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Management of **major bleeding complications** in patient on treatment with **direct oral anticoagulants** in an emergency department

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DEA II livello Dipartimento Emergenza di Alta Specializzazione

The laboratory

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Emergency Department of the Poliambulanza Foundation, Brescia

35 major bleeding events - 2 urgent procedure (January-November 2017)

ISTH criteria

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

N Engl J Med 2009; 361:1139-51

5 Dabigatran (1 procedure)
7 Apixaban
1 Rivaroxaban
24 AVK (1 procedure)

35 major bleeding events

- 10 gastro-intestinal bleeding (4 dabigatran:1 upper, 3 lower; 6 AVK)
- Intestinal infarction in AVK (procedure)
- 17 cerebral hemorrhages
- Upper mesenteric artery
- Left epigastric artery
- Esophageal aortic fistula
- Hemoperitoneum in pelvis fracture
- Hemopericardium
- Urosepsis in dabigatran (procedure)
- Hepatic hematoma

1: The relative risk of major GI bleeding in the non-valvular atrial fibrillation population: take home points.

1. Adjusted-dose warfarin increases the risk of major GI bleeding approximately three-fold compared with placebo.
2. The addition of aspirin or other anti-platelet agents to warfarin increases the risk of major GI bleeding approximately two-fold (compared with warfarin alone).
3. Compared with warfarin, rivaroxaban and dabigatran (at the 150 mg twice daily dose) increase the risk of major GI bleeding approximately 1.5 fold.
4. Compared with warfarin, apixaban does not significantly alter the risk of major GI bleeding.
5. Compared with warfarin, dabigatran 110 mg twice daily does not significantly alter the risk of major GI bleeding.
6. Concurrent use of anti-platelet agents increases the risk of major GI bleeding associated with rivaroxaban and of major extra-cranial bleeding (presumably including major GI bleeding) associated with dabigatran. Data related to impact of anti-platelet agents on apixaban-related major GI bleeding are not yet available.

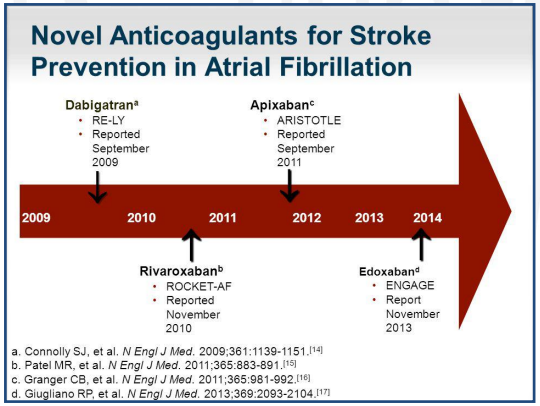


Table 3: The rates of major GI bleeding in the non-valvular atrial fibrillation population from the three pivotal trials.

	Dabigatran 150 mg twice daily	Rivaroxaban 20 mg daily	Apixaban 5 mg twice daily
Total patients (n)	6076	7131	9088
Major GI bleeding (n)	223	224	105
Major GI bleeding (%/year)	1.85	2.00	0.76
Hazard ratio for major GI bleeding (vs. warfarin)	1.49 [CI 1.21–1.84]	1.61 [CI 1.30–1.99]	0.89 [CI 0.70–1.15]

8 Direct FXa inhibitors → PT – APTT were normal

↓

PCCs

5 Dabigatran → PT- APTT were prolonged

↓

Idarucizumab

DOAC anticoagulant activity *should be measured*...

- ***Bleeding or thromboembolic events***
  - Before surgery or invasive procedures
  - Thrombolytic therapy in stroke

2% DOAC → ischaemic stroke

..testing *could be useful* in...

- Renal, liver disease
- Interaction with other drugs
- Extreme body weight
- Adherence to the therapy
- Undercoagulation or overcoagulation is suspected

Thromb Haemost 2011; 106: 868-76
Blood 2013; 121: 4032-5

- Appropriate administration in immediate reversal of anticoagulation

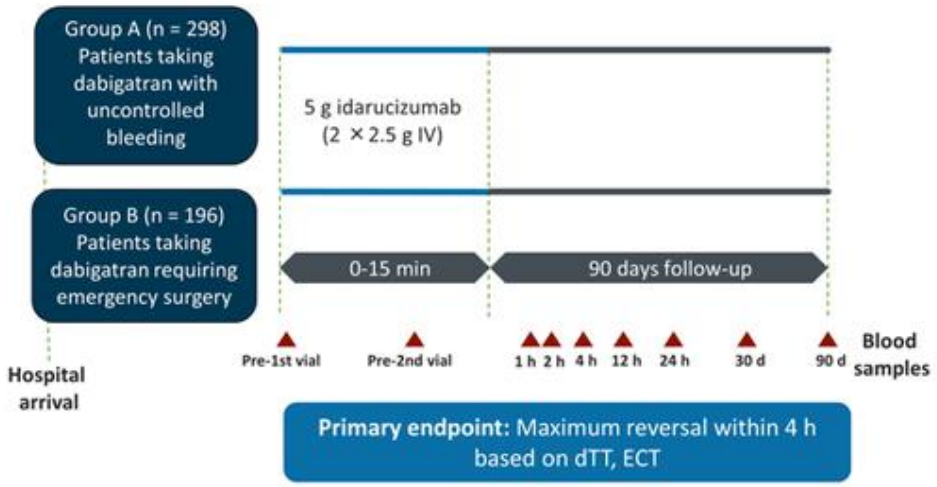
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Idarucizumab for Dabigatran Reversal

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Peter Verhamme, M.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D., Frank W. Sellke, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., M.M.E., Bushi Wang, Ph.D., Chak-Wah Kam, M.D., and Jeffrey I. Weitz, M.D.

REVERSE-AD: Trial Design



Pollack CV, et al. *Thromb Haemost*. 2015;114:198-205.

	Group A (N=51)	Group B (N=39)	Total (N=90)
Elevated dilute thrombin time at baseline — no. (%)	40 (78)	28 (72)	68 (76)
Elevated ecarin clotting time at baseline — no. (%)	47 (92)	34 (87)	81 (90)
Type of bleeding — no. (%)§			
Intracranial	18 (35)		18 (20)
Trauma-related	9 (18)		9 (10)
Gastrointestinal	20 (39)		20 (22)
Other	11 (22)		11 (12)

11 normal dTT → 64%
40 elevated dTT → 28%

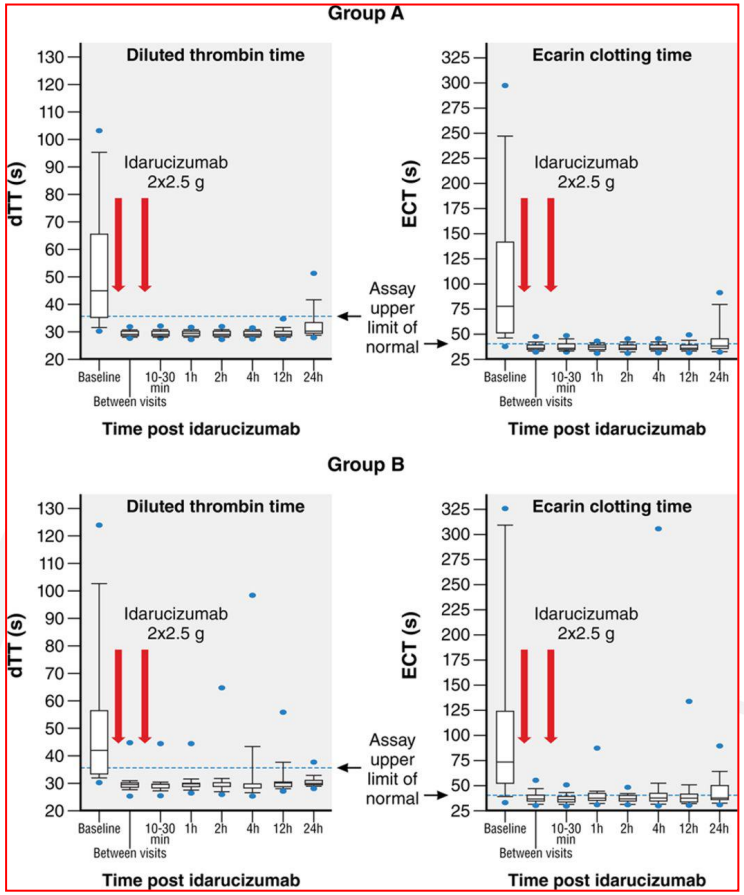
Pollack N Engl J Med 2015

25% Dabigatran concentrations were relatively low before administration of Idarucizumab

↑ [dabigatran]

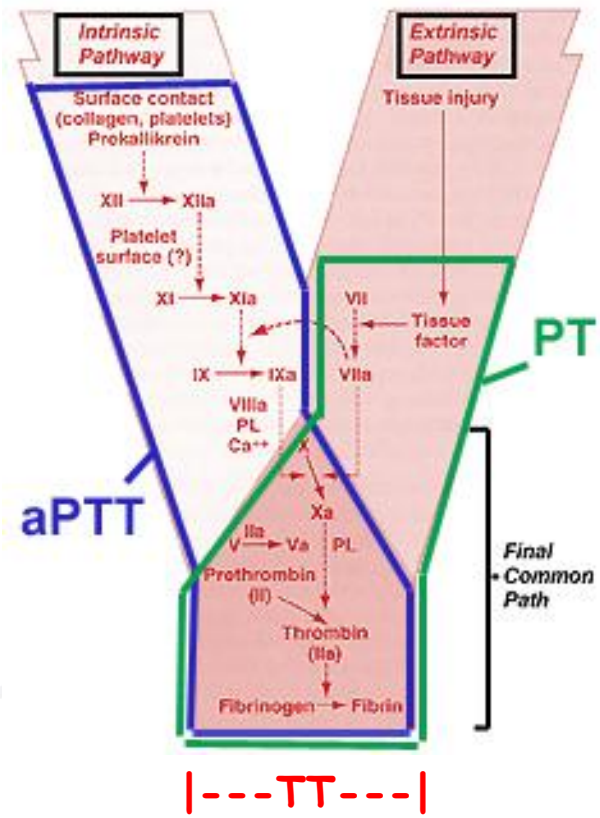
6 patients 12 hours after Idarucizumab

16 patients 24 hours after Idarucizumab



Pollack N Engl J Med 2015

Global Tests



Specific Tests

Table II - Recommendations on tests to be used for direct oral anticoagulants.

Drug	PT	APTT	TT	dTT	Ecarin	Anti-FXa
Dabigatran	[a]No	[b]No	[c]Yes	Yes	[d]Yes	No
Rivaroxaban	[e]No	[f]No	No	No	No	Yes
Apixaban	[f]No	[f]No	No	No	No	Yes
Edoxaban	[f]No	[f]No	No	No	No	Yes

PT: prothrombin time; APTT: activated partial thromboplastin time; TT: thrombin time; dTT: dilute thrombin time; anti-FXa: anti-factor Xa activity.
[a]: Poorly responsive to increasing drug concentration and reagent-dependent; [b]: Responsive to increasing drug concentration and reagent-dependent; [c]: Strongly responsive even to low levels of the drug. If normal, it may be used to rule out significant circulating drug levels; [d]: Clotting or chromogenic; [e]: Moderately responsive to increasing drug concentration, but reagent-dependent; [f]: Poorly responsive to increasing drug concentration and reagent-dependent.

Tripodi et al. Blood Transfus. 2017

Monitoring ≠ Measuring

Management of **major bleeding complications** in patient on treatment with **direct oral anticoagulants** in an emergency department

Journal of Thrombosis and Haemostasis, **16**: 565–570 DOI: 10.1111/jth.13949

BRIEF REPORT

Interlaboratory variability in the measurement of direct oral anticoagulants: results from the external quality assessment scheme

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Table 2 Parameters of coagulation and interlaboratory variation as observed by participants when measuring common freeze-dried plasmas without (plasma A) or with direct oral anticoagulants (DOACs) (dabigatran, plasma E; rivaroxaban, plasma D; or apixaban, plasma C (Survey II).

	PT ratio		APTT ratio		TT ratio		Concentration (ng mL^{-1})	
Dabigatran								
Plasma	A	E	A	E	A	E	A	E
No. of participants	233	232	221	219	83	45	81	81
Mean*	1.00	1.23	0.99	1.85	1.03	Unclottable	5.3	177
CV*	4.0	3.9	6.2	5.8	11.9	Undefined	–	8.7
%†	–	–	–	–	–	–	98	
Rivaroxaban								
Plasma	A	D	A	D	A	D	A	D
No. of participants	233	233	221	221	83	82	71	71
Mean*	1.00	1.17	0.99	1.16	1.03	1.03	4.2	81
CV*	4	6.2	6.2	8.3	11.9	8.5	–	8.4
%†	–	–	–	–	–	–	96	–
Apixaban								
Plasma	A	C	A	C	A	C	A	C
No. of participants	233	233	221	221	83	83	67	67
Mean*	1.00	1.07	0.99	1.08	1.03	1.03	5.4	66
CV*	4.0	4.6	6.2	7.4	11.9	8.5	–	10.3
%†	–	–	–	–	–	–	99	–

…the use of PT or APTT in clinical practice to evaluate DOAC anticoagulant activity could case ***dangerous misinterpretations !***

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