VII CONGRESSO NAZIONALE ANEU

CONTROVERSIE IN NEUROLOGIA D'EMERGENZA E URGENZA

STRATEGIE DI REVERSAL NEI SANGUINAMENTI MAGGIORI IN CORSO DI ANTI-FXA: *PRIMI DATI REAL WORD*

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OSPEDALE MAGGIORE

Istituto delle Scienze Neurologiche
Istituto di Ricovero e Cura a Carattere Scientifico

Associazione Neurologia Emergenza Urgenza

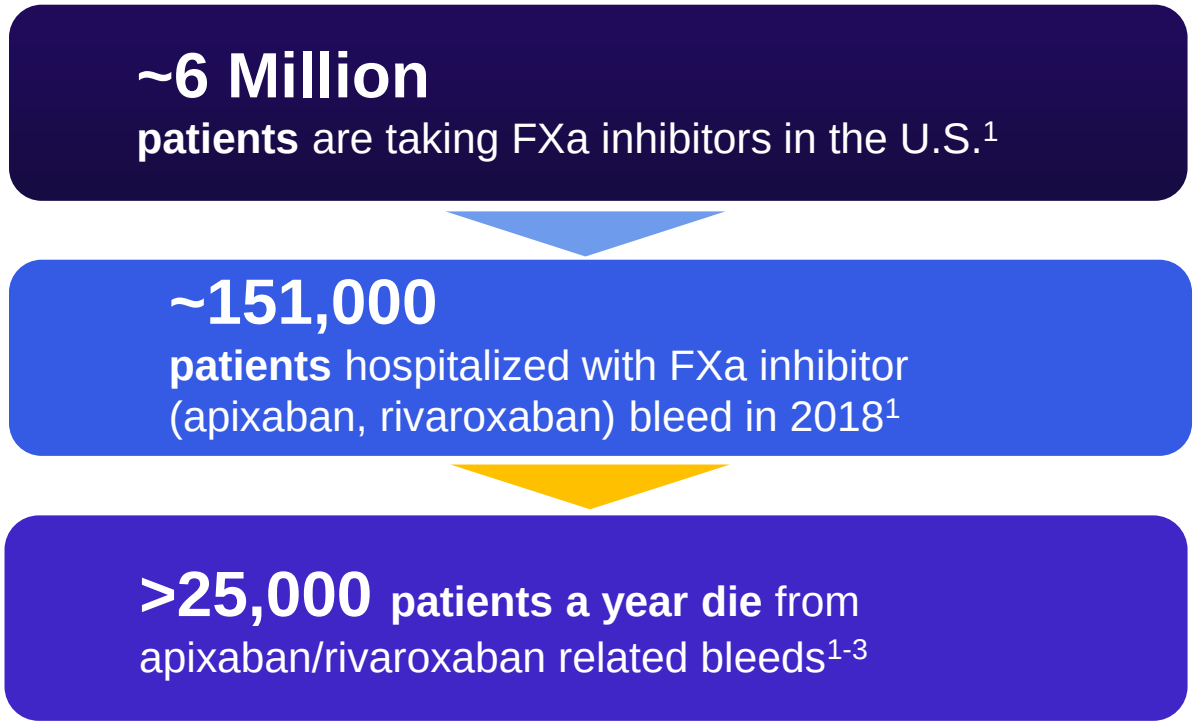
Conflitti di interesse

- ALEXION – ASTRA ZENECA
- BOEHRINGER INGELHEIM
- CLS-BEHRING
- ANGELS
- BAYER

Lettura con il contributo non condizionante di ASTRAZENECA

Dimensione del problema

PREVALENCE OF BLEEDING WITH FACTOR Xa INHIBITORS



1. IQVIA MIDAS Data, IBM Truven Health Analytics: Bleeding Events Report, ending Sept 2019; 2. Piccini JP, et al. *Eur Heart J*. 2014;35(28):1873-1880; 3. Held C, et al. *Eur Heart J*. 2015;36(20):1264-1272.

The Use of DOACs Has Increased Significantly Since Approval

ANTICOAGULANTS, CONSUMPTION (DDD / 1000 INHABITANTS PER DAY) IN ITALY: COMPARISON 2014-2019[2]

SUBGROUPS	2014	2015	2016	2017	2018	2019	Δ % 19-18
DOACs	1,6	3,4	5,3	7,3	9,4	11,7	25,0
LMWH	9,7	9,7	9,5	9,2	8,9	8,7	-2,0
Anti-thrombotic	0,0	0,0	0,0	0,0	0,0	0,0	2,2
Fondaparinux	0,3	0,4	0,4	0,5	0,5	0,5	2,6
Heparin and heparinoids	0,6	0,4	0,5	0,4	0,4	0,4	-3,1
Vitamin K Antagonists	6,5	6,1	5,6	5,1	4,6	4,1	-10,6
Anticoagulants	**18,8**	**20,1**	**21,4**	**22,6**	**23,7**	**25,4**	**7,0**
enoxaparin	7,5	7,6	7,7	7,3	7,2	7,6	6,0
apixaban	0,2	0,8	1,6	2,3	3,0	3,6	22,2
rivaroxaban	0,6	1,5	2,3	2,8	3,2	4,1	28,9
dabigatran	0,8	1,1	1,4	1,8	2,2	2,4	10,2
edoxaban	0,0	0,0	0,0	0,4	1,0	1,6	51,7
nadroparina calcica	1,4	1,4	1,2	1,2	1,1	0,8	-27,1
fondaparinux	0,3	0,4	0,4	0,5	0,5	0,5	2,6
parnaparina	0,5	0,5	0,5	0,6	0,5	0,3	-50,9
alteplasi	0,0	0,0	0,0	0,0	0,0	0,0	5,2
eparina	0,6	0,4	0,4	0,4	0,4	0,4	-3,0

2. https://www.aifa.gov.it/-/rapporto-osmed-2019

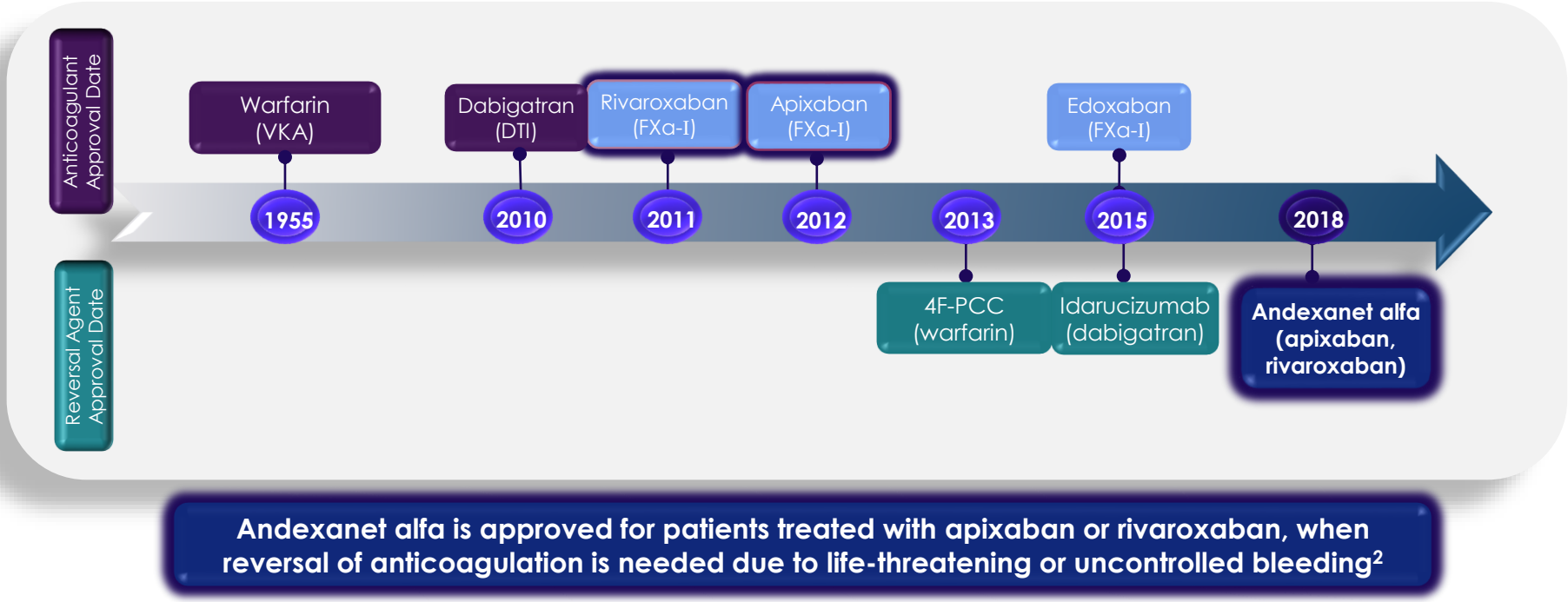
The Use of DOACs Has Increased Significantly Since Approval

1.2 MILLION PATIENTS WITH DOAC WERE INITIATED FOR THE NVAF INDICATION AS OF DECEMBER 31, 2019 IN ITALY

	Apixaban		Dabigatran		Edoxaban		Rivaroxaban		Totale	
	N	%	N	%	N	%	N	%	N	%
Patients	371978	31,0	289759	24,1	153354	12,8	385100	32,1	1200191	100
Age, Median (range)	79,8 (18 – 109)		77,2 (18 – 103)		79,7 (19 – 106)		77,8 (18 – 108)		78,5 (18-109)	
<65	28974	7,8	35889	12,4	12960	8,5	47941	12,4	125764	10,5
65-74	83643	22,5	82535	28,5	34722	22,6	100477	26,1	301377	25,1
75-84	163024	43,8	125718	43,4	64654	42,2	163736	42,5	517132	43,1
≥85	96337	25,9	45617	15,7	41018	26,7	72946	18,9	255918	21,3
Gender										
Female	194648	52,3	132772	45,8	81335	53	186823	48,5	595578	49,6
Male	177330	47,7	156987	54,2	72019	47	198277	51,5	604613	50,4

2. https://www.aifa.gov.it/-/rapporto-osmed-2019

ANDEXANET ALFA ANSWERS AN UNMET NEED FOR A SPECIFIC REVERSAL AGENT FOR FXA INHIBITOR-ASSOCIATED BLEEDING[1]



Andexanet alfa is approved for patients treated with apixaban or rivaroxaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding[2]

DOAC = direct oral anticoagulant; FXa = factor Xa; Fxa-I = Factor Xa Inhibitor; PCC = prothrombin complex concentrate; VKA = vitamin K antagonist.

1. Kustos SA et al. *Medicines*. 2019;6(4):103; 2. Andexanet alfa - Summary of product characteristics. Astrazeneca AB; June 22.

Unmet medical need for a reversal agent for FXa inhibitors

FXa-induced major bleeding

- Rates of bleeding with rivaroxaban and apixaban in NVAF trials

	Major bleed (%/year)	ICH (%/year)	GI bleed[a] (%/year)
Rivaroxaban[1] **ROCKET-AF**	**3.6%**	**0.5%**	3.2%
Apixaban[2] **ARISTOTLE**	**2.1%**	**0.3%**	0.8%

Rivaroxaban and apixaban were compared with warfarin across NVAF trials. Due to differences in trial designs and patient populations, no direct comparisons between agents can be made

Table adapted from Deitelzweig *et al.* 2017

[a]Investigators defined GI bleeds as major bleeds[1,2]

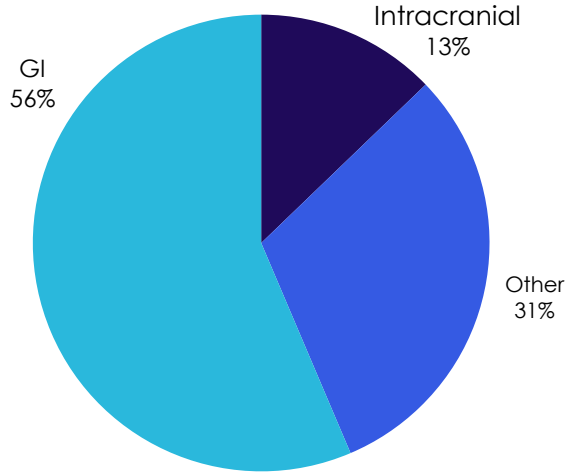
FXa, factor Xa; GI, gastrointestinal; ICH, intracranial haemorrhage; NVAF, nonvalvular atrial fibrillation

1. Patel MR, *et al. N Engl J Med* 2011;365:883–91; 2. Granger CB, *et al. N Engl J Med* 2011;365:981–92

Unmet medical need for a reversal agent for FXa inhibitors

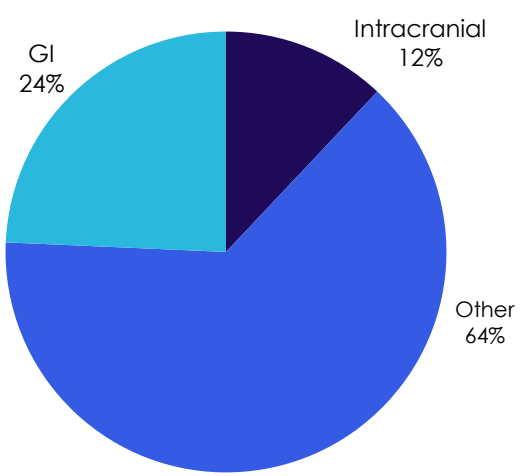
Distribution of FXa-inhibitor-associated major bleeds

Rivaroxaban[1]



Overall rate of major bleeding: 3.6%/**year**[2]

Apixaban[3]



Overall rate of major bleeding: 2.1%/**year**[3]

Figures created from data in Piccini *et al.* 2011 & Granger *et al* 2011

Rates are calculated as percent of all major bleeds
DOAC, direct oral anticoagulant; FXa, factor Xa; GI, gastrointestinal
1. Piccini JP, *et al. Eur Heart J* 2014;35:1873–80; 2. Patel MR, *et al. N Engl J Med* 2011;365:883–91; 3. Granger CB, *et al. N Engl J Med* 2011;365:981–92

Scopo

- **Per le seguenti categorie**
  - ICH
  - altri major bleeding
- **avere un antidoto per:**
  - Interrompere attività Anti–Factor Xa
  - Ridurre concentrazione plasmatica di Xabani
  - Interrompere ICH expansion e major bleeding expansion
  - Ridurre mortalità e disabilità

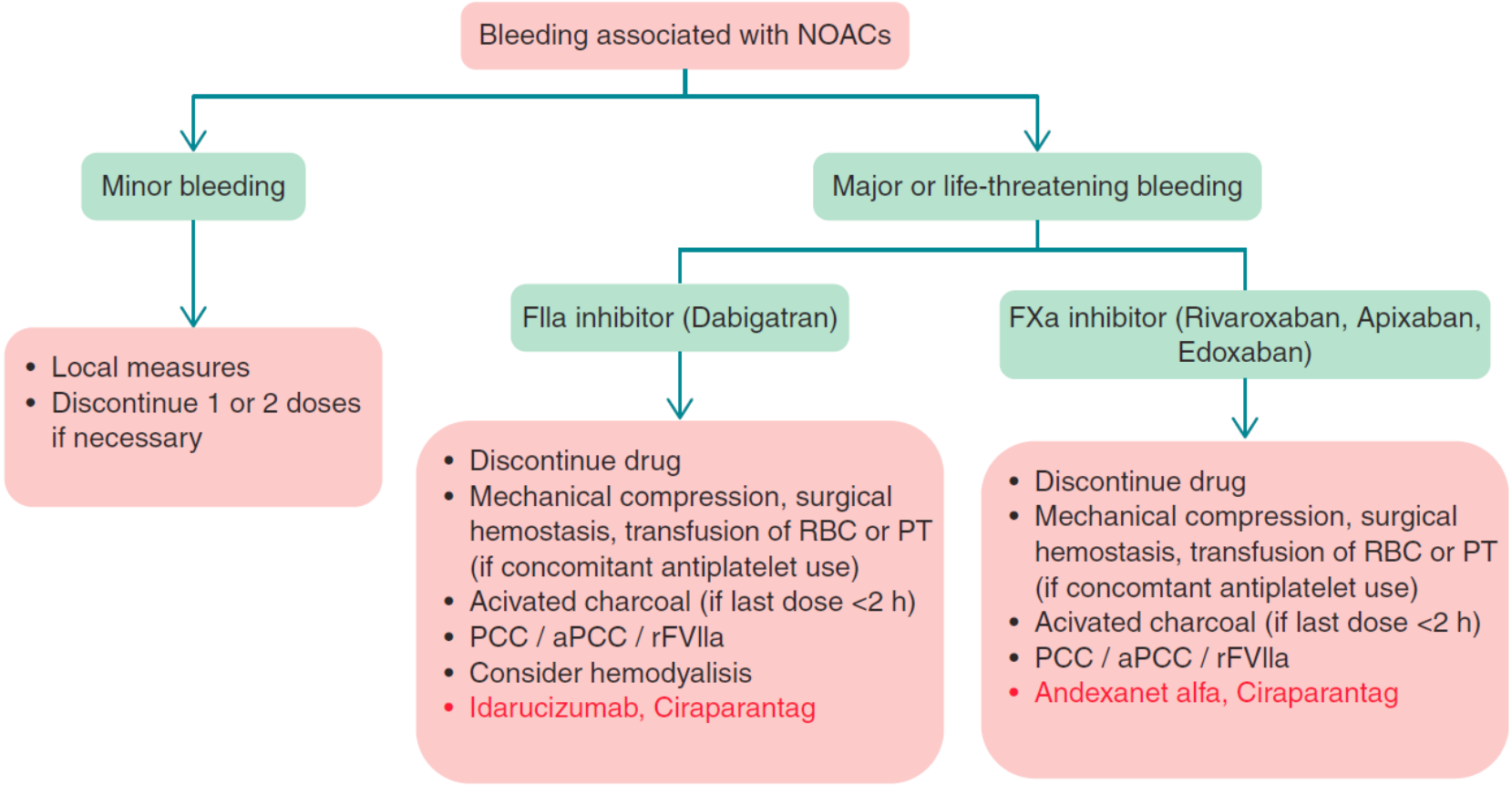
Nel passato...

Strategies for anticoagulation reversal in bleeding associated with warfarin and new oral anticoagulants

	Warfarin	Dabigatran	Rivaroxaban, apixaban, and edoxaban
General measures	Drug discontinuation, mechanical compression, surgical haemostasis, transfusional support	Drug discontinuation, mechanical compression, surgical haemostasis, transfusional support	Drug discontinuation, mechanical compression, surgical haemostasis, transfusional support
Activated charcoal	Consider if last dose <2 h	Consider if last dose <2 h	Consider if last dose <2 h
Haemodialysis	No benefits (highly protein bound)	Removes 62–68% of circulating drug	No benefits (highly protein bound)
Coagulation factors	PCC (25 U/kg, repeat if necessary) FFP (10–15 ml/kg) rFVIIa (90 ug/kg)	PCC (25 U/kg, repeat if necessary) rFVIIa (90 ug/kg)	PCC (25 U/kg, repeat if necessary) or FEIBA (50 IE/kg, max 200 IE/day) rFVIIa (90 ug/kg)
Specific inhibitors	Vitamin K (5–10 mg IV)	Idarucizumab (Phase 1) Ciraparantag (preclinical)	Andexanet alfa (Phases 1–3) Ciraparantag (Phase 1)

Enriquez A, Europace 2015

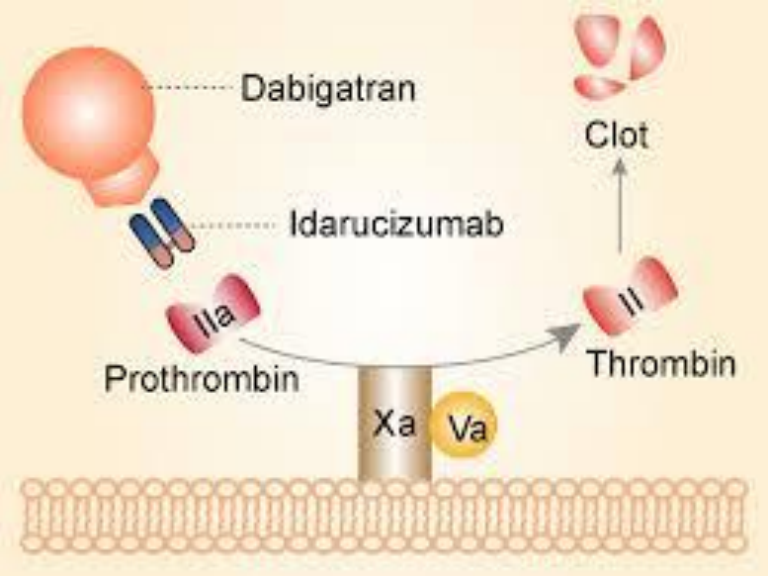
Management of bleeding associated with NOACs



Enriquez A, Europace 2015

Nel passato...

"Antidoti"



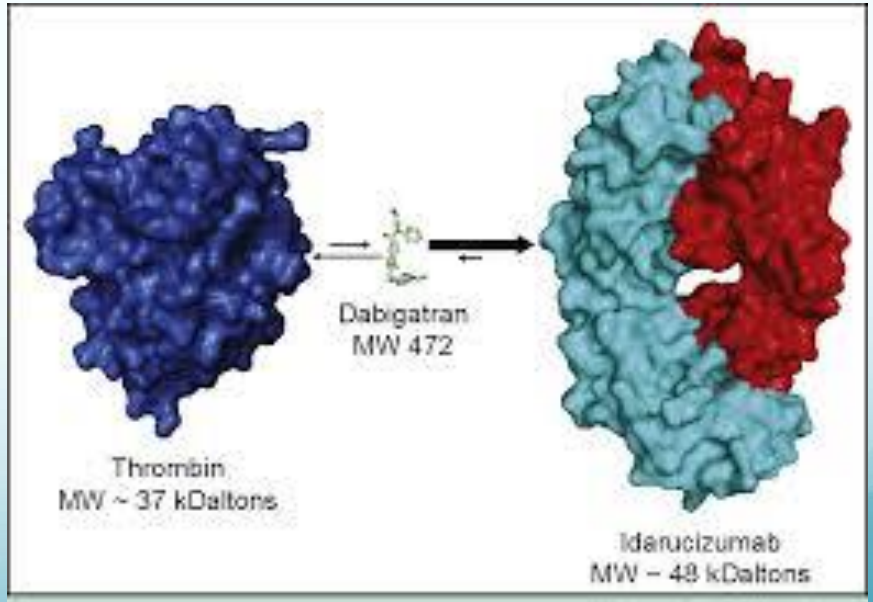
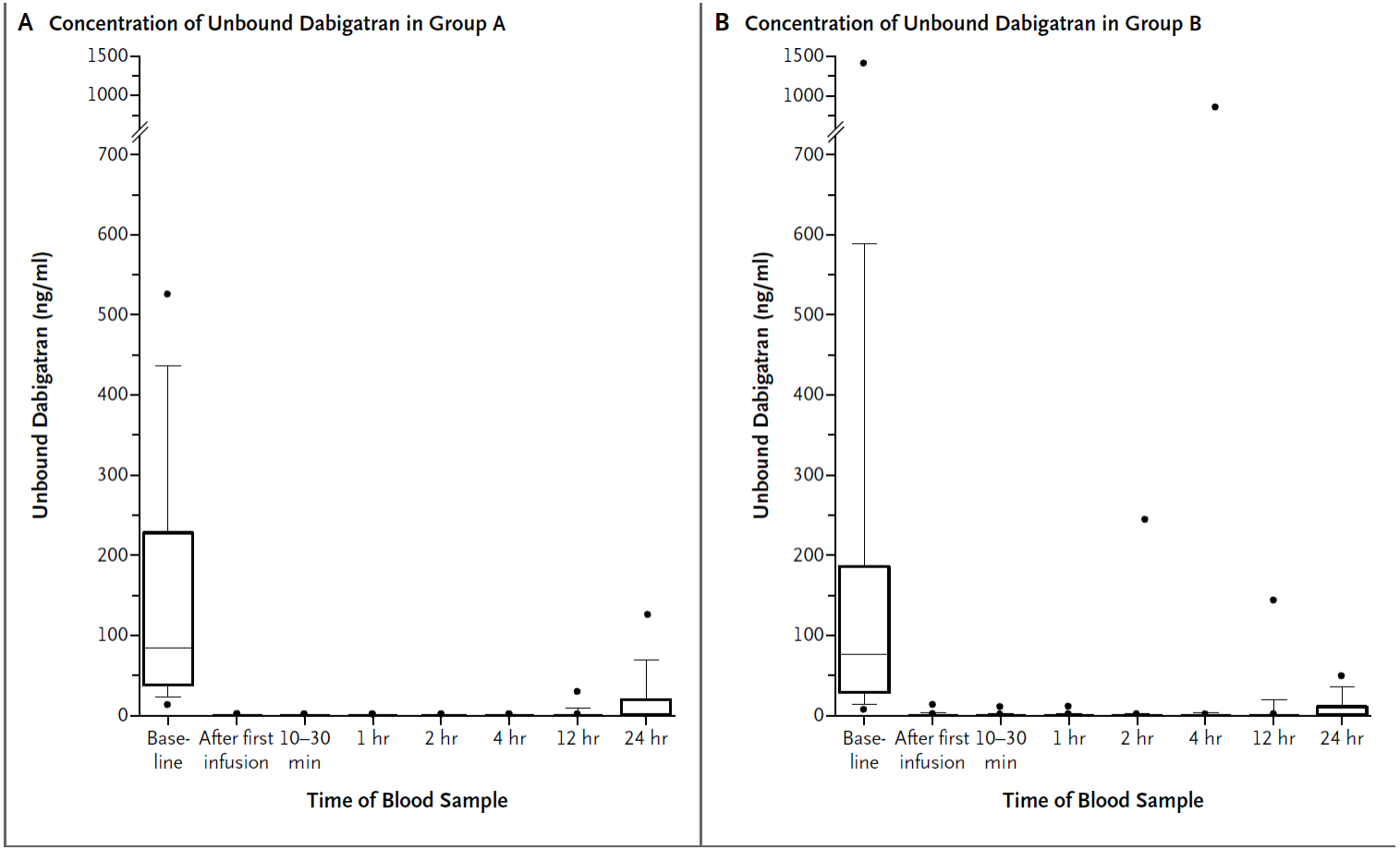


Figure 1 Structure and relative sizes of thrombin (FIIa), dabigatran, and idarucizumab. Reprinted

Trauman JM, AJEM 2016

Time Courses of Plasma Concentrations of Unbound Dabigatran before and after the Administration of Idarucizumab

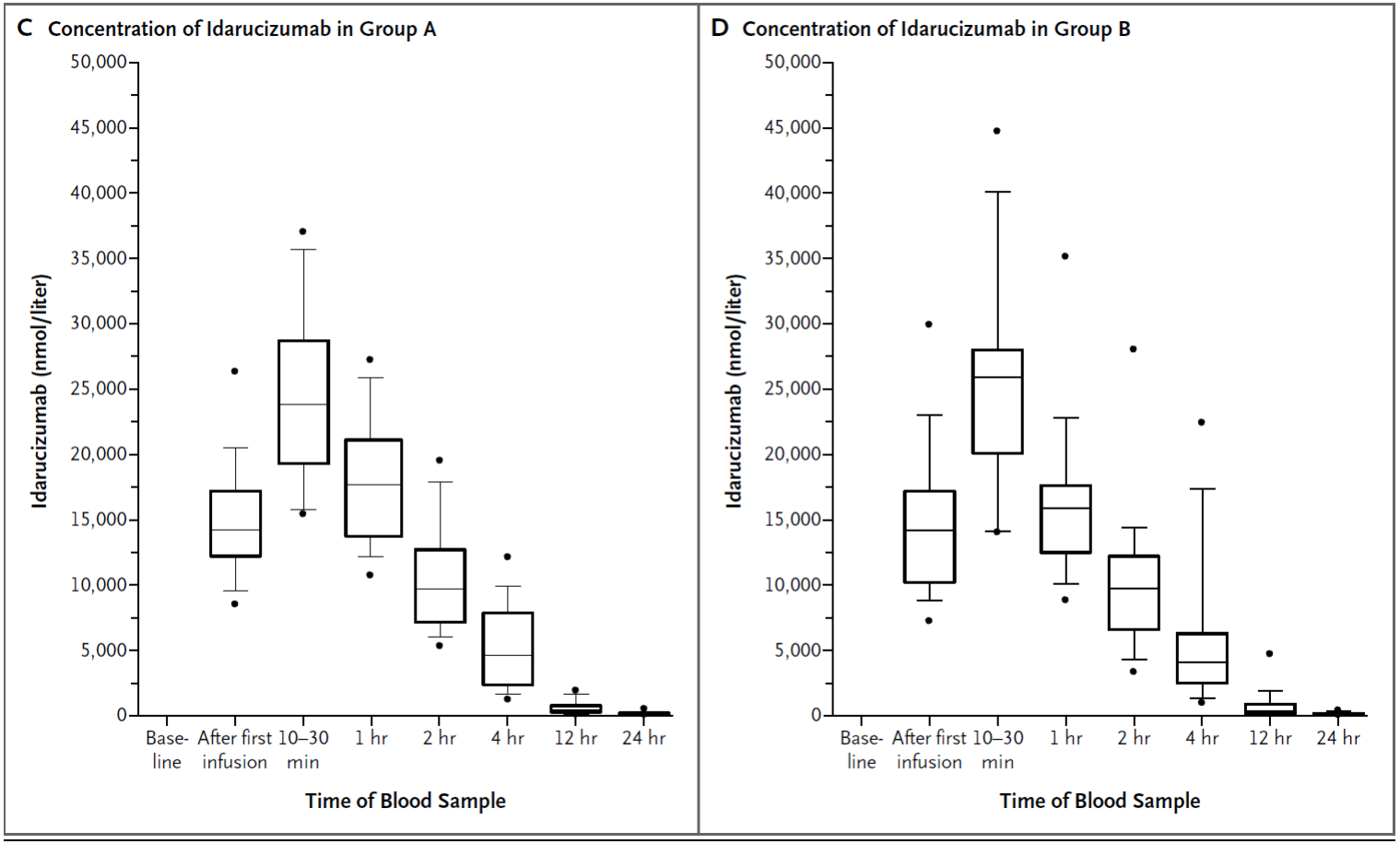


patients who had serious bleeding

patients who required urgent surgery

Pollack V, NEJM 2015

Time Courses of Plasma Concentrations of Idarucizumab before and after the Administration of Idarucizumab



patients who had serious bleeding

patients who required urgent surgery

Pollack V, NEJM 2015

"Antidoti"

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

S.J. Connolly, M. Crowther, J.W. Eikelboom, C.M. Gibson, J.T. Curnutte, J.H. Lawrence, P. Yue, M.D. Bronson, G. Lu, P.B. Conley, P. Verhamme, J. Schmidt, S. Middeldorp, A.T. Cohen, J. Beyer-Westendorf, P. Albaladejo, J. Lopez-Sendon, A.M. Demchuk, D.J. Pallin, M. Concha, S. Goodman, J. Leeds, S. Souza, D.M. Siegal, E. Zotova, B. Meeks, S. Ahmad, J. Nakamya, and T.J. Milling, Jr., for the ANNEXA-4 Investigators*

Connolly SJ,*et al. N Engl J Med* 2019

Reversal of FXa inhibitors: andexanet alfa

Specific reversal agent for FXa inhibitors

- Andexanet alfa designed to reverse anticoagulant effects of FXa inhibitors
- Andexanet alfa acts as an FXa decoy
- It's a recombinant, modified, inactive form of human FXa produced in CHO cells
- It binds and sequesters FXa inhibitor molecules

Design of andexanet alfa compared to native FXa

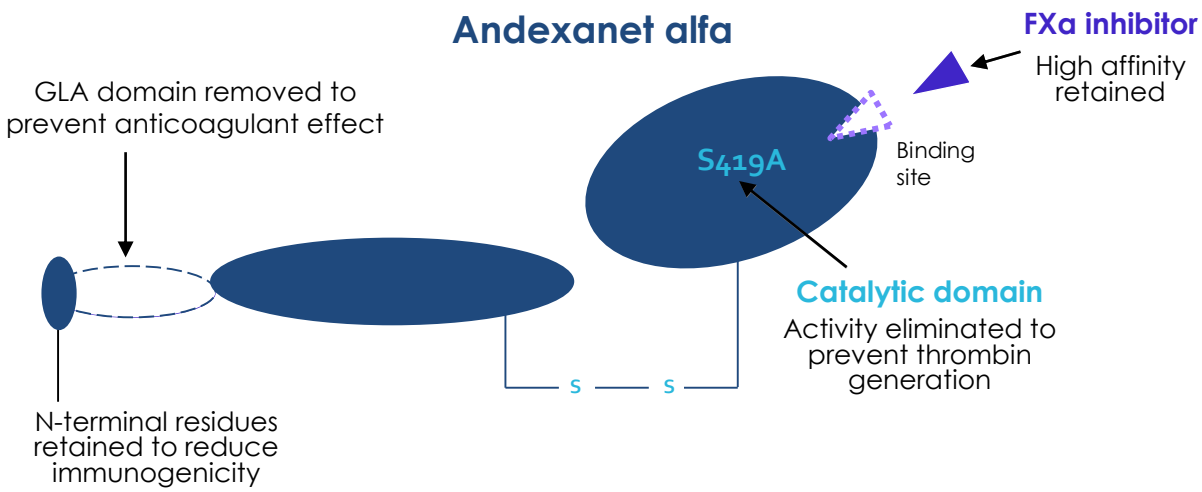


Figure adapted from Lu *et al.* 2013

Andexanet alfa is a specific reversal agent that binds and sequesters FXa inhibitors, therefore restoring native FXa activity[a]

FXa, factor Xa; CHO, Chinese hamster ovary; GLA, γ-carboxyglutamate

Lu G, *et al. Nat Med* 2013;19:446–451

BINDING OF ANDEXANET ALFA TO FACTOR Xa INHIBITORS

1. Reversible binding[1-2]

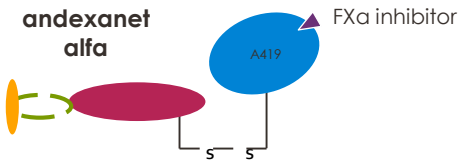
- 1:1 binding stoichiometry
- Need > 1:1 stoichiometric molar ratio of andexanet alfa : FXa inhibitor to shift binding equilibrium and reverse the effects of the FXa inhibitor

2. High affinity binding (subnanomolar range)[3]

- Relative potency of binding is in the same order of magnitude as the inhibition constants reported in the literature for FXa inhibitors against plasma-derived FXa

3. Competitive binding:[1-3]

- Direct FXa inhibitors:
  - Native FXa and andexanet alfa compete for binding to FXa inhibitors
- Indirect FXa inhibitors:
  - ***Native FXa and andexanet alfa compete for binding to the AT-III/FXa inhibitor complex***



Graphic adapted from: Lu G et al. EMJ Cardiol 2018;6[1]:47-51

Affinity of andexanet alfa for direct FXa inhibitors[3]

Inhibitor	r-Antidote K_d (nM)	FXa K_i (nM)
Rivaroxaban	1.53 ± 0.22	0.400
Apixaban	0.58 ± 0.02	0.100

Andexanet alfa has not been shown to be effective for, and is not indicated for, the treatment of bleeding related to any FXa inhibitors other than apixaban or rivaroxaban

AT-III, antithrombin III; **FXa,** Factor Xa; **K_d;** potency; **K_i,** inhibition constants; **nM,** nanomoles; **r-antidote;** recombinant antidote.

1. Siegal D et al. *Blood Adv*. 2017;1(21): 1827-1838. **2.** Lu G et al. *Blood Adv*. 2020;4(4):728-739. **3.** Lu G et al. *Nat Med.* 2013;19(4):446-451.

The NEW ENGLAND JOURNAL of MEDICINE

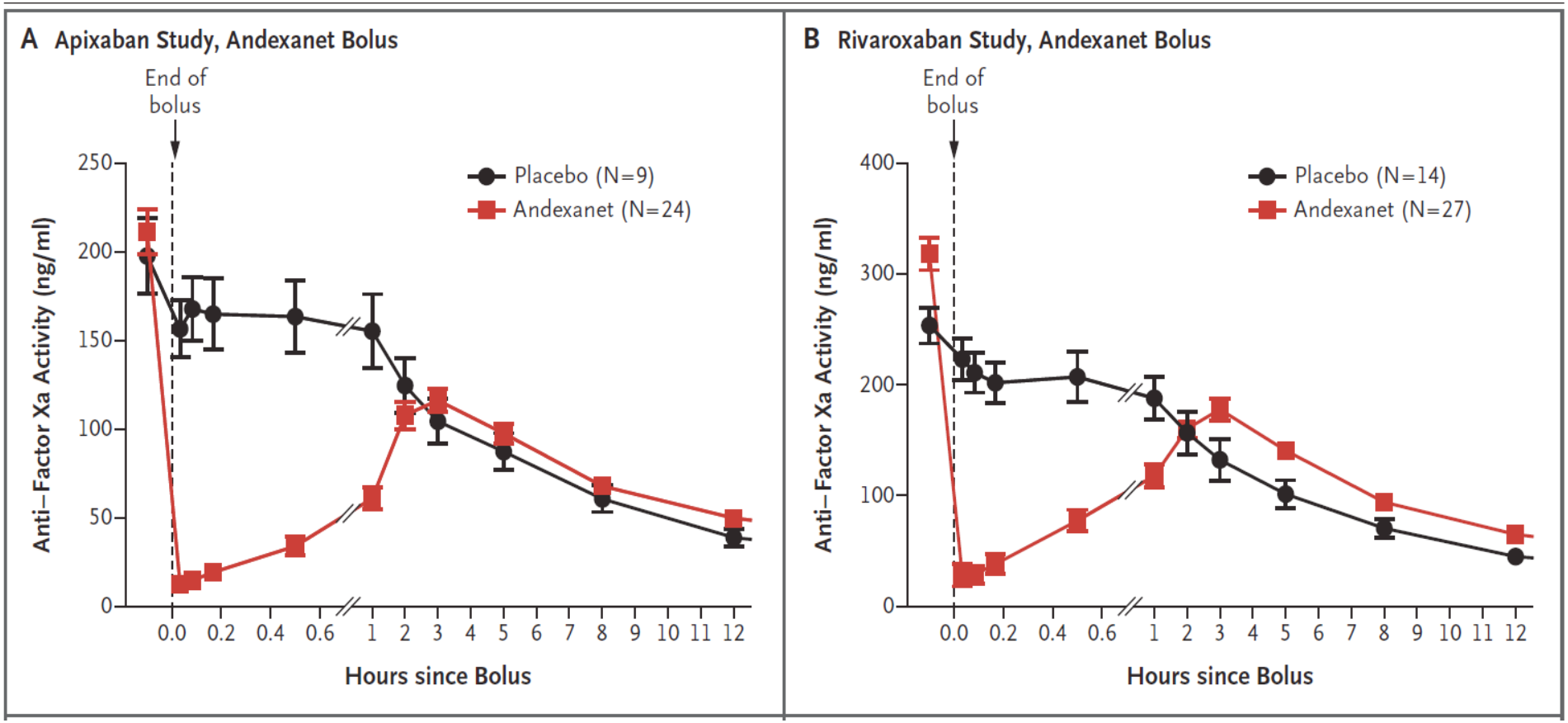
ORIGINAL ARTICLE

Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity

Deborah M. Siegal, M.D., John T. Curnutte, M.D., Ph.D., Stuart J. Connolly, M.D., Genmin Lu, Ph.D., Pamela B. Conley, Ph.D., Brian L. Wiens, Ph.D., Vandana S. Mathur, M.D., Janice Castillo, B.S., Michele D. Bronson, Ph.D., Janet M. Leeds, Ph.D., Florie A. Mar, Ph.D., Alex Gold, M.D., and Mark A. Crowther, M.D.

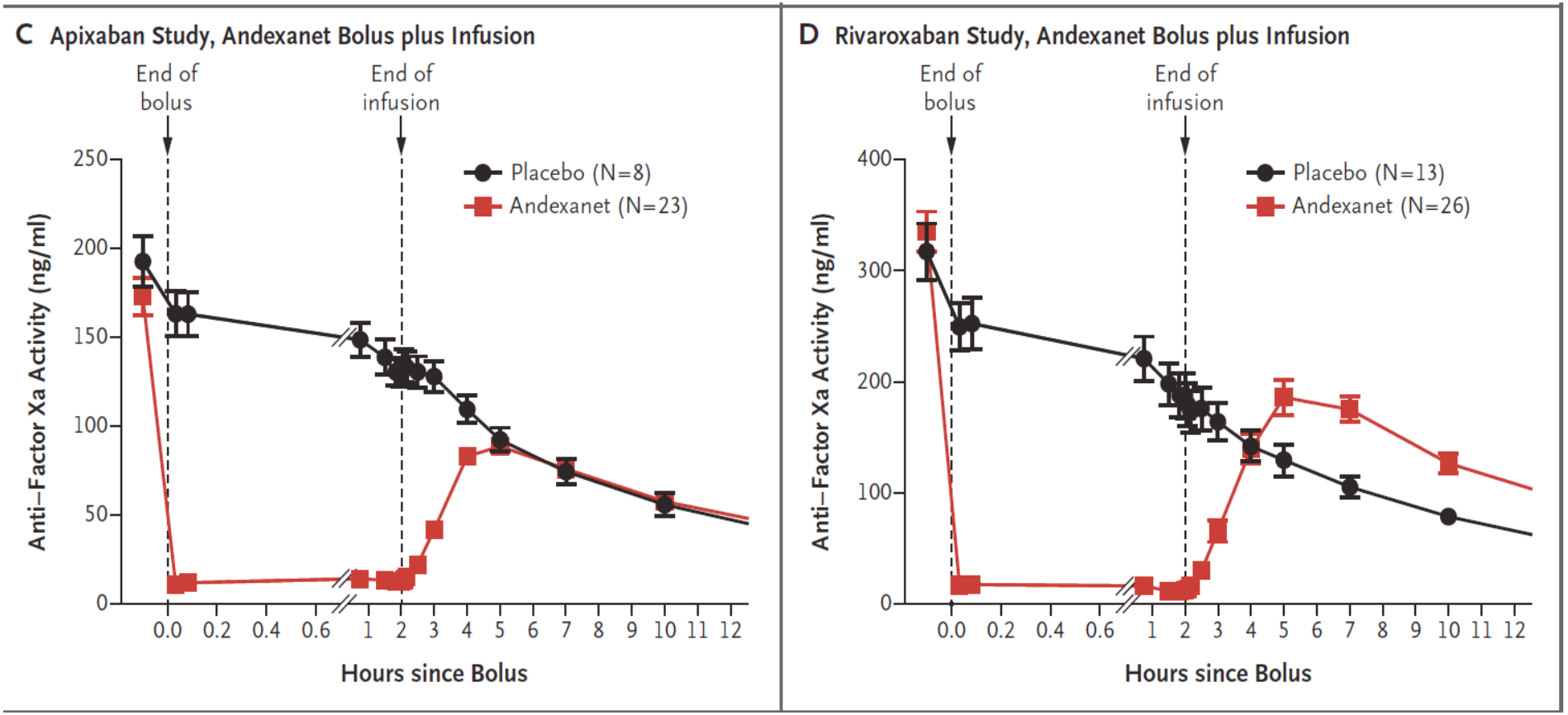
Siegal D, NEJM 2015

Time Courses of Anti–Factor Xa Activity before and after Administration of Andexanet



Siegal D, NEJM 2015

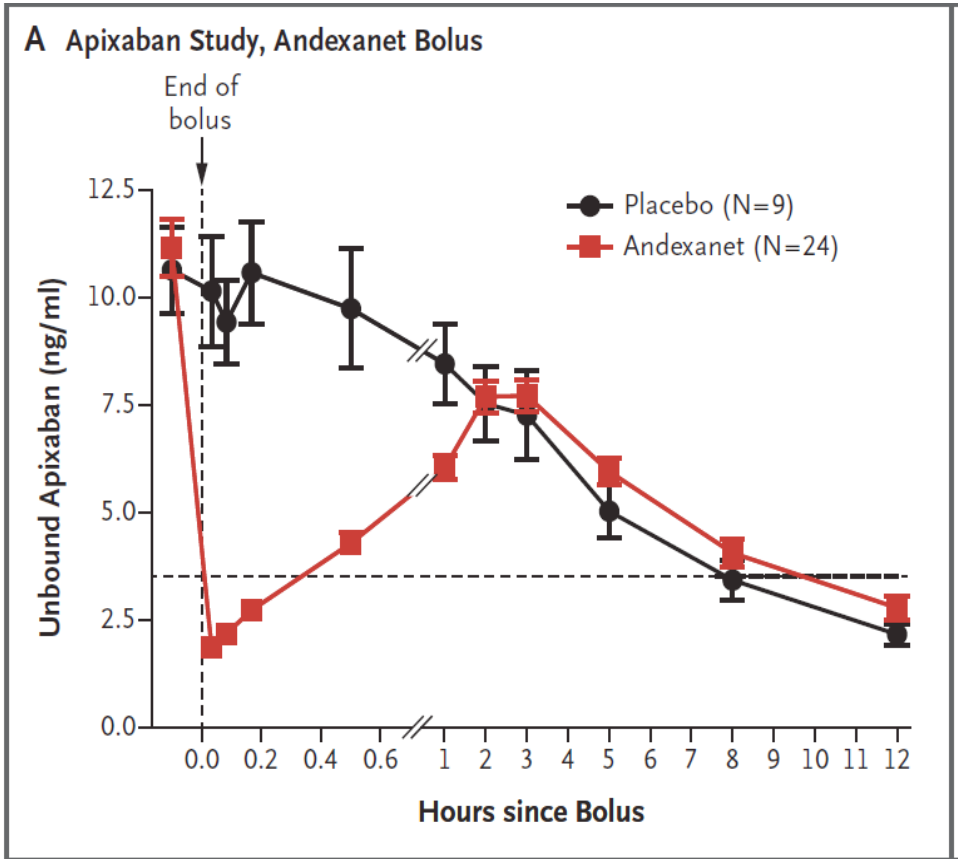
Time Courses of Anti–Factor Xa Activity before and after Administration of Andexanet

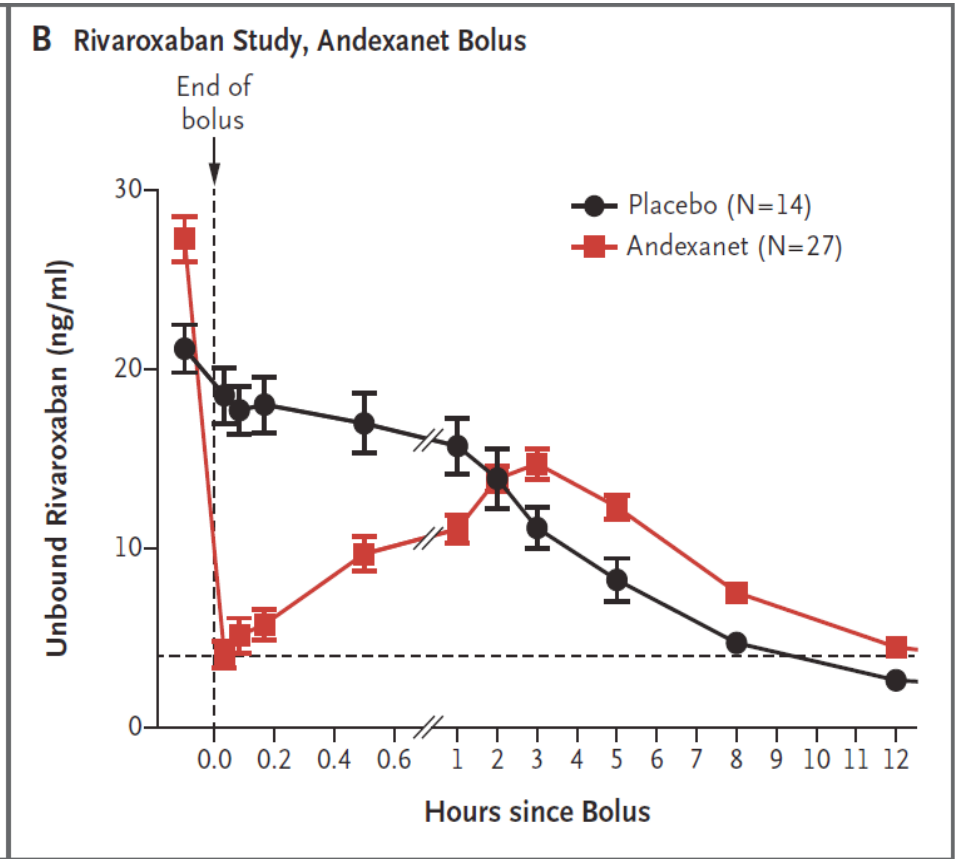


Hours of bleeding expansion!

Siegal D, NEJM 2015

Time Courses of Plasma Concentrations of Unbound Apixaban or Rivaroxaban before and after Administration of Andexanet





Siegal D, NEJM 2015

CLINICAL TRIALS OVERVIEW

Phase 3 → Phase 3b/4 → Phase 4 Ongoing study

ANNEXA-A and ANNEXA-R[1]

Efficacy and safety of andexanet alfa for the **reversal of anticoagulation with apixaban** or **rivaroxaban** in healthy volunteers

Primary endpoint:
- Anti-FXa activity from baseline to nadir

Secondary endpoint:
- Thrombin generation from baseline to its peak after treatment

Safety outcomes:
- Drug-related AEs
- Thrombotic events
- Antibodies to FX, FXa, or andexanet alfa

ANNEXA-4[2]

Efficacy and safety of andexanet alfa in patients with **acute major bleeding** and administration of a FXa inhibitor within 18 hours[a]

Co-Primary efficacy endpoint:
- Anti-FXa activity from baseline after treatment
- Excellent or good hemostatic efficacy 12 hours after treatment[b]

Safety outcomes:
- Thrombotic events
- Antibodies to FX and FXa, or andexanet alfa
- 30-day mortality

ANNEXA-I[3]

Efficacy and safety of andexanet alfa vs. usual care in patients with **intracerebral hemorrhage** anticoagulated with a FXa inhibitor[a]

Primary endpoint:
- Excellent or good hemostatic efficacy[b]

Secondary endpoint:
- Anti-FXa activity from baseline to nadir

Safety outcomes:
- Thrombotic events
- Mortality

[a]FXa inhibitors included apixaban, rivaroxaban, edoxaban, or enoxaparin (≥1mg/kg/day); [b]Hemostatic efficacy as rated by an independent adjudication committee.[2,3]

AE = adverse events; FX = factor X; Fxa = factor Xa; IV = intravenous; SQ = subcutaneous.

1. Siegal DM et al. *N Engl J Med*. 2015;373(25):2413-2424; 2. Connolly SJ et al. Article and supplementary appendix. *N Engl J Med.* 2019;380(14):1326-1335; 3. Study NCT03661528. ClinicalTrials.gov website.

Andexanet Alfa - Real-world Effectiveness of Andexanet Alfa in Factor Xa Inhibitor Reversal

Real World Evidence

Andexanet Alfa in All Bleed Types

- Real-world management of oral FXa inhibitor-related bleeds with reversal or replacement agents including andexanet alfa and 4F-PCC: a multicenter study
- Andexanet alfa is associated with a significant reduction in in-hospital mortality compared to 4F-PCC in a real-world analysis
- 30-day mortality following andexanet alfa in ANNEXA-4 compared with PCC therapy in the ORANGE study for life threatening NOAC-related bleeding

Andexanet Alfa in Brain Hemorrhages

- Hematoma expansion and clinical outcomes in patients with FXa inhibitor-related atraumatic intracerebral hemorrhage treated within the ANNEXA-4 trial vs. real-world usual care
- Andexanet alfa versus 4F-PCC for the reversal of apixaban- or rivaroxaban-associated intracranial hemorrhage: a propensity score-overlap weighted analysis

Background

Prior to US approval of andexanet alfa, clinicians often relied on **off-label use of 4F-PCC** to manage FXai-associated major bleeding events

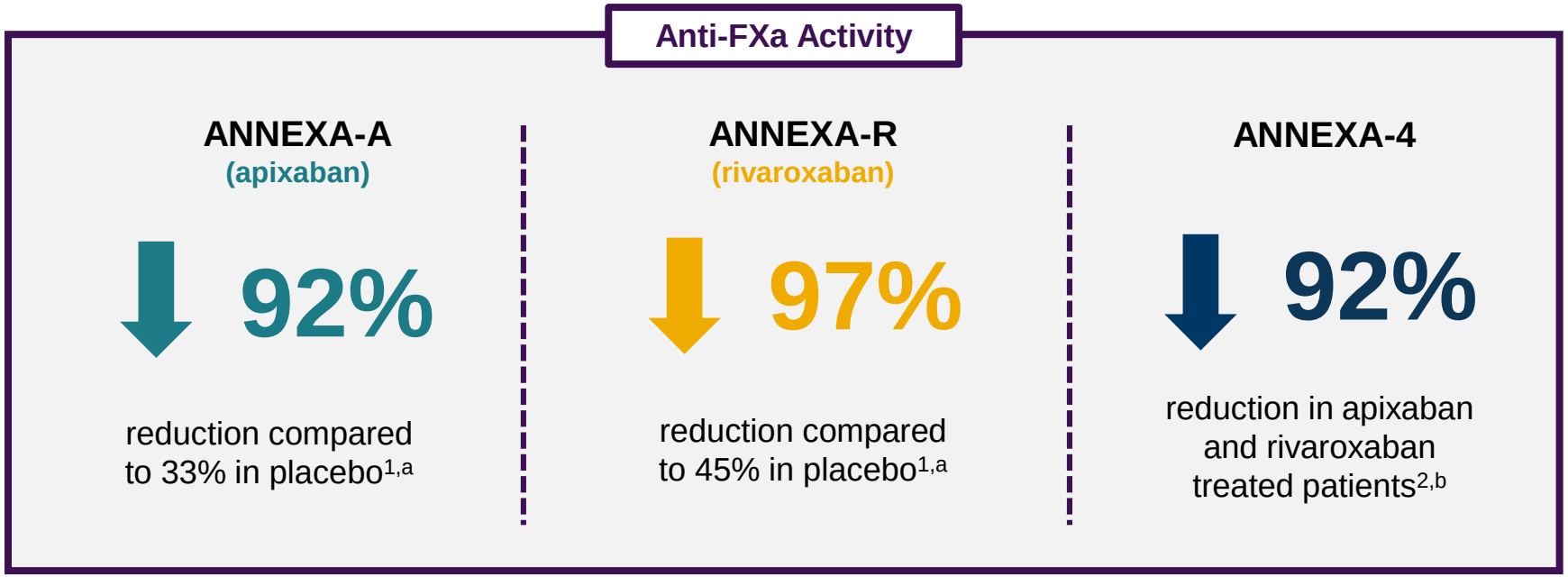
In **May 2018**, Andexanet alfa was **approved by the FDA** as a specific reversal agent for FXa inhibitors apixaban and rivaroxaban for life threatening or uncontrolled bleeding[1] based on healthy volunteer studies and a single-arm trial

To date, studies comparing outcomes for andexanet alfa and 4F-PCC have been limited to **small case series**[2]
RETRACE and ORANGE indirect comparison studies in Germany and UK

EMA approval of andexanet alfa in **April 2019**

1. Andexanet alfa prescribing information. 2. Barra et al. *J Thromb Haemost*. 2020; 18: 1637– 1647. https://doi.org/10.1111/jth.14838

Results From Phase III/IV Clinical Trials Demonstrated Direct and Rapid Reversal of Anticoagulation With Andexanet Alfa



[a]Patients included were healthy volunteers ranging from 50-75 years of age. The modified intention-to-treat population included all participants who underwent randomization, who received any amount of andexanet alfa or placebo, and for whom a baseline measurement of anti-FXa and at least one measurement of anti-FXa activity after treatment administration was available; [b]Efficacy-evaluable population included 234 patients taking either apixaban (n=134) or rivaroxaban (n=100). The total efficacy analysis set included 254 patients.

1. Siegal DM et al. *N Engl J Med*. 2015;373(25):2413-2424; 2. Connolly SJ et al. *N Engl J Med.* 2019;380(14):1326-1335.

Hemostatic Effectiveness and Mortality Rates in Clinical Trials Evaluating FXa Inhibitor-associated Bleeding

ANNEXA-4[1]

Hemostatic Effectiveness[a]

82%

achieved excellent/good hemostasis at 12 hours

Overall Mortality

14%

overall mortality rate at 30 days

ICrH-related Mortality

15%

ICrH-related mortality rate at 30 days

Other Clinical Studies[2,3]

ICrH-related Mortality[b]

45% to **48%**

ICrH-related mortality rates in apixaban- and rivaroxaban-treated patients receiving standard of care in other clinical studies

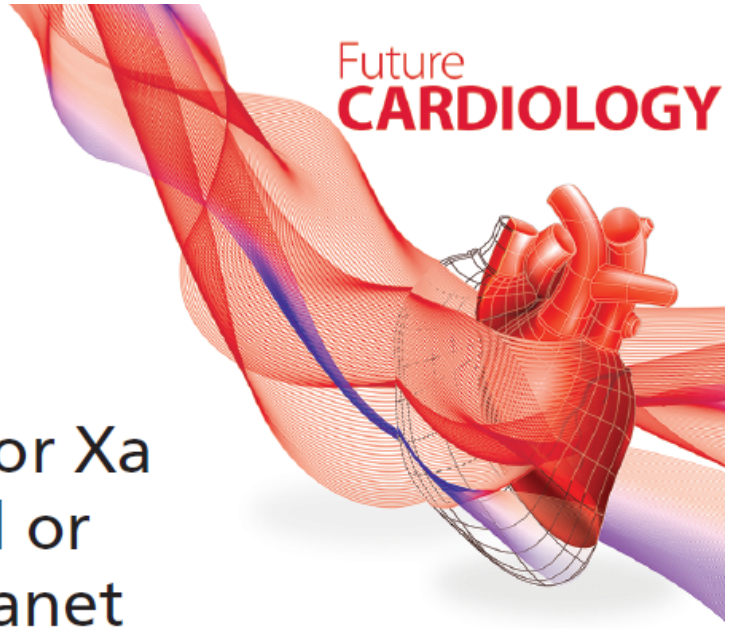
[a]Of the 254 patients in the efficacy analysis set, 249 could be evaluated for hemostatic efficacy[1]; [b]30-day mortality rates were reported in apixaban-treated patients and overall morality rates throughout the study duration were reported in rivaroxaban-treated patients.

ICrH = intracranial hemorrhage.

1. Connolly SJ et al. *N Engl J Med.* 2019;380(14):1326-1335; 2. Held C et al. *Eur Heart J.* 2015;36(20):1264-1272; 3. Hankey GJ et al. *Stroke.* 2014;45(5):1304-1312.

Andexanet Alfa in All Bleed Types

Short Communication 2021



Real-world management of oral factor Xa inhibitor-related bleeds with reversal or replacement agents including andexanet alfa and four-factor prothrombin complex concentrate: a multicenter study

Craig I Coleman*,[1], Paul P Dobesh[2], Sherry Danese[3], Julie Ulloa[3] & Belinda Lovelace[4]

Coleman CI et al. *Future Cardiol.* 2021;17(1):127-135.

Study Design

Search Strategy

Multicenter, observational, retrospective study identified patients hospitalized for oral FXa inhibitor-related bleeding between January 2016 and September 2019 through EMR data from **45 hospitals in the US (N=3030)**

Patient Selection Criteria

Patients were included in the analysis if they:

- Were an adult patient hospitalized for anticoagulation-related bleeding with ICD-10 indicative of bleeding due to extrinsic factors at the time of inpatient admission or during the hospital stay
- Received an oral FXa inhibitor prior to admission

Outcomes and Analysis

- Outcomes evaluated included:
  - Patient demographics
  - Bleed type[a]
  - Length of hospital stay
  - Level of care (inpatient vs. ICU)
  - Anticoagulant administered prior to the bleed
  - Reversal or replenishing agent[b]
  - In-hospital mortality status

[a]Bleed type categorized as GI bleed, ICrH, critical compartment bleed, traumatic not otherwise specified or other; [b]Reversal or replacement agents include andexanet alfa, 4F-PCC, fresh frozen plasma, and other agents. EMR = electronic medical record;

Coleman CI et al. *Future Cardiol.* 2021;17(1):127-135.

Baseline Characteristics

	Total sample N=3,030	Andexanet alfa n=342	4F-PCC n=733	FFP n=925	All other[a] n=794	No reversal Administered n=438
Age	67.6	69.1	70.1	66.9	66.8	67.3
Gender, n (%)						
Male	1,605 (53)	188 (55)	369 (50)	474 (51)	452 (57)	224 (51)
Female	1,424 (47)	154 (45)	364 (50)	451 (49)	341 (43)	214 (49)
FXa Inhibitor						
Apixaban	45%	47%	51%	42%	46%	39%
Edoxaban	6%	3%	8%	6%	5%	5%
Rivaroxaban	49%	50%	41%	52%	49%	56%
Other	<1%	0%	0%	<1%	0%	0%
Bleed Type						
GI	48%	40%	41%	50%	53%	52%
ICrH	17%	20%	23%	16%	14%	11%
Critical compartment	4%	3%	29%	27%	23%	19%
Traumatic	26%	31%	4%	4%	4%	3%
Other	6%	6%	3%	3%	6%	15%

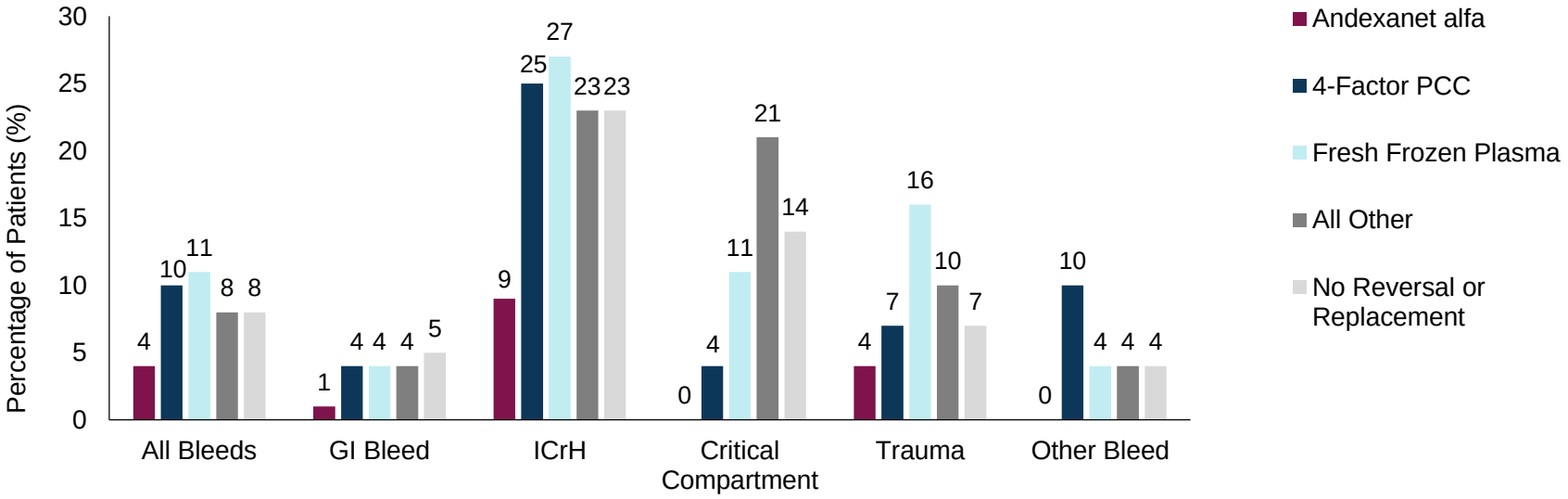
[a]All other reversal or replacement agents include 3F-PCCs, recombinant factor VIIa, activated 4F-PCC, tranexamic acid and vitamin K.

3F-PCC = three-factor prothrombin complex concentrate; 4F-PCC = four-factor prothrombin complex concentrate; FFP = fresh frozen plasma; FXa = factor Xa; GI = gastrointestinal; ICrH = intracranial hemorrhage.

Coleman CI et al. *Future Cardiol.* 2021;17(1):127-135.

Lower In-hospital Mortality Observed With Andexanet Alfa Versus Other Coagulation Agents Across US Hospitals

Inpatient Mortality by Bleed Type and Reversal or Replacement Agent Administered[a]



Observed inpatient mortality for patients managed with andexanet alfa (n=342) was **4%** and 8-11% for patients managed with other supportive care options (n=2688)

[a]Prior to admission, 49% of patients had been treated with rivaroxaban and 45% of patients had been treated with apixaban.
4F-PCC = four-factor prothrombin complex concentrate; GI = gastrointestinal; ICrH = intracranial hemorrhage; US = United States.
Coleman CI et al. *Future Cardiol.* 2021;17(1):127-135.

Andexanet Alfa is Associated With a Significant Reduction in In-hospital Mortality Compared to 4F-PCC in a Real-world Analysis

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July 12, 2022

Dobesh PP et al. Presented at: International Society on Thrombosis and Haemostasis (ISTH) Congress; July 9-13, 2022; London, UK

Study Design

Search Strategy

Multicenter, retrospective, observational chart review study identified hospitalized patients who were administered andexanet alfa or 4F-PCC for oral FXa inhibitor- or enoxaparin-related bleeding between May 17, 2018 and September 30, 2021 from **184 hospitals in the US (N=2830)**

Patient Selection Criteria

Patients were included in the analysis if they:

- ≥18 years of age and hospitalized for anticoagulation-related bleeding with an ICD-10 indicative of bleeding due to extrinsic factors at the time of inpatient admission
- Received an oral FXa inhibitors or enoxaparin prior to admission and were managed with andexanet alfa or 4F-PCC
- Had a documented discharge disposition

Outcomes and Analysis

Outcomes evaluated included:

- In-hospital mortality, adjusted using a multivariate logistic regression model
- Treatment patterns
- Hospital utilization
- Clinical outcomes

4F-PCC = four-factor prothrombin complex concentrate; FXa = factor Xa; ICD-10 = International Classification of Diseases, Tenth Revision; US = United States.

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Baseline Characteristics

	Andexanet alfa (n = 1366)	4F-PCC (n = 1464)	p-value[a]
Age, years, mean; median (IQR)	64; 65 (19)	65; 66 (20)	0.092
Sex, n (%)			
Male	754 (55)	834 (57)	0.343
Female	612 (45)	630 (43)	0.343
Anticoagulant use, n (%)			
Apixaban	543 (40)	591 (40)	0.738
Rivaroxaban	383 (28)	372 (25)	0.114
Edoxaban	69 (5)	48 (3)	0.018
Enoxaparin	370 (27)	449 (31)	0.036
Time since last dose, n (%)			
<8 hrs	570 (42)	590 (40)	0.441
8-18 hrs	569 (42)	615 (42)	0.849
>18 hrs	227 (17)	259 (18)	0.449
Alteration in mental status (yes), n (%)	444 (33)	497 (34)	0.415
Do not resuscitate order (yes), n (%)	292 (21)	332 (23)	0.404
Systolic BP (first measurement), mmHg, mean; median (IQR)	133; 134 (46)	128; 130 (45)	<0.001

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Baseline Characteristics (continued)

	Andexanet alfa (n = 1366)	4F-PCC (n = 1464)	p-value[a]
Comorbidities, n (%)			
Hypertension	709 (52)	796 (54)	0.189
Diabetes	537 (39)	652 (45)	0.005
Chronic kidney disease	315 (23)	345 (24)	0.751
Heart failure	310 (23)	343 (23)	0.643
Prior stroke	271 (20)	284 (19)	0.768
Peptic ulcer disease	197 (14)	210 (14)	0.953
Liver disease	174 (13)	193 (13)	0.725
None of the above	146 (11)	120 (8)	0.023
Unknown	132 (10)	99 (7)	0.005
Bleed location, n (%)			
CI	836 (61)	861 (59)	0.195
ICrH	360 (26)	394 (27)	0.737
Critical compartment/non-compressible bleed	156 (11)	174 (12)	0.700
Other bleed	14 (1)	35 (2)	0.005
Cause of bleed, n (%)			
Spontaneous	751 (55)	842 (58)	0.174
Trauma	451 (33)	457 (31)	0.305
Other	4 (<1)	8 (1)	0.300
Unknown	160 (12)	157 (11)	0.405

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Healthcare Resource Utilization

	Andexanet alfa (n = 1366)	4F-PCC (n = 1464)	p-value[a]
Length of stay, days, mean; median (IQR)[b]	6; 5 (5) (n = 1288)	6; 5 (5) (n = 1343)	0.56
Length of ICU stay, days, mean; median (IQR)[b]	3; 2 (3) (n = 848)	3; 2 (3) (n = 941)	0.404
In-hospital mortality (yes), n (%)	78 (6)	121 (8)	0.008
Discharge disposition, n (%)			
Home	719 (53)	761 (52)	0.728
Other destination	381 (28)	362 (25)	0.056
Death	78 (6)	121 (8)	0.008
Unknown	188 (14)	220 (15)	0.339

[a]Unadjusted analysis; [b]Assessed in patients surviving to discharge.

4F-PCC = four-factor prothrombin complex concentrate; ICU = intensive care unit; IQR = interquartile range.

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Factors Associated With an Increased Risk of In-hospital Mortality

Factor		Adjusted OR (95% CI)
Anticoagulant Use	Oral FXa inhibitor (vs enoxaparin)	1.26 (0.86 to 1.87)
Bleed Subtype	**ICrH (vs GI bleed)**	3.46 (2.35 to 5.16)
	Critical compartment (vs GI bleed)	0.93 (0.42 to 1.87)
	Other (vs GI bleed)	2.28 (0.61 to 6.72)
Bleed Cause	Trauma (vs spontaneous)	1.36 (0.96 to 1.94)
Patient characteristics	Age (per year)	1.01 (1.00 to 1.02)
	Male (vs female)	1.10 (0.78 to 1.55)
	Systolic blood pressure (per mmHg)	1.00 (1.00 to 1.01)
	Impaired mental status (vs none)	4.62 (3.03 to 7.26)
	Do not resuscitate order (vs no)	3.28 (2.29 to 4.74)
Comorbid Conditions	Liver disease (vs no)	1.23 (0.78 to 1.88)
	Chronic kidney disease (vs no)	2.00 (1.38 to 2.88)
	Heart failure (vs no)	1.15 (0.79 to 1.66)
	Diabetes (vs no)	1.02 (0.72 to 1.45)
Oral Anticoagulant	8-18 hrs since oral anticoagulant (vs >18 hrs)	1.51 (0.92 to 2.55)
	<8 hrs since oral anticoagulant (vs >18 hrs)	1.41 (0.86 to 2.38)

Key factors associated with higher odds of death include:

- **ICrH bleeds**
- **Impaired mental status**
- **DNR order**
- **Presence of chronic kidney disease**

Note: Sample excludes patients who used both andexanet alfa and 4F-PCC and those without a value for baseline impaired mental status.
4F-PCC = four-factor prothrombin complex concentrate; CI = confidence interval; DNR = do not resuscitate; FXa = factor Xa; GI = gastrointestinal; hrs = hours; ICrH = intracranial hemorrhage; OR = odds ratio.
Dobesh PP et al. Presented at: International Society on Thrombosis and Haemostasis (ISTH) Congress; July 9-13, 2022; London, UK.

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Treatment With Andexanet Alfa is Associated With a Lower In-hospital Mortality Risk Versus 4F-PCC

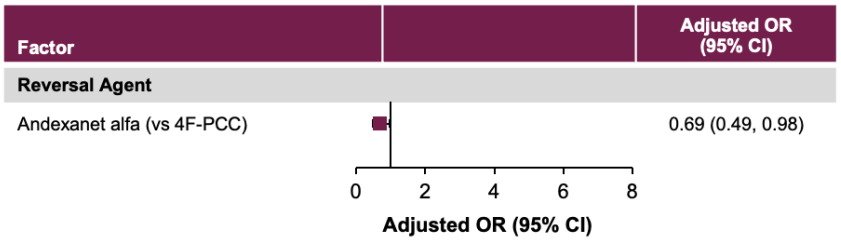
Unadjusted Baseline Characteristics By Bleed Location

	Andexanet alfa (n=1366)	4F-PCC (n=1464)	p-value
Bleed location, n (%)			
GI	836 (61)	861 (59)	0.195
ICrH	360 (26)	394 (27)	0.737
Critical compartment/non-compressible bleed	156 (11)	174 (12)	0.700
Other bleed	14 (1)	35 (2)	0.005

Unadjusted In-hospital Mortality

	Andexanet alfa (n=1366)	4F-PCC (n=1464)	p-value
In-hospital mortality, n (%)	78 (6)	121 (8)	0.008

Adjusted Odds Ratio of In-hospital Mortality for Andexanet Alfa vs. 4F-PCC[a]



Treatment with andexanet alfa was associated with a **31% lower likelihood of in-hospital mortality risk** versus 4F-PCC (OR, 0.69; 95% CI, 0.49-0.98)

[a]Models were adjusted for anticoagulants used, time since last dose, bleed type, trauma vs. spontaneous, age, sex, systolic blood pressure, mental status, do not resuscitate status, and comorbid liver, kidney disease, heart failure and diabetes.

4F-PCC = four-factor prothrombin complex concentrate; CI = confidence interval; GI = gastrointestinal; ICrH = intracranial hemorrhage; OR = odds ratio.

Dobesh PP et al. Presented at: International Society on Thrombosis and Haemostasis (ISTH) Congress; July 9-13, 2022; London, UK.

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ORIGINAL RESEARCH

General Medicine

Thirty-day mortality with andexanet alfa compared with prothrombin complex concentrate therapy for life-threatening direct oral anticoagulant-related bleeding

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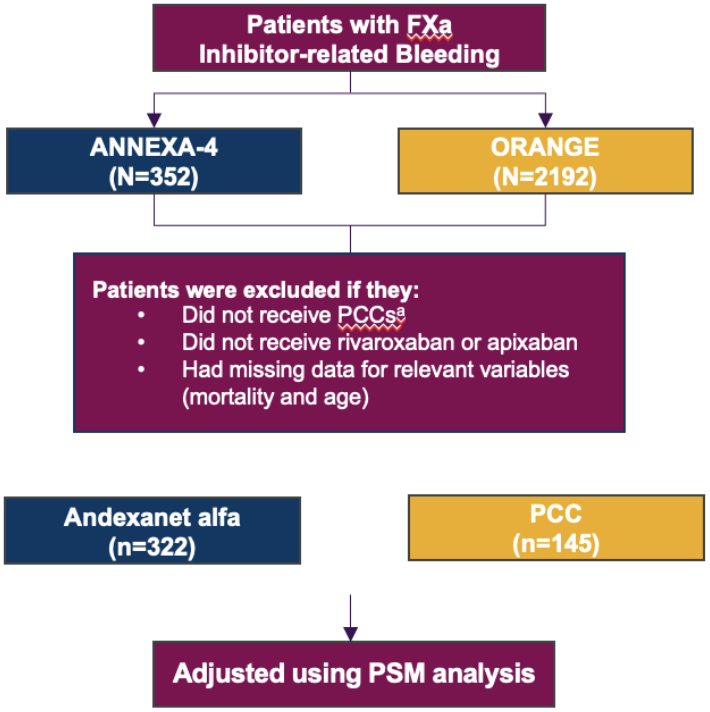
1. Cohen AT et al. *JACEP Open.* 2022;3(2):e12655; 2. Cohen AT et al. Poster presented at: American College of Cardiology 2020; March 28-30, 2020; Chicago, IL.

Study Design[1]



Outcomes and Analysis

- 30-day mortality was analyzed by entire cohort and by bleed type (ICrH, GI, and other major bleeds)
- PSM was conducted using the NICE Decision Support Unit technical support document 17

Differences in Study Populations

- ORANGE did not have exclusion criteria while ANNEXA-4 did[1]
- Volume of blood products received was sufficient for inclusion in ORANGE[2]
- Hemodynamic compromise was sufficient for inclusion in ANNEXA-4[3]

[a]Patients in the ORANGE registry study only.

ANNEXA-4 = The Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors-4; FXa = factor Xa; GI = gastrointestinal; ICrH = intracranial hemorrhage; NICE = National Institute for Health and Care Excellence; ORANGE = ORal ANticoagulant aGEnt-associated bleeding events reporting system; PCC = prothrombin complex concentrate; PSM = propensity score matching.

1. Cohen AT et al. *JACEP Open.* 2022;3(2):e12655; 2. Green L et al. *Haematologica.*2018;103(4):738-745; 3. Connolly SJ et al. *N Engl J Med.* 2019;380(14):1326-1335.

Baseline Characteristics

	Before PSM			After PSM		
	Andexanet alfa	PCC	Abs dif	Andexanet alfa	PCC	Abs dif
Total (N)	322	145	--	322	88	--
Age, years, mean ± SD	77.7 ± 10.79	81.0 ± 9.47	-3.3	77.7 ± 10.79	74.9 ± 9.96	2.9
Bleed Type (%)						
ICrH	64.9	50.3	14.6	64.9	67.1	-2.2
GI bleed	25.5	37.9	-12.5	25.5	28.6	-3.1
Other major bleeds[a]	9.6	11.7	-2.1	9.6	4.4	5.3
Medical History (%)						
Stroke	18.9	6.2	12.7	18.9	15.2	3.7
CAD	13.0	22.8	-9.7	13.0	7.5	5.6
TIA	7.5	24.1	-16.7	7.5	7.1	0.3
AF	83.9	77.9	5.9	83.9	78.9	5.0
Hypertension	78.3	55.9	22.4	78.3	72.7	5.6
Diabetes	30.4	22.1	8.4	30.4	26.7	3.7
Renal dysfunction	23.3	15.2	8.1	23.3	24.5	-1.2
Cancer	26.7	16.6	10.2	26.7	17.7	9.0

[a]Bleed types other than ICrH or GI bleeds.
Abs dif = absolute difference; AF = atrial fibrillation; CAD = coronary artery disease; GI = gastrointestinal; ICrH = intracranial hemorrhage; PCC = prothrombin complex concentrate; PSM = propensity score matching; TIA = transient ischemic attack.
Cohen AT et al. *JACEP Open.* 2022;3(2):e12655.

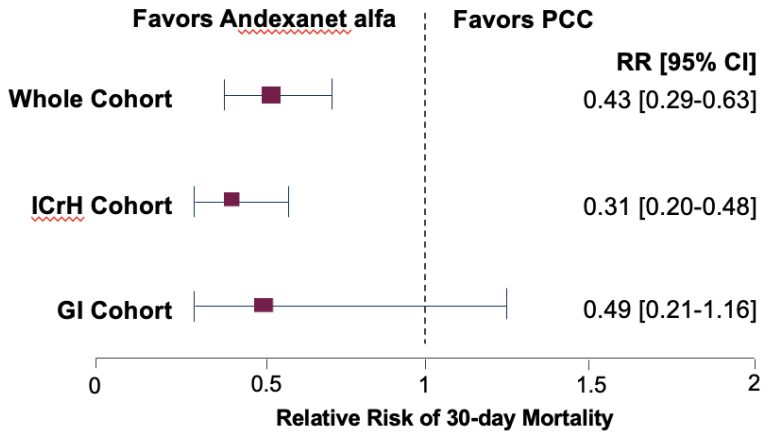
1. Cohen AT et al. *JACEP Open.* 2022.

Lower Overall and ICrH Mortality Observed With Andexanet Alfa in a PSM Analysis of ANNEXA-4 and ORANGE Patients

Adjusted 30-day Mortality Rate by Bleed Type[1,2,a]

Population	Number of Matches	30-day Mortality (%)		Relative Reduction (%)	p-value
		Andexanet alfa	PCC		
Whole cohort	Andexanet alfa = 322 PCC = 88	14.60	34.09	-57.17	<0.001
ICrH subgroup	Andexanet alfa = 209 PCC = 47	15.31	48.94	-68.72	<0.001
GI subgroup	Andexanet alfa = 82 PCC = 28	12.20	25.00	-51.20	0.11
Other bleeds subgroup	Andexanet alfa = 31 PCC = 8	16.13	12.50	29.04	0.79

Relative Risk of 30-day Mortality by Bleed Type[1,a,b]



30-day mortality was **reduced by 57%** in patients receiving andexanet alfa versus matched patients receiving PCC **across the whole patient population**

[a]Adjusted using propensity score matching for age, bleed site, and medical history of atrial fibrillation, hypertension, diabetes, cancer, renal dysfunction, stroke, coronary artery disease, and transient ischemic attack; [b]Confidence intervals could not be obtained for the other bleeds subgroup due to the low number of matches n<10.

ANNEXA-4 = The Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors-4; CI = confidence interval; DOAC = direct oral anticoagulant; ICrH = intracranial hemorrhage; GI = gastrointestinal; ORANGE = ORal ANticoagulant aGEnt-associated bleeding events reporting system; PCC = prothrombin complex concentrate; PSM = propensity score-matched; RR = relative risk.

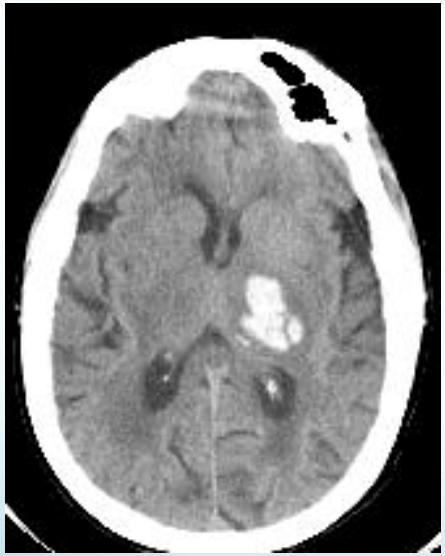
1. Cohen AT et al. *JACEP Open.* 2022;3(2):e12655; 2. Cohen AT et al. Poster presented at: American College of Cardiology 2020; March 28-30, 2020; Chicago, IL.

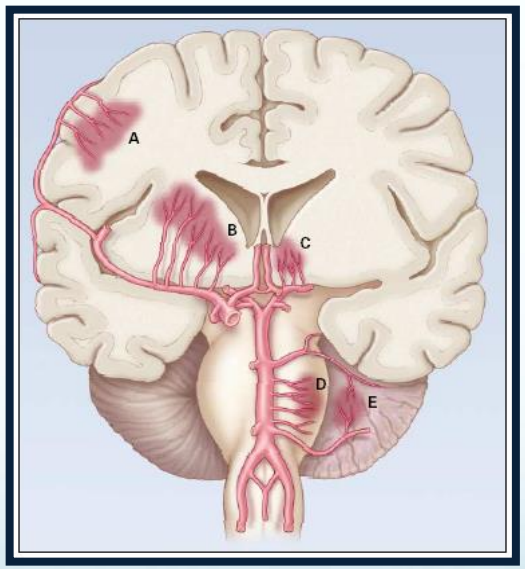
Andexanet Alfa in Brain Hemorrhages

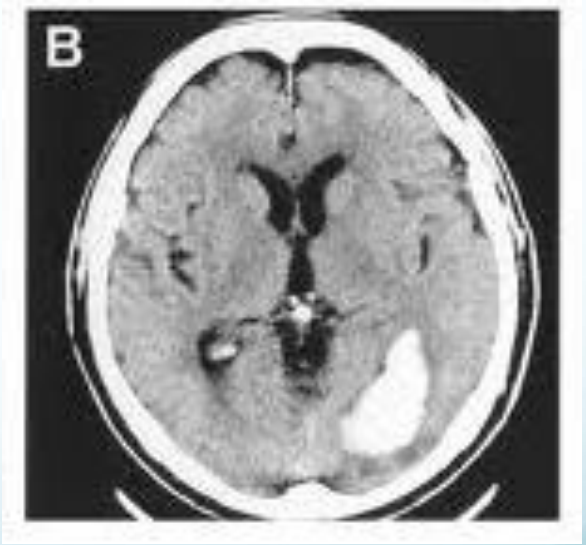
Emorragia cerebrale (ICH)

Profonda

Lobare

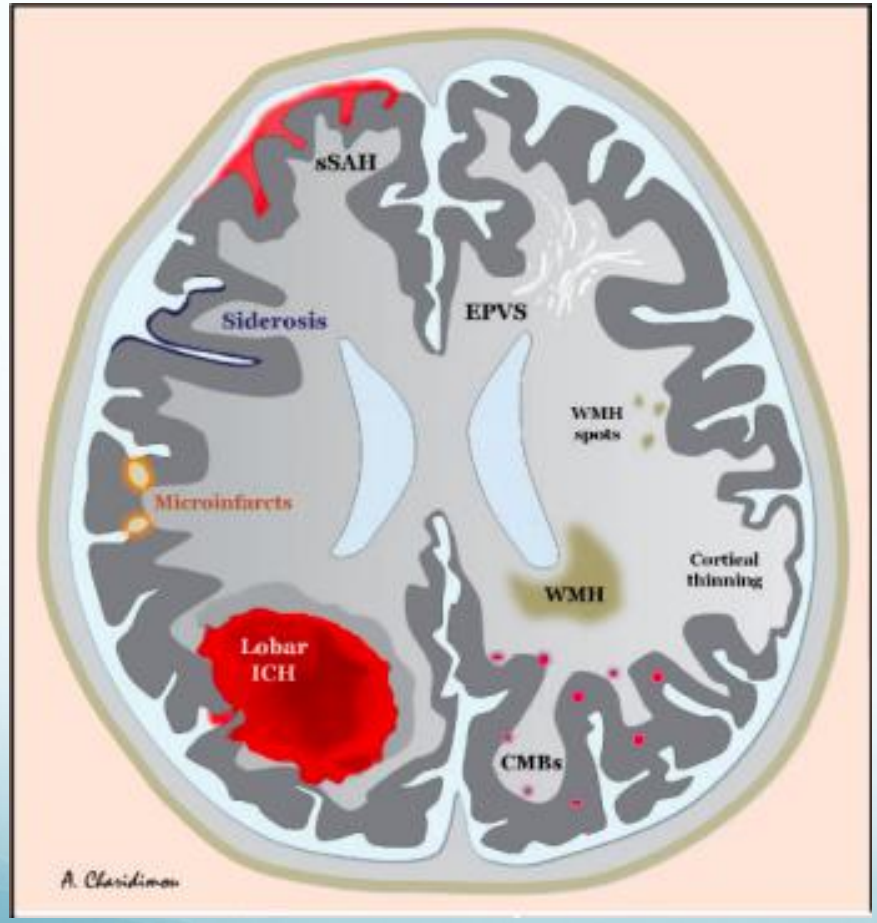






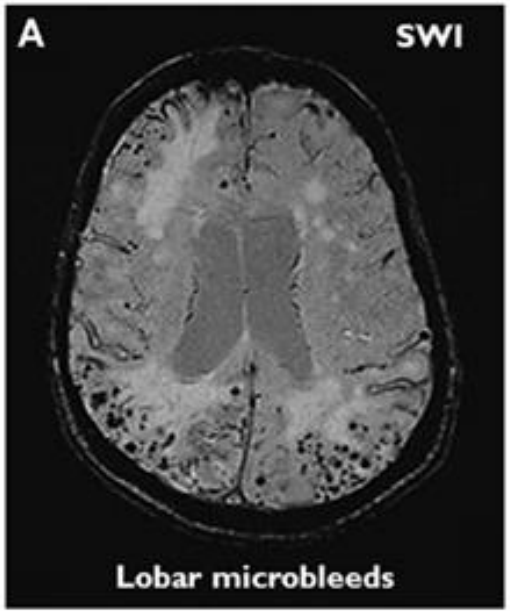
Qureshi AI, Tuhrim S, Broderick JP, Batjer HH, Hondo H, Hanley DF. Spontaneous intracerebral hemorrhage. N Engl J Med 2001;344:1450-60.

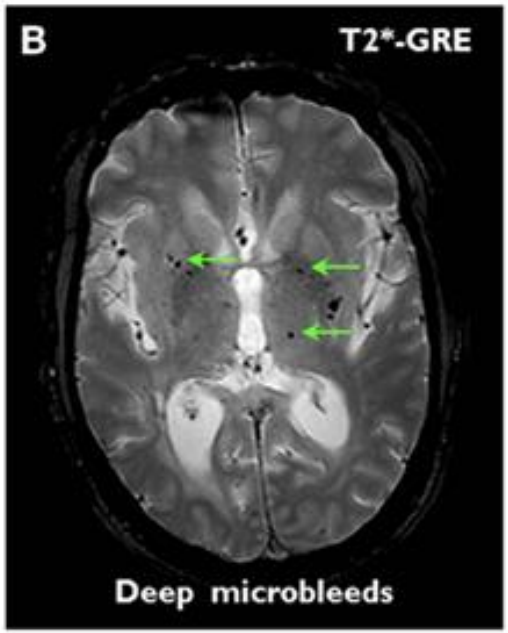
Angiopatia amiloide cerebrale (CAA)

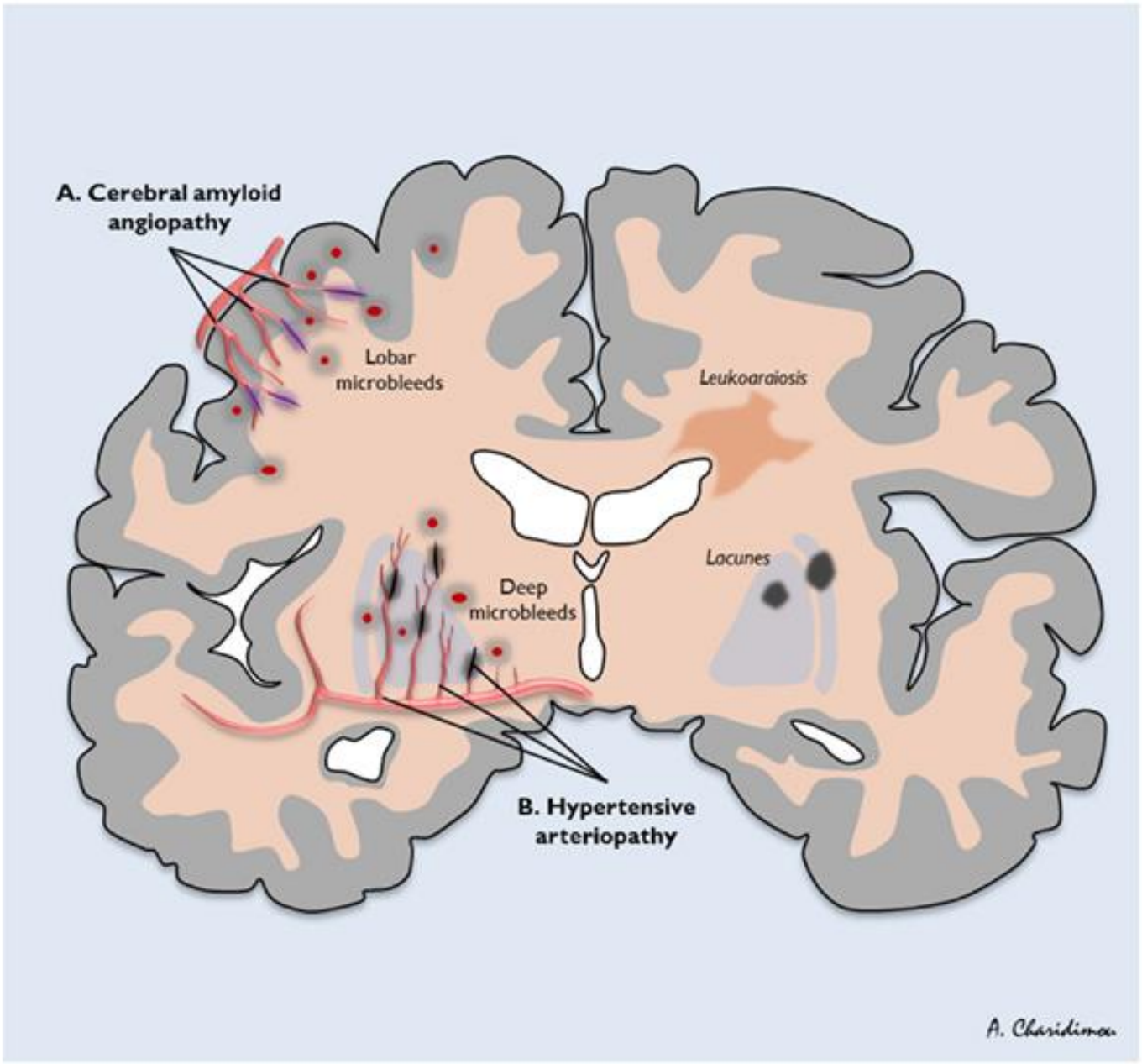


Emorragiche	Ischemiche
Emorragie intracerebrali lobari- ICH	Leucoencefalopatia ischemica
Microbleeds- CMBs	Microinfarti
Emorragie subaracnoidee (convessità)- sSAH	Lacune
Siderosi corticale superficiale - cSS	

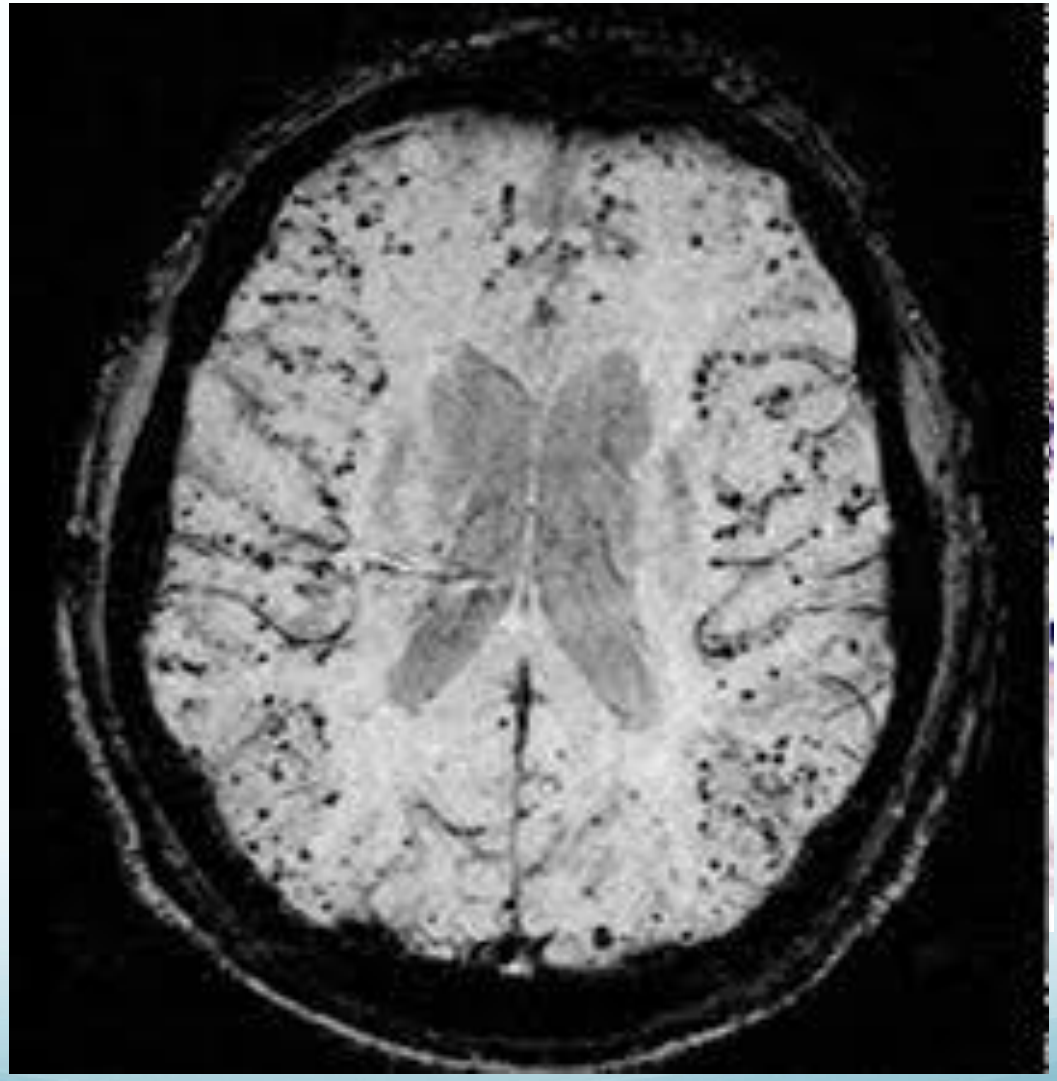
Microbleeds



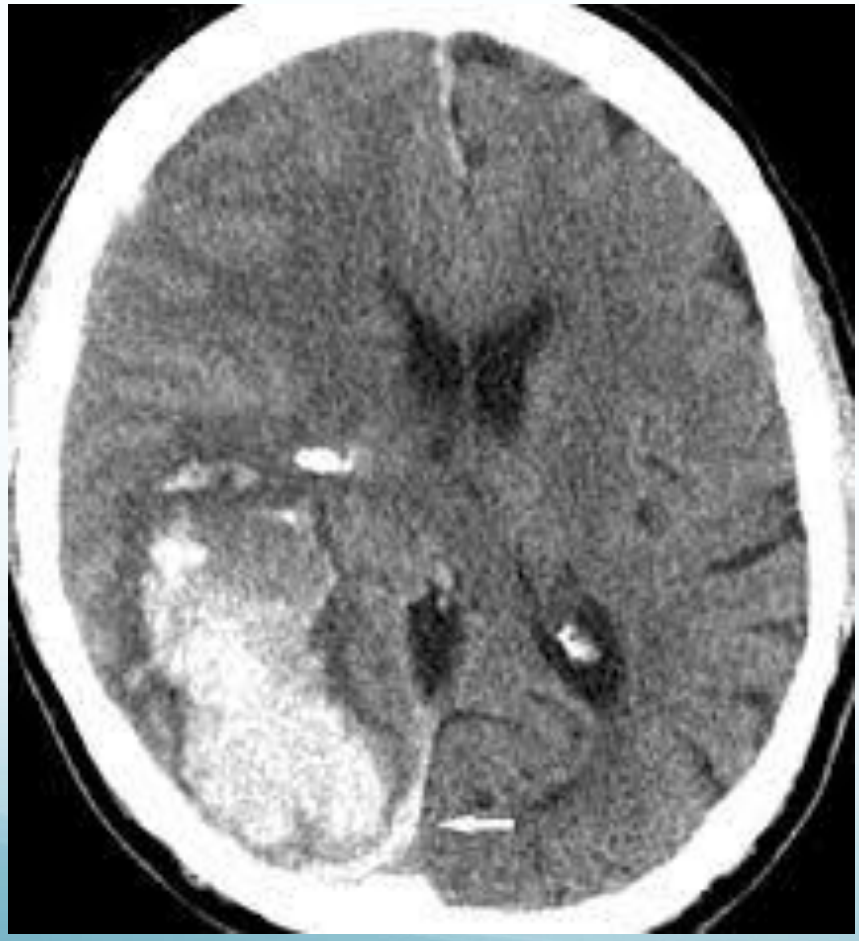


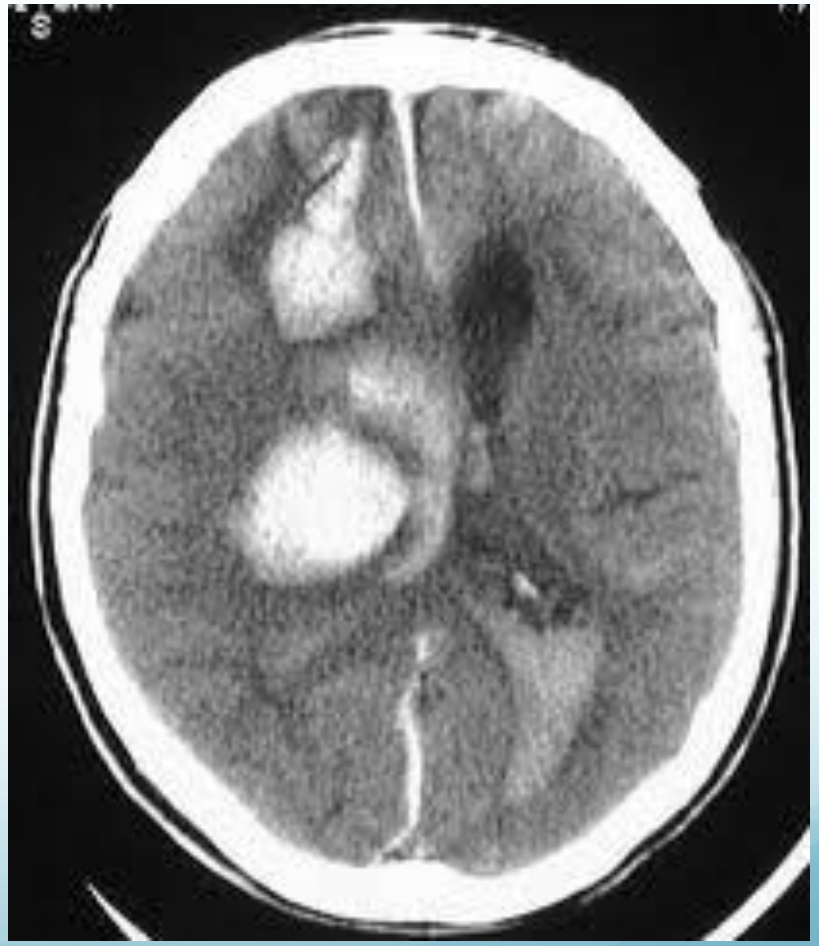


Emorragia cerebrale lobare: angiopatia amiloide

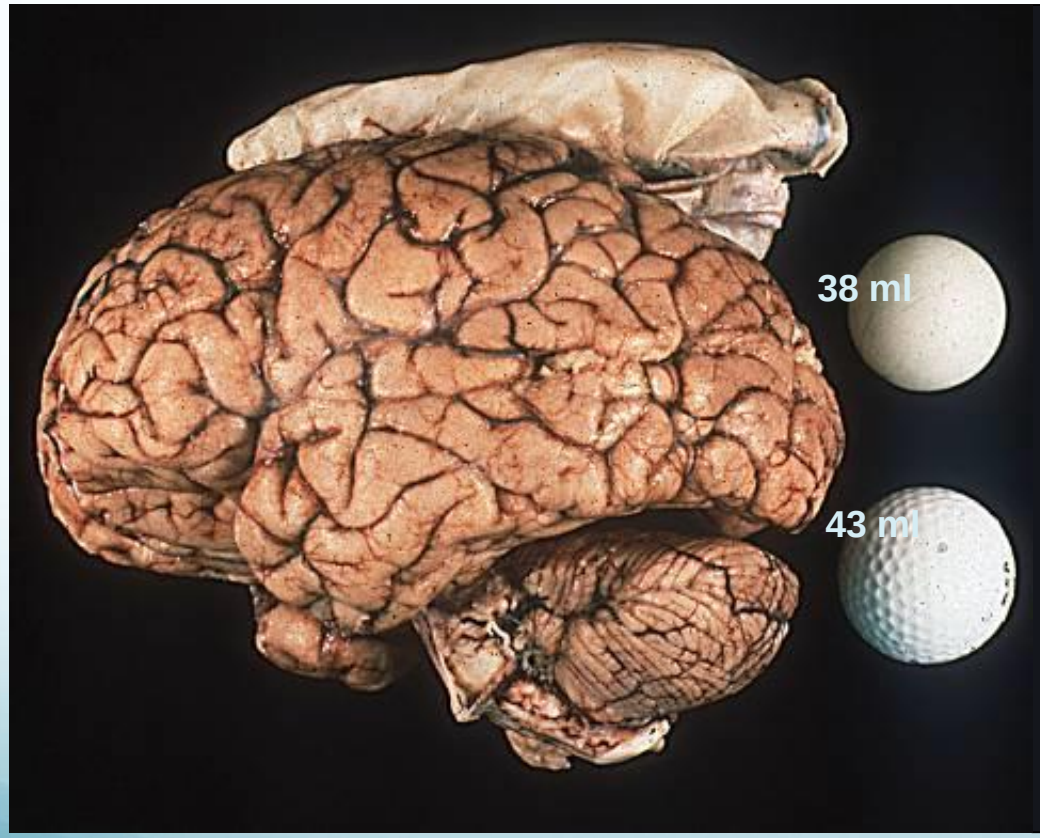


Emorragia cerebrale lobare: angiopatia amiloide





Size is the most important **predictor** for patient outcome



- **A patient with a haemorrhage the size of a ping pong ball is likely to have a better outcome that a patient with a haemorrhage the size of golf ball:**
  - mortality on ’ping pong’ size: app. 40%
  - mortality on ’golf ball’ size: app. 70%

Davis SM et al. Neurology 2006;66:1175-1181

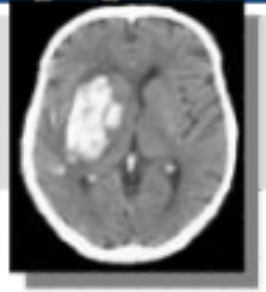
Volume dell'ematoma

- Mortalità più alta nei primi 3 giorni.
- Danno tissutale diretto da parte dell'ematoma, con dislocazione del parenchima ed erniazione, proporzionale al volume stesso.

Volume, ml	Mortalità a 30 giorni,%
< 30	7- 23
30-60	60-64
> 60	71-93

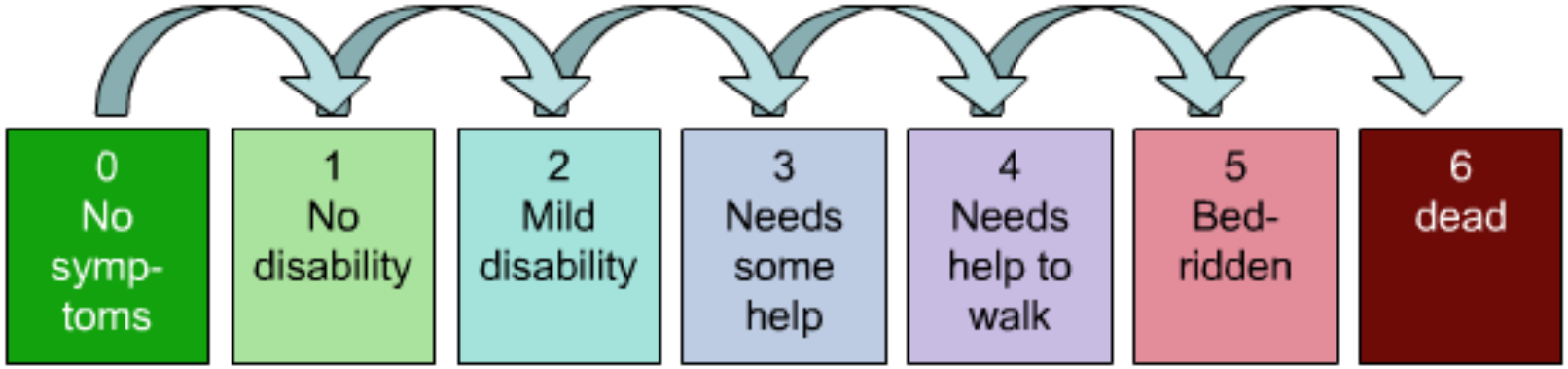
Broderick JP et al. Stroke 1993; 24: 617-21

Baseline volume and outcome



Each ml increase

⇒ 6% more likely to get worse by 1 point



Modified Rankin Score

Davis SM et al. Neurology 2006;66:1175-1181

COSA SAPEVAMO DAI TRIAL: ANNEXA-4 SUBSTUDY

Stroke

CLINICAL AND POPULATION SCIENCES

Hemostatic Efficacy and Anti-FXa (Factor Xa) Reversal With Andexanet Alfa in Intracranial Hemorrhage

ANNEXA-4 Substudy

Andrew M. Demchuk, MD; Patrick Yue, MD; Elena Zotova, PhD; Juliet Nakamya, PhD; Lizhen Xu, PhD; Truman J. Milling, Jr, MD; Tomoyuki Ohara, MD; Joshua N. Goldstein, MD, PhD; Saskia Middeldorp, MD; Peter Verhamme, MD, PhD; Jose Luis Lopez-Sendon, MD; Pamela B. Conley, PhD; John T. Curnutte, MD, PhD; John W. Eikelboom, MD; Mark Crowther, MD; Stuart J. Connolly, MD; on behalf of the ANNEXA-4 Investigators

1. Demchuk AM et al. *Stroke*. 2021;52:00-00; 2. Demchuk AM et al. *Stroke*. 2021;52:00-00 (Suppl).

ANNEXA-4 SUBSTUDY: INTRACRANIAL HEMORRHAGE

HEMOSTATIC EFFICACY CRITERIA[1-2]

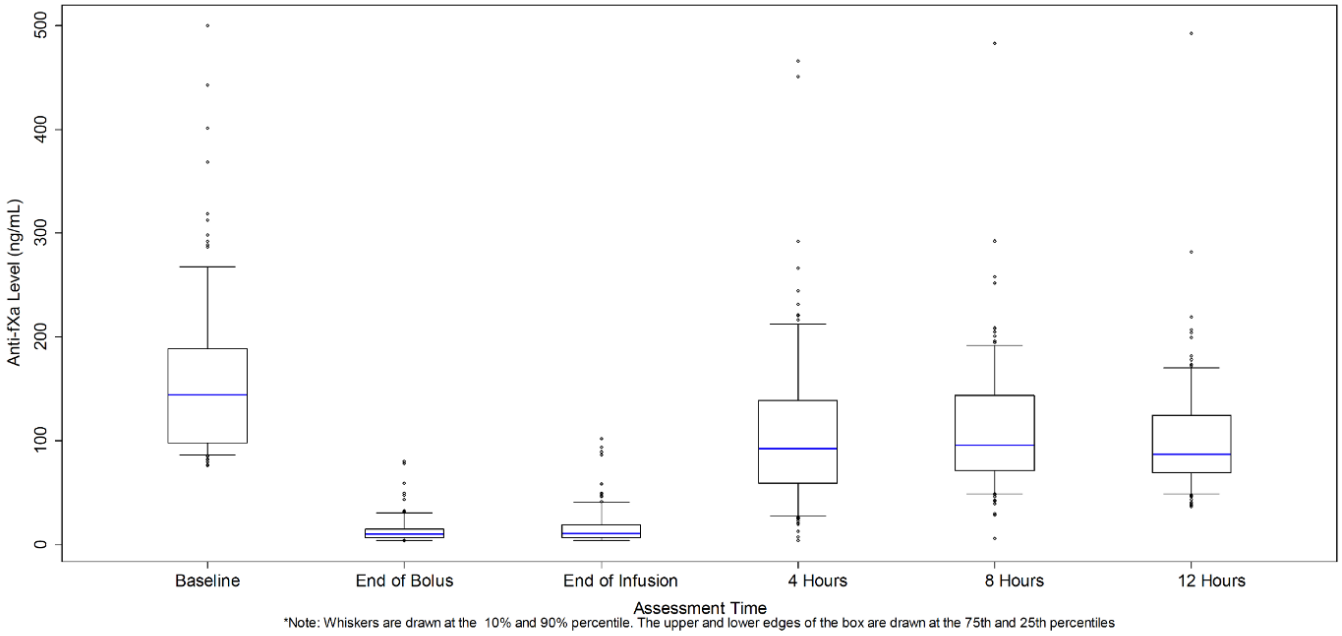
Excellent†* (effective)	Good† (effective)	Poor/None‡ (not effective)
•Intracerebral hemorrhage: ≤20% increase in hematoma volume compared to baseline on a repeat CT or MRI scan performed at both the 1- and 12-hour post-infusion time points.	**•Intracerebral hemorrhage:** >20% but ≤35% increase in hematoma volume compared to baseline on a repeat CT or MRI scan performed at +12-hour time point.	**•Intracerebral hemorrhage:** >35% increase in hematoma volume on a CT or MRI compared to baseline on a repeat CT or MRI scan at +12-hour time point.
•Subarachnoid bleeding: ≤20% increase in maximum thickness using the most dense area on the follow-up versus baseline at both the 1- and 12-hour post-infusion time points.	**•Subarachnoid bleeding:** >20% but <35% increase in maximum thickness using the most dense area on the follow-up +12-hours versus baseline.	**•Subarachnoid bleeding:** >35% increase in maximum thickness using the most dense area on the +12 hours versus at baseline.
•Subdural hematoma: ≤20% increase in maximum thickness at both the 1- and 12-hour post-infusion assessments compared to baseline.	**•Subdural hematoma:** >20% but <35% increase in maximum thickness at +12-hours compared to baseline.	**•Subdural hematoma:** >35% increase in maximum thickness at +12 hours compared to baseline.

1. Connolly et al. *N Engl J Med.* 2019;380(14):1326-1335; 2. Protocol for: Connolly SJ, Crowther M, Eikelboom JW, et al. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. *N Engl J Med*. DOI: 10.1056/NEJMoa1814051.

ANNEXA-4 SUBSTUDY: INTRACRANIAL HEMORRHAGE

ANTI-FXA ACTIVITY FOR APIXABAN-TREATED PATIENTS

Anti-FXa Activity for Apixaban Patients
- Efficacy population - All ICH subset



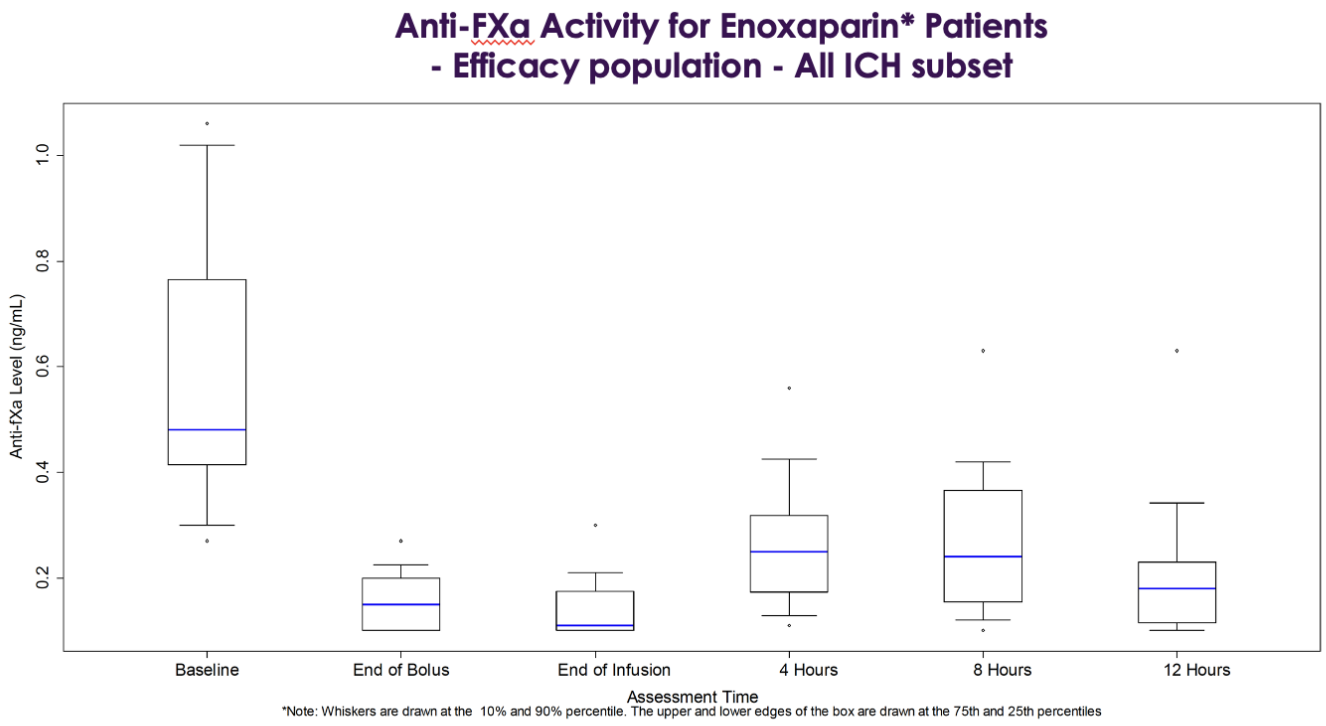
*Note: Whiskers are drawn at the 10% and 90% percentile. The upper and lower edges of the box are drawn at the 75th and 25th percentiles

Anti-FXa activity over time for patients with either spontaneous and traumatic intracranial hemorrhage who had received apixaban. The horizontal lines represent the median values. Median baseline anti-FXa activity levels were **144.2 ng/mL** at baseline and **9.6 ng/mL** at the lowest value post-andexanet treatment. The median percentage decrease from baseline to nadir was **-93.8% (95% CI: -94.6% to -92.6%).**

1. Demchuk AM et al. *Stroke*. 2021;52:00-00; 2. Demchuk AM et al. *Stroke*. 2021;52:00-00 (Suppl).

ANNEXA-4 SUBSTUDY: INTRACRANIAL HEMORRHAGE

ANTI-FXA ACTIVITY FOR ENOXAPARIN*-TREATED PATIENTS

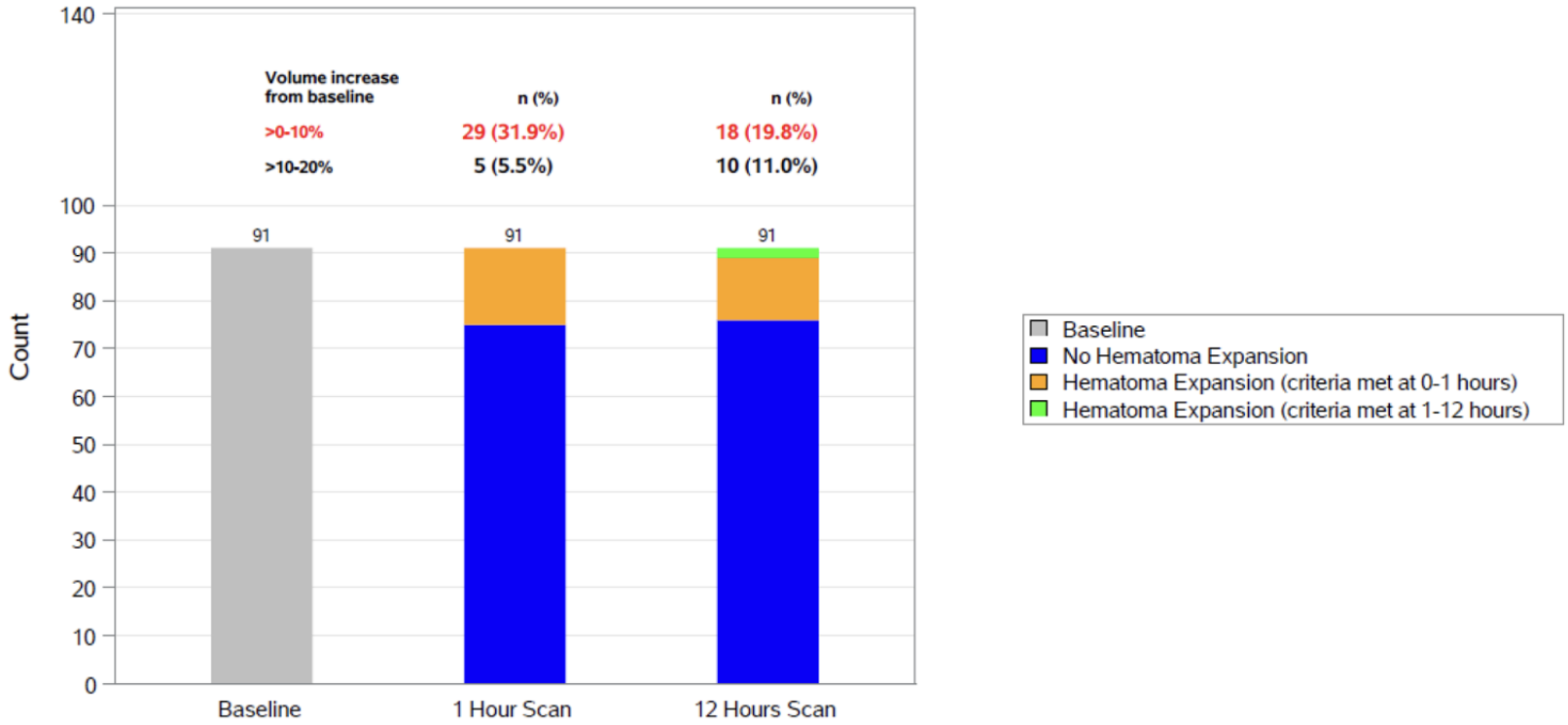


Anti-FXa activity over time for patients with spontaneous and traumatic intracranial hemorrhage who had received enoxaparin. The horizontal lines represent the median value. Median baseline anti-FXa activity levels were **0.5 IU/mL** at baseline and 0.1 IU/mL at the lowest value post-andexanet treatment. The median percentage decrease from baseline to nadir was **-75.4% (95% CI: -79.4% to -66.7%).**

1. Demchuk AM et al. *Stroke*. 2021;52:00-00; 2. Demchuk AM et al. *Stroke*. 2021;52:00-00 (Suppl).

ANNEXA-4 SUBSTUDY: INTRACRANIAL HEMORRHAGE

HEMATOMA EXPANSION IN SPONTANEOUS INTRACEREBRAL/IVH BLEEDS (SAFETY POPULATION)



Hematoma expansion defined as greater than 35% increase in hematoma volume relative to baseline at the specific time indicated in the figure. The plot only includes subjects with no missing values at baseline, 1 hour, and 12 hours scan. Eight patients were excluded due to missing data.

1. Demchuk AM et al. *Stroke*. 2021;52:00-00; 2. Demchuk AM et al. *Stroke*. 2021;52:00-00 (Suppl).

REAL WORLD EVIDENCE:

Stroke - 2022

ORIGINAL CONTRIBUTION

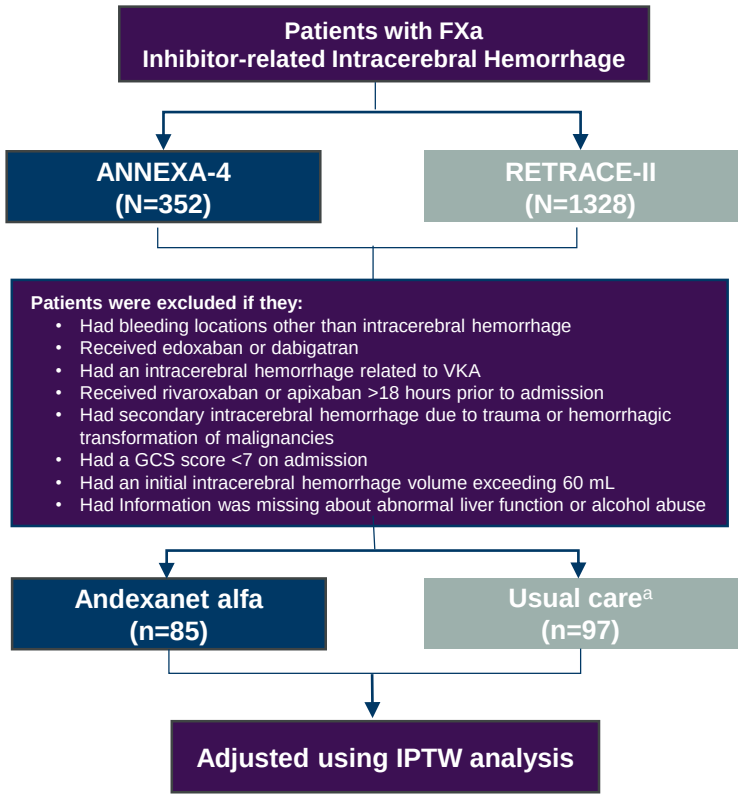
Hematoma Expansion and Clinical Outcomes in Patients With Factor-Xa Inhibitor–Related Atraumatic Intracerebral Hemorrhage Treated Within the ANNEXA-4 Trial Versus Real-World Usual Care

Hagen B. Huttner, MD, PhD*; Stefan T. Gerner, MD*; Joji B. Kuramatsu, MD; Stuart J. Connolly, MD; Jan Beyer-Westendorf, MD; Andrew M. Demchuk, MD; Saskia Middeldorp, MD; Elena Zotova, PhD, CCRP; Julia Altevers, MPH; Frank Andersohn, MD; Mary J. Christoph, PhD, MPH; Patrick Yue, MD; Leonhard Stross, PhD; Stefan Schwab, MD

Huttner HB et al. *Stroke.* 2022;53(2):532-543.

Study Design

German-Wide Multicenter Analysis of Oral Anticoagulant-Associated Intracerebral Hemorrhage - Part II



Outcomes and Analysis

- **Primary outcome:** proportion of patients with hematoma expansion[b] 12 hours post baseline in ANNEXA-4 and at first follow-up imaging in RETRACE-II
- **Secondary outcomes:** mean absolute change in hematoma volume between initial and follow-up imaging, in-hospital mortality, and functional outcome at discharge[c]
- Propensity score-adjusted analyses were performed using the IPTW approach

[a]Usual care included any reversal treatment, PCC, vitamin K, fresh frozen plasma, tranexamic acid, antithrombin, and platelet concentrates; [b]Hematoma expansion was defined as an increase ≥35% in intracerebral hemorrhage volume between baseline and follow-up imaging; [c]Functional outcome was based on the mRS at discharge or at day 30 and were dichotomized as favorable (mRS score: 0-3) versus unfavorable (mRS score: 4-6).

ANNEXA-4 = The Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors-4; FXa = factor Xa; GCS = Glasgow Coma Scale; IPTW = inverse probability of treatment weighting; mRS = modified Rankin Scale;

PCC = prothrombin complex concentrate; RETRACE-II = German-wide Multicenter Analysis of Oral Anticoagulant-associated Intracerebral Hemorrhage; VKA = vitamin K antagonist.

Huttner HB et al. *Stroke.* 2022;53(2):532-543.

Baseline Characteristics

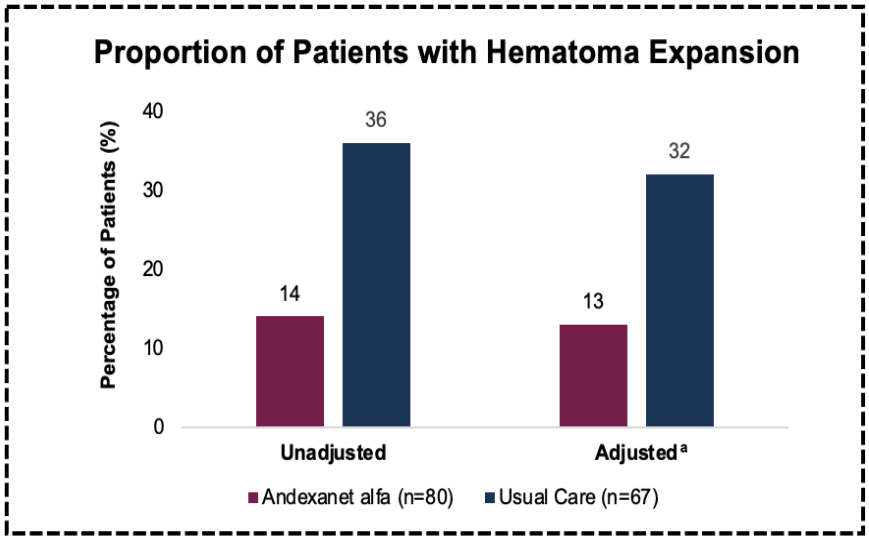
	ANNEXA-4 (n=85)	RETRACE-II (n=97)	ASD[a]	p-value
Demographics				
Age, years, mean (SD)	78.8 (9.0)	78.4 (7.6)	0.055	0.57
Female sex, n (%)	36 (42)	51 (53)	0.206	0.17
DOAC exposure, n (%)				
Apixaban	49 (58)	19 (20)	0.849	<0.001
Rivaroxaban	36 (42)	78 (80)	0.849	<0.001
Comorbidities, n (%)				
Hypertension	75 (88)	87 (91)	0.078	0.60
Diabetes mellitus	35 (41)	32 (33)	0.163	0.28
Dyslipidemia	41 (48)	32 (33)	0.307	0.041
Prior MI	9 (11)	12 (13)	0.060	0.69
Congestive heart failure	11 (13)	19 (20)	0.186	0.22
Abnormal kidney function	13 (15)	18 (19)	0.092	0.54
Prior ischemic stroke or TIA	28 (33)	28 (30)	0.075	0.62
Prior hemorrhagic stoke or major bleed	6 (7)	8 (8)	0.048	0.75
Peripheral arterial occlusive disease	3 (4)	4 (4)	0.033	>0.99
Prior use of statins	47 (55)	27 (28)	0.566	<0.001
Prior use of antiplatelets	26 (31)	12 (13)	0.451	0.003
Clinical status on admission				
Glasgow Coma Scale, mean (SD)	13.5 (2.1)	13.0 (2.5)	0.217	0.32
NIHSS, mean (SD)	8.11 (6.50)	10.17 (6.93)	0.308	0.093
Intracerebral characteristics				
Intracerebral hemorrhage score, mean (SD)	1.15 (1.02)	1.44 (1.10)	0.273	0.076
Initial intracerebral volume (cm^3): mean (SD)	13.6 (14.0)	16.1 (17.0)	0.163	0.73
Intraventricular hemorrhage, n (%)	11 (13)	38 (40)	0.644	<0.001
Infratentorial bleeding, n (%)	17 (20)	11 (11)	0.055	0.57

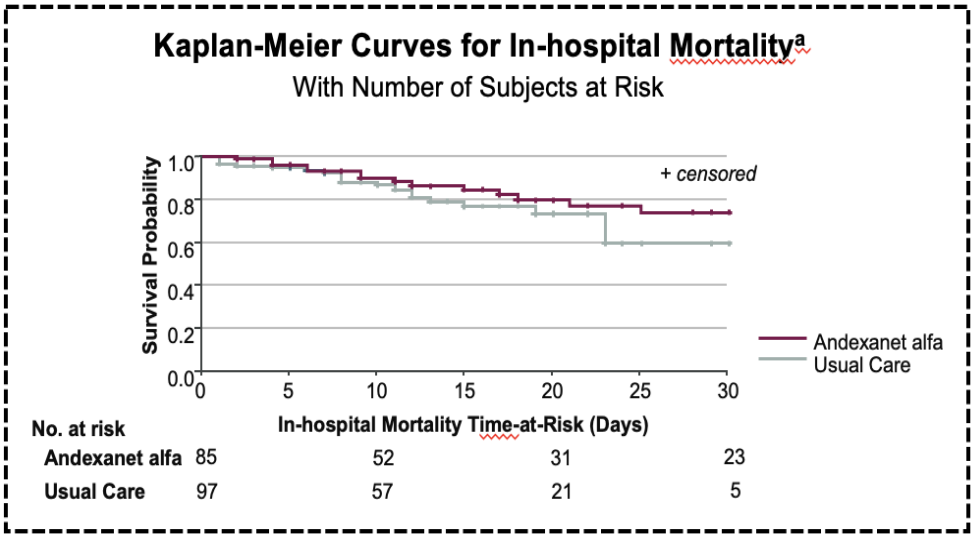
[a]Differences between treatment groups were reported as absolute standardized differences.

ANNEXA-4 = The Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors-4; ASD = absolute standardized differences; DOAC = direct oral anticoagulant; MI = myocardial infarction; NIHSS = National Institute of Health Stroke Scale; RETRACE-II = German-wide Multicenter Analysis of Oral Anticoagulant-associated Intracerebral Hemorrhage; SD = standard deviation; TIA = transient ischemic attack.

Huttner HB et al. *Stroke.* 2022;53(2):532-543.

IPTW Analysis of ANNEXA-4 and RETRACE-II Patients Suggests Less Hematoma Expansion With Andexanet Alfa



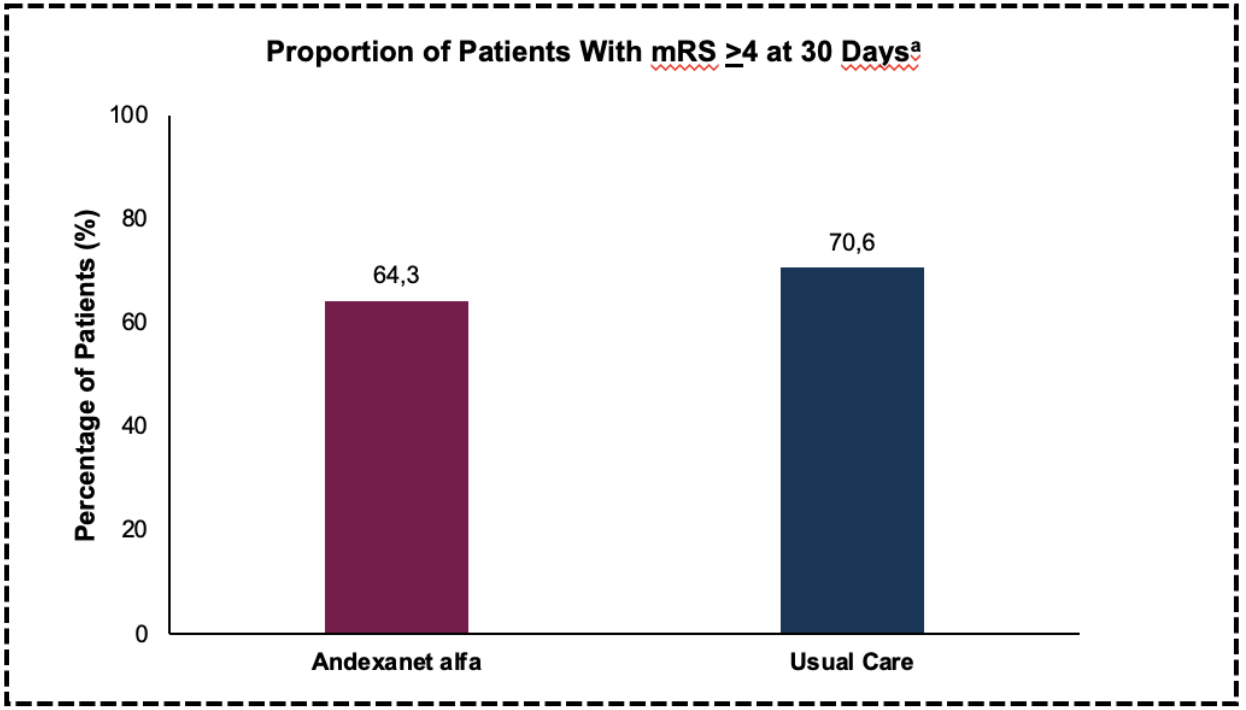


The relative risk of hematoma expansion was **60% lower in patients treated with andexanet alfa** (aRR, 0.40; 95% CI, 0.20-0.78; p=0.005)

Patients treated with andexanet alfa trended toward a **lower rate of mortality** versus usual care (HR, 0.49; 95% CI, 0.24-1.04; p = 0.06)

Huttner HB et al. *Stroke.* 2022;53(2):532-543.

Functional Outcomes Observed at 30 Days With Andexanet Alfa and Usual Care



[a]Adjusted using IPTW analysis.

ANNEXA-4 = The Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors-4; CI = confidence interval; IPTW = inverse probability of treatment weighting; mRS = modified Rankin Scale; RETRACE-II = German-wide Multicenter Analysis of Oral Anticoagulant-associated Intracerebral Hemorrhage; RR = relative risk.

Huttner HB et al. *Stroke.* 2022;53(2):532-543.

Huttner HB et al. *Stroke.* 2022;53(2):532-543.

Costa *et al. Critical Care* (2022) 26:180
https://doi.org/10.1186/s13054-022-04043-8

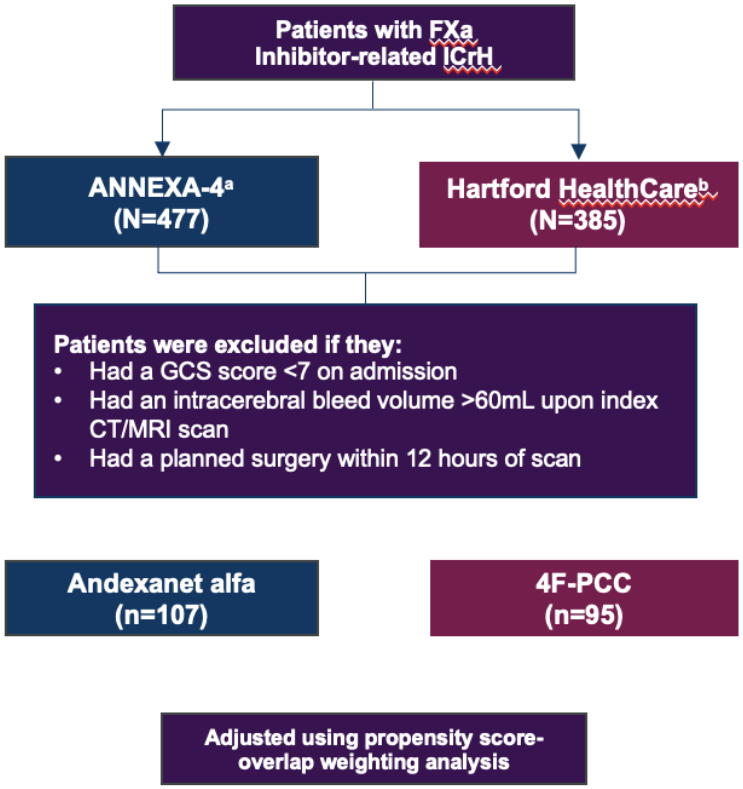
Critical Care

RESEARCH Open Access

Andexanet alfa versus four-factor prothrombin complex concentrate for the reversal of apixaban- or rivaroxaban-associated intracranial hemorrhage: a propensity score-overlap weighted analysis

Olivia S. Costa[1,2], Stuart J. Connolly[3,4], Mukul Sharma[3,4], Jan Beyer-Westendorf[5], Mary J. Christoph[6], Belinda Lovelace[6] and Craig I. Coleman[1,2*]

Study Design



Outcomes and Analysis

- **Co-primary outcomes:** Hemostatic effectiveness and 30-day all-cause mortality[c]
- **Secondary outcomes:** Occurrence of thrombotic event during the first 5 days after reversal agent administration[d]
- A propensity score-overlap weighting analysis was used

[a]Only US patients enrolled in the ANNEXA-4 trial were included in this analysis; [b]The synthetic control arm used EHR data from Hartford Healthcare; [c]Excellent/good hemostasis was defined as a ≤35% increase in hematoma size from index to repeat scan at approximately 12 hours after reversal administration; [d]The five-day time frame for thrombotic events was selected as it was a time point specifically reported in ANNEXA-4.
4F-PCC = four factor-prothrombin complex concentrate; ANNEXA-4 = The Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors-4; CT = computed tomography; EHR = electronic health record; FXa = factor Xa; GCS = Glasgow Coma Scale; ICrH = intracranial hemorrhage; MRI = magnetic resonance imaging; US = United States.

Costa OS. *Crit Care*. 2022;26(1):180.

BASELINE CHARATERISTICS

	Andexanet alfa (n=107)	4F-PCC (n=95)
Demographics		
Age, years, mean ± SD	79 ± 8	77 ± 11
Male (%)	49.5	52.6
GCS score[a]	14 ± 1	14 ± 2
ICrH characteristics		
Initial imaging to reversal start, hours, mean ± SD	2.6 ± 1.8	2.1 ± 1.9
End of reversal to repeat imaging, hours, mean ± SD	12.4 ± 1.1	8.1 ± 5.1
Traumatic onset (%)	53.3	64.2
Infratentorial location (%)	16.8	12.6
Size of bleed ≥10 mL/mm (%)	33.6	14.7
Single compartment bleed (%)	77.6	85.3
Intracerebral and/or intraventricular bleed[b] (%)	59.8	48.4
Subdural bleed[b] (%)	32.7	40.0
Subarachnoid bleed[b] (%)	31.8	27.4

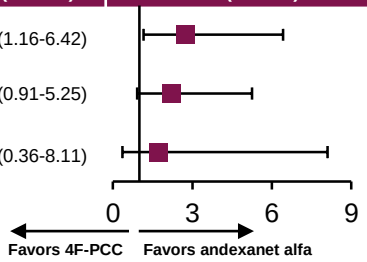
Costa OS. *Crit Care*. 2022;26(1):180.

Note: There were relevant differences in baseline characteristics of patients receiving andexanet alfa and 4F-PCC as evidenced by most covariates having an ASD >0.1 except the male and GCS score characteristics. [a]Not included in the propensity score model due to lack of heterogeneity at baseline; [b]ICrH types add up to >100% given that a portion of patients had multicompartment bleeds..

Improved Clinical and Safety Outcomes Associated With Andexanet Alfa in Real-world Indirect Comparative Effectiveness Study

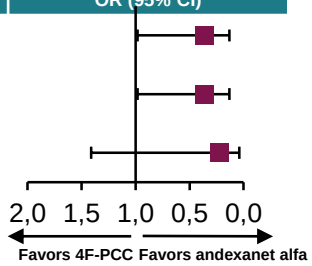
Adjusted Odds of Hemostatic Effectiveness for Andexanet Alfa vs. 4F-PCC[a]

	Weighted Incidence, % (95% CI)			
Hemostatic Effectiveness	Andexanet alfa (n=107)	4F-PCC (n=95)	OR (95% CI)	OR (95% CI)
Overall Cohort Analysis	85.8 (77.7-91.8)	68.1 (57.7-77.3)	2.73 (1.16-6.42)	
Sensitivity Analysis Adjudicating Missing Scans	85.0 (76.9-91.2)	72.2 (62.1-80.2)	2.19 (0.91-5.25)	
Intracerebral and/or Intraventricular Subgroup (AA, n=47; 4F-PCC, n=37)	78.2 (69.1-85.6)	67.7 (57.4-76.9)	1.71 (0.36-8.11)	



Adjusted Odds of 30-day Mortality for Andexanet Alfa vs. 4F-PCC[a]

	Weighted Incidence, % (95% CI)			
All-cause 30-day Mortality	Andexanet alfa (n=107)	4F-PCC (n=95)	OR (95% CI)	OR (95% CI)
Overall Cohort Analysis	7.9 (3.6-13.8)	19.6 (12.1-24.0)	0.36 (0.13-0.98)	
Sensitivity Analysis Adjudicating Missing Scans	7.9 (4.2-15.9)	19.3 (11.9-28.7)	0.36 (0.13-0.98)	
Intracerebral and/or Intraventricular Subgroup (AA, n=47; 4F-PCC, n=37)	7.5 (3.3-14.2)	26.7 (18.2-36.7)	0.22 (0.04-1.41)	



Incidence of **excellent/good hemostatic effectiveness** in the overall cohort analysis

85.8% for andexanet alfa **vs.** **68.1%** for 4F-PCC

30-day all-cause mortality in the overall cohort analysis

7.9% for andexanet alfa **vs.** **19.6%** for 4F-PCC

[a]Adjusted using propensity scores overlap weighting.

4F-PCC = four-factor prothrombin complex concentrate; AA = andexanet alfa; ANNEXA-4 = The Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors-4; CI = confidence interval; EMR = electronic medical record; FXa = factor Xa; ICrH = intracranial hemorrhage; OR = odds ratio.

Costa OS. *Crit Care*. 2022;26(1):180.

Summary
Real World Evidence

- **Improved survival rates** and **lower in-hospital mortality**
- Lower 30-day mortality rates observed in patients **with life-threatening** or uncontrolled major bleeding
- **Reduced** the rate of **hematoma expansion** demonstrated in FXa inhibitor-related intracerebral hemorrhage
- **Hemostatic effectiveness** achieved in **>85%** of patients with ICH

Grazie per l’ attenzione