Strategie di reversal in urgenza

Daniela Poli

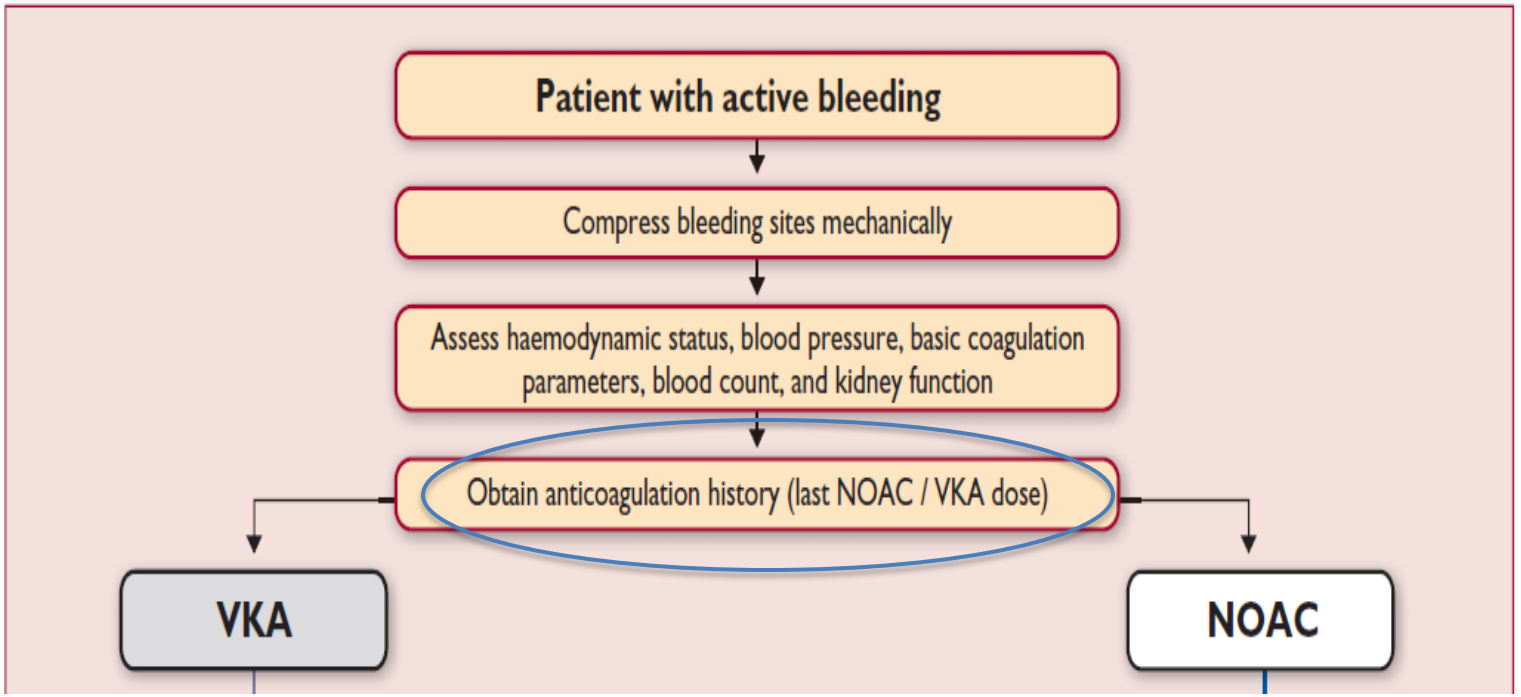
Diclosures

Fees for collaboration and advisory board membership:

- Daiichi Sankyo
- Pfizer BMS
- Bayer

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)



European Heart Journal, 2016

Possible measures to take in case of bleeding

	Direct thrombin inhibitors (dabigatran)	FXa inhibitors (apixaban, edoxaban, and rivaroxaban)
None life-threatening bleeding	Inquire last intake + dosing regimen. Estimate normalization of haemostasis: Normal renal function: 12–24 h CrCl 50–80 mL/min: 24–36 h CrCl 30–50 mL/min: 36–48 h CrCl < 30 mL/min: ≥48 h Maintain diuresis. Local haemostatic measures. Fluid replacement (colloids if needed). RBC substitution if necessary. Platelet substitution (in case of thrombocytopenia ≤60 × 10^9/L or thrombopathy). Fresh frozen plasma as plasma expander (not as reversal agent) Tranexamic acid can be considered as adjuvans. Desmopressin can be considered in special cases (coagulopathy or thrombopathy) Consider dialysis (preliminary evidence: −65% after 4 h).[122] Charcoal haemoperfusion can be considered (based on preclinical data)	Inquire last intake + dosing regimen. Normalisation of haemostasis: 12–24 h Local haemostatic measures. Fluid replacement (colloids if needed). RBC substitution if necessary. Platelet substitution (in case of thrombocytopenia ≤60 × 10^9/L or thrombopathy). Fresh frozen plasma as plasma expander (not as reversal agent) Tranexamic acid can be considered as adjuvans. Desmopressin can be considered in special cases (coagulopathy or thrombopathy)

EHRA ESC 2015

Management options:

Supportive mesures

Specifical reversal strategies

Reduction of drug exposure

- Delay or stop next dose of DOAC
- Hold antiplatelet therapy
- Active charcoal orally if last dose < 3 h
- [Hemodialysis (dabigatran)]

Support for circulation and oxygenation

Intravenous access

- Volume expanders
- Other hemodynamic support
- Oxygen on mask or nasal prongs
- Red cells concentrates
- Correct acidosis
- Counteract hypothermia

Local measures

- Compression of bleeding source (if possible)
- Apply topical thrombin or fibrin glue
- Invasive maneuvers
- Coiling or regional embolization
- Surgical intervention

Activated Charcoal

- In vitro it absorbs 99.9% of dabigatran suspended in acidic water
- its adminstration should be done within 1–2 h after intake of the drug
  (van Ryn et al. Thromb Haemost 2010)

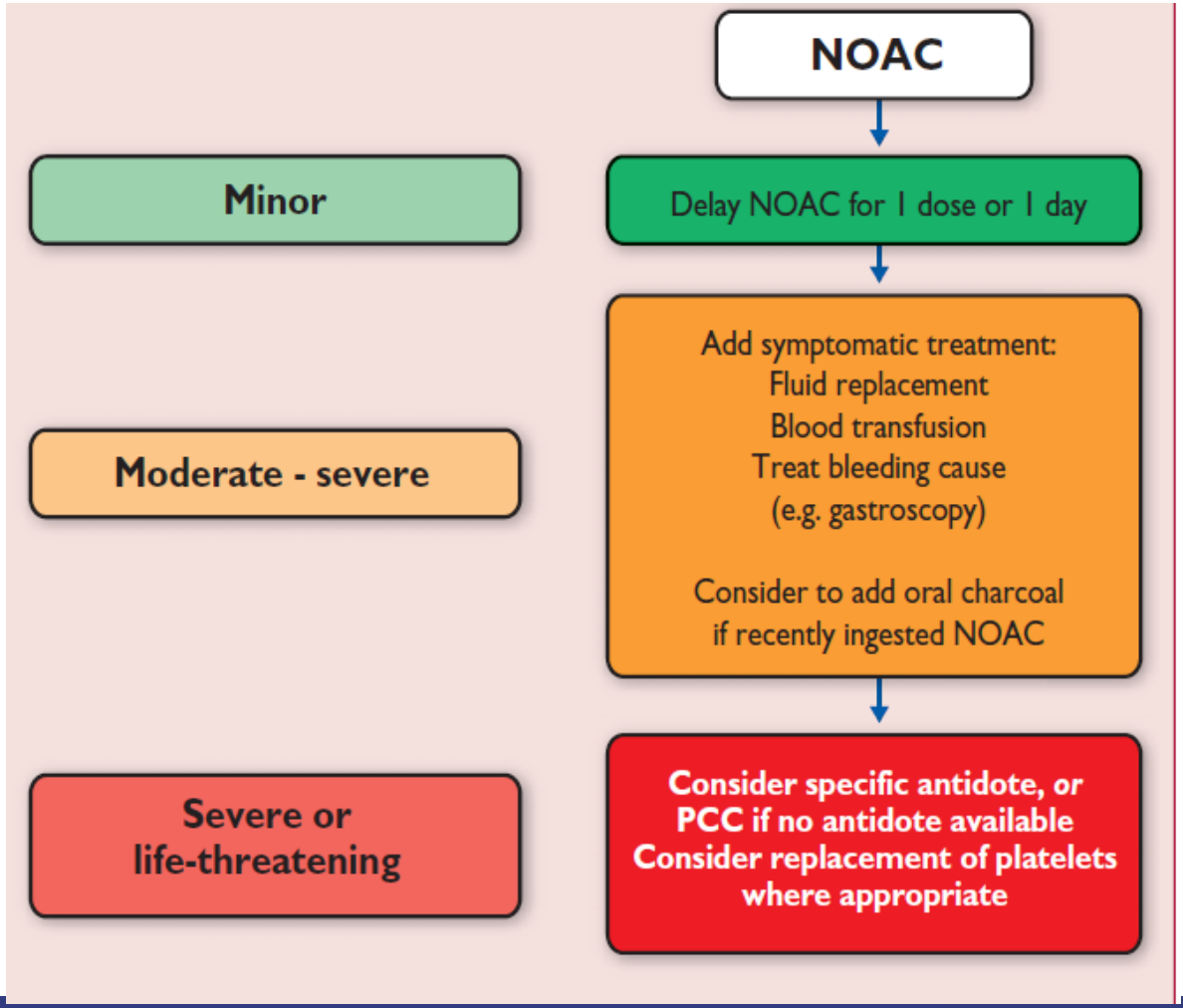
Possible measures to take in case of bleeding: reversal strategies

	dabigatran	Factor Xa inhibitors
Life-threatening bleeding	All of the above. Prothrombin complex concentrate (PCC) 50 U/kg (with additional 25 U/kg if clinically needed) (but no clinical ata). 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)	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)

EHRA ESC 2015

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)



Eur Heart J, 2016

ANTIDOTES

- Dabigatran — Idarucizumab
- Factor Xa inhibitors — Andexanet alfa
- (Universal inhibitor — Ciraparantag)

Idarucizumab

Pharmacokynetics

- Humanized monoclonal antibody fragment
- High affinity for dabigatran and dabigatran metabolites
- Cleared by kidney
- Half life 45’ (normal renal function)

Therapeutic dosages

- 2 intravenous infusion of 2.5 g (5-10’ within 15’ each other)

The NEW ENGLAND JOURNAL of MEDICINE

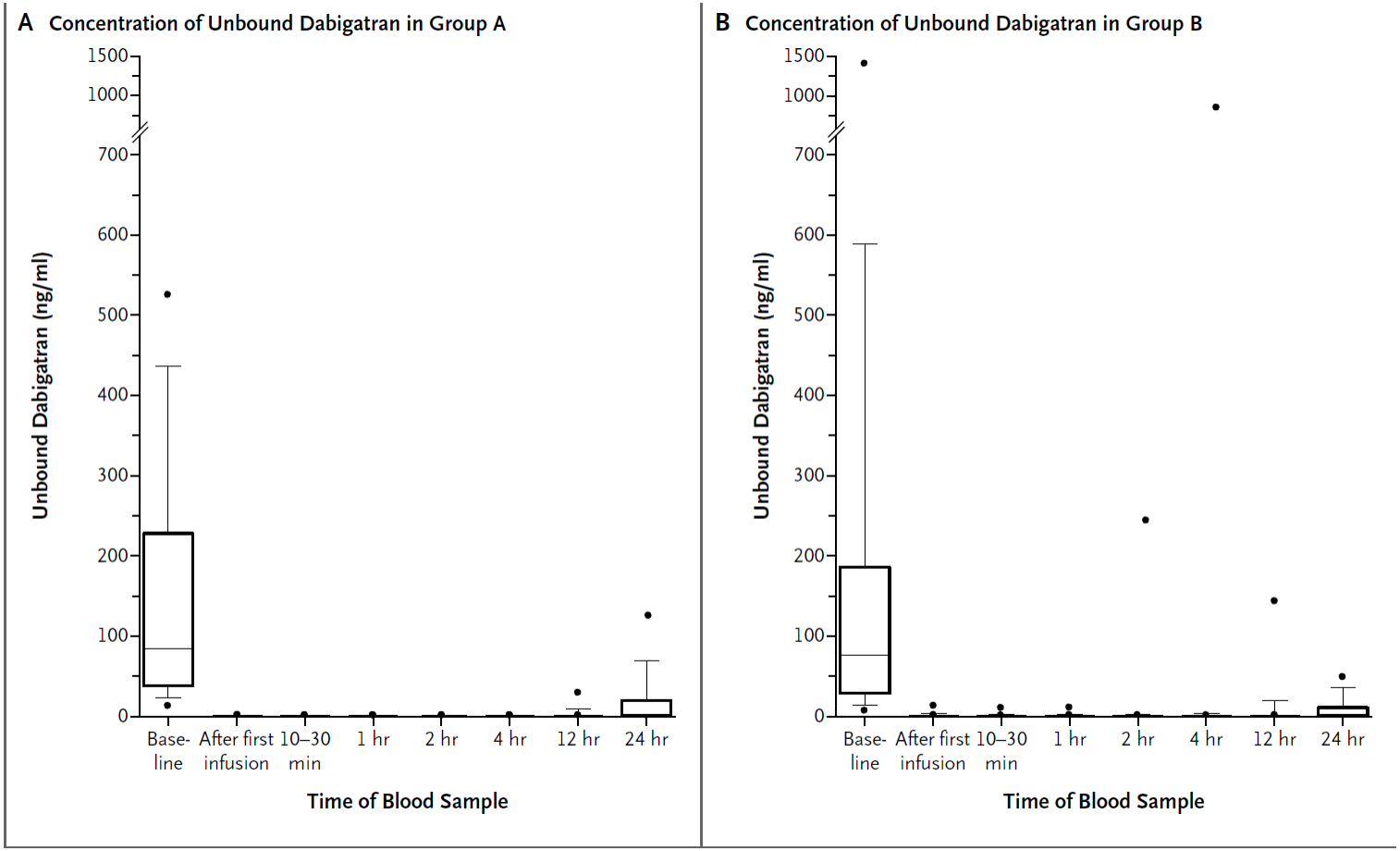
ORIGINAL ARTICLE

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.

N Engl J Med, 2015

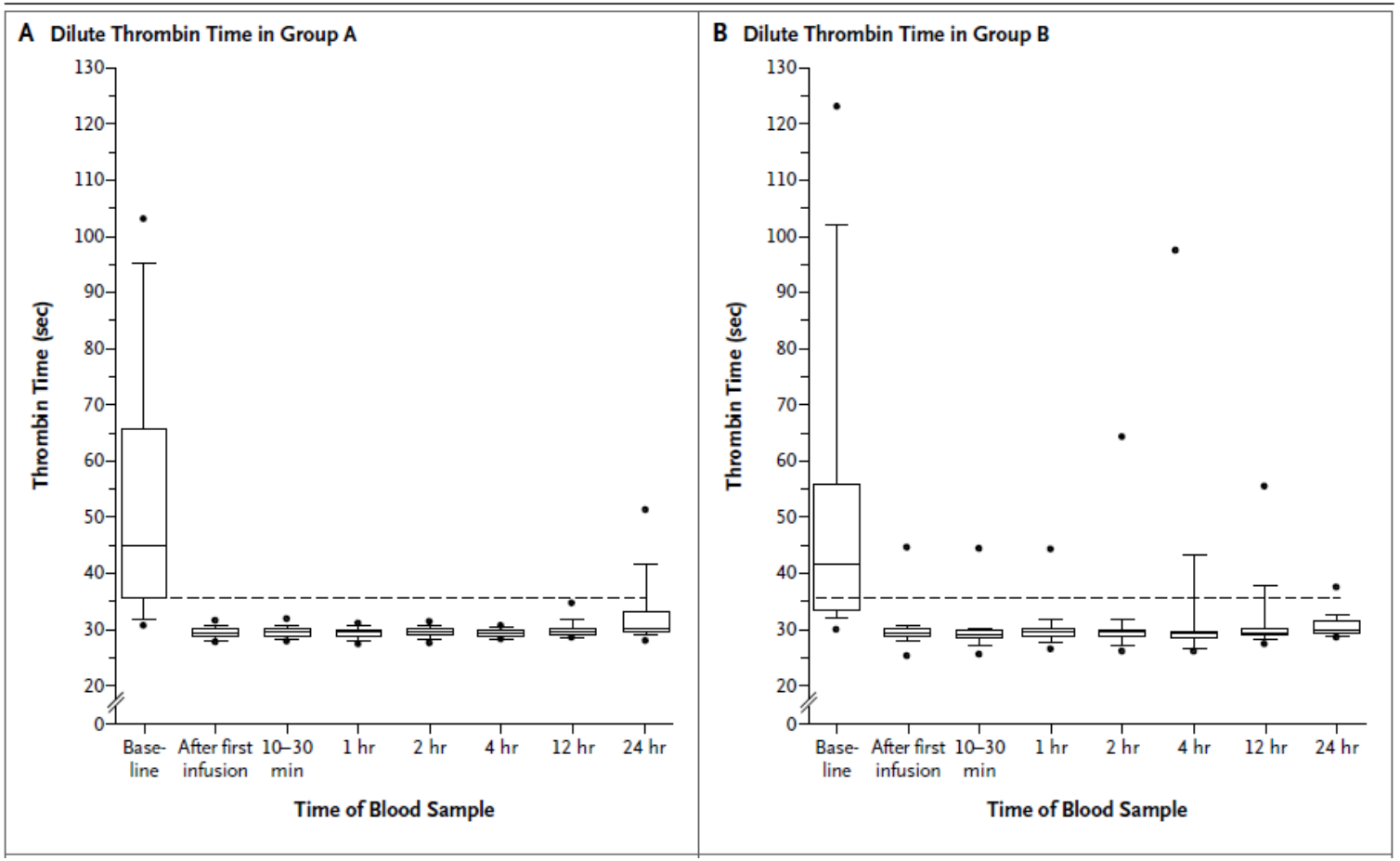
Time Courses of Plasma Concentrations of Unbound Dabigatran before and after the Administration of Idarucizumab



patients who had serious bleeding

patients who required urgent surgery

Time Courses of Plasma Concentrations of Diluted Thrombin Time before and after the Administration of Idarucizumab



patients who had serious bleeding

patients who required urgent surgery

Pollack V, NEJM 2015

Idarucizumab for Dabigatran Reversal

Table 1. Clinical Characteristics of the Patients.*

Characteristic	Group A (N=51)	Group B (N=39)	Total (N=90)
Age — yr			
Median	77.0	76.0	76.5
Range	48–93	56–93	48–93
Male sex — no. (%)	32 (63)	18 (46)	50 (56)
Type of bleeding — no. (%)§			
Intracranial	18 (35)	—	18 (20)
Trauma-related	9 (18)	—	9 (10)
Gastrointestinal	20 (39)	—	20 (22)
Other	11 (22)	—	11 (12)

Group A outcome
9 death: 4 whithin 96 h, 3 ICH

N Engl J Med, 2015

Idarucizumab for dabigatran reversal

- Rapidly and complete reversal of the anticoagulant activity of dabigatran in 88 to 98% of patients

- No safety concerns among the 90 patients involved in this study — including patients who were given idarucizumab on clinical grounds but were later found to have had normal results on clotting tests at baseline — or among the more than 200 volunteers who were administered idarucizumab in previous studies

Pollack V, NEJM 2015

Andexanet alfa

Pharmacokynetics

- Recombinant modified human factor Xa decoy protein catalytically inactive
- Binds factor Xa inhibitors (apixaban, edoxaban, rivaroxaban, heparin and fondaparinux) in the active site with high affinity (1:1 ratio).
- Binds and sequesters factor Xa inhibitors within the vascular space, restoring the activity of endogenous factor Xa and reducing levels of anticoagulant activity.
- Binds also TFPI with transient elevation of F1+2 and Ddimer
- Half life ≈ 1 hour

Andexanet alfa

Therapeutic dosages

Apixaban:	bolus of 400 mg iv in 30’
	followed by 4 mg/min/120’ (480 mg)
Rivaroxaban:	bolus of 800 mg iv in 30’
(edoxaban)	followed by 8 mg/min/120’ (960 mg)

Ciraparantag

- Universal reversal agent
- Synthetic cationic small molecule
- Binds dabigatran, apixaban, edoxaban, rivaroxaban, heparin via non-covalent hydrogen bonds
- Proposed dose: single 100 mg IV dose in 30’
- Renal excretion
- Restored baseline hemostasis within 10–30 minutes and effects were sustained for 24 hours.
- Phase 3 studies under way

ANTIDOTES

Small studies

Possible adverse events

Costs

Inadequate use

Usefulness of the laboratory in emergency

Measurement of circulating DOAC

To establish if bleeding or thrombosis is due to elevated or low drug levels

To assess residual circulating drug before surgery/invasive procedures

To make decision on thrombolysis in stroke patients

To make decision on antidotes

Tripodi A, 2016

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

*Duke University School of Medicine, Durham, NC, USA; †University of Insubria, Varese, Italy; ‡Monash University, Clayton, Vic., Australia; §McMaster University and the Thrombosis and Atherosclerosis Research Institute, Hamilton, ON, Canada; and ¶University of Leuven, Leuven, Belgium

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

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

*Duke University School of Medicine, Durham, NC, USA; †University of Insubria, Varese, Italy; ‡Monash University, Clayton, Vic., Australia; §McMaster University and the Thrombosis and Atherosclerosis Research Institute, Hamilton, ON, Canada; and ¶University of Leuven, Leuven, Belgium

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

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

Managing reversal of direct oral anticoagulants in emergency situations

Anticoagulation Education Task Force White Paper

Walter Ageno[1]; Harry R. Büller[2]; Anna Falanga[3]; Werner Hacke[4]; Jeroen Hendriks[5,6]; Trudie Lobban[7]; Jose Merino[8]; Ivan S. Milojevic[9]; Francisco Moya[10]; H. Bart van der Worp[11]; Gary Randall[12]; Konstantinos Tsioufis[13]; Peter Verhamme[14]; A. John Camm[15,16]

Table 3: Who should control access to reversal agents?

• Investigate whether there is a hospital bleeding management protocol – if not contact relevant departments: haematology, cardiology, neurology, etc.
• Check that the reversal agent has been incorporated into the hospital formulary – if not take steps for the reversal agent to be considered by the appropriate committee.
• Redraft the policy and flow chart(s) regarding the management of bleeding related to DOACs.
• Discuss with relevant staff where the reversal agent should be stored ([accident and] emergency department, pharmacy, etc).

Thromb Haemost 2016

Managing reversal of direct oral anticoagulants in emergency situations

Anticoagulation Education Task Force White Paper

Walter Ageno[1]; Harry R. Büller[2]; Anna Falanga[3]; Werner Hacke[4]; Jeroen Hendriks[5,6]; Trudie Lobban[7]; Jose Merino[8]; Ivan S. Milojevic[9]; Francisco Moya[10]; H. Bart van der Worp[11]; Gary Randall[12]; Konstantinos Tsioufis[13]; Peter Verhamme[14]; A. John Camm[15,16]

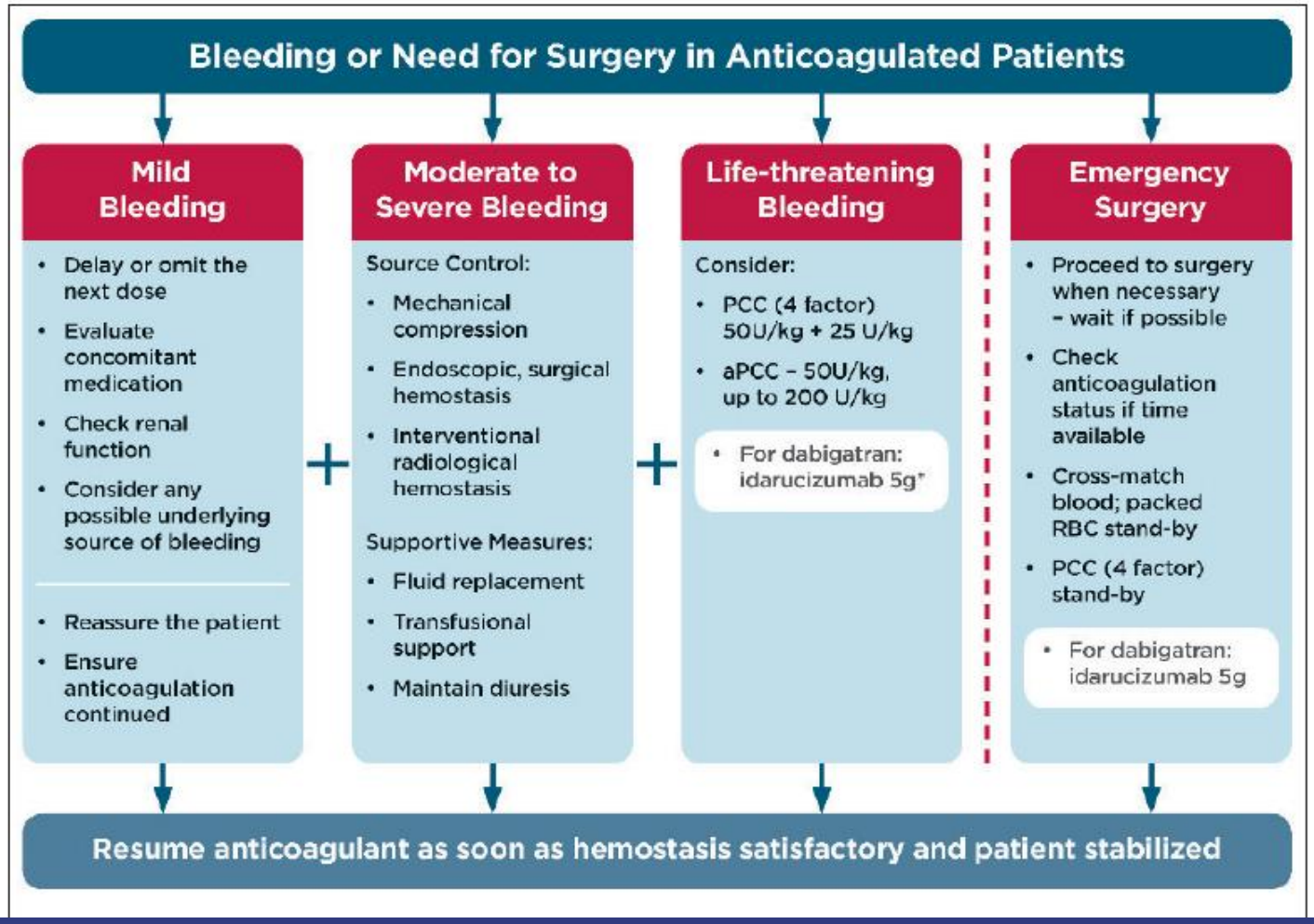
- Arrange a supply of the reversal agent via the pharmacy or contact with the pharmaceutical company.
- All appropriate hospital staff members should be made aware of the availability of specific reversal agent therapy.
- Where applicable, a patient prescribed DOAC therapy should be informed of the availability of a specific reversal agent.
- After use of the reversal agent inform the pharmacy (and the pharmaceutical company) that a new supply is needed.
- Maintain a log on the use of the reversal agent and consider joining a local, national or international registry of post-marketing experience with the reversal agent.

Thromb Haemost 2016

Managing reversal of direct oral anticoagulants in emergency situations

Anticoagulation Education Task Force White Paper

Walter Ageno[1]; Harry R. Büller[2]; Anna Falanga[3]; Werner Hacke[4]; Jeroen Hendriks[5,6]; Trudie Lobban[7]; Jose Merino[8]; Ivan S. Milojevic[9]; Francisco Moya[10]; H. Bart van der Worp[11]; Gary Randall[12]; Konstantinos Tsioufis[13]; Peter Verhamme[14]; A. John Camm[15,16]



Thromb Haemost 2016

Grazie per l’attenzione