15% TV surales ou du bras)
Récidives = 9.3% - Génotypage sur 85% des cas

Six Months vs Extended Oral Anticoagulation After a First Episode of Pulmonary Embolism: The PADIS-PE Randomized Clinical Trial. *Couturaud F. JAMA 2015;314:31-40.*



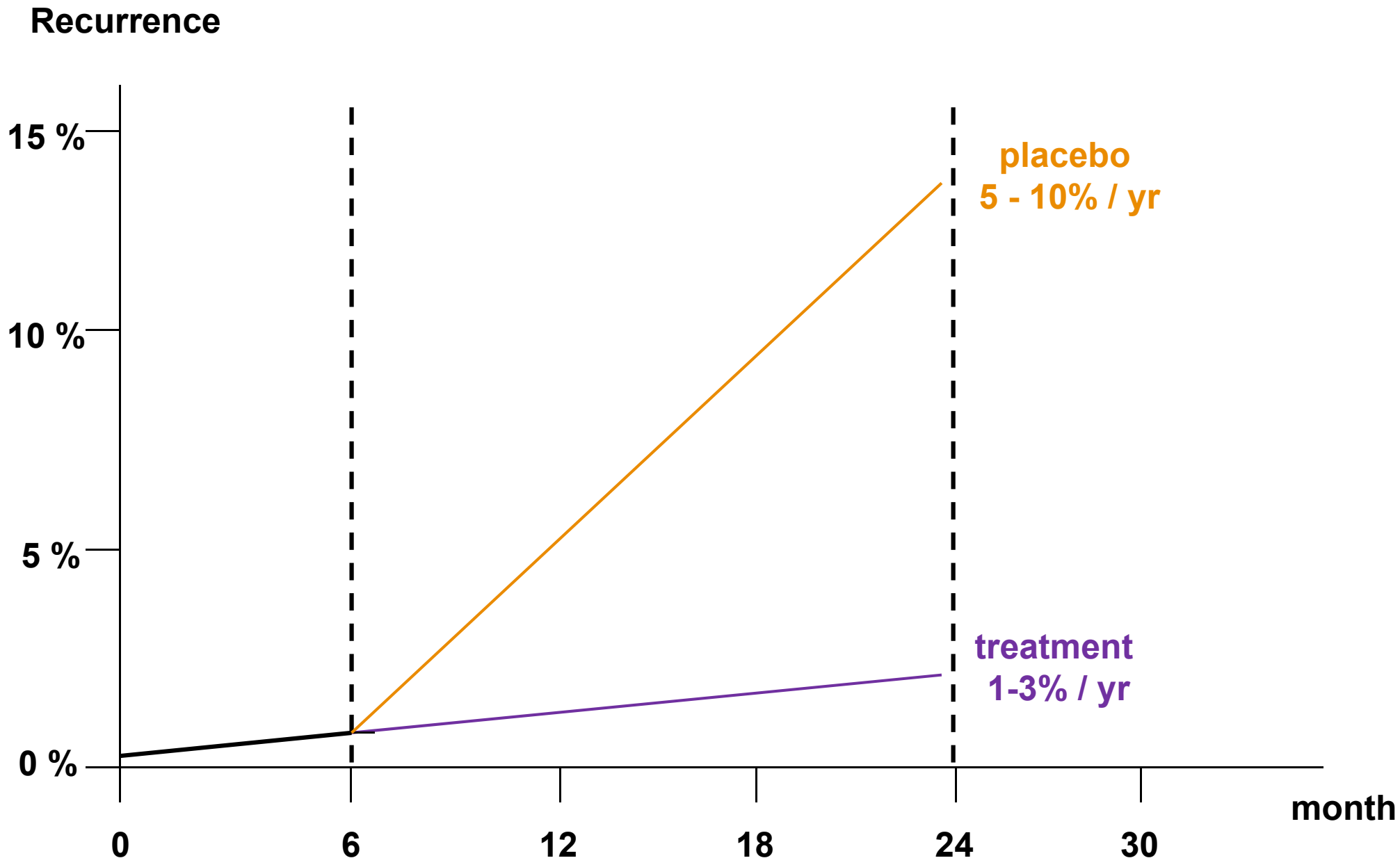
No. at risk

Placebo	187	170	162	158	155	141	117	105
Warfarin	184	182	180	174	168	150	120	110



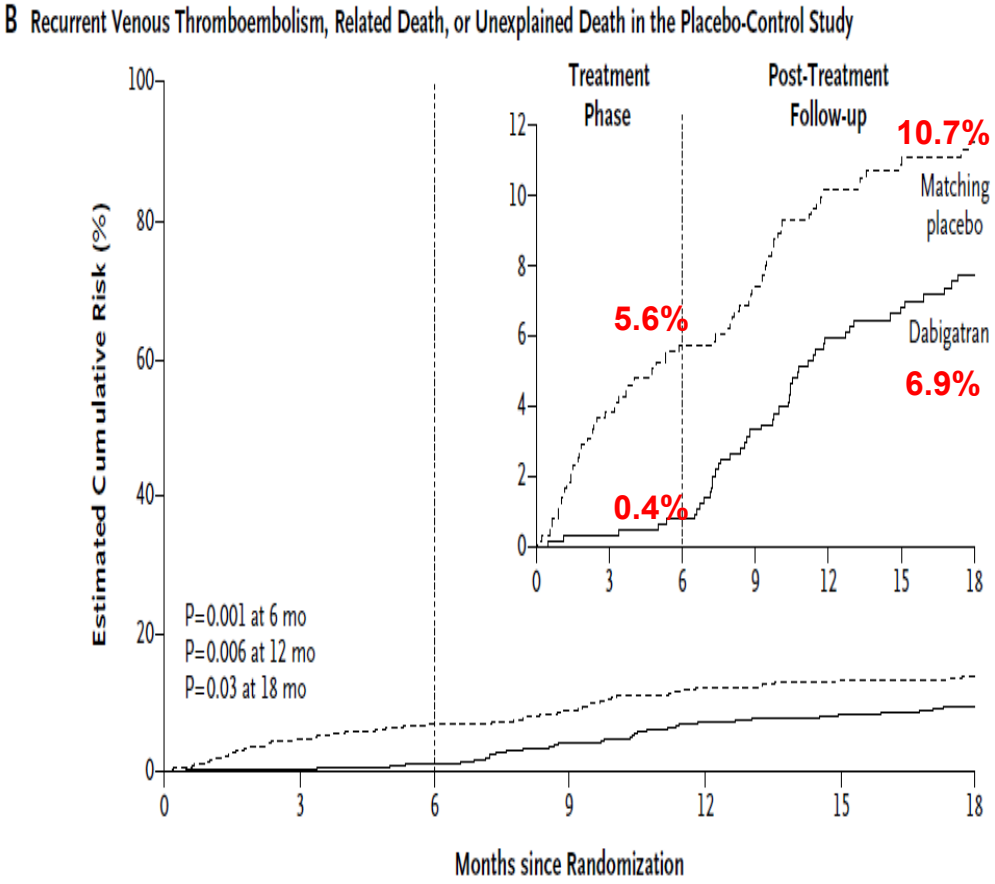
No. at risk

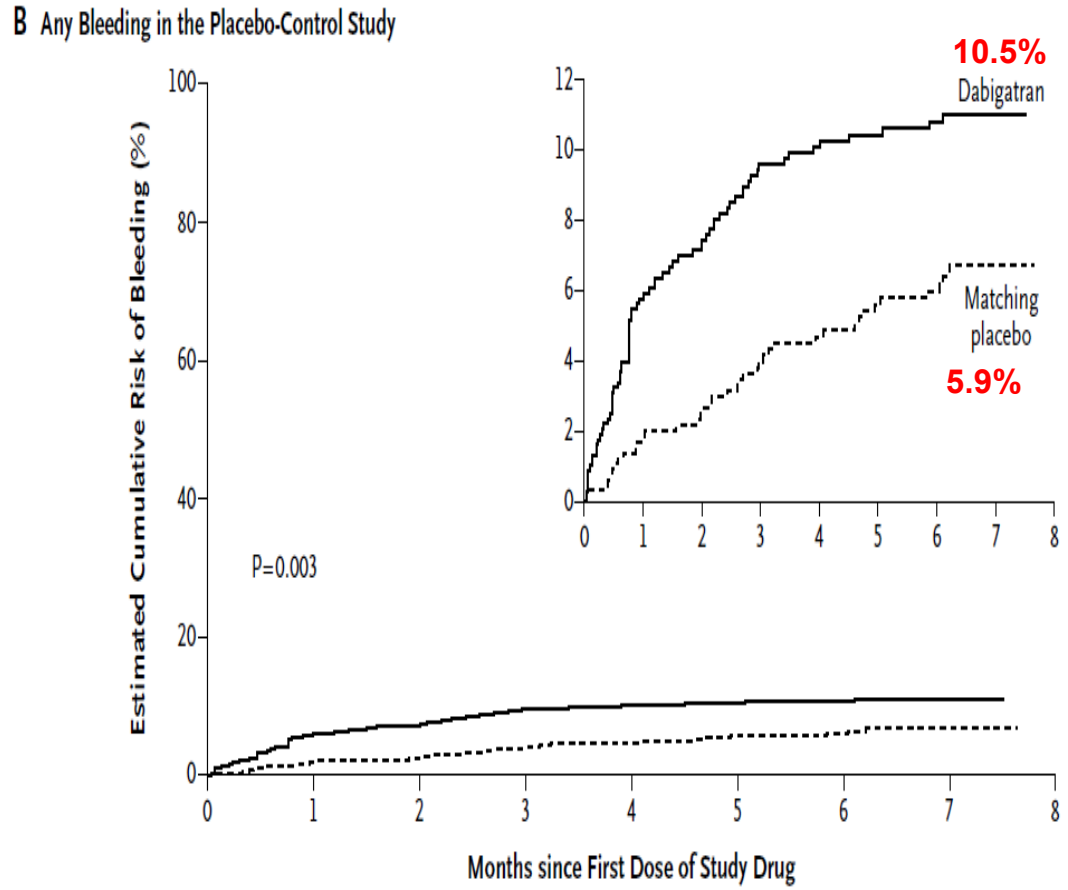
Placebo	187	185	183	182	181	170	148	130
Warfarin	184	182	180	177	176	162	138	126


Recurrence
15 %
10 %
5 %
0 %
placebo
5 - 10% / yr
treatment
1-3% / yr
month
0
6
12
18
24
30

Extended Use of Dabigatran, Warfarin or Placebo in VTE.
Schulman S et al. RE-MEDY and RE-SONATE Trials Investigators.
N Engl J Med 2013;368:709-18.

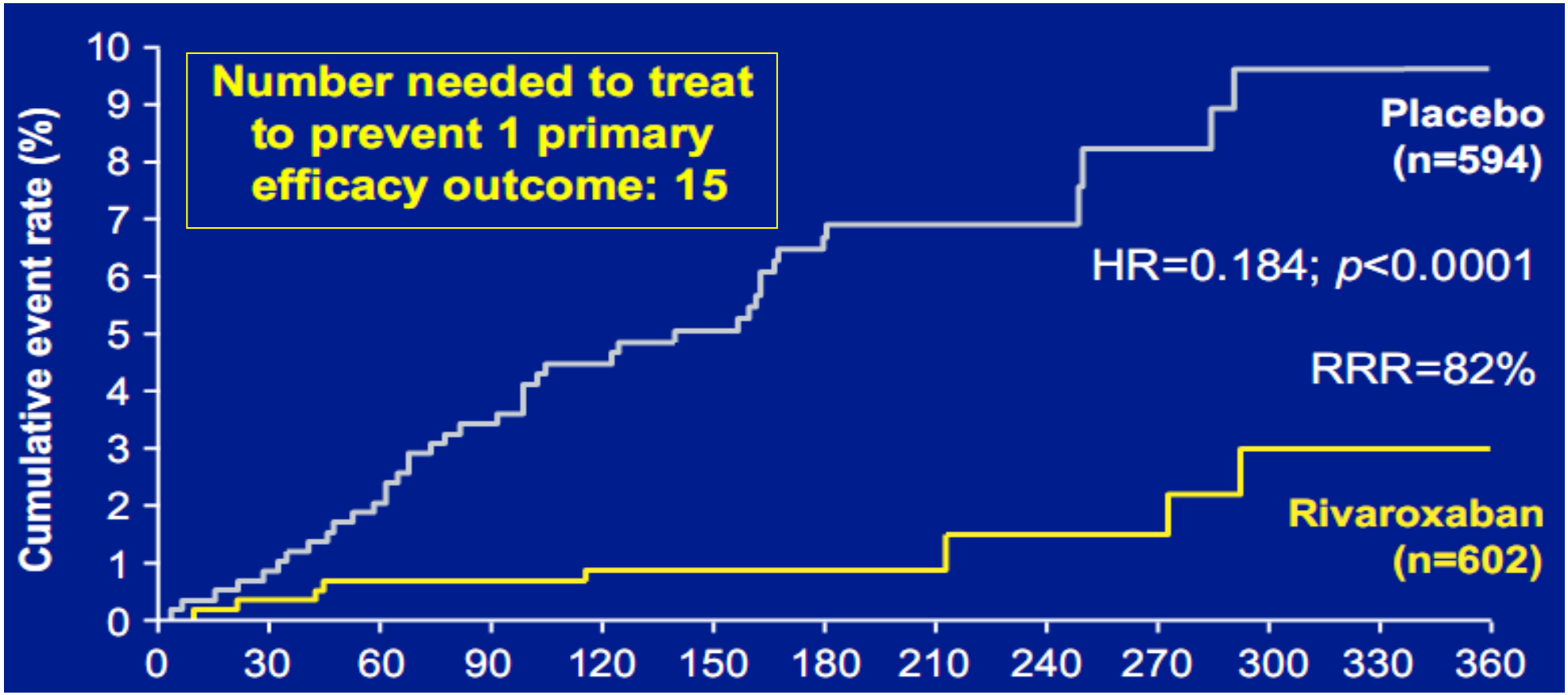
RE-SONATE : Efficacy and safety outcomes





Once-daily oral rivaroxaban versus placebo in the long-term prevention of recurrent symptomatic VTE. The EINSTEIN Extension study. ***Büller HR et al. N Engl J Med 2010;363:2499510***

Primary efficacy outcome analysis



Number needed to harm : approximately 140.
34 recurrent events were prevented, at the cost of 4 major bleeding events.

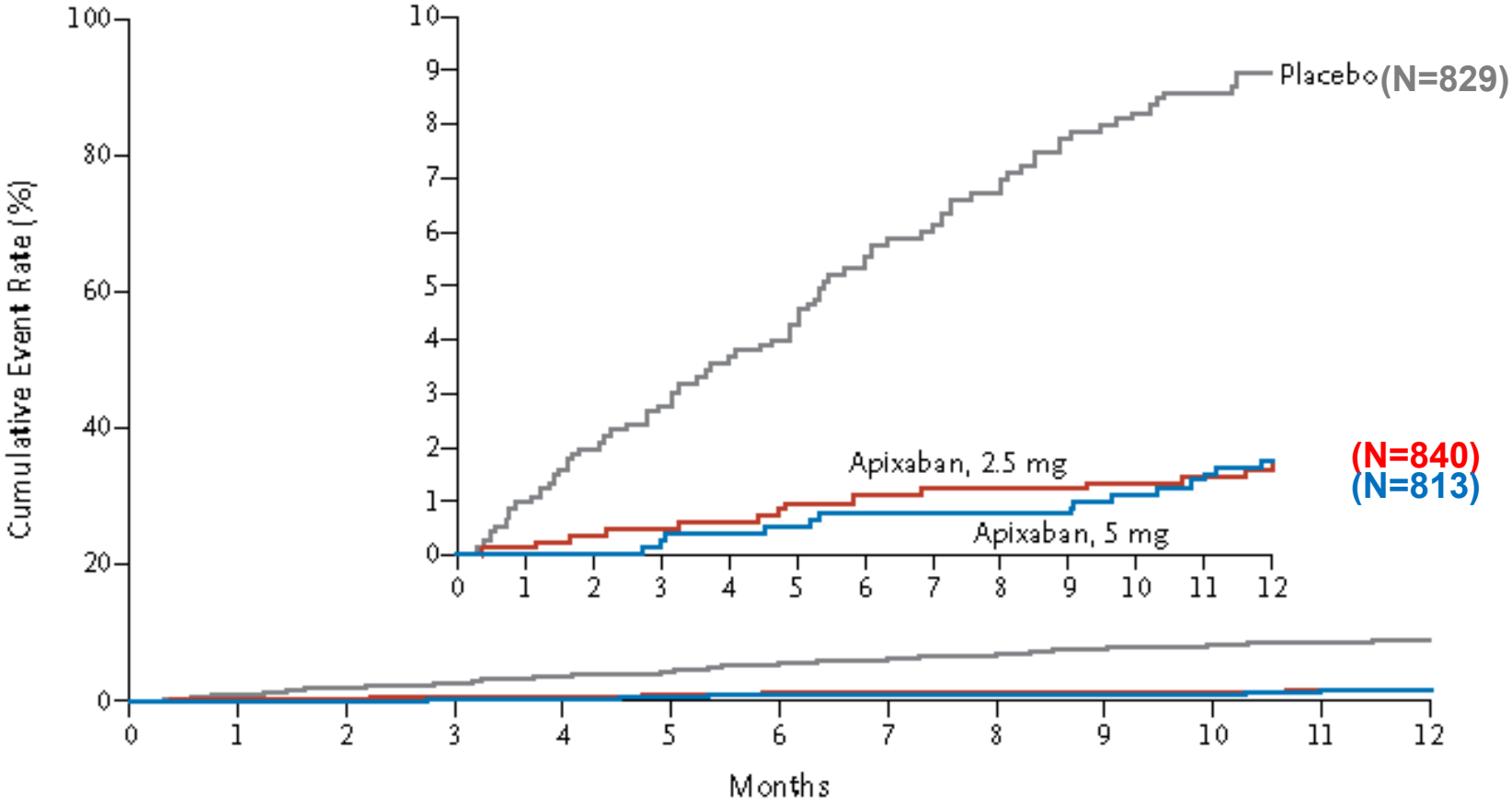
But x4 concerning clinically non-major bleedings.

Apixaban for extended treatment of Venous Thromboembolism.
Agnelli G. for the AMPLIFY-EXT study group. *N Engl J Med 2013;368:699-708.*

- **Randomized, double-blind study.**
- **To compare two doses of apixaban (2.5 mg and 5 mg, twice daily) with placebo in patients with VTE who had completed 6 to 12 months of anticoagulation therapy.**
- **Patients for whom there was clinical equipoise regarding the continuation or cessation of anticoagulation therapy and if they had not had a symptomatic recurrence during prior anticoagulation therapy.**
- **The study drugs were administered for 12 months.**

Apixaban for extended treatment of Venous Thromboembolism.
Agnelli G. for the AMPLIFY-EXT study group. *N Engl J Med 2013;368:699-708.*

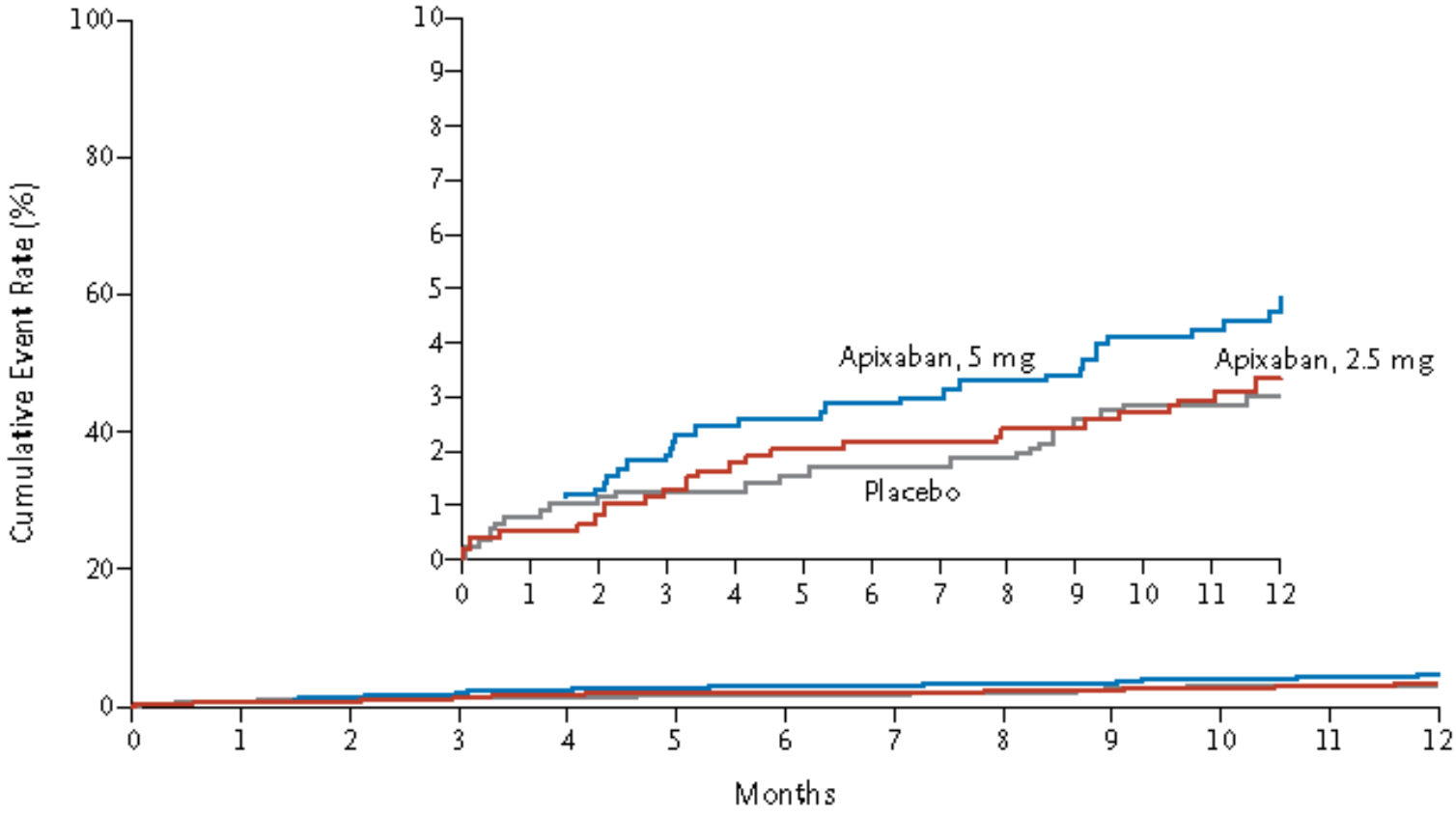
Symptomatic recurrent VTE or VTE-related death



No. at Risk					
Apixaban, 2.5 mg	840	836	825	818	533
Apixaban, 5 mg	813	807	799	791	513
Placebo	826	796	768	743	471

Apixaban for extended treatment of Venous Thromboembolism.
Agnelli G. for the AMPLIFY-EXT study group. *N Engl J Med 2013;368:699-708.*

Major or Clinically Relevant Nonmajor Bleeding



No. at Risk					
Apixaban, 2.5 mg	840	786	759	737	354
Apixaban, 5 mg	811	751	716	689	331
Placebo	823	749	687	651	298

Summary of secondary prevention with AOD

Drugs (Study)	VTE Recurrence			Major or Clinically Relevant Bleeding		
	Intervention Arm Annualized Rate (n events/N)	Placebo Arm Annualized Rate (n events/N)	Relative Risk (95% CI)	Intervention Arm Annualized Rate (n events/N)	Placebo Arm Annualized Rate (n events/N)	Relative Risk (95% CI)
Rivaroxaban 20 mg (EINSTEIN Extension)[10]	≈2.2/100 p-y† (8/602)	≈12.2/100 p-y† (42/594)	0.18 (0.09–0.39)	≈10.1/100 p-y† (36/602)	≈2.0/100 p-y† (7/594)	5.19 (2.3–11.7)
Apixaban 2.5 or 5 mg twice daily (AMPLIFY Extension)[11]	≈1.8/100 p-y† (14/840) ≈1.8/100 p-y† (14/813)	≈ 9.9/100 p-y† (73/829)	0.19 (0.11–0.48) 0.20 (0.11 to 0.34)	≈3.8/100 p-y† (27/840) ≈5.1/100 p-y† (35/813)	≈3.3/100 p-y† (22/829)	1.20 (0.69–2.10) 1.62 (0.96 to 2.73)
Dabigatran 150 mg twice daily (RE-SONATE)[7]	≈0.9/100 p-y† (3/681)	≈11.9/100 p-y† (37/662)	0.08 (0.02–0.25)	≈12.5/100 p-y† (36/681)	≈4.2/100 p-y† (12/662)	2.92 (1.52–5.60)
	1 - 2 %/y	**10 - 12 %/y**	**0.20**	**10 - 12 %/y** **4 %/y**	**2-4 %/y** **2-4 %/y**	**3 - 5 [if full dose]** **1.2 [if low dose]**

Adapted from Blondon & Bounameaux Circulation 2015

CHEST 2016 update Supplement

ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

Antithrombotic Therapy for VTE Disease

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

- **In patients with a proximal DVT of the leg or PE provoked by surgery, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B), (ii) treatment of a longer time-limited period (e.g. 6, 12 or 24 months) (Grade 1B), or (iii) extended therapy (no scheduled stop date) (Grade1B).**

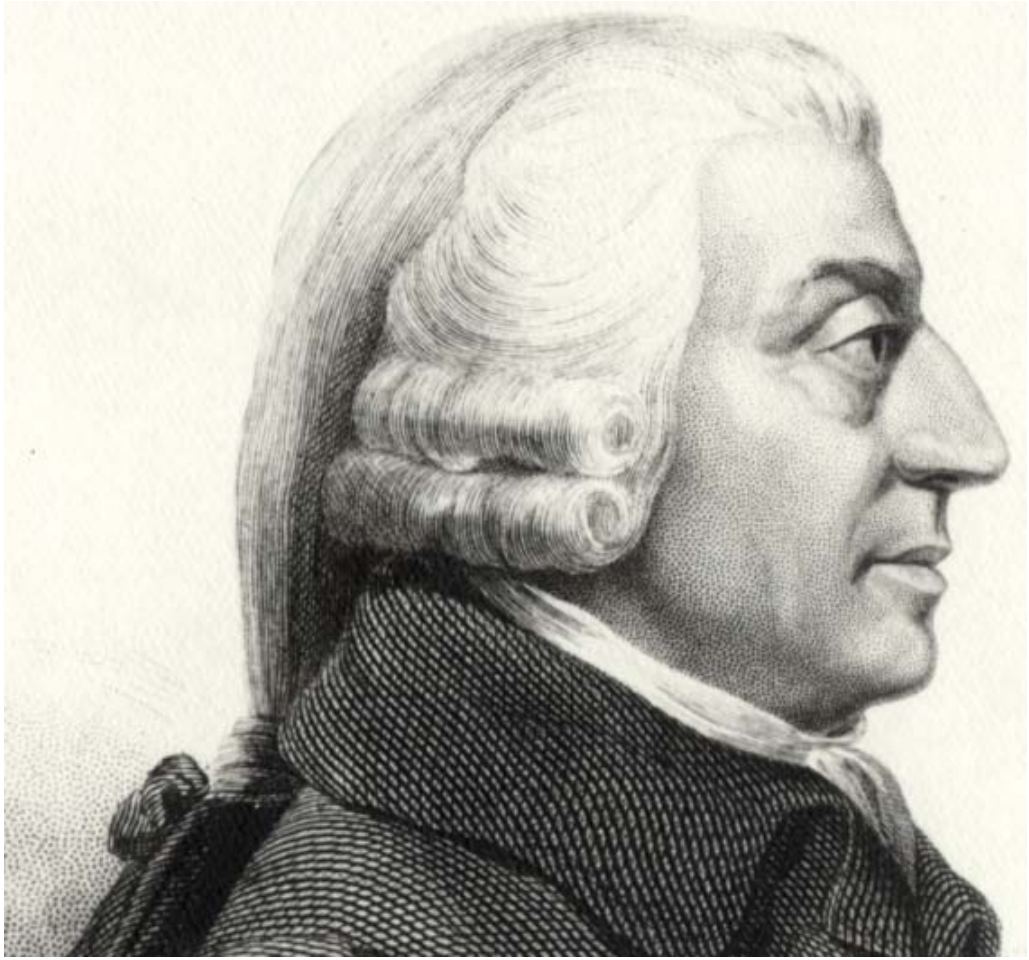
- **In patients with a proximal DVT of the leg or PE provoked by a nonsurgical transient risk factor, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B), and (ii) treatment of a longer time limited period (e.g. 6, 12 or 24 months) (Grade 1B). We suggest treatment with anticoagulation for 3 months over extended therapy if there is a low or moderate bleeding risk (Grade 2B), and recommend treatment for 3 months over extended therapy if there is a high risk of bleeding (Grade 1B).**

- **In patients with a first VTE that is an unprovoked proximal DVT of the leg or PE and who have a (i) low or moderate bleeding risk (see text), we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 2B), and a (ii) high bleeding risk (see text), we recommend 3 months of anticoagulant therapy over extended therapy (no scheduled stop date) (Grade 1B).**

- **In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over catheter-directed thrombolysis (CDT) (Grade 2C).**

Adam SMITH 1723 - 1790

Division du travail
&
Extension des richesses



« La quantité de chaque marchandise mise sur le marché se proportionne naturellement d'elle-même à la demande effective.

C'est l'intérêt de tous ceux qui emploient leur terre, leur travail ou leur capital à faire venir quelque marchandise au marché, que la quantité n'en excède jamais la demande effective ; et c'est l'intérêt de tous les autres, que cette quantité ne tombe jamais au-dessous. »

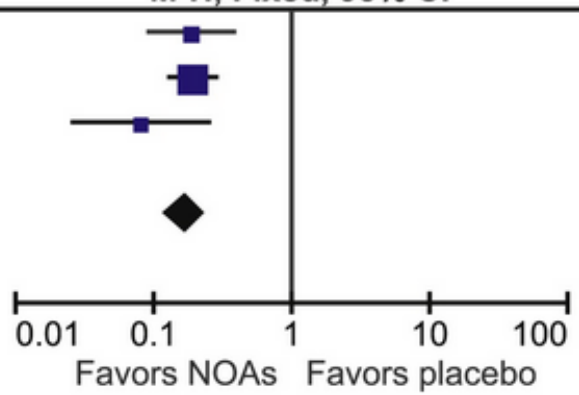
Efficacy of DOAs in secondary prevention of VTE.

Kakkos SK et al. 2014

Study or Subgroup	NOAs Events	NOAs Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
EINSTEIN-extension	8	602	42	594	24.0%	0.19 [0.09, 0.40]	2010
AMPLIFY-EXT	28	1653	73	829	55.2%	0.19 [0.13, 0.30]	2012
RE-SONATE	3	681	36	662	20.7%	0.08 [0.03, 0.26]	2013
Total (95% CI)		**2936**		**2085**	**100.0%**	**0.17 [0.12, 0.24]**	
Total events	39	**1.32 %**	151	**7.24 %**			

Heterogeneity: Chi² = 1.95, df = 2 (P = 0.38); I² = 0%

Test for overall effect: Z = 9.75 (P < 0.00001)

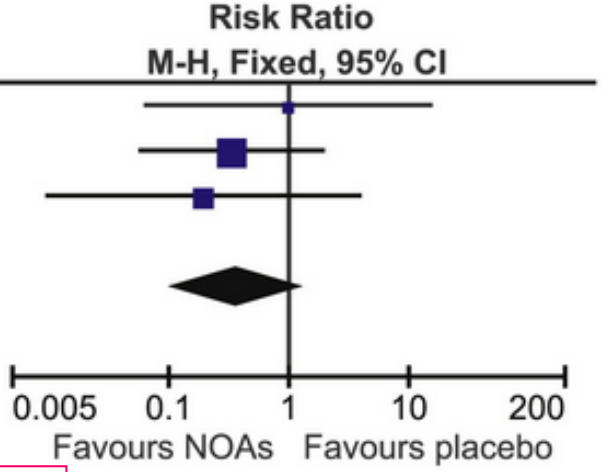


VTE recurrence

Study or Subgroup	NOAs Events	NOAs Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
EINSTEIN-extension	1	598	1	590	13.4%	0.99 [0.06, 15.74]	2010
AMPLIFY-EXT	2	1653	3	829	53.0%	0.33 [0.06, 2.00]	2012
RE-SONATE	0	681	2	662	33.6%	0.19 [0.01, 4.04]	2013
Total (95% CI)		**2932**		**2081**	**100.0%**	**0.37 [0.10, 1.38]**	
Total events	3	**0.1 %**	6	**0,29 %**			

Heterogeneity: Chi² = 0.66, df = 2 (P = 0.72); I² = 0%

Test for overall effect: Z = 1.48 (P = 0.14)



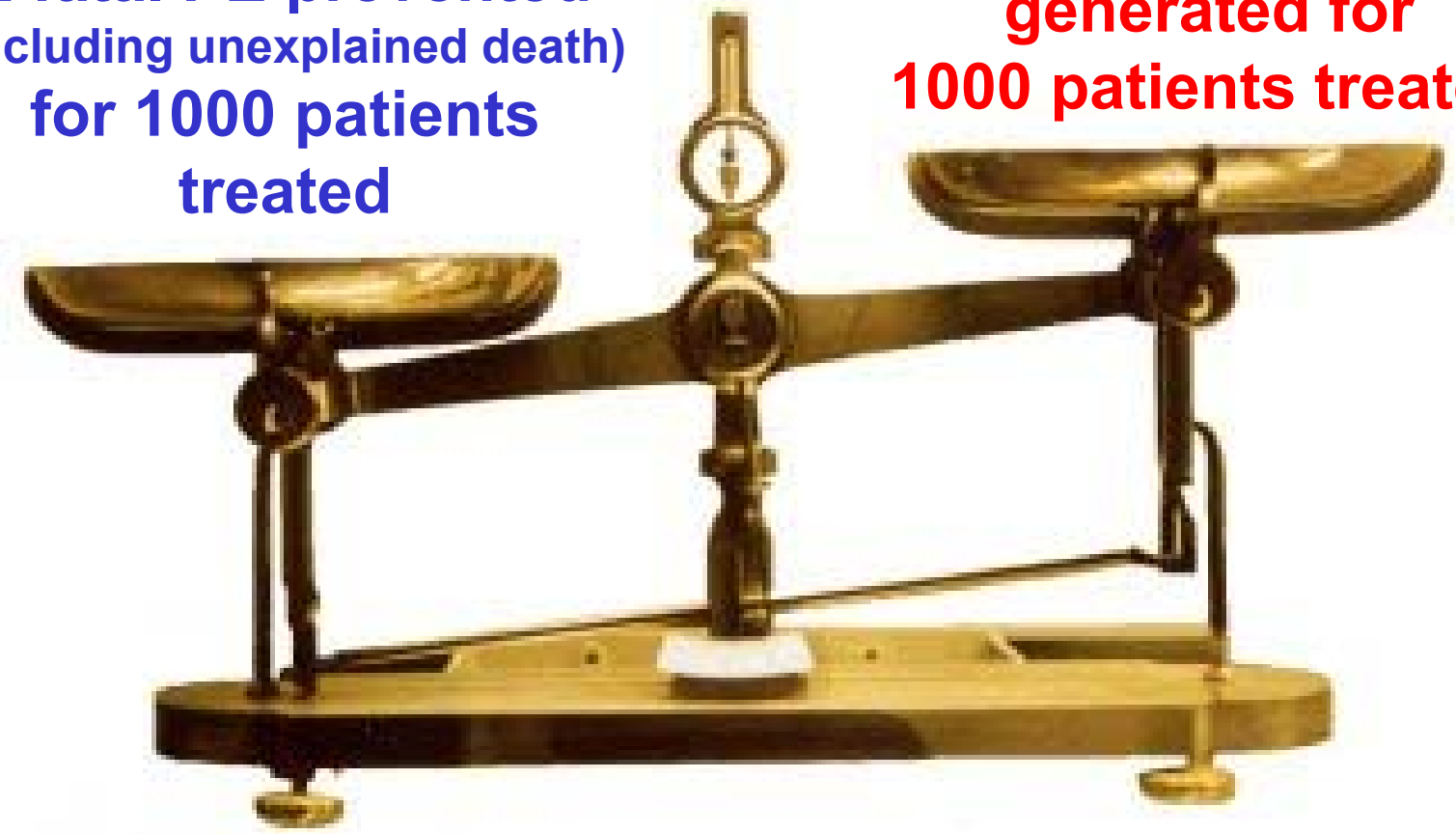
Fatal PE (including unexplained deaths)

2 fatal PE prevented
(including unexplained death)
for 1000 patients treated

1 major bleeding

(+25 clinically relevant non-major bleed.)

generated for 1000 patients treated



The case-fatality rate of recurrent VTE is lower (5.1%) than the case-fatality rate of major bleeding (9.1-11%).
[Carrier M et al. 2010 ; Linkins LA et al. 2003; Douketis JD et al. 1998]

Autres stratégies de prévention secondaire

EINSTEIN CHOICE.

Weitz JL et al. Thromb Haemost 2015;114:645-50

- The EINSTEIN CHOICE study is a multicentre, randomised, double-blind, active-controlled, event-driven study comparing the efficacy and safety of two once daily doses of rivaroxaban (20 and 10 mg) with aspirin (100 mg daily) for the prevention of recurrent VTE in patients who completed 6-12 months of anticoagulant therapy for their index acute VTE event.

- All treatments will be given for 12 months. The primary efficacy objective is to determine **whether both doses of rivaroxaban are superior to aspirin for the prevention of symptomatic recurrent VTE**, while the **principal safety outcome is the incidence of major bleeding**.

- The trial is anticipated to enrol 2,850 patients from 230 sites in 31 countries over a period of 27 months.

AMPLIFY-EXT	Apixaban 2,5 mg	Apixaban 5 mg	Placebo	ASA 100 mg
Rate of death from any cause	**0.8%**	**0.5%**	**1,7%**	?

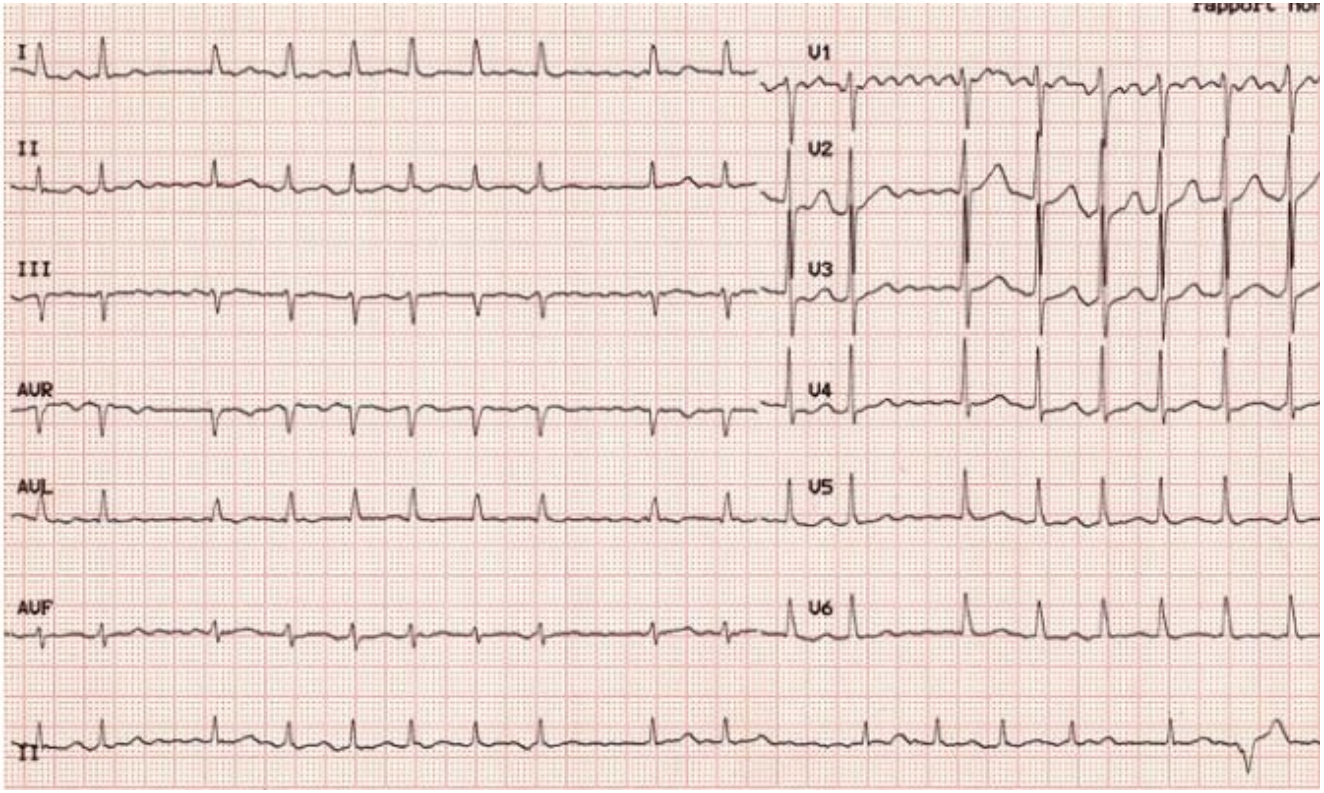
1. Données sur les indications des anticoagulants oraux dans la MTEV.

2. AOD et prévention secondaire de la MTEV

3. Données sur les indications des anticoagulants oraux dans la FA

4. AOD et prévention de la TV en chirurgie orthopédique

5. Ce qui n'est pas (encore) une indication des anticoagulants oraux directs



- La FA est le trouble du rythme cardiaque le plus fréquent.
- L'estimation actuelle de sa prévalence est de 1,5 à 2% de la population générale dans les pays dits développés, avec un âge moyen des patients avec FA qui augmente et qui est compris entre 75 et 85 ans.

- Les données épidémiologiques de la FA montrent que l'âge est fortement associé à sa prévalence qui est <0,5% entre 40 et 50 ans mais atteint 5 à 15% à 80 ans.
- La FA est associée, en l'absence de traitement anticoagulant efficace, à un risque d'accident vasculaire cérébral (AVC) multiplié par 5 ; on estime qu'un AVC sur cinq est dû à une FA.

Stroke risk assessment with CHA_2DS_2-VASc

CHA_2DS_2-VASc criteria	Score
Congestive heart failure/ left ventricular dysfunction	1
Hypertension	1
Age ≥75 yrs	2
Diabetes mellitus	1
Stroke/transient ischaemic attack/TE	2
Vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque)	1
Age 65–74 yrs	1
Sex **c**ategory (i.e. female gender)	1

Total score	Patients (n=7329)	Adjusted stroke rate (%/year)*
0	1	**0.0**
1	422	**1.3**
2	1230	**2.2**
3	1730	**3.2**
4	1718	**4.0**
5	1159	**6.7**
6	679	**9.8**
7	294	**9.6**
8	82	**6.7**
9	14	**15.2**

Lip G. Chest 2010;137:263-72; Lip G. Stroke 2010; 41:2731–8; Camm J. Eur Heart J 2010; 31: 2369–429; Hart RG. Ann Intern Med 2007;146:857–67

Recommandations ESC$_{2016}$

Risk category	$CHA_2DS_2VAS_C$ score	Recommended antithrombotic therapy
One ‘major’ risk factor **or** ≥ 2 ‘clinically relevant non major ‘ risk factor	≥ 2	OAC
One ‘clinically relevant non major ‘	1	Either OAC or aspirin 75-325 mg daily. Preferred: OAC rather than aspirin
No risk factor	0	Either aspirin 75- 325 mg daily or no antithrombotic therpy. Preferred: no antithrombotic therapy rather than aspirin

Camm J. Eur Heart J. 2010 ; 31:2369-429.

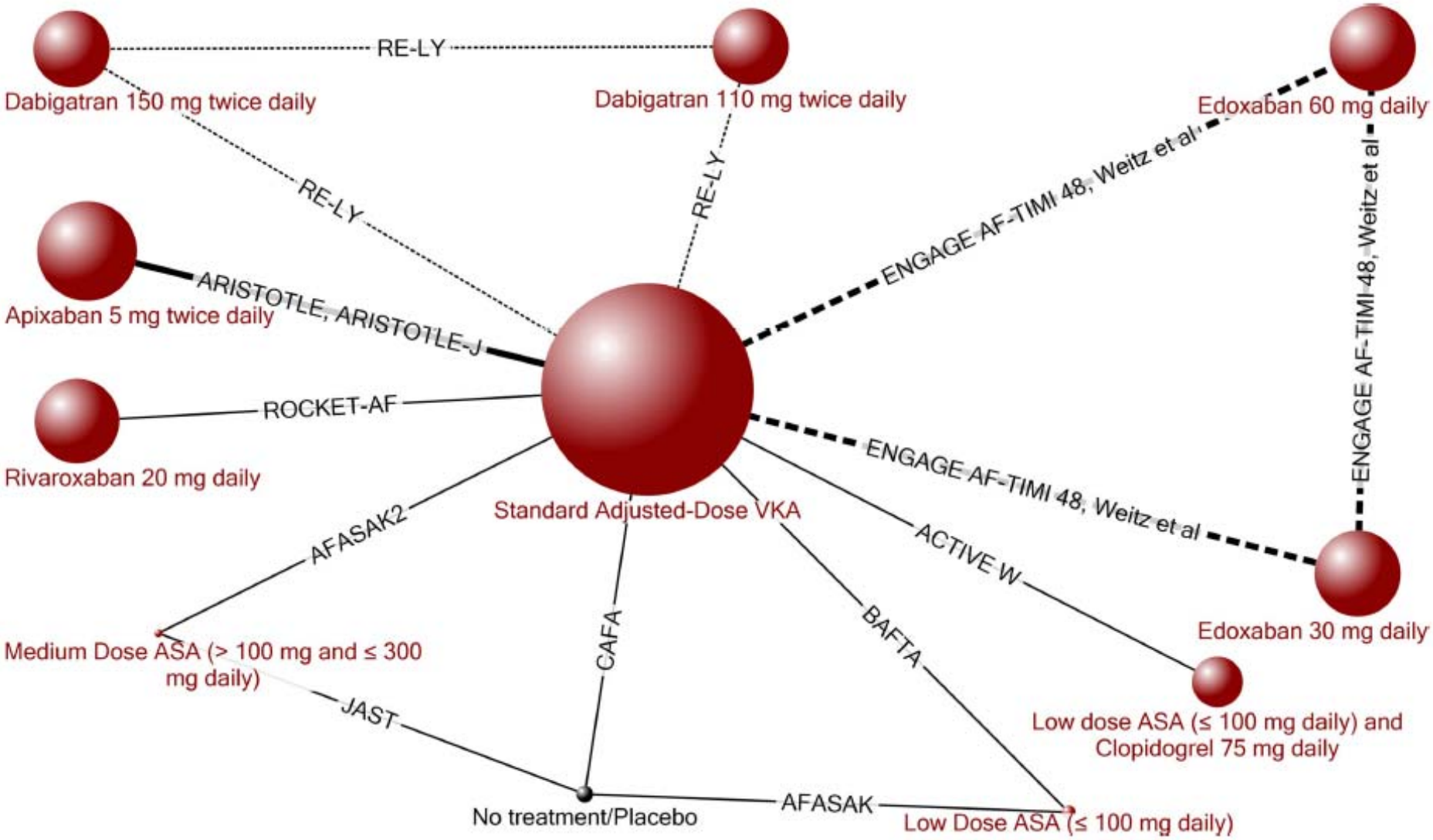
Bleeding Score HAS-BLED (max : 9)

Letter	Clinical characteristics	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INR	1
E	Elderly (e.g age> 65 years)	1
D	Drugs or alcool (1 point each)	1 or 2
		Maximum 9 points

Score of ≥3 indicates “high risk“, and some caution and regular review of the patient is needed following the initiation of antithrombotic therapy.

Camm J. Eur Heart J. 2010 ; 31:2369-429.

Les antithrombotiques et la FA

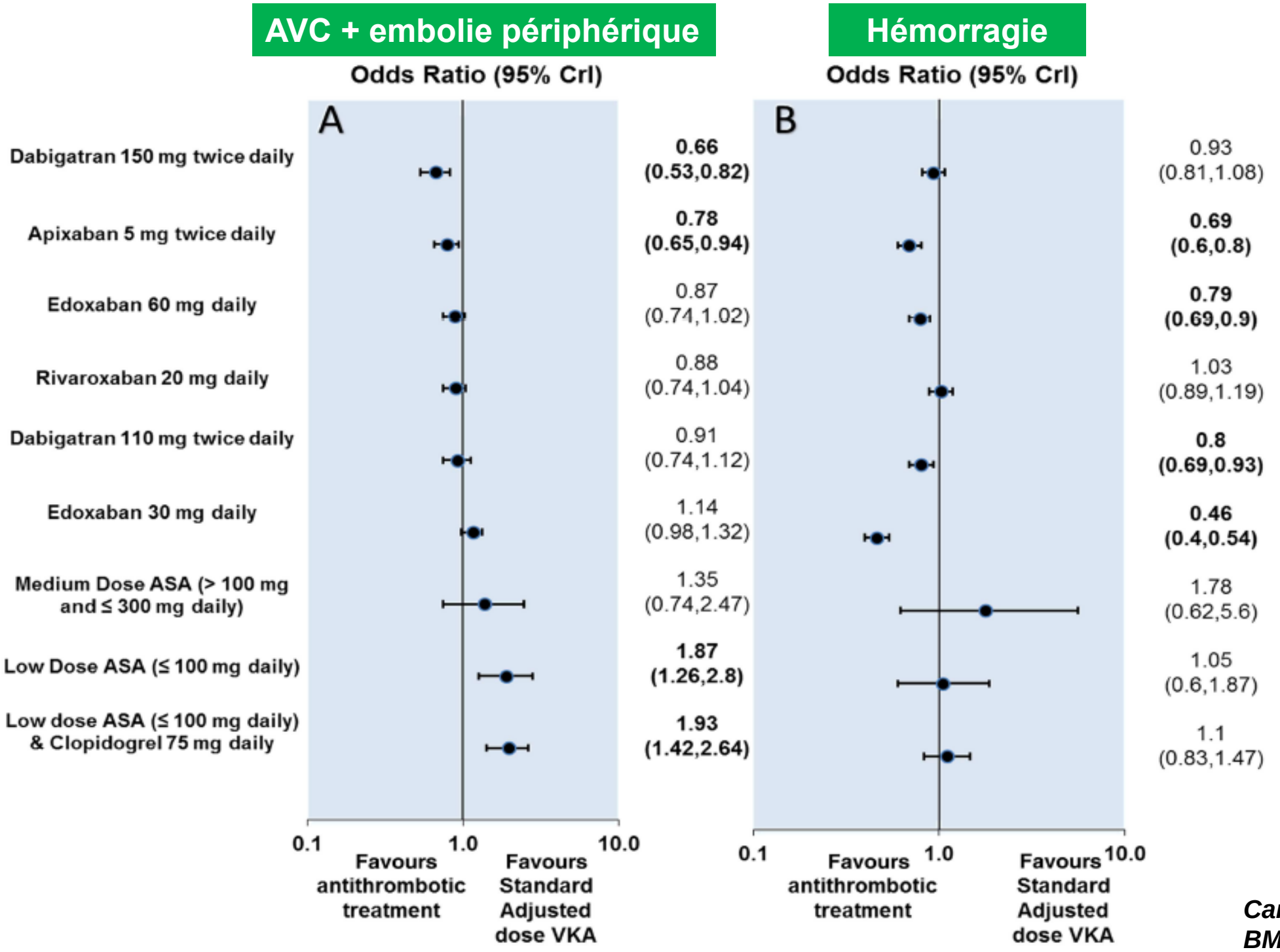


Cameron et al, BMJ Open 2014

ESC Guidelines for FA - 2016

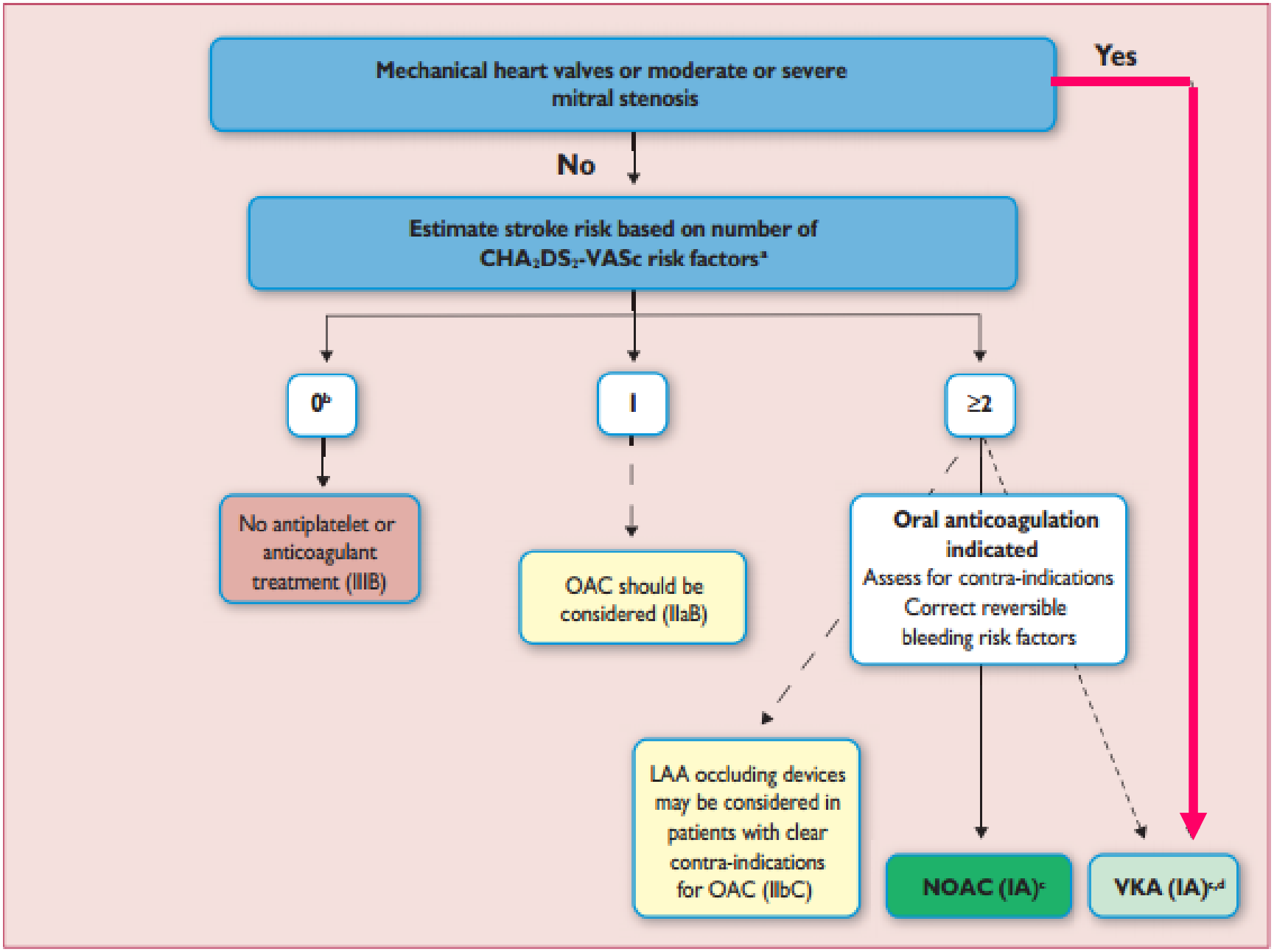
	Dabigatran (RE-LY)	Rivaroxaban (ROCKET-AF)	Apixaban (ARISTOTLE)	Edoxaban (ENGAGE AF-TIMI 48)
Mechanism	Oral direct thrombin inhibitor	Oral direct factor Xa inhibitor	Oral direct factor Xa inhibitor	Oral direct factor Xa inhibitor
Bioavailability, %	6	66 fasting, 80–100 with food	50	62
Time to peak levels, hours	3	2–4	3	1–2
Half-life, hours	12–17	5–13	9–14	10–14
Excretion	80% renal	66% liver, 33% renal	27% renal	50% renal
Dose	150 mg twice daily or 110 mg twice daily	20 mg once daily	5 mg twice daily	60 mg once daily or 30 mg once daily
Dose reduction in selected patients		Rivaroxaban 15 mg once daily if CrCl 30-49 mL/min	Apixaban 2.5 mg twice daily if at least 2 of age ≥80 years, body weight ≤60 kg or serum creatinine level ≥1.5 mg/dL (133 µmol/L)	Edoxaban 60 mg reduced to 30 mg once daily, and edoxaban 30 mg reduced to 15 mg once daily, if any of the following: creatinine clearance of 30–50 mL/min, body weight ≤60 kg, concomitant use of verapamil or quinidine or dronedarone
Study design	Randomized, open-label	Randomized, double-blind	Randomized, double-blind	Randomized, double-blind
Number of patients	18 113	14 264	18 201	21 105 (71683)
Follow-up period, years	2	1.9	1.8	2.8
Randomized groups	Dose-adjusted warfarin vs. blinded doses of dabigatran (150 mg twice daily, 110 mg twice daily)	Dose-adjusted warfarin vs. rivaroxaban 20 mg once daily	Dose-adjusted warfarin vs. apixaban 5 mg twice daily	Dose-adjusted warfarin vs. edoxaban (60 mg once daily, 30 mg once daily)
Age, years	71.5 ± 8.7 (mean ± SD)	73 (65–78) [median (interquartile range)]	70 (63–76) [median (interquartile range)]	72 (64–78) [median (interquartile range)]
Male sex, %	63.6	60.3	64.5	61.9
$CHADS_2$ score (mean)	2.1	3.5	2.1	2.8

	Dabigatran (RE-LY)			Rivaroxaban (ROCKET-AF)		Apixaban (ARISTOTLE)		Edoxaban (ENGAGE AF-TIMI 48)		
	Warfarin	Dabigatran 150	Dabigatran 110	Warfarin	Rivaroxaban	Warfarin	Apixaban	Warfarin	Edoxaban 60	Edoxaban 30
	n = 6022	*n* = 6076	*n* = 6015	*n* = 7133	*n* = 7131	*n* = 9081	*n* = 9120	*n* = 7036	n = 7035	*n* = 7034
	Event rate, %/year	Event rate, %/year (RR vs. warfarin)	Event rate, %/year (RR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year (HR vs. warfarin)
Stroke/systemic embolism	1.72	1.12 (0.65, 0.52–0.81; *P* for non-inferiority and superiority <0.001)	1.54 (0.89, 0.73–1.09; *P* for non-inferiority <0.001)	2.4	2.1 (0.88, 0.75–1.03; *P* for non-inferiority <0.001, *P* for superiority = 0.12)	1.60	1.27 (0.79, 0.66–0.95; *P* <0.001 for non-inferiority, *P* = 0.01 for superiority)	1.80	1.57 (0.87, 0.73–1.04; *P* <0.001 for non-inferiority, *P* = 0.08 for superiority)	2.04 (1.13, 0.96–1.34; *P* = 0.005 for non-inferiority, *P* = 0.10 for superiority)
Ischaemic stroke	1.22	0.93 (0.76, 0.59–0.97; *P* = 0.03)	1.34 (1.10, 0.88–1.37; *P* = 0.42)	1.42	1.34 (0.94; 0.75–1.17; *P* = 0.581)	1.05	0.97 (0.92, 0.74–1.13; *P* = 0.42)	1.25	1.25 (1.00, 0.83–1.19; *P* = 0.97)	1.77 (1.41, 1.19–1.67; *P* <0.001)
Haemorrhagic stroke	0.38	0.10 (0.26, 0.14–0.49; *P* <0.001)	0.12 (0.31, 0.17–0.56; *P* <0.001)	0.44	0.26 (0.59; 0.37–0.93; *P* = 0.024)	0.47	0.24 (0.51, 0.35–0.75; *P* <0.001)	0.47	0.26 (0.54, 0.38–0.77; *P* <0.001)	0.16 (0.33, 0.22–0.50; *P* <0.001)
Major bleeding	3.61	3.40 (0.94, 0.82–1.08; *P* = 0.41)	2.92 (0.80, 0.70–0.93; *P* = 0.003)	3.45	3.60 (1.04; 0.90-2.30; *P* = 0.58)	3.09	2.13 (0.69, 0.60–0.80; *P* <0.001)	3.43	2.75 (0.80, 0.71–0.91; *P* <0.001)	1.61 (0.47, 0.41–0.55; *P* <0.001)
Intracranial bleeding	0.77	0.32 (0.42, 0.29–0.61; *P* <0.001)	0.23 (0.29 0.19–0.45; *P* <0.001)	0.74	0.49 (0.67; 0.47–0.93; *P* = 0.02)	0.80	0.33 (0.42, 0.30–0.58; *P* <0.001)	0.85	0.39 (0.47, 0.34–0.63; *P* <0.001)	0.26 (0.30, 0.21–0.43; *P* <0.001)
Gastrointestinal major bleeding	1.09	1.60 (1.48, 1.19–1.86; *P* <0.001)	1.13 (1.04, 0.82–1.33; *P* = 0.74)	1.24	2.00 (1.61; 1.30-1.99; *P* < 0.001)	0.86	0.76 (0.89, 0.70–1.15; *P* = 0.37)	1.23	1.51 (1.23, 1.02–1.50; *P* = 0.03)	0.82 (0.67, 0.53–0.83; *P* <0.001)
Myocardial infarction	0.64	0.81 (1.27, 0.94-1.71; *P* = 0.12)	0.82 (1.29, 0.96-1.75; *P* = 0.09)	1.12	0.91 (0.81; 0.63–1.06; *P* = 0.12)	0.61	0.53 (0.88, 0.66–1.17; *P* = 0.37)	0.75	0.70 (0.94, 0.74–1.19; *P* = 0.60)	0.89 (1.19, 0.95–1.49; *P* = 0.13)
Death from any cause	4.13	3.64 (0.88, 0.77–1.00; *P* = 0.051)	3.75 (0.91, 0.80–1.03; *P* = 0.13)	2.21	1.87 (0.85; 0.70–1.02; *P* = 0.07)	3.94	3.52 (0.89, 0.80–0.99; *P* = 0.047)	4.35	3.99 (0.92, 0.83–1.01; *P* = 0.08)	3.80 (0.87, 0.79–0.96; *P* = 0.006)

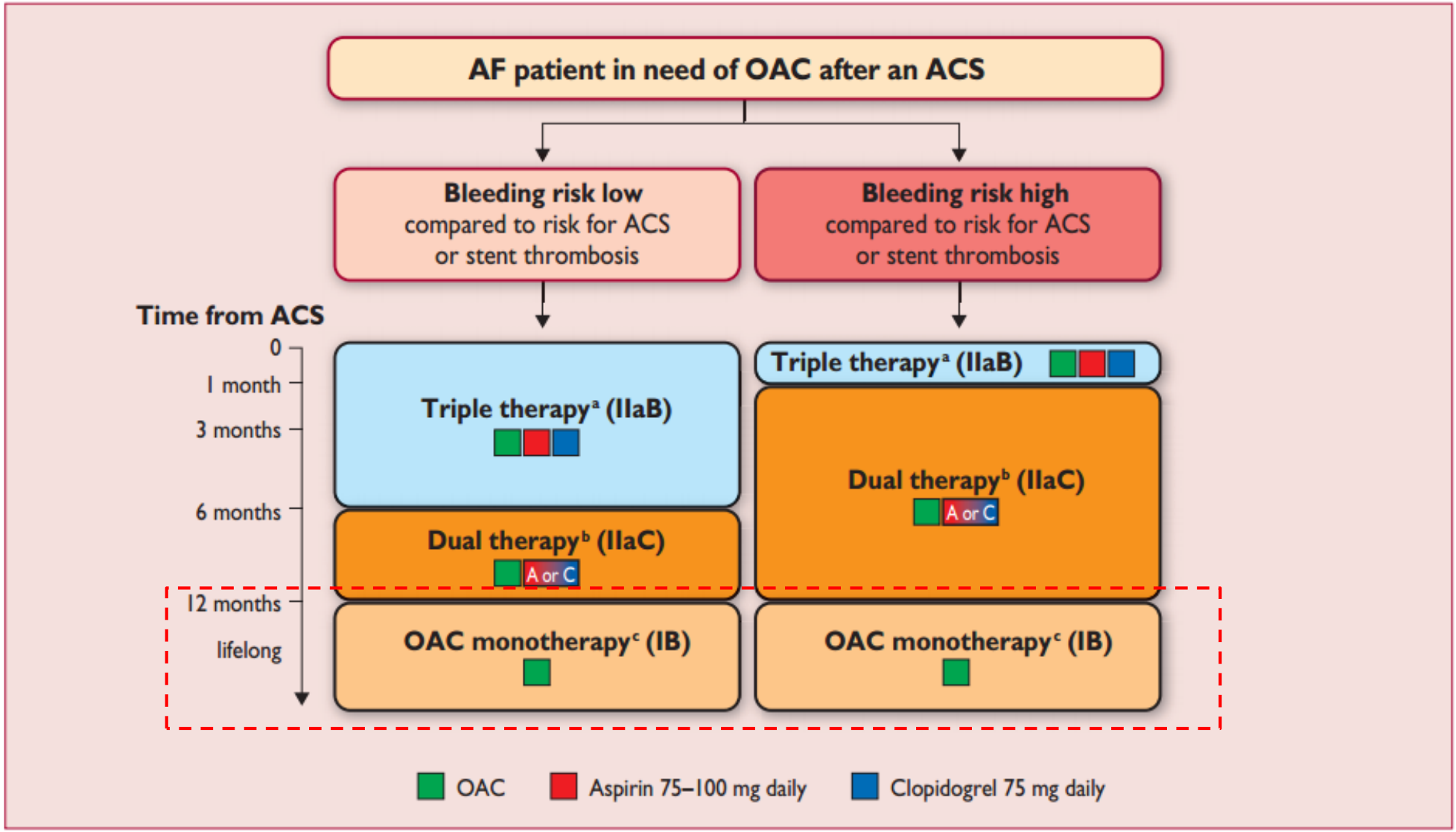


Cameron et al, BMJ Open 2014

ESC Guidelines for FA - 2016



ESC Guidelines for FA - 2016



ACS = acute coronary syndrome; AF = atrial fibrillation; OAC = oral anticoagulation (using vitamin K antagonists or non-vitamin K antagonist oral anticoagulants); PCI = percutaneous coronary intervention.

[a]Dual therapy with OAC and aspirin or clopidogrel may be considered in selected patients, especially those not receiving a stent or patients at a longer time from the index event.

[b]OAC plus single antiplatelet.

[c]Dual therapy with OAC and an antiplatelet agent (aspirin or clopidogrel) may be considered in patients at high risk of coronary events.

1. Données sur les indications des anticoagulants oraux dans la MTEV.

2. AOD et prévention secondaire de la MTEV

3. Données sur les indications des anticoagulants oraux dans la FA

4. AOD et prévention de la TV en chirurgie orthopédique

5. Ce qui n'est pas (encore) une indication des anticoagulants oraux directs

Bon usage des antithrombotiques

PREVENTION ET DUREE DE TRAITEMENT EN CHIRURGIE ORTHOPEDIQUE

Risque chirurgical		Traitement
Faible	Arthroscopie du genou, hallux valgus, hernie discale, arthroscopie diagnostique ou méniscectomie	Pas de prophylaxie (1-)
Modéré	Fracture extrémité distale du membre inférieur (tibia péroné, cheville et pied) rupture Tendon d'Achille, plâtre **sans appui : durée immobilisation (2+)** Arthrodèse de rachis, lésion ligamentaire genou ou cheville, tubérosité tibiale antérieure (TTA) **= 8-10 jours (2+)**	HBPM (2+)
Elevé trauma	Fracture diaphyse fémorale = **42 jours ou** **Fracture du col du fémur = 35 jours** Fracture du Plateau et pilon tibial = **durée immobilisation**	HBPM utilisable au-delà du 14ème jour (2+) Fondaparinux (1+)
Elevé	PTH = **35 à 42 jours (1+)** PTG = **14 jours (1+)**, voire 35 jours (2+) Reprises de PTH et PTG : mêmes durées Que ce soit pour la PTH ou la PTG, **un écho-Doppler systématique réalisé avant la sortie n'est pas recommandé** (1-)	HBPM Fondaparinux Dabigatran Rivaroxaban Apixaban **Première intention, sans différence**
	Ostéotomie tibiale = 42 jours ou **durée immobilisation**	HBPM (2+)

PTH : prothèse totale hanche, PTG : prothèse totale genou

Dabigatran etexilate for thromboprophylaxis in orthopaedic surgery

Study	Indication	Study arm	Main efficacy outcome*
RE-NOVATE (N=3494)	Total hip arthroplasty	Enoxaparin 40 mg o.d.	6.7%
		Dabigatran 150 mg o.d.	8.6%
		Dabigatran 220 mg o.d.	6.0%
RE-MODEL (N=2076)	Total knee arthroplasty	Enoxaparin 40 mg o.d.	37.7%
		Dabigatran 150 mg o.d.	40.5%
		Dabigatran 220 mg o.d.	36.4%
RE-MOBILIZE (N=2715)	Total knee arthroplasty	Enoxaparin 30 mg b.i.d.	25.3%
		Dabigatran 150 mg o.d.	33.7%**
		Dabigatran 220 mg o.d.	31.1%

* Composite of total venographic and symptomatic VTE and death from all causes

** Non-inferiority criterion not met

MVTE : prévention en chirurgie orthopédique
Pooled Analysis Major VTE and VTE-Related Death

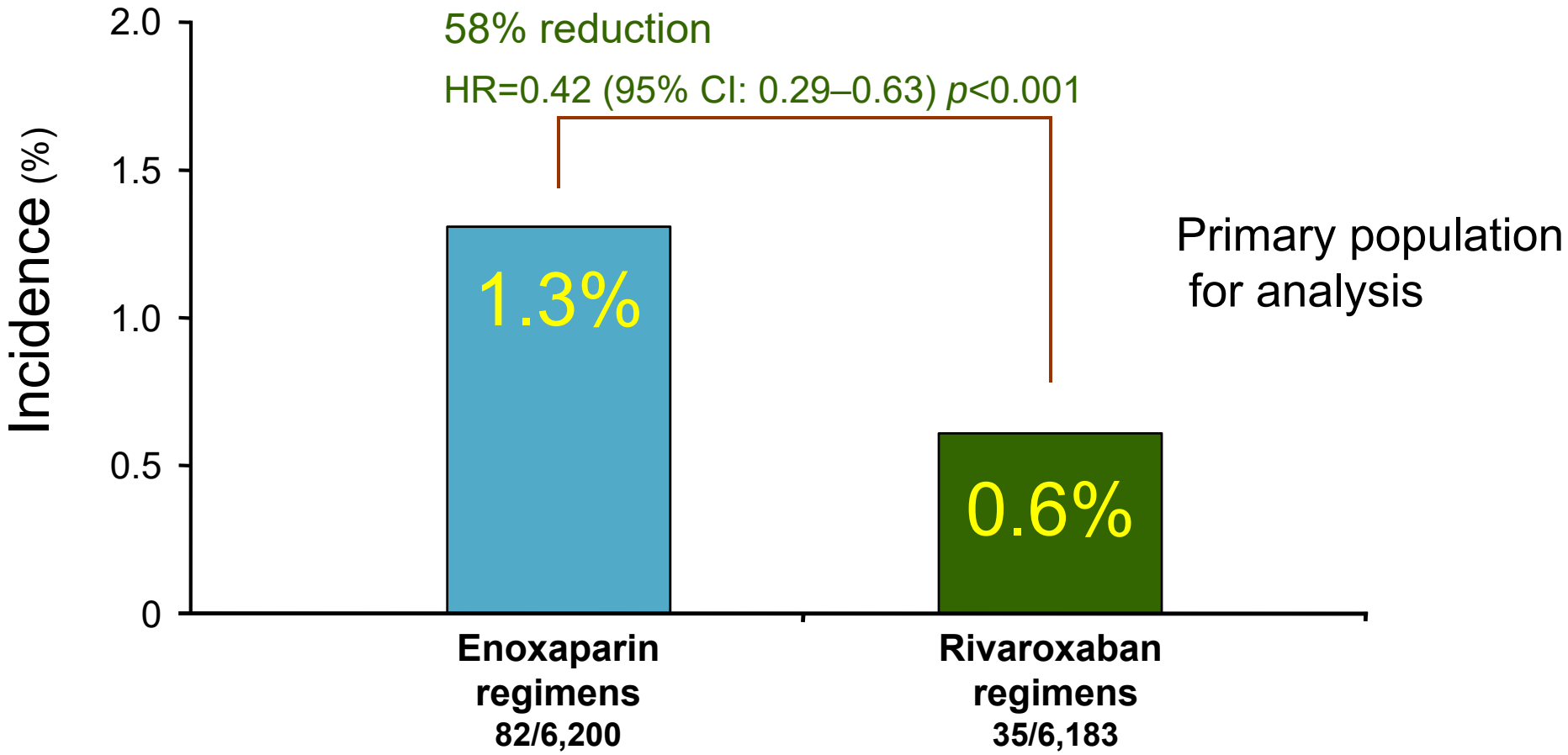
Study	Dabigatran 150 mg	Dabigatran 220 mg	Enoxaparin
RE-NOVATE* (THR)	4.3%	3.1%	3.9%
RE-MODEL (TKR)	3.8%	2.6%	3.5%
RE-MOBILIZE (TKR)	3.0%	3.4%	2.2%
Pooled	**3.8%**	**3.0%**	**3.3%**
Absolute risk difference	0.5	-0.2	
(Dabigatran – Enoxaparin) [95% CI]	[-0.6 to 1.6]	[-1.3 to 0.9]	

Eriksson BI. *Lancet* 2007;370:949-56

RECORD 1-4: Primary efficacy outcome
Total treatment duration pool

RECORD

Symptomatic VTE + all-cause mortality

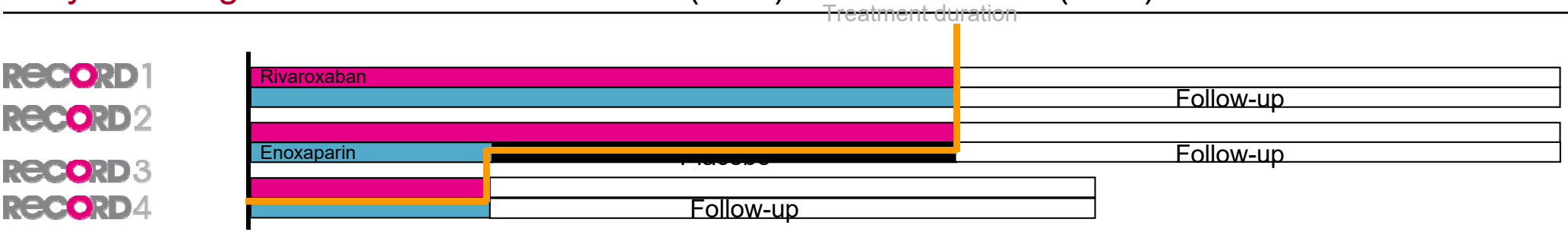


Homogeneity test, *p*=0.313; safety population, n=12,383

Turpie AG.

Treatment-emergent bleeding

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

Apixaban or Enoxaparin for Thromboprophylaxis after Knee Replacement

Michael Rud Lassen, M.D., Gary E. Raskob, Ph.D., Alexander Gallus, M.D., Graham Pineo, M.D., Dalei Chen, Ph.D., and Ronald J. Portman, M.D.

N Engl J Med 2009;361:594-604

2.5 mg of apixaban orally twice daily or 30 mg of enoxaparin SC every 12 hours
Overall rate of primary events much lower than anticipated.

Outcome	Patients with Events				Relative Risk (95% CI)	Difference in Risk (95% CI)
	Apixaban		Enoxaparin			
	no./total no. (%)	*95% CI*	*no./total no. (%)*	*95% CI*		
Intended treatment period						
All VTE and death from any cause	104/1157 (9.0)	7.47–10.79	100/1130 (8.8)	7.33–10.66	1.02 (0.78 to 1.32)	0.11 (–2.22 to 2.44)
Major VTE and death from any cause†	26/1269 (2.0)	1.39–3.01	20/1216 (1.6)	1.06–2.55	1.25 (0.70 to 2.23)	0.36 (–0.68 to 1.40)
Symptomatic VTE and VTE-related death	19/1599 (1.2)	0.75–2.95	13/1596 (0.8)	0.46–1.41	1.46 (0.72 to 2.95)	0.38 (–0.30 to 1.06)

Composite incidence of **major bleeding and clinically relevant non-major bleeding:** 2.9% with apixaban and 4.3% with enoxaparin (P = 0.03).

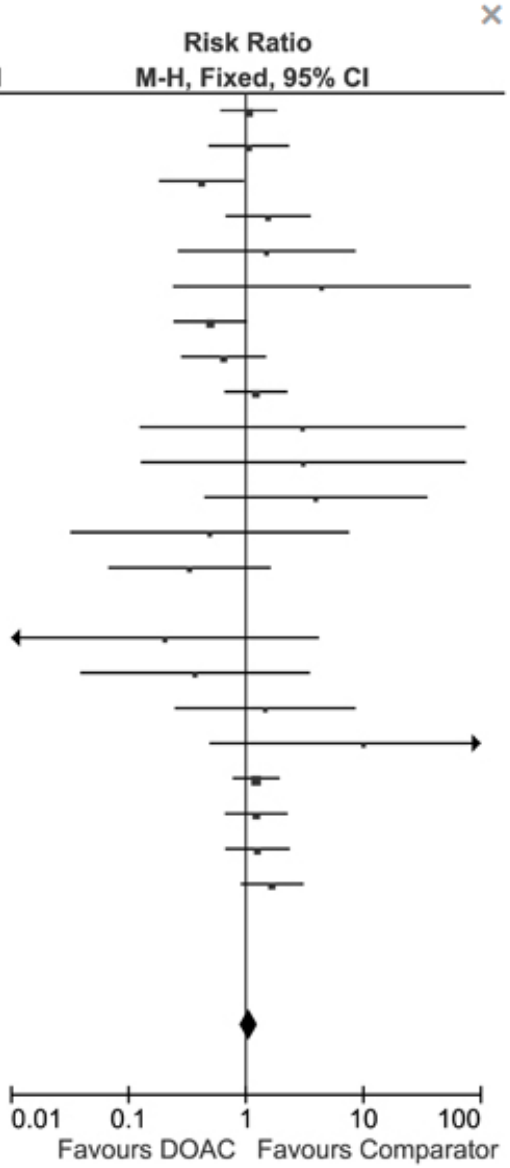
Lassen MR. N Engl J Med. 2009;361:594-604

Major Bleeding and Case Fatality Rate with the Direct Oral Anticoagulantsin Orthopedic Surgery: A Systematic Review and Meta-Analysis. *Riva N et al. Semin Thromb Haemost 2016;42:42-54*

Study or Subgroup	DOAC Events	DOAC Total	LMWH/fondaparinux Events	LMWH/fondaparinux Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RE-NOVATE	38	2309	18	1154	11.0%	1.06 [0.60, 1.84]
RE-MODEL	19	1382	9	694	5.5%	1.06 [0.48, 2.33]
RE-MOBILIZE	10	1728	12	868	7.3%	0.42 [0.18, 0.97]
RE-NOVATE II	14	1010	9	1003	4.1%	1.54 [0.67, 3.55]
Mirdamadi	3	45	2	45	0.9%	1.50 [0.26, 8.55]
APROPOS	4	305	0	149	0.3%	4.41 [0.24, 81.41]
ADVANCE-1	11	1596	22	1588	10.1%	0.50 [0.24, 1.02]
ADVANCE-2	9	1501	14	1508	6.4%	0.65 [0.28, 1.49]
ADVANCE-3	22	2673	18	2659	8.3%	1.22 [0.65, 2.26]
Raskob	1	170	0	172	0.2%	3.04 [0.12, 73.98]
STARS J-2	1	85	0	87	0.2%	3.07 [0.13, 74.32]
STARS E-3	4	354	1	349	0.5%	3.94 [0.44, 35.11]
STARS J-4	1	59	1	29	0.6%	0.49 [0.03, 7.58]
STARS J-5	2	303	6	301	2.8%	0.33 [0.07, 1.63]
Fuji	0	22	0	20		Not estimable
ODIXa-KNEE	0	102	2	104	1.1%	0.20 [0.01, 4.20]
ODIXa-OD-HIP	1	142	3	157	1.3%	0.37 [0.04, 3.50]
ODIXa-HIP 2006	3	136	2	132	0.9%	1.46 [0.25, 8.57]
ODIXa-HIP 2007	2	80	0	162	0.2%	10.06 [0.49, 207.14]
RECORD1	40	2209	33	2224	15.0%	1.22 [0.77, 1.93]
RECORD2	22	1228	18	1229	8.2%	1.22 [0.66, 2.27]
RECORD3	21	1220	17	1239	7.7%	1.25 [0.67, 2.37]
RECORD4	27	1526	16	1508	7.4%	1.67 [0.90, 3.08]
NCT01205932 (R1)	0	298	0	98		Not estimable
NCT01206972 (R2)	0	224	0	74		Not estimable
Total (95% CI)		**20707**		**17553**	**100.0%**	**1.07 [0.89, 1.29]**
Total events	255		203			

Heterogeneity: Chi² = 24.14, df = 21 (P = 0.29); I² = 13%

Test for overall effect: Z = 0.74 (P = 0.46)



| **Fig. 2** Forest plot evaluating major bleeding during anticoagulant treatment, comparing the direct oral anticoagulants with LMWH/fondaparinux. LMWH, low-molecular-weight heparin.|

Major Bleeding and Case Fatality Rate with the Direct Oral Anticoagulantsin Orthopedic Surgery: A Systematic Review and Meta-Analysis. ***Riva N et al. Semin Thromb Haemost 2016;42:42-54***

- **There was no significant difference between the DOACs and LMWHs in the risk of :**
  - **Major bleeding (1.23 vs. 1.16%; RR: 1.07, 95% CI: 0.89–1.29),**
  - **Fatal bleeding (0.02 vs. 0.01%; RR: 1.63, 95% CI: 0.39–6.77),**
  - **Intracranial bleeding (0 vs. 0.01%; RR: 0.33, 95% CI: 0.03–3.18).**
- **The weighted mean CFR of major bleeding was 3.3% (95% CI, 1.5–5.7) and 2.3% (95% CI, 0.7–4.6), respectively.**
- **Bleeding complications and the associated CFR during prophylactic anticoagulation in orthopedic surgery were very low and not significantly different between the DOACs and LMWHs.**

Bon usage des antithrombotiques

Dabigatran 150 mg/jour et 220 mg/jour, est non inférieur aux HBPM en termes d'efficacité sur les évènements thromboemboliques veineux (ETEV) majeurs.
L'incidence des hémorragies majeures apparait plus faible avec la dose de 150 mg/jour (NS).
Pour les patients âgés de plus de 75 ans et les patients insuffisants rénaux modérés, la dose de 150 mg/jour est suggérée (2+).
En cas de risque thromboembolique surajouté (risque lié au patient, en dehors de l'âge élevé), nous suggérons de ne pas utiliser le dabigatran à la dose de 150 mg/jour (2-).

1 à 4h post-op

Rivaroxaban 10 mg/jour, est supérieur aux HBPM en termes d'efficacité sur les ETEV majeurs et symptomatiques avec une tendance à l'augmentation du risque hémorragique.
En cas de risque thromboembolique surajouté (risque lié au patient), nous suggérons d'utiliser le rivaroxaban à cette dose (2+). En cas de risque hémorragique élevé (risque lié au patient), nous suggérons de ne pas utiliser le rivaroxaban à cette dose (2-).

8h post-op

Apixaban 2,5 mg 2 /jour, est supérieur aux HBPM sur les ETEV majeurs, sans réduction des événements symptomatiques.
L'incidence des hémorragies n'est pas différente de celle observée avec les HBPM. En conséquence, en cas de risque thromboembolique surajouté (risque lié au patient), nous suggérons d'utiliser l'apixaban à cette dose (2+).

12 à 14h post-op

1. Données sur les indications des anticoagulants oraux dans la MTEV.

2. AOD et prévention secondaire de la MTEV

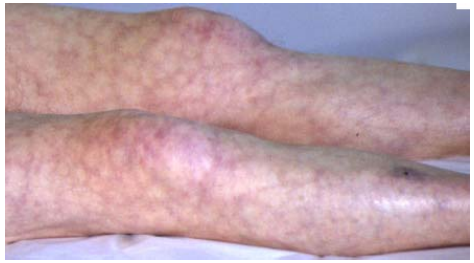
3. Données sur les indications des anticoagulants oraux dans la FA

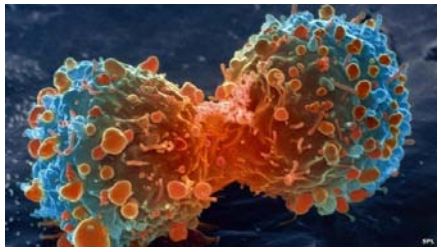
4. AOD et prévention de la TV en chirurgie orthopédique

5. Ce qui n'est pas (encore) une indication des anticoagulants oraux directs

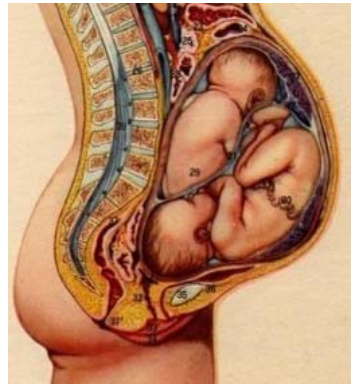
- La fibrillation atriale valvulaire

- Les prothèses valvulaires mécaniques
- Le SAPL.

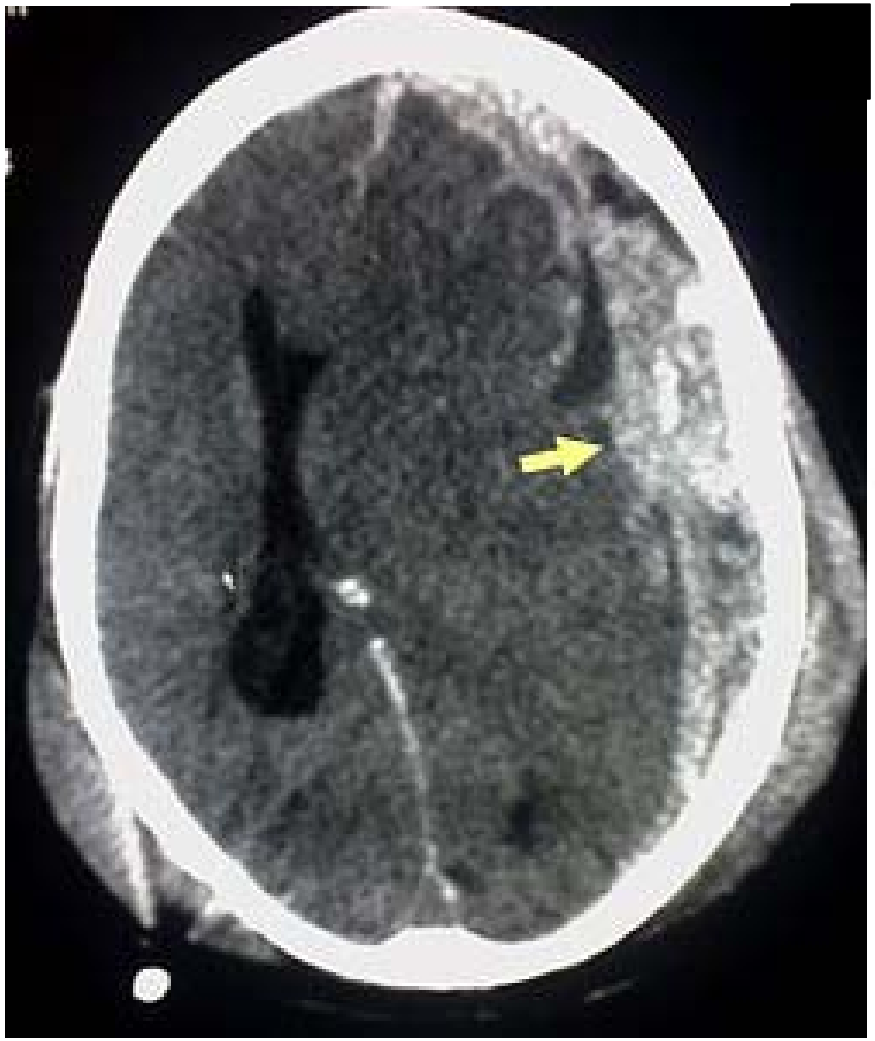


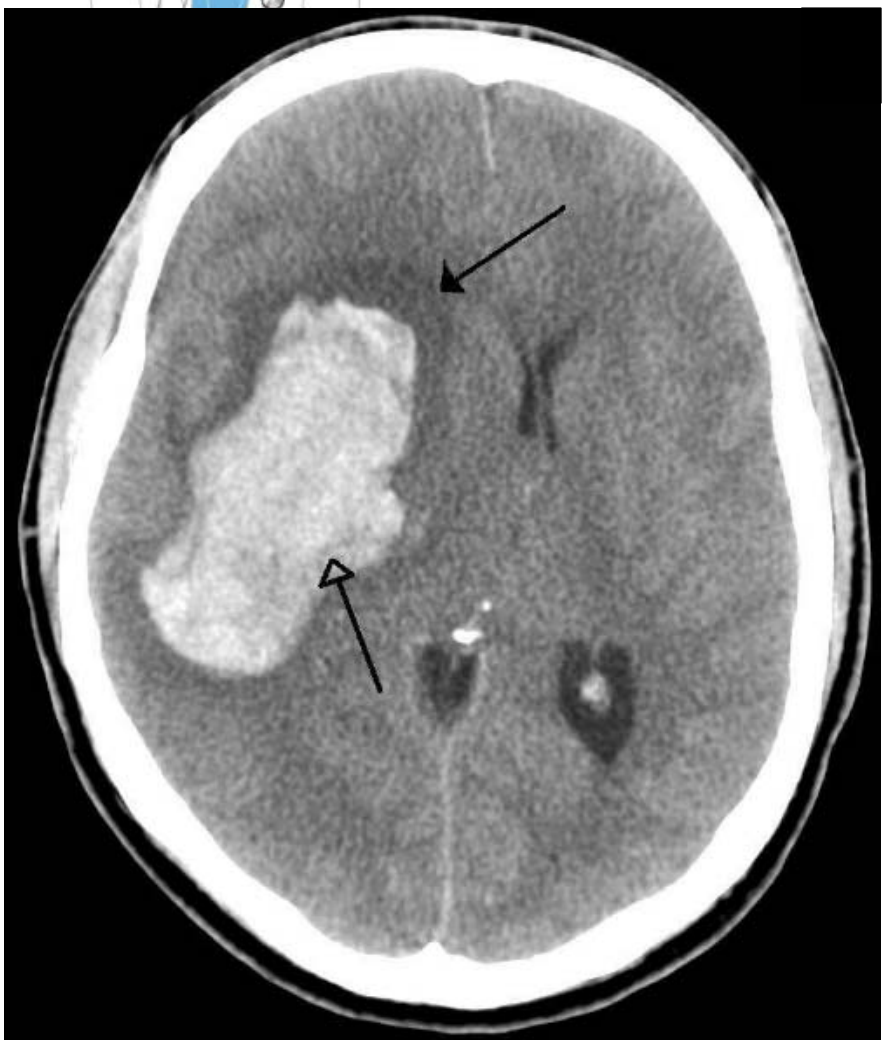


- Les thromboses associées au K.
- La prévention en médecine



- La femme enceinte (HBPM ++)





HSD

HIC

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Bon usage des antithrombotiques

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Schémas posologiques

MTEV

Dabigatran	150 mg x 2 après HBPM/HNF 5 jours
Rivaroxaban	15 mg x 2 pendant 21 jours puis 20 mg une fois par jour
Apixaban	10 mg x 2 pendant 7 jours puis 5 mg x 2
Edoxaban	60 mg x 1 après HBPM/HNF 5 jours

FA

Dabigatran	110 mg x 2 ou 150 mg x 2 (75 mg x 2 si IR ?!)
Rivaroxaban	20 mg une fois par jour (15 mg si Cl Cr 30-49)
Apixaban	5 mg x 2 (2,5 mg x 2 in selected patients)