ESO Guidelines for the Management of ICH in the Anticoagulated Patient

Thorsten Steiner, MD, PhD, MME

Head of Department of Neurology

Varisano Klinik Frankfurt Höchst, Frankfurt

Faculty member, Department of Neurology, Heidelberg University Hospital

Heidelberg, Germany

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

MedEd On The Go®

www.mededonthego.com

Disclaimer

The views and opinions expressed in this educational activity are those of the faculty and do not necessarily represent the views of Total CME, LLC, the CME providers, or the companies providing educational grants. This presentation is not intended to define an exclusive course of patient management; the participant should use their clinical judgment, knowledge, experience, and diagnostic skills in applying or adopting for professional use any of the information provided herein. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patient's conditions and possible contraindications or dangers in use, review of any applicable manufacturer’s product information, and comparison with recommendations of other authorities. Links to other sites may be provided as additional sources of information.

Structure of the Topics of Haemostatic Therapies in Acute ICH

Haemostatic therapies

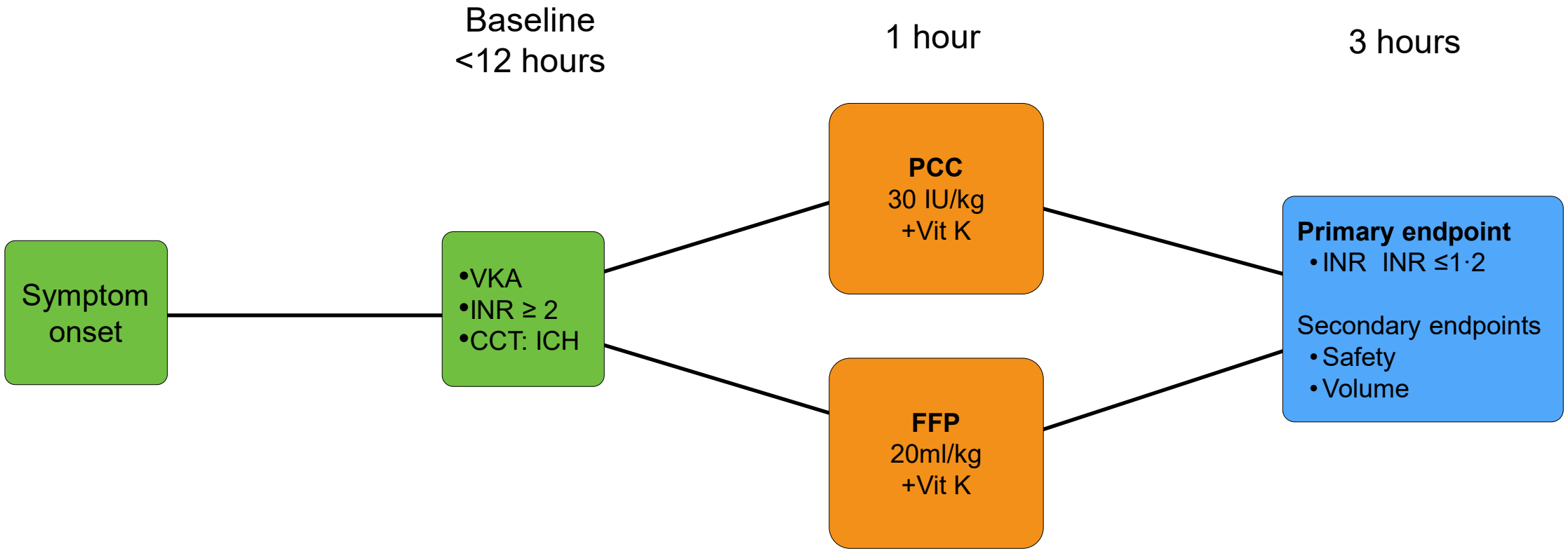
1. **Spontaneous** ICH
    1. not associated with antithrombotic drug use
        1. FVIIa
        2. Antifibrinolytic drugs
    2. associated with antiplatelet drug use
        1. Platelet transfusion
2. **Anticoagulant**-associated ICH
        1. PCC versus FFP for anticoagulant-associated ICH (vitamin K-antagonists)
        2. Andexanet vs. usual care for anticoagulant-associated ICH factor Xa inhibitors
        3. Tranexamic acid vs. usual care for anticoagulant-associated ICH factor Xa inhibitors
        4. Idarucizumab for anticoagulant-associated ICH (factor IIa inhibitor)

Haemostatic Therapies

Haemostatic therapies

1. Spontaneous ICH
    1. not associated with antithrombotic drug use
        1. FVIIa
        2. Antifibrinolytic drugs
    2. associated with antiplatelet drug use
        1. Platelet transfusion
2. **Anticoagulant-associated ICH**
        1. **PCC versus FFP for anticoagulant-associated ICH (vitamin K-antagonists)**
        2. Andexanet vs. usual care for anticoagulant-associated ICH factor Xa inhibitors
        3. Tranexamic acid vs. usual care for anticoagulant-associated ICH factor Xa inhibitors
        4. Idarucizumab for anticoagulant-associated ICH (factor IIa inhibitor)

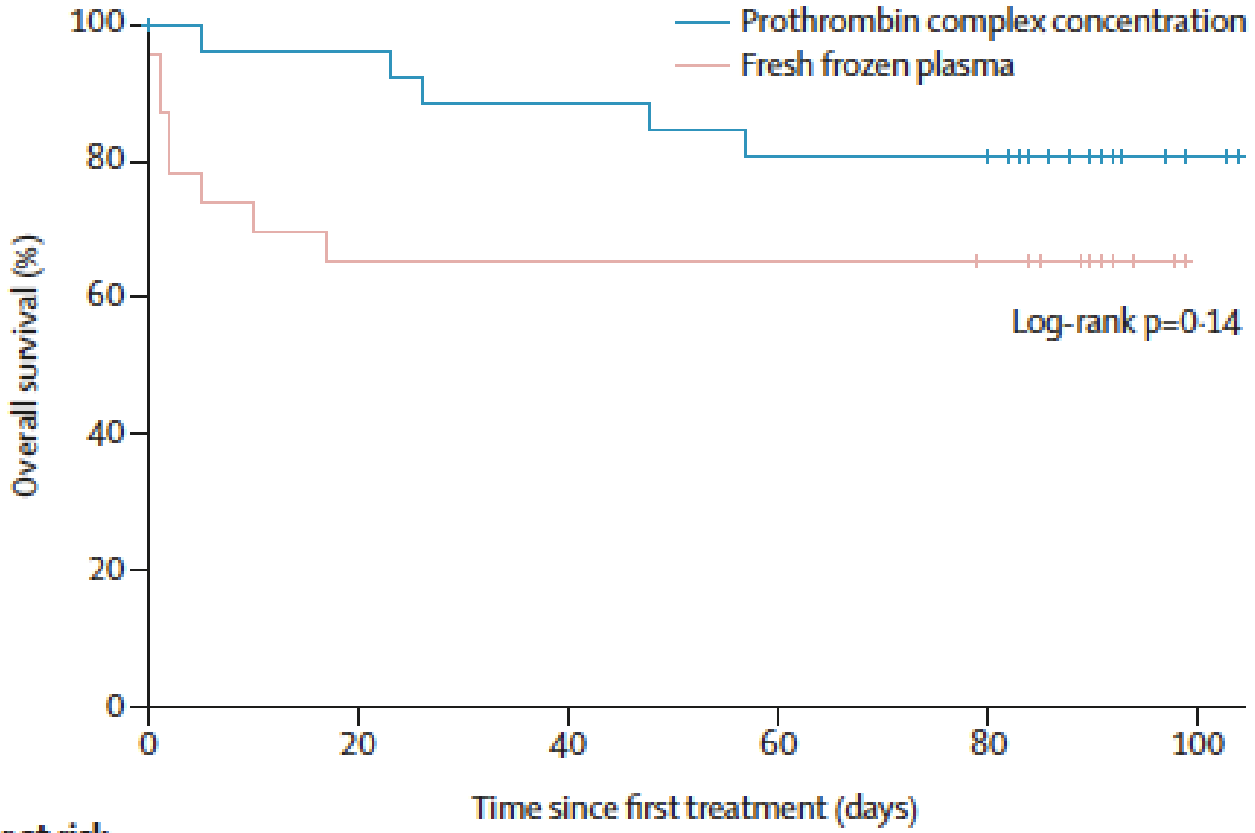
Design and Intervention



PCC: 4-factor PCC; FFP: Fresh Frozen Plasma; INR: international Normalized Ratio; VKA: Vitamin K antagonists; ICH: Intracranial Hemorrhage; CCT cerebral computed tomography, mRS: modified Rankin Score

Steiner T, Poli S, Griebe M, et al. *Lancet Neurol*. 2016;15(6):566-73.

Survival



Number at risk							
Prothrombin complex concentration	27	25	23	23	21	21	14
Fresh frozen plasma	23	16	15	15	15	15	10

4-factor PCC:
30 IU/kg if INR ≥ 2.0 and
10 IU/kg if 1.3 ≤ INR < 2.0
+Vit-K 10 mg

Steiner T, Poli S, Griebe M, et al. *Lancet Neurol*. 2016;15(6):566-73.

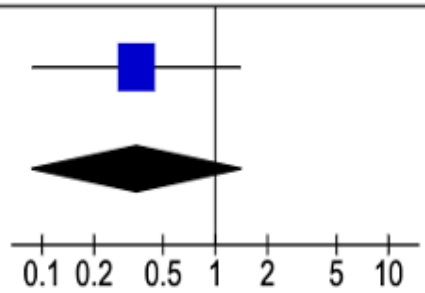
PICO 3.1.1: Haemorrhage Expansion by 24 Hours

Study or Subgroup	Prothrombin complex concentrates Events	Total	Fresh frozen plasma Events	Total	Weight	Odds ratio M-H, Random, 95% CI
Steiner, 2016 (INCH)	6	21	8	15	100.0%	0.35 [0.09 , 1.40]
Total (95% CI)		**21**		**15**	**100.0%**	**0.35 [0.09 , 1.40]**
Total events:	6		8			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.48 (P = 0.14)

Test for subgroup differences: Not applicable



Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

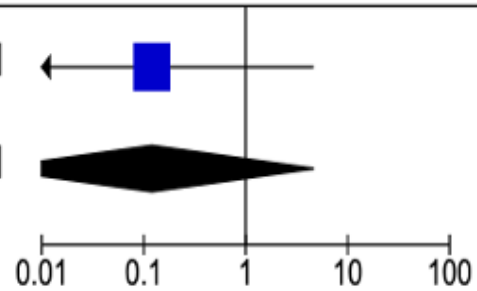
(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

3.1.1: All Serious Adverse Events

Study or Subgroup	Prothrombin complex concentrates Events	Total	Fresh frozen plasma Events	Total	Weight	Odds ratio M-H, Random, 95% CI	Odds ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Boulis, 1999	0	2	2	3	100.0%	0.12 [0.00 , 4.61]		? ? - - - ?
Total (95% CI)		**2**		**3**	**100.0%**	**0.12 [0.00 , 4.61]**		
Total events:	0		2					



Heterogeneity: Not applicable

Test for overall effect: Z = 1.14 (P = 0.25)

Test for subgroup differences: Not applicable

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

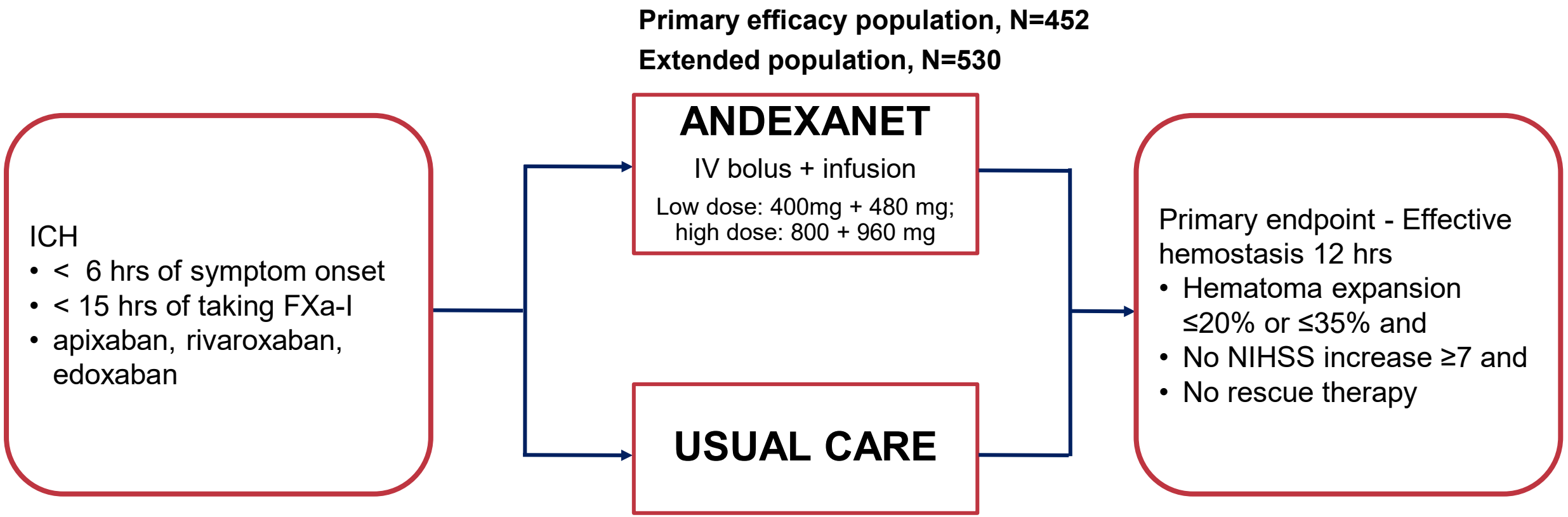
(G) Other bias

Haemostatic Therapies

Haemostatic therapies

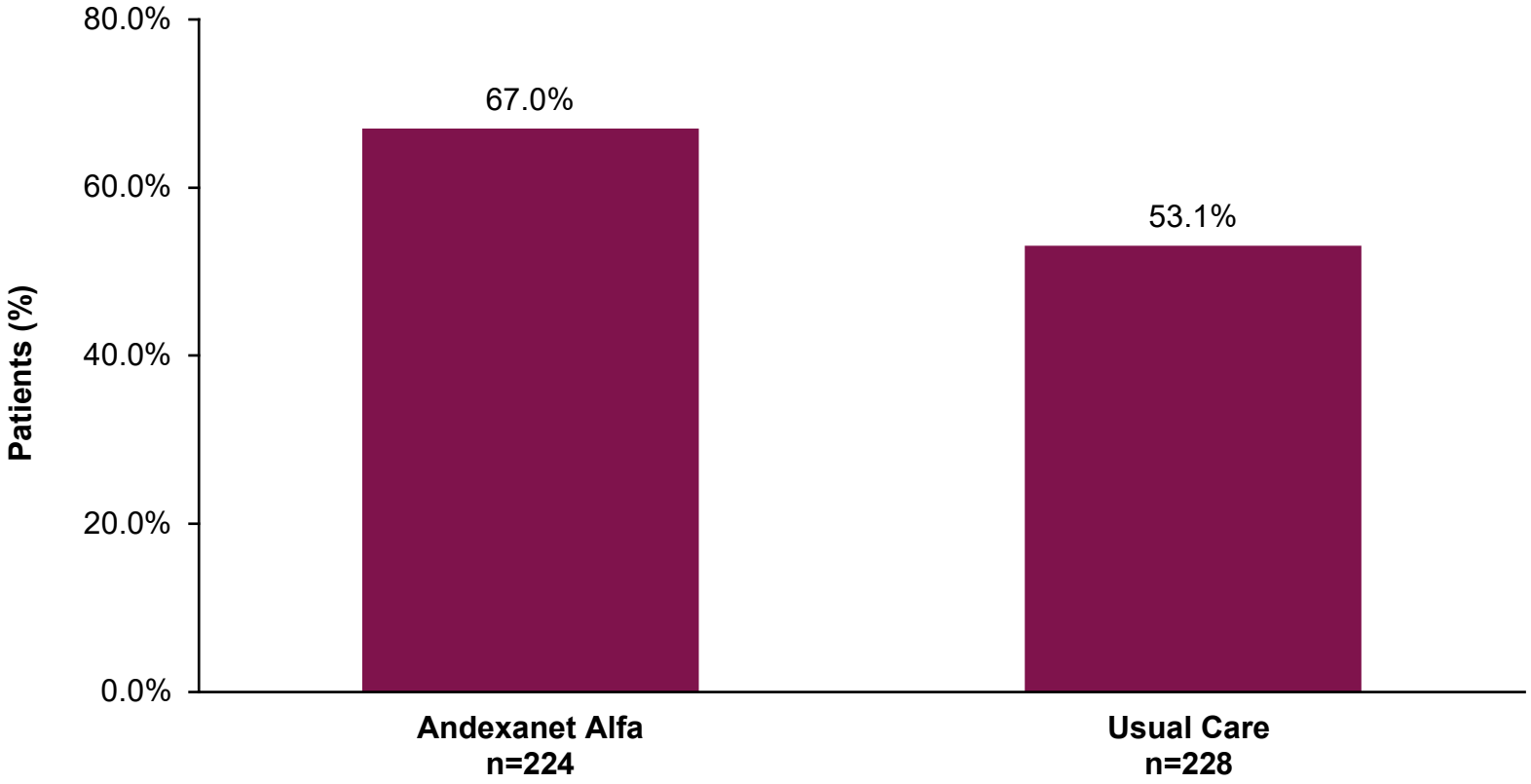
1. Spontaneous ICH
    1. not associated with antithrombotic drug use
        1. FVIIa
        2. Antifibrinolytic drugs
    2. associated with antiplatelet drug use
        1. Platelet transfusion
2. Anticoagulant-associated ICH
        1. PCC versus FFP for anticoagulant-associated ICH (vitamin K-antagonists)
        2. **Andexanet** vs. usual care for anticoagulant-associated ICH factor Xa inhibitors
        3. Tranexamic acid vs. usual care for anticoagulant-associated ICH factor Xa inhibitors
        4. Idarucizumab for anticoagulant-associated ICH (factor IIa inhibitor)

ANNEXa-I Study Design



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

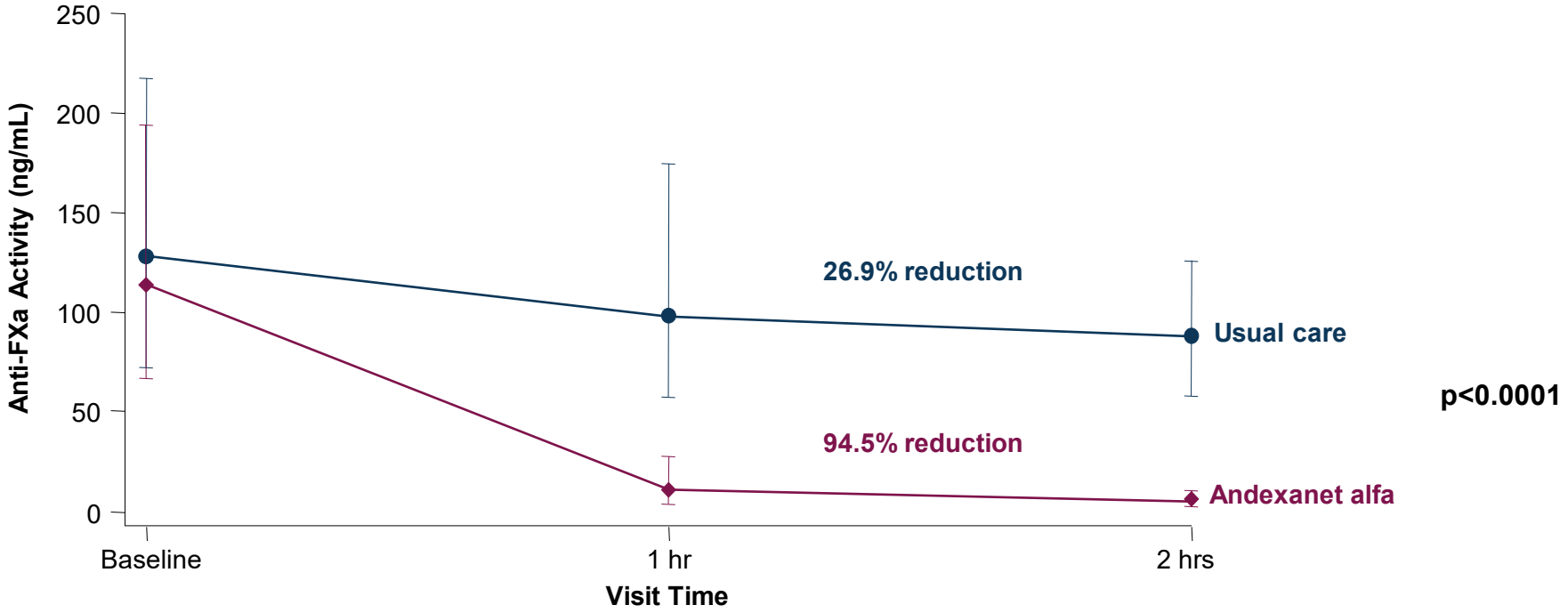
Primary Efficacy Endpoint: Effective Hemostasis at 12 Hours, (N=452)



13.4%
adjusted absolute increase
in **effective hemostasis**
with **andexanet alfa**
vs **usual care**[b]
95% CI, 4.6-22.2
p=0.003

[a]As determined by a blinded adjudication committee[2];
[b]Analysis was performed using a CMH test stratified by time from symptom onset to baseline imaging assessment (<180 minutes vs ≥180 minutes).
CI = confidence interval; CMH = Cochran-Mantel-Haenszel.
Connolly SJ. Presented at: World Stroke Congress (WSC); October 10-12, 2023

Secondary Endpoint: Median Reduction in Anti-FXa Activity From Baseline to Nadir at 2 Hours[a,b]



	Andexanet alfa (n=224)	Usual care (n=228)
	Change from baseline (%), median (IQR)[b]	**Change from baseline (%), median (IQR)[b]**
Apixaban (N=254)	-94.2 (-96.3, -89.8)	-20.5 (-41.7, -6.2)
Rivaroxaban (N=115)	-96.4 (-97.9, -93.3)	-48.7 (-66.8, -20.9)
Edoxaban (N=43)	-71.8 (-77.8, -59.6)	-17.0 (-38.0, -4.6)

[a]Nadir was defined as the minimum value of the post 1- and 2-hour assessment. If either value was missing, then the nadir was missing; [b]Analysis was performed with ANCOVA on the ranked data, including time from symptom onset to baseline imaging scan (<180 minutes vs ≥180 minutes) and baseline anti-FXa activity as covariates. Patients with missing anti-FXa levels were excluded and missing values at 1 and 2 hours were imputed by multiple imputations (100 times).

ANCOVA = Analysis of Covariance; FXa = factor Xa; hr = hour; ICH = intracerebral hemorrhage; IQR = interquartile range.

Connolly et al. *N Engl J Med*. 2024. In press (Supplementary materials).

Safety Data: Thrombotic Events and Mortality

Parameter	Total (N = 503) n (%)	Andexanet (N=263) n (%)	Usual care (N=267) n (%)	Increase with andexanet per 100 patients (95% CI)	P-value+
No pts with at ≥ 1 TE	42 (7.9)	27 (10.3)	15 (5.6)	4.6 (0.1, 9.2)	**0.048**
TIA	0	0 (0)	0 (0)	-	
Ischemic Stroke	21 (4.0)	**17 (6.5)**	4 (1.5)	5.0 (1.5, 8.8)	
MI	15 (2)	**11 (4.2)**	4 (1.5)	2.7 (-0.2, 6.1)	
DVT	3 (0.6)	1 (0.4)	2 (0.7)	-0.4 (-2.4, 1.5)	
Pulmonary Embolism	7 (1.3)	1 (0.4)	6 (2.2)	-1.9 (-4.5, 0.2)	
Arterial Systemic Embolism	5 (0.9)	3 (1.1)	2 (0.7)	0.4 (-1.7, 2.7)	
Death	141 (26.6)	73 (27.8)	68 (25.5)	2.3 (-5.2, 9.8)	0.512

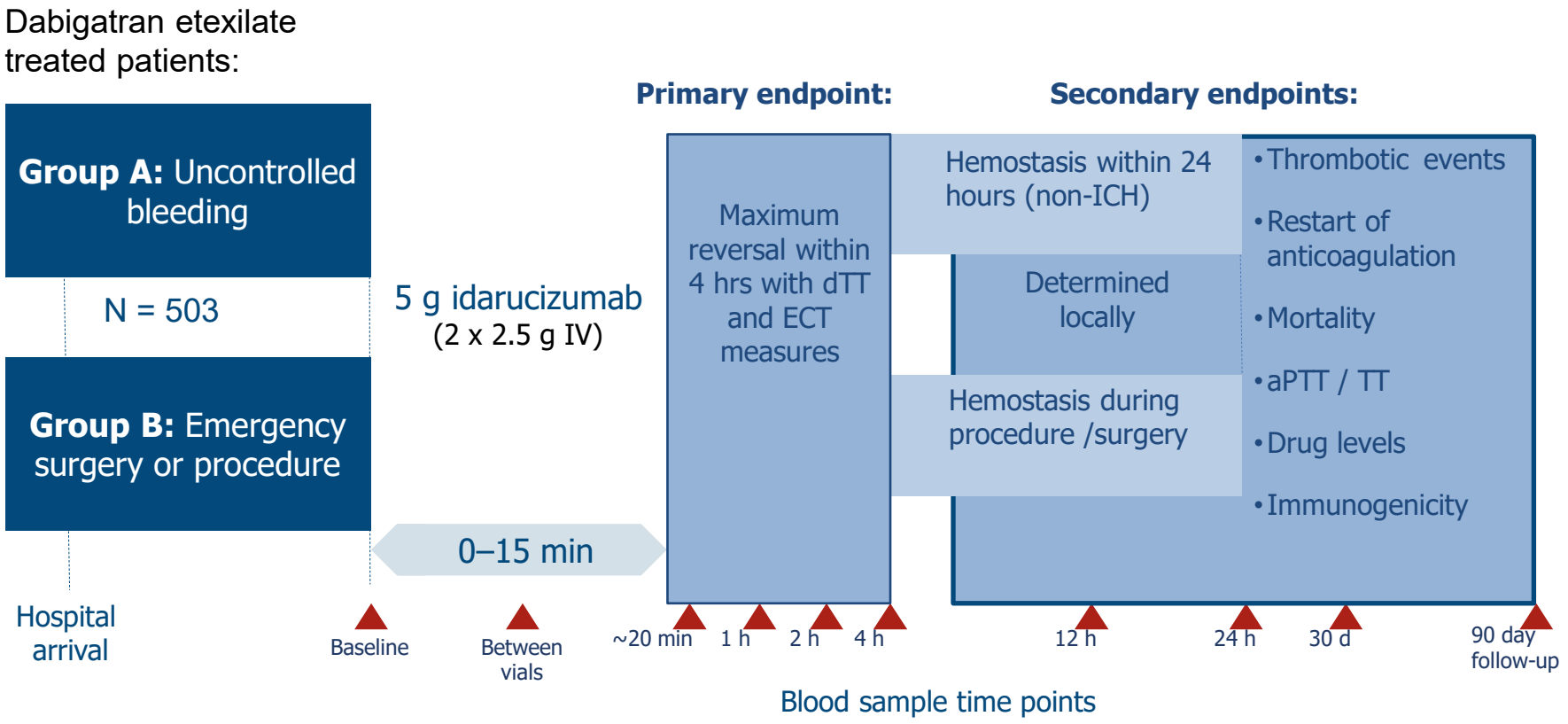
Connolly SJ. Presented at: World Stroke Congress (WSC); October 10-12, 2023

Haemostatic Therapies

Haemostatic therapies

1. Spontaneous ICH
    1. not associated with antithrombotic drug use
        1. FVIIa
        2. Antifibrinolytic drugs
    2. associated with antiplatelet drug use
        1. Platelet transfusion
2. Anticoagulant-associated ICH
        1. PCC versus FFP for anticoagulant-associated ICH (vitamin K-antagonists)
        2. Andexanet vs. usual care for anticoagulant-associated ICH factor Xa inhibitors
        3. Tranexamic acid vs. usual care for anticoagulant-associated ICH factor Xa inhibitors
        4. **Idarucizumab** for anticoagulant-associated ICH (factor IIa inhibitor)

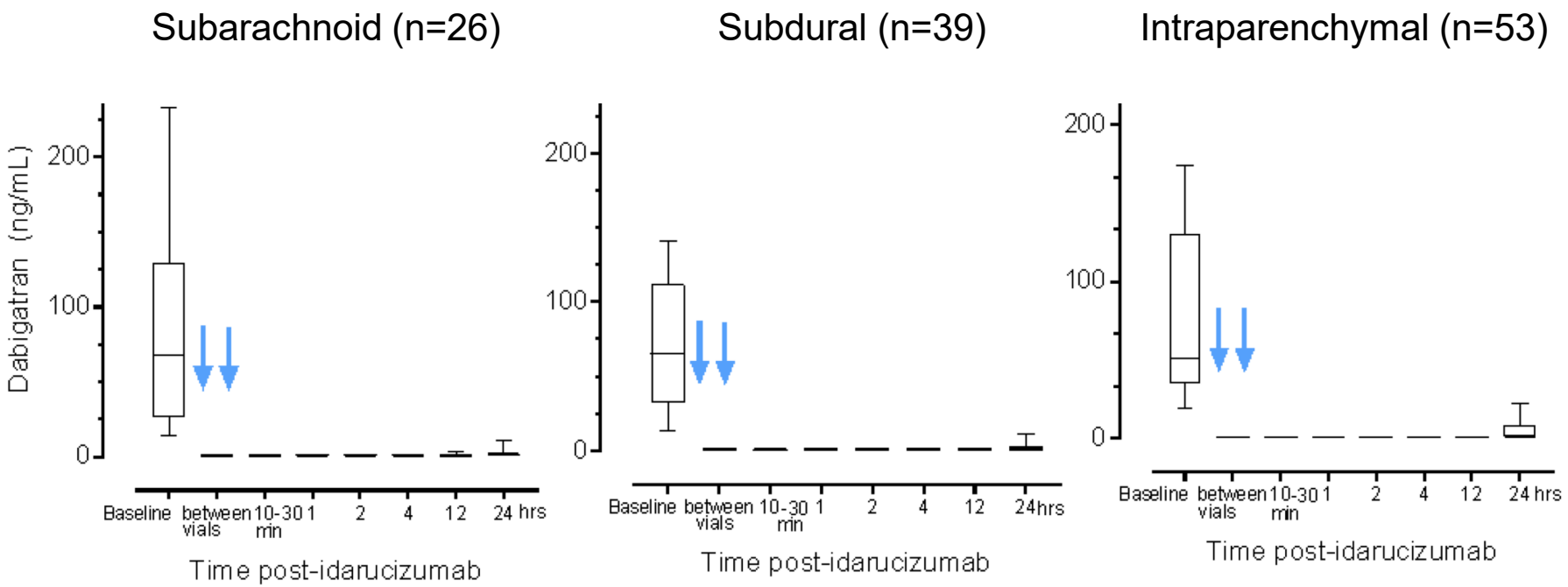
Multicentre, Prospective, Open-label, Single-arm Phase III Study



173 sites in 39 countries

Pollack CV Jr, Reilly PA, van Ryn J, et al. *N Engl J Med*. 2017;377(5):431-441.

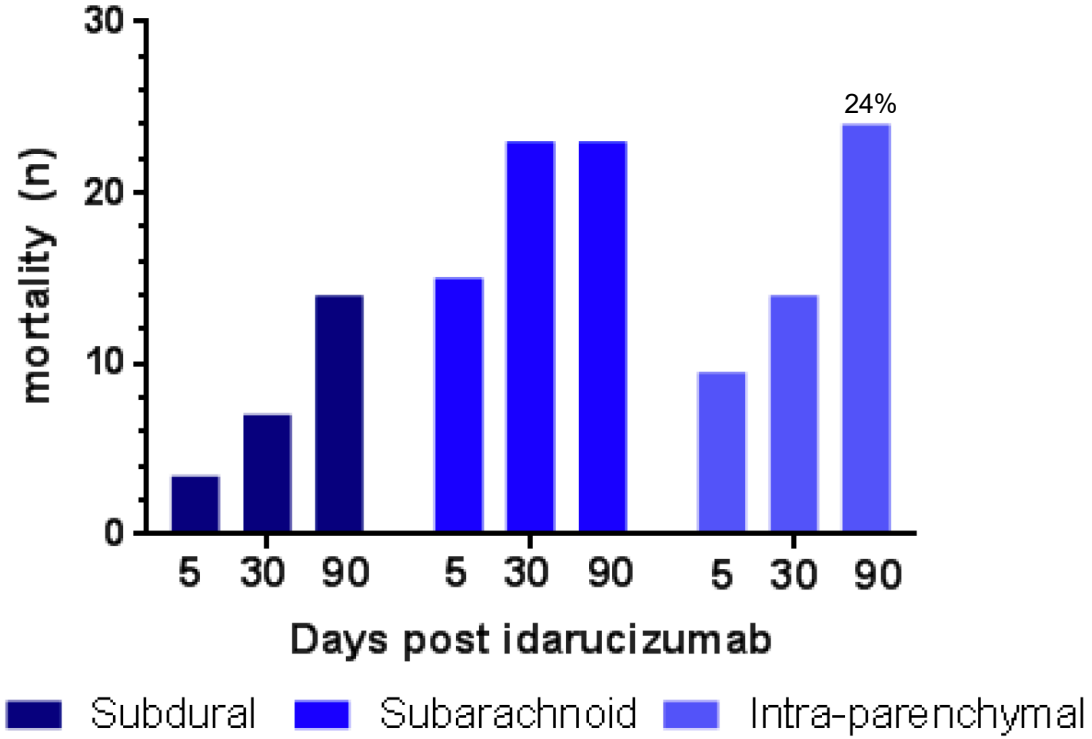
Idarucizumab in 118 Patients with Intracranial Hemorrhage from REVERSE-Trial, N=503

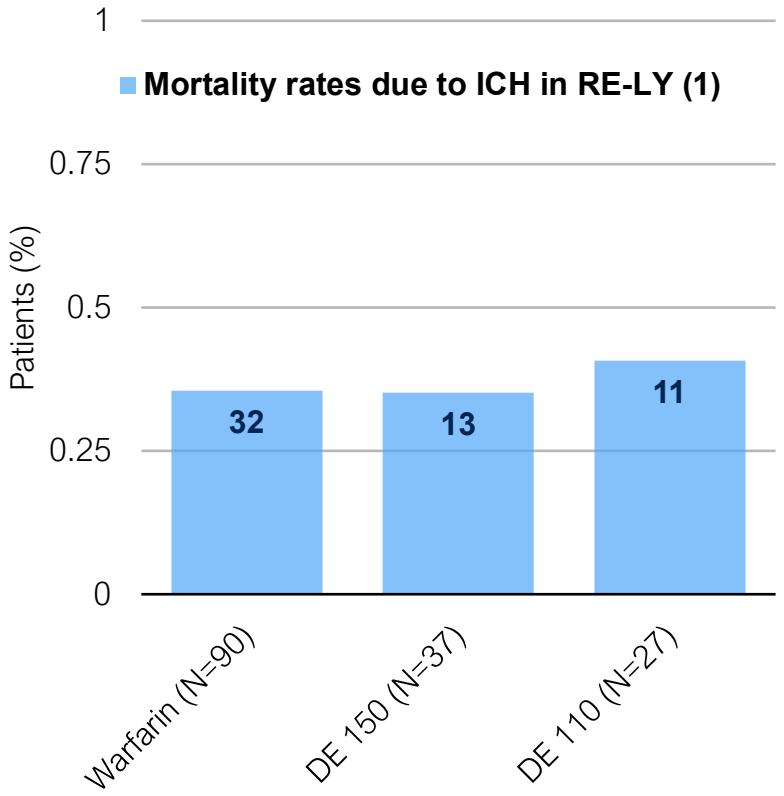


- Complete reversal of dTT and ECT was observed in 100% and >90% of evaluable patients, respectively
- TT was also reversed to normal levels post-idarucizumab
- No patients required two doses of idarucizumab

T. Steiner, P.A. Reilly, J. van Ryn, J.I. Weitz, C.V. Pollack and R.A. Bernstein, NCC 2018

Secondary Outcomes: Mortality





T. Steiner, P.A. Reilly, J. van Ryn, J.I. Weitz, C.V. Pollack and R.A. Bernstein, NCC 2018; Hart RG, Diener HC, Yang S, et al. *Stroke*. 2012;43(6):1511-7.

Multiple Choice Question

Which combination of dosages of antidotes for the treatment of cerebral hemorrhage associated with oral anticoagulants and used in randomized clinical trials is correct?

A. 20 U/kg PCC; 10 mg iv Vit-K; low dose andexanet alfa; 1 x 5 g idarucizumab

B. 30 U/kg PCC; no Vit-K; low dose andexanet alfa; 1 x 5 g idarucizumab

C. 30 U/kg PCC; 10 mg iv Vit-K; low/high dose andexanet alfa; 2 x 2,5 g idarucizumab

D. 50 U/kg PCC; 20 mg iv Vit-K; high dose andexanet alfa; 2 x 5 g idarucizumab

Looking for more resources on this topic?

MedEd ON THE GO

- CME/CE in minutes
- Congress highlights
- Late-breaking data
- Quizzes
- Webinars
- In-person events
- Slides & resources

www.MedEdOTG.com