Mot de passe du 22 février 2013 : **patient2202**
Password, February 22, 2013 : **patient2202**

AVC et la FA en 2013: les nouveaux AC

Gestion des saignements et des interventions

Perspectives en salle d'urgence

Le Groupe de Travail sur la Thrombose du Canada
www.tigc.org

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SSVQ
Société des sciences vasculaires du Québec

- Les test de coagulation: leur utilisation et leurs limites actuelles
- Gestion pratique des saignements
- Anticoagulation et interventions

André Roussin MD

Conflits d'intérêt potentiels 2012-2013

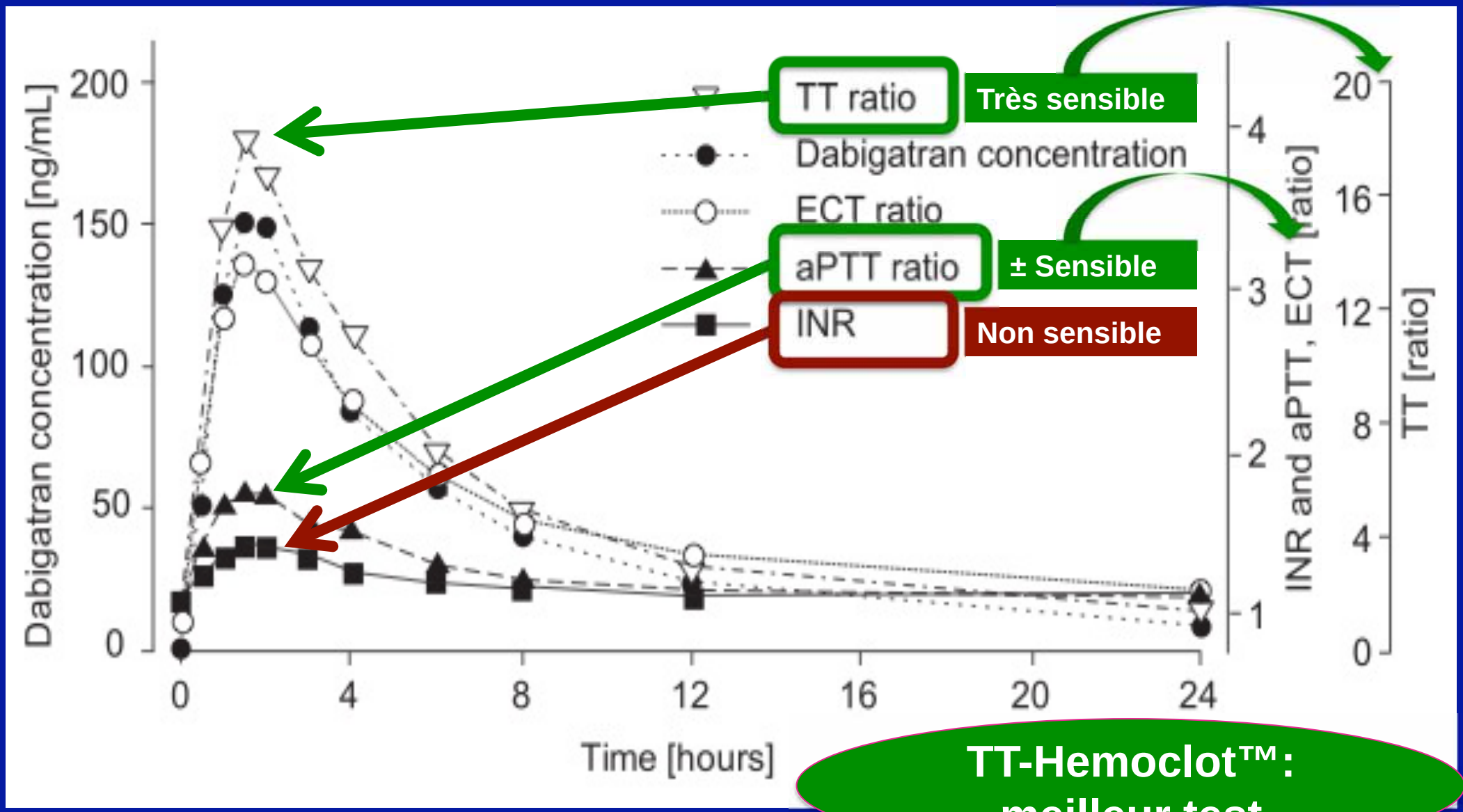
J'ai reçu des honoraires et/ou des fonds de recherche et/ou participé à des comités aviseurs pour les compagnies suivantes:

- AstraZeneca
- Bayer
- Bristol-Myers Squibb
- Boehringer-Ingelheim
- Covidien
- Pendopharm
- Pharmaprix
- Pfizer
- Sanofi
- Sunovion

Adapté et modifié de: J.Eikelboom et al. Circulation. 2010;121:1523-1532	Apixaban (Eliquis™)	Rivaroxaban (Xarelto™)	Dabigatran (Pradaxa™)
Mécanisme d'action	Inhibiteurs directs du FXa		Inhibiteur direct du FIIa
Biodisponibilité orale	~50 %	80 %	6,5 %
Schéma d'administration	Deux fois par jour dans toutes les indications (pETEV, tETEV, FA, SCA)	Une fois par jour (pETEV, tETEV, FA) Deux fois par jour (SCA)	Deux fois par jour dans toutes les indications (pETEV, tETEV, FA)
Prodrogue	Non		Oui
Effet de l'alimentation	Non		
Clairance rénale	~27 %	36 %	85 %
ASC: ClCr 15-29 ml/min	↑ 1,44X	↑ 1,60X	↑ 6X (ClCr 10-30ml/min)
Demi-vie moyenne (t1/2)	~12h	7–11 h	14–17 h
tmax	3 h	2–4 h	0,5–2 h
Interactions médicamenteuses	Inhibiteurs de CYP 3A4 et de gp-P Inducteurs de CYP 3A4	Inhibiteurs de CYP 3A4 et de gp-P Inducteurs de CYP 3A4	Inhibiteurs de gp-P Amiodarone

Dabigatran: tests de coagulation

Temps de Thrombine (TT), Temps de Céphaline (PTT ou TCa) et PT-INR

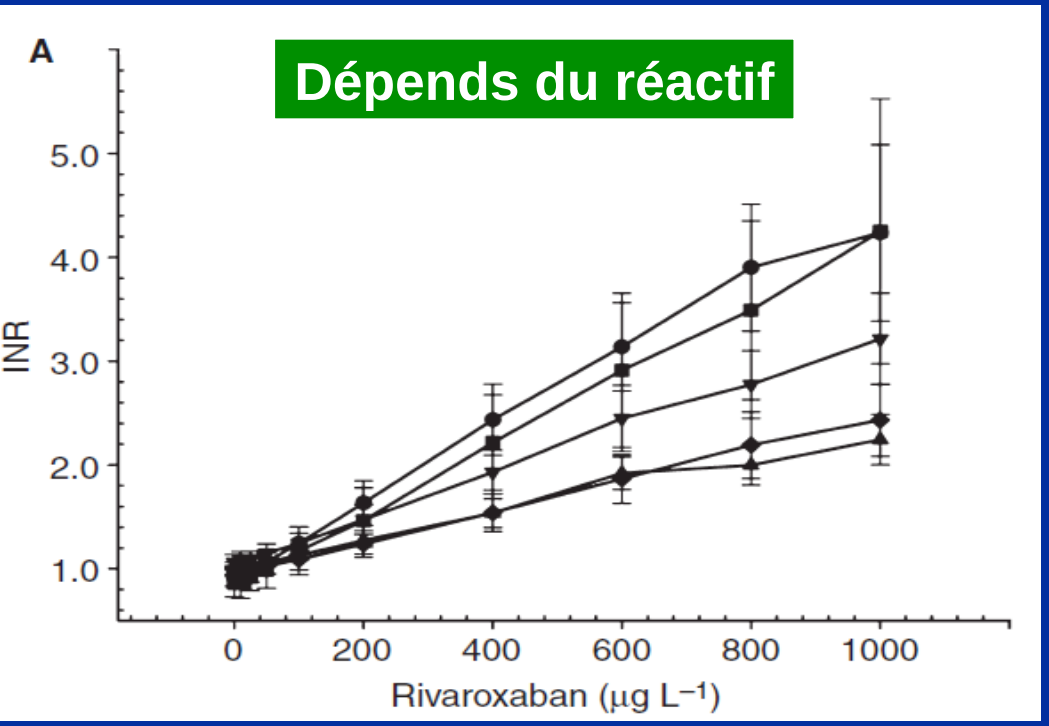


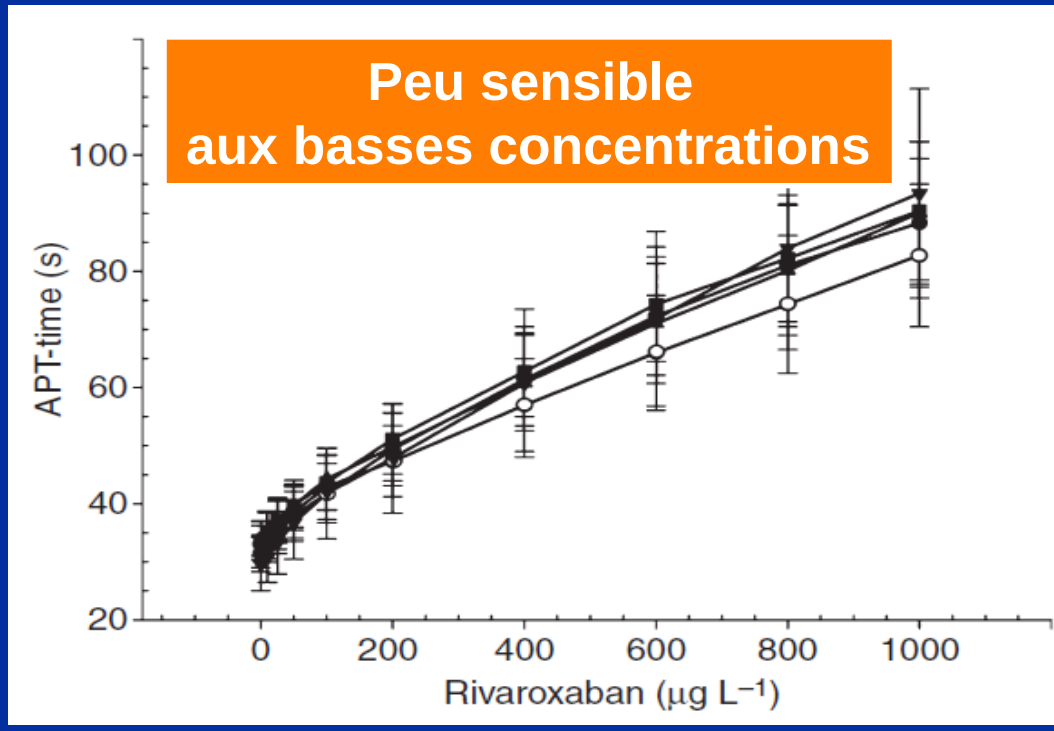
TT-Hemoclot™: meilleur test

Adapté de: Van Ryn J et al. Thromb Haemost 2010; 103: 1116-27

Rivaroxaban: tests de coagulation
PT-INR et PTT (TCa)

PT-INR **Mieux que…** **PTT (TCa)**





Adapté de: Hillarp A, et al. J Thromb Hemost 2011; 9: 133-9

PT-INR, TT (Temps de Thrombine) et PTT (TCA)
Dabigatran, Rivaroxaban et Apixaban

Table 1.
Sensitivity and Utility of Current Coagulation Assays for Dabigatran, Rivaroxaban, and Apixaban

Assay	Dabigatran		Rivaroxaban / ± Apixaban	
	Sensitivity	Utility	Sensitivity	Utility
PT-INR	Relatively insensitive	Not ideal; widely available	More sensitive at higher concentrations	Widespread availability makes PT useful
dPT	More sensitive than PT	Not widely available; lacks FDA approval	Variability between thromboplastin reagents	Not widely available; lacks FDA approval
TT	Too sensitive, inaccurate at high concentrations	Sensitivity limits utility in quantifying anticoagulation	No effect	Not useful
Hemoclot™				
Ecarin clotting time	Sensitive at all concentrations	Limited availability; lacks FDA approval	No effect	Not useful
PTT (TCA)	More sensitive than PT	Availability and sensitivity support use	Less sensitive than PT	Not ideal; widely available

Adapté de: Miyares MA, Davis K. Am J Health-Syst Pharm 2012; 69: e28-39

TT dilué calibré (Haemoclot™), Anti Xa (Rotachrom™) Dabigatran, Rivaroxaban et Apixaban

Table 2 Effect of novel oral anticoagulants on commonly used coagulation tests

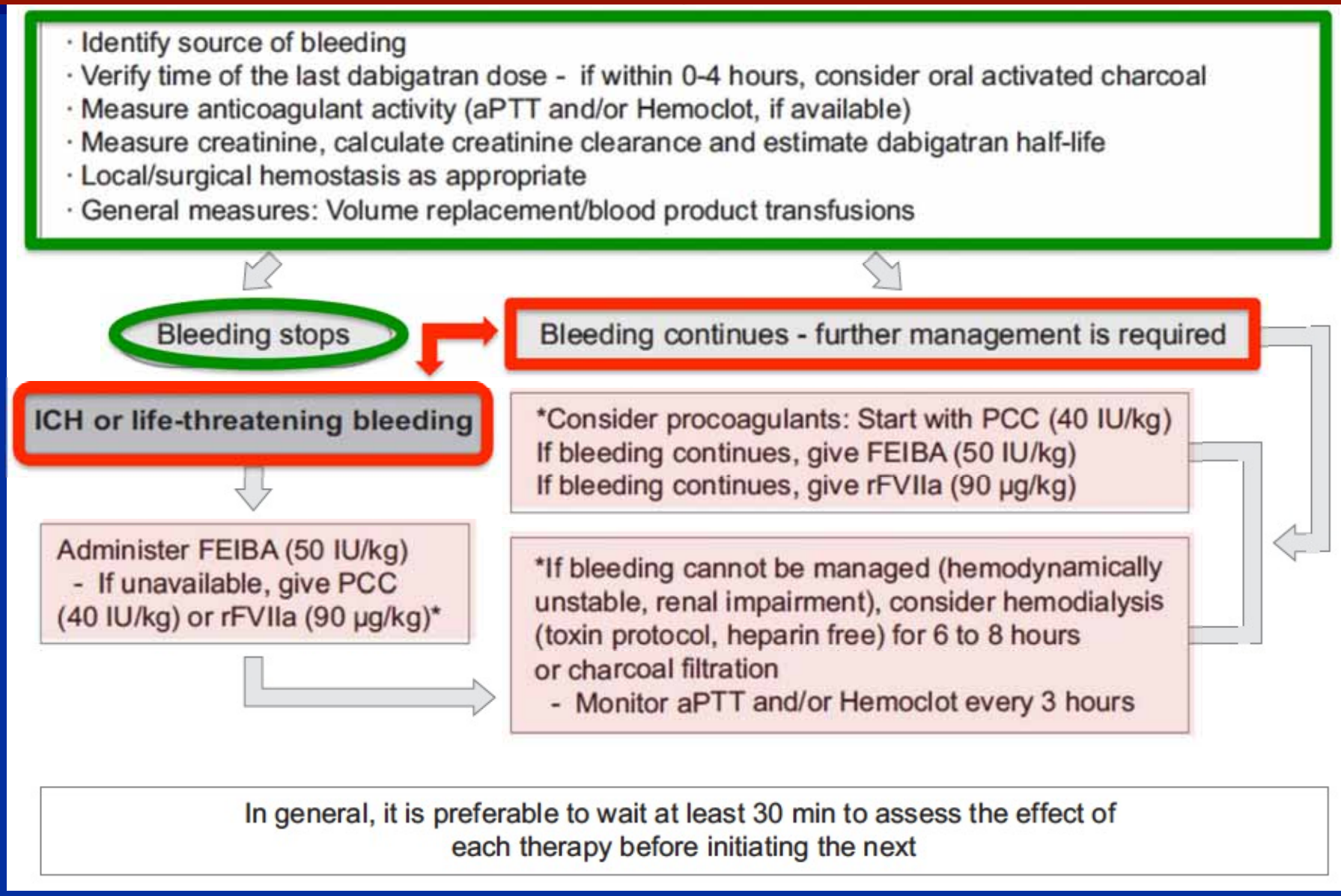
Novel anticoagulant	Prothrombin time (PT)	Activated partial thromboplastin time (aPTT)	Thrombin clotting time (TCT)	Ecarin clotting time	Haemoclot assay	Anti-factor Xa activity	
						Clot-based	Chromogenic
							Rotachrom™
Dabigatran	↑ or no change (low sensitivity, varies with reagents)	↑ (varies with reagents)	↑	↑	↑[a]	↑	ND
Rivaroxaban	↑ or no change (not sensitive at low concentrations, varies with reagents)	↑ or no change (less sensitive than PT)	—	—	—	↑	↑[a] (sensitive and specific when calibration curve used)
Apixaban	↑ or no change (other tests more sensitive, may vary with reagents)	↑ or no change (other tests more sensitive, may vary with reagents)	—	—	—	↑[a]	↑[a]

ND, no data.
[a]Preferred test. Adapted from previously published review articles.[41,59]

Adapté de: Siegal DM, Crowther MA. EHJ dec 2012

Renversement suggéré du dabigatran

Saignements modérés à sévères: arrêt du dabigatran



Eitz JI. Circulation 2012; 126: 2428-32

Renversement suggéré du rivaroxaban
Pas de preuve d'efficacité pour les saignements humains

- If bleeding cannot be controlled by the symptomatic measures, consider administration of procoagulants
  - activated prothrombin complex concentrate (APCC)
  - prothrombin complex concentrate (PCC)
  - recombinant factor VIIa (rFVIIa)

Feiba™ 50 UI/kg
Beriplex™ 40 UI/kg
rFVIIa 90 µg/kg

- Administration of APCC or rFVIIa can rapidly attenuate hemostasis impairment after rivaroxaban overdose in baboons
- On completion of activated prothrombin complex concentrate (APCC, FEIBA) infusion, bleeding time returned to baseline and PT was reduced.
- Infusion of recombinant activated Factor VII (rFVIIa, NovoSeven) reduced bleeding time by 34%, and PT was also shortened.*

Adapté de: Xarelto® Product Monograph, 2008

* Gruber, et al., ASH, 2008, abs 3825

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Renversement suggéré de l'apixaban
Pas de preuve d'efficacité pour les saignements humains

- In the event of hemorrhagic complications in a patient receiving ELIQUIS, treatment must be discontinued, and the source of bleeding investigated. Appropriate standard treatment, e.g. surgical hemostasis as indicated and blood volume replacement, should be undertaken. In addition, consideration may be given to the use of fresh whole blood or the transfusion of fresh frozen plasma.
- If bleeding cannot be controlled by the above measures, consider administration of one of the following procoagulants:
  - activated prothrombin complex concentrate (APCC), e
  - prothrombin complex concentrate (PCC)
  - recombinant Factor-VIIa (rFVIIa)

Feiba™ 50 UI/kg
Beriplex™ 40 UI/kg
rFVIIa 90 µg/kg

- However, there is currently only very limited experience with [illegible] of these products in individuals receiving ELIQUIS.

Adapté de: Monographie Eliquis™ (apixaban) 2012

Renversement de l'apixaban
Gestion des saignements: ce qui n'est pas utile

- Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of ELIQUIS.
- There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving ELIQUIS.
- There is neither scientific rationale for benefit or experience with the systemic hemostatics, e.g., desmopressin and aprotinin in individuals receiving ELIQUIS.

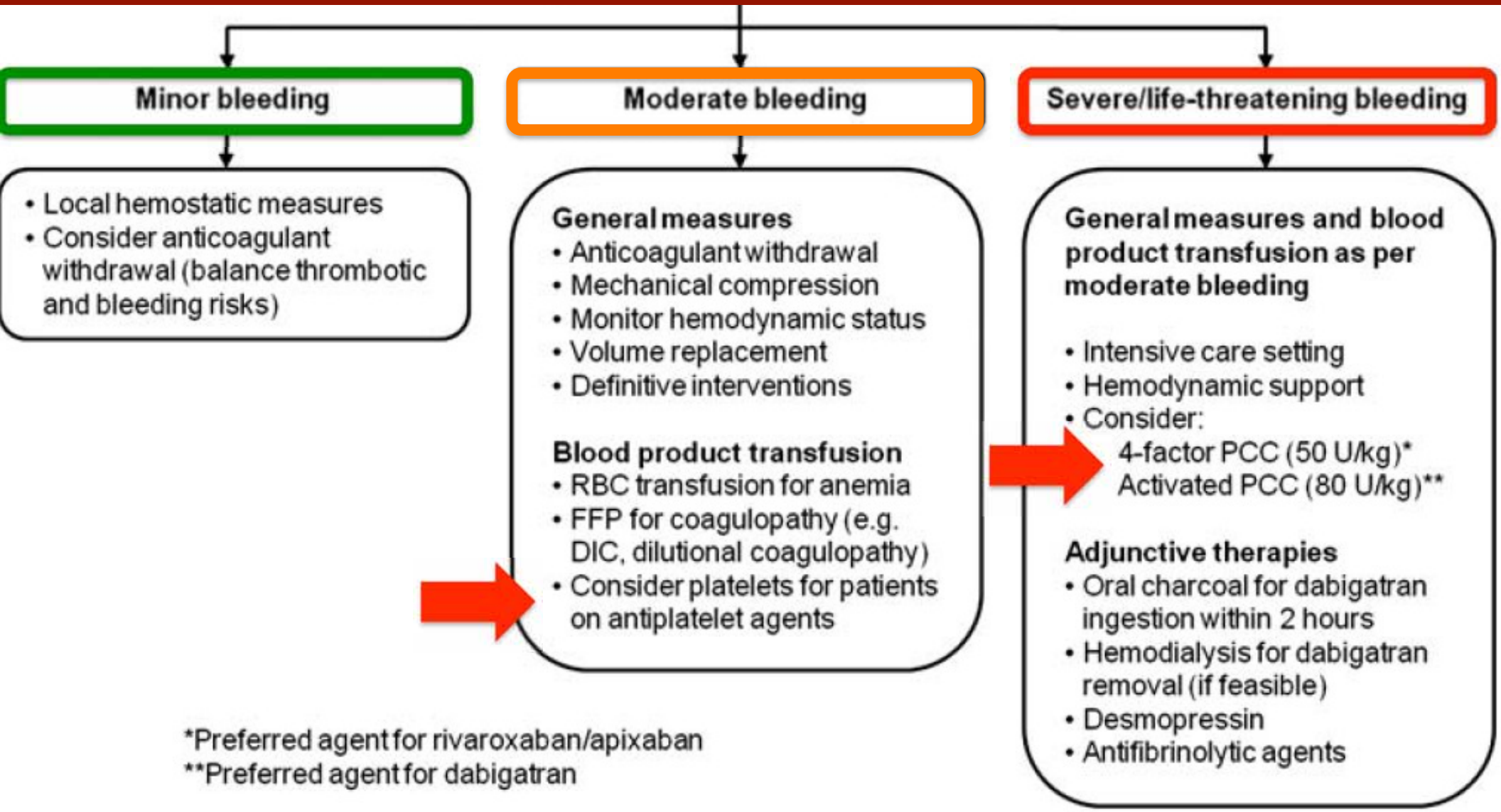
Adapté de: Monographie Eliquis™ (apixaban) 2012

Renversement de l'apixaban
Anesthésie spinale ou épidurale et ponctions lombaires

- **Indwelling epidural or intrathecal catheters must be removed at least 5 hours prior to the first dose of ELIQUIS.**
- **The *(neurological)* risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, the administration of ELIQUIS should be delayed for 24 hours.**

Adapté de: Monographie Eliquis™ (apixaban) 2012

Renversement du dabigatran, rivaroxaban et apixaban
Stratification du risque de saignement



Les facteurs concentrés injectables (PCC et PCCa)
Disponibles au Canada

Composition of Prothrombin Complex Concentrates[61-68]

Prothrombin Complex Concentrate	Factor II	Factor VII	Factor IX	Factor X	Heparin	Human Antithrombin III	Protein C	Protein S
Feiba	1.3 IU/IU	0.9 IU/IU **Activé**	1.4 IU/IU	1.1 IU/IU	...[c]	...	1.1 IU/IU	...
Profilnine SD[a] (Grifols Biologicals)	NMT 150 units/100 factor IX units	NMT 35 units/100 factor IX units	100 units	NMT 100 units/100 factor IX units	...	...	...	...
Bebulin[a] (Baxter Healthcare)	24–38 IU/mL	<5 IU/mL	24–38 IU/mL	24–38 IU/mL	<0.15 IU/IU factor IX	...	...	...
Beriplex	19–40 IU/mL	10–25 IU/mL	20–31 IU/mL	25–51 IU/mL	0.5 IU/mL	0.6 IU/mL	21–41 IU/mL	12–34 IU/mL
Kanokad (Sanquin)	14–35 IU/mL	7–20 IU/mL	25 IU/mL	14–35 IU/mL	...	...	...	...
Octaplex	14–38 IU/mL	9–24 IU/mL	25 IU/mL	18–30 IU/mL	5–12.5 IU/mL	...	13–31 IU/mL	12–32 IU/mL

Adapté de: Miyares MA, Davis K. Am J Health-Syst Pharm 2012; 69: e28-39

Dabigatran et chirurgie selon le risque de saignement

Nombre de jours d'arrêt pré-opératoire

Before Invasive Procedures Such as Elective Surgery in Patients R... ...Twice-Daily Dosing With a Standa...

1 - 2 - 4

Clearance

Saignement

Renal Function (Creatinine Clearance), mL/min	Half-Life, h*	Timing of Discontinuation of Dabigatran Before Surgery: Standard Risk of Bleeding	Timing of Discontinuation of Dabigatran Before Surgery: High Risk of Bleeding†
>80	13 (11–22)	24 h	2–4 d
>50–≤80	15 (12–34)	24 h	2–4 d
>30–≤50	18 (13–23)	≥2 d (48 h)	4 d
≤30	27 (22–35)	2–5 d	>5 d

Adapté de: Hankey Gj, Eikelboom JW. Circulation 2011; 123: 1436-1450

Et monographie 2012

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Rivaroxaban et chirurgie selon le risque de saignement

Nombre de jours d'arrêt pré-opératoire

1 à 2 - 4

Selon le risque de saignement

Adapté de: Monographie 2012

Apixaban et chirurgie selon le risque de saignement

Nombre de jours d'arrêt pré-opératoire

1 à 2 au moins

Selon le risque de saignement

Adapté de: Monographie 2012

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Références

Le Groupe de Travail sur la Thrombose du Canada
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SSVQ .org
Société des sciences vasculaires du Québec