Emorragia e DOAC

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Agenda

- ✔The issue
- ✔Giuseppe & Marta
- ✔Reversal agents
- ✔Conclusions

XIII congresso nazionale
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US Emergency Department Visits for Outpatient Adverse Drug Events, 2013-2014

US Emergency Department (ED) Visits for Adverse Drug Events (ADEs) by Drug Class, 2013-2014[a]

Drug Class	ED Visits for ADEs		ED Visits for ADEs Resulting in Hospitalization[b]	
	No. of Cases	National Estimate, % (95% CI)[c]	No. of Cases Hospitalized	National Estimate, % Hospitalized (95% CI)[c]
Hematologic Agents				
Anticoagulants	7211	17.6 (14.1-21.0)	3691	48.8 (42.0-55.5)
Vitamin K antagonists (warfarin)	6179	15.1 (12.3-17.9)	3156	48.5 (41.8-55.1)
Factor Xa inhibitors	580	1.4 (0.9-2.0)	300	50.4 (43.0-57.8)
Unfractionated and low-molecular-weight heparins	450	0.8 (0.6-1.1)	224	46.5 (38.7-54.4)
Direct thrombin inhibitors (oral)	173	0.5 (0.2-0.7)	107	63.8 (49.8-77.8)
Antiplatelets	2656	6.6 (4.7-8.5)	1312	44.4 (35.7-53.2)
Platelet $P2Y_{12}$ receptor antagonists[d]	1837	4.6 (3.0-6.2)	942	47.8 (37.7-57.9)
Aspirin with or without dipyridamole	1545	3.6 (2.2-5.0)	753	41.2 (32.6-49.8)
Systemic Antimicrobial Agents[e]				
Antibiotics	6426	16.1 (14.4-17.8)	481	7.1 (5.3-9.0)
Amoxicillin-containing penicillins	2198	4.8 (4.2-5.4)	96	3.7 (2.3-5.2)
Sulfonamide-containing agents	1174	3.2 (2.7-3.7)	108	8.9 (6.2-11.5)
Cephalosporins	776	2.0 (1.7-2.4)	63	6.7 (4.2-9.2)
Quinolones	592	1.7 (1.4-1.9)	77	14.5 (11.0-18.0)
Erythromycins and macrolides	410	1.2 (1.0-1.3)	24	5.5 (2.6-8.3)
Lincosamides (clindamycin)	396	1.0 (0.8-1.2)	28	5.5 (2.1-8.8)
Tetracyclines	286	0.7 (0.6-0.8)	16	NA
Metronidazole	195	0.4 (0.3-0.5)	18	NA
Other antibiotics	439	1.1 (0.9-1.3)	68	12.1 (7.6-16.6)
Antivirals and antiretrovirals	148	0.3 (0.2-0.4)	14	NA
Other systemic antimicrobial agents	123	0.3 (0.2-0.4)	16	NA
Hormone-Modifying Agents				
Diabetes agents	5995	13.3 (10.8-15.8)	2314	38.5 (31.4-45.7)

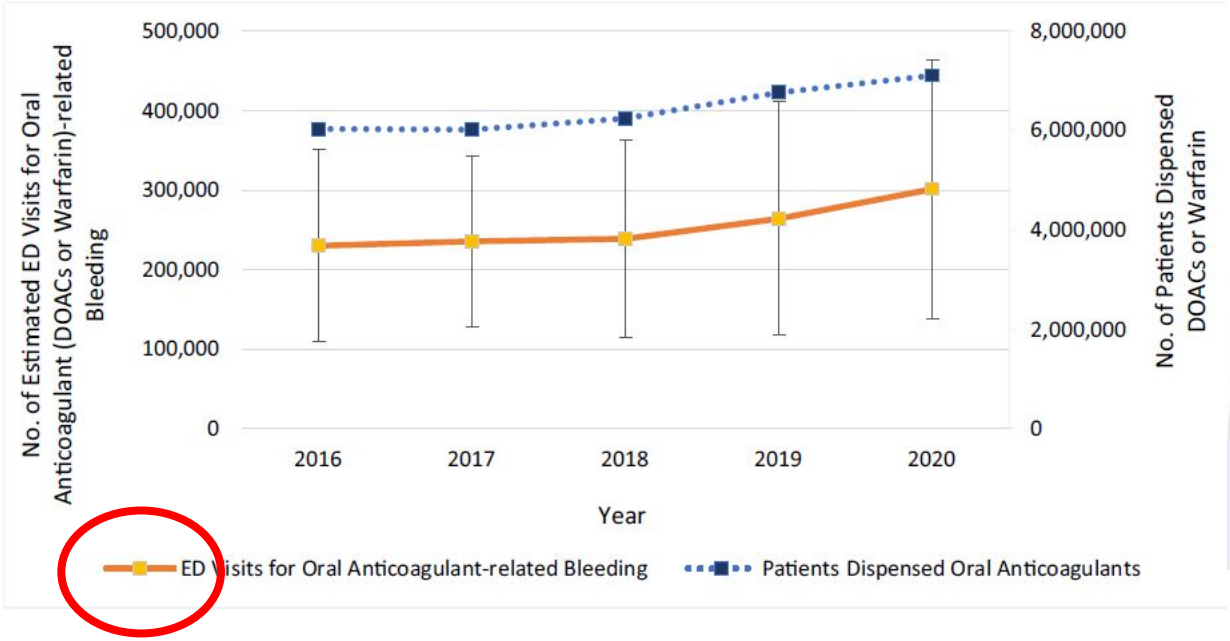
Adverse Event Manifestation[b]	ED Visits for ADEs	
	No. of Cases	National Estimate, % (95% CI)[c]
Anticoagulants (n = 6290)		
Hemorrhage	5101	79.4 (75.2-83.6)
Central nervous system[d]	262	2.8 (1.4-4.2)
Pulmonary	149	2.3 (1.7-3.0)
Gastrointestinal	1577	27.0 (21.0-32.9)
Genitourinary	547	9.5 (6.6-12.4)
Epistaxis	815	15.0 (11.7-18.3)
Skin, wound, or other minor	1418	18.8 (13.2-24.4)
Other hemorrhage types	333	4.1 (2.5-5.6)
Laboratory abnormality only (eg, elevated international normalized ratio) or unspecified overdose	1116	19.5 (15.5-23.6)
Other or unspecified effect	73	1.1 (0.7-1.5)

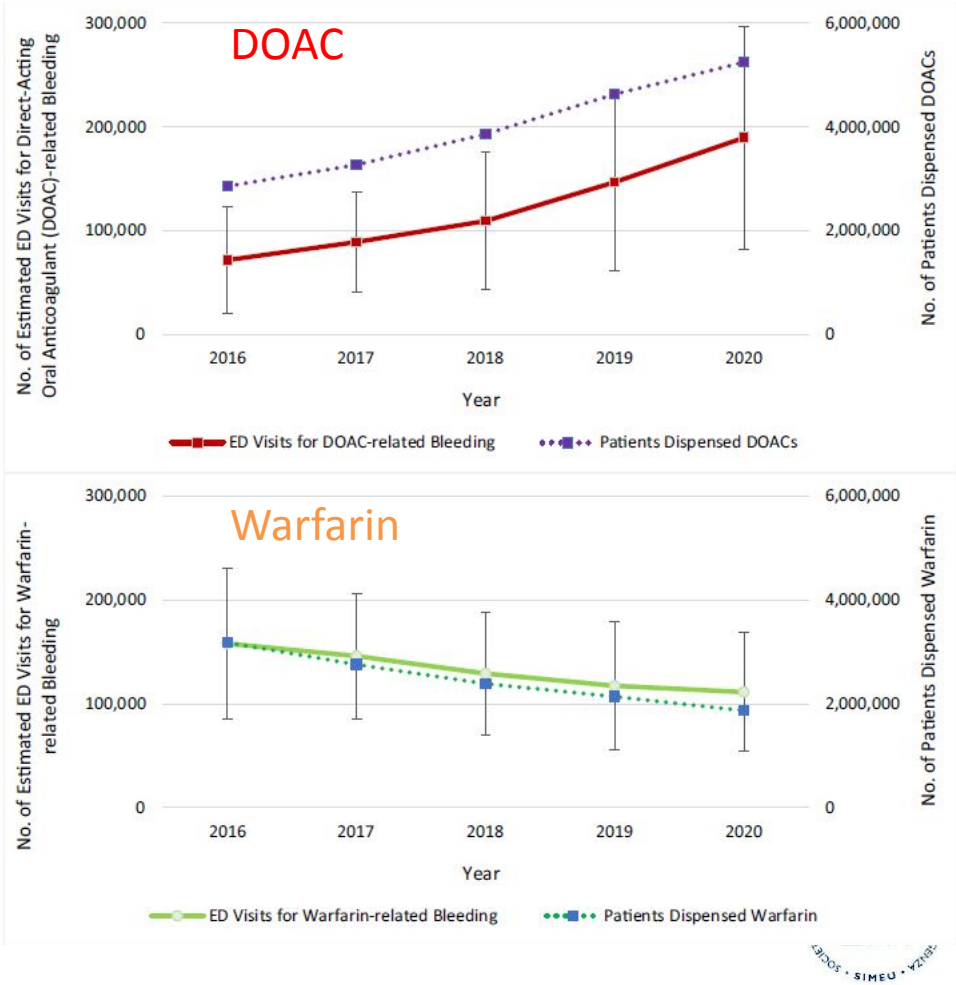
58 EDs in the United States:
prevalence of ED visits for adverse drug events was 4 per 1000 individuals in 2013 and 2014.
The most common drug classes implicated were anticoagulants, antibiotics, diabetes agents, and opioid analgesics.

Shehab, JAMA 2016

Bleeding related to oral anticoagulants: Trends in US emergency department visits, 2016-2020

The number of patients prescribed any OAC increased 17.8 %



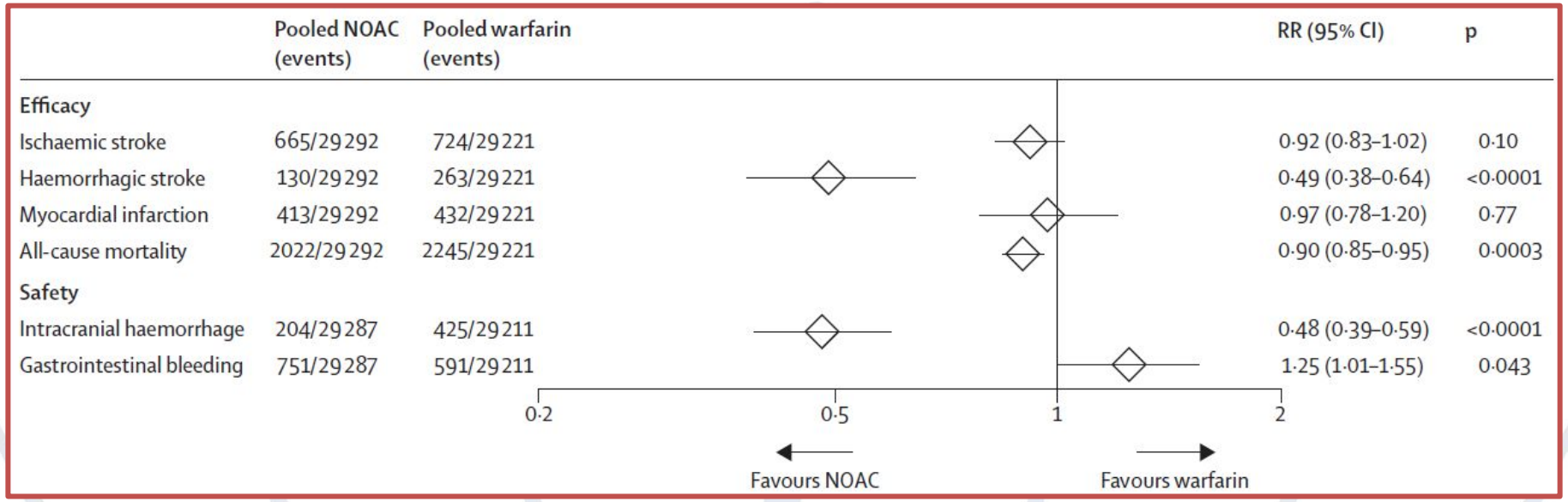


DOAC: 5.9 ED visits per 100 patients dispensed DOACs

Warfarin: 13.0 ED visits per 100 patients dispensed warfarin

Geller, Thromb Res 2023

Bleeding warfarin vs DOAC



ICH	Incidence (% per year)	Case fatality rate (%)
Warfarin	0.2 - 0.4	45-50
DOAC	0.1 – 0.2	59

Raval, Circulation 2017
Chai-Adisaksopha, JTH 2015

Ruff, Lancet 2014

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Giuseppe 85 y

March 24th admitted (11.00 p.m.) for melena for 5 days and hypotension.

Medical history: systemic arterial hypertension, atrial fibrillation, previous AMI, abdominal aortic aneurysm, PAD, diverticulosis of the colon, chronic renal failure (stage 3). Last edoxaban 30 mg intake h 8.00 a.m. (15 h before admission)

Clinical examination: alert, conscious, mild epigastric abdominal pain. BP 89/70 mmHg, HR 88 bpm, SpO2 92% room air

Blood sample: WBC 8720/uL, Hb 7.7g/dL, PLT 220000/uL, creatinine 1.36 mg/dl (CrCl 39 ml/min), INR 1.37

How would you manage this patient?

Andexanet alpha (PCC if not available)

Fluids and red blood cell transfusions

Fresh frozen plasma and vitamin K

Norepinephrine and tranexamic acid

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

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Potential indication for use

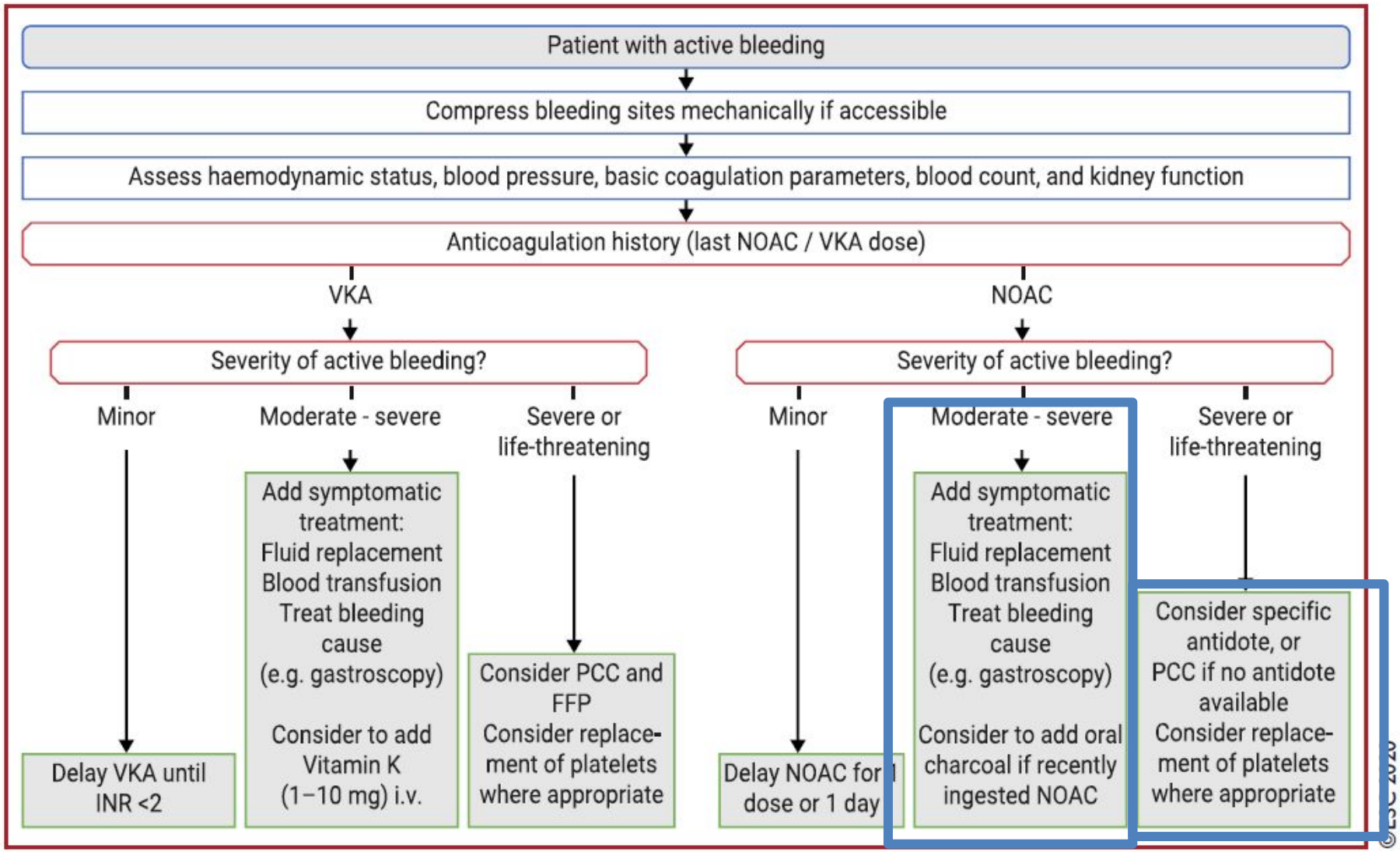
- Need for urgent surgery or intervention in patients with acute renal failure

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

J Thromb Haemost 2016

2020 ESC Guidelines for the diagnosis and management of AF



Hindricks, Eur Heart J 2021

Timing for reversal

Main inclusion criteria

- ✓ *Last Fxa inhibitor intake < 18 h (ANNEXA-4)*
- ✓ *Last Fxa inhibitor intake < 15 h (ANNEXA-I)*
- ✓ *FIIa inhibitor, group B intervention < 8 h (REVERSE-AD)*

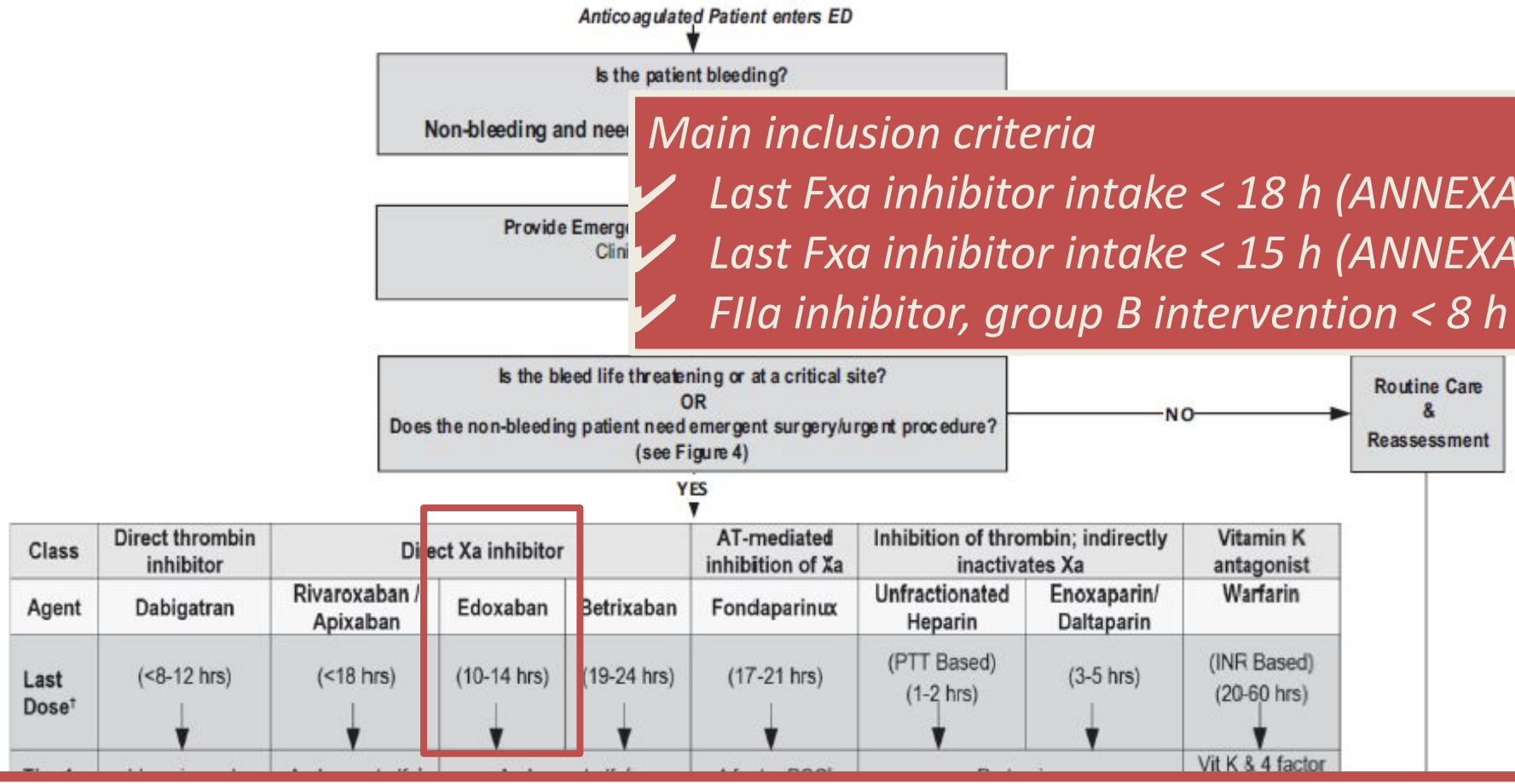


TABLE 4A Estimated Drug Half-Life Based on CrCl

	Dabigatran					Apixaban, Betrixaban, Edoxaban, or Rivaroxaban		
CrCl, mL/min	≥80	50-79	30-49	15-29	<15	≥30	15-29	<15
Estimated drug half-life, h	13	15	18	27	30 (off dialysis)	• Apixaban, edoxaban, rivaroxaban: 6-15 • Betrixaban: 19-27	• Apixaban: 17 • Edoxaban: 17 • Rivaroxaban: 9	• Apixaban: 17 (off dialysis) • Edoxaban: 10-17 (off dialysis) • Rivaroxaban: 13 (off dialysis)

CrCl = creatinine clearance.

Baugh, Ann Emerg Med 2019

Marta 68 y

Feb 19th admitted (11.00 a.m.) for major trauma (pedestrian against car).

118 territorial emergency administered tranexamic acid + pelvic binder applied.

Clinical examination: alert but confused, unable to provide her medical history or medications, complains of pelvic pain. BP 105/65 mmHg, HR 110 bpm, SpO2 94% room air.

Blood sample: WBC 9130/uL, Hb 10.9g/dL, PLT 310000/uL, creatinine 0.87 mg/dl, INR 1.1, aPTTR 0.9, fibrinogen 256 mg/dl.

- **CT scan:** fracture of the pelvis, hematoma of the psoas muscle and the left quadriceps femoris muscle, no signs of active bleeding. Small subdural hematoma (7 mm).
- **Medical history (husband):** systemic arterial hypertension, atrial fibrillation, current smoker. Last apixaban 5 mg intake at 8 a.m. (3 hours before).

How would you manage this patient?

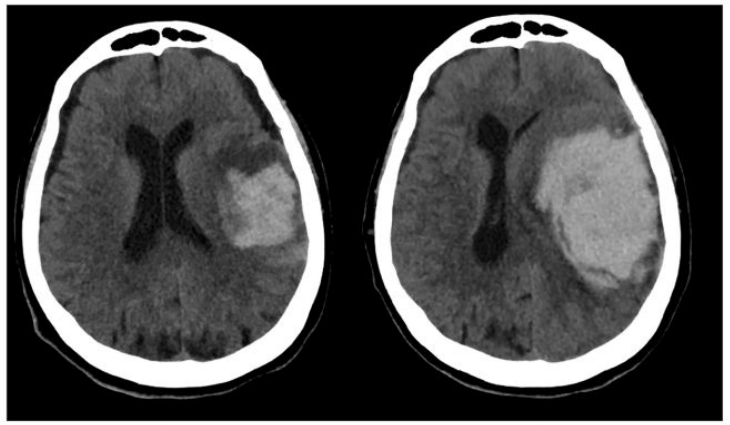
Andexanet alpha (PCC if not available)

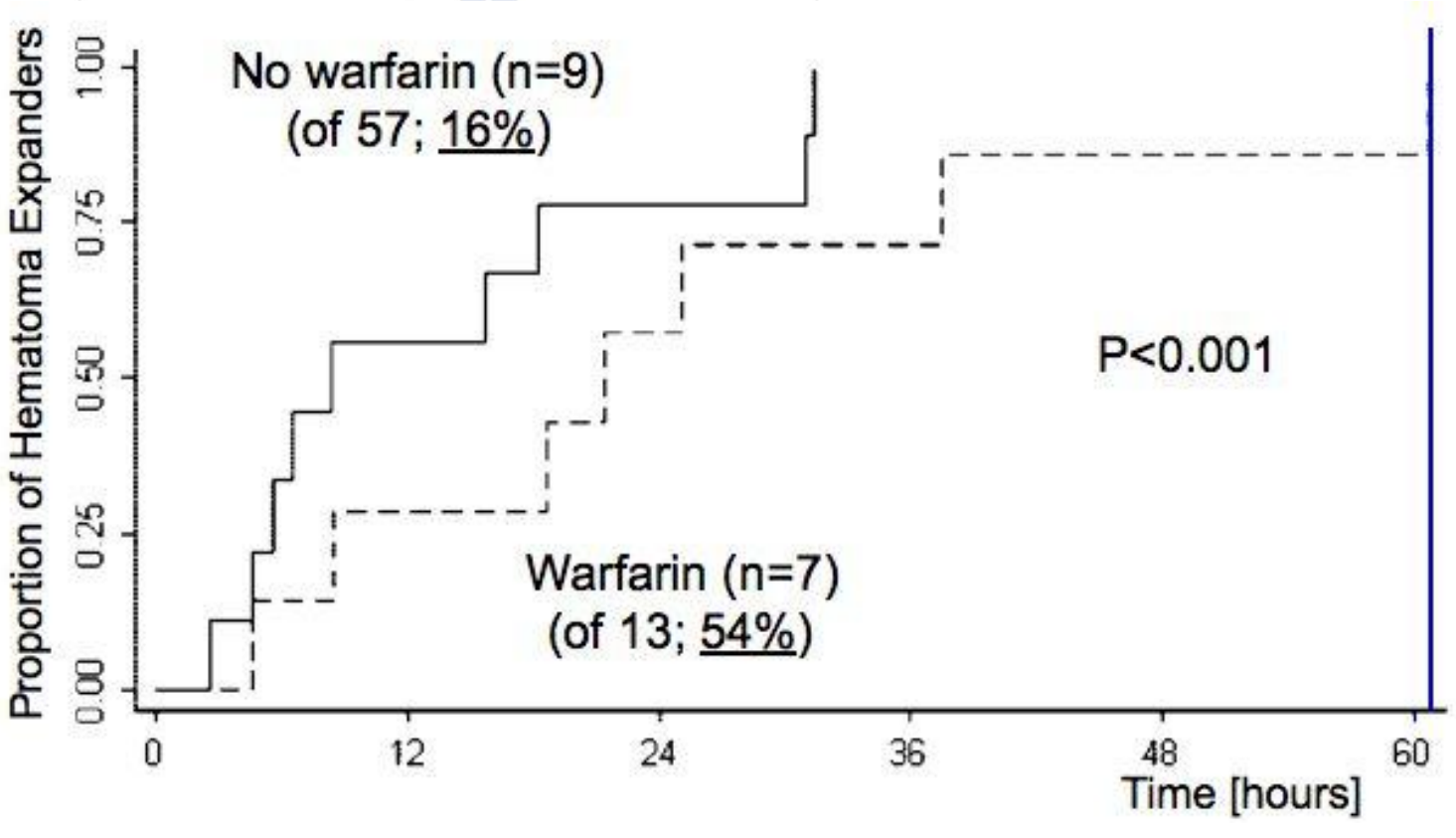
Fluids and red blood cell transfusions

Fresh frozen plasma and vitamin K

Norepinephrine and tranexamic acid

“Growth” occurs more often and over a longer time period in OAT-ICH compared to S-ICH





Adapted from: Flibotte, Neurology 2004

Predictors of severe intracerebral hemorrhage expansion

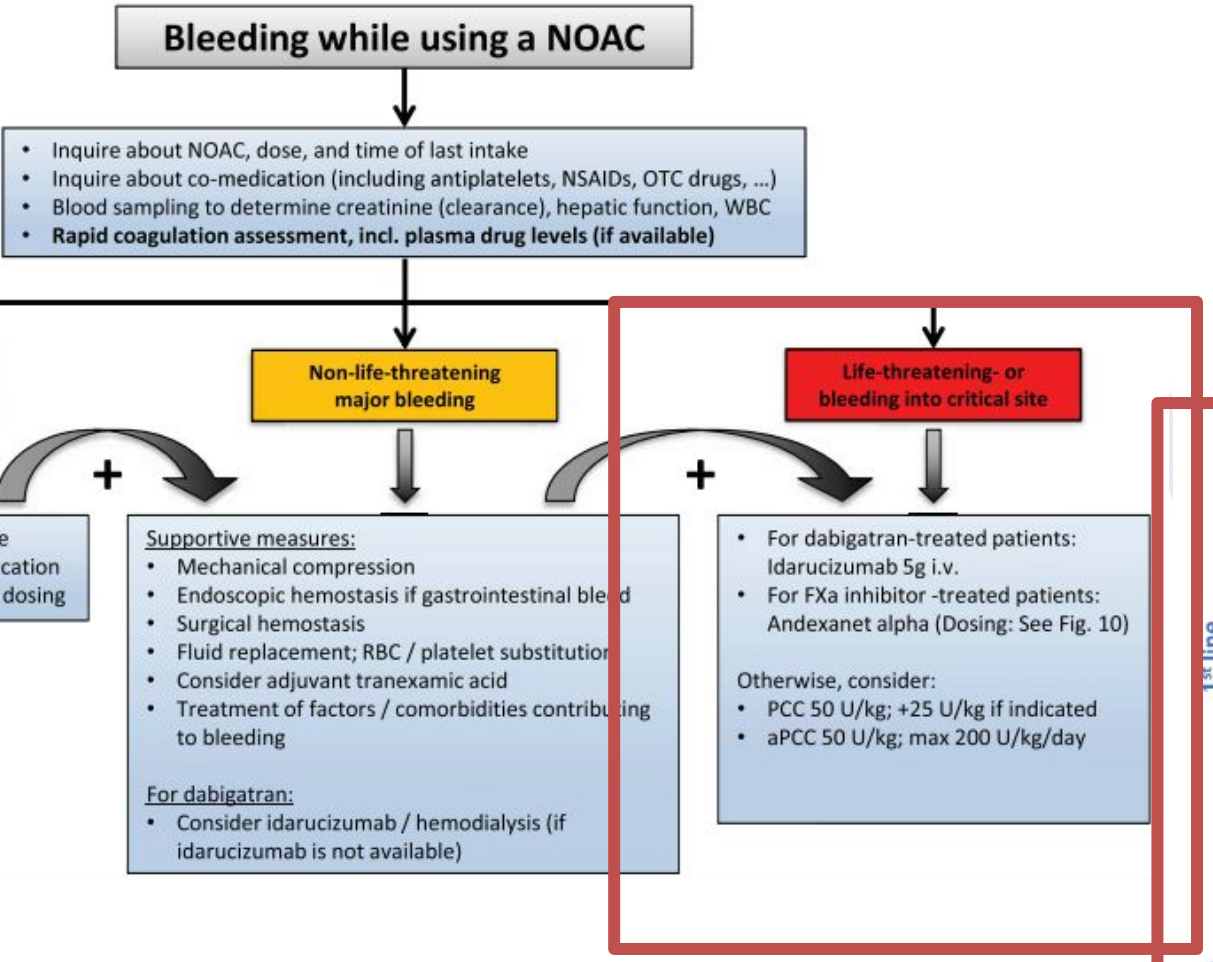
A total of 1472 patients with spontaneous ICH were included, of whom 223 (15.2%) had sHE.

Table 2. Predictors of severe ICH expansion.

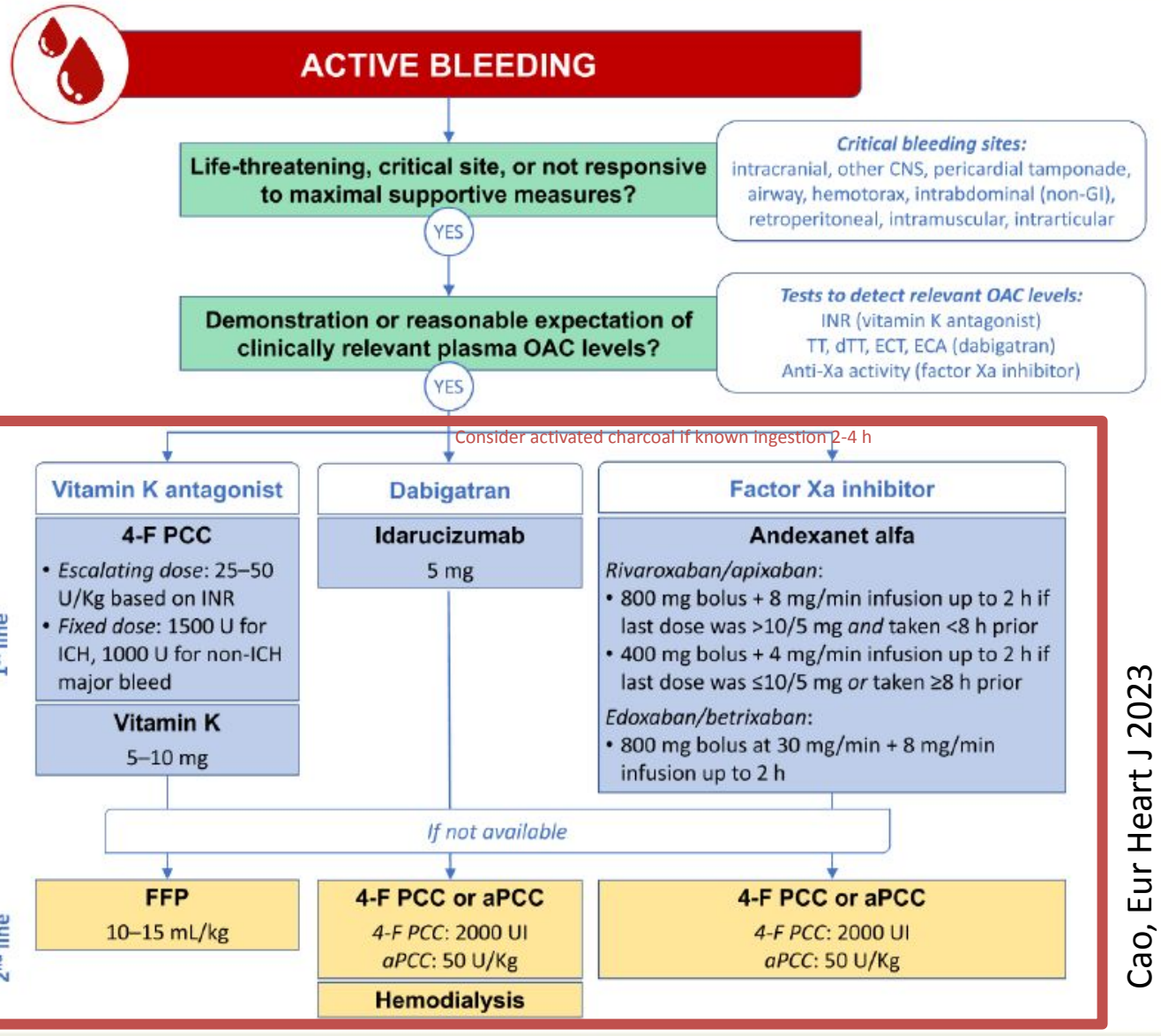
	OR (95% CI)	*p*
Age, years	1.02 (1.01–1.04)	0.001
Anticoagulant treatment	3.00 (2.09–4.31)	<0.001
GCS	0.93 (0.89–0.98)	0.002
Time from onset/LKW to NCCT, h	0.96 (0.93–0.99)	0.009
Baseline ICH volume, mL	1.02 (1.02–1.03)	<0.001

Morotti, European Stroke Journal 2024

European Guidelines and Consensus



Steffel, Europace 2021



Cao, Eur Heart J 2023

Specific reversal

Idarucizumab (reversal of dabigatran)

5g i.v. divided in two 2.5g-doses, given within up to 15 minutes apart

Suppression of dTT

0 min; 15 min — 24 h

Andexanet Alfa *is administered as an IV bolus at a target rate of 30 mg/min over 15-30 min, followed by a continuous infusion of 4 mg/min* ***(low dose)*** *or 8 mg/min* ***(high dose)*** *for 2 hours*

LOW dose: 400 mg i.v. bolus over 15 min, followed by 480 mg i.v. infusion (4mg/min) over 2 h.

HIGH dose: 800 mg i.v. bolus over 30 min, followed by 960 mg i.v. infusion (8mg/min) over 2 h.

FXa inhibitor	Last dose	Timing of the last dose	
		<8 hours or unknown	≥8 hours
Apixaban	≤5 mg	LOW dose	LOW dose
	>5 mg or unknown	HIGH dose	
Rivaroxaban	≤10 mg	LOW dose	LOW dose
	>10 mg or unknown	HIGH dose	

Suppression of FXa level

0 min — 2 h — 24 h

Hindricks, Eur Heart J 2021

PATIENTS

WHO

530 adults

Mean age, 78.9 years

Men: 54%; Women: 46%

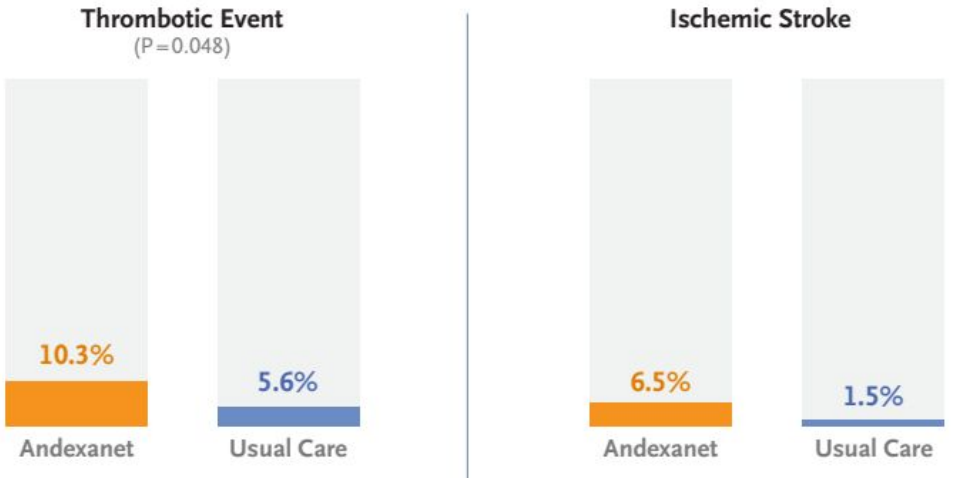
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 16/23, 2024 VOL. 390 NO. 19

Andexanet for Factor Xa Inhibitor–Associated Acute Intracerebral Hemorrhage

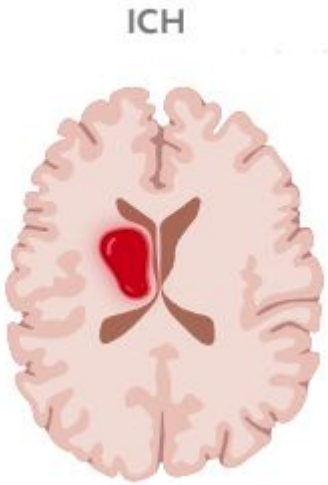
Table 2. Efficacy End Points.

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)	



The trial did not have sufficient power or information to draw conclusions about the effect of andexanet on mortality: 30-day death A=27.8% vs UC=25.5%

Connolly, NEJM 2024



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 16/23, 2024 VOL. 390 NO. 19

Andexanet for Factor Xa Inhibitor–Associated Acute Intracerebral Hemorrhage

…Before the protocol was amended, 34 patients in whom the primary site of hemorrhage was subdural or subarachnoid were enrolled (22 patients [9.8%] in the Andexanet group and 12 patients [5.3%] in the usual-care group). **Subsequently, only patients with intracerebral hemorrhage were eligible…**

Connolly, NEJM 2024

Main exclusion criteria

- ✔ Hematoma volume > 60 ml
- ✔ NIHSS > 35
- ✔ Glasgow Coma Scale < 7
- ✔ Surgery planned < 12 h

Specific reversal

	Idarucizumab	Andexanet alfa
Type of molecule	Humanized mouse monoclonal antibody fragment	Catalytically inactive recombinant form of factor Xa derived from Chinese hamster ovarian cells
Mechanism of action	Binds with both free and thrombin-bound dabigatran with high affinity	Binds to factor Xa inhibitors with high affinity
Procoagulant activity	No	Uncertain
Terminal half-life	10 h	5–7 h
FDA approved indications	Patients treated with dabigatran who require rapid reversal of the anticoagulant effects during emergency surgery or urgent procedures or in life-threatening or uncontrolled bleeding	Patients treated with rivaroxaban or apixaban who require reversal of the anticoagulant effects in life-threatening or uncontrolled bleeding

Chaudhary JTT 2019

RE-VERSE-AD

Idarucizumab for Dabigatran Reversal — Full Cohort Analysis

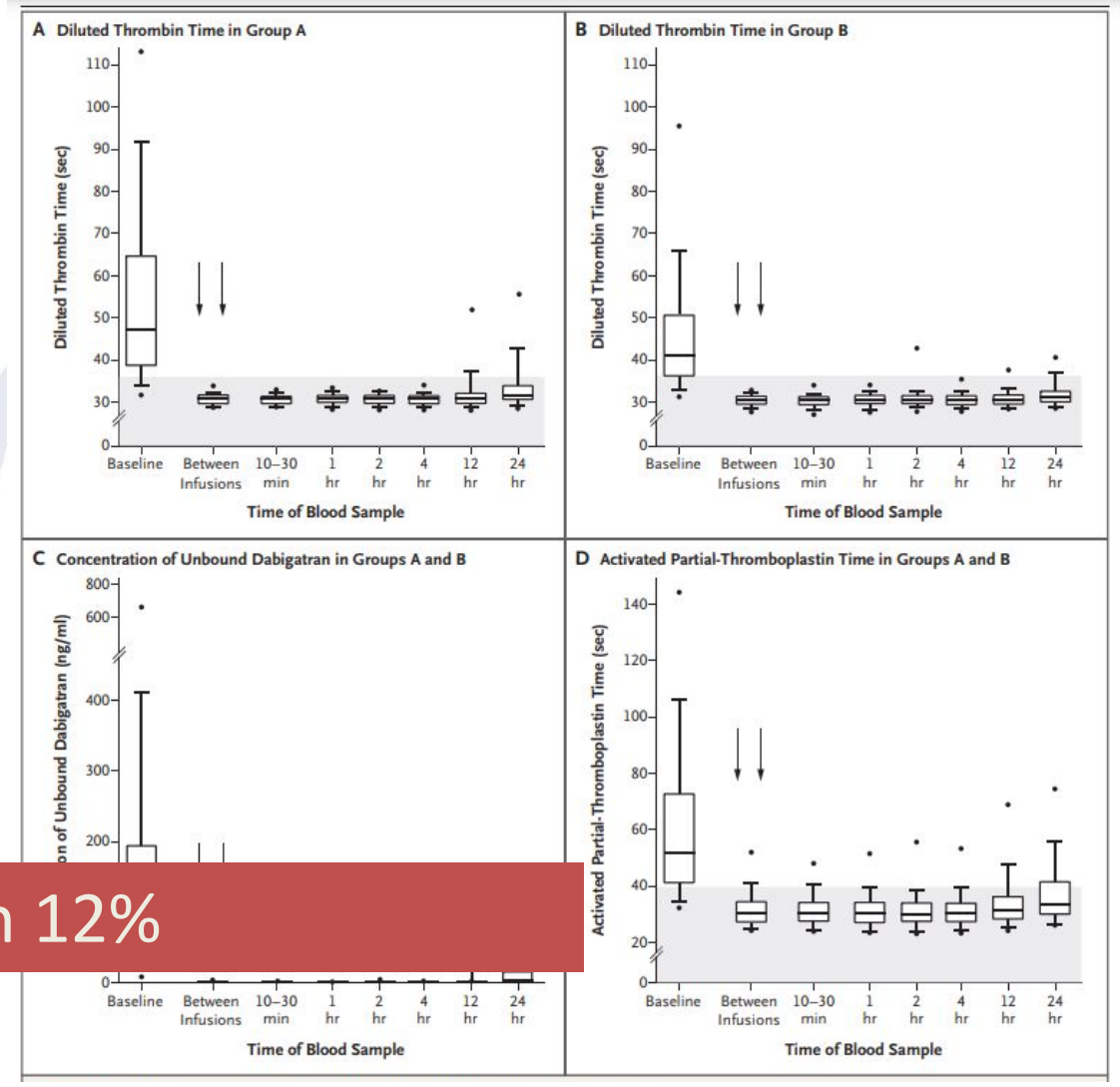
503 patients were enrolled: 301 in group A (uncontrolled bleeding), and 202 in group B (urgent procedure within 8h).

Group A (45.5% GI bleeding and 32.6% ICH) median time to the cessation of bleeding was 2.5 hours.

Group B median time to the initiation of the intended procedure was 1.6 h

Plasma concentration of unbound

30-day death 12%



Pollack, NEJM 2017

ANNEXA-4

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

342 patients who had **acute MB** within 18 hours since last dose (factor Xa inhibitor).

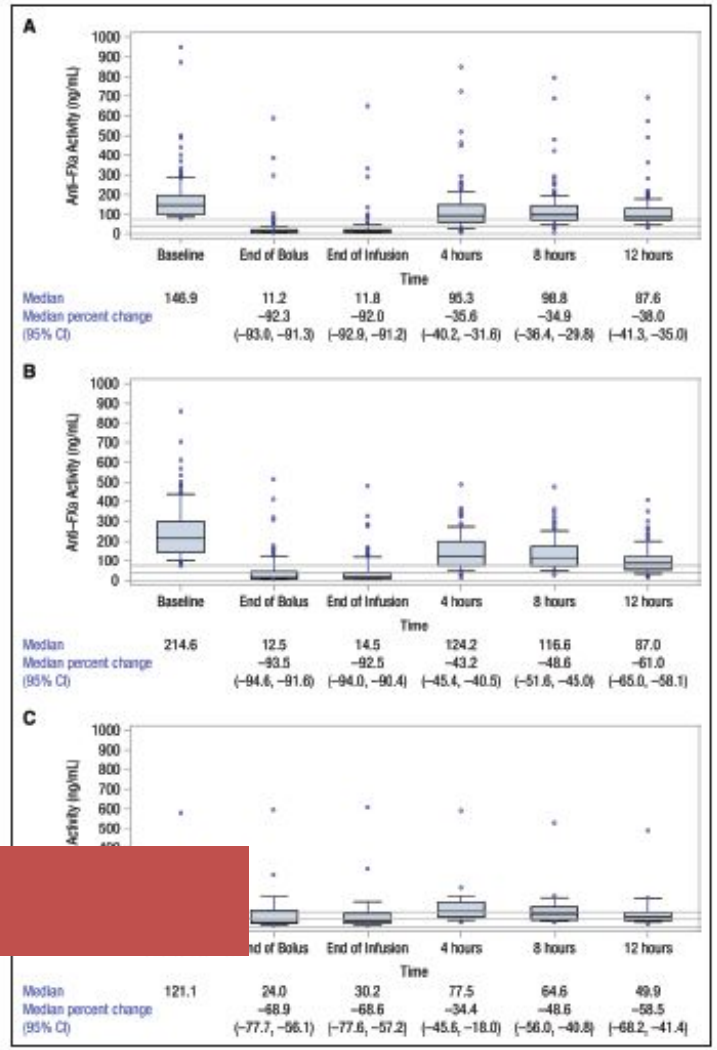
ICH 71.3%, GI bleeding 22.3%.

Andexanet markedly reduced anti–factor Xa activity, and 82% of patients had excellent or good hemostatic efficacy at 12 hours.

Apixaban

Rivaroxaban

Edoxaban



30-day deaths 15.7%

Milling, Circulation 2023

Prothrombin Complex Concentrate for Major Bleeding on Factor Xa Inhibitors: A Prospective Cohort Study

Patients on apixaban or rivaroxaban with a major bleed received PCC 2,000 U (fixed dose) P.O. To evaluate the haemostatic effectiveness at day one

66 patients included: rivaroxaban 56%, apixaban 44%

Outcome	(*n* = 66)
Haemostatic effectiveness rating[a]	
Good	43 (65)
Moderate	13 (20)
Poor/None	10 (15)

ICH= 36	GIB= 16
%	%
67	69
17	12
17	19

PCC may have a beneficial effect, the risk of thromboembolism after reversal has to be taken into account (5 major thromboembolic events).

Schulman, Thromb Haemost 2018

Reversal agents for oral anticoagulant-associated major or life-threatening bleeding

Table 5 Comparison of major oral anticoagulation-reversal studies

Trial	Reversal agent	Anticoagulant	Number of patients		Hemostatic Efficacy (95% CI)	Thrombotic event rate at 30 days (%)	Mortality at 30 days (%)
			Total	% ICH			
ANNEXA-4 (2019)	Andexanet	FXa inhibitors (enoxaparin,	352	64	82% (77–87)	10	14
ANNEXA-I	Andexanet		263	263		10.3	27.8
	Usual care		267	267		5.6	25.5
RE-VERSE AD (2017)	Idarucizumab	Dabigatran	301	32.6	67.7%[a]	4.8	12
Sarode (2013)	4F-PCC	Warfarin	98	12	72% (64–81)	7.8[b]	5.8
	Plasma		104	12	65% (56–75)	6.4[b]	4.6

4F-PCC four factor prothrombin complex concentrate

[a]Hemostatic efficacy reported only in patients without intracranial hemorrhage

[b]Events evaluated at 45 days

Moia, Intern Emerg Med 2019

Reversal agents for oral anticoagulant-associated major or life-threatening bleeding

Table 2 7-Element bundle for managing OA-associated major or life-threatening bleeding

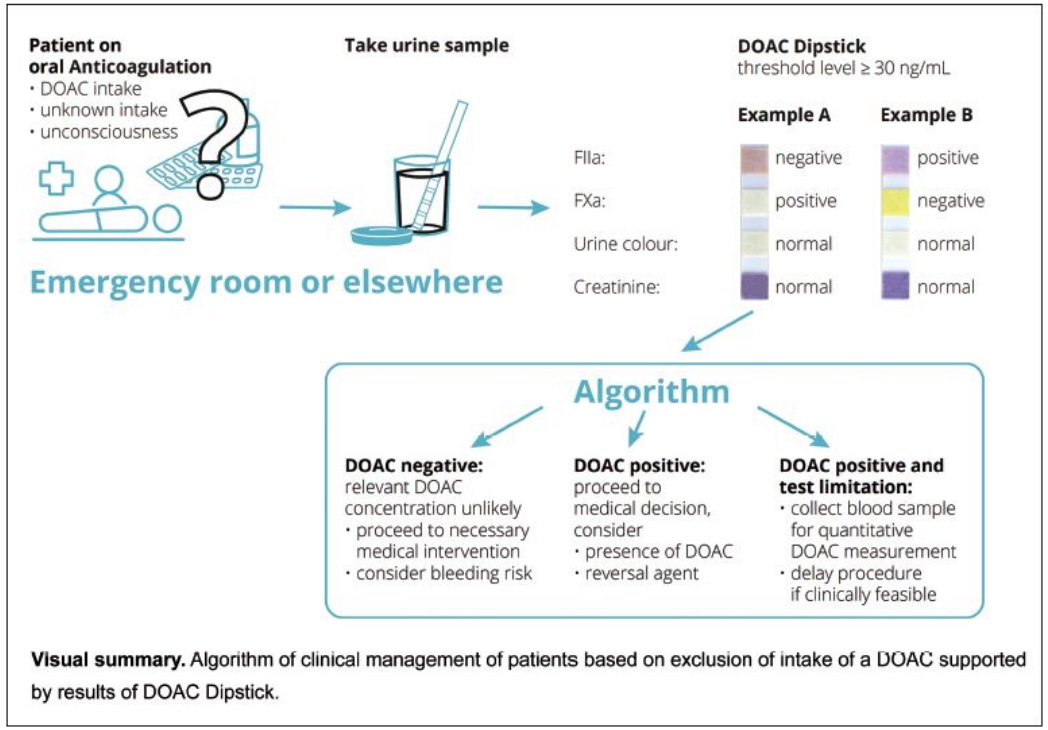
1	Cessation of the OA
2	Fluid replacement, to support the cardiovascular system and renal function
3	blood tests, to check for hemoglobin level, platelet count, renal function, liver function, PT, aPTT, and DOACs' plasma level
4	Red blood cell transfusion, and eventually platelet and/or fresh frozen plasma transfusion when necessary; consider tranexamic acid
5	Any local hemostatic measure, such as endoscopy, interventional radiology procedure or surgical intervention
6	Check and management of any additional bleeding risk factor, such as uncontrolled hypertension, excessive alcohol intake, acute renal insufficiency, low platelet count, antithrombotic therapies, in particular antiplatelet drugs, NSAIDs and glucocorticoids
7	If DOAC: plasma measurement of the DOAC level and reversal agent administration (idarucizumab, Andexanet alfa or 4F-PCC) only when the anticoagulant drug is active in patient's plasma in measurable quantities If VKA: INR measurement and vitamin K administration plus reversal with PCC (FFP if PCC unavailable)

OC oral anticoagulant, *DOAC* direct oral anticoagulant, *VKA* vitamin K antagonist, *4F-PCC* 4-factor prothrombin complex concentrate, *INR* international normalized ratio, *FFP* fresh frozen plasma

Moia, Intern Emerg Med 2019

Algorithm for Rapid Exclusion of Clinically Relevant Plasma Levels of Direct Oral Anticoagulants in Patients Using the DOAC Dipstick: An Expert Consensus Paper

Job Harenberg[1,2] Robert C. Gosselin[3] Adam Cuker[4] Cecilia Becattini[5] Ingrid Pabinger[6] Sven Poli[7,8] Jeffrey Weitz[9,10] Walter Ageno[11] Rupert Bauersachs[12] Ivana Celap[13,14] Philip Choi[15,16] James Douketis[10] Jonathan Douxfils[17,18] Ismail Elalamy[19,20] Anna Falanga[21,22] Jawed Fareed[23] Emmanuel J. Favaloro[24,25] Grigorios Gerotziafas[26,27] Harald Herkner[28] Svetlana Hetjens[29] Lars Heubner[30] Robert Klamroth[31] Forian Langer[32] Gregory Y. H. Lip[33,34] Brian Mac Grory[35] Sandra Margetić[12,36] Anne Merrelaar[28] Marika Pikta[37,38] Thomas Renne[39,40] Sam Schulman[20,41] Michael Schwameis[28] Daniel Strbian[42] Alfonso Tafur[43,44] Julie Vassart[17] Francesco Violi[45] Jeanine Walenga[46] Christel Weiss[29]



Visual summary. Algorithm of clinical management of patients based on exclusion of intake of a DOAC supported by results of DOAC Dipstick.

842 patients in 5 studies

	Direct oral factor Xa inhibitors Mean (95% CI)	Direct oral thrombin inhibitor Mean (95% CI)
Sensitivity	97.8 (95.6–99.0)	98.3 (91.0–100)
Negative predictive value	86.6 (76.0–93.7)	99.6 (97.7–100)
Positive predictive value	87.2 (83.7–90.1)	73.4 (63.7–83.2)
Specificity	50.0 (40.2–59.0)	91.8 (87.7–94 0.9)

Thromb Haemost 2024

Thromboembolic and BLEEding events while on DOAC treatment: role of DOAC tests in the Emergency Department.

PIEMONTE

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T-BLEEDOAC

Conclusions

- ✔Knowing the type and last intake of anticoagulant treatment is crucial
- ✔The decision-making should be based on bleeding severity
- ✔Local assets/resources should be known
- ✔Future studies should assess the clinical role of DOAC levels and reversal agents

THANK YOU