

## Available Strategies to Reverse Anticoagulant Medications

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## Objectives

- Describe the pharmacological agents and therapeutic strategies available for use in patients who experience major bleeds
- Discuss the risk and limitations of current agents available for reversal
- Construct treatment plans to manage severe bleeds in a patients anticoagulation therapy

## Disclosure

Anuja Rizal and I have no actual or potential conflict of interest associated with this presentation

## Background

- Anticoagulation is the cornerstone of treatment for thrombosis and thromboembolic complications
- In the United States, over six million patients are on anticoagulation therapy
- Evidence is limited on the management of bleeding and reversal of anticoagulation therapy
  - Reversing therapy is a **risk** (thrombosis) verses **risk** (bleeding) decision
  - Involves fully informed clinical decision making

Tamaselli GF, et al. J Am Coll Cardiol 2017; 70(24): 3042-3067

## Reversal Decision Pathway

1. Assess Bleeding
2. Determine Anticoagulation Therapy
3. Rapid Laboratory Testing

## Assess Bleeding Severity

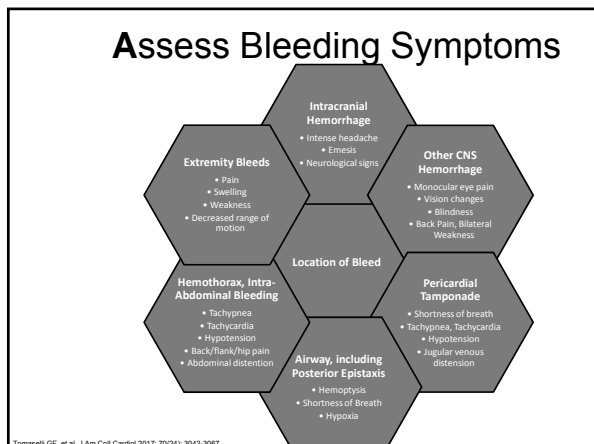
### Major

- Hemodynamically unstable
- Bleeding in an anatomically critical location
- Requires transfusion
  - ≥ 2 units of RBCs
- Decrease of hemoglobin
  - ≥ 2 g/dL drop in Hgb

### Non-major

- All other bleeding not classified as major
- Patient may require intervention or hospitalization

Tamaselli GF, et al. J Am Coll Cardiol 2017; 70(24): 3042-3067



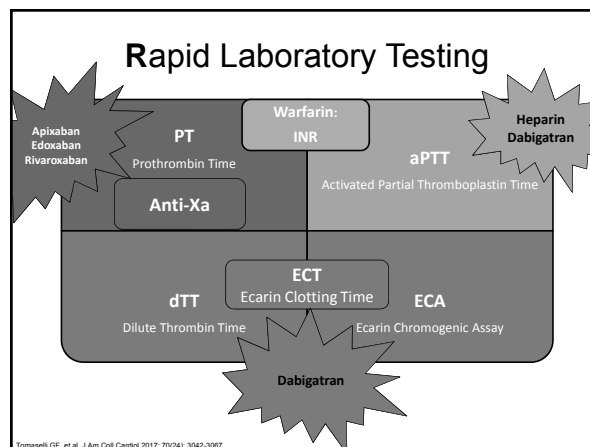
- ### Determine Anticoagulation Therapy
- Medication Reconciliation
    - Dose of medication
    - Timing since last administered
    - Monitoring parameters
    - Use of additional anticoagulants/anti-platelet agents

### Determine Anticoagulation Therapy

- Timing since last administered

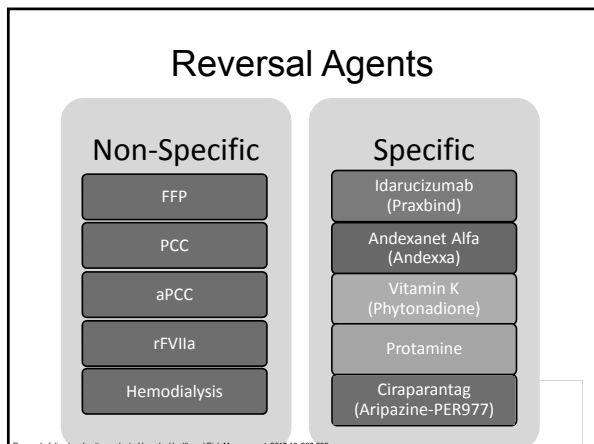
Half Life	Time to resolve anticoagulation
Dabigatran – 12 to 17 hours	elapsed by day 2.5 to 3.5 after the last dose
Rivaroxaban – 5 to 9 hours	elapsed by day 1 to 2 after the last dose
Apixaban – 8 to 15 hours	elapsed by day 1.5 to 3 after the last dose
Edoxaban – 6 to 11 hours	elapsed by day 1.3 to 2 after the last dose

https://www.upToDate.com/contents/management-of-bleeding-in-patients-receiving-direct-oral-anticoagulants?search=fresh%20open%20sum%20dosing%20for%2000AC%20reversal&source=search\_result&selectedTitle=1~150&usage\_type=default&display\_rank=1



- ### Rapid Laboratory Testing
- Hgb/HCT
  - Platelet count
  - Renal function
  - Liver function
  - DIC tests
- https://www.upToDate.com/contents/management-of-bleeding-in-patients-receiving-direct-oral-anticoagulants?search=fresh%20open%20sum%20dosing%20for%2000AC%20reversal&source=search\_result&selectedTitle=1~150&usage\_type=default&display\_rank=1

- ### Knowledge Check!
- A patient comes into the Emergency Department with a BP of 93/67, abdominal distention and recently was started on anticoagulation therapy
    - What steps would you take to triage this patient?
    - What acronym can you use to remember the decision pathway?
    - What laboratory values would be important to order?



## Non-Specific Reversal Agents

### Fresh Frozen Plasma (FFP)

- Indication:** alternative reversal agent for patients on warfarin when preferred agents are unavailable
- Mechanism of action:** direct plasma transfusion

**Dosing**

Depends upon the patient's size and clinical situation. The typical 70 kg adult dose is 4 to 6 units (approximately 10 mL/kg) infused at 10ml/min

- Caution:** hypervolemia with PE or cardiac failure, disease transmission, transfusion reactions associated with antibody generation, higher incidence of thrombosis
- Contraindications:** not indicated for volume expansion only, not recommended as a protein or fibrinogen source

Fresh Frozen Plasma. Lexi-Comp. Wolters Kluwer Health | Lippincott Williams & Wilkins. Available at: <https://online.lexi.com/coactiondocretrieve?docId=9382046>. Reversal of direct oral anticoagulants. Vascular Health and Risk Management. 2017;13:287-292.

### 3 Factor Prothrombin Complex Concentrate (PCC) Profilnine®

- Indication:** reversal in patients with severe, life-threatening bleeds or need for urgent and invasive surgery when other agents are not available
- Mechanism of action:** replaces deficient coagulation factors II, IX and X

**Dosing**

Dosing is individualized based on severity of factor IX deficiency, extent and location of bleeding and clinical status; factor IX 1 unit/kg will increase the plasma factor IX level by 1%

- **Onset and Duration:** raises factor IX levels 20-30% (moderate bleeding) or 30-50% (major bleeding) every 16 to 24 hours, continued until hemostasis is achieved
- Caution:** antibody formation, hypersensitivity reactions, thrombotic events
- Contraindications:** none listed in manufacturer's labeling

Factor IX Complex (Human) (Factors II, IX, X). Lexi-Comp. Wolters Kluwer Health | Lippincott Williams & Wilkins. Available at: <https://online.lexi.com/coactiondocretrieve?docId=9382046>. Reversal of direct oral anticoagulants. Vascular Health and Risk Management. 2017;13:287-292.

### 4 Factor Prothrombin Complex Concentrate (PCC) Octaplex® KCentra®

- Indication:** reversal in patients with severe, life-threatening bleeds or need for urgent and invasive surgery
  - Warfarin; associated with 1.4% increase in thrombotic events
  - DOACs; used off-label; rivaroxaban, edoxaban, and apixaban
- Mechanism of action:** replaces coagulation factors II, VII, IX and X and protein C and S
  - **Onset:** rapid decline within 10 minutes
  - **Duration:** ~6 to 8 hours
- Contraindication:** hypersensitivity to concentrate, history of heparin induced thrombocytopenia
- US Boxed Warning:** administration of prothrombin complex concentrate (PCC) may predispose the patient to thromboembolic complications

Prothrombin Complex Concentrate (Human) (Factors II, VII, IX, X, Protein C, and Protein S). Lexi-Comp. Wolters Kluwer Health | Lippincott Williams & Wilkins. Available at: <https://online.lexi.com/coactiondocretrieve?docId=9382046>. Reversal of direct oral anticoagulants. Vascular Health and Risk Management. 2017;13:287-292.

### 4 Factor Prothrombin Complex Concentrate (PCC) Octaplex® KCentra®

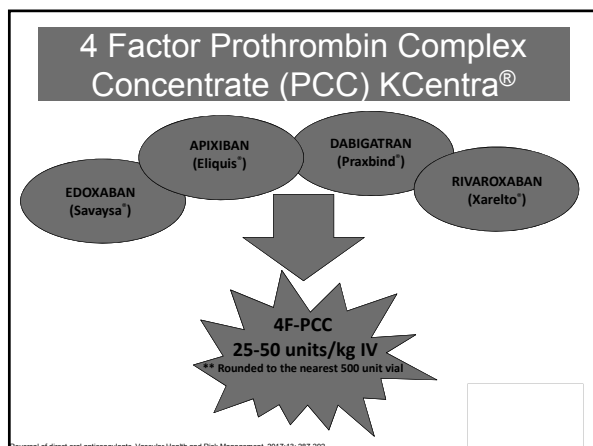
#### Warfarin Fixed Dosing

#### 4PCC 1500 units IV x 1 dose

Optional: additional 1000 units IV, repeated dosing is not usually necessary

80-84	250 mL	20 min
85-89	250 mL	22 min
90-94	250 mL	23 min
95-99	250 mL	24 min
>100 (max)	250 mL	25 min

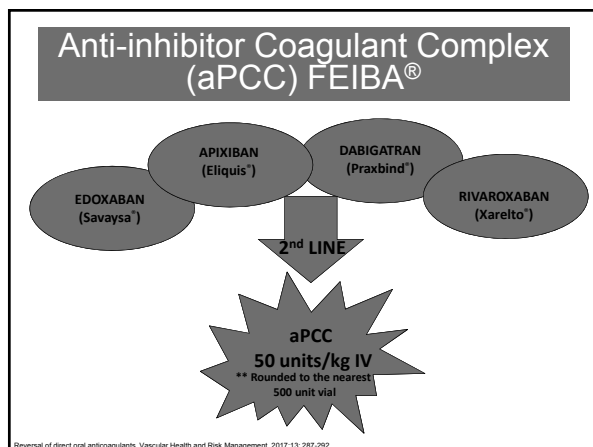
Management of Anticoagulation. Wolters Kluwer Health | Lippincott Williams & Wilkins.



### Anti-inhibitor Coagulant Complex (aPCC) FEIBA®

- **Indication:** for reversal in in hemophilia A and B patients with uncontrolled bleeding, used off-label or oral anticoagulation associated bleeding
- **Mechanism of action:** replaces coagulation factors II, VII (activated and more potent), IX and X
  - Onset: within 15 to 30 minutes
  - Duration: ~ 8 to 12 hours
- **Contraindications:** hypersensitivity to FEIBA or its components, disseminated intravascular coagulation (DIC), acute thrombosis or embolism
- **US Boxed Warnings:** thromboembolic events, especially following doses >200 units/kg/day; monitor patients for signs and symptoms of thromboembolic events
- **Warnings:** anaphylaxis and hypersensitivity reactions may occur

Anti-inhibitor Coagulant Complex. Lexi-Comp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at [https://online.lexi.com/coaction/docretrieve/docid/patch\\_#6365](https://online.lexi.com/coaction/docretrieve/docid/patch_#6365)  
Reversal of direct oral anticoagulants. Vascular Health and Risk Management. 2017;13:287-292.



### Recombinant Factor VII (rFVIIa) Novoseven®

- **Indication:** promoting hemostasis through the extrinsic pathway of the coagulation cascade
- **Mechanism of action:** vitamin K-dependent glycoprotein promotes hemostasis through intrinsic pathway

	Dosing
DOAC- associated bleeding	90 ug/kg/dose IV *no clinical studies have evaluated the reversal of DOACs with rFVIIa, we generally avoid use if possible

- Onset varies: administration required every 2 hours until hemostasis is achieved
- Duration: ½ life ~2 to 3 hours
- **Contraindications:** none listed in manufacturer's labeling
- **US Boxed Warning:** serious thromboembolic events are associated with use, monitor patients for signs and symptoms of thrombosis
- **Warning:** antibody formation, hypersensitivity reactions

Factor VIIa (Recombinant). Lexi-Comp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at [https://online.lexi.com/coaction/docretrieve/docid/patch\\_#6885#ch](https://online.lexi.com/coaction/docretrieve/docid/patch_#6885#ch)  
Reversal of direct oral anticoagulants. Vascular Health and Risk Management. 2017;13:287-292.

### Hemodialysis

- Reversal of dabigatran is associated with life-threatening bleeding
  - Dabigatran: protein bound ~35%
  - Hemodialysis removes up to 68% of dabigatran DOAC activity
- Edoxaban is protein bound (~50%),
  - However trials did not demonstrate hemodialysis as an effective method for removal

Reversal of direct oral anticoagulants. Vascular Health and Risk Management. 2017;13:287-292.

### Specific Reversal Agents

### Vitamin K (Phytonadione)

- Mechanism of Action:**

### Vitamin K (Phytonadione)

- Indication:** reverse elevated INRs associated with active bleeding episodes on vitamin K antagonists; warfarin (Coumadin, Jantoven)

Route of Administration	Dosing
PO	1 to 10mg PO
IV Infusion	1 to 10mg in NS or D5W IV over 30 minutes

- Onset**
  - PO 6 to 10 hours
  - IV 1 to 2 hours
- Duration**
  - SC and IM not recommended
- US Boxed Warning:** Fatal hypersensitivity reactions have occurred with parenteral use. Avoid IV and IM administration unless subcutaneous administration is not feasible and the serious risk is justified.

Management of Bleeding in Patients on Oral Anticoagulants. Am College of Cardio. Protamine sulfate. Lexi-Comp, Lexicomp, Wolters Kluwer Health, Inc. Bluecross, ©. Available at https://online.lww.com/txaction/doi/10.1097/00000539-201405000-00004

### Vitamin K (Phytonadione)

- Caution/Warnings**
  - Infuse at maximum rate of 1mg/min
    - Rapid IV push can cause hypotension or anaphylaxis
- Monitor**
  - BP, INR, active bleeding
- Contraindications**
  - Hypersensitivity to phytonadione or any component of the formulation

Management of Bleeding in Patients on Oral Anticoagulants. Am College of Cardio

### Protamine

- Indication:** reverses enoxaparin
- Mechanism of action:** In the presence of LMWH, protamine incompletely reverses the antifactor-Xa activity of LMWH

Enoxaparin Last Administered	Dose
Previous 8 hours	1mg IV protamine sulfate/1 mg of enoxaparin
> 8 hours ago or if aPTT remains prolonged	0.5mg IV of protamine/ 1mg of enoxaparin

Protamine sulfate. Lexi-Comp, Lexicomp, Wolters Kluwer Health, Inc. Bluecross, ©. Available at https://online.lww.com/txaction/doi/10.1097/00000539-201405000-00004

### Protamine

**Inactive Ionic Complex**

### Protamine

- Indication:** reverses unfractionated heparin and enoxaparin, dalteparin, tiazaparin, nadroparin
- Mechanism of action:** protamine given in the presence of heparin or LMWH forms a stable salt bond and the anticoagulant activity of both drugs is nullified

Heparin Last Administered	Dose	Enoxaparin Last Administered	Dose
Immediate	1mg to 1.5 mg IV protamine sulfate/100 units of heparin	Previous 8 hours	1mg IV protamine sulfate/1 mg of enoxaparin
30 to 60 min	0.5 to 0.75mg IV protamine sulfate/100 units of heparin	> 8 hours ago or if aPTT remains prolonged	0.5mg IV of protamine/ 1mg of enoxaparin
> 2 hours	0.25 to 0.375mg IV protamine sulfate/ 100 units of heparin		
Unknown	25mg to 50mg IV SINGLE dose		

Protamine sulfate. Lexi-Comp, Lexicomp, Wolters Kluwer Health, Inc. Bluecross, ©. Available at https://online.lww.com/txaction/doi/10.1097/00000539-201405000-00004

## Protamine

- **Dosing dalteparin, tiazaparin, nadroparin**

Regardless of administration time

1mg IV protamine sulfate/100 anti-factor Xa units of LMWH

- **Onset:** ~5 minutes
- **Duration:** ½ life ~7 minutes
- **Warnings/Precautions:**
  - Heparin rebound
  - Hypersensitivity reactions
    - Have epinephrine available, consider co-administration with diphenhydramine or hydrocortisone
  - Infusion reactions can cause severe hypotensive and anaphylactic-like reactions
- **Contraindications:** hypersensitivity to components
- **US Boxed Warning:** Hypotension, cardiovascular collapse, non-cardiogenic pulmonary edema, pulmonary vasoconstriction, and pulmonary hypertension may occur

Protamine sulfate, Leadi-Drugs, Lexcomp, Wolters Kluwer Health, Inc. Riverwoods, IL. Available at [https://online.lexel.com/facollection/retrievedocs/path\\_15560927](https://online.lexel.com/facollection/retrievedocs/path_15560927)  
Reversal of direct oral anticoagulants, Vascular Health and Risk Management, 2017, 13, 287-292

## Idarucizumab (Praxbind)

**Administer 5g IV** (typically two separate vials)

- IV Push (preferred): Inject 5 g via syringe
- Infusion: Hang both vials and administer 5g as two consecutive infusions no later than 15 minutes apart

**Mechanism of action:** humanized monoclonal antibody fragment (Fab) that binds and sequesters dabigatran

Idarucizumab, Leadi-Drugs, Lexcomp, Wolters Kluwer Health, Inc. Riverwoods, IL. Available at [https://online.lexel.com/facollection/retrievedocs/path\\_15560927](https://online.lexel.com/facollection/retrievedocs/path_15560927)  
Reversal of direct oral anticoagulants, Vascular Health and Risk Management, 2017, 13, 287-292

## Idarucizumab (Praxbind)

- **Warning/Precautions**
  - Hereditary fructose intolerance, thromboembolic risk; dabigatran can be reinitiated 24 hours after administration if appropriate
  - Hypersensitivity reactions
  - Thromboembolic risk
- **Contraindications**
  - None listed in manufacturer’s labeling

Idarucizumab, Leadi-Drugs, Lexcomp, Wolters Kluwer Health, Inc. Riverwoods, IL. Available at [https://online.lexel.com/facollection/retrievedocs/path\\_15560927](https://online.lexel.com/facollection/retrievedocs/path_15560927)  
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## Andexanet Alfa (Andexxa)

**Mechanism of action:** Binds and sequesters Factor Xa inhibitors, inhibits Tissue Factor Pathway

DOAC	Last Dose	Timing of last DOAC before Andexanet alfa administration	
		<8 Hours or Unknown	≥8 Hours
Apixaban (Eliquis)	≤5 mg	Low Dose	Low Dose
	>5 mg/unknown	High Dose	
Rivaroxaban (Xarelto)	≤10 mg	Low Dose	Low Dose
	>10 mg/unknown	High Dose	

Low dose: 400 mg IV bolus followed by 4 mg/minute IV infusion for up to 120 minutes  
High dose: 800 mg IV bolus followed by 8 mg/minute IV infusion for up to 120 minutes

Andexanet alfa, Leadi-Drugs, Lexcomp, Wolters Kluwer Health, Inc. Riverwoods, IL. Available at [https://online.lexel.com/facollection/retrievedocs/path\\_15560927](https://online.lexel.com/facollection/retrievedocs/path_15560927)  
Reversal of direct oral anticoagulants, Vascular Health and Risk Management, 2017, 13, 287-292

## Andexanet Alfa (Andexxa)

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1844444/>

## Andexanet Alfa (Andexxa)

- **Warnings/Precautions**
  - Anti-factor Xa activity re-elevation
  - Thromboembolic and ischemic risks
  - >10% Immunologic antibody development, infusion related reaction
  - 1 to 10% DVT, stroke, MI, cardiac failure, UTI, pneumonia, acute respiratory failure
- **Monitor**
  - Signs and symptoms of hemostasis or thrombosis
- **Contraindications**
  - None listed in manufacturer’s labeling

Andexanet alfa, Leadi-Drugs, Lexcomp, Wolters Kluwer Health, Inc. Riverwoods, IL. Available at [https://online.lexel.com/facollection/retrievedocs/path\\_15560927](https://online.lexel.com/facollection/retrievedocs/path_15560927)  
Reversal of direct oral anticoagulants, Vascular Health and Risk Management, 2017, 13, 287-292

### Ciraparantag (Aripazine-PER977)

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

Reversal of direct oral anticoagulants. Vascular Health and Risk Management. 2017;13:287-292.

### Managing Major Bleeding

- Anticoagulants and antiplatelet agents should be held
- Airway and IV access secured
- Obtaining and administering reversal agents must not delay resuscitation and local hemostatic measures
  - Volume resuscitation
  - Pressure/Packing
  - Supportive measures (blood product transfusion when appropriate)

### Resumption of Anticoagulation

- Benefits of resuming anticoagulation vs. the risk of recurrent bleeding
- Risk assessment of recurrent thrombosis
  - Utilize guidelines based on underlying indication for anticoagulation
  - Assess specific risk patient factors
    - Site of bleeding
    - Past medical history
    - Clotting disorders, etc.

### Conclusion

- Evidence is limited on the reversal of anticoagulation agents
  - Many agents are available and pharmacist are a key promoter for the right reversal agent for the correct anticoagulation agent
  - Each agent comes with risks and limitations that are important to inform the patients and providers
- Utilize this presentation when developing treatment plans to manage severe bleeds

### Knowledge Check!

- A 87 yo male reports to the anticoagulation clinic. You see him on a monthly basis as his INR is always within goal of 2-3. Today is the day after St. Patrick's Day. He reports of increased alcohol intake yesterday, and his INR comes back at 3.8. How will you manage this patient?

### Knowledge Check!

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  - **Assess patients bleeding**
  - **Hold Warfarin dose x 1**
  - **Counsel on signs and symptoms of bleeding**
  - **Follow up with patient within the week**

### Knowledge Check!

- A 76 yo female reports to the anticoagulation clinic with complaints of abdominal pain and distension. He reports feeling dizzy and weak the past 24 hours and has apparent tachypnea. His INR comes back at 4.7, what is your clinical suspicion, how should you proceed?

### Knowledge Check!

- A 76 yo female reports to the clinic with complaints of abdominal pain and distension. He reports feeling dizzy and weak the past 24 hours and has apparent tachypnea. His INR comes back >4 and is unable to be detected on a POCT. What is your clinical suspicion, how should you proceed?
  - Immediately refer to the Emergency Room
  - Intravenous INR draw
  - High clinical suspicion for intra-abdominal bleed
  - Select appropriate agent based on agents available at your institution

### Knowledge Check!

- A 54 yo male is hospitalized status post coronary artery bypass grafting (CABG)
  - Heparin infusion at 1200 u/hr is administer for 3 hours
  - Patient begins complaining of lower extremity swelling and pain
  - A Doppler is ordered to rule out DVT and extremity bleeding is suspected
  - The provider wants to reverse the heparin, what do you recommend?

### Knowledge Check!

- The provider wants to reverse the heparin, what do you recommend?
  - Stop heparin drip
  - Recommend Protamine 1mg/100units of heparin
    - 1200 units heparin x 3 hours = 3,600 units / 100 units
    - 36mg of Protamine
  - If bleeding persists consider another dose of protamine
  - Monitor for signs and symptoms of thrombosis

### Knowledge Check!

- A 67yo male comes into the Emergency Department at 10:36am on Rivaroxaban 20mg nightly for nonvalvular atrial fibrillation. Upon CT scan, the patient shows evidence of an intracranial hemorrhage. Assuming the **patient took the medication last night and all available reversal agents are available at your institution**, what medication and dose would you recommend as the most effective agent?
  - KCentra 1500 units IV once
  - Andexxa 400 mg IV bolus followed by 4 mg/minute IV infusion for up to 120 minutes
  - Vitamin K 10mg IV once
  - Protamine 10mg

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  - KCentra 1500 units IV once
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  - Protamine 10mg



## Applying your knowledge

- Utilize the information provided for reversal of anticoagulation therapy to construct treatment plans and manage severe bleeds at your institution

Requirement	EP 2: The [hospital/organization] uses approved protocols and evidence-based practice guidelines for reversal of anticoagulation and management of bleeding events related to each anticoagulant medication.
Rationale	Bleeding is the most common complication of all anticoagulants. In addition to heparin and warfarin, each of the direct oral anticoagulants have different reversal mechanisms. It is important for organizations to use evidence-based practice guidelines when developing protocols to manage bleeding events. For timely and appropriate management, providers need to be aware of the variations in presentation severity (e.g., location and severity of bleeding, indication for reversal) and appropriate reversal agents (e.g., drug discontinuation, use of concentrated clotting therapy) for each anticoagulation medication used by patients coming to their organization.
References	Tomaselli GF, et al. "2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways." <i>Journal of the American College of Cardiology</i> 70, no. 24 (Dec 19, 2017): 3042-67.  Samuelson BT and Cuker A. "Measurement and Reversal of the Direct Oral Anticoagulants." <i>Blood Reviews</i> 31, no. 1 (Jan 2017): 77-84.

Thank you for your attention!

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May 2019

Please see  
"Direct Oral Anticoagulants and  
Factor IIa and Xa Inhibitors"  
CE presentation for additional  
information on Oral Anticoagulants