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Nuove evidenze nel Reversal: lo studio ANNEXA-I

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Disclosures

- Advisory Board, presentazioni a congresso, workshops
  - Abbott
  - Alexion
  - Astra Zeneca
  - Bayer
  - Boehringer Ingelheim
  - Bristol Myers Squibb
  - Daiichi Sankyo
  - Medtronic
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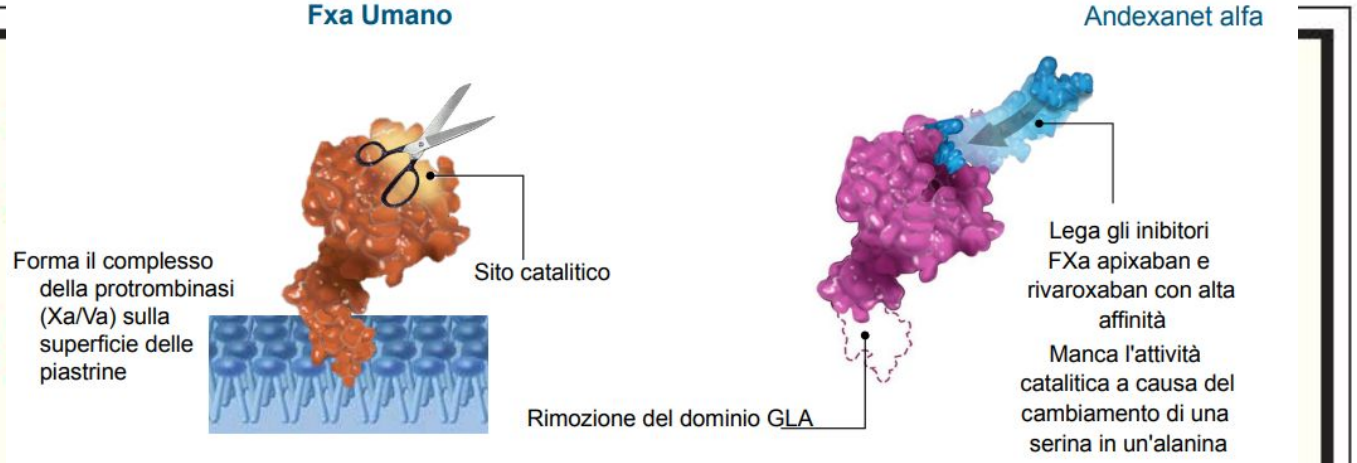
- Unrestricted research grant
  - Boehringer Ingelheim

The NEW JOURNAL

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



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*

N Engl J Med 2024;390:1745-55

ANNEXa-I Study Design

Phase 4, multicenter, prospective, randomized, open-label, blinded-endpoint trial in patients with acute ICrH treated with FXa inhibitors[1]

Primary Efficacy Population (N=452)[2]
Extended Population (N=530)[2]

Patients ≥18 years old with acute ICrH within 6 hours of symptom onset and within 15 hours following the last dose of apixaban, rivaroxaban, or edoxaban[1]

R 1:1

- **Andexanet alfa**
- **Usual care[a]**

Primary Efficacy Endpoint: Effective Hemostasis at 12 Hours[1,b]
Defined as meeting **all 3** of the following criteria:

1. ≤35% hematoma volume expansion at 12 hours
2. NIHSS score increase of <7 at 12 hours
3. No rescue therapy administered between 3 and 12 hours after randomization

Secondary Efficacy Endpoint:

- Percent change from baseline to nadir in anti-FXa activity during the first 2 hours post-randomization[c]

Select Safety Endpoints:

- Thrombotic events at 30 days
- 30-day mortality

[a]Usual care: any treatment(s), including no treatment, other than andexanet alfa administered within 3 hours post-randomization that the investigator and/or treating physicians considered to be appropriate
[b]Effective hemostasis defined as "good" or "excellent" hemostatic efficacy as determined by a blinded adjudication committee
[c]Nadir defined as the minimum anti-FXa activity post-randomization

Additional Key Inclusion and Exclusion Criteria

Key Inclusion Criteria
Acute intracerebral hematoma of 0.5 mL to 60 mL on CT/MRI[a]
NIHSS score ≤35 at time of consent
Negative pregnancy test and not lactating

Key Permissible Planned Surgeries/Procedures

- Neurological interventions for reasons beyond hematoma evacuation (ie: Burr hole/craniotomy for ICP monitoring)
- Lumbar punction
- Pericardial drainage or thoracentesis
- Embolization
- CT-guided abscess drainage

Key Exclusion Criteria

Recent history of a diagnosed TE or clinically relevant symptom including VTE, MI, DIC, CVA, TIA, ACS, or arterial systemic[b]

Acute decompensated HF, cardiogenic or septic shock, or severe sepsis

Receipt of a VKA, dabigatran, PCC, rfVIIa, FEIBA, FFP, or whole blood within 7 days

GCS <7 at time of consent

Past use of andexanet alfa

Any tumor-related bleeding

Expected survival of <1 month (not related to intracranial bleed)

Planned surgery within 12 hours after randomization

[a]Patients may have extracerebral bleeding (subdural, subarachnoid, epidural) or extracranial (GI, intraspinal), but the ICH must be considered the most clinically significant bleed at the time of enrollment;

[b]Recent history is defined as within 2 weeks.

ACS = acute coronary syndrome; CT = computed tomography; CVA = cerebral vascular accident; DIC = disseminated intravascular coagulation; EBV = estimated blood volume; FEIBA = anti-inhibitor coagulant complex; FFP = fresh frozen plasma; GCS = Glasgow Coma Scale; GI = gastrointestinal; HF = heart failure; ICH = intracerebral hemorrhage; ICP = intracranial pressure; MI= myocardial infarction; MRI = magnetic resonance imaging; NIHSS = National Institutes of Health Stroke Scale;

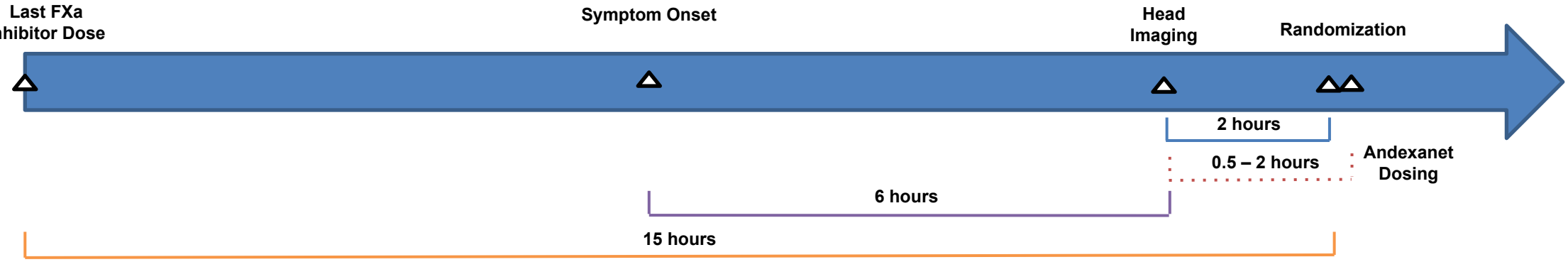
Key Timing Considerations

Head CT or MRI

- Must occur within 2 hours prior to randomization
- Required within 6 hours of bleeding symptom onset

Treatment

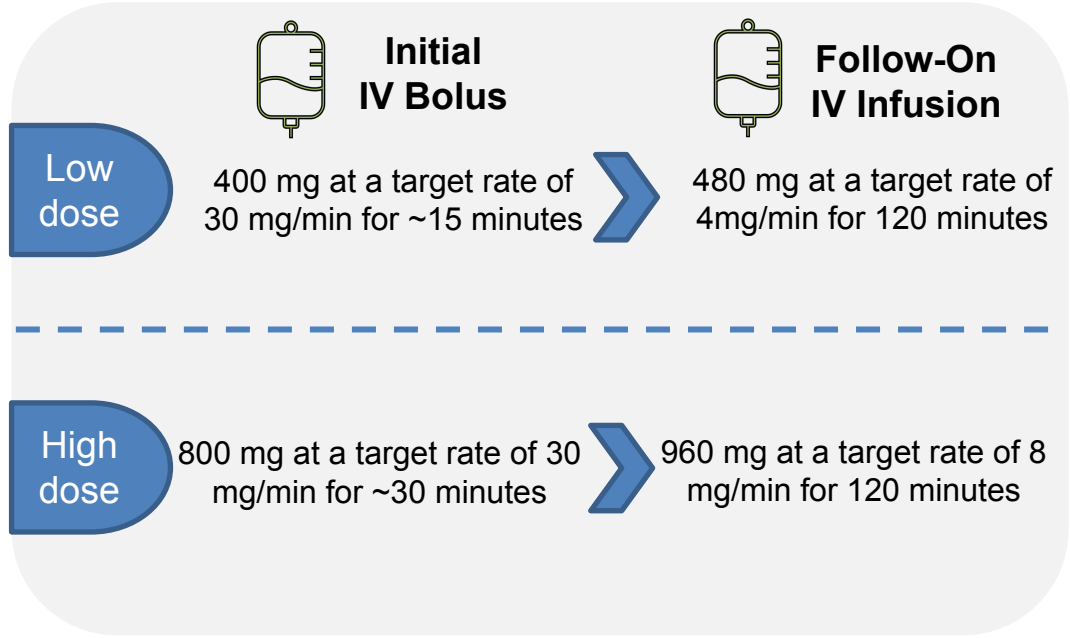
- Last oral FXa inhibitor dose occurred within 15 hours of randomization
- If last FXa inhibitor dose is unknown or >15 hours, a local and standard anti-FXa activity level must be performed within 2 hours of consent
- Andexanet alfa dosing initiated between 0.5 to 2 hours of baseline CT/MRI
- All patients initiate treatment as soon as possible after randomization



Randomization1:1 to Andexanet Alfa vs Usual Care

Andexanet alfa dose is based on the specific FXa inhibitor, dose of FXa inhibitor and time since the patient's last dose

FXa Inhibitor	FXa Inhibitor Last Dose	Timing of FXa Inhibitor Last Dose before Andexanet alfa Initiation[a]	
		<8 hours	≥8 hours
Rivaroxaban	10 mg	Low dose	Low dose
	>10 mg	High dose	
Apixaban	≤5 mg	Low dose	
	>5 mg	High dose	
Edoxaban	30 mg	Low dose	
	>30 mg	High dose	



Usual care consisted of any treatment(s), including no treatment, other than andexanet alfa, that is initiated within 3 hours post-randomization[b]

[a]High dose andexanet alfa administered if >15 hours or unknown timing since last FXa inhibitor dose, only if local anti-fXa activity >100 ng/mL and was obtained within 2 hours prior to consent and performed as per standard of care;

[b]Patients randomized to usual care may receive platelets and/or PRBCs at any time, pro-coagulant blood products (3F-PCC, 4F-PCC, aPCC, rfVIIa, FFP, FEIBA, whole blood, local/systemic hemostatics (ie: aminocaproic acid) according to standard institutional/local practice guidelines.

3F-PCC = 3-factor prothrombin complex concentrate; 4F-PCC; 4-factor prothrombin complex concentrate; aPCC = activated prothrombin complex concentrate; FEIBA = anti-inhibitor coagulant complex; FXa = Factor Xa; IV = intravenous; PRBC = packed red blood cells; rfVIIa = recombinant Factor VIIa.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Andexanet (N=224)	Usual Care (N=228)
Hemorrhage location — no. (%)		
Intracerebral	198 (88.4)	214 (93.9)
Intraventricular	3 (1.3)	1 (0.4)
Subarachnoid	9 (4.0)	8 (3.5)
Subdural	13 (5.8)	4 (1.8)
Hemorrhage preceded by trauma — no. (%)	26 (11.6)	33 (14.5)
Systolic blood pressure in patients with intracerebral hemorrhage — mm Hg	161.2±27.0	159.8±27.7
Median hematoma volume (IQR) — ml	10.5 (4.1–24.9)	9.0 (3.1–22.8)
Median Glasgow Coma Scale score (IQR)‡	15.0 (13.0–15.0)	15.0 (13.0–15.0)
Median NIHSS score (IQR)§	9.0 (5.0–16.0)	9.0 (4.0–14.0)
Median time from symptom onset to baseline scan (IQR) — hr	2.3 (1.5–4.0)	2.4 (1.4–3.8)
Median time from baseline scan to randomization (IQR) — hr	1.1 (0.7–1.5)	1.2 (0.7–1.7)
Median time from hospital presentation to receipt of treatment (IQR) — hr¶	2.1 (1.5–2.9)	2.3 (1.7–3.1)
Patients receiving high-dose andexanet — no. (%)	45 (20.1)	—
Patients receiving low-dose andexanet — no. (%)	175 (78.1)	—
Patients receiving PCC within 3 hr — no. (%)	—	195 (85.5)

Figure S1. Reduction in Median Anti-FXa Activity From Baseline to Nadir at 2 Hours

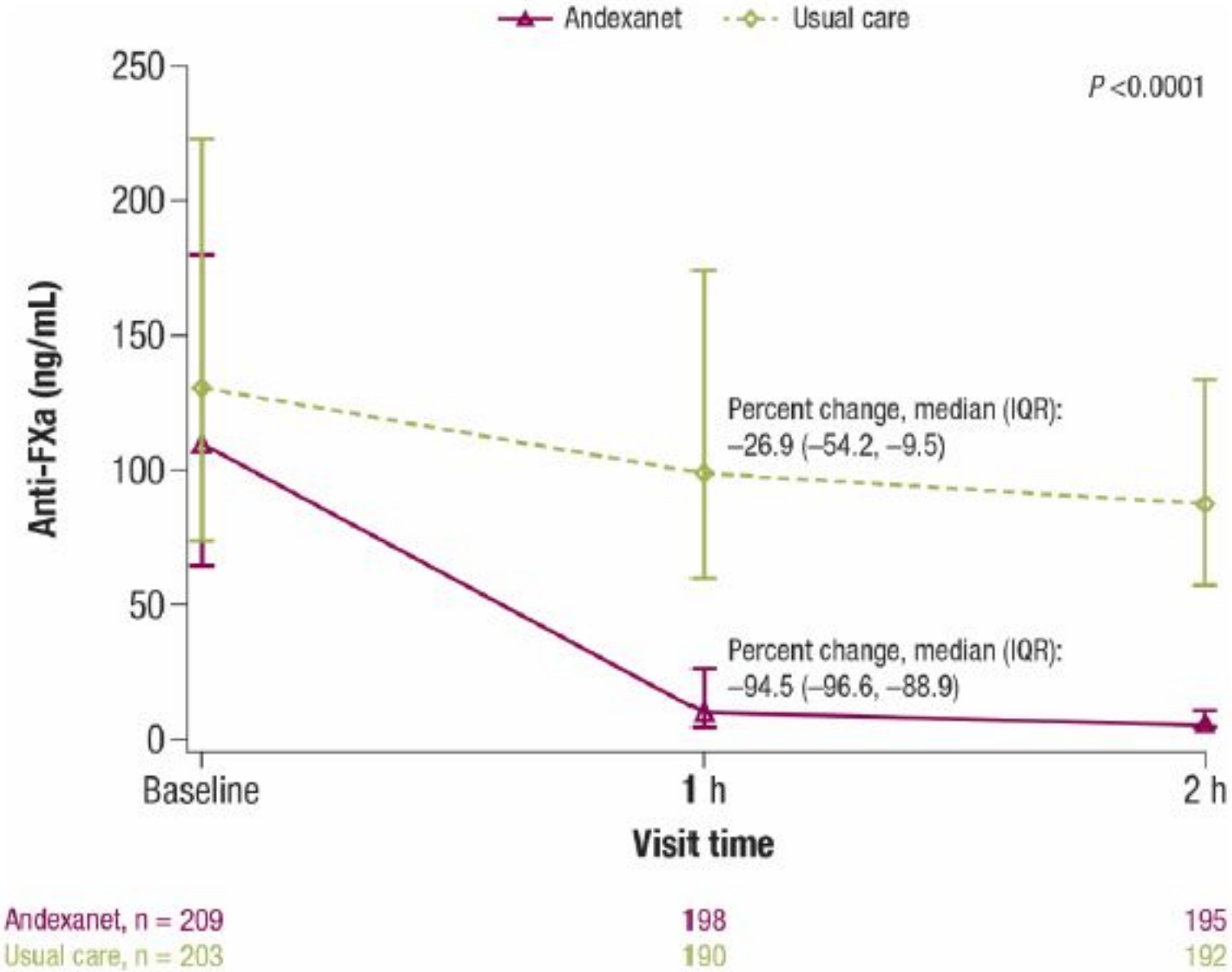


Table 2. Efficacy End Points.

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)	

Effective hemostasis

Subgroup	Andexanet	Usual Care	Adjusted Difference (95% CI)
	no. of patients with hemostatic efficacy/ total no. (%)		
Anti-FXa activity at baseline			
<30 ng/ml	8/14 (57)	9/13 (69)	−13.3 (−49.2 to 22.5)
≥30 ng/ml	132/195 (68)	95/190 (50)	17.1 (7.6 to 26.6)
<75 ng/ml	48/69 (70)	30/53 (57)	13.5 (−3.6 to 30.7)
≥75 ng/ml	92/140 (66)	74/150 (49)	15.3 (4.2 to 26.3)
ICH score at baseline			
<3	129/193 (67)	112/198 (57)	10.2 (0.8 to 19.6)
≥3	19/28 (68)	9/29 (31)	34.4 (9.5 to 59.3)
Volume of hematoma at baseline			
<30 ml	125/180 (69)	109/192 (57)	12.0 (2.4 to 21.6)
≥30 ml	25/44 (57)	12/35 (34)	22.8 (1.5 to 44.1)
<0.5 ml	5/7 (71)	6/9 (67)	14.1 (−26.1 to 54.2)
≥0.5 ml	145/217 (67)	115/218 (53)	13.7 (4.7 to 22.6)
Hemorrhage location at baseline			
Intracerebral	131/198 (66)	111/214 (52)	13.8 (4.5 to 23.1)
Intraventricular	2/3 (67)	0/1 (0)	—
Subdural	9/13 (69)	4/4 (100)	−24.6 (−51.2 to 2.0)
Subarachnoid	8/9 (89)	6/8 (75)	15.1 (−19.4 to 49.5)
Time to randomization since last administration of FXa			
<8 hr	51/86 (59)	43/99 (43)	14.6 (0.4 to 28.8)
≥8 hr	96/133 (72)	78/129 (60)	12.2 (0.9 to 23.4)
Andexanet dose			
Low	126/175 (72)	121/228 (53)	18.2 (9.0 to 27.4)
High	24/45 (53)	121/228 (53)	0.8 (−14.9 to 16.5)
Usual care received			
PCC	150/224 (67)	101/195 (52)	14.7 (5.5 to 23.9)
Non-PCC	150/224 (67)	18/30 (60)	6.8 (−11.5 to 25.1)

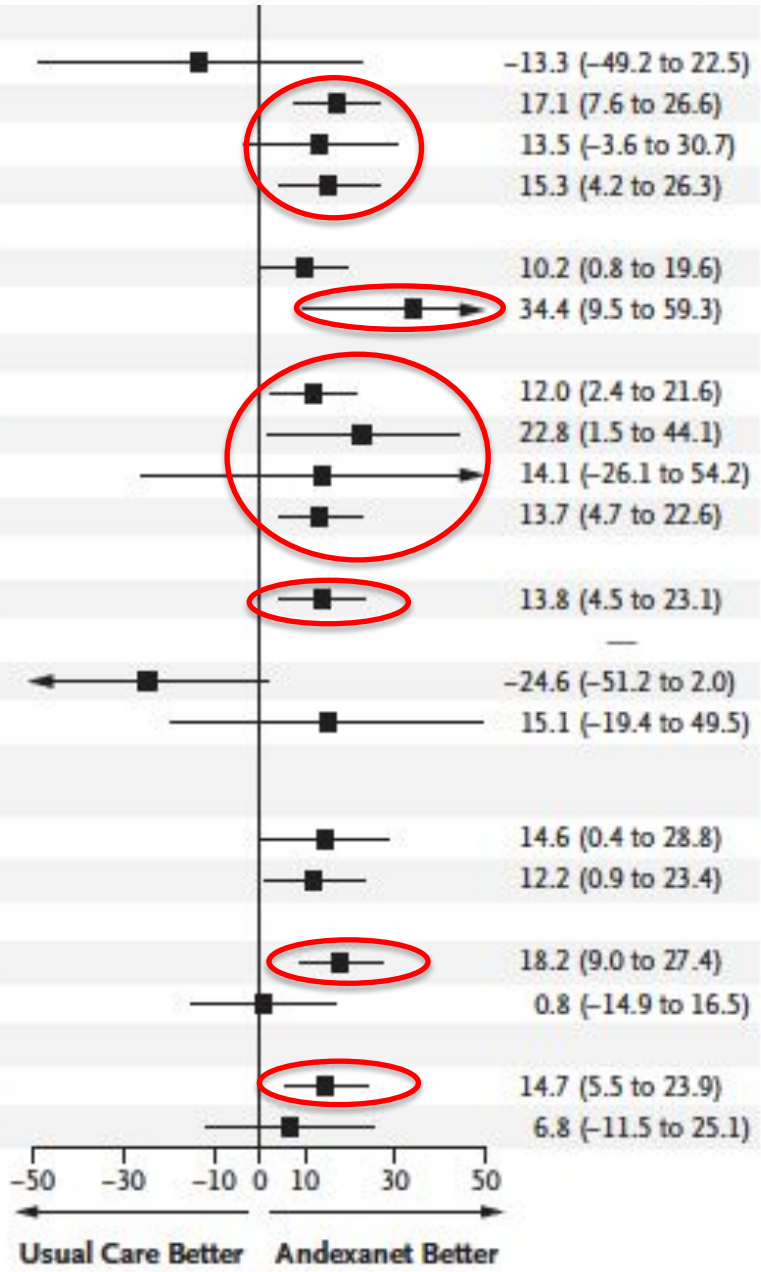


Table 3. Thrombotic Events and Deaths at 30 Days.*

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

69 (28.0) 79 (30.9) -2.9 (-10.9, 5.2)

MULTIVARIABLE MODELS FOR RISK OF HEMATOMA EXPANSION AT 12 HOURS

Parameter	Odds ratio (95% CI)	*P* value
Model 1		
Andexanet versus usual care*	0.45 (0.30, 0.71)	<0.001
Symptom onset to treatment, hours	0.72 (0.62, 0.83)	<0.001
Anti-FXa activity, per 100 ng/mL	1.19 (1.00, 1.43)	0.056
Hematoma volume, mL	1.01 (1.00, 1.02)	0.025
Model 2		
Andexanet versus usual care*	0.51 (0.34, 0.76)	<0.001
Pre-scan hematoma growth rate, mL/hour	1.02 (1.01, 1.04)	0.001

Shoamanesh A et al, ISC 2024

*Usual care is the reference.
CI, confidence interval; FXa, Factor Xa; ICH, intracerebral hemorrhage.

RATES OF HEMATOMA EXPANSION

Group	Andexanet (n = 224)	Usual care (n = 235)	Decrease with andexanet per 100 patients (95% CI)*
Pre-scan hematoma growth rate, mL/hour			
Q1: <1.2	4/50 (8.0)	**13/65 (20.0)**	-12.0 (-24.3, 0.3)
Q2: 1.2 to <4.1	15/57 (26.3)	**22/58 (37.9)**	-11.6 (-28.5, 5.3)
Q3: 4.1 to <11.4	19/62 (30.6)	**22/53 (41.5)**	-10.9 (-28.4, 6.7)
Q4: ≥11.4	19/55 (34.5)	**35/59 (59.3)**	-24.8 (-42.5, -7.0)

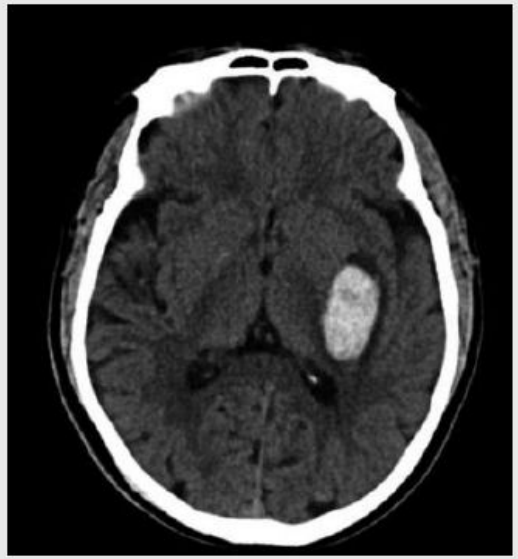
Shoamanesh A et al, ISC 2024

*The decrease with andexanet per 100 patients is estimated from the proportion difference, and the 95% CIs are Wald CIs.
CI, confidence interval; Q, quartile.

Case 1

75-year-old woman with atrial fibrillation on apixaban presenting with left putaminal ICH (volume: 24 mL) 2 hours following symptom onset. Pre-scan hematoma growth rate = 12 mL/hour (24/2)

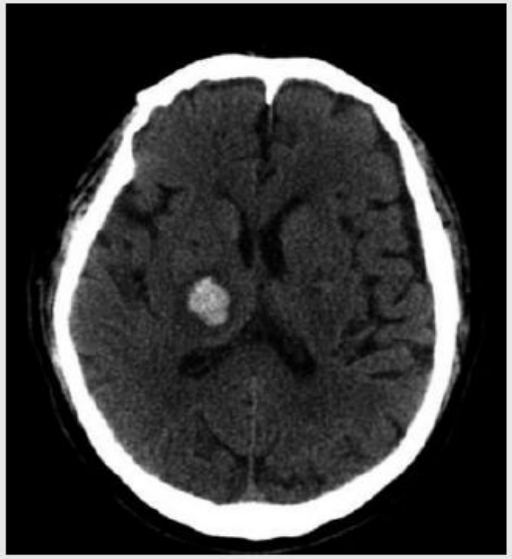
- **Risk of expansion***: 59%
- **NNT with andexanet to prevent expansion**: 4
- **NNH to cause thrombotic event**: ~26



Case 2

81-year-old man with remote history of unprovoked DVT on rivaroxaban presenting with right thalamic ICH (volume: 5.9 mL) 5 hours following symptom onset. Pre-scan hematoma growth rate = 1.18 mL/hour (5.9/5)

- **Risk of expansion***: 20%
- **NNT with andexanet to prevent expansion**: 8
- **NNH to cause thrombotic event**: ~26



*Risk of expansion is based on estimation from subgroup analysis of rate of hematoma expansion by pre-scan hematoma growth rate quartile presented previously (slide 14).

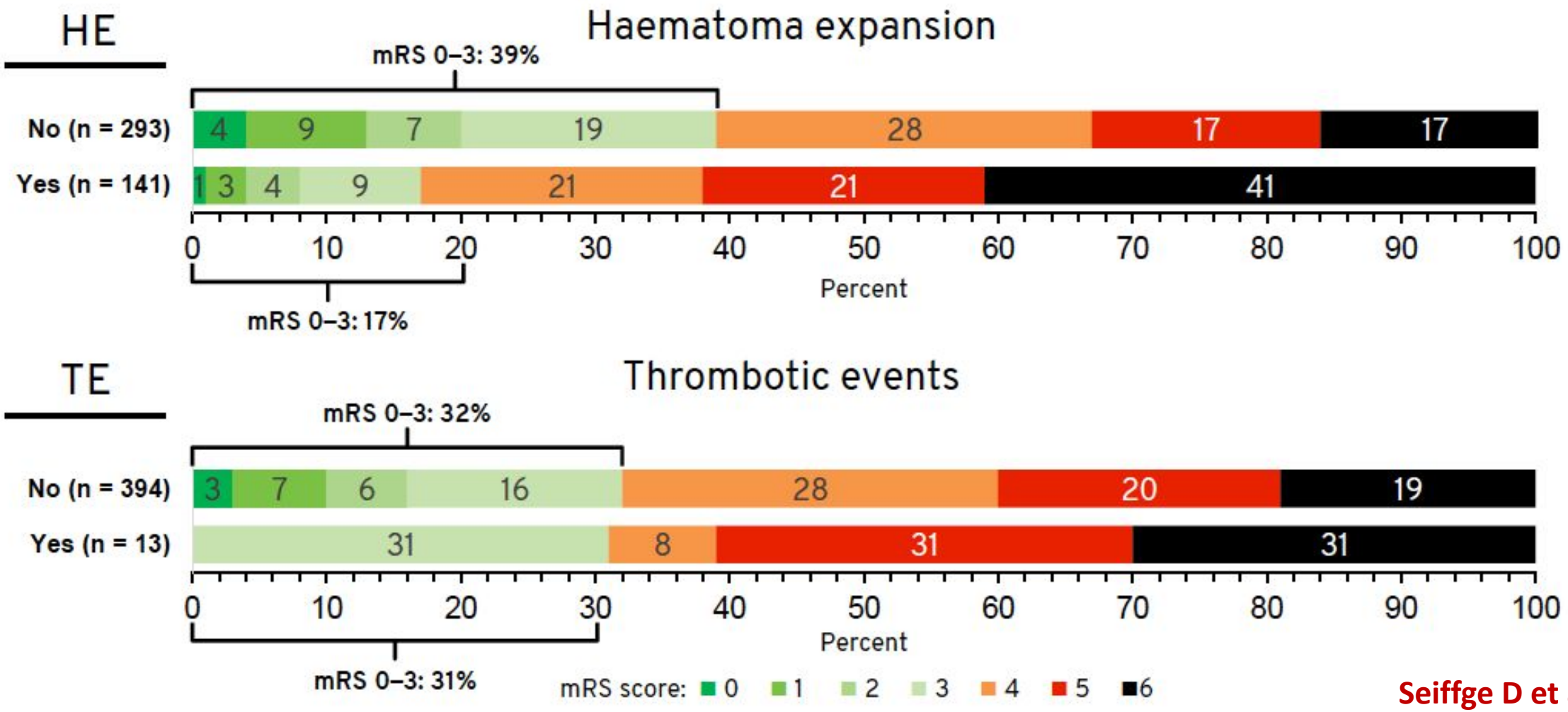
DVT, deep vein thrombosis; ICH, intracerebral hemorrhage; NNH, number needed to harm; NNT, number needed to treat.

Objective

To evaluate the clinical consequences of haematoma expansion and thrombotic events on all-cause mortality and functional outcomes to inform risk/benefit analyses

Seiffge D et al, 2024

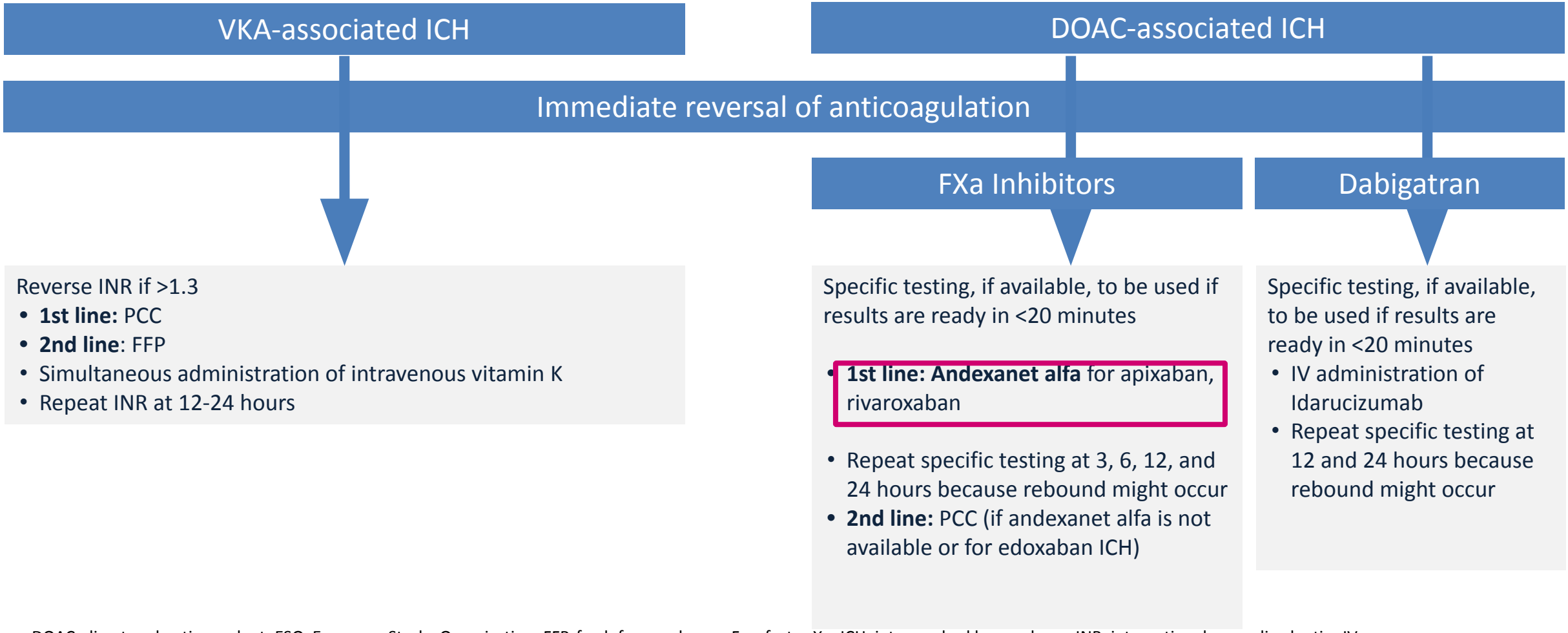
Landmark Analysis: mRS Scores at Day 30



Seiffge D et al, 2024

*For haematoma expansion, mRS was evaluable in 434 patients. For thrombotic events, mRS was evaluable in 407 patients.
HE, haematoma expansion; mRS, modified Rankin Scale; TE, thrombotic event.

ESO: Guidelines on Management of Anticoagulation-Related Intracerebral Hemorrhage

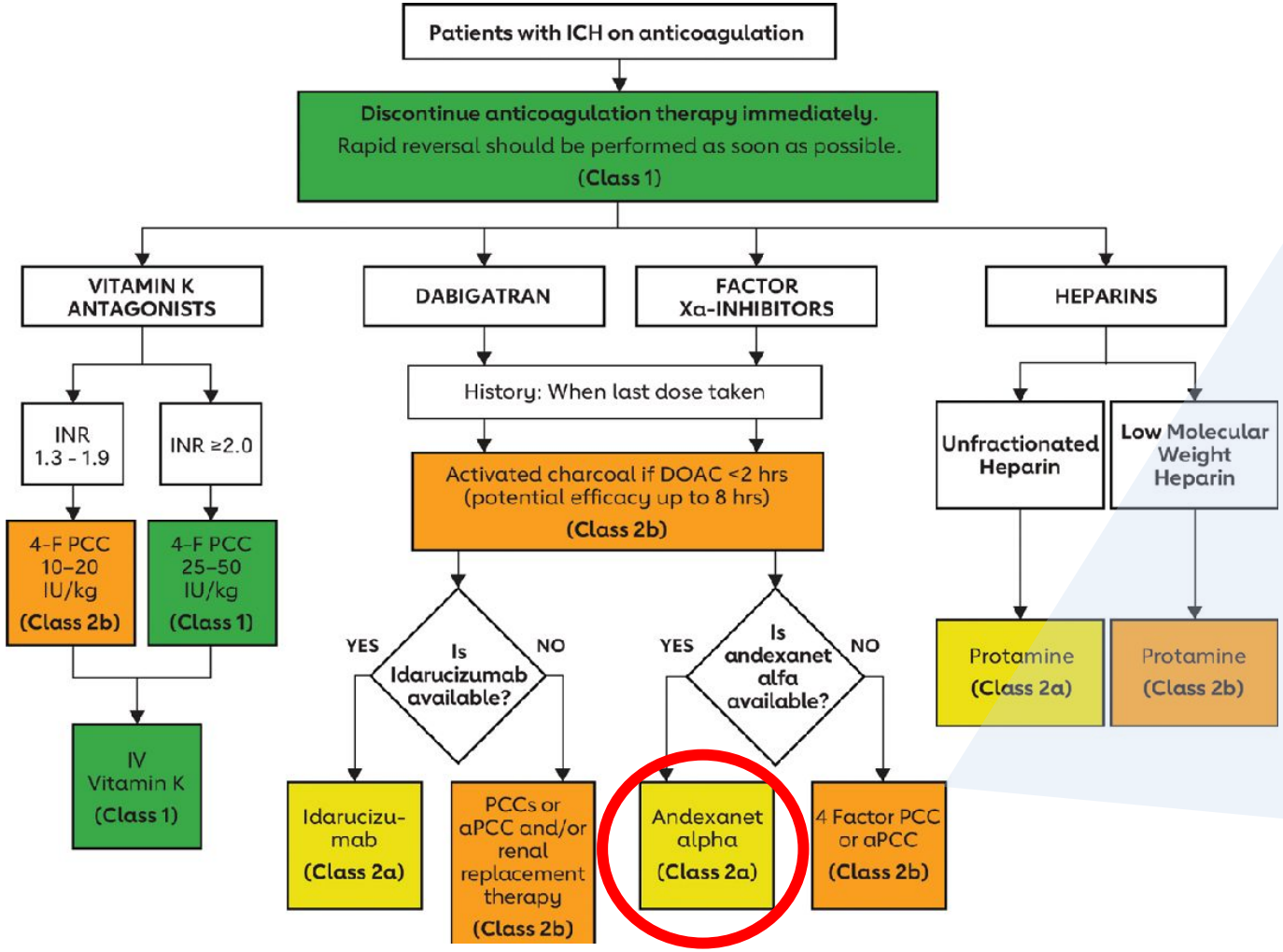


DOAC, direct oral anticoagulant; ESO, European Stroke Organization; FFP, fresh frozen plasma; Fxa, factor Xa; ICH, intracerebral hemorrhage; INR, international normalized ratio; IV, intravenous; PCC, prothrombin complex concentrate; VKA, vitamin k antagonist.

Christensen H et al. *Eur Stroke J*. 2019;4(4):294-306.

AHA/ASA 2022 Guideline for the Management of Patients With Spontaneous Intracerebral Hemorrhage

A Guideline From the American Heart Association/American Stroke Association



CLASS (STRENGHTS) of RECOMMENDATION

CLASS 2a (MODERATE) — **Benefit >> Risk**

Suggested phrases for writing recommendations:

- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

CLASS 2b (WEAK) — **Benefit ≥ Risk**

Suggested phrases for writing recommendations:

- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well-established

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

Greenberg 2022 - Stroke. 2022;53:00–00

Conclusioni

- ANNEXa-I è il solo RCT su agente reversal vs usual care nell'emorragia cerebrale da DOAC
- Andexanet alfa ha consentito di raggiungere emostasi efficace rispetto alla usual care
- Mortalità a 30 gg +2.3% e mRS 0-2 a 30 gg - 2.9%, ma:
  - ✔ Follow-up a 30 giorni poco indicativo: meglio a 90 o 180 giorni
  - ✔ Pazienti andexanet alfa con più FA e diabete e volume basale ematoma di poco maggiore
  - ✔ Somministrazione ultra-precoce forse più efficace: door-to-needle come per trombolisi?
- Eventi trombotici: +4.6%, ma:
  - ✔ Usual care: 14.5% no PCC (nulla o che altro?)
  - ✔ PCC: dose a scelta dei clinici (possibile sottodosaggio)
  - ✔ Effetto reversal PCC molto scarso: riduzione attività antiXa solo 23%
  - ✔ Timing evento trombotico rispetto a ripresa/non ripresa di terapia anticoagulante?
- Andexanet alfa unico agente reversal per apixaban e rivaroxaban approvato da FDA/EMA per pazienti con emorragie da anti-Xa: farmaco "disease modifying" con effetti a medio-lungo termine da verificare in registri di "mondo reale"
- Terapia reversal non trattamento "standalone" ma parte integrante di un "bundle of care" con controllo/terapia di pressione arteriosa, glicemia, temperatura corporea, eventuale Nch