Treatment of Factor Xa Inhibitor-Associated Bleeding with Andexanet Alfa: Full Results of ANNEXA-4

Stuart J. Connolly M.D., Mark Crowther M.D. , John W. Eikelboom M.D., C. Michael Gibson M.D., John T. Curnutte M.D. Ph.D., John H. Lawrence M.D., Patrick Yue M.D., Michele D. Bronson Ph.D., Genmin Lu Ph.D., Pamela B. Conley Ph.D., Peter Verhamme M.D. Ph.D., Jeannot Schmidt M.D., Saskia Middeldorp M.D., Alexander T. Cohen M.D., Jan Beyer-Westendorf M.D., Pierre Albaladejo M.D., Jose Lopez-Sendon M.D., Andrew M. Demchuk M.D., Daniel J. Pallin M.D., Shelly Goodman R. N., Janet Leeds Ph. D., Sonia Souza Ph.D., Deborah M. Siegal M.D., Elena Zotova Ph.D., Brandi Meeks M.Sc., Juliet Nakamya Ph.D., and Truman J. Milling Jr. M.D.

On behalf of the ANNEXA-4 Investigators

- Connolly SJ et al. *New Eng J Med*; 2019 Article in Press

Conflict of Interest Statement

Consulting; Significant; Population Health Research Institute at McMaster University.

Speakers' Bureau; Significant; Janssen.

Honoraria; Significant; CSL Behring.

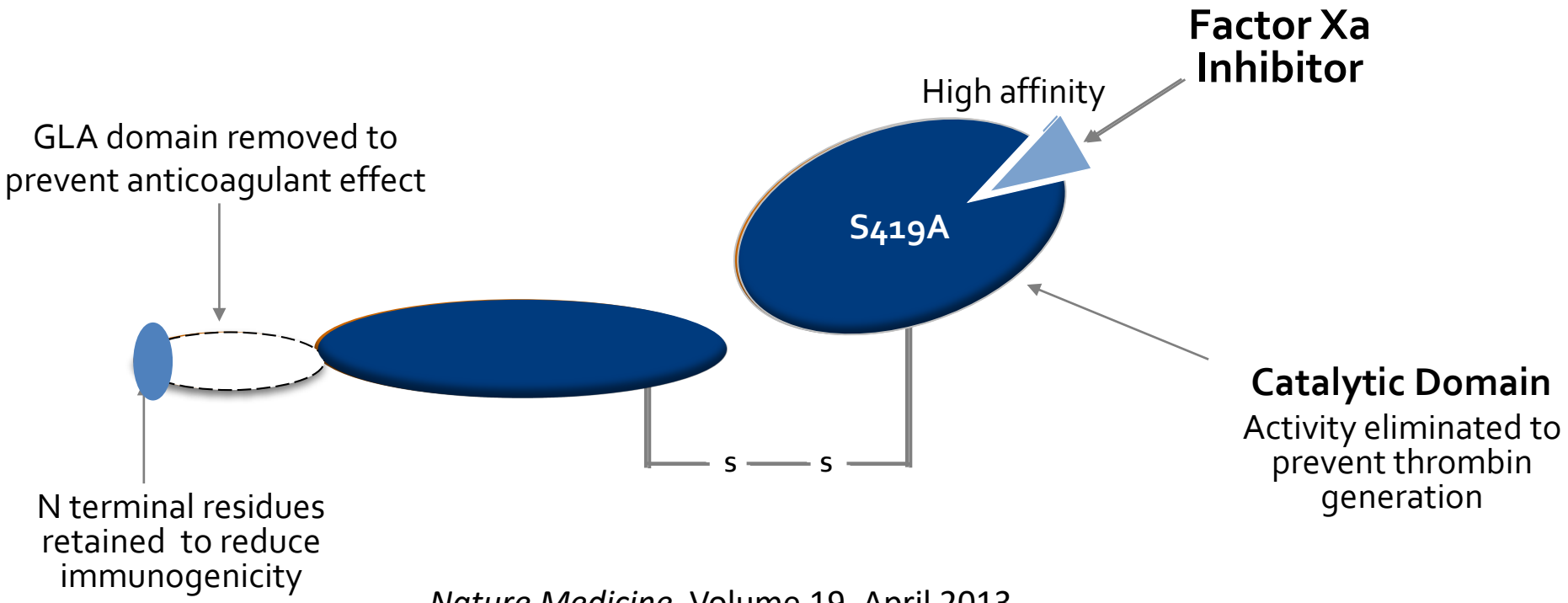
Consultant/Advisory Board; Modest; Octapharma, Portola

Background

- Factor Xa (fXa) inhibitors are effective, but can cause serious bleeding
- No other approved specific reversal agent available for fXa inhibitors
- Andexanet alfa developed as a specific reversal agent for direct oral fXa inhibitors
- It rapidly and safely reversed anti-fXa activity in healthy volunteers and in early interim results from bleeding patients

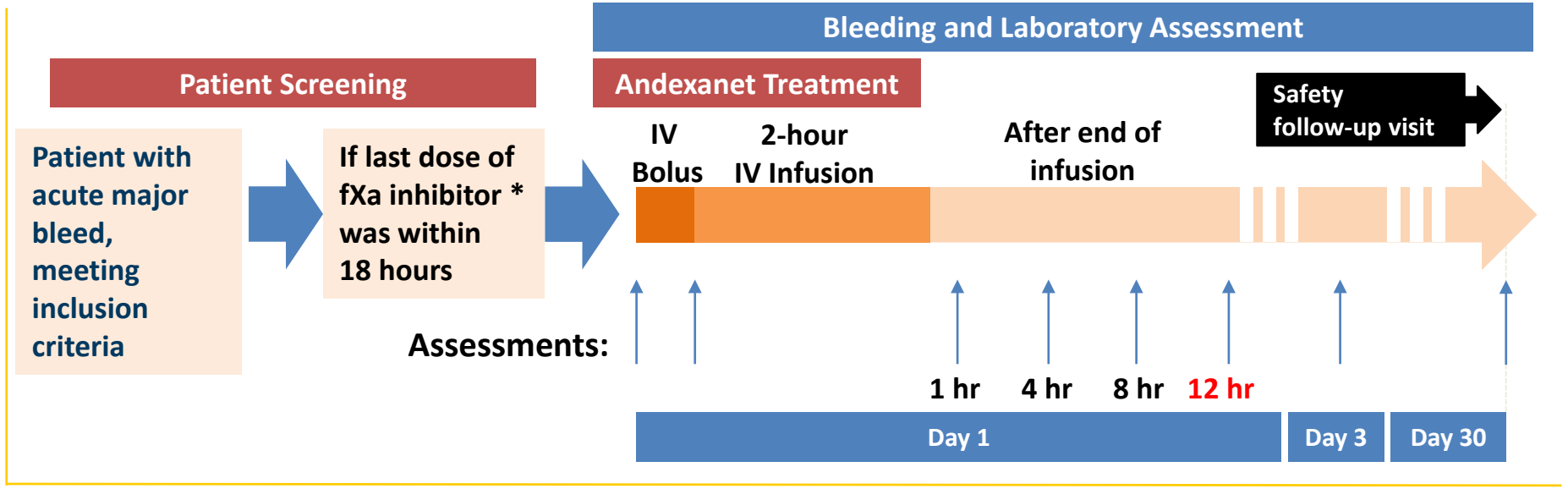
Andexanet alfa: Recombinant Modified Human Factor Xa

- Specifically designed to reverse anticoagulant effects of fXa inhibitors
- Acts as a fXa decoy to bind molecules that target and inhibit fXa



Nature Medicine, Volume 19, April 2013

ANNEXA-4 Study Design



Efficacy Measurements

- Change in anti-fXa activity
- Clinical hemostatic efficacy through 12 hours

Safety Measurements

- Thrombotic events
- Antibodies to fX, fXa, andexanet
- 30-day mortality

* apixaban, rivaroxaban, enoxaparin, or edoxaban

ANNEXA-4: Design and Analysis Plan

- **Criteria for Major Acute Bleeding**
  - Life-threatening bleeding with hemodynamic compromise
  - Bleeding with hemoglobin drop of >2 gm/dl, or falling below 8 gm/dl
  - Critical organ bleeding, such as intracranial, intra-spinal, etc.
- **Analysis Populations**
  - **Safety** population includes all patients receiving andexanet
  - **Efficacy** population excludes patients with baseline anti-fXa activity <75 ng/ml (0.25IU/ml for enoxaparin) and patients deemed not to meet acute major bleeding criteria by central academic adjudication committee
- **Full Analysis**
  - Includes 352 patients enrolled up to June 1, 2018

Assessment of Clinical Hemostatic Efficacy

- All cases assessed by independent committee
- Specific efficacy criteria for each type of bleed
- Independent Core Lab interpreted brain CT and MRI
- Cases rated as excellent vs. good vs. poor/none
  - For ICH, hematoma volume increase of 0-20% = excellent, 20-35% = good, > 35% = poor/none
- Based on method developed for assessment of PCC in warfarin reversal*

* Sarode R et al, *Circulation* 2013; 128: 1234-43.

Baseline Characteristics

	Safety Population N=352	Efficacy Population N=254
Age (yr), mean ± SD	77(±11)	77 (±11)
Male	187 (53%)	129 (51%)
Time from presentation to Andexanet (mean hrs)	4.7	4.8
Estimated creatinine clearance < 30 mL/min	33 (9%)	27 (11%)
Indication for anticoagulation		
Atrial fibrillation	280 (80%)	201 (79%)
Venous Thromboembolic Disease	61 (17%)	46 (18%)
Medical History		
Myocardial infarction	48 (14%)	36 (14%)
Stroke	69 (20%)	57 (22%)
Heart Failure	71 (20%)	56 (22%)

Site of Initial Bleeding

Safety Versus Efficacy Population	352	254
Intracranial Bleeding	**227 (64%)**	**171 (67%)**
Non-traumatic	128	99
Glasgow Coma Scale, mean	14	14
NIHSS, mean	5.7	5.2
mRS, mean	2.8	2.8
Trauma related	99	72
Intracerebral site	137	104
Hematoma Volume ≤10cc	84	66
Hematoma Volume 11-60 cc	53	38
Sub-dural site	75	58
Subarachnoid site	57	43
Time from baseline scan to drug admin, hours (SD)	2.4 (1.6)	2.4 (1.6)
Gastrointestinal Bleeding	**90 (26%)**	**62 (24%)**
Upper	27	21
Lower	21	14
Unknown	42	27
Other Bleeding site	**35 (10%)**	**21 (8%)**

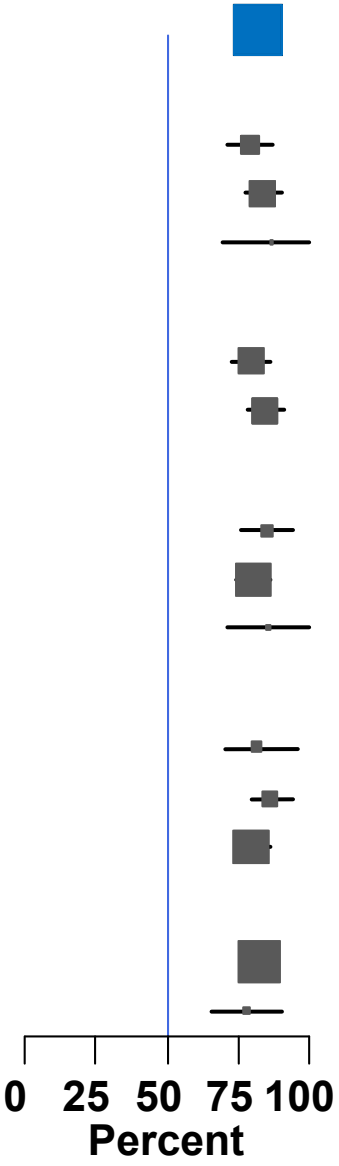
Main Results:
Effective Hemostasis at 12 Hours Post Andexanet

Number of Major Bleeds Adjudicated	Number of Patients who Achieved Excellent or Good Hemostasis	Percent of Patients who Achieved Excellent or Good Hemostasis	Binomial Exact 95% Confidence Interval
249	204*	82%	77% – 87%

** Of 204 patients, 171 (84%) were "excellent" and 33 (16%) were "good"*

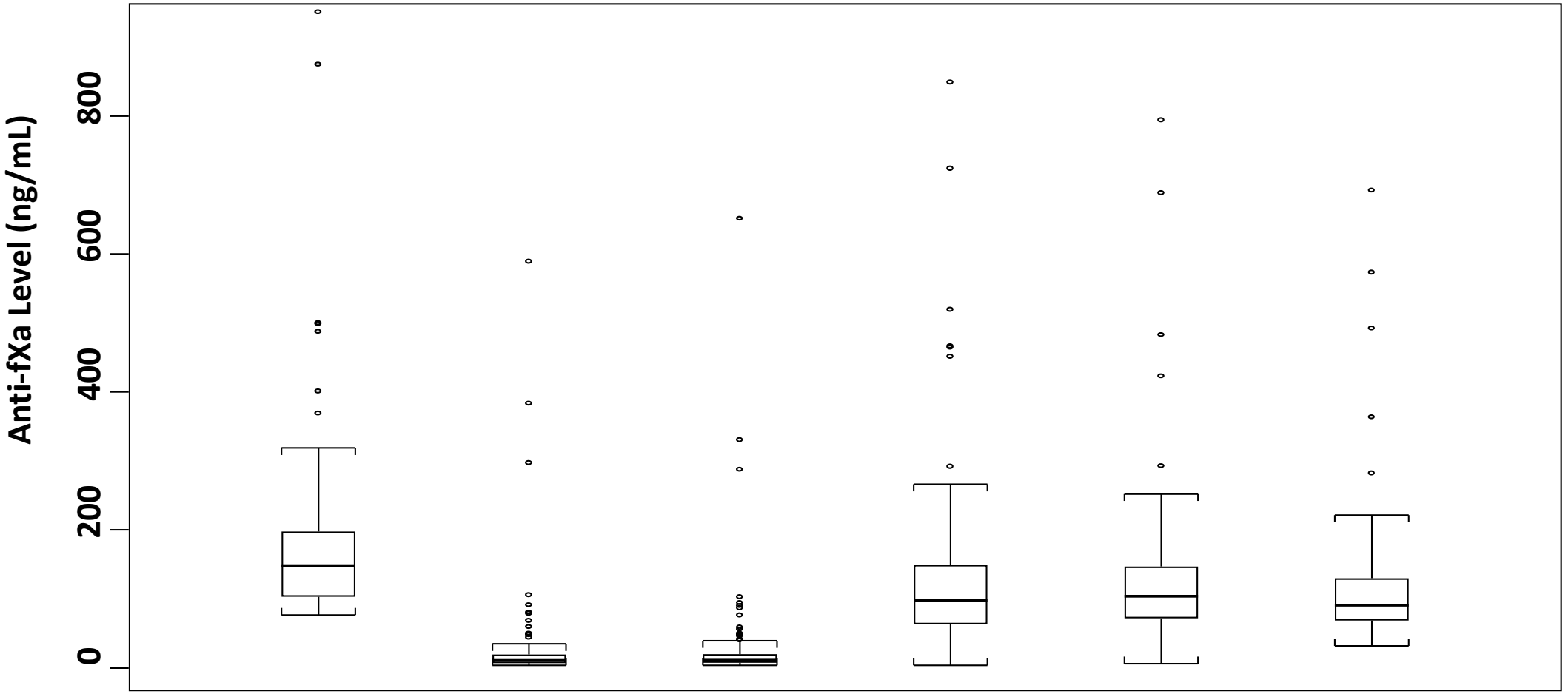
Subgroups

Group	No. of Patients	Excellent or Good Hemostasis (95%CI)
Overall	**204**	**82% (77- 87)**
Drug		
Rivaroxaban	79	80% (72-88)
Apixaban	109	83% (77-90)
Enoxaparin	13	87% (69-100)
Sex		
Male	101	80% (73-87)
Female	103	84% (78-91)
Site of bleeding		
Gastrointestinal	51	85% (76-94)
Intracranial	135	80% (74-86)
Other	18	86% (71-100)
Age		
<65 yr	23	82% (68-96)
65-75 yr	57	86% (78-95)
>75 yr	124	80% (74-86)
Andexanet dose		
Low	172	83% (78-88)
High	32	78% (65-91)



Anti-fXa Activity in Efficacy Population (N=254)

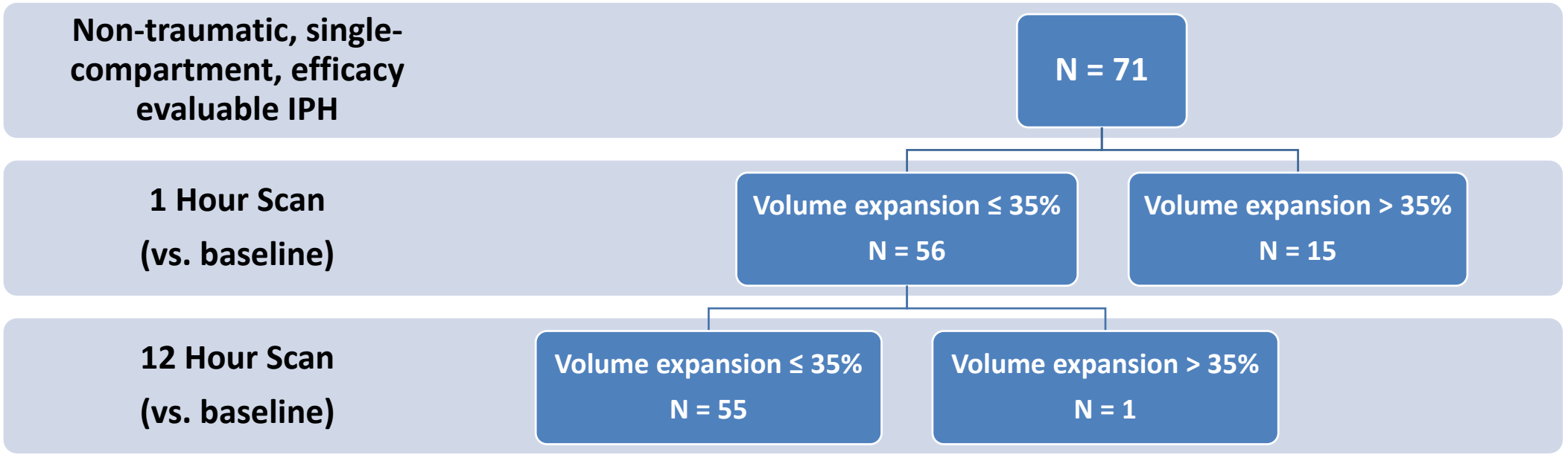
Example here is apixaban



	Baseline	End of Bolus	End of Infusion	4 Hours	8 Hours	12 Hours
Median	149.7	11.1	11.5	97.2	104.6	91.3
Percent Change		-92%	-92%	-32%	-34%	-38%
(95% CI)		(-93 to -91)	(-93 to -91)	(-38 to -29)	(-36 to -27)	(-41 to -34)

ICH Hematoma Expansion Between 1 and 12 hours

- 71 efficacy evaluable patients had non-traumatic, single-compartment, intraparenchymal hemorrhages
- Of these, 56 had volume expansion ≤ 35% from baseline at 1 hour
- Of these, ***55 of 56 (98%)*** had no additional hematoma expansion at 12 hours *

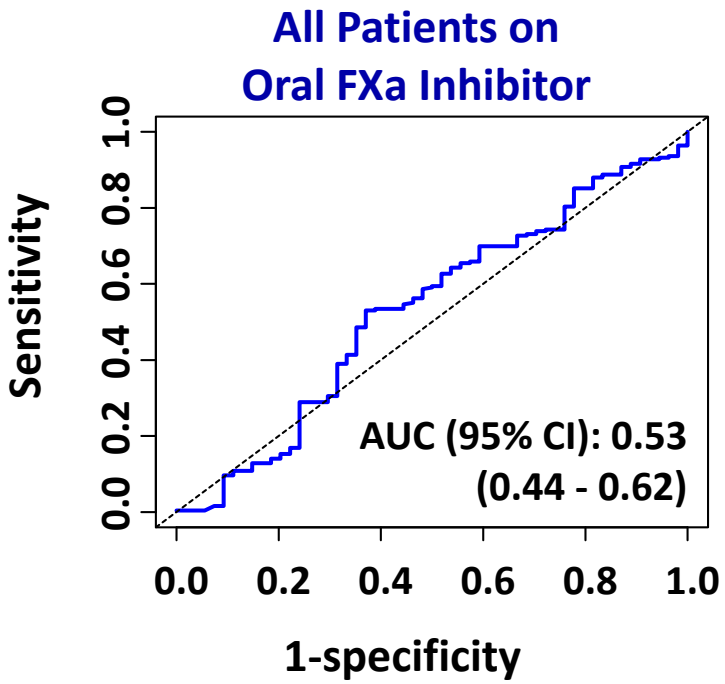


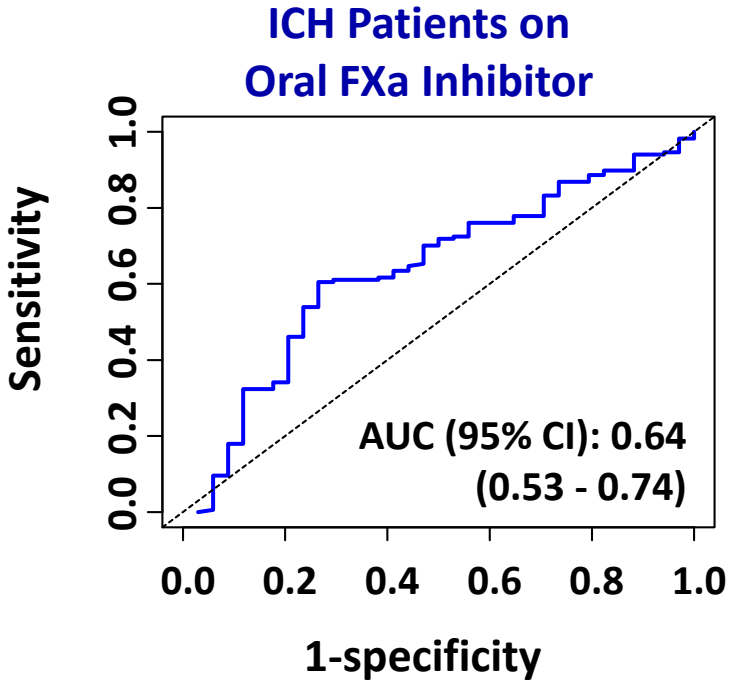
* Hematoma volume remained ≤ 35% vs. baseline

Biomarker-Efficacy Correlation

- Whole treated population – no significant relationship between hemostatic efficacy and reduction in anti-factor Xa activity

- ICH patients – anti-factor Xa activity reduction magnitude was a predictor of hemostatic efficacy





Safety – Thrombotic Events

Patients in Safety Analysis (N=352)	Total	<6 days after bolus	6-14 days after bolus	15-30 days after bolus
Patients with at least one thrombotic event within 30 days	**34 (9.7%)**	**11**	**11**	**12**
Myocardial Infarction	7	6	1	0
Ischemic Stroke (or uncertain etiology)	14	5	6	3
Transient Ischemic Attack	1	0	0	1
Deep Vein Thrombosis	13	1	5	7
Pulmonary Embolism	5	1	0	4

Safety – Restarting Anticoagulation

Thrombotic Events

34 (9.7%)

Before oral anticoagulation restart or never restarted

0

After oral anticoagulation restart

Patients in Safety Analysis (n=352)	Total	<6 days after bolus	6-14 days after bolus	15-30 days after bolus
Restart of any anticoagulation (includes prophylactic dose heparins)	220 (62%)	145	46	29
Restart of oral anticoagulation	100 (28%)	31	37	32

Safety – Mortality

Patients in Safety Analysis (N=352)	Total	<6 days after bolus	6-14 days after bolus	15-30 days after bolus
Deaths within 30 days	**49 (13.9%)**	**8**	**21**	**20**
Cardiovascular	35	7	15	13
Non-Cardiovascular	12	1	5	6
Uncertain Cause	2	0	1	1

Mortality Rate by Bleed Type: ICH (15.0%); GI (11.1%)

Conclusions

- Andexanet infusion rapidly reversed anti-fXa activity
- Effective hemostasis adjudicated to occur in 82% of patients
- ICH 30-day mortality was 15%
- Hemostatic efficacy correlated with Anti-fXa reduction in ICH patients but not the general study population
- Thrombotic events at 30 days (9.7%) were in the expected range for the study population and were mitigated by restarting anticoagulation

The NEW ENGLAND JOURNAL of MEDICINE

ANNEXa4

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*