Gli **antidoti dei DOACs**

Eloise Beggiato

Bleeding risk and reversal strategies for old and new anticoagulants and antiplatelet agents

Time until restoration of hemostasis after cessation of therapeutic dose

	Time until restoration of hemostasis after cessation of therapeutic dose	Reversing agent	Remark
Vitamin K antagonists	Warfarin: 60–80 h Acenocoumarol: 18–24 h Phenprocoumon: 8–10 days	Vitamin K i.v.; reversal in 12–16 h Vitamin K orally; reversal in 24 h PCC's; immediate reversal	Dose of vitamin K or PCCs depend on INR and bodyweight
Heparin	3–4 h	Protamine sulphate 25–30 mg; immediate reversal	1 mg of protamin per 100 anti-Xa units given in the last 2–3 h
LMW heparin	12–24 h	(Partially) protamine sulphate 25–50 mg; immediate (partial) reversal	1 mg of protamine per 100 anti-Xa units given in the last 8 h
Pentasaccharides	Fondaparinux: 24–30 h Idraparinux: 5–15 days Idrabiotaparinux: 5–15 days	Recombinant factor VIIa 90 μg kg^{-1}; immediate thrombin generation* Avidin for idrabiotaparinux*	Based on laboratory endpoints, no systematic experience in bleeding patients
Oral factor Xa inhibitors	Dependent on compound, usually within 12 h	Prothrombin complex concentrate (3000 U)*	Based on laboratory endpoints, no systematic experience in bleeding patients
Oral thrombin inhibitors	Dependent on compound, usually within 12 h	None so far	
Aspirin	5–10 days (time to produce unaffected platelets)	DDAVP (0.3–0.4 μg kg^{-1}) and/or platelet concentrate; reversal in 15–30 min	Cessation not always required, also dependent on clinical situation and indication
Clopidogrel Prasugrel	1–2 days	Platelet concentrate, possibly in combination with DDAVP (0.3–0.4 μg kg^{-1}); reversal in 15–30 min	Cessation not always desirable, also dependent on clinical situation and indication

Levi et M al. JTH 2011; 9:1705-12

Management of Bleeding With Non–Vitamin K Antagonist Oral Anticoagulants in the Era of Specific Reversal Agents

GENERAL PRINCIPLES AND SUPPORTIVE MEASURES

Minimize the Risk of Bleeding

Dose, emivita,funzionalità renale

Supportive Measures

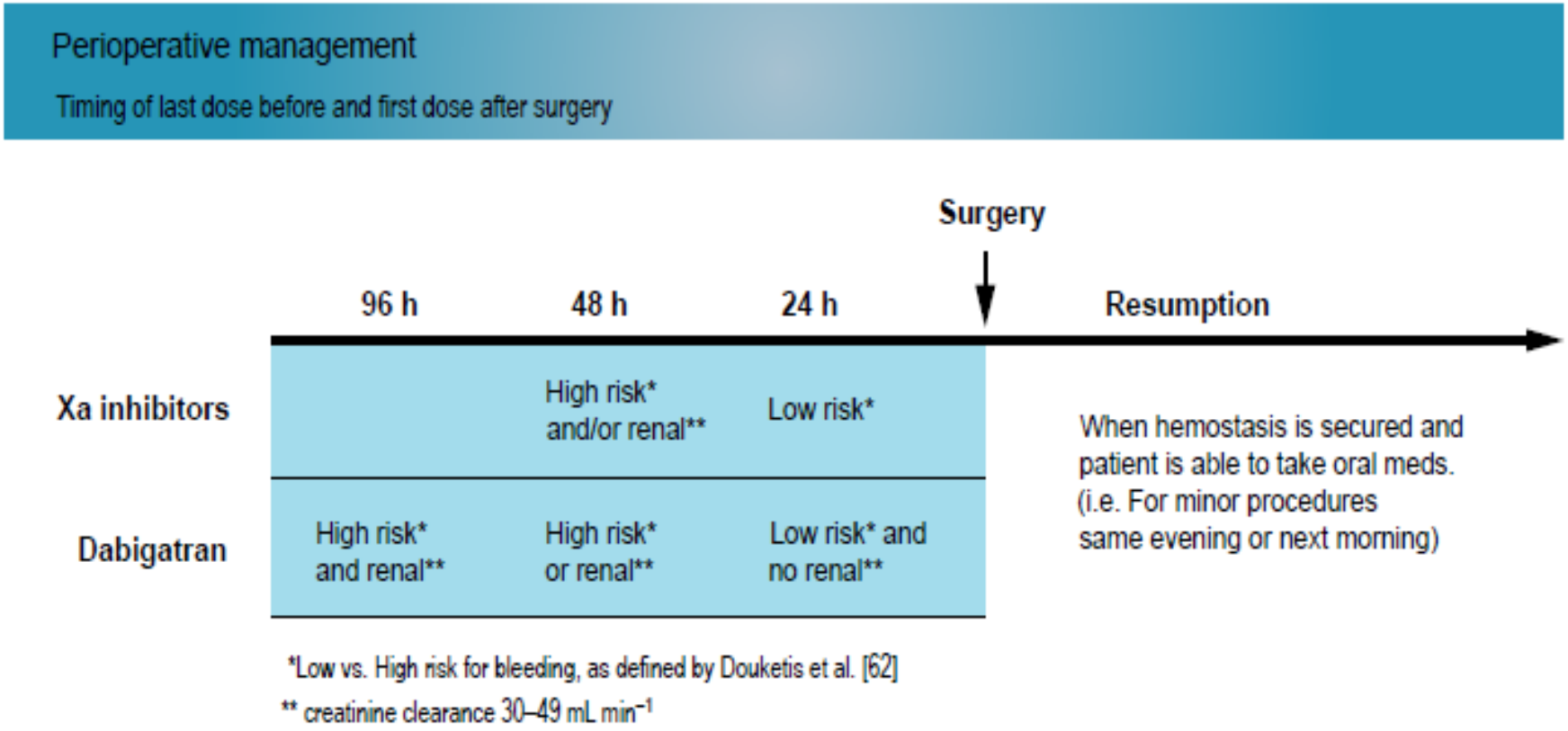
Laboratory Measurements

NONSPECIFIC HEMOSTATIC AGENTS

SPECIFIC REVERSAL AGENTS

Circulation 2016

LA GESTIONE PERIOPERATORIA



Schulman S, J Intern Med 2013

Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation

Table 10 Last intake of drug before elective surgical intervention

	Dabigatran		Apixaban–edoxaban–rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. ≥12 or 24 h after last intake)			
	Low risk	High risk	Low risk	High risk
CrCl ≥ 80 mL/min	≥24 h	≥48 h	≥24 h	≥48 h
CrCl 50–80 mL/min	**≥36 h**	**≥72 h**	≥24 h	≥48 h
CrCl 30–50 mL/min[a]	**≥48 h**	**≥96 h**	≥24 h	≥48 h
CrCl 15–30 mL/min[a]	Not indicated	Not indicated	**≥36 h**	**≥48 h**
CrCl < 15 mL/min	No official indication for use			

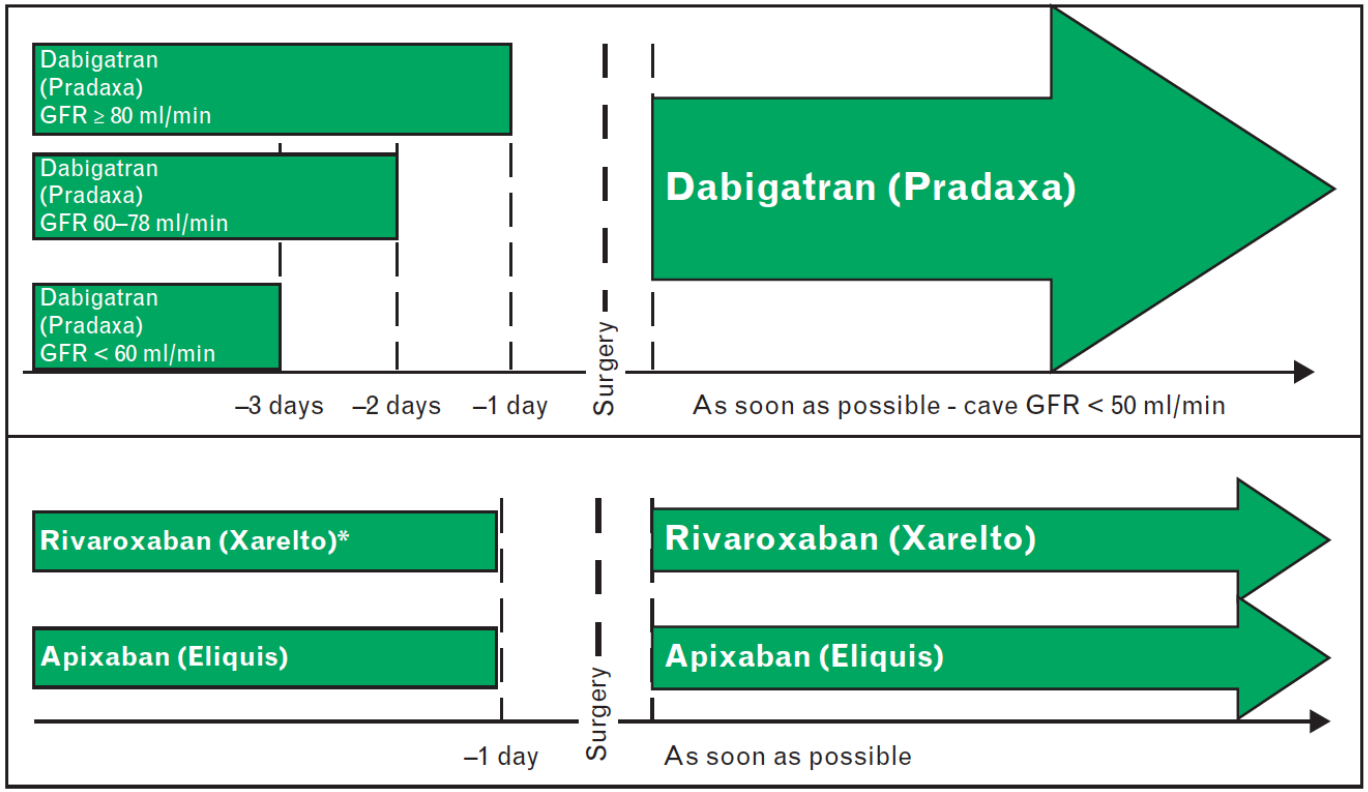
There is no need for bridging with LMWH/UFH

Heidbuchel H. Europace 2015; doi:10.1093/europace/euv309

'New' direct oral anticoagulants in the perioperative setting

Low bleeding risk:

(minimal bleeding, uncritical localization, easy to manage)

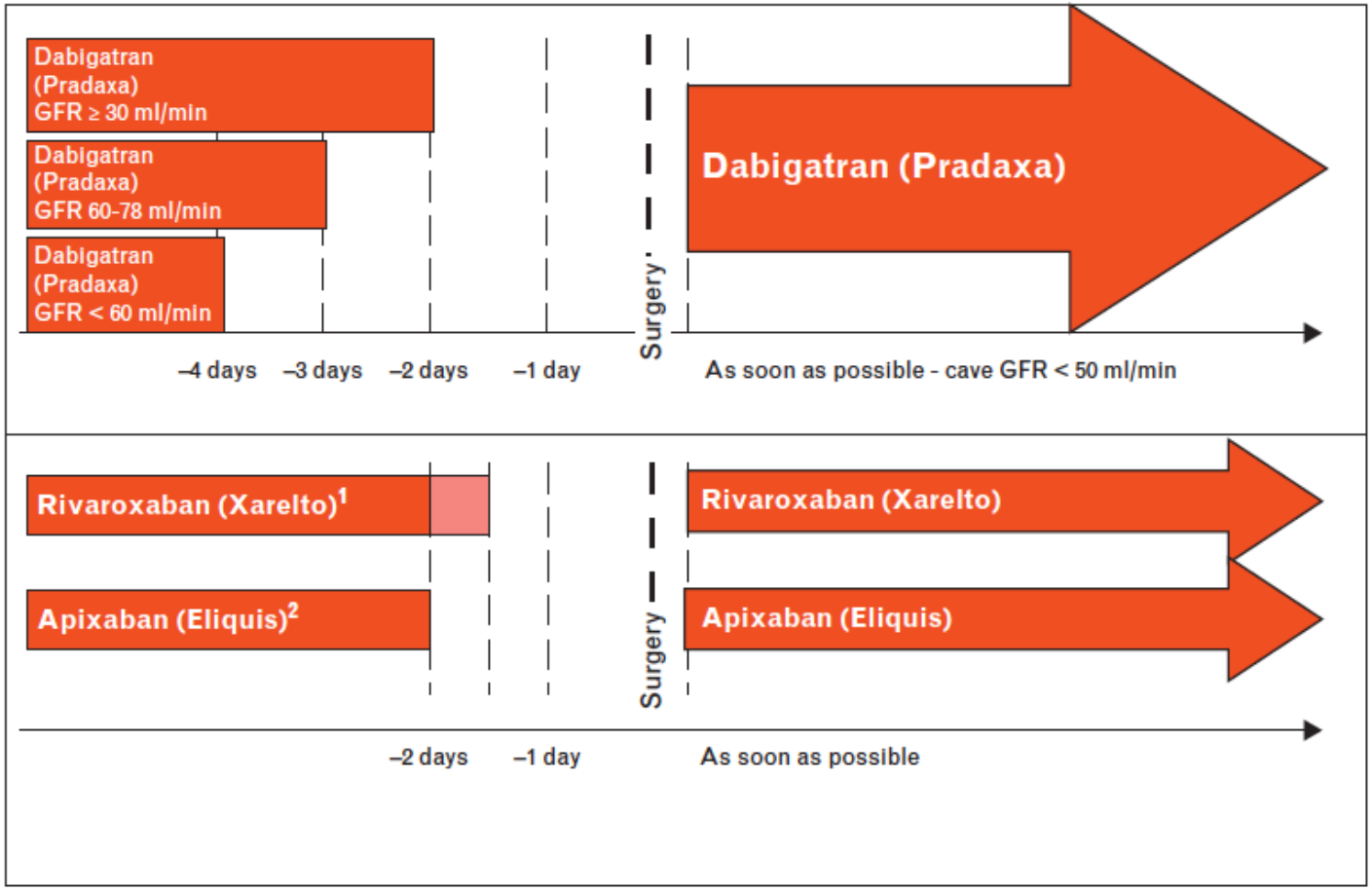


Breuer G et al. Curr Opin Anesthesiol. 2014; 27:409-19

'New' direct oral anticoagulants in the perioperative setting

High bleeding risk:

(risk of bleeding not acceptable, relevant bleeding could not be precluded)



Breuer G et al. Curr Opin Anesthesiol. 2014; 27:409-19

Management of Bleeding With Non–Vitamin K Antagonist Oral Anticoagulants in the Era of Specific Reversal Agents

GENERAL PRINCIPLES AND SUPPORTIVE MEASURES

Minimize the Risk of Bleeding

Supportive Measures

Laboratory Measurements

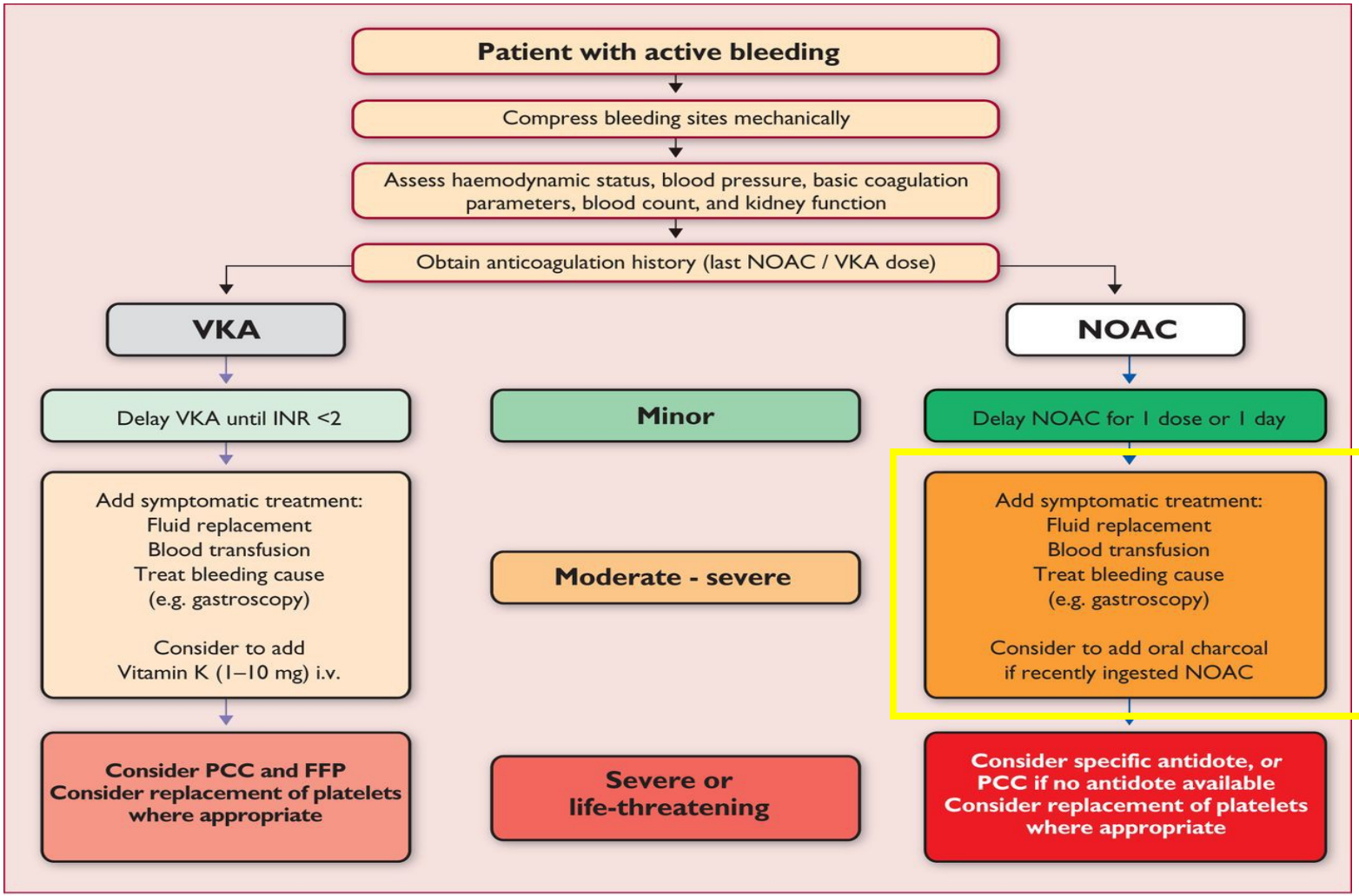
NONSPECIFIC HEMOSTATIC AGENTS

SPECIFIC REVERSAL AGENTS

European Heart Journal
doi:10.1093/eurheartj/ehw210

2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC)



FFP = fresh frozen plasma; INR = international normalized ratio; i.v. = intravenous; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulation; PCC = prothrombin complex concentrates; VKA = vitamin K antagonist.

Kirchhof et al; EHJ 2016

Table 2. Management of NOAC-Related Bleeding

	Mild	Moderate	Severe/Life Threatening*	
			Dabigatran	FXa Inhibitors
Supportive measures				
Delay or discontinue NOAC	X	X	X	X
Discontinue (or reverse) other antithrombotics	X	X	X	X
Decrease absorption-activated charcoal if last dose 2–4 h		X	X	X
Maintain diuresis/volume support (fluids)		X	X	X
Mechanical compression/intervention to establish hemostasis		X	X	X
Transfusion: PRBCs, FFP (as plasma expander), platelets		X	X	X
Dialysis			X†	
Nonspecific hemostatic agents				
PCC > aPCC > rFVIIa				X‡
Specific reversal agents				
Indarucizumab			X	
Andexanet alfa				If approved
Ciraparantag			If approved	If approved

aPCC indicates activated prothrombin complex concentrate; FFP, fresh-frozen plasma; FXa, activated Factor X; NOAC, non–vitamin K oral anticoagulant; PCC, prothrombin complex concentrate; PRBCs, packed red blood cells; and rFVIIa, recombinant activated factor VII.

*Includes bleeding causing hemodynamic compromise, intracranial hemorrhage, bleeding into a critical organ or closed space, persistent bleeding despite general supportive measures and local hemostatic support, risk of recurrent bleeding because excess NOAC drug exposure attributable to delayed clearance of NOAC (acute renal failure) or overdose.

†Only consider in patients on dabigatran with renal failure if specific reversal agent not available.

‡Specific reversal agents preferred if approved.

Management of Bleeding With Non–Vitamin K Antagonist Oral Anticoagulants in the Era of Specific Reversal Agents

GENERAL PRINCIPLES AND SUPPORTIVE MEASURES

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Supportive Measures

Laboratory Measurements

NONSPECIFIC HEMOSTATIC AGENTS

SPECIFIC REVERSAL AGENTS

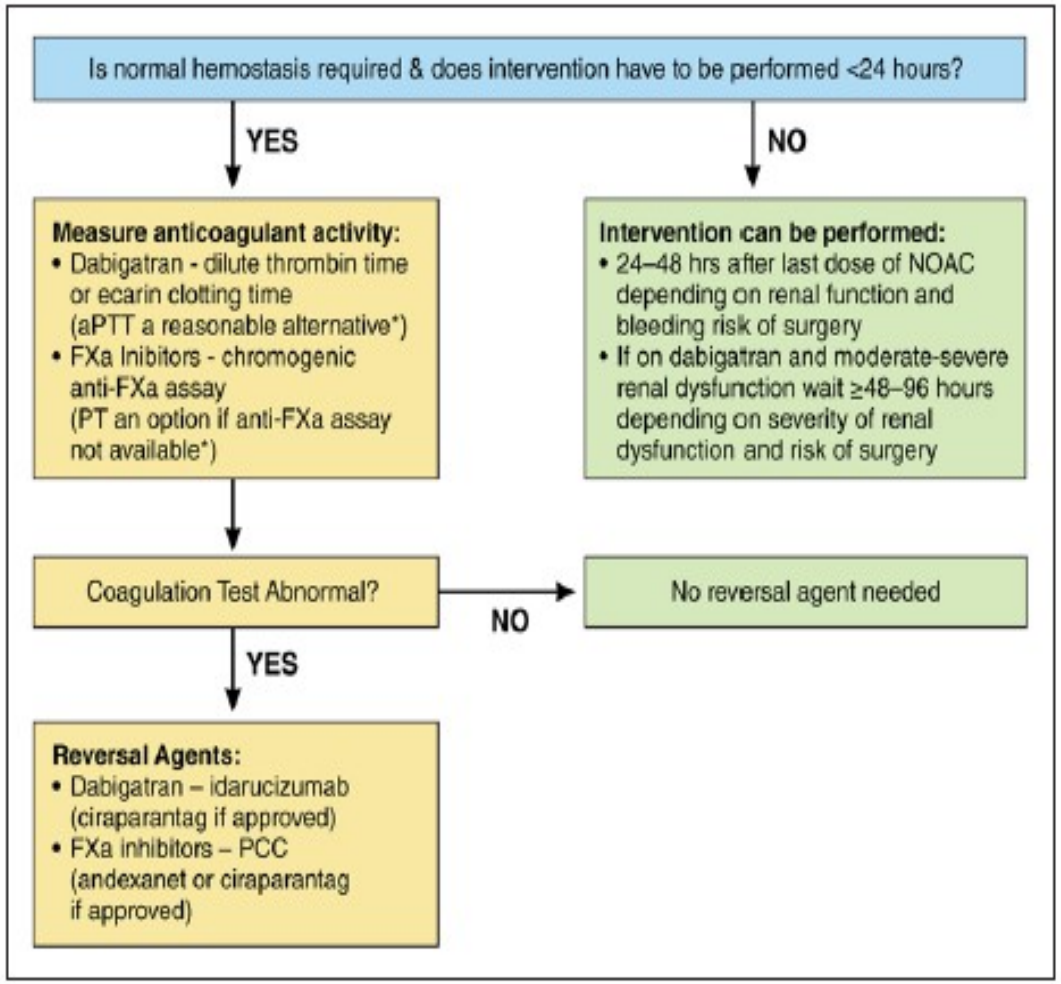

Figure 4. Management of NOAC-treated patients who require invasive procedures.

*A prolonged activated partial thromboplastin time (aPTT) indicates an anticoagulant effect of dabigatran, and a prolonged prothrombin time (PT) indicates an anticoagulant effect of the FXa inhibitors. However, the clinical utility of these common tests is limited because a normal aPTT or PT does not exclude clinically relevant plasma levels of dabigatran and FXa inhibitors, respectively. In particular, there is considerable variability in the sensitivity of the PT across the FXa inhibitors, and this test is less sensitive to apixaban than rivaroxaban and edoxaban. aPTT indicates activated partial thromboplastin time; FXa, activated Factor X; NOAC, non–vitamin K antagonist oral anticoagulants; PCC, prothrombin complex concentrate; and PT, prothrombin time.

Management of Bleeding With Non–Vitamin K Antagonist Oral Anticoagulants in the Era of Specific Reversal Agents

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SPECIFIC REVERSAL AGENTS

Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation

! **2015** !

Life-threatening bleeding	All of the above Prothrombin complex concentrate (PCC) 25 U/kg (may be repeated once or twice) (but no clinical evidence) Activated PCC 50 IE/kg; max 200 IE/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC if available Activated factor VII (rFVIIa; 90 μg/kg) no data about additional benefit + expensive (only animal evidence)	Life-threatening bleeding	All of the above Prothrombin complex concentrate (PCC) 25 U/kg (may be repeated once or twice) (but no clinical evidence) Activated PCC 50 IE/kg; max 200 IE/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC if available Activated factor VII (rFVIIa; 90 μg/kg) no data about additional benefit + expensive (only animal evidence)

All of the above.

Prothrombin complex concentrate (PCC) 50 U/kg
(with additional 25 U/kg if clinically needed)
(healthy volunteer data)

Activated PCC 50 U/kg; max 200 U/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC if available.

Activated factor VII (rFVIIa; 90 μg/kg) no data about additional benefit + expensive (only animal evidence)

Idarucizumab 5 g IV (approval waiting) … *for Dabigatran*

Heidbuchel H. Europace 2015; doi:10.1093/europace/euv309

Efficacy Results to Date

It is important to underscore that there are limited data supporting the efficacy and safety of using these nonspecific hemostatic agents in bleeding patients taking NOACs. It is unclear that normalizing coagulation parameters in healthy volunteers translates to improved outcomes in patients who are actively bleeding. Furthermore, the use of these agents in managing bleeding caused by VKA or in hemophiliac patients has been associated with an increased risk of thrombotic complications.[58–60] This risk may be higher when activated factors are used. For these reasons, hemostatic agents should be reserved for patients taking NOACs who present with life-threatening bleeding despite general supportive measures or patients who require emergency surgery before expected clearance of the NOAC.[20–23]

Neither nonspecific nor specific reversal agents are recommended in cases of elective procedures (to foreshorten the time to an elective procedure) or when procedures can be delayed until the anticoagulant is cleared. Moreover, these agents should not be used in patients with a gastrointestinal hemorrhage who is responding to supportive measures, or in patients with supratherapeutic drug levels without bleeding.[61]

Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients

International Society on Thrombosis and Haemostasis

Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients

MAJOR BLEEDING

1. Fatal bleeding

and/or

2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartmentsyndrome,

and/or

3. Bleeding causing a fall in hemoglobin level of 2 g/dL or more, or leading to transfusion of two or more units of whole blood or red cells.

Schulman S et al. JTH 2005; 3:692-694

Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients

LIFE THREATENING BLEEDING

1. Fatal bleeding

and/or

2. intracranial bleeding

and/or

3. Bleeding causing a fall in hemoglobin level of 5 g/dL or more, or leading to transfusion of 4 or more units of whole blood or red cells or inotropic agents or necessitating surgery

Schulman S et al. JTH 2005; 3:692-694

Schulman S et al. JTH 2005; 3:692-694

Management of Bleeding With Non–Vitamin K Antagonist Oral Anticoagulants in the Era of Specific Reversal Agents

GENERAL PRINCIPLES AND SUPPORTIVE MEASURES

Minimize the Risk of Bleeding

Supportive Measures

Laboratory Measurements

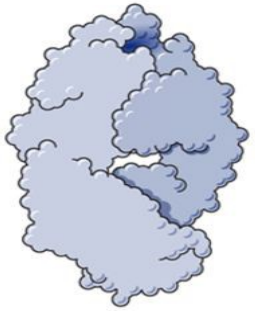
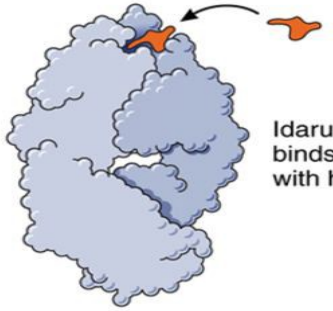
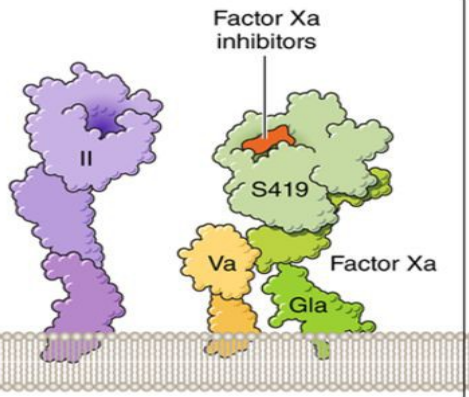
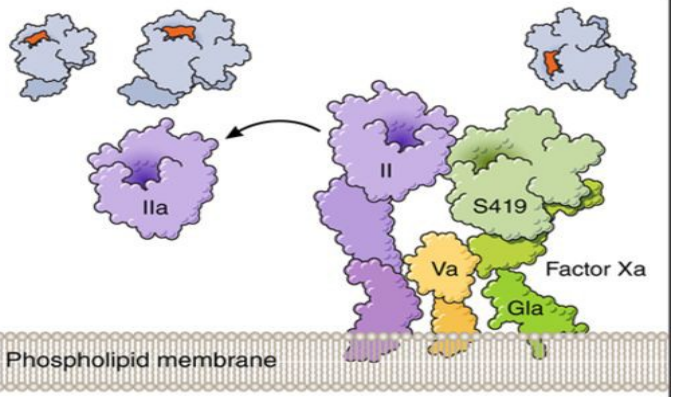
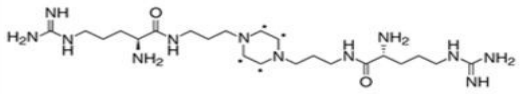
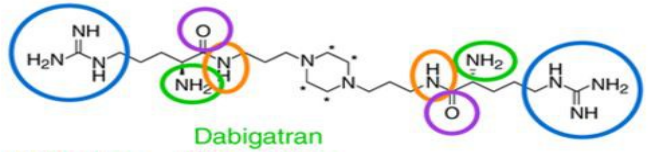
NONSPECIFIC HEMOSTATIC AGENTS

SPECIFIC REVERSAL AGENTS

NOAC reversal agents: stages of development

- **1.** Adapted from Greinacher et al. Thromb Haemost 2015; **2.** Clinicaltrials.gov: NCT02104947; **3.** Pollack et al. Thromb Haemost 2015; **4.** US FDA press release 16 Oct 2015; **5.** European Commission Community Register of Medicinal Products for Human Use 20 November 2015; **6.** ClinicalTrials.gov Identifier: NCT02329327; **7.** ClinicalTrials.gov Identifier: NCT02207257

DOACs: Antidoti

NOAC reversal agent	Target	Mechanism
 Idarucizumab	 Dabigatran	 Idarucizumab binds Dabigatran with high affinity
 Andexanet alpha	 Factor Xa inhibitors; II; S419; Va; Factor Xa; Gla	 IIa; II; S419; Va; Factor Xa; Gla; Phospholipid membrane
 Ciraparantag (PER977)	Apixaban Argatroban Edoxaban Dabigatran Rivaroxaban UFH LMWH Fondaparinux	 Dabigatran Rivaroxaban Apixaban Argatroban UFH/LMWH Fondaparinux; Edoxaban Dabigatran Rivaroxaban UFH/LMWH Fondaparinux; Dabigatran Rivaroxaban UFH/LMWH Fondaparinux; Edoxaban Apixaban Computer-aided energy minimization modeling predicts 8 non-covalent binding sites on ciraparantag for NOACs or heparins

Management of Bleeding With Non–Vitamin K Antagonist Oral Anticoagulants in the Era of Specific Reversal Agents

Table 1. Comparison of Specific NOAC Reversal Agents

	Idarucizumab	Andexanet alfa	Ciraparantag
Alternate names	aDabi-Fab, BI655075	PRT064445	Aripazine, PER977
Company	Boehringer Ingelheim	Portola Pharmaceuticals	Perosphere Inc.
Chemical structure	Humanized monoclonal antibody fragment	Recombinant truncated human factor Xa variant (decoy)	Synthetic water-soluble cationic small molecule consisting of 2 L-arginine units connected with a piperazine-containing linker chain
Molecular mass	47 766 Da	39 000 Da	512 Da
Binding	Noncompetitive binding to dabigatran	Competitive binding to direct factor Xa inhibitors or to indirect factor Xa inhibitor–activated antithrombin	Covalent hydrogen bonding
Target affinity	≈350× greater affinity for dabigatran than factor IIa	Affinity for direct factor Xa inhibitors similar to that of native factor Xa	Not reported
Onset	<5 min	2 min	5–10 min
Half-life	Initial: 47 min	Terminal: ≈6 h	Duration of action 24 h
	Terminal: 10.3 h		
Elimination	Kidney (protein catabolism)	Not reported	Not reported
Anticoagulant(s) reversed	Dabigatran	Direct and indirect factor Xa inhibitors*	Dabigatran
			Argatroban
			Low-molecular-weight heparins
			Unfractionated heparin
			Oral and parenteral factor Xa inhibitors
Route and dose in clinical studies	5 g administered as 2 doses of 2.5 g IV over 5–10 min, 15 min apart (repeat dosing can be considered if recurrent bleeding or require second emergent procedure if elevated coagulation parameters)	400–800 mg intravenous bolus (30 mg/min) followed by infusion of 4–8 mg/min†	100–300 mg intravenous bolus
Storage	Refrigerated	Refrigerated	Room temperature

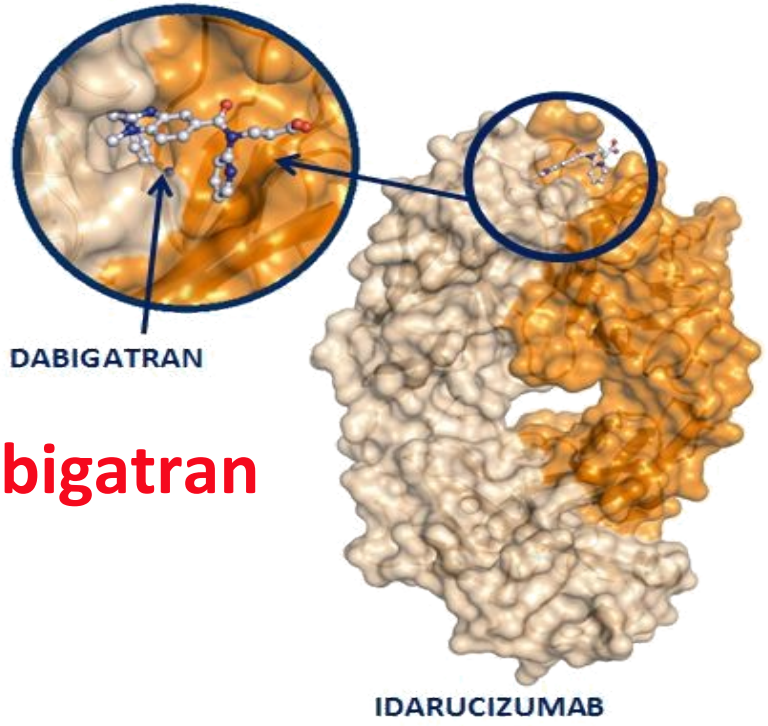
NOAC indicates non-vitamin K oral anticoagulant.

*For the indirect factor Xa inhibitors, andexanet alfa likely to completely reverse fondaparinux, which only inhibits factor Xa, but not low-molecular-weight heparins that also inhibit factor IIa.

†Lower dose to reverse apixaban, higher dose to reverse rivaroxaban.

Idarucizumab

(frammento di anticorpo monoclonale)



Dabigatran

Idarucizumab is in late-stage development and has not yet been approved for clinical use

Idarucizumab

Humanized Fab fragment

Binding affinity ~350× higher than dabigatran to thrombin

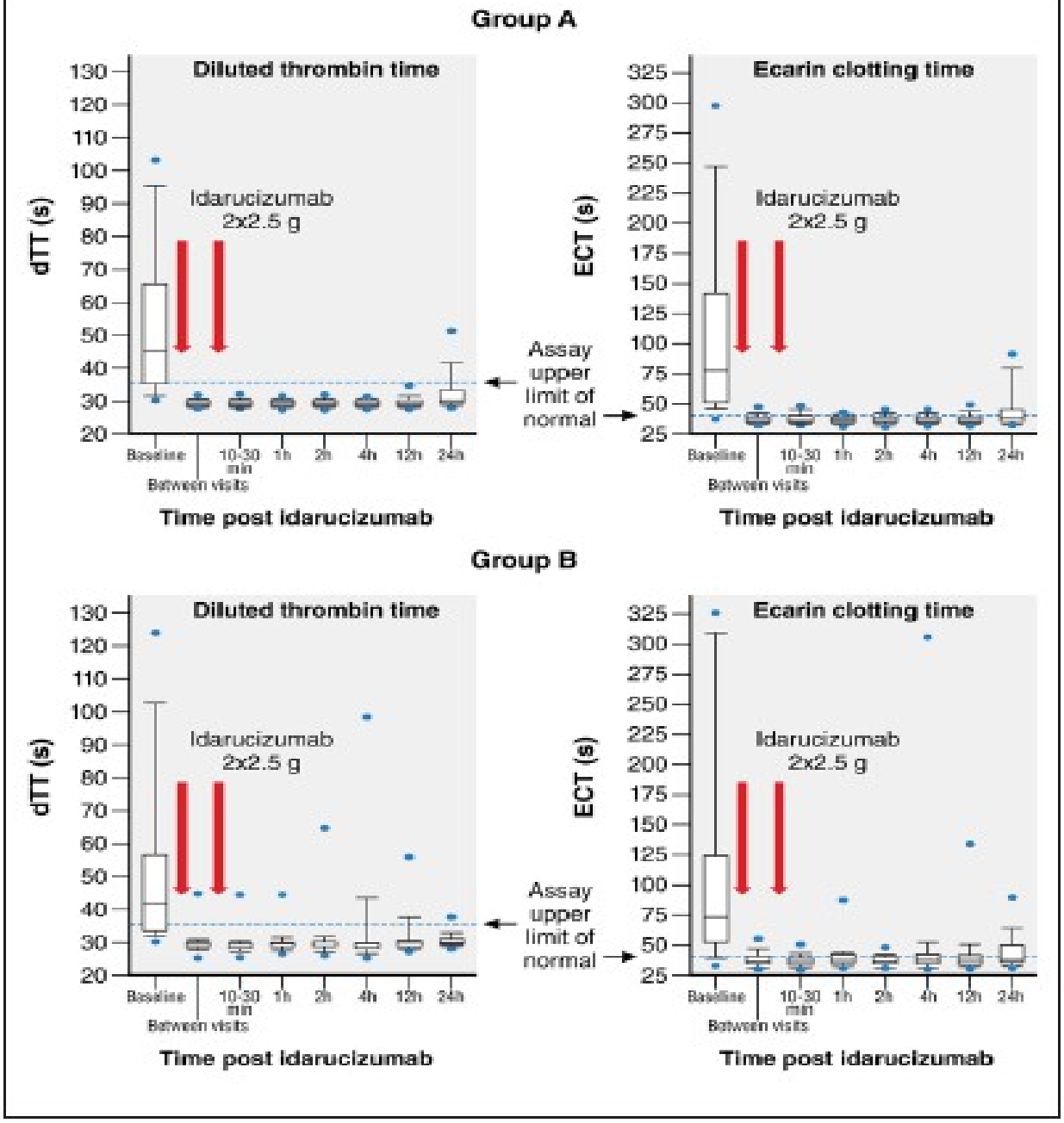
No intrinsic procoagulant or anticoagulant activity

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

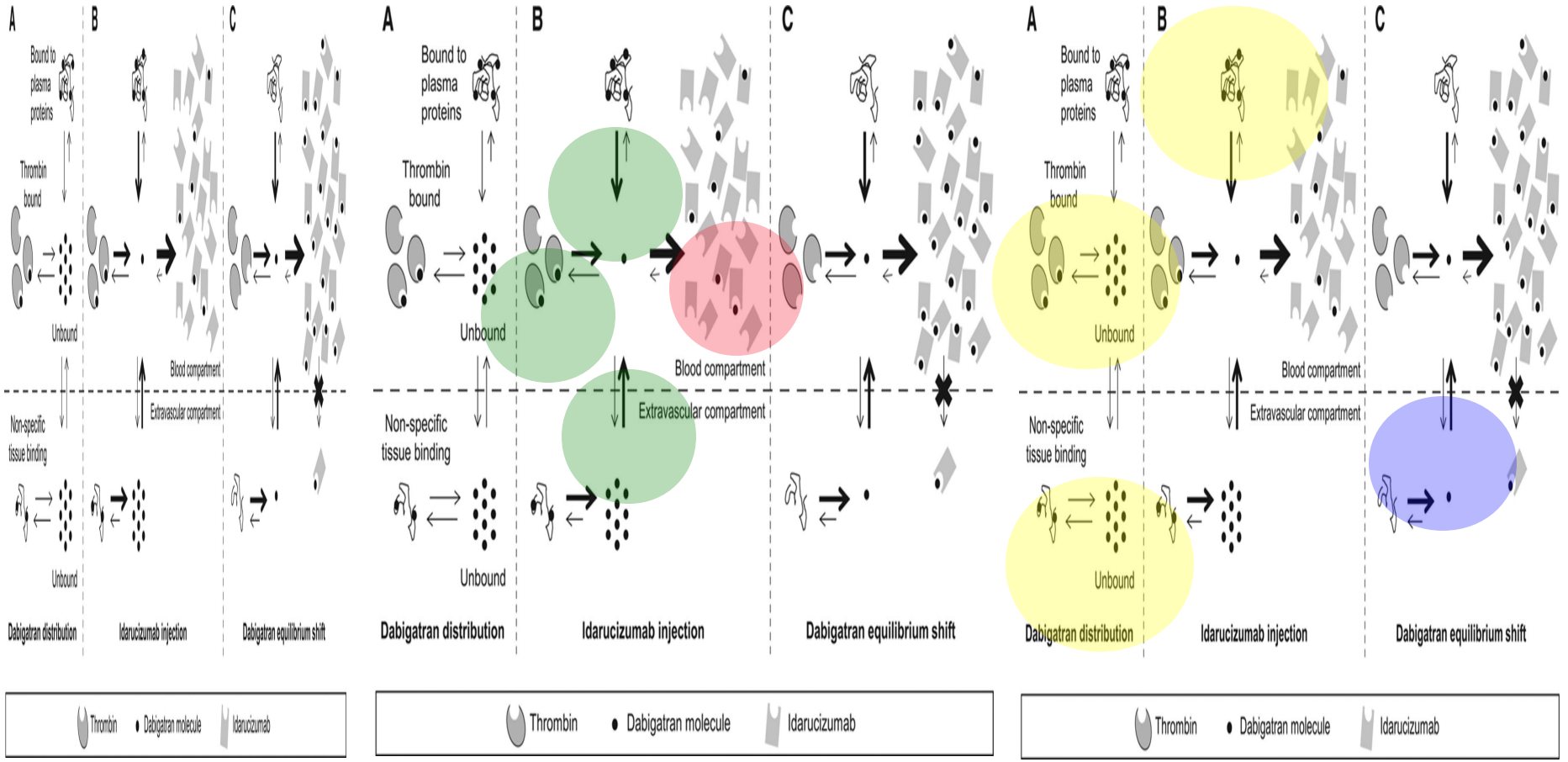
Short half-life

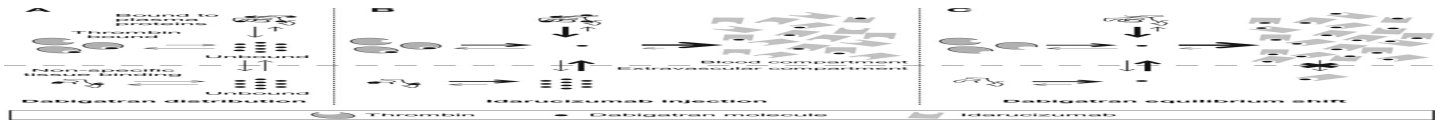
- Schiele et al. Blood 2013; Stangier et al. OR 320; presented at ISTH 2015

RE-VERSE AD: reversal of dabigatran with idarucizumab.



Idarucizumab



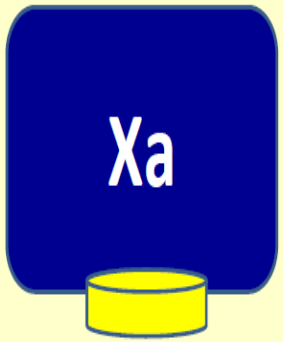


Eikelboom et al; Circulation 2015

Factor Xa inhibitor antidote (andexanet alpha, PRT064445, Annexa™-A)

Possibile antidoto

Non ha il residuo Gla



Fattore Xa normale. Ha il residuo Gla da carbossilare da parte della vitamina K. In questo modo è coagulabile.

Greinacher A et al. Thromb Haemost 2015; 113: 931-942

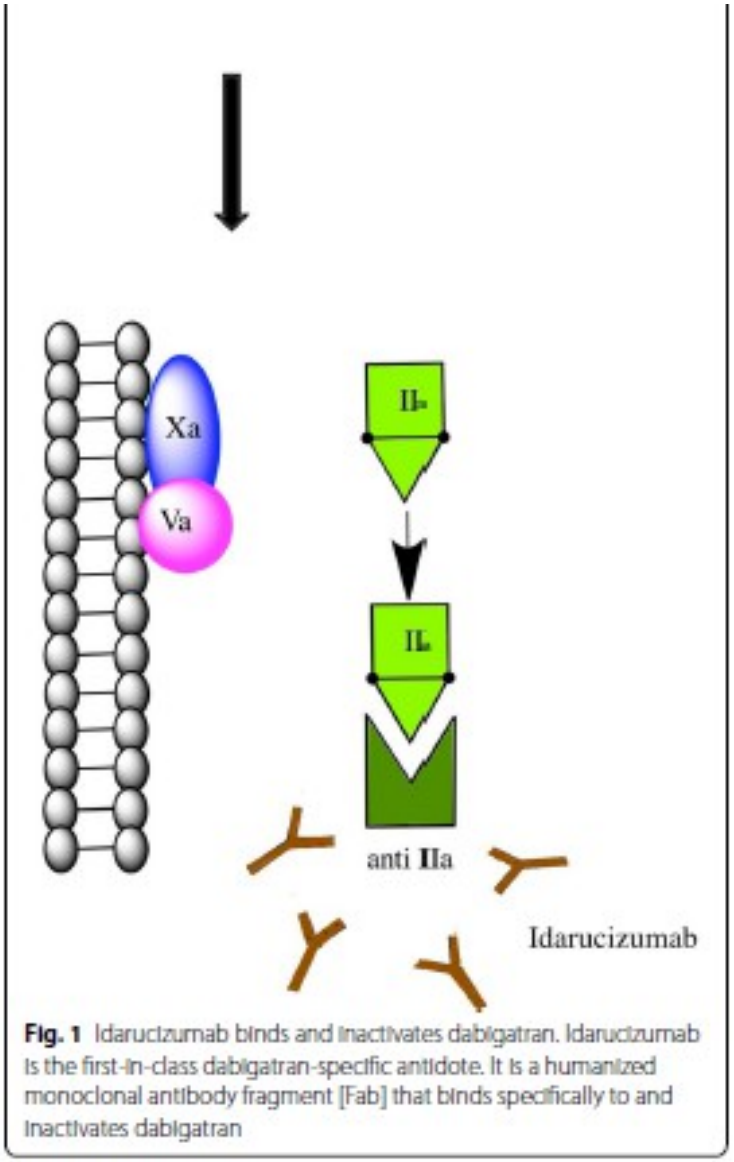
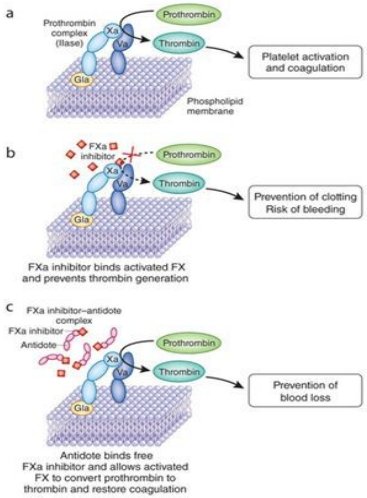


Fig. 1 Idarucizumab binds and inactivates dabigatran. Idarucizumab is the first-in-class dabigatran-specific antidote. It is a humanized monoclonal antibody fragment [Fab] that binds specifically to and inactivates dabigatran

Andexanet alfa

Andexanet Alfa

Future Antidote for Factor Xa Inhibitors



- Recombinant Fxa decoy
- No coagulant activity
- Neutralizes anti-Fxa inhibitors
- Effective w/in 2-5 min
- Need 2h infusion for sustained suppression
- Starting Phase 3b-4 study

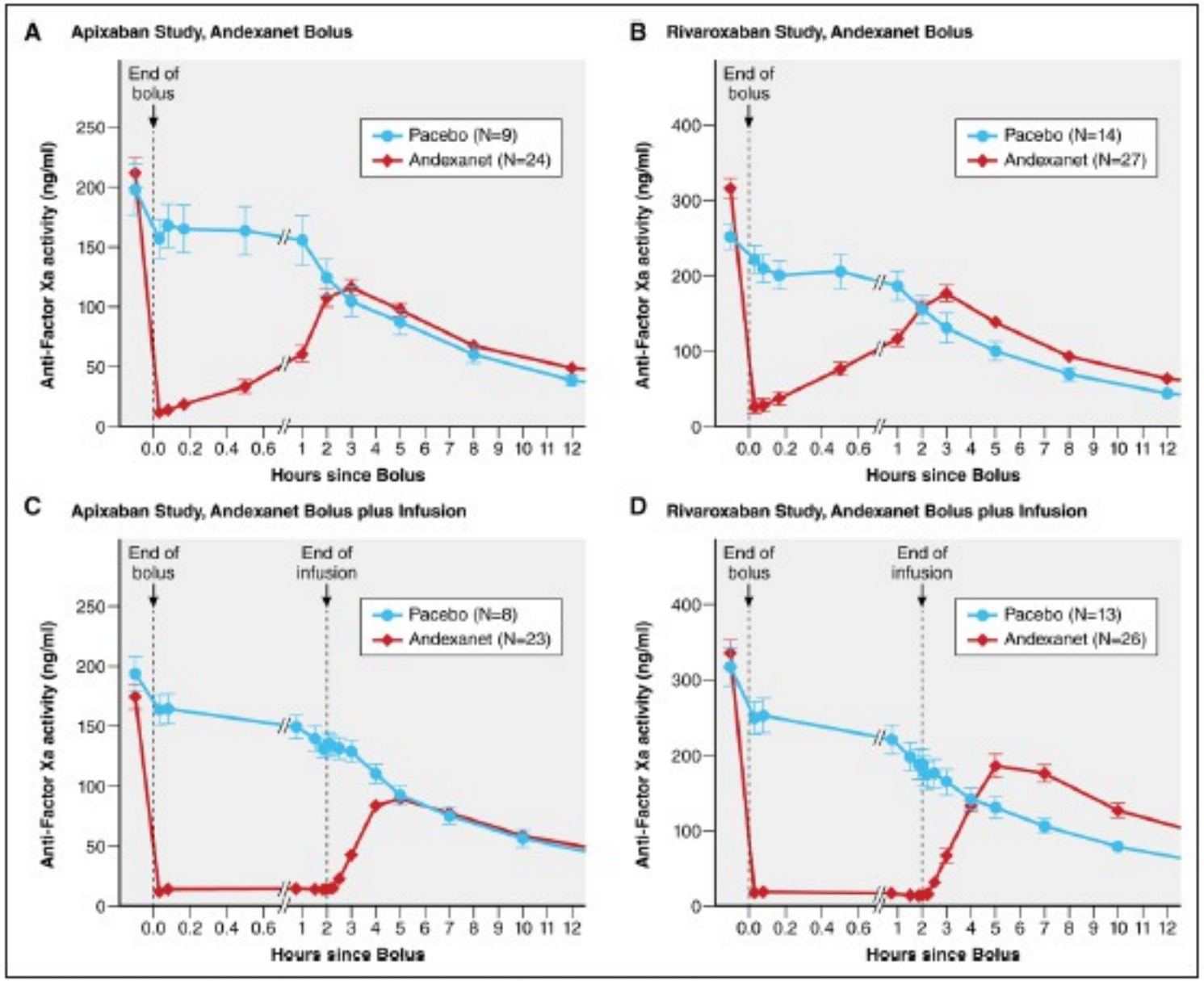


Figure 3. ANNEXA-A and -R: reversal of factor Xa inhibitors with andexanet.

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

International Society on Thrombosis and Haemostasis

Indications for use

Bleeding

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

Surgery

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

Levy JH et al. JTH 2016; 14:623-7

CONCLUSIONI:

- ✓ Nello studio RE-VERSE AD il **28%** dei pazienti ha ricevuto l'idarucizumab nonostante valori di TTd non elevato
- ✓ Gli eventi trombotici a 30 gg sono risultati del **5.6**%
- ✓ **L'andexanet** è capace di riportare una buona emostasi nell'**80%** dei pazienti con emorragia e **l'idarucizumab** nel **90%** dei pazienti chirurgici
- ✓ L'**ETP** è aumentato dopo somministrazione di andexanet
- ✓ Gli eventi trombotici a 30 gg sono risultati del **18%**