NAO e sanguinamenti

- *Cos'è cambiato*
- *Quali emorragie trattare*
- *Il Laboratorio*
- *La terapia delle emorragie*

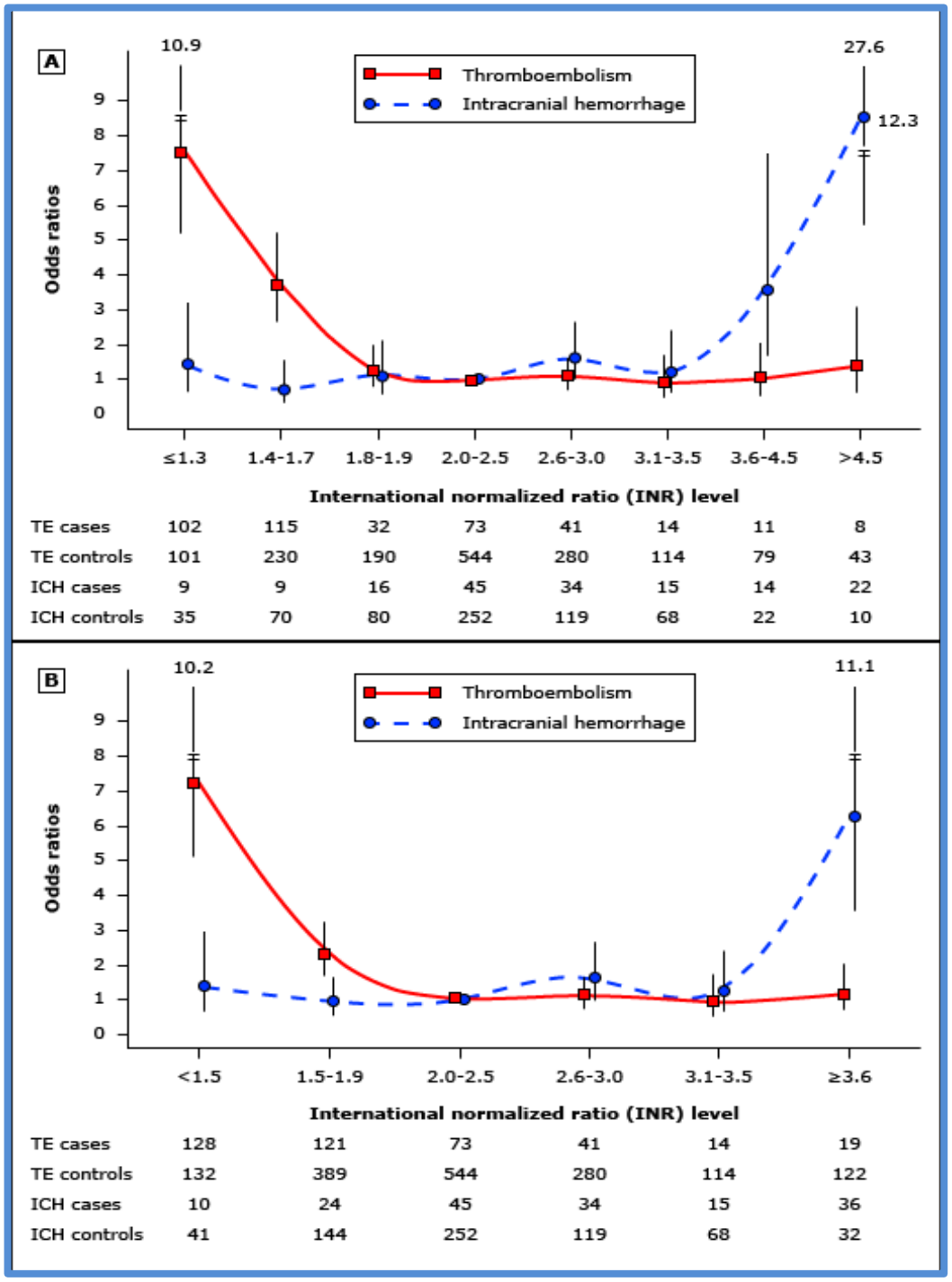
Dr. Franco Cominotto
Direttore FF SOC Pronto Soccorso Medicina d'Urgenza ASUITS

Emorragie maggiori e TAO

- L'incidenza annuale di complicanze emorragiche maggiori in pazienti in terapia anticoagulante è compresa tra 1% e 4%
- Le sedi più frequenti sedi delle manifestazioni emorragiche sono gastrointestinali (15 - 60%)
- Il 15% circa delle emorragie cerebrali spontanee si verifica in corso di TAO
- L'ICH è responsabile del 90% delle morti e delle maggiori invalidità dei pazienti con sanguinamento in terapia anticoagulante

Palareti et al. Lancet 1996, 348; 423-428 (ISCOAT trial)

Levy, Anesthesiology, 2008



Rischio emorragico e tromboembolico ed anticoagulazione ottimale nel paziente con FANV

ATRIA study. Singer DE,
Circ Cardiovasc Qual Outcomes 2009; 2:297.

Warfarin-Associated Intracerebral Hemorrhage Is Inadequately Treated at Community Emergency Departments

Eric M. Liotta, MD; Rajeev K. Garg, MD; Richard E. Temes, MD; Sayona John, MD; Vivien H. Lee, MD; Thomas P. Bleck, MD; Shyam Prabhakaran, MD, MS

Background and Purpose—The purpose of this study was to investigate time delays, adherence to guidelines, and their impact on outcomes in patients with warfarin-associated intracerebral hemorrhage transferred from community emergency departments to a comprehensive stroke center.

Methods—We collected demographic, clinical, transfer time, treatment, and outcome data for patients transferred to our institution with warfarin-associated intracerebral hemorrhage from community emergency departments.

Results—Among 928 patients with intracerebral hemorrhage, 56 (6%) with warfarin-associated intracerebral hemorrhage (median international normalized ratio, 2.55) were transferred to the comprehensive stroke center. Twenty patients received no acute reversal therapy before transfer, only 4 of whom had international normalized ratios ≤1.4 in the community emergency department. Median time of emergency department stay was 3.66 hours and median time to initiation of acute reversal therapy was 4.48 hours. Those who received ≥3 U of fresh–frozen plasma or recombinant activated Factor VIIa (11 patients) before transfer had lower repeat international normalized ratios and better discharge dispositions than those treated less aggressively.

Conclusions—Treatment of warfarin-associated intracerebral hemorrhage in community emergency departments is often suboptimal and does not adhere to published guidelines. Treating coagulopathy aggressively before interhospital transfer may improve outcomes and warrants further investigation. (***Stroke*. 2012;43:2503-2505.)**

Key Words: anticoagulation ■ comprehensive stroke centers ■ intracerebral hemorrhage

---

50% ICH TAO correlate non ricoagulate

REVERSAL THERAPY DEI VKA

Agente	Dosaggio	Tempo di somministrazione	Tempo di neutralizzazione
CCP*	INR < 2.0 20UI/kg INR 2.0-3.0 30 UI/Kg INR 3.0-4.0 40 UI/Kg INR >4.0 50UI/kg	10-15'	15-30'
PFC	15-30 ml/Kg	2-6 h	6-12 h
FVIIra	90-120 microg/kg	5'	15'
VK1 ev	10 mg in sol. Fisiol. 250 cc ripetibile	1 mg/min	Inizio dopo 2 h Max effetto dopo 12-16 ore
Sola sospensione della TAO	/	/	3-5 giorni

*variabile a seconda del CCP utilizzato

CONCENTRATI di COMPLESSO PROTROMBINICO UMANO disponibili in Italia, composizione e dosaggi

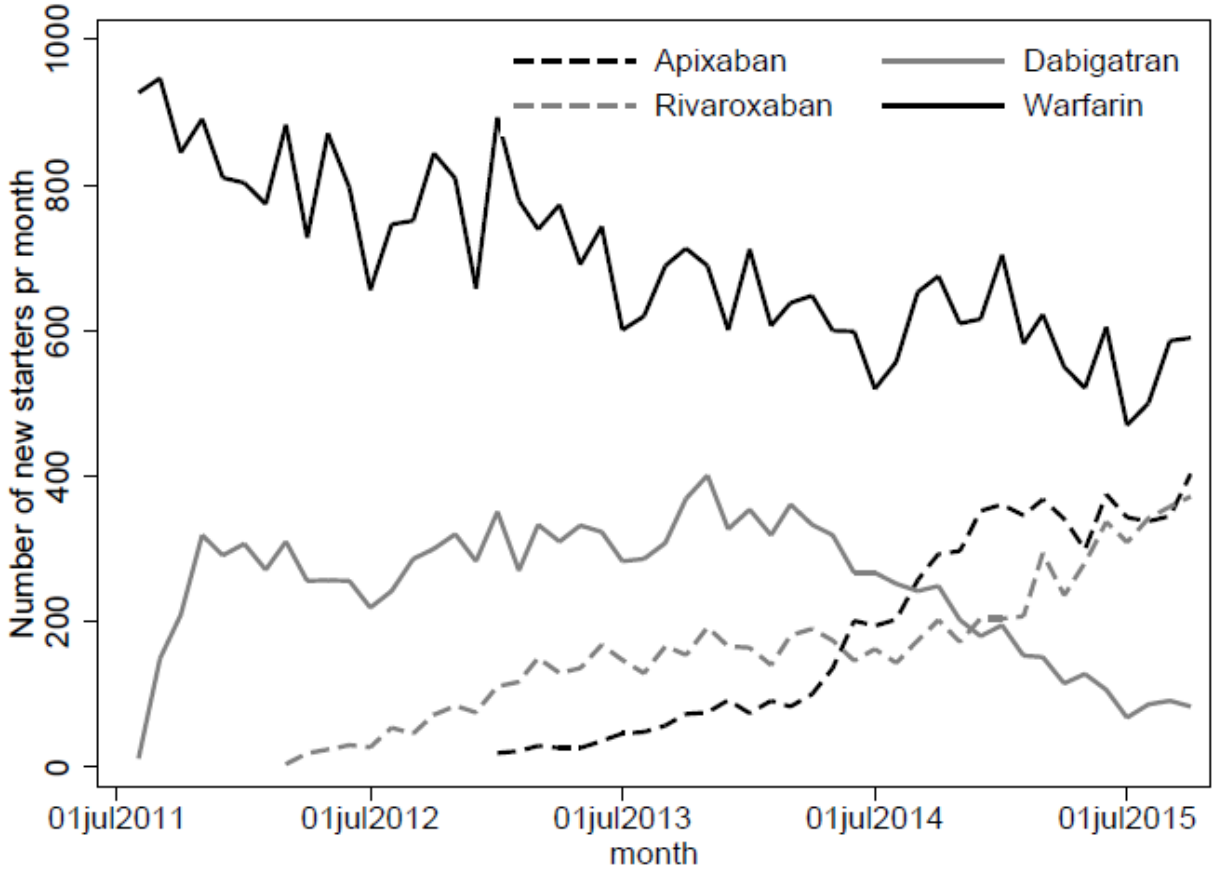
ATC B02BD - Fattori della coagulazione del sangue
ATC B02BD01 - Fattori IX, II, VII e X di coagulazione in associazione
Complesso protrombinico umano

CCP	N. di fattori presenti	Tipo di fattori presenti	Contenuto	Altri fattori presenti Eccipienti
Kedcom® Kedrion S.p.A. **UmanComplex®** Kedrion S.p.A.	3	II, IX, X	Fattore II 25UI/ml Fattore IX 25UI/ml Fattore X 20UI/ml	Eparina Antitrombina III
Protromplex Tim3® Baxalta Italy S.r.l.	3	II, IX, X	Fattore II 30UI/ml Fattore IX 30UI/ml Fattore X 30UI/ml	Eparina
Pronativ® Octapharma Italy S.p.A.	4	II, VII, IX, X	Fattore II 14-38UI/ml Fattore VII 9-24UI/ml Fattore IX 25UI/ml Fattore X 18-30UI/ml	Proteina C Proteina S Eparina
Confidex® Behring S.p.A.	4	II, VII, IX, X	Fattore II 20-48UI/ml Fattore VII 10-25UI/ml Fattore IX 20-31UI/ml Fattore X 22-60UI/ml	Proteina C Proteina S Eparina Albumina umana Antitrombina III umana

NAO e sanguinamenti

- *Cos'è cambiato*
- *Quali emorragie trattare*
- *Il Laboratorio*
- *La terapia delle emorragie*

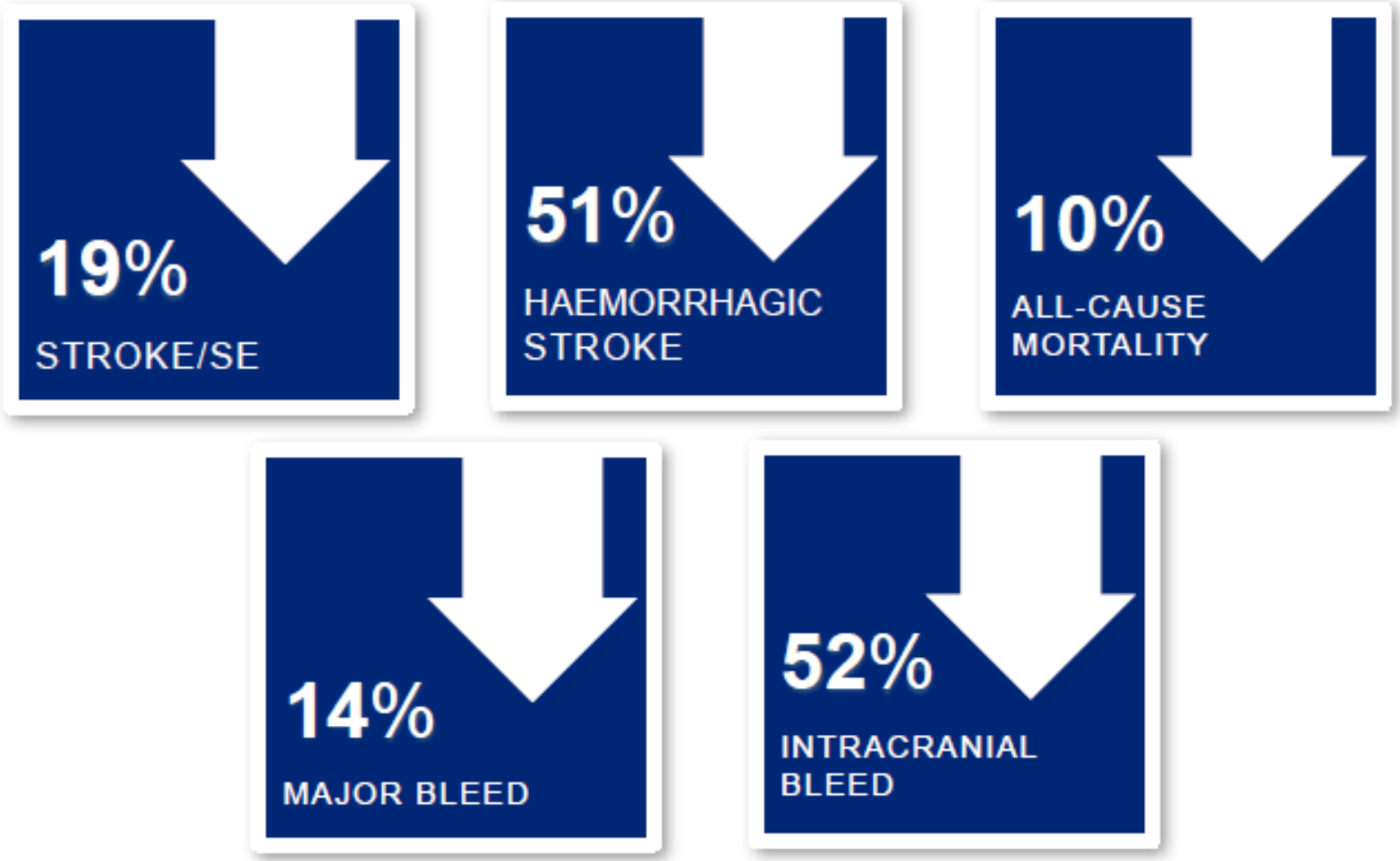
Trend di trattamento dei pazienti con FANV



BMJ 2016;353:i3189

NOACs POWER

In clinical trials, NOACs have demonstrated favourable safety and efficacy profiles compared with warfarin



Meta-analysis of data from RE-LY®, ROCKET AF, ARISTOTLE, ENGAGE AF-TIMI 48; Ruff et al. Lancet 2014

Major Bleeding/life threating bleeding

The International Society on Thrombosis and Haemostasis

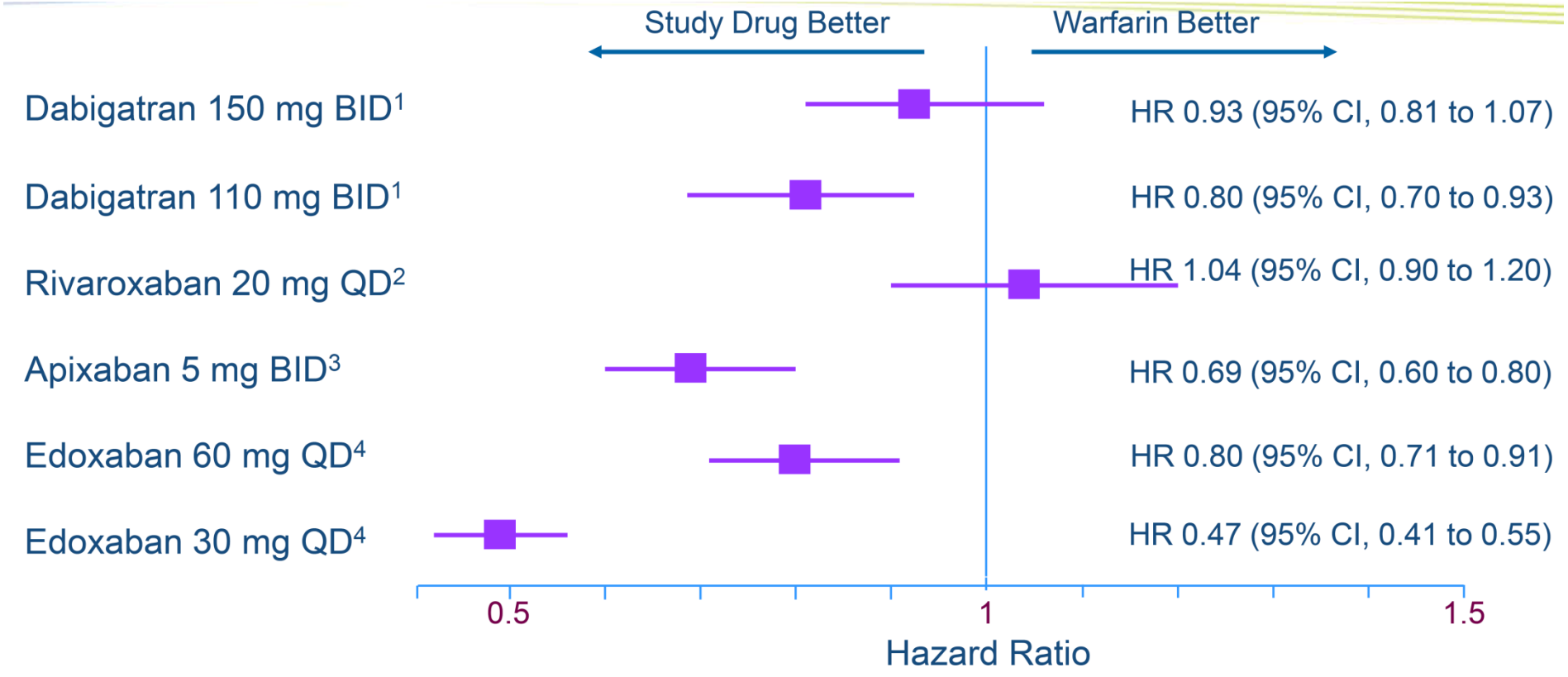
Table 2: Definitions of bleeding used in pivotal NOAC trials.

Major bleeding	Life-threatening bleeding
• Decrease in haemoglobin of ≥ 2 g/dl, or • Transfusion of ≥ 2 units of packed RBCs, or • Bleeding into a critical site (intracranial, intra-spinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal)	• Fatal bleeding, or • Symptomatic intra-cranial bleeding, or • Bleeding with decrease of haemoglobin of ≥ 5 g/dl, or • Bleeding requiring inotropic support, or • Bleeding requiring surgery, or • Transfusion of ≥ 4 units of packed RBCs

Gastrointestinal bleeding with the new oral anticoagulants – defining the issues and the management strategies

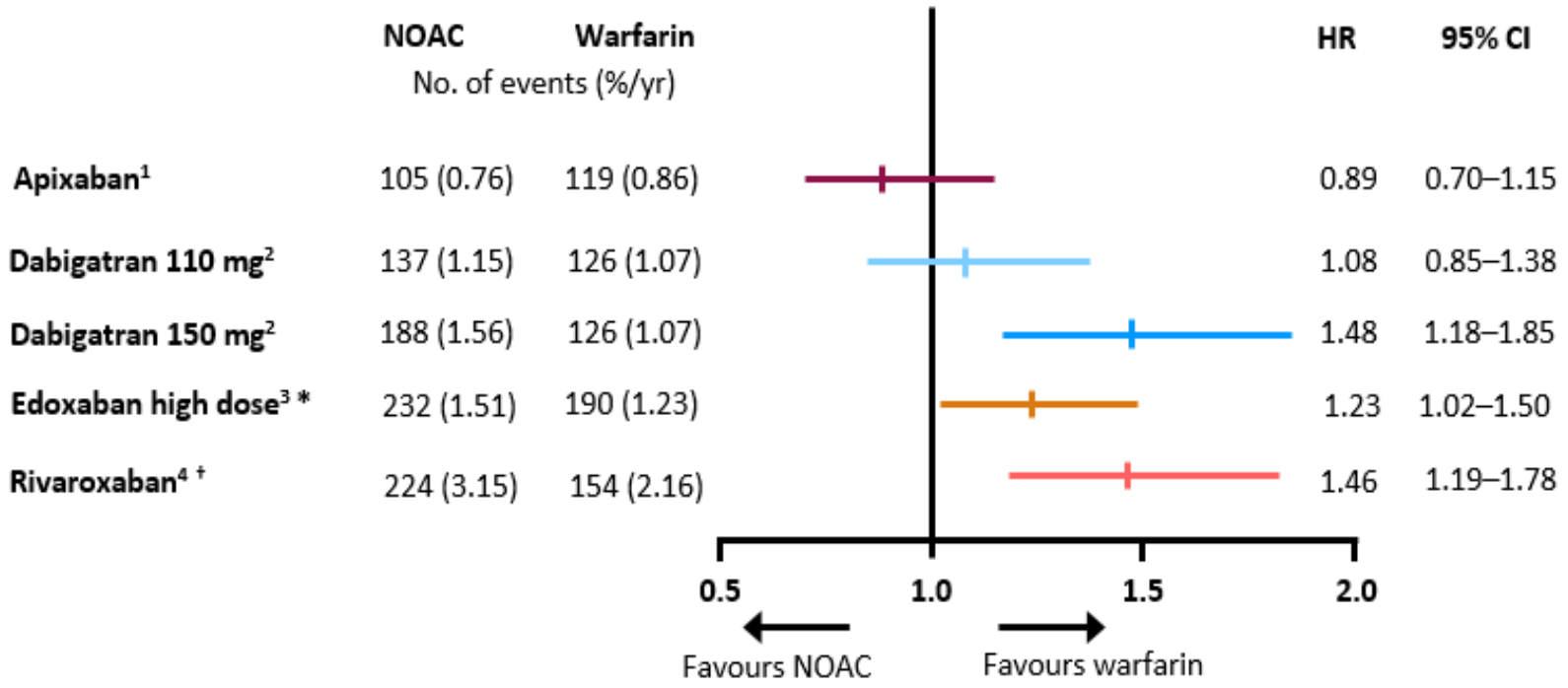
Jay Desai[1]; Jennifer M. Kolb[2]; Jeffrey I. Weitz[3]; James Aisenberg[2]

“Major Bleeding”sintesi dei confronti con Warfarin (RCT)



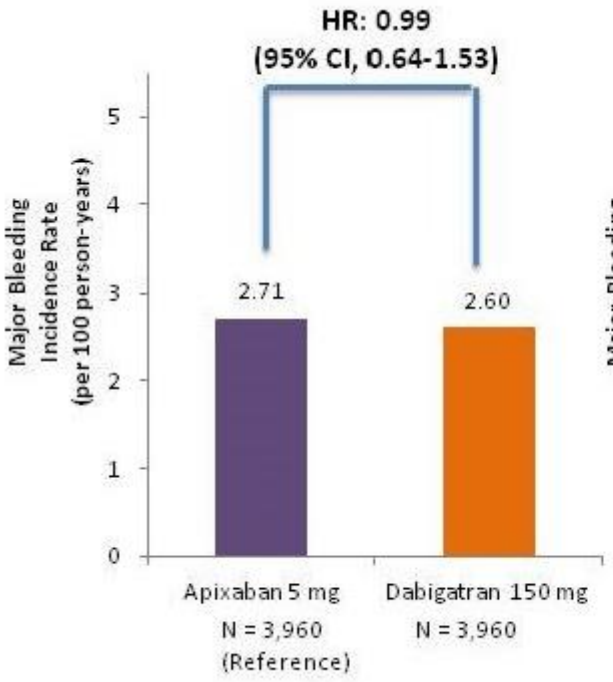
1.Granger *et al. N Engl J Med* 2011;365:981-92; 2. Connolly *et al. N Engl J Med* 2010;363:1875-6, suppl app;
3. Giugliano *et al. N Engl J Med* 2013;369:2093-104; 4. Patel *et al. N Engl J Med* 2011;365:883-91, suppl app.
5. Desai J et al, Thromb Haemost 2013; 110: 205–212

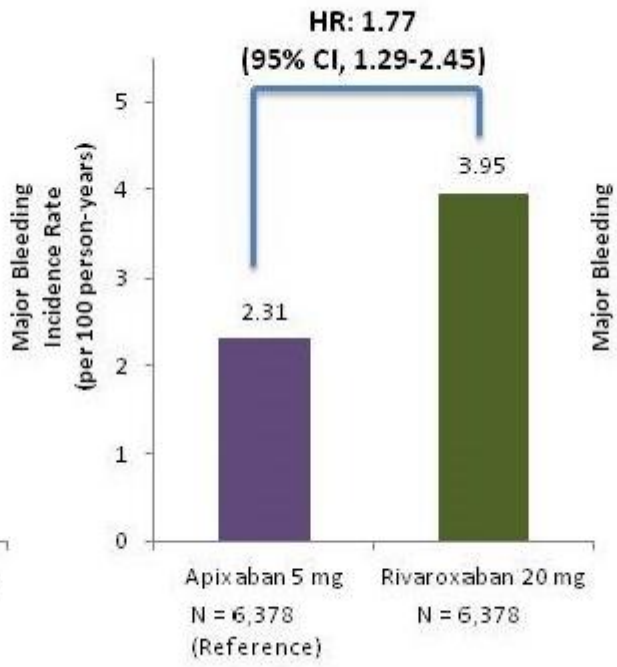
“Gastrointestinal bleeding” dai RCT DOAC vs warfarin

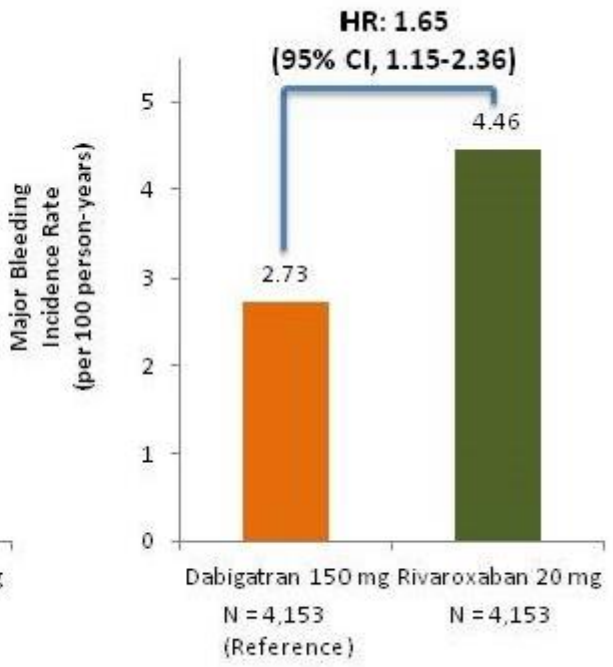


1.Granger *et al. N Engl J Med* 2011;365:981-92; 2. Connolly *et al. N Engl J Med* 2010;363:1875-6, suppl app;
3. Giugliano *et al. N Engl J Med* 2013;369:2093-104; 4. Patel *et al. N Engl J Med* 2011;365:883-91, suppl app.
5. Desai J et al, Thromb Haemost 2013; 110: 205–212

Supplementary Material to Lip et al. ***"Real-world comparison of major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban, or warfarin. A propensity score matched analysis"***







(Thromb Haemost 2016; 116.5)

Gastrointestinal Safety of Direct Oral Anticoagulants: A Large Population-Based Study

Neena S. Abraham,[1,2,3] Peter A. Noseworthy,[2,4] Xiaoxi Yao,[2] Lindsey R. Sangaralingham,[2] and Nilay D. Shah[2,3,5]

[1]Division of Gastroenterology and Hepatology, Department of Medicine, Mayo Clinic, Scottsdale, Arizona; [2]Mayo Clinic

incidenza di sanguinamento per 100 pazienti per anno

Table 4. Stratified Analysis in Propensity Score Matched Rivaroxaban vs Dabigatran Users

	Rivaroxaban (n = 15,787)		Dabigatran (n = 15,787)		Rivaroxaban vs dabigatran (n = 31,574)	
Variable	Events, n	IR	Events, n	IR	HR (95% CI)	*P* for interaction
Overall	222	2.74	215	2.02	1.20 (1.00–1.45)	
Age						
18–64 y	26	1.05	14	0.46	2.03* (1.06–3.90)	.10
65–74 y	66	2.54	54	1.56	1.44* (1.00–2.06)	
≥75 y	130	4.29	147	3.54	1.06 (0.84–1.34)	

-20%

Table 5. Stratified Analysis in Propensity Score Matched Apixaban vs Dabigatran Users

	Apixaban (n = 6542)		Dabigatran (n = 6542)		Apixaban vs dabigatran (n = 13,084)	
Variable	Events, n	IR	Events, n	IR	HR (95% CI)	*P* for interaction
Overall	33	1.38	121	2.73	0.39*** (0.27–0.58)	
Age						
18–64 y	2	0.34	7	0.73	0.38 (0.08–1.84)	.54
65–74 y	5	0.69	29	2.12	0.25** (0.10–0.65)	
≥75 y	26	2.43	85	4.06	0.45*** (0.29–0.71)	

+61%

Table 6. Stratified Analysis in Propensity Score–Matched Apixaban vs Rivaroxaban Users

	Apixaban (n = 6565)		Rivaroxaban (n = 6565)		Apixaban vs rivaroxaban (n = 13,130)	
Variable	Events, n	IR	Events, n	IR	HR (95% CI)	*P* for interaction
Overall	32	1.34	116	3.54	0.33*** (0.22–0.49)	
Age						
18–64 y	2	0.34	6	0.81	0.38 (0.08–1.89)	.36
65–74 y	5	0.69	32	3.24	0.18*** (0.07–0.47)	
≥75 y	25	2.32	78	5.05	0.39*** (0.25–0.61)	

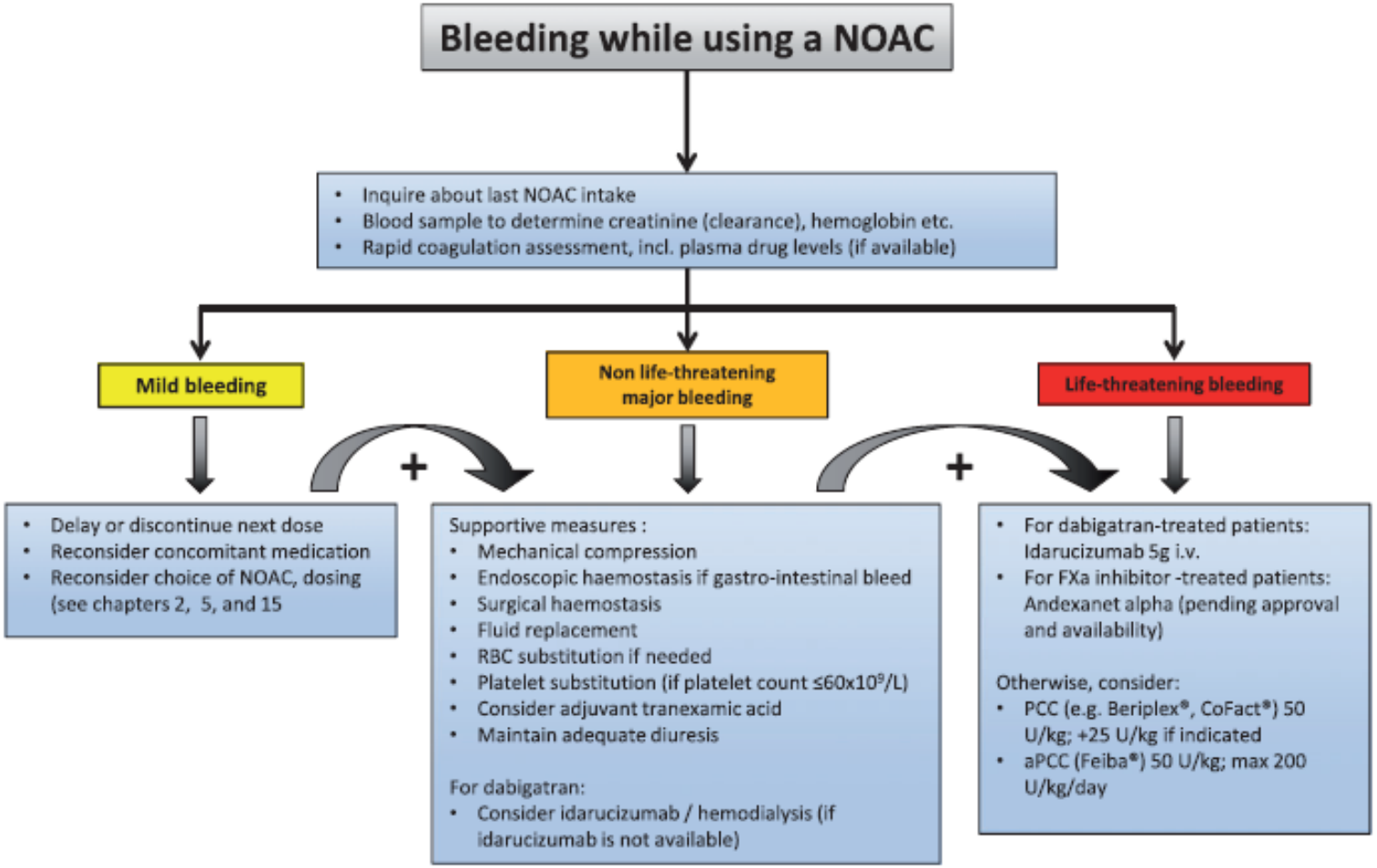
+66%

NOTE. *P* value in the table is for interaction; ***$P < .001$ indicates significance for the HR.
IR, incidence rate per 100 person-years.

Gastroenterology 2017;152:1014–1022

- *Cos'è cambiato*
- *Quali emorragie trattare*
- *Il Laboratorio*
- *La terapia delle emorragie*

NOACs: trattamento delle emorragie



Skill base

a) Emivita degli anticoagulanti orali
b) Stima della funzione renale e categorie di disfunzione
c) NOACs: emivita nel paz. con insufficienza renale
d) DATA/ORA dell'ultima assunzione

Emivita degli anticoagulanti orali

Agente	Emivita, ore
Warfarin	media 40
Dabigatran	12-17
Rivaroxaban	5-13
Apixaban	12
Edoxaban	10-14

Ageno W et al. Thrombosis and Haemostasis, 2016

NOACs: emivita nel paz. con insufficienza renale

Table 7 Estimated drug half lives and effect on AUC NOAC plasma concentrations in different stages of CKD compared to healthy controls

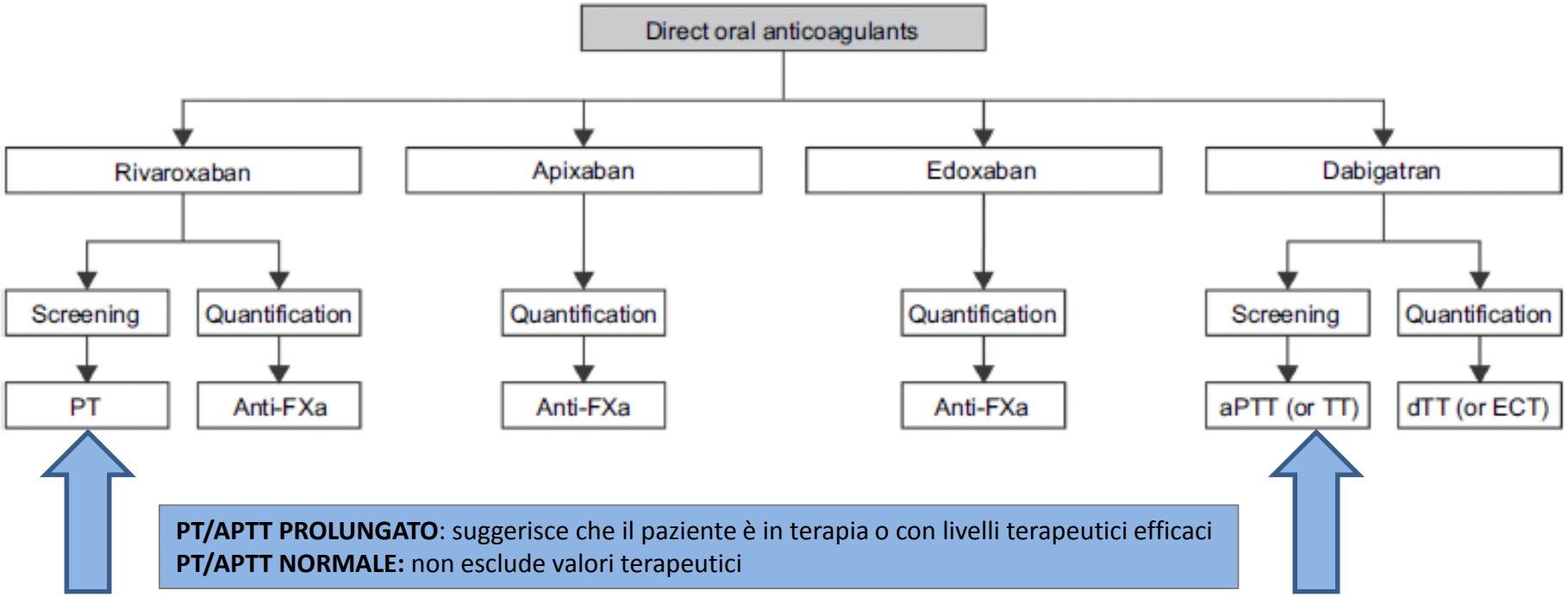
	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
CrCl >80 mL/min	12-17	12 h	10–14 h[51,65]	5–9 h (young) 11–13 h (elderly)
CrCl 50–80 mL/min CKD Stages I and II	~17 h[122] (+50%)	~14.6 h[123] (+16%)	~8.6 h[124] (+32%)[SmPC]	~8.7 h[125] (+44%)[126]
CrCl 30–50 mL/min CKD Stage III	~19 h[122]	~17.6 h (+29%)	~9.4 h[124] (+74%)[SmPC]	~9.0 h (+52%)[126]
CrCl 15–30 mL/min CKD Stage IV	28	~17.3 h (+44%)	~16.9 h[124] (72%)[SmPC]	~9.5 h (+64%)[126]
CrCl ≤ 15 mL/min CKD Stage V; off-dialysis	No data	– (+36%)	– (+93%)[SmPC]	– (+70%)[127]

CKD, chronic kidney disease; CrCl, creatinine clearance.

EUROPEAN SOCIETY OF CARDIOLOGY®
Europace (2015) **17**, 1467–1507
doi:10.1093/europace/euv309

- *Cos'è cambiato*
- *Quali emorragie trattare*
- ***Il Laboratorio***
- *La terapia delle emorragie*

DOAC: QUALI TEST?



PT/APTT PROLUNGATO: suggerisce che il paziente è in terapia o con livelli terapeutici efficaci
PT/APTT NORMALE: non esclude valori terapeutici

	Anti-FXa (ng/mL)[a]
C_{trough}	44 (12–137)
C_{max}	249 (184–343)

	Anti-FXa (ng/mL)[b]
C_{trough}	103 (41–230)
C_{max}	171 (91–321)

	Anti-FXa (ng/mL)[c]
C_{trough}	21 (2.5)
C_{max}	241 (1.2)

	dTT (ng/mL)[d]
C_{trough}	91 (61–143)
C_{max}	175 (117–275)

JACC 2017, vol70.n°24; 3043-3061

Vascular health and risk management 2017:13 457-467

DOAC: QUALI TEST?

FARMACO	METODO DI DOSAGGIO DELL'ATTIVITA' ANTICOAGULANTE
Dabigatran (Ng/Ml)	**dTT** **ECT /**ECA (**TEST QUANTITATIVO calibrato specificamente sull'attività anticoagulante del Dabigatran. Esprime la concentrazione di farmaco circolante**
Rivaroxaban (Ng/Ml) **Apixaban (Ng/Ml)** **Edoxaban (Ng/Ml)**	**aXa**

La misura dell'attivita' anticoagulante deve essere espressa in ng/ml. In condizioni stabili le concentrazioni farmacologiche devono essere misurate prima della somministrazione successiva del farmaco.

Pengo V et al, T&H 2011; Douxfils J et al, T&H 2012, 2013; Baglin T, JT&H 2013, Tripodi A, 2013

Misurare l'anticoagulazione?

- Prima di procedura o chirurgia urgente con trattamento nelle ultime 24 ore
- Sanguinamento attivo
- Sospetto sovradosaggio
- Sospetta mancata aderenza alla terapia
- Insufficienza renale imprevista
- Trombosi acuta
- Incoscienza del paziente

- *Cos'è cambiato*
- *Quali emorragie trattare*
- *Il Laboratorio*
- *La terapia delle emorragie*

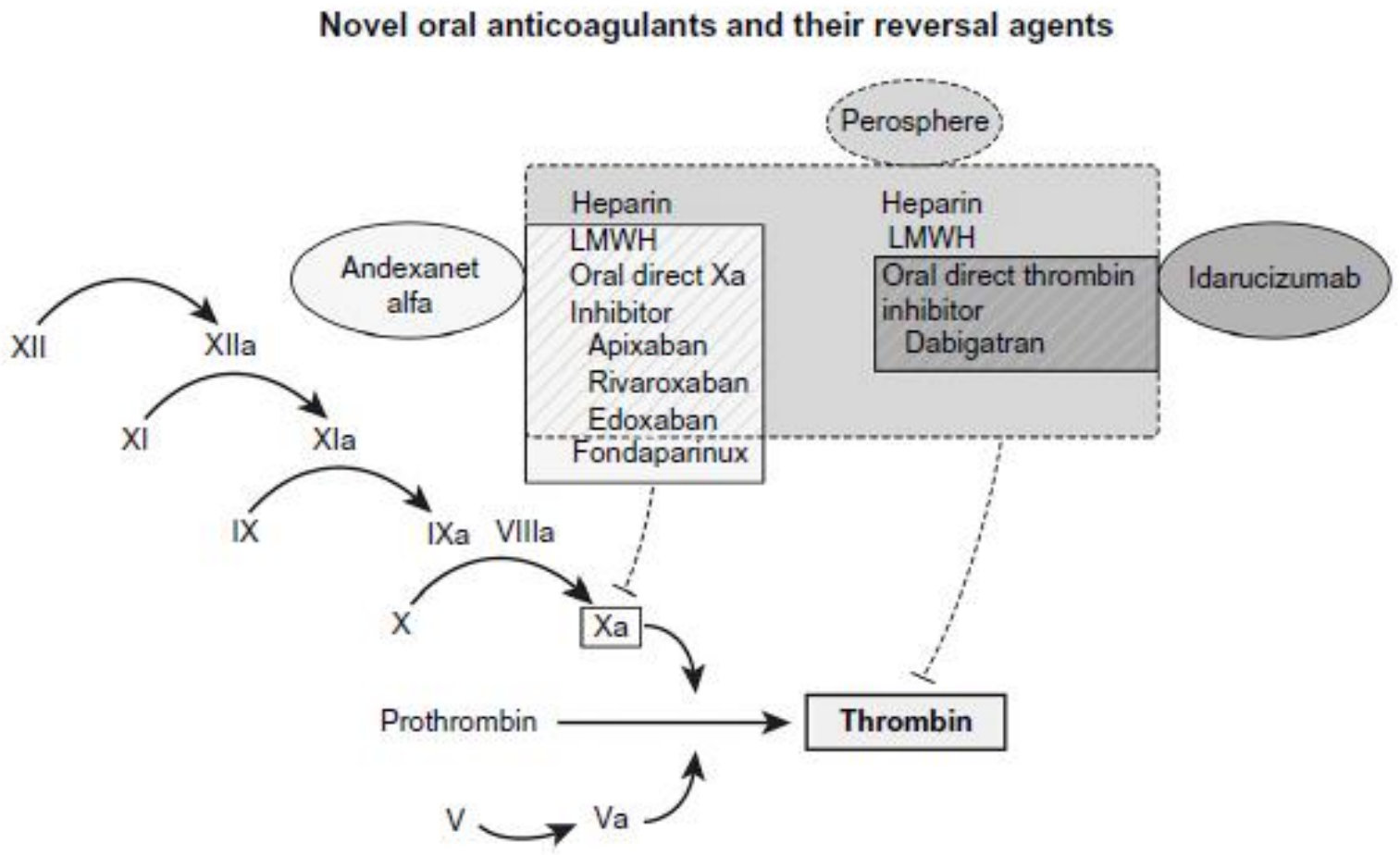
Misure non specifiche per neutralizzare l'effetto anticoagulante dei NOACs

Interruzione farmaco/attesa, mantenere diuresi	**Rimozione del farmaco con dialisi** (solo per dabigatran)	**Attivazione della coagulazione** (PCC, aPCC, rFVIIa)
Richiesti tempi lunghi **Necessaria funzionalità renale sufficiente**	**Necessari infrastrutture e tempi prolungati** **Difficoltosa in compromissione emodinamica**	**rFVIIa, FEIBA rschio protrombotico; benefici incerti specie per inibb. FXa** **PCC non specifico e azione non immediata** **PCC: 4F non ubiquitariamente disponibile, tempo di ricombinazione**

Ageno W et al. Thrombosis and Haemostasis, 2016

What is an ideal reversal agent?		
	No procoagulant effects	**Easy to use**
	Specifically targets the NOAC	**Predictable**
	Acts immediately	**Effect is sustained**

Misure specifiche per neutralizzare i NOACs



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, M.D., Ph.D.,
Robert Dubiel, Hylek, M.D.,
Pieter W. Kam Levy, M.D.,
Frank W. Sellke D., M.M.E.,
Bushi W M.D.

Frammento di anticorpo umanizzato

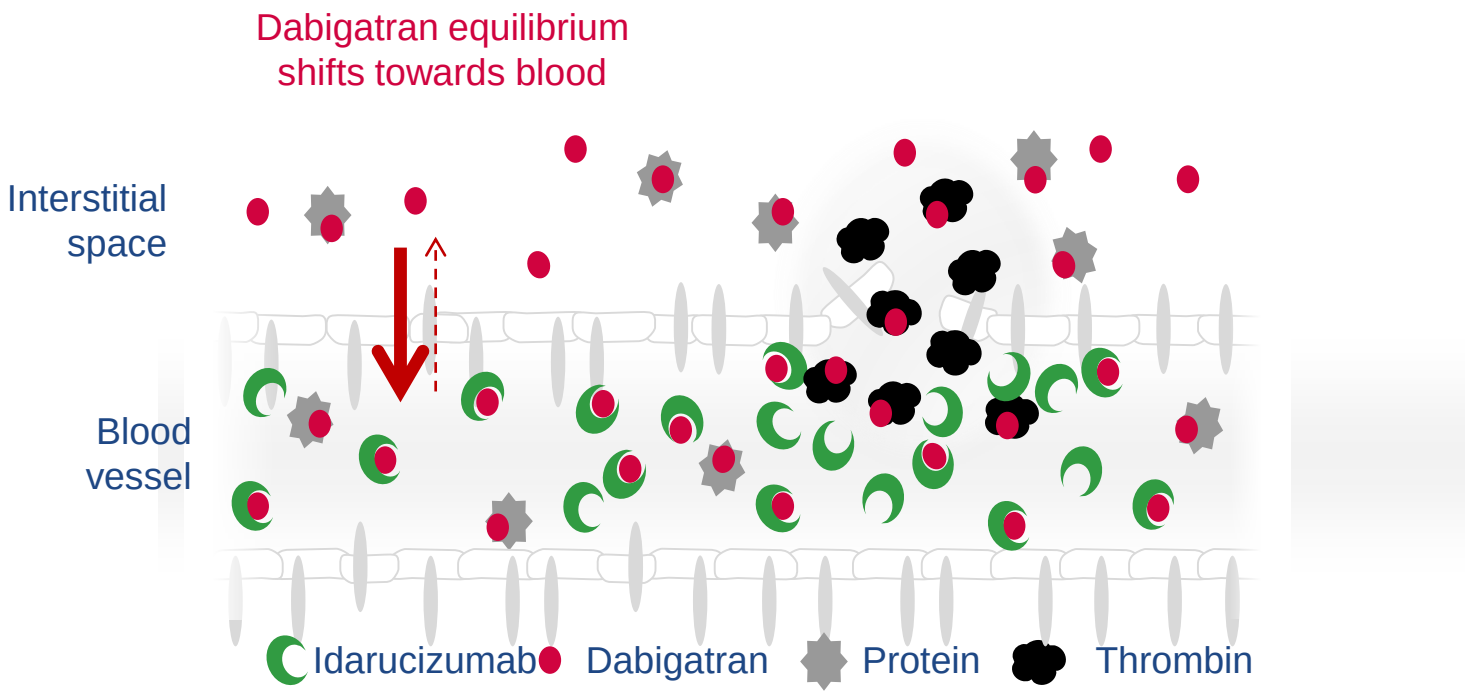
Affinità di legame 350 volte superiore a quella di dabigatran per la trombina

Nessuna attività procoagulante o anticoagulante

Somministrazione ev in bolo o con infusione rapida

Insorgenza d'azione immediata Emivita breve, eliminazione renale

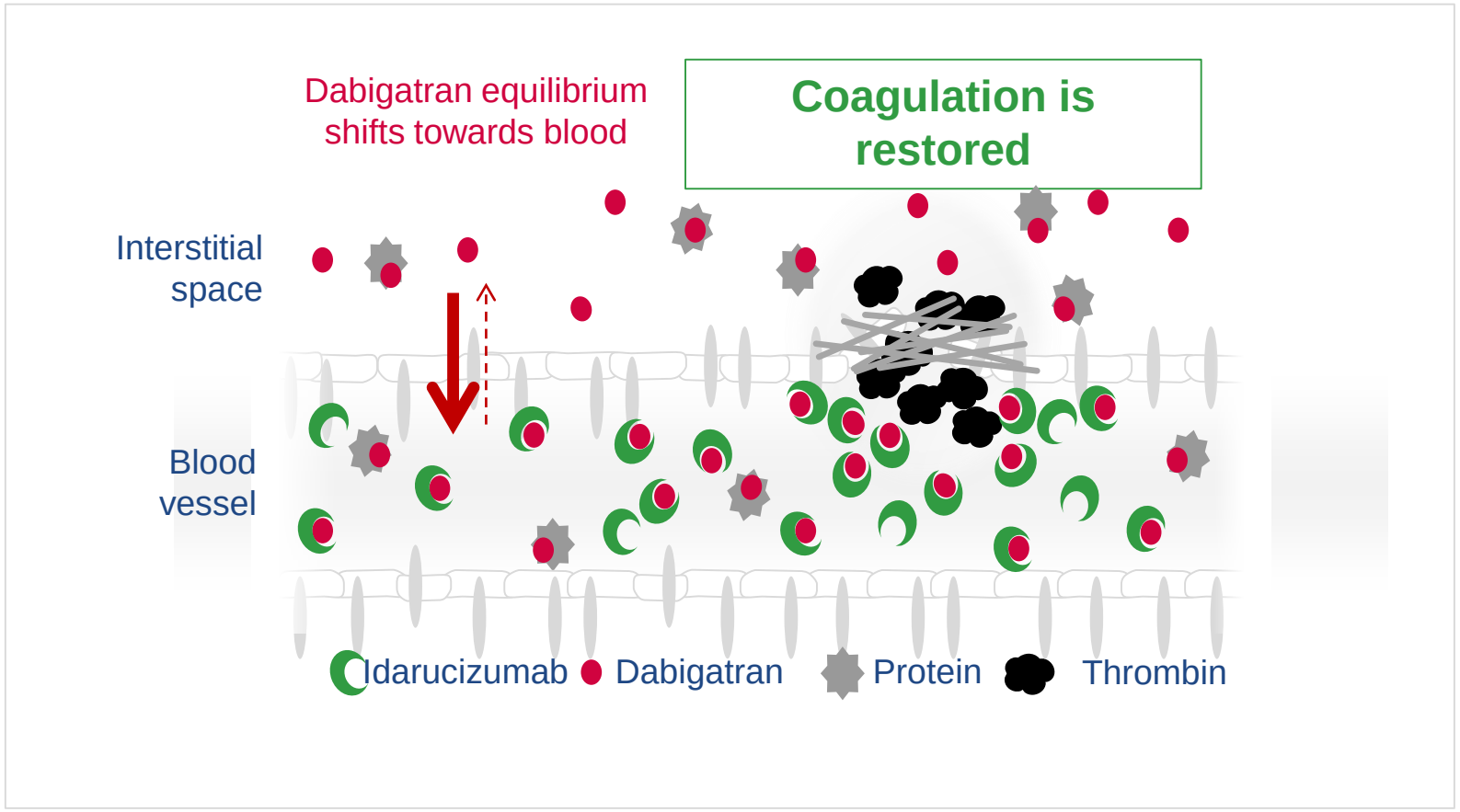
Idarucizumab e ricoagulazione



- When idarucizumab is administered, it binds rapidly to free dabigatran in plasma
- Some idarucizumab molecules remain unbound and have the potential to bind to dabigatran

Eikelboom Circulation. 2015;132:2412-2422.

Idarucizumab e ricoagulazione



Eikelboom Circulation. 2015;132:2412-2422.

Studio RE-VERSE AD™

Pollack et al. N Engl J Med 2015

AHA Meeting,New Orleans 2016

ORIGINAL ARTICLE

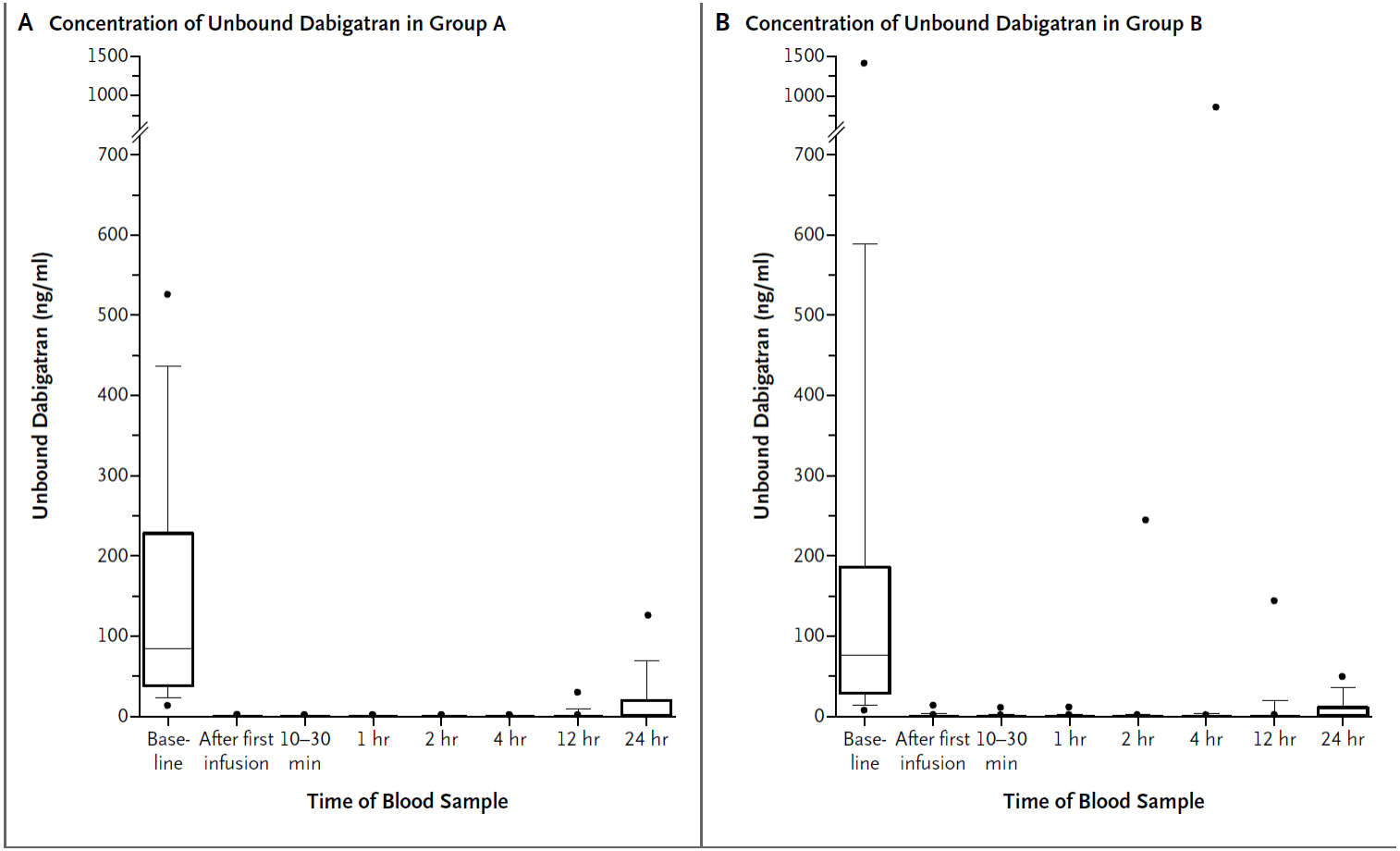
Idarucizumab for Dabigatran Reversal — Full Cohort Analysis

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., Joanne van Ryn, Ph.D.,

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	33 (11.0)	
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)

Concentrazioni plasmatiche di dabigatran “libero” dopo infusione di Idarucizumab



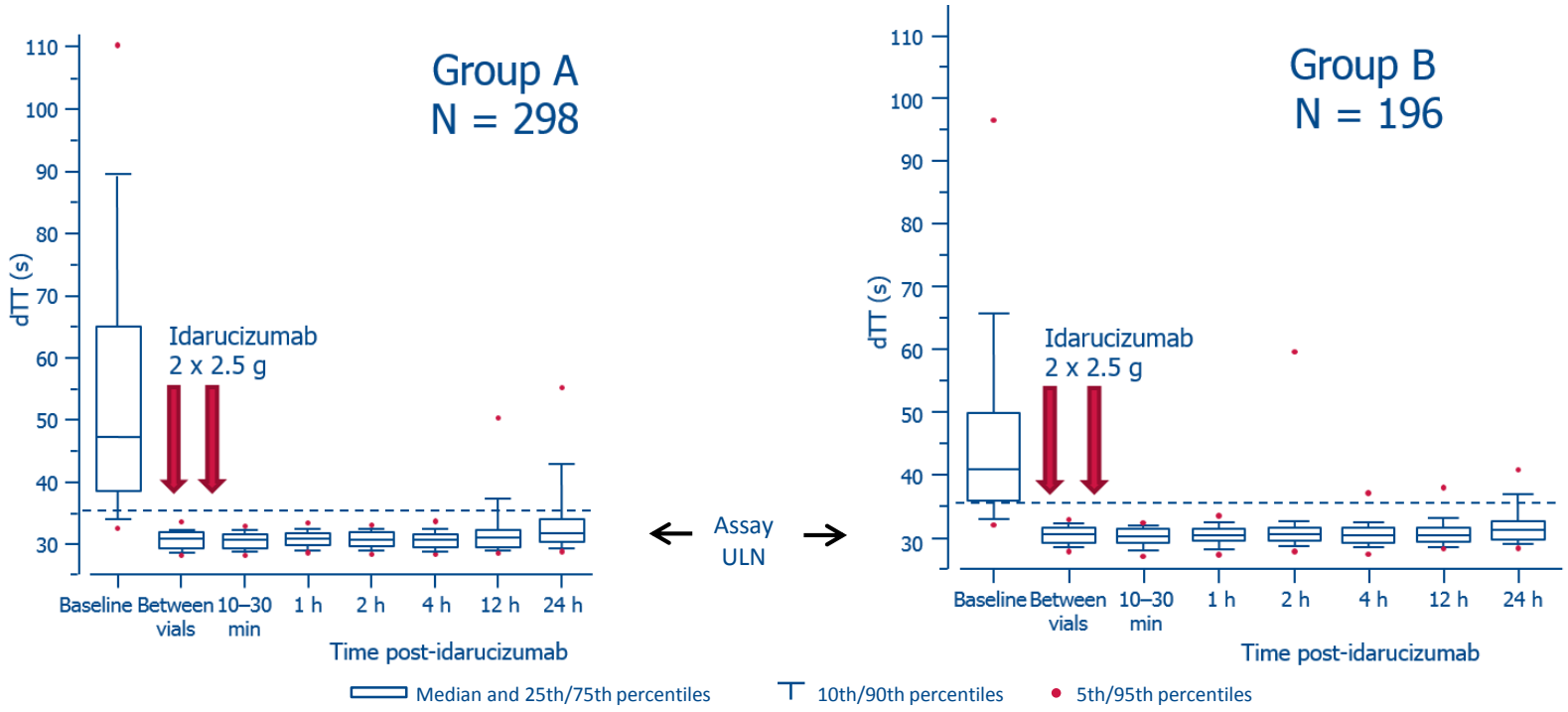
A)patients who had serious bleeding

B) patients who required urgent surgery

Pollack V, NEJM 2015

Studio RE-VERSE AD™ risultati principali

Reversal completo dell'attività anticoagulante di dabigatran in 5 min.

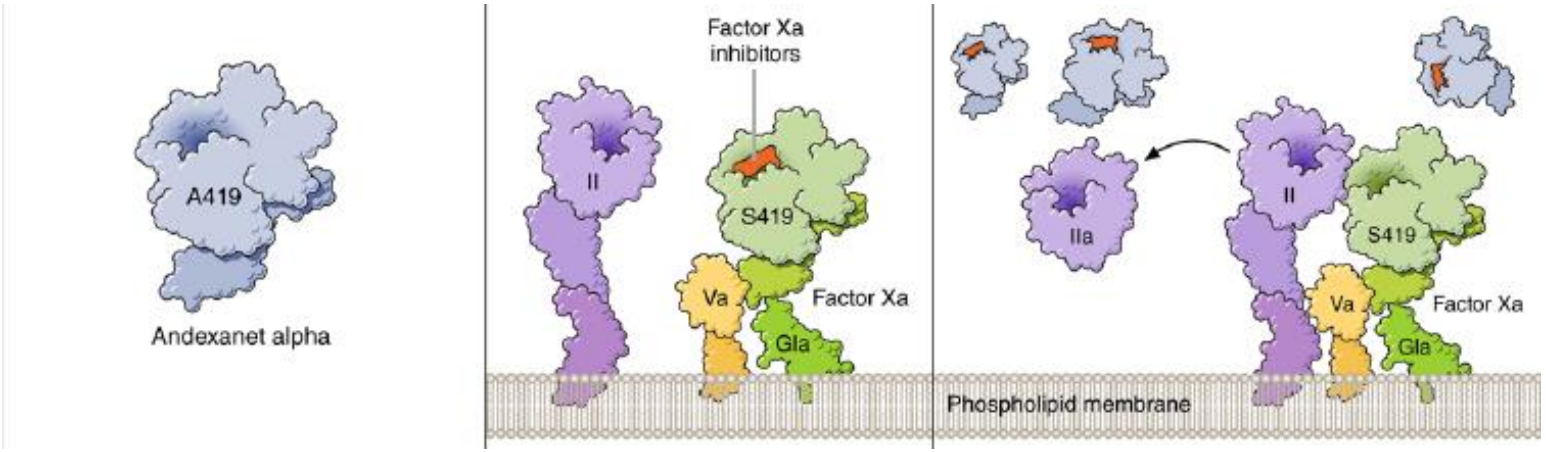


dTT, tempo di trombina diluita; ECT, tempo di ecarina;

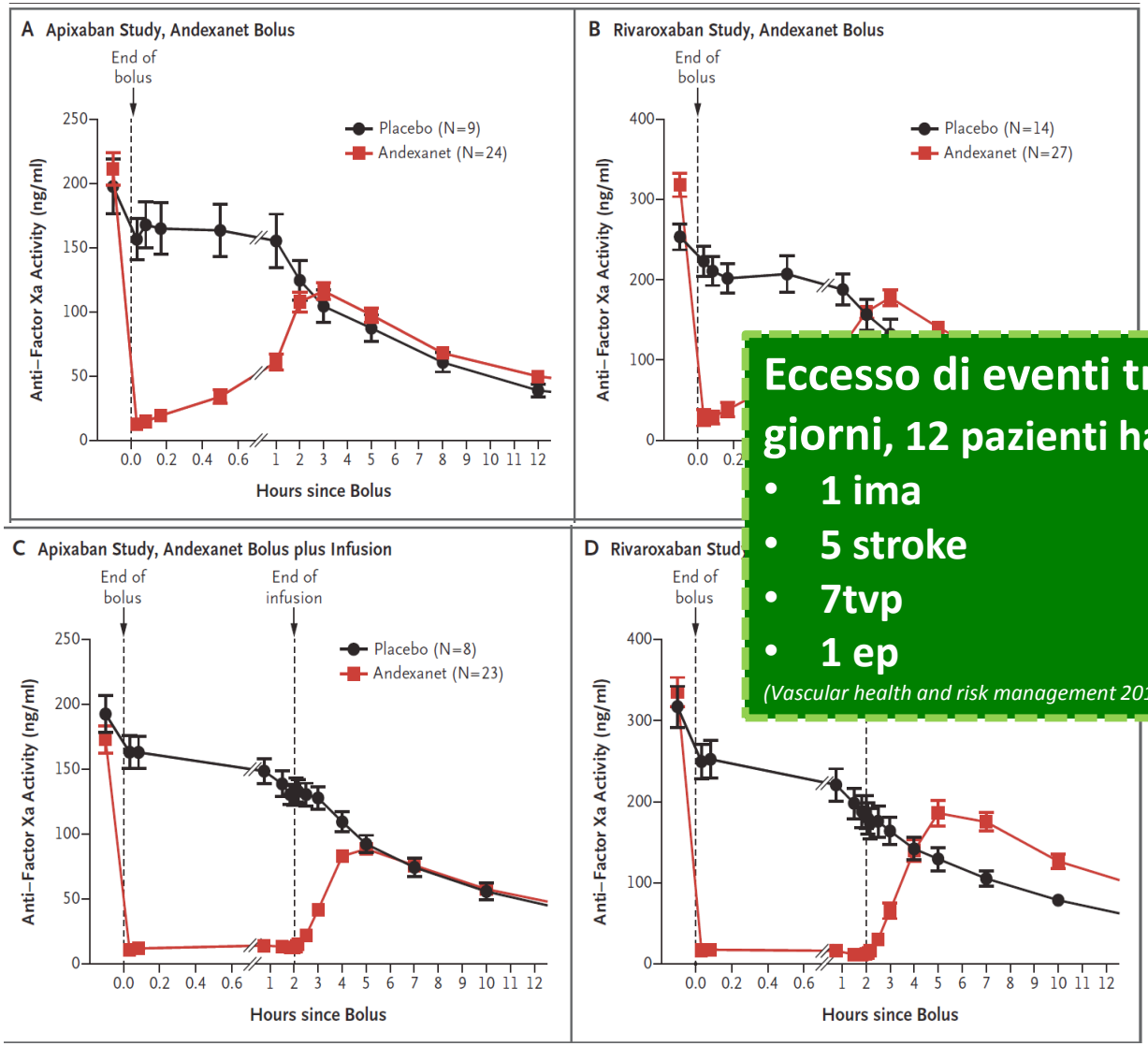
Pollack et al. AHA 2016--N. ENGL J MED 377; 5, August 1, 2017

Andexanet ALFA

- Antidoto specifico per inibitori diretti del fattore X (rivaroxaban, apixaban, edoxaban)
- Si lega agli inibitori del fattore X con la stessa affinità del fattore X stesso



ANNEXA A-R bolo e infusione di Andexanet



Eccesso di eventi trombotici entro 30 giorni, 12 pazienti hanno avuto trombosi:

- **1 ima**
- **5 stroke**
- **7tvp**
- **1 ep**

(Vascular health and risk management 2017: 13 287-292)<

Siegal D, NEJM 2015

Annexa 4 risultati

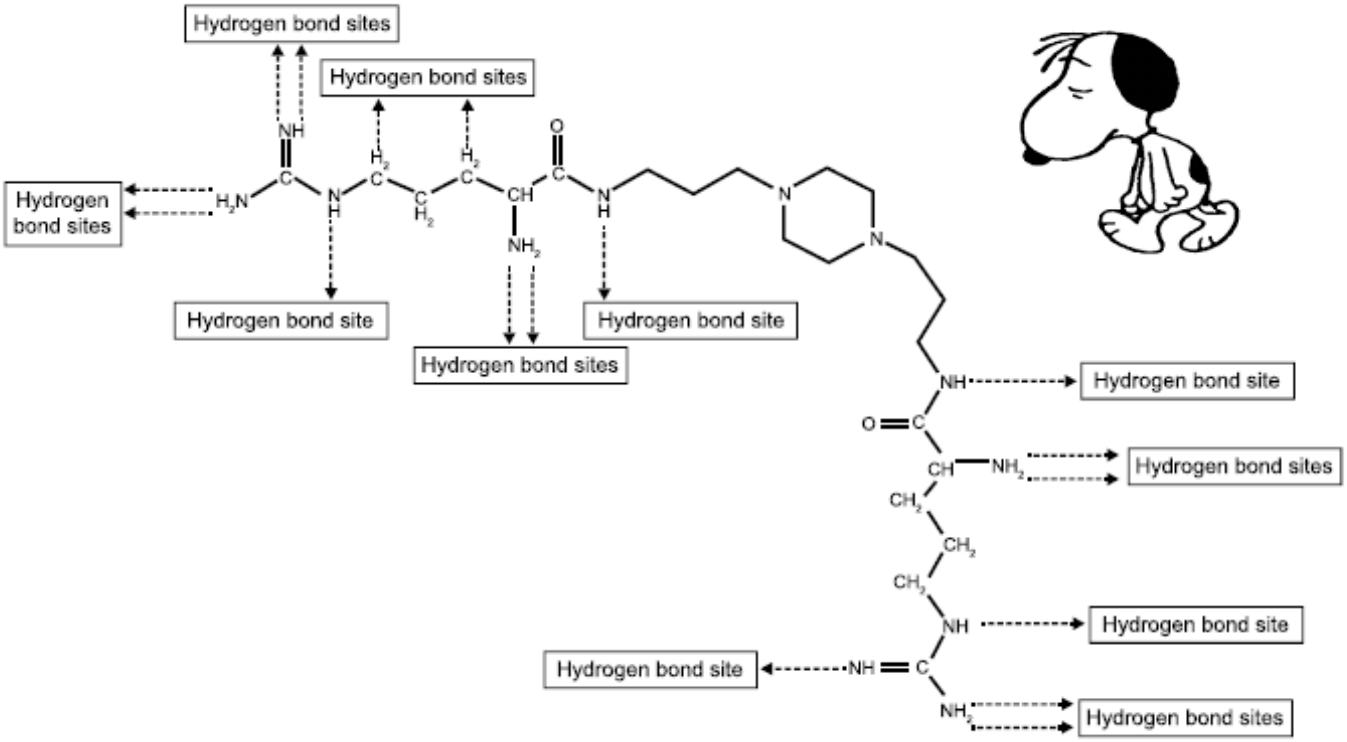
- 228 pazienti arruolati, di cui 137 trattati
- età media di 77 aa
- Dopo il bolo di andexanet la percentuale di attività anti Xa è:
  - diminuita del 92% (95% CI, 87 to 94) tra i pazienti trattati con apixaban,
  - diminuita del 87% nel gruppo rivaroxaban
  - diminuita del 73% per quelli in enoxaparina
- Emostasi buona o eccellente a 12 ore in 109 paz (83%)
- A 30 giorni 24 pazienti hanno presentato evento trombotico (11%) e 27 decessi (12%)

Interim Report on the ANNEXA-4 Study: Andexanet For Reversal of Anticoagulation in Factor Xa - Associated Acute Major Bleeding. March 12, 2018

AMERICAN COLLEGE of CARDIOLOGY

Ciraparantag

- Molecola idrosolubile sintetica che mediante legami non coovalenti lega molecole complesse (dabigatran, apixaban, rivaroxaban, fondaparinux, LMWE) e ne previene il legame con i target endogeni



Ciraparantag (PER977)

Ciraparantag (PER977) at a glance	
Mechanism of action	Universal reversal agent
	Synthetic molecule binds:
	Direct Xa inhibitors (apixaban, rivaroxaban, and edoxaban)
	Direct thrombin inhibitors (dabigatran)
	Unfractionated and low molecular weight heparin
Proposed dose	Single 100 mg IV dose*
Time to effect	30 minutes: restoration of WBCT and mean fibrin–fibrin diameter**
Adverse effects	Mild perioral and facial flushing, dysgeusia**
	PT remains elevated
	Does not appear to be sensitive marker for PER977-mediated anticoagulation reversal*
	No prothrombotic effect§
Possible indications	Life threatening hemorrhage
	Emergent surgery
	Elective procedures to minimize time off anticoagulation

Notes: *Dose being investigated in Phase II trial; **data from Laulicht et al;[50] §data from Ansell et al.[38]
Abbreviations: FDA, Food and Drug Administration; PT, prothrombin time; WBCT, whole-blood clotting time; IV, intravenous.

- 80 volontari sani ai quali è stato somministrato, 3 ore dopo assunzione di edoxaban 60 mg, 100/300 mg di PER977
- Misurato CT clotting time) ai tempi 0-10,30, 24 h: normalizzato il CT e mantenuto nelle 24 ore

ESC European Society of Cardiology
European Heart Journal (2018) **00**, 1–64
doi:10.1093/eurheartj/ehy136

The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation

Life-threatening bleeding	• All of the above
	• Direct reversal: Idarucizumab 5 g i.v. in two doses a 2.5 g i.v. no more than 15 min apart
		• All of the above
		• Direct reversal: Andexanet alpha (if available and approved)[a]
		  • Bolus over 15–30 min, followed by 2-h infusion
		  • Rivaroxaban (last intake >7 h before) or apixaban: 400 mg bolus, 480 mg infusion @ 4 mg/min
		  • Rivaroxaban (last intake <7 h before or unknown) or enoxaparin or edoxaban: 800 mg bolus, 960 mg infusion @ 8 mg/min

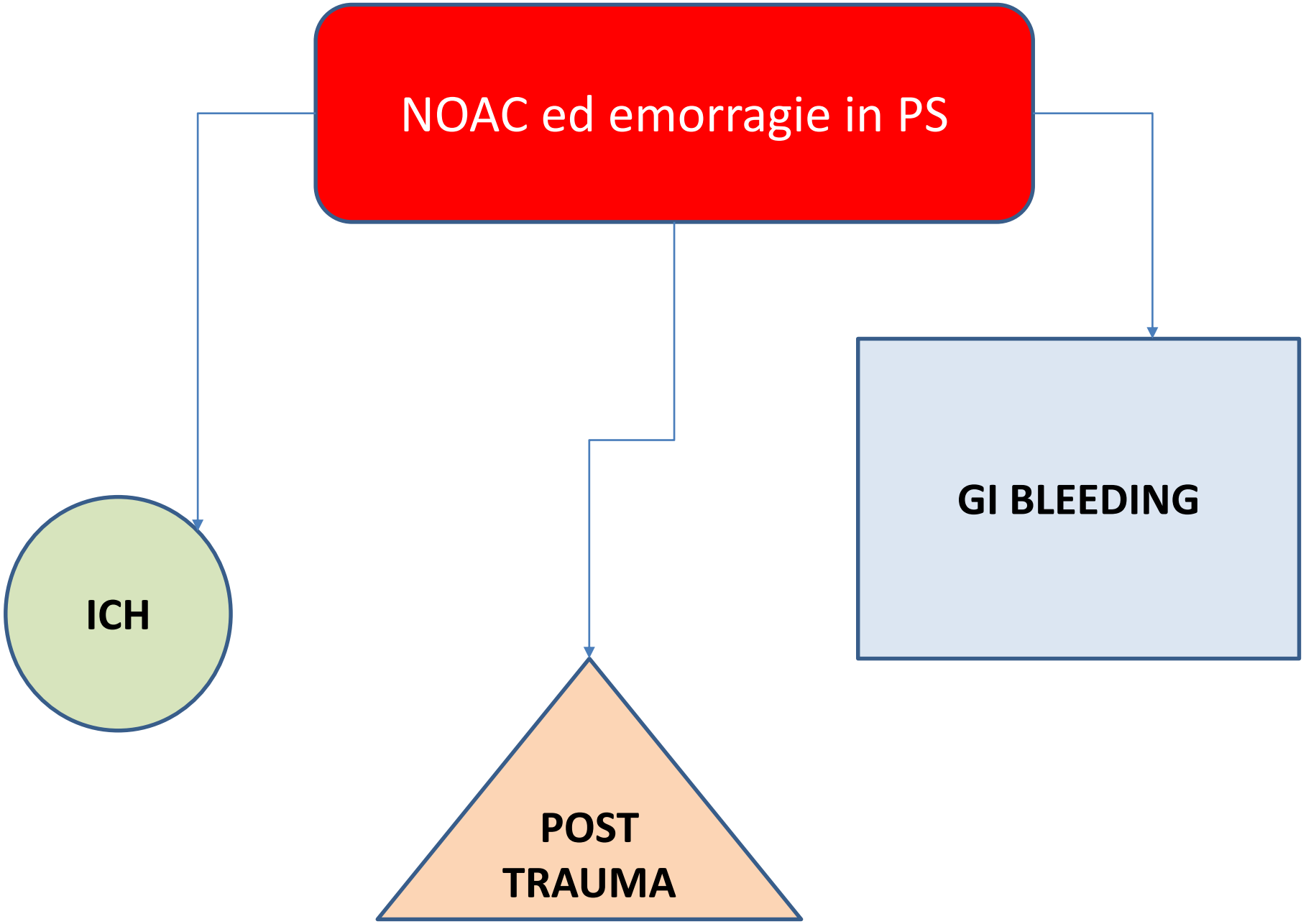
	• Prothrombin complex concentrate (PCC) 50 U/kg (with additional 25 U/kg if clinically needed) • Activated PCC 50 U/kg; max 200 U/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC, if available	

ESC European Society of Cardiology
European Heart Journal (2018) **00**, 1–64
doi:10.1093/eurheartj/ehy136

Table 10 **Possible measures to take in case of bleeding**

	Direct thrombin inhibitors (dabigatran)	FXa inhibitors (apixaban, edoxaban, rivaroxaban)
Non life-threatening major bleeding	• Inquire about last intake + dosing regimen • Local haemostatic measures • Fluid replacement • RBC substitution, if necessary • Platelet substitution (in case of thrombocytopenia ≤60 × 109/L or thrombopathy) • Fresh frozen plasma not as reversal agent (may be considered as plasma expander) • Tranexamic acid can be considered as adjuvant (1 g i.v., repeat every 6 h, if necessary) • Desmopressin can be considered in special cases such as coagulopathy or thrombopathy; 0.3 µg/kg i.v. infusion (max dose 20 µg)	

	• Estimate normalization of plasma levels:
	  • 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
	• Consider idarucizumab (see below)
		• Normalization of plasma levels: 12–24 h


NOAC ed emorragie in PS
ICH
POST TRAUMA
GI BLEEDING

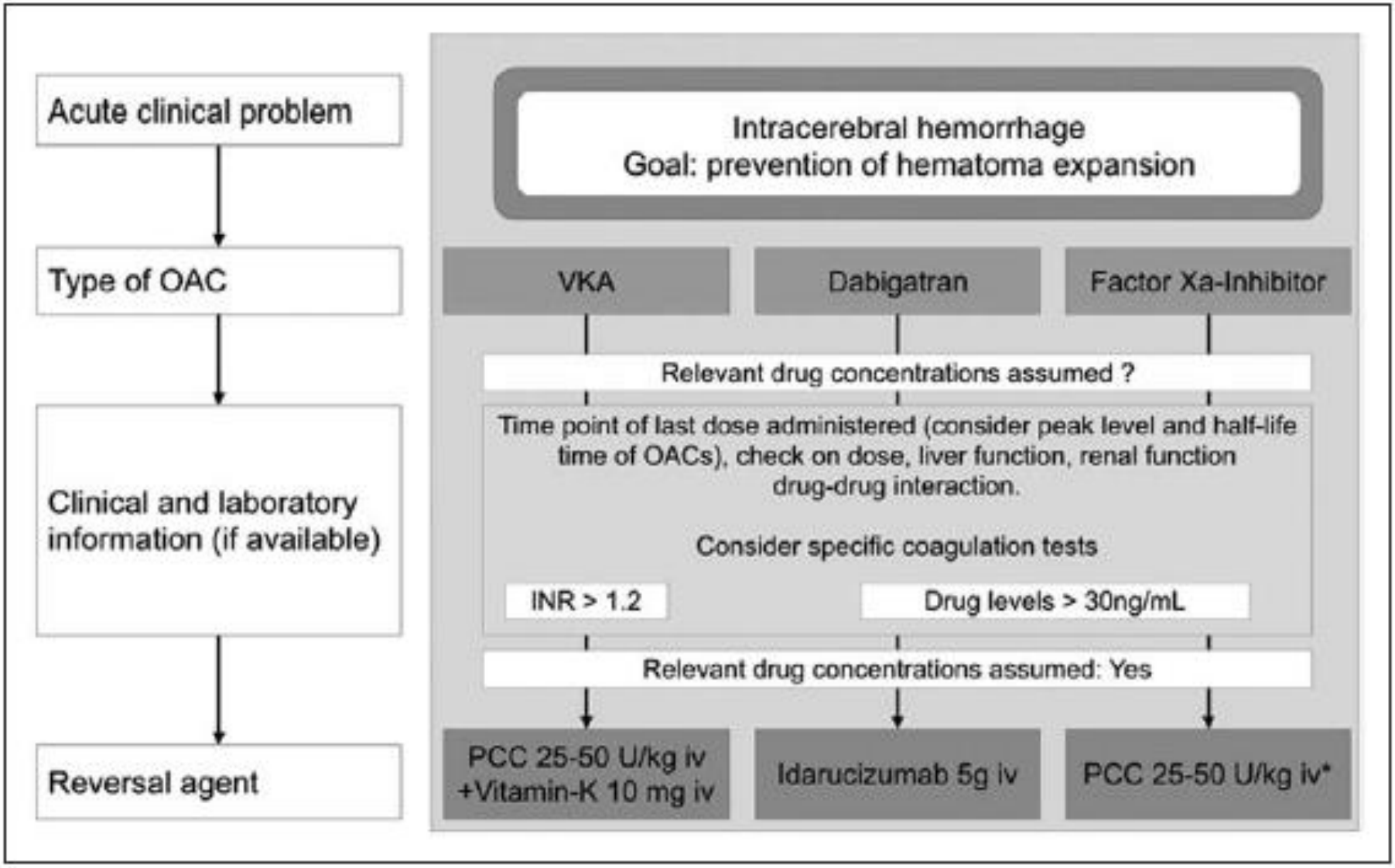
Anticoagulant-Associated Intracranial Hemorrhage in the Era of Reversal Agents

Thorsten Steiner, MD, MME; Jeffrey I. Weitz, MD; Roland Veltkamp, MD

Consequently, hematoma expansion seems to be a common complication of intracerebral hemorrhage regardless of whether patients are taking VKAs or DOACs. Therefore, once the diagnosis of intracerebral bleeding is established, anticoagulant reversal should be undertaken as soon as possible.[13]

ICH

(*Stroke*. 2017;48:00-00. DOI: 10.1161/STROKEAHA.116.013343.)



(*Stroke*. 2017;48:00-00. DOI: 10.1161/STROKEAHA.116.013343.)

Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage

A Statement for Healthcare Professionals from the Neurocritical Care Society and Society of Critical Care Medicine

Recommendations for Direct Thrombin Inhibitor Reversal

(1) We recommend discontinuing direct thrombin inhibitors when intracranial hemorrhage is present or suspected. (Good Practice statement)

(2) We recommend assessing the time and amount of the last ingested dose, renal function, and possible medication interactions to assist in estimating the degree of anticoagulation exposure. (Good Practice statement)

(3) We suggest that pharmacological reversal of direct thrombin inhibitors should be guided primarily by bleeding (major or intracranial) and not primarily by laboratory testing. (Conditional recommendation, low-quality evidence)

(4) We suggest administering activated charcoal (50 g) to intubated intracranial hemorrhage patients with enteral access and/or those at low risk of aspiration who present within 2 h of ingestion of an oral direct thrombin inhibitor. (Conditional recommendation, very low-quality evidence)

(5) We recommend administering idarucizumab (5 g IV in two divided doses) to patients with intracranial hemorrhage associated with dabigatran if:

(a) the dabigatran was administered within a period of 3–5 half-lives and there is no evidence of renal failure (Strong recommendation, moderate quality of evidence) or

(b) there is renal insufficiency leading to continued drug exposure beyond the normal 3–5 half-lives (Strong recommendation, moderate quality of evidence)

(6) We suggest administering aPCC (50 units/kg) or 4-factor PCC (50 units/kg) to patients with intracranial hemorrhage associated with direct thrombin inhibitors if idarucizumab is not available or if the hemorrhage is associated with a DTI other than dabigatran if:

(a) the direct thrombin inhibitor was administered within a period of 3–5 half-lives and there is no evidence of renal failure (Conditional recommendation, low-quality evidence) or

(b) there is renal insufficiency leading to continued drug exposure beyond the normal 3–5 half-lives. (Conditional recommendation, low-quality evidence)

(7) In patients with dabigatran-associated intracranial hemorrhage and renal insufficiency or dabigatran overdose, we suggest hemodialysis if idarucizumab is not available. (Conditional recommendation, low-quality data)

(8) In patients with dabigatran-associated intracranial hemorrhage who have already been treated with idarucizumab, PCC, or aPCC, with ongoing evidence of clinically significant bleeding, we suggest consideration of redosing idarucizumab and/or hemodialysis. (Conditional recommendation, low-quality evidence)

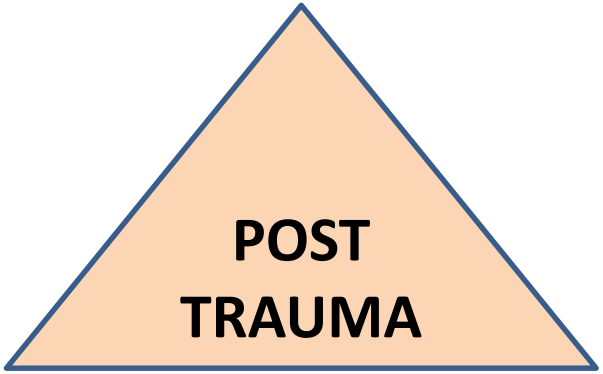
(9) We recommend against administration of rFVIIa or FFP in direct thrombin inhibitor-related intracranial hemorrhage. (Strong recommendation, low-quality evidence)

Neurocrit Care (2016) 24:6–46

Management of Patients on Non–Vitamin K Antagonist Oral Anticoagulants in the Acute Care and Periprocedural Setting

A Scientific Statement From the American Heart Association

There is no clinical trial evidence to guide the management of patients with traumatic brain injury while on anticoagulants. An initial head CT is typical; however, the role of repeated CT or inpatient observation with neurological assessment remains controversial when the initial head CT is negative. Until further data become available, NOAC reversal for traumatic ICH should be considered similar to nontraumatic ICH.



NOACs may be held during the period of clinic assessment or until hemostasis has been achieved in trauma patients without bleeding and with mild bleeding, or bleeding from easily controllable foci. Maintaining adequate urine output and specific NOAC reversal strategies (NOAC reversal) should be considered in trauma patients with moderate or severe bleeding, or suspected bleeding that requires further evaluation.

Review Article

Management of anticoagulation in patients with acute gastrointestinal bleeding

GI BLEEDING

Franco Radaelli[a,*], Francesco Dentali[b], Alessandro Repici[c], Arnaldo Amato[a], Silvia Paggi[a], Emanuele Rondonotti[a], Jean Marc Dumonceau[d]

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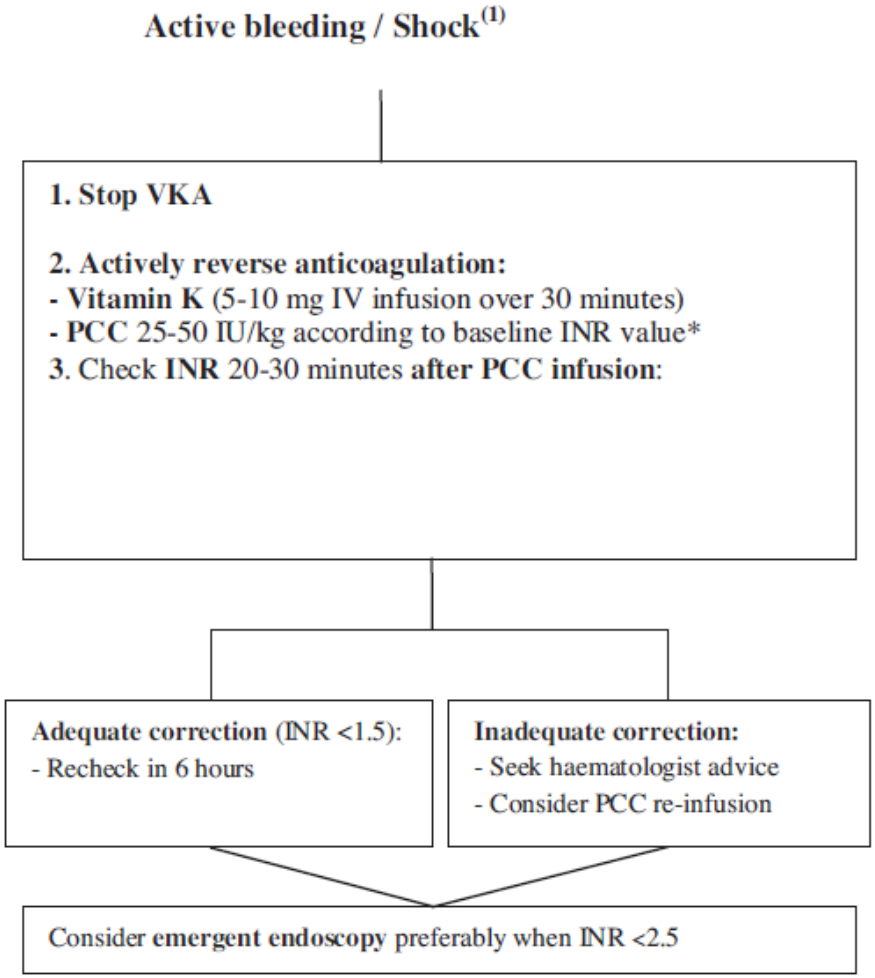
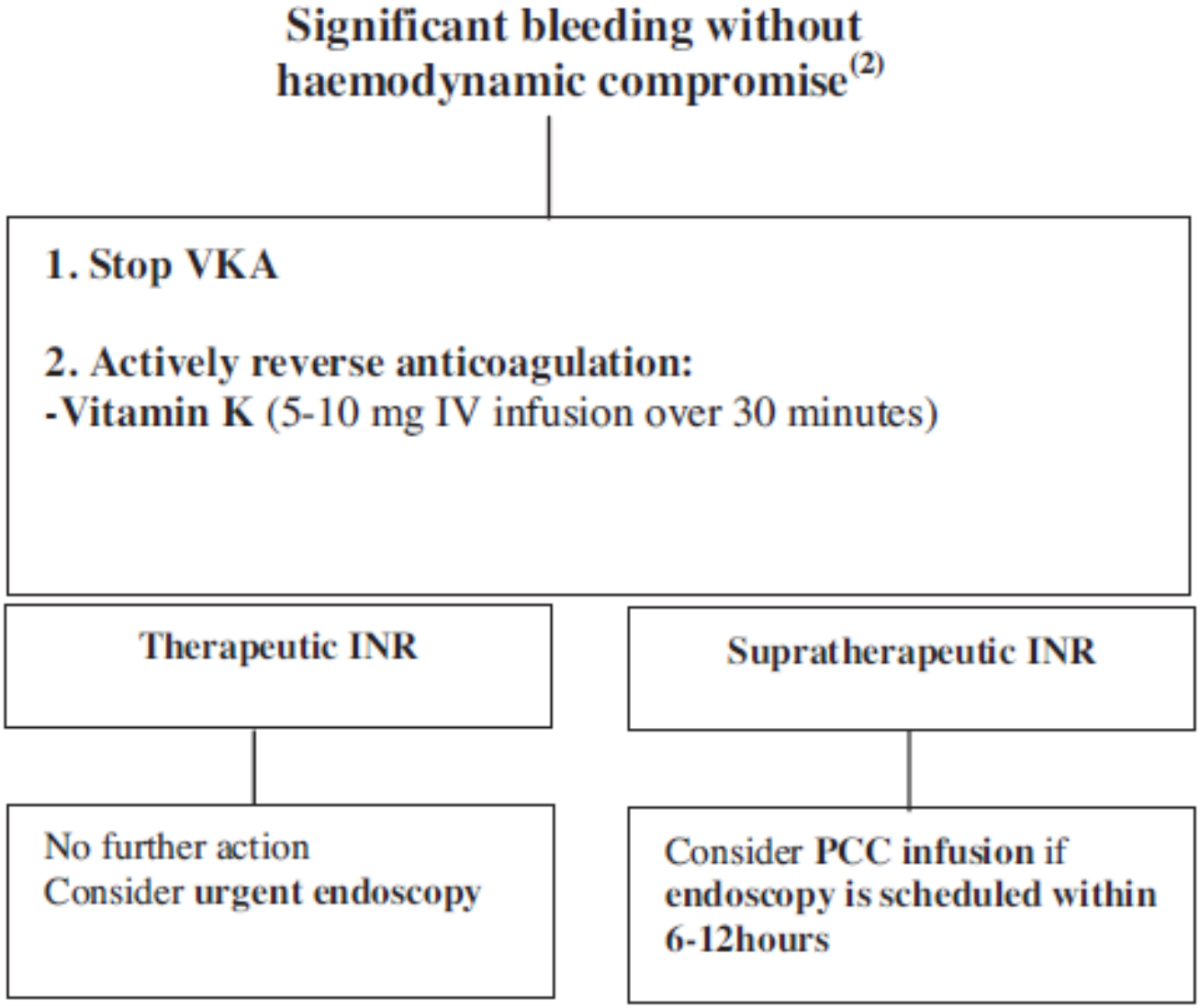
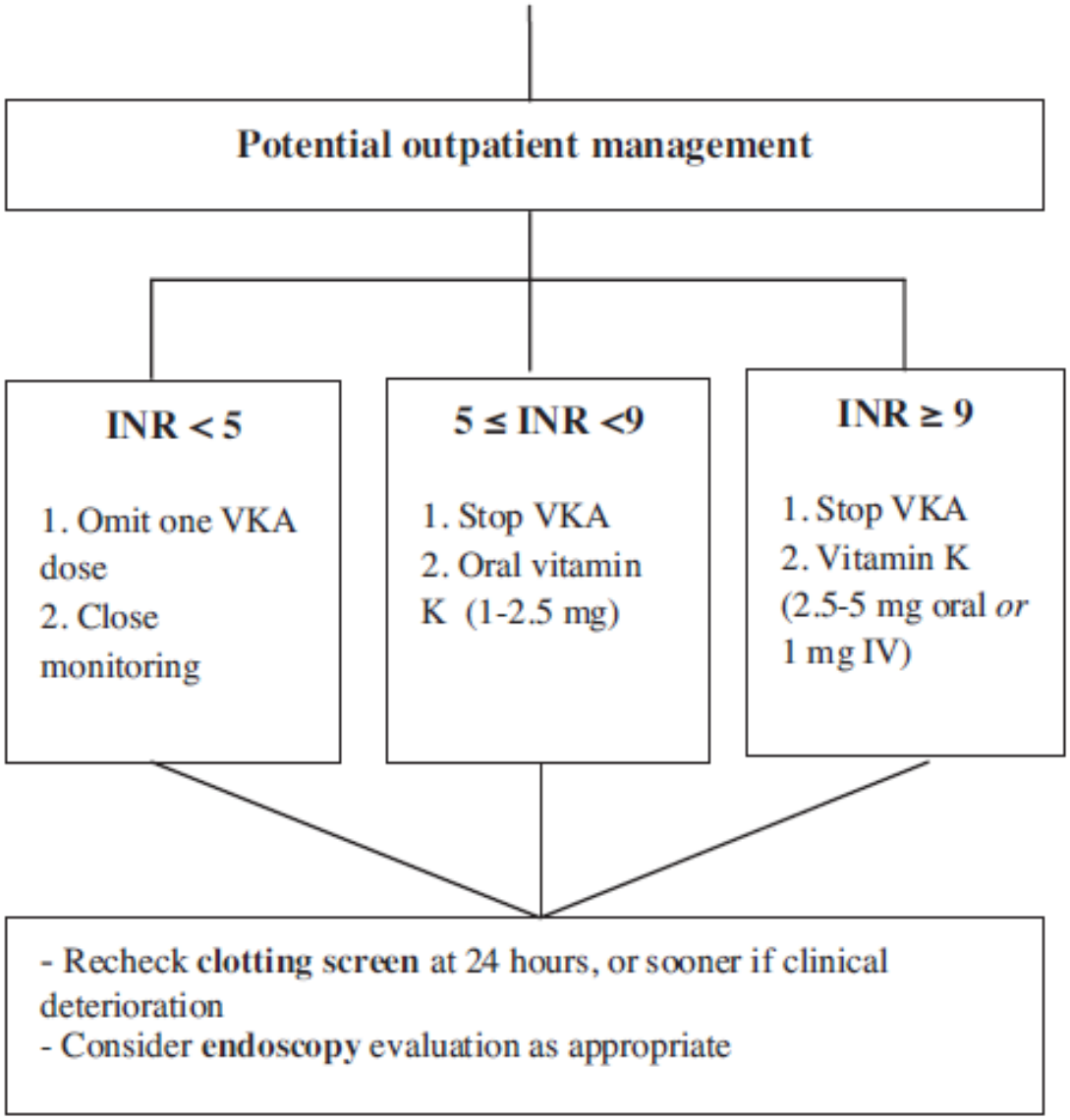


Digestive and Liver Disease 47 (2015) 621–627



Digestive and Liver Disease 47 (2015) 621–627

Minor rectal bleeding [3]



GI BLEEDING

Journal of Thrombosis and Haemostasis, **14**: 623–627 DOI: 10.1111/jth.13227

RECOMMENDATIONS AND GUIDELINES

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

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

EXAMPLE of a "Serious Bleeding on NOAC PROTOCOL"

General Measures

- mechanical compression if possible
- two sites of IV access
- determine timing of last NOAC dose
- CBC, BUN, Creatinine, liver enzymes
- plasma expanders/PRBC's as necessary
- consider activated charcoal if NOAC ingestion <2hours
- notify on-call hematologist
- Refer to chart below for specific measures

NOAC	Blood tests for NOAC presence or effect	Specific Antidote	Alternative Treatments Options
Dabigatran	PTT , TT	Idarucizumab 5 grams IV (2 infusions of 2.5 grams)	4 Factor PCC *(Kcentra®)* 50 IU/kg IV Factor VIIa 90µg/kg IV every 2 hours Tranexamic acid 15-30 mg/kg IV Hemodialysis
Rivaroxaban	Anti-Factor Xa	Unavailable in the U.S.	4 Factor PCC *(Kcentra®)* 50 IU/kg IV Factor VIIa 90µg/kg IV every 2 hours Tranexamic acid 15-30 mg/kg IV
Apixaban	Anti-Factor Xa	Unavailable in the U.S.	PCC *(Kcentra®)* 50 IU/kg IV Factor VIIa 90µg/kg IV every 2 hours Tranexamic acid 15-30 mg/kg IV
Edoxaban	Anti-Factor Xa	Unavailable in the U.S.	PCC *(Kcentra®)* 50 IU/kg IV Factor VIIa 90µg/kg IV every 2 hours Tranexamic acid 15-30 mg/kg IV

TT = thrombin time, PTT = partial thromboplastin time, PCC = prothrombin complex concentrate

Editorial

EXPERT OPINION

Antidotes to non-vitamin K oral anticoagulants: necessary or not?

Marco Proietti & Gregory YH Lip†

In life-threatening situations, the possibility to barely immediately reverse the anticoagulation effect of NOACs could have importance.

For example, **when hemodynamic stability has been compromised during hemorrhagic shock, stopping active bleeding could be necessary in trying to stabilize vital functions.**

Proietti M, JTT 2015

Conclusioni

- Riconosciamo e stabilizziamo le emorragie gravi, «major/life threating»?
- Siamo certi che sia necessario usare l'antidoto?
- Il dosaggio dell'attività del NOAC puo' essere di ausilio?
- Una volta ricoagulato dobbiamo riscoagularlo?