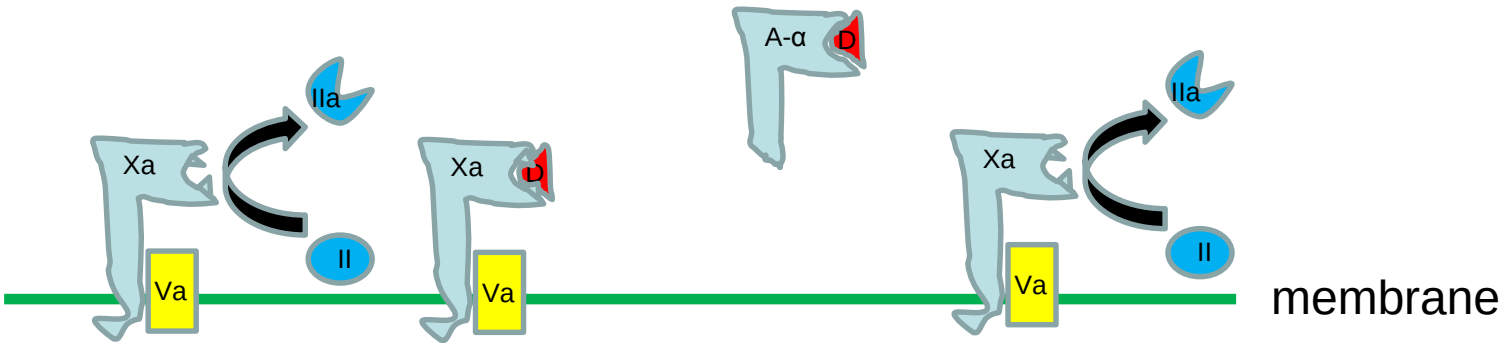
ANDEXANET ALFA FOR FACTOR Xa INHIBITOR REVERSAL

- Andexanet alfa is a modified recombinant factor Xa lacking procoagulant activity and membrane-binding domain
- Binds factor Xa inhibitors with high affinity and thus acts as a “decoy protein”
- Also blocks LMWH effect
- Short half-life: given as bolus plus a 1-2 hour infusion (prevents rebound)
- VERY expensive - $25-58K per treatment!
- FDA approval in 2018 (Andexxa®)
- Approved for UW formulary 2019


A-α
D
IIa
Xa
Xa
D
Xa
IIa
II
Va
Va
Va
II
membrane
No drug
With drug
With drug +
Andexanet-α

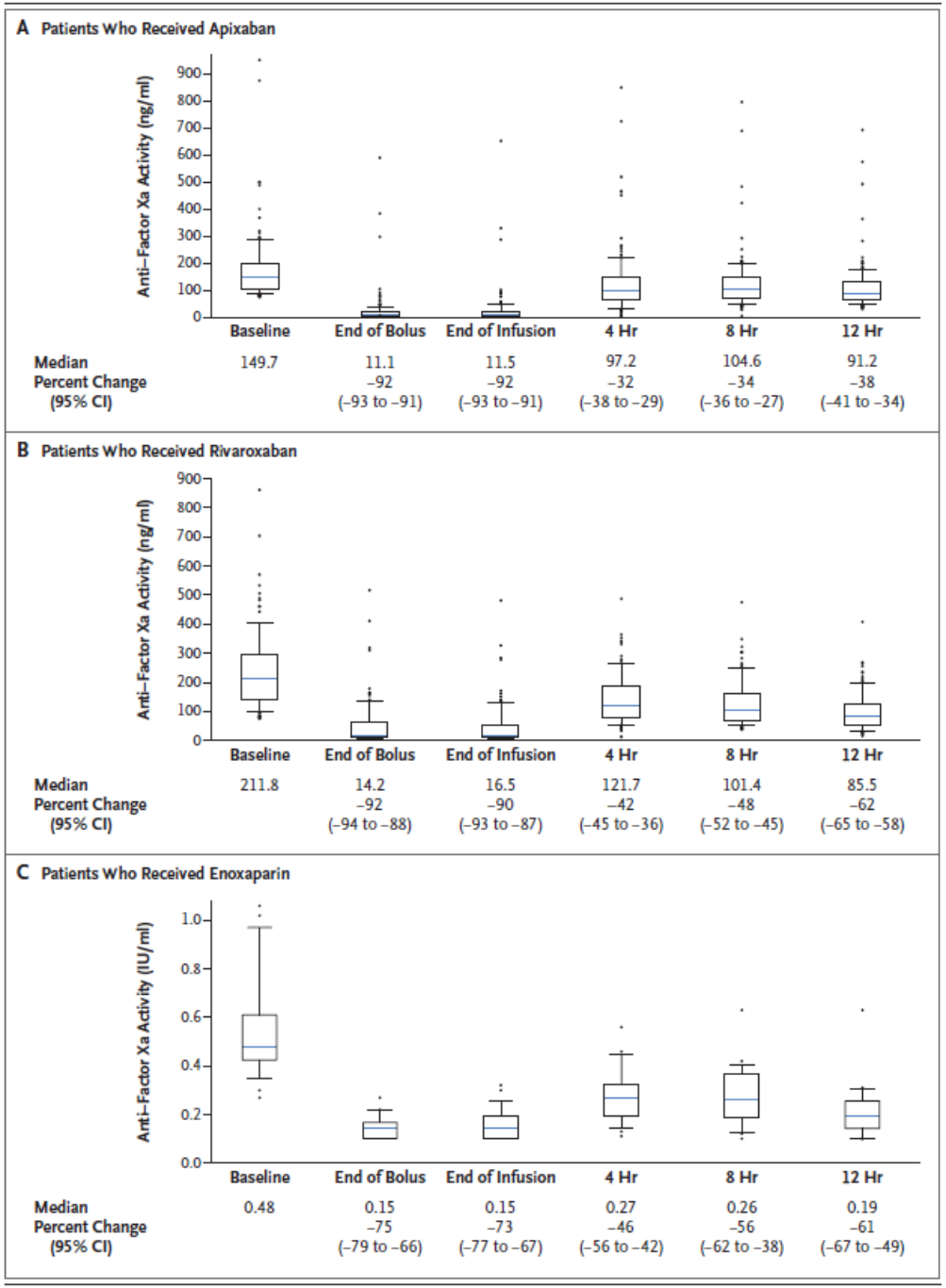
Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors

- **352 patients with acute major bleeding within 18 hours of taking Xa inhibitor**
- **64% had intracranial bleed, 26% GI bleed**
- **Mean age 77 y**
- **No control group (randomized trial is planned)**
- **Treatment: andexanet bolus 400-800 mg followed by 2 hour infusion of 480-960 mg**
  - **Dosing will depend on which drug taken, what dose, and time since last dose taken (if known) per pharmacy protocol**

Connolly et al, NEJM 2019, in press

Dosing Table

	Dose Taken	Timing of last dose	
		< 8 hours or unknown	≥ 8 hours
Apixaban	> 5 mg or unknown	800 mg bolus then 8 mg/min for 120 mins	400 mg bolus then 4 mg/min for 120 minutes
	≤ 5 mg	400 mg bolus then 4 mg/min for 120 mins	
Rivaroxaban	> 10 mg or unknown	800 mg bolus then 8 mg/min for 120 mins	
	≤ 10 mg	400 mg bolus then 4 mg/min for 120 mins	
Edoxaban	Any dose	800 mg bolus then 8 mg/min for 120 mins	

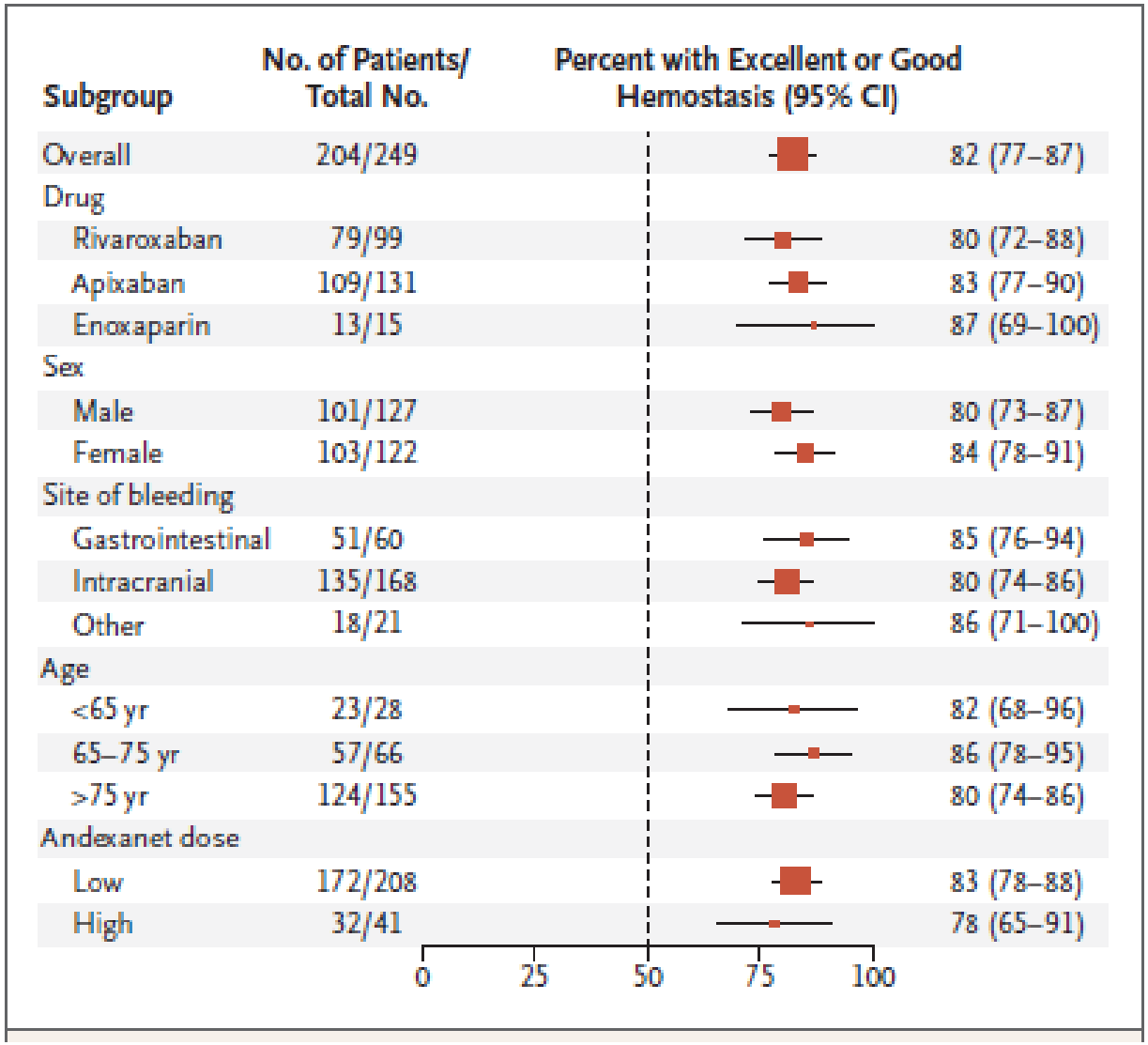


Drug levels drop rapidly with andexanet administration but rebound within a few hours

No significant relationship between reduction of anti-Xa activity during treatment and “hemostatic efficacy”

Connolly et al, NEJM 2019

Hemostatic efficacy



Subgroup	No. of Patients/ Total No.	Percent with Excellent or Good Hemostasis (95% CI)
Overall	204/249	82 (77–87)
Drug		
Rivaroxaban	79/99	80 (72–88)
Apixaban	109/131	83 (77–90)
Enoxaparin	13/15	87 (69–100)
Sex		
Male	101/127	80 (73–87)
Female	103/122	84 (78–91)
Site of bleeding		
Gastrointestinal	51/60	85 (76–94)
Intracranial	135/168	80 (74–86)
Other	18/21	86 (71–100)
Age		
<65 yr	23/28	82 (68–96)
65–75 yr	57/66	86 (78–95)
>75 yr	124/155	80 (74–86)
Andexanet dose		
Low	172/208	83 (78–88)
High	32/41	78 (65–91)

Connolly et al, NEJM 2019

Hemostatic efficacy vs anti-Xa activity

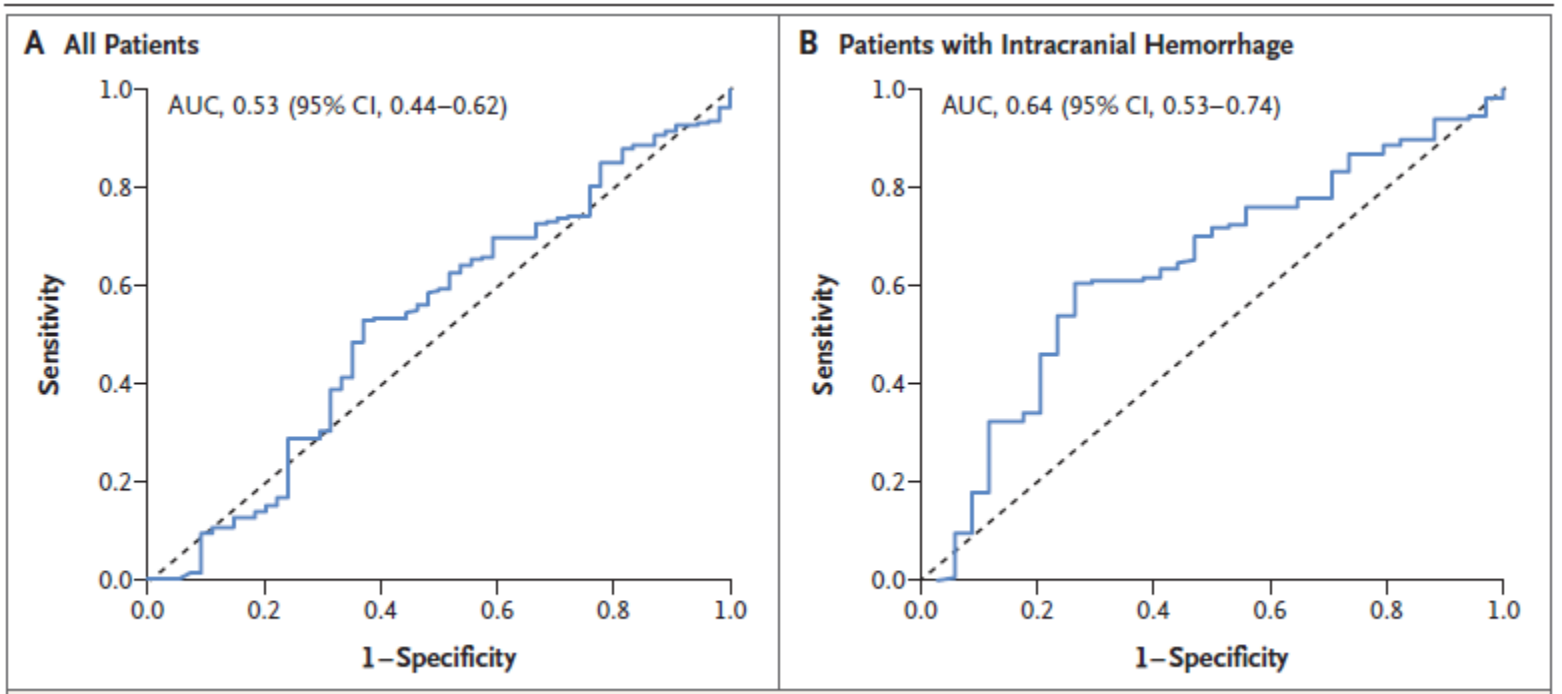


Figure 3. Receiver-Operating-Characteristic (ROC) Curves for Hemostatic Efficacy.

Connolly et al, NEJM 2019

Rating System for Hemostatic Efficacy

Bleed Type	Excellent (effective)	Good (effective)	Poor/none (not effective)
Visible	Cessation of bleeding ≤ 1 hour after end of infusion and no plasma, coagulation factor or blood products (excludes pRBCs).[1]	Cessation of bleeding between > 1 and ≤ 4 hours after end of infusion and ≤ 2 units plasma, coagulation factor or blood products (excludes pRBCs).[4]	Cessation of bleeding > 4 hours after end of the infusion and /or >2 units plasma, coagulation factor or blood products (excludes pRBCs).[5]
Muscular/skeletal	pain relief or no increase in swelling or unequivocal improvement in objective signs of bleeding ≤1 hour after the end of infusion; and the condition has not deteriorated during the 12-hour period	pain relief or no increase in swelling or unequivocal improvement in objective signs of bleeding >1 and ≤4 hours after end of infusion; and the condition has not deteriorated during the 12-hour period	No improvement by 4 hours after end of infusion and/or condition has deteriorated during the 12-hour period
Intracerebral hematoma	≤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	>20% but ≤35% increase in hematoma volume compared to baseline on a repeat CT or MRI scan at +12-hour time point	>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 bleed	≤20% increase in maximum thickness using the most dense area on the follow-up vs baseline at both the 1 and 12 hour post infusion time points	>20% but <35% increase in maximum thickness using the most dense area on the follow-up at +12h vs baseline	>35% increase in maximum thickness using the most dense area on the +12h vs at baseline
Subdural hematoma	≤20% increase in maximum thickness at both the 1 and 12 hour post infusion assessments compared to baseline	>20% but < 35% increase in maximum thickness at +12h compared to baseline	>35% increase in maximum thickness at +12h compared to baseline
Pericardial	No increase in the size of pericardial effusion on repeat echocardiogram done within 12 hours of the end of infusion	<10% increase in the size of pericardial effusion on repeat echocardiogram done within 12 hours of the end of infusion	10% or more increase in the size of pericardial effusion on repeat echocardiogram done within 12 hours of the end of infusion
Intra-spinal	No increase in hematoma size on repeat CT or MRI scan done within 12 hours of the end of infusion	<10% increase in hematoma size on repeat CT or MRI scan done within 12 hours of the end of infusion	10% or more increase in hematoma size on repeat CT or MRI scan done within 12 hours of the end of infusion
GI, Urinary or non-visible bleeding not described above	≤10% decrease in both corrected hemoglobin/hematocrit at 12 hours[2,3] compared to baseline	>10 % to ≤20% decrease in both corrected hemoglobin/hematocrit at 12 hours compared to baseline[2,3]	>20% decrease in both corrected hemoglobin/hematocrit[2,3]

Note that death from bleeding not included as a factor in this rating system

Connolly et al, NEJM 2019

Table 2. Timing of Thrombotic Event and Restarting of Anticoagulation.*

Variable	Safety Population (N=352)			
	Total	<6 Days after Bolus	6–14 Days after Bolus	15–30 Days after Bolus
	number of patients (percent)			
≥1 Thrombotic event within 30 days†	34 (10)	11	11	12
Myocardial infarction	7	6	1	0
Ischemic stroke or stroke of uncertain classification	14	5	6	3
Transient ischemic attack	1	0	0	1
Deep-vein thrombosis	13	1	5	7
Pulmonary embolism	5	1	0	4
Death within 30 days‡	49 (14)	8	21	20
Cardiovascular cause	35	7	15	13
Noncardiovascular cause	12	1	5	6
Uncertain cause	2	0	1	1
Restart of any anticoagulation§	220 (62)	145 (41)	46 (13)	29 (8)
Thrombotic event before restart¶	26 (7)			
Thrombotic event after restart	8 (2)			
Restart of oral anticoagulation‖	100 (28)	31 (9)	37 (11)	32 (9)
Thrombotic event before restart¶	34 (10)			
Thrombotic event after restart	0			

Connolly et al, NEJM 2019

Workflow for andexanet administration

- Only patients with acute, life-threatening bleeding should get andexanet
- It should NOT be given to reverse drug effect prior to elective surgery
- A stat anti-Xa level (not drug-specific) should be drawn immediately (20 minute turnaround time at UWH)
- Drug-specific anti-Xa level drawn (result not required prior to andexanet approval)
- If bleeding is intracranial neurosurgery will determine if andexanet should be given
  - Hematology consult attending will make this determination for all other types of bleeding

Exclusion criteria

- Anticipated use of heparin or LWMH within 12 h
- Already received PCC, factor VIIa or other factor-based reversal agent
- Expected survival < 1 mo
- Reversal of enoxaparin (protamine can be used instead)
- Reversal for planned procedure
- No detectable anti-Xa activity (UWH only)
- Bleeding could reasonably be managed with volume replacement, PRBC transfusion