Course n° : *Course 3*
Sub-category: *3.6.4.*
Date: *11-09-2014)*
Language: Romana
City: Chisinau
Country:Republica Moldova
Speaker: *Sanda Maria Copotoiu*

Managementul perioperator al noilor anticoagulante orale directe

Martie 2008 Dabigatran

Boehringer Ingelheim

Septembrie 2008 Rivaroxaban

Bayer HealthCare Pharmaceuticals

Mai 2011 Apixaban

Bristol-Myers Squibb Company

15.01.2014 Epixaban EMA

Daiichi-Sankyo

Indicații terapeutice

2008

•*Profilactic* - termen scurt

TVP ortopedie șold/genunchi

2014

•Curativ: TVP, EP

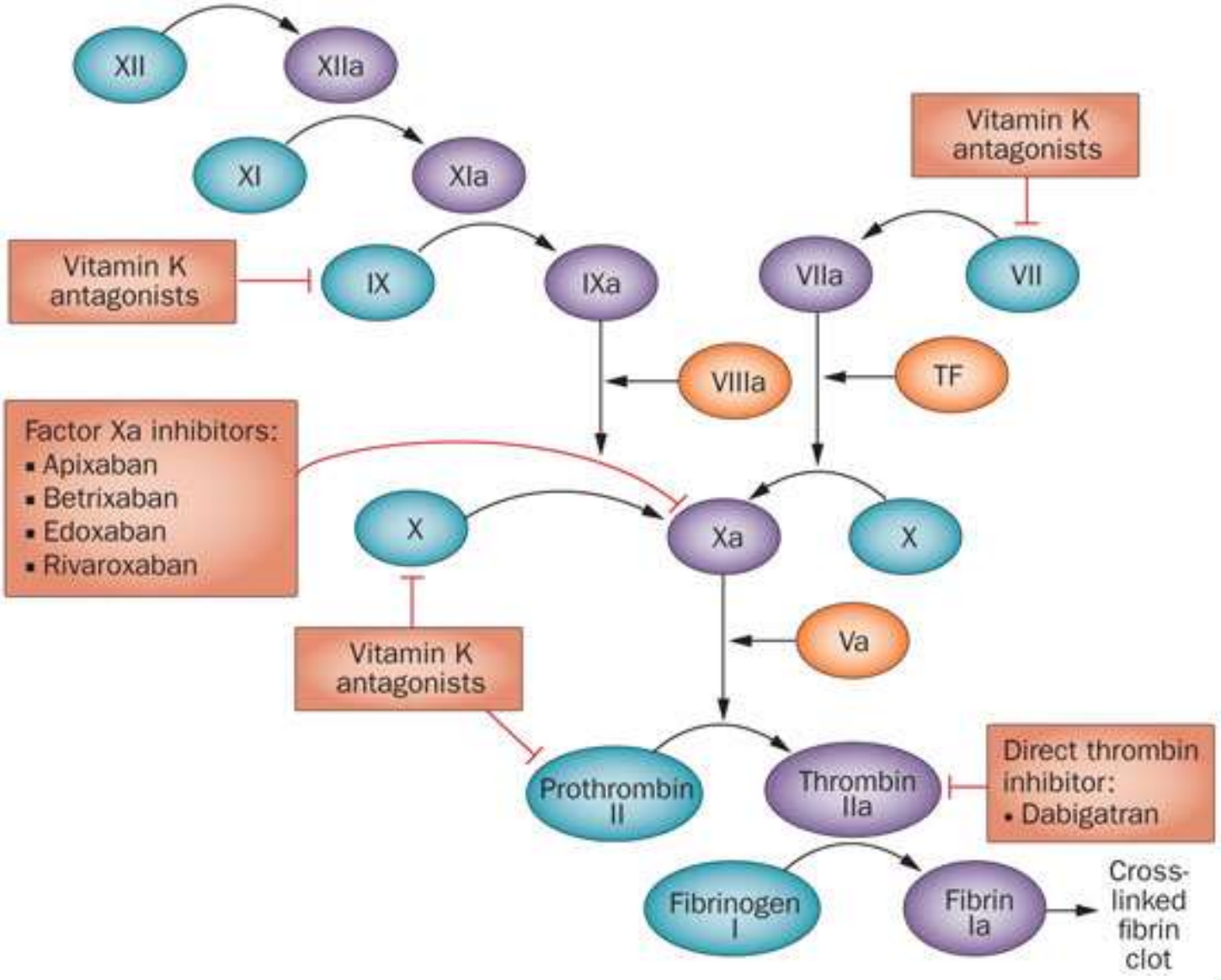
•Profilactic termen lung: BTE

•Preventiv: AVC în FA nonvalvulară

Studii Clinice

	Profilaxie TVP	Tratament TVP	Fibrilație atrială	SCA
Dabigatran	Ortopedie **RE-NOVATE** **RE-MODEL** **RE-MOBILIZE** Profilaxie secundară **RE-MEDY**	**RE-COVER** **RE-COVER II** **RE-SONATE**	**RE-LY** **RE-LY ABLE**	RE-DEEM
Rivaroxaban	Ortopedie **RECORD I** **RECORD II** **RECORD III** **RECORD IV** Medicină internă **MAGELLAN** Profilaxie secundară **EINSTEIN-Ext**	**EINSTEIN-DVT** **EINSTEIN-PE**	**ROCKET-AF**	ATLAS-TIMI 46 **ATLAS-TIMI 51**
Apixaban	Ortopedie **ADVANCE-1** **ADVANCE-2** **ADVANCE-3** Medicină internă **ADOPT** Profilaxie secundară **AMPLIFY-Ext NCT00633893**	**AMPLIFY**	**AVERROES** **ARISTOTLE**	APPRAISE **APPRAISE-2**
Edoxaban	**NCT00986154**		**ENGAGE-AF TIMI 46**	

Locul de acțiune al NACO



	Dabigatran
Prodrog	Da
Mod de acțiune	Anti IIa
Biodisponibilitate	6-8%
Legare de proteine	35%
Dializabil	Da
Vârf plasmatic	2h
T1/2	12-17 h
Eliminare	Renal (nemodificat) 80% Bilă 5-10%
Metabolizare	P-gp
Doze TVP ortopedie	 220mgx1/zi sau 150mgx1/zi șold 28-35 zile, genunchi 10 zile
Tratament TVP/EP, prevenție pe termen lung	150mgx2/zi
Prevenție AVC în FA nonvalvulară	150mg x 2/zi sau 110mg x2/zi

	Rivaroxaban
Prodrog	Nu
Mod de acțiune	AntiXa
Biodisponibilitate	66% a jeun 100% masă
Legare de proteine	95%
Dializabil	Nu
Vârf plasmatic	2-4h
T1/2	5-9h tineri 11-13h vârstnici
Eliminare	Renal (1/2 inactiv) 66% Fecale 33%
Metabolizare	P-gp/CYP3A4
Doze TVP ortopedie	 10 mgx1/zi șold 5 săptămâni genunchi 2 săptămâni
Tratament TVP/EP, prevenție pe termen lung	15mgx2/zi (3 săptămâni), urmat de 20mgx1/zi
Prevenție AVC în FA nonvalvulară	20mg x 1/zi sau 15mg x 1/zi (Cl Cr 30-49ml/min)

	Apixaban
Prodrog	Nu
Mod de acțiune	AntiXa
Biodisponibilitate	50%
Legare de proteine	87%
Dializabil	Nu
Vârf plasmatic	3-4h
T1/2	8-15h
Eliminare	Renal 25-30% Fecale 56%
Metabolizare	P-gp/CYP3A4
Doze TVP ortopedie	 2.5 mg x 2/zi șold 32-38 zile genunchi 10-14 zile
Tratament TVP/EP, prevenție pe termen lung	10mgx2/zi (7 zile) urmat de 5mgx2/zi
Prevenție AVC în FA nonvalvulară	5mg x 2/zi (2.5mg x 2/zi dacă sunt îndeălinite 2 din criteriile următoare: vârstă>80 ani, G≤60kg, cretinină ≥ 133 µmpl/l

	Edoxaban
Prodrog	Nu
Mod de acțiune	AntiXa
Biodisponibilitate	62%
Legare de proteine	
Dializabil	Nu
Vârf plasmatic	1.5h
T1/2	8-10h
Eliminare	Renal 35% Fecale 60%
Metabolizare	P-gp/CYP3A4
Doze TVP ortopedie	 30mg/60mg 15 mg la Clcr<20
Tratament TVP/EP, prevenție pe termen lung	
Prevenție AVC în FA nonvalvulară	30mg/zi

Interacțiuni medicamentoase

Questions and answers on the use of dabigatran and perpectives on the use of other new oral anticoagulants in patients with atrial fibrillation

A consensus document of the Italian Federation of Thrombosis Centers (FCSA)

Vittorio Pengo[1]; Luciano Crippa[2]; Anna Falanga[3]; Guido Finazzi[4]; Francesco Marongiu[5]; Gualtiero Palareti[6]; Daniela Poli[7]; Sophie Testa[8]; Eros Tiraferri[9]; Alberto Tosetto[10]; Armando Tripodi[11]; Cesare Manotti[12]

doi:10.1160/TH11-05-0358
Thromb Haemost 2011; 106: 868–876

	Dabigatran	Rivaroxaban, edoxaban, apixaban
P-glycoprotein inhibitors (amiodarone, phenotiazin, carboxylic acid, azole antifungals, verapamil, antimalarial, cyclosporine, thioxanthenes)	Yes	Yes
P-glycoprotein inducers (dexamethasone, rifampicin, St. John's Wort)	Yes	Yes
CYP3A4 inhibitors (phenotiazin, carboxylic acid, azole antifungals, verapamil, erythromycin, telithromycin, nefazodone, antimalarial, cyclosporine, thioxanthenes)	No	Yes
CYP3A4 inducers (carbamazepine, efavirenz, nevirapine, phenytoin, phenobarbitone, rifabutin, rifapentine, rifampicin, St. John's Wort, alcohol, eucalyptol)	No	Yes
NSAIDS (aspirin, naproxen, diclofenac)	Yes	Yes
Antiplatelet agents (clopidogrel)	Yes	Yes

> 40% din populatia tinta

Journal of Thrombosis and Haemostasis, **8**: 2069–2091

LETTERS TO THE EDITOR

The frequency of prescription of P-glycoprotein-affecting drugs in atrial fibrillation

L. JUNGBAUER, C. DOBIAS, C. STÖLLBERGER and F. WEIDINGER
2nd Medical Department, Krankenanstalt Rudolfstiftung, Wien, Österreich, Austria

Interactions between dabigatran and P-gp-affecting drugs have only been studied in phase I trials in healthy volunteers [6]. Verapamil and amiodarone elevated dabigatran concentrations by 50–60% and clarithromycin by 19% [6]. Food–drug and herb–drug interactions with dabigatran are unknown.

We conclude that 42% of hospitalized AF patients and 48% of VKA-receiving patients take P-gp-affecting drugs. Although

Dabigatran bleed risk with closed head injuries: are we prepared?

Clinical article

MICHAEL W. PARRA, M.D.,[1,2] LLOYD ZUCKER, M.D.,[1] ERIC S. JOHNSON, D.O.,[1,2] DIANE GULLETT, R.N., B.S.N., M.P.H.,[1] CRISTINA AVILA, B.S.,[1,2] ZACHARY A. WICHNER, D.O., M.P.H.,[1,2] AND CANDACE R. KOKABAM, M.S.N.[1]

[1]Delray Medical Center/Provisional Level I Trauma Center, Delray Beach; and [2]Nova Southeastern University College of Osteopathic Medicine, Fort Lauderdale-Davie, Florida

Fatal Association of Mechanical Valve Thrombosis With Dabigatran

A Report of Two Cases

Shaul Atar, MD; Alice Wishniak, MD; Alexander Shturman, MD; Sewaed Shtiwi, MD; and Marc Brezins, MD

Hemopericardium and Cardiac Tamponade Associated with Dabigatran Use

Eliza A Dy and Dane L Shiltz

Hemodialysis for the Treatment of Pulmonary Hemorrhage From Dabigatran Overdose

Betty C. Chen, MD,[1] Nijal R. Sheth, MD,[2] Kobena A. Dadzie, MD,[2] Silas W. Smith, MD,[1] Lewis S. Nelson, MD,[1] Robert S. Hoffman, MD,[1] and James F. Winchester, MD[2]

Wound Complications Following Rivaroxaban Administration

A Multicenter Comparison with Low-Molecular-Weight Heparins for Thromboprophylaxis in Lower Limb Arthroplasty

Simon S. Jameson, MRCS, Monika Rymaszewska, MRCS, Philip James, Ignacio Serrano-Pedraza, PhD, Scott D. Muller, MD, FRCSCTr&Orth), Anthony C.W. Hui, MA, FRCSEd(Orth), and Mike R. Reed, MD, FRCSCTr&Orth)

Hemorrhagic complications associated with dabigatran use

BETTY C. CHEN,[1] AARON D. VINY,[2] FIONA M. GARLICH,[1] PAUL BASCIANO,[3] MARY ANN HOWLAND,[1,4] SILAS W. SMITH,[1] ROBERT S. HOFFMAN,[1] and LEWIS S. NELSON[1]

[1]*New York City Poison Control Center, Bellevue Hospital Center, New York University, New York, USA*
[2]*Department of Medicine, Weill Cornell Medical Center, New York, USA*
[3]*Division of Hematology and Oncology, Weill Cornell Medical Center, New York, USA*
[4]*St. John's University College of Pharmacy, New York, USA*

Safety Alerts

21.3.2012

Bleeding Reports Prompt Pradaxa Label Changes in Canada

Health Canada
www.hc-sc.gc.ca

Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

Warnings and Alerting
Severe haemorrhages
in patients treated with Prazaxa

12.08.2011

FDA

7.12.2011

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18/11/2011

European Medicines Agency
updates on safety of Pradaxa

(Pradaxa®): Recommendation to use with caution in the elderly and renally impaired patients

Pharmac attacked for rushing drug

Australian Government
Department of Health and Ageing

03.11.2011

Alerts

Dabigatran (Pradaxa): risk of bleeding relating to use

Nov.2011
Reuters

Boehringer says about 260 deaths related to Pradaxa

Le Monde science&médecine

Fabriquer des organes Une technique qui permet de faire pousser un bourgeon de foie humain, transplanté chez la souris, illustre le foisonnement des recherches en bio-ingénierie. PAGE 2

Un échec russe en trompe-l'œil L'explosion de la fusée Proton est une mauvaise nouvelle pour l'industrie spatiale russe, mais ses concurrents savent qu'il faut compter avec elle. PAGE 3

Symphonie thyroïdienne La Galloise Barbara Demeneix, biologiste et violoniste, se passionne pour une hormone qui est le « chef d'orchestre » de nos métamorphoses. PAGE 7

Les trop belles promesses des nouveaux anticoagulants

Selon la Haute Autorité de santé, ces médicaments n'apportent pas de progrès global. De plus, ils pourraient induire un surcoût annuel de 150 millions d'euros pour l'Assurance-maladie. Enquête.

PAGES 4-5

Un anticoagulant mis en cause après quatre décès

AFP 9 OCTOBRE 2013 À 07:37

Des gélules de Pradaxa du laboratoire allemand Boehringer Ingelheim (Photo Philippe Huguen. AFP)

Les proches de quatre personnes âgées ayant succombé à des hémorragies alors qu'elle prenaient du Pradaxa ont saisi la justice face au laboratoire allemand ayant développé le médicament.

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Pradaxa Lawsuits

The attorneys at Morgan and Morgan are investigating lawsuits on behalf of patients who suffered severe bleeding, including gastrointestinal bleeds and cerebral hemorrhaging, while taking the blood thinner Pradaxa. Thousands of lawsuits have already been filed, and we are expecting that many more claims will surface over the next several months. **If you or a loved one suffered a severe bleed while taking Pradaxa, you may be able to join this growing litigation** and sue the drug's manufacturer for financial compensation to cover your medical bills and other losses.

Jump to:

To find out if you are eligible for a Pradaxa lawsuit, complete the form on the right hand side of this page. Morgan and Morgan will evaluate your claim – at no cost to you - to determine whether you have legal recourse.

Important Information

Morgan & Morgan is no longer accepting claims for these cases. The information here is for reference only.

Up-to-date information and resources can be found in our current consumer alerts.

LexisNexis Martindale-Hubbell Peer Review Rated For Ethical Standards and Legal Ability

LexisNexis Martindale-Hubbell AV RATED

Related Resources

Pradaxa

General Information › Manufacturer ›

Pradaxa Lawsuits and Settlements

Pradaxa › Pradaxa Lawsuits and Settlements

More than 4,000 people will receive money from drug maker Boehringer Ingelheim as part of an MDL settlement related to Pradaxa. People who want to collect their settlement money soon can inquire about pre-settlement funding.

Thousands of people who took Pradaxa suffered side effects, and hundreds of people died. These people and their families filed lawsuits for compensation.

More than 4,000 people who suffered damaging side effects from the blood thinner Pradaxa – including gastrointestinal, rectal and brain bleeding – filed lawsuits against the drug's manufacturer, Boehringer Ingelheim Pharmaceuticals. Because Pradaxa was marketed heavily as safe and effective, doctors wrote millions of prescriptions for the new blood thinner after the U.S. Food and Drug Administration (FDA) approved it in October 2010.

But in 2011, more than 540 patients lost their lives after using Pradaxa, and

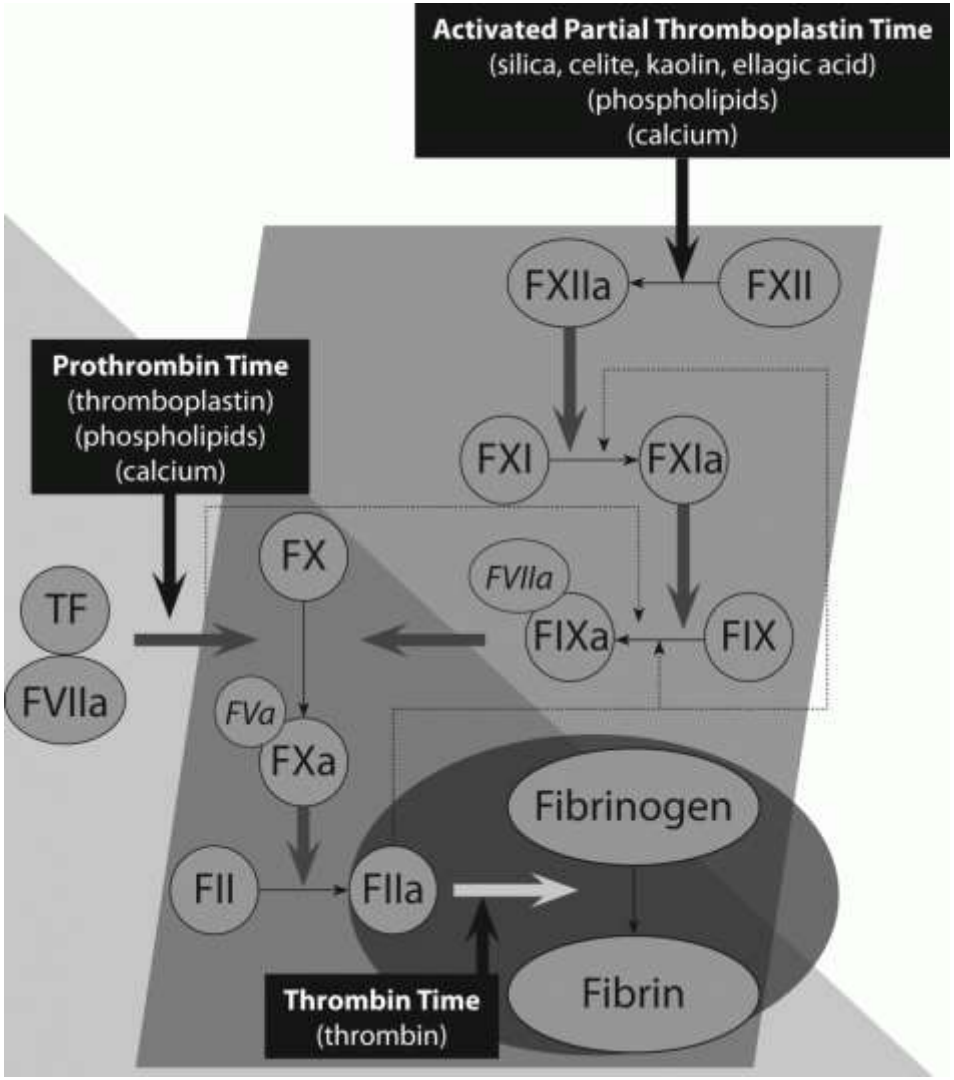
CEEA

European Society of Anaesthesiology ESA

World Federation of Societies of Anaesthesiologists


STOP

Teste de laborator



Teste de laborator

Laboratory assessment of new anticoagulants.

Samama, MM; Guinet, C

Clinical Chemistry & Laboratory Medicine. 49(5):761-772, May 2011.

Dabigatran

- Ecarin clotting time, **Haemoclot** or anti-IIa
- PT, aPTT and TT modified according to the reagent *(aPTT more sensitive)*

Rivaroxaban

- **anti-FXa activity**
- PT and aPTT modified according to the reagent *(PT more sensitive)*

Apixaban

- **anti-FXa activity**
- PT and aPTT not really prolonged

In press

Contents lists available at ScienceDirect

Thrombosis Research

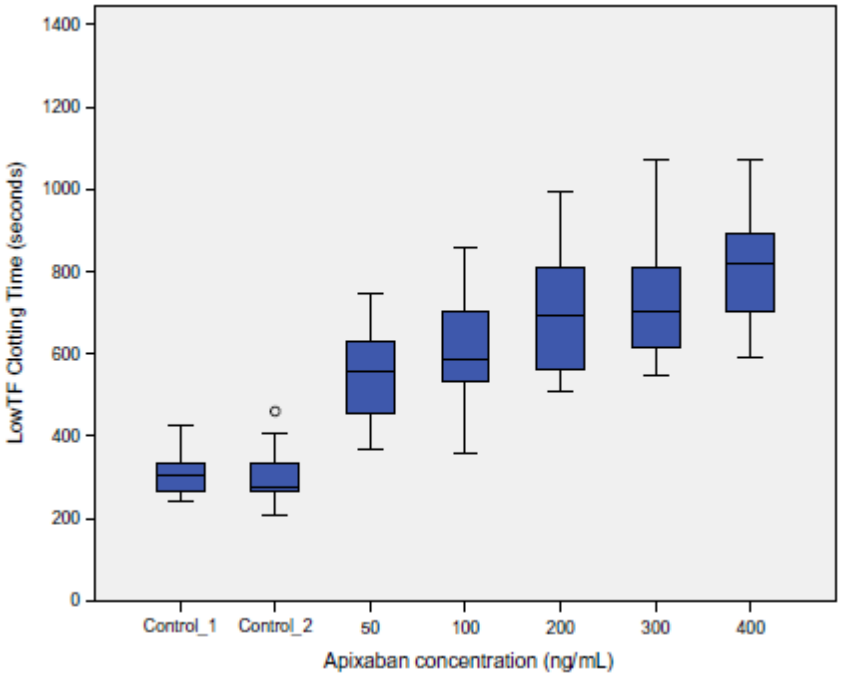
journal homepage: www.elsevier.com/locate/thromres

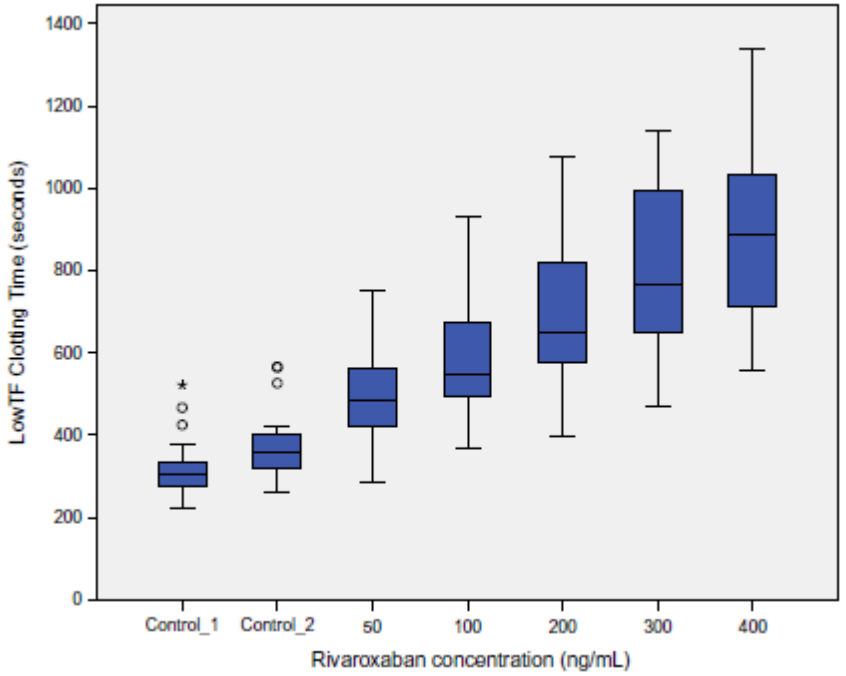
Regular Article

Measuring the activity of apixaban and rivaroxaban with rotational thrombelastometry ☆

Dieter Adelmann [a], Marion Wiegele [a], Rudolf Karl Wohlgemuth [a], Stefan Koch [a], Sophie Frantal [b], Peter Quehenberger [c], Gisela Scharbert [a], Sibylle Kozek-Langenecker [d], Eva Schaden [a,*]

Received 16 September 2013
Received in revised form 28 July 2014
Accepted 10 August 2014
Available online xxxx





Conclusions: LowTF–ROTEM® could be a valuable diagnostic tool for rapid determination of the effect of apixaban and rivaroxaban at the point of care.

În practică

Conservator

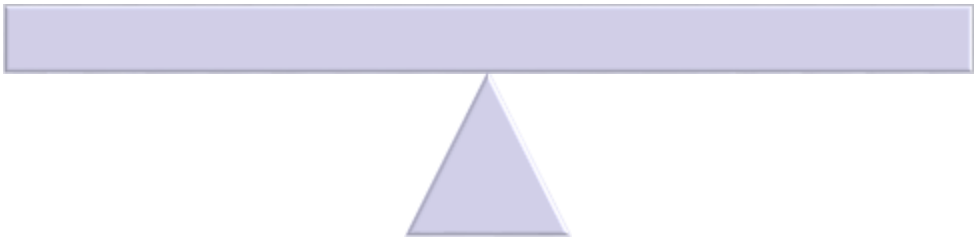
Logic

GIHP/GEHT

EHRA

AVK

Farmacocinetic



Intervenții chirurgicale elective
Conservator

Le Praticien en anesthésie réanimation (2014) **18**, 52—59

Disponible en ligne sur
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

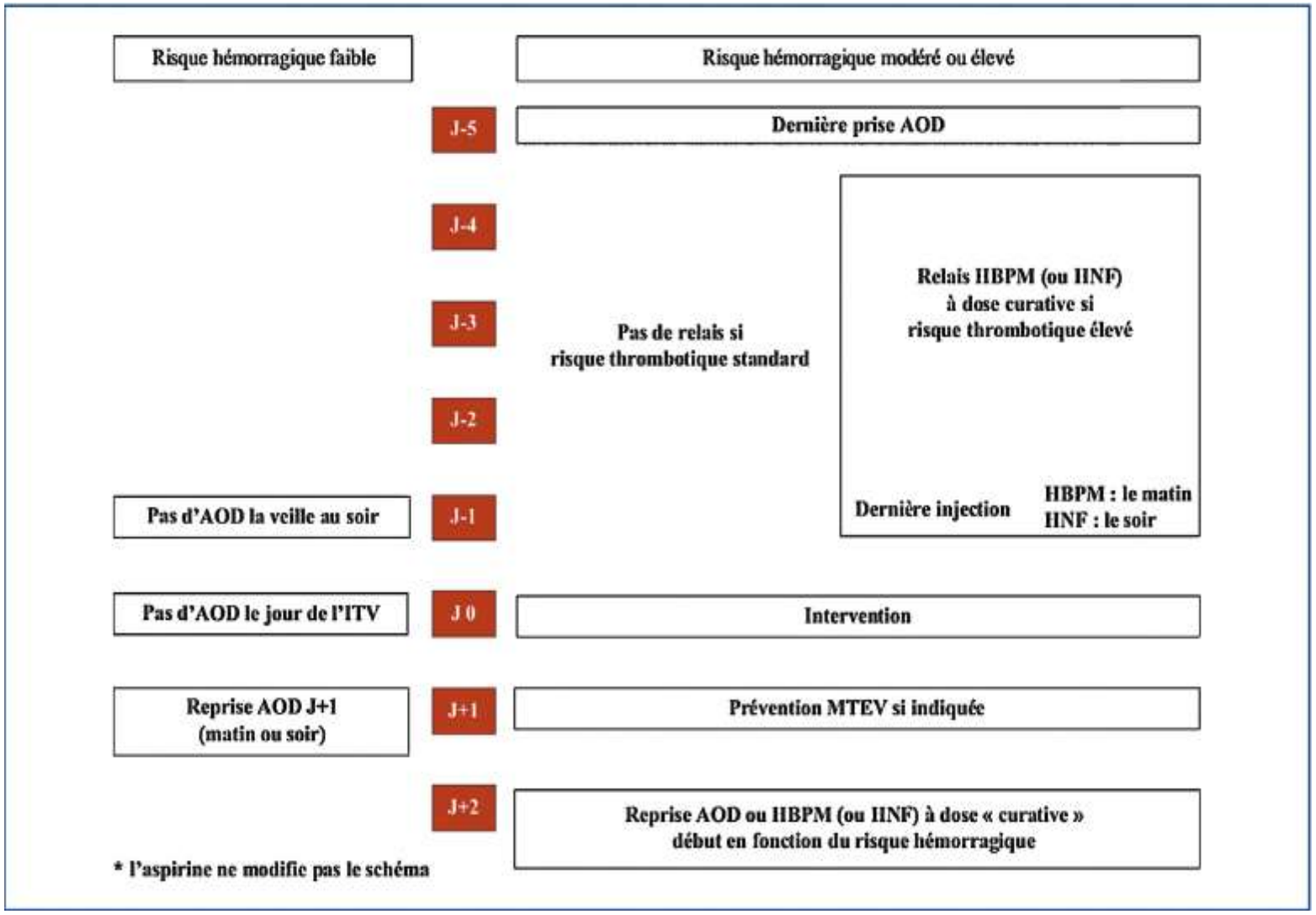
RUBRIQUE PRATIQUE

Gestion périopératoire des nouveaux anticoagulants

CrossMark

Perioperative management of new oral anticoagulants

Intervenții chirurgicale elective
Conservator



Intervenții chirurgicale elective
Farmacocinetic

Review

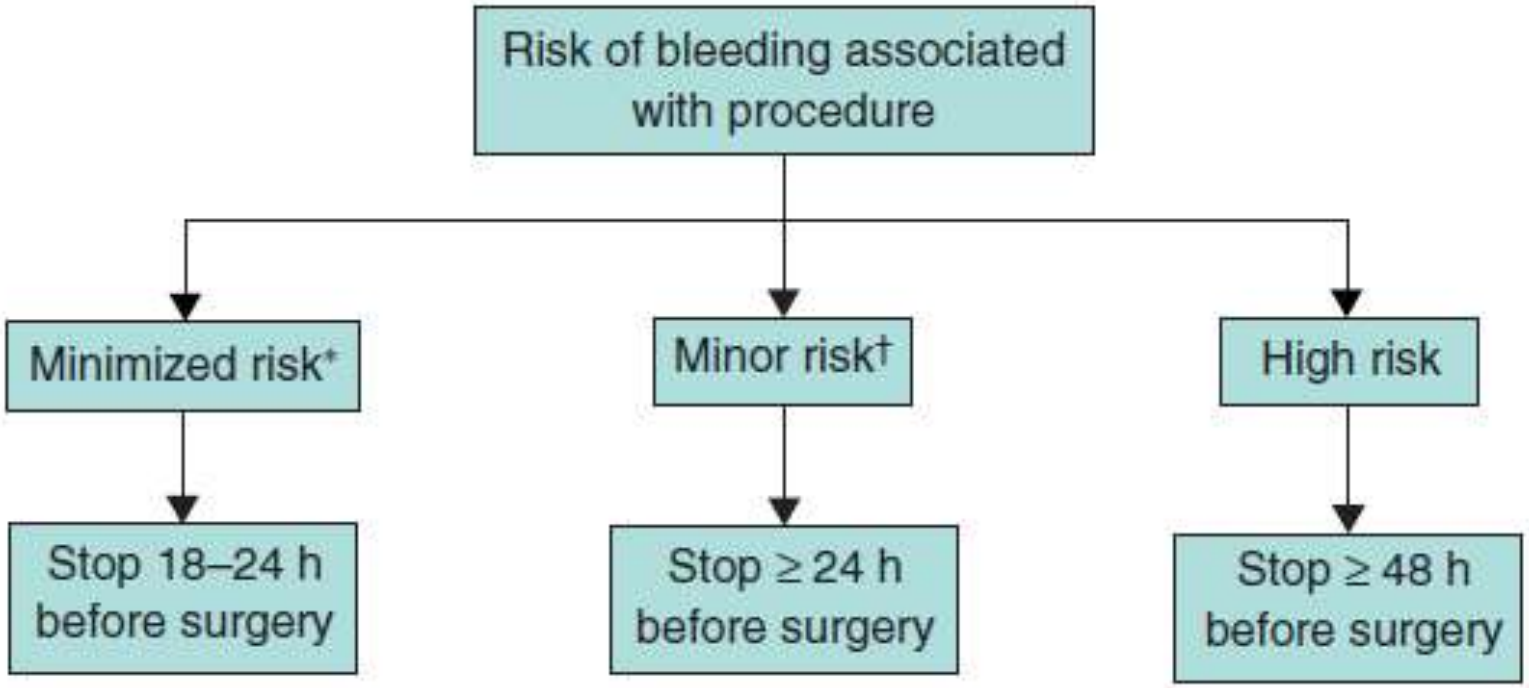
Perioperative management of patients on new oral anticoagulants

A. Lai[1], N. Davidson[2], S. W. Galloway[3] and J. Thachil[4]

Paper accepted 31 January 2014
Published online 29 April 2014 in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.9485

BJS 2014; **101**: 742–749

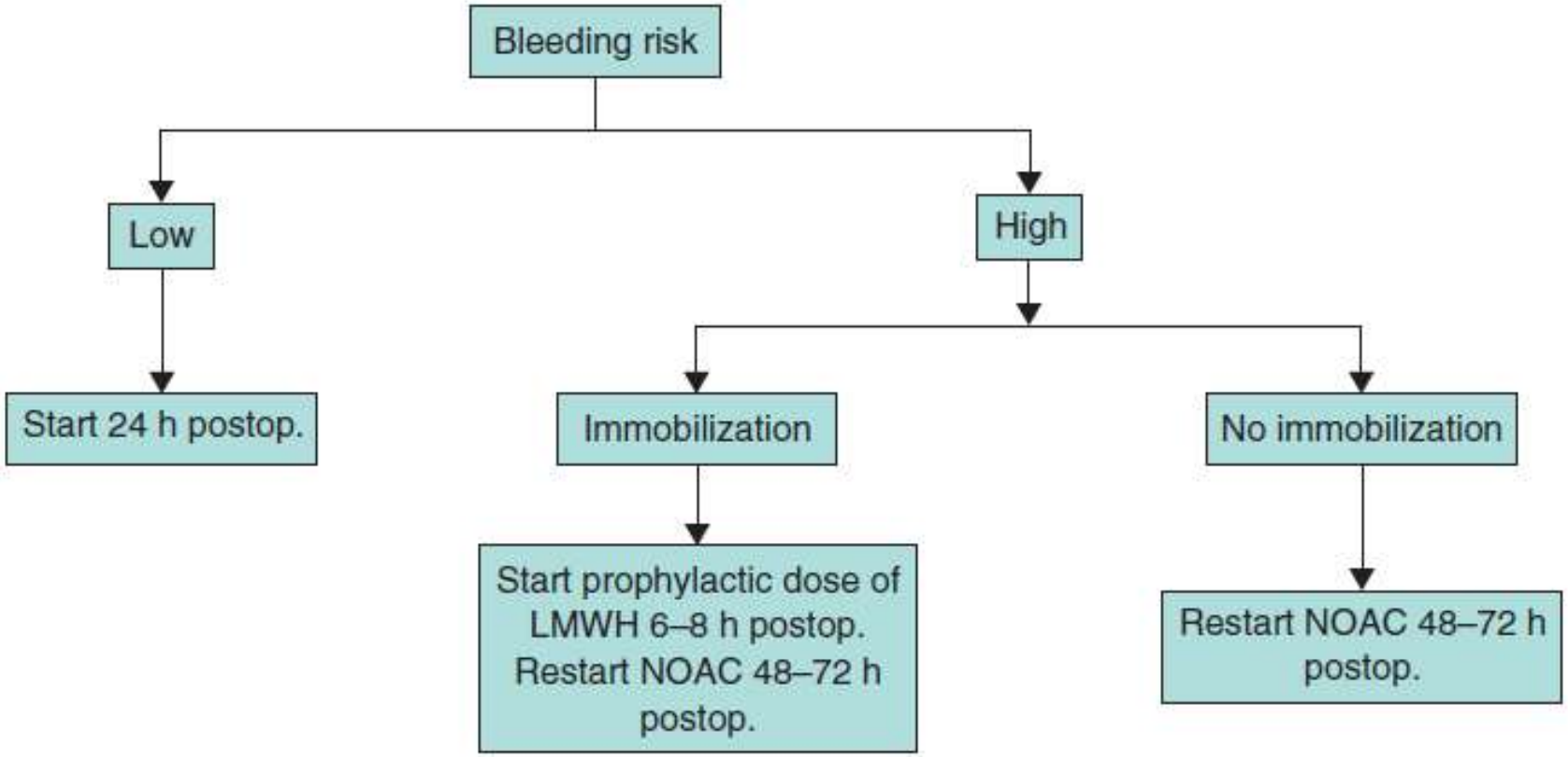
Intervenții chirurgicale elective
Farmacocinetic



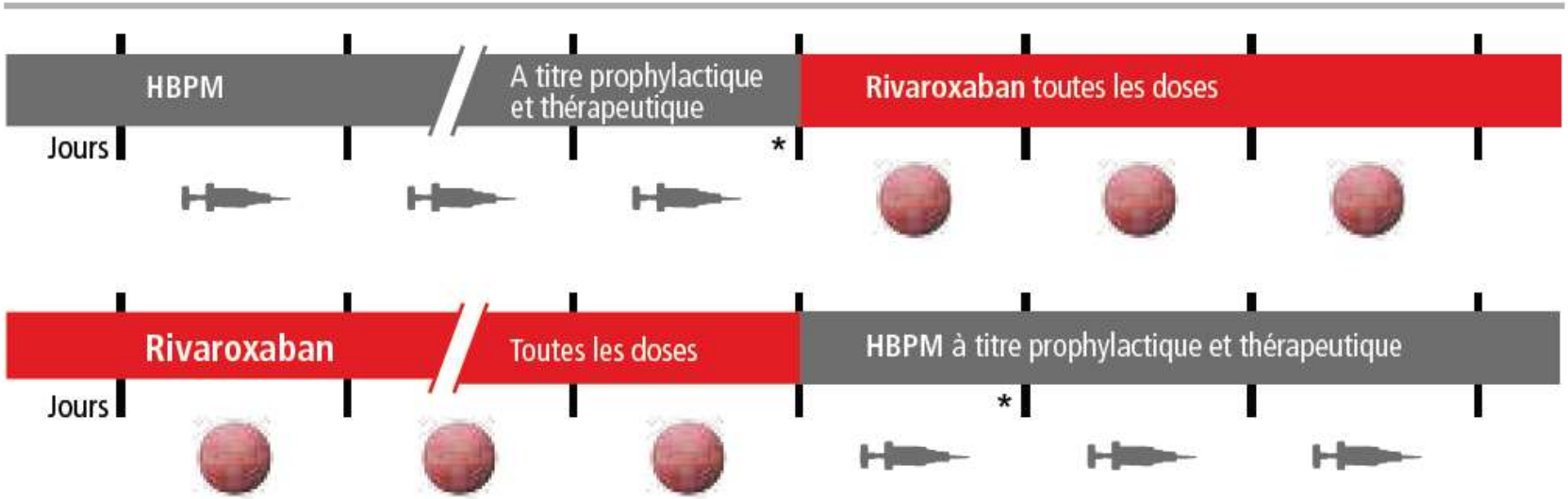
Intervenții chirurgicale elective
Farmacocinetic (ct)

Creatinine clearance (ml/min)	Risk of bleeding	Suggested interruption (h)		
		Rivaroxaban	Apixaban	Dabigatran
≥ 80	Low	≥ 24	≥ 24	≥ 24
	High	≥ 48	≥ 48	≥ 48
50–79	Low	≥ 24	≥ 24	≥ 36
	High	≥ 48	≥ 48	≥ 72
30–49	Low	≥ 24	≥ 24	≥ 48
	High	≥ 48	≥ 48	≥ 96
15–29	Low	≥ 36	≥ 36	Not indicated
	High	≥ 48	≥ 48	Not indicated
< 15	No indication for any agent			

Reluare tratament NACO postoperator



Trecerea de la un anticoagulant parenteral la NACO si viceversa



*Important : Les HBPM peuvent s'accumuler chez les patients avec insuffisance rénale → DV plus longue

CEEA

De dabigatran à un anticoagulant parentéral:

Arrêter la prise de dabigatran

Première injection

12 h après la dernière prise

D'un anticoagulant parentéral au dabigatran

Dernière injection

Première administration de dabigatran

0-2 h avant la prochaine injection prévue

Intervenții chirurgicale în urgență
Conservator

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

Intervenții chirurgicale în urgență
Conservator

Urgent surgery and RIVAROXABAN (XARELTO®)

[Rivaroxaban] ≤ 30 ng/ml	•• Operate
30 ng/ml < [Rivaroxaban] ≤ 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 < [Rivaroxaban] ≤ 400 ng/ml	• Wait up to12-24 h and obtain new dosage** or (if time is not compatible with emergency) • Maximum delay surgery • Operate, if abnormal bleeding : antagonise ***
[Rivaroxaban] > 400 ng/ml	• Overdose – Major haemorrhagic risk

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- Reversal by CCP or FEIBA does not fully correct the abnormalities of haemostasis tests
- rFVIIa is not considered first-line

Intervenții chirurgicale în urgență
Conservator

Urgent surgery and DABIGATRAN (PRADAXA®)

There is a worse proposal in case of unavailability of immediate dosage.
It does not guarantee the absence of formal haemorrhagic complications

Ratio aPTT ≤ 1.2 and ratio PT ≤ 1.2	•• Operate
Ratio 1.2 < aPTT ≤ 1.5 or ratio PT > 1.2	•• Wait up to12 h* and obtain specific dosage / new aPTT - PT **or** (if time is not compatible with emergency) •• Operate, if abnormal bleeding : antagonise the anticoagulant effect**
Ratio aPTT > 1.5	•• Wait up to 12–24 h and obtain specific dosage / new aPTT - PT or (if time is not compatible with emergency) • If CkrCl Cockcroft < 50 ml/mn, obtained specific dosage to detect overdose and discuss haemodialysis • Maximum delay surgery • Operate, if abnormal bleeding : antagonise **

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 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

Note: PT and aPTT can be disrupted for reasons other than the anticoagulant effect. We can use in a second step the analysis of the thrombin time, if available, that when normal, excludes the presence of dabigatran.

Intervenții chirurgicale în urgență
Conservator

Urgent surgery and RIVAROXABAN (XARELTO®)

There is a worse proposal in case of unavailability of immediate dosage.
It does not guarantee the absence of formal haemorrhagic complications

Ratio aPTT ≤ 1.2 and ratio PT ≤ 1.2	•• Operate
Ratio 1.2 < aPTT ≤ 1.5 or ratio PT > 1.2	•• Wait up to12 h* and obtain specific dosage / new aPTT - PT **or** (if time is not compatible with emergency) •• Operate, if abnormal bleeding : antagonise the anticoagulant effect**
Ratio aPTT > 1.5	•• Wait up to 12–24 h and obtain specific dosage **or** (if time is not compatible with emergency) • Maximum delay surgery • Operate, if abnormal bleeding : antagonise **

In case of renal insufficiency, half-life of rivaroxaban 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 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

Note: PT and aPTT can be disrupted for reasons other than the anticoagulant effect. We can use in a second time the anti-Xa activity analysis, if available, and if it is normal, consider rivaroxaban concentration <30 ng/mL

CEEA
Blood Coagulation, Fibrinolysis and Cellular Haemostasis

Received: August 21, 2012
Accepted after major revision: November 29, 2012
Prepublished online: February 7, 2013
doi:10.1160/TH12-08-0573
Thromb Haemost 2013; 109: ■■■

Effective elimination of dabigatran by haemodialysis

A phase I single-centre study in patients with end-stage renal disease

Dmytro Khadzhynov[1]*; Frank Wagner[2]*; Stephan Formella[3]; Erol Wiegert[2]; Viktoria Moschetti[3]; Torsten Slowinski[1]; Hans-H. Neumayer[1]; Karl-Heinz Liesenfeld[3]; Thorsten Lehr[3]; Sebastian Härtter[3]; Jeffrey Friedman[4]; Harm Peters[1#]; Andreas Clemens[3#]

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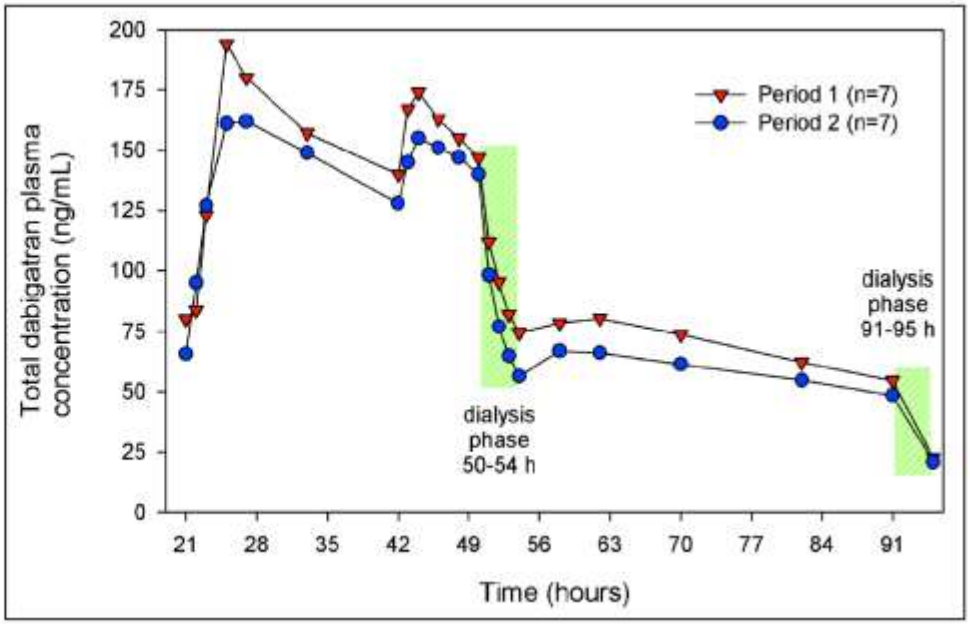
Four hours of haemodialysis removed 48.8% and 59.3% of total dabigatran from the central compartment with 200 and 400 ml/minute targeted blood flow, respectively. The anticoagulant activity of dabigatran was linearly related to its plasma levels.There was a minor redistribution of dabigatran (<16%) after the end of the haemodialysis session.



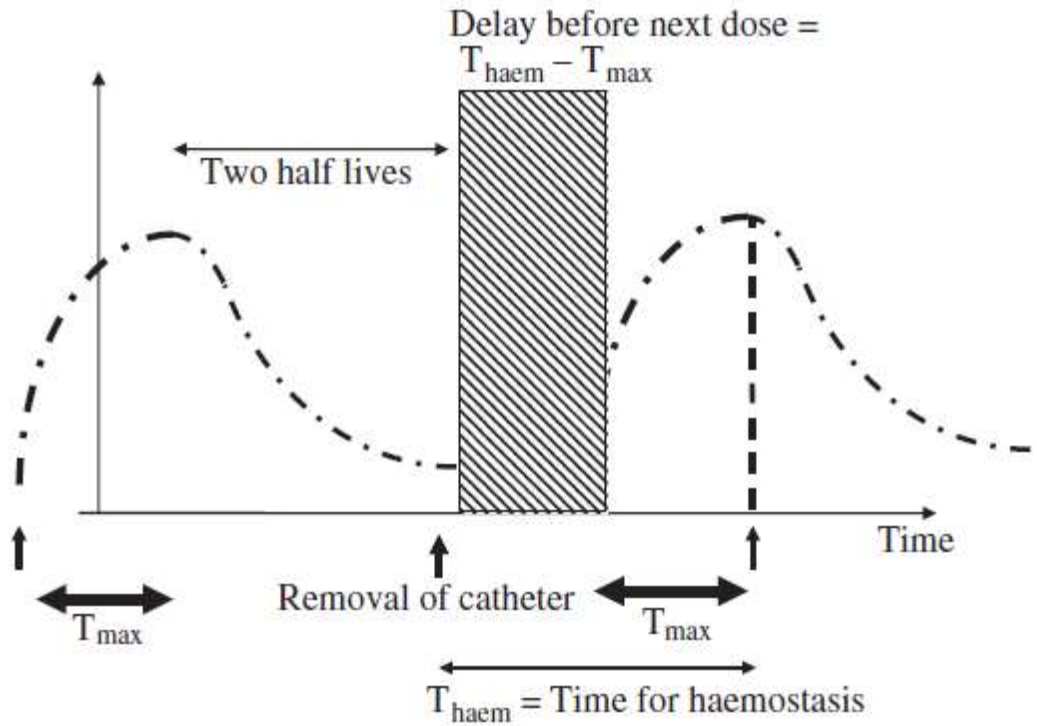
Anestezia loco-regională

Anaesthesia, 2007, **62**, pages 1154–1160 doi:10.1111/j.1365-2044.2007.05195.x

REVIEW ARTICLE

Selected new antithrombotic agents and neuraxial anaesthesia for major orthopaedic surgery: management strategies

N. Rosencher,[1] M.-P. Bonnet[1] and D. I. Sessler[2]



Anestezia loco-regională

Anaesthesia 2013, 68, 966–972 doi:10.1111/anae.12359

Guidelines

Regional anaesthesia and patients with abnormalities of coagulation

The Association of Anaesthetists of Great Britain & Ireland
The Obstetric Anaesthetists' Association
Regional Anaesthesia UK

Anestezia loco-regională

Table 2 Relative risk related to neuraxial and peripheral nerve blocks in patients with abnormalities of coagulation.

	Block category	Examples of blocks in category
Higher risk	Epidural with catheter	
	Single-shot epidural	
	Spinal	
	Paravertebral blocks	Paravertebral block
		Lumbar plexus block
		Lumbar sympathectomy
		Deep cervical plexus block
	Deep blocks	Coeliac plexus block
		Stellate ganglion block
		Proximal sciatic block (Labat, Raj, sub-gluteal)
		Obturator block
		Infraclavicular brachial plexus block
		Vertical infraclavicular block
		Supraclavicular brachial plexus block
	Superficial perivascular blocks	Popliteal sciatic block
		Femoral nerve block
		Intercostal nerve blocks
		Interscalene brachial plexus block
		Axillary brachial plexus block
	Fascial blocks	Ilio-inguinal block
		Ilio-hypogastric block
		Transversus abdominis plane block
		Fascia lata block
	Superficial blocks	Forearm nerve blocks
		Saphenous nerve block at the knee
		Nerve blocks at the ankle
		Superficial cervical plexus block
		Wrist block
		Digital nerve block
		Bier's block
Normal risk	Local infiltration	

ALR

Drug	Time to peak effect	Elimination half-life	Acceptable time after drug for block performance	Administration of drug while spinal or epidural catheter in place[1]	Acceptable time after block performance or catheter removal for next drug dose
Rivaroxaban prophylaxis[5] ($CrCl > 30\ ml.min^{-1}$)	3 h	7–9 h	18 h	Not recommended	6 h
Rivaroxaban treatment[5] ($CrCl > 30\ ml.min^{-1}$)	3 h	7–11 h	48 h	Not recommended	6 h
Dabigatran prophylaxis or treatment[7]					
($CrCl > 80\ ml.min^{-1}$)	0.5–2.0 h	12–17 h	48 h	Not recommended	6 h
($CrCl\ 50–80\ ml.min^{-1}$)	0.5–2.0 h	15 h	72 h	Not recommended	6 h
($CrCl\ 30–50\ ml.min^{-1}$)	0.5–2.0 h	18 h	96 h	Not recommended	6 h
Apixaban prophylaxis	3–4 h	12 h	24–48 h	Not recommended	6 h

Tableau 1 Doses préventives en orthopédie et anesthésie locorégionale axiale (rachianesthésie, péridurale).

	Délai avant la ponction ou l'ablation du cathéter	Délai après la ponction ou l'ablation du cathéter	Tests biologiques
Rivaroxaban (Xarelto®) (prophylaxie, 10 mg/j)	18–26 h	4–6 h	Anti-Xa spécifique
Apixaban (Eliquis®) (prophylaxie, 2,5 mg × 2)	20–30 h	4–6 h	Anti-Xa spécifique
Dabigatran (Pradaxa®) (prophylaxie, 150–220 mg)	34 h	6 h	Temps de thrombine diluée (Haemoclot®)

Intervenții chirurgicale în urgență
Conservator

Table 2 Definition of serious or potentially serious bleeding with vitamin K antagonists, according to the French Health Authority [27].

Serious or potentially serious bleeding in the context of treatment with a VKA is defined by the presence of at least one of the following criteria
- Externalized bleeding uncontrollable by conventional procedure
- Haemodynamic instability
  - SBP < 90 mmHg or
  - 40 mmHg decrease in SBP compared with usual or
  - Mean arterial pressure < 65 mmHg or
  - Signs of shock
- Need for urgent haemostatic surgery, interventional radiology, endoscopy
- Need for blood transfusion
- Threatening or functional location
  - Intracranial or intraspinal haemorrhage
  - Retro-orbital and intraocular bleeding
  - Haemothorax, haemoeritoneum and retroperitoneum, haemopericardium
  - Deep muscular haematoma and/or compartment syndrome
- Acute gastrointestinal bleeding
- Haemarthrosis

SBP: systolic blood pressure; VKA: vitamin K antagonist.

Intervenții chirurgicale în urgență
Conservator

Haemorrage and DABIGATRAN (PRADAXA®) or RIVAROXABAN (XARELTO®)

Bleeding into a critical organ (intracranial, acute subdural, intraocular...)	1) FEIBA® 30-50 UI / kg* or 2) PCC 50 UI / kg*
Serious bleeding according to the French Health Authority (2008) (excluding previous cases)	•• If [ ]** ≤ 30 ng/ml : no reversal •• Prefer haemostatic procedure if feasible •• If no haemostatic procedure is appropriate and If [ ]** > 30ng/ml ► Discuss reversal*** (not always necessary)

* Depending on availability. No data available on the thrombotic risk of high doses of PCC or FEIBA in these patients
** [ ] means concentration
*** PCC=25-50 UI/kg ou FEIBA=30-50 UI/Kg
rFVIIa is not considered first-line

Intervenții chirurgicale în urgență
Conservator

Haemorrage and DABIGATRAN (PRADAXA®) or RIVAROXABAN (XARELTO®)

Bleeding into a critical organ (intracranial, acute subdural, intraocular...)	1) FEIBA® 30-50 UI / kg* or 2) PCC 50 UI / kg*
Serious bleeding according to the French Health Authority (2008) (excluding previous cases)	•• If ratio aPTT ≤ 1.2 and ratio PT ≤ 1.2: no reversal •• Prefer haemostatic procedure if feasible •• If no haemostatic procedure is appropriate and if ratio aPTT > 1.2 (isolated) or ratio PT > 1.2 ► Discuss reversal** (not always necessary) and obtain specific dosage

* Depending on availability. No data available on the thrombotic risk of high doses of PCC or FEIBA in these patients
*** PCC=25-50 UI/kg or FEIBA=30-50 UI/Kg
rFVIIa is not considered first-line

Drug	Com-parator	Endpoint	Efficacy vs comparator	Bleeding-related safety vs comparator			
				Major bleeding	Gastrointestinal bleeding	Intracranial haemorrhage	Fatal/life-threaten-ing bleeding
Direct FIIa inhibitors							
Dabigatran (38)	Warfarin	Prevention of stroke of systemic embolism in patients with AF	Superior 1.11% vs 1.69%	3.11% vs 3.36%	1.51% vs 1.02%	0.30% vs 0.74%	1.45% vs 1.80%
Dabigatran (41)	Warfarin	Prevention of recurrent VTE in patients with acute VTE	Non-inferior 2.4% vs 2.1%	1.6% vs 1.9%	4.2% vs 2.8%	0.0% vs 0.2%	0.08% vs 0.08%
Direct FXa inhibitors							
Rivaroxaban (40)	Warfarin	Prevention of stroke and non-CNS systemic embolism in patients with AF	Non-inferior 1.7% vs 2.2%	3.6% vs 3.4%	No data available	0.5% vs 0.7%	0.2% vs 0.5%
Rivaroxaban (59)	Warfarin	Prevention of stroke and non-CNS systemic embolism in patients with AF	Superior 1.26% vs 2.61%	3.00% vs 3.59%	0.9% vs 1.9% (major GI bleeding)	0.8% vs 1.6%	0.16% vs 0.47% (fatal)
Rivaroxaban (60)	Enoxaparin	Prevention of recurrent VTE in patients with pulmonary embolism	Non-inferior 2.1% vs 1.8%	1.1% vs 2.2%	No data available	<0.1% vs 0.4% (non-fatal)	<0.1% vs 0.1%
Apixaban (61, 62)	Warfarin	Prevention of stroke or systemic embolism in patients with AF	Superior 1.27% vs 1.60%	2.13% vs 3.09%	0.76% vs 0.86%	0.33% vs 0.80%	No data available
Apixaban (63)	Enoxaparin	Prevention of DVT and PE (knee surgery patients)	Did not meet non-inferiority criteria (9.0% vs 8.8%)	0.7% vs 1.4%	<0.1% vs 0.4%	0.0% vs <0.1%	0.0% vs <0.1%
Apixaban (64)	Enoxaparin	Prevention of DVT and PE (hip surgery patients)	Superior 1.4% vs 3.9%	0.8% vs 0.7%	0.1% vs 0.0%	No data available	0.0% vs 0.0%
Edoxaban (39)	Enoxaparin	Prevention of VTE (hip surgery patients)	Superior 2.4% vs 6.9%	2.6% vs 3.7%*	No data available	No data available	No data available
		Prevention of VTE (knee surgery patients)	Superior 7.4% vs 13.9%	6.2% vs 3.7%*			

doi:10.1160/TH13-05-0431
Thromb Haemost 2014; 111: 189–198

Reversing the new oral anticoagulants with prothrombin complex concentrates (PCCs): what is the evidence?

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- PCCs (including activated PCCs) **show promise** for reversing the anticoagulant effects of the new oral anticoagulants.
- **Conventional laboratory assays do not correlate well with bleeding or reversal of anticoagulation** in this setting; thrombin generation assays appear to have the best predictive value. However, it should be noted that there are significant differences in the methods for conducting such assays, which can complicate comparisons between studies.
- Both activated (e.g. FEIBA®) and non-activated PCCs **correct most parameters of thrombin generation assays** (initial rate, peak and ETP) **in vitro.** However, non-activated PCCs seem to lack the ability to correct the lag time before onset of thrombin generation while FEIBA® partially corrects the lag time.
- **The dosing** and effectiveness of a strategy for reversal of the new oral anticoagulants **probably depends on the level of the anticoagulant present.**

- ***No studies have yet examined the effectiveness of any reversal strategy in bleeding human patients.***

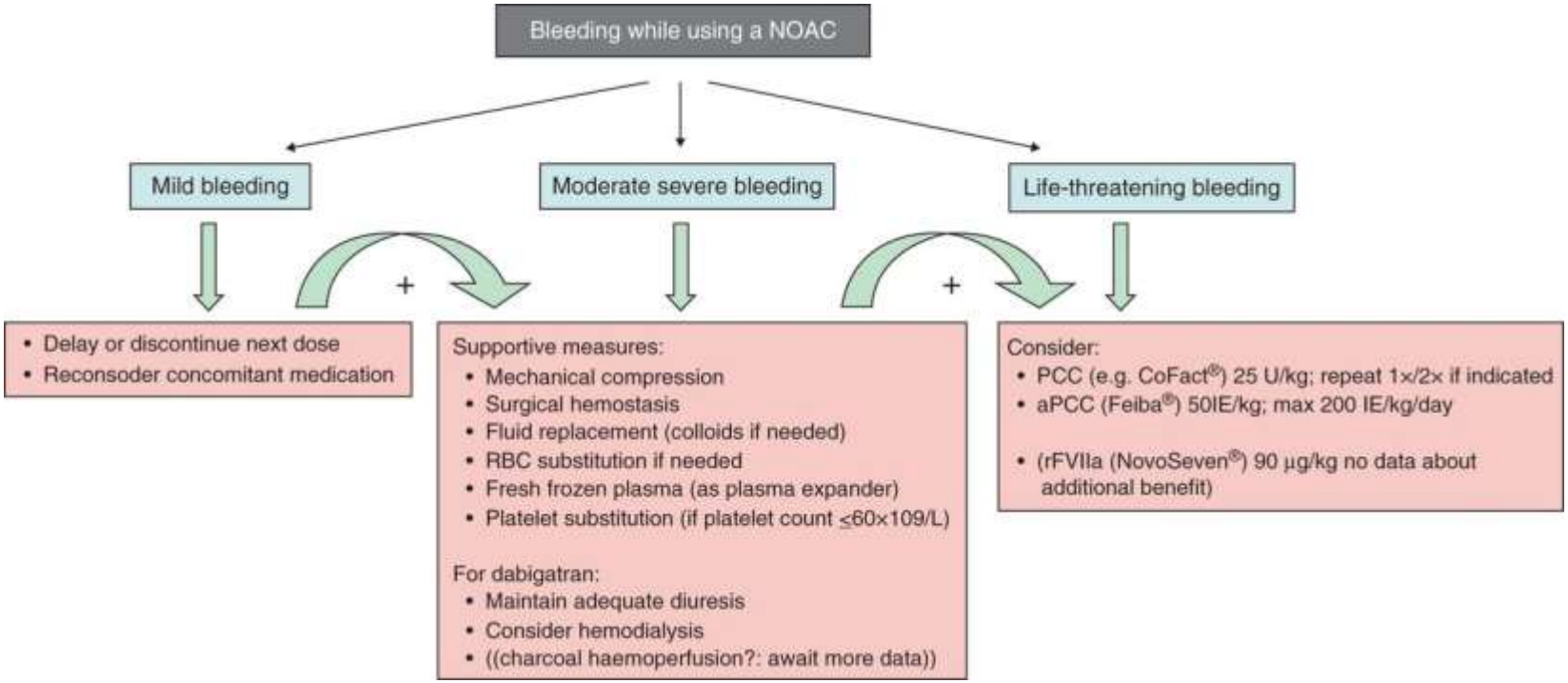
Dabigatran (Pradaxa)

- Emergency v. Urgency
- Activated charcoal if 1-2 hours
- Hemodialysis
- aPTT
- PCC v. FFP
- FVIIa

- Emergency v. Urgency
- Activated charcoal if 1-2 hours
- PCC v. FFP
- FVIIa

Rivaroxaban (Xeralta)
Apixaban (Eliquis)

Management of bleeding in patients taking NOACs. Possible therapeutic measures in case of minor or severe bleeding in patients on NOAC therapy.



Heidbuchel H et al. Europace 2013;15:625-651

CEEA

European Society of Anaesthesiology ESA

World Federation of Societies of Anaesthesiologists

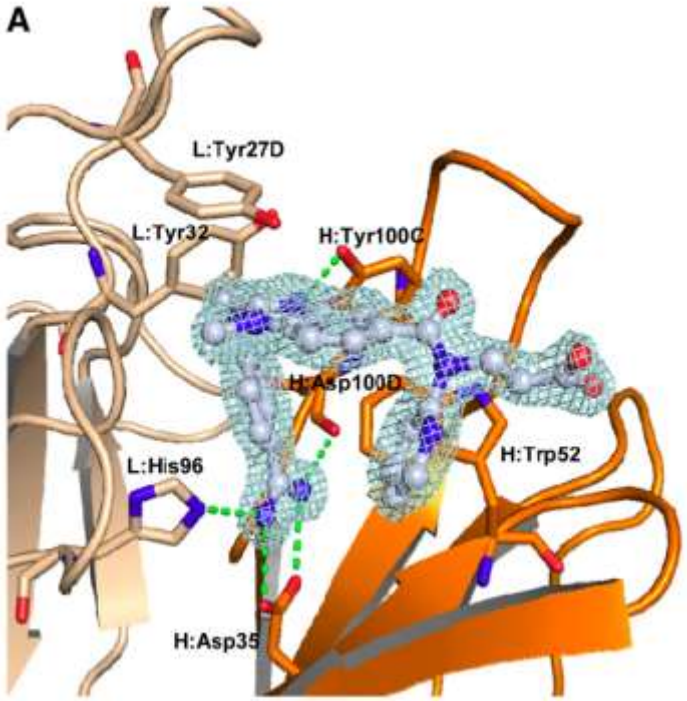
Blood. 2013;121(18):3554-3562

A specific antidote for dabigatran: functional and structural characterization

Felix Schiele,[1] Joanne van Ryn,[2] Keith Canada,[3] Corey Newsome,[3] Eliud Sepulveda,[3] John Park,[4] Herbert Nar,[1] and Tobias Litzenburger[4]

[1]Structural Research Group, and [2]CardioMetabolic Diseases Research, Boehringer Ingelheim GmbH & Co. KG, Biberach, Germany; [3]Biotherapeutics, Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT; and [4]New Biological Entity Discovery, Boehringer Ingelheim GmbH & Co. KG, Biberach, Germany

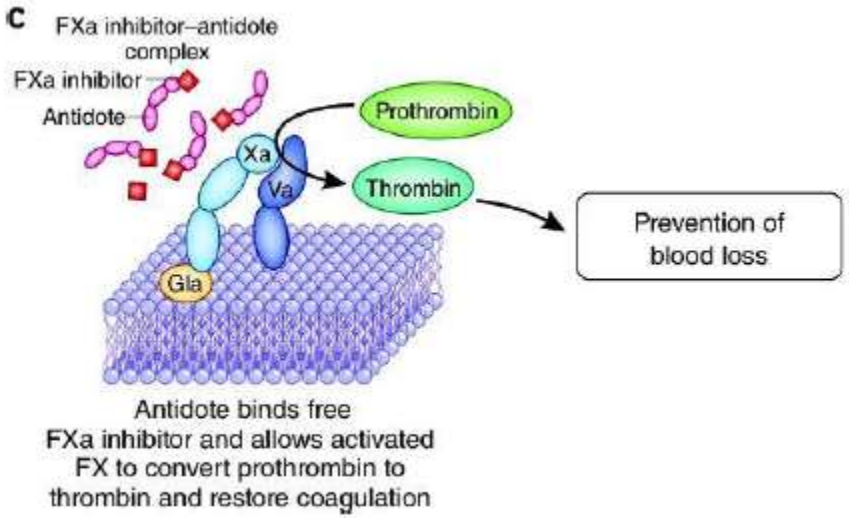
By a tighter network of interactions, the antidote achieves an affinity for dabigatran that is ≅ 350 times stronger than its affinity for thrombin



Nature Medicine, April 2013, Volume 19 No 4 pp446 - 451

A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor Xa

Genmin Lu[1], Francis R DeGuzman[2], Stanley J Hollenbach[2], Mark J Karbarz[1], Keith Abe[2], Gail Lee[2], Peng Luan[1], Athiwat Hutchaleelaha[3], Mayuko Inagaki[3], Pamela B Conley[1], David R Phillips[1] & Uma Sinha[1]



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- r-antidote does not interfere with normal fXa function
- r-antidote with no anticoagulant or procoagulant activity
- Rapid onset of action & complete reversal of fXa-inhibitors activity
- Normalises hemostasis from anticoagulant drugs targeting fXa
- Universal antidote for direct & indirect fXa inhibition

Limitations

- Possible that used in vitro system are not sensitive enough
- Preclinical data based on animal model, difficulties to extrapolate to humans
- unidentified interactions with other proteins
- immunogenicity


AVK?


NACO?