

Nouveaux anticoagulants et prévention des AVC ischémiques

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AVC et FA: un Buzz !

citations medline

atrial fibrillation and stroke / atrial fibrillation

- 1978 : 9 / 191 (5 %)
- 2002 : 260 / 1381 (19 %)
- 2009 : 567 / 2545 (22 %)
- 2019 : 2075 / 6273 (33 %)

Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: The Framingham Study

Philip A. Wolf, M.D., Thomas R. Dawber, M.D., M.P.H., H. Emerson Thomas, Jr., M.D., and William B. Kannel, M.D., M.P.H.

Oral Anticoagulants vs Aspirin in Nonvalvular Atrial Fibrillation An Individual Patient Meta-analysis

Carl van Walraven, MD, MSc, FRCPC

Robert C. Hart, MD

Daniel E. Singer, MD

Context: Patients with nonvalvular atrial fibrillation (AF) have an increased risk of stroke and other vascular events.

Objective: To compare the risk of vascular and bleeding events in patients with AF treated with vitamin K inhibitors, oral anticoagulants, or aspirin.

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*

AVC et FA

Plus de 5 articles par jour !!!

AVC et FA

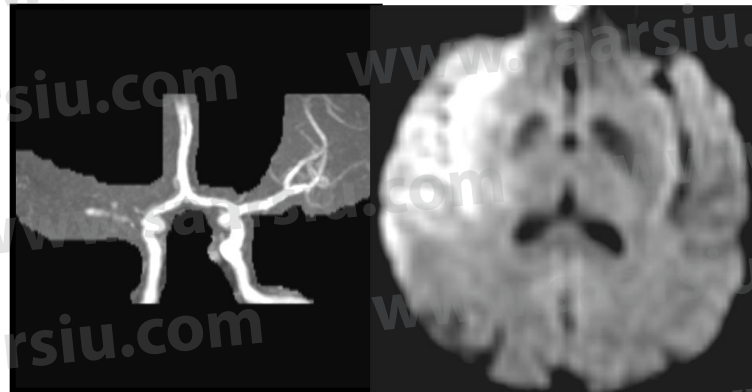
- Beaucoup plus fréquente qu'on ne le pensait dans les AIC et les AIT
- AVK sous prescrits et sous dosés
 - Le risque d'AIC est sous estimé
 - Celui d'hémorragie cérébrale est surestimé
- Anticoagulants oraux directs (AOD)
 - supérieurs à la Warfarine
 - Dans les essais ... et la vraie vie
- La FA paroxystique
 - Quand on cherche on trouve
 - Mais il faut être patient



La sténose de la carotide ne protège pas de la FA ...
... même si elle est chirurgicale

Classiquement

- 10 à 20 % des infarctus cérébraux sont dus à une fibrillation auriculaire

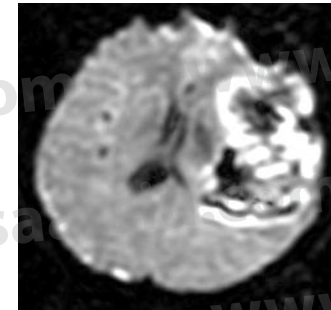


410 patients thrombolysés ≥ 65 ans

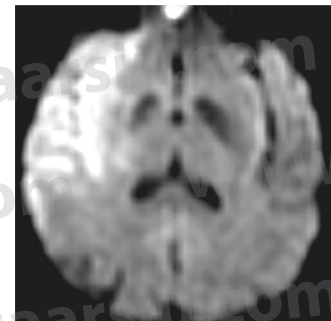
- AC/FA : 49.3 %
- 90 % non anticoagulées

Anticoagulants sous-utilisés et sous-dosés

Par crainte des hémorragies



... Le résultat : des infarctus!!!



1159 AVC < 12 h
(≥ 65 ans)

- 2,3 % : hématomes sous anticoagulants

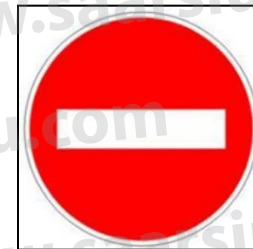
38 % : infarctus & AC/FA
(76 % non anticoagulés)

Les Anticoagulants Oraux Directs

- Pradaxa, Xarelto, Eliquis, Lixiana
- Pas besoin de surveillance coagulation
- Pas d'interférence alimentaire
- Durée d'action courte
- Attention à l'insuffisance rénale

Cockcroft

< 30 ml/min Pradaxa
< 15 ml/min Xarelto



* Sauf Pradaxa

Essais des AOD

- Dabigatran (Re-Ly, 2009)
 - 150 mg*2 Supérieur à la Warfarine
 - 110 mg*2 Non inférieur
- Rivaroxaban (Rocket, 2011)
 - 20 mg Non inférieur
- Apixaban (Aristotle, 2011)
 - 5 mg*2 Supérieur à la Warfarine
- Apixaban (Averroes, 2011)
 - 5 mg*2 supérieur Aspirine
- Edoxaban (Engage AF-Timi 2013)
 - 30 and 60 mg non inferieur Warf



77 284 patients
inclus dans les essais

Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials

Christian T Ruff, Robert P Giugliano, Eugene Braunwald, Elaine B Hoffman, Naveen Deenadayalu, Michael D Ezekowitz, A John Camm, Jeffrey I Weitz, Basil S Lewis, Alexander Parkhomenko, Takeshi Yamashita, Elliott M Antman

Lancet 2014; 383: 955-62

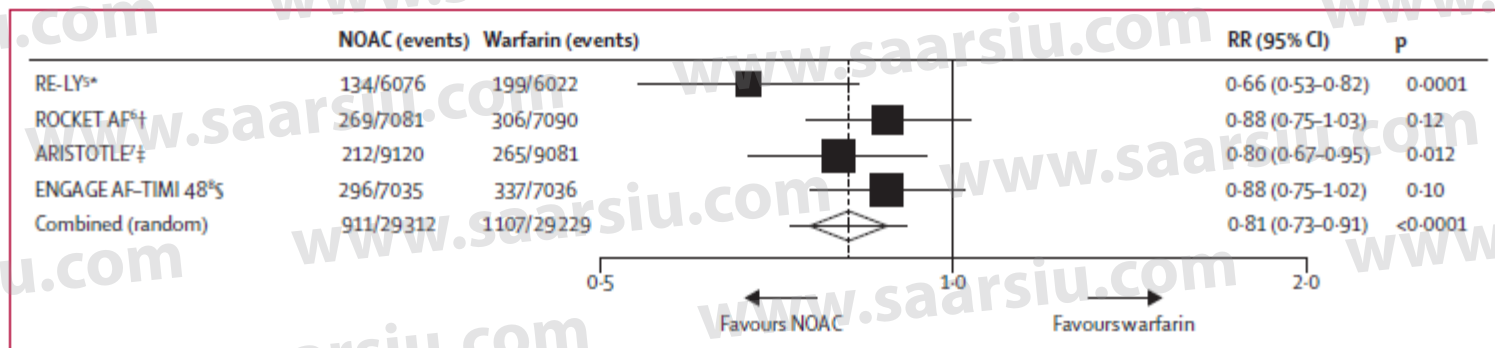


Figure 1: Stroke or systemic embolic events

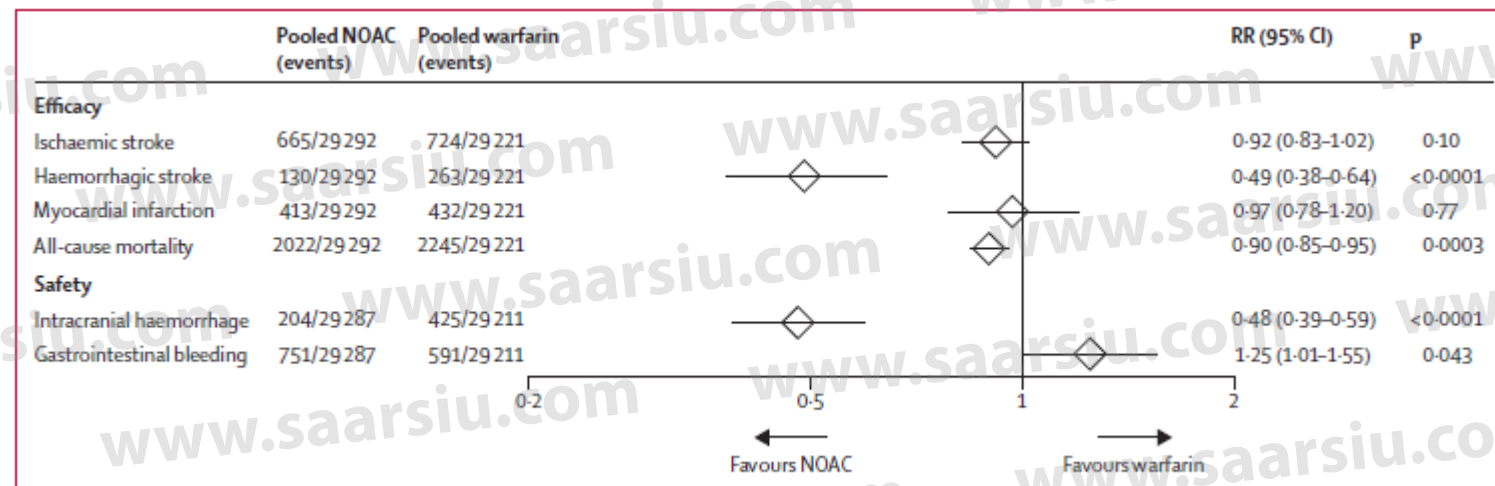


Figure 2: Secondary efficacy and safety outcomes

ATCD AVC-AIT

% patients-years (mean, range)	Aspirin	Warfarin	AOD
All Stroke	8.3	2.8 (2.5-3.2)	2.4 (1.9-3.1)
Brain Hemorrhage	1.1	0.7 (0.5-1.0)	0.3 (0.1-0.4)
Disabling fatal stroke	6.3	1.5 (1.2-1.9)	1.4 (1-1.9)
Major bleeding	2.9	3.8 (3.2-4.2)	3.2 (2-4.2)
Death	7.9	4.3 (3.8-4.6)	4.2 (3.2-5.8)

*Sub-groups Rely, Rocket, Averroes, Aristotle, Lancet Neurol 2010-12
Engage Stroke 2016 (n=21 264)*

Les AOD

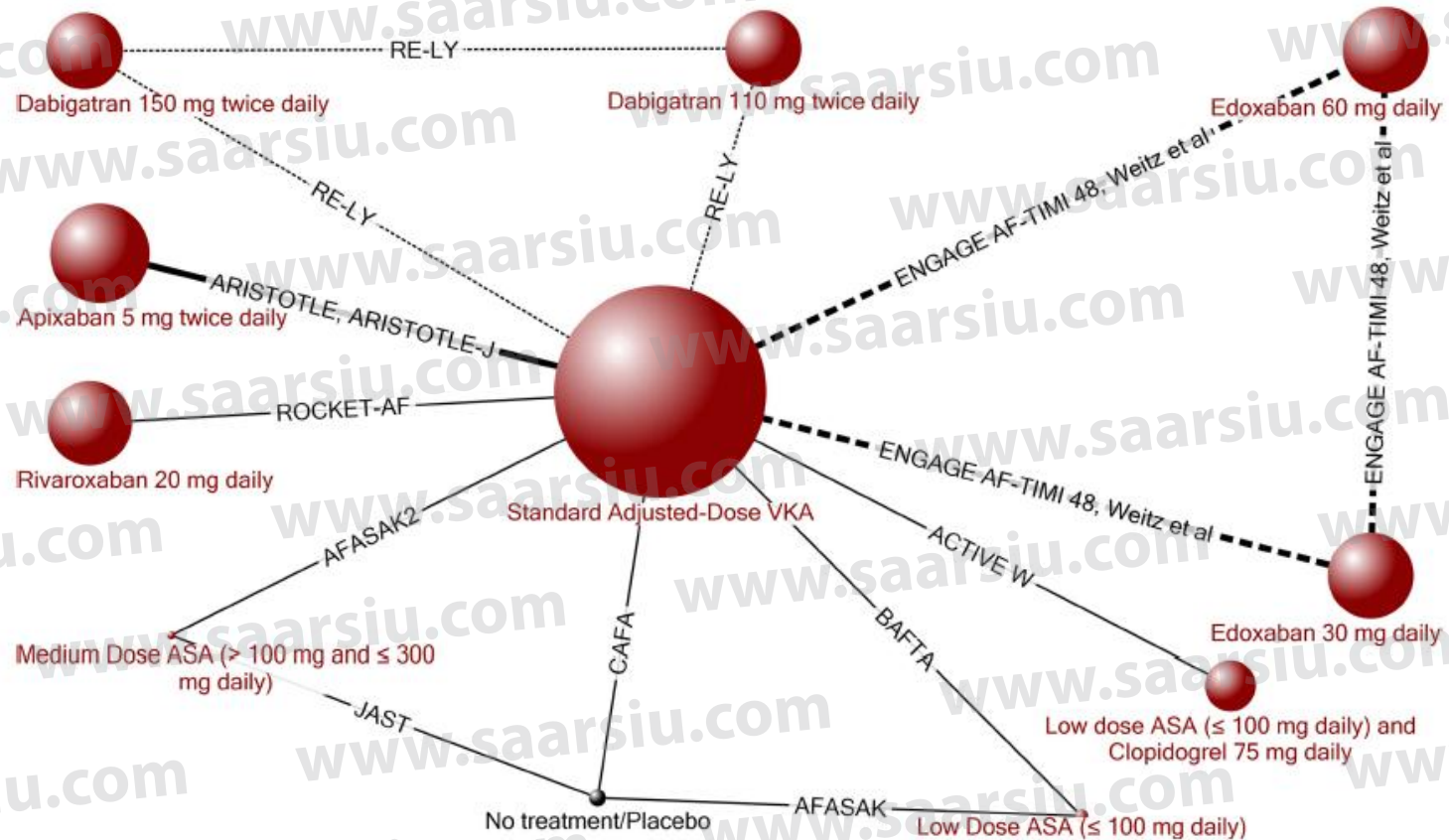
- Quatre fois moins d'AVC
- Trois fois moins d'hémorragies cérébrales
- Deux fois moins de morts

Que l'ASPIRINE

(en cas de FA après un AVC/ AIT)

Network meta-analysis

(Cameron et al. BMJ open 2014)



Anti-agregeants

Hémorragies graves

Standard Adjusted-Dose VKA	0.93 (0.81,1.08)	0.69 (0.6,0.8)	0.79 (0.69,0.9)	1.03 (0.89,1.19)	0.8 (0.69,0.93)	0.46 (0.4,0.54)	1.78 (0.62,5.6)	1.05 (0.6,1.87)	1.1 (0.83,1.47)
0.66 (0.53,0.82)	Dabigatran 150 mg twice daily	0.74 (0.6,0.91)	0.84 (0.69,1.03)	1.1 (0.9,1.35)	0.86 (0.74,1.003)	0.5 (0.4,0.61)	1.91 (0.66,6.08)	1.13 (0.63,2.04)	1.18 (0.85,1.63)
0.78 (0.65,0.94)	1.19 (0.89,1.58)	Apixaban 5 mg twice daily	1.14 (0.93,1.38)	1.49 (1.21,1.82)	1.16 (0.94,1.43)	0.67 (0.54,0.83)	2.57 (0.89,8.18)	1.52 (0.85,2.75)	1.59 (1.16,2.2)
0.87 (0.74,1.02)	1.31 (1.002,1.73)	1.11 (0.87,1.41)	Edoxaban 60 mg daily	1.31 (1.08,1.59)	1.02 (0.83,1.25)	0.59 (0.5,0.69)	2.27 (0.78,7.17)	1.34 (0.75,2.41)	1.4 (1.02,1.92)
0.88 (0.74,1.04)	1.33 (1.01,1.76)	1.12 (0.87,1.43)	1.01 (0.8,1.28)	Rivaroxaban 20 mg daily	0.78 (0.63,0.96)	0.45 (0.37,0.56)	1.74 (0.6,5.48)	1.02 (0.57,1.85)	1.07 (0.78,1.48)
0.91 (0.74,1.12)	1.38 (1.11,1.74)	1.17 (0.88,1.53)	1.05 (0.81,1.37)	1.04 (0.8,1.36)	Dabigatran 110 mg twice daily	0.58 (0.47,0.72)	2.22 (0.77,7.03)	1.31 (0.73,2.37)	1.37 (0.99,1.9)
1.14 (0.98,1.32)	1.73 (1.32,2.26)	1.45 (1.15,1.84)	1.31 (1.13,1.54)	1.3 (1.04,1.63)	1.25 (0.97,1.61)	Edoxaban 30 mg daily	3.85 (1.32,12.18)	2.27 (1.26,4.1)	2.38 (1.72,3.3)
1.35 (0.74,2.47)	2.04 (1.08,3.9)	1.72 (0.92,3.24)	1.56 (0.84,2.91)	1.54 (0.83,2.88)	1.48 (0.79,2.8)	1.18 (0.64,2.21)	Medium Dose ASA (> 100 mg and ≤ 300 mg daily)	0.59 (0.17,1.94)	0.62 (0.19,1.84)
1.87 (1.26,2.8)	2.84 (1.81,4.5)	2.39 (1.55,3.72)	2.16 (1.42,3.34)	2.14 (1.4,3.31)	2.05 (1.32,3.23)	1.64 (1.08,2.53)	1.39 (0.74,2.61)	Low Dose ASA (≤ 100 mg daily)	1.05 (0.55,1.97)
1.93 (1.42,2.64)	2.93 (2.01,4.3)	2.46 (1.73,3.54)	2.23 (1.58,3.17)	2.2 (1.55,3.14)	2.11 (1.46,3.07)	1.69 (1.21,2.4)	1.43 (0.73,2.81)	1.03 (0.62,1.7)	Low dose ASA (≤ 100 mg daily) & Clopidogrel 75 mg daily

AVC ischémiques/embolies

Network meta-analysis, Cameron et al.
BMJ Open 2014

● Mieux

○ NS

● Moins bien

AVK

Hémorragies graves

Standard Adjusted-Dose VKA	0.93 (0.81,1.08)	0.69 (0.6,0.8)	0.79 (0.69,0.9)	1.03 (0.89,1.19)	0.8 (0.69,0.93)	0.46 (0.4,0.54)	1.78 (0.62,5.6)	1.05 (0.6,1.87)	1.1 (0.83,1.47)
0.66 (0.53,0.82)	Dabigatran 150 mg twice daily	0.74 (0.6,0.91)	0.84 (0.69,1.03)	1.1 (0.9,1.35)	0.86 (0.74,1.003)	0.5 (0.4,0.61)	1.91 (0.66,6.08)	1.13 (0.63,2.04)	1.18 (0.85,1.63)
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AVC ischémiques/embolies

● Mieux

○ NS

● Moins bien

Network meta-analysis, Cameron et al.

BMJ Open 2014

APIXABAN 5/DABI 150

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AVC ischémiques/embolies

Network meta-analysis, Cameron et al.
BMJ Open 2014

● Mieux

○ NS

● Moins bien

La vraie vie : le registre danois

Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study

Torben Bjerregaard Larsen,^{1,2} Flemming Skjøth,^{2,3} Peter Brønnum Nielsen,² Jette Nordstrøm Kjældgaard,² Gregory Y H Lip^{2,4}

the **bmj** | *BMJ* 2016;353:i3189 | doi:10.1136/bmj.i3189

61 678 patients

1/8/2011-30/11/2015

AOD doses standards

Pas de contrôle de l'observance

Ischaemic and haemorrhagic stroke associated with non-vitamin K antagonist oral anticoagulants and warfarin use in patients with atrial fibrillation: a nationwide cohort study

Laila Staerk^{1*}, Emil Loldrup Fosbøl^{2,3}, Gregory Y.H. Lip⁴, Morten Lamberts^{1,2}, Anders Nissen Bonde¹, Christian Torp-Pedersen⁵, Brice Ozenne⁶, Thomas Alexander Gerds⁶, Gunnar Hilmar Gislason^{1,3,7,8}, and Jonas Bjerring Olesen^{1,9}

European Heart Journal (2016) 0, 1–9
doi:10.1093/eurheartj/ehw496

43 299 patients

22/8/2011-31/12/2015

AOD toutes doses

Contrôle de l'observance

pas d'arrêt de prescription > 30 jours

OBSERVANCE

AVK : 51 %

Dabi : 59 %

Rivaro : 56 %

Api : 69 %

De l'importance de l'observance (Suivi à un an)

Pas d'arrêt de prescription
> 30 jours

	Warf 18094	Dabi 12613	Rivaro 5693	Api 6899
AIC	1.07	1.04	1.08	1.22
Hemorr intra- Cranienne	0.60	0.26	0.47	0.40

Résultats très proches des
essais randomisés

Pas de contrôle de l'observance
(qui varie de 50 à 70 %)

	Warf 35436	Dabi 12701	Rivaro 7192	Api 6349
AIC	3.01	3.68	2.95	3.72
Hemorr intra- Cranienne	0.55	0.22	0.31	0.40

Trois fois plus d'AVC ischémiques

Meta-analyse des registres occidentaux

AVC Ischémiques

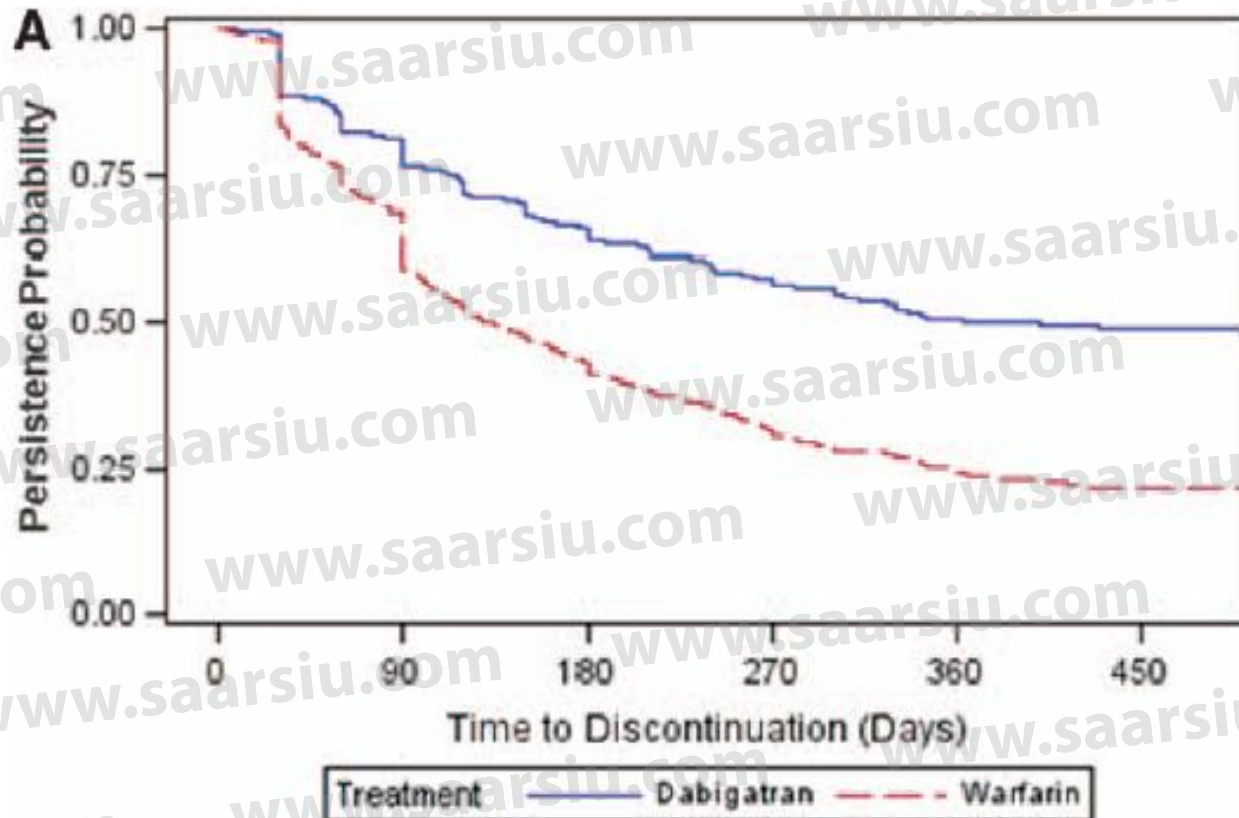
	Tous AOD	AVK
Observance contrôlée	0.9 % (n=264 780)	1.3 % (n=85 301)
Observance non contrôlée	3.4 % (n=26 242)	3 % (n=35 436)

Mortalité

	Tous AOD	AVK
Observance contrôlée	2.3 % (n=186 098)	3.8 % (n=67 207)
Observance non contrôlée	5.4 % (n=28 780)	7.4 % (n=35 436)

Larsen BMJ 2016, Maura Circulation 2015, Graham JAMA int med 2016, Circulation 2015, Yao J AHA 2016, Halvorsen EHJ CPAA 2016, Lip thromb hemost 2016, Coleman CMRO 2016.

New AF patients treated by Warfarin or Dabigatran (discontinuation rate)



La FA paroxystique
est sous-diagnostiquée

5575 AF-free stroke patients

New AF detection rate during one year
Post-discharge in real life ?

- 1 %
- 2 %
- 5 %
- 10 %
- 15 %

?

2 %

Kamel et al J stroke cerebrovasc dis 2012

Freedom from AT/AF

24 h Holter

Cardiomemo*

Loop recording **

Cristal AF > 65 years***

Prior TE Patients

Other Risk Factor Patients

Median time to first detection: 1.7 months (IQR 1.2-2.4)

Months

28

28 %

Median time to first detection: 1.7 months (IQR 0.4-6.7)

Numbers at Risk: 163
1428

127
1091

111
949

106
856

67
592

Prior TE
Other Risk Factors

Time from Device Implant (months)

Ziegler, P. D. et al. Stroke 2010;41:256-260

* Gaillard Neurology 2010, ** Flint Stroke 2012

*** Sanna NEJM 2014

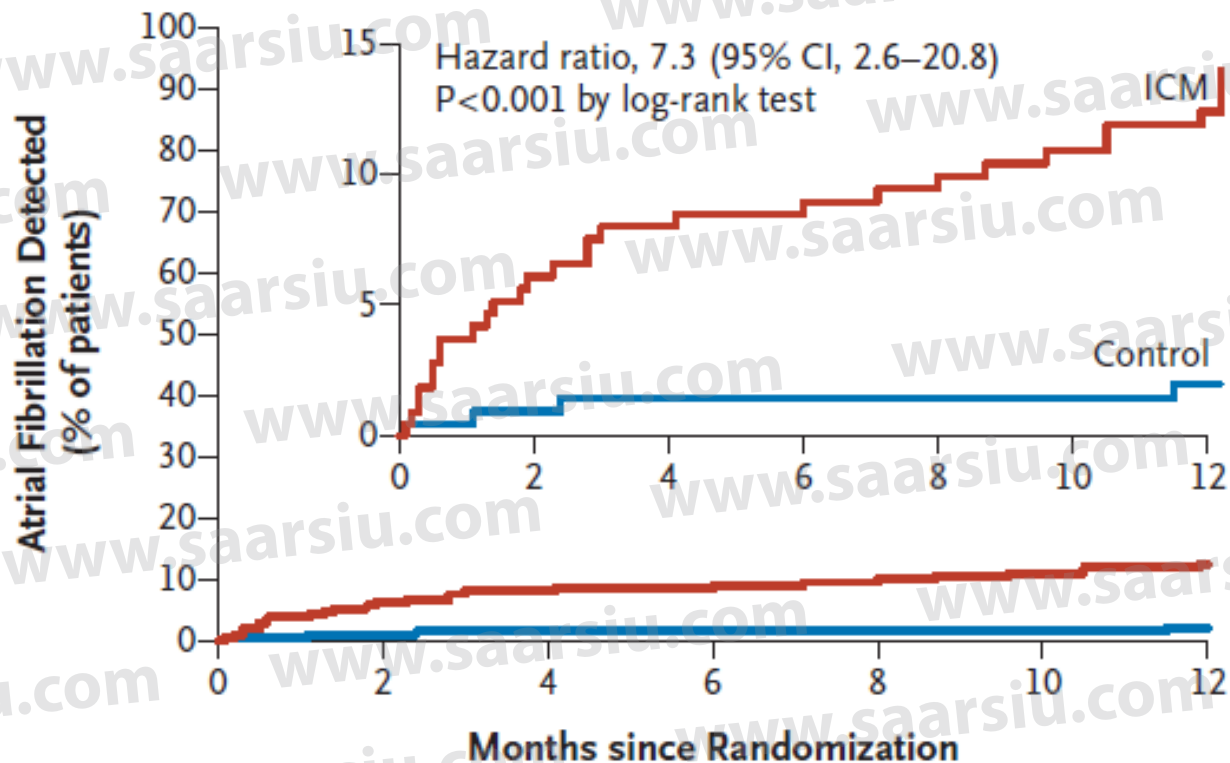


American Heart Association | American Stroke Association

Learn and Live.

Cristal AF (NEJM 2014)

B Detection of Atrial Fibrillation by 12 Months



Nouveaux médicaments ...

... Nouvelles technologies !



Un cadeau d'anniversaire de 60 ans



et un ECG sur tel portable

Un cours
“take your pulse”



apprendre à prendre son pouls



Très rapide ou Irrégulier = ECG



Arrêt bref des Anticoagulants ?

- 1584 interruptions chez 1024 patients (2 ans)
 - 82 % pour gestes mineurs (coloscopie, soins dentaires, chirurgie ophtalmo)
 - 84 % < 6 jours
- 690 interruptions chez patients en AC/FA
 - 97.5 % sans bridging
 - 1.6 % d'évènements à 1 mois (1 patient sur 63)
 - 0.7 % thrombo-emboliques
 - 0.9 % hémorragies

Mon dentiste veut que j'arrête
mon traitement anticoagulant,
Que dois je faire ?

Changez de dentiste !

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation

James D. Douketis, M.D., Alex C. Spyropoulos, M.D., Scott Kaatz, D.O.,
Richard C. Becker, M.D., Joseph A. Caprini, M.D., Andrew S. Dunn, M.D.,
David A. Garcia, M.D., Alan Jacobson, M.D., Amir K. Jaffer, M.D., M.B.A.,
David F. Kong, M.D., Sam Schulman, M.D., Ph.D., Alexander G.G. Turpie, M.B.,
Vic Hasselblad, Ph.D., and Thomas L. Ortel, M.D., Ph.D.,

for the BRIDGE Investigators*

Table 3. Study Outcomes.

Outcome	No Bridging (N=918) <i>number of patients (percent)</i>	Bridging (N=895) <i>number of patients (percent)</i>	P Value
Primary			
Arterial thromboembolism	4 (0.4)	3 (0.3)	0.01*, 0.73†
Stroke	2 (0.2)	3 (0.3)	
Transient ischemic attack	2 (0.2)	0	
Systemic embolism	0	0	
Major bleeding	12 (1.3)	29 (3.2)	0.005†
Secondary			
Death	5 (0.5)	4 (0.4)	0.88†
Myocardial infarction	7 (0.8)	14 (1.6)	0.10†
Deep-vein thrombosis	0	1 (0.1)	0.25†
Pulmonary embolism	0	1 (0.1)	0.25†
Minor bleeding	110 (12.0)	187 (20.9)	<0.001†

* P value for noninferiority.

† P value for superiority.

Composite Endpoint
Stroke, death, MI, DVT, PE
Major bleeding

Number to harm

39

17

Perioperative bridging anticoagulation during dabigatran or warfarin interruption among patients who had an elective surgery or procedure

Substudy of the RE-LY trial

James D. Douketis¹; Jeff S. Healey^{1,2}; Martina Brueckmann^{3,4}; John W. Eikelboom^{1,2}; Michael D. Ezekowitz⁵; Mandy Fraessdorf³; Herbert Noack³; Jonas Oldgren⁶; Paul Reilly⁷; Alex C. Spyropoulos⁸; Lars Wallentin⁶; Stuart J. Connolly^{1,2}

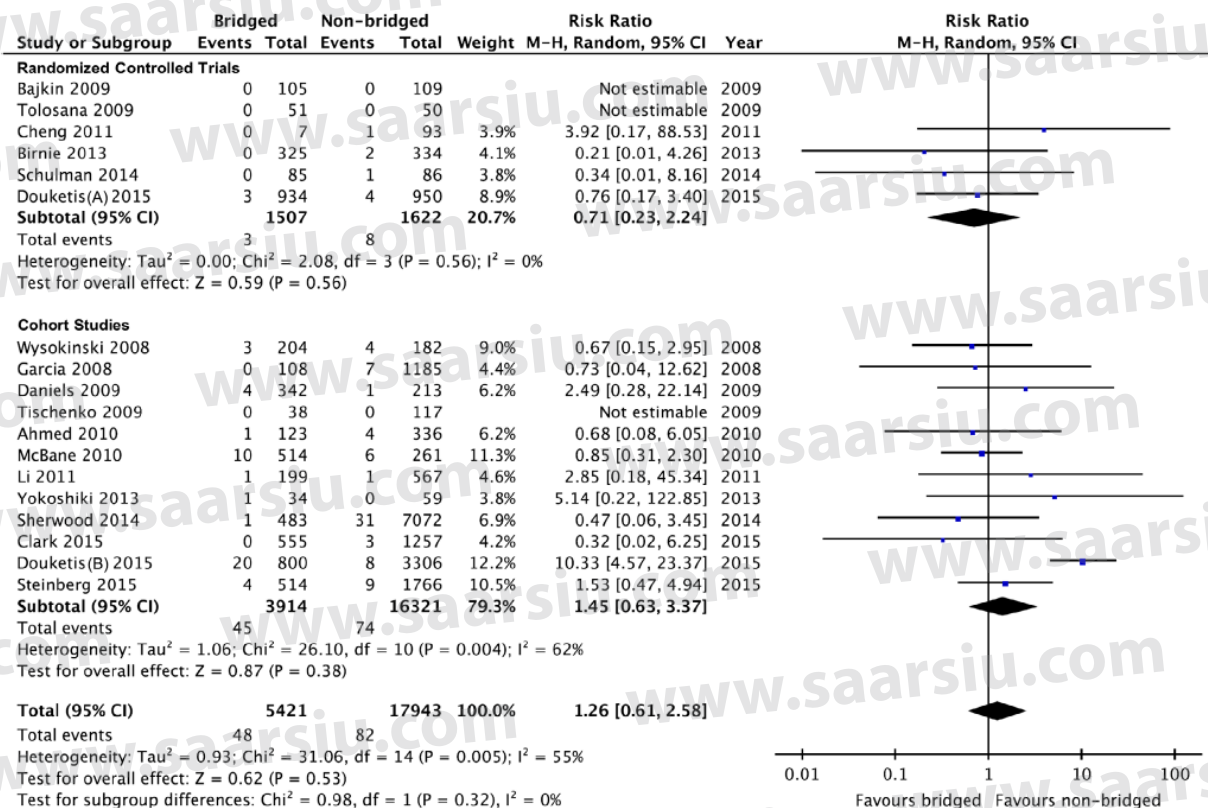
Thrombo-embol + major bleeding
Number to harm

	Bridging	No bridging
Warfarin	12	54
Dabigatran	10	41

Thromboembolic and bleeding risk of periprocedural bridging anticoagulation: A systematic review and meta-analysis

Hsien-Cheng Kuo^{1,2} | Feng-Lin Liu^{1,2} | Jui-Tai Chen^{1,2} | Yih-Giun Cherng^{1,2} |
Ka-Wai Tam^{3,4,5} | Ying-Hsuan Tai^{1,2}

Thromboembolic events



Saignements majeurs

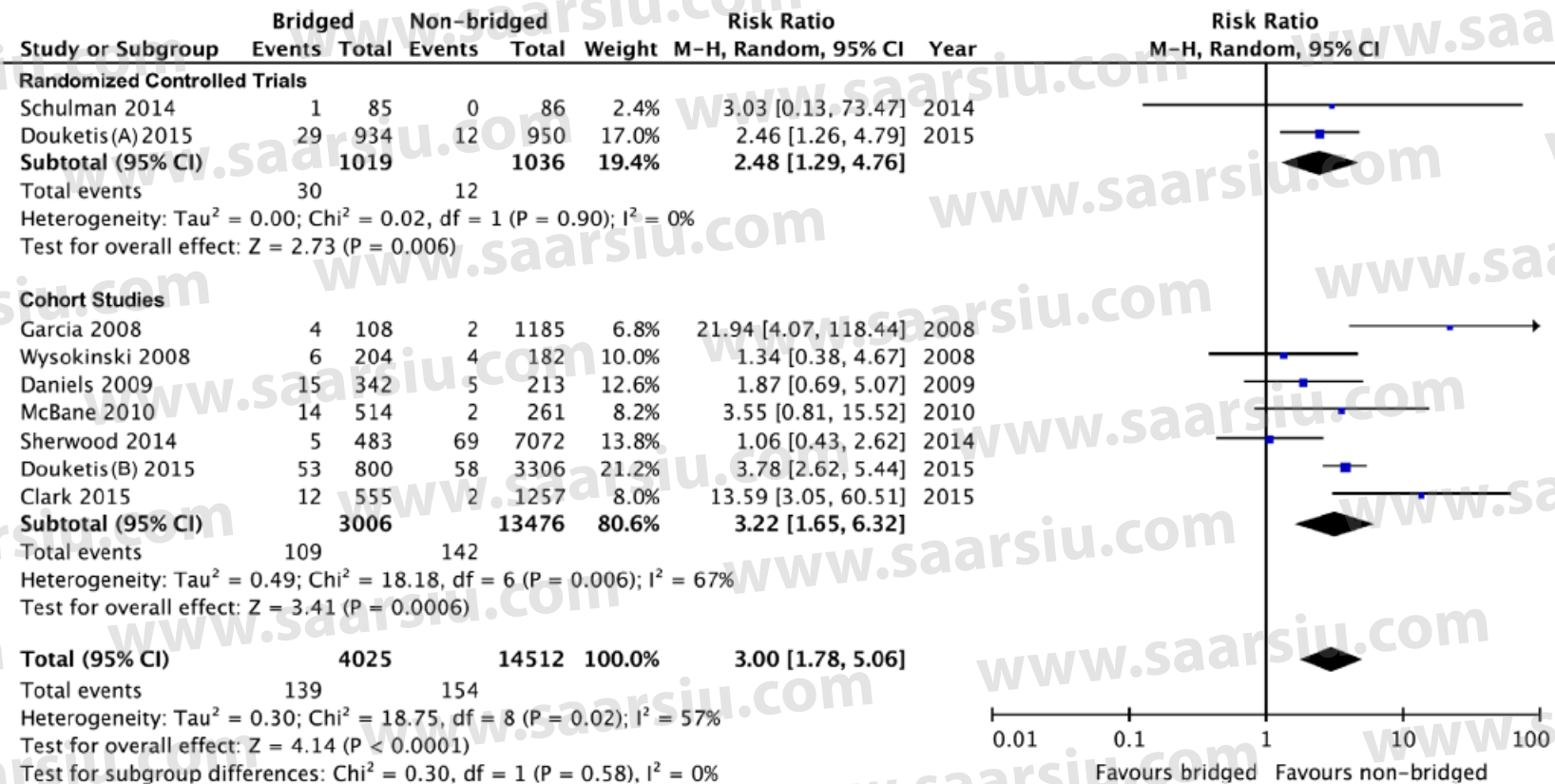


FIGURE 4 Forest plot of major bleeding between bridged and non-bridged groups. CI, confidence interval; M-H, Mantel-Haenszel

Les AOD : pas d'Antidote !!!

- C'est de moins en moins vrai.....

Pradaxa® : Idarucizumab (Praxbind ®)

Eliquis®, Xarelto® : Andexanet Alfa

ORIGINAL ARTICLE

Idarucizumab for Dabigatran Reversal — Full Cohort Analysis

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., Joanne van Ryn, Ph.D.,
John W. Eikelboom, M.B., B.S., Stephan Glund, Ph.D.,
Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D.,
Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Chak-Wah Kam, M.D.,
Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D.,
Gordon Royle, M.D., Frank W. Sellke, M.D., Joachim Stangier, Ph.D.,
Thorsten Steiner, M.D., Peter Verhamme, M.D., Bushi Wang, Ph.D.,
Laura Young, M.D., and Jeffrey I. Weitz, M.D.

CONCLUSIONS

In emergency situations, idarucizumab rapidly, durably, and safely reversed the anti-coagulant effect of dabigatran. (Funded by Boehringer Ingelheim; RE-VERSE AD ClinicalTrials.gov number, NCT02104947.)

Thrombotic events : 6.8 %, 30-day mortality: 13 %

CONCLUSIONS

In patients with acute major bleeding associated with the use of a factor Xa inhibitor, treatment with andexanet markedly reduced anti-factor Xa activity, and 82% of patients had excellent or good hemostatic efficacy at 12 hours, as adjudicated according to prespecified criteria. (Funded by Portola Pharmaceuticals; ANNEXA-4 ClinicalTrials.gov number, NCT02329327.)

Thrombotic events : 10 %, 30-day mortality: 12 %

ORIGINAL ARTICLE

Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors

S.J. Connolly, M. Crowther, J.W. Eikelboom, C.M. Gibson, J.T. Curnutte,
J.H. Lawrence, P. Yue, M.D. Bronson, G. Lu, P.B. Conley, P. Verhamme,
J. Schmidt, S. Middeldorp, A.T. Cohen, J. Beyer-Westendorf, P. Albaladejo,
J. Lopez-Sendon, A.M. Demchuk, D.J. Pallin, M. Concha, S. Goodman, J. Leeds,
S. Souza, D.M. Siegal, E. Zotova, B. Meeks, S. Ahmad, J. Nakamya,
and T.J. Milling, Jr., for the ANNEXA-4 Investigators*

Sans INR comment contrôler l'observance ?

... ce qui compte ce n'est pas l'INR, c'est la qualité de l'éducation thérapeutique globale (HTA, statines, anti-thrombotiques, mode de vie)

Qualité du contrôle INR

(éducation patient, autres facteurs de risque)

Nombre de patients à traiter pour que survienne un AVC par an

INR 2-3 (% du temps)	Apixaban	Warfarin
24-60 “pays mal éduqués »	58	42
71-83 “pays bien éduqués”	110	96
	52	54