

DOAC vs "Good Old" Warfarin

In

Defending Warfarin

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Objectives

- **1. Recognize the benefits and harms associated with DOACs for the prevention and treatment of thromboembolic events**
- **2. Recognize the benefits and harms associated with warfarin for the prevention and treatment of thromboembolic events**
- **3. Compare and contrast the benefits and harms of DOACs versus warfarin in complex patients with multiple co-morbidities**

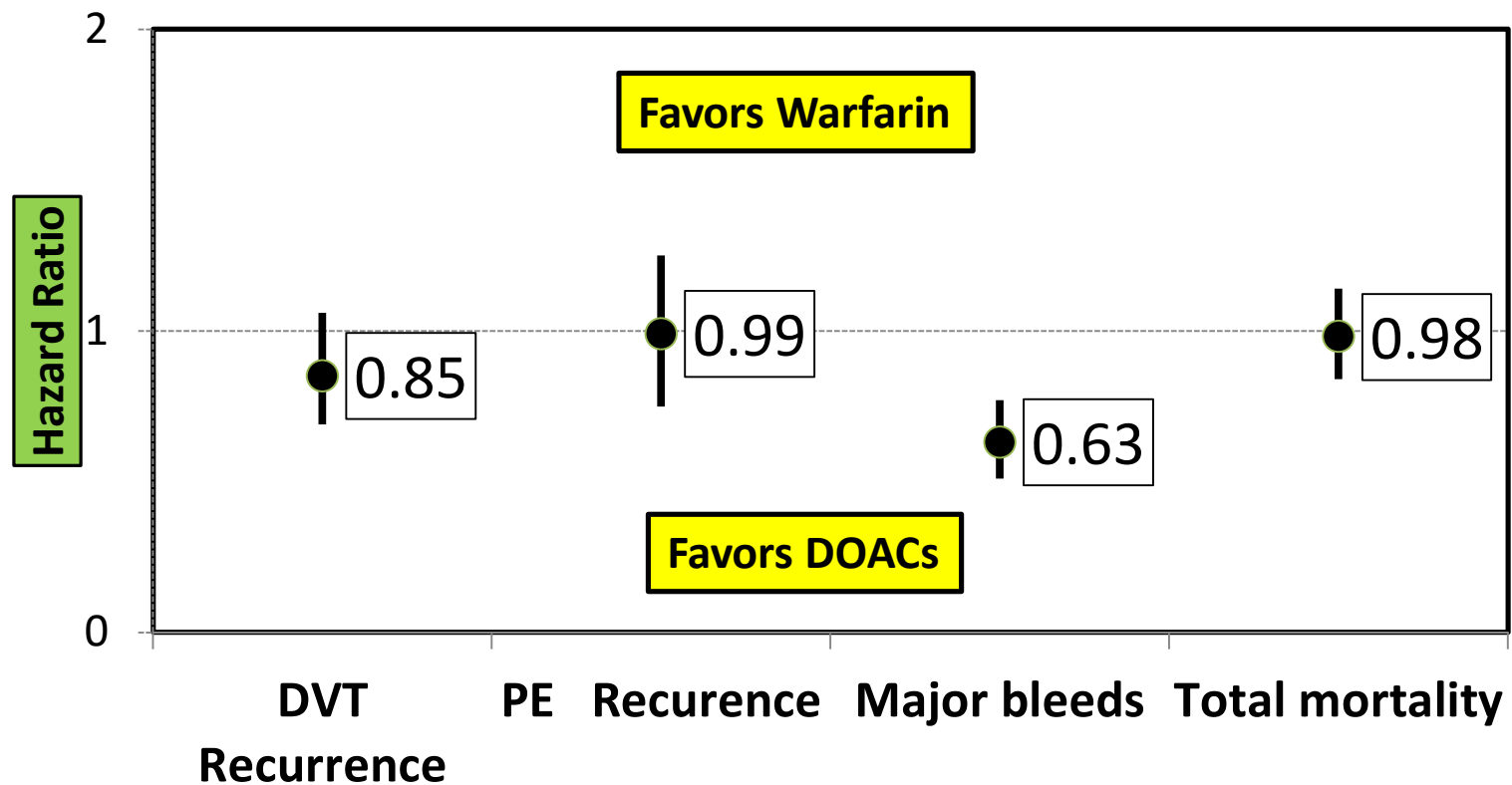


DOACs vs Warfarin

	Warfarin	DOACs
Therapeutic target	II, VII, IX, et X	II ou X
Biological half life	Long (\approx 40 hours)	Short (\approx 10 hours)
Dependant of renal function	No	Yes
Antidote ?	Yes	No
Paramètre de suivi	Yes	No
Prix	About 10 cents/day	More than 3 \$/day

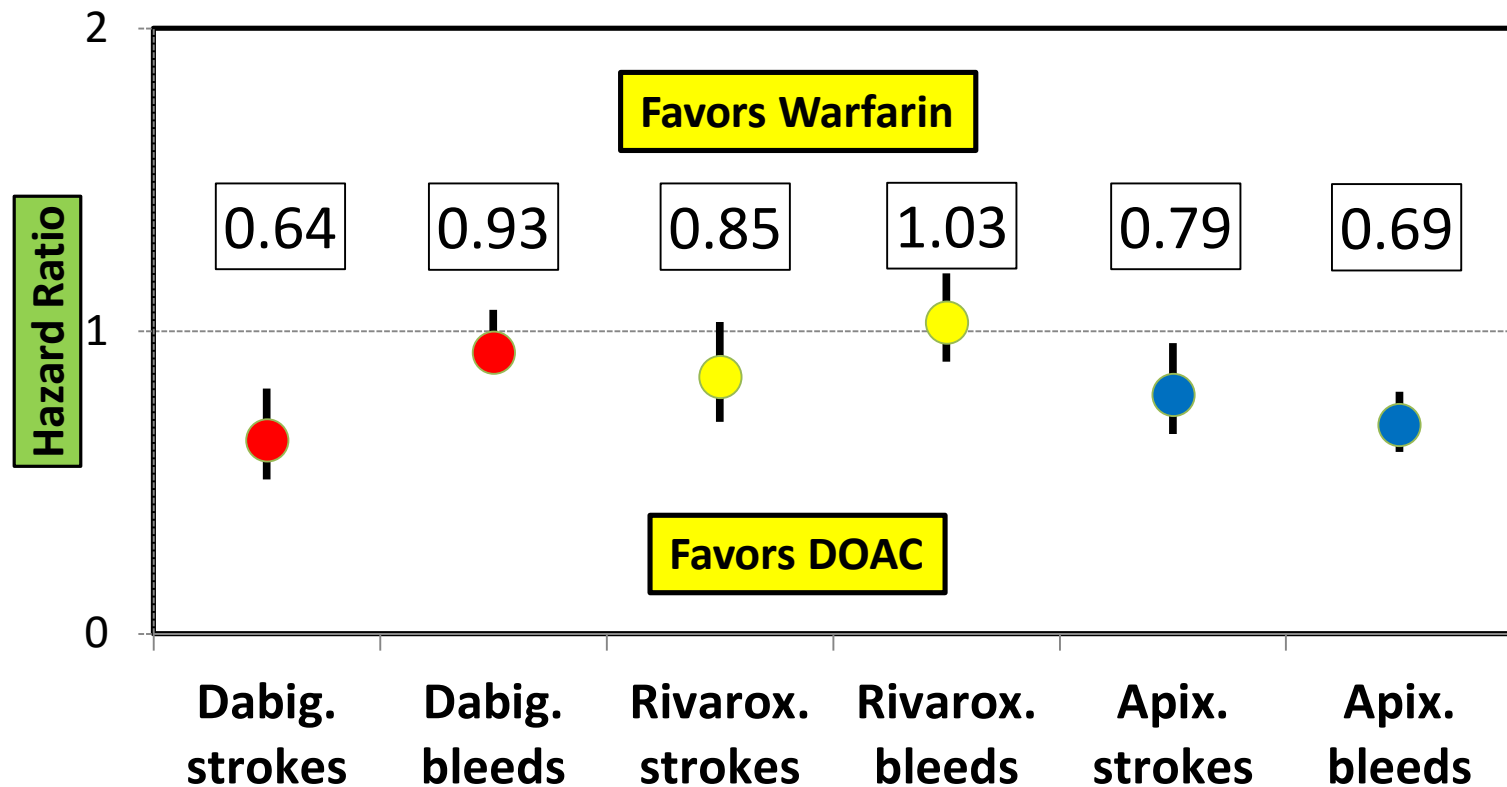
Clinical trials in DVT/PE trials

Méta analysis of DVT/PE clinical trials. (N=38000)



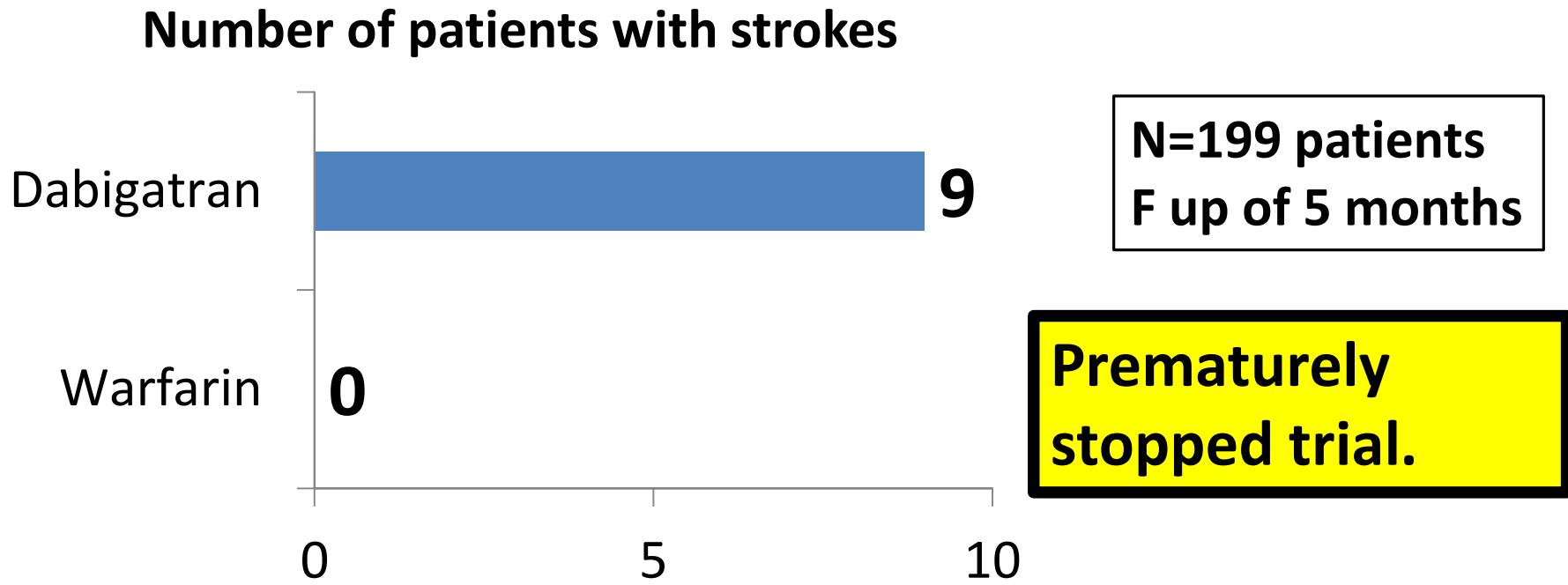
Clinical trials in atrial fibrillation

Meta analysis of atrial fibrillation clinical trials (N=96826).



REALIGN

RCT comparing dose adjusted dabigatran and warfarin in patients with recently (<7 days) implanted metal aortic or mitral valve.



**How do we use oral
anticoagulants?**

Before

(Warfarin)

Personalized care

- **Close follow-up (every 2 months)**
- **Regular reevaluation of the risk to benefit ratio**
- **Easy access to a medical team**

Now?

Warfarin

Personalized as always

DOACs, research

**Personalized monthly dedicated
follow up**

DOACs, usual care

**Close follow up?
Easy access to a medical team?**

Patient compliance

Anticoagulant non compliance?



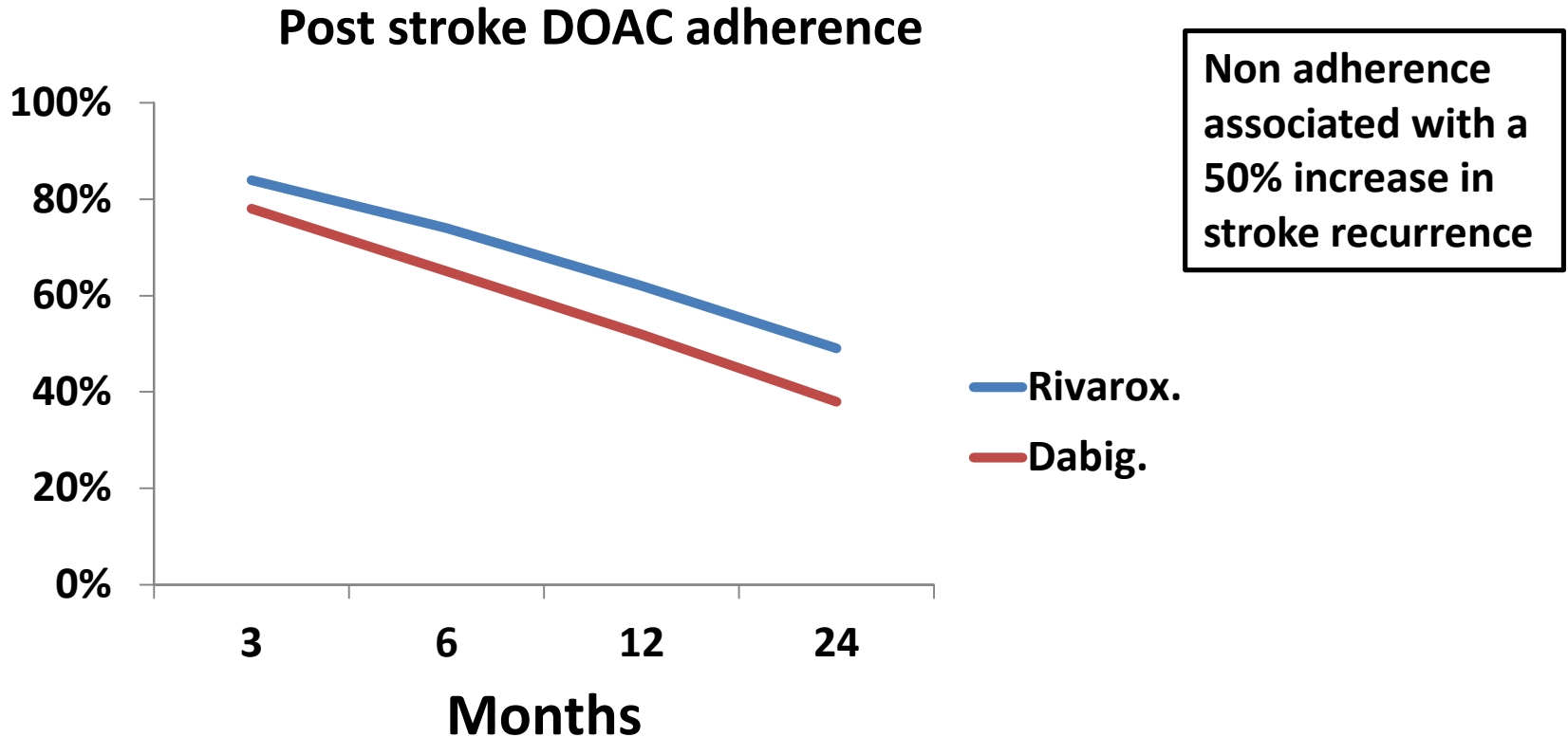
Anticoagulant non compliance or non adherence?

Post stroke anticoagulation.

Only 1% of patients decided on their own to stop their anticoagulant.

36% forget to take at least 20% of their anticoagulant doses.

DOACs non adherence



CI Coleman. Int J Cardiol. 2016;212:171

MJ Alberts. Int J Cardiol. 2016;215:11

Anticoagulant non adherence

Warfarin	DOACs
Patients well aware.	In the dispill.
Regular follow up.	Close follow up?
Easy access to medical care.	Easy access to medical care.
Available monitoring .	Monitoring unavailable.
Long half life (useful for missed doses.	Short half life

Patient selection

RCT patient selection

Exclusions in RCT

Valvular atrial fibrillation

DVT/PE and cancer

Filters and thrombolysis

Extreme weights

Plt < 100 and Hb < 100

High bleeding risk

BP > 180/110

GFR < 30 cc/min

Real life



RCT vs Real life patient selection

**Multidisciplinary
time consuming
(> 1 hour)
patient selection**

**Close and
dedicated follow
up with frequent
lab tests**

**Individual
pharmacologic
reevaluation at
the end of the
trial**

**« You have
DVT/PE? You are
preselected »
« I have 5 min. to
decide »**

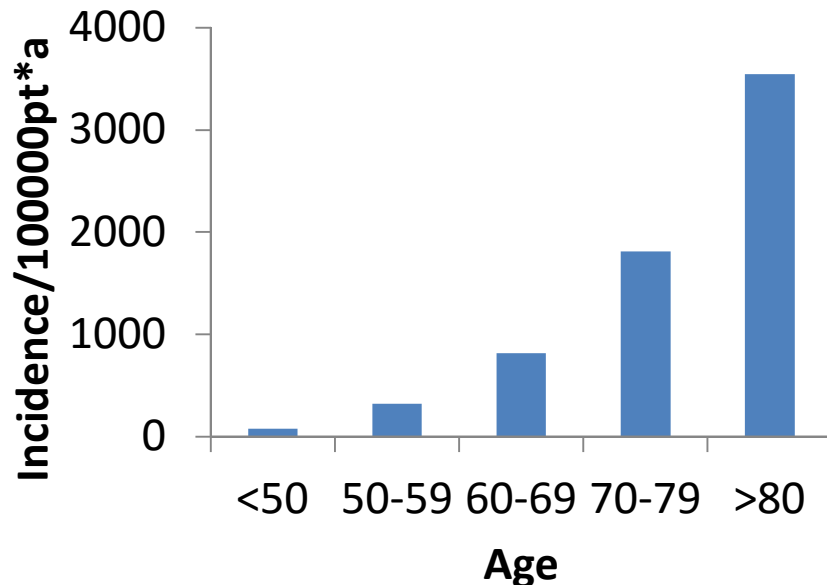
**FP follow up?
How much time?
Frequency? ATC
will only be one
of the topics.**

**If long term.
Regular
reevaluation of
treatment?...**

Elderly patients

- Decreased GFR and going down with years
- Increased risk of acute renal failure

Age dependant ARF incidence



Stratified ARF risk

TFG cc/min	Risque
45-60	X 2
30-45	X 6

Post marketing studies

Post marketing study in atrial fibrillation

Danish observational nationwide cohort study. 61 678 patients with non-valvular atrial fibrillation naïve to oral anticoagulants.

Patient characteristics

	Apixaban	Dabigatran	Rivaroxaban	Warfarin
Age	71,3	67,6	71,8	72,4
CHADS VASC	2,8	2,2	2,8	2,8
HAS BLED	2,3	2,0	2,2	2,2

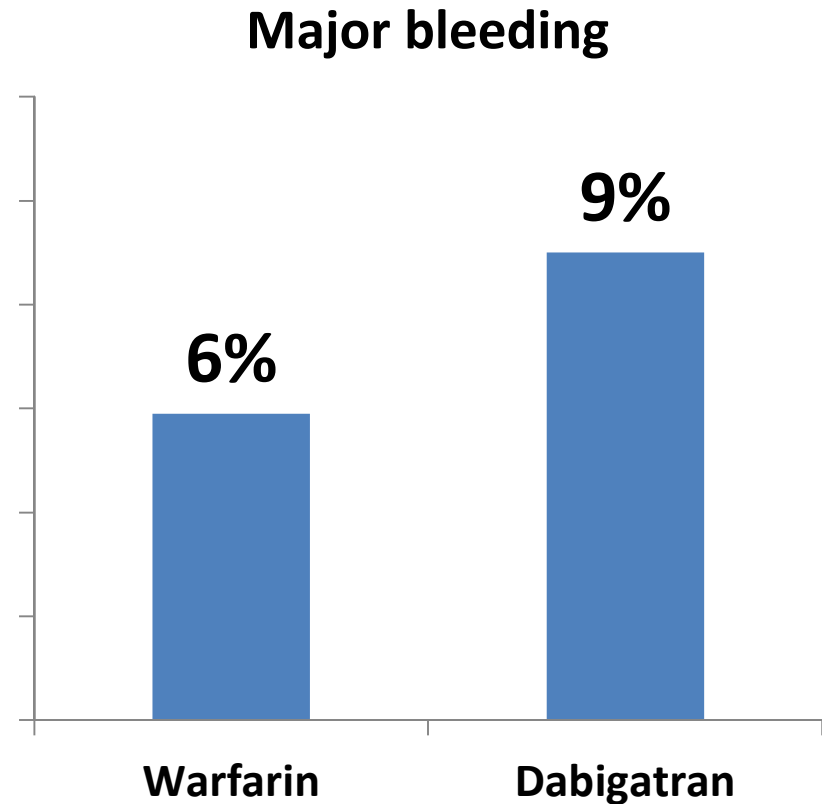
Outcomes yearly rates over a 2.5 year follow up

	Apixaban	Dabigatran	Rivaroxaban	Warfarin
Stroke/Embol.	4,08	1,84	2,34	2,39
Major bleed	2,67	2,01	3,63	3,46

Post marketing studies

Medicare retrospective cohort study in atrial fibrillation

	Warfarin	Dabig.
Age	75	76
IRC	34,2%	23,5%
Diabetes	45,0%	36,1%
Past bleed	12%	7%
Recent hospit.	27,9%	13,3%

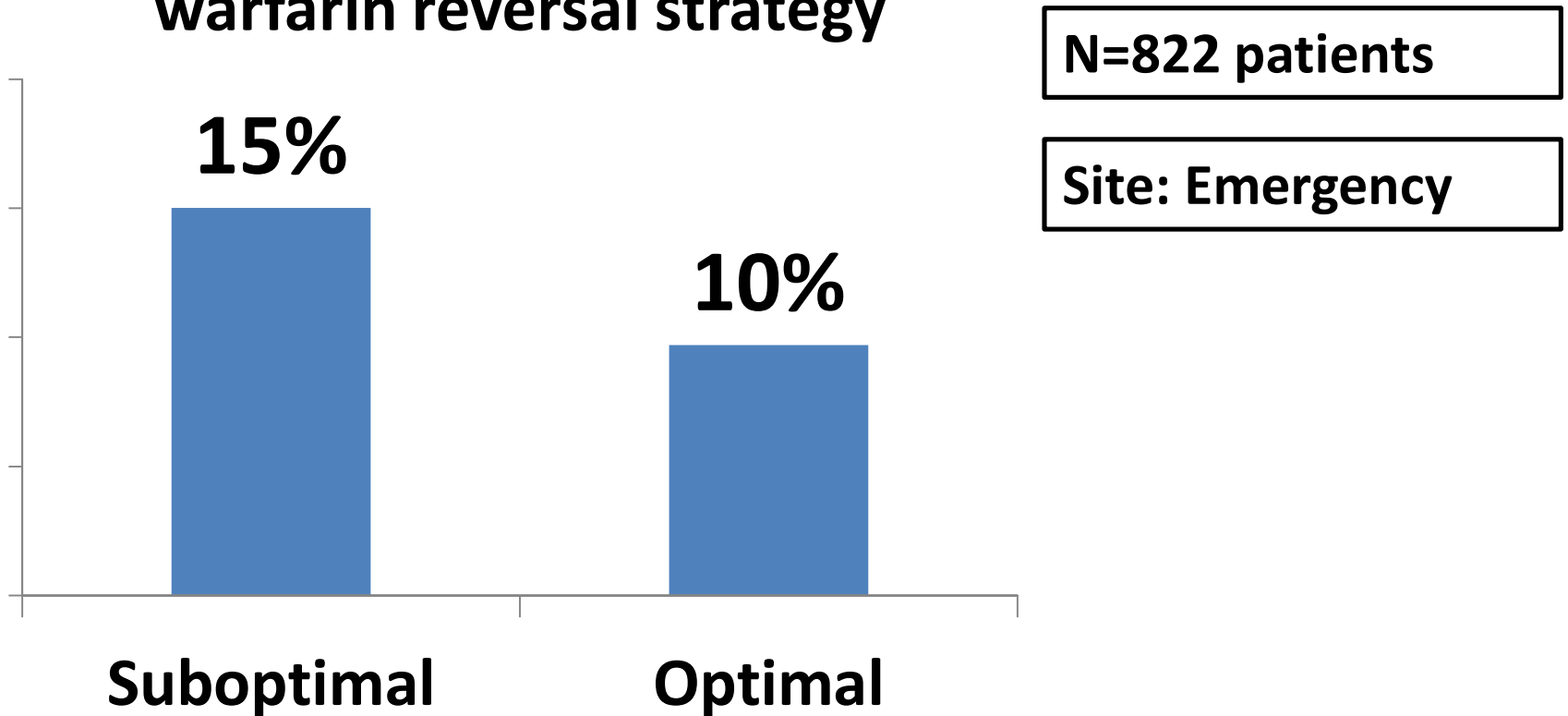


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Antidotes and other practical issues

Impact of warfarin antidotes in major bleeding

7 day mortality according to warfarin reversal strategy

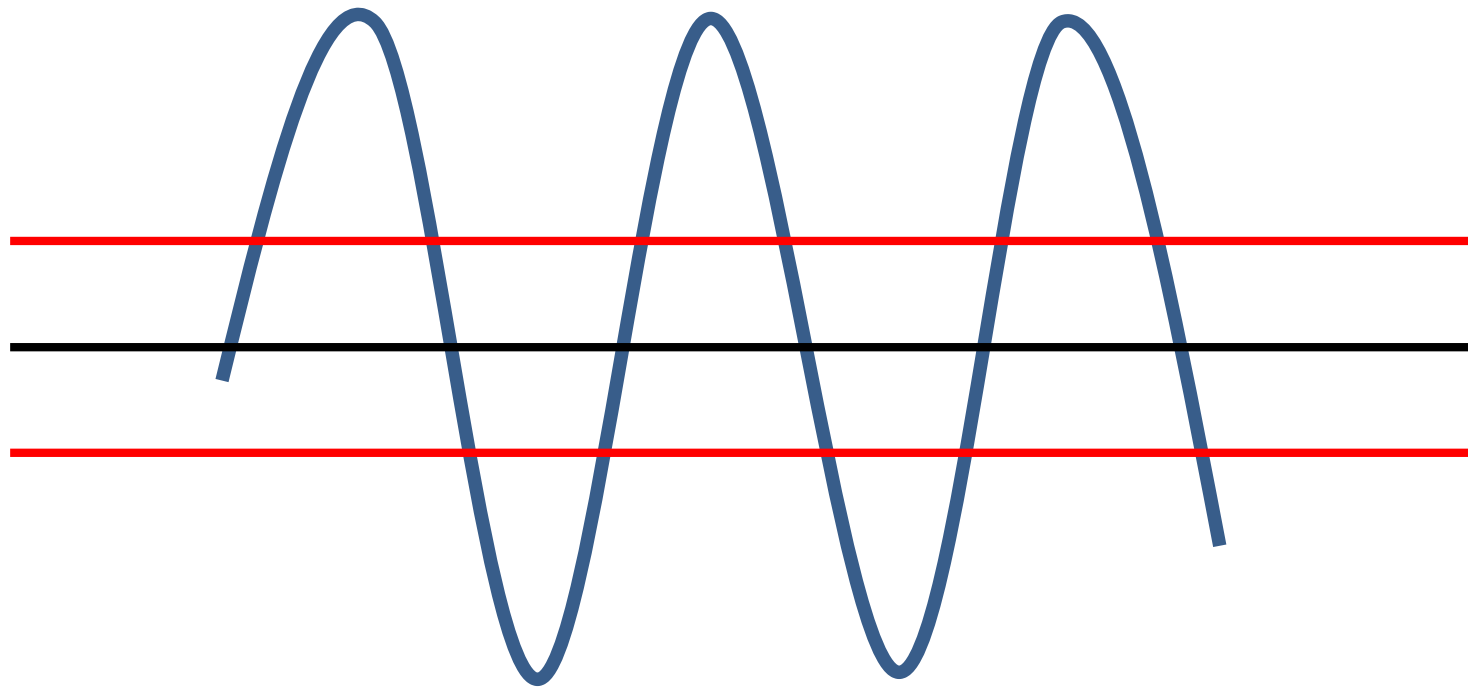


Practical problems (real and recent cases)

**Anticoagulated with rivaroxaban and recurring DVT.
Effectiveness issue? Compliance issue? Absorption issue?**

**Anticoagulated with apixaban, last dose this morning and
appendicitis. Operation? The sooner the better.
The surgeon (and me) would like to measure drug
concentration and have a safe zone cutoff.
An antidote would be nice ...**

**More protection and less bleeding.
A paradox?**



But:
The INR variability index does not seem to have an impact on embolic outcomes

DOACs have a more predictable
pharmacokinetic profile?

Rivaroxaban

C_{max} : 10-600 ng/ml

15 hrs post dose : 10-250 ng/ml

24 hr post dose : 5-50 ng/ml

Less intracranial bleeding

NOACs do not decrease factor VII levels or activity, therefore tissue factor initiated coagulation is preserved

Tissue factor initiated coagulation is involved in deep vein thrombosis and atrial clotting pathophysiology. Why are NOACs effective in this context?

NNT (6-12 months) between 200 and 1000

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Cost effective?

Monthly price
(Including follow up costs)

Warfarin = 35\$

Dabigatran = 96\$

Rivaroxaban = 85\$

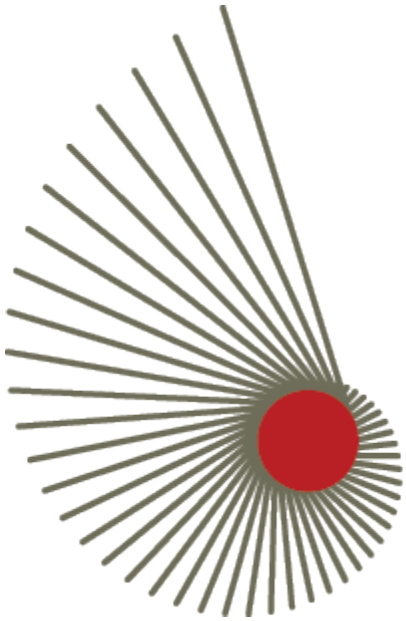
Apixaban = 96\$

From INESSS's recommendations

Conclusion

The perfect anticoagulant

Wish list	Warfarin	DOACs
Effective	✓	✓
Monitoring possibilities	✓	
Long half life but reversible	✓	
Cheap	✓	
No follow up		



WARE

Wisconsin Alumni Research Foundation

Pharmacocinétiques des NACO

	Dabigatran	Rivaroxaban	Apixaban
Absorption	7 %	80-100 % (nourr)	50 %
T Max	2 h	2-3 h	2-3 h
Demi vie	12-17 h	7-11 h	9-14 h
Elimination rénale	80 %	33 %	27 %
Mét. hépatique	Non	Oui Princ. 3A4	Oui Princ. 3A4

Les NACO sont généralement contre indiqués si insuffisance rénale avec une Cl Créat de moins de 30 cc/min.

Le rivaroxaban et l'apixaban sont contre indiqués si insuffisance hépatique avec coagulopathie ou avec classification Child B ou C.

NACOs moins variables?

Déviatiun standard de la moyenne du paramètre de mesure

Valeur moyenne du paramètre de mesure

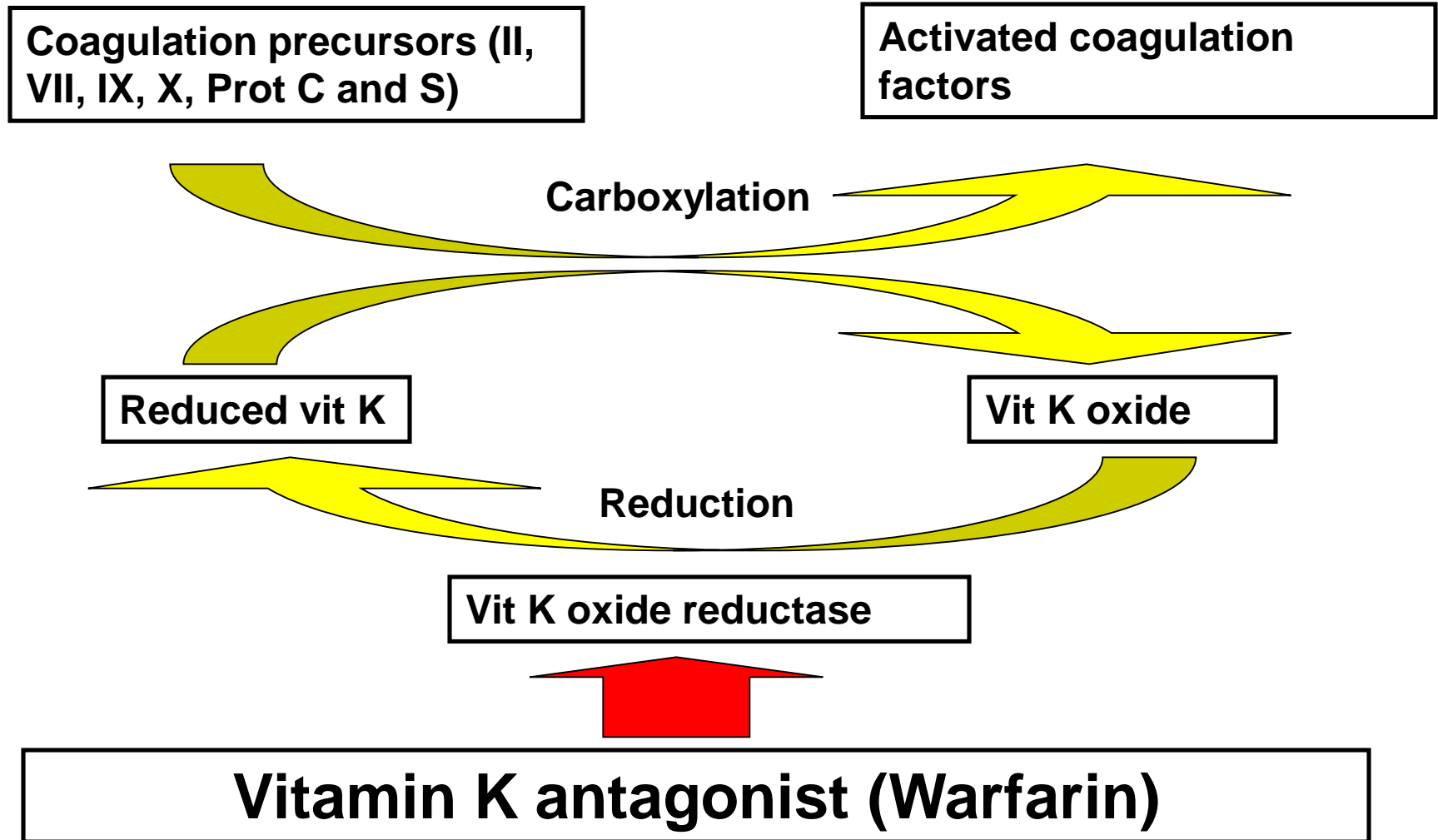
Warfarin - INR \approx 20%

Cmax ou AUC Rivaroxaban \approx 20%

Données internes pour le warfarin

Xu Steven Xu. Br J Pharmacol. 2012;74:86

Warfarin



Safety and effectiveness of oral rivaroxaban versus standard anticoagulation for the treatment of symptomatic deep-vein thrombosis (XALIA): an international, prospective, non-interventional study



Walter Ageno, Lorenzo G Mantovani, Sylvia Haas, Reinhold Kreutz, Danja Monje, Jonas Schneider, Martin van Eickels, Martin Gebel, Elizabeth Zell, Alexander G G Turpie

Summary

Background The efficacy and safety of the anticoagulant rivaroxaban for the treatment and secondary prevention of deep-vein thrombosis and pulmonary embolism has been shown in phase 3 trials. However, data about rivaroxaban *Lancet Haematol* 2016; 3: e12-21
Published Online

Xalia study. Prospective non randomized non interventional study. 5142 patients with DVT±PE were included and treatment (rivaroxaban vs warfarin) decided by their treating physician. Research grade follow up for all.

After age stratification

**Similar bleeding risk between rivaroxaban and warfarin
Similar risk of DVT±PE recurrence**