Optimizing Your Pharmacologic Approach to Reversing Anticoagulation for ICH

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Resource Information

About This Resource

These slides are one component of a continuing education program available online at MedEd On The Go titled What's New in Treating the Anticoagulated Patient with ICH?

Program Learning Objectives:

- Describe the various therapies necessary to manage the care of anticoagulated patients with ICH in the neurocritical care setting, including reversal and repletion
- Illustrate the latest neurosurgical clinical trial data to optimize care for patients with ICH
- Categorize the specific recommendations from the recent ESO guidelines on the management of ICH in the anticoagulated patient and describe approaches to implement them
- Outline the 3 elements of ICH care bundling and how each optimizes the care of the anticoagulated patient

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Poll: What is the most important criteria for a reversal agent for the treatment of anticoagulation-associated ICH?

A. Hemostatic efficacy
B. Safety
C. Availability
D. Price/costs

David Seiffge
@DavidSeiffge

What is the most important criteria for a reversal agent to be used to treat hyperacute intracerebral haemorrhage in a patient on therapeutic anticoagulation?

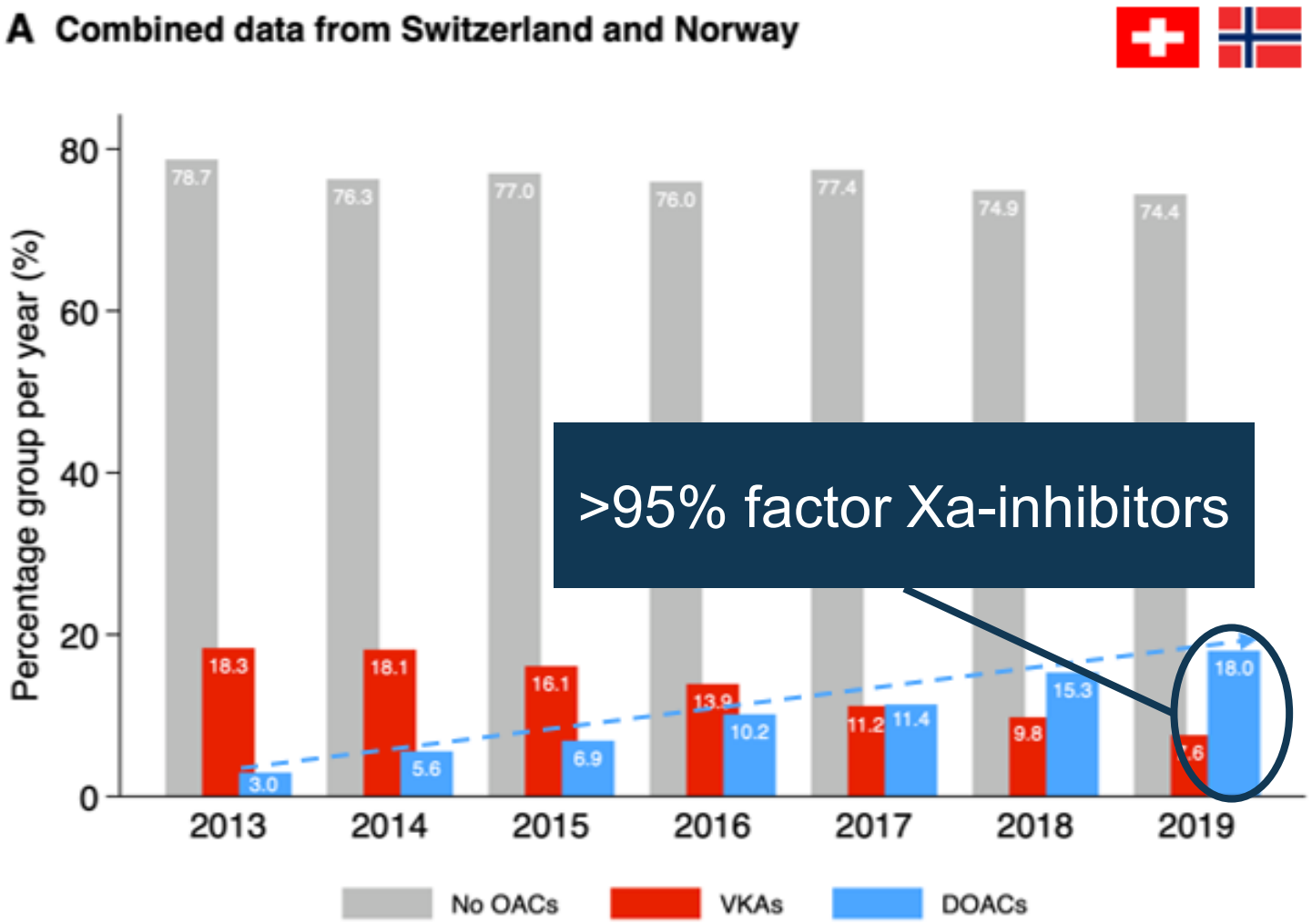
Post übersetzen

Haemostatic efficacy	51%
Safety	23%
Price/costs	5%
Availability	21%

167 Votes · 2 Tage 13 Stunden übrig

09:44 · 04.05.24 Aus Earth · **2.1K** Mal angezeigt

The Changing Spectrum of OAC–ICH



Siepen BM, Forfang E, Branca M, et al. *Stroke Vasc Neurol*. 2024:svn-2023-002813.

Prothrombin Complex Concentrate (PCC)

Specifications:

- Contains Vit K dependent coagulation factors derived from human plasma
- Standardized on factor IX only, virtually no factor X
- No direct effect on anti-FXa activity
- Approved for repletion of acquired coagulation factor deficiency induced by Vit K antagonists
- Not approved for treatment of FXa inhibitors

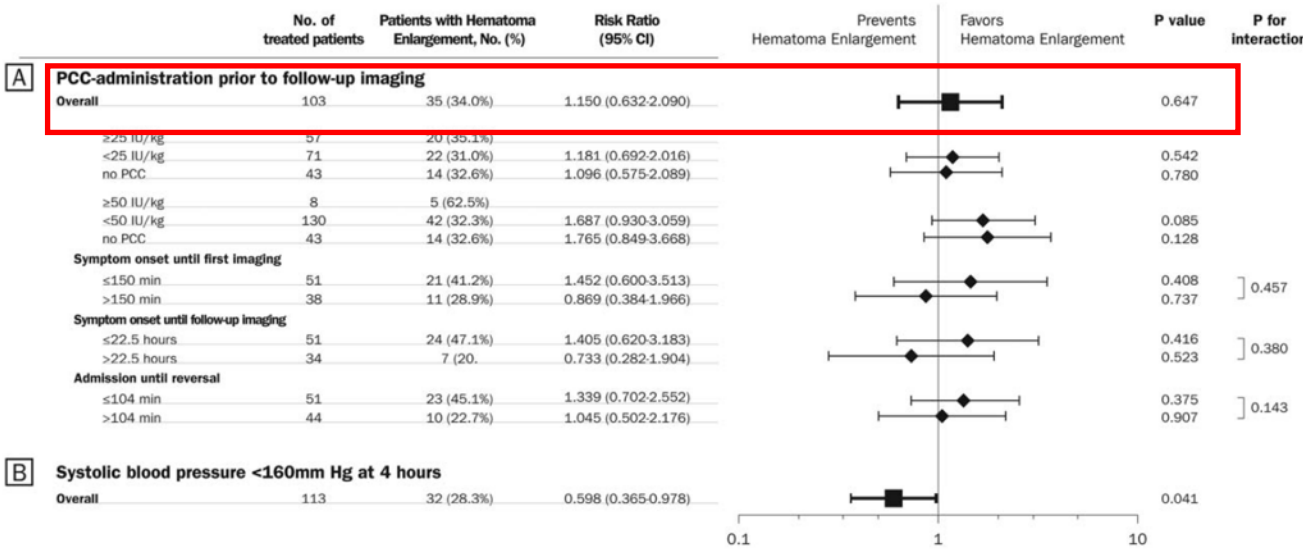


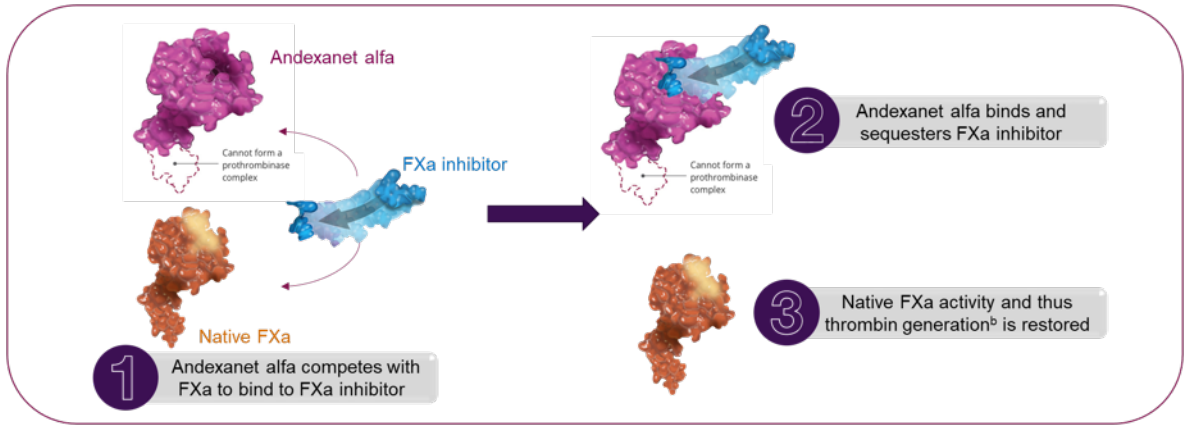
Table 2. Weighted Regression of Study Outcomes

Outcomes	Prothrombin complex concentrate (n = 85) vs conservative management (referent, n = 97) aOR (95% CI)	*P* value
Good neurological recovery at 90 d	0.62 (0.33-1.16)	.14
Mortality at 90 d	1.03 (0.70-1.53)	.88
In-hospital mortality	1.11 (0.69-1.79)	.66
Hematoma expansion[a]	0.94 (0.38-2.31)	.90

No effect of PCC on outcomes in FXaI-ICH in observational studies

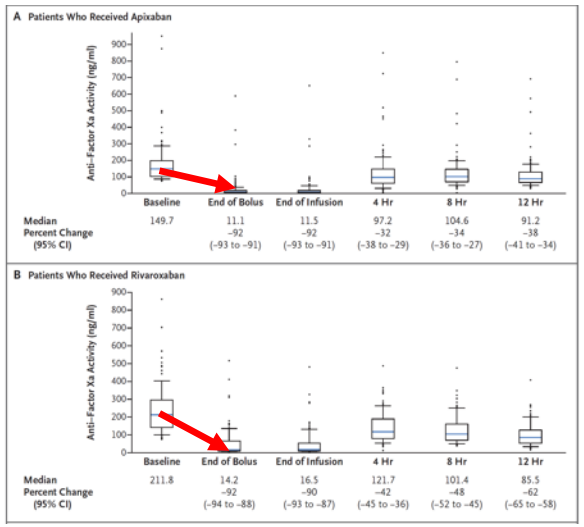
Gerner ST, Kuramatsu JB, Sembill JA,et al. *Ann Neurol*. 2018;83(1):186-196.
Ip B, Pan S, Yuan Z, et al. *JAMA Netw Open*. 2024;7(2):e2354916.

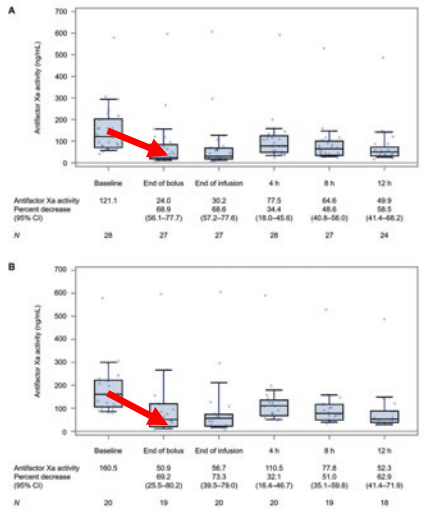
Andexanet Alfa - Recombinant Modified Human Factor Xa



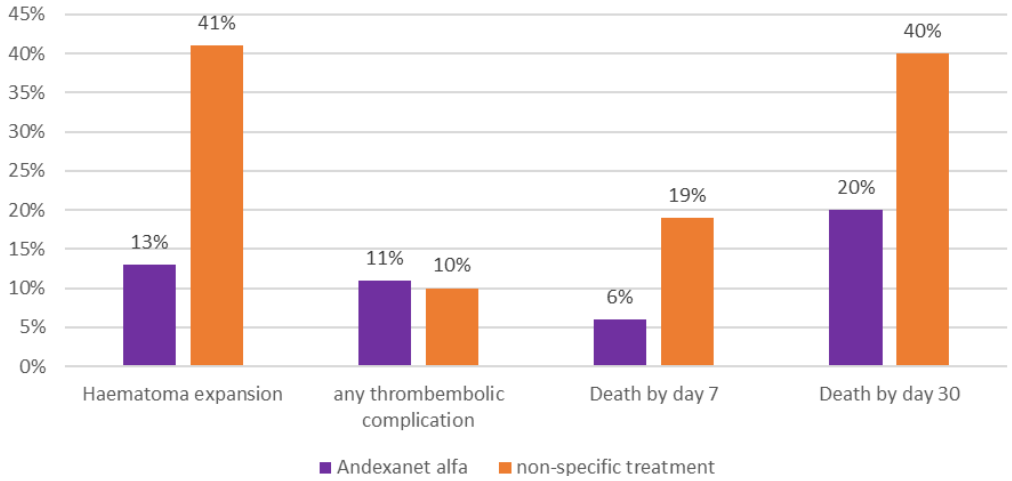
Specifications:

- Designed to reverse anticoagulant effects of FXa inhibitors
- Acts as a FXa decoy to bind molecules that target and inhibit FXa





Matched comparison:
ANNEXA-4 vs. non-specific treatment (TICH-NOAC)



Connolly SJ, Crowther M, Eikelboom JW, et al. *N Engl J Med*. 2019;380(14):1326-1335; Benz AP, Xu L, Eikelboom JW, et al. *Thromb Haemost*. 2022;122(6):998-1005; Siepen BM, Forfang E, Branca M, et al. *Stroke Vasc Neurol*. 2024:svn-2023-002813.

ANNEXA-I RCT

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:[1]

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

Select Safety Endpoints:[2]

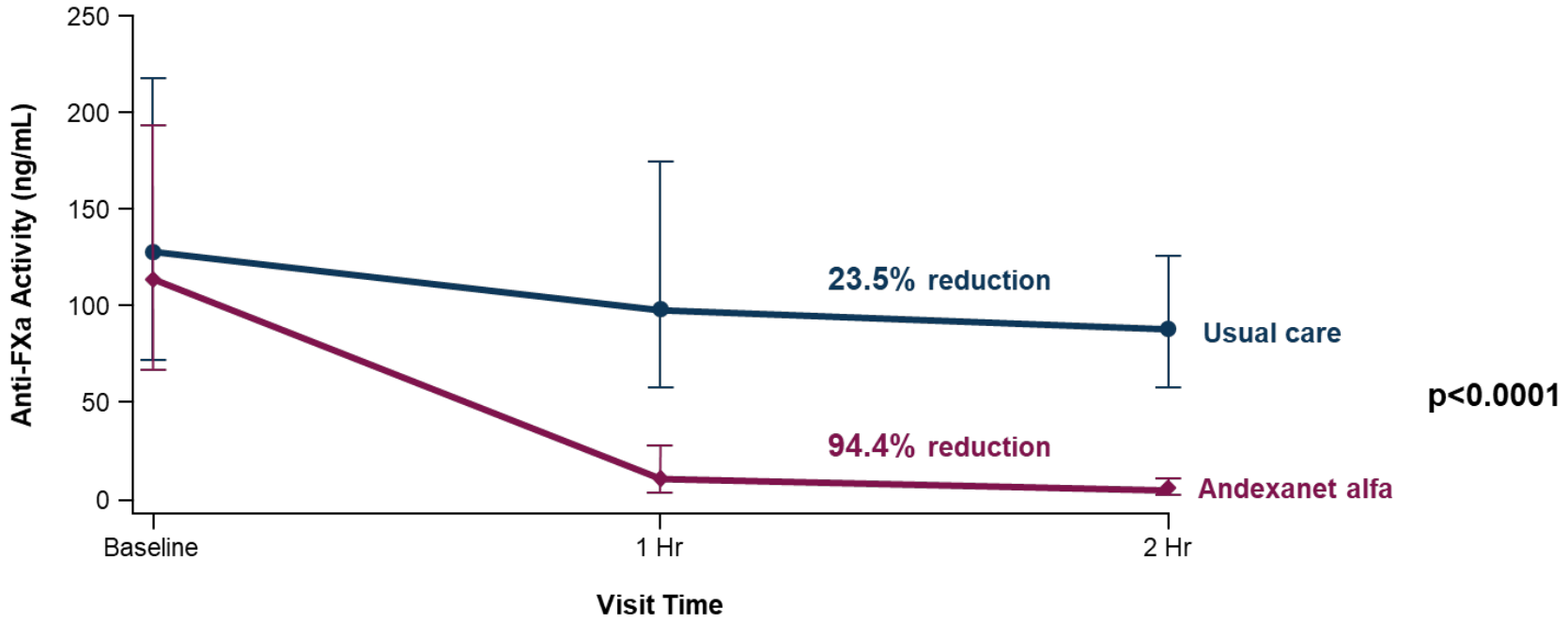
- Thrombotic events at 30 days
- 30-day mortality

ICrH, intracranial hemorrhage; NIHSS, National Institutes of Health Stroke Scale; R, randomized; RCT, randomized controlled trial.

1. Study NCT03661528. ClinicalTrials.gov website: https://clinicaltrials.gov/study/NCT03661528. 2. Connolly SJ. Presented at: World Stroke Congress (WSC); October 10-12, 2023; Toronto, Canada.

Anti-FXa Activity Was Significantly Reduced in Patients Treated with Andexanet Alfa Versus Usual Care

Secondary Endpoint: Change in Anti-FXa Activity From Baseline to Nadir at 2 Hours[1,a]



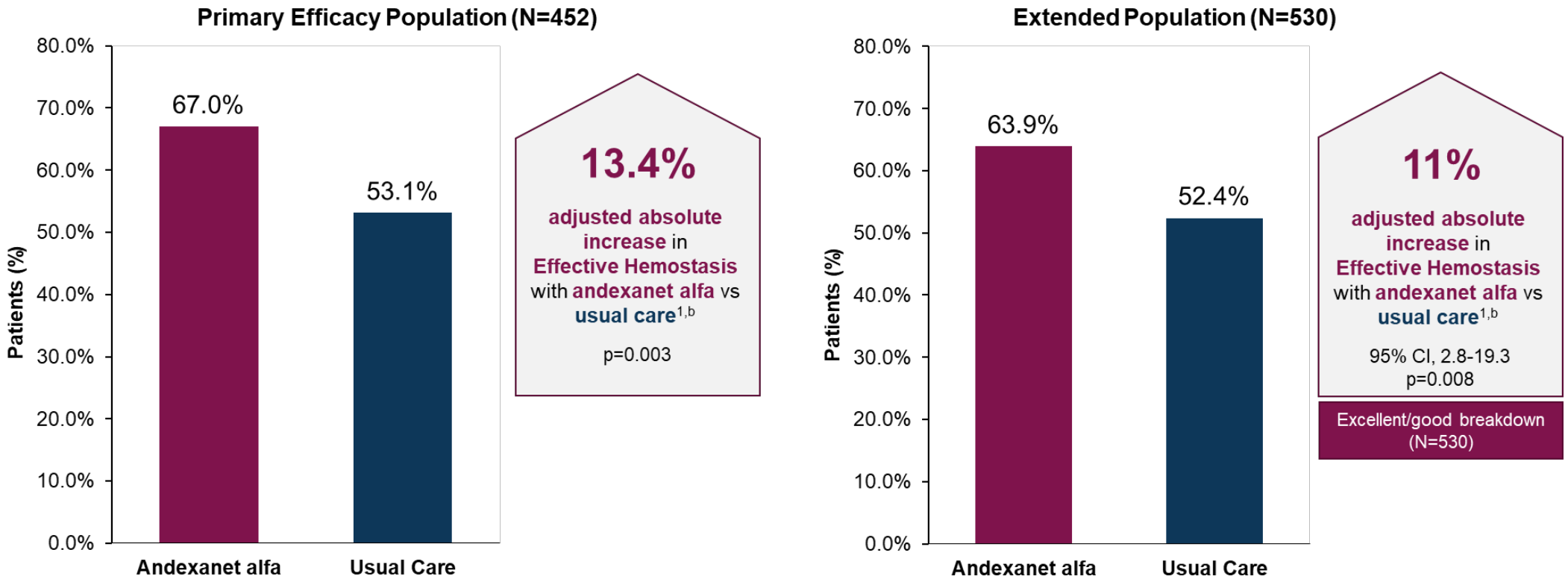
	Andexanet alfa	Usual care	Anti-FXa activity reduction with andexanet alfa (%), median (IQR)[a,b]
Patients on apixaban, n (%)	162 (61.6%)	158 (59.2%)	94.0% (96.4, 88.8)
Patients on rivaroxaban, n (%)	79 (30.0%)	75 (28.1%)	96.4% (97.9, 93.2)
Patients on edoxaban, n (%)*	22 (8.4%)	31 (11.6%)	72.3% (78.9, 37.4)

IQR, interquartile range.

1. Connolly SJ. Presented at: World Stroke Congress (WSC); October 10-12, 2023; Toronto, Canada.

Achievement of Effective Hemostasis Was Significantly Higher in Patients Treated With Andexanet Alfa Versus Usual Care

Primary Endpoint: Effective Hemostasis at 12 Hours[1,a]



[a]As determined by a blinded adjudication committee[2]; [b]Analysis was performed using a CMH test stratified by lime from symptom onset to baseline imaging assessment (<180 min)[3]
CI = confidence interval; CMH = Cochran-Mantel-Haenszel; FXa = factor Xa; ICrH = intracranial hemorrhage.

1. Connolly SJ. Presented at: World Stroke Congress (WSC); October 10-12, 2023; Toronto, Canada. 2. Study NCT03661528. ClinicalTrials.gov website: https://clinicaltrials.gov/study/NCT03661528. 3. Data on File. CSL ALXN2070 18-513.

Additional Outcomes

Extended Population (N=530)

	Andexanet alfa (n=263)	Usual care (n=267)	Adjusted absolute increase with andexanet alfa (95% CI)[d]
Excellent/good, n (%)[a]	**168 (63.9)**	**140 (52.4)**	**11.0 (2.8, 19.3)**
Excellent, n (%)[b]	147 (55.9)	121 (45.3)	10.6 (2.1, 19.0)
Good, n (%)[c]	21 (8.0)	19 (7.1)	0.9 (-3.6, 5.4)

	Andexanet alfa (n=263)	Usual care (n=267)	Absolute difference with andexanet alfa (95% CI)
Hematoma increase ≥12.5 mL, n (%)	29 (11.6)	48 (19.0)	-7.4 (-13.7, -1.1)
mRS score ≤3 at 30 days, n (%)	69 (28.0)	79 (30.9)	-2.9 (-10.9, 5.2)[a]

[a]Analysis for 30-day mRS score was performed using a CMH test stratified by time from symptom onset to baseline imaging assessment (<180 min vs ≥ 180 min). [b]Primary objective of study met at interim. [c]Excellent hemostatic efficacy was defined as NIHSS score of <7 from baseline to 12 hours plus a ≤20% increase in hematoma volume on repeat CT/MRI at 12 hours plus no rescue therapies administered between 3- and 12-hours post-randomization. [d]Analysis was performed using a CMH test stratified by time from symptom onset to baseline imaging assessment (<180 min vs ≥180 min).

CI = confidence interval; FXa = factor Xa; ICrH = intracranial hemorrhage; mRS = modified Rankin Scale

Connolly SJ. Presented at: World Stroke Congress (WSC); October 10-12, 2023; Toronto, Canada.

Safety Endpoints

Extended Population (N=530)

	Andexanet alfa (n=263)	Usual care (n=267)	Absolute difference with andexanet alfa (95% CI)[c]
Patients with ≥1 thrombotic event, n (%)[a,b]	27 (10.3)	15 (5.6)	4.6 (0.1, 9.2)
Transient ischemic attack, n (%)	0 (0)	0 (0)	-
Ischemic stroke, n (%)	17 (6.5)	4 (1.5)	5.0 (1.5, 8.8)
Myocardial infarction, n (%)	11 (4.2)	4 (1.5)	2.7 (-0.2, 6.1)
Deep vein thrombosis, n (%)	1 (0.4)	2 (0.7)	-0.4 (-2.4, 1.5)
Pulmonary embolism, n (%)	1 (0.4)	6 (2.2)	-1.9 (-4.5, 0.2)
Arterial systemic embolism, n (%)	3 (1.1)	2 (0.7)	0.4 (-1.7, 2.7)
All-cause mortality, n (%)[a,b]	73 (27.8)	68 (25.5)	2.3 (-5.2, 9.8)

[a]As determined by a blinded adjudication committee. [b]Evaluated through 30 days post-randomization.[2] [c]Analysis was performed using a CMH test stratified by time from symptom onset to baseline imaging assessment (<180 min vs ≥180 min).

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; FXa = factor Xa; ICrH = intracranial hemorrhage

1. Connolly SJ. Presented at: World Stroke Congress (WSC); October 10-12, 2023; Toronto, Canada. 2. Data on File. SAP 18-513

Rate of Thrombotic Events in Different Reversal Trials

Fresh frozen plasma versus prothrombin complex concentrate in patients with intracranial haemorrhage related to vitamin K antagonists (INCH): a randomised trial

Thorsten Steiner*, Sven Poli*, Martin Griebe, Johannes Hüsing, Jacek Hajda, Anja Freiberger, Martin Bendszus, Julian Bösel, Hanne Christensen, Christian Dohmen, Michael Hennerici, Jennifer Kollmer, Henning Stetefeld, Katja E Wartenberg, Christian Weimar, Werner Hacke, Roland Veltkamp

	FFP (n=23)		PCC (n=27)	Odds ratio (95% CI)*	p value†
	FFP only (n=4)‡	FFP plus PCC (after 3 h; n=19)‡§			
Number of patients with at least one SAE	2	8	16	0·65 (0·16–2·49)	0·55
Number of SAEs	5	15	23	N/A	N/A
SAE classified as haematoma expansion	2	7	7	N/A	N/A
SAE classified as haematoma expansion leading to death	2	4	1	N/A	N/A
Thromboembolic events¶					
Myocardial infarction	0	..	0	N/A	N/A
Ischaemic stroke	1	1	2	N/A	N/A
Pulmonary embolism	0	0	4	N/A	N/A
Deep vein thrombosis	0	0	1	N/A	N/A

FFP=fresh frozen plasma. N/A=not applicable. PCC=prothrombin complex concentrate. SAE=serious adverse event. *FFP plus PCC *vs* PCC only. †Fisher's exact test. ‡Two of 21 patients who did not reach the primary endpoint in the FFP did not receive PCC (protocol violation). §According to the protocol, patients in whom the international normalised ratio after 3 h was not below or equal to 1·2 received PCC. ¶One stroke in the FFP only group and one stroke and one pulmonary embolism in the PCC group occurred within the first 3 days after start of treatment.

Table 3: Safety outcomes

18%

Stroke

CLINICAL TRIAL

Tranexamic Acid for Intracerebral Hemorrhage in Patients on Non-Vitamin K Antagonist Oral Anticoagulants (TICH-NOAC): A Multicenter, Randomized, Placebo-Controlled, Phase 2 Trial

Alexandros A. Polymeris, MD, PhD; Grzegorz M. Karwacki, MD; Bernhard M. Siepen, MD; Sabine Schaedelin, MSc; Dimitrios A. Tsakiris, MD; Christoph Stippich, MD; Raphael Guzman, MD; Christian H. Nickel, MD; Nikola Sprigg, DM; Georg Kägi, MD; Jochen Vehoff, MD; Filip Baranka, MD, PhD; Sebastian Thilemann, MD; Marina Maurer; Benjamin Wagner, MD; Christopher Traenka, MD; Henrik Gensicke, MD; Gian Marco De Marchis, MD, MSc; Leo H. Bonati, MD; Urs Fischer, MD, MSc; Werner J. Z'Graggen, MD; Krassen Nedeltchev, MD; Susanne Wegener, MD; Philipp Baumgartner, MD; Stefan T. Engelter, MD*; David J. Seiffge, MD*; Nils Peters, MD*; Philippe A. Lyrer, MD*; for the TICH-NOAC Investigators†

Table 2. Primary and Secondary Outcomes in the Intention-to-Treat Population

	TXA (n=32)	Placebo (n=31)	Effect size (95% CI)	*P* value
Primary outcome				
HE*	12 (38%)	14 (45%)	0.63 (0.22 to 1.82)†	0.40
Secondary outcomes				
Symptomatic HE*	9 (28%)	9 (29%)	0.86 (0.28 to 2.66)†	0.79
Absolute hematoma volume change, mL*	3.3 (0.6–8.8)	1.8 (0.1–8.7)	−0.33 (−3.80 to 3.14)†	0.85
Ordinal mRS score at 90 d			1.11 (0.44 to 2.80)†	
0	0 (0%)	0 (0%)		
1	2 (6%)	3 (10%)		
2	3 (9%)	3 (10%)		
3	3 (9%)	3 (10%)		
4	6 (19%)	7 (23%)		
5	3 (9%)	2 (6%)		
6	15 (47%)	13 (42%)		
mRS score 0–4 at 90 d	14 (44%)	16 (52%)	0.81 (0.29 to 2.27)†	0.69
mRS score 0–3 at 90 d	8 (25%)	9 (29%)	0.87 (0.28 to 2.70)†	0.81
In-hospital death‡	8 (25%)	6 (19%)	1.30 (0.39 to 4.39)†	0.67
Death within 90 d‡	15 (47%)	13 (42%)	1.07 (0.37 to 3.04)†	0.91
Major thromboembolic events within 90 d	4 (13%)	2 (6%)	1.86 (0.37 to 9.50)	0.45
Ischemic stroke	0	2		
Myocardial infarction	2§	0		
Deep vein thrombosis/pulmonary embolism	3§	0		
Neurosurgical intervention up to day 2	2 (6%)	0 (0%)	...	...

10%

ANNEXa I

Extended Population (N=530)

	Andexanet alfa (n=263)	Usual care (n=267)	Absolute difference with andexanet alfa (95% CI)
Patients with ≥1 thrombotic event, n (%)	27 (10.3)	15 (5.6)	4.6 (0.1, 9.2)
Transient ischemic attack, n (%)	0 (0)	0 (0)	-
Ischemic stroke, n (%)	17 (6.5)	4 (1.5)	5.0 (1.5, 8.8)
Myocardial infarction, n (%)	11 (4.2)	4 (1.5)	2.7 (-0.2, 6.1)
Deep vein thrombosis, n (%)	1 (0.4)	2 (0.7)	-0.4 (-2.4, 1.5)
Pulmonary embolism, n (%)	1 (0.4)	6 (2.2)	-1.9 (-4.5, 0.2)
Arterial systemic embolism, n (%)	3 (1.1)	2 (0.7)	0.4 (-1.7, 2.7)
All-cause mortality, n (%)	73 (27.8)	68 (25.5)	2.3 (-5.2, 9.8)

Andexanet alfa

10%

Usual care

6%

Steiner T, Poli S, Griebe M, et al *Lancet Neurol*. 2016;15(6):566-73; Polymeris AA, Karwacki GM, Siepen BM, et al. *Stroke*. 2023;54(9):2223-2234; Connolly SJ. Presented at: World Stroke Congress (WSC); October 10-12, 2023; Toronto, Canada.

Multiple Choice Question

For patients enrolled in the ANNEXa-I trial with ICH who received andexanet alfa, which of the following was NOT observed when compared to usual care patients:

A. Anti-Factor Xa levels were reduced by 94.4%
B. No rescue therapy was necessary between 3 and 12 hours after randomization
C. An increase in intracranial hematoma size occurred in more patients
D. Clinical outcomes were defined as excellent (55.9%) and good (8%)

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