EVMS Emergency Medicine Journal Club
Therapy Worksheet

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CITATION: Siegal, DM et al. Andexanet Alfa for the reversal of Factor Xa Inhibitor Activity. N Engl J of Med 2015; 373: 2413-24.

A. What is being studied? (Answer below)	**Comments**
1. Study Objective	To establish the efficacy and safety of Andexanet for reversal of anticoagulation with Apixaban (ANNEXA-A) or Rivaroxaban (ANNEXA-R).
2. Study Design	1. Parallel studies, ANNEXA-A and ANNEXA-R. 2. Randomized, double blinded, and placebo controlled. 3. 1 clinical site per study in US. Private research companies. 4. Assignment in 3:1 ratio in ANNEXA- A, 2:1 ratio in ANNEXA-R. 5. Part 1 bolus alone, part 2 bolus + drip 2 hour. 6. Housed at study site for 8 days. 7. Safety outcomes assessed at day 15, 36, 43 after administration. 8. Independent safety committee monitored trial and was aware of allocation. 9. Sponsored by Protola pharmaceuticals, non-disclosure agreements, additional support from Bayer, BM Squibb, J&J, Pfizer.

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3. Inclusion Criteria	1. Health volunteers. 2. 50-75 years old.
4. Exclusion Criteria	1. None listed.
5. Interventions Compared	ANNEXA-A: 1. 5mg of Apixaban twice daily for 3.5 days. 2. 3 hours after last dose of Apixaban Andexanet administered in 2 ways; Part 1: 400 mg bolus, Part 2: 400 mg bolus followed by 120 minutes of 4 mg/min (480 +400 mg total). ANNEXA-R: 1. 20 mg of Rivaroxaban daily for 4 days. 2. 4 hours after the last dose of Rivaroxaban Andexanet administered in 2 ways; Part 1: 800 mg bolus, Part 2 : 800 mg bolus + infusion of 8 mg per minute for 120 minutes (960 + 800 mg total). Does not discuss placebo Dose determined by phase 2 that established the stoichiometric ratio needed for reversal.
6. Outcomes Evaluated	1. Primary outcome was percent change of anti-factor Xa activity (measured by validated method) from baseline (defined as before administration of Andexanet or placebo) to nadir. Nadir defined in part 1 as lower of anti-factor Xa activity at 2 or 5 minutes after the end of the bolus and defined in

	Part 2 as smallest value between 10 minutes before and 5 minutes after end of continuous infusion. Secondary outcomes 1. Proportion of participants with an 80% or greater reduction in anti factor Xa activity from baseline. 2. Change in unbound inhibitor plasma concentration from baseline to nadir. 3. Change in thrombin generation from baseline to peak measured as change in endogenous thrombin potential. 4. Occurrence of an endogenous thrombin potential above the lower limit of the baseline derived range at its peak after administration of Andexanet or placebo. 5. Part 2 studies a secondary outcome was also percent change in anti factor Xa activity from baseline to the post bolus nadir. 6. Followed for evaluation of clinical outcomes of symptomatic thrombosis and bleeding. No clinically validated reference range for endogenous thrombin potential; so, the baseline was prospectively defined as the mean endogenous thrombin potential at baseline on day before anticoagulant administration plus or minus one standard deviation.
B. Are the results of the study valid? Answer questions below	

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1. Were patients randomized?	Yes
2. Was randomization concealed (Blinded)	It states it was but doesn't go into detail about how, safety monitors not blinded.
3. Were patients analyzed in the groups to which they were randomized?	Modified intention to treat analysis; all participants who underwent randomization, received any amount of Andexanet, who had a baseline and at least one measurement of anti factor Xa activity after administration of Andexanet or placebo were included.
4. Were patients in the treatment and control groups similar with respect to known prognostic factors?	Stated as yes, table 1 in the supplementary appendix.
C. Did experimental and control groups retain a similar prognosis after the study started (answer the questions below)?	
1. Were patients aware of group allocation?	No description of how blinding occurred
2. Were clinicians aware of group allocation?	No description of how blinding occurred

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3. Were outcome assessors aware of group allocation?	No description of how they were blinded. Safety committee was NOT blinded
4. Was follow-up complete?	Yes
D. What were the results?	
1. How large was the treatment effect? (difference between treatment and control group).	Anti factor Xa activity was significantly reduced with Andexanet when compared to placebo in all trials: (Part 1: Apixaban 94% vs 21%; (+/-11% and no CI's reported) rivaroxaban 92% vs 18%) (+/- 15% and no CI's reported) (Part 2: Apixaban 92% vs 33%; Rivaroxaban 97% vs 45%) All patients who received Andexanet had at least 80% reversal of anti factor Xa activity w/ exception of 1 patient that had malfunction of medication delivery equipment and none of the patients that received the placebo had at least an 80% reversal of anti factor Xa activity. Thrombin generation was restored significantly more with Andexanet than with placebo. Mean thrombin generation increased to above the baseline mean in the Andexanet treated groups. Returned to within 2 standard deviations within 30 minutes after Andexanet. Unbound Apixaban and Rivaroxaban significantly reduced after Andexanet when compared to placebo. Safety outcomes: no serious or severe adverse events and no thrombotic events.

	Presence of non-neutralizing antibodies in 17% of Andexanet treated patients as compared to 2% in placebo treated patients.
2. How precise was the estimated treatment effect at a 95% confidence interval?	No CI's were reported though SD's were fairly large.
D. How can I apply the results to patient care	
IV. Were the study patients similar to my patients?	No, healthy volunteers. Average BMI 26 creatinine 0.8
1. Were all clinically important outcomes considered?	The outcomes make sense for this trial it would have been nice if the safety outcomes were better defined although I am not sure the safety outcomes good or bad are generalizable to non-healthy patients. No actual clinical outcomes in active bleeding performed.
2. Are the likely treatment benefits worth the potential harms and costs?	Not a treatment study. No identified harms in this study, however the safety outcome analysis was poorly defined, and there is a hint at possible reactions in the future with the increased non-neutralizing antibodies.

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Limitations:
1. healthy volunteers not patients with bleeding complications.
2. poorly defined safety outcomes.
3. Conflicts of interest. Researchers were either employees or patent holders of the sponsoring company.

4. Extremely short period of efficacy with reversal of effect in 1 hour in bolus group) or 2 hours after continuous infusion ended.

Clinical Bottom Line: Andexanet chemically reverses anti-factor Xa activity with Apixaban and Rivaroxaban in healthy patients for short durations of time. No proven efficacy in clinical setting with actively bleeding patients.