Direct Oral Anticoagulants: Recent Updates

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Disclosure

- I have no relevant financial interests or conflicts of interest to disclose.

Overview/Learning Objectives

Describe	Describe the FDA indications and dosing considerations for the Direct Oral Anticoagulants (DOACs)
Describe	Describe recent updates to CHEST anticoagulation guidelines as it relates to DOACs in atrial fibrillation
Compare	Compare safety and efficacy profiles of the DOACs
Discuss	Discuss reversal strategies for apixaban and rivaroxaban

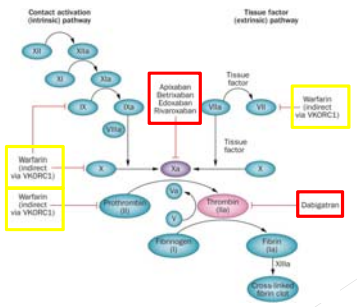
DOAC, NOAC, TSOAC….oh my

- DOAC – Direct Oral AntiCoagulant
- NOAC – Novel Oral AntiCoagulant
- NOAC – New Oral AntiCoagulant
- NOAC – Non-vitamin k Oral AntiCoagulant
- TSOAC – Target Specific Oral AnticCoagulant

- Apixaban, Betrixaban, Edoxaban, Rivaroxaban and Dabigatran

https://i.ytimg.com/vi/NecK4MwOfaI/hqdefault.jpg

Coagulation Cascade



DOACs vs Warfarin

DOAC Advantages

- No need for INR monitoring
- Standardized dosing and dose adjustments
- Less drug/food interactions
- Wider therapeutic window
- Faster onset/offset
  - Advantage in initiation of therapy and holding for procedures

Warfarin Advantages

- Populations for which DOACs are not approved (mechanical valve replacement etc.)
- Often lower cost to patient
- More experience with reversal

Dabigatran (Pradaxa®)

- Indications/Dosing

Indication	Dosing
Stroke Prevention in non-valvular atrial fibrillation	• 150 mg twice daily • 75 mg twice daily for CrCl 15-30 ml/min • 75 mg twice daily for CrCl 30-50 ml/min and strong P-gp inhibitor (ketoconazole and dronedarone)
Treatment of DVT/PE	• 150 mg twice daily after 5-10 days of parenteral anticoagulation • Avoid use in patients with CrCl <30 ml/min • Avoid use in patients with CrCl <50 and P-gp inhibitors
Prevention of DVT/PE following hip or Knee Replacement	• 110 mg first day, then 220 mg once daily • Avoid use in patients with CrCl <30 ml/min • Avoid use in patients with CrCl <50 and P-gp inhibitors

- Interacts with P-glycoprotein (P-gp)

Pradaxa [Package Insert]. Ridgefield, CT; 2018

Rivaroxaban (Xarelto®)

- Indications/Dosing

Indication	Dosing
Stroke Prevention in non-valvular atrial fibrillation	• 20 mg daily • 15 mg daily for CrCl 15-50 ml/min
Treatment of DVT/PE	15 mg twice daily for 21 days then 20 mg once daily
Prevention of DVT/PE following hip or Knee Replacement	10 mg daily for 35 days (hip) or 12 days (knee)
Reduction of Risk of Major Cardiovascular Events Chronic Coronary Artery Disease (CAD) or Peripheral Artery Disease (PAD)	2.5 mg twice daily plus aspirin (75-100 mg)

- 20 mg and 15 mg doses should be taken with food
- DVT/PE treatment/prevention -> avoid use in patients with CrCl <30 ml/min
- Avoid use with combined P-gp and CYP 3A4 Inducers/Inhibitors

Xarelto [Package Insert]. Titusville, NJ; 2019

Apixaban (Eliquis®)

- Indications/Dosing

Indication	Dosing
Stroke Prevention in non-valvular atrial fibrillation	• 5 mg twice daily • 2.5 mg if at least two of (Age ≥80, Weight ≤ 60 kg or SCr ≥1.5 mg/dl) • 2.5 mg twice daily if taken with strong inhibitors of CYP3A4 and P-gp
Treatment of DVT/PE	10 mg twice daily for 7 days, then 5mg twice daily
Prevention of DVT/PE following hip or Knee Replacement	2.5 mg twice daily for 35 days (hip) or 12 days (knee)

- Avoid use with combined P-gp and CYP 3A4 Inducers and Dose Reduce with P-gp and CYP 3A4 Inhibitors

Eliquis [Package Insert]. Princeton, NJ; 2018

Edoxaban (Savaysa®)

- Indications
  - Stroke Prevention in non-valvular atrial fibrillation
  - Treatment of DVT/PE
- Dosing

Stroke Prevention	DVT/PE Treatment
60 mg once daily (if CrCl is > 50-95 ml/min)	60 mg once daily after initial 5-10 days of parenteral anticoagulant therapy (if CrCl is > 50ml/min)
30 mg once daily (if CrCl is 15-50 ml/min)	30 mg once daily after initial 5-10 days of parenteral anticoagulant therapy if: • CrCl is 15-50 ml/min • Patient weight is < 60kg • Taking certain concomitant P-gp inhibitors
NOTE: Contraindicated if CrCl is > 95ml/min	

- Interacts with P-glycoprotein (P-gp)

Savaysa [Package Insert]. Basking Ridge, NJ; 2017

Betrixaban (Bevyxxa®)

- Indication:
  - Extended VTE prophylaxis (35-42 days) in adults hospitalized for acute medical illness
- Dosing:
  - 160mg x1 dose, then 80mg daily for 35-42 days in patients with CrCl > 30 ml/min
  - 80mg x1 dose, then 40mg daily for 35-42 days patients with CrCl 15-30 ml/min or taking concomitant P-gp inhibitors
- Interacts with P-glycoprotein (P-gp)

Bevyxxa [Package Insert]. South San Francisco, CA; 2017

P-Glycoprotein and CYP3A4 Inducers and Inhibitors for Rivaroxaban and Apixaban

Combined P-gp inhibitor and strong CYP3A4 inhibitor

- Significant increase in rivaroxaban/apixaban levels
- Increased Risk of Bleeding
- cobicistat, conivaptan, indinavir, itraconazole, ketoconazole, nefazodone, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole

Combined P-gp inducer and strong CYP3A4 inducer

- Significant reduction in rivaroxaban/apixaban levels
- Increased Risk of Clotting
- carbamazepine, dexamethasone, rifampin, St John's wort, phenytoin

P-Glycoprotein and CYP3A4 Inducers and Inhibitors for Rivaroxaban and Apixaban

Combined P-gp inhibitor and strong CYP3A4 inhibitor

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- **carbamazepine**, dexamethasone, rifampin, St John's wort, **phenytoin**

P-Glycoprotein Interactions Dabigatran, Betrixaban and Edoxaban

Inhibitors – Increase Concentration of medication

alfentanil, amiodarone, azithromycin, carvedilol, clarithromycin, cobicistat, conivaptan, cyclosporine, diltiazem, dronedarone, duloxetine, erythromycin, fenofibrate, grapefruit, all HIV protease inhibitors, itraconazole, ivacaftor, ketoconazole, lapatinib, lomitapide, mefloquine, nicardipine, nifedipine, nilotinib, posaconazole, progesterone, propafenone, quinidine, quinine, ranolazine, sunitinib, tacrolimus, tamoxifen, telithromycin, ticagrelor, tolvaptan, vemuranfenib, verapamil

Inducers – Reduce concentration of medication

carbamazepine, dexamethasone, penobarbital, phenobarbital, rifampin, St John's wort, tipranavir

P-Glycoprotein Interactions Dabigatran, Betrixaban and Edoxaban

Inhibitors – Increase Concentration of medication

alfentanil, **amiodarone, azithromycin, carvedilol**, clarithromycin, cobicistat, conivaptan, **cyclosporine, diltiazem**, dronedarone, **duloxetine**, erythromycin, fenofibrate, grapefruit, all HIV protease inhibitors, itraconazole, ivacaftor, **ketoconazole**, lapatinib, lomitapide, mefloquine, nicardipine, nifedipine, nilotinib, posaconazole, **progesterone**, propafenone, quinidine, quinine, ranolazine, sunitinib, **tacrolimus**, **tamoxifen**, telithromycin, ticagrelor, tolvaptan, vemuranfenib, verapamil

Inducers – Reduce concentration of medication

carbamazepine, dexamethasone, penobarbital, phenobarbital, **rifampin**, St John's wort, tipranavir

Some Take home points

- Apixaban and Rivaroxaban can be used for the treatment of DVT/PE without having to use an injectable anticoagulant such as heparin or enoxaparin
  - Great for the ED for patients that have no other reason for hospitalization
- Overall less food interactions than warfarin but rivaroxaban Afib and DVT/PE doses should be taken with food
- Overall less drug interactions than warfarin but watch for interactions with P-GP and CYP3A4 inducers and inhibitors
- Don't use edoxaban in patients with good kidney function
- There is growing evidence in the literature for use after percutaneous coronary intervention (dabigatran, apixaban, rivaroxaban) and in special populations (renal dysfunction (rivaroxaban and apixaban) and DVT prophylaxis in cancer (apixaban, edoxaban and rivaroxaban))

DOACs in Atrial Fibrillation

2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation

Background – Atrial Fibrillation and Stroke Risk

- Individuals with atrial fibrillation have an increased risk of:
  - Stroke (4-5x increase)
  - Heart Failure (2-3x increase)
  - Mortality (2x increase)
- Preferred tool for stroke risk for atrial fibrillation patients is the CHA_2DS_2-VASc
  - Points for age, gender, CHF, HTN, History of Stroke or Vascular Disease and Diabetes

January, Craig T., et al. "2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation." *Circulation*, 2019, doi:10.1161/cir.0000000000000665.

AHA/ACC/HRS Strength of Recommendations and Level of Evidence

CLASS (STRENGTH) OF RECOMMENDATION

CLASS I (STRONG) — Benefit >>> Risk

Suggested phrases for writing recommendations:
- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

LEVEL (QUALITY) OF EVIDENCE‡

LEVEL A
- High-quality evidence‡ from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

LEVEL B-R (Randomized)
- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

January, Craig T., et al. "2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation." *Circulation*, 2019, doi:10.1161/cir.0000000000000665.

2019 AHA/ACC/HRS Focused Update of the Guideline for the Management of Patients With Atrial Fibrillation

COR	LOE	Recommendations
I	A	1. For patients with AF and an elevated CHA_2DS_2-VASc score of 2 or greater in men or 3 or greater in women, oral anticoagulants are recommended. Options include: • Warfarin (LOE: A) (S4.1.1-5–S4.1.1-7) • Dabigatran (LOE: B) (S4.1.1-8) • Rivaroxaban (LOE: B) (S4.1.1-9) • Apixaban (LOE: B) (S4.1.1-10), or • Edoxaban (LOE: B-R) (S4.1.1-11) **MODIFIED**: This recommendation has been updated in response to the approval of edoxaban, a new factor Xa inhibitor. More precision in the use of CHA_2DS_2-VASc scores is specified in subsequent recommendations. The LOEs for warfarin, dabigatran, rivaroxaban, and apixaban have not been updated for greater granularity as per the new LOE system. (Section 4.1. in the 2014 AF Guideline) The original text can be found in Section 4.1 of the 2014 AF guideline. Additional information about the comparative effectiveness and bleeding risk of NOACs can be found in Section 4.2.2.2.
	B	
	B	
	B-R	

January, Craig T., et al. "2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation." *Circulation*, 2019, doi:10.1161/cir.0000000000000665.

2019 AHA/ACC/HRS Focused Update of the Guideline for the Management of Patients With Atrial Fibrillation

COR	LOE	Recommendations
I	A	2. NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) are recommended over warfarin in NOAC-eligible patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) (S4.1.1-8–S4.1.1-11). **NEW**: Exclusion criteria are now defined as moderate-to-severe mitral stenosis or a mechanical heart valve. When the NOAC trials are considered as a group, the direct thrombin inhibitor and factor Xa inhibitors were at least noninferior and, in some trials, superior to warfarin for preventing stroke and systemic embolism and were associated with lower risks of serious bleeding.

January, Craig T., et al. "2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation." *Circulation*, 2019, doi:10.1161/cir.0000000000000665.

DOAC Efficacy and Safety Comparison

Overview

- No direct, head to head prospective, randomized controlled trials have been conducted between the various DOACs and warfarin
- The initial trials for the DOACs were designed to show non-inferiority to warfarin
- Recently there have been several large studies using Centers for Medicare and Medicaid (CMS) and or insurance claims databases that compared the DOACs amongst each other and/or warfarin
  - ARISTOPHANES [Lip et al.] (2018)- CMS and 4 claims databases comparing Apixaban, Rivaroxaban, Dabigatran and Warfarin
  - Noseworthy et al. (2016) – 1 claims database comparing Apixaban, Dabigatran, Rivaroxaban
  - Graham et al. (2019) – CMS database comparing Apixaban, Rivaroxaban, Dabigatran and Warfarin
- Looked at efficacy (prevention of ischemic stroke/systemic embolism) and safety (major bleeding)

Comparison of Noseworthy et al. (2016), ARISTOPHANES [Lip et al](2018), & Graham et al. (2019)

	Noseworthy et al.	ARISTOPHANES (Lip et al.)	Graham et al.
Agents Compared	apixaban, dabigatran and rivaroxaban	apixaban, dabigatran, rivaroxaban, and warfarin	apixaban, dabigatran, rivaroxaban, and warfarin
Patients	26,214 across 3 matched cohorts	285,292 across 6 matched cohorts	448,944 patients spread across the agents • 2 propensity matched groups (warfarin pts vs All DOACs)
Databases Used	1 commercial claims database	CMS Database & 4 commercial claims databases	CMS Database
Safety Outcome Trend	Rivaroxaban may be associated with higher bleed risk	Rivaroxaban may be associated with higher bleed risk than warfarin	All 3 DOACs had lower incidence of bleed than warfarin, apixaban and dabigatran were favored over rivaroxaban
Efficacy Outcome Trend	Similar effectiveness for all 3 agents	All 3 DOACs had lower incidence of stroke than warfarin	All 3 DOACs had lower incidence of stroke than warfarin
Quirks	Didn't include warfarin		Propensity matched into 2 groups, but compared outcomes across all 4 agents

ARISTOPHANES

A Closer Look at the Results

Methods and Outcomes Measured

- Patients had at least one claim for apixaban, dabigatran, rivaroxaban or warfarin in the study period and a diagnosis of atrial fibrillation (AF) before the date of the first claim
  - Exclusion criteria included valvular heart disease, history of VTE, transient AF, heart valve replacement during the study period, pregnancy and/or a knee/hip replacement during the study period
- Patients were matched 1:1 in each data set based on propensity scores generated by logistic regression based on demographics, Charlson Comorbidity Index score, baseline bleeding and stroke/SE history, comorbidities, and other medications
- Time to event was measured based on hospitalization with stroke, systemic embolism or major bleeding as the principal diagnosis
  - Stroke and Systemic Embolism (Ischemic, Hemorrhagic and Systemic Embolism)
  - Major Bleeding (Gastrointestinal, Intracranial and All Other)

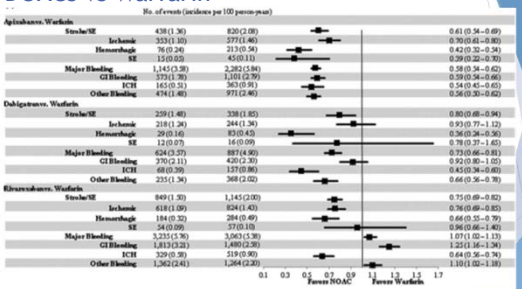
Lip, Gregory Y.h., et al. "Effectiveness and Safety of Oral Anticoagulants Among Nonvalvular Atrial Fibrillation Patients. The ARISTOPHANES Trial" Stroke, vol. 49, no. 12, 2018, pp. 2933-2944., doi:10.1161/strokeaha.118.020232.

ARISTOPHANES Cohorts

- Apixaban vs. Warfarin
  - 57,929 patients in each arm
  - Average Age ~74
  - CHA2DS2-VASc Score 3.7
  - HAS-BLED 3
- Dabigatran vs. Warfarin
  - 26,838 patients in each arm
  - Average Age ~72
  - CHA2DS2-VASc Score 3.4
  - HAS-BLED 2.7
- Rivaroxaban vs. Warfarin
  - 83,007 patients in each arm
  - Average Age ~74.5
  - CHA2DS2-VASc Score 3.7
  - HAS-BLED 2.9
- Apixaban vs. Dabigatran
  - 27,096 patients in each arm
  - Average Age ~71.5
  - CHA2DS2-VASc Score 3.3
  - HAS-BLED 2.6
- Apixaban vs. Rivaroxaban
  - 62,619 patients in each arm
  - Average Age ~73
  - CHA2DS2-VASc Score 3.5
  - HAS-BLED 2.8
- Dabigatran vs. Rivaroxaban
  - 27,538 patients in each arm
  - Average Age ~71.4
  - CHA2DS2-VASc Score 3.3
  - HAS-BLED 2.6

Lip, Gregory Y.h., et al. "Effectiveness and Safety of Oral Anticoagulants Among Nonvalvular Atrial Fibrillation Patients. The ARISTOPHANES Trial" Stroke, vol. 49, no. 12, 2018, pp. 2933-2944., doi:10.1161/strokeaha.118.020232.

DOACs vs Warfarin



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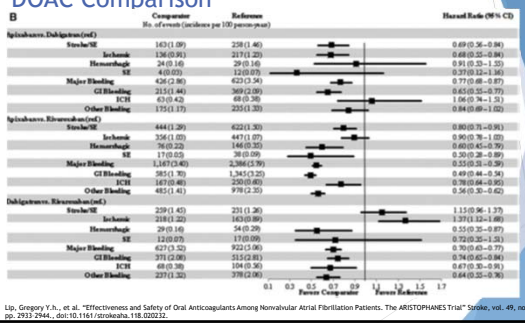
DOAC Comparison



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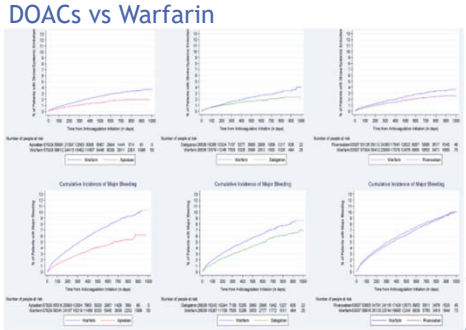
DOACs vs Warfarin



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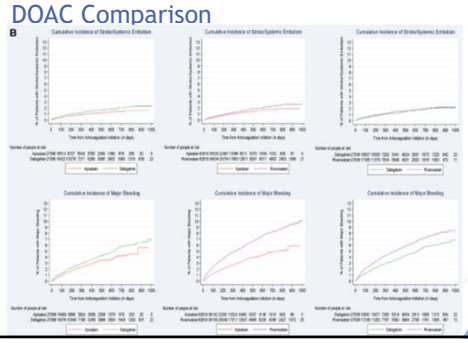
DOAC Comparison



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Take Home Points - ARISTOPHANES

- Some limitations by using a retrospective claims database
  - No evaluation of correct dose reductions
  - No examination of time in therapeutic INR for warfarin
  - No accounting for individual providers' practice
- Potentially shows a trend that favors apixaban and dabigatran over rivaroxaban and warfarin
- Authors very clear that, "NOAC versus NOAC comparisons are for hypotheses generating only. Those results should be interpreted with caution and need to be confirmed by findings from NOAC versus NOAC RCTs which are expected to be released in the upcoming years (eg, DARING-AF trial [Comparison of Efficacy and Safety Among Dabigatran, Rivaroxaban, and Apixaban in Non-Valvular Atrial Fibrillation).

Lip, Gregory Y.h., et al. "Effectiveness and Safety of Oral Anticoagulants Among Nonvalvular Atrial Fibrillation Patients. The ARISTOPHANES Trial" Stroke, vol. 49, no. 12, 2018, pp. 2933-2944., doi:10.1161/strokeaha.118.020232.

Reversal Options – Apixaban and Rivaroxaban

Andexanet Alfa

4 Factor Prothrombin Complex Concentrate

Andexanet Alfa (Andexxa®)

Andexanet Alfa (Andexxa®) Background

- Andexanet alfa
  - Modified recombinant inactive form of human factor Xa
  - MOA: binds and blocks the FXa inhibitors
    - Thought to also bind and inhibit the activity of Tissue Factor Pathway Inhibitor (TFPI)
      - Increasing tissue factor-initiated thrombin generation
- Pharmacokinetics
  - Half-life 5-7 hours
  - Anti-factor Xa activity increases to placebo levels ~2 hours after completion of the infusion
    - HOWEVER -- Elevation of tissue factor-initiated thrombin generation above pretreatment baseline occurs within 2 minutes after administration and is sustained for at least 22 hours
- Cost:
  - Low dose: ~$29,000
  - High dose: ~$58,000

Andexxa [Package Insert]. South San Francisco, CA; 2018
Siegal DM, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. *N Engl J Med*. 2015

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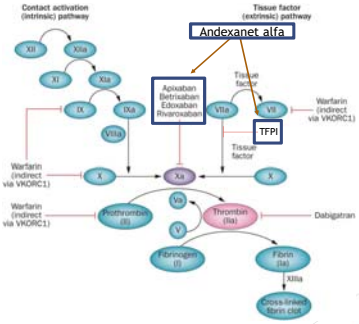

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FDA Approved Dosing

Dose	Initial IV Bolus	Follow-up IV infusion
Low Dose	**400 mg**	4 mg/min x 120 min
High Dose	**800 mg**	8 mg/min x 120 min

Fxa Inhibitor	Fxa Inhibitor Last Dose	<8 hours or unknown	≥8 hours
rivaroxaban	≤ 10 mg	Low	Low
rivaroxaban	> 10 mg or UNKNOWN	High	
apixaban	≤ 5 mg	Low	
apixaban	> 5 mg or UNKNOWN	High	

Andexxa [Package Insert]. South San Francisco, CA; 2018

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Anticoagulation Effects of Factor Xa Inhibitors (ANNEXA-4) study

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Study Design

- Multicenter
- Prospective
- Open-label
- Single-group study


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

S.J. Connolly, M. Crowther, J.W. Eikelboom, C.M. Gibson, J.T. Curnutte, J.H. Lawrence, P. Yue, M.D. Bronson, G. Lu, P.B. Conley, P. Verhamme, J. Schmidt, S. Middeldorp, A.T. Cohen, J. Beyer-Westendorf, P. Albaladejo, J. Lopez-Sendon, A.M. Demchuk, D.J. Pallin, M. Concha, S. Goodman, J. Leeds, S. Souza, D.M. Siegal, E. Zotova, B. Meeks, S. Ahmad, J. Nakamya, and T.J. Milling, Jr., for the ANNEXA-4 Investigators*

Connolly SJ, et al. Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. *New England Journal of Medicine*. 2019.

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Study Population

- 352 patients were enrolled - 63 Centers in North America and Europe
- Enrolled patients from April 2015 – May 2018
  - July 2016-August 2017 only ICH
  - AFTER August 2017, patients with ALL types of bleeding EXCEPT visible, musculoskeletal or intraarticular bleeding were enrolled

Connolly SJ, et al. Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. *New England Journal of Medicine*. 2019.

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Study Population

Inclusion	Exclusion
18 years of age	Surgery within 12 hours AFTER andexanet treatment (exception of minimally invasive procedures)
Acute major bleeding	ICH with a GCS < 7 OR an estimated hematoma volume > 60 mL
Within 18 hours of taking: apixaban, rivaroxaban, edoxaban or enoxaparin (1 mg/kg/day)	Expected survival < 1 month
	Occurrence of thrombotic event within 2 weeks BEFORE enrollment
	Previous 7 days taken: Vitamin K antoganist, dabigatran, PCC, recombinant factor VIIa, whole blood, or plasma

Connolly SJ, et al. Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. *New England Journal of Medicine*. 2019.

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Study Procedures

Time and Medication	Bolus	Infusion
>7 hours since rivaroxaban ALL apixaban	400 mg	480 mg
<7 hours since rivaroxaban ALL edoxaban ≥ 1 mg/kg of enoxaparin	800 mg	960 mg

Connolly SJ, et al. Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. *New England Journal of Medicine*. 2019.

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Study Procedures

Fxa Inhibitor	Fxa Inhibitor Last Dose	Timing of Last Dose of Fxa Inhibitor	
		< 8 hours or Unknown	≥ 8 hours
Rivaroxaban	≤ 10 mg	Low	Low
	> 10 mg or unknown	High	
Apixaban	≤ 5 mg	Low	
	> 5 mg or unknown	High	
Enoxaparin	≤ 40 mg	Low	
	> 40 mg or unknown	High	
Edoxaban	≤ 30 mg	Low	
	> 30 mg or unknown	High	
Unknown	Unknown	High	

Connolly SJ, et al. Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. *New England Journal of Medicine*. 2019.[43]

Data Collection

- Blood samples - measure anti-factor Xa activity
  - Levels were drawn at baseline, immediately following the bolus, and 4, 8, and 12 hours after the end of the treatment
- ICH
  - CT/MRI of the head
    - Within 2 hours before andexanet treatment
    - And at 1 hour and 12 hours after the END of the andexanet
- GI/other types of bleeds
  - Hgb/Hct - baseline and 12 hours following treatment
  - Infusion of blood products

Connolly SJ, et al. Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. *New England Journal of Medicine*. 2019.[44]

Hemostatic Efficacy

- According to: Sarode R, et al. Efficacy and Safety of a 4-Factor Prothrombin Complex Concentrate in Patients on Vitamin K Antagonists Presenting With Major Bleeding. *Circulation*. 2013

Bleed Type	Excellent (effective)	Good (effective)	Poor/None (not effective)
Intracranial hematoma	**≤20% increase** in hematoma volume compared to baseline on repeat CT/MRI 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/MRI at 12+ hour time point	**>35% increase** in hematoma volume on the CT/MRI at 12+ hour time point
Subarachnoid bleed	**≤20% increase** in maximum thickness compared to baseline at both the 1 and 12 hour post infusion	**>20% but ≤35% increase** in maximum thickness compared to baseline at 12+ hour	**>35% increase** in maximum thickness compared to baseline at 12+ hour
GI, Urinary, or non-visible bleeding	**≤10% decrease** in both corrected hgb/hct at 12 hours compared to baseline	**>10% but ≤20% decrease** in both corrected hgb/hct at 12 hours compared to baseline	**>20% decrease** in both corrected hgb/hct

Connolly SJ, et al. Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. *New England Journal of Medicine*. 2019.

Study Outcomes

Two Co-primary efficacy outcomes:

- % change from baseline in anti-factor Xa activity after andexanet treatment
- % of patients with excellent or good hemostatic efficacy 12 hours AFTER andexanet infusion

Primary safety outcomes:

- Death
- Thrombotic events
- Development of antibodies to andexanet or to native factor X and factor Xa

Followed patients for 30 days or death

Connolly SJ, et al. Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. *New England Journal of Medicine*. 2019.

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Statistical Analysis

- Safety Outcomes:
  - ALL patients that received andexanet alfa
- Efficacy Outcomes:
  - Only included patients who retrospectively met two criteria:
    - Baseline anti-factor Xa activity of ≥ 75 ng/mL or ≥ 25 IU/mL for enoxaparin
    - AND confirmed major bleeding at presentation determined by the adjunction committee

Connolly SJ, et al. Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. *New England Journal of Medicine*. 2019.[47]

Results - Patient Characteristics

	Safety Population (n=352)	Efficacy Population (n=254)
Age	77.4 ± 10.8	77.1 ± 11.1
Male Sex	187 (53%)	129 (51%)
White Race	307 (87%)	222 (87%)
Body-Mass Index	27.0 ± 5.9	27.0 ± 6.2
Primary Indication for Anticoagulation		
Atrial Fibrillation	280 (80%)	201 (79%)
Venous Thromboembolism	61 (17%)	46 (18%)
Other	11 (3%)	7 (3%)

Connolly SJ, et al. Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. *New England Journal of Medicine*. 2019.[48]

Results - Patient Characteristics cont.

	Safety Population (n=352)	Efficacy Population (n=254)
Factor Xa Inhibitor		
rivaroxaban	128 (36%)	100 (39%)
apixaban	194 (55%)	134 (53%)
enoxaparin	20 (6%)	16 (6%)
edoxaban	10 (3%)	4 (2%)
Site of Bleeding		
Gastrointestinal	90 (26%)	62 (24%)
Intracranial	227 (64%)	171 (67%)
Other	35 (10%)	21 (8%)

Connolly SJ, et al. Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. *New England Journal of Medicine*. 2019.

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What does anti-factor Xa activity mean?

- Anti-factor Xa (anti-Xa) assay
  - Functional assay that facilitates the measurement of antithrombin (AT)-catalyzed inhibition of factor Xa
- Billoir P, et al. Anti-Xa Oral Anticoagulant Plasma Concentration Assay in Real Life: Rivaroxaban and Apixaban Quantification in Emergency With LMWH Calibrator
  - 210 patients (June 2013-October 2017)
  - Rivaroxaban and apixaban
    - 41 (20%) VTE indication, 169 (80%) Nonvalvular Afib

	Peak	Trough
rivaroxaban	249 ng/mL	44 ng/mL
apixaban	171 ng/mL	103 ng/mL

Billoir P, et al. Anti-Xa Oral Anticoagulant Plasma Concentration Assay in Real Life: Rivaroxaban and Apixaban Quantification in Emergency With LMWH Calibrator. *Annals of Pharmacotherapy*. 2018

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Results – Anti-Factor Xa Activity

	Average Baseline FXa Level	*Average FXa - End of the Bolus (% Reduction)*	*Median Value from baseline % reduction 4 hours POST infusion*	*Median Value from baseline % reduction 8 hours POST infusion*	*Median Value from baseline % reduction 12 hours POST infusion*
Apixaban	149.7 ng/mL	11.1 ng/mL (92%)	32%	34%	38%
Rivaroxaban	211.8 ng/mL	14.2 ng/mL (92%)	42%	48%	62%
Enoxaparin	0.48 IU/mL	0.15 IU/mL (75%)			

Connolly SJ, et al. Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. *New England Journal of Medicine*. 2019.

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Results – Hemostatic Efficacy

	Good/Excellent Hemostatic Efficacy at 12 hours
Overall patients	204/252 **(82%)**
GI bleeding	51/60 **(85%)**
Intracranial	135/168 **(80%)**

Bleed Type	Excellent (effective)	Good (effective)
Intracranial hematoma	≤20% increase in hematoma volume compared to baseline on repeat CT/MRI 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/MRI at 12+ hour time point
Subarachnoid bleed	≤20% increase in maximum thickness compared to baseline at both the 1 and 12 hour post infusion	>20% but ≤35% increase in maximum thickness compared to baseline at 12+ hour
GI, Urinary, or non-visible bleeding	≤10% decrease in both corrected hgb/hct at 12 hours compared to baseline	>10% but ≤20% decrease in both corrected hgb/hct at 12 hours compared to baseline

Connolly SJ, et al. Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. *New England Journal of Medicine*. 2019.

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Results – Poor/No Hemostatic Efficacy

	# Patients in Efficacy Analysis	Poor/None
Overall	249	45 (18%)
FXa Inhibitors		
Apixaban	131	22 (16.8%)
Rivaroxaban	99	20 (20%)
Enoxaparin	15	2 (13.3)
Edoxaban	4	1 (25)
Site of Bleeding		
GI	60	9 (15%)
ICH	168	33 (19.6%)
Other	21	3 (14.3%)

	# Patients in Efficacy Analysis	Poor/None
Dose of Andexanet alfa		
Low Dose	208	36 (17.3%)
High Dose	41	9 (22%)

Connolly SJ, et al. Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. *New England Journal of Medicine*. 2019.

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Results – Safety Outcomes

- 49 patients (14%) died within 30 days
  - 35 cardiovascular causes
  - 12 non-cardiovascular causes
  - 2 unknown
- 2 infusion reactions
  - 91 yo female enrolled for ICH, developed a fever
    - Treated with APAP
    - Completed course with no interruptions
  - 85 yo male enrolled for ICH, developed rigors, severe chills, HTN, fever, confusion, and oxygen desaturation (~45 minutes into 2 hour infusion)
    - Treated with diphenhydramine, prednisone, haloperidol, paracetamol (APAP), and supplemental O2
    - CI not resumed

Connolly SJ, et al. Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. *New England Journal of Medicine*. 2019.

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Results – Safety Outcomes

- 34 patients (10%) had thrombotic event during the 30-day follow-up

	< 6 days	6-14 days	15-30 days
Total	**11**	**11**	**12**
Myocardial Infarction	6	1	0
Ischemic stroke or stroke of uncertain classification	5	6	3
Transient ischemic attack	0	0	1
Deep-vein thrombosis	1	5	7
Pulmonary embolism	1	0	4

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Connolly SJ, et al. Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. *New England Journal of Medicine*. 2019.

Resumption of Anticoagulation

	Total (n=352)	< 6 days after bolus	6-14 days after bolus	15-30 days after bolus
Resumption of **ANY** anticoagulation	220 (62%)	145 (41%)	46 (13%)	29 (8%)

Timing	Total (n=352)
Thrombotic event **BEFORE** restarting anticoagulation OR **NOT** resuming anticoagulation	26 (7%)
Thrombotic event **AFTER** restarting anticoagulation	8 (2%)

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Connolly SJ, et al. Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. *New England Journal of Medicine*. 2019.

Authors Conclusions

- No significant relationship between hemostatic efficacy and a reduction in anti-factor Xa activity during andexanet alfa treatment
- Treatment with andexanet alfa resulted in an excellent or good hemostatic efficacy at 12 hours in 82% of the patients

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Connolly SJ, et al. Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. *New England Journal of Medicine*. 2019.

Early Experience with Andexxa

- Culbreth and colleagues published their institution's (Brigham and Women's Hospital, Boston, MA) with the first 15 patients that they used andexanet alfa on.
- Average time from order to administration: 66 minutes
  - Challenges with reconstitution and preparation of the medication, up to 18 vials and product slow to dissolve
- No thrombotic events
- 40% inpatient mortality (5 from initial bleed, 1 from infection)
- Deviated from their use guidelines and FDA indications in many of the patients, including combining with 4F-PCC and procedures within 12 hours of administration
- 7/15 had worsening hemorrhages on repeat CT

Culbreth, Sarah E., et al. "Andexanet Alfa-The First 150 Days." *American Journal of Hematology*, vol. 94, no. 1, 2018, doi:10.1002/ajh.25326.

Four Factor Prothrombin Concentrate (Kcentra®)

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Kcentra – Prothrombin complex concentrate

- FDA Approved Indication: reversal of vitamin K antagonist therapy in adult patient with either an acute bleed or need for urgent surgery
- Contains the vitamin-K dependent factors II, VII, IX, and X together known as the prothrombin complex, and the Antithrombotic Protein C and Protein S
- FDA Approved Dosing

Pre-Treatment INR	2 - < 4	4 - 6	> 6
Dose (units/kg)	25	35	50
Max dose (units)	2500	3500	5000

- Cost
  - $7,250 (2500 units) - $14,500 (5000 units)

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Kcentra [Package Insert]. Kankakee, IL; 2013

Recent Studies using 4F-PCC of Xa reversal

	Majeed et al. (n=84)	Schulman et al. (n=66)
Reversal Agent	4factor PCC, ~25u/kg	4factor PCC 2000 units
Average Age	75	76.9
Xa Inhibitor	Rivaroxaban 53.6% Apixaban 46.4%	Rivaroxaban 56% Apixaban 44%
Primary Bleed Site	ICH (n=59) 70% GI (n=13) 15%	ICH (n=36) 55% GI (n=16) 24%
Time from last dose of Xa inhibitor to reversal	Median: 12.5 hours	Median: 16.9 hours+
Hemostatic Response	Effective 69.1%	Effective 85%
Hemostatic Response/ Outcomes in ICH patients	Effective 72.9%	Effective 84%
Thromboembolism	N=2 (2.4%) within 30 days Both stroke	N=5 (8%), within 30 days 3 stroke, 1 peripheral arterial occlusion, 1 VTE
Mortality	N=27 (32%) within 30 days	N=9 (14%) within 30 days

Consensus Guidelines for the Reversal of Direct Factor Xa Inhibitors

- Neurocritical Care Society and the Society for Critical Care Medicine (2015)
  - Recommend Activated charcoal (50 g) within 2 h of ingestion
  - Activated PCC (FEIBA) 50 units/kg IV OR 4 factor PCC 50 units/kg IV
- American Society for Hematology (2018)
  - For patients with life-threatening bleeding during oral direct Xa inhibitor treatment of VTE, the ASH guideline panel *suggests* using *either* 4-factor PCC administration as an addition to cessation of oral direct Xa inhibitor *or* cessation of oral direct Xa inhibitor alone (conditional recommendation based on very low certainty in the evidence about effects).
  - For patients with life-threatening bleeding during oral direct Xa inhibitor treatment of VTE, the ASH guideline panel suggests using coagulation factor Xa (recombinant), inactivated-zhzo in addition to cessation of oral direct Xa inhibitor rather than no coagulation factor Xa (recombinant), inactivated-zhzo (conditional recommendation based on very low certainty in the evidence about effects).
  - **Remark:** This recommendation does not apply to non-life-threatening bleeding. No data are available comparing the efficacy of 4-factor PCC and coagulation factor Xa (recombinant), inactivated-zhzo. The guideline panel offers no recommendation for 1 approach over the other.

Frontera, Jennifer A., et al. "Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage." Critical Care Medicine, vol. 44, no. 12, 2016, pp. 2251-2257., doi:10.1097/ccm.0000000000002057.

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Summary

- Use of Direct Oral Anticoagulants (DOACs) is expanding into more patient populations and with stronger recommendations in guidelines
- Individual characteristics and potential medication interactions need to be considered when choosing a DOAC
- Reversal options for DOAC related bleeding include andexanet alfa and 4 factor prothrombin complex concentrate

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