Lo stroke emorragico all'epoca dei DOACs: quali le armi a disposizione

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Agenda

- Cenni sulle caratteristiche dei DOAC
- Antidoti a disposizione
- Dati *real world*
- Indicazioni da linee guida

DOAC - caratteristiche

Table 4 Absorption and metabolism of the different NOACs

	Dabigatran[106,376]	Apixaban[517]	Edoxaban[518]	Rivaroxaban[519,520]
Bioavailability	3–7%	50%	62%	15 mg/20 mg: 66% without food, 100% with food
Prodrug	Yes	No	No	No
Clearance non-renal/renal of absorbed dose	20%/80%	73%/27%	50%/50%	65%/35%
Plasma protein binding	35%	87%	55%	95%
Dialysability	50–60% (In part dialysable)	14% (Not dialysable)	NA (Not dialysable)	NA (Not dialysable)
Metabolism	Glucoronic acid conjugation	CYP3A4 (25%), CYP1A2, CYP2J2, CYP2C8, CYP2C9 CYP2C19	CYP3A4 (<4% of elimination)	CYP2A4 (18%)[519], CYP2J2
Absorption with food	No effect	No effect	6–22% more; minimal effect on exposure	+39% more (see above)
Absorption with H2B/PPI	−12% to 30% (not clinically relevant)	No effect	No effect	No effect
Time to peak levels (h)	3	3	2–4	2–4
Elimination half-life (h)	12–17	12	10–14	5–9 (young) 11–13 h (elderly)

NOAC, non-vitamin K antagonist oral anticoagulant.

DOAC - caratteristiche

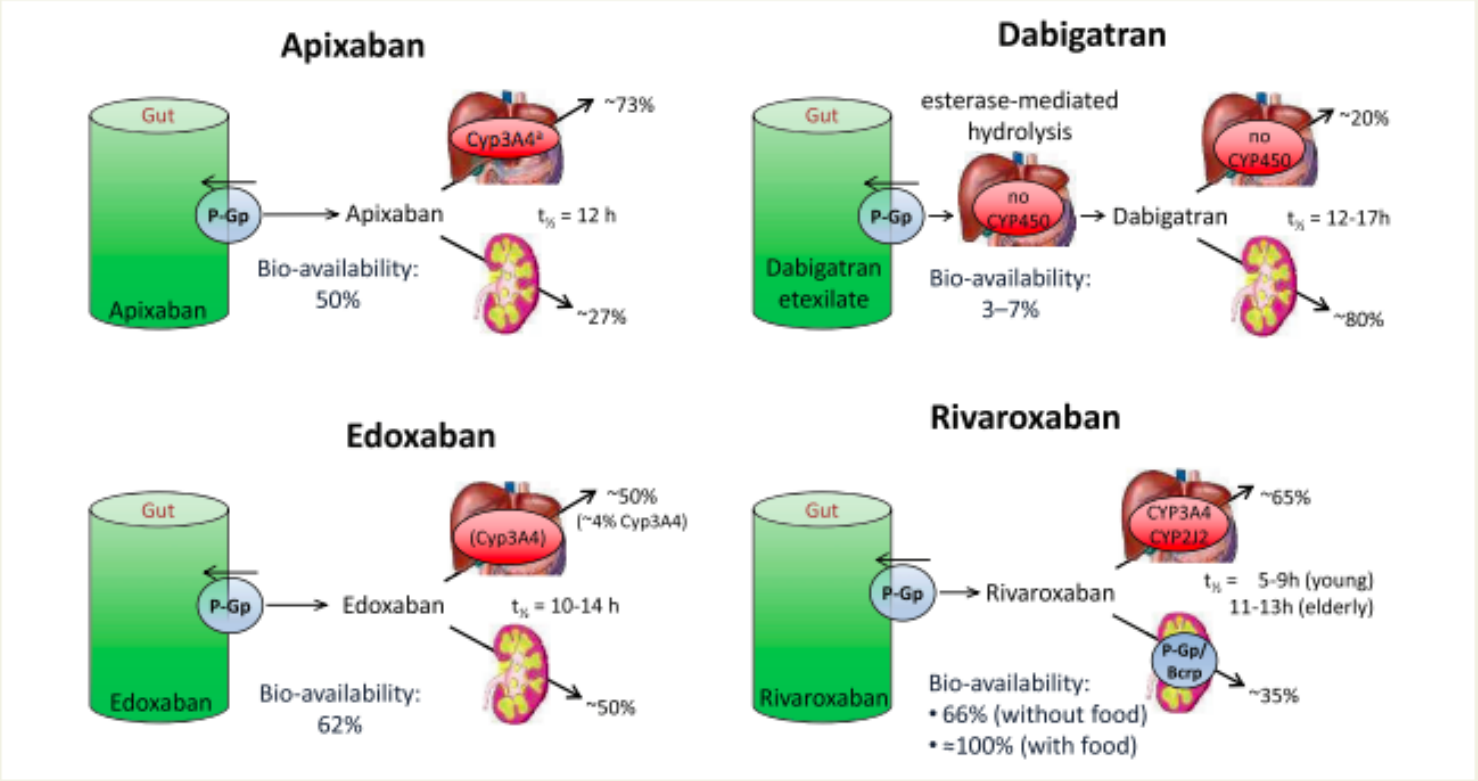


Figure 5 Absorption and metabolism of the different NOACs. There are interaction possibilities at the level of absorption or first transformation, and at the level of metabolization and excretion. [a]Also via CYP1A2, CYP2J2, CYP2C8, CYP2C9, and CYP2C19. NOAC, non-vitamin K antagonist oral anticoagulant.

DOAC - utilizzo

- I DOAC sono ampiamente utilizzati per il trattamento e la prevenzione degli eventi trombotici.
- Il trattamento antitrombotico aumenta il rischio emorragico (emorragia maggiore, CRNMB, emorragie minori)
- **L'emorragia cerebrale** è una delle possibili complicanze del loro uso, ed è associata a elevata morbilità e mortalità

Emorragia maggiore (sec. ISTH)

- Fatale: che determina o concorre a determinare il decesso del paziente
- In sede critica: **intracranica**, intraoculare, retroperitoneale, pericardica, spinale, muscolare con sd. compartimentale, intraarticolare
- Che richieda intervento chirurgico o manovra invasiva
- Con calo Hb > 2 g/dl o con necessità di terapia trasfusionale con almeno 2 U GRF

Schulman et al, JTH 2005

CRNMB ed emorragia minore (sec. ISTH)

- Emorragia che non ricade nella definizione di emorragia maggiore ma che presenta almeno uno di questi criteri:

1. Che richiede intervento sanitario
2. Che porta a ospedalizzazione o aumento delle cure
3. Che porta il paziente a ricercare una visita medica face to face (i.e. non la sola comunicazione telefonica o via mail)

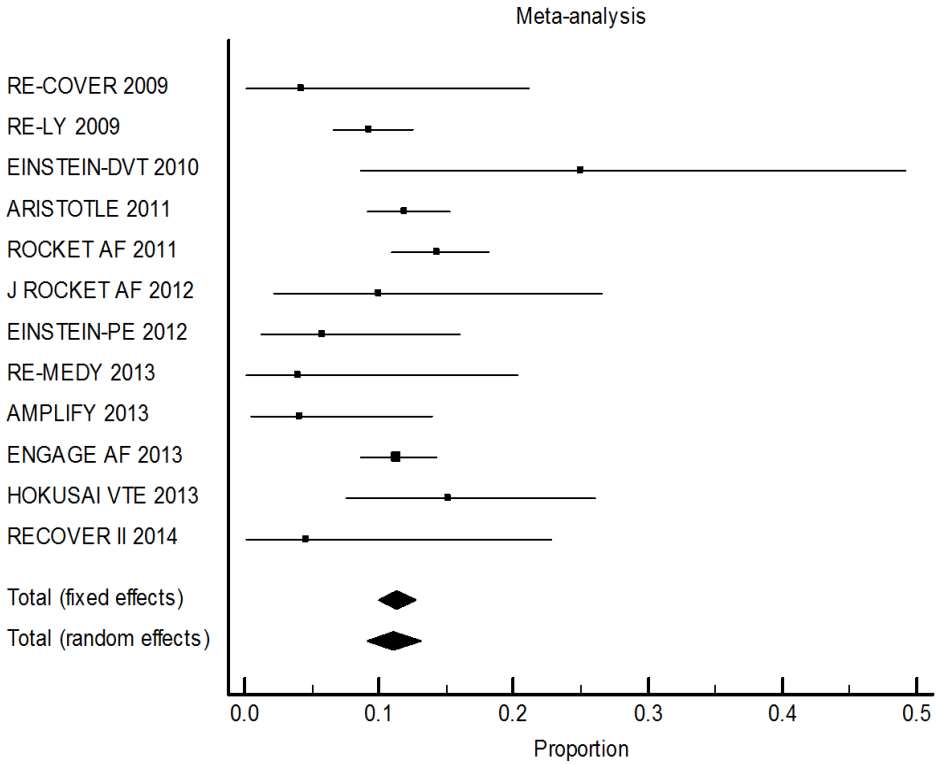
- Emorragia minore: ogni altro tipo di emorragia

Kaatz et al, JTH 2015

ORIGINAL ARTICLE

Mortality outcomes in patients receiving direct oral anticoagulants: a systematic review and meta-analysis of randomized controlled trials

Major Bleeding Case Fatality Rate of AVKs



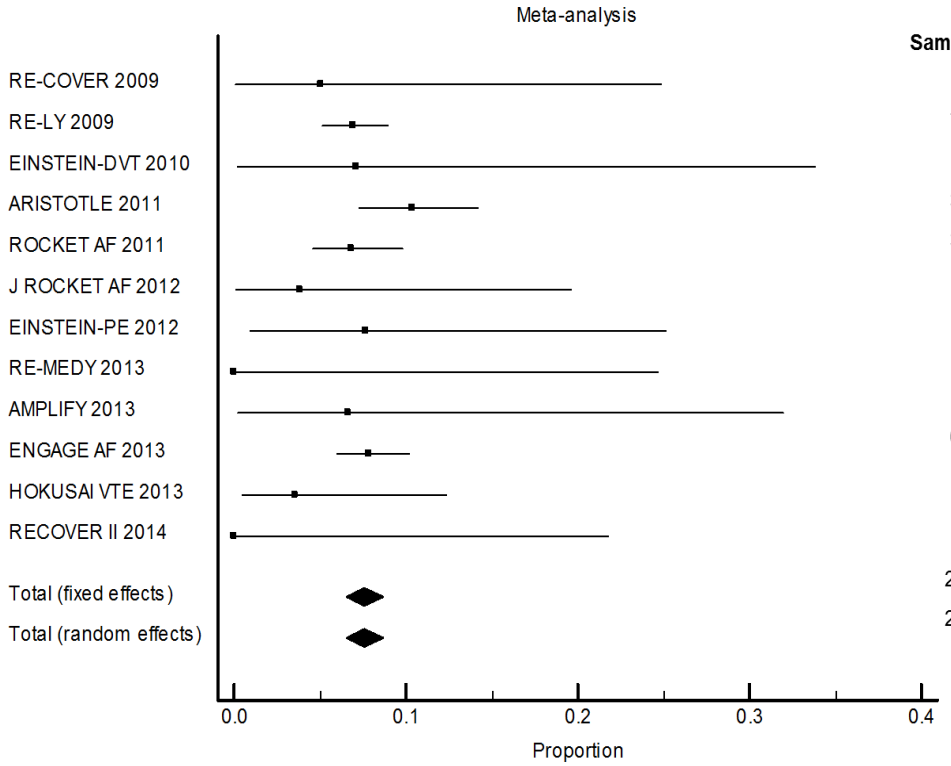
	Sample size	Proportion (%)	95% CI
RE-COVER 2009	24	4.167	0.105 to 21.120
RE-LY 2009	421	9.264	6.670 to 12.446
EINSTEIN-DVT 2010	20	25.000	8.657 to 49.105
ARISTOTLE 2011	462	11.905	9.095 to 15.213
ROCKET AF 2011	386	14.249	10.918 to 18.139
J ROCKET AF 2012	30	10.000	2.112 to 26.529
EINSTEIN-PE 2012	52	5.769	1.206 to 15.947
RE-MEDY 2013	25	4.000	0.101 to 20.352
AMPLIFY 2013	49	4.082	0.498 to 13.979
ENGAGE AF 2013	524	11.260	8.683 to 14.283
HOKUSAI VTE 2013	66	15.152	7.512 to 26.104
RECOVER II 2014	22	4.545	0.115 to 22.844
Total (fixed effects)	2081	11.306	9.980 to 12.741
Total (random effects)	2081	11.045%	9.169 to 13.073

Chai-adisaksopha et al. JTH 2015

ORIGINAL ARTICLE

Mortality outcomes in patients receiving direct oral anticoagulants: a systematic review and meta-analysis of randomized controlled trials

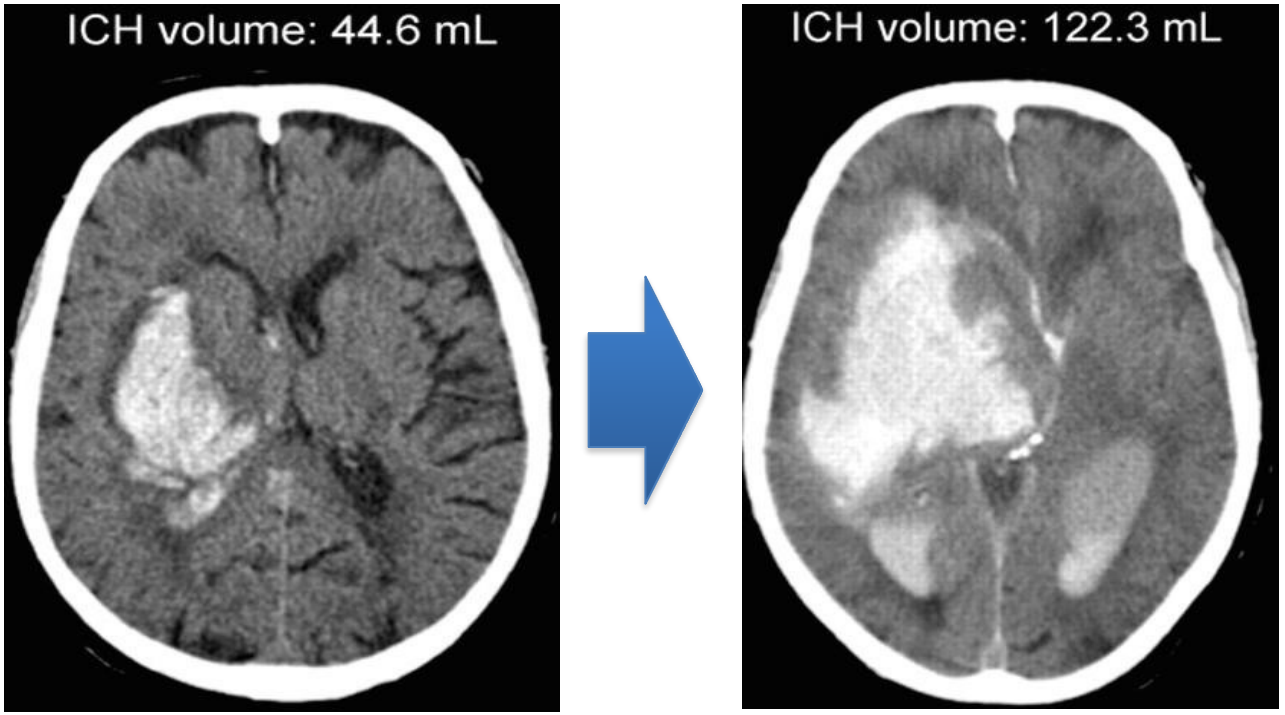
Major Bleeding Case Fatality Rate of DOACs



	Sample size	Proportion (%)	95% CI
RE-COVER 2009	20	5.000	0.127 to 24.873
RE-LY 2009	741	6.883	5.167 to 8.950
EINSTEIN-DVT 2010	14	7.143	0.181 to 33.868
ARISTOTLE 2011	327	10.398	7.309 to 14.226
ROCKET AF 2011	395	6.835	4.553 to 9.790
J ROCKET AF 2012	26	3.846	0.0973 to 19.637
EINSTEIN-PE 2012	26	7.692	0.946 to 25.130
RE-MEDY 2013	13	0.000	0.000 to 24.705
AMPLIFY 2013	15	6.667	0.169 to 31.948
ENGAGE AF 2013	672	7.887	5.963 to 10.190
HOKUSAI VTE 2013	56	3.571	0.435 to 12.313
RECOVER II 2014	15	0.000	0.000 to 21.802
Total (fixed effects)	2320	7.568	6.527 to 8.717
Total (random effects)	2320	7.568%	6.530 to 8.676

Chai-adisaksopha et al. JTH 2015

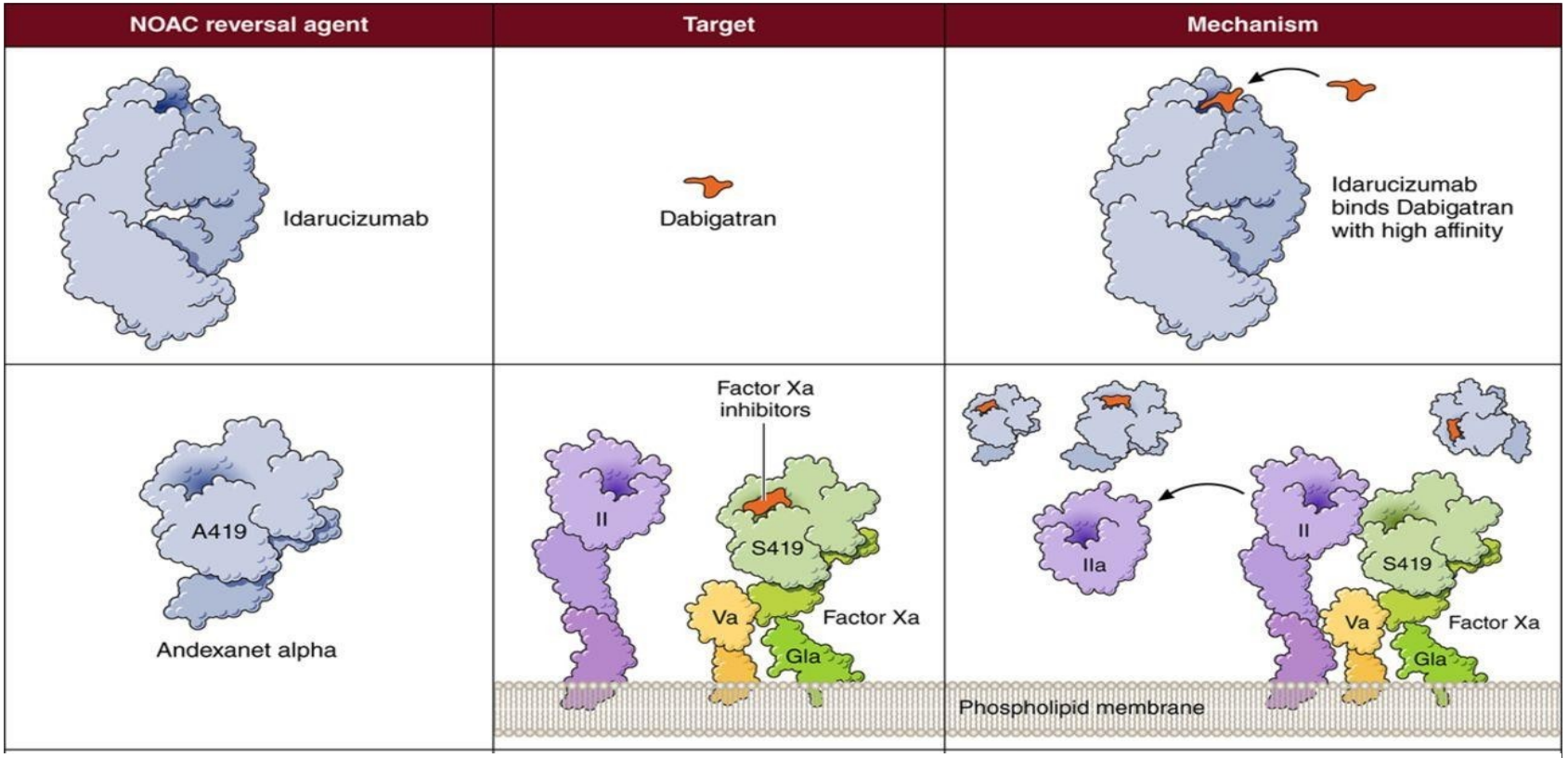
Time is Brain in ICH



Predittori di outcome sfavorevole sono l'età del paziente, il volume iniziale dell'ematoma e la sua espansione nel breve termine

Huttner et al. Stroke 2006

DOACs: Antidoti



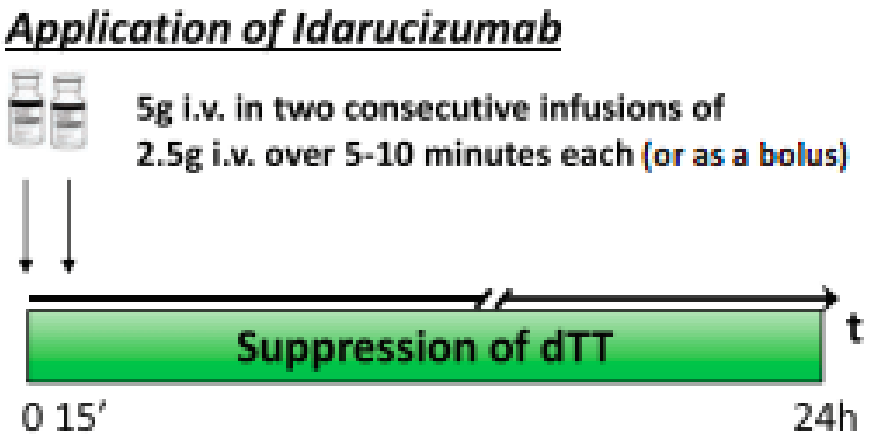
Ruff et al. Circulation 2016

Antidoti specifici disponibili

	Idaracizumab	Andexanet alfa
Alternate names	aDabi-Fab, BI655075	PRT064445
Company	Boehringer Ingelheim	Portola Pharmaceuticals
Chemical structure	Humanized monoclonal antibody fragment	Recombinant truncated human factor Xa variant (decoy)
Molecular mass	47 766 Da	39 000 Da
Binding	Noncompetitive binding to dabigatran	Competitive binding to direct factor Xa inhibitors or to indirect factor Xa inhibitor–activated antithrombin
Target affinity	≈350× greater affinity for dabigatran than factor IIa	Affinity for direct factor Xa inhibitors similar to that of native factor Xa
Onset	<5 min	2 min
Half-life	Initial: 47 min	Terminal: ≈6 h
	Terminal: 10.3 h	
Elimination	Kidney (protein catabolism)	Not reported
Anticoagulant(s) reversed	Dabigatran	Direct and indirect 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†
Storage	Refrigerated	Refrigerated

NEUTRALIZZAZIONE DI DABIGATRAN con Idarucizumab (Praxbind®)

- Frammento di anticorpo umanizzato
- Crea un complesso con dabigatran neutralizzando il suo effetto anticoagulante



- Determina un'inversione immediata e completa dell'attività anticoagulante del dabigatran (normalizzazione dei tempi di coagulazione)
- La sua azione dura 24 ore

INDICAZIONI A IDARUCIZUMAB

4.1 Indicazioni terapeutiche

Praxbind è un inattivatore specifico per dabigatran ed è indicato nei pazienti adulti trattati con Pradaxa (dabigatran etexilato) nei casi in cui si rende necessaria l'inattivazione rapida dei suoi effetti anticoagulanti:

- negli interventi chirurgici di emergenza/nelle procedure urgenti;
- nel sanguinamento potenzialmente fatale o non controllato.

4.2 Posologia e modo di somministrazione

Limitato esclusivamente all'uso ospedaliero.

Posologia

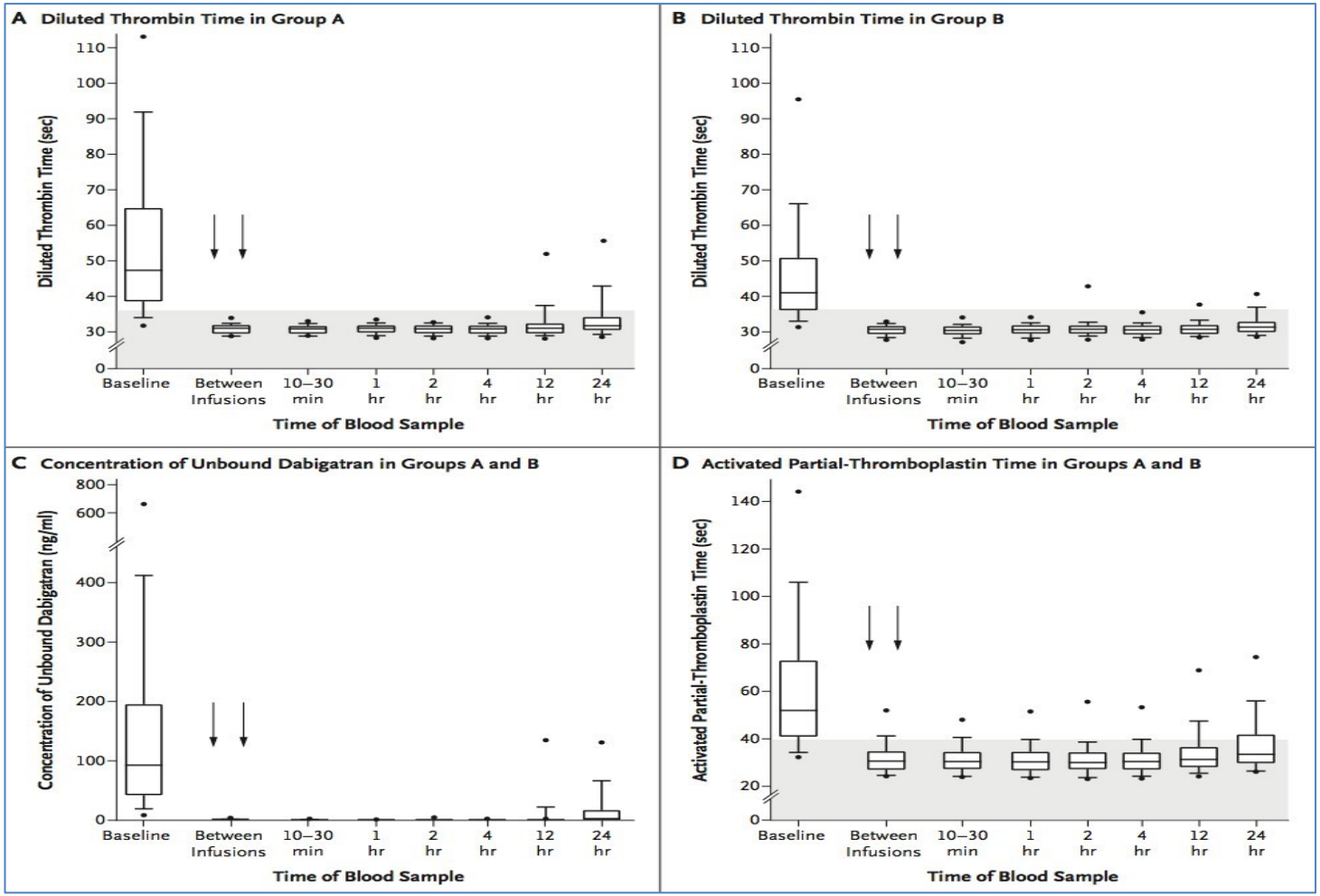
La dose raccomandata è di 5 g di idarucizumab (2 flaconcini da 2,5 g/50 mL).

Agenzia Italiana

Idarucizumab for Dabigatran Reversal — Full Cohort Analysis

Gruppo A: pazienti con emorragia non controllata

Gruppo B: pazienti candidati a procedura urgente



Pollack et al. NEJM 2017

Dabigatran Reversal With Idarucizumab in Patients With Renal Impairment

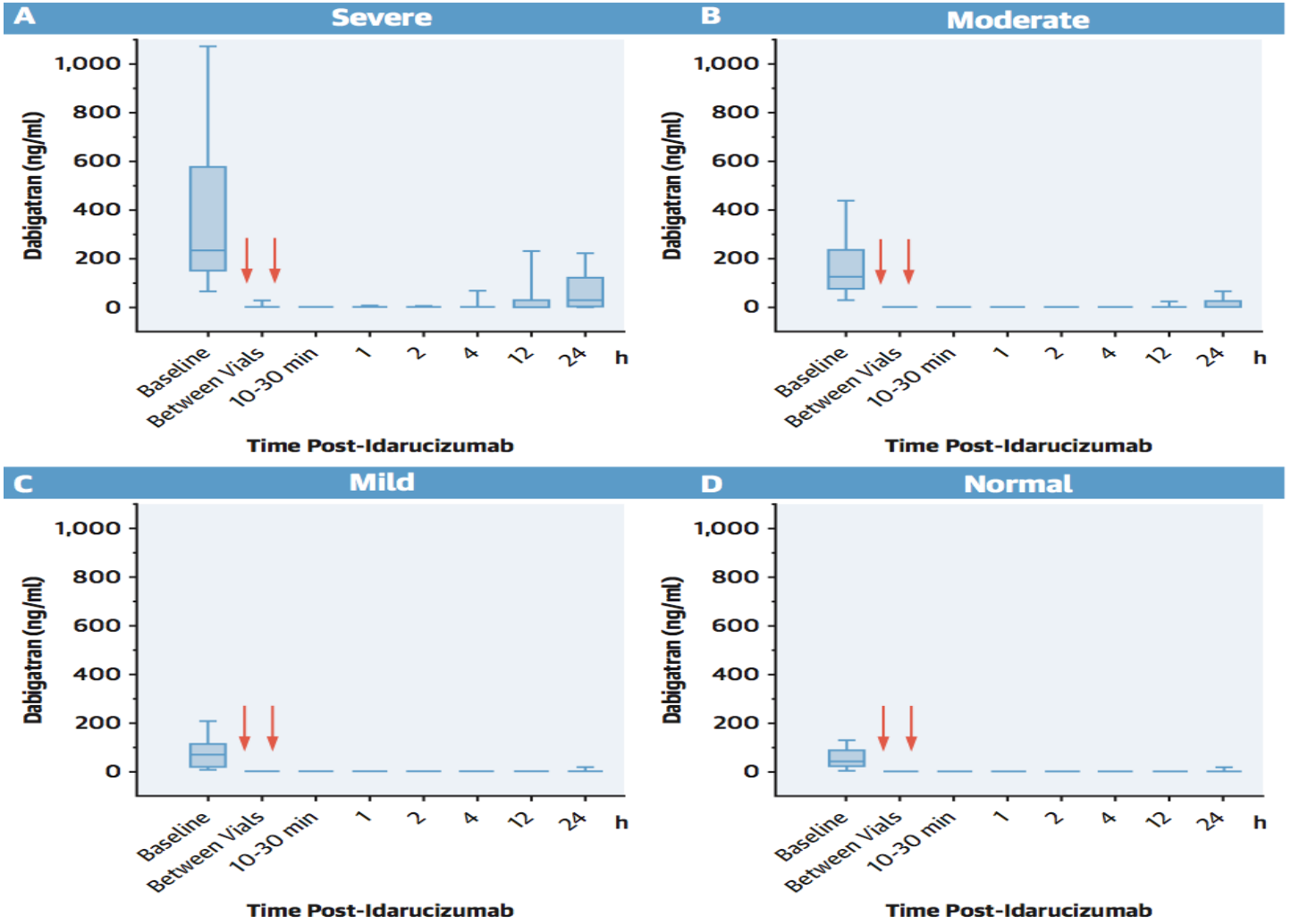
	Renal Function					
	Normal ≥80 ml/min	Mild 50 to <80 ml/min	Moderate 30 to <50 ml/min	Severe <30 ml/min	Missing*	Total
dTT						
Evaluable patients	64	122	113	85	12	396
Maximum reversal within 4 h	100 (100-100)	100 (100-100)	100 (100-100)	100 (100-100)	100 (100-100)	100 (100-100)
Proportion of patients achieving 100% reversal	63 (98.4)	121 (99.2)	112 (99.1)	83 (97.6)	12 (100.0)	391 (98.7)
Proportion of patients achieving 80% reversal	63 (98.4)	121 (99.2)	112 (99.1)	84 (98.8)	12 (100.0)	392 (99.0)
Dabigatran concentration†						
Evaluable patients	77	139	116	87	14	433
Patients achieving 100% reversal within 4 h	77 (100.0)	137 (98.6)	115 (99.1)	86 (98.9)	14 (100.0)	429 (99.1)
Patients restarted on dabigatran within 24 h	5 (6.5)	2 (1.4)	2 (1.7)	0 (0.0)	2 (14.3)	11 (2.5)
Dabigatran levels† at 12/24 h‡						
Dabigatran plasma levels at baseline	70 ± 85	106 ± 173	217 ± 320	447 ± 494	98 ± 87	190 ± 315
Individual maximum dabigatran plasma level at 12-24 h	7.4 ± 16	15.0 ± 106	46.7 ± 202	124 ± 225	7.7 ± 19	41.1 ± 159

Values are n, n (%), median (95% confidence interval), or mean ± SD. Reversal of unbound dabigatran concentration was defined as levels below 20 ng/ml. Reversal is shown for all patients with at least 1 post-dose value and with pre-dose dTT levels above the upper limit of normal (35.5 s). *Fourteen patients could not be categorized according to renal function because their creatinine data were missing. †Unbound dabigatran. ‡The maximum value from 12 or 24 h was taken for each patient.

dTT = diluted thrombin time.

Eikelboom et al. JACC 2019

Dabigatran Reversal With Idarucizumab in Patients With Renal Impairment



Eikelboom et al. JACC 2019

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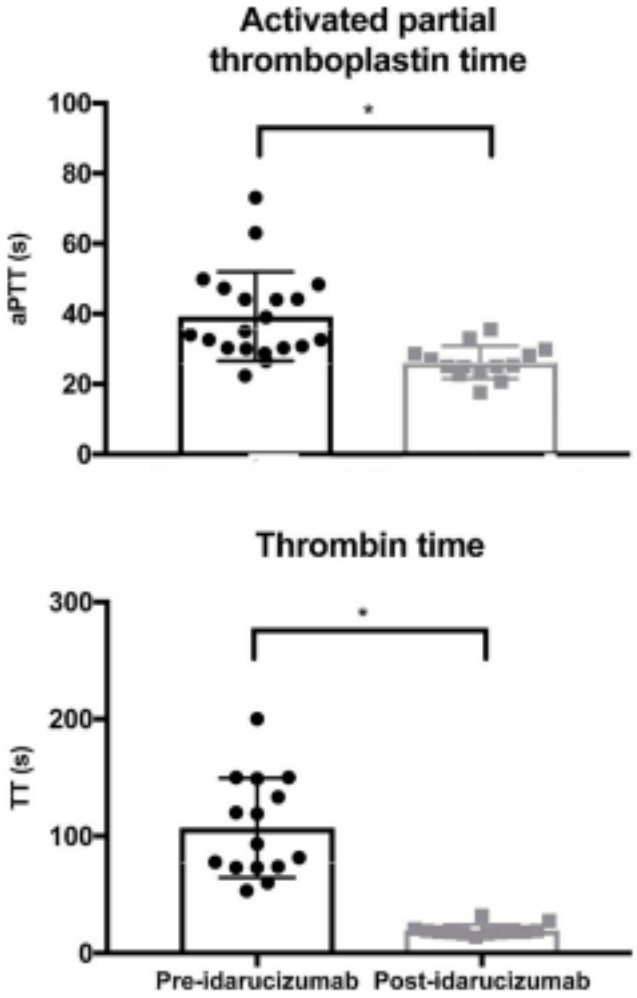
Dabigatran reversal by idarucizumab in the setting of intracranial hemorrhage: A systematic review of the literature

Victor M. Lu[a,*], Kevin Phan[a,b], Prashanth J. Rao[a,b], Sunjay V. Sharma[c], Ekkehard M. Kasper[d]

Table 1
Study and demographic characteristics. ICH, intracranial hemorrhage; SDH, subdural hemorrhage; SAH, subarachnoid hemorrhage; ICbH, intracerebral hemorrhage; MVA, motor vehicle accident; NR, not reported.

						ICH presentation			
Study	Country	Design	Cases (n)	Mean age (yrs)	Females (n)	SDH	SAH	ICbH	Etiology
Arai et al. [19]	Japan	Case report	1	79	0	1	.	.	1 Fall
Balakumar et al. [20]	US	Case report	1	86	1	.	1	.	1 Fall
Edwards et al. [21]	Australia	Case report	2	70	0	2	.	.	1 MVA, 1 Fall
Gendron et al. [22]	France	Case report	1	80	0	1	.	.	1 Fall
Goriacko et al. [23]	US	Case report	1	79	0	.	.	1	1 Spontaneous
Hieber et al. [25]	Germany	Case report	1	83	1	1	.	.	1 Spontaneous
Kermer et al. [17]	Germany	Case series	12	75	6	3	1	8	NR
Quintavalla et al. [24]	Italy	Case report	1	82	1	1	.	.	NR
Vosko et al. [18]	Europe	Case series	3	73	1	1	1	1	3 Spontaenous
		Sum (% total)	23	76.2 (average)	10 (43%)	10 (43%)	3 (13%)	10 (43%)	.



Our systematic review highlights that the use idarucizumab is effective in reversing the anticoagulation effect of dabigatran in patients presenting specifically with ICH. A 5 g dose of idarucizumab was sufficiently effective to decrease/normalize anticoagulation parameters as inferred by aPTT and TT values across all presentations. Stabilization or resolution of hemorrhage occurred in 87% of cases in the pooled cohort with no medication-related adverse effects. The in-hospital mortality rate of 4% compares favorably to the corresponding rate of up to 30% in those ICH patients receiving dabigatran not treated by idarucizumab [28,29], as well as the 9% mortality rate reported for idarucizumab-reversed ICH by the RE-VERSE AD study [14]. These values are sup-

NEUTRALIZZAZIONE DEI Farmaci Inibitori del Fattore Xa

- **Andexanet alfa**
- **Complesso protrombinico a 4 fattori II-VII,IX, X (50U/Kg) per <u>Rivaroxaban, Apixaban, Edoxaban *</u>.**
- Complesso protrombinico concentrato attivato (40U/Kg) FEIBA per Rivaroxaban ed Apixaban
- Fattore VIIa ricombinante NOVOSEVEN (90-100mcg/kg)

*E. S. Eerenberg, et al., "Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects," Circulation, vol. 124, no. 14, pp. 1573–1579, 2011

INDICAZIONI A ANDEXANET ALFA

4.1 Indicazioni terapeutiche

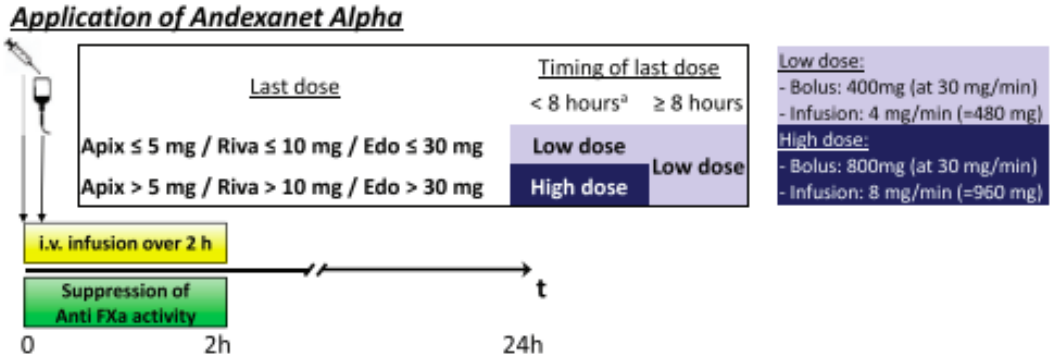
Per pazienti adulti trattati con un inibitore diretto del fattore Xa (FXa) (apixaban o rivaroxaban), quando è richiesta l'inversione della terapia anticoagulante a causa di emorragie potenzialmente fatali o incontrollate.

4.2 Posologia e modo di somministrazione

Uso esclusivamente ospedaliero.

Posologia

Andexanet alfa viene somministrato sotto forma di bolo endovenoso a una velocità target di circa 30 mg/min in 15 minuti (dose bassa) o 30 minuti (dose elevata), seguito da un'infusione continua di 4 mg/min (dose bassa) o 8 mg/min (dose elevata) per 120 minuti (vedere tabella 1). La posologia di andexanet alfa si basa su modelli di farmacocinetica/farmacodinamica ed esercizi di simulazione (vedere paragrafi 5.1 e 5.2).



APIXABAN

Inversione di apixaban

Il regime posologico raccomandato di Ondexxya si basa sulla dose di apixaban somministrata al paziente al momento dell'inversione della terapia anticoagulante e sul tempo trascorso dall'ultima dose di apixaban (vedere tabella 2). Se il dosaggio dell'ultima somministrazione di anticoagulante o l'intervallo tra l'ultima dose e l'episodio emorragico non sono noti, non è disponibile alcuna raccomandazione sulla dose. La decisione clinica di iniziare il trattamento deve essere sostenuta dalla misurazione del livello di anti-FXa al basale (se tale livello è disponibile entro un tempo accettabile).

Tabella 2: Riassunto delle dosi per l'inversione di apixaban

Inibitore del FXa	**Ultima dose**	**Tempo dall'ultima dose prima dell'inizio di Ondexxya**	
		< 8 ore	**≥ 8 ore**
Apixaban	≤ 5 mg	Dose bassa	Dose bassa
	> 5 mg	Dose elevata	

Collegio Italiano dei Farmaco

RIVAROXABAN

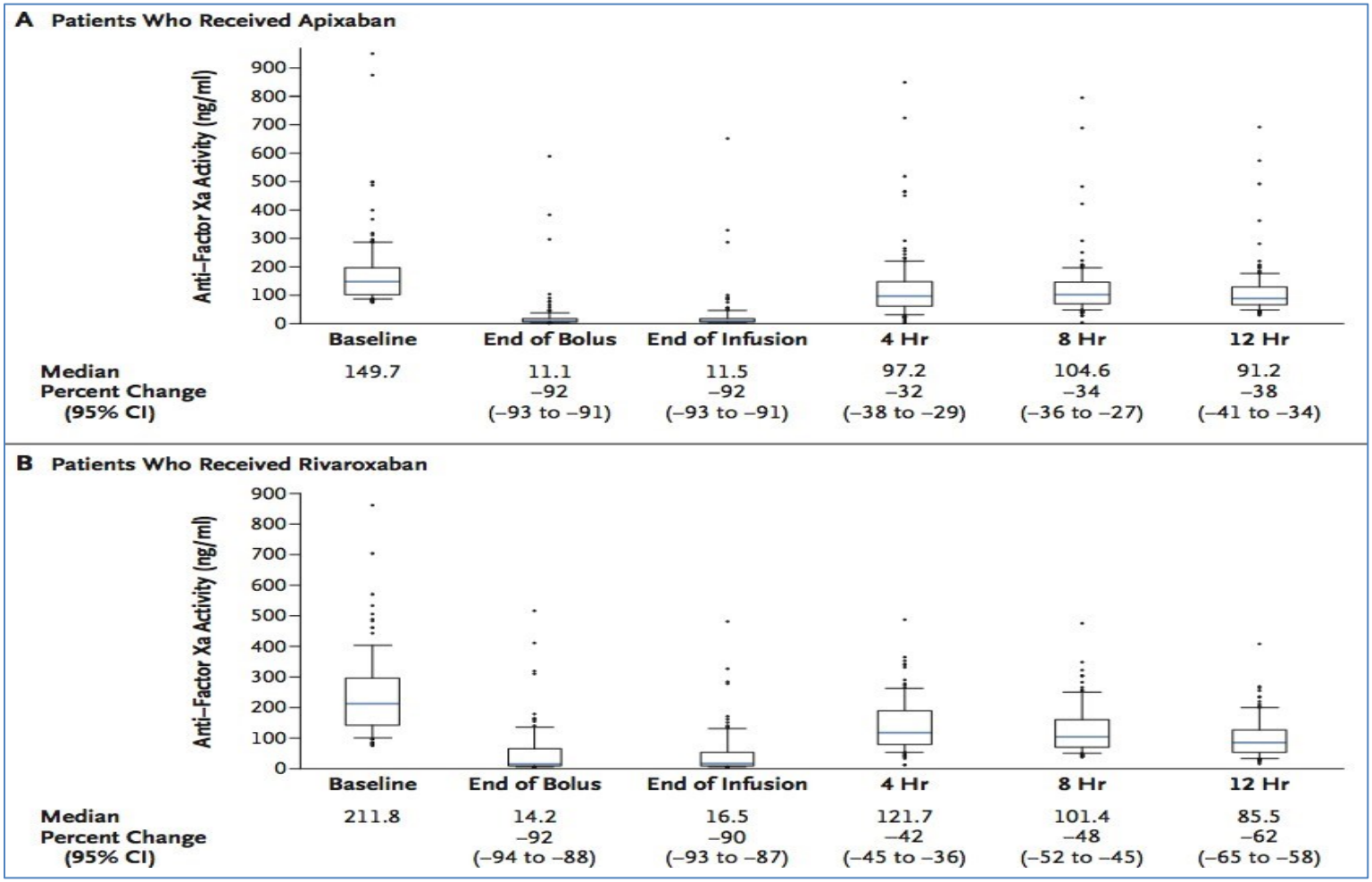
Inversione di rivaroxaban

Il regime posologico raccomandato di Ondexxya si basa sulla dose di rivaroxaban somministrata al paziente al momento dell'inversione della terapia anticoagulante e sul tempo trascorso dall'ultima dose di rivaroxaban (vedere tabella 3). Se il dosaggio dell'ultima somministrazione di anticoagulante o l'intervallo tra l'ultima dose e l'episodio emorragico non sono noti, non è disponibile alcuna raccomandazione sulla dose. La decisione clinica di iniziare il trattamento deve essere sostenuta dalla misurazione del livello di anti-FXa al basale (se tale livello è disponibile entro un tempo accettabile).

Tabella 3: Riassunto delle dosi per l'inversione di rivaroxaban

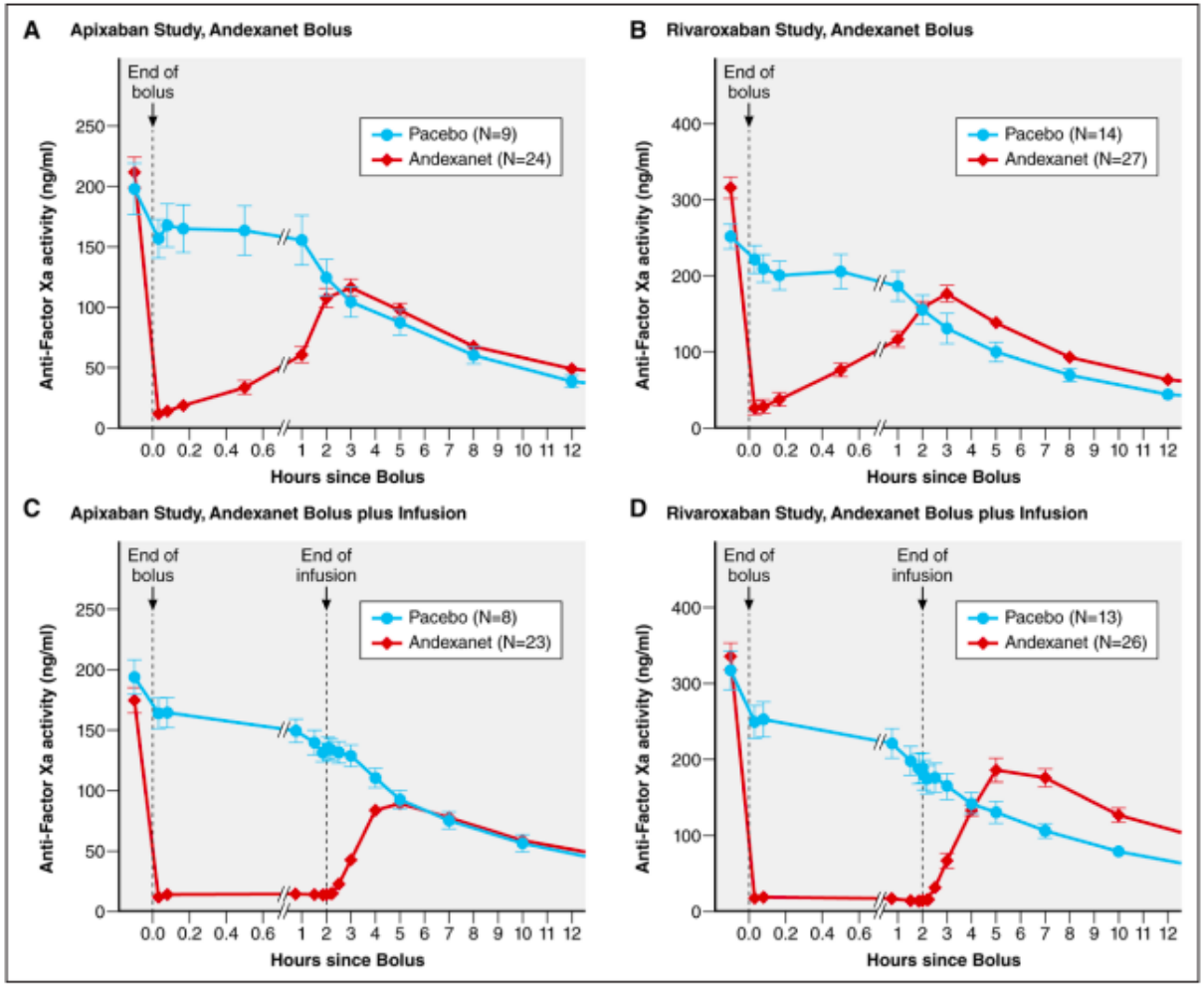
Inibitore del FXa	**Ultima dose**	**Tempo dall'ultima dose prima dell'inizio di Ondexxya**	
		< 8 ore	**≥ 8 ore**
Rivaroxaban	≤ 10 mg	Dose bassa	Dose bassa
	> 10 mg	Dose elevata	

Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors



Connoly et al. NEJM 2019

Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors



Siegal et al. NEJM 2015

I CONCENTRATI DI COMPLESSO PROTROMBINICO (CCP)

- I CCP sono emoderivati in cui sono concentrati fattore II, fattore X e fattore IX, e talora FVII, PC e PS.
- Sono disponibili sotto forma di prodotti liofilizzati da infondere ev una volta ricostruiti: non presentano rischio di sovraccarico di liquidi per il piccolo volume ed il loro effetto è immediato.
- *Rappresentano attualmente il trattamento di scelta per il reverse rapido della terapia con antagonisti della vitamina K (warfarin, acenocumarolo)*
- I CCP contenenti anche FVII sono noti come CCP a 4 fattori, mentre i prodotti senza FVII sono CCP a 3 fattori.

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.

Clinical Trial Registration—URL: http://www.trialregister.nl. Unique identifier: NTR2272. (***Circulation*. 2011;124:1573-1579.**)

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Andexanet for Factor Xa Inhibitor–Associated Acute Intracerebral Hemorrhage

S.J. Connolly, M. Sharma, A.T. Cohen, A.M. Demchuk, A. Członkowska, A.G. Lindgren, C.A. Molina, D. Bereczki, D. Toni, D.J. Seiffge, D. Tanne, E.C. Sandset, G. Tsivgoulis, H. Christensen, J. Beyer-Westendorf, J.M. Coutinho, M. Crowther, P. Verhamme, P. Amarenco, R.O. Roine, R. Mikulik, R. Lemmens, R. Veltkamp, S. Middeldorp, T.G. Robinson, T.J. Milling, Jr., V. Tedim-Cruz, W. Lang, A. Himmelmann, P. Ladenvall, M. Knutsson, E. Ekholm, A. Law, A. Taylor, T. Karyakina, L. Xu, K. Tsiplova, S. Poli, B. Kallmünzer, C. Gumbinger, and A. Shoamanesh, for the ANNEXA-I Investigators*

Table 2. Efficacy End Points.

End Point	Andexanet (N = 224)	Usual Care (N = 228)	Adjusted Difference per 100 Patients (95% CI)*	P Value*
	no./total no. (%)		*percentage points*	
Hemostatic efficacy	150/224 (67.0)	121/228 (53.1)	13.4 (4.6 to 22.2)	0.003
Hematoma volume change ≤35%†	165/215 (76.7)	137/212 (64.6)	12.1 (3.6 to 20.5)	
NIHSS score change <7 points	188/214 (87.9)	181/218 (83.0)	4.6 (–2.0 to 11.2)	
No receipt of rescue therapy between 3 hr and 12 hr	218/224 (97.3)	213/228 (93.4)	3.8 (–7.6 to 0.0)	
Hematoma volume increase ≥12.5 ml‡	24/216 (11.1)	36/214 (16.8)	–5.6 (–12.0 to 0.8)	
Hemostatic efficacy, excluding patients nonevaluable for administrative reasons	150/218 (68.8)	121/225 (53.8)	14.5 (5.7 to 23.4)	

Table 3. Thrombotic Events and Deaths at 30 Days.*

Event	Andexanet (N = 263)	Usual Care (N = 267)	Increase per 100 Patients (95% CI)†	P Value†
	no. of patients (%)		*percentage points*	
≥1 Thrombotic event	27 (10.3)	15 (5.6)	4.6 (0.1 to 9.2)	0.048
Transient ischemic attack	0	0	—	
Ischemic stroke	17 (6.5)	4 (1.5)	5.0 (1.5 to 8.8)	
Myocardial infarction	11 (4.2)	4 (1.5)	2.7 (–0.2 to 6.1)	
Deep-vein thrombosis	1 (0.4)	2 (0.7)	–0.4 (–2.4 to 1.5)	
Pulmonary embolism	1 (0.4)	6 (2.2)	–1.9 (–4.5 to 0.2)	
Arterial systemic embolism	3 (1.1)	2 (0.7)	0.4 (–1.7 to 2.7)	
Death	73 (27.8)	68 (25.5)	2.5 (–5.0 to 10.0)	0.51

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Recommendation

We recommend idarucizumab to reverse effects of dabigatran in adult patients with ICH occurring during use of dabigatran. Evidence for effects on clinical endpoints is limited.
Quality of evidence: *Low* ⊕⊕
Strength of recommendation: *Strong* ↑↑

Christense et al. ESJ 2019

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Recommendation

We recommend using andexanet alfa if available – in adult patients with ICH occurring during use of rivaroxaban or apixaban. We also recommend randomising into trials as based on the low quality of evidence, there is significant uncertainty whether desirable outweigh undesirable effects.
Quality of evidence: *Low* ⊕⊕
Strength of recommendation: *Weak* ↑

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Recommendations

PICO 6: In patients with ICH occurring during use of NOAC and when specific reversal agents are not available we recommend considering the use of four-factor PCC (37.5–50 IU/kg) to normalise coagulation tests.
Quality of evidence: *Very low* ⊕
Strength of recommendation: *Weak* ↑

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fXa-inhibitors

In some centres specific testing is available. To be used if results are ready in <20 min

1. line

andexanet alfa* (for apixaban, rivaroxaban)

Last dose>7 hours: bolus 400 mg, infusion 480 mg over 120 minutes

Last dose <7 hours:bolus 800 mg, infusion 960 mg over 120 minutes

Repeat specific testing after 3, 6, 12 and 24 hours because rebound might occur

2. line

PCC 50 IU/kg

(if andexanet is not available or for edoxaban-ICH)

dabigatran

In some centres specific testing is available. To be used if results are ready in <20 min

Idarucizumab

2.5 g x 2 IV

Repat specific testing after 12 and 24h because rebound might occur

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PICO 7: In patients with ICH occurring during use of NOAC, we recommend against using FFP to improve outcome, reduce mortality, decrease haematoma expansion or reverse the effects of NOAC.

Quality of evidence: *Very low* ⊕

Strength of recommendation: *Weak* ↓

Christense et al. ESJ 2019

EHRA practical guidelines 2021

ESC European Society of Cardiology

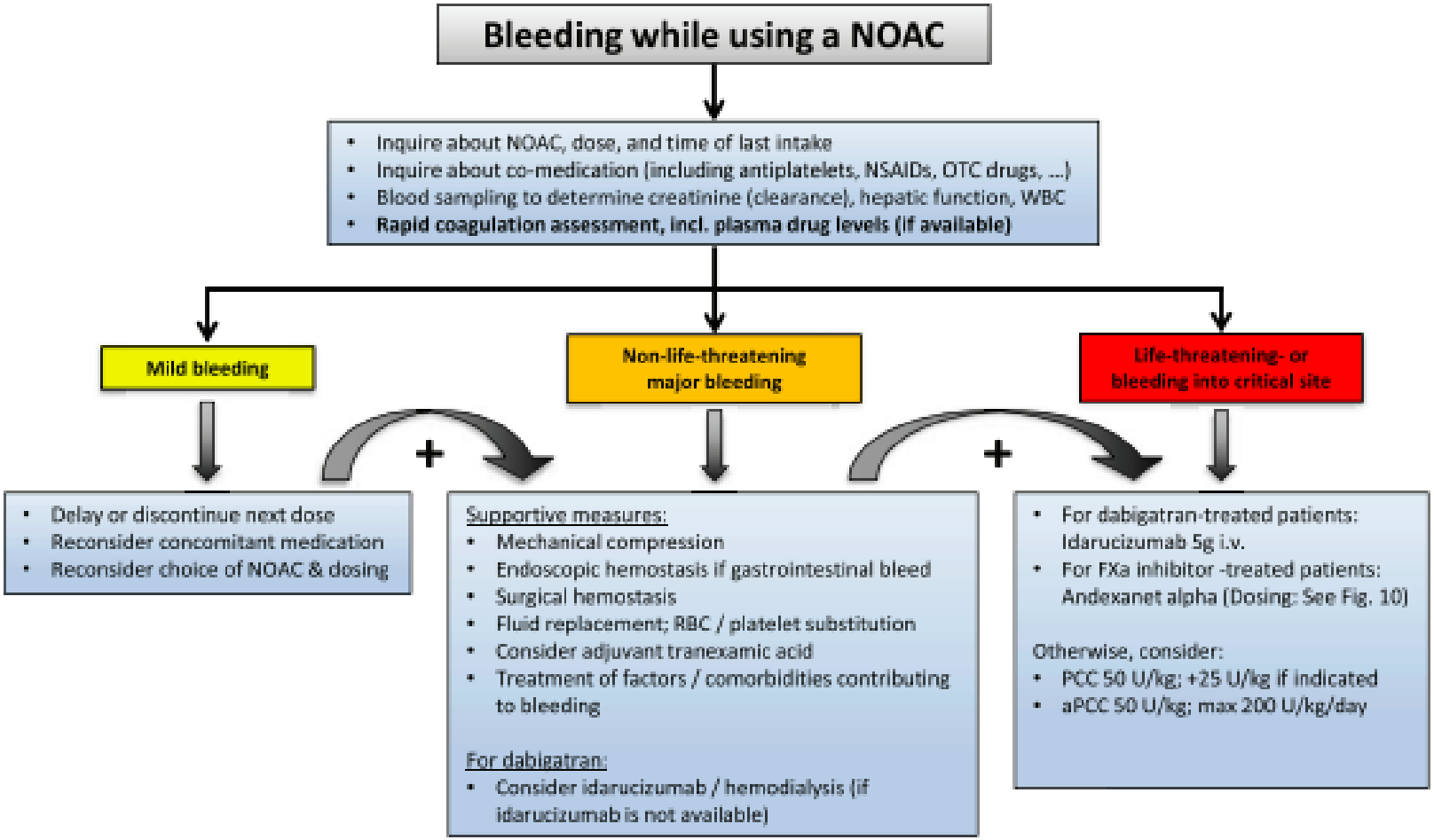
Europace (2021) **23**, 1612–1676
doi:10.1093/europace/euab065

POSITION PAPER
EHRA Practical Guide

2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation

Jan Steffel[1]*, Ronan Collins[2], Matthias Antz[3], Pieter Cornu[4], Lien Desteghe[5,6], Karl Georg Haeusler[7], Jonas Oldgren[8], Holger Reinecke[9], Vanessa Roldan-Schilling[10], Nigel Rowell[11], Peter Sinnaeve[12], Thomas Vanassche[12], Tatjana Potpara[13], A. John Camm[14], and Hein Heidbüchel[5,6]

EHRA practical guidelines 2021



Stroke

AHA/ASA GUIDELINE

2022 Guideline for the Management of Patients With Spontaneous Intracerebral Hemorrhage: A Guideline From the American Heart Association/American Stroke Association

Reviewed for evidence-based integrity and endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons.

Endorsed by the Society of Vascular and Interventional Neurology

The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.

Endorsed by the Neurocritical Care Society

Steven M. Greenberg, MD, PhD, FAHA, Chair; Wendy C. Ziai, MD, MPH, FAHA, Vice Chair; Charlotte Cordonnier, MD, PhD; Dar Dowlatshahi, MD, PhD, FAHA; Brandon Francis, MD, MPH; Joshua N. Goldstein, MD, PhD, FAHA; J. Claude Hemphill III, MD, MAS, FAHA; Ronda Johnson, MBA; Kiffon M. Keigher, MSN, ACNP-BC, RN, SCRN; William J. Mack, MD, MS, FAHA*; J. Mocco, MD, MS, FAHA†; Eileena J. Newton, MD; Ilana M. Ruff, MD‡; Lauren H. Sansing, MD, MS, FAHA; Sam Schulman, MD, PhD; Magdy H. Selim, MD, PhD, FAHA; Kevin N. Sheth, MD, FAHA*§; Nikola Sprigg, MD; Katharina S. Sunnerhagen, MD, PhD; on behalf of the American Heart Association/American Stroke Association

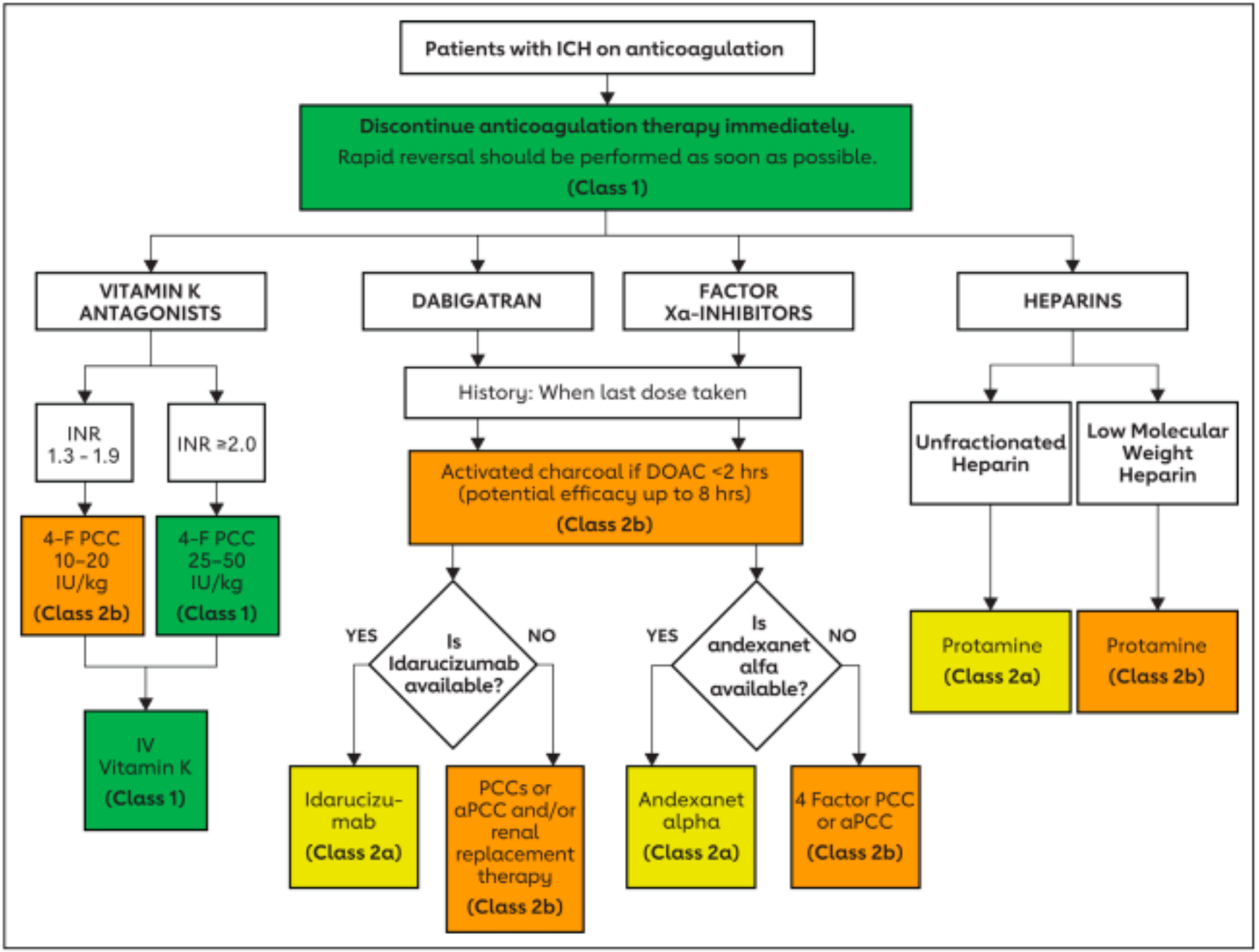
5.2.1. Anticoagulant-Related Hemorrhage

Recommendations for Anticoagulant-Related Hemorrhage
Referenced studies that support recommendations are summarized in Data Supplements 18 and 19.

COR	LOE	Recommendations
1	C-LD	1. In patients with anticoagulant-associated spontaneous ICH, anticoagulation should be discontinued immediately and rapid reversal of anticoagulation should be performed as soon as possible after diagnosis of spontaneous ICH to improve survival.[162]
VKAs		
1	B-R	2. In patients with VKA-associated spontaneous ICH and INR ≥2.0, 4-factor (4-F) prothrombin complex concentrate (PCC) is recommended in preference to fresh-frozen plasma (FFP) to achieve rapid correction of INR and limit HE.[163]
1	C-LD	3. In patients with VKA-associated spontaneous ICH, intravenous vitamin K should be administered directly after coagulation factor replacement (PCC or other) to prevent later increase in INR and subsequent HE.[164,165]
2b	C-LD	4. In patients with VKA-associated spontaneous ICH with INR of 1.3 to 1.9, it may be reasonable to use PCC to achieve rapid correction of INR and limit HE.[162,164]
DOACs		
2a	B-NR	5. In patients with direct factor Xa inhibitor–associated spontaneous ICH, andexanet alfa is reasonable to reverse the anticoagulant effect of factor Xa inhibitors.[166,167]
2a	B-NR	6. In patients with dabigatran-associated spontaneous ICH, idarucizumab is reasonable to reverse the anticoagulant effect of dabigatran.[168]

Recommendations for Anticoagulant-Related Hemorrhage (Continued)

COR	LOE	Recommendations
2b	B-NR	7. In patients with direct factor Xa inhibitor–associated spontaneous ICH, a 4-F PCC or activated PCC (aPCC) may be considered to improve hemostasis.[169–171]
2b	C-LD	8. In patients with dabigatran- or factor Xa inhibitor–associated spontaneous ICH, when the DOAC agent was taken within the previous few hours, activated charcoal may be reasonable to prevent absorption of the DOAC.[172–174]
2b	C-LD	9. In patients with dabigatran-associated spontaneous ICH, when idarucizumab is not available, aPCC or PCCs may be considered to improve hemostasis.[175,176]
2b	C-LD	10. In patients with dabigatran-associated spontaneous ICH, when idarucizumab is not available, renal replacement therapy (RRT) may be considered to reduce dabigatran concentration.[177]
Heparins		
2a	C-LD	11. In patients with unfractionated heparin (UFH)–associated spontaneous ICH, intravenous protamine is reasonable to reverse the anticoagulant effect of heparin.[178]
2b	C-LD	12. In patients with low-molecular-weight heparin (LMWH)–associated spontaneous ICH, intravenous protamine may be considered to partially reverse the anticoagulant effect of heparin.[178]


Patients with ICH on anticoagulation
Discontinue anticoagulation therapy immediately.
Rapid reversal should be performed as soon as possible.
(Class 1)
VITAMIN K ANTAGONISTS
DABIGATRAN
FACTOR Xa-INHIBITORS
HEPARINS
INR 1.3 - 1.9
INR ≥2.0
4-F PCC 10–20 IU/kg
(Class 2b)
4-F PCC 25–50 IU/kg
(Class 1)
IV Vitamin K
(Class 1)
History: When last dose taken
Activated charcoal if DOAC <2 hrs
(potential efficacy up to 8 hrs)
(Class 2b)
YES
Is Idarucizumab available?
NO
Idarucizu-mab
(Class 2a)
PCCs or aPCC and/or renal replacement therapy
(Class 2b)
YES
Is andexanet alfa available?
NO
Andexanet alpha
(Class 2a)
4 Factor PCC or aPCC
(Class 2b)
Unfractionated Heparin
Low Molecular Weight Heparin
Protamine
(Class 2a)
Protamine
(Class 2b)

Grazie per l’attenzione