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Safe and effective reversal of enoxaparin with andexanet alfa in healthy volunteers and in patients with acute major bleeding

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ANNEXa 4

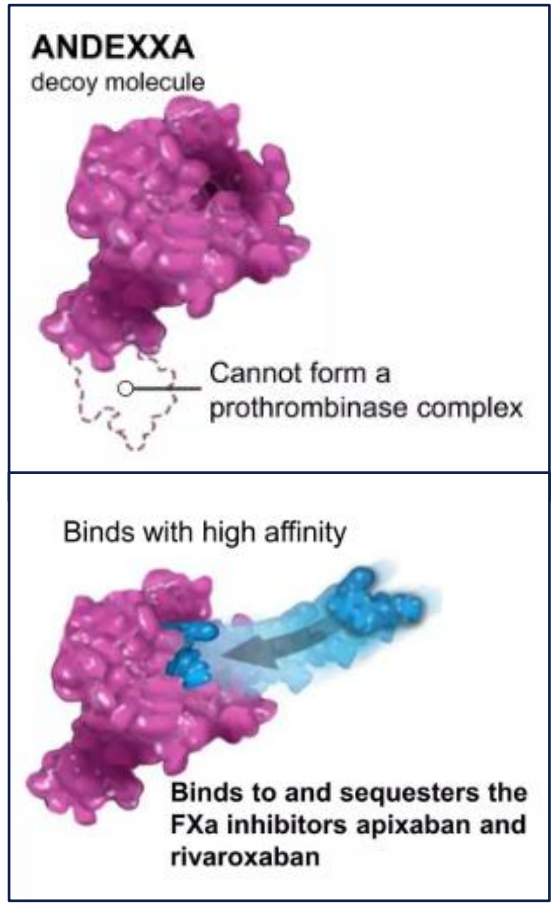
On behalf of the ANNEXA-4 investigators

Disclosures for Thijs F. van Haaps

- No disclosures

Andexanet alfa (andexanet)

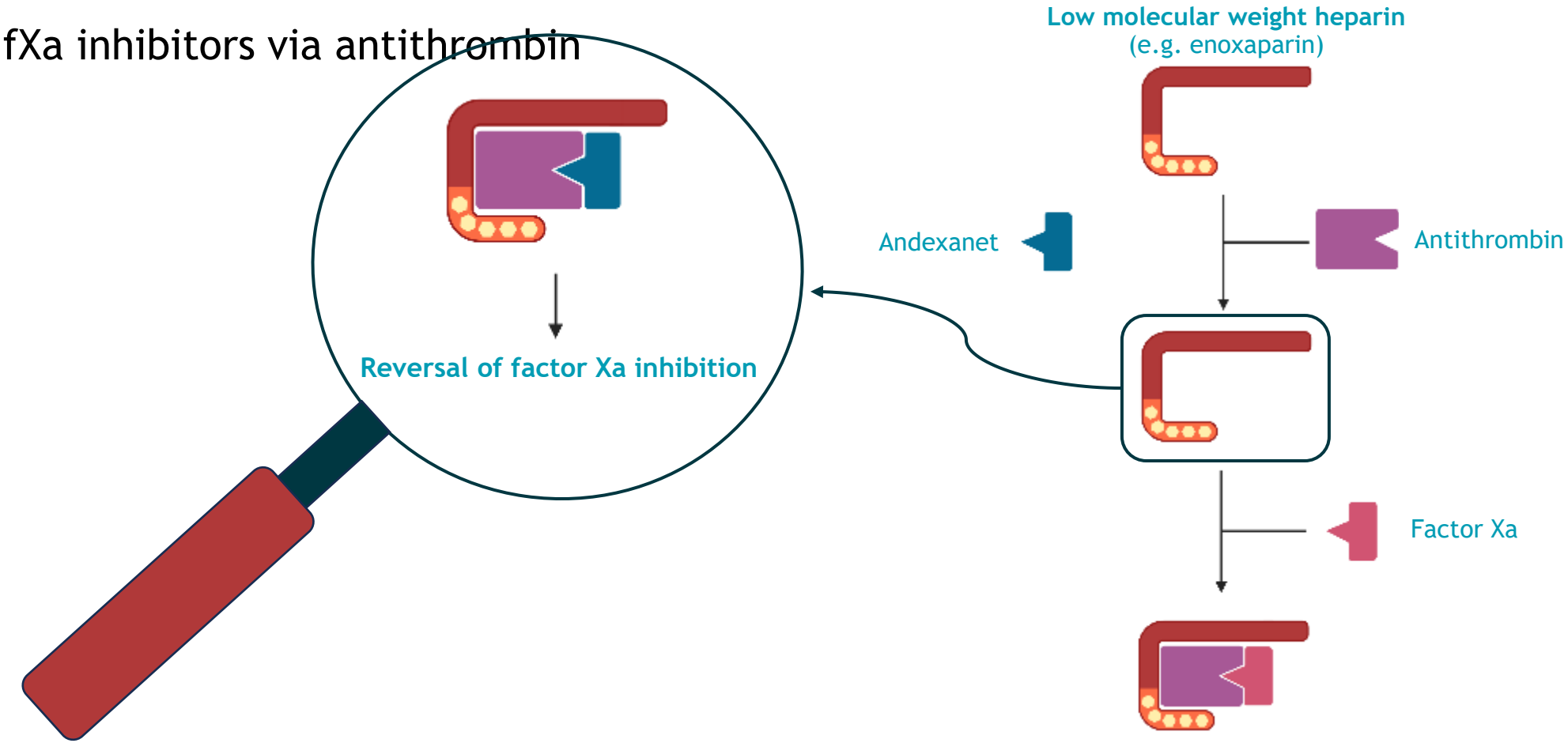
- Andexanet registered reversal agent for apixaban / rivaroxaban:
  - “Decoy fXa”
  - 479 patients enrolled in ANNEXA-4 study:
    - 93% reduction anti-Xa activity
    - 80% achieved good or excellent hemostasis
    - 10% thrombotic events
    - 16% mortality



Connolly, N Eng J Med 2019;380-1326
Milling Jr, Circulation 2023;147:1026–1038.

Reversal of heparins

- Indirect fXa inhibitors via antithrombin



Makris, BJH 2012;160;35-46
Ourri, ACS Chem. Biol. 2019;14;2512-2526
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Aims

- Effects of andexanet in persons treated with indirect fXa inhibitor enoxaparin:
  - **On biomarkers:** anti-Xa activity, thrombin generation
    - **Part 1**: Healthy volunteers
  - **On clinical outcomes of acute major bleeding**
    - **Part 2**: Subset of enoxaparin treated participants of ANNEXA-4

Part 1: Healthy volunteer study

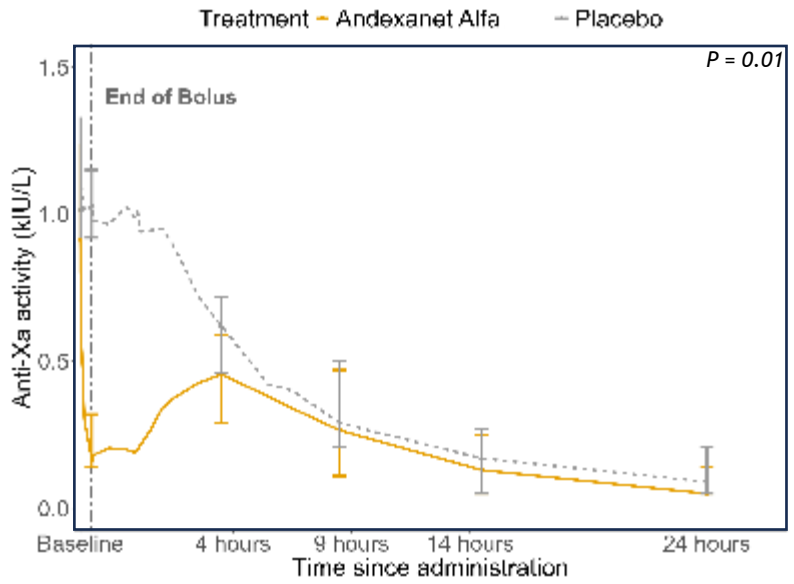
- Double-blind randomized healthy volunteer study
- Dosed to steady-state enoxaparin (1 mg/kg, b.i.d.)
- Randomized between:
  - Andexanet High dose +3h
  - Andexanet Low dose +8h
  - Placebo

Last given dose	Timing of last dose	
	<8h or unknown	≥8h
≤ 40 mg	Low dose	Low dose
> 40 mg / Unknown	High dose	

Part 1: Change in anti-Xa activity

High dose

Andexanet 3 hours post-enoxaparin



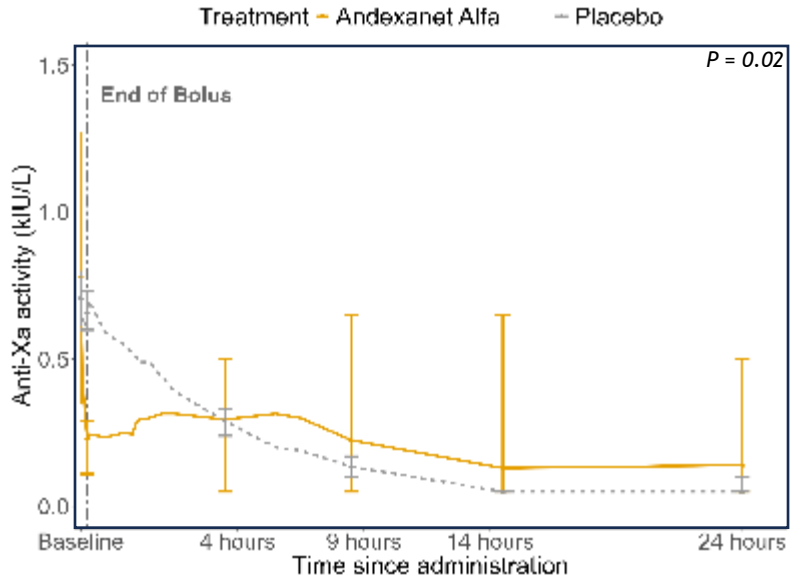
N = 16: n = 12 Andexanet
n = 4 Placebo

Decrease anti-Xa:

Andexanet 83%; placebo 14%

Low dose

Andexanet 8 hours post-enoxaparin



N = 15: n = 12 Andexanet
n = 3 Placebo

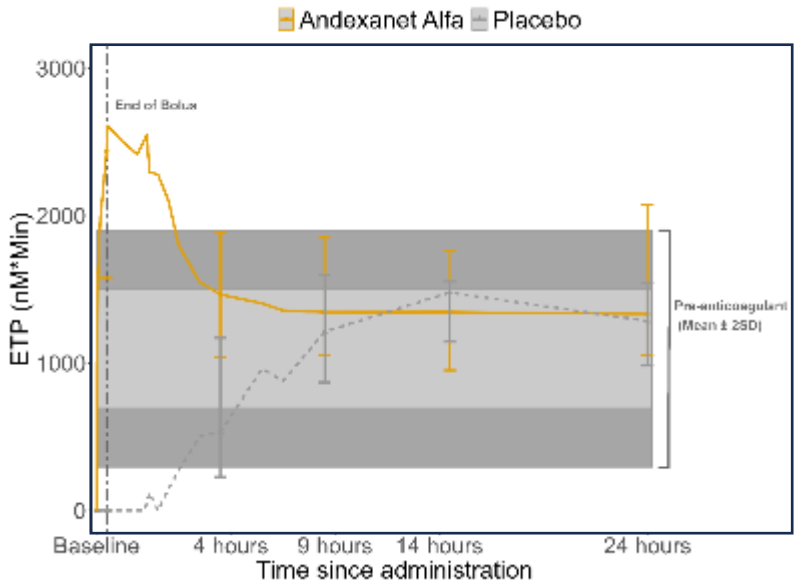
Decrease anti-Xa:

Andexanet 73%; placebo 26%

Part 1: Thrombin generation

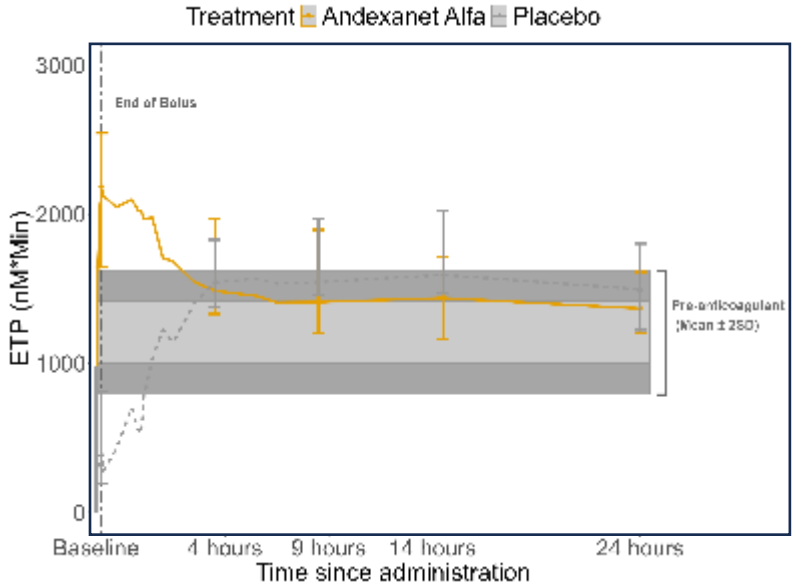
High dose

Andexanet 3 hours post-enoxaparin



Low dose

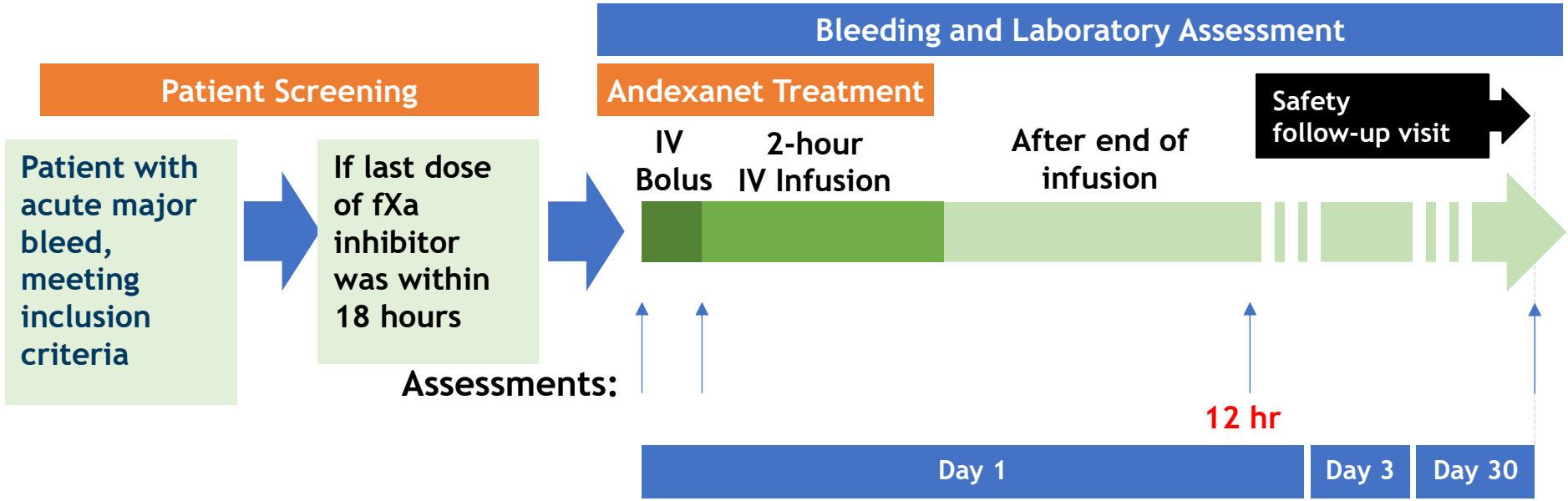
Andexanet 8 hours post-enoxaparin



- Endogenous Thrombin Potential increases after andexanet administration

- Normalizes to pre-anticoagulant state **immediately** without (partial) **return**

Part 2: ANNEXA-4 study



Outcomes

Efficacy:

- Change in anti-Xa activity
- Hemostatic efficacy @ 12 h

Safety:

- Thrombotic events
- 30-day mortality

479 included patients

- **22 treated with enoxaparin**

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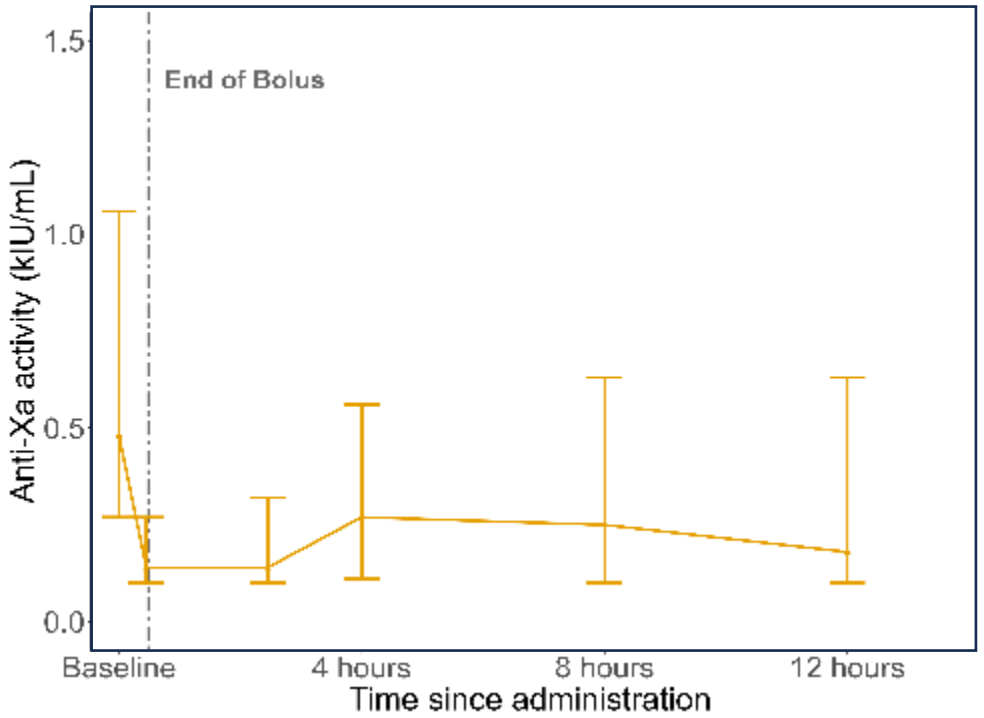
Part 2: Patients on enoxaparin (N = 22)

Age (years), mean (SD)	68.0 ±9.4
Women, no. (%)	10 (46)
Primary Site of bleeding, no. (%)	
Intracranial	11 (50)
Gastrointestinal	7 (32)
Other	4 (18)
Enoxaparin dosing	
Daily dose (mg/kg bodyweight) - mean (SD)	1.6 ±0.5
Twice daily dosed – no. (%)	18 (82)
Indication for anticoagulation, no. (%)	
Venous thromboembolism	14 (64)
Atrial fibrillation	6 (27)
Other	2 (9)



Decrease anti-Xa (median):
-> 75% @ End of Bolus
-> 63% @ 12 h

Part 2: Clinical outcomes

- Safety population -> all patients receiving Andexanet: n = 22
- Efficacy population -> anti-Xa activity ≥ 0.25 IU/mL
  -> confirmed major bleeding event
  } n = 16

	Effective hemostasis	Thrombotic complication	Death
Proportion of participants, % (95% CI) n/N	88 (62 - 98) 14 / 16	5 (1 - 22) 1 / 22	9 (3 - 28) 2 / 22
Site of bleeding Intracranial, n/N (%) Non-intracranial, n/N (%)	 8 / 10 (80) 6 / 6 (100)	 0 / 22 (0) 1 / 22 (5)	 2 / 22 (9) 0 / 22 (0)

Conclusions

Biomarkers:

- Immediate large reduction anti-Xa activity, partial rebound after End-of-Infusion
- Thrombin generation increase to pre-anticoagulant levels, without rebound

Clinical Outcome:

- >80% Good or excellent hemostatic efficacy

- **Results mirror those obtained for reversal of rivaroxaban / apixaban**
- **Similar efficacy/safety may be expected in patients treated with LMWH**

Discussion

- Modest number of patients treated with enoxaparin
  - Probably too low for regulatory approval
- ANNEXA-4 excluded ICH-patients with Glasgow Coma Scale <7 or large hematoma volume
  - Improvement on hemostatic efficacy?
- Not compared with standard-of-care
  - High quality studies on efficacy of protamine currently absent…
- Fate on andexanet alfa is uncertain (may not be fully approved or even withdrawn)

Questions

Thank you for your attention