1-11-2020

What a Blood Bath! Andexxa® Makes a Splash! Current Trends in Anticoagulation Reversal

Michael Pasqualicchio
Baptist Hospital of Miami, michaelpa@baptisthealth.net

What a Blood Bath!
Andexxa® Makes a Splash!
Current Trends in Anticoagulation Reversal

Michael Pasqualicchio, Pharm.D., BCPS
PGY-2 Critical Care Pharmacy Resident
Baptist Hospital of Miami
MichaelPa@Baptisthealth.net

Disclosures

The author of this presentation has no relevant financial or non-financial relationships in the products described and reviewed in this presentation.

Objectives

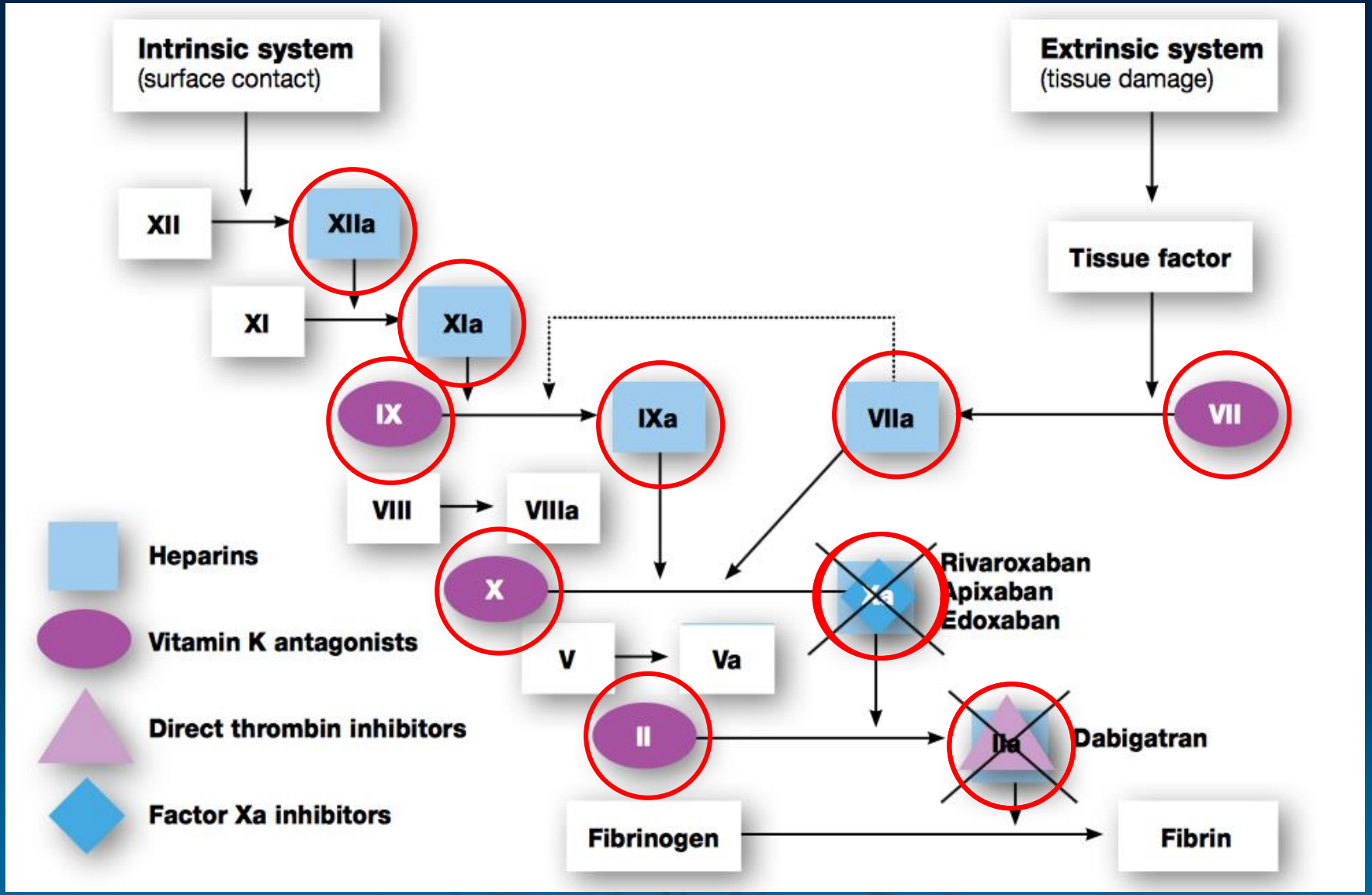
- Discuss various pharmacological management and reversal options for direct acting oral anticoagulation agents
- Review the mechanism of action and dosing of prothrombin complex concentrate (Kcentra®) and andexanet alfa (Andexxa®)
- Review available studies in practice facilitating the approval of andexanet alfa
- Evaluate and compare literature regarding the safety and efficacy of prothrombin complex concentrate and andexanet alfa for the reversal of oral anticoagulation

Classification of Anticoagulants

Route	Class	Agents
Oral	Vitamin K antagonist	Warfarin (Coumadin®)
	Direct thrombin inhibitor	Dabigatran (Pradaxa®)
	Factor Xa inhibitors	Apixaban (Eliquis®) Betrixaban (Bevyxxa®) Edoxaban (Savaysa®) Rivaroxaban (Xarelto®)
Parenteral	Thrombin/Factor Xa inhibitors	Heparin Enoxaparin (Lovenox®)
	Direct thrombin inhibitors	Bivalirudin Argatroban
	Factor Xa Inhibitor	Fondaparinux (Arixtra®)

Direct Oral Anticoagulants (DOACs)

Mechanism of DOACs



Drager, WE. Managing and reversing direct oral anticoagulants: A discussion guide. *American Society of Health-System Pharmacists.*

Direct Oral Anticoagulants

- Estimated over 6 million patients in the United States are treated with anticoagulants
- DOACs are now the most widely prescribed oral anticoagulants
- Major bleeding reported in 2.1% to 3.6% of patients in phase III trials
- Apixaban and rivaroxaban are among the top ten drugs contributing to emergency department visits in the United States

Cucker A, Burnett A, Triller D, Crowther M, Ansell J, Van Cott EM, Wirth D, Kaatz S. Reversal of direct acting oral anticoagulants: guidance from the anticoagulation forum. *American Journal of Hematology*. 2019: 94(6):697-709.

Management of DOAC-Related Bleed

1. Assess and identify severity of bleed
2. Manage and control bleed
3. Determine whether and when to restart anticoagulation

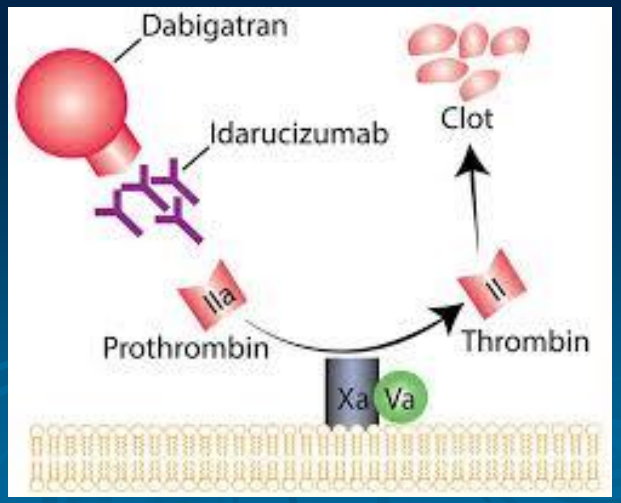
Tomaselli GF, Mahaffey KW, Cuker A, et al. 2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants. *Journal of the American College of Cardiology*. 2017;70(24):3042-3067.

DOAC Reversal Agents

Idarucizumab (Praxbind®)

Dabigatran (Pradaxa®) Reversal

- Idarucizumab (Praxbind®)
- Mechanism of action: Humanized monoclonal antibody fragment that binds specifically to dabigatran and its metabolites
  - Binds with affinity 350 times greater than that of thrombin



Drager, WE. Managing and reversing direct oral anticoagulants: A discussion guide. *American Society of Health-System Pharmacists.*

Idarucizumab (Praxbind®)

- Dosing: 2.5 grams IV over 5 to 10 minutes for 2 doses
  - Second vial no later than 15 minutes following administration of first vial
- Onset of action within minutes/hemostasis restored within 12 hours
- Renal elimination

Drager, WE. Managing and reversing direct oral anticoagulants: A discussion guide. *American Society of Health-System Pharmacists.*

RE-VERSE AD

Idarucizumab for Dabigatran Reversal — Full Cohort Analysis

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., Joanne van Ryn, Ph.D., John W. Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Chak-Wah Kam, M.D., Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., et al.

- Two groups of patients:
  - Uncontrollable or life-threatening bleed
  - Surgery or invasive procedure that could not be delayed
- Primary outcome: maximum percentage reversal of diluted thrombin time or the ecarin clotting time (ECT)

Pollack CV Jr, Reilly PA, van Ryn J. et al. Idarucizumab for dabigatran reversal - full cohort analysis. *N Engl J Med*. 2017;377(5):431-441.

RE-VERSE AD

- Inclusion criteria:
  - ≥18 years old
  - On dabigatran
- Exclusion criteria:
  - Group A:
    - Patients with minor bleeding
    - Patients with no clinical signs of bleeding
    - Hypersensitivity to reversal agent
  - Group B:
    - Low risk procedure
    - Elective procedure
    - Hypersensitivity to reversal agent

Pollack CV Jr, Reilly PA, van Ryn J. et al. Idarucizumab for dabigatran reversal - full cohort analysis. *N Engl J Med*. 2017;377(5):431-441.

RE-VERSE AD

- Idarucizumab reversed anticoagulation rapidly and completely in more than 98% of patients
  - Reversal maintained for 24 hours
  - Cessation of bleeding within 2.5 hours
  - Surgery enabled in 197 of 202 patients
  - 4.8% of patients had thrombotic event within 30 days

Pollack CV Jr, Reilly PA, van Ryn J. et al. Idarucizumab for dabigatran reversal - full cohort analysis. *N Engl J Med*. 2017;377(5):431-441.

DOAC Reversal Agents

Prothrombin complex concentrate (Kcentra®)

PCC General Information

- Purified, lyophilized, non-activated 4-factor concentrate prepared from human plasma
- Contains the following:
  - Factor II
  - Factor VII
  - Factor IX
  - Factor X
  - Protein C and S

Cada DJ, Levien TL, Baker DE. Prothrombin complex concentrate. *Hosp Pharm*. 2013;48(11):951–957.

PCC General Information

- Approved indication: Vitamin K antagonist reversal in patients with
  - Acute major bleeding
  - Need for urgent surgery/invasive procedure
- Weight-based dosing:

INR	PCC Dose
INR 2 to <4	25 units/kg (Max 2500 units)
INR 4 to 6	35 units/kg (Max 3500 units)
INR ≥6	50 units/kg (Max 5000 units)

- Administered IV at a rate of 0.12 ml/kg/minute
- Warnings/precautions:
  - Thromboembolic events
  - Hypersensitivity reactions
  - Contains heparin (contraindicated in patients with Heparin Induced Thrombocytopenia)

Cada DJ, Levien TL, Baker DE. Prothrombin complex concentrate. *Hosp Pharm*. 2013;48(11):951–957.

PCC for DOAC Reversal

- Off-label
- Initial dosing recommendation from European Heart Rhythm Association: 50 units/kg IV (additional 25 units/kg if clinically necessary)
  - 12 healthy subjects received rivaroxaban for 2.5 days all achieving immediate reversal
  - 15 healthy subjects received apixaban for 3.5 days all achieving immediate reversal

Eerenberg ES Kamphuisen PW Sijpkens MK Meijers JC Buller HR Levi M. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. *Circulation* 2011;124:1573-9.
Perlstein I Wang Z Song Y Wang J Bedford B Chang Met al. Reversal of apixaban anticoagulation by 4-factor prothrombin complex concentrates in healthy subjects. *Blood* 2014; 124:345.

Fixed Dose PCC

Yasaka M, Sakata T, Naritomi H, Minematsu K (2005)	Khorsand N, Veeger NJ, Muller M, et al (2011)	Khorsand N, Veeger NJ, van Hest RM, Ypma PF, Heidt J, Meijer K (2012)	Klein L, Peters J, Miner J, Gorlin J (2015)
Insufficient: 200 units and 500 units Reversed INR in all patients: 1000 units and 1500 units	Extra-cranial hemorrhage treated with 1040 units: Successful clinical outcome in 91% of patients	Variable dosing: 88% positive clinical response 1040 units fixed dose: 96% positive clinical response	1500 units reversed INR to less than 2.0 in 92.3% of patients and less than 1.5 in 71.8% of patients

- Ongoing PROPER3 trial evaluating variable vs. fixed dosing (1000 units) in vitamin K antagonist related extra-cranial bleeding

UPRATE Study

Management of rivaroxaban- or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study

Ammar Majeed,[1-4] Anna Ågren,[1,3] Margareta Holmström,[1,3] Maria Bruzelius,[1,3] Roza Chaireti,[3,5,6] Jacob Odeberg,[1,3,7] Eva-Lotta Hempel,[1,3] Maria Magnusson,[6,8,9] Tony Frisk,[10] and Sam Schulman[11,12]

- Published in 2017 assessing the use of PCC for apixaban and rivaroxaban reversal
- Fixed dose PCC regimen of either 1,500 or 2,000 IV units based on weight

Majeed A, Argen A, Holmstrom M, et al. Reversal of rivaroxaban or apixaban associated major bleeding with prothrombin complex concentrates: a cohort study. *Blood.* 2017;130:1706-1712.

UPRATE Study

- Population: patients with acute and active major bleeding while on rivaroxaban or apixaban
  - Last dose within 24 hours
- Excluded patients:
  - Reduced hemoglobin without source
  - Preoperative reversal
  - Acute coronary syndrome or ischemic stroke in past 30 days
  - Other hemostatic agents administered

Majeed A, Argen A, Holmstrom M, et al. Reversal of rivaroxaban or apixaban associated major bleeding with prothrombin complex concentrates: a cohort study. *Blood.* 2017;130:1706-1712.

UPRATE Study

- Prothrombin complex concentrate dosing
  - <65 kg: 1500 units IV
  - >65 kg: 2000 units IV
- Efficacy/safety assessment:

Non-intracerebral hemorrhage (ICH) bleeding	Intracerebral hemorrhage (ICH) bleeding
▪ Hemoglobin trend ▪ Transfusion of blood products ▪ Need for surgery or intervention ▪ Administration of other hemostatic agents	▪ Follow up CT within 24 hours ▪ Change in neurological status ▪ Surgical intervention
Safety assessment: arterial or venous thromboembolism and 30-day mortality	

Majeed A, Argen A, Holmstrom M, et al. Reversal of rivaroxaban or apixaban associated major bleeding with prothrombin complex concentrates: a cohort study. *Blood.* 2017;130:1706-1712.

UPRATE Results

- 84 total patients (39 apixaban and 45 rivaroxaban)
  - 70.2% ICH
- 26 patients (30.9%) had ineffective hemostatic effect post PCC
  - 61.5% suffered from ICH
- Death occurred in 15 patients (18%)
  - 13 patients (86.7%) had ICH
- Thromboembolism in 3 patients (2.4%)
  - 1 patient on thromboprophylaxis

Majeed A, Argen A, Holmstrom M, et al. Reversal of rivaroxaban or apixaban associated major bleeding with prothrombin complex concentrates: a cohort study. *Blood.* 2017;130:1706-1712.

UPRATE Conclusions

- Limitations:
  - Observational study
  - No control group for comparison
  - Subjective effectiveness

- Majority of patients treated with 2,000 units PCC for the management of major bleeding event on rivaroxaban or apixaban achieved effective bleeding control

Majeed A, Argen A, Holmstrom M, et al. Reversal of rivaroxaban or apixaban associated major bleeding with prothrombin complex concentrates: a cohort study. *Blood.* 2017;130:1706-1712.

PCC for Factor Xa Inhibitor Reversal

Prothrombin Complex Concentrate for Major Bleeding on Factor Xa Inhibitors: A Prospective Cohort Study

Sam Schulman[1,2] Peter L. Gross[1] Bruce Ritchie[3] Susan Nahirniak[4] Yulia Lin[5] Lani Lieberman[6] Marc Carrier[7] Mark A. Crowther[1] Indy Ghosh[8] Alejandro Lazo-Langner[9] Michelle Zondag[10] On Behalf of the Study Investigators*

- Published in 2018 assessing the use of PCC for apixaban and rivaroxaban reversal
- Fixed dose of 2,000 units studied

Schulman S, Gross PL, Ritchie B, et al. Prothrombin complex concentrate for major bleeding on factor Xa inhibitors: a prospective cohort study. *Thromb Haemost.* 2018;118:842-851.

PCC for Factor Xa Inhibitor Reversal

- Inclusion criteria:
  - Received 2,000 units of PCC for major bleeding on apixaban or rivaroxaban
  - No other hemostatic agents
- Exclusion criteria
  - Drop in hemoglobin without source
  - Acute coronary syndrome or stroke within 30 days

Schulman S, Gross PL, Ritchie B, et al. Prothrombin complex concentrate for major bleeding on factor Xa inhibitors: a prospective cohort study. *Thromb Haemost.* 2018;118:842-851.

PCC for Factor Xa Inhibitor Reversal

- 66 patients (29 apixaban and 37 rivaroxaban)
  - 55% ICH
- 10 patients (15%) did not achieve hemostatic efficacy
- 5 patients (8%) experienced thromboembolism within 30 days
  - 0 of the 4 patients with thromboembolism during first 12 days were on anticoagulation
  - 62% of patients were restarted on anticoagulation within 5 days

Schulman S, Gross PL, Ritchie B, et al. Prothrombin complex concentrate for major bleeding on factor Xa inhibitors: a prospective cohort study. *Thromb Haemost.* 2018;118:842-851.

Study Conclusions

- Limitations:
  - Retrospective recruitment of patients
  - No control group for comparison
  - Not all patients received 2000 units
  - Subjective effectiveness

- Good hemostatic efficacy was achieved in 65% of patients and moderate hemostatic efficacy was achieved in 20% of patients

Schulman S, Gross PL, Ritchie B, et al. Prothrombin complex concentrate for major bleeding on factor Xa inhibitors: a prospective cohort study. *Thromb Haemost.* 2018;118:842-851.

DOAC Reversal Agents

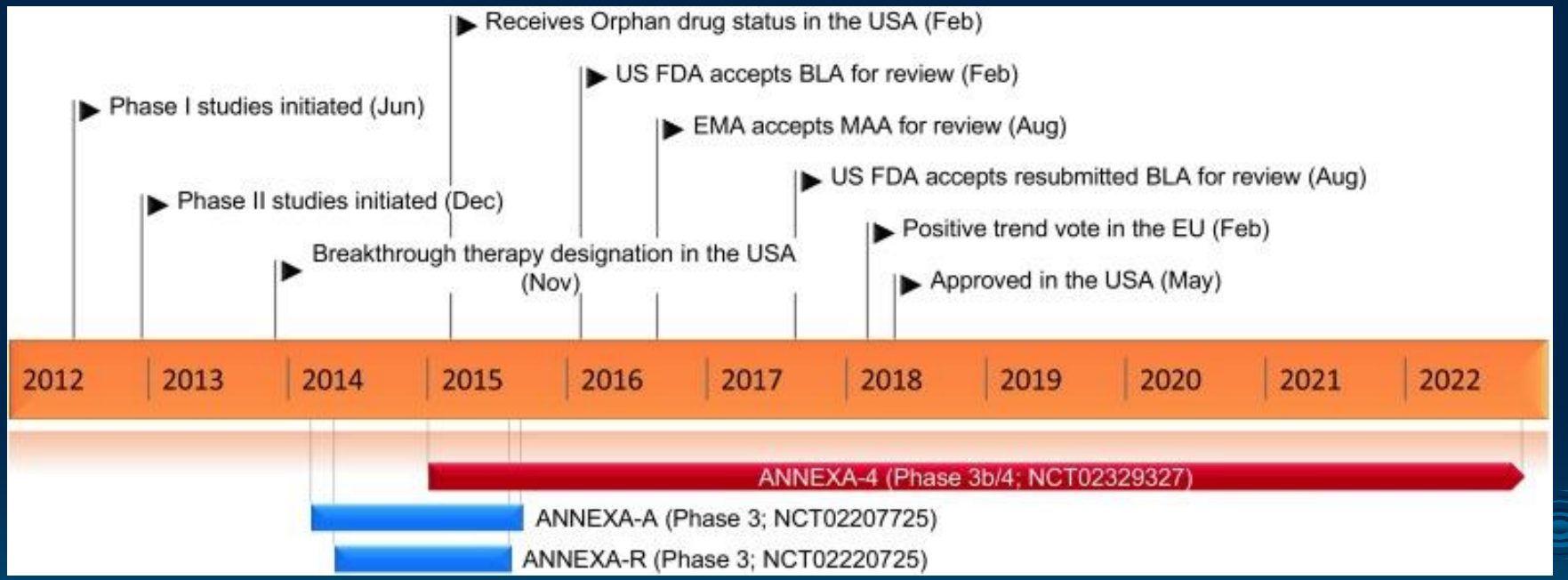
Andexanet Alfa (Andexxa®)

Andexanet Alfa General Information

- Indication: FDA accelerated approval in May 2018 for the reversal of anticoagulation in patients treated with apixaban (Eliquis®) or rivaroxaban (Xarelto®) in the setting of:
  - Life-threatening or uncontrolled bleeding
  - Emergency surgery

Heo YA. Andexanet Alfa: First Global Approval [published correction appears in Drugs. 2018 Aug;78(12):1285]. *Drugs*. 2018;78(10):1049–1055.

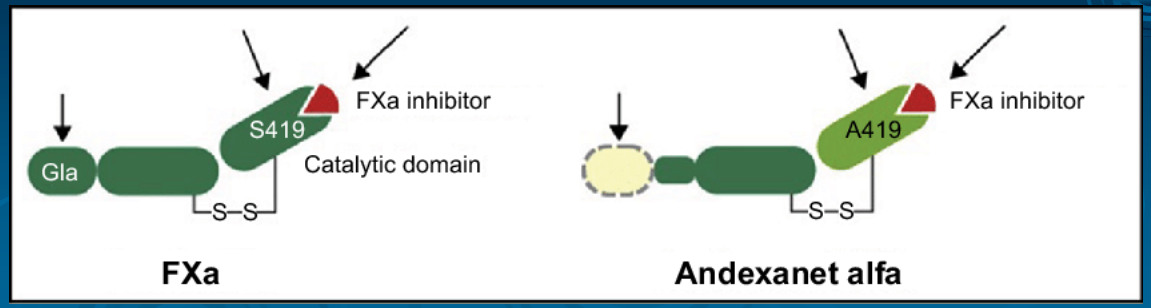
Andexanet Alfa General Information



Heo YA. Andexanet Alfa: First Global Approval [published correction appears in Drugs. 2018 Aug;78(12):1285]. *Drugs*. 2018;78(10):1049–1055.

Mechanism of action

- Recombinant modified human factor Xa decoy protein
  - Catalytically inactive (no coagulation activity)
  - Binds to factor Xa inhibitors at their site with a higher affinity than endogenous factor Xa
    - 1:1 stoichiometric ratio
    - Sequesters the inhibitor within the vascular space allowing endogenous factor Xa to be active



Kaatz S, Bhansali H, Gibbs J, Lavender R, Mahan CE, Paje DG. Reversing factor Xa inhibitors - clinical utility of andexanet alfa. *J Blood Med*. 2017;8:141–149. Published 2017 Sep 13.

ANNEXA-A/ANNEXA-R trial

Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity

Deborah M. Siegal, M.D., John T. Curnutte, M.D., Ph.D., Stuart J. Connolly, M.D., Genmin Lu, Ph.D., Pamela B. Conley, Ph.D., Brian L. Wiens, Ph.D., Vandana S. Mathur, M.D., Janice Castillo, B.S., Michele D. Bronson, Ph.D., Janet M. Leeds, Ph.D., Florie A. Mar, Ph.D., Alex Gold, M.D., et al.

- ANNEXA-A and ANNEXA-R trials published in 2015 evaluated the ability of andexanet alfa to reduce anti-factor Xa levels in healthy volunteers
  - Compared andexanet alfa to placebo
  - Compared bolus to bolus with infusion

Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity. *The New England journal of medicine.* 2015;373:2413-2424.

ANNEXA-A/ANNEXA-R

- Randomized, double-blind, placebo controlled trial
- Healthy volunteers
- Primary endpoint: percent change in anti-factor Xa activity from baseline to post-administration

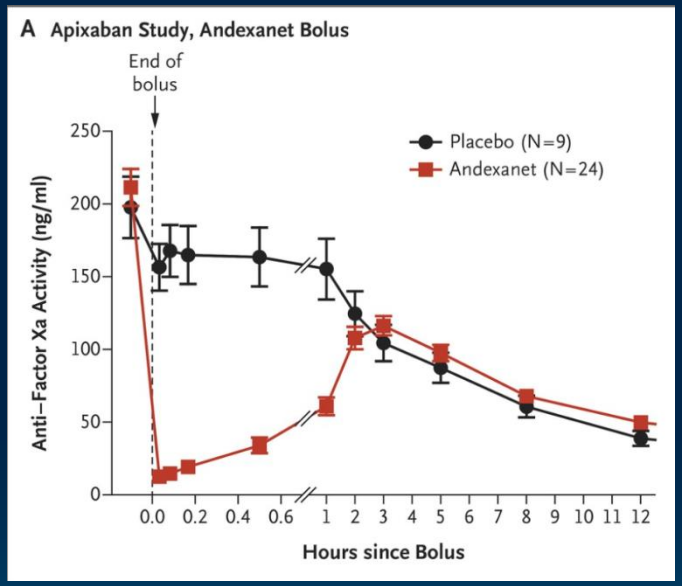
Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity. *The New England journal of medicine.* 2015;373:2413-2424.

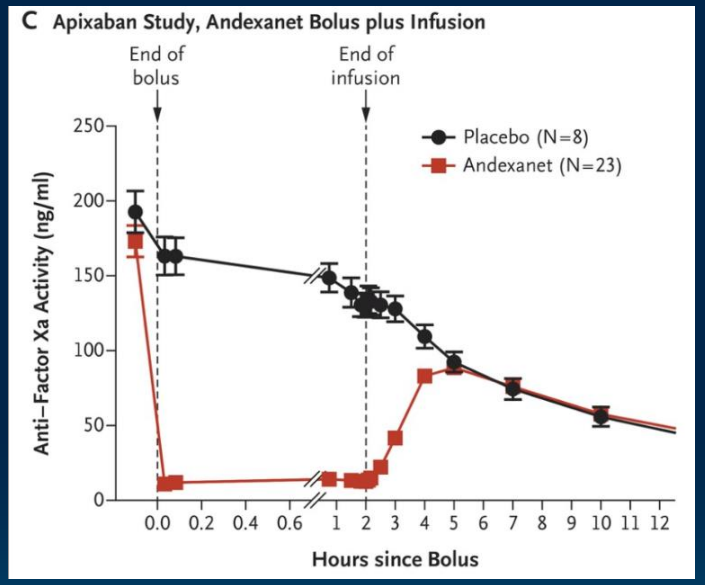
Trial design

- ANNEXA-A
  - Apixaban 5 mg twice daily for 3.5 days
  - Low dose andexanet alfa regimen administered on day four, 3 hours after the last apixaban
    - Bolus vs. bolus with infusion
- ANNEXA-R
  - Rivaroxaban 20 mg daily for 4 days
  - High dose andexanet alfa regimen administered on day four, 4 hours after the last rivaroxaban
    - Bolus vs. bolus with infusion

Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity. *The New England journal of medicine.* 2015;373:2413-2424.

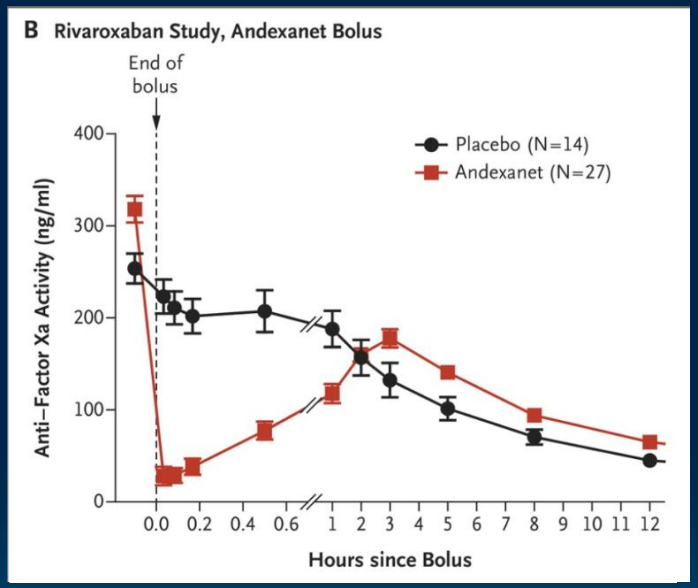
ANNEXA-A Results

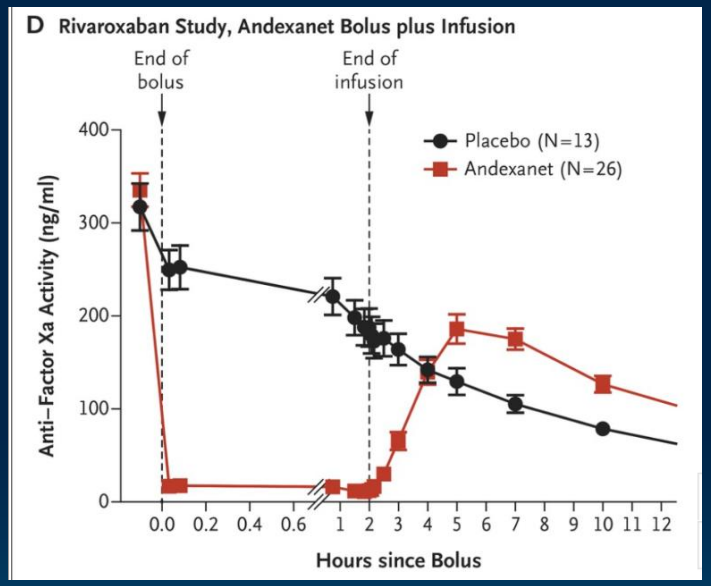




Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity. *The New England journal of medicine.* 2015;373:2413-2424.

ANNEXA-R Results





Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity. *The New England journal of medicine.* 2015;373:2413-2424.

ANNEXA-A/ANNEXA-R Safety Data

- No serious safety events and no thrombotic events reported
- One patient discontinued treatment after 35 minutes – allergic reaction
- No antibodies to factor X or factor Xa developed

Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity. *The New England journal of medicine.* 2015;373:2413-2424.

ANNEXA-A/ANNEXA-R Conclusions

- Andexanet alfa effectively reverses the anticoagulant effects of apixban and rivaroxaban within minutes of administration
- Bolus with continuous infusion dosing results in prolonged suppression of anti-factor Xa activity

Andexanet Alfa Dosing Regimens

- Two dosing regimens
  - Low dose:
    - 400 mg IV bolus administered at 30 mg/minute
    - 4 mg/minute IV infusion 2 minutes after for up to 120 minutes
  - High dose:
    - 800 mg IV bolus administered at 30 mg/minute
    - 8 mg/minute IV infusion 2 minutes after for up to 120 minutes
- Andexanet alfa available as 100 mg and 200 mg vial

Andexxa (andexanet alfa) [package insert]. South San Francisco, Ca. *Portola Pharmaceuticals.*

Regimen Selection

Andexanet alfa dose based on apixaban or rivaroxaban dose			
FXa inhibitor	FXa inhibitor last dose	Timing of FXa inhibitor last dose before andexanet alfa initiation	
		<8 Hours or Unknown	≥8 Hours
Apixaban	≤5 mg	Low dose	Low dose
	>5 mg/unknown	High dose	
Rivaroxaban	≤10 mg	Low dose	
	>10 mg/unknown	High dose	

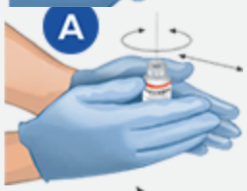
Andexxa (andexanet alfa) [package insert]. South San Francisco, Ca. *Portola Pharmaceuticals.*

Dose Preparation

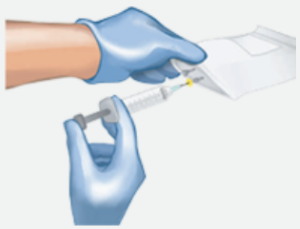
IV Bolus Preparation

200 mg vials: Reconstitute the 200 mg vial of ANDEXXA with 20 mL of Sterile Water for Injection USP (SWFI).

- Use a 20-mL (or larger) syringe and 20-gauge (or higher) needle.
- Slowly inject the SWFI directing the solution onto the inside wall of the vial to minimize foaming.
- To reduce the total reconstitution time needed during preparation, reconstitute all required vials in succession.



- To ensure dissolution of the cake or powder, gently swirl each vial until complete dissolution of powder occurs (A). Do not shake (B); shaking could lead to foaming. Typical dissolution time for each vial is approximately 3 to 5 minutes. If dissolution is incomplete, discard the vial and do not use the product.
- Upon reconstitution, the parenteral drug product should be inspected visually for particulate matter and discoloration prior to administration.



- Use 60-mL or larger syringe with a 20-gauge (or higher) needle to withdraw the reconstituted ANDEXXA solution from each of the vials until the required dosing volume is achieved. Note the total volume withdrawn into the syringe.
- Transfer the ANDEXXA solution from the syringe into an empty polyolefin or polyvinyl chloride IV bag with a volume of 250 mL or less.
- Discard the syringe and needle.
- Discard the vials, including any unused portion.

Andexxa (andexanet alfa) [package insert]. South San Francisco, Ca. *Portola Pharmaceuticals.*

ANNEXA-4 Trial

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

Stuart J. Connolly, M.D., Mark Crowther, M.D., John W. Eikelboom, M.D., C. Michael Gibson, M.D., John T. Curnutte, M.D., Ph.D., John H. Lawrence, M.D., Patrick Yue, M.D., Michele D. Bronson, Ph.D., Genmin Lu, Ph.D., Pamela B. Conley, Ph.D., Peter Verhamme, M.D., Ph.D., Jeannot Schmidt, M.D., et al., for the ANNEXA-4 Investigators*

- Patients enrolled from April 2015 to May 2018
  - Preliminary results published September 2016 (67 patients)
  - Final results published April 2019

Connolly SJ, Milling TJ, Eikelboom JW, et al. Full Study Report of Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors. *The New England journal of medicine*.2019: 380:1326-1335.

ANNEXA-4 Trial

- Multicenter, prospective, open-label, single-group study
- Received within 18 hours one of the following
  - Apixaban
  - Rivaroxaban
  - Edoxaban
  - Enoxaparin at least 1 mg/kg/day
- Acute major bleeding

Connolly SJ, Milling TJ, Eikelboom JW, et al. Full Study Report of Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors. *The New England journal of medicine*.2019: 380:1326-1335.

ANNEXA-4 Acute Major Bleeding

- Life-threatening bleeding with signs/symptoms of hemodynamic compromise
- Bleeding associated with hemoglobin decrease of at least 2 g/dL
- Bleeding in a critical area or organ
- July 2016 to August 2017 only patients with intracranial hemorrhage were enrolled

Connolly SJ, Milling TJ, Eikelboom JW, et al. Full Study Report of Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors. *The New England journal of medicine*.2019: 380:1326-1335.

ANNEXA-4 Exclusion Criteria

ANNEXA-4 Exclusion criteria
Planned surgery within 12 hours
Intracranial hemorrhage in patient with Glasgow Coma Scale score of less than 7
Estimated hematoma volume greater than 60 mL
Expected survival of less than 1 month
Thrombotic event within 2 weeks of enrollment
Vitamin K antagonist, dabigatran, PCC, recombinant factor VIIa, whole blood, or plasma administered within last 7 days

Connolly SJ, Milling TJ, Eikelboom JW, et al. Full Study Report of Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors. *The New England journal of medicine*.2019: 380:1326-1335.

ANNEXA-4

- Dosing based on time since anticoagulant for rivaroxaban only
  - <8 hours = low dose regimen
  - ≥8 hours = high dose regimen
- Primary outcomes:
  - Percent change in anti-factor Xa activity
  - Rate of excellent or good hemostatic efficacy 12 hours post infusion
  - Safety outcome of death, thrombotic event, development of antibodies

Connolly SJ, Milling TJ, Eikelboom JW, et al. Full Study Report of Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors. *The New England journal of medicine*.2019: 380:1326-1335.

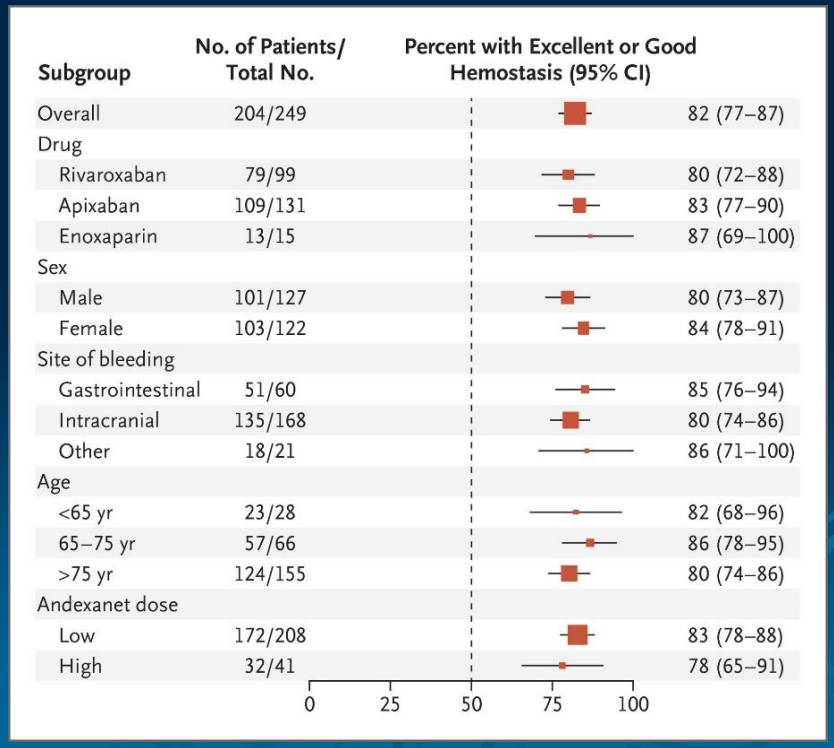
ANNEXA-4 Study Population

Characteristic	Safety (N=352)	Efficacy (N=254)
Age - yr	77.4 ± 10.8	77.1 ± 11.1
Indication for anticoagulation – no. (%)		
▪ Atrial fibrillation	280 (80)	201 (79)
▪ Venous thromboembolism	61 (17)	46 (18)
▪ Other	11 (3)	7 (3)
Factor Xa inhibitor – no. (%)		
▪ Rivaroxaban	128 (36)	100 (39)
▪ Apixaban	194 (55)	134 (53)
▪ Enoxaparin	20 (6)	16 (6)
▪ Edoxaban	10 (3)	4 (2)
Site of bleeding – no. (%)		
▪ Gastrointestinal	90 (26)	62 (24)
▪ Intracranial	227 (64)	171 (67)
▪ Other	35 (10)	21 (8)

Connolly SJ, Milling TJ, Eikelboom JW, et al. Full Study Report of Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors. *The New England journal of medicine*.2019: 380:1326-1335.

ANNEXA-4 Efficacy Results

- Anti-factor Xa activity at end of bolus administration
  - Apixaban 92% reduction
  - Rivaroxaban 92% reduction
- Hemostatic efficacy:



Connolly SJ, Milling TJ, Eikelboom JW, et al. Full Study Report of Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors. *The New England journal of medicine*.2019: 380:1326-1335.

ANNEXA-4 Safety Results

- 34 (10%) patients had at least 1 thrombotic event during 30-day follow up
  - 34 (100%) occurred prior to restart of oral anticoagulant
  - 26 (76%) occurred prior to restart of any anticoagulant at any dose

Connolly SJ, Milling TJ, Eikelboom JW, et al. Full Study Report of Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors. *The New England journal of medicine*.2019: 380:1326-1335.

ANNEXA-4 Limitations

- 41 of 249 patients received the high dose regimen
  - 99 patients were on rivaroxaban
- No comparison – single group cohort
- Patients on average had a Glascow Coma Score (GCS) of 14 and hematoma volume of <10 mL
- Excluded patients with surgery within 12 hours
- Subjective primary outcome

Connolly SJ, Milling TJ, Eikelboom JW, et al. Full Study Report of Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors. *The New England journal of medicine*.2019: 380:1326-1335.

ANNEXA-4 Conclusions

- Andexanet alfa reduced anti-factor Xa levels and achieved hemostasis in the majority of patients
- Increased risk of thrombotic events
  - May be dependent on restart of anticoagulation

Anticoagulation Reversal Recommendations

Guidance from the American Journal of Hematology

- Reversal agents only indicated if bleeding is life-threatening or not controlled by supportive measures
- Reversal agents should only be administered pre-operatively if the surgery cannot be performed or delayed
- DOAC overdose without bleeding is not an indication for reversal

Cucker A, Burnett A, Triller D, Crowther M, Ansell J, Van Cott EM, Wirth D, Kaatz S. Reversal of direct acting oral anticoagulants: guidance from the anticoagulation forum. *American Journal of Hematology*. 2019: 94(6):697-709.

Guidance from the American Journal of Hematology - Dabigatran

- Patients with dabigatran associated major bleeding or requiring emergent surgery should be treated with idarucizumab 5 grams IV
  - PCC can be used at 50 units/kg if idarucizumab is not available
  - Hemodialysis removes up to 68% but often impractical

Cucker A, Burnett A, Triller D, Crowther M, Ansell J, Van Cott EM, Wirth D, Kaatz S. Reversal of direct acting oral anticoagulants: guidance from the anticoagulation forum. *American Journal of Hematology*. 2019: 94(6):697-709.

Guidance from the American Journal of Hematology – Factor Xa Inhibitors

- Patients with rivaroxaban or apixaban associated bleeding warranting reversal should be treated with andexanet alfa
  - PCC 2,000 units can be used if andexanet alfa is not available

Cucker A, Burnett A, Triller D, Crowther M, Ansell J, Van Cott EM, Wirth D, Kaatz S. Reversal of direct acting oral anticoagulants: guidance from the anticoagulation forum. *American Journal of Hematology*. 2019: 94(6):697-709.

Guidance from the American Journal of Hematology – Factor Xa Inhibitors

- Patients with edoxaban-associated or betrixaban-associated major bleeding warranting reversal should be treated with either high dose andexanet alfa or PCC 2,000 units

Cucker A, Burnett A, Triller D, Crowther M, Ansell J, Van Cott EM, Wirth D, Kaatz S. Reversal of direct acting oral anticoagulants: guidance from the anticoagulation forum. *American Journal of Hematology*. 2019: 94(6):697-709.

Andexanet alfa vs. PCC

Study result	ANNEXA-4 S - N=352 E - N=254	UPRATE N=84	Schulman et al. N=66
Anticoagulant	Xa inhibitors	Xa inhibitors	Xa inhibitors
Reversal agent	Andexanet alfa	PCC	PCC
Dosing		1500 units or 2000 units	2000 units
Age, yrs	77.4 ± 10.8	75 (70.0–83.0)	76.9 ± 10.4
Intracranial hemorrhage – no, (%)	227 (64)	59 (70.2)	36 (55)
Efficacy endpoint met – no, (%)	204 (82)	58 (69.1)	56 (85)
Thromboembolism – no, (%)	34 (10)	3 (3.6)	5 (7.6)

Abbreviations:
S = safety
E = efficacy

Investigational Agent

Ciraparantag

(Aripazine-PER977)

Ciraparantag (Aripazine-PER977)

- Direct sequestering of heparin, direct factor Xa and thrombin inhibitors
- Small synthetic water-soluble molecule
- Single dose forms strong ionic, noncovalent bonds and large complex molecules that bind anticoagulation agents
- Under evaluation in Phase II clinical trials

Ansell JE, Bakhru SH, Laulicht BE, et al. Single-dose ciraparantag safely and completely reverses anticoagulant effects of edoxaban. *Thromb Haemost*. 2017;117(2):238–245.

Restarting Anticoagulation

Restarting Anticoagulation

- Reassess indication for anticoagulation
  - Paroxysmal atrial fibrillation with CHA2DS2-VASc ≤1
  - Temporary indication (postsurgical prophylaxis, provoked VTE >3 months prior, etc.)
- Risk/benefit assessment to restart
  - Reversible factors contributing to bleed
  - High thrombotic risk (Mechanical valve prosthesis, atrial fibrillation, left ventricular assist device, venous thromboembolism)
- Timing of restart
  - High re-bleeding risk – initiate parenteral anticoagulant
  - Dependent on thrombotic/bleed risk

Tomaselli GF, Mahaffey KW, Cuker A, et al. 2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants. *Journal of the American College of Cardiology*. 2017;70(24):3042-3067.

Assessment Questions

1. The ANNEXA-4 trial included patients with severe neurologic compromise as well as those requiring urgent surgery. (T/F)
2. According to a guidance document published in the American Journal of Hematology, a fixed dose of 2000 units of prothrombin complex concentrate is preferred to weight-based dosing in factor Xa inhibitor associated bleeding. (T/F)
3. Reversal agents for direct acting oral anticoagulant associated bleeding, should be administered to patients with bleeds that are life threatening, located in a critical organ, or uncontrolled by supportive measures. (T/F)
4. Investigational drug, ciraparantag is capable of reversing all anticoagulants including warfarin, argatroban, DOACs, heparin, LMWH, and fondaparinux. (T/F)

References

- Andexxa (andexanet alfa) [package insert]. South San Francisco, Ca. *Portola Pharmaceuticals*
- Ansell JE, Bakhru SH, Laulicht BE, et al. Single-dose ciraparantag safely and completely reverses anticoagulant effects of edoxaban. *Thromb Haemost*. 2017;117(2):238–245.
- Cada DJ, Levien TL, Baker DE. Prothrombin complex concentrate. *Hosp Pharm*. 2013;48(11):951–957.
- Connolly SJ, Milling TJ, Eikelboom JW, et al. Full Study Report of Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors. *The New England journal of medicine*.2019: 380:1326-1335.
- Cucker A, Burnett A, Triller D, Crowther M, Ansell J, Van Cott EM, Wirth D, Kaatz S. Reversal of direct acting oral anticoagulants: guidance from the anticoagulation forum. *American Journal of Hematology*. 2019: 94(6):697-709.
- Drager, WE. Managing and reversing direct oral anticoagulants: A discussion guide. *American Society of Health-System Pharmacists.*
- Eerenberg ES Kamphuisen PW Sijpkens MK Meijers JC Buller HR Levi M. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. *Circulation* 2011;124:1573-9.
- Heo YA. Andexanet Alfa: First Global Approval [published correction appears in Drugs. 2018 Aug;78(12):1285]. *Drugs*. 2018;78(10):1049–1055.
- Kaatz S, Bhansali H, Gibbs J, Lavender R, Mahan CE, Paje DG. Reversing factor Xa inhibitors - clinical utility of andexanet alfa. *J Blood Med*. 2017;8:141–149. Published 2017 Sep 13.
- Majeed A, Argen A, Holmstrom M, et al. Reversal of rivaroxaban or apixaban associated major bleeding with prothrombin complex concentrates: a cohort study. *Blood.* 2017;130:1706-1712.
- Perlstein I Wang Z Song Y Wang J Bedford B Chang Met al. Reversal of apixaban anticoagulation by 4-factor prothrombin complex concentrates in healthy subjects. *Blood* 2014; 124:345.
- Pollack CV Jr, Reilly PA, van Ryn J. et al. Idarucizumab for dabigatran reversal - full cohort analysis. *N Engl J Med*. 2017;377(5):431-441.
- Schulman S, Gross PL, Ritchie B, et al. Prothrombin complex concentrate for major bleeding on factor Xa inhibitors: a prospective cohort study. *Thromb Haemost.* 2018;118:842-851.
- Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity. *The New England journal of medicine.* 2015;373:2413-2424.
- Tomaselli GF, Mahaffey KW, Cuker A, et al. 2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants. *Journal of the American College of Cardiology*. 2017;70(24):3042-3067.