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Factor Xa Inhibitor Reversal: Considerations for Algorithm Development

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Disclosure

- I have no conflicts of interest to disclose
- I will discuss off-label use of four-factor prothrombin complex concentrate (4F-PCC) and factor eight bypass inhibitor activity (FEIBA)

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Objectives

- Identify factors to consider prior to pharmacologic intervention
- Describe the roles of prothrombin complex concentrates (PCCs) and andexanet alfa
- Design a comprehensive reversal strategy that incorporates various patient scenarios

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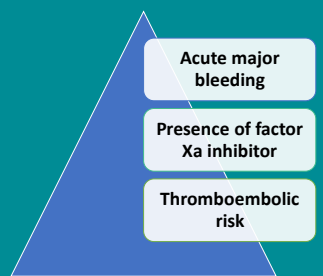

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International Society of Thrombosis and Haemostasis

Definition of major bleeding

As general principles, a definition of major bleeding needs to be based on objective criteria, and major bleeds are those that result in death, are life-threatening, cause chronic sequelae or consume major health-care resources. With this in mind, the Control of Anticoagulation Subcommittee recommends the following criteria for major bleeding in non-surgical patients:

1 Fatal bleeding, and/or
2 Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or
3 Bleeding causing a fall in hemoglobin level of 20 g L^{-1} (1.24 mmol L^{-1}) or more, or leading to transfusion of two or more units of whole blood or red cells.

Schulman S, et al. *J Thromb Haemost 2005*; 3:692-694

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Defining Acute Major Bleeding

Shulman	▪ International Society of Thrombosis and Haemostasis
Majeed (UPRATE)	▪ International Society of Thrombosis and Haemostasis ▪ Active ▪ Evidence of blood loss or decreasing hemoglobin ▪ ICH → deteriorating neurologic symptoms within 48 hours + radiologic evidence of ICH
Connolly (ANNEXA-4)	▪ ONE or more of the following: ▪ Potentially life-threatening bleeding w/ hemodynamic compromise ▪ Severe hypotension, poor skin perfusion, mental confusion, or low cardiac output not otherwise explained ▪ Bleeding associated with a ≥2 g/dL decrease (or ≤8 g/dL if no baseline was available ▪ Bleeding in a critical area or organ (e.g., retroperitoneal, intra-articular, pericardial, epidural, intracranial, or intramuscular w/ compartment syndrome)

Schulman S, et al. *Thromb Haemost* 2018; 118:842-851
Majeed A, et al. *Blood* 2017; 130:1706-1712
Connolly SJ, et al. *N Engl J Med* 2019; 380:1326-1335

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Defining Need for Urgent Procedure/Surgery

Goldstein	▪ Urgent surgical or invasive procedure within 24 hours ▪ Made by clinical care teams
Pollack (REVERSE-AD)	▪ Required surgery or other invasive procedures that could not be delayed for at least 8 hours AND for which normal hemostasis was required
Connolly (ANNEXA-4)	----

Goldstein JN, et al. *Lancet* 2015; 385:2077-2087
Pollack CV, et al. *N Engl J Med* 2015; 373:511-520
Connolly SJ, et al. *N Engl J Med* 2019; 380:1326-1335

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Is Factor Xa Inhibitor Still Present?

- Agent
- Renal Function
- Time Since Last Dose
- Dose
- Half-life
- Drug Interactions

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Assessing Appropriateness of Reversal Based on Time of Last Dose and Renal Function

Reverse: This recommendation is based on an assumption that drug is present due to approximately 3 half-lives or less elapsing since the last dose

		Time Since Last Dose			
Factor Xa Inhibitor	Renal Function	≤24 Hours	25 to 48 Hours	49 to 72 Hours	73 to 96 Hours
Apixaban (Eliquis®)	Normal Mild impairment Moderate impairment Severe impairment Hemodialysis or CrCl <15 mL/min	REVERSE	REVERSE	DO NOT REVERSE DO NOT REVERSE REVERSE REVERSE REVERSE	DO NOT REVERSE
Rivaroxaban (Xarelto®)	Normal Mild impairment Moderate impairment Severe impairment Hemodialysis or CrCl <15 mL/min	REVERSE	REVERSE ONLY IF AGE ≥60 YEARS REVERSE ONLY IF AGE ≥60 YEARS REVERSE REVERSE REVERSE	DO NOT REVERSE CONSIDER REVERSAL (LIMITED DATA)	
Edoxaban (Savaysa®)	Normal Mild impairment Moderate impairment Severe impairment Hemodialysis or CrCl <15 mL/min	REVERSE	REVERSE	DO NOT REVERSE CONSIDER REVERSAL (LIMITED DATA)	
Betrixaban (Bevyxxa®)	Normal Mild impairment Moderate impairment Severe impairment Hemodialysis or CrCl <15 mL/min	REVERSE			

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Table 2: ANDEXXA Dose Based on Rivaroxaban or Apixaban Dose (Timing of Last Dose of FXa Inhibitor before ANDEXXA Initiation)

FXa Inhibitor	FXa Inhibitor Last Dose	< 8 Hours or Unknown	≥ 8 Hours
Rivaroxaban	≤ 10 mg	Low Dose	Low Dose
	> 10 mg or Unknown	High Dose	
Apixaban	≤ 5 mg	Low Dose	
	> 5 mg or Unknown	High Dose	

Andexxa [package insert]. San Francisco, CA: Portola Pharmaceutical, Inc.; 2018

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Thromboembolic Risk

	Contraindications	Boxed warning
4-factor PCC (Kcentra)	▪ Disseminated intravascular coagulation (DIC) ▪ Heparin-induced thrombocytopenia	▪ Arterial and venous thromboembolic complications ▪ Not studied in TE event, MI, DIC, CVA, TIA, unstable angina or severe peripheral vascular disease WITHIN THE PRIOR 3 MONTHS ▪ May not be suitable in patients with thromboembolic events in the prior 3 months
Factor eight inhibitor bypass activity (FEIBA)	▪ DIC ▪ Acute thrombosis or embolism, including myocardial infarction	▪ Thromboembolic complications, particularly in patients with thrombotic risk factors
Andexanet	▪ None	▪ Arterial and venous thromboembolic events ▪ Ischemic events (myocardial infarction and ischemic stroke) ▪ Cardiac arrest ▪ Sudden death

Kcentra [package insert]. Kankakee, IL: CSL Behring; 2018
FEIBA [package insert]. Lexington, MA: Baxalta US Inc.; 2018
Andexxa [package insert]. San Francisco, CA: Portola Pharmaceuticals, Inc.; 2018

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Thromboembolic Risk: Exclusion Criteria

Schulman	Majeed	Connolly
• Acute coronary syndrome or ischemic stroke within 30 days	• Acute coronary syndrome or ischemic stroke within 30 days	• Thrombotic event within 2 weeks

Schulman S, et al. *Thromb Haemost* 2018; 842–851
Majeed A, et al. *Blood* 2017; 130:1706-1712
Connolly SJ, et al. *N Engl J Med* 2019;380:1326-1335

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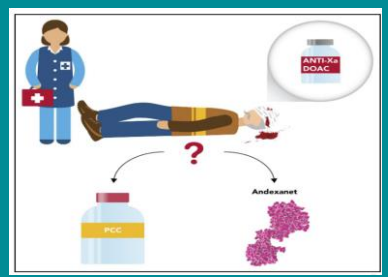

Hunt BJ, et al. *Blood 2018*; 132:2441-2445

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Prothrombin Complex Concentrates

Non-activated	Activated
• 3-factor • Factors II, IX, and X • Factor VII content is low or non-therapeutic • 4-factor • Factors II, VII, IX, and X	• Factor eight inhibitor bypass activity (FEIBA) • Factors II, VII, IX, and X • Only the factor VII component is activated

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Pharmacology

- Circulating factor Xa inhibitors will inhibit activated clotting factors produced from prothrombin complex concentrate
- Goal is to overwhelm this inhibitory effect by providing additional quantities of coagulation factors
- Not a true neutralizing agent

Am J Health-Syst Pharm 2016; 73(suppl 2):S5-13

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4-factor PCC

Reference	Design	Population Factor Xa inhibitor	Product/Dose	Time Since Last Dose	Efficacy	TE Complications
Schulman	Prospective, multicenter	n=66 Major bleeding (ICH, GIB) Rivaroxaban & apixaban	Beriplex/Octaplex 1000 to 4200 units (intended dose was 2000 units; 25 units/kg in 80kg patient)	18 hours *Time from last dose to PCC*	Hemostasis (good) 65%	8% Ischemic stroke, peripheral arterial occlusion, VTE
Majeed (UPRATE)	Prospective, multicenter	n=84 Major bleeding (ICH most common, GIB second most common) Rivaroxaban & apixaban	Confidex/Octaplex 1500 units (<65kg) 2000 units (>65 kg) *~25 units/kg; repeat dosing occurred in n=3*	13 hours *Time from last dose to treatment*	Hemostatic efficacy 69%	4% Ischemic stroke

Schulman S, et al. *Thromb Haemost* 2018; 118:842-851
Majeed A, et al. *Blood* 2017; 130:1706-1712

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FEIBA

Reference	Design	Population Factor Xa inhibitor	Product/Dose	Time Since Last Dose	Efficacy	TE Complications
Dager	Retrospective, single center	n=48 ICH and non-ICH Rivaroxaban/ apixaban	Low dose: 10 units/kg Moderate dose: 24 units/kg Some instances of repeat dosing	Serum levels (n=44) 18% w/ values <40 ng/mL	No need for repeat dosing 90% Excellent or good hemostasis for GIB 92%	6% VTE
Frontera	Neurocritical Care Society/ SCCM Guidelines	ICH	50 units/kg if ICH occurred within 3 to 5 terminal half-lives of drug exposure *Conditional recommendation, low quality of evidence*		Available data are insufficient to support the efficacy of available hemostatic agents; however, correction of coagulopathy is advisable.	

Dager WE, et al. *Thromb Res* 2019; 173:71-76
Frontera, JA, et al. *Neuro Crit Care* 2016; 24:6-46

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Pharmacologic Agents for Anticoagulation Reversal

Factor Xa Inhibitor Reversal NO HEPARIN ALLERGY			Factor Xa Inhibitor Reversal HEPARIN ALLERGY
Kcentra			FEIBA
ICH	Life-threatening hemorrhage (not ICH)	Urgent surgery or procedure	ICH
50 units/kg	25 units/kg	25 units/kg	50 units/kg

PCC: Key Considerations

- Hemostatic efficacy demonstrated
- Use described for urgent surgery/invasive procedures
- Duration of effect is 6 to 8 hours
- Moderate cost and operational complexity
- Not a specific reversal agent
- Thromboembolic risk exists

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Andexanet alfa

coagulation factor Xa [recombinant], inactivated-zhzo

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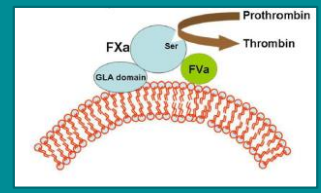
Factor Xa: Mechanism of Action



- GLA domain facilitates binding of factor Xa to phospholipids
- Serine at position 419 catalyzes prothrombin to thrombin conversion

Sartori M, et al. J Thromb Thrombolysis 2018;45:345-352

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Pharmacology

- Recombinant modified factor Xa decoy molecule
- Modifications still allow binding of factor Xa inhibitors
- Does not activate the coagulation cascade
- GLA domain removed (cannot form prothrombinase complex)
- Serine 419 replaced with alanine 419 (cannot cleave prothrombin and generate thrombin)

Kaatz s, et al. J Blood Med 2017;8:141-149

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ANNEXA-4

Design	Patients	Intervention	Efficacy Outcomes	Safety Outcomes
▪ Prospective ▪ Multicenter (n=63) ▪ Single cohort ▪ Open-label	▪ Acute major bleeding ▪ Apixaban, rivaroxaban, edoxaban, or enoxaparin within 18 hours	▪ Andexanet bolus + infusion ▪ Stratified by time since dose (<=7 hours or >7 hours) ▪ Modification described in Supplementary Appendix	▪ Percent change from baseline in anti-factor Xa activity ▪ Percentage of patients with excellent or good hemostatic efficacy 12 hours after infusion	▪ Death ▪ Thrombotic events ▪ Development of antibodies to andexanet or to native factor X and Xa

Connolly SJ, et al. *N Engl J Med* 2019;380:1326-1335

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ANNEXA-4: Baseline Characteristics

Characteristic	Safety Population (N=352)	Efficacy Population (N=254)
Primary indication for anticoagulation, n (%)		
▪ Atrial fibrillation	280 (80)	201 (79)
▪ Venous thromboembolism	61 (17)	46 (18)
▪ Other	11 (3)	7 (3)
Factor Xa inhibitor, n (%)		
▪ Rivaroxaban	128 (36)	100 (39)
▪ Apixaban	194 (55)	134 (53)
▪ Enoxaparin	20 (6)	16 (6)
▪ Edoxaban	10 (3)	4 (2)
Site of bleeding, n (%)		
▪ Gastrointestinal	90 (26)	62 (24)
▪ Intracranial	227 (64)	171 (67)
▪ Other	35 (10)	21 (8)

72% of patients met criteria met for efficacy population

Connolly SJ, et al. *N Engl J Med* 2019;380:1326-1335

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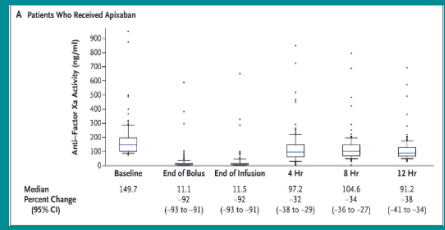
ANNEXA-4: Anti-factor Xa Activity



Connolly SJ, et al. *N Engl J Med* 2019;380:1326-1335

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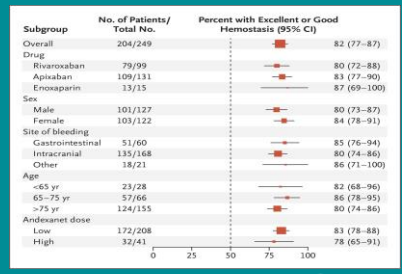
ANNEXA-4: Hemostatic Efficacy



Connolly SJ, et al. *N Engl J Med* 2019;380:1326-1335

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ANNEXA-4: Intracranial Hemorrhage

Population	ICH Demographics	Hemostasis (Excellent or Good)	Death
Safety (n=227) Efficacy (n=171) Exclusions: • Planned surgery within 12 hours of andexanet (changed to 1 day in amendment 1) • ICH with a GCS <7 or estimated hematoma volume of >60mL NOTE: multiple changes to exclusion criteria in amendment 2 specific to ICH	Mean GCS=14 *Efficacy population* Intracerebral (n=104) • Hematoma volume ≤10mL (63%) 11 to 60mL (37%) SDH (n=58) • Maximal thickness <10mm (57%) >10mm (43%) SAH (n=43)	• Excellent: ICH hematoma volume ≤20% increase in hematoma volume compared to baseline at both 1 and 12 hours • Good: ICH hematoma volume >20 to ≤35% increase in hematoma volume compared to baseline at 12 hours • Scoring for SAH/SDH: similar, except maximal thickness used 80% (74-86)	Not reported specific to ICH

Connolly SJ, et al. *N Engl J Med* 2019;380:1326-1335

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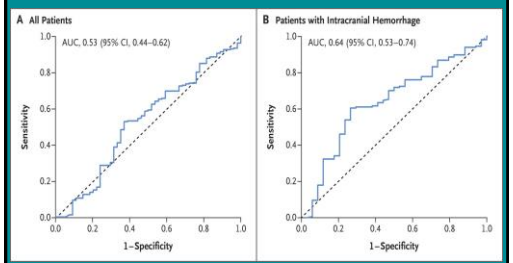
Hemostatic Efficacy and Change in Anti-factor Xa Activity



Connolly SJ, et al. *N Engl J Med* 2019;380:1326-1335

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ANNEXA-4: Thrombotic Events

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

Variable	Total	Safety Population (N=352) <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 SJ, et al. *N Engl J Med* 2019;380:1326-1335

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Tissue Factor Pathway Inhibitor (TFPI)

- Endogenous inhibitor of factor Xa
- Andexanet binding to TFPI
  - Formation of a non-productive andexanet-TFPI complex
  - Reduces TFPI activity
  - Transient increases in prothrombin fragments, thrombin-antithrombin complex, and D-dimer
  - Elevations typically return to normal within 1 to 3 days
- Additional study needed

Kaatz s, et al. J Blood Med 2017;8:141-149

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Product Information

ANDEXXA is indicated for patients treated with rivaroxaban and apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.

This indication is approved under accelerated approval based on the change from baseline in anti-FXa activity in healthy volunteers. An improvement in hemostasis has not been established. Continued approval for this indication may be contingent upon the results of studies to demonstrate an improvement in hemostasis.

Limitation of Use:

ANDEXXA has not been shown to be effective for, and is not indicated for, the treatment of bleeding related to any FXa inhibitors other than apixaban and rivaroxaban.

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Andexxa [package insert]. San Francisco, CA: Portola Pharmaceuticals; 2018

Andexanet alfa: Key Considerations

- Specific reversal agent (reduces anti-factor Xa activity)
- NOT studied for use in urgent surgery/invasive procedures
- ONLY for use with apixaban and rivaroxaban
- Short pharmacodynamic half-life → ? rebound bleeding
- Very high cost and operational complexity
- Thromboembolic risk exists

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Criteria for use

Coagulation factor Xa (recombinant,inactivated, Andexxa) is currently only FDA approved for the reversal of apixaban and rivaroxaban in the setting of life-threatening or uncontrolled major bleeding.

Criteria	Critical life-threatening bleeding and rivaroxaban/apixaban ingested <18 h ago	Critical life-threatening bleeding	Emergency surgery/ procedures[a]	Betrixaban, edoxaban, enoxaparin reversal	Less severe bleeding
Indications	For critical life-threatening bleeding defined as bleeding that causes hemodynamic compromise, threatens a vital organ, or may result in disability, that does not respond to conventional measures	AND dose ingested >18 h ago OR patient received alternative reversal strategies at outside hospital (eg, PCC)	Not FDA approved for patients requiring urgent/ emergent procedures. Consider use of 4F-PCC	Not FDA approved, limited data exist	Not approved for less severe bleeding
Approval required	No approval required for apixaban or rivaroxaban reversal for critical life threatening major bleeding	Requires hematology review and approval			Not approved for this indication
Laboratory monitoring	Baseline CBC, anti-Xa (UFH/LMWH); Draw prior to administration; do not wait for results	Anti-Xa (UFH/LMWH) Draw immediately for consideration of administration			Not applicable

[a] If urgent or emergent surgery is required and there is insufficient time to allow the anticoagulant effect to dissipate, reversal strategies with prothrombin complex concentrates may be appropriate. Decisions regarding the need for reversal are individualized based on the urgency and bleeding risk of the procedure.

Culbreth SE, et al. *Am J Hematol* 2018. https://doi.org/10.1002/ajh.25326

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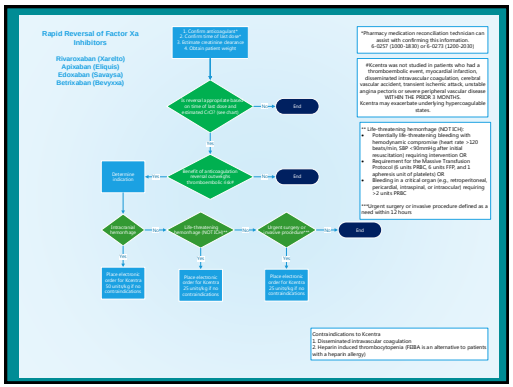

Comprehensive Reversal Strategy

Factors to consider prior to pharmacologic intervention

Agent selection

Anticoagulation resumption

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Conclusions

- Acute major bleeding should be clearly defined
- An assessment for the presence of residual factor-Xa inhibitor activity is necessary
- Comparative data between prothrombin complex concentrates and andexanet are lacking
- Important caveats for use exist for each option
- Protocol development should include a close examination of the existing data, cost, and operational considerations

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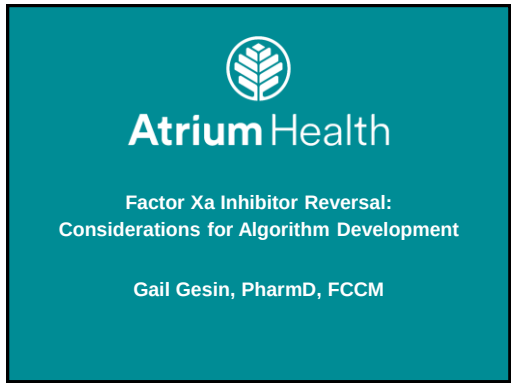
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