Les nouveaux anticoagulants monitorage et antidote

Dr Olfa Kaabachi –
Dr Khaireddine Raddaoui
Journées STAAR-ATR, 28Mai 2016

HAUTE AUTORITÉ DE SANTÉ

- **6 janvier 2015 Communiqué de Presse**
- Les « NACO », anticoagulants d'action directe, n'ont pas tous démontré la même efficacité
- La Commission de la Transparence de la HAS a réévalué les trois anticoagulants oraux d'action directe (NACO), en particulier dans la prévention des accidents vasculaires cérébraux et embolies systémiques chez les malades ayant une fibrillation atriale non valvulaire. Sur la base des données disponibles, elle a hiérarchisé ces médicaments. **La nécessité ou pas de suivre l'anticoagulation ainsi que l'absence d'antidote sur le marché l'ont poussé à positionner ces médicaments en 2ème intention après les antivitaminesK, qui restent le traitement de référence.**

PRADAXA : remboursé à 30 % !

Ce que nous savons

- Héparine non fractionnée :
  - neutralisation complète par le sulfate de protamine
- HBPM :
  - neutralisation incomplètes par le sulfate de protamine
- Fondaparinux :
  - pas d'antidote
- AVK :
  - antidote mais 5000 morts / an ?
- Aspirine :
  - pas d'antidote
- Clopidogrel, Ticagrelor et Prasugrel :
  - pas d'antidote

Le risque hémorragique

Tazarourte et al. Critical Care 2014, 18:R81
http://ccforum.com/content/18/2/R81

CRITICAL CARE

RESEARCH Open Access

Guideline-concordant administration of prothrombin complex concentrate and vitamin K is associated with decreased mortality in patients with severe bleeding under vitamin K antagonist treatment (EPAHK study)

Karim Tazarourte[1], Bruno Riou[2], Benjamin Tremey[3], Charles-Marc Samama[4], Éric Vicaut[5], Bernard Vigué[6*] and EPAHK study group

Key messages

- In patients on VKA therapy presenting with severe hemorrhage, international guidelines recommend, as soon as the diagnosis is confirmed, the administration of PCC (≥20 UI/kg) and vitamin K (≥5 mg) to normalize coagulation (post-reversal INR ≤1.5).
- A guideline-concordant administration dose of PCC and vitamin K administrated in the first eight hours was associated with a two-fold decrease in seven-day mortality overall and with a three-fold decrease in the ICH subgroup
- The guideline-concordant reversal was performed in 38% of the patients within eight hours after admission
- Whereas pre-reversal INR is not absolutely necessary, post-reversal INR is essential to evaluate treatment efficacy
- The post-reversal INR target must be performed systematically and immediately after PCC administration

- Meta-analysis comparing the safety and efficacy of the four newer oral agents to warfarin in patients with atrial fibrillation. They were found to be equally effective in the prevention of stroke. More importantly the incidence of intracranial hemorrhage was reduced by almost 50 % and there was a significant reduction in all cause mortality. However, an increase in gastrointestinal bleeding was observed

[Ruff CT. Lancet. 2014;383(9921):955–62.].

PLOS | ONE

RESEARCH ARTICLE

Risk of Fatal Bleeding in Episodes of Major Bleeding with New Oral Anticoagulants and Vitamin K Antagonists: A Systematic Review and Meta-Analysis

Joel Skaistis*, Travis Tagami

Authors' Conclusions

Major bleeds occurring on NOAC therapy are statistically significantly less likely to lead to death than bleeds occurring with VKAs. This reduction in fatal bleeding is due to the decreased incidence of intracranial bleeding with NOAC agents compared to VKAs. Odds of fatal bleeding given occurrence of a major bleed at any given anatomic site showed no detectable difference between NOAC and VKA groups. Despite poor understanding of anticoagulation reversal with the NOAC agents, there is no additional mortality risk detected during bleeding events compared to VKAs.

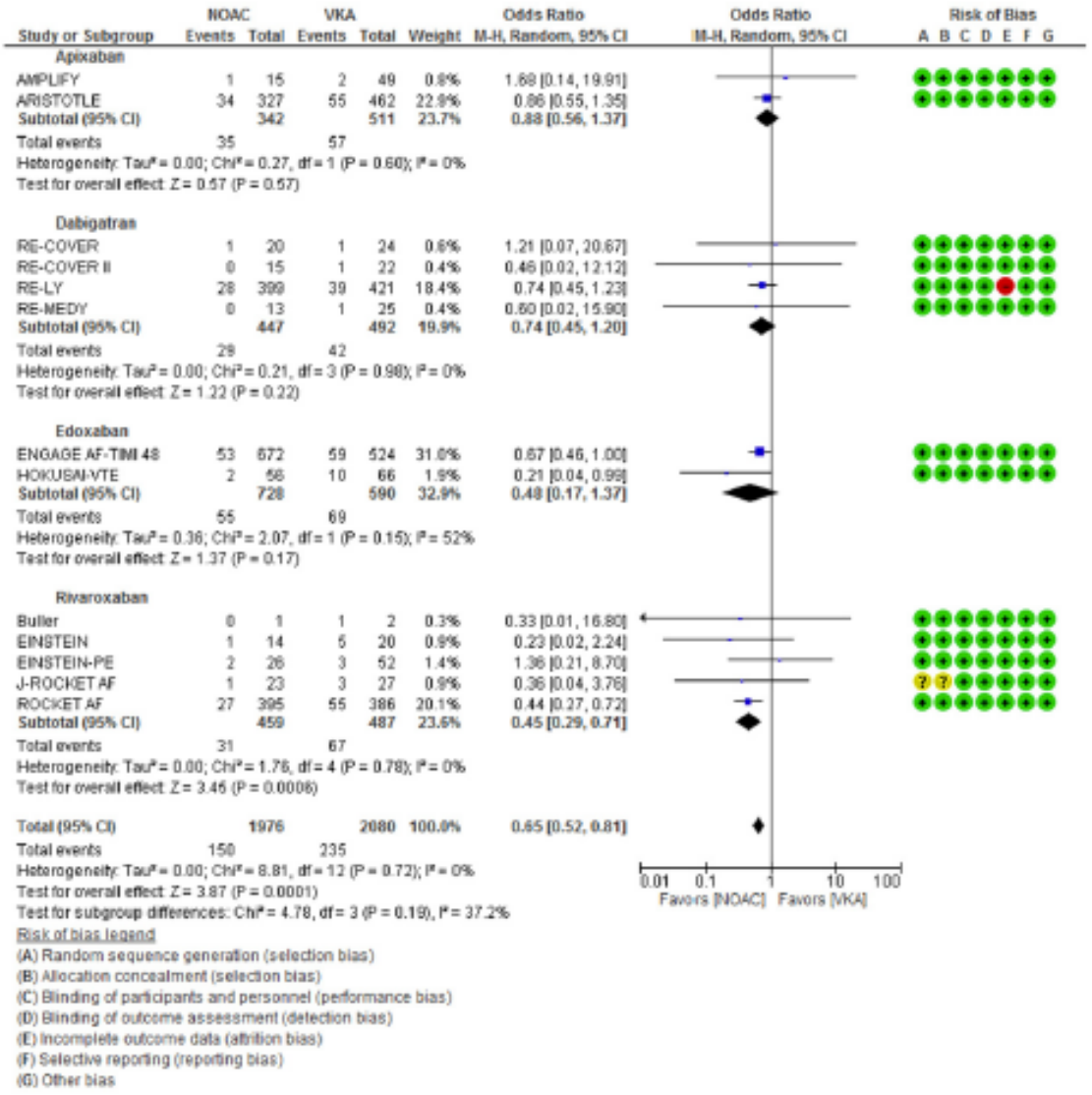


Fig 2. Relative Odds of Fatal Bleeding Given Occurrence of Major Bleed. Odds ratios and 95% confidence intervals are given for the relative odds that major bleeding events will lead to fatal bleeding events.

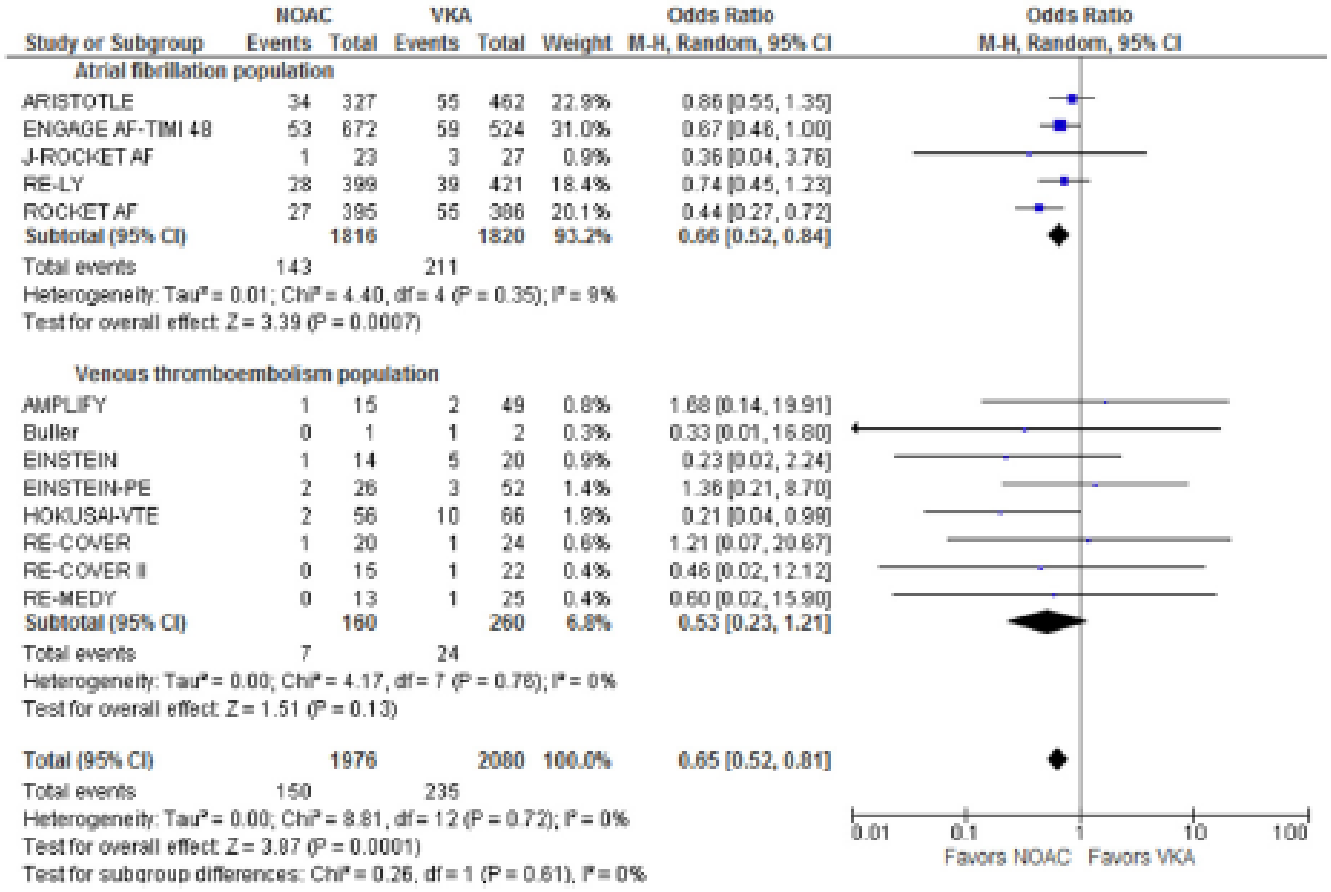


Fig 3. Relative Odds for fatal bleeding in treatment indication subgroups. Odds ratios and 95% confidence intervals are given for the relative odds that major bleeding events will lead to fatal bleeding events. Subgroups are determined by the indication for anticoagulation and fall into two categories, treatment of acute venous thromboembolism or stroke prophylaxis in atrial fibrillation.

Antidotes for Bleeding Caused by Novel Oral Anticoagulants

Charles V. Pollack, Jr., MA, MD

(*Circulation*. 2016;133:e18-e19.

Table. Performance Profile of the 4 NOACs (Dabigatran, Apixaban, Edoxaban, and Rivaroxaban) Taken Together Compared With Warfarin in Clinical Trials of Stroke Prevention in Patients With Atrial Fibrillation[2]

End Point (Effectiveness or Safety)	Relative Risk Reduction with NOACs Over Warfarin, %
Stroke or clot embolus to elsewhere in the body (effectiveness)	19
Major bleeding (safety)	14
Bleeding into or around the brain (safety)	52

Meta-Analysis of Efficacy and Safety of New Oral Anticoagulants (*Dabigatran*, *Rivaroxaban*, *Apixaban*) Versus *Warfarin* in Patients With Atrial Fibrillation

Corey S. Miller, BA[a,c], Sonia M. Grandi, MSc[a], Avi Shimony, MD[a,b,d], Kristian B. Filion, PhD[a], and Mark J. Eisenberg, MD, MPH[a,b,c,*]

(Am J Cardiol 2012;110:453–460)

In conclusion, the new oral anticoagulants are more efficacious than warfarin for the prevention of stroke and systemic embolism in patients with AF. With a **decreased risk for intracranial bleeding**, they appear to have a favorable safety profile, making them promising alternatives to warfarin.

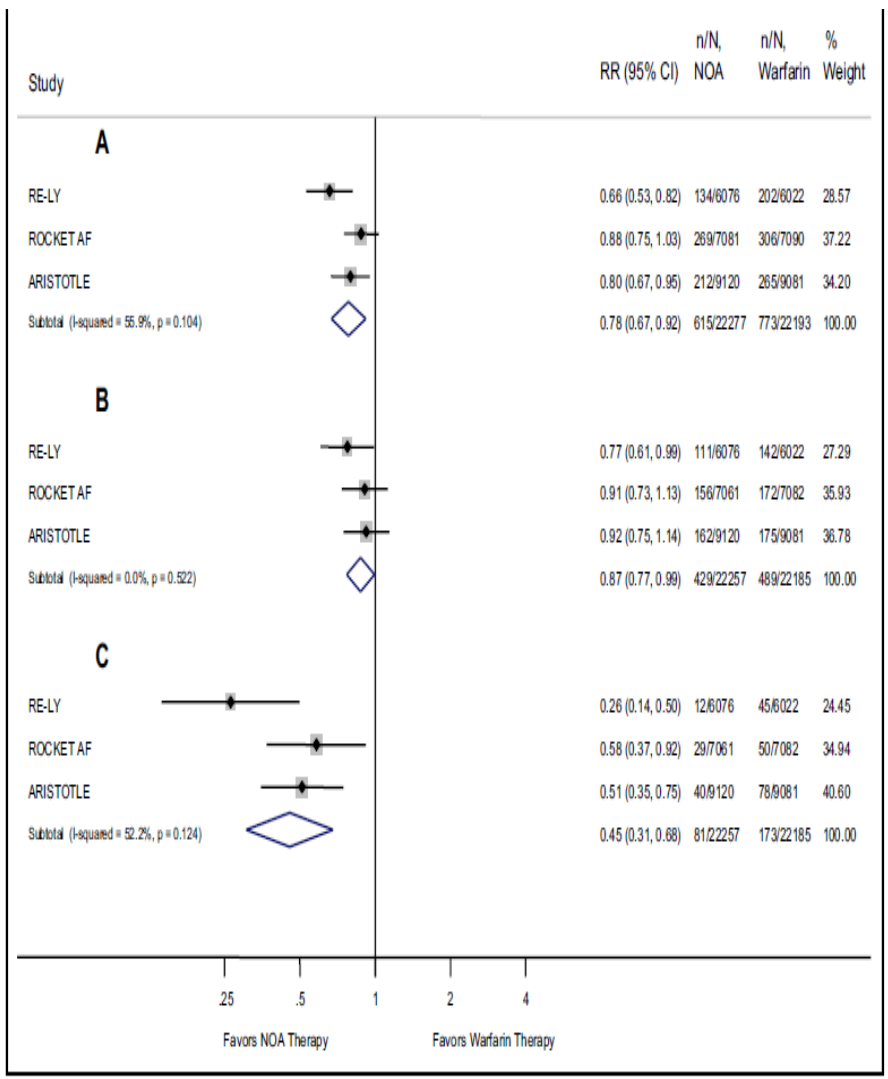


Figure 2. Forest plot for *(A)* all-cause stroke and systemic embolism, *(B)* ischemic and unspecified stroke, and *(C)* hemorrhagic stroke, new oral anticoagulants (NOA) versus warfarin in patients with AF.

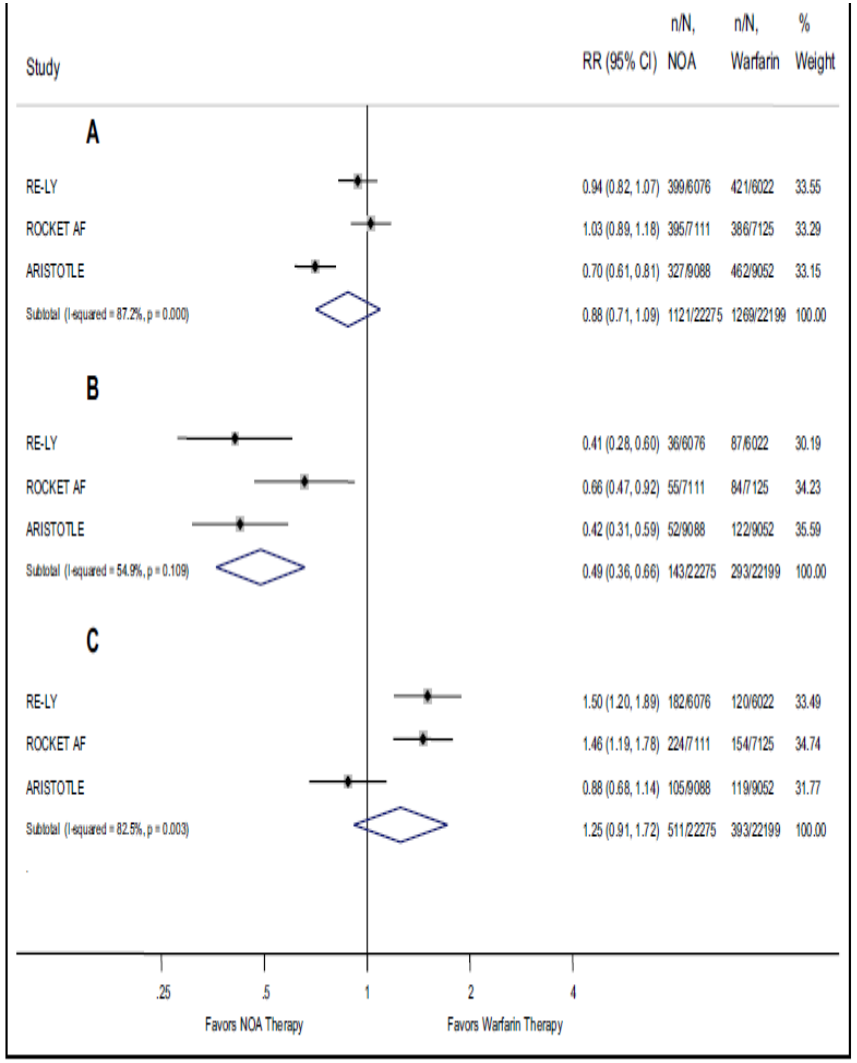


Figure 3. Forest plot for *(A)* major bleeding, *(B)* intracranial bleeding, and *(C)* gastrointestinal bleeding, new oral anticoagulants (NOA) versus warfarin in patients with AF.

Circulation. 2015 July 21; 132(3): 194–204. doi:10.1161/CIRCULATIONAHA.114.013267.

Efficacy and harms of direct oral anticoagulants in the elderly for stroke prevention in atrial fibrillation and secondary prevention of venous thromboembolism: systematic review and meta-analysis

Manuj Sharma, M Clin Res[1,2], **Victoria R Cornelius, PhD**[1], **Jignesh P Patel, PhD**[3,4], **J Graham Davies, PhD**[4], and **Mariam Molokhia, PhD**[1]

Conclusion—DOACs demonstrated at least equal efficacy to VKA in managing thrombotic risks in the elderly however bleeding patterns were distinct. In particular, dabigatran was associated with a higher risk of gastrointestinal bleeding than VKA. Insufficient published data for apixaban, edoxaban and rivaroxaban indicates further work is needed to clarify their bleeding risks in the elderly.

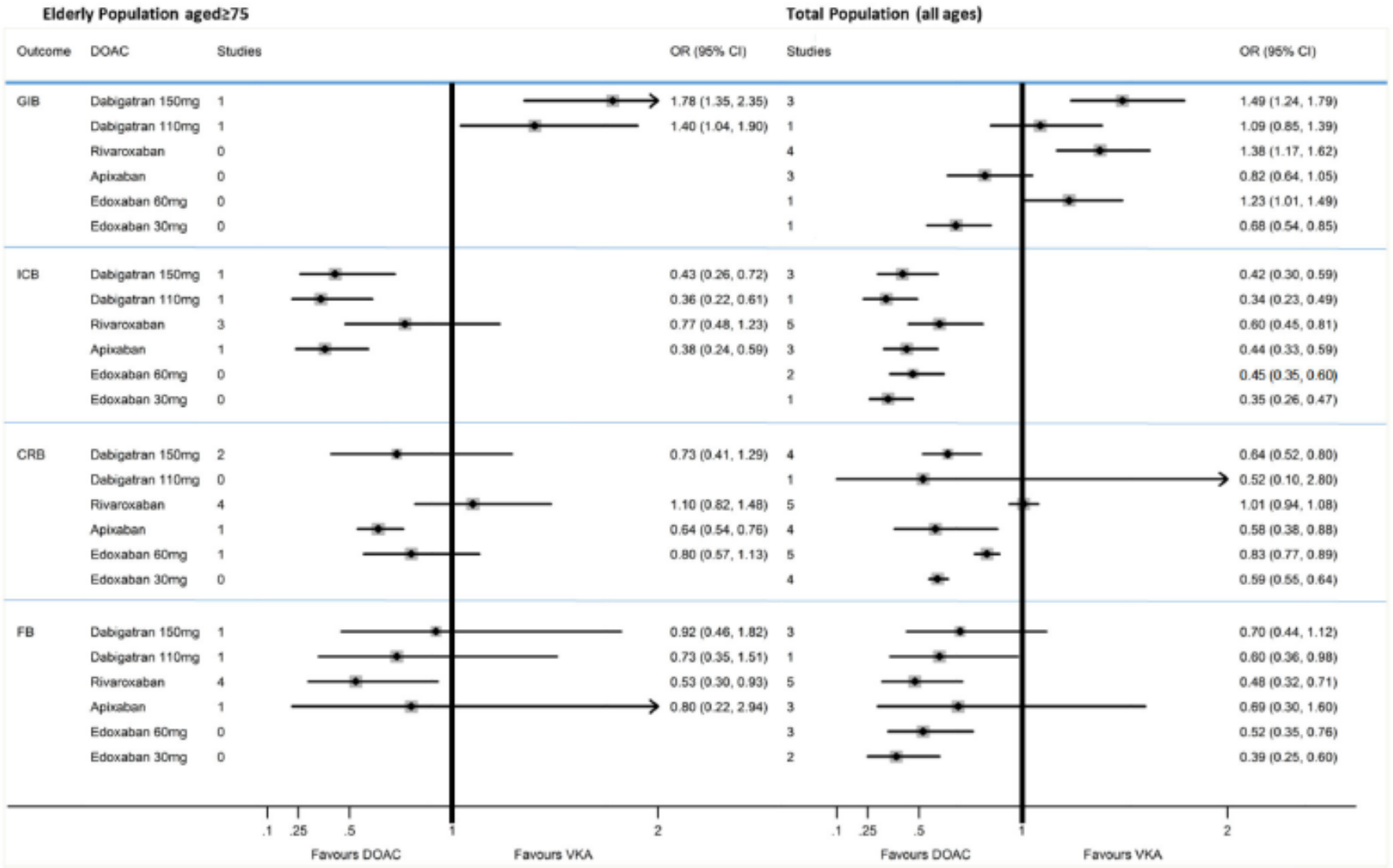


Figure 6. Risk of secondary outcomes in elderly (left) and total population (right)
GIB= Gastrointestinal bleeding; ICB = Intracranial Bleeding; CRB= Clinically Relevant Bleeding; FB= Fatal Bleeding

Comparison of the Short-Term Risk of Bleeding and Arterial Thromboembolic Events in Nonvalvular Atrial Fibrillation Patients Newly Treated With Dabigatran or Rivaroxaban Versus Vitamin K Antagonists

A French Nationwide Propensity-Matched Cohort Study

(*Circulation*. 2015;132:1252-1260.

In conclusion, in this study based on medico-administrative data, no statistically significant difference was observed between NOACs, dabigatran or rivaroxaban, and VKAs in terms of the risk of bleeding or arterial thromboembolic events during the early phase of anticoagulant therapy in nv-AF patients. The same level of clinical caution is therefore required when initiating either NOACs or VKAs. Similar analyses should be extended to other NOACs such as apixaban, and observational studies should now focus on NOAC head-to-head comparison in a noninferiority design.

Table 3. Events, Person-Years at Risk, and Crude Event Rates Among NOAC New Users and Matched VKA New Users

	Dabigatran All Doses	VKA D-All Doses Matched	Dabigatran 75–110	VKA D75–110 Matched	Dabigatran 150	VKA D75–110 Matched	Rivaroxaban All Doses	VKA R-All Doses Matched	Rivaroxaban 10–15	VKA R10–15 Matched	Rivaroxaban 20	VKA R20 Matched
Bleeding events	55/1684/3.3	122/3292/3.7	43/1195/3.6	101/2368/4.3	12/489/2.5	30/1054/2.8	31/848/3.7	68/1913/3.6	16/328/4.9	36/734/4.9	15/520/2.9	40/1178/3.4
Bleeding events or death	158/1684/9.4	341/3292/10.4	137/1195/11.5	295/2368/12.5	21/489/4.3	56/1054/5.3	75/848/8.8	161/1913/8.4	43/328/13.1	89/734/12.1	32/520/6.2	80/1178/6.8
Ischemic stroke or SE	33/1687/2	58/3300/1.8	28/1198/2.3	37/2376/1.6	5/490/1	14/1056/1.3	12/851/1.4	28/1918/1.5	6/329/1.8	13/736/1.8	6/521/1.2	15/1182/1.3
Ischemic stroke or SE or death	136/1687/8.1	280/3300/8.5	121/1198/10.1	243/2376/10.2	15/490/3.1	43/1056/4.1	60/851/7.1	125/1918/6.5	37/329/11.2	66/736/9	23/521/4.4	56/1182/4.7

Values are events/ person-years at risk/crude event rate/100 person-years. D, dabigatran; NOAC, non–vitamin K antagonist oral anticoagulants; R, rivaroxaban; SE, systemic embolism; and VKA, vitamin K antagonist.

Risk of Bleeding With Dabigatran in AtrialFibrillation FREE

Inmaculada Hernandez et al. *JAMA Intern Med.* 2015;175(1):18-24.

- Dabigatran was associated with a higher risk of bleeding relative to warfarin, with hazard ratios of 1.30 (95% CI, 1.20-1.41) for any bleeding event, 1.58 (95% CI, 1.36-1.83) for major bleeding, and 1.85 (95% CI, 1.64-2.07) for gastrointestinal bleeding.

Beyer-Westendorf J. Blood. 2014;124(6):955–62

- A recent analytical study was conducted in Germany using data from a prospective, noninterventional oral anticoagulation registry. 43 % of the 1776 patients on rivaroxaban reported bleeding and of those 6.1 % were classified as major bleeding.

Suivi du traitement

- Comme pour tout traitement anticoagulant, une surveillance clinique appropriée est recommandée pendant toute la durée du traitement, à la recherche d'éventuels signes de saignement extériorisé ou de signes pouvant évoquer un saignement non extériorisé (asthénie, dyspnée, polypnée, pâleur, hypotension, tachycardie, céphalée ne cédant pas au traitement, malaise, chute brutale du taux d'hémoglobine, etc.).

Evaluation de la fonction rénale

Tableau 9 : données pharmacocinétiques des AOD dans les populations particulières

	Dabigatran		Rivaroxaban	Apixaban
Insuffisance rénale				
ClCr normale (ClCr ≥ 80 mL/min)		$t_{1/2\,max}$ 13,4h (11,0–21,6)		
Légère (50 ≤ ClCr < 80 mL/min)		$t_{1/2\,max}$ 15,3h (11,7–34,1)	ASC + 40 %	ASC + 16 %
Modérée (30 ≤ ClCr < 50 mL/min)	ASC + 80–130 %	$t_{1/2\,max}$ 18,4h (13,3–23,0)	ASC + 50 %	ASC + 29 %
Sévère (15 ≤ ClCr < 30 mL/min)	ASC + 500 %	$t_{1/2\,max}$ 27,2h (21,6–35,0)	ASC + 60 %	ASC + 44 %
Sujets âgés (≥ 75–80 ans)				
ASC	ASC + 40–60 %		ASC + 50 %	ASC + 32 %
Cmax	C max + 25 %			Pas d'augmentation Cmax
Cmin	C min + 31 %			

Tableau 10 : populations particulières des AOD et conduites à tenir recommandées

Populations particulières		Dabigatran		Rivaroxaban			Apixaban	
		ETEV	FA	ETEV	FA	TVP/EP	ETEV	FA
Insuffisance rénale ClCr (Cockcroft) en mL/min	ClCr < 15	Contre Indiqué	Contre Indiqué	Déconseillé	Déconseillé	Déconseillé	Déconseillé	Déconseillé
	15 < ClCr < 30	Contre Indiqué	Contre Indiqué	Prudence	Prudence ↘ posologie	Prudence ↘ posologie > J21 *si besoin*	Prudence	Prudence ↘ posologie
	30 < ClCr < 50	Prudence ↘ posologie	Prudence ↘ posologie *si besoin*		Prudence ↘ posologie	Prudence ↘ posologie > J21 *si besoin*		
	$Cr_{sérique}$ ≥ 133 µM/L + ≥ 80 ans ou ≤ 60 kg							Prudence ↘ posologie

Evaluation de la fonction hépatique

Tableau 9 : données pharmacocinétiques des AOD dans les populations particulières

	Dabigatran	Rivaroxaban	Apixaban
Insuffisance hépatique			
Légère (stade A de Child et Pugh)	Pas d'influence. Non recommandé	ASC + 20 %	Prudence
Modérée (stade B de Child et Pugh)	Pas d'influence. Non recommandé	ASC + 130 %	Prudence
Sévère (stade C du Child et Pugh)	Contre-indiqué	Contre-indiqué si coagulopathie associée, y compris Child B et C	Non recommandé sauf si coagulopathie : contre-indiqué

Tableau 10 : populations particulières des AOD et conduites à tenir recommandées

Populations particulières		Dabigatran		Rivaroxaban			Apixaban	
		ETEV	FA	ETEV	FA	TVP/EP	ETEV	FA
Atteinte hépatique (AT)	IH ou MH	Contre Indiqué	Contre Indiqué					
	AT + coagulopathie et RSCS			Contre Indiqué	Contre Indiqué	Contre Indiqué	Contre Indiqué	Contre Indiqué
	ASAT/ALAT > 2 x LSN	Déconseillé	Déconseillé				Prudence	Prudence
	IH sévère						Déconseillé	Déconseillé
	IH légère/modérée						Prudence	Prudence

Surveillance biologique de l'activité anticoagulante dans les situations particulières

- L'utilisation du dabigatran, du rivaroxaban et de l'apixaban ne requiert pas de suivi de l'activité anticoagulante **en routine.**

Surveillance biologique de l'activité anticoagulante dans les situations particulières

- Cependant, dans certaines situations telles que les situations de surdosage, d'hémorragies, d'interventions urgentes ou d'inobservance, la mesure de l'anticoagulation liée à ces molécules peut être utile.

Surveillance biologique de l'activité anticoagulante dans les situations particulières

- Il n'existe pas à ce jour de recommandations précises validées concernant la surveillance biologique des AOD, la prise en charge des saignements graves, des interventions urgentes ou programmées chez les patients recevant un AOD.

Quels tests ?

- Dans les situations d'urgence (saignement grave, acte invasif devant être réalisé en urgence), **une première mesure** devra être effectuée rapidement et devra être « datée » **en fonction de l'heure de la dernière prise de l'AOD et/ou de la prise suivante prévue**, afin de déterminer où se situe la mesure dans l'intervalle de doses (comparaison approximative aux valeurs maximales de référence et/ou aux valeurs résiduelles de référence).

- Dans la mesure du possible, **une deuxième mesure** devra être réalisée à la fin de l'intervalle de doses (Tmin), afin de permettre une comparaison plus précise aux valeurs résiduelles de référence.

Comment interpréter les tests ?

- Pour une bonne interprétation des tests, on doit connaître :
  - l'heure de la mesure par rapport à la prise de l'AOD,
  - l'indication et la dose d'AOD absorbée par le patient,
  - les caractéristiques du patient (âge, poids, fonction rénale, etc.).

Review Article

Novel Anticoagulants in Atrial Fibrillation: Monitoring, Reversal and Perioperative Management

BioMed Research International
Volume 2015, Article ID 424031, 8 pages

Fadi Shamoun,[1] Hiba Obeid,[2] and Harish Ramakrishna[3]

Novel Oral Anticoagulants
Efficacy, Laboratory Measurement, and Approaches to Emergent Reversal
Eric Gehrie, MD.Arch Pathol Lab Med—Vol 139, May 2015

Dabigatran

- A recent study comparing different tests for monitoring dabigatran levels in patients with AF found a strong correlation between the total and free dabigatran plasma levels measured by **liquid chromatography-tandem mass-spectrometry (LC-MS/MS)** and indirect measurements by Hemoclot Thrombin Inhibitor (HTI) and ecarin clotting time (ECT) assays.
- **This correlation suggests that HTI and ECT assays** are **highly sensitive** for the assessment of dabigatran activity when compared to standard coagulation tests (aPTT, PT).

[M. Skeppholm. *Thrombosis Research, vol. 134, no. 4, pp. 783–789*, 2014]

Dabigatran

- Measured the dabigatran concentrations by the Hemoclot assay and correlated the results with aPTT and thrombin time (TT)
  - TT was very sensitive to the presence of the drug and that aPTT is useful as a qualitative test (**to determine whether dabigatran is having an anticoagulant effect in the patient**),
  - but both TT and aPTT had only moderate correlation with the drug levels.
- This could be useful in preparing patients for surgery in settings where HTI or ECT assays are not available.
- The study recommended measuring aPTT and TT before elective surgery in patients taking dabigatran.

[G. Hapgood; *Thrombosis and Haemostasis, vol. 110, no. 2, pp. 308–315, 2013.*]

Dabigatran

- aPTT may not be used to assess dabigatran therapy if the patient has a lupus anticoagulant or an intrinsic clotting factor deficiency, as the aPTT prolongation from these conditions will mask the effect of dabigatran on the aPTT.

Dabigatran

- ***Quantitative assessment of dabigatran levels*** can be obtained with the dilute thrombin time (dTT), the ecarin clotting time [TEMPS Escarine], or the ecarin chromogenic assay.

- These assays are not generally available.
- No FDA approval.

Rivaroxaban and Apixaban

- Rivaroxaban and apixaban have been shown to affect routine coagulation tests, including the aPTT, activated clotting time, PT, and chromogenic anti– factor Xa assay.

- The PT provides a relatively more sensitive assessment of rivaroxaban and apixaban than the aPTT or the activated clotting time.

- No therapeutic ranges exist, complicating the interpretation of the results of these tests.

Rivaroxaban and Apixaban

- ***Qualitative assessment of direct oral factor Xa inhibitors*** : suggest using either the PT or the chromogenic anti–factor Xa assay.
- At present, no assays or calibration reagents are FDA approved for the measurement of the direct oral factor Xa inhibitors.

Apixaban

- Similar to other factor Xa inhibitors, chromogenic antifactor Xa assays can be used to measure the plasma concentrations of edoxaban when drug-specific calibrators are available.

Effect of direct oral anticoagulants on routine haemostasis assays and thrombophilia screening.		
Assay	Rivaroxaban, apixaban, edoxaban	Dabigatran
aPTT	↑	↑
Prothrombin time	↓	↓
Fibrinogen	↔	↓
Thrombin time	↔	↓
Anti-Xa activity	↑	↔
Anti-IIa activity	↔	↑
Genetic analysis	Possible	
Antithrombin, proteins C and S (activity)	Not possible (false negative)	
Lupus anticoagulant	Not possible (false positive)	
Anticardiolipin and anti-B_2GP_1 antibodies	Possible	
aPPT = activated partial thromboplastin time; B_2GP_1 = β_2 glcoprotein-1		

Table 2. Laboratory Monitoring of US Food and Drug Administration–Approved Oral Anticoagulants

Property/Drug	Warfarin (Coumadin, Bristol-Meyers Squibb, Princeton, New Jersey)	Dabigatran (Pradaxa, Boehringer Ingelheim Pharmaceuticals, Ridgefield, Connecticut)	Rivaroxaban (Xarelto, Janssen Pharmaceuticals Inc, Titusville, New Jersey)	Apixaban (Eliquis, Bristol-Meyers Squibb, Princeton, New Jersey)
Routine monitoring required?	Yes	No	No	No
Qualitative assessment of NOAC levels	N/A	aPTT[a], PT[a], TT[a]	PT[a]	PT[a]
Quantitative assessment of NOAC levels	PT/INR	dTT[b], ECA[b], ECT[b]	Chromogenic anti–factor Xa[c]	Chromogenic anti–factor Xa[c]

Abbreviations: aPTT, activated partial thromboplastin time; dTT, dilute thrombin time; ECA, ecarin chromogenic assay; ECT, ecarin clotting time; FDA, US Food and Drug Administration; INR, international normalized ratio; N/A, not applicable; NOAC, novel oral anticoagulant; PT, prothrombin time; TT, thrombin time.

Recommendations for monitoring and reversal of NOACs.

NOAC	Trial name	Most accurate monitoring tests	Qualitative monitoring tests
Dabigatran	RE-LY	HTI ECT	TT aPTT
Rivaroxaban	ROCKET AF	Antifactor Xa chromogenic assays	PT
Apixaban	AVERROES ARISTOTLE		
Edoxaban	ENGAGE AF-TIMI		

*Those reversal agents are still under evaluation.

Quels tests ?

Tableau I2: tests de l'hémostase recommandés dans les situations particulières

Test	Dabigatran	Rivaroxaban	Apixaban
INR	NA	NA	NA
Temps Quick – TP (PT*) Test non spécifique	NA	Test qualitatif Peu sensible	NA
TCA (aPTT*) Test non spécifique	Test qualitatif Non linéaire à doses élevées	NA	NA
Temps Thrombine – TT Test non spécifique	NA	NA	NA
Temps Thrombine Modifié Test spécifique	Test quantitatif	NA	NA
Temps Ecarine – ECT Test non spécifique	Test quantitatif	NA	NA
Anti-IIa Test spécifique	Test quantitatif	NA	NA
Anti-Xa chromogénique Test spécifique	NA	Test quantitatif	Test quantitatif

Tableau 13 : valeurs résiduelles de référence des AOD (moyennes géométriques, percentiles ou intervalles de confiance (IC) – Source RCP

Test	Dabigatran	Rivaroxaban	Apixaban
Temps Quick – TP		Prévention AVC 20 mg 1x/j : Percentiles 5–95 : 12 – 26 s 15 mg 1x/j : Percentiles 5–95 : 12 – 26 s	
		Traitement ETEV 15 mg 2x/j : Percentiles 5–95 : 14 – 24 s 20 mg 1x/j : Percentiles 5–95 : 13 – 20 s	
Concentrations ou activités anti-Xa Temps Thrombine Modifié Temps Ecarine – ECT Anti-IIa Anti-Xa chromogénique	Prévention ETEV 220 mg 1x/j 22 ng/mL Percentiles 25–75 : 13,0–35,7 ng/mL	Prévention ETEV 10 mg 1x/j 14 ug/L IC90 % 4 – 51	Prévention ETEV 2,5 mg 2x/j 0,84 UI/mL Percentiles 5–95 : 0,37–1,8 UI/mL
	Prévention AVC 150 mg 2x/j 91,0 ng/mL Percentiles 25–75 : 61,0–143 ng/mL	Traitement ETEV 20 mg 1x/j 32 ug/L IC90 % 6 – 239	Prévention AVC 5 mg 2x/j 1,54 UI/mL Percentiles 5–95 : 0,61 – 3,43 UI/mL 2,5 mg 2x/j 1,18 UI/mL Percentiles 5–95 : 0,51 – 2,42 UI/mL

Tableau 14 : valeurs résiduelles de référence des AOD pouvant être associées à un risque accru de saignement (concentrations ou ratio par rapport aux valeurs normales) – Source RCP

Test	Dabigatran Valeurs correspondant au 90e percentile des valeurs minimales observées présentées dans le tableau ci-dessus	Rivaroxaban	Apixaban
Temps Quick – TP Test non spécifique		Non disponibles	
TCA Test non spécifique	Prévention ETEV 220 mg 1x/j > 1.3 x LSN (soit allongement 51 sec)		
	Prévention AVC 150 mg 2x/j > 2 x LSN (soit allongement 80 sec)		
Temps Ecarine – ECT Test non spécifique	Prévention AVC 150 mg 2x/j > 3 x LSN (soit allongement 103 sec)		
Temps Thrombine Modifié Anti-IIa Anti-Xa chromogénique Tests spécifiques	Prévention ETEV 220 mg 1x/j > 67 ng/mL	Non disponibles	Non disponibles
	Prévention AVC 150 mg 2x/j > 200 ng/mL		

LSN : limite supérieure de la normale

Tableau 15 : valeurs maximales de références des AOD – Source RCP

Test	Dabigatran	Rivaroxaban	Apixaban
Temps Quick – TP (PT)		Prévention ETEV 10 mg 1x/j Percentiles 5–95 : 13 – 25 s	
		Prévention AVC 20 mg 1x/j : Percentiles 5–95 : 14 – 40 s 15 mg 1x/j : Percentiles 5–95 : 10 – 50 s	
		Traitement ETEV 15 mg 2x/j : Percentiles 5–95 : 17 – 32 s 20 mg 1x/j : Percentiles 5–95 : 15 – 30 s	
Concentrations ou activités anti-Xa Temps Thrombine Modifié Temps Ecarine – ECT Anti-IIa Anti-Xa chromogénique	Prévention ETEV 220 mg 1x/j 70,8 ng/mL Percentiles 25–75 : 35,2–162 ng/mL	Prévention ETEV 10 mg 1x/j 101 ug/L IC90 % 7 – 273	Prévention ETEV 2,5 mg 2x/j 1,3 UI/mL Percentiles 5–95 : 0,67–2,4 UI/mL
	Prévention AVC 150 mg 2x/j 175 ng/mL Percentiles 25–75 : 117–275 ng/mL	Traitement ETEV 20 mg 1x/j 215 ug/L IC90 % 22 – 535	Prévention AVC 5 mg 2x/j 2,55 UI/mL Percentiles 5–95 : 1,36 – 4,79 UI/mL 2,5 mg 2x/j 1,84 UI/mL Percentiles 5–95 : 1,02 – 3,29 UI/mL

En cas d'hémorragie / chirurgie

Adaptation posologie

- âge
- Fonctions rénale et hépatique
- Pathologie

Respecter les contre indications

Table 1: Recommendation for NOACs cessation before elective procedure.

	Dabigatran		Apixaban		Rivaroxaban	
	No important bleeding risk and/or adequate local hemostasis possible: perform at trough level (i.e., ≥12 hours or 24 hours after last intake)					
Creatinine clearance	Low risk	High risk	Low risk	High risk	Low risk	High risk
≥80 mL/min	≥24 hours	≥48 hours	≥24 hours	≥48 hours	≥24 hours	≥48 hours
50–80 mL/min	**≥36 hours**	**≥72 hours**	≥24 hours	≥48 hours	≥24 hours	≥48 hours
30–50 mL/min	**≥48 hours**	**≥96 hours**	≥24 hours	≥48 hours	≥24 hours	≥48 hours
15–30 mL/min	Not indicated	Not indicated	**≥36 hours**	**≥48 hours**	**≥36 hours**	**≥48 hours**
<15 mL/min	No official indication for use					

5

Massive human rivaroxaban overdose

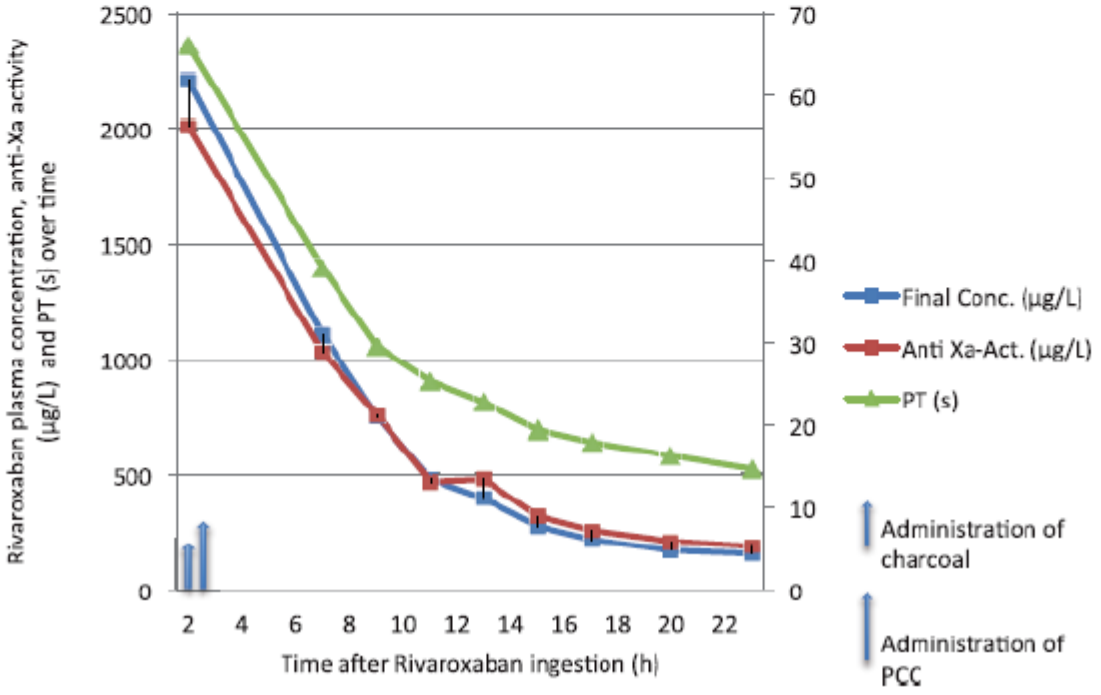
Thomas Lehmann[1]; Katharina E. Hofer[2]; Michael Baumann[1]; Karin Hasler[3]; Alessandro Ceschi[2]; Hugo Kupferschmidt[2]; Gabriele Rohde[4]; Wolfgang Korte[1]

[1]Center of Laboratory Medicine and Hemostasis and Hemophilia Center St. Gallen, St. Gallen, Switzerland; [2]Swiss Toxicological Information Centre, Associated Institute of the Zurich University, Zurich, Switzerland; [3]Department of Emergency, Kantonsspital St. Gallen, Switzerland; [4]Bioanalytik, Bayer Pharma AG, Leverkusen, Germany

Homme de 63 ans , coronarien et HTA, pas d'insuffisance rénale

TS : 1960 mg rivaroxaban (98 cp à 20 mg) + 90 mg diazepan, 50 mg zolpidem,1 g quetiapine

Admission : conscient, 127 000 plaquettes, Hb normale, TQ = 66 sec, ***concentration rivaroxaban 2207 µg/l (40)*** *. H + 3 : traitement par charbon activé, CCP…Pas d'accidents hémorragiques*



General management of bleeding in patients on NOACs

- In the absence of US FDA-approved NOAC antidotes and prospective data to guide bleed management in the setting of NOAC use, several hemostatic therapies have been described. There is little data on the efficacy of these in NOAC-associated bleeding. Strategies can be categorized as follows:
- Alter pharmacokinetics: reduce the absorption or remove from circulation
- Antifibrinolytic agents – tranexamic acid and ε-aminocaproic acid
- Therapy with plasma factors: prothrombin complex concentrates (PCCs), fresh frozen plasma, and cryoprecipitate
- Specific antidotes: ciraparantag (PER977), andexanet alfa, and idarucizumab

Antifibrinolytic agents

- In the case of major bleeding, antifibrinolytic agents such as tranexamic and ε-aminocaproic acid may be used.
- Although the efficacy of these agents in case of NOAC-associated bleeding is unknown, these are inexpensive agents with a favorable safety profile.

Altering pharmacokinetics of NOACs

- For major bleeding associated with **apixaban and dabigatran**, administration of **activated charcoal** may reduce continued absorption of the anticoagulant.
- Limited data shows that charcoal administered up to **6 hours** after **apixaban** reduces its plasma concentration, with best effects when administered within 2 hours from ingestion.
- Similarly, activated charcoal may be useful in decreasing **dabigatran** levels when given within **2–3 hours** of ingestion.
- Limited ex vivo data but no human data are available for dabigatran.
- Although there are **no specific studies available for rivaroxaban or edoxaban,** activated charcoal may be efficacious for these agents too.

Altering pharmacokinetics of NOACs

- **Hemodialysis** is a possible treatment for **dabigatran**-associated bleeding, given dabigatran's low protein-bound state and lipophilic profile.
- **Rivaroxaban and apixaban** are more highly protein-bound and thus are **unlikely to be successfully dialyzed**.
- **It is unclear if edoxaban may be removed by dialysis**.
- Small case series and case reports have described.
- Dialysis is challenging in cases with major bleeding and hemodynamic instability, and is most likely to be of the greatest utility in instances of dabigatran overdose or emergent need for surgery in otherwise hemodynamically stable patients.

[Warkentin TE. Blood. 2012;119(9):2172–4.- Hankey GJ. Int J Hematol. 2015;101(6):594–7.].

POTENTIAL REVERSAL OF NOVEL ORAL ANTICOAGULANTS

- A **4-factor prothrombin complex concentrate (PCC)** was recently **FDA approved for the reversal of warfarin** in patients with acute major bleeding;

- At present, reversal of TSOAs **is usually attempted** by the administration of:
  - prothrombin complex concentrates (PCC). They contain Factor II, IX and X.
  - The four Factor PCC also contains Factor VII.
- These agents are supposed to reverse the effect of the novel oral anticoagulants by saturating their action.
- Also this method does not neutralize the risk of thromboembolism.

[Honickel M. Thromb Haemost. 2015;113(4):728–40.].

Dabigatran

- ***A murine modes*** of dabigatran-associated bleeding :
  - rFVIIa and combinations of rFVIIa plus a 4-factor PCC (Factor II, IX , X + VII) **improved the aPTT**, but not blood loss volume.
  - Treatment with either the combination of rFVIIa plus a 4-factor PCC or treatment with factor eight inhibitor bypass activity (FEIBA, an activated PCC) **improved the bleeding time** but had an insignificant effect on blood loss.
  - 4-factor PCC, but not rFVIIa, **reduced expansion of intracranial hematomas.**

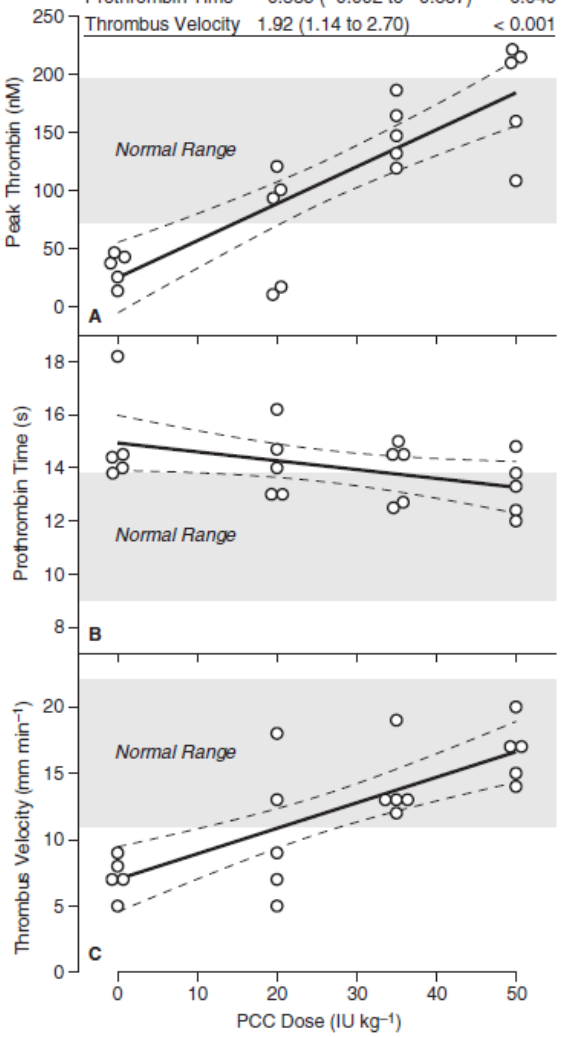
Journal of Thrombosis and Haemostasis, **10**: 1841–1848 DOI: 10.1111/j.1538-7836.2012.04859.x

ORIGINAL ARTICLE

Reversal of dabigatran anticoagulation by prothrombin complex concentrate (Beriplex P/N) in a rabbit model

I. PRAGST,* S. H. ZEITLER,* B. DOERR,* F. J. KASPEREIT,* E. HERZOG,* G. DICKNEITE* and J. VAN RYN†

Parameter	Slope (CI) per 10 IU kg^{-1}	*P*
Peak Thrombin	31.9 (22.1 to 41.7)	< 0.001
Prothrombin Time	–0.335 (–0.002 to –0.667)	0.049
Thrombus Velocity	1.92 (1.14 to 2.70)	< 0.001



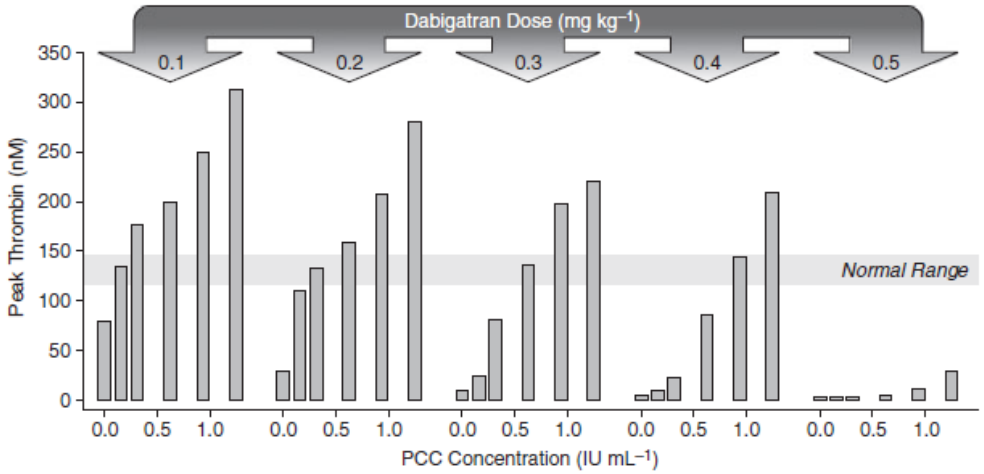


Fig. 2. Peak thrombin generation after spiking *in vitro* with PCC of plasma samples from animals treated *in vivo* with 0.1, 0.2, 0.3, 0.4 or 0.5 mg kg^{-1} dabigatran i.v. (one animal per dose). Indicated PCC concentrations *in vitro* after spiking are equivalent to those produced *in vivo* by PCC doses of 12.5, 25, 50, 75 and 100 IU kg^{-1}.

4-factor PCC **reduced blood loss and improved bleeding time**

Dabigatran

- **There are several case reports of patients** with life threatening bleeding associated with dabigatran therapy.
- Many of the reports seem to indicate that treatment with FFP, rFVIIa, PCCs, fibrinogen, and/or platelets were not helpful in achieving clinically relevant levels of hemostasis, with a few **reports suggesting a benefit from rFVIIa, hemodialysis, or PCC therapy**.
- There is one report of what appears to be a dramatic response to FEIBA.

[Lindahl Tl et al. Thromb Res. 2015 Mar;135(3):544-7]

Dabigatran

- One study shows that three- and four-factor PCCs are similarly effective for dabigatran reversal. Idarucizumab also reversed the effects of dabigatran and, unlike PCCs, was not associated with over-correction of thrombin generation.

[Honickel M et al .Thromb Haemost. 2015 Apr;113(4):728-40]

Recommendations to achieve "reversal" of dabigatran in bleeding patients.

- **Pretreatment laboratory tests** (PT/ INR, PTT, TT, and a complete blood count)
- In the event of an overdose within the past 2 hours => administration of activated charcoal.
- If the patient has mild bleeding => supportive care and careful observation.

Recommendations to achieve "reversal" of dabigatran in bleeding patients.

- If the patient has life-threatening bleeding :
  - **hemodialysis** if (1) the patient's creatinine clearance is below 30 mL/min, (2) the patient has acute kidney injury, and (3) the last dose of dabigatran was more than 2 but less than 12 hours before presentation.
  - If criteria for hemodialysis are not met =>
    - delaying/ discontinuing dabigatran, fluid support (including blood product support) as needed,
    - the consideration of offlabel use of **4-factor PCC (25 units/kg, dose not to exceed 2500 units).**
    - We do not recommend redosing the 4-factor PCC, nor do we recommend providing rFVIIa or FEIBA within 24 hours of a dose of the 4-factor PCC owing to our concern for possible thromboembolic complications.

Rivaroxaban and Apixaban

- ***A rabbit model*** of rivaroxaban-induced bleeding :
  - a 4-factor PCC and recombinant factor VIIa (rFVIIa) improved coagulation laboratory studies but did not significantly reduce bleeding.
- ***A rat model*** of rivaroxaban-induced bleeding :
  - 4-factor PCC, FEIBA, and rFVIIa improved laboratory assessments of coagulation and reduced bleeding.
- ***A baboon model*** of rivaroxaban- associated bleeding :
  - potential utility of FEIBA and rFVIIa in rivaroxaban reversal.

Thrombosis Research 133 (2014) 671–681

Contents lists available at ScienceDirect

Thrombosis Research

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

Regular Article

Reversal of rivaroxaban-induced anticoagulation with prothrombin complex concentrate, activated prothrombin complex concentrate and recombinant activated factor VII *in vitro* ☆☆

Elisabeth Perzborn *, Stefan Heitmeier, Volker Laux, Anja Buchmüller

In summary, all three haemostatic agents – rFVIIa, aPCC and PCC – were partially effective in reversing rivaroxaban-induced anticoagulation. In the clotting assays, rFVIIa and aPCC had a higher reversal potential than PCC, but reversal was not complete and reached a plateau. This limited reversal effect may partly be caused by the effect of the agent itself on the measurement (by accelerating the initiation phase of coagulation), suggesting that clotting times may not correspond to the clinical effects, and clotting assays may not precisely predict the reversal potential of haemostatic agents (in particular PCC). ETP measurements may be more predictive for assessing the reversal potential of PCC or aPCC, but not of rFVIIa. Data from this study indicate that PT, CT and TG assays cannot predict the exact dose of a reversal agent required to reverse anticoagulation given a specific plasma concentration of rivaroxaban. Therefore, more studies are required to establish the safety, efficacy and clinical utility of these agents for reversing the anticoagulant effect of rivaroxaban in clinical practice.

Rivaroxaban and Apixaban

Human clinical trials :

- A randomized, placebo-controlled study of young, healthy volunteers treated with 20 mg of rivaroxaban, dosed twice daily.
  - A 4-factor PCC led to normalization of the PT and the endogenous thrombin potential.
- In vitro study using human plasma obtained from healthy donors found that :
  - rFVIIa was superior to a 4-factor PCC at normalizing laboratory coagulation studies.

[Marlu R et al. Thromb Haemost. 2012 Aug;108(2):217-24]

recommendations to achieve reversal of rivaroxaban or apixaban in bleeding patients

- Pretreatment laboratory tests (PT/INR, PTT, and a complete blood count)
- In the event of an overdose within the past 2 hours, the
- administration of activated charcoal.
- If the patient has mild bleeding => supportive care and careful observation.
- If the patient has life-threatening bleeding =>
  - delaying/discontinuing the drug in question,
  - fluid support (including blood product support) as needed,
  - off-label use of a one-time dose **of the 4- factor PCC (25 units/kg, dose not to exceed 2500 units).**
  - As with dabigatran reversal, we do not recommend redosing the 4-factor PCC, nor do we recommend providing rFVIIa or FEIBA within 24 hours of a dose of the 4-factor PCC.

Thrombosis Research 134 (2014) 909–913

Contents lists available at ScienceDirect

Thrombosis Research

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

Regular Article

Ex vivo reversal of the anticoagulant effects of edoxaban ☆

Abdel-Baset Halim [a,1], Meyer M. Samama [b,c], Jeanne Mendell [a,*]

Conclusions

Based on PT, aPTT, and anti-FXa activity, low therapeutic concentrations of rFVIIa and FEIBA showed significant and rapid reversal of the anticoagulant effects of supratherapeutic concentrations of edoxaban. However, minimal reversal was observed for intrinsic FX activity. In addition, no dose response was observed for rFVIIA or FEIBA. Further clinical studies are needed to determine the efficacy and safety of rFVIIa and FEIBA for the reversal of edoxaban-mediated anticoagulant effects in clinical practice and the optimal dosage required across different patient populations.

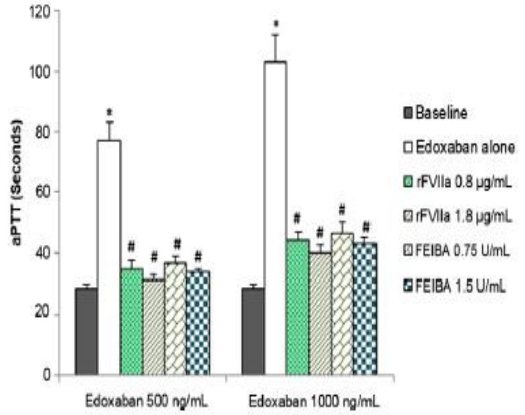


Fig. 3. Reversal of edoxaban-mediated aPTT prolongation by rFVIIa or FEIBA after 15 minutes of incubation. Error bars represent the standard deviation of the mean. aPTT, activated partial thromboplastin time; FEIBA, factor VIII bypass activity; rFVIIa, recombinant factor VIIa. *p < 0.0001 vs baseline; #p < 0.0001 vs edoxaban alone.

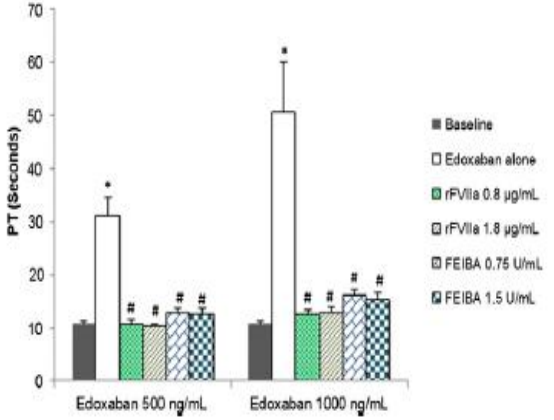


Fig. 2. Reversal of edoxaban-mediated PT prolongation by rFVIIa or FEIBA after 15 minutes of incubation. Error bars represent the standard deviation of the mean. FEIBA, factor VIII inhibitor bypass activity; PT, prothrombin time; rFVIIa, recombinant factor VIIa. *p < 0.0001 vs baseline; #p < 0.0001 vs edoxaban only.

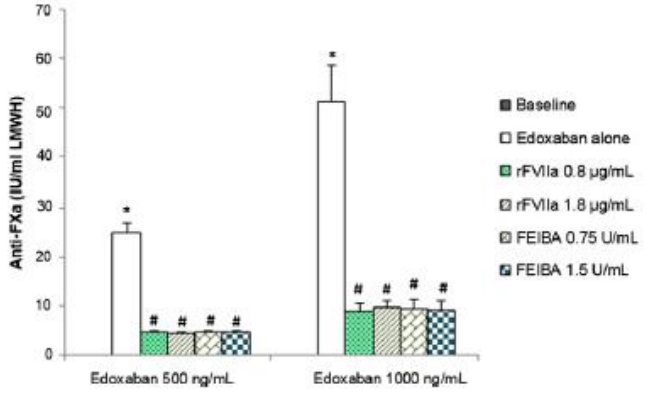


Fig. 4. Reversal of edoxaban-mediated effects on anti-FXa by rFVIIa or FEIBA after 15 minutes of incubation. Error bars represent the standard deviation of the mean. FEIBA, factor VIII inhibitor bypass activity; FXa, activated factor X; LMWH, low-molecular-weight heparin; rFVIIa, recombinant factor VIIa. *p < 0.0001 vs baseline; #p < 0.0001 vs edoxaban alone.

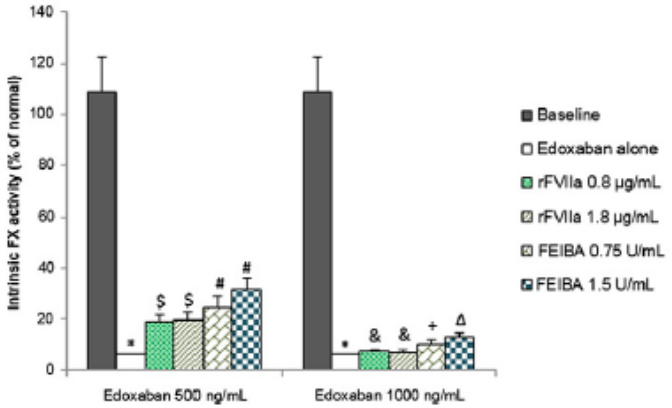


Fig. 5. Reversal of edoxaban-mediated effects on intrinsic FX activity by rFVIIa or FEIBA after 15 minutes of incubation. Error bars represent the standard deviation of the mean. FEIBA, factor VIII inhibitor bypass activity; FX, factor X; rFVIIa, recombinant factor VIIa. *p < 0.0001 vs baseline; #p < 0.0001, $p < 0.0002, Δ p < 0.0005, + p < 0.002, or &p < 0.05.

Table 1 General management of bleeding in patients on novel oral anticoagulant therapy

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Minor bleeding	Mechanical compression, interrupt anticoagulation if appropriate			
Major bleeding	IV fluids, correct anemia, thrombocytopenia, source control. Stop agent			
Activated charcoal	Yes*	Unknown	Yes*	Unknown
Hemodialysis	Yes[§]	No	No	Unknown
Antifibrinolytics	Tranexamic acid and ε-aminocaproic acid[¬]			
Plasma factors	PCC, aPCC and recombinant FVIIa			

Notes: *Activated charcoal may be useful in apixaban and dabigatran overdose if administered early, especially within 2–3 hours of ingestion; [§]dabigatran has low protein binding and can be dialyzed unlike rivaroxaban and apixaban; [¬]limited data but inexpensive and favorable safety profile.

Abbreviations: aPCC, activated prothrombin complex concentrate; FVIIa, recombinant factor VII activated; PCC, prothrombin complex concentrate; IV, intravenous.

Table 3. Considerations in the Emergent Reversal of Oral Anticoagulants in the Setting of Moderate to Severe Hemorrhage

Property/Drug	Warfarin (Coumadin, Bristol-Meyers Squibb, Princeton, New Jersey)	Dabigatran (Pradaxa, Boehringer Ingelheim Pharmaceuticals, Ridgefield, Connecticut)	Rivaroxaban (Xarelto, Janssen Pharmaceuticals Inc, Titusville, New Jersey)	Apixaban (Eliquis, Bristol-Meyers Squibb, Princeton, New Jersey)
Blood Product				
Platelets	No[a]	No[a]	No[a]	No[a]
FFP	Yes[b]	No[a]	No[a]	No[a]
Cryoprecipitate	No[a]	No[a]	No[a]	No[a]
3-Factor PCC	No	Consider[c,d]	Consider[c,d]	Consider[c,d]
4-Factor PCC	Yes[b,e]	Consider[d]	Consider[d]	Consider[d]
FEIBA	No	Consider[c,d]	Consider[c,d]	Consider[c,d]
rFVIIa	No	Consider[c,d]	Consider[c,d]	Consider[c,d]
Antifibrinolytics	No	No[d]	No[d]	No[d]
Drug Removal				
Activated charcoal	No	Recommend[f]	Recommend[f]	Recommend[f]
Hemodialysis	No	Recommend	No	No
Other Therapy				
Vitamin K	Yes[b,e]	No	No	No

Abbreviations: FEIBA, factor eight inhibitor bypass activity; FFP, fresh frozen plasma; PCC, prothrombin complex concentrate; rFVIIa, recombinant factor VIIa.

[a] The use of FFP, platelets, or cryoprecipitate may be indicated owing to blood loss, but these therapies would not be expected to be helpful as monotherapy in the reversal of the novel oral anticoagulants.

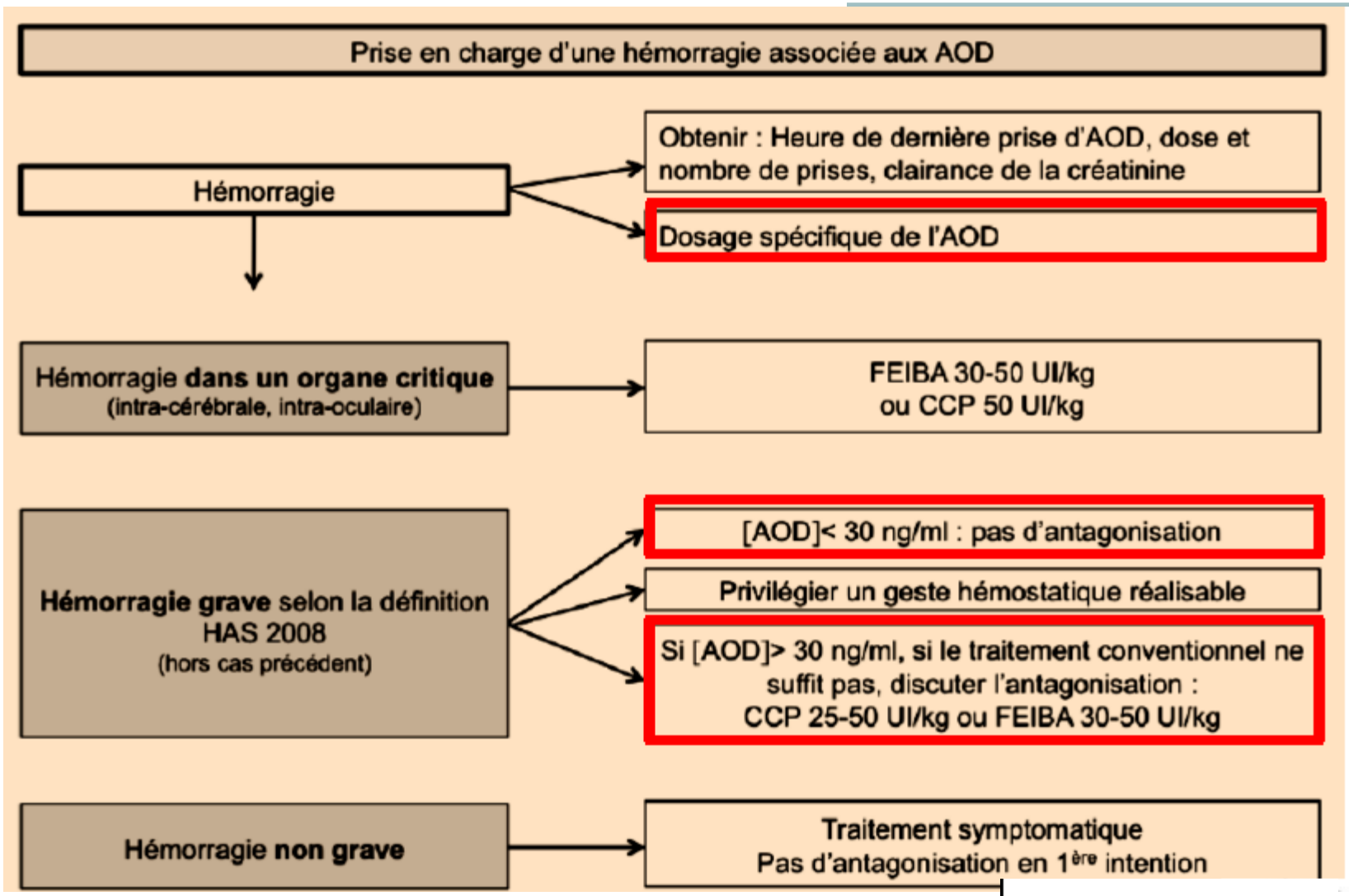
[b] Consult Guyatt et al[22] for specific recommendations.

[c] At hospitals where 4-factor PCC is not available, the blood bank may consider using a 3-factor PCC or an activated product (FEIBA or rFVIIa). For details, see Winkler and Tormey.[16] Activated factors may be more thrombogenic than the 4-factor PCC.

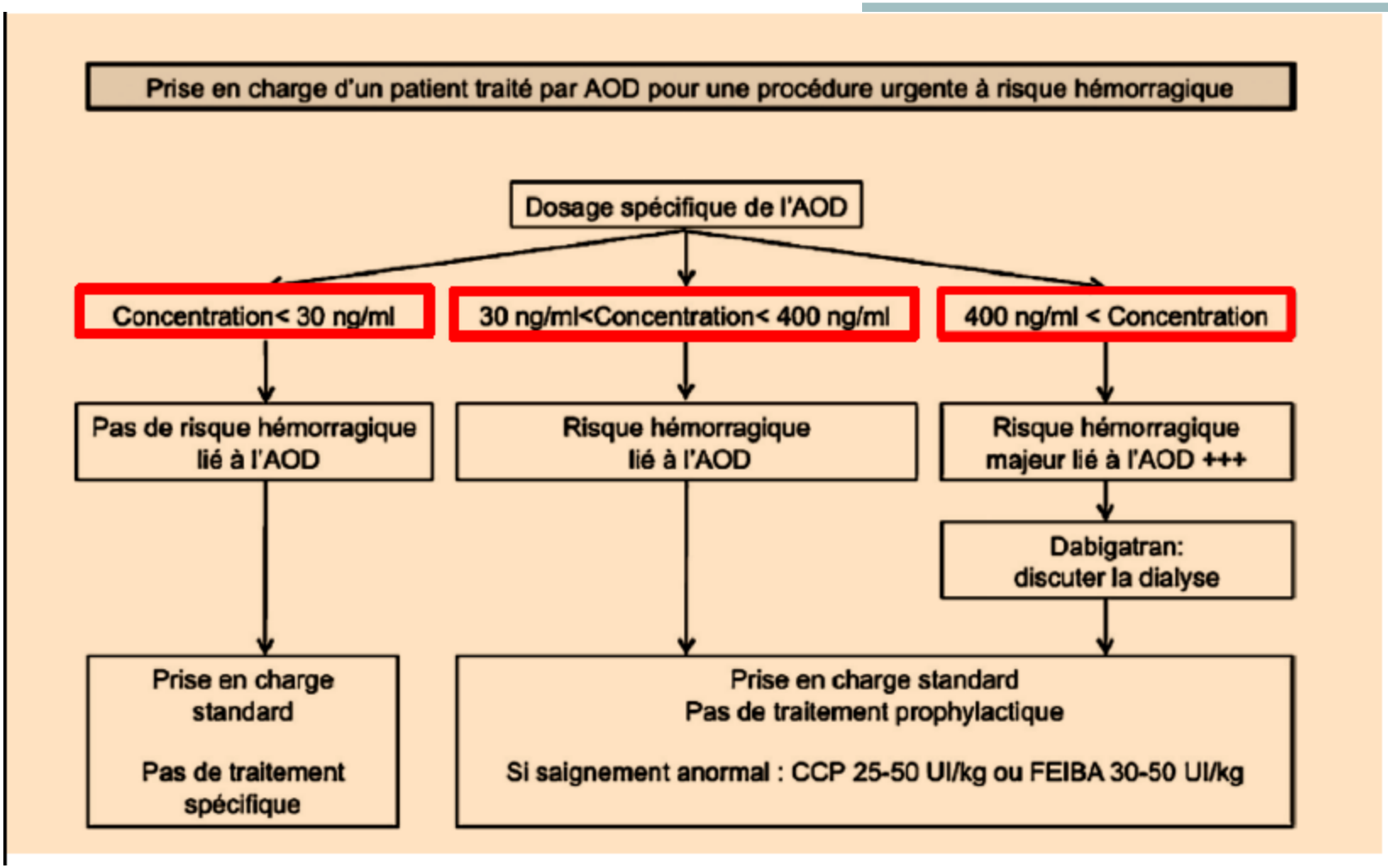
[d] To date, no clinical trial has been performed to assess the efficacy of this approach.

[e] A 4-factor PCC that is intended to be administered with vitamin K was recently approved by the US Food and Drug Administration for the purpose of treating major bleeding in patients taking vitamin K antagonists.[23]

[f] Only thought to be effective if the last dose was within 1 to 2 hours (eg, in an overdose).



GIHP Groupe d'intérêt en hémostase péri-opératoire



GIHP Groupe d'intérêt en hémostase péri-opératoire

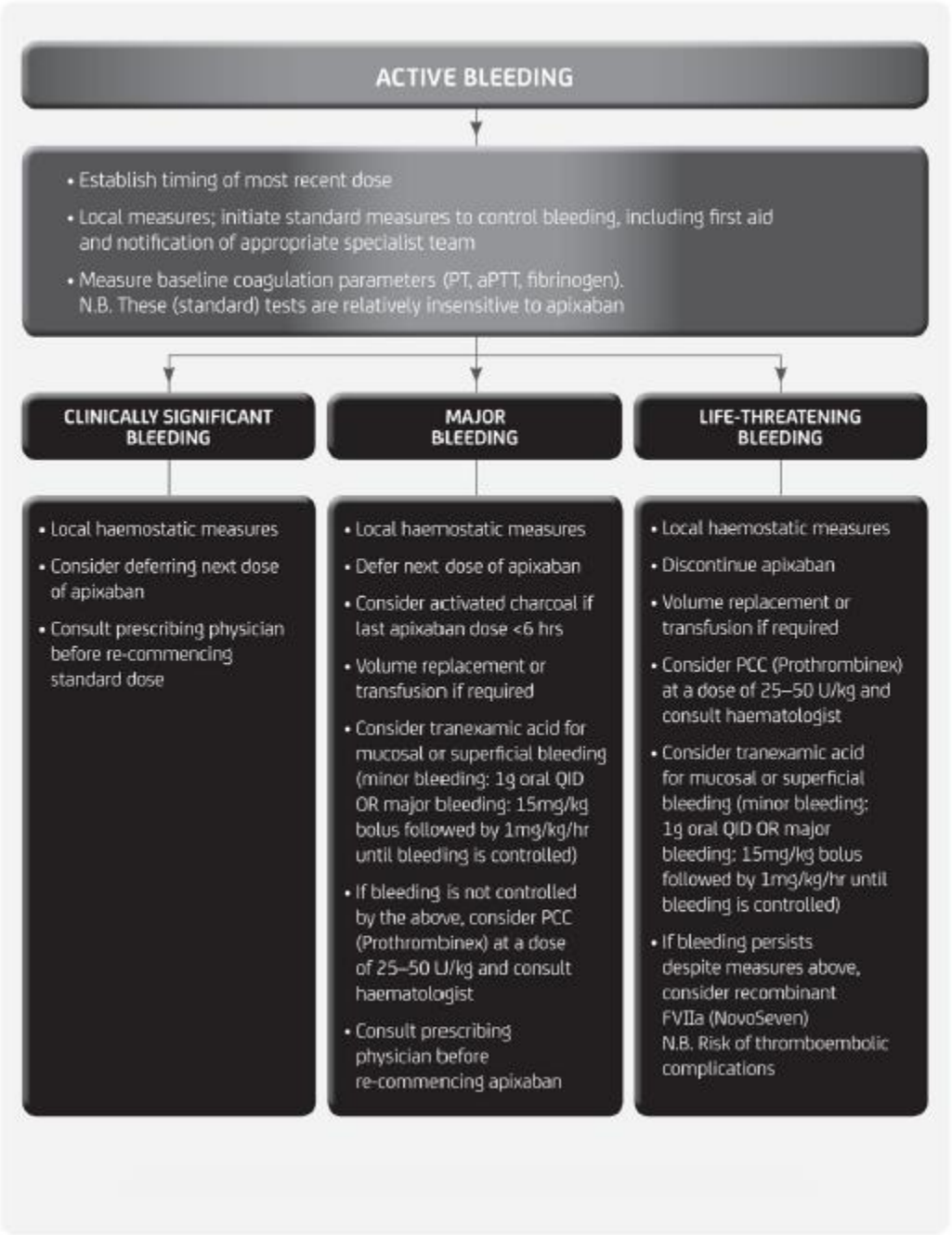
Ward et al. Thrombosis Journal 2013, 11:27
http://www.thrombosisjournal.com/content/11/1/27

THROMBOSIS JOURNAL

REVIEW Open Access

Practical management of patients on apixaban: a consensus guide

Christopher Ward[1*], Greg Conner[2], Geoffrey Donnan[3], Alexander Gallus[4] and Simon McRae[5]



1 Considerations for the management of bleeding, based on expert consensus.

Activated Prothrombin Complex Concentrates for the Reversal of Anticoagulant-Associated Coagulopathy

Nadia I. Awad, PharmD; and Craig Cocchio, PharmD, BCPS

Vol. 38 No. 11 • November 2013 • P&T®

- three-factor PCC products contain three coagulation factors (II, IX, and X)
- four-factor PCC products contain four coagulation factors (II, VII, IX and X)
- activated PCC (aPCC) products contain four coagulation factors (in inactive and activated forms)

CONCLUSION

The use of aPCC products for reversing the anticoagulant effects of dabigatran, rivaroxaban, and fondaparinux remains subject to further investigation. Conflicting preclinical evidence exists regarding the ability of aPCC products to shorten bleeding times that are prolonged by anticoagulant agents. Furthermore, the safety of aPCC products for use in off-label indications has not been adequately assessed in human subjects. Both the potential benefits, as well as the theoretical risks of thrombosis in human subjects, and the cost of these products themselves must be carefully considered.

Although conventional therapies to reverse the anticoagulant effects of warfarin are still used, novel agents will be needed as anticoagulant pharmacotherapy continues to evolve.

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Reversal of new, factor-specific oral anticoagulants by rFVIIa, prothrombin complex concentrate and activated prothrombin complex concentrate: a review of animal and human studies.

Lee FM et al. Thromb Res. 2014 May;133(5):705-13

- CONCLUSION: While preclinical studies may hint at a role for these haemostatic agents in reversing the anticoagulant effects of oral, factor-specific anticoagulants, existing trials offer **inconclusive evidence** to guide a clinical decision among individual agents with respect to **potency and thrombosis risk**.

Les antidotes

Dabigatran and idarucizumab

- Idarucizumab (aDabi-Fab, BI 655075, UNII- 97RWB5S1U6) is the first dabigatran specific antidote under study. It is a humanized monoclonal antibody fragment [Fab] that binds specifically to dabigatran (It has an affinity for dabigatran that is ~350 times greater than that of thrombin.

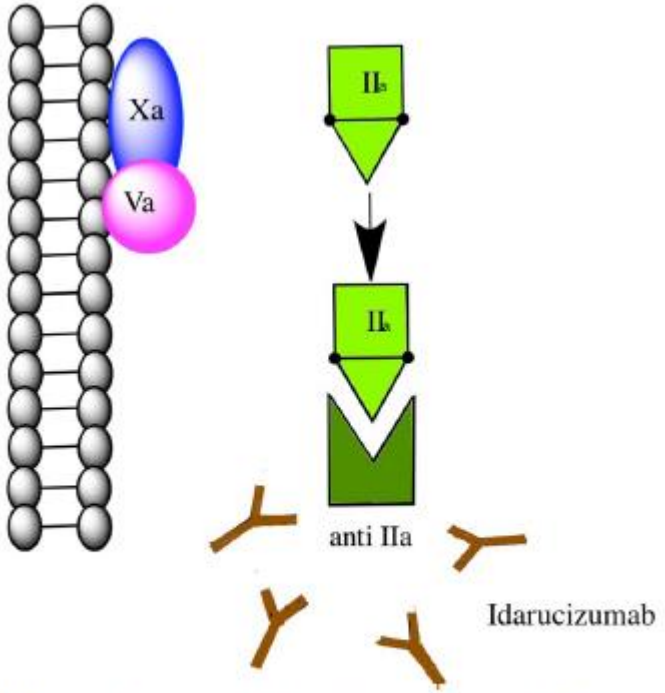


Fig. 1 Idarucizumab binds and inactivates dabigatran. Idarucizumab is the first-in-class dabigatran-specific antidote. It is a humanized monoclonal antibody fragment [Fab] that binds specifically to and inactivates dabigatran

Dabigatran and idarucizumab

- ***In ex vivo studies in rats***,
- Steady state dabigatran levels of ~200 ng were completely reversed within 1 min of an intravenous bolus of idarucizumab.
- Strong similarities were noted in the binding pattern of idarucizumab to dabigatran and thrombin to dabigatran.

Dabigatran and idarucizumab

- ***phase 1, first-in-human***,
- 110 healthy volunteers was conducted to assess the pharmacokinetics, safety and tolerability of idarucizumab .
- Idarucizumab was found to attain peak plasma levels rapidly. However its concentration decreased to 5 % or less of the peak level within 4 h secondary to renal elimination.
- It was found that it had to be dosed in **1:1 ratio with dabigatran for its complete efficacy.**
- Also of importance is the fact that it had **no impact on the coagulation profile** of subjects who received placebo.

[Glund S. Thromb Haemost. 2015;113(5):943–51. Lancet. 2015 Aug 15;386(9994):680-90].

Dabigatran and idarucizumab

- ***A phase 3 trial***
- In patients treated with dabigatran who have uncontrolled bleeding or require emergency surgeries or procedures (REVERSE AD trial) [Pollack CV. Curr Drug Saf. 2015;10:PMID 25877809.- Am J Emerg Med. 2012;30(9):2046–54].
- Showed that the anticoagulant effect of dabigatran was **completely reversed within minutes** by idarucizumab.

An interim analysis (90 patients)

- The primary end point of this study was the maximum percentage reversal of the anticoagulant effect of dabigatran within 4 h after the administration of 5 g of IV idarucizumab.

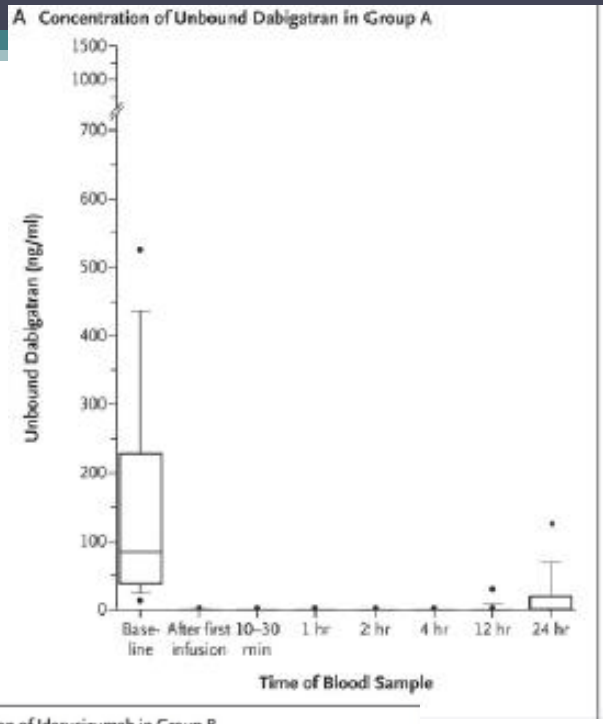
- This was determined by measuring the dilute thrombin time (elevated in 68 patients in the analysis) or ecarin clotting time (elevated in 81 patients) at a central laboratory.

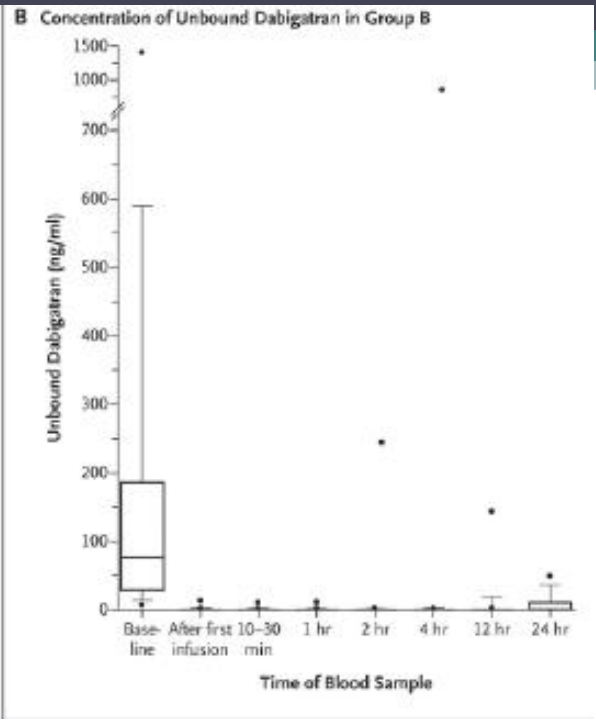
- The median maximum percentage reversal was 100 % (95 % confidence interval, 100–100) in these patients with elevated coagulation profile.

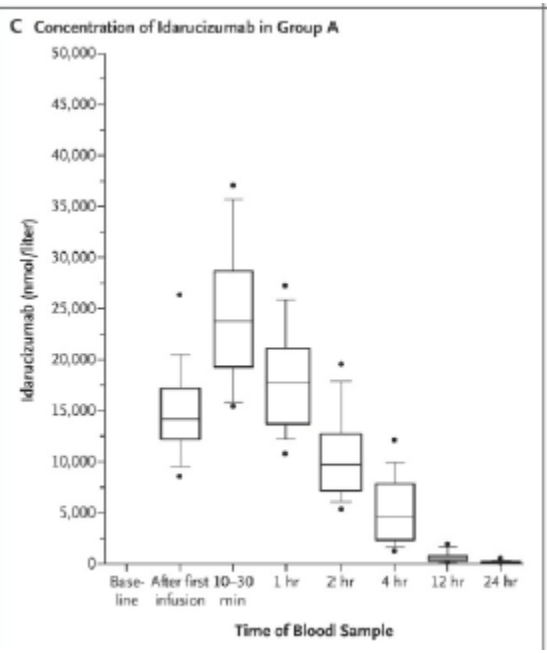
[Pollack CV. N Engl J Med. 2015;373:511–20].

Figure 2. Time Courses of Plasma Concentrations of Unbound Dabigatran and Idarucizumab before and after the Administration of Idarucizumab.

The analyses included 51 patients who had serious bleeding (group A; Panels A and C) and 39 who required urgent surgery or intervention (group B; Panels B and D). Data are







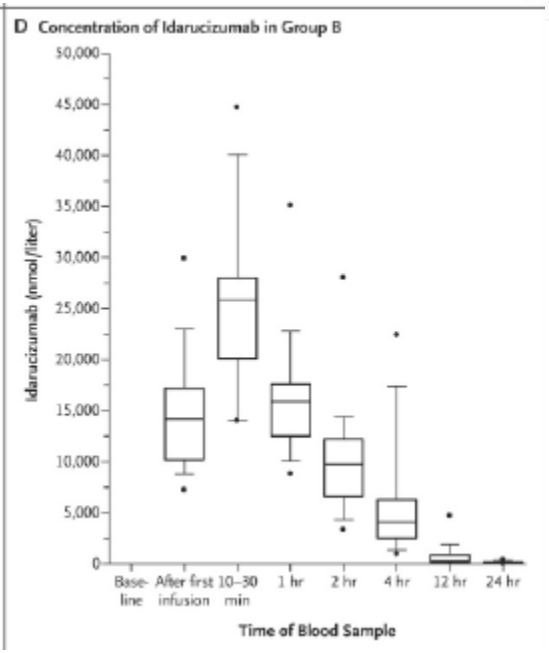
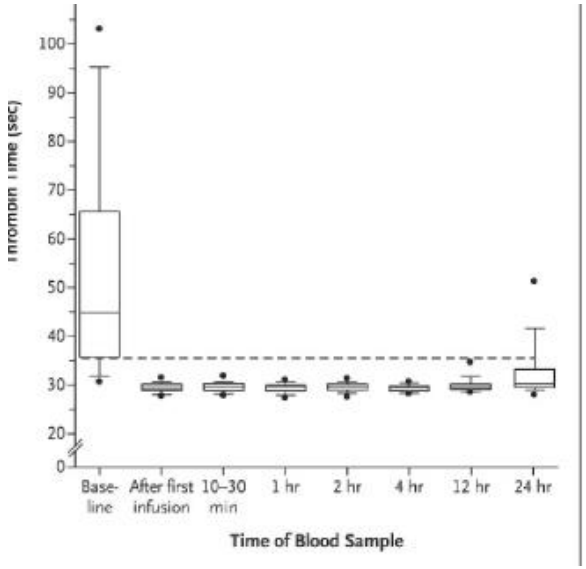
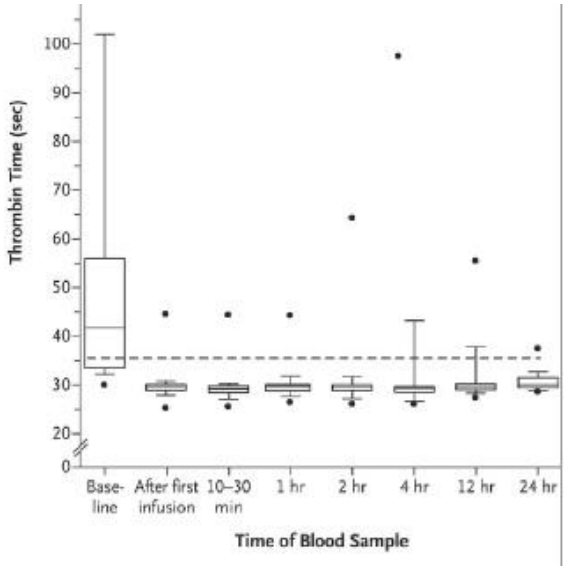
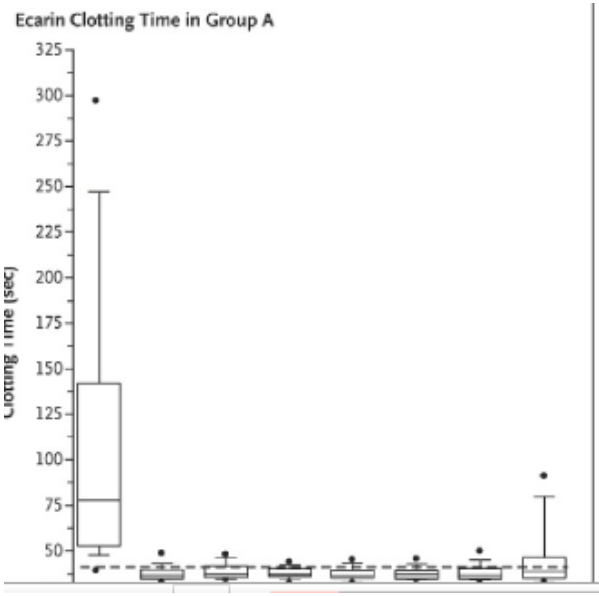


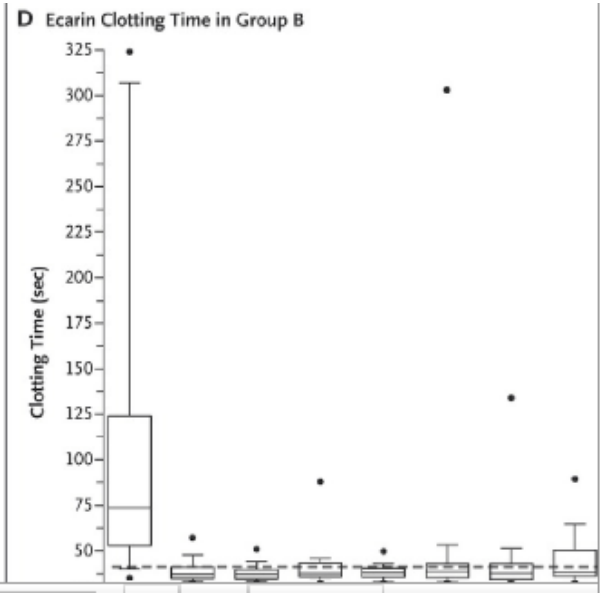
Figure 1. Time Course of the Dilute Thrombin Time and Ecarin Clotting Time before and after the Administration of Idarucizumab.

The analyses included 51 patients who had serious bleeding (group A; Panels A and C) and 39 who required urgent surgery or intervention (group B; Panels B and D). Idarucizumab









Dabigatran and idarucizumab

- In conclusion, this study shows that three- and four-factor PCCs are similarly effective for dabigatran reversal. Idarucizumab also reversed the effects of dabigatran and, unlike PCCs, was not associated with over-correction of thrombin generation.

[Honickel M et al .Thromb Haemost. 2015 Apr;113(4):728-40]

Idarucizumab was US FDA approved in October 2015.

Safety and adverse events

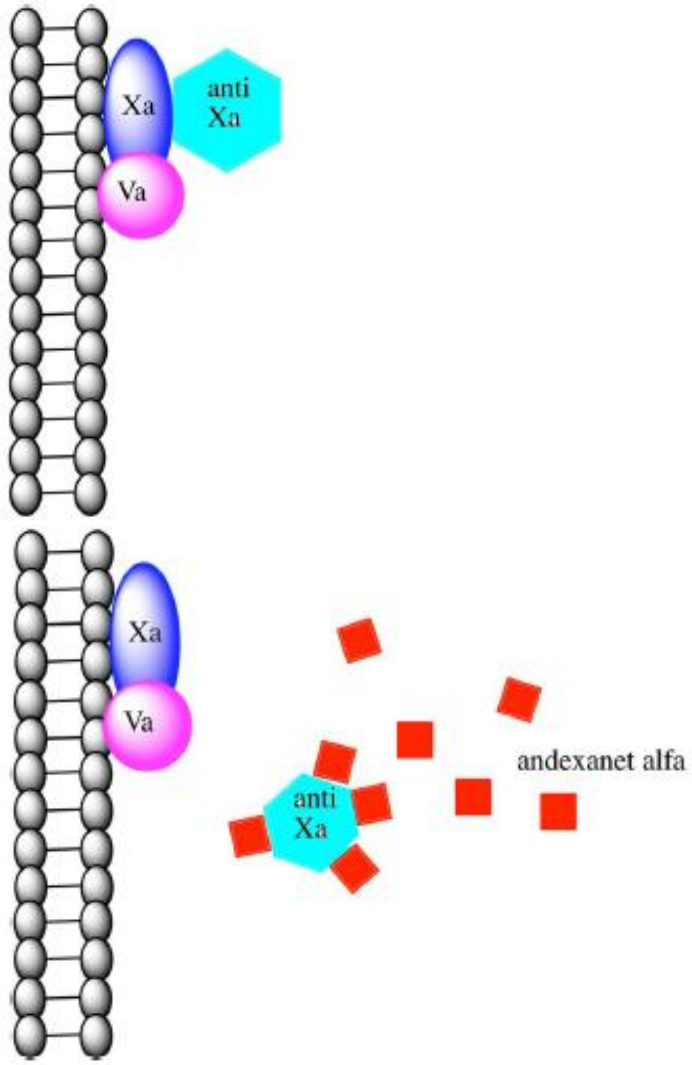
- In the interim analysis of the Phase III study, thrombotic events occurred in five patients. None of the patients were receiving anticoagulant therapy at the time of thrombotic event. In the absence of a placebo group, it is not possible to link these events to idarucizumab administration. The data from Phase I studies are reassuring with regard to the safety of idarucizumab. **Postmarket surveillance will be vital to identify currently unknown adverse events**.

Factor Xa inhibitors and andexanet alfa

- Andexanet alfa (PRT064445, r-Antidote; Portola Pharmaceuticals) is a 39 kDa, recombinant modified decoy of Factor Xa produced in Chinese hamster ovary cells. The amino acid serine is replaced by alanine at position 419.

- This recombinant protein retains the ability to bind direct FXa inhibitors as well as antithrombin activated by low molecular weight heparin or fondaparinux

[Gomez-Outes A. Recent Pat Cardiovasc Drug Discov. 2014;9(1):2–10.].



Factor Xa inhibitors and andexanet alfa

- ***In a rabbit model,***
- andexanet alfa was found to reverse the action of direct Factor Xa inhibitors in a dose dependent manner.

[Lu G. Nat Med. 2013;19(4):446–51.].

Factor Xa inhibitors and andexanet alfa

- ***The phase II studies***
- In healthy subjects : bolus dose of andexanet α antagonized the anti-Xa activity of apixaban and rivaroxaban (5 mg twice daily, 11 doses) with a decrease in activity of Factor Xa by 53 and 20 % respectively.

Crowther M KM. J Thromb Haemost. 2013;11(Suppl 2): AS20.1.
Crowther M LG. J ThrombHaemost. 2014;12(Suppl 1): COA01 (abstract).
Crowther M LG. Eur Heart J 2014;35(Suppl.1): P738 (abstract).
Crowther MMV. Blood 2013;122(21):3636.

Factor Xa inhibitors and andexanet alfa

- **Phase III trials** are ongoing to evaluate the safety and efficacy of andexanet alfa in reversing apixaban-(ANNEXA-A study) and rivaroxaban-(ANNEXA-R study) induced anticoagulation in healthy volunteers.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity

Deborah M. Siegal, M.D., John T. Curnutte, M.D., Ph.D., Stuart J. Connolly, M.D., Genmin Lu, Ph.D., Pamela B. Conley, Ph.D., Brian L. Wiens, Ph.D., Vandana S. Mathur, M.D., Janice Castillo, B.S., Michele D. Bronson, Ph.D., Janet M. Leeds, Ph.D., Florie A. Mar, Ph.D., Alex Gold, M.D., and Mark A. Crowther, M.D.

N ENGL J MED 373;25 NEJM.ORG DECEMBER 17, 2015

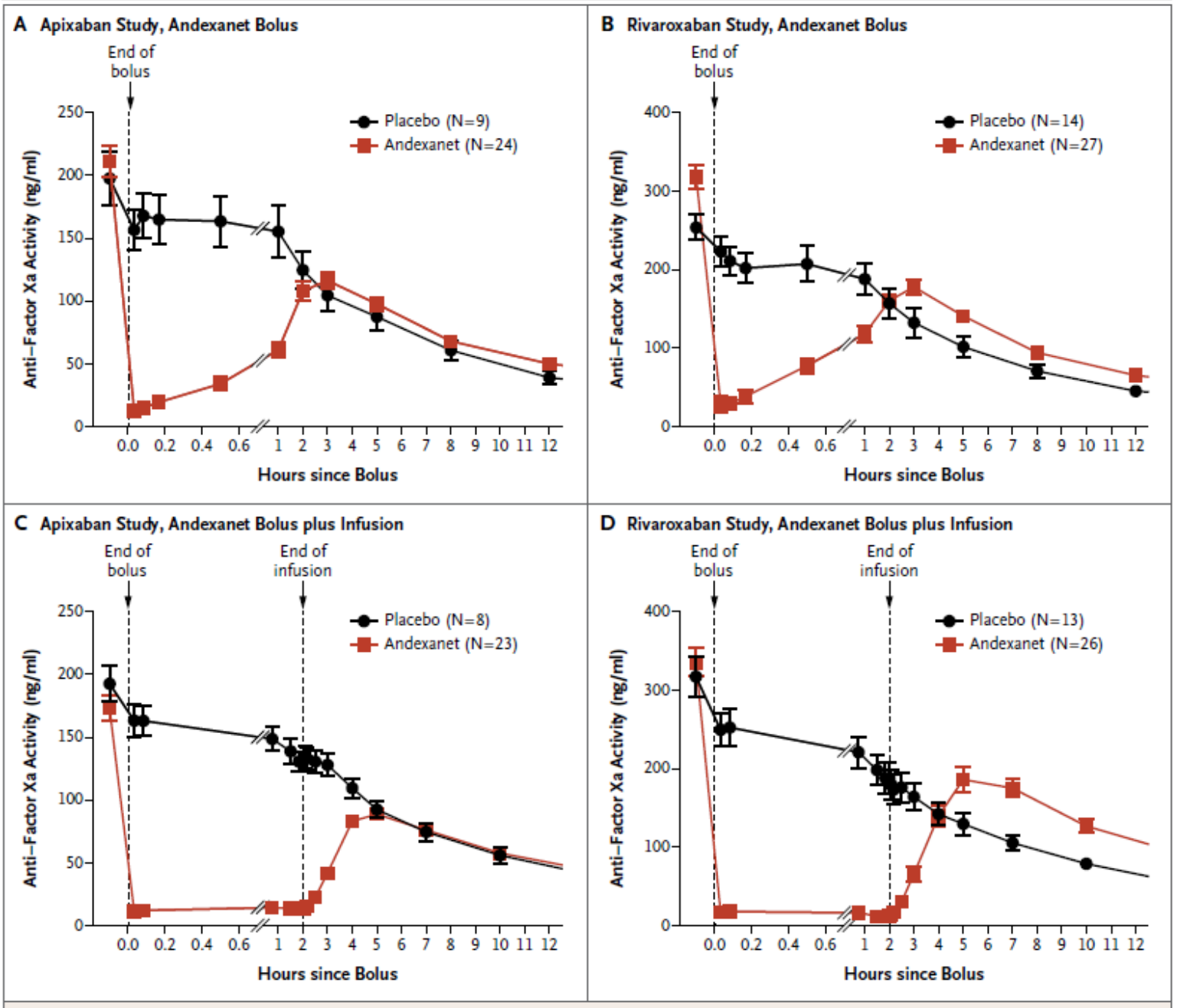


Figure 1. Time Courses of Anti–Factor Xa Activity before and after Administration of Andexanet.

In conclusion, andexanet is a specific, rapidly acting antidote that is being developed for urgent reversal of factor Xa inhibitor anticoagulant activity. In our studies, andexanet rapidly restored factor Xa activity and thrombin generation and reduced unbound factor Xa inhibitor concentrations in apixaban-treated and rivaroxaban-treated older participants. The reversal of anticoagulation with andexanet was not associated with safety concerns or thrombotic events. The ability of andexanet to reverse anticoagulation markers in participants undergoing anticoagulation with apixaban, rivaroxaban, edoxaban, or enoxaparin makes it a potential universal antidote for both direct and indirect factor Xa inhibitors.[8-11] The rapid onset and offset of action of andexanet and the ability to administer it as a bolus or as a bolus plus an infusion may provide flexibility with regard to the restoration of hemostasis when urgent factor Xa inhibitor reversal is required. The ongoing ANNEXA-4 phase 3b–4 study (ClinicalTrials.gov number, NCT02329327) is evaluating the efficacy and safety of andexanet in patients with factor Xa inhibitor–associated acute major bleeding.

Andexanet alfa is undergoing review for FDA approval.

Target specific oral anticoagulants and PER977

- PER977 (arapazine, ciraparantag; Perosphere Inc.) is a small, 512 Da, synthetic, water soluble molecule that binds to direct inhibitors of factor Xa and IIa as well as to heparin-based anticoagulants through non-covalent hydrogen bonding and charge interactions.
- It is reported to antagonize the effects of all anticoagulants except VKAs and agratroban.

[Gomez-Outes A. Recent Pat Cardiovasc Drug Discov. 2014;9(1):2–10.].

Target specific oral anticoagulants and PER977

- ***In an animal model***, rats were overdosed with rivaroxaban, apixaban, edoxaban and dabigatran. PER977 was noted to reduce bleeding within 30 min of administration.

[Bakhru S. Ciuculation. 2013;128:A18809.].

Target specific oral anticoagulants and PER977 Ciraparantag

- **In the first human trial of PER977** (NCT01826266),
- It was tested on 80 volunteers who were either untreated or pretreated with 60 mg of edoxaban.
- the pharmacokinetics and pharmacodynamics were studied with escalating doses of PER977 (100–300 mg).
- A dose of intravenous bolus of 300 mg PER977 was found to normalize whole blood clotting time within 10–30 min and the effect was sustained for over 24 h.

[Ansell JE. N Engl J Med. 2014;371(22):2141–2.].

Use of PER977 to Reverse the Anticoagulant Effect of Edoxaban

NEJM371;22 november 27, 2014

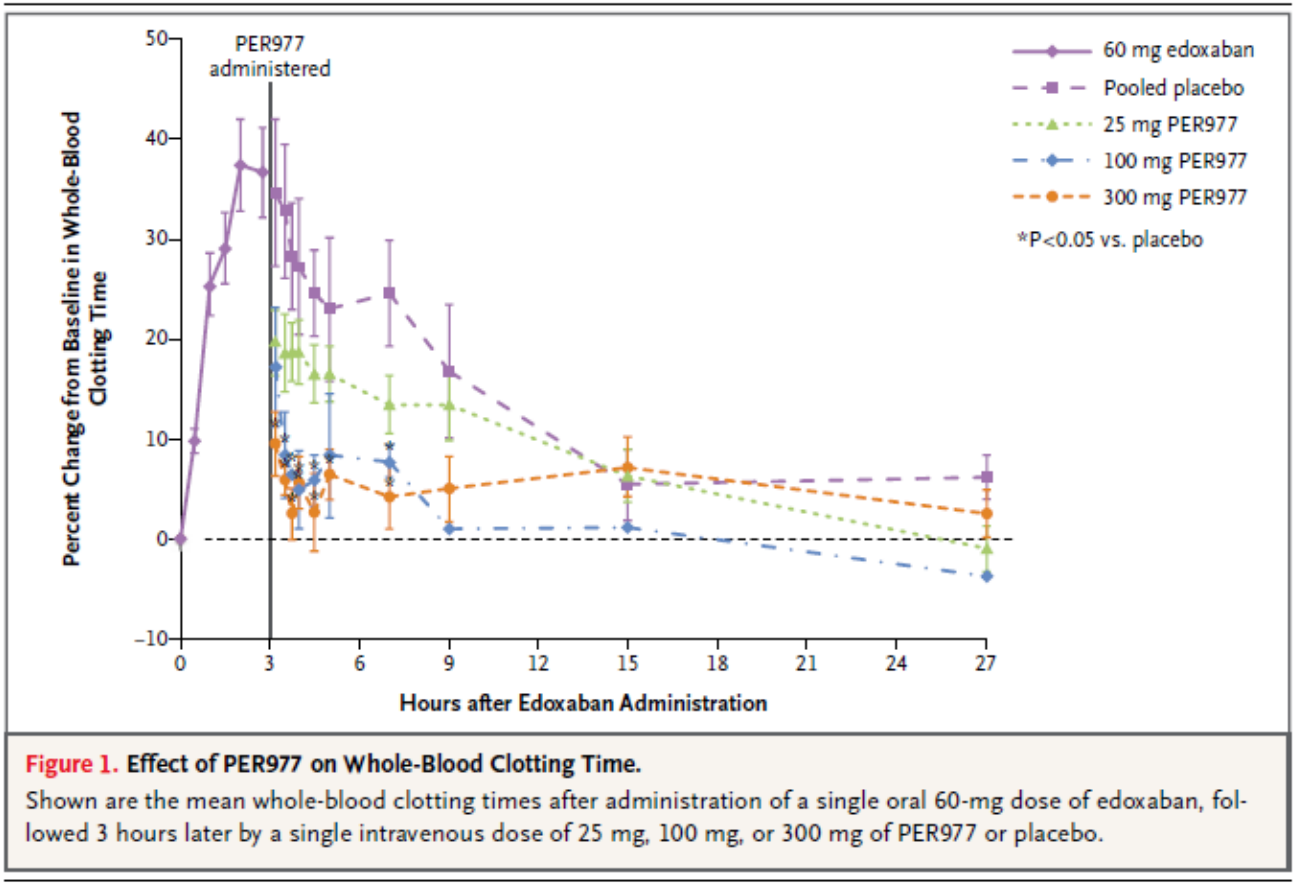


Figure 1. Effect of PER977 on Whole-Blood Clotting Time.

Shown are the mean whole-blood clotting times after administration of a single oral 60-mg dose of edoxaban, followed 3 hours later by a single intravenous dose of 25 mg, 100 mg, or 300 mg of PER977 or placebo.

Vascular Health and Risk Management

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REVIEW

Reversing anticoagulant effects of novel oral anticoagulants: role of ciraparantag, andexanet alfa, and idarucizumab

Vascular Health and Risk Management 2016:12 35–44

Conclusion

- **Postmarket surveillance will be vital to identify currently unknown adverse events.**
- **Ceci est valable aussi bien pour les nouveaux ACO et leur antidote.**