The University of Texas at Austin
Dell Medical School

Andexanet vs. PCC for fXa Inhibitor associated Life-Threatening Bleeding

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Seton
Healthcare Family

Conflict of Interest Statement

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

Honoraria; Significant; CSL Behring.

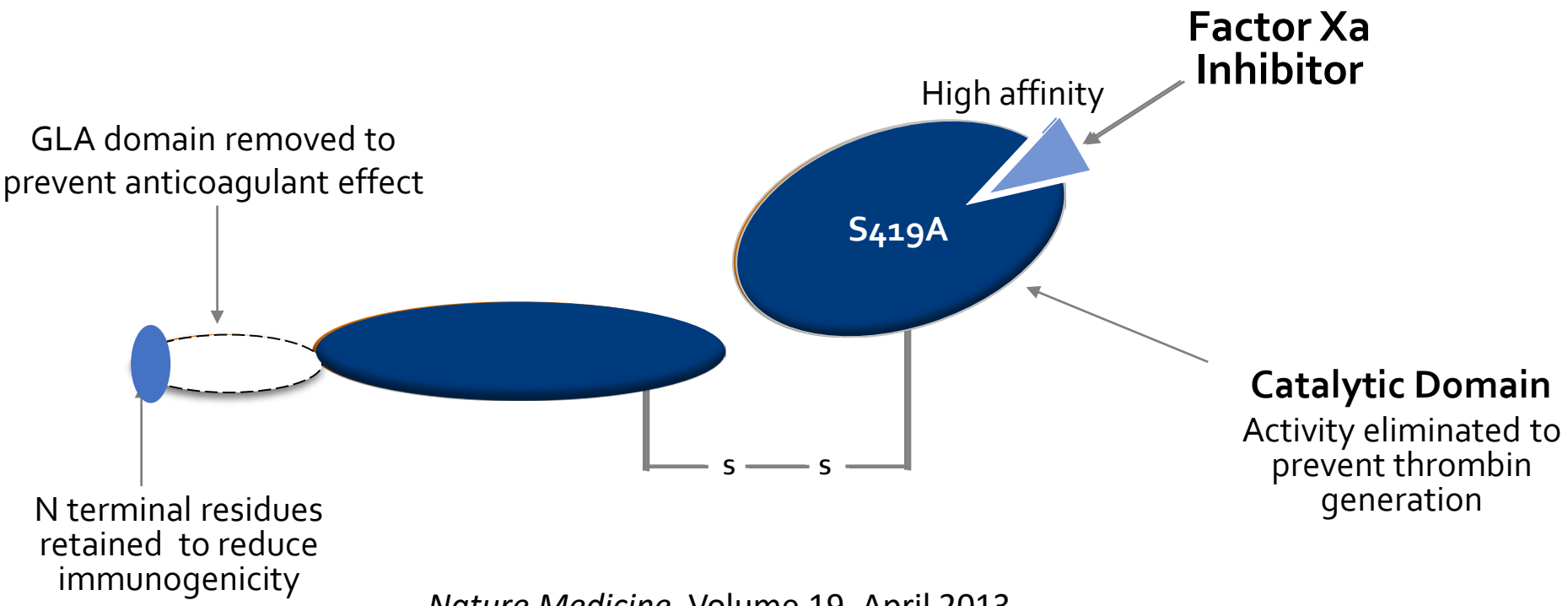
Consultant/Advisory Board; Modest; Octapharma, Portola

Timeline

1960s-2000s – Warfarin era, only 50% of a fib patients who should be anticoagulated actually are (=200,000 unnecessary strokes per year)
2010 – First DOAC approved
2012 – Trauma Centers', others' and patients' outcry about lack of reversibility, slowing uptake of new and better drugs
2013 – Kcentra Approved for warfarin reversal
2014 -- ANNEXA4 and REVERSE AD cohort studies launched
2015 – FDA approves idarucizumab
2017 – Majeed PCC study published
2018 – FDA approves andexanet alfa, Schulman PCC study published
2019 – ANNEXA-I study launched

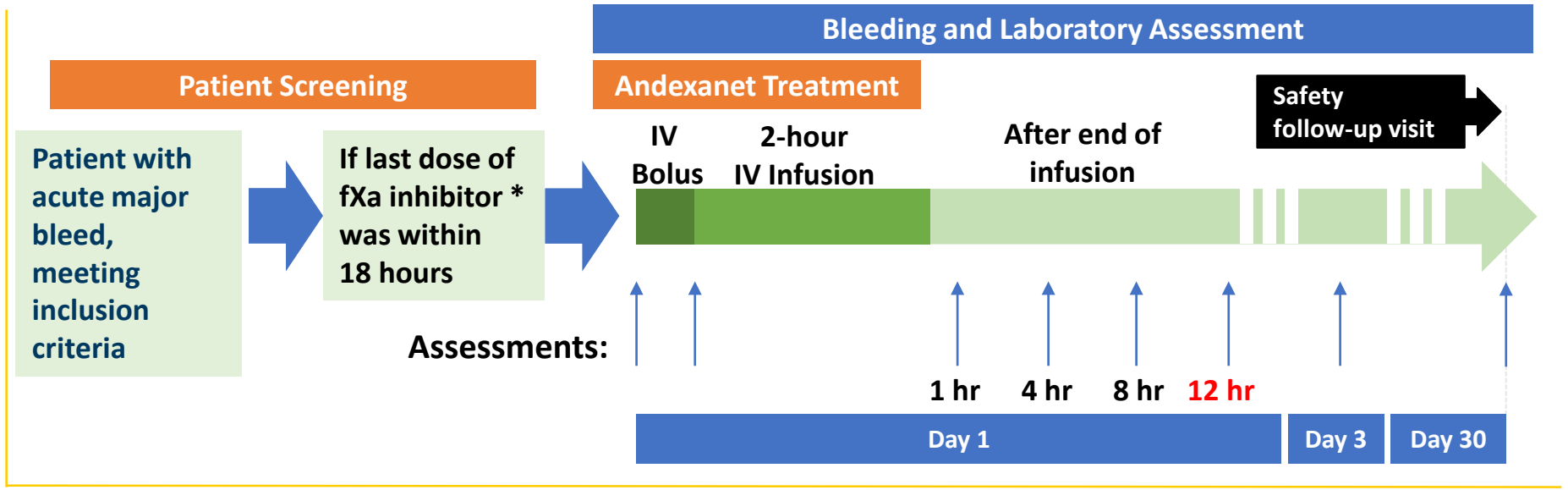
Andexanet alfa: Recombinant Modified Human Factor Xa

- 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, Milling T et al, *Circulation* 2013; 128: 1234-43.

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%)**

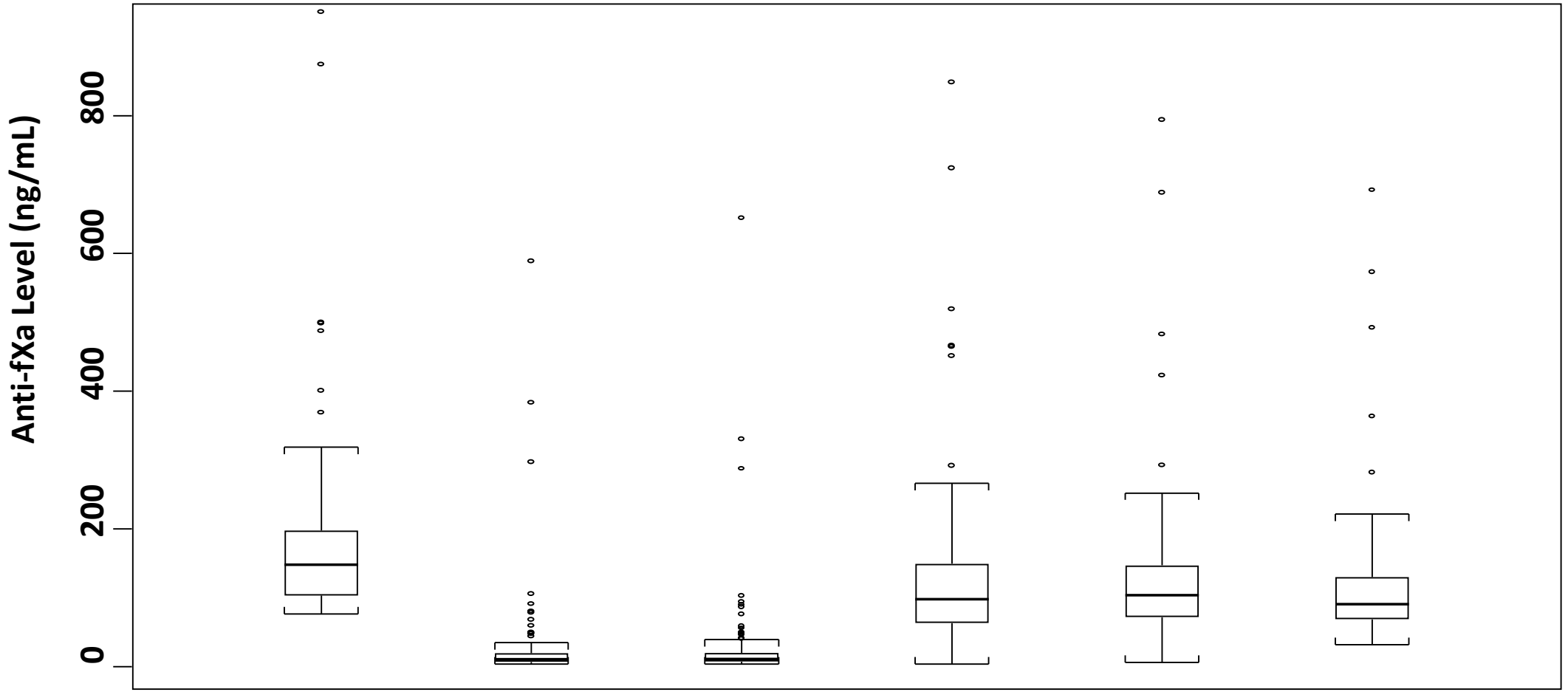
Main Results:
Effective Hemostasis at 12 Hours Post Andexanet

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"***

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

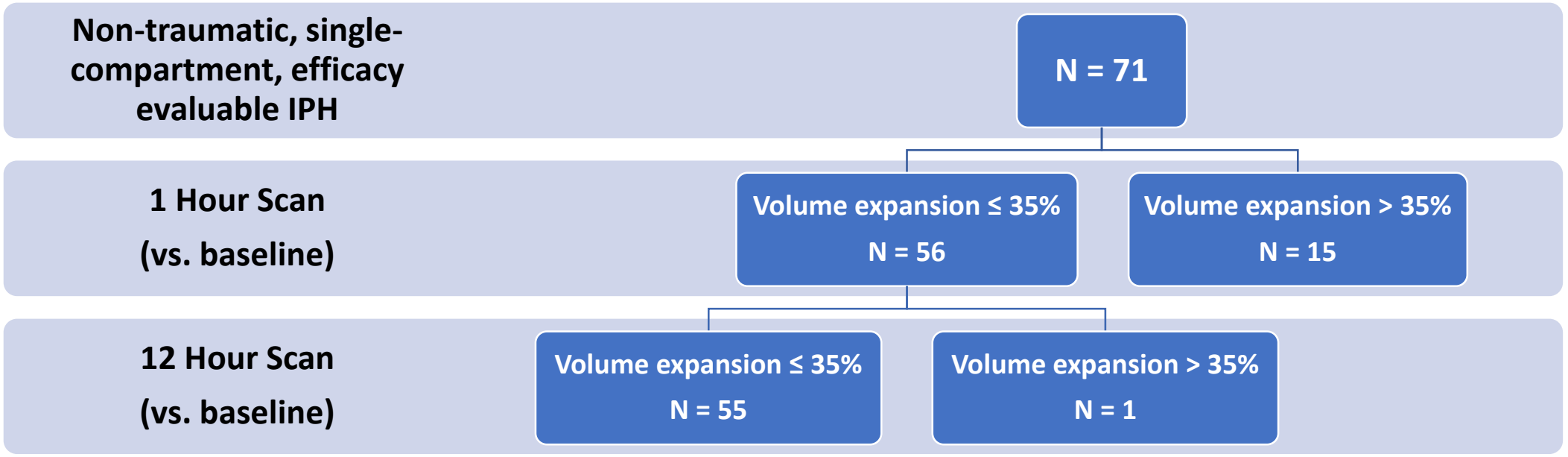
Example here is apixaban



	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

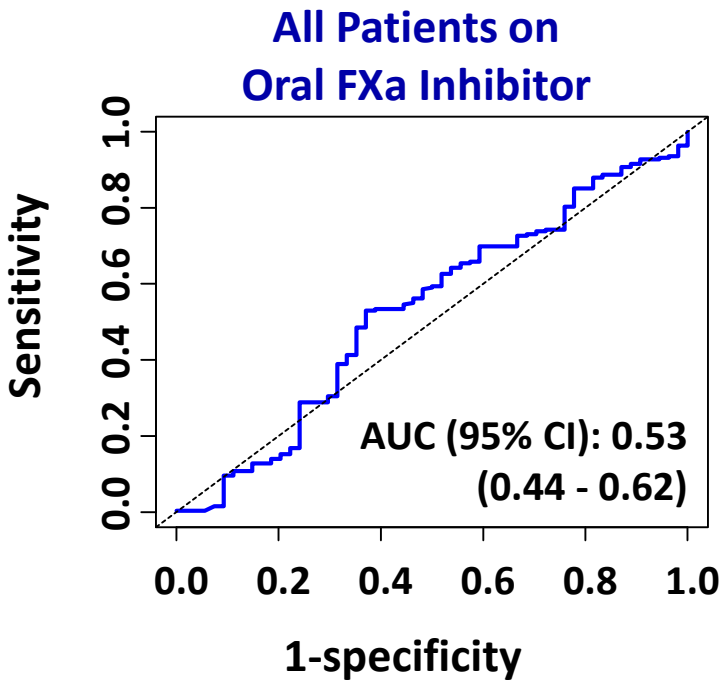
- 71 efficacy evaluable patients had non-traumatic, single-compartment, intraparenchymal hemorrhages
- Of these, 56 had volume expansion ≤ 35% from baseline at 1 hour
- Of these, ***55 of 56 (98%)*** remained ≤ 35% from baseline at 12 hours *

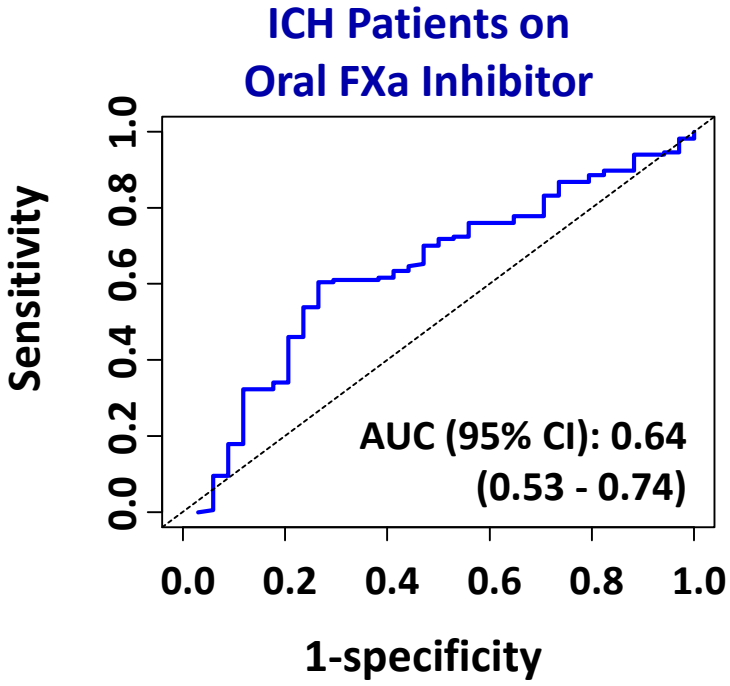


Biomarker-Efficacy Correlation

- 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

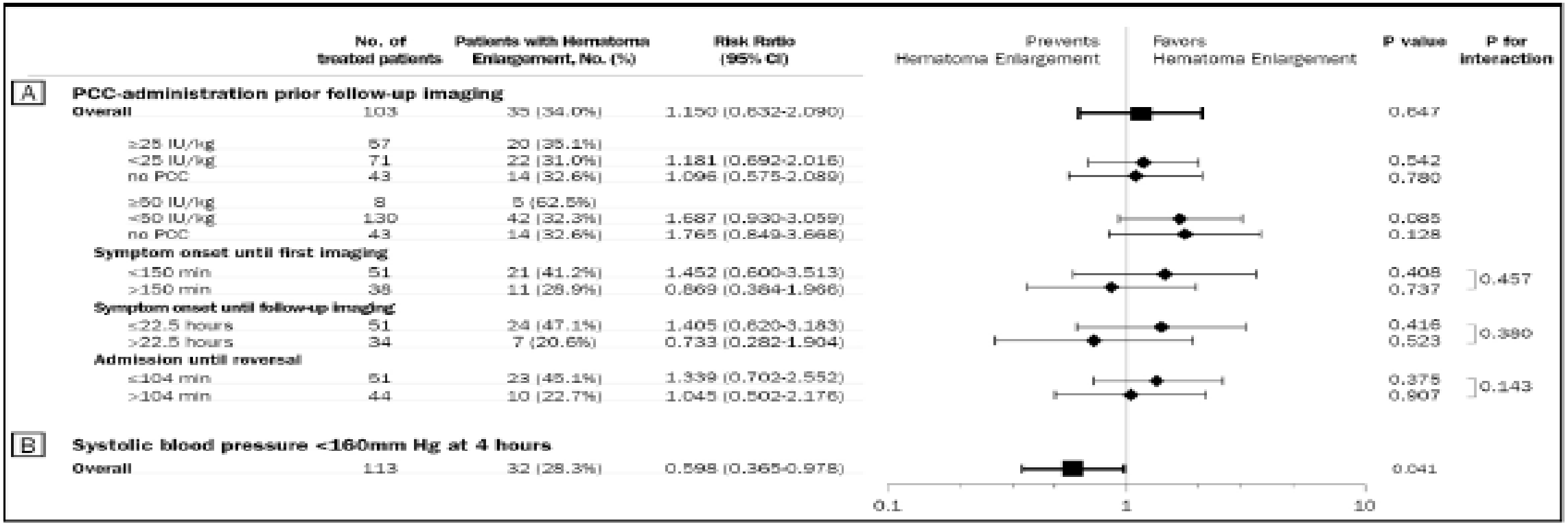
Mortality Rate by Bleed Type: ICH (15.0%); GI (11.1%)

Off-Label PCC use in DOAC bleeding

Study (Ref.) Characteristic or outcome	Sarode et al[16] (*N* = 104)	Sarode et al[16] (*N* = 98)	ANNEXA-4[8] (*N* = 67)	Majeed et al[14] (*N* = 84)	This study (*N* = 66)
Anticoagulant	Warfarin	Warfarin	Xa inhibitors	Xa inhibitors	Xa inhibitors
Reversal agent	Plasma	PCC	Andexanet alfa	PCC	PCC
Exclusion for poor prognosis	Expected survival <3 d	Expected survival <3 d	Expected survival <1 mo	DNR order given	DNR order given
Age, mean (SD)	69.8 (13.9)	69.8 (12.8)	77.1 (10.0)	75 (10.9)	76.9 (10.4)
Male sex	51 (49)	50 (51)	35 (52)	48 (57)	42 (67)
ICH	12 (12)	12 (12)	28 (42)	59 (70)	36 (55)
GI bleed	64 (62)	63 (64)	33 (49)	13 (16)	16 (24)
Time last dose Xa inhibitor to PCC, median (IQR)	N.A.	N.A.	(Mean ± SD) R: 12.8 ± 4.2 A: 12.1 ± 4.7	12.5 (9–16)	16.9 (12–21)
Effectiveness assessment according to Sarode et al[16] for CNS bleeds					
Excellent or Good[a]	7 (58)	5 (42)	16 (80)	Not done	25 (76)[b]
Effectiveness assessment according to ISTH criteria[18] for CNS bleeds					
Effective[a]	Not done	Not done	Not done	43 (73)	25 (69)
Safety outcomes during 30 d					
Thromboembolism	7 (6)	8 (8)	12 (18)	3 (4)	5 (8)
Death	5 (5)	6 (6)	10 (15)	27 (32)	9 (14)

Schulman S, et al. *Thromb Haemost.* 2018; 118(5):842-851.

Off-Label PCC use



	No. of treated patients	Patients with Hematoma Enlargement, No. (%)	Risk Ratio (95% CI)	P value	P for interaction
A **PCC-administration prior follow-up imaging**					
Overall	103	35 (34.0%)	1.150 (0.632-2.090)	0.647	
≥25 IU/kg	57	20 (35.1%)			
<25 IU/kg	71	22 (31.0%)	1.181 (0.692-2.016)	0.542	
no PCC	43	14 (32.6%)	1.096 (0.575-2.089)	0.780	
≥50 IU/kg	8	5 (62.5%)			
<50 IU/kg	130	42 (32.3%)	1.687 (0.930-3.059)	0.085	
no PCC	43	14 (32.6%)	1.765 (0.849-3.668)	0.128	
Symptom onset until first imaging					
≤150 min	51	21 (41.2%)	1.452 (0.600-3.513)	0.408	0.457
>150 min	38	11 (28.9%)	0.869 (0.384-1.966)	0.737	
Symptom onset until follow-up imaging					
≤22.5 hours	51	24 (47.1%)	1.405 (0.620-3.183)	0.416	0.390
>22.5 hours	34	7 (20.6%)	0.733 (0.282-1.904)	0.523	
Admission until reversal					
≤104 min	51	23 (45.1%)	1.339 (0.702-2.552)	0.375	0.143
>104 min	44	10 (22.7%)	1.045 (0.502-2.176)	0.907	
B **Systolic blood pressure <160mm Hg at 4 hours**					
Overall	113	32 (28.3%)	0.598 (0.365-0.978)	0.041	

Gerner ST, et al. *Ann Neurol.* 2018; 83(1): 186-196.

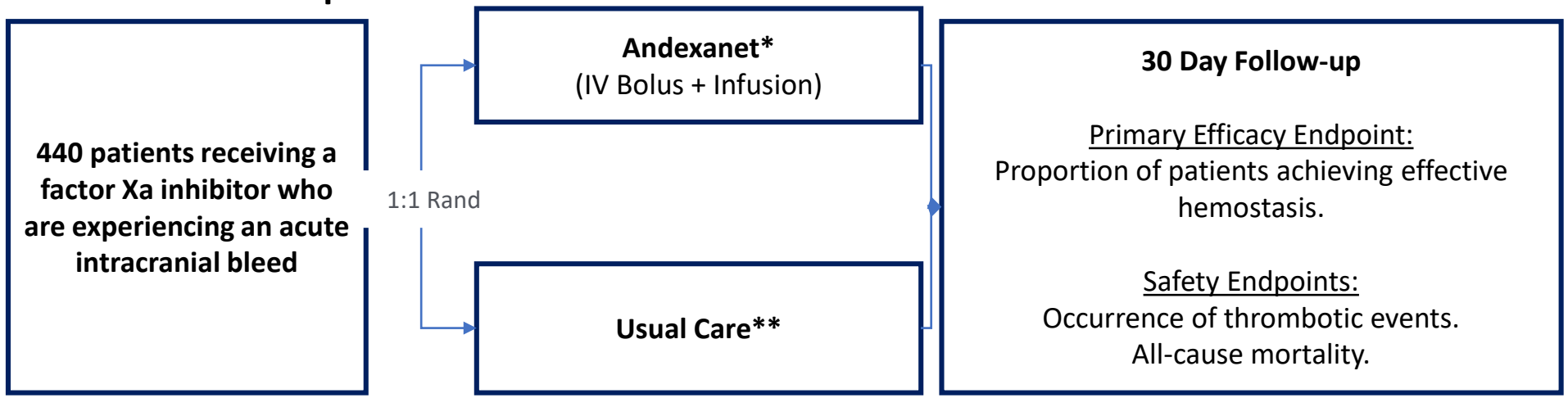
Differences Between ANNEXA4 and PCC Studies

- FDA Oversight
- Sample Size
- Independent adjudication for eligibility/efficacy/TE
- Serial CT scans
- Exclusion from efficacy analysis for anti-Xa <75 ng/ml
- PCC mechanism not understood
- Stoichiometry off by as much as 2 orders of magnitude

ANNEXA-I enrolled 30 patients of 450

ANNEXA-I Study Design

- Randomized Clinical Trial of AndexXA® in Acute Intracranial Hemorrhage in Patients Receiving an Oral Factor Xa Inhibitor (Last dose ≤ 15 hours and symptom onset ≤ 12 hours)
- Primary objective is to evaluate the rate of hemostatic efficacy of andexanet compared to usual care



*Andexanet

Patients will receive one of two dosing regimens of andexanet based on which FXa inhibitor they received and the amount and timing of the most recent dose.

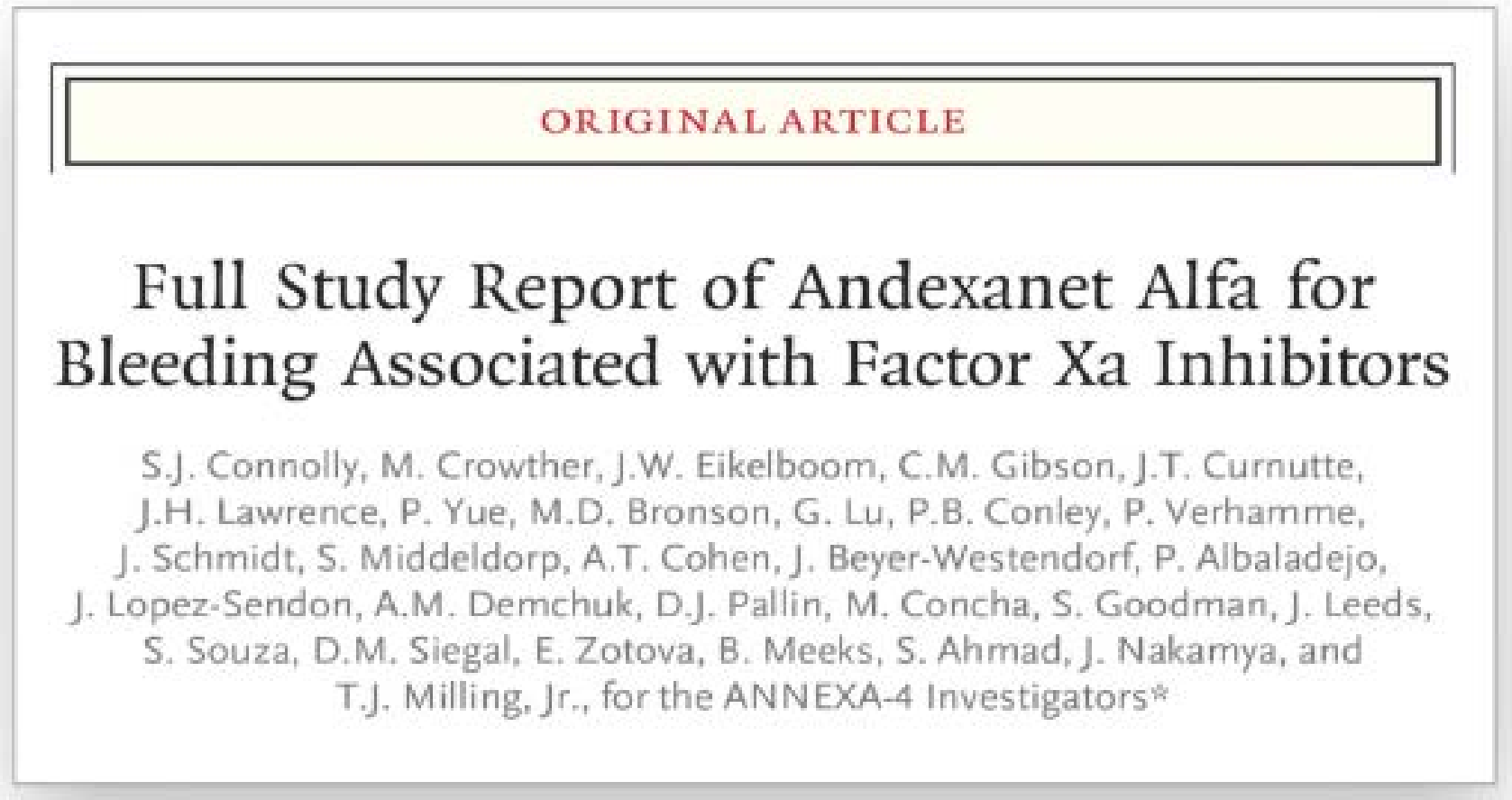
**Usual Care

Consists of any treatment(s) (including no treatment) other than andexanet that the Investigator and/or other treating physicians consider to be appropriate.

Main Points –
"Four 3rd graders do not a 12th grader make"

- PCC mechanism not understood
- Stoichiometry does not make sense
- PCC clinical data lacks rigor of FDA regulated trial, e.g. missing follow up CT scans, no anti-Xa levels
- Most antidotes, like andexanet, do not have randomized controlled evidence in sick patients (Just a well understood mechanism and a little safety data)
  - Idarucizumab -- dabigatran
  - Crofab – crotaline envenomation
  - Fomepizole – toxic alcohols
  - Hydroxycobalamin – cyanide
- Andexanet's mechanism is well understood. It has been studied in multiple small and large animal models, 145 healthy normal and older adults in a placebo controlled RCT, 352 patients with acute major bleeding and ANNEXA-I is ongoing

Questions?



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*