IX EDIZIONE

Giornate Mediche di Santa Maria Nuova 2017

LA DIMISSIONE OSPEDALIERA "RITARDATA":
Complicanze intraospedaliere e criticità gestionali

5-6 Ottobre 2017

La reverse therapy nel paziente emorragico: una facilitazione nella gestione della terapia anticoagulante

LUCA MASOTTI

DIRETTORE SOSTITUTO

MEDICINA INTERNA II

OSPEDALE SAN GIUSEPPE, EMPOLI

REVERSE

=

neutralizzare l'attività di un farmaco anticoagulante ripristinando una efficace emostasi

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 2: Situations in which to consider use of a reversal agent.

Clinical situation	Definite need for a reversal agent	Reversal agent possibly helpful (patient-dependent)	Reversal agent generally not needed
Life-threatening bleeding (e.g., intracranial haemorrhage, symptomatic or expanding extradural haemorrhage, or uncontrollable haemorrhage)	X		
Bleeding in a closed space or critical organ (e.g., intracranial, intraspinal, intraocular, pericardial, pulmonary, retroperitoneal, or intramuscular with compartment syndrome)	X		
Persistent major bleeding despite local haemostatic measures, or risk of recurrent bleeding because of delayed DOAC clearance or DOAC overdose	X		
Need for urgent intervention that is associated with a high risk of bleeding and that cannot be delayed to allow for drug clearance	X		
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	X		
Need for urgent surgery or intervention in patients with acute renal failure		X	
Elective surgery			X
Gastrointestinal bleeds that respond to supportive measures			X
High drug levels or excessive anticoagulation without associated bleeding			X
Need for surgery or intervention that can be delayed long enough to permit drug clearance			X

DOACs, non-Vitamin K oral anticoagulants. Adapted from Levy et al. 2015 (31).

Perché il reverse urgente?

- Interrompere un sanguinamento
- Ridurre il rischio dell'espansione di un ematoma
- Permettere un'eventuale intervento chirurgico d'emergenza
- Migliorare l'outcome

Definizione di emorragie maggiori/a rischio di vita in corso di terapia antitrombotica: criteri ISTH

- Emorragia intracranica ed altro sanguinamento in organi critici (midollo spinale, peritoneo, retro-peritoneo, tratto gastro-enterico, torace, articolazioni, occhio, sindrome compartimentale)
- Emorragie che determinano un calo di 2 g/dl di Hb o che richiedono almeno 2 sacche di GR per trattarle
- Emorragie che richiedono l'intervento chirurgico o manovre invasive per arrestarle
- Emorragie fatali

Schulman S et al. JTH 205

frontiers in Neurology

REVIEW
published: 07 April 2017
doi: 10.3389/fneur.2017.00074

Secondary Hematoma Expansion and Perihemorrhagic Edema after Intracerebral Hemorrhage: From Bench Work to Practical Aspect

*Krista Lim-Hing[1] and Fred Rincon[1,2]**

TABLE 1 | Phases of ICH and proposed pathophysiologic events [with permission from Rincon and Mayer (59)].

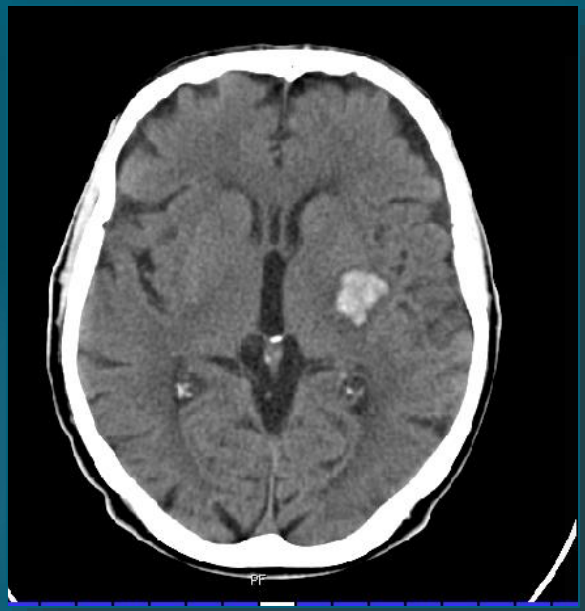
Phase	Event	Time	Implicated mechanism
I	Vascular rupture	1–10 s	Chronic vascular changes: lipohyalinosis, amyloid angiopathy, hypocholesterolemia
II	Hematoma formation	<1 h	Blood pressure, coagulation abnormalities
III	Hematoma expansion	1–6 h	Blood pressure, perihematomal vascular + tissue injury
IV	Edema formation	24–72 h	Cellular and humoral toxicity, blood degradation products

Espansione dell'ematoma

- **L'espansione si verifica in circa il 40% dei casi**
  - √ **2/3 nella prime 1-3 ore dopo la formazione dell'ematoma**
  - √ **1/3 nelle restanti 20 ore**

- **Ciò corrisponde generalmente ad un deterioramento del GCS (early neurological deterioration END or worsening ENW)**

- **Più rara è la espansione dopo le prime 24 ore e la recidiva emorragica**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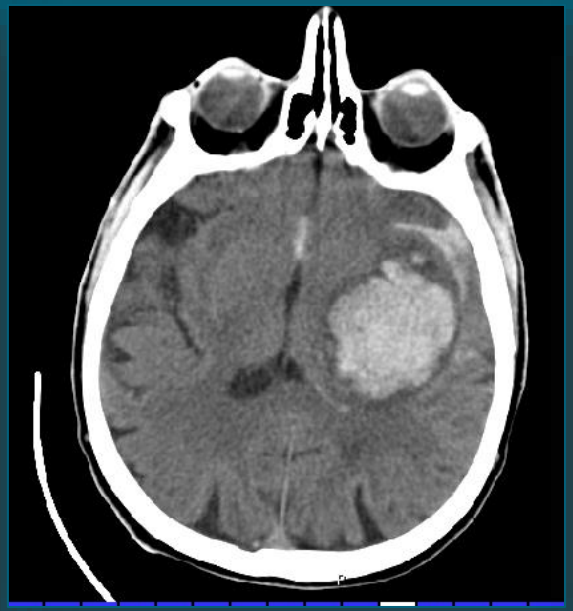
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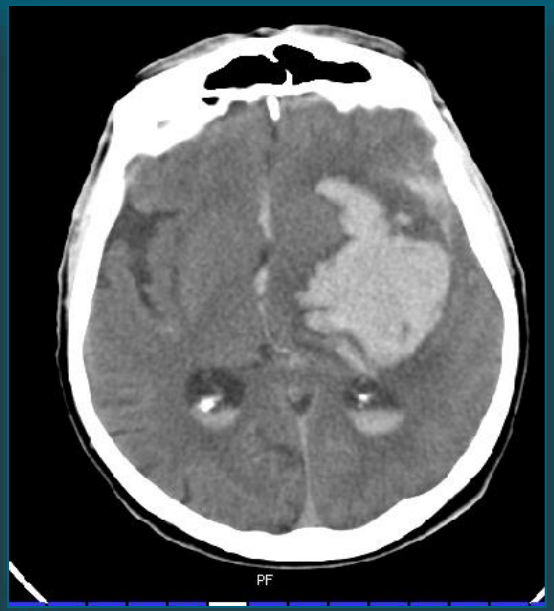
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Outcome of intracerebral hemorrhage associated with different oral anticoagulants

Neurology® 2017;88:1693-1700

Figure 1 Flowchart of study design and patient selection

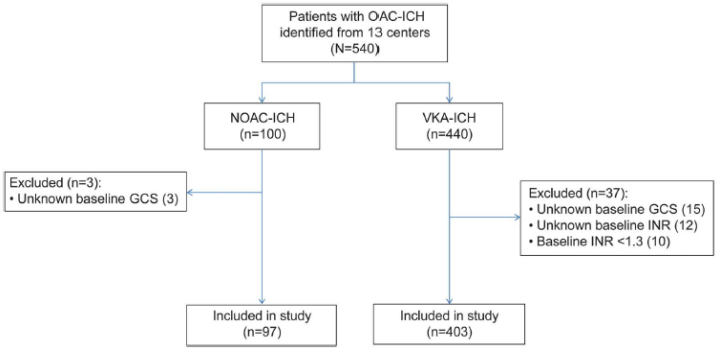


Table 2 Characteristics of participants with non-vitamin K antagonist oral anticoagulant (NOAC)-associated intracerebral hemorrhage (ICH) and vitamin K antagonist (VKA)-associated ICH

Variable	NOAC-ICH (n = 97)	VKA-ICH (n = 403)
Age, y, median (IQR)	80 (74-85)	80 (72-85)
Male sex, n (%)	53 (55)	196 (49)
ICH location		
Lobar area	38 (39)	158 (39)
Supratentorial deep areas	40 (41)	198 (49)
Cerebellum	13 (13)	26 (6)
Brainstem	6 (6)	21 (5)
Glasgow Coma Scale, median (IQR)	14 (12-15)	15 (13-15)
Acute neurosurgery, n (%)	7 (7)	24 (6)
IVH extension, n (%)	42 (43)	146 (36)
Premorbid mRS, median (IQR)[a]	1 (0-3)	0 (0-2)
Early palliation, n (%)	11 (13)	28 (7)
Anticoagulation for atrial fibrillation, n (%)	85/86 (99)	267/332 (80)

Neurology® 2017;88:1693-1700

Figure 2 Survival curve comparing non-vitamin K oral antagonist anticoagulant (NOAC)-associated intracerebral hemorrhage (ICH) and vitamin K antagonist anticoagulant (VKA)-associated ICH 90-day mortality

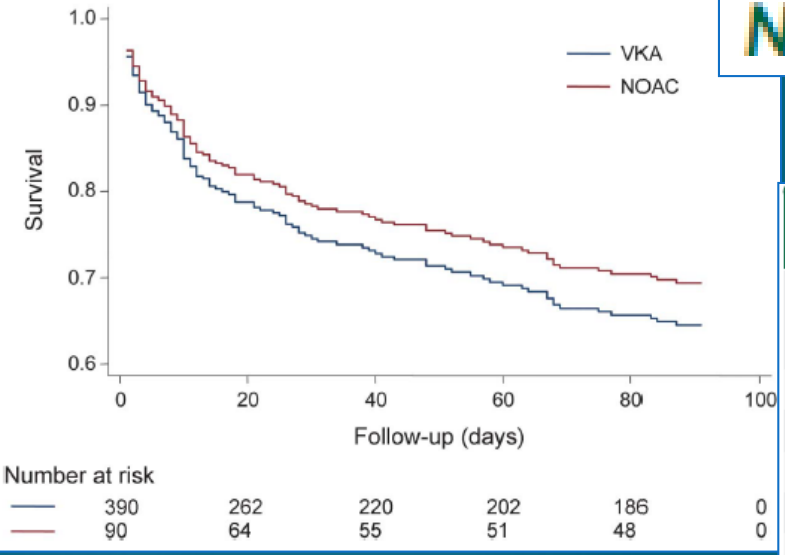
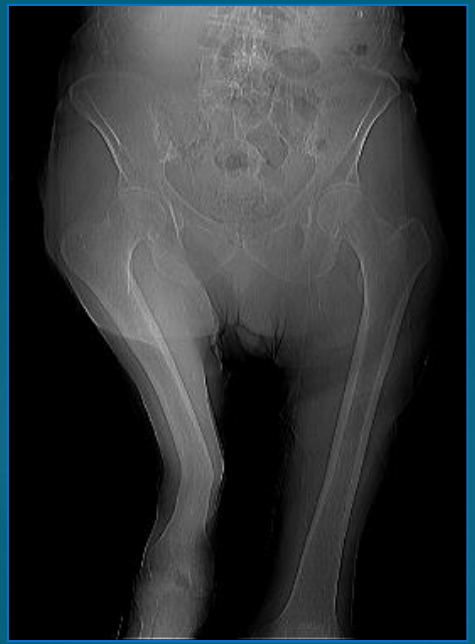
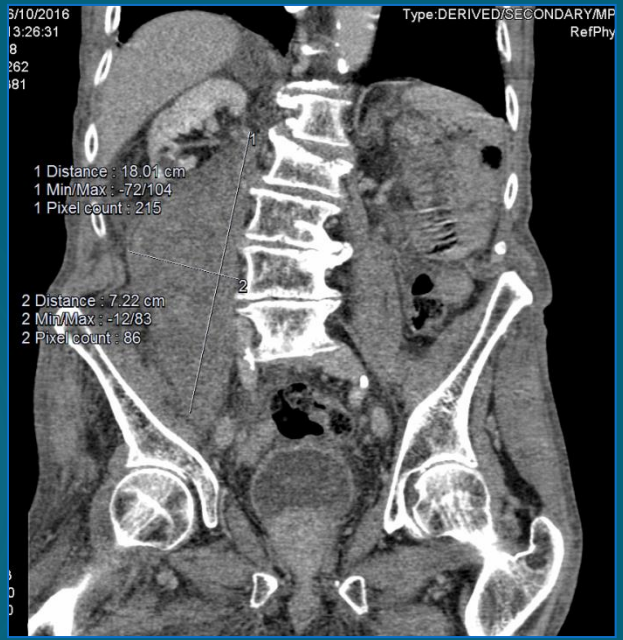


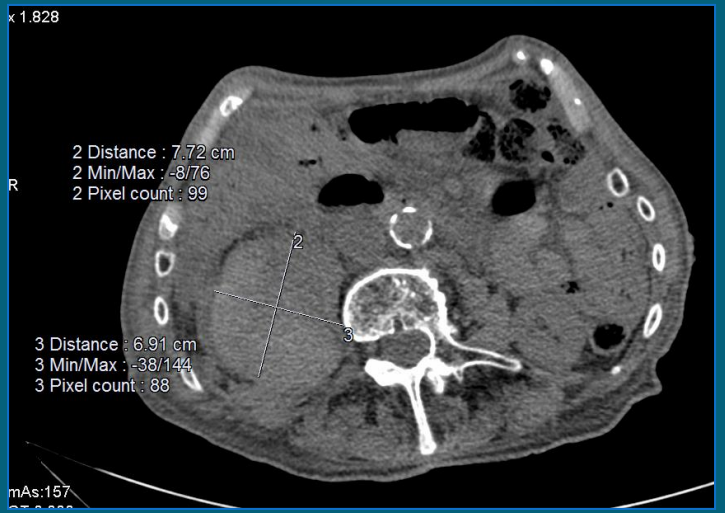
Table 3 Cox proportional hazards models: univariable and multivariable analyses for the primary outcome of 90-day mortality

		Univariable model		Multivariable model	
Variables	**Units**	**HR (95% CI)**	**p Value**	**HR (95% CI)**	**p Value**
Sex	Female	1.00 (reference)		1.00 (reference)	
	Male	1.08 (0.77-1.51)	0.65	0.92 (0.68-1.32)	0.654
Age	Per year	1.04 (1 .02-1.06)	0.001	1.04 (1.01-1.06)	0.002
GCS	Per point	0.81 (0.78-0.85)	0.001	0.85 (0.80-0.89)	0.001
ICH volume	Per (log) mL	1.58 (1.38-1.82)	0.001	1.38 (1.17-1.64)	0.001
IVH volume	Per (log) mL	1.525 (1.37-1.70)	0.001	1.18 (0.98-1.44)	0.081
ICH location	Lobar area	1.00 (reference)		1 (reference)	
	Supratentorial deep areas	0.94 (0.67-1.32)	0.74	1.26 (0.83-1.90)	0.277
	Cerebellum	0.73 (0.36-1.49)	0.39	1.31 (0.59-2.93)	0.514
	Brainstem	0.94 (0.42-2.14)	0.89	3.36 (1.30-8.70)	0.012
Neurosurgery	vs no neurosurgery	0.84 (0.41-1.71)	0.63	0.45 (0.20-1.00)	0.051
Anticoagulant type	VKA	1.00 (reference)		1 (reference)	
	NOAC	1.10 (0.73-1.67)	0.65	0.93 (0.52-1.64)	0.792

Caso clinico: ematoma retro-peritoneale in paziente in AVK





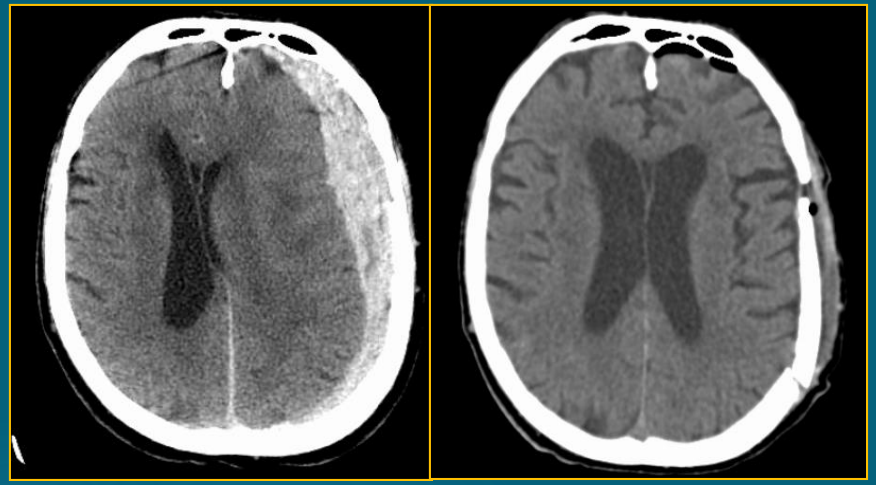


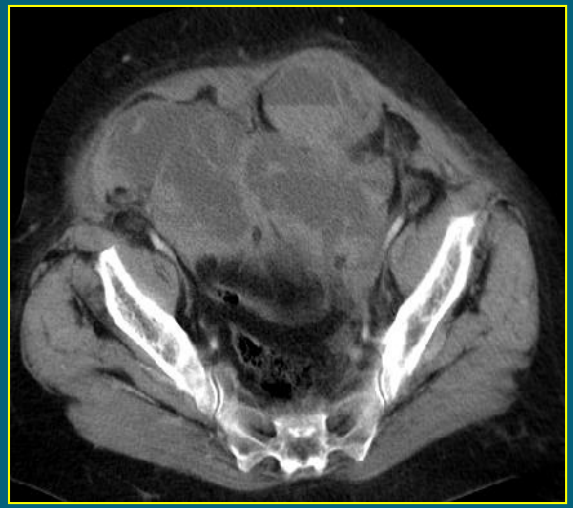
Rapporto tra AO e chirurgia in emergenza-urgenza

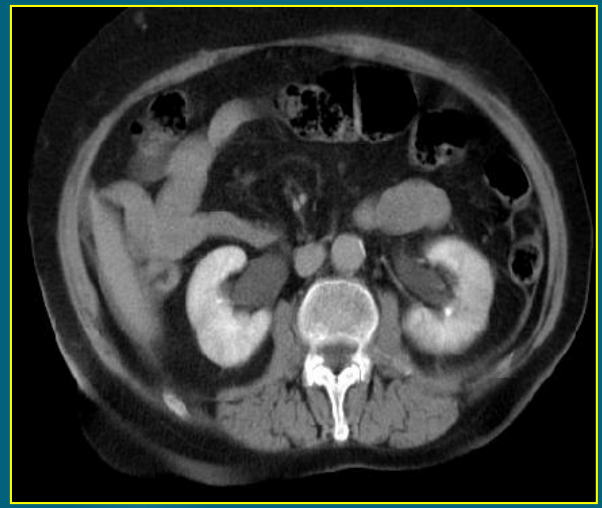
Emorragia maggiore AO-correlata richiedente l'intervento chirurgico per arrestarla-risolverla (emorragia intracranica, digestiva, retroperitoneale, peritoneale ecc.)

L'intervento chirurgico in emergenza/urgenza (entro 4-6 ore) richiede la neutralizzazione urgente della AO, ma non è finalizzato all'arresto di una emorragia (esempio intervento che prevede una laparotomia ecc.)

Situazioni in cui la prosecuzione della AO può condurre all'intervento chirurgico d'urgenza (trauma grave non immediatamente chirurgico, esempio poli-trauma ecc)



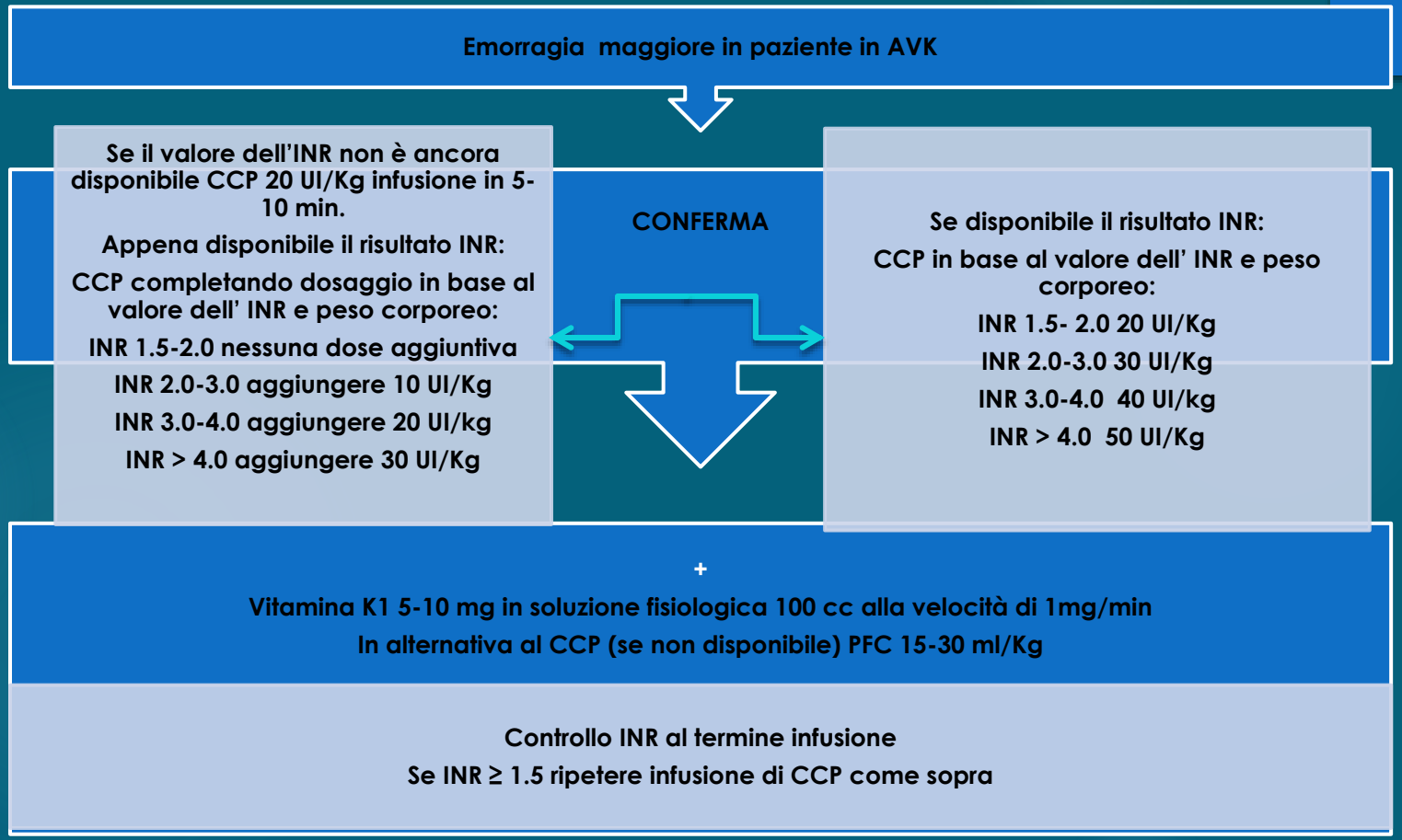




Reversal therapy: attuali opzioni

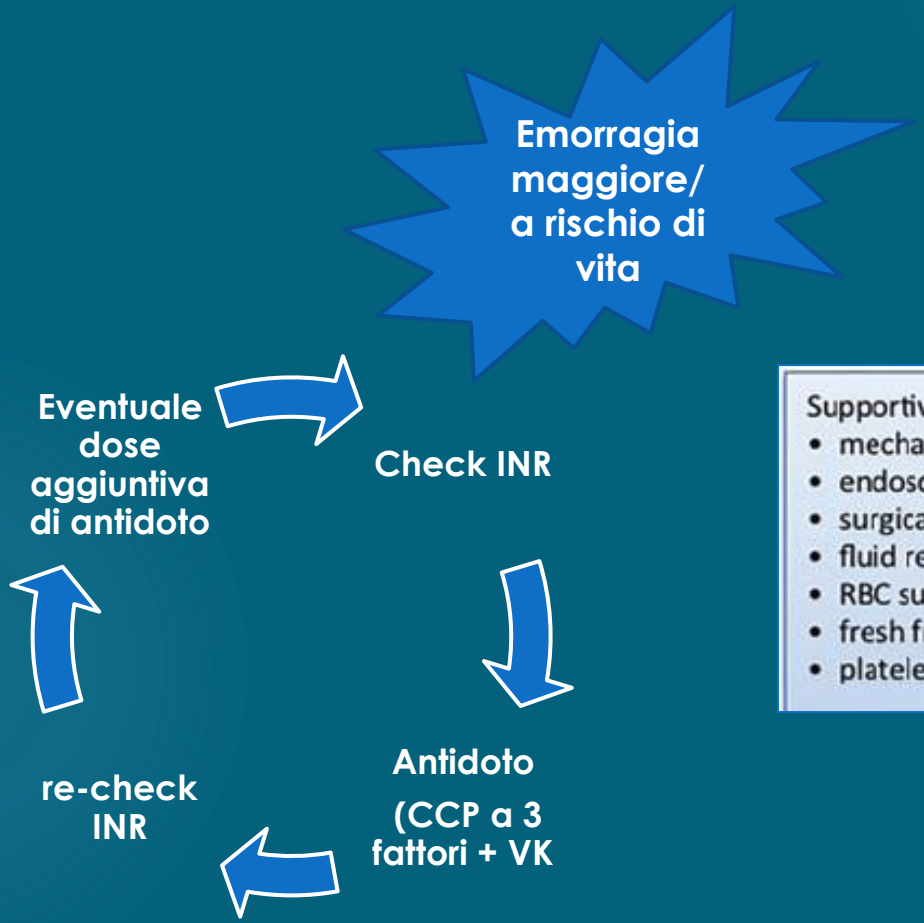
Farmaco	**Sito d'azione**	**Antidoti specifici**	**Possibili strategie**
rtPA	plasminogeno	No	Acido tranexamico, PFC, concentrati di fibrinogeno o crioprecipitati
ENF	Factori Xa e IIa (rapporto antiXa/antilla 1:1)	**Solfato di protamina**	Solfato di protamina
EBPM	Fattori Xa e IIa (rapporto antiXa/antilla 4:1)	No	Solfato di protamina a dose aumentata del 50% rispetto alla ENF
Fondaparinux	Fattore Xa	No	FVIIra
AVK	Fattori II, VII, IX, X	**VK1**	CCP 3 o 4 fattori; PFC; VK1
Dabigatran	Fattore IIa,	**Idarucizumab**	Idarucizumab; CCP 3 o 4 fattori; FEIBA; FVIIra
DOAC antiXa	Fattore Xa	No	CCP 3 o 4 fattori; FEIBA; FVIIra
Antiaggreganti	Inibizione ciclo-ossigenasi (COX), R ADP, P2Y12	No	Trasfusioni piastriniche, desmopressina

Flow chart per la corretta neutralizzazione dell'INR nelle emorragie maggiori AVK correlate



Modificato da Masotti L. et al. Reviews in Health Care 2011; 2: 9-8

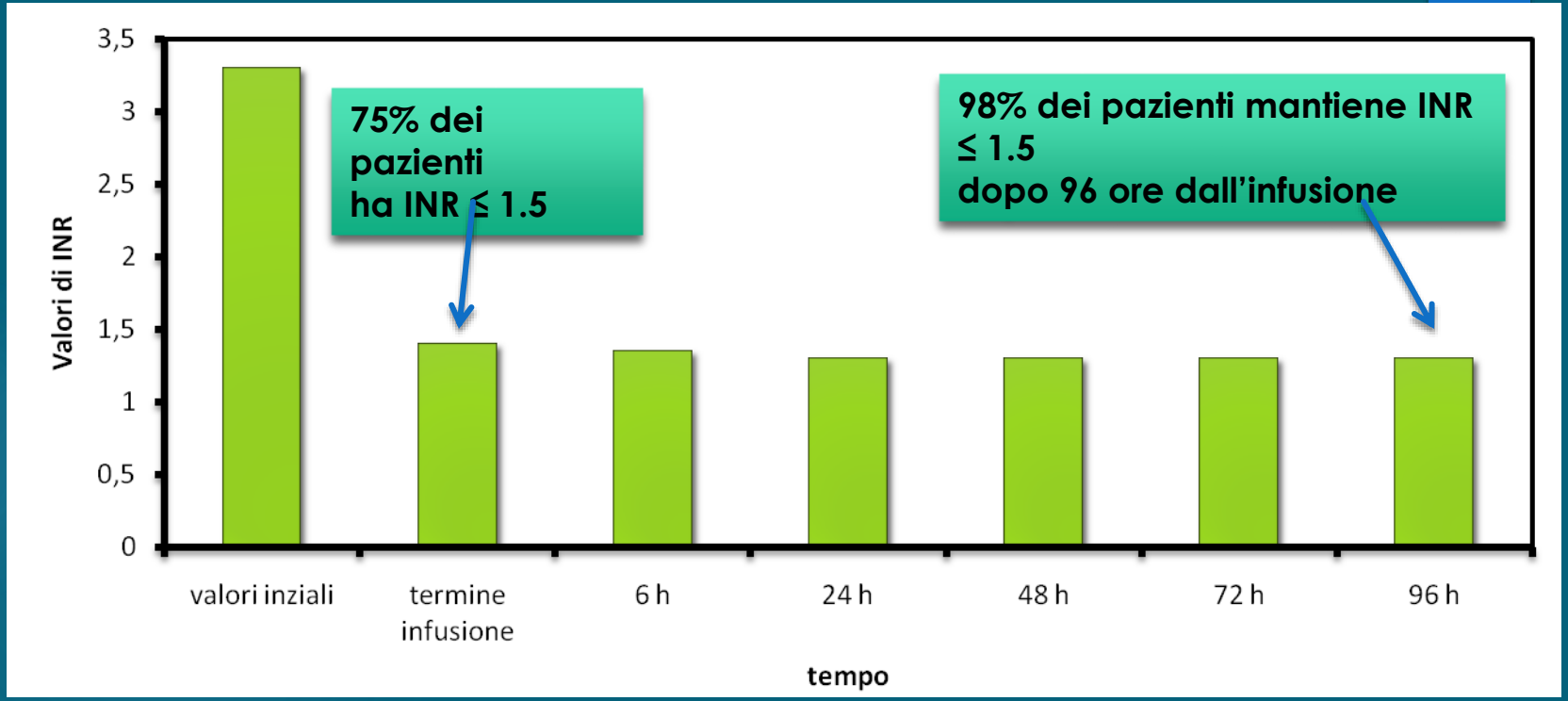
Reverse dei farmaci AVK



Supportive measures :

- mechanical compression
- endoscopic hemostasis if gastro-intestinal bleed
- surgical hemostasis
- fluid replacement (colloids if needed)
- RBC substitution if needed
- fresh frozen plasma (as plasma expander)
- platelet substitution (if platelet count $\leq 60 \times 10^9$/L)

Effetto del CCP a 3 fattori sul reverse degli AVK e sua durata



Imberti D et al. Pathophysiol Haemost Thromb 2007-08; 36: 259-265

Quando il CCP a 4 fattori nell'emorragie da farmaci AVK?

E' stato dimostrato che in caso di valori molto elevati di INR il CCP a 4 fattori potrebbe essere più efficace del CCP a 3 fattori nel neutralizzare l'INR

Pertanto se ne raccomanda l'uso nei casi di emorragia maggiore con valori di INR almeno ≥ 4

Original Investigation

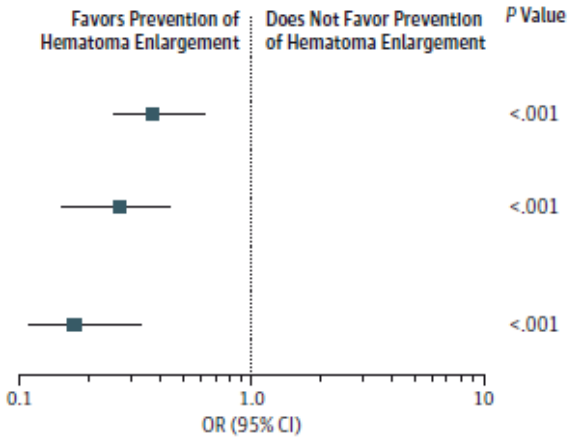
Anticoagulant Reversal, Blood Pressure Levels, and Anticoagulant Resumption in Patients With Anticoagulation-Related Intracerebral Hemorrhage

JAMA. 2015;313(8):824-836.

Joji B. Kuramatsu, MD; Stefan T. Gerner, MD; Peter D. Schellinger, MD; Jörg Glahn, MD; Matthias Endres, MD; Jan Sobesky, MD; Julia Flechsenhar, MD; Hermann Neugebauer, MD; Eric Jüttler, MD; Armin Grau, MD; Frederick Palm, MD; Joachim Röther, MD; Peter Michels, MD; Gerhard F. Hamann, MD; Joachim Hüwel, MD; Georg Hagemann, MD; Beatrice Barber, MD; Christoph Terborg, MD; Frank Trostdorf, MD; Hansjörg Bäzner, MD; Aletta Roth, MD; Johannes Wöhrle, MD; Moritz Keller, MD; Michael Schwarz, MD; Gernot Reimann, MD; Jens Volkmann, MD; Wolfgang Müllges, MD; Peter Kraft, MD; Joseph Classen, MD; Carsten Hobohm, MD; Markus Horn, MD; Angelika Milewski, MD; Heinz Reichmann, MD; Hauke Schneider, MD; Eik Schimmel, MD; Gereon R. Fink, MD; Christian Dohmen, MD; Henning Stetefeld, MD; Otto Witte, MD; Albrecht Günther, MD; Tobias Neumann-Haefelin, MD; Andras E. Racs, MD; Martin Nueckel, MD; Frank Erbguth, MD; Stephan P. Kloska, MD; Arnd Dörfler, MD; Martin Köhrmann, MD; Stefan Schwab, MD; Hagen B. Huttner, MD

Figure 3. Adjusted Graphical Regression Analysis of Combined Associations of INR Reversal, Systolic Blood Pressure, and Timing With Hematoma Enlargement

	No. of Patients	Patients With Hematoma Enlargement, No. (%)	OR (95% CI)	P Value
INR <1.3				
Achieved	432	116 (26.9)	0.37 (0.26-0.59)	<.001
Did not achieve	421	191 (45.4)		
INR <1.3 within 4 hours				
Achieved	217	43 (19.8)	0.27 (0.15-0.43)	<.001
Did not achieve	636	264 (41.5)		
INR <1.3 within 4 hours and systolic BP <160 mm Hg within 4 hours				
Achieved	193	35 (18.1)	0.17 (0.11-0.33)	<.001
Did not achieve	498	220 (44.2)		



Multivariable model for the combined associations, ie, extent and timing of international normalized ratio (INR) reversal and systolic blood pressure (BP), with hematoma enlargement. Hematoma enlargement was defined as relative volume increase of >33% on follow-up imaging. Adjustments consisted of all nonmodifiable parameters associated with hematoma enlargement, ie, time from symptom onset to imaging, deep intracerebral hemorrhage location, National Institutes of Health Stroke Scale score, and comorbidity (eTable 2 in the Supplement). OR indicates odds ratio.

Safety of prothrombin complex concentrates for rapid anticoagulation reversal of vitamin K antagonists

A meta-analysis

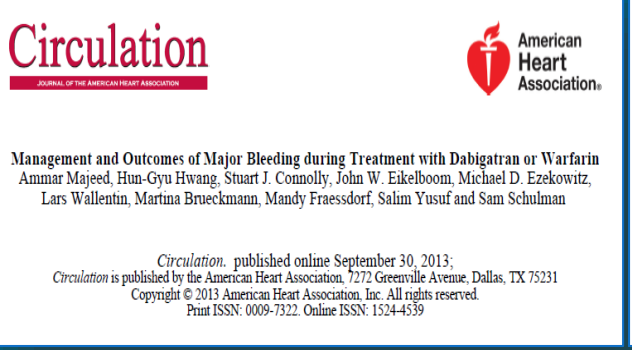
Francesco Dentali[1]; Chiara Marchesi[1]; Matteo Giorgi Pierfranceschi[2]; Mark Crowther[3]; David Garcia[4]; Elaine Hylek[5]; Daniel M. Witt[6,7]; Nathan P. Clark[6]; Alessandro Squizzato[1]; Davide Imberti[8]; Walter Ageno[1]

[1]University of Insubria, Varese, Italy; [2] Hospital of Piacenza, Piacenza, Italy; [3]McMaster University, Hamilton, Ontario, Canada; [4]University of New Mexico School of Medicine, Albuquerque, New Mexico, USA; [5]Boston University School of Medicine, Massachusetts, USA; [6]Kaiser Permanente Colorado Clinical Pharmacy Anticoagulation Service, Aurora, Colorado, USA; [7]Kaiser Permanente Colorado Clinical Pharmacy Research Team, Aurora, Colorado, USA; [8]Hospital of Ferrara, Ferrara, Italy

Table 2: Rate of complications.

	Rate (95% CI)
TE events	1.4% (0.8–2.1)
Death for all causes	10.6% (5.9–16.6)
TE events in pts treated for bleeding	1.9% (1.0–3.1)
TE events in pts treated before urgent surgery or invasive procedures	0.8% (0.1–2.0)
TE events in pts treated with 4-factor PCCs	1.8% (1.0–3.0)
TE events in pts treated with 3-factor PCCs	0.7% (0.0–2.4)
TE events in high quality studies	2.3% (0.5–5.4)
Viral transmission after PCC administration	1.9% (0.3–4.9)

TE, thromboembolic, pts: patients, PCCs: prothrombin concentrates.


Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

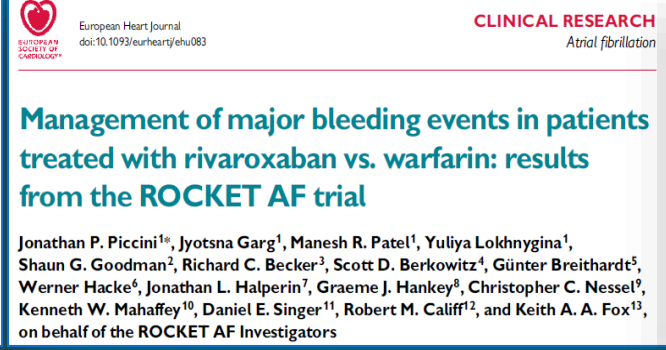
American Heart Association.

Management and Outcomes of Major Bleeding during Treatment with Dabigatran or Warfarin

Ammar Majeed, Hun-Gyu Hwang, Stuart J. Connolly, John W. Eikelboom, Michael D. Ezekowitz, Lars Wallentin, Martina Brueckmann, Mandy Fraessdorf, Salim Yusuf and Sam Schulman

Circulation. published online September 30, 2013;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

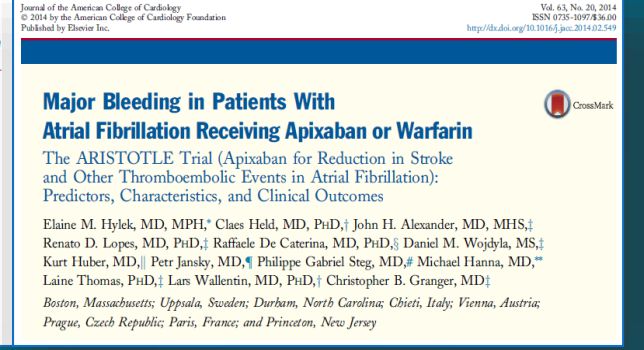
Print ISSN: 0009-7322. Online ISSN: 1524-4539


European Heart Journal
doi:10.1093/eurheartj/ehu083

CLINICAL RESEARCH
Atrial fibrillation

Management of major bleeding events in patients treated with rivaroxaban vs. warfarin: results from the ROCKET AF trial

Jonathan P. Piccini[1]*, Jyotsna Garg[1], Manesh R. Patel[1], Yuliya Lokhnygina[1], Shaun G. Goodman[2], Richard C. Becker[3], Scott D. Berkowitz[4], Günter Breithardt[5], Werner Hacke[6], Jonathan L. Halperin[7], Graeme J. Hankey[8], Christopher C. Nessel[9], Kenneth W. Mahaffey[10], Daniel E. Singer[11], Robert M. Califf[12], and Keith A. A. Fox[13], on behalf of the ROCKET AF Investigators


Journal of the American College of Cardiology
© 2014 by the American College of Cardiology Foundation
Published by Elsevier Inc.
Vol. 63, No. 20, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2014.02.549

Major Bleeding in Patients With Atrial Fibrillation Receiving Apixaban or Warfarin

CrossMark

The ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation): Predictors, Characteristics, and Clinical Outcomes

Elaine M. Hylek, MD, MPH,* Claes Held, MD, PhD,† John H. Alexander, MD, MHS,‡ Renato D. Lopes, MD, PhD,‡ Raffaele De Caterina, MD, PhD,§ Daniel M. Wojdyla, MS,‡ Kurt Huber, MD,‖ Petr Jansky, MD,¶ Philippe Gabriel Steg, MD,# Michael Hanna, MD,** Laine Thomas, PhD,‡ Lars Wallentin, MD, PhD,† Christopher B. Granger, MD‡

Boston, Massachusetts; Uppsala, Sweden; Durham, North Carolina; Chieti, Italy; Vienna, Austria; Prague, Czech Republic; Paris, France; and Princeton, New Jersey

- Emorragie maggiori meno frequenti (drammatica riduzione delle EIC)
- Emorragie meno gravi in termini di mortalità
- Emorragie gestibili nella maggior parte dei casi con misure di supporto generale
- Emorragie che impattano meno sui costi (meno emoderivati usati, meno procedure invasive e/o interventi) e sulla ospedalizzazione (ridotta durata di degenza)

Levi *Critical Care* (2016) 20:249
DOI 10.1186/s13054-016-1413-3

Critical Care

REVIEW Open Access

Management of bleeding in patients treated with direct oral anticoagulants

Marcel Levi[1,2]

Circulation. 2011;124:1573-1579.

Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate

A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects

Elise S. Eerenberg, MD; Pieter W. Kamphuisen, MD; Meertien K. Sijpkens, BSc; Joost C. Meijers, PhD; Harry R. Buller, MD; Marcel Levi, MD

Background—Rivaroxaban and dabigatran are new oral anticoagulants that specifically inhibit factor Xa and thrombin, respectively. Clinical studies on the prevention and treatment of venous and arterial thromboembolism show promising results. A major disadvantage of these anticoagulants is the absence of an antidote in case of serious bleeding or when an emergency intervention needs immediate correction of coagulation. This study evaluated the potential of prothrombin complex concentrate (PCC) to reverse the anticoagulant effect of these drugs.

Methods and Results—In a randomized, double-blind, placebo-controlled study, 12 healthy male volunteers received rivaroxaban 20 mg twice daily (n=6) or dabigatran 150 mg twice daily (n=6) for 2½ days, followed by either a single bolus of 50 IU/kg PCC (Cofact) or a similar volume of saline. After a washout period, this procedure was repeated with the other anticoagulant treatment. Rivaroxaban induced a significant prolongation of the prothrombin time (15.8±1.3 versus 12.3±0.7 seconds at baseline; $P<0.001$) that was immediately and completely reversed by PCC (12.8±1.0; $P<0.001$). The endogenous thrombin potential was inhibited by rivaroxaban (51±22%; baseline, 92±22%; $P=0.002$) and normalized with PCC (114±26%; $P<0.001$), whereas saline had no effect. Dabigatran increased the activated partial thromboplastin time, ecarin clotting time (ECT), and thrombin time. Administration of PCC did not restore these coagulation tests.

Conclusion—Prothrombin complex concentrate immediately and completely reverses the anticoagulant effect of rivaroxaban in healthy subjects but has no influence on the anticoagulant action of dabigatran at the PCC dose used in this study.

12 volontari sani
6 rivaroxaban
6 dabigatran
CCP 50 UI/Kg

Vascular Health and Risk Management

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REVIEW

Reversal of direct oral anticoagulants

Mosaad Almegren

Table 1 Summary of specific reversal agents for DOACs

	Idarucizumab	Andexanet alfa	Ciraparantag
Target	Thrombin inhibitor (dabigatran)	Direct factor Xa inhibitors (rivaroxaban, apixaban, edoxaban), LMWH, fondaparinux	Dabigatran, rivaroxaban, apixaban, edoxaban, LMWH, fondaparinux
Mechanism of action	Noncompetitive binding to dabigatran	Binding to direct and indirect factor Xa inhibitors	Noncovalent hydrogen bonding binds to the target drug
Onset of action	Immediate	2–5 minutes	10 minutes
Administration and dose	5 g intravenously as two doses of 2.5 g each, not more than 15 minutes apart*	400–800 mg intravenous bolus followed by 4–8 mg/min infusion[§]	100–300 mg intravenous bolus[‡]
Elimination	Renal	Not reported	Not reported

Notes: *FDA-approved dose. [§]Doses used in clinical trials but not approved. [‡]Dose used in Phase I clinical trial.
Abbreviations: DOACs, direct oral anticoagulants; FDA, US Food and Drug Administration; LMWH, low molecular weight heparin.

Idarucizumab is a humanized monoclonal antibody fragment

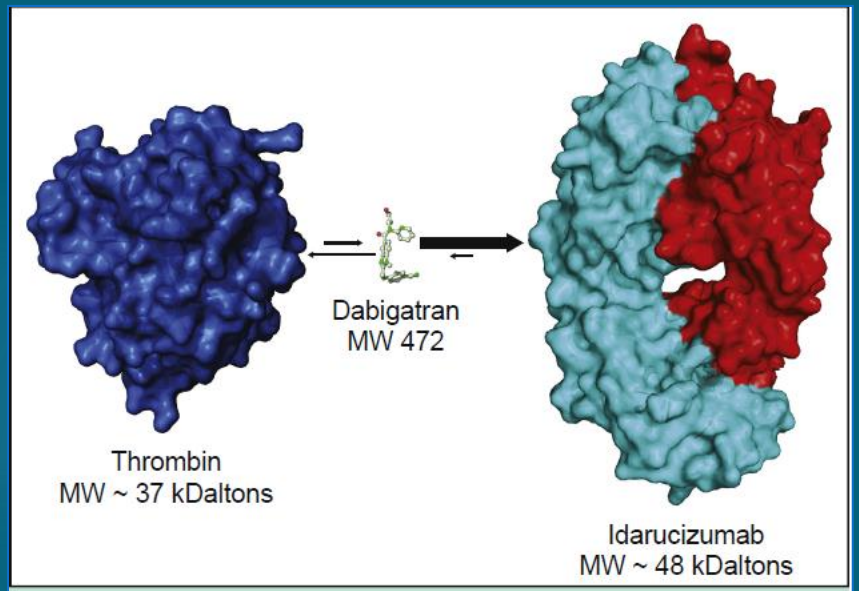

Figure 1 Structure and relative sizes of thrombin (FIIa), dabigatran, and idarucizumab. Reprinted with permission from Pollack et al.[14]

- Humanized Fab fragment
- Binding affinity **around 350 times higher** than dabigatran to thrombin
- No intrinsic pro-coagulant or anticoagulant activity
- IV dosing by bolus or rapid infusion (2 x 2.5 g in 50 mL in 15 minutes);
  immediate onset of action (in minutes)
- Short half-life (45 minutes-4h)

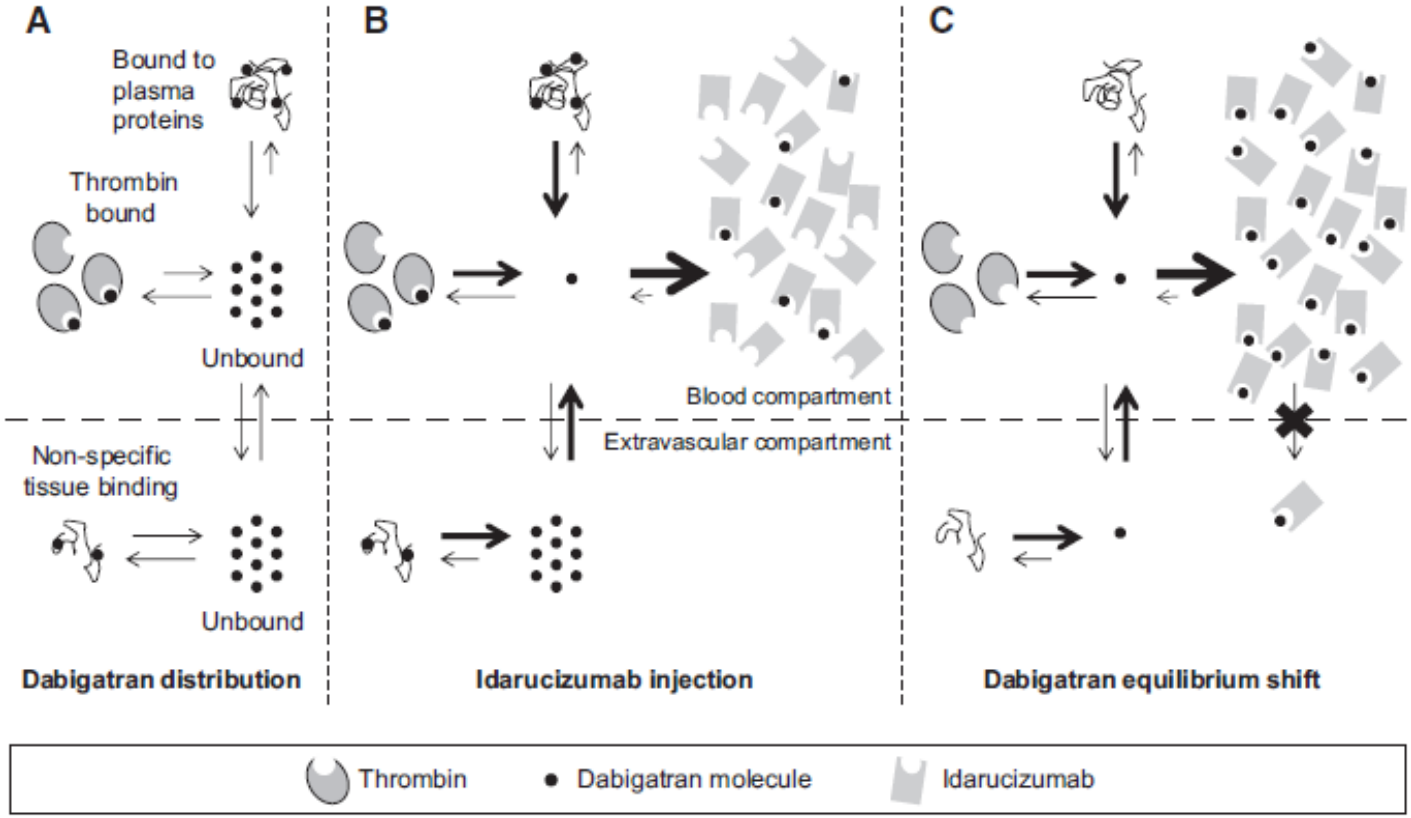

Figure 3. Changes in the distribution of dabigatran after idarucizumab administration. **A**, Circulating dabigatran exists in a state of equilibrium between the plasma and the extravascular compartments. Only unbound dabigatran in the plasma is able to bind thrombin and to inhibit coagulation. **B**, Idarucizumab rapidly binds dabigatran in the plasma. This alters the equilibrium, causing dabigatran in the extravascular compartment to move into the plasma and to potentially dissociate from thrombin (larger arrows). **C**, Because of the high affinity of idarucizumab for dabigatran, thrombin is no longer inhibited, and it regains its capacity to trigger clotting.

The NEW ENGLAND JOURNAL of MEDICINE

This article was published on July 11, 2017, at NEJM.org.

ORIGINAL ARTICLE

Idarucizumab for Dabigatran Reversal — Full Cohort Analysis

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Group A (N=301)	Group B (N=202)	Total (N=503)
Age — yr			
Median	79	77	78
Range	24–96	21–96	21–96
Male sex — no. (%)	172 (57.1)	102 (50.5)	274 (54.5)
Weight — kg			
Median	74	77	75
Range	35–231	39–169	35–231

Table 1. (Continued.)

Characteristic	Group A (N = 301)	Group B (N = 202)	Total (N = 503)
Time since last intake of dabigatran — hr‡			
Median	14.6	18.0	15.6
Range	1.5–90.4	2.6–105.8	1.5–105.8
Elevated ecarin clotting time at baseline — no. (%)	276 (91.7)	185 (91.6)	461 (91.7)
Elevated diluted thrombin time at baseline — no. (%)	244 (81.1)	152 (75.2)	396 (78.7)
Elevated ecarin clotting time or diluted thrombin time at baseline — no. (%)	276 (91.7)	185 (91.6)	461 (91.7)

Table 2. Indications for Dabigatran Reversal.

Indication	Group A (N=301)*	Group B (N=202)†
	no. of patients (%)	
Bleeding		
Intracranial	98 (32.6)	
Subdural	39 (13.0)	
Subarachnoid	26 (8.6)	
Intracerebral	53 (17.6)	
Gastrointestinal	137 (45.5)	
Lower	47 (15.6)	
Upper	52 (17.3)	
Unknown	42 (14.0)	
Intramuscular	9 (3.0)	
Retroperitoneal	10 (3.3)	
Intrapericardial	7 (2.3)	
Intraarticular	5 (1.7)	
Intraocular	1 (0.3)	
Other	52 (17.3)	
Not identified	4 (1.3)	
Trauma-related	78 (25.9)	
Reason for procedure‡		
Abdominal condition or infection: hernia, peritoneal infection		49 (24.3)
Fracture or septic arthritis: involvement of the hip or femur		41 (20.3)
Cardiovascular condition: pacemaker implantation, aneurysm repair		37 (18.3)
Central nervous system condition: craniotomy		17 (8.4)
Pancreatic or hepatobiliary disease: cholecystitis, cholangitis		14 (6.9)
Respiratory condition: chest trauma		14 (6.9)
Kidney and urinary tract condition: acute renal failure		11 (5.4)
Septicemia or sepsis		8 (4.0)
Skin condition: abscess, hematoma		6 (3.0)
Postoperative complications		3 (1.5)
Uterine condition		1 (0.5)
Poisoning: deliberate overdose		1 (0.5)

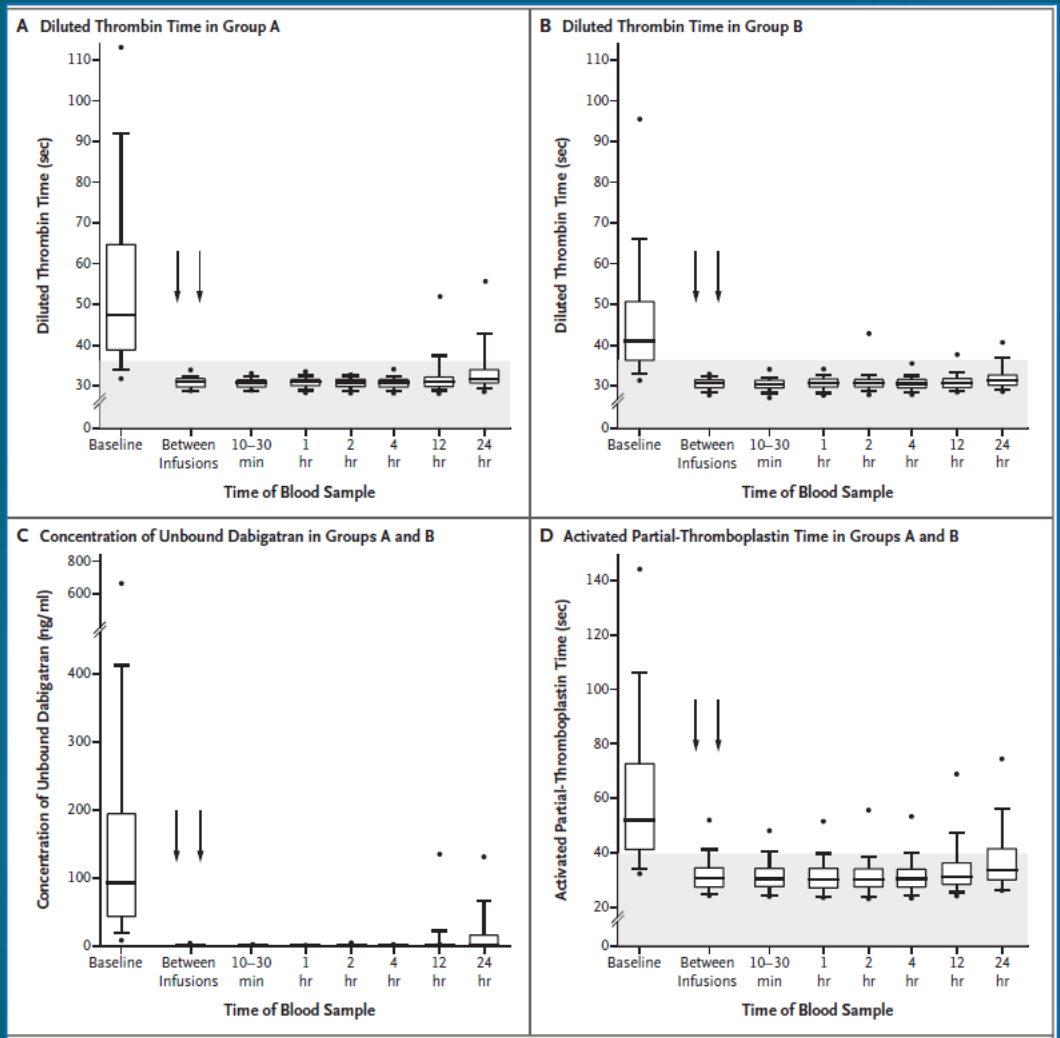

Figure 1. Key Measurements before and after the Administration of Idarucizumab.

Table 3. Patients Who Received More Than One Dose of Idarucizumab.*

Patient No.	Age	Sex	Previous Dose of Dabigatran	Index Event	Baseline Level of Unbound Dabigatran	Creatinine Clearance	Approximate Time to Additional Dose	Reason for Additional Dose
	yr		*mg twice daily*		*ng/ml*	*ml/min*		
Group A								
1	60	Male	110	Gastrointestinal bleeding	955	25.7	48 hr	Recurrent bleeding
2	79	Male	110	Gastrointestinal bleeding	325	43.4	36 hr	Recurrent bleeding
3	76	Male	110	Hematuria	1360	15.2	24 hr	Recurrent bleeding
4	73	Male	110	Gastrointestinal bleeding	329	29.0	24 hr	Recurrent bleeding
Group B								
5	85	Female	75	Intestinal occlusion	51	31.2	5 days	New procedure
6	73	Female	150	Ischemic large bowel	1630	34.0	12 hr	Postoperative bleeding
7	82	Female	110	Catheter placement for dialysis	271	8.0	6 days	Postoperative bleeding
8	70	Male	110	Catheter placement for dialysis	240	18.6	3 days (dose 2); 8 days (dose 3)	Postoperative bleeding and new procedure

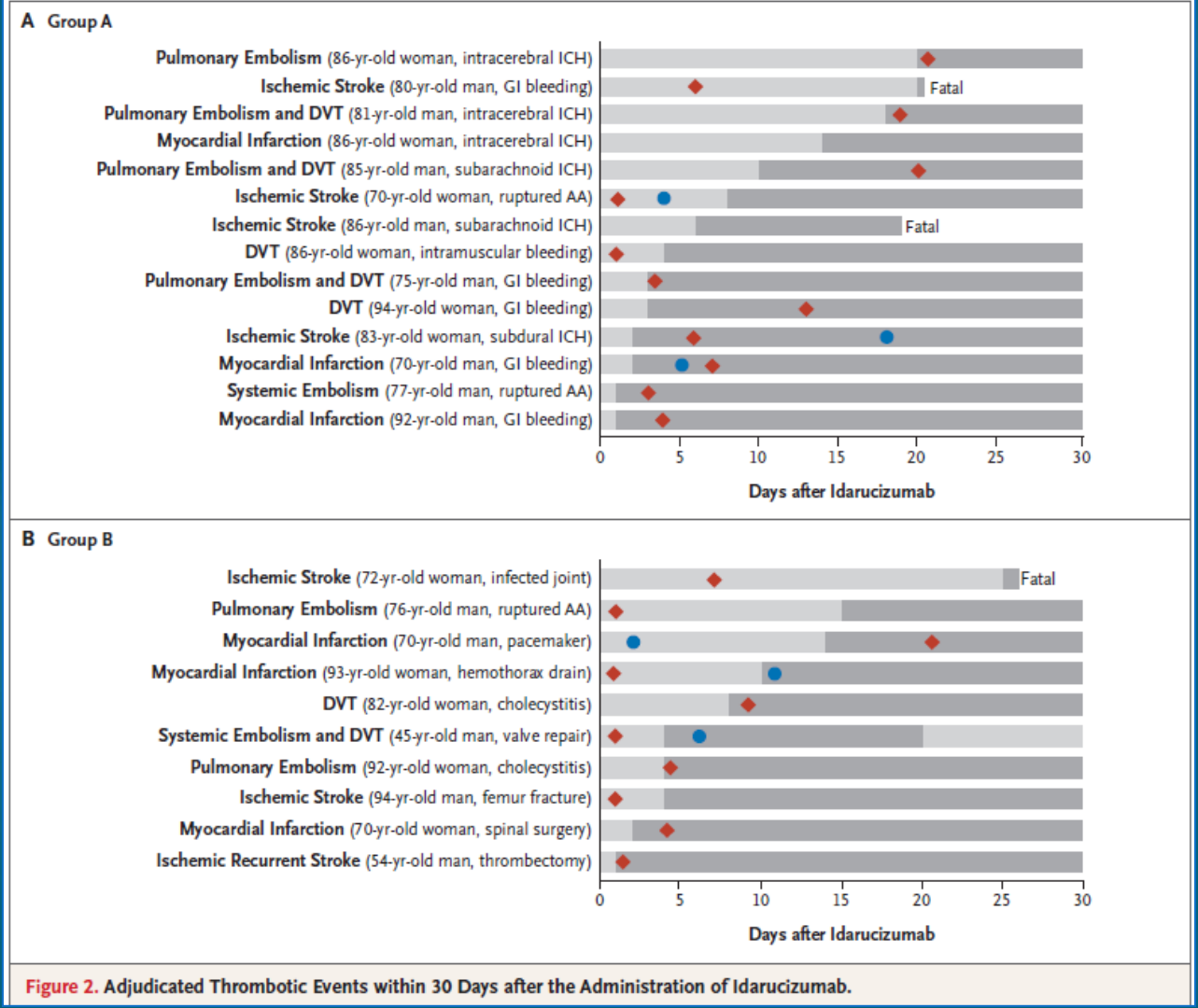

Figure 2. Adjudicated Thrombotic Events within 30 Days after the Administration of Idarucizumab.

4.8% a 30 gg
6.8% a 90 gg

62.5% non aveva ripreso terapia Anticoagulante (78.5% gruppo A)

Idarucizumab

The Antidote for Reversal of Dabigatran

John W. Eikelboom, MBBS, FRCPC; Daniel J. Quinlan, MBBS; Joanne van Ryn, PhD; Jeffrey I. Weitz, MD, FRCPC

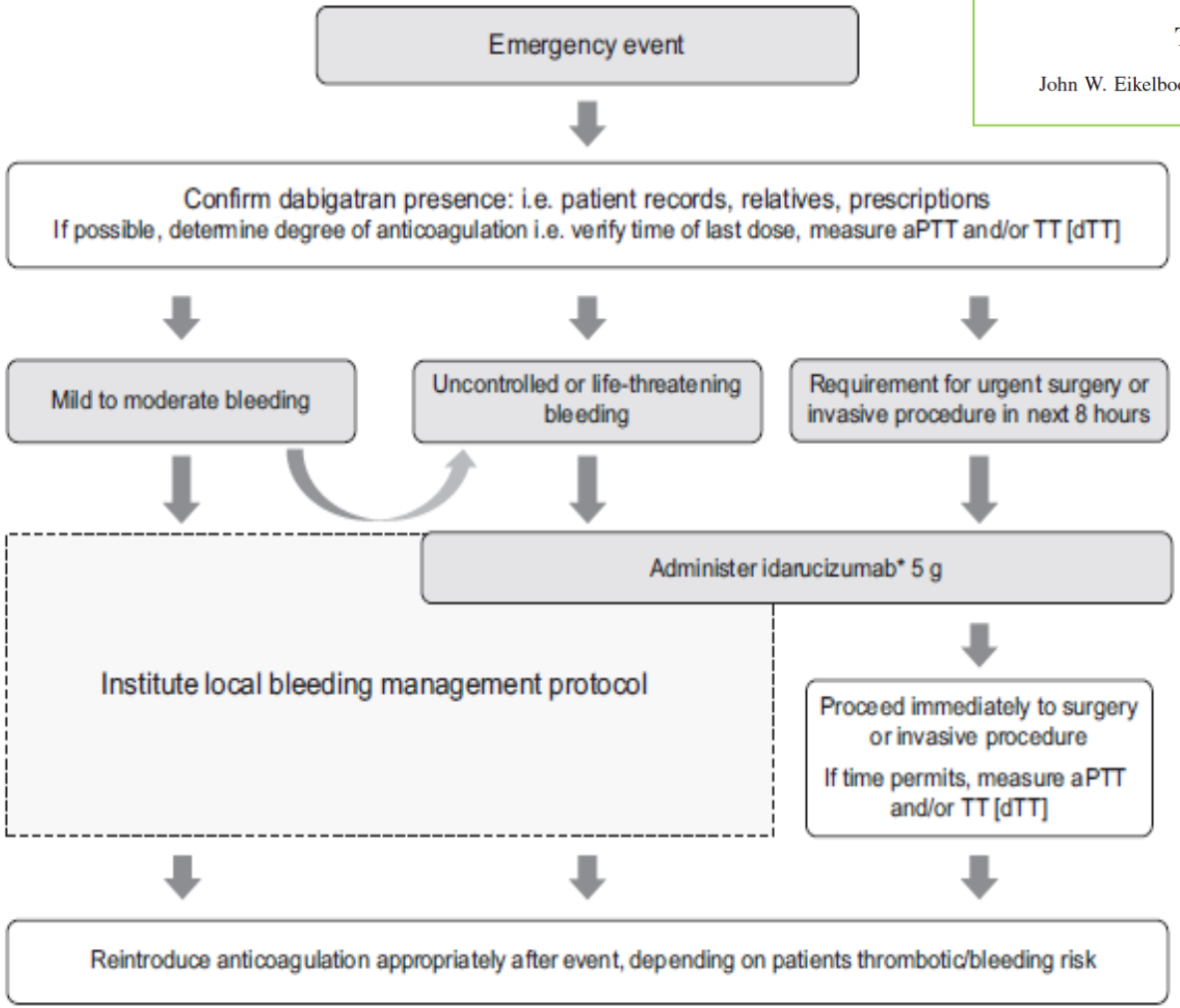

Figure 7. Proposed algorithm for management of patients treated with dabigatran who present with bleeding episodes or require urgent surgery/invasive procedures. *Administer two 50-mL vials of idarucizumab (each containing 2.5 g) intravenously. In rare cases when dabigatran anticoagulation remains present after idarucizumab and bleeding continues in the patient, a second 5-g dose of idarucizumab may be considered. aPTT indicates activated partial thromboplastin time; dTT, diluted thrombin time; and TT, thrombin time.

Circulation. 2015;132:2412-2422.

Journal of Stroke WSO

Antagc
idaruci
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Germa

Pawel Ker
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and Rober

Table 2. Idarucizumab for reversal of Dabigatran activity in patients with intracranial bleeding

Case No.	Sex	Age	Dabigatran dose	Indication for OAC	ICH type	CrCl	aPTT admission	aPTT post Idarucizumab	TT admission	TT post Idarucizumab	Restart ATT (drug)	Volume Adm. (ml)	Hematoma growth	NIHSS Ad.	NIHSS Dis.	mRS Ad.	mRS Dis.
1	M	71	150 mg bid	NVAF	SAH	90.8	30.3	20.7	>120	18.1	36 h Enox 40 mg	n.a.	n.a.	10	0	5	1
2	M	56	150 mg bid	NVAF	ICB	104.8	26.5	22.7	53.4	18.2	12 h Enoxaparin 20 mg	29	+27 ml Intraventricular extension	2	3	3	3
3	F	86	110 mg bid	NVAF	ICB	59.8	34	n.a.	>200	n.a.	None	7	No	4	2	4	3
4	F	78	150 mg bid	NVAF	ICB	n.a.	44	n.a.	n.a.	n.a.	None	134.5	n.a.	33	n.a.	5	6
5	F	83	110 mg bid	NVAF	SDH	112	30	27	73.1	17.6	Enoxaparin Dose not specified	R: 155.05 L: 36.4	No	6	0	5	1
6	M	78	110 mg bid	NVAF	SDH	75	47.3	29.9	n.a.	n.a.	24 h ASA 100 mg	n.a.	No	n.a.	n.a.	2	3
7	F	82	110 mg bid	NVAF	ICB Pons	n.a.	44.2	n.a.	>150	n.a.	n.a.	10	None	4	2	3	2
8	F	74	110 mg bid	NVAF	ICB	66.8	30.3	23.9	81.6	20.6	n.a.	6.2 × 3.9 × 5.8 cm	No	18	9	5	5
9	M	76	110 mg bid	NVAF	ICB	64.6	32.6	28.2	77.8	n.a.	n.a.	3.7 × 3.5 × 2.0 cm	No	32	22	5	5
10	M	83	110 mg bid	NVAF	ICB	69	n.a.	n.a.	119	n.a.	n.a.	8 ml + ventricular extension	No	9	9	2	3
11	F	73	150 mg bid	NVAF	ICB	58	22.4	25	n.a.	n.a.	n.a.	45 × 24 × 26 mm	Yes 24h following admission	8	12	5	5
12	M	65	150 mg bid	NVAF	SDH bilateral	108	28.8	25.3	93.3	19.1	24 h 3.000 IE Certoparin		No	1	0	1	0

International Journal of Stroke
2017, Vol. 12(4) 383–391

DOI: 10.1177/1747493017701944
journals.sagepub.com/home/wso
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Antagonizing dabigatran by idarucizumab in cases of ischemic stroke or intracranial hemorrhage in Germany – A national case collection

Pawel Kermer[1], Christoph C Eschenfelder[2], Hans-Christoph Diener[3], Martin Grond[4], Yasser Abdalla[5], Katharina Althaus[6], Jörg Berrouschot[7], Hakan Cangür[8], Michael Daffertshofer[9], Sebastian Edelbusch[10], Klaus Gröschel[11], Claus G Haase[12], Andreas Harloff[13], Valentin Held[14], Andreas Kauert[15], Peter Kraft[16], Arne Lenz[17], Wolfgang Müllges[16], Mark Obermann[18], Someieh Partowi[19], Jan Purrucker[20], Peter A Ringleb[20], Joachim Röther[21], Raluca Rossi[22], Niklas Schäfer[23], Andreas Schneider[12], Ramona Schuppner[24], Rüdiger J Seitz[25], Kristina Szabo[14] and Robert Wruck[9]

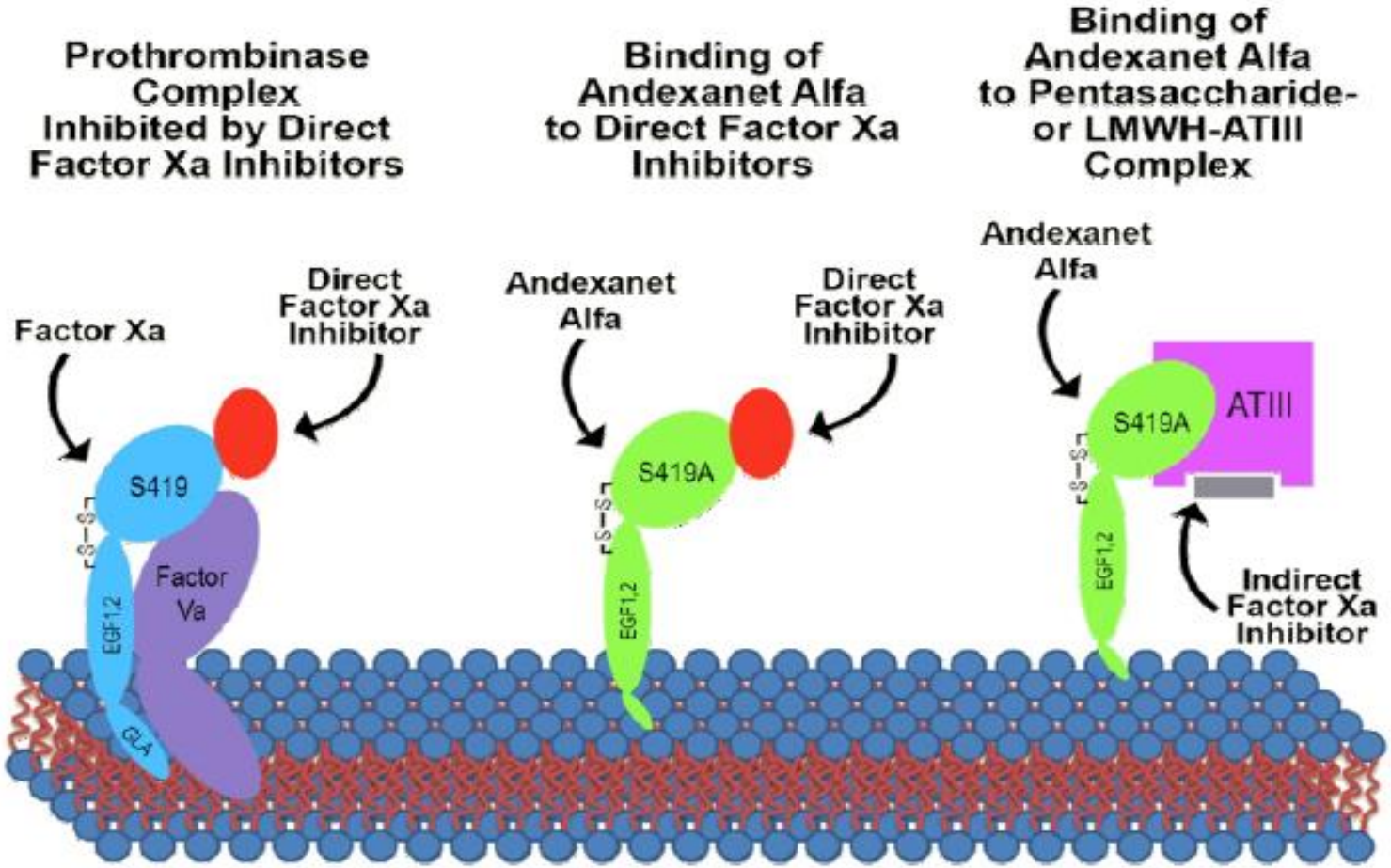
Table 1. Idarucizumab for reversal of Dabigatran activity prior to iv. rt-PA treatment of acute ischemic stroke

Case No.	Sex	Age	Dabigatran dose	Indication for OAC	CrCl (ml/min)	aPTT Adm (s)	aPTT Post Idarucizumab (s)	TT Adm (s)	TT Post Idarucizumab (s)	Restart Antithrombotic Treatment (drug)	NIHSS Ad.	NIHSS Dis.	mRS Ad.	mRS Dis.
1	M	75	110 mg bid	NVAF	69.2	38.0	31.9	66.8	n.a	24 h D1 10 mg bid	5	1	3	1
2	F	40	110 mg bid	CMP†	102	24.3	24.1	69.1	n.a	7 d VKA	12	1	4	0
3	M	83	110 mg bid	NVAF	58.4	34.6	30.9	45.4	17	8 d D1 10 mg bid	4	2	2	1
4	M	76	110 mg bid	NVAF	75	73	n.a.	218	n.a.	3 d D1 50 mg bid	11	1	4	1
5	F	67	150 mg bid	NVAF	n.a.	26	n.a.	129.8	n.a.	10 d Apixaban 2.5 mg bid 20 d Apixaban 5 mg bid	10	8	4	4
6	F	86	110 mg bid	NVAF	52.2	34.6	35.7	n.a.	n.a.	24 h D1 10 mg bid	5	2	2	1
7	F	86	110 mg bid	NVAF	n.a.	45	28	n.a.	n.a.	Edoxaban Dose not specified	12	2	4	1
8	F	58	150 mg bid	ESUS†	89	35.8	26.8	87.5	0,0	3 d Argatroban	3		3	
9*	M	53	150 mg bid	NVAF	112	25.9	28.1	19.2	n.a.	n.a.	17	n.a.	5	6
10	F	75	110 mg bid	NVAF	64	35.6	n.a.	>150	n.a.	24 h ASA 100 mg 21d-28 d OAC not specified	7	18	5	5
11	M	80	110 mg bid	NVAF	47	59	33	>150	17	24 h D1 10 mg bid	5	2	2	0
12	F	94	110 mg bid	NVAF	48.3	69	33	>150	n.a	30 h D1 50 mg bid	6	0	4	0

(continued)

Table 1. Continued

Case No.	Sex	Age	Dabigatran dose	Indication for OAC	CrCl (ml/min)	aPTT Adm (s)	aPTT Post Idarucizumab (s)	TT Adm (s)	TT Post Idarucizumab (s)	Restart Antithrombotic Treatment (drug)	NIHSS Ad.	NIHSS Dis.	mRS Ad.	mRS Dis.
13	M	85	150 mg bid	NVAF	73.5	48	29	n.a	n.a.	24 h ASA 100 mg Certoparin 3.000 IE 7 d D1 50 mg bid	7	1	3	1
14	F	78	110 mg bid	NVAF	52	84	35	n.a	n.a.	48 h D1 50 mg bid	7	1	2	1
15	F	84	110 mg bid	NVAF	112	25.6	n.a.	n.a.	n.a.	48 h ASA 100 mg	14	14	4	4
16	M	77	110 mg bid	NVAF	79	43.6	n.a.	n.a.	n.a.	48 h D1 50 mg bid	4	1	4	1
17	M	54	150 mg bid	NVAF	72	26.1	38.5	24.1	n.a.	24 h D1 50 mg bid	11	2	3	2
18	F	89	110 mg bid	NVAF	57.5	38.9	28.2	n.a.	n.a.	8 d D1 10 mg bid	5	2	2	2
19	F	90	110 mg bid	NVAF	64	37	n.a.	>120	n.a.	24 h ASA 100 mg 7d D1 10 mg bid	7	3	3	1



Original artwork by: Mohammad A. Rattu, PharmD

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity

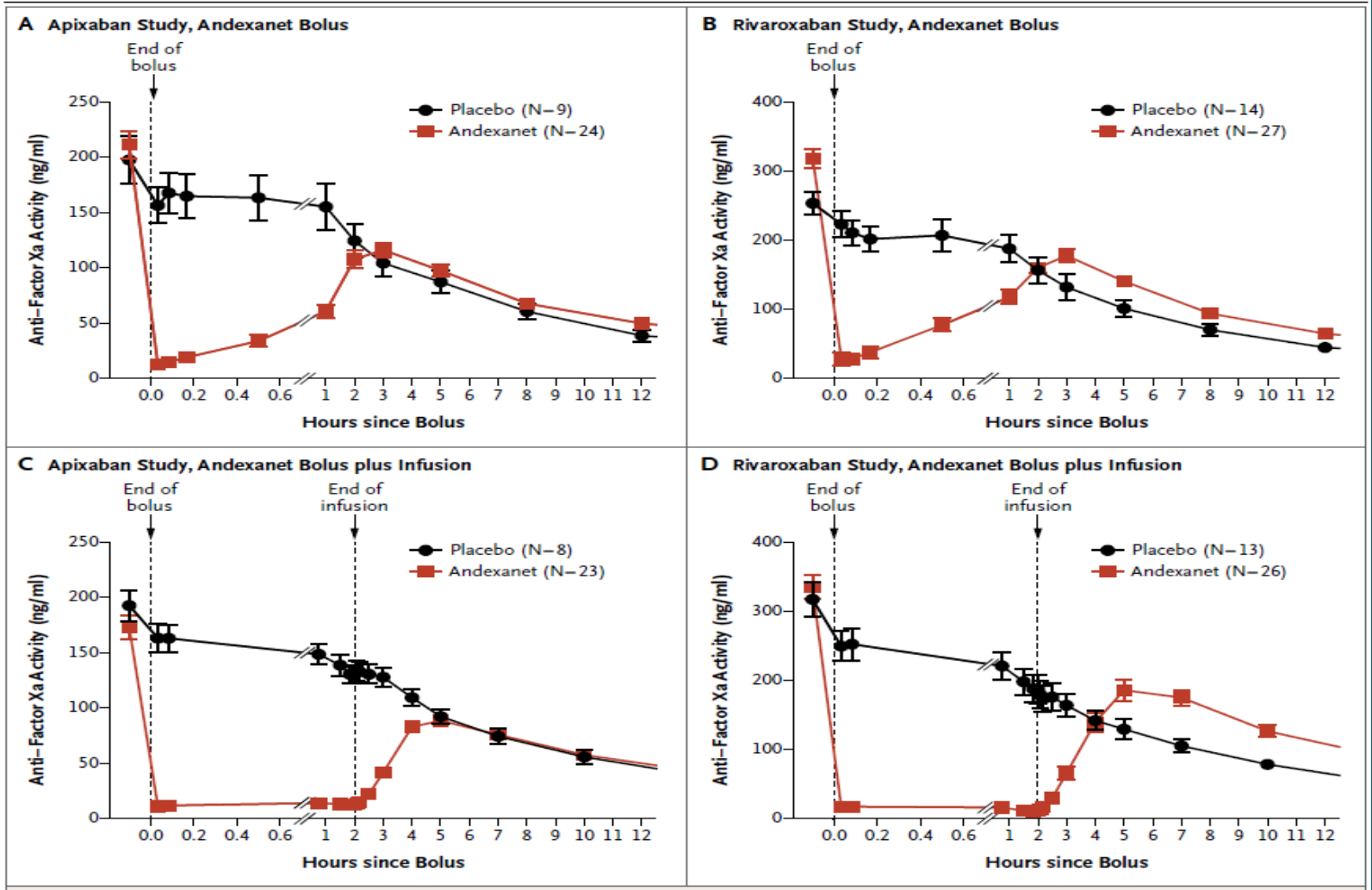


Figure 1. Time Courses of Anti–Factor Xa Activity before and after Administration of Andexanet.

The NEW ENGLAND JOURNAL of MEDICINE

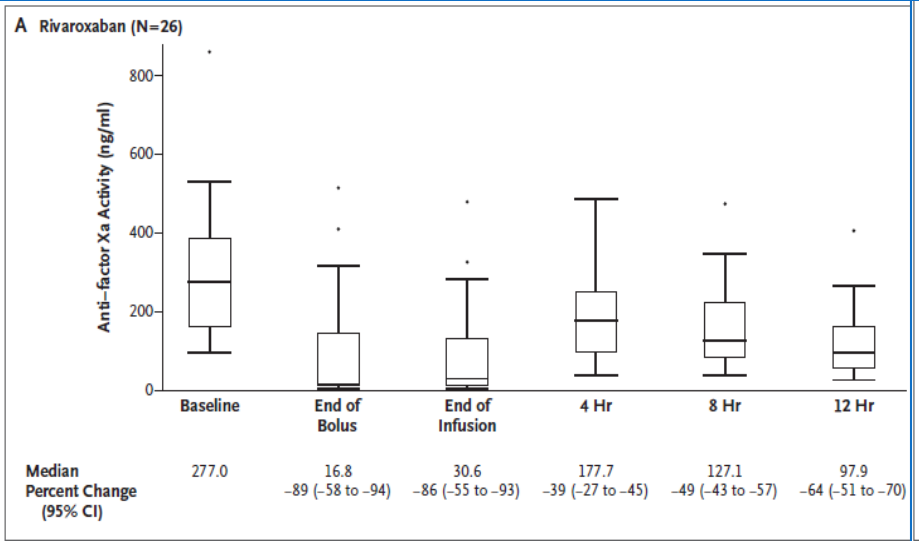
ORIGINAL ARTICLE

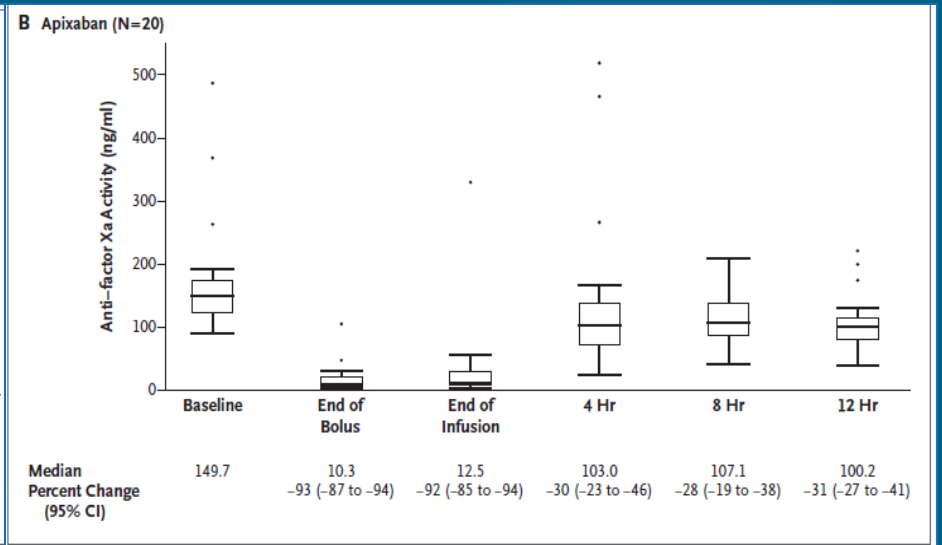
Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

on the basis of predefined criteria. Of 47 patients in efficacy population, 37 had excellent or good hemostasis (79%; 95% CI, 64%–89%). Of 67 patients in safety population, 12 had thrombotic events (18%) within 30 days after andexanet alfa was administered. The thromboses included one myocardial infarction, five strokes, seven deep vein thrombosis, and one pulmonary embolism.[31]

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Safety Population (N=67)	Efficacy Population (N=47)

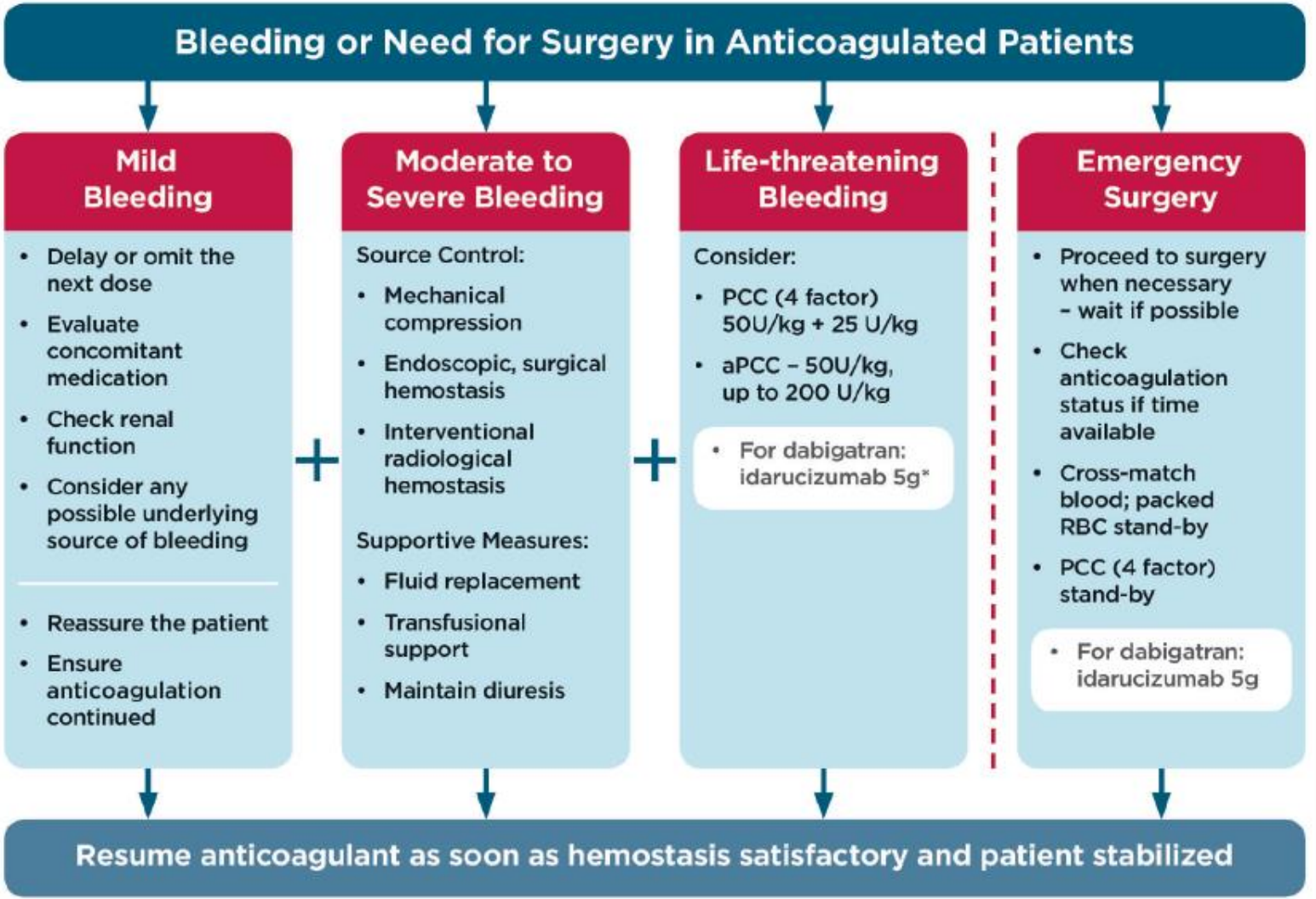




Managing reversal of direct oral anticoagulants in emergency situations

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;

Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial

M Irem Baharoglu*, Charlotte Cordonnier*, Rustam Al-Shahi Salman*, Koen de Gans, Maria M Koopman, Anneke Brand, Charles B Majoie, Ludo F Beenen, Henk A Marquering, Marinus Vermeulen, Paul J Nederkoorn, Rob J de Haan, Yvo B Roos, for the PATCH Investigators†

	Platelet transfusion group (n=97)	Standard care group (n=93)	Odds ratio (95%CI)	p value
Alive at 3 months (survival)	66 (68%)	72 (77%)	0·62 (0·33–1·19)	0·15
mRS score 4–6 at 3 months	70 (72%)	52 (56%)	2·04 (1·12–3·74)	0·0195
mRS score 3–6 at 3 months	86 (89%)	76 (82%)	1·75 (0·77–3·97)	0·18
Median ICH growth at 24 h (mL)*	2·01 (0·32–9·34)	1·16 (0·03–4·42)	--	0·81

Data are n (%) or median (IQR). mRS=modified Rankin Scale. ICH=intracerebral haemorrhage. *n=80 in platelet transfusion group and 73 in standard care group.

Table 2: Secondary outcomes in the intention-to-treat population

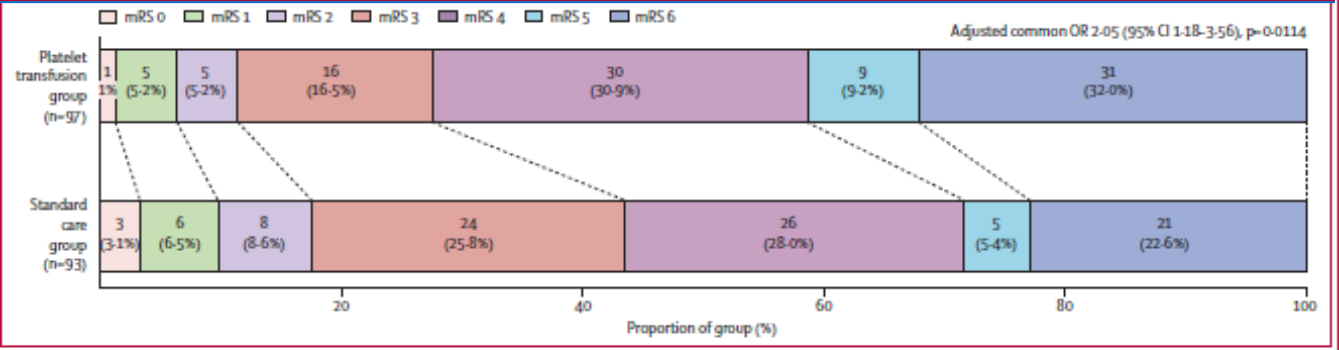


Figure 2: Distribution of mRS score at 3 months
mRS=modified Rankin Scale. OR=odds ratio.

	Platelet transfusion group (n=97)	Standard care group (n=93)
Mean age (years)	74·2 (49–94)	73·5 (40–92)
Men	55 (57%)	57 (61%)
Women	42 (43%)	36 (39%)
Vascular comorbidities		
Ischaemic stroke or TIA	38/94 (40%)	40 (43%)
ICH	4 (4%)	5/92 (5%)
Hypertension	68/94 (72%)	67/92 (73%)
Diabetes mellitus	15 (15%)	17/90 (19%)
Hypercholesterolaemia	46/94 (49%)	40/84 (48%)
Ischaemic heart disease	23/96 (24%)	22/90 (24%)
Peripheral arterial disease	16 (16%)	4/91 (4%)
Coagulation disorder	1/96 (1%)	2/91 (2%)
Antiplatelet therapy pre-ICH*		
COX inhibitor alone	71 (73%)	78 (84%)
COX inhibitor and dipyridamole	18 (19%)	13 (14%)
ADP inhibitor alone	4 (4%)	1 (1%)
COX inhibitor and ADP inhibitor	3 (3%)	1 (1%)
None	1 (1%)	0
Statin therapy pre-ICH	54/96 (56%)	48/92 (52%)
Median GCS score	14 (13–15)	15 (13–15)
Median NIHSS score	12 (7–19)	13 (7–17)
Mean platelet count (×10⁹/L)	229 (120–622)	241 (91–461)
Country of inclusion*		
Netherlands (27 centres)	63 (65%)	57 (61%)
France (9 centres)	19 (20%)	20 (22%)
UK (5 centres)	15 (15%)	16 (17%)
ICH location		
Supratentorial deep	62/96 (65%)	70/92 (76%)
Supratentorial lobar	32/96 (33%)	22/92 (24%)
Infratentorial	2/96 (2%)	0
Median ICH volume (mL)	13·1 (5·4–42·4)	8·0 (4·4–25·8)
Intraventricular extension	12/95 (13%)	20/92 (22%)
Median total ICH Score†	1 (0–2)	1 (0–1)
Age >80 years	28 (29%)	34 (37%)
GCS score		
5–12	19 (20%)	11 (12%)
3–4	1 (1%)	0
ICH volume >30 mL	32 (34%)	19 (21%)
Intraventricular extension	12 (13%)	20 (22%)
Infratentorial ICH location	2 (2%)	0

Data are mean (range), n (%), or median (IQR), unless noted otherwise. TIA=transient ischaemic attack. ICH=intracerebral haemorrhage. COX=cyclooxygenase. ADP=adenosine diphosphate. GCS=Glasgow Coma Scale. NIHSS=National Institutes of Health Stroke Scale. *Stratification variable. †3 participants missing in the platelet transfusion group and 2 missing in the standard care group.

Table 1: Baseline characteristics of the intention-to-treat population

Take home messages

- Il reverse urgente rappresenta il cornerstone del management pratico dei sanguinamenti maggiori/a rischio di vita in corso di terapia anticoagulante in combinazione con misure generali
- Avere a disposizione un antidoto rappresenta una facilitazione ed una "sicurezza" per la gestione della terapia anticoagulante
- I CCP in associazione alla VK1 sono misure consolidate per il reverse urgente degli AVK
- Frequenza e gravità dei sanguinamenti in corso di DOACs sono minori rispetto alla terapia con AVK
- L'uso di misure di supporto generale sembra essere efficace nella maggior parte dei casi di sanguinamento da DOACs, specie per le emorragie extracraniche
- In attesa di avere a disposizione antidoti per tutti i DOACs, oggi è già disponibile un antidoto specifico per dabigatran che ci permette di superare uno dei maggiori gap iniziali di questi farmaci