Journée d'études de l'ASMA (Association scientifique de médecine d'assurance)

Les NACOs: "tout" ce que vous devez en savoir actuellement

Pr. François Mullier
Associate head of laboratory of clinical biology, CHU UCL Namur

Yvoir
March 16th, 2016

NTHC
Namur Thrombosis & Hemostasis Center

CHU UCL NAMUR

Content

- Introduction
- PK and PD
- Indications and posology
- Interactions
- Adherence/persistance
- Specific populations
- Monitoring?
- Gestion périopératoire
- Antidotes
- Conclusions

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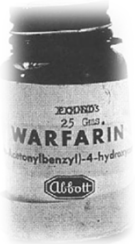
Traditional anticoagulants Main disadvantages

- **UFH[1]**
  - Parenteral administration
  - Frequent monitoring and dose adjustment
  - HIT
- **LMWH[1]**
  - Parenteral administration
  - Weight adjusted titration

- **VKA[1]**
  - Narrow therapeutic range
  - Food and drugs interactions
  - Frequent monitoring and dose adjustment

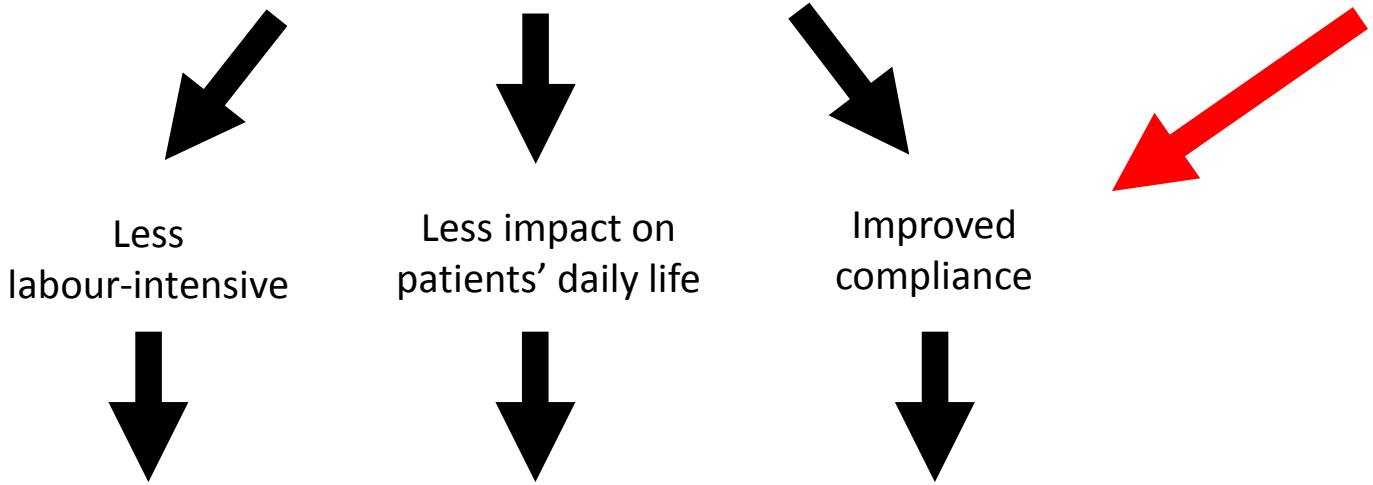


1. Hirsh J *et al*. *Chest* 2008;133;141S–159S; 2. Ansell J *et al*. *Chest* 2008;133;160S–198S

The promises of DOACs

- **Simplified dosing regimen**
- **No dietary restrictions**
- **Predictable anticoagulation and no need for routine coagulation monitoring**
- **Can be given at fixed doses**

Reduced potential for food and drug interactions



1. Raghaven N *et al. Drugs Metab Dispos* 2009;37:74–81;
2. Shantsila E & Lip GY. *Curr Opin Investig Drugs* 2008;9:1020–1033;
3. Mueck W *et al. Clin Pharmacokinet* 2008;47:203–216;
4. Mueck W *et* al. *Thromb Haemost* 2008;100:453–461; 5. Mueck W *et al*. *Int J Clin Pharmacol Ther* 2007;45:335–344

Results for primary outcome versus warfarin

	ARISTOTLE *(apixaban)*	**RE-LY** *(dabigatran)*		**ROCKET-AF** *(rivaroxaban)*	**ENGAGE AF-TIMI 48** *(edoxaban)*	
		2 x 110mg	2 x 150mg		1 x 30mg	1 x 60mg
Primary outcome : stroke and systemic embolism	2 x 5mg and 2 x 2,5 mg Superiority HR 0,79 (CI: 0,66-0,95) **NNT= 303**	Non-inferiority	Superiority RR 0,65 (CI: 0,52-0,81) **NNT= 172**	1 x 20mg non- inferiority	Non-inferiority HR 1,13 (CI: 0,96-1,34)	Non-inferiority HR 0,87 (CI: 0,73-1,04)
Primary outcome safety: major bleedings and non major bleedings	Less with apixaban HR 0,69 (IC: 0,60-0,80)	Less with dabigatran RR 0,80 (CI: 0,70-0,93)	No difference	No difference	Less with edoxaban HR 0,62 (CI: 0,57-0,67)	Less with edoxaban HR 0,86 (CI:0,80-0,92)
Myocardial infarction %/year	0,53 vs 0,61 HR 0,88 (0,66- 1,17)	0,72 vs 0,53 RR 1,35 (0,98-1,87)	0,74 vs 0,53 RR 1,38 (1,0-1,91) NNH= 476	0,91 vs 1,12 HR 0,81 (063-1,06)	0,89 vs 0,70 HR 1,19 (CI: 0,95-1,49)	0,75 vs 0,70 HR 0,94 (CU: 0,74-1,19)
Haemorrhagic stroke %/year	0,24 vs 0,47 HR 0,51 (0,35-0,75) **NNT= 435**	0,12 vs 0,83 RR 0,31 (0,17-0,56) **NNT= 384**	0,10 vs 0,38 RR 0,26 (0,14-0,49) **NNT= 357**	0,26 vs 0,44 HR 0,59 (0,37-0,93) **NNT= 555**	0,16 vs 0,47 HR 0,33 (0,22-0,50) **NNT= 322**	0,26 vs 0,47 HR 0,54 (0,38-0,77) **NNT= 476**
Intracranial bleeding %/year	0,33 vs 0,80 HR 0,42 (0,30-0,58) **NNT= 213**	0,23 vs 0,74 RR 0,31 (0,20-0,47) **NNT= 196**	0,30 vs 0,74 RR 0,40 (0,20-0,60) **NNT= 227**	0,5 vs 0,7 HR 0,67 (0,47-0,93) **NNT = 500**	0,26 vs 0,85 HR 0,30 (0,21-0,43) **NNT= 169**	0,39 vs 0,85 HR 0,47 (0,34-0,63) **NNT= 217**
Gastrointestinal bleeding %/year	0,76 vs 0,86 HR 0,89 (0,70- 1,15)	1,12 vs 1,02 RR 1,10 (0,86 – 1,41)	1,51 vs 1,02 RR 1,36 (1,09-1,70) **NNH= 204**	3,15 vs 2,16 HR 1,46 (1,19-1,78) **NNH = 101**	0,82 vs 1,23 HR 0,67 (0,53-0,83) **NNT= 243**	1,51 vs 1,23 HR 1,23 (1,02-1,5) **NNH= 357**
Death %/year	3,52 vs 3,94 HR 0,89 (0,80- 0,99) **NNT= 238**	3,75 vs 4,13 RR 0,91 (0,80-1,03)	3,64 vs 4,13 RR 0,88 (0,77-1,00)	1,78 vs 2,21 HR 0,85 (0,70-1,02)	3,80 vs 4,35 HR 0,87 (0,79-0,96) **NNT= 181**	3,99 vs 4,35 HR 0,92 (0,83-1,01)

P. Chevalier, Minerva 2012;11:84-85. Granger CB et al. NEJM 2011;365:981-92. Connoly SJ et al. NEJM 2009;361:1139-51.
Patel MR et al. NEJM 2011;365:883-91. Giugliano RP et al. NEJM 2013;368:2093-104

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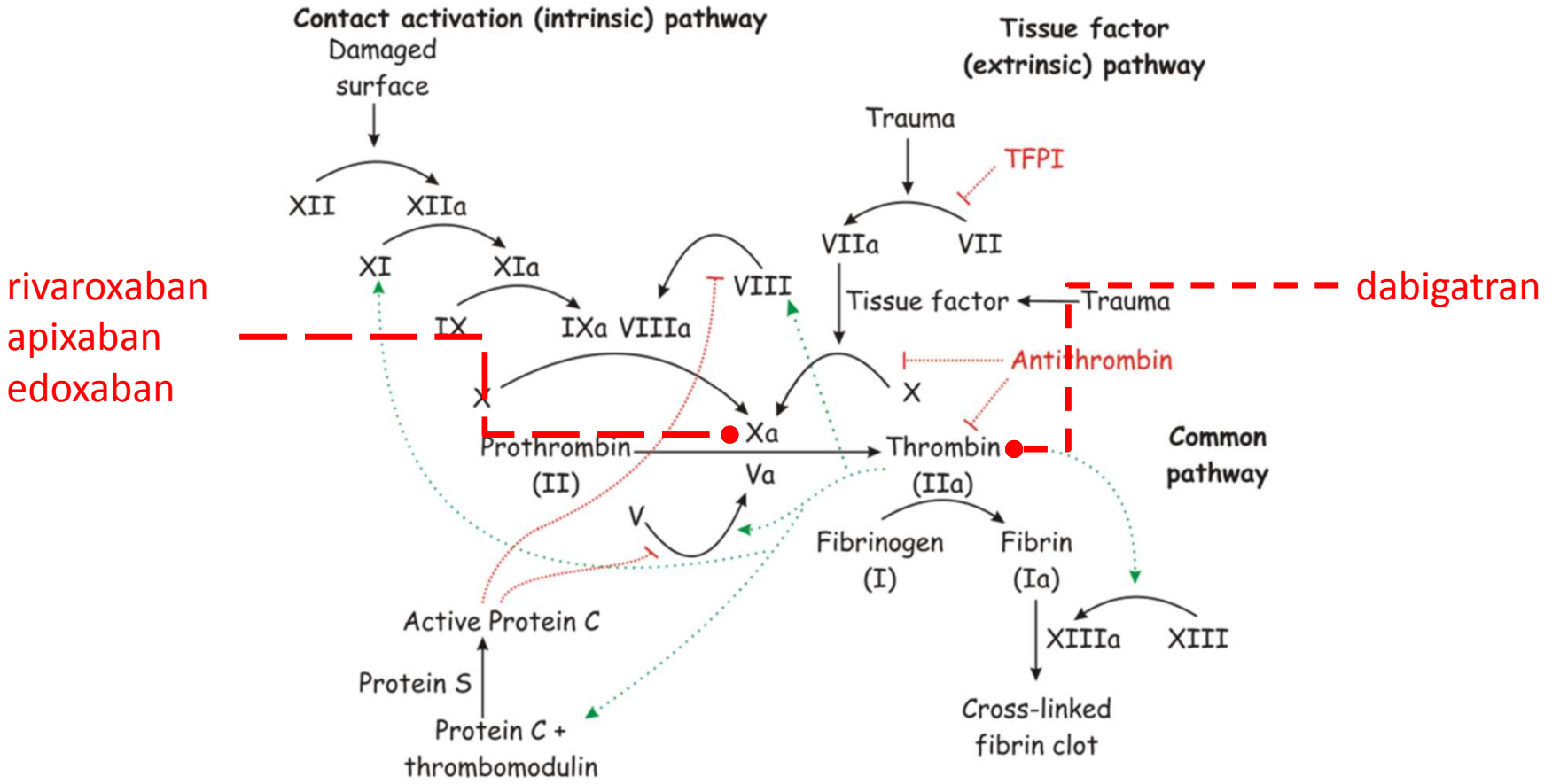
PK and PD


Contact activation (intrinsic) pathway
Damaged surface
XII
XIIa
XI
XIa
IX
IXa VIIIa
VIII
X
Xa
Prothrombin (II)
Va
V
Active Protein C
Protein S
Protein C + thrombomodulin
Tissue factor (extrinsic) pathway
Trauma
TFPI
VIIa
VII
Tissue factor
Trauma
Antithrombin
X
Thrombin (IIa)
Common pathway
Fibrinogen (I)
Fibrin (Ia)
XIIIa
XIII
Cross-linked fibrin clot
rivaroxaban
apixaban
edoxaban
dabigatran

PK and PD

	dabigatran etexilate (PRADAXA®)	rivaroxaban (XARELTO®)	apixaban (ELIQUIS®)	edoxaban (LIXIANA®)
Target	Thrombin	Factor Xa	Factor Xa	Factor Xa
Bioavailability (%)	3-7% Not affected by food	- 80 to 100% for the 10 mg - 66% for the 15 and 20 mg (fasted)*	50% Not affected by food	62% Not affected by food
Prodrug	Yes – activated by esterase (CES1)	No	No	No
Half-life (hours)	11-13	5-13	8-15	10-14
T_{MAX} (hours)	0.5-2.0	2.0-4.0	3.0-4.0	1.0-2.0
Renal clearance	80%	33%	25%	50%
Metabolism	P-gp	P-gp CYP3A4	P-gp CYP3A4/5, 1A2, 2J2	P-gp CYP3A4/5

* these dose regimen have to be taken with food.

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Indications

VTEx

PE

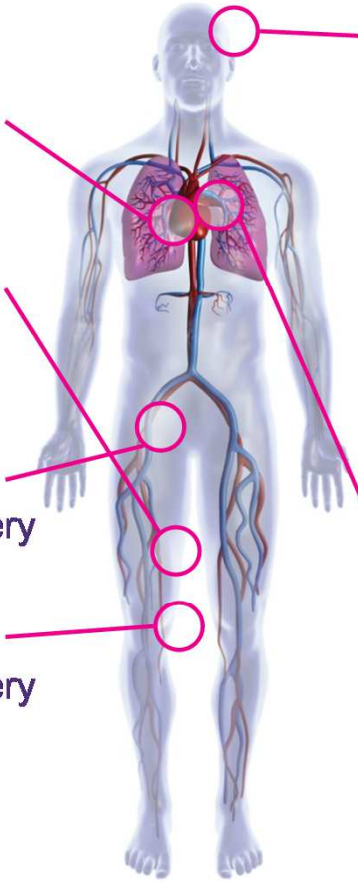
- Pulmonary embolism (PE)
  500,000 deaths per year in Europe

DVT

- Deep venous thrombosis (DVT)
  1 event every 12 seconds

VTEp

- Elective hip replacement surgery
  DVT risk: 42–57%
- Elective knee replacement surgery
  DVT risk: 41–85%



- Ischemic Stroke
  15% due to atrial fibrillation

SPAF

- Unstable angina and myocardial infarction
  1 death every 17 seconds

ACS

Fibrillation auriculaire (FA)

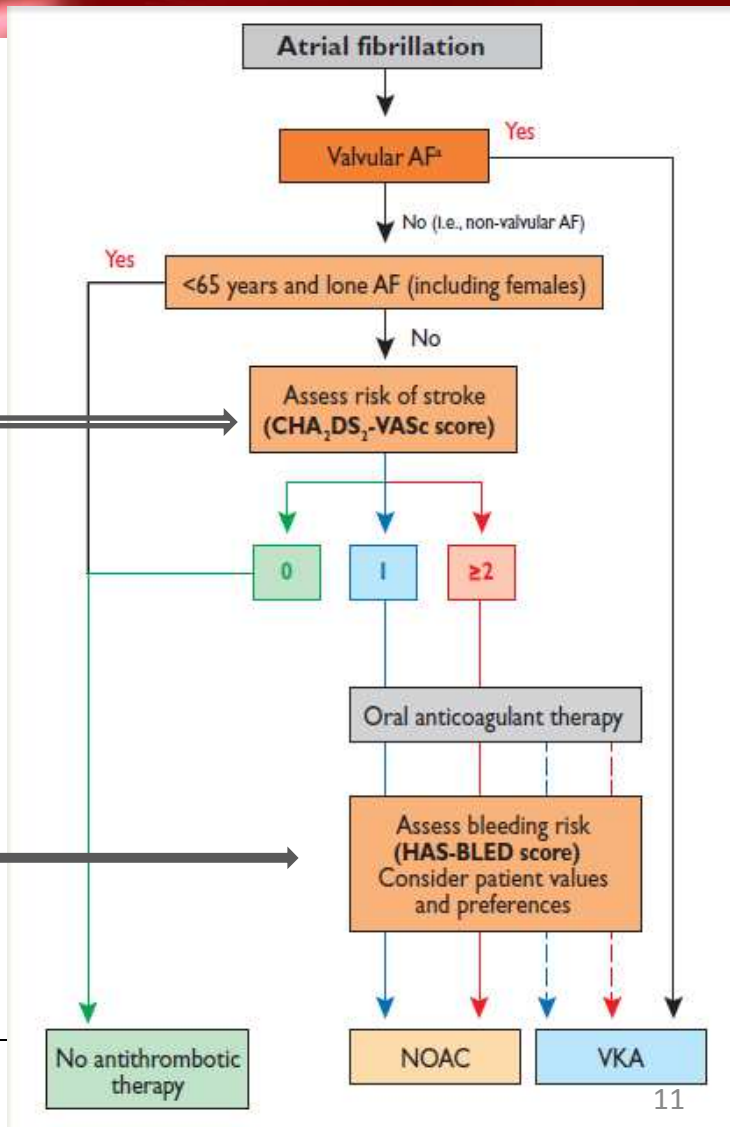
- Quand faut-il anticoaguler?

(b) Risk factor-based approach expressed as a point based scoring system, with the acronym CHA_2DS_2-VASc
(Note: maximum score is 9 since age may contribute 0, 1, or 2 points)

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease[a]	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	**9**

HAS-BLED bleeding risk score

Letter	Clinical characteristic[a]	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 INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points



Camm AJ, Lip GYH, De Caterina R et al. European Heart Journal 2012;33:2719-2747

Fibrillation auriculaire (FA)

- Evaluation du risque thrombotique (bénéfice)

(b) Risk factor-based approach expressed as a point based scoring system, with the acronym CHA_2DS_2-VASc (Note: maximum score is 9 since age may contribute 0, 1, or 2 points)	
Risk factor	**Score**
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease[a]	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	**9**

(c) Adjusted stroke rate according to CHA_2DS_2-VASc score		
CHA_2DS_2-VASc score	**Patients (*n*=7329)**	**Adjusted stroke rate (%/year)[b]**
0	1	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%

Camm J, Kirchhof P, Lip G et al. European Heart Journal 2010;31:2369-2429

Fibrillation auriculaire (FA)

- Evaluation du risque hémorragique (risque)

HAS-BLED bleeding risk score

Letter	Clinical characteristic[a]	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 INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

Absence de cut-off limitant. Risque élevé si score ≥ 3

Camm AJ, Kirchhof P, Lip GYH et al. European Heart Journal 2010;31:2369-2429

Fibrillation auriculaire (FA)

- Critères de remboursement
  - Cat B Chap IV

a) La spécialité suivante fait l'objet d'un remboursement s'il est démontré qu'elle est administrée dans la prévention de l'accident vasculaire cérébral (AVC) et de l'embolie systémique (ES) chez les patients adultes présentant une fibrillation auriculaire non valvulaire associée à un ou plusieurs autres facteurs de risque suivants:

- Antécédent d'AVC, d'accident ischémique transitoire ou d'embolie systémique;
- Fraction d'éjection ventriculaire gauche < 40 %;
- Insuffisance cardiaque symptomatique, classe > ou = 2 New York Heart Association (NYHA);
- Age > ou = 75 ans;
- Age > ou = 65 ans associé à l'une des affections suivantes : diabète, coronaropathie ou hypertension artérielle.

  - Absence de consensus sur la définition de FA VALVULAIRE:
    - Valve mécanique = CI formelle (dabigatran); quid des bioprothèses valvulaires?
    - Sténose mitrale modérée à sévère

De Caterina R and Camm AJ. European Heart Journal (2014) 35, 3328–3335, www.cbip.be

DOAC patient selection criteria

Table 3 DOAC patient selection criteria

Criteria for DOAC use	Comment(s)
Patient preference for and willingness to take DOAC	Patients should be presented will all therapeutic options and their respective perceived advantages and disadvantages (See Table 2)
No contraindication to DOAC therapy	E.g. pregnancy, breastfeeding, mechanical heart valve
Adequate organ function	Clinicians should regularly monitor renal function, particularly for DOACs with greater reliance on renal elimination (see Tables 5, 6 and 12) and, if there are other factors that may increase DOAC exposure (e.g. age, unavoidable use of concomitant p-gp/CYP3A4 inhibitors). Avoid in moderate or severe hepatic dysfunction
No significant drug–drug interactions	See Tables 13 and 14 for detailed guidance
	Patients taking *any* anticoagulant with antiplatelet agents or NSAIDs have a significantly higher risk of bleeding. To minimize bleeding, avoid these drug combinations when possible
No significant disease state interactions	VTE patients with a history of GI bleeding or at risk for GI bleeding may be better candidates for warfarin, apixaban, or edoxaban, as there may be a higher risk of bleeding or GI adverse effects with dabigatran and rivaroxaban
Highly likely to be adherent with DOAC therapy and follow-up plan	See Table 4 for further details
Confirmed ability to obtain DOAC on a longitudinal basis from a financial, insurance coverage and retail availability standpoint	The drug costs of DOACs may be prohibitive for some patients, as compared with generic warfarin plus laboratory monitoring
	There are patient assistance programs available via the pharmaceutical companies, and this should be arranged prior to prescribing

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Patient adherence assessments when choosing anticoagulant therapies

Table 4 Patient adherence assessments when choosing anticoagulant therapies [118–123]

Taking medications	**How often does the patient miss or forget to take doses of their medication(s)?**
	• If a warfarin patient frequently misses doses, switching to a shorter half-life DOAC may more rapidly predispose the patient to risk of thrombosis
	• Often, a subtherapeutic INR is a reliable indicator to the clinician and patient that warfarin doses have been missed
	• Without the requirement for laboratory monitoring with the DOACs, there is no such alert to indicate opportunities to improve adherence
	Is a once-daily or a twice-daily medication dosing frequency preferred?
	• If patient is adherent with other twice daily medications, any of the DOACs may be appropriate
	• Conversely, if patient prefers once daily medications, rivaroxaban or edoxaban may be preferred
Laboratory monitoring	**Is laboratory access difficult?**
	• Patients with transportation challenges, difficult venous access, inflexible work or school schedules or other reasons for difficulty complying with INR monitoring may significantly benefit from DOAC therapy
	• Clinicians should remind DOAC patients that renal function and a complete blood count should be monitored at least annually or more frequently as the clinical situation dictates
Health care responsibility	**Is the patient reliable to notify health care providers about changes to health and pertinent medical issues?**
	• It is important for the patient to make all health care providers aware he or she is taking an anticoagulant medication, as this information will aid in:
	– design of peri-procedural anticoagulation plans
	– addressing medication interactions
	– consideration of other health status changes
	• Patients who may be unreliable to report pertinent issues to the clinician may be better suited to warfarin so that at least some of these may be uncovered during INR follow-up
	• DOAC patients and their clinicians may elect to interact via clinic visit, phone, or electronic media at a regular interval

INR International normalized ratio, *DOAC* direct oral anticoagulant

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Fibrillation auriculaire (FA)

- AVK ou DOAC?
  - Calcul du score SAME-TT2R2 pour évaluer le contrôle d'anticoagulation sous AVK (% du temps passé dans le range thérapeutique → INR:2-3)

Table 1 The SAME-TT_2R_2 Score

S	Sex (female)	1
A	Age (<60 years)	1
M	Medical history*	1
e		
T	Treatment (rhythm control strategy)	1
T	Tobacco use (within 2 years)	2
R	Race (non-Caucasian)	2

*Defined as more than 2 of the following: hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, hepatic or renal disease.

Faibles score : 0-1, Borderline : 2, Haut score ≥ 3

CLINICAL SIGNIFICANCE

- In a "real world" cohort of consecutive patients with nonvalvular atrial fibrillation, a high SAMe-TT_2R_2 score (reflecting poor anticoagulation control with poor time-in-therapeutic range [TTR]) was associated with more bleeding, adverse cardiovascular events, and mortality during follow-up.
- The SAMe-TT_2R_2 score, an easy, simple prediction of which atrial fibrillation patients are likely to do well on vitamin K antagonists (VKA) (with good average TTR), could guide decision-making between using VKAs and non-VKA oral anticoagulants.

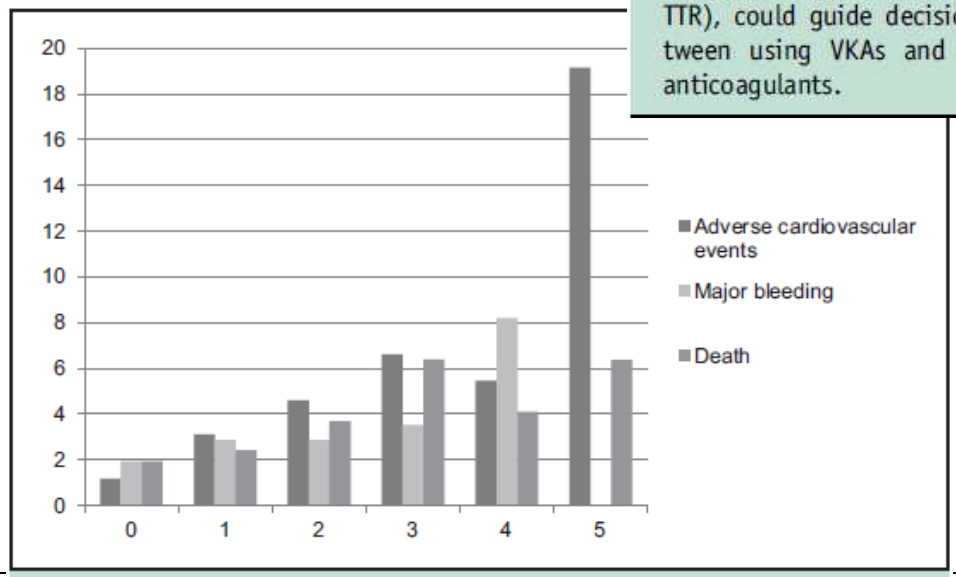

Figure Adverse events according to SAMe-TT_2R_2 score at baseline.

Gallego P et al. The American Journal of Medicine (2014) 127, 1083-1088

Indications	dabigatran etexilate Pradaxa®	rivaroxaban Xarelto®	apixaban Eliquis®	edoxaban Lixiana®
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	- 220 mg/day (2 caps of 110 mg od) - 150 mg/day (2 caps of 75 mg od)) if CrCl between 30-50 ml/min, if >75 years, if verapamil, amiodarone or quinidine	- 10 mg/day (1 tablet of 10 mg od)	- 5 mg/day (1 tablet of 2.5 mg bid)	/
Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors	- 300 mg/day (1 caps of 150 mg bid) - 220 mg/jour (1 caps of 110 mg bid) If >80 years or treated with verapamil	- 20 mg/day (1 tablet of 20 mg od) - 15 mg/day (1 tablet of 15 mg od) if CrCl between 15-49 ml/min	- 10 mg/day (1 tablet of 5 mg bid) - 5 mg/day (1 tablet of 2.5 mg bid) if at least 2 of the following: ≥80 years ≤60 kg serum creat. ≥ 1,5 mg/dl or if CrCl 15-29 ml/min	- 60 mg/day (1 tablet of 60 mg od) - 30 mg/day (1 tablet of 30 mg od) if CrCl between 15-50 ml/min or ≤60 kg or P-gp inhibitors (cyclosporin, dronedarone, erythromycin, ketoconazole)
Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.	<u>After initial treatment of 5 days with LMWH</u> - 300 mg/day (1 caps of 150 mg bid) - 220 mg/jour (1 caps of 110 mg bid) If >80 years or treated with verapamil	<u>Treatment phase:</u> - 30 mg/day (1 tablet of 15 mg bid) during 21 days <u>Secondary prevention:</u> - 20 mg/day (1 tablet of 20 mg od) - 15 mg/day (1 tablet of 15 mg od) if CrCl between 15-49 ml/min	<u>Treatment phase:</u> - 20 mg/day (1 tablet of 10 mg bid) during 7 days - 10 mg/day (1 tablet of 5 mg bid) for at least 3 months <u>Secondary prevention:</u> - 5 mg/day (1 tablet of 2.5 mg bid) following completion of 6 months of treatment for DVT or PE	<u>After initial treatment of 5 days with LMWH</u> - 60 mg/day (1 tablet of 60 mg od) - 30 mg/day (1 tablet of 30 mg od) if CrCl between 15-50 ml/min or ≤60 kg or P-gp inhibitors (cyclosporin, dronedarone, erythromycin, ketoconazole)

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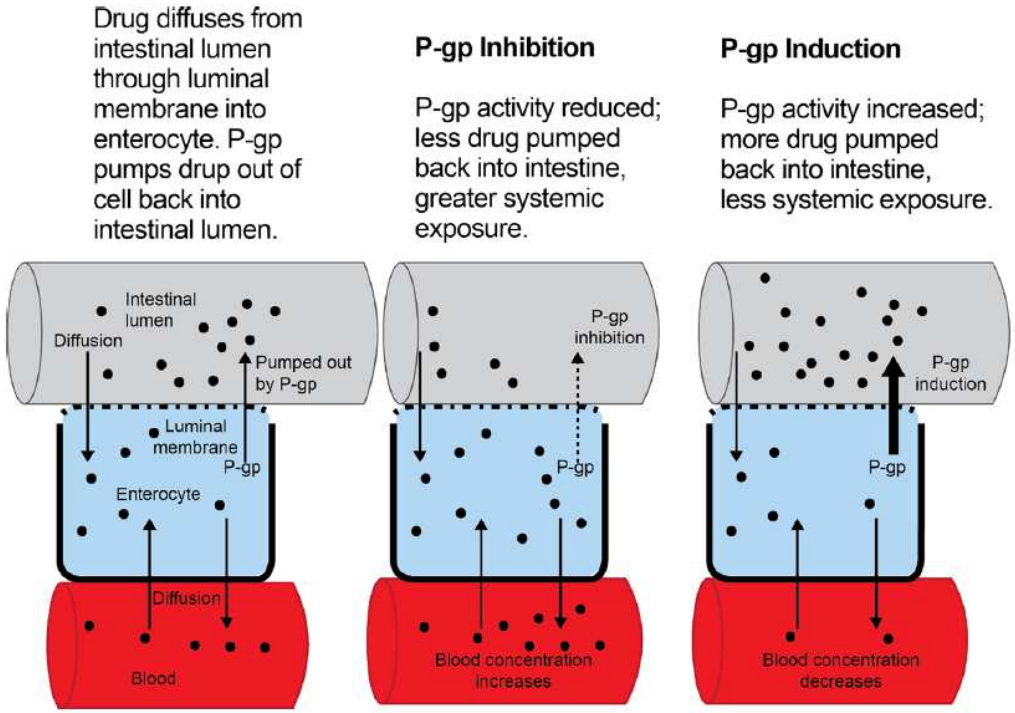
Drug interactions

	dabigatran etexilate (PRADAXA®)	rivaroxaban (XARELTO®)	apixaban (ELIQUIS®)	edoxaban (LIXIANA®)
CYP substrate	×	✓ 3A4, 2J2 + cyp-independent mechanism	✓3A4/5, 1A2, 2J2 + cyp-independent mechanism	✓ 3A4/5 + cyp-independent mechanism
Transport substrate	✓ P-gp	✓ P-gp	✓ P-gp	✓ P-gp
Anti-H_2/proton pump inhibitors	30% reduction of the AUC No impact on efficacy in RCT	No impact	No impact	No impact

Eu-SmPC Pradaxa® Xarelto® Eliquis® Lixiana®

Drug interactions: P-glycoprotein



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Drug interactions

	dabigatran etexilate (PRADAXA®)	rivaroxaban (XARELTO®)	apixaban (ELIQUIS®)	edoxaban (LIXIANA®)
CYP substrate	×	✓ 3A4, 2J2 + cyp-independent mechanism	✓3A4/5, 1A2, 2J2 + cyp-independent mechanism	✓ 3A4/5 + cyp-independent mechanism
Transport substrate	✓ P-gp	✓ P-gp	✓ P-gp	✓ P-gp

Strong P-gp inhibitors	Moderated P-gp inhibitors	Strong P-gp inducers
Contraindicated	Caution!	Caution!
Ketoconazole Itraconazole Dronédarone Ciclosporine Tacrolimus	Amiodarone Verapamil Quinidine Clarithromycin	Rifampicin St John's wort Carbamazepine Phenytoin

+ **PD interactions**

ASA
Clopidogrel
NSAIDs
SSRI and SNERI
Concomitant treatment with other anticoagulant

CI

Dose tailoring:

- VTE prevention post TKR/THR: max 150 mg/day (2 caps of 75 mg od)
- SPAF: max 220 mg/day (1 caps 110 mg bid)

Eu-SmPC Pradaxa®

Drug interactions rivaroxaban

	dabigatran etexilate (PRADAXA®)	rivaroxaban (XARELTO®)	apixaban (ELIQUIS®)	edoxaban (LIXIANA®)
CYP substrate	×	✓ 3A4, 2J2 + cyp-independent mechanism	✓3A4/5, 1A2, 2J2 + cyp-independent mechanism	✓ 3A4/5 + cyp-independent mechanism
Transport substrate	✓ P-gp	✓ P-gp	✓ P-gp	✓ P-gp

Strong P-gp and CYP3A4 inhibitors	Moderated P-gp inhibitors	Strong P-gp inducers
Not-recommended	Caution!	Caution!
Ketoconazole Itraconazole Voriconazole Posaconazole Protease inhibitors (ritonavir,…)	Amiodarone* Verapamil* Quinidine* Clarithromycin Erythromycin	Rifampicin St John's wort Carbamazepine Phenytoin Phenobarbital

No dose adjustment

+ **PD interactions**

ASA
Clopidogrel
NSAIDs
SSRI and SNERI
Concomitant treatment with other anticoagulant

CI

*not indicated in the SmPC

Eu-SmPC Xarelto®

Drug interactions rivaroxaban

- **<u>Grapefruit juice</u>**

Lack of data but…

- Grapefruit juice is classified as moderate to strong CYP3A4 inhibitor, similar to erythromycin.
- Increases in rivaroxaban exposure upon grapefruit juice consumption are not expected to exceed the 1.3-fold increase observed on average in healthy subjects when pre- and co-treated with erythromycin 500 mg tid.
- This increase is within the magnitude of normal inter-individual variability of AUC and Cmax and is considered as clinically not relevant.
- No inclusion of grapefruit juice in the SmPC.

[1]Variation de type II H-C-000944-II-0023, Commission decision 05/08/2013.

Drug interactions apixaban

	dabigatran etexilate (PRADAXA®)	rivaroxaban (XARELTO®)	apixaban (ELIQUIS®)	edoxaban (LIXIANA®)
CYP substrate	×	✓ 3A4, 2J2 + cyp-independent mechanism	✓3A4/5, 1A2, 2J2 + cyp-independent mechanism	✓ 3A4/5 + cyp-independent mechanism
Transport substrate	✓ P-gp	✓ P-gp	✓ P-gp	✓ P-gp

Strong P-gp and CYP3A4 inhibitors	Moderated P-gp inhibitors	Strong P-gp inducers
Not-recommended	Caution!	Caution!
Ketoconazole Itraconazole Voriconazole Posaconazole Protease inhibitors (ritonavir,…)	Amiodarone* Verapamil* Quinidine* Clarithromycin Erythromycin	Rifampicin St John's wort Carbamazepine Phenytoin Phenobarbital

No dose adjustment

+ **PD interactions**

ASA
Clopidogrel
NSAIDs
SSRI and SNERI
Concomitant treatment with other anticoagulant

CI

*not indicated in the SmPC

Eu-SmPC Eliquis®

Drug interactions edoxaban

	dabigatran etexilate (PRADAXA®)	rivaroxaban (XARELTO®)	apixaban (ELIQUIS®)	edoxaban (LIXIANA®)
CYP substrate	×	✓ 3A4, 2J2 + cyp-independent mechanism	✓3A4/5, 1A2, 2J2 + cyp-independent mechanism	✓ 3A4/5 + cyp-independent mechanism
Transport substrate	✓ P-gp	✓ P-gp	✓ P-gp	✓ P-gp

Strong P-gp and CYP3A4 inhibitors	Moderated P-gp inhibitors	Strong P-gp inducers
Dose reduction	Caution!	Caution!
Cyclosporine Dronedarone Erythromycin Ketoconazole	Amiodarone Verapamil Quinidine	Rifampicin St John's wort Carbamazepine Phenytoin Phenobarbital

SPAF and DVT/PE:
- edoxaban 30 mg od

No dose adjustment

+ **PD interactions**

ASA
Clopidogrel
NSAIDs
SSRI and SNERI
Concomitant treatment with other anticoagulant

CI

*not indicated in the SmPC

Eu-SmPC Lixiana®

Content

- Introduction
- PK and PD
- Indications and posology
- Interactions
- Specific populations
- Monitoring?
- Conclusions

Hepatic impairment

- Recommendation:

Prior to initiating DOACs, liver function testing should be performed.

Renal impairment

	dabigatran etexilate (PRADAXA®)	rivaroxaban (XARELTO®)	apixaban (ELIQUIS®)	edoxaban (LIXIANA®)
Mild renal impairment (CrCl: 50 to 80 mL/min)	No recommendation*	No dose adjustment is required	No dose adjustment is required	No dose adjutement is required FDA warning: Lixiana should not be used in patients with CrCl >95mL/min
Moderate renal impairment (CrCl: 30 to 50 mL/min)	**SPAF and VTEt:** High bleeding risk patients 220 mg/day 1 caps. of 110 mg bid	**SPAF:** 15 mg/day 1 tablet of 15 mg od **VTEt:** 15 mg/day 1 tablet of 15 mg od if the risk of bleeding outwieghts risk of recurence	No dose adjustement is required	**SPAF and VTEt:** 30 mg/day 1 tablet of 30 mg od
Severe renal impairment (CrCl: 10-30 mL/min)	Contraindicated * Renal function should be assessed during treatment with Pradaxa at least once a year in patients with mild to moderate renal impairment and in patients aged over 75 years. Renal function should also be assessed when a decline in renal function is suspected	**SPAF:** 15 mg/day 1 tablet of 15 mg od **VTEt:** 15 mg/day 1 tablet of 15 mg od if the risk of bleeding outwieghts risk of recurence **Not recommended in CrCl<15 mL/min**	**VTEt:** Caution **SPAF:** patients should receive the lower dose of apixaban 2.5 mg bid if at least two of the following conditions is encountered: if at least 2 of the following: ≥80 years ≤60 kg serum creat. ≥ 1,5 mg/dl or if CrCl 15-29 ml/min **Not recommended in CrCl<15 mL/min**	**SPAF and VTEt:** 30 mg/day 1 tablet of 30 mg od **Not recommended in CrCl<15 mL/min and on dialysis**

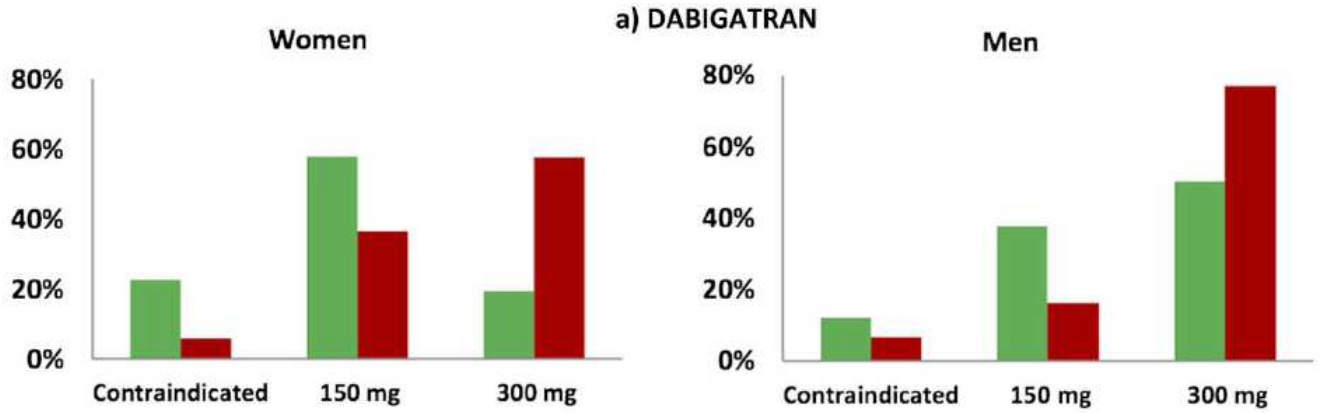
Renal impairment
How to monitor?

- RCT in SPAF: eligibility and posology based on the Cockcroft-Gault method
- MDRD overestimates low renal function

- Thus, many old SPAF patients are:

1. Either eligible to receive DOAC whereas they don't
2. Or receive higher dose regimen

by using MDRD instead of Cockcroft-Gault



MacCallum et al., BMJ Open. 2013

Renal impairment

- Renal function should be assessed in all patients by calculating the CrCl prior to initiation of treatment with DOACs
- Renal function should be assessed using the Cockcroft-Gault method
- Algorythm for the monitoring of the renal function has been proposed*
  - 60 mL/min should be assessed every 6 months
  - 50 mL/min should be assessed every 5 months
  - 40 mL/min … every 4 months
  - etc…

* There iare several proposals for the monitoring of the kidney function, but in any case, yearly monitoring is probably not sufficient in patients with impaired renal function.

Eu-SmPC Pradaxa® Xarelto® Eliquis® and Lixiana®
Heidbuchel et al. Europace. 2015

Extreme body weight

	dabigatran etexilate (PRADAXA®)	rivaroxaban (XARELTO®)	apixaban (ELIQUIS®)	edoxaban (LIXIANA®)
Low body weight (<50-60 kg)	No dose adjustment required Limited clinical data are available for patients <50 kg	No dose adjustment required Variation of less than 25% of the exposure	**VTEt:** No dose adjustment required **SPAF:** Dose reduction: 2.5 mg bid if at least 2 of the following: ≥80 years ≤60 kg serum creat. ≥ 1,5 mg/dl or if CrCl 15-29 ml/min 30 % increase of the exposure	Dose reduction: 30 mg od C_{MAX} and AUC increased by 40% and 13%, respectively
High body weight (>120 kg)	No dose adjustment required Trough dabigatran concentrations were 20% lower in patients >100 kg compared to the 50-100 kg group	No dose adjustement is required Variation of less than 25% of the exposure	No dose adjustement required 30% reduction of the exposure	No information

Other special populations

	dabigatran etexilate (PRADAXA®)	rivaroxaban (XARELTO®)	apixaban (ELIQUIS®)	edoxaban (LIXIANA®)
Elderly	**SPAF:** Patients between 75-80 years should be treated with a daily dose of 300 mg taken as one 150 mg capsule twice daily. A dose of 220 mg taken as one 110 mg capsule twice daily can be individually onsidered, at the discretion of the physician, when the thromboembolic risk is low and the bleeding risk is high Patients aged 80 years or above should be treated with a daily dose of 220 mg taken as one 110 mg capsule twice daily due to the increased risk of bleeding in this population.	Elderly patients exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 1.5 fold higher, mainly due to reduced (apparent) total and renal clearance. No dose adjustment is necessary.	VTEt: No dose adjustment required **SPAF:** Dose reduction: 2.5 mg bid if at least 2 of the following: **≥80 years** ≤60 kg serum creat. ≥ 1,5 mg/dl or if CrCl 15-29 ml/min Elderly patients (above 65 years) exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 32% higher and no difference in C_{MAX}.	After taking renal function and body weight into account, age had no additionnal clinically significant effect on edoxaban pharmacokinets
Ethnic origin and race	No clinically relevant ethnic differences among Caucasians, African-American, Hispanic, Japanese or Chinese patients were observed. However, 32.8% of the white European participants of the RE-LY study presented a particular SNP that decreased trough concentrations to the rate of the 110mg BID dose	No clinically relevant inter-ethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding rivaroxaban pharmacokinetics and pharmacodynamics.	The results across phase 1 studies showed no discernible difference in apixaban pharmacokinetics between White/Caucasian, Asian and Black/African American subjects.	In a population pharmacokinetic analysis of the ENGAGE AF-TIMI 48 study, peak and total exposure in Asian patients and non-Asian patients were comparable.

OD vs BD, adherence, persistance

- **An OD dosing** regimen was related to greater adherence vs. BID regimens in cardiovascular patients, and in AF patients (for diabetes and hypertension drugs).

- It is likely that also for NOACs an OD dosing regimen is best from a total pill count perspective, but it is unknown whether any regimen is superior in guaranteeing the clinical thrombo-embolic preventive effects and safety profile as seen in the clinical trials.

- There is modelling data suggesting that there is potentially a larger decrease in anticoagulant activity occuring **when a single pill is omitted** from an OD dosing regimen compared with when a single or even two pills are omitted from a BID regimen. **The clinical relevance of these fluctuations is unknown**

- It is essential to ensure that drugs are taken acccording to the prescibed regimen to obtain the results observed in the clinical trials.

Content

- Introduction
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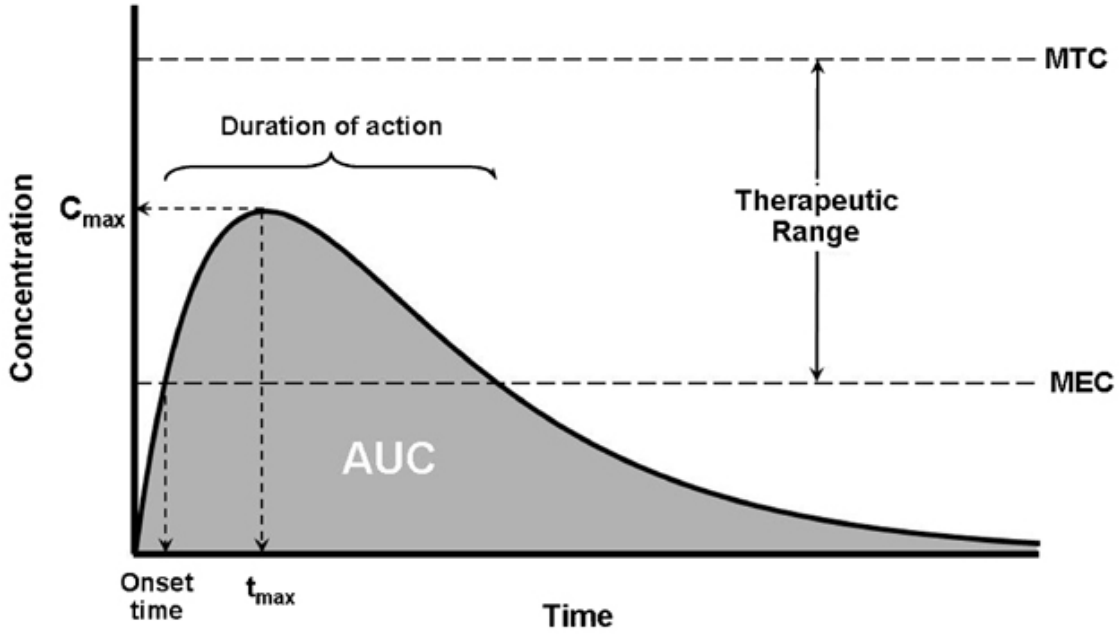
- Indications and posology
- Interactions
- Specific populations
- Monitoring?
- Conclusions

Brief reminder…



	dabigatran etexilate (PRADAXA®)	rivaroxaban (XARELTO®)	apixaban (ELIQUIS®)	edoxaban (LIXIANA®)
T_{MAX} (hours)	0.5-2.0	2.0-4.0	3.0-4.0	1.0-2.0
T_{TROUGH} (hours)	12.0	24.0	12.0	24.0

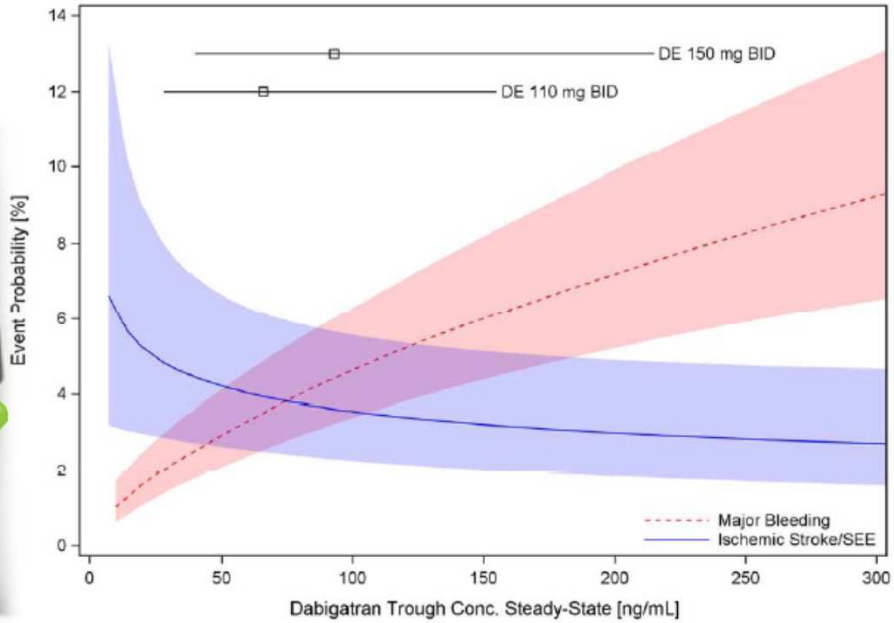
Pro or cons monitoring?

- Cons:
  - PK-PD studies: preditable response
  - All RCT were performed without monitoring
  - Large therapeutic range

Freyburger et al., 2011; Mani et al., 2013; Samama et al., 2013

Pro or cons monitoring?

- Pro:
  - Example: dabigatran etexilate (same for edoxaban)
  - Correlation between clinical events and plasmatic dabigatran concentrations
  - Possible improvement of the B/R balance



Reilly PA et al., JACC 2013; Douxfils et al., Exp. Op. Drug Saf. 2015.

Pro or cons monitoring?

- Pro:
  - Example: dabigatran etexilate
    - >90th percentile at trough = risk of bleeding
    - cut-off proposed: 200 ng/mL
    - Important variation of plasmatic concentration (up to 5-fold at trough)
    - Response can be infra- or supra-therapeutic

EMA SmPC 2013; Ten Cate, H. Thromb Haemost 2012; Ten Cate, H. Thromb J 2013; Reilly PA et al. JACC 2013; Chan et al. JTH 2015; Douxfils et al. JTH 2015; Douxfils et al. Exp. Op. Drug. Saf. 2015

How to? Monitoring

- First step:
  - Definition of therapeutic concentration ranges
- Second step:
  - Which test(s) could/should be used in these concentration ranges?
- Third step:
  - How to interpret?

Absence of therapeutic range

Absence of therapeutic range,

But expected plasma concentration or

on-therapy range

Table III. Expected plasma concentrations of Oral Direct Inhibitors.

Drug	Dose	Peak levels mean and range	Trough levels mean and range	References
Apixaban	2·5 mg bd	0·062 mg/l (CV 37%)	0·021 mg/l (CV 17%)	Frost *et al* (2013)
Apixaban	5 mg bd	0·128 mg/l (CV 10%)	0·050 mg/l (CV 20%)	Frost *et al* (2013)
Dabigatran	150 mg bd	0·184 mg/l (95% CI 0·064–0·443)	0·090 mg/l (0·031–0·225)	Van Ryn *et al* (2010)
Rivaroxaban	10 mg od	0·125 mg/l (0·091–0·195)	0·009 mg/l (0·001–0·038)	Mueck *et al* (2008)
Rivaroxaban	20 mg od	0·223 mg/l (0·16–0·36)	0·022 mg/l (0·004–0·096)	Mueck *et al* (2008)

CV, coefficient of variation; 95% CI, 95% confidence interval.

Kitchen S, *et al*. Br J Haematol. 2014

When? Patients or situations requiring an assessment of the response

- Bleeding or recurrence of thrombosis
- Before an invasive procedure (elective or urgent surgery at risk of bleeding, thrombolysis)
- In patients with potential drug interactions that affect the pharmacokinetics of DOACs (P-gp)
- In patients with extreme body weight (< 50 or > 110 kg)
- In elderly patients (> 75 years of age) with renal failure
- In patients with genetic mutations (i.e., rs2244613 minor allele carriers → dabigatran etexilate only)
- In case of accumulating interfering factors
- ~~Effect of Antidotes~~

Douxfils *et al.* Exp. Op. Drug. Saf. 2015.

Evidence regarding laboratory measurement: a systematic review

TABLE 6 Suggestions for Laboratory Measurement of Non-Vitamin K Oral Anticoagulants

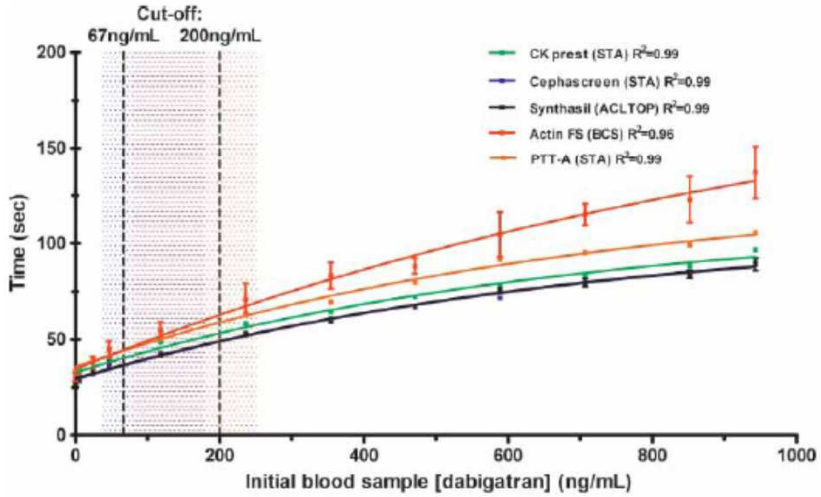
Drug	Clinical Objective: Determine If Clinically Relevant Below On-Therapy Drug Levels Are Present — Suggested Test	Determine If Clinically Relevant Below On-Therapy Drug Levels Are Present — Interpretation	Clinical Objective: Estimate Drug Levels Within On-Therapy Range — Suggested Test	Estimate Drug Levels Within On-Therapy Range — Interpretation	Clinical Objective: Determine If Above On-Therapy Drug Levels Are Present — Suggested Test	Determine If Above On-Therapy Drug Levels Are Present — Interpretation
Dabigatran	TT	Normal TT likely excludes clinically relevant drug levels	Dilute TT, ECA, ECT	—	APTT, dilute TT, ECA, ECT	Normal APTT likely excludes excess drug levels; only dilute TT, ECA, and ECT are suitable for quantitation
Rivaroxaban	Anti-Xa	Normal anti-Xa activity likely excludes clinically relevant drug levels	Anti-Xa	—	Anti-Xa, PT	Normal PT likely excludes excess drug levels; only anti-Xa is suitable for quantitation
Apixaban	Anti-Xa	Normal anti-Xa activity likely excludes clinically relevant drug levels	Anti-Xa	—	Anti-Xa	—

Suggestions for laboratory measurement of the anticoagulant activity of dabigatran, rivaroxaban, and apixaban are based on the clinical objective. Typical on-therapy drug levels are shown in Table 1. Abbreviations as in Table 2.

Cuker *et al.* J Am Coll Cardiol. 2014.

Dabigatran and aPTT

- Dabigatran
  - aPTT: in vitro study



B) In atrial fibrillation (AF): dabigatrain etexilate 150 mg bid

Reagent	Clotting time corresponding to a risk a bleeding in AF at C_{trough} (i.e. 200 ng/ml) (15)	
	Sec	Ratio
Actin FS®	62.5	2.06
Cephascreen®	48.6	1.77
CKPrest®	53.0	1.74
PTT-A®	58.6	1.77
Synthasil®	49.0	1.78
Hemoclot Thrombin Inhibitor®	54.7	1.64

Adapted from Douxfils J, Mullier F *et al.* Thromb Haemost. 2012

Table 2: Coagulation test thresholds at trough that may be associated with an increased risk of bleeding.

Test (trough value)	Indication	
	pVTEp orthopaedic surgery	SPAF and DVT/PE
dTT [ng/mL]	> 67	> 200
ECT [x-fold upper limit of normal]	No data	> 3
aPTT [x-fold upper limit of normal]	> 1.3	> 2
INR	Should not be performed	Should not be performed

EU-SmPC – Pradaxa available on the EMA website

How to? Monitoring

- **aPTT should not be used except for screening a bleeding patient on dabigatran etexilate**
- **Normal APTT and/or PT don't exclude presence of therapeutic levels of DOACs**
- **Normal TT excludes clinical relevant dabigatran level**
- **Importance of delay between last administration and sampling**
- **Specific tests should be preferred**

Douxfils J, et al. Thromb Res. 2012; Douxfils J, et al. Thromb Haemost 2013
Lessire S. et al Thromb Res 2015

Interprétation
Cas pratique: Xarelto®

- Femme: 66 ans, FA, HTA, dyslipidémie, appendicectomie, amygdalectomie, hysterectomie radicale totale
  - **Traitements:**
    rivaroxaban 20mg; flécaïnide; rosuvastatine; losartan; pantoprazole
  - Taille : 160 cm, poids 63 kg, Créat 1,05 mg/dL, CG* : 52,4 mL/min
  - 09/07/2014 :
    - 24 h: 70 ng/mL (thérapeutique)
    - 120 min : 446 ng/mL (supra-thérapeutique)
    - 180 min : 476 ng/mL (supra-thérapeutique)

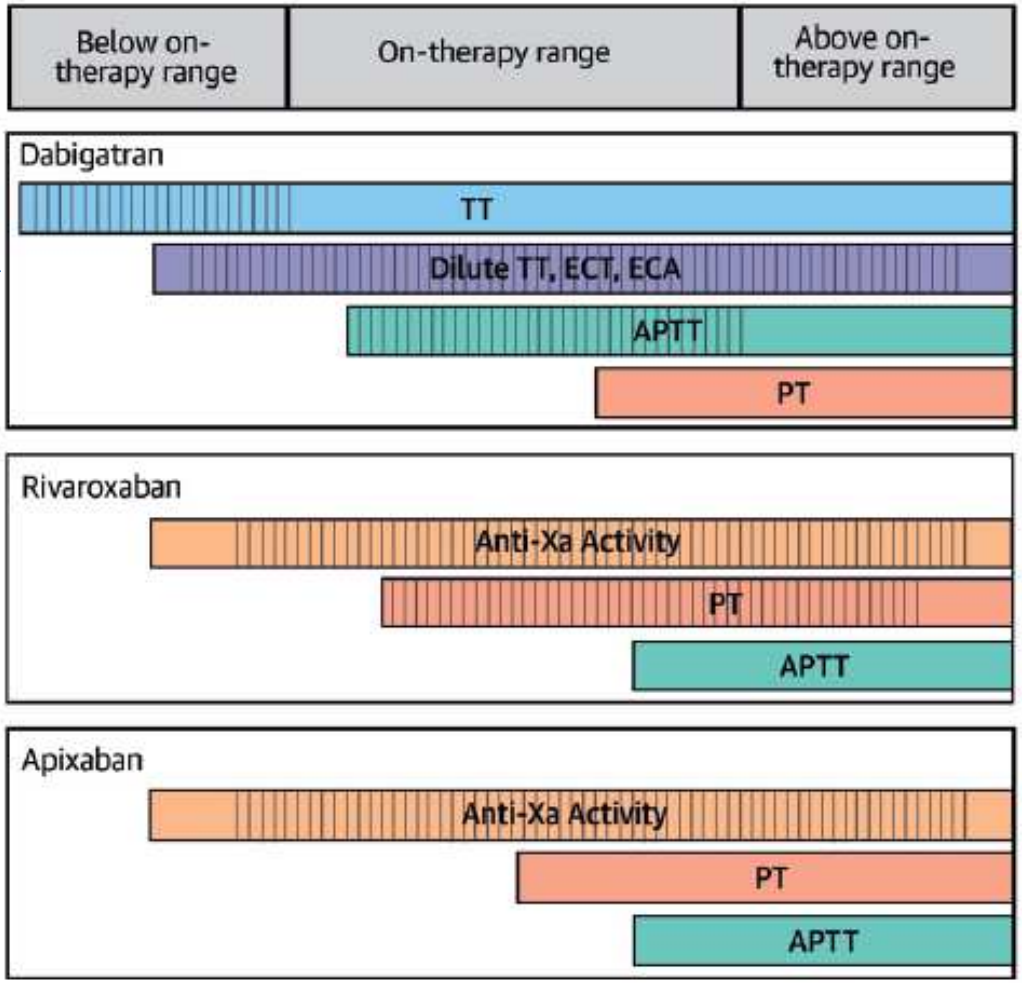
  - Diminution de la dose à **15mg/ jour**

CG* < 49ml/min → rivaroxaban 15mg/jour

*CG: Cockcroft and Gault

Coagulation tests and NOACs

Adaptations of the specific assays should be performed for the low concentration range (perioperative management)



Cuker and coll. J. Am. Coll. Cardiol. 2014
Lessire S. Submitted
Douxfils J, Lessire S et al. Thromb Haemost 2015

Preoperative assessment: Anemia and NOACs

Anemia predicted (RE-LY):

- bleeding complications (2x increase for critical area or organ, 2.5x increase for GI bleeding)
- temporary and permanent discontinuation of the RE-LY study medication
- hospitalizations for new malignancies
- thromboembolic events (stroke, CV hospit, all cause mortality)

➔close monitoring, rather than dose adjusting or discontinuation of AC.

Association was stronger for younger patients VS older patients.

Westenbrink BD and coll. JTH 2015

Preop assessment (in CHU UCL Namur)

- Is my patient at risk of being in supratherapeutic levels?
  - Age, body weight
  - Renal function (Creat Cl Cockcroft-Gault), liver function
  - Co-medications
  - Right dose for the patient (Off label)?
- Anemia present?

- If yes: preoperative dosage (which NOAC, indication and doses, timing of last intake…)

Timing of discontinuation

Periods of interruption before surgery/invasive procedures depend on:

- Stratification of the bleeding risk of the procedure
- Renal function

The timing of NOACs discontinuation remains a permanent balance between bleeding and TE risk

Dincq AS and coll. Biomed Res Int. 2014;
Beyer-Westendorf J and coll. Eur Heart J 2014 Jul

Surgery/procedure and bleeding risks

1.Interventions not requiring discontinuation of anticoagulation (i.e. dental, ophthalmology, and superficial surgeries)

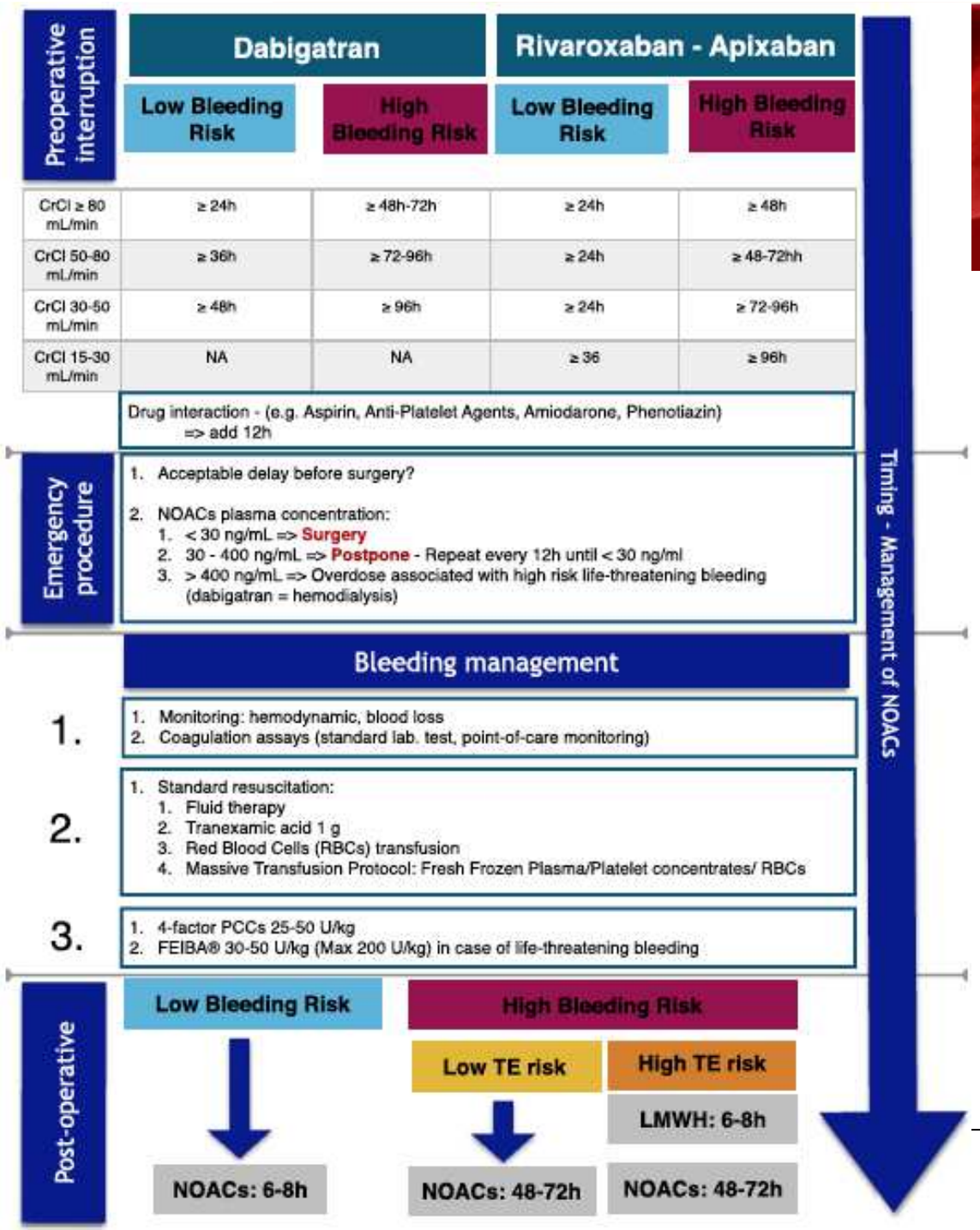
2.Intervention with low bleeding risk (i.e.prostate or bladder biopsy, angiography, pacemaker implementation);

➔ **stop NOACs 24 hours**

3.Intervention with high bleeding risk (spinal or epidural anesthesia, lumbar diagnostic puncture, cardiothoracic surgery, abdominal surgery, major orthopedic surgery, liver biopsy, transurethral prostate resection, and kidney biopsy);

➔ **stop at least 48h to 96 hours**

Faraoni and coll. Critical care 2015
Dincq AS and coll. Biomed Res Int. 2014;



Faraoni and coll. Critical care 2015

Bridging or not?

- Increase in major bleeding without decrease of thrombotic events in patients group bridged with heparins during the perioperative interruption of oral anticoagulants

- Recent updated guidelines recommend to bridge only patient at high risk of thrombo-embolic events, especially as these were under-represented in clinical trials analysing the benefit or harm of bridging therapies (e.g. the BRIDGE clinical trial.
- Using a protocol, best way to keep risk of bleeding and TE low vs individual physician preferences and experiences

Beyer-Westendorf J, *European heart journal*. 2014; 35; Douketis JD, *Thrombosis and haemostasis*. 2015; Siegal D, *Circulation*. 2012; Steinberg BA, *Circulation*. 2015; Douketis JD, *The New England journal of medicine*. 2015;Douketis JD, *Chest*. 2012; Mar PL, *Int J Cardiol*. 2016; Douketis JD, J Thromb Haemost 2016

Recommendations before invasive procedures

- Expert Opinions (the “threshold” at which the haemorrhagic risk of patients on NOACs would be comparable to untreated ones is unknown)

- `The Working Group on Perioperative Haemostasis (GIHP) :
  - 30 ng/ml = threshold for safe haemostasis
    =12.5% of mean peak concentration at steady state
    (SmPc: 175 ng/ml))
    = 3 half lifes

- EMA: dabigatran concentration < 48 ng/mL is equivalent to elimination of at least 75% of dabigatran and should be reached before invasive intervention.

Sié P and coll. Arch. Cardiovasc Dis 2011
Samama CM and coll. (GIHP) EMC –2014

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000829/WC500110875.pdf

Urgent surgery and DABIGATRAN (PRADAXA®)

[Dabigatran] ≤ 30 ng/ml	•• Operate
30 ng/ml < [Dabigatran] ≤ 200 ng/ml	•• Wait up to12 h* and obtain new dosage** or (if time is not compatible with emergency) •• Operate, if abnormal bleeding : antagonise the anticoagulant effect***
200 ng/ml < [Dabigatran] ≤ 400 ng/ml	• Wait up to12 h* and obtain new dosage** or (if time is not compatible with emergency) • Maximum delay surgery • Discuss haemodialysis, especially if CkrCl < 50 ml/mn • Operate, if abnormal bleeding : antagonise ***
[Dabigatran] > 400 ng/ml	• Overdose – Major haemorrhagic risk • Discuss haemodialysis before surgery

In case of renal insufficiency, half-life of dabigatran is clearly increased

* It is not possible to accurately determine the time to reach a threshold of 30 ng/ml, so the sentence "until 12h"

** This second assay can be used to estimate the time required to obtain the threshold of 30 ng/ml

*** This proposal applies primarily to emergency situations where you cannot wait :

- PCC 25-50 UI/kg or FEIBA=30-50 UI/Kg depending on the availability
- No data are available on the thrombotic risk of high doses of PCC or FEIBA in these patients
- Reversal by CCP or FEIBA does not fully correct the abnormalities of haemostasis tests
- rFVIIa is not considered first-line

Pernod and coll. Arch Cardiovasc Dis 2013

Preoperative interruption

	Dabigatran		Rivaroxaban - Apixaban	
	Low Bleeding Risk	High Bleeding Risk	Low Bleeding Risk	High Bleeding Risk
CrCl ≥ 80 mL/min	≥ 24h	≥ 48h-72h	≥ 24h	≥ 48h
CrCl 50-80 mL/min	≥ 36h	≥ 72-96h	≥ 24h	≥ 48-72hh
CrCl 30-50 mL/min	≥ 48h	≥ 96h	≥ 24h	≥ 72-96h
CrCl 15-30 mL/min	NA	NA	≥ 36	≥ 96h

Drug interaction - (e.g. Aspirin, Anti-Platelet Agents, Amiodarone, Phenotiazin)
=> add 12h

Emergency procedure

1. Acceptable delay before surgery?
2. NOACs plasma concentration:
   1. < 30 ng/mL => **Surgery**
   2. 30 - 400 ng/mL => **Postpone** - Repeat every 12h until < 30 ng/ml
   3. > 400 ng/mL => Overdose associated with high risk life-threatening bleeding (dabigatran = hemodialysis)

Bleeding management

1.
   1. Monitoring: hemodynamic, blood loss
   2. Coagulation assays (standard lab. test, point-of-care monitoring)
2.
   1. Standard resuscitation:
      1. Fluid therapy
      2. Tranexamic acid 1 g
      3. Red Blood Cells (RBCs) transfusion
      4. Massive Transfusion Protocol: Fresh Frozen Plasma/Platelet concentrates/ RBCs
3.
   1. 4-factor PCCs 25-50 U/kg
   2. FEIBA® 30-50 U/kg (Max 200 U/kg) in case of life-threatening bleeding

Post-operative

Low Bleeding Risk → **NOACs: 6-8h**

High Bleeding Risk

Low TE risk	High TE risk
	LMWH: 6-8h
NOACs: 48-72h	NOACs: 48-72h

Timing - Management of NOACs

4. Idarucizumab 5 g for dabigatran life-treatening bleeding (à suivre, pas encore remboursé)

Faraoni and coll. Critical care 2015

Antidotes: Current status

Antidote	Data available for	Ex vivo	Animal	Phase 1 & 2 trials*	Phase 3	References	ClinicalTrials.gov numbers
andexanet alpha, PRT064445	apixaban	+	+	+#	+	21,25,27,29#	NCT02207725 NCT02220725 NCT02329327
	betrixaban	+	+	+	+	21,25	
	rivaroxaban	+	+	+	+	21,23,24,26	
	edoxaban	n.d.	n.d.	+	+	27	
		+	+	n.d.	+	21	
		+	+	+	+	21,25	
idarucizumab	dabigatran	+	+	+	+	32–39	NCT02028780 NCT02104947
modified thrombin (γT -S195A-IIa)	dabigatran	+	+	n.d.	n.d.	22	
aripazine (PER977)	apixaban	+	+	n.d.	n.d.	48,49,50,51	NCT02206100 NCT02205905 NCT01826266 NCT02207257 NCT02206087
	rivaroxaban	+	+	n.d.	n.d.	23,48,50,51	
	edoxaban	+	+	+	n.d.	49,50,51,52	
	enoxaparin	+	+	n.d.	n.d.	49,50	
	dabigatran	+	+	n.d.	n.d.	48,51	
	heparin	n.d.	n.d.	planned	n.d.	n.d.	

*as these antidotes are all tested in volunteers in whom real bleeding studies are not possible, the differentiation between phase 1 and 2 studies is difficult. # this trial is named phase 3 trial but it enrolls elderly volunteers and measures surrogate markers and not the efficacy of the antidote in patients with acute bleeding or acute invasive interventions. n.d.: no data available; planned: study does not recruit patients; +: completed or ongoing studies.

Autorisé depuis le 12/2015, pas encore remboursé en Belgique

Greinacher A and coll. Thromb Haemost 2015

Resuming NOACs

- Delay the first doses of prophylactic anticoagulation until after major surgery is effective and safe

- Results of phase III trials VTE prophylaxis with NOACs ➔ acceptable efficacy and safety can be achieved when appropriate first dose of anticoagulant is given at least 6 hours after surgery.

Paikin JS and coll. CHEST 2015

Resuming NOACs

- <u>Full dose anticoagulation:</u>
  - risk of postop bleeding > the risk of TE event ➔ full dose anticoagulation might be resumed 48 or 72 hours after the procedure.

- If immobilization and increased risk of TE event
  - ➔ thromboprophylaxis using LMWH or UFH should be started within 6 to 8 h post op
  - ➔therapeutic anticoagulation with NOACs should be delayed for 48 to 72 hours.

- Following major orthopedic surgery: use prophylactic doses of NOACs until the patient can resume full dose of NOAC.

Faraoni and coll. Critical Care 2015

Content

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CONCLUSIONS (1/2)

- Un pas en avant dans la gestion de l'anticoagulation
- Importance de connaitre et comprendre la pharmacocinétique
- Importance de vérifier les interactions médicamenteuses et les populations spéciales (poids, âge, fonction rénale (Cockroft))
- Le patient doit adhérer à son traitement
- Une mesure de la concentration en anticoagulant peut être utile dans certaines situations cliniques (TT et tests spécifiques)

CONCLUSIONS (2/2)

- La gestion périopératoire de ces anticoagulants est complexe et reste débattue
- L'intérêt du bridging est actuellement remis en cause (SAUF pour les populations à haut risque thrombotique)
- Les antidotes arrivent mais coût élevé, conditions de remboursement très strictes et attention aux effets secondaires

Conclusions

Europace Advance Access published August 31, 2015
Europace
doi:10.1093/europace/euv309
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]

Table 3 Checklist during follow-up contacts of AF patients on anticoagulation[a]

	Interval	Comments
1. Adherence	Each visit	Instruct patient to bring NOAC card and remaining medication: make note and assess average adherence Re-educate on importance of strict intake schedule Inform about adherence aids (special boxes, smartphone applications, etc.)
2. Thromboembolism	Each visit	Systemic circulation (TIA, stroke, and peripheral) Pulmonary circulation
3. Bleeding	Each visit	'Nuisance' bleeding: preventive measures possible? (PPI, haemorrhoidectomy, etc.). Motivate patient to diligently continue anticoagulation Bleeding with impact on quality of life or with risk: prevention possible? Need for revision of anticoagulation indication or dose?
4. Other side effects	Each visit	Carefully assess relation with NOAC: decide for continuation (and motivate), temporary cessation (with bridging), or change of anticoagulant drug
5. Co-medications	Each visit	Prescription drugs; over-the-counter drugs, especially aspirin and NSAID (see 'Drug–drug interactions and pharmacokinetics of non-vitamin K antagonist anticoagulants' section) Careful interval history: also temporary use can be risky!
6. Blood sampling	Yearly 6-monthly x-monthly On indication	Haemoglobin, renal and liver function $\geq$75–80 years (especially if on dabigatran or edoxaban), or frail[b] If renal function $\leq$60 mL/min: recheck interval = CrCl/10 If intercurrent condition that may impact renal or hepatic function

TIA, transient ischaemic attack; PPI, proton pump inhibitor; CrCl, creatinine clearance (preferably measured by the Cockcroft method).
[a]For frequency of visits: see *Figure* 2.
[b]Frailty is defined as three or more criteria of unintentional weight loss, self-reported exhaustion, weakness assessed by handgrip test, slow walking speed, or low physical activity.[34] On online frailty calculator can be found at http://www.biomedcentral.com/1471-2318/10/57 under Additional Files.

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19h30-20h00	State of the art lecture : Reversal strategies for DOACs Pr Peter Verhamme, Center for Molecular and Vascular Biology, Department of Cardiovascular Sciences, KU Leuven
20h00-20h30	Table ronde animée par le Pr Philippe Hainaut, Cliniques Universitaires Saint-Luc , UCL Bruxelles Intervenants: Pr Jean-Michel Dogné, Pr Peter Verhamme, Dr Sarah Lessire, Pr Maximilien Gourdin, Dr Jonathan Douxfils
20h30- ...	Repas

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E-Mail : francois.mullier@uclouvain.be
GSM : +32479 49 79 15

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