Terapie Anticoagulanti
Evidenze ed Opinioni a confronto
Cremona, 4 Marzo 2016

Agenti antiemorragici

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Quante complicanze emorragiche aspettarsi con i farmaci anticoagulanti orali ?

Bleeding risk for patients on OAT

- Major bleeding 1- 5 % pt/year
- Fatal 0 - 0.5% pt/ year (up to 1-5% pt/year in some studies)
- Correlation with INR and duration; x 2-3 first months
- Occult anatomical reasons
- Concomitant drugs
- Major bleeding: > 75 year old 5.1% pt/year
  young 1% pt/year

THROMBOSIS AND HEMOSTASIS

Rates, management, and outcome of rivaroxaban bleeding in daily care: results from the Dresden NOAC registry

BLEEDING RATES PER 100 PATIENT-YEARS

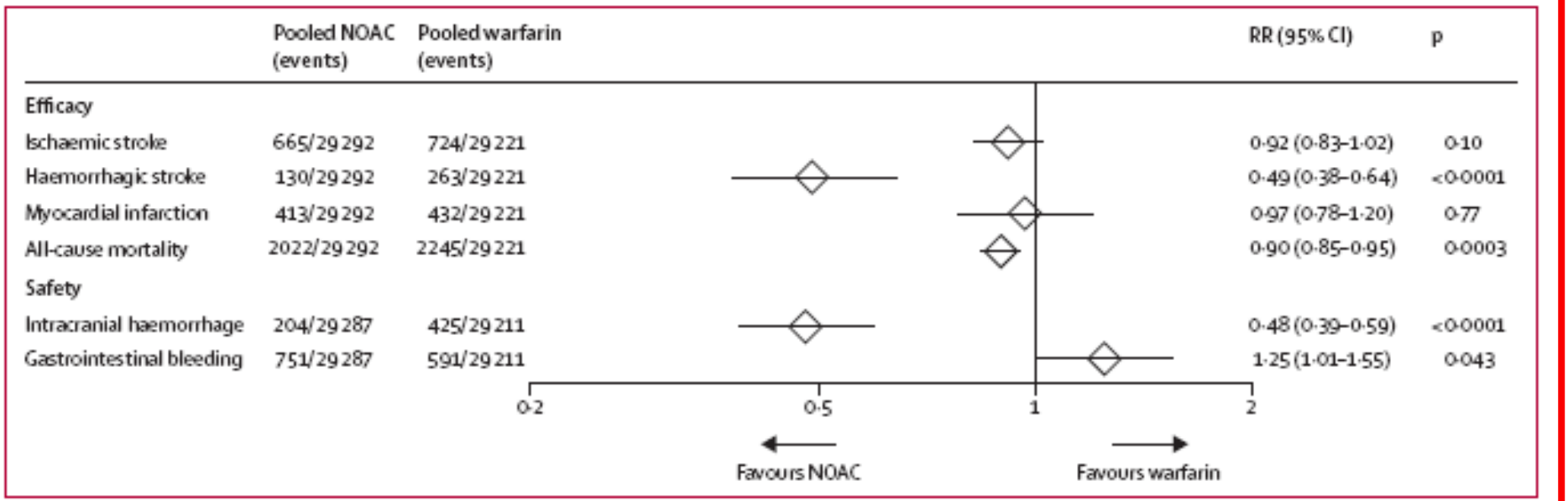
	All patients	SPAF	VTE	*P* value: SPAF vs VTE
n (%)	1775 (100)	1200 (67.6)	575 (32.4)	
Any bleeding, % (95% CI)	59.4 (55.2-63.9)	59.3 (54.4-64.6)	59.6 (51.7-68.4)	.4989
Minor bleeding, % (95% CI)	36.3 (33.2-39.7)	35.8 (32.2-39.7)	37.8 (31.8-44.6)	.4199
NMCR bleeding, % (95% CI)	19.7 (17.6-22.1)	20.7 (18.1-23.5)	17.2 (13.5-21.6)	.1585
Major bleeding, % (95% CI)	3.4 (2.6-4.4)	3.1 (2.2-4.3)	4.1 (2.5-6.4)	.2849

Beyer-Westendorf J, Blood 2014

Quali complicanze emorragiche aspettarsi con i farmaci anticoagulanti orali ?

Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials

SICUREZZA ED EFFICACIA



REVERSIBILITA' DELL'EFFETTO ANTICOAGULANTE AVK (ANTIDOTI /ANTIEMORRAGICI)

AZIONE	EFFETTO
Sospensione TAO	3-7 gg
Vit.K x os	24 ore
Vit.K ev	10-12 ore
Plasma Fresco congelato	3-6 ore
CCP	5 minuti

PLASMA FRESCO CONGELATO (FFP)

- Contiene tutti i fattori vit.K dipendenti
- E' "l'antidoto" più utilizzato negli USA
- Presenta molti importanti limiti:
  - Ritardo per test di compatibilità AB0, riscaldamento, tempo di infusione
  - Richiede volumi notevoli con rischio di sovraccarico
  - Pericolo di reazioni allergiche
  - Rischio di Transfusion-Related Acute Lung Injury
  - Emodiluizione con aggravamento del sanguinamento

CONCENTRATI DEL COMPLESSO PROTROMBINICO (CCP)

Emoderivati ottenuti da un pool di plasma di donatori, in cui sono concentrati in piccoli volumi FII, FIX, FX, ± FVII

Caratteristiche principali:

- Effetto è immediato
- Infusione rapida (8 ml/ min)
- Effetti avversi rari
- Virus-inattivati

CCP SONO SCARSAMENTE USATI :

Timori di complicanze trombotiche, mancanza di disponibilità immediata, non conoscenza

(Dentali F . et al, JTH 2006)

Efficacy and Safety of a 4-Factor Prothrombin Complex Concentrate in Patients on Vitamin K Antagonists Presenting With Major Bleeding

A Randomized, Plasma-Controlled, Phase IIIb Study

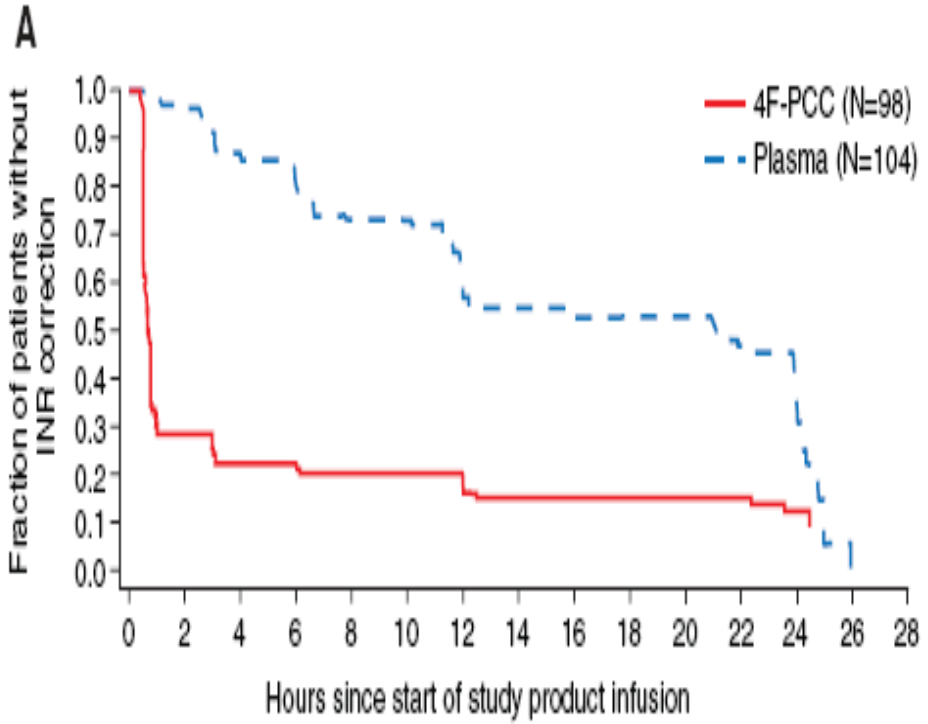
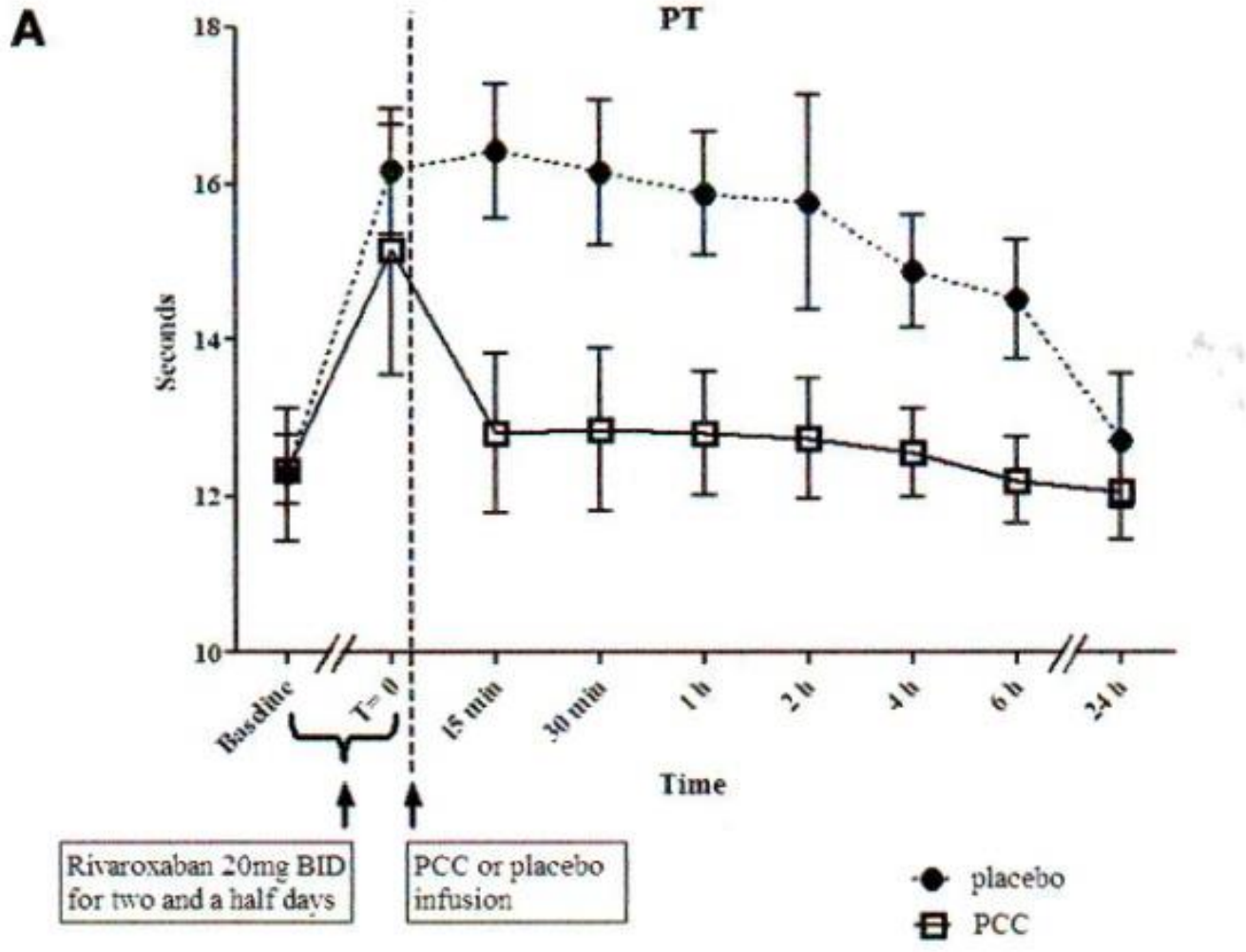


Table 7. Rapid INR Reduction (Intention-to-Treat Efficacy Population)

	No. (%) of Patients [95% CI]		
	4F-PCC (n=98)	Plasma (n=104)	Difference 4F-PCC Minus Plasma, % (95% CI)
Rapid INR reduction*	61 (62.2) [52.6 to 71.8]	10 (9.6) [3.9 to 15.3]	52.6† (39.4 to 65.9)

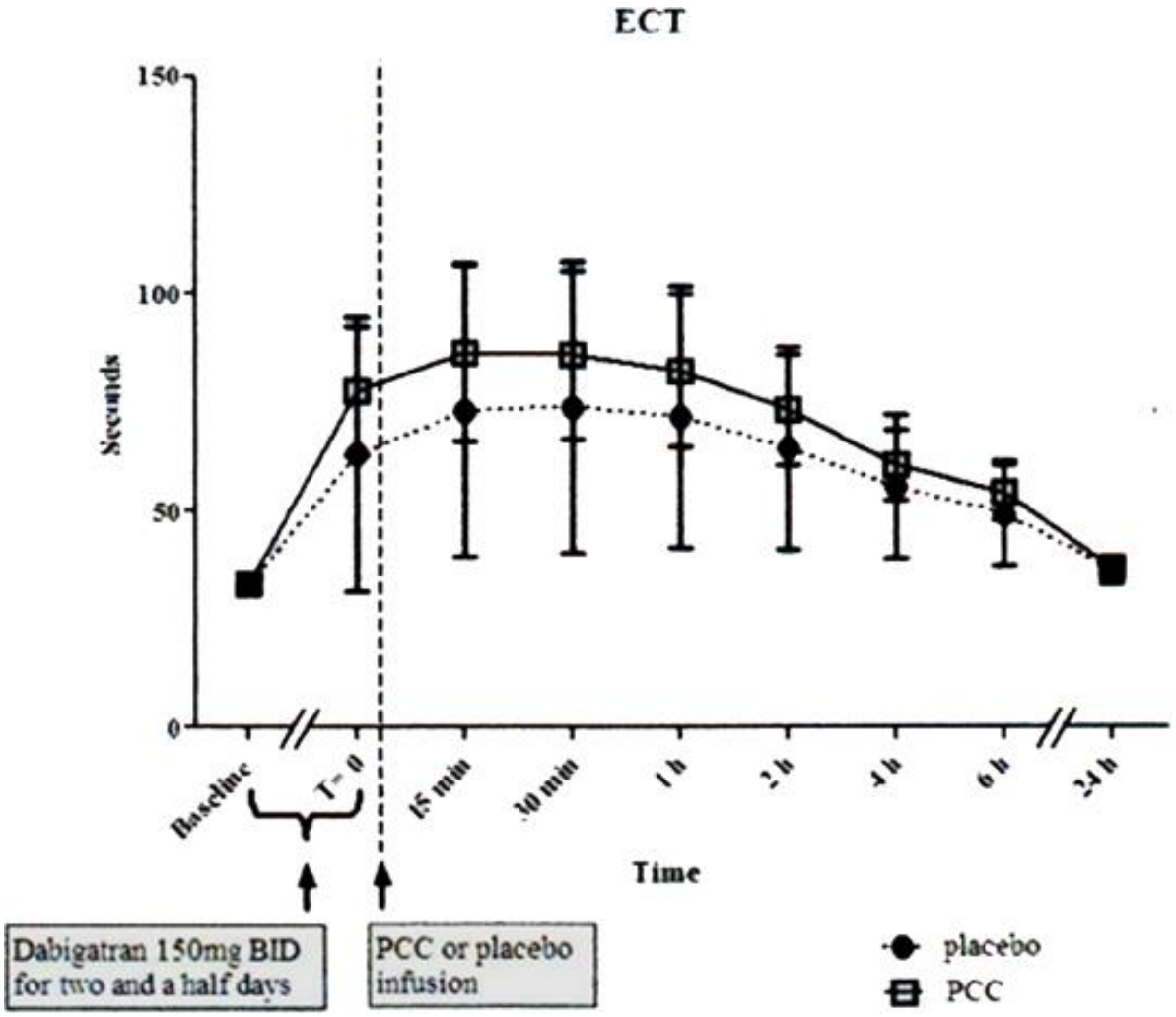
Sarade R et al, Circulation 2013

Four-factor PCC reverses rivaroxaban



Eeremberg ES. et al. Circulation 2011

Four-factor PCC does not reverse dabigatran



Eeremberg ES. et al. Circulation 2011

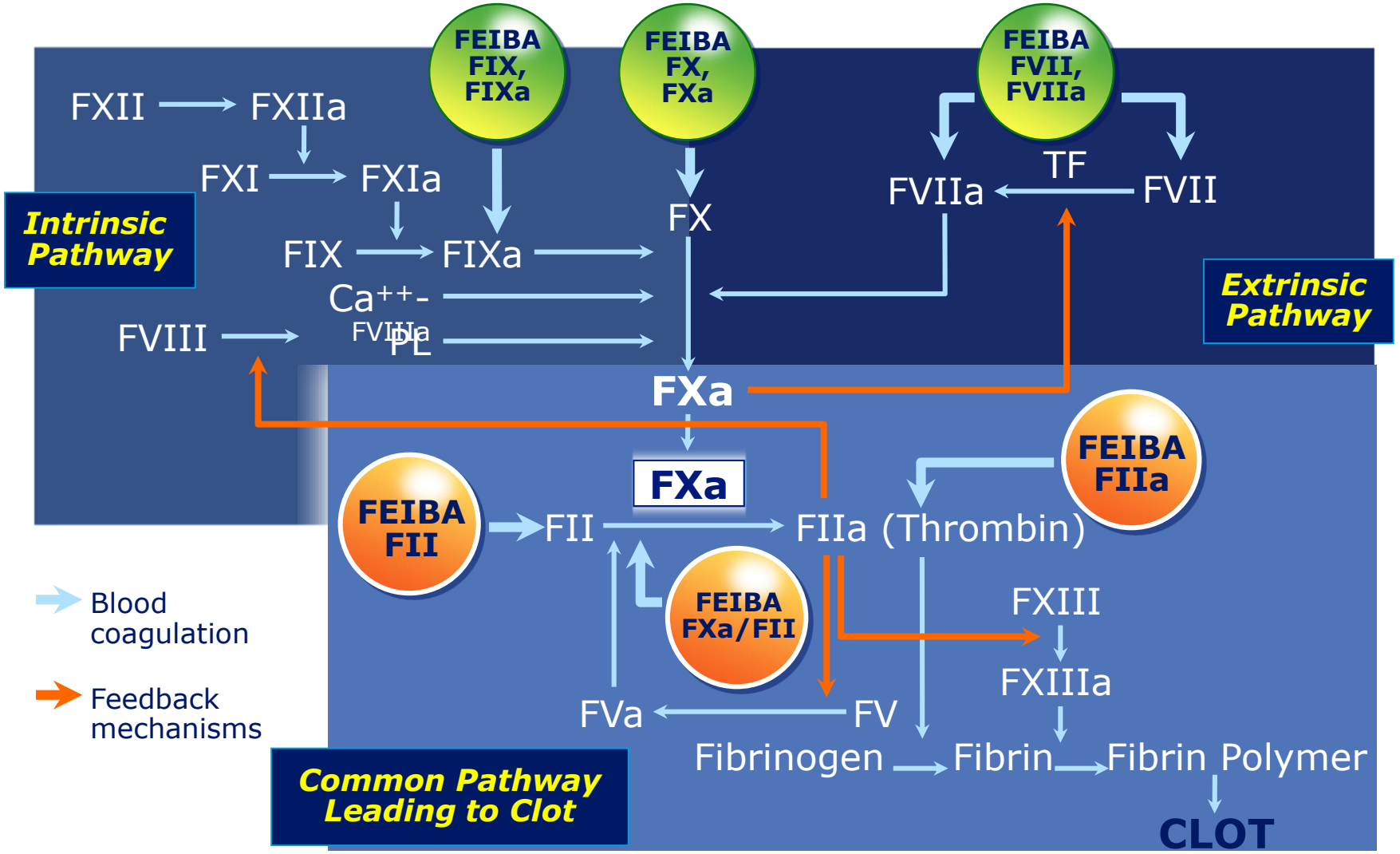
Emergenza in corso di terapia con dabigatran

- Se ultima dose < 2 hr somministare carbone attivo e/o gastrolusi

- Plasma, PCC, rFVII non hanno effetto dimostrato a migliorare i tempi di coagulazione

- Emodialisi
- APCC (25-50 U/kg) possibilmente efficace?

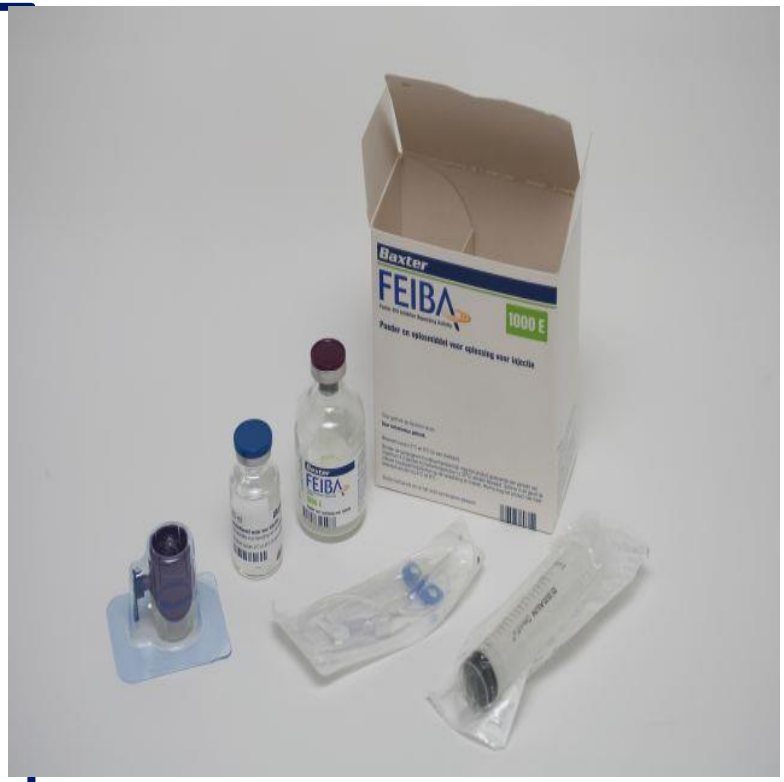
FEIBA® : Sites of Action



Turecek PL et al. Vox Sang 1999; 77 (suppl 1): 72-79.

FEIBA® : Factor Eight Inhibitor Bypass Activity

- FEIBA® contains mainly **non-activated factors II, IX, and X** and mainly **activated factor VII** and 1 to 6 U/ml **FVIII**
- 1000 U/20 mL, dose standard (50 U/kg) ~ 80 mL
- **Thrombotic risk**
  - Ehrlich 2002: 4 thrombotic AE per 100,000 FEIBA® infusions (**81% previous thrombotic risk factors, 50% used overdose**)
  - Aledort 2004: 8.24 thrombotic AE per 100,000 FEIBA® infusions
  - Berg 2014: 70 thrombotic and embolic events reported in global safety database (1975–2013)



FEIBA™ for Reversal of Direct Oral Anticoagulant Associated Major Bleeding

Patient (Age and Gender)	Indication for DOAC	DOAC and Dosage	Site of Bleeding	Intervention/ Procedure	Units of RBCs Transfused	Additional Treatment	FEIBA™ Dose (IU) (1st/2nd)	Adverse Events post-FEIBA™	Survived Hospitalization
85 Male	AF (2)	Rivaroxaban 20 mg daily	Epistaxis	Nasal Packing	0	--	3275	--	Yes
86 Male	AF (2)	Rivaroxaban 20 mg daily	LGIB	Angiogram, no embolization performed	10	Vitamin K	3159/ 2952	--	Yes
84 Male	AF (2)	Dabigatran 110 mg BID	Orbital vitreous hemorrhage	Surgical repair of ruptured globe	0	--	1812	--	Yes
92 Male	AF (6)	Apixaban 5 mg BID	Left hand	Conservative management	1	Tranexamic acid	2718	TIA	Yes
85 Male	VTE	Rivaroxaban 20 mg daily	LGIB	Conservative management	2	Vitamin K	1740	--	Yes
90 Female	AF (5)	Rivaroxaban 20 mg daily	SDH	Conservative management	0	--	3275	--	No; died of major bleed
93 Female	AF (6)	Apixaban 2.5 mg BID	LGIB	Conservative management	4	--	2241	--	No
93 Male	AF (3)	Rivaroxaban 15 mg daily	UGIB	Upper endoscopy, no intervention	4	Vitamin K	3000	--	No; died of major bleed and septic shock
81 Male	AF (4)	Dabigatran 110 mg BID	LGIB	Upper endoscopy and colonoscopy, no interventions	4	--	3362	--	No

Shaw et al, ASH 2014

Bleeding and antidotes in new oral anticoagulants

Ammar Majeed, MD [a], Sam Schulman, MD, PhD [a,b,c,*]

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[b] *Department of Medicine, McMaster University, Hamilton, ON, Canada*
[c] *Thrombosis and Atherosclerosis Research Institute, Hamilton, ON, Canada*

- **Idarucizumab (Praxbind):** antidoto specifico per il dabigatran (frammento di anticorpo monoclonale-Fab), alta affinità di legame, rapidità di azione dose-dipendente, durata dell'effetto 6 ore dopo somministrazione ev. Registrato in USA e Europa
- **Andrexanet alfa:** antidoto universale degli inibitori del Fxa, proteina ricombinante simile al FXa che si lega ai farmaci anti-Xa con effetto rapido e durata d'azione fino a 3 ore (studi di fase II)
- **Ciraparantag (PER977):** piccola molecola sintetica (Perosphere Inc) che si lega a diversi NOA, compreso dabigatran, rivaroxaban, apixaban e edoxaban

Best Practice & Research Clinical Haematology 26 (2013) 191–202

The NEW ENGLAND JOURNAL of MEDICINE

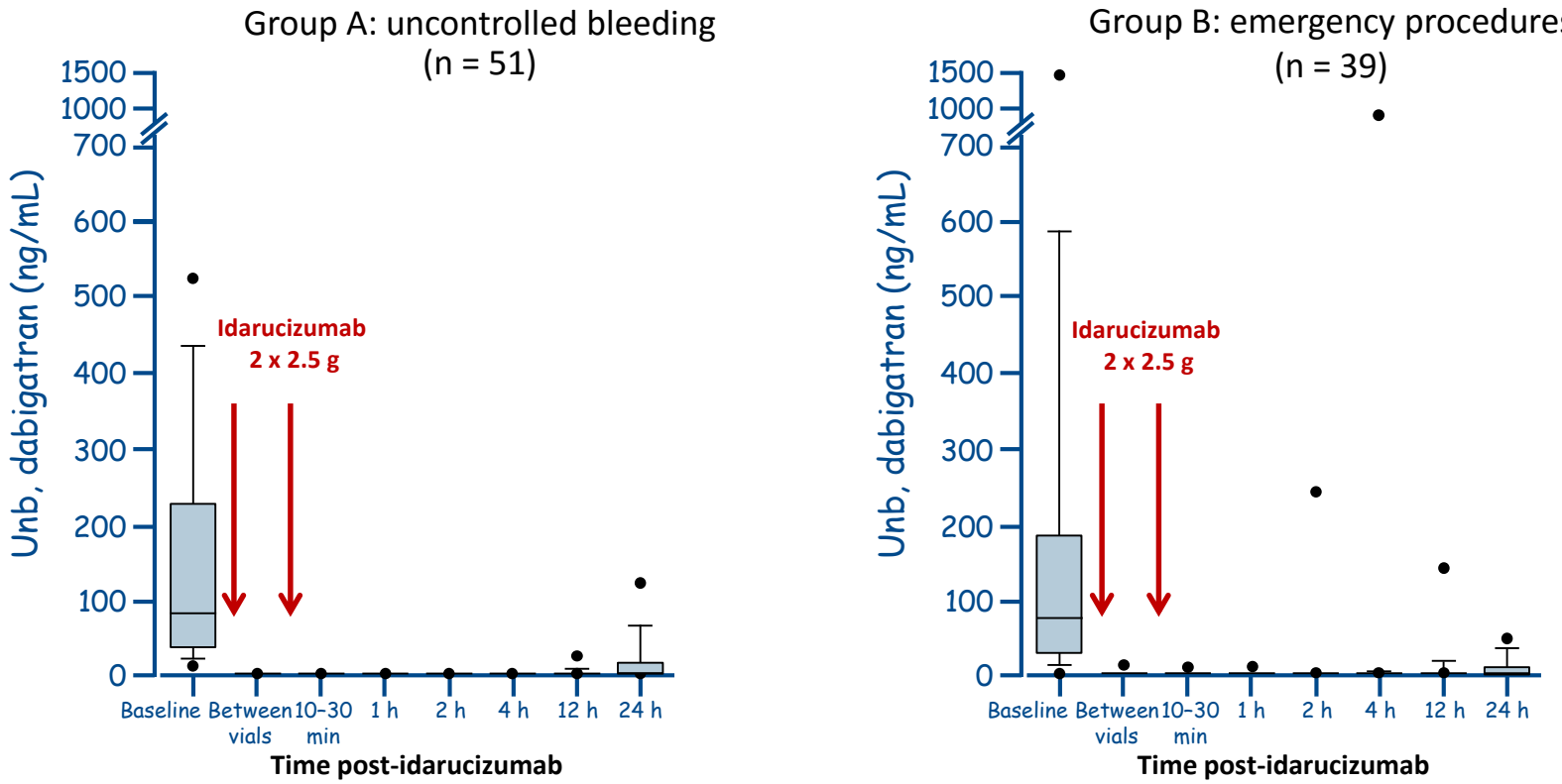
ORIGINAL ARTICLE

Idarucizumab for Dabigatran Reversal

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Peter Verhamme, M.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D., Frank W. Sellke, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., M.M.E., Bushi Wang, Ph.D., Chak-Wah Kam, M.D., and Jeffrey I. Weitz, M.D.

Re-verse AD trial: Idarucizumab reverses the anticoagulant effects of dabigatran in patients in an emergency setting of major bleeding, urgent surgery, or interventions

Dabigatran levels drop immediately after Idarucizumab administration



Dabigatran levels were <20 ng/mL* in 89/90 patients after infusion of first vial, in 77/83 at 12 hours and 62/78 patients at 24 hours

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

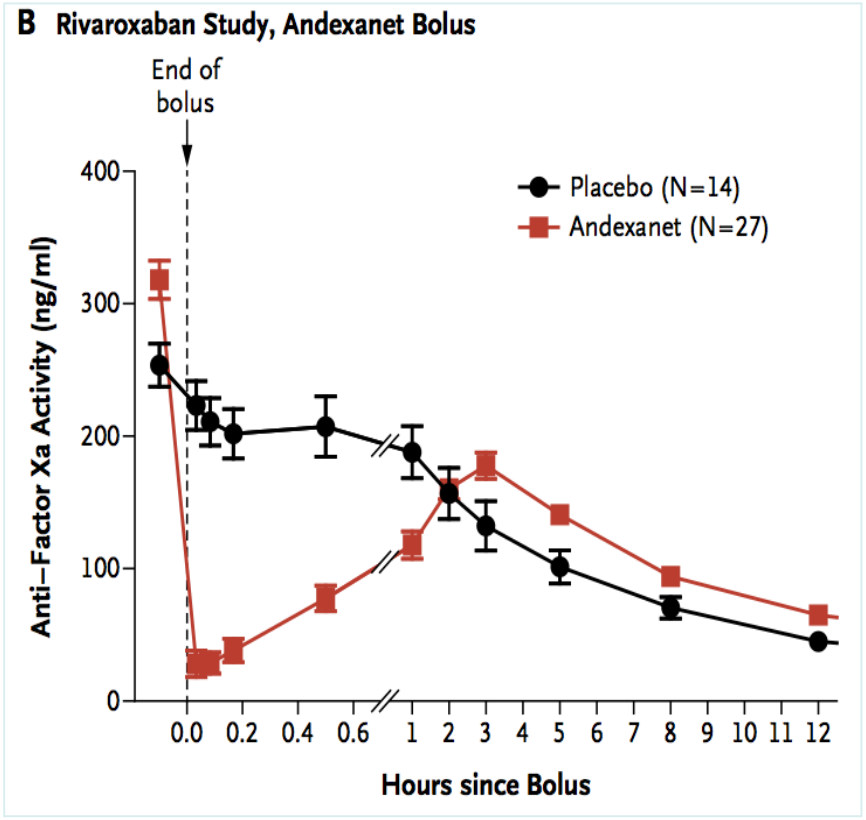
Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity

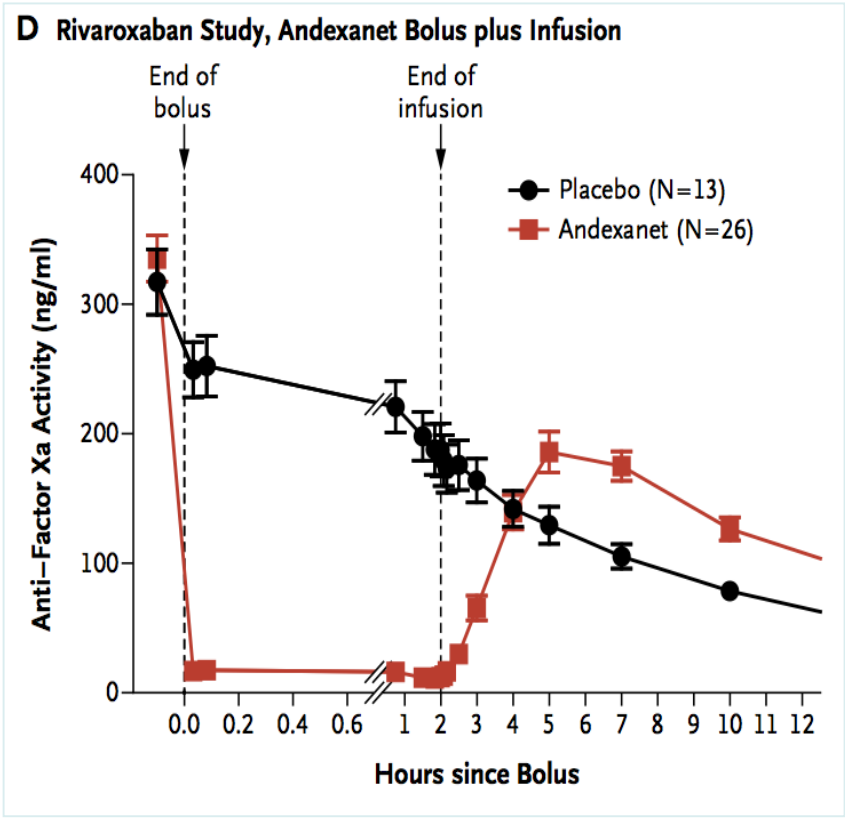
Deborah M. Siegal, M.D., John T. Curnutte, M.D., Ph.D., Stuart J. Connolly, M.D., Genmin Lu, Ph.D., Pamela B. Conley, Ph.D., Brian L. Wiens, Ph.D., Vandana S. Mathur, M.D., Janice Castillo, B.S., Michele D. Bronson, Ph.D., Janet M. Leeds, Ph.D., Florie A. Mar, Ph.D., Alex Gold, M.D., and Mark A. Crowther,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

ANNEXA™-A PART 2: A Phase 3 Randomized, Double-blind, Placebo-controlled Trial Demonstrating Sustained Reversal Of Apixaban-induced Anticoagulation In Older Subjects By Andexanet ALFA

ANNEXA-R

Anti-Factor Xa activity: bolus/: bolus plus infusion





When and how to use antidotes for the reversal of direct oral anticoagulants: guidance from the SSC of the ISTH

J. H. LEVY,* W. AGENO,† N. C. CHAN,‡ M. CROWTHER,§ P. VERHAMME¶ and J. I. WEITZ,§ FOR THE SUBCOMMITTEE ON CONTROL OF ANTICOAGULATION

Table 1 Indications for use or non-use of the antidotes

Indications for use	• Life-threatening bleeding: Intracranial hemorrhage, symptomatic or expanding extradural hemorrhage, or uncontrollable hemorrhage • Bleeding in a closed space or critical organ: Intraspinal, intraocular, pericardial, pulmonary, retroperitoneal, or intramuscular with compartment syndrome • Persistent major bleeding despite local hemostatic measures, or risk of recurrent bleeding because of delayed DOAC clearance or DOAC overdose • Need for urgent intervention that is associated with a high risk of bleeding and that cannot be delayed to allow for drug clearance • Emergency surgery or intervention in patients at high risk for procedural bleeding: Neurosurgery (intracranial, extradural, or spinal), lumbar puncture, cardiac or vascular surgery (aortic dissection/aneurysm repair), hepatic or other major organ surgery
Potential indication for use	• Need for urgent surgery or intervention in patients with acute renal failure
Antidotes should not be used	• Elective surgery • Gastrointestinal bleeds that respond to supportive measures • High drug levels or excessive anticoagulation without associated bleeding • Need for surgery or intervention that can be delayed long enough to permit drug clearance

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HEMOSTATIC EFFECT OF TRANEXAMIC ACID MOUTHWASH IN ANTICOAGULANT-TREATED PATIENTS UNDERGOING ORAL SURGERY

STEEN SINDET-PEDERSEN, D.D.S., GÖRAN RAMSTRÖM, D.D.S., STENER BERNVIL, M.D., AND MARGARETA BLOMBÄCK, M.D.

Abstract We carried out a placebo-controlled, double-blind, randomized study of the hemostatic effect of tranexamic acid mouthwash after oral surgery in 39 patients receiving anticoagulant agents because of the presence of cardiac valvular stenosis, a prosthetic cardiac valve, or a vascular prosthesis. Surgery was performed with no change in the level of anticoagulant therapy, and treatment with the anticoagulant agent was continued after surgery. Before it was sutured, the operative field was irrigated in 19 patients with 10 ml of a 4.8 percent aqueous solution of tranexamic acid (an inhibitor of fibrinolysis) and in 20 patients with a placebo solution. For seven days thereafter, patients were instructed to rinse their mouths with 10 ml of the assigned solution for two minutes four times a day.

There were no significant differences between the two treatment groups in base-line variables, including the level of anticoagulation at the time of surgery. Eight patients in the placebo group had a total of 10 postoperative bleeding episodes, whereas only 1 patient in the tranexamic acid group had a bleeding episode ($P = 0.01$). There were no systemic side effects.

We conclude that local antifibrinolytic therapy is effective in preventing bleeding after oral surgery in patients who are being treated with anticoagulants. (N Engl J Med 1989; 320:840-3.)

ORAL anticoagulant agents (vitamin K antagonists, including warfarin and dicumarol) prevent thromboembolism by reducing the plasma concentrations of coagulation factors II, VII, IX, and X. Because patients with mechanical cardiac-valve prostheses are at high risk for thromboembolism, lifelong oral anticoagulant therapy has been recommended for them.[1,2] Before oral surgery is performed in patients taking oral anticoagulants, it is common practice to reduce or discontinue the anticoagulant medication in order to lower the risk of bleeding. Before operating on such patients, then, the surgeon must choose between exposing them to the risk of thromboembolism and exposing them to the risk of bleeding.

It was recently demonstrated that bleeding complications and transfusion requirements after oral surgery and gingival bleeding in patients with hemophilia were significantly reduced by local treatment with the antifibrinolytic agent tranexamic acid, administered as a mouthwash.[3,4] Orally administered tranexamic acid that is swallowed does not appear in the saliva at detectable levels[5]; its concentration in saliva after use of the mouthwash remains sufficiently high to suppress fibrinolysis for hours, however, although only insignificant levels are detected in the plasma.[5] The aim of the present study was to compare the hemostatic effect of tranexamic acid mouthwash with that of a placebo after oral surgery in patients with valvular heart disease, a cardiac-valve prosthesis, or a vascular prosthesis who were being treated with anticoagulants at a therapeutic level.

From the Department of Oral and Maxillofacial Surgery (S.S.-P.) and the Coagulation Laboratory, Department of Clinical Immunology (S.B.), Aarhus University Hospital, Aarhus, Norrebrogade, Denmark, and the Department of Oral and Maxillofacial Surgery (G.R.) and the Coagulation Laboratory, Department of Clinical Chemistry and Blood Coagulation (M.B.), Karolinska Hospital, Stockholm, Sweden. Address reprint requests to Dr. Sindet-Pedersen at the Department of Oral and Maxillofacial Surgery, Aarhus University Hospital, Norrebrogade, DK-8000 Aarhus C, Denmark.

METHODS

Patients with a cardiac-valve stenosis, a cardiac-valve prosthesis, or a vascular prosthesis who were being treated with an oral anticoagulant agent at a therapeutic level and who were to undergo oral surgery were enrolled in the study. The study was performed in two centers, Aarhus University Hospital in Aarhus, Denmark, and Kar-

Same effect with NOAs ?

Conclusioni

- La gestione delle complicanze emorragiche e dell'emergenza nei pazienti in TAO richiede un approccio multidisciplinare e conoscenze approfondite dei meccanismi d'azione dei farmaci
- Necessità di più dati sui trattamenti anti-emorragici (sicurezza ed efficacia)
- Sviluppo di antidoti sia per gli inibitori del FII che del FX
- Idarucizumab registrato USA e approvato dall'EMA
- In studi randomizzati su volontari Andexanet sicuro ed efficace

Conclusioni

- Sviluppo di antidoti sia per gli inibitori del FII che del FX
- Idarucizumab ha ricevuto approvazione dall'EMA
- In studi su randomizzati su volontari Andexanet sembra essere sicuro ed efficace

CONSIDERAZIONI CONCLUSIVE (I)

- Mancanza di studi clinici e di esperienza sulla gestione dei pz da sottoporre a chirurgia in elezione o in urgenza
- Le attuali raccomandazioni peri-operatorie sono principalmente basate sulle caratteristiche farmacocinetiche dei DOA nel paziente "standard"
- CCP a 4 fattori normalizzano il PT INR di rivaroxaban alle dosi di 50UI/kg
- CCP a 4 fattori non modificano l'allungamento del PTT indotto da dabigatran
- In corso di valutazione antidoti specifici

CONSIDERAZIONI CONCLUSIVE (II)

- Alterazioni della farmacocinetica dei DOA possono richiedere tempi più lunghi di sospensione
- Il dosaggio specifico dell'attivita' anticoagulante e' raccomandabile e tutti i laboratori devono attrezzarsi
- Urgenza/Emergenza …

E' AUSPICABILE L'APPROCCIO CONDIVISO MULTIDISCIPLINARE E LA DEFINIZIONE DI PROTOCOLLI COMUNI *("PERCORSI RAGIONATI")*

(Anestesisti/Rianimatori, Chirurghi, Cardiologi, Neurologi,

Esperti in Emostasi e Trombosi…)

Oral anticoagulants: time to reverse

	Lag-time (hours)	$t_{1/2}$ (hours)	Time to reverse (Lag+2 $t_{1/2}$)	Time to reverse CrCl<30 ml/h
Warfarin	30	50	130 (5.4 days)	-
Dabigatran	-	13	≈26	60
Rivaroxaban	-	7-11	≈20	? 1.5x?
Apixaban	-	9-14	≈24	? 1.5x?
Edoxaban	-	9-11	≈24	? 1.5x?

Garcia, Blood 2010
Stangier, Clin Pharmacokin 2010
Ageno, Chest 2012

Bleeding in Patients with Atrial Fibrillation Treated with Non Vitamin K Antagonist Oral Anticoagulants: A Population-Based Study

	VKA	Dabigatran 150 mg	Dabigatran 110 mg	Rivaroxaban	Overall
Number of patients	9,564	1,806	4,170	2,709	18,249
Serum creatinine mg/dL	1.2 (0.3-11.6)	1.0 (0.5-4.4)	1.2 (0.4-4.1)	1.3 (0.5-3.5)	1.2 (0.3-11.6)
$CHADS_2$ score Median (Range)	3 (0-6)	3 (1-6)	4 (1-6)	4 (2-6)	3 (0-6)
Anti-platelet use (%)	52	50	35	55	48
Bleeds per 100 patient years (N)	3.9 (372)	2.8 (50)	4.6 (191)	4.3 (116)	729
Fatalities within 1 month of hemorrhage	**44 (0.5 %)**	8 (0.44 %)	15 (0.36 %)	3 (0.11 %)	70
Intracranial hemorrhage	**67 (0.7 %)**	4 (0.22 %)	16 (0.38 %)	3 (0.11 %)	90
Gastrointestinal hemorrhage	**178 (1.9 %)**	20 (1.1 %)	**108 (2.6 %)**	26 (0.96 %)	332

Ellis et al, ASH 2014

What is major bleeding?

Any bleeding that

- Require hospitalization, or
- Require transfusion of at least 2 units of packed red blood cells, or
- Involve a body cavity, intracranial or retroperitoneal, or
- Fatal

Linkins et al, Ann Int Med 2003

Major bleeding and anticoagulation

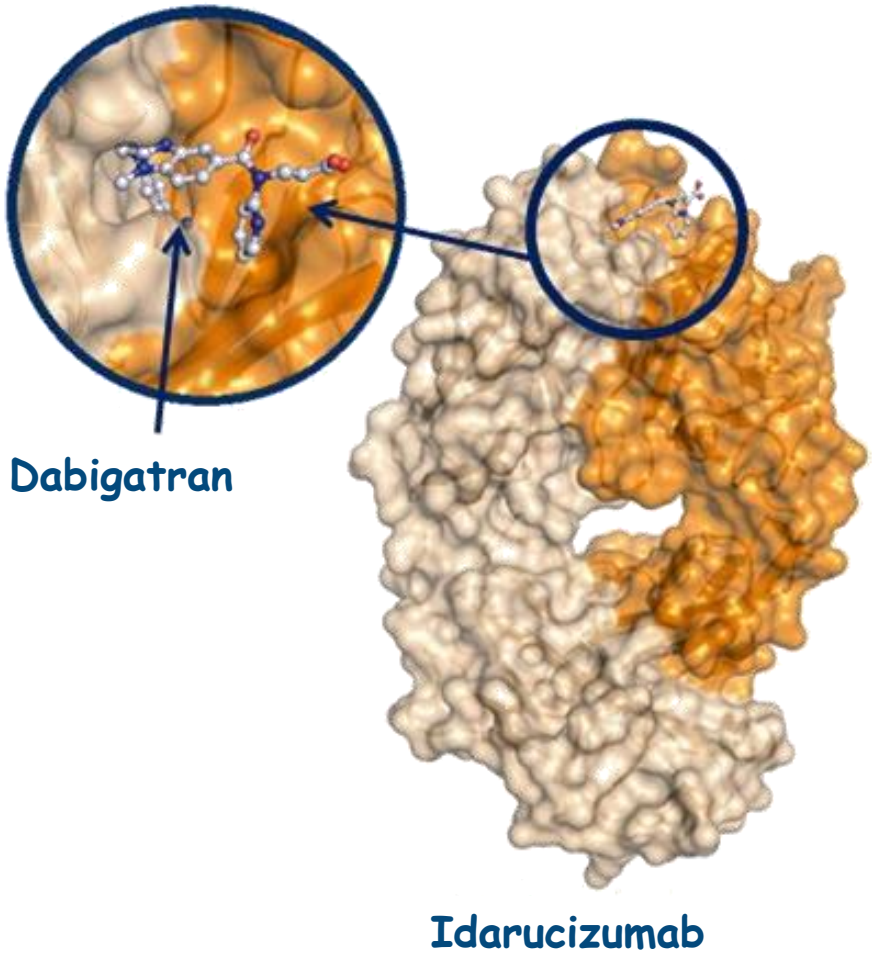
- GI bleeding
  - The risk of GI bleeding is two-fold higher in patients taking dabigatran
  - The risk of re-bleeding is particularly high for GI bleeding (52-56%)

- Intracerebral hemorrhage
  - Epidural and subdural hemorrhages primarily related to trauma; no major controindication for restarting anticoagulation (unless subject at risk of trauma, e.g. elderly)
  - Subarachnoid/intracerebral hemorrhage: control risk factors; very high risk recurrence; risk is lower with dabigatran/rivaroxaban/apixaban than warfarin

Pharmaco-kinetic & dynamic

	Dabigatran	Rivaroxaban	Apixaban
Target	IIa	Xa	Xa
Prodrug	Yes	No	No
Hours to Cmax	2	2-4	1-3
Bioavailability	7%	80%	66%
Protein binding	35%	>90%	87%
Half-life (Hours)	12-14	9-13	8-15
CYP metabolism	No	Yes[1]	Yes[2]
P-gp interaction	Yes	Yes	Yes
Renal elimination	80%	66%	25%
Dosing	Twice a day	Once a day	Twice a day

[1] CYP3A4/A5, CYP2J2; [2] CYP3A4, CYP1A2, CYP2J2



Humanized Fab fragment

Binding affinity ~350× higher than dabigatran to thrombin

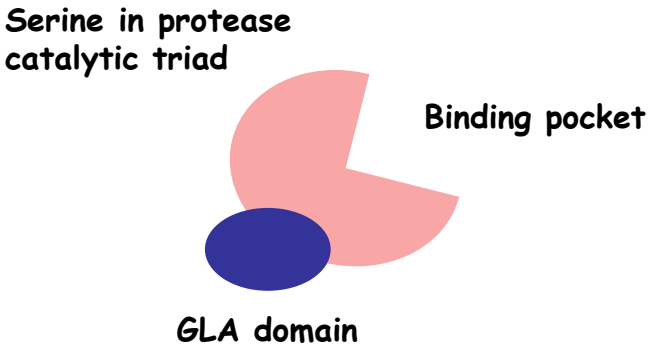
No intrinsic procoagulant or anticoagulant activity

IV dosing by bolus or rapid infusion, immediate onset of action

Short half-life

- Schiele et al. Blood 2013; Stangier et al. OR 320; presented at ISTH 2015

Normal Factor Xa molecule



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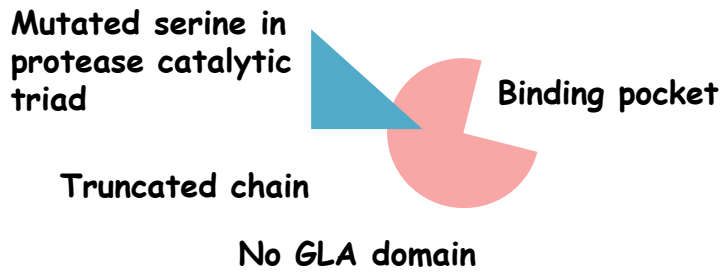

- Andexanet alfa reduces the non-protein-bound free fraction of the Factor Xa inhibitor ⇨ anticoagulant effect caused by a direct Factor Xa inhibitor is rapidly neutralized by administration of andexanet alfa
- Andexanet alfa is inactivated Factor Xa
  - Lower molecular weight owing to truncated chain
  - No GLA domain
  - Mutated serine
  - Active binding site to Factor Xa substrates
- The molecule has no catalytic activity and does not bind to the protaminase complex
- Intact binding site allows binding to:
  - Direct Factor Xa inhibitors, e.g. rivaroxaban
  - ATIII activated by LMWH or fondaparinux

FEIBA™ for Patients on Direct Oral Anticoagulants Requiring Urgent Surgery

Patient (Age and Gender)	Indication For DOAC [AF(CHADS2); VTE]	DOAC and Dosage	Surgery/ Procedure	Units of PRBCs Transfused	FEIBA™ Dose (IU)	Adverse Events post-FEIBA™ administration	Survived Hospitalization
91 Female	AF (4)	Rivaroxaban 15 mg daily	Femur fracture ORIF	3, intra-operatively	1812	--	Yes
50 Male	VTE	Apixaban 5 mg BID	Laparotomy for SBO	0	1350	--	Yes
50 Female	AF (4)	Apixaban 2.5 mg BID	Angiography + SMA stent for ischemic bowel	0	3918	--	Yes
77 Male	AF (2)	Rivaroxaban 20 md daily	Laparotomy for incarcerated hernia/SBO	0	3241	Venous oozing intra-operatively	Yes
78 Male	AF (3)	Dabigatran 110 mg BID	SBO/ Femoral hernia repair	0	6000	--	Yes

The use of FEIBA™ for reversal of DOAC effect for urgent surgery in this cohort of patients was effective and not associated with adverse thrombotic complications.

Shaw, ASH 2014

Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials

Nick van Es,[1] Michiel Coppens,[1] Sam Schulman,[2] Saskia Middeldorp,[1] and Harry R. Büller[1]

Key Points

- DOACs have similar efficacy as VKAs in the treatment of acute symptomatic VTE, but significantly reduce the risk of major bleeding.
- The efficacy and safety of DOACs in the treatment of acute VTE are consistent in clinically important subgroups.

Blood 2014

Bleeding Risk, Management and Outcome in Patients Receiving Non-VKA Oral Anticoagulants (NOACs)

Trial	Included patients (*n*)	Major bleeding: NOAC	Major bleeding: VKA
RE-LY [44]	18,113	2.71 %/year (110 mg BID) 3.11 %/year (150 mg BID)	3.36 %/year
ARISTOTLE [45]	18,201	2.13 %/year	3.09 %/year
ENGAGE-AF [46]	21,105	2.75 %/year (60 mg) 1.61 %/year (30 mg)	3.43 %/year
ROCKET-AF [47]	14,264	5.6/year	5.4/year
SPAF meta-analysis [15]	71,683	RR for NOAC 0.86 (95 % CI 0.73–1.00)	
RECOVER 1 + 2 [48]	5107	1.4 %	2.0 %
EINSTEIN DVT + PE [23]	8282	1.0 %	1.7 %
AMPLIFY [49]	5395	0.6 %	1.8 %
HOKUSAI [50]	8240	1.4 %	1.6 %
VTE meta-analysis [14]	24,455	RR for NOAC 0.60 (95 % CI 0.41–0.88)	

Werth S et al, Am J Cardiovasc Drugs 2015