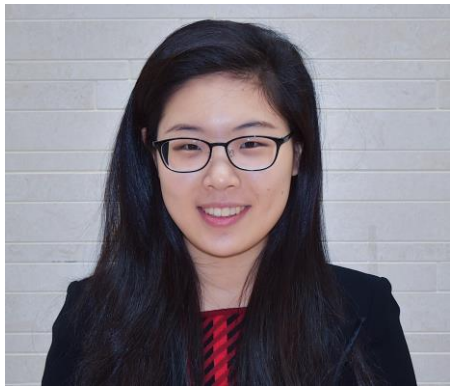
# Four-Factor Prothrombin Complex Concentrate (4F-PCC) Off-Label Uses: A Dive into the Guidelines & Literature

A presentation for HealthTrust Members
April 26, 2023



MIN SUN (MINNY) JEONG, PHARMD,
PGY2 MEDICATION-USE SAFETY & POLICY PHARMACY RESIDENT

ERNEST MARIO SCHOOL OF PHARMACY, RUTGERS UNIVERSITY/ROBERT WOOD JOHNSON UNIVERSITY HOSPITAL – NEW BRUNSWICK

# Disclosures

- The presenter and her preceptor have no financial relationships with any commercial interests pertinent to this presentation.

- This program may contain the mention of drugs, brands, or suppliers presented in a case study or comparative format using evidence-based research. Such examples are intended for educational and informational purposes and should not be perceived as an endorsement of any drug, brand, or supplier.

- This program includes both FDA-labeled and off-label uses of 4F-PCC.

# Pharmacist Learning Objectives

1

Recall the pharmacology of four-factor prothrombin complex concentrate (4F-PCC) and its place in current guidelines.

2

Identify recent studies that assess the safety and efficacy of 4F-PCC off-label uses.

3

Recognize the role of the pharmacist in evaluating the appropriateness of 4F-PCC use.

# Acronyms

**4F-PCC:** Four-Factor Prothrombin Complex Concentrate

**ACC:** American College of Cardiology

**AGA:** American Gastroenterology Association

**aPTT:** activated Partial Thromboplastin Time

**BARC:** Bleeding Academic Research Consortium

**CT:** Computed Tomography

**DIC:** Disseminated Intravascular Coagulation

**DOAC:** Direct Oral Anticoagulant

**EMR:** Electronic Medical Record

**FDA:** Food and Drug Administration

**FFP:** Fresh Frozen Plasma

**HIT:** Heparin-Induced Thrombocytopenia

**ICH:** Intracranial Hemorrhage

**INR:** International Normalized Ratio

**IU:** International Units

**ISTH:** International Society on Thrombosis and Hemostasis

**IV:** Intravenous

**PCCs:** Prothrombin Complex Concentrates

**PT:** Prothrombin Time

**rFVIIa:** Recombinant Factor VIIa

**SWFI:** Sterile Water for Injection

**VKA:** Vitamin K Antagonist

# Background on 4F-PCC

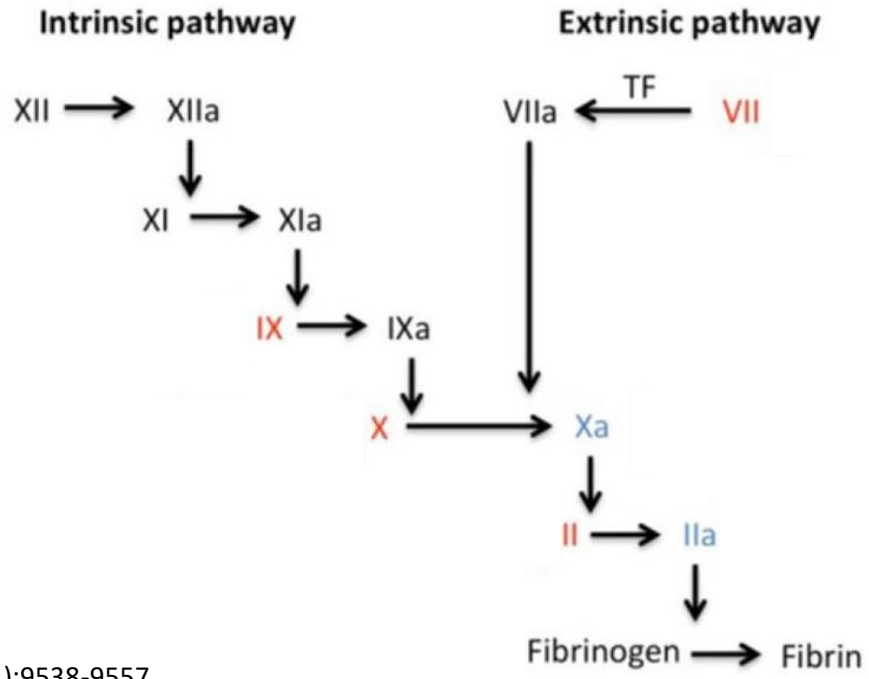
4F-PCC PHARMACOLOGY & PLACE IN GUIDELINES

# Pharmacology

**Four-Factor** Prothrombin Complex Concentrate

Purified vitamin-K dependent factors II, VII, IX, and X and antithrombotic Proteins C and S

- Contains heparin



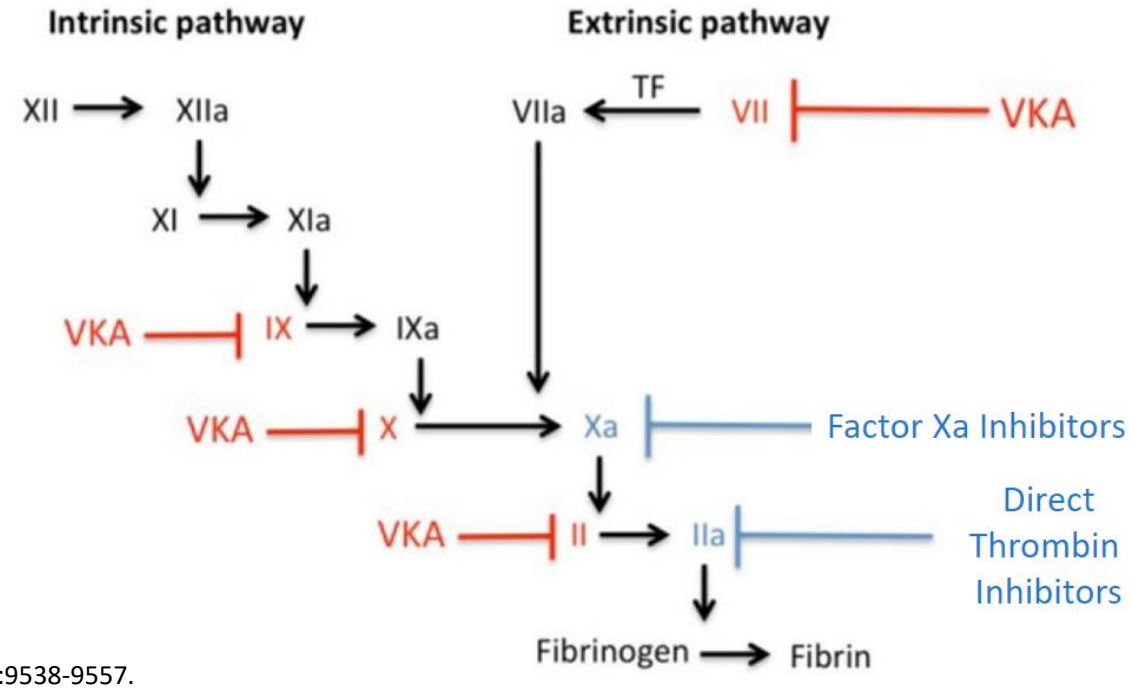

Sources: Van Gorp RH, Schurgers LJ. *Nutrients.* 2015;7(11):9538-9557.
Baskaran J, et al. Prothrombin Complex Concentrate. *StatPearls.* Updated 2022 Dec 19.

# Pharmacology

**Four-Factor** Prothrombin Complex Concentrate

Purified vitamin-K dependent factors II, VII, IX, and X and antithrombotic Proteins C and S

- Contains heparin




Sources: Van Gorp RH, Schurgers LJ. *Nutrients.* 2015;7(11):9538-9557.
Baskaran J, et al. Prothrombin Complex Concentrate. *StatPearls.* Updated 2022 Dec 19.

# FDA-Labeled Indications

## Reversal of Warfarin Anticoagulation

For the urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonist (VKA) (i.e, warfarin) therapy in adult patients with:

- Acute major bleeding
- Need for an urgent surgery/invasive procedure

Source: Kcentra®. Prothrombin complex concentration (human) prescribing information. 2020.

# Cautions

**Contraindications**

- Known anaphylactic or severe systemic reactions to 4F-PCC or its components including:
  - Factors II, VII, IX, X, Proteins C and S, heparin, antithrombin III and human albumin
- Known heparin-induced thrombocytopenia (HIT)
- Disseminated intravascular coagulation (DIC)

**Warnings and Precautions**

- Hypersensitivity reactions
- Arterial and venous thromboembolic complications **(US Boxed Warning)**
- May not be suitable in patients with thromboembolic events in the prior 3 months
- May carry a risk of transmitting infectious agents

Source: Kcentra®. Prothrombin complex concentration (human) prescribing information. 2020.

# Place in Guidelines: FDA-Labeled Indication

- Rapid reversal of anticoagulation (with correction of the INR) is recommended in patients with major bleeding associated with VKAs.
- Standard practice: Discontinue VKA and administer IV vitamin K. Consider reversal strategy.
- Although fresh frozen plasma (FFP) traditionally has been used, PCCs may provide advantages such as:
  - More rapid reduction of INR
  - Reduced drug preparation time
  - Reduced risk of anaphylaxis and transmission of infectious pathogens
  - Lower volume requirement - may be preferred in fluid-restricted patients

Sources: Levy JH, et al. *Anesthesiology*. 2018; 129:1171-1184.
Keeling D, et al. *Br J Haematol*. 2016; 175:602-613.
Kozek-Langenecker SA, et al. *Eur J Anaesthesiol*. 2017; 34:332-395.
Hornor MA, et al. *J Am Coll Surg*. 2018; 227:521-536.e1.

# Dosage and Administration

## FDA-labeled dosing: weight-based

- Dose of Prothrombin Complex Concentrate (Human) Required for Reversal of VKA Anticoagulation in Patients with Acute Major Bleeding or Need for Urgent Surgery/Invasive Procedure

| Pre-treatment INR | 2 - <4 | 4-6 | >6 |
|---|---|---|---|
| Dose (units†) / kg body weight* | 25 | 35 | 50 |
| Maximum dose (units†) | 2500 | 3500 | 5000 |

## Guideline recommended dosing**: low-dose fixed

| Use | Non-intracranial major bleeding | Intracranial hemorrhage |
|---|---|---|
| Dose (units†) | 1000 | 1500-2000 |

Source: Kcentra®. Prothrombin complex concentration (human) prescribing information. 2020.
**Tomaselli GF, et al. *J Am Coll Cardiol.* 2020;76(5):594-622.
**Gilbert BW, et al. *Am J Emerg Med*. 2020; 38:806-809.
**Schwebach AA, Waybright RA, Johnson TJ. *Pharmacotherapy*. 2019; 39:599-608.

* Dosing is based on actual body weight up to but not exceeding 100 kg. For patients weighing more than 100 kg, maximum dose should not be exceeded.
† Units refer to International Units

# Assessment Question 1

4F-PCC does **NOT** contain which of the following?

A. Factor X
B. Proteins C and S
C. Factor V
D. Heparin

# Assessment Response 1

4F-PCC does **NOT** contain which of the following?

A. Factor X
B. Proteins C and S
**C. Factor V**
D. Heparin

# 4F-PCC Off-Label Uses*

## GUIDELINE RECOMMENDATIONS AND ASSESSMENT OF SAFETY AND EFFICACY

*Currently not included in the labeling approved by the US Food and Drug Administration

# 4F-PCC Off-label Uses

## Urgent direct oral anticoagulant (DOAC) reversal

- In patients experiencing life-threatening bleeding
- For perioperative management and prevention of bleeding

## Coagulopathy reversal in patients with liver disease

# Place in Guidelines: Off-Label Uses

**Guidelines / Guidance Documents / Expert Recommendations**

- 2022 Guideline for the Management of Patients With Spontaneous Intracerebral Hemorrhage: A Guideline From the American Heart Association/American Stroke Association
- 2021 European Consensus Statement on Use of 4F-PCC for Cardiac and Non-Cardiac Surgical Patients
- 2020 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants
- 2020 The American College of Emergency Physicians Expert Panel: Anticoagulant Reversal Strategies in the Emergency Department Setting
- 2019 Anticoagulation Forum Guidance on Reversal of Direct Oral Anticoagulants
- 2018 American Society of Hematology guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy.
- 2018 American College of Surgeons' Guidelines for the Perioperative Management of Antithrombotic Medication.
- 2016 Management of severe perioperative bleeding: guidelines from the European Society of Anesthesiology
- 2012 American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis.

# Definitions*

| LIFE-THREATENING BLEED |
| --- |
| Composite of BARC Type 3a & 3b definitions:<br>• Hemoglobin drop ≥5 g/dL from a recent (premorbid) known value (provided hemoglobin drop is related to bleed) PLUS transfusion OR<br>• Uncontrolled bleeding requiring procedural intervention (e.g., Interventional Radiology, endoscopic, surgical)* OR<br>• Hemodynamic instability: bleeding requiring intravenous vasoactive agents |

*Excluding dental/nasal/skin/hemorrhoid

| CRITICAL SITES |
| --- |
| • Brain*<br>• Eye**<br>• Spine<br>• Airway<br>• Pericardium<br>• Aorta<br>• Closed space with concern for compartment syndrome |

*Does not include microbleeds or hemorrhagic transformation
**Intraocular with vision compromise

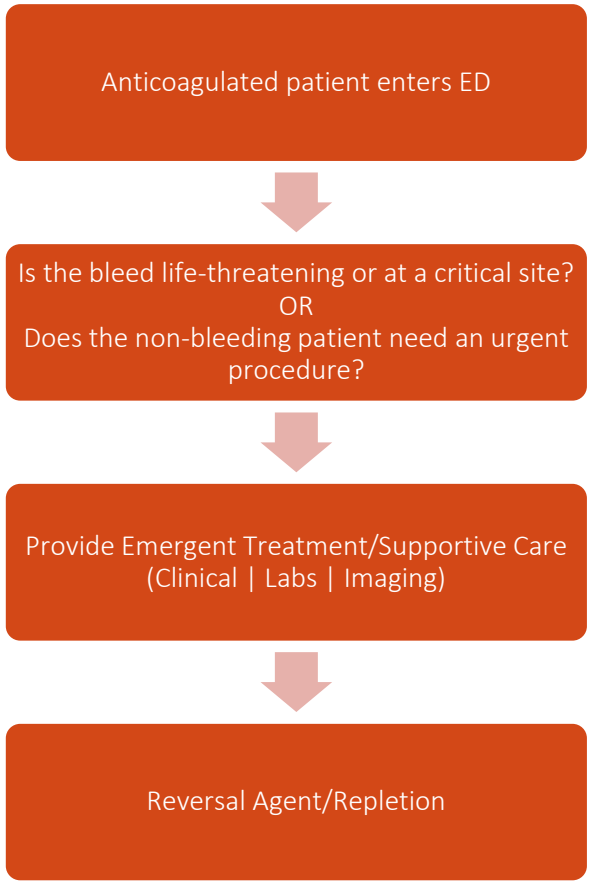
| EMERGENCY SURGERY OR URGENT PROCEDURE |
| --- |
| Invasive procedure with significant risk of life-threatening bleeding or bleeding at critical site that cannot be reasonably delayed beyond the length of the anticoagulant's therapeutic effect (i.e. >2 half-lives depending on clinical scenario) while empiric medical treatment is delivered. |

*NOTE: Definitions of a life-threatening bleeding event or critical site may vary significantly.

Source: Baugh CW, et al. *Ann Emerg Med*. 2020;76(4):470-485.

BARC: Bleeding Academic Research Consortium

# Guidance Statement for Anticoagulant Reversal or Factor Replacement*




| Class | Direct Thrombin Inhibitor | Direct Xa Inhibitor | | |
|---|---|---|---|---|
| Agent | Dabigatran | Rivaroxaban/ Apixaban | Edoxaban | Betrixaban |
| Last Dose | (<8-12hrs) | (<18hrs) | (19-24hrs) | (17-21hrs) |
| Tier 1 | Idarucizumab | Andexanet alfa | | |
| Tier 2 | PCC† \| Dialysis | PCC† | | |

**Reassess:** Clinical | Labs | Imaging

*Adapted from The 2020 Anticoagulant Reversal Strategies in the Emergency Department Setting: Recommendations of a Multidisciplinary Expert Panel (*Annals of Emergency Medicine)*

† Not FDA-approved for indication

Source: Baugh CW, et al. *Ann Emerg Med*. 2020;76(4):470-485.

# Definition of Hemostatic Effectiveness

***ISTH Scientific and Standardization Subcommittee (SSC)***

- Good effectiveness is achieved when **ALL** criteria are met:

| Non-Visible Bleed* | Intracranial Bleed |
|---|---|
| • Invasive interventions avoided or carried out with blood loss not exceeding expected amount<br>• No unscheduled (re-)interventions needed for bleeding management<br><br>At 48 hours from initial management/at discharge:<br>• Hemoglobin level has not dropped > 10%<br>• No need for further treatment with hemostatic agents or transfusion of blood products | • Invasive interventions avoided or carried out with blood loss not exceeding the expected amount<br>• Hematoma volume stable or increased by <35% as compared to baseline volume<br>• No deterioration of the Extended Glasgow Outcome Scale (GOS-E) or any validated scoring system<br><br>Within 48 hours from initial management:<br>• No need for further treatment with hemostatic agents or transfusion of blood products<br>• No unscheduled (re-)interventions are needed for bleeding management |

Source: Khorsand N, et al. *J Thromb Haemost*. 2021;19(4):1112-1115.

*All bleeds that do not classify as visible, musculoskeletal, or intracranial bleeds. (Includes gastrointestinal (GI) bleeds when the bleeding site is not visible to the naked eye, regardless of visible (e.g., melena) signs.)

# Urgent DOAC Reversal

- Complex laboratory measurement of anticoagulant activity
  - Minimum DOAC level that may contribute to bleeding or surgical bleeding risk is unknown
- 2015 ISTH recommendations for anticoagulant reversal
  - Serious bleeding and a DOAC level >50ng/mL
  - Patients requiring an invasive procedure with high bleeding risk and DOAC level >30ng/mL
- Many facilities have variability in lab testing and limited capacity to measure DOAC levels

Source: Khorsand N, et al. *J Thromb Haemost*. 2021;19(4):1112-1115.

ISTH: International Society on Thrombosis and Hemostasis

# Guideline-Based Dosing*

**DOAC reversal for patients with major bleeding or those requiring urgent procedure*

**Weight-based: 50 IU/kg**

- 2020 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants
- 2018 American College of Surgeons' Guidelines for the Perioperative Management of Antithrombotic Medication

**Fixed/Weight-based (depending on DOAC): 2,000 IU or 50 IU/kg**

- 2019 Guidance from the Anticoagulation Forum: Reversal of direct oral anticoagulants

| Class | 4F-PCC Dosing |
|---|---|
| Factor Xa inhibitors | 2,000 IU |
| Direct Thrombin Inhibitor | 50 IU/kg |

Sources: Tomaselli GF et al. *J Am Coll Cardiol*. 2020; 76:594-622.
Hornor MA, et al. *J Am Coll Surg*. 2018; 227:521-536.e1.
Cuker A, et al. *Am J Hematol*. 2019; 94:697-709.

# Urgent DOAC Reversal

## Management of rivaroxaban or apixaban-associated major bleeding with prothrombin complex concentrates

| | |
|---|---|
| **Study Design** | Prospective observational study conducted from January 1, 2014 to October 1, 2016 |
| **Population** | (n=84) Patients who received PCCs for the reversal of rivaroxaban or apixaban due to a major bleeding event. |
| **Methods** | • Effectiveness of PCCs: assessed by using the International Society of Thrombosis and Hemostasis (ISTH) Scientific and Standardization Subcommittee criteria<br>• Safety outcomes: thromboembolic events and all-cause mortality within 30 days after treatment with PCCs |
| **Results** | • PCCs were given at a median (interquartile range) dose of 2000 IU (1500-2000 IU)<br>• Intracranial hemorrhage (ICH) was the most common site of bleeding requiring reversal (n=59; 70.2%), followed by gastrointestinal bleeding (n=13; 15.5%)<br>• Management with PCCs was assessed as effective in 58 (69.1%) patients and ineffective in 26 (30.9%) patients. |

**Conclusion:** The administration of PCCs for the management of major bleeding events associated with rivaroxaban or apixaban is effective in most cases and is associated with a low risk of thromboembolism.

Source: Majeed A, et al. *Blood*. 2017;130:1706-12.

# Urgent DOAC Reversal – *continued*

**Prothrombin complex concentrate for major bleeding on factor Xa inhibitors: a prospective cohort study**

| | |
|---|---|
| **Study Design** | Prospective, observational, multicenter, cohort study performed at non-Canadian hospitals |
| **Population** | (n=66) Patients on apixaban (n=29) or rivaroxaban (n=37), suffering a major bleed, who were treated with PCC |
| **Methods** | • Dosing was based on existing hospital protocol with a fixed dose of PCC 2,000 units<br>• The treating physician evaluated the hemostatic effectiveness as observed during the first day as good, moderate, or poor/ none, using an assessment guide<br>• Safety outcomes were thromboembolism or death |
| **Results** | The effectiveness was assessed as good in 65% (95% confidence interval [CI], 53–77), moderate in 20% (95% CI, 10–30) and poor/ none in 15% (95% CI, 6–24)<br>• For the 36 patients with intracranial hemorrhage (n=36), the corresponding ratings were 67, 17 and 17%<br>• For 16 patients with gastrointestinal bleeding they were 69, 12 and 19%, respectively. There were nine deaths (14%) by 30 days, and five (8%) major thromboembolic events.<br>In a post hoc analysis, according to the ISTH criteria, reversal was effective in 68% and ineffective in 32% |

**Conclusion:** For major bleeding associated with oral Factor Xa inhibitors, PCC may have a beneficial effect.

Source: Schulman S, et al. *Thromb Haemost*. 2018;118:842-51.

# Fixed Low-dose vs. Weight-based Dosing

**Comparison of Hemostatic Outcomes in Patients Receiving Fixed-Dose vs. Weight-Based 4-Factor Prothrombin Complex Concentrate**

| | |
|---|---|
| **Study Design** | Single-center, retrospective cohort study performed at a 433-bed tertiary care hospital in Kentucky |
| **Population** | (n=72) Patients 18 years or older who received 4F-PCC for hemostasis of oral anticoagulation |
| **Methods** | Effectiveness was assessed by determining if clinically effective hemostasis was achieved after receiving a fixed-dose (n=34) vs. a weight-based dose (n=38) of 4F-PCC |
| **Results** | • Results yielded no statistical difference in clinically effective hemostasis using a fixed-dose vs. weight-based dosing, 91.2% and 78.9%, respectively (p = 0.150). There was no significant difference in adverse events, length of stay, or in-hospital mortality between groups; however, significant acquisition cost savings was realized. |

**Conclusion:** A fixed-dose regimen of ~2000 units of 4F-PCC may be a reasonable approach to achieve hemostasis in patients receiving warfarin or factor Xa inhibitors.

Source: Kim C, et al. *J Emerg Med.* 2020;59(1):25-32.

# 4F-PCC vs. Andexanet alfa: Summary

**2020 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants**

- Suggests andexanet alfa is preferable to 4F-PCC for treatment of patients with major bleeding on oral direct Factor Xa inhibitors

Data regarding comparing 4F-PCC and andexanet alfa in ICH is conflicting

Data regarding comparative efficacy in cardiovascular procedures is extremely limited

- No clinical trials dedicated to studying 4F-PCC versus andexanet alfa in this setting

Source: Tomaselli GF et al. *J Am Coll Cardiol*. 2020; 76:594-622.

# 4F-PCC vs. Andexanet alfa: Studies

| Reference | Methods | Results | Conclusions |
|---|---|---|---|
| **Ammar AA, et al (2021)** | Retrospective review of adult patients with DOAC-related ICH (n=44) who received either andexanet alfa (n=28) or 4F-PCC (n=16) | **CT Stability at 6h post-reversal**<br>• Andexanet alfa = 78%; 4F-PCC = 71%<br><br>**CT Stability at 24h post-reversal**<br>• Andexanet alfa = 88%; 4F-PCC = 60% | **No difference** in neuroimaging stability, functional outcome, and thrombotic events when comparing andexanet alfa and 4F-PCC with DOAC-related ICH. |
| **Parsels KA, et al (2022)** | Retrospective, matched (baseline ICH volume), cohort analysis conducted at a single healthcare system | **Good or Excellent ICH Hemostasis**<br>• Andexanet alfa (n=24) = 92.3%<br>• 4F-PCC (n=24) = 88.5% | **No significant differences** in good or excellent ICH hemostasis within 24h or new thrombotic events within 14-days |

Sources: Ammar AA, et al. *Neurocrit Care.* 2021;35(1):255-261.
Parsels KA, et al. *Am J Emerg Med*. 2022;55:16-19

# 4F-PCC vs. Andexanet alfa: Studies

| Reference | Methods | Results | Conclusions |
|---|---|---|---|
| **Barra ME, et al (2020)** | Retrospective, single-center case series of rivaroxaban or apixaban-associated ICH (n=29) between 2016 to 2019 treated with andexanet alfa (n=18) or 4F-PCC (n=11) | **Excellent or Good Hemostasis**<br>• Andexanet alfa = 88.9%; 4F-PCC = 60%<br>**Good Functional Outcome at hospital discharge**<br>• Andexanet alfa = 55.6%; 4F-PCC = 9.1%<br>**Thrombotic Complications within 30 days**<br>• Andexanet alfa = 16.7%; 4F-PCC = 9.1%<br>**Median Cost of Therapy**<br>• Andexanet alfa = $29970/patient<br>• 4F-PCC = $6925/patient | Higher rates of occurrence of **good or excellent hemostasis** and **better functional outcome**s at discharge **with andexanet alfa** compared to 4F-PCC, but **higher rates of thrombotic complications.** |
| **Vestal ML, et al (2022)** | Retrospective, single-center, case series evaluating hemostatic efficacy of patients receiving andexanet alfa (n=21) or 4F-PCC (n=35) for reversal or apixaban or rivaroxaban after ICH | **Good or Excellent ICH Hemostasis**<br>• Andexanet alfa = 64.7%; 4F-PCC = 54.8%<br>**Thrombotic Events**<br>• Andexanet alfa = 14.3%; 4F-PCC = 31.4%<br>**30-Day All-Cause Mortality**<br>• Andexanet alfa = 30%; 4F-PCC = 45.2% | Reversal with andexanet alfa and 4F-PCC **differed in terms of hemostatic efficacy and thrombotic events** after ICH in patients anticoagulated with apixaban or rivaroxaban. |

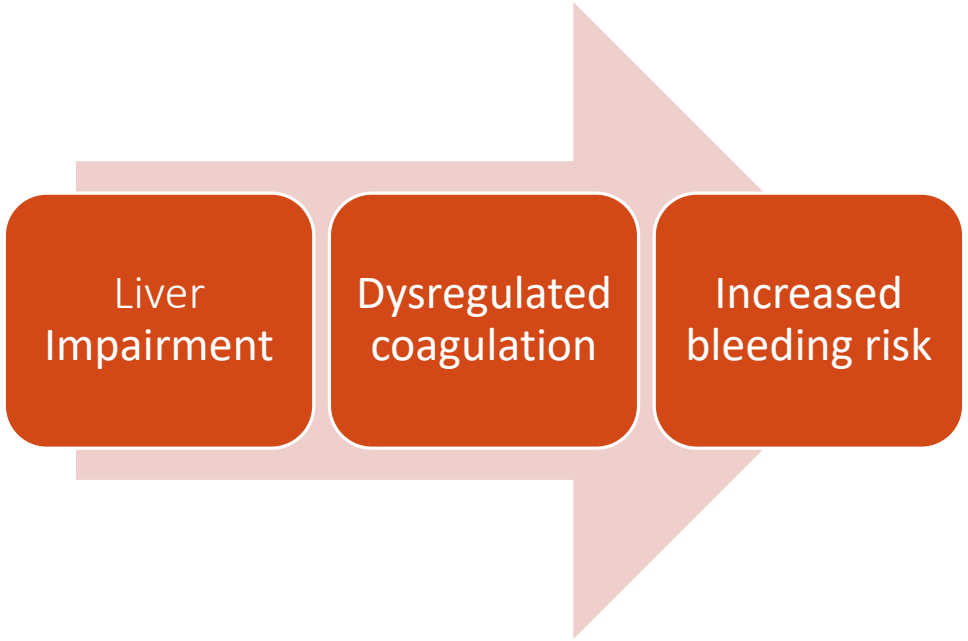
Sources: Barra ME, et al. *J Thromb Haemost*. 2020;18(7):1637-1647.
Vestal ML, et al. *J Thromb Thrombolysis*, 2022;53(1):167-175

# Key Takeaway

- Guidelines recommend 4F-PCC when the respective reversal agents for DOACs are not available.
- There is variability in guideline recommendations for dosing strategies for DOAC reversal.
- There are limited comparative studies on 4F-PCC and andexanet alfa.

# Coagulopathy Reversal in Non-Anticoagulated Patients with Liver Disease

The indication for 4F-PCC administration in patients with liver-related coagulopathies is unclear.




Source: Gish RG, Stravitz RT. *Gastroenterol Hepatol.* 2021;17(1 Suppl 1):16-23.

# Guideline Recommendations

**2019 AGA Clinical Practice Update: Coagulation in Cirrhosis**

- 4F-PCC contains both pro- and anticoagulant factors
- Offers an attractive low-volume therapy to rebalance hemostatic system
- Dosage is based on INR, which is problematic in cirrhosis
- Published experience in liver disease is limited

**2020 Society of Critical Care Medicine: Guidelines for the Management of Adult Acute and Acute-on-Chronic Liver Failure in the ICU**

- "There is insufficient evidence to issue a recommendation for or against PCC”

Sources: O’Leary JG, et al. *Gastroenterology*. 2019;157(1):34-43.e1.
Nanchal R et al. *Crit Care Med* 2020;48(3):e713-e191.

# Comparison of FFP, 4F-PCC, and rFVIIa in Critically Ill Patients with Liver Disease

| | |
|---|---|
| **Study Design** | Retrospective cohort study conducted at a large university-affiliated teaching hospital between September 1, 2011, and December 31, 2015 |
| **Population** | (n=45) Critically ill adults with hepatic impairment (admission INR≥1.5) who received either FFP alone (n=15), PCCs (n=15), or rFVIIa (n=15) prior to a surgical intervention or procedure |
| **Methods** | • **Primary outcomes:** rates of achieving an INR <1.5 at the time of the procedure and an absolute change in INR from 12 hours before the procedure to the time of the procedure<br>• **Secondary outcomes:** time to the procedure, blood product use, bleeding rates, and adverse events |
| **Results** | • INR < 1.5 was more likely to occur with PCCs (80%, p=0.03) and rFVIIa (87%, p=0.01) compared with FFP (27%)<br>• Administered 2.1 ± 1.4 hours (p<0.05, FFP vs PCCs or rFVIIa), 1.3 ± 0.5 hours, and 1.3 ± 0.6 hours before the procedure, respectively.<br>• Hypervolemia was less likely to occur in the PCCs (40%, p=0.02) or rFVIIa (33%, p<0.01) groups than in the FFP group (93%). Overall, 33 (73%) of the 45 patients experienced minor bleeding. |

**Conclusion:** PCC reduced INR faster and more effectively than FFP in critically-ill patients with coagulopathy associated with liver impairment. Bleeding rates were similar across all groups.

Source: Kwon et al. *Pharmacotherapy.* 2016;36(10):1047-1054.

# Prothrombin Complex Concentrates for Coagulopathy in Liver Disease

| | |
|---|---|
| **Study Design** | Retrospective, single-center study conducted in London, United Kingdom from January 2008 to June 2012 |
| **Population** | (n=105 patients; 194 4F-PCC administrations*) adults with liver-related coagulopathy |
| **Methods** | • The effect of PCC on coagulation was analyzed in patients for whom coagulation results were available 7 hours before and after PCC. |
| **Results** | Median dose of PCC administered: 22 IU/kg (~1,500 IU)<br>Types of liver failure: Acute (23%), chronic (77%)<br>Indication for PCC: Bleeding (52%), pre-procedure prophylaxis (48%)<br>**Efficacy**<br>• PCC therapy resulted in statistically significant reductions in INR from baseline regardless of the administration of cryoprecipitate/fibrinogen concentrate (2.3 vs. 1.8 ($p<0.001$))<br>**Safety**<br>• No cardiovascular adverse events or strokes during the 4-week follow up period after administration of PCC<br>• Three patients (~3%) developed venous thromboembolic events<br>• 46 patients died of causes determined to be unrelated to PCC treatment (44%) |

**Conclusion:** PCC was effective in improving coagulation tests without an excess of thrombotic events

Source: Drebes et al. *Hepatol Commun*. 2019; 3(4):513-524.

*Beriplex P/N® & Octaplex® used

# Key Takeaway

- PT, INR, and aPTT may not be reliable measures of hemostatic function in patients with liver disease.
- Guidelines have no specific recommendations for or against the use of 4F-PCC in patients with liver disease.
- There are limited studies on the use of 4F-PCC in patients with liver disease.

# Assessment Question 2

Which of the following has been demonstrated in recent studies regarding the safety and efficacy of 4F-PCC off-label use for factor Xa inhibitor-associated major bleeding?

A. Fixed-dose regimen of 2000 units has been shown to be superior to weight-based dosing.
B. The administration of PCCs for the management of major bleeding events is associated with a high risk of thromboembolism.
C. According to the ISTH criteria, reversal was effective in more than half of the patients treated with PCCs.
D. There were better functional outcomes at discharge with 4F-PCC compared to andexanet alfa in patients with intracranial hemorrhage.

# Assessment Response 2

Which of the following has been demonstrated in recent studies regarding the safety and efficacy of 4F-PCC off-label use for factor Xa inhibitor-associated major bleeding?

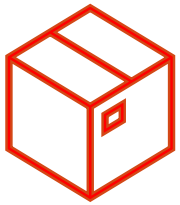
A. Fixed-dose regimen of 2000 units has been shown to be superior to weight-based dosing.
B. The administration of PCCs for the management of major bleeding events is associated with a high risk of thromboembolism.
C. **According to the ISTH criteria, reversal was effective in more than half of the patients treated with PCCs.**
D. There were better functional outcomes at discharge with 4F-PCC compared to andexanet alfa in patients with intracranial hemorrhage.

# Role of the Pharmacist

# Pharmacist Role

1. Ensure appropriate storage, preparation, and administration
2. Obtain patient history
3. Assess patient-specific bleeding and thrombus risk
4. Monitor for potential adverse reactions
5. Develop anticoagulant reversal protocol

# Storage, Preparation, and Administration

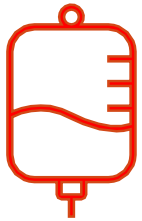


## Storage

Store between 2-25°C (36-77°F)

**Do not freeze**

Store in original carton and protect **from light**

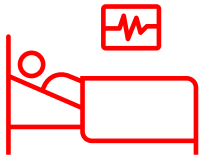


## Preparation

For single-use only

Discard partially used vials

Reconstitute **with provided diluent (SWFI)**



## Administration

Must be used within 4 hours following reconstitution

Should be warmed to room temperature **(20–25°C)** prior to administration

Should be administered through a separate infusion line

Source: Kcentra®. Prothrombin complex concentration (human) prescribing information. 2020.

# Obtaining Adequate History

- History of HIT
- History of DIC
- Past medical history
- Past surgical history
- Prior medications

# Patient-Specific Criteria – Risk Analysis

## Patient specific bleeding risk

- HAS-BLED parameters*
- Bleeding history
- Platelet abnormalities
- INR above therapeutic range

## Patient specific thrombus risk

- Mechanical heart valve
- Stroke risk factors/history

*HAS-BLED: Hypertension (Uncontrolled, >160 mmHg systolic), Abnormal renal/liver function (dialysis, transplant, Cr >2.26 mg/dL) (Cirrhosis or bilirubin >2x normal with AST/ALT/AP >3x normal), Stroke history, Bleeding history or predisposition, Labile INR (Unstable/high INRs, time in therapeutic range <60%), Elderly (>5 years), Drug/alcohol usage (Aspirin, clopidogrel, NSAIDs, or ≥8 drinks/week)

Sources: Doherty JU, et al. *J Am Coll Cardiol.* 2017;69(7):871-898
Douketis JD, et al. *Chest*. 2022;162(5):e207-e243.

# Anticoagulant Reversal Protocol

- Include purpose, inclusion/exclusion criteria, table of contents, standardized definitions, and anticoagulant-specific management and monitoring.

- Requirements for the use of anticoagulation reversal agents should rely on:
  - Specific bleeding criteria
  - Timing of last ingestion of anticoagulant
  - Pharmacokinetics of specific anticoagulant ingested

- Build protocol as an order set within the electronic medical record (EMR)

- Consider 4F-PCC fixed-dosing strategy based on guideline recommendations

Source: National Patient Safety Goals Effective January 2023. The Joint Commission.

# EMR Order Set Template*

## The Anticoagulation Forum (AC Forum)

- **Labs**
  - Complete blood count (CBC)
  - Metabolic panel including liver and kidney function
  - Prothrombin time/International Normalized Ratio (PT/INR)
  - activated Partial Thromboplastin Time (aPTT)

- **Medication**
  - Reversal Agent**
    - Time of ingestion
      - Dose

*For adults with DOAC-related, life-threatening bleeding
**Reversal agents are prioritized per guideline recommendations and should be used in the order listed, based on availability

Source: Reversal & Hemostatic Therapies for DOAC-related, Life-Threatening Bleeding. *Anticoagulation Forum.* 2023

# Assessment Question 3

What factors should a pharmacist consider prior to verifying and preparing an order for 4F-PCC in a patient undergoing an urgent procedure?

A. The last DOAC dose/administration (if applicable)
B. History of Heparin Induced Thrombocytopenia (HIT)
C. History of bleeding and/or thromboembolism
D. All of the above

# Assessment Response 3

What factors should a pharmacist consider prior to verifying and preparing an order for 4F-PCC in a patient undergoing an urgent procedure?

A. The last DOAC dose/administration (if applicable)
B. History of Heparin Induced Thrombocytopenia (HIT)
C. History of bleeding and/or thromboembolism
**D. All of the above**

# Summary

- 4F-PCC has been used for various FDA-labeled and off-label uses.
- Guideline recommendations on its off-label uses are primarily based on observational studies.
- Patient-specific factors must be considered when determining the clinical appropriateness of 4F-PCC use.

# References


1. Van Gorp RH, Schurgers LJ. New Insights into the Pros and Cons of the Clinical Use of Vitamin K Antagonists (VKAs) Versus Direct Oral Anticoagulants (DOACs). Nutrients. 2015;7(11):9538-9557. Published 2015 Nov 17. doi:10.3390/nu7115479
2. Baskaran J, Lopez RA, Cassagnol M. Prothrombin Complex Concentrate. [Updated 2022 Dec 19]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK539716/
3. CSL Behring LLC. Kcentra®. Prothrombin complex concentration (human) prescribing information. Kankakee, IL; 2020 July.
4. Tomaselli GF, Mahaffey KW, Cuker A, et al. 2020 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants. *J Am Coll Cardiol.* 2020;76(5):594-622.
5. Gilbert BW, Morton L, Huffman JB et al. Modified version of the American College of Cardiology's recommendation for low-dose prothrombin complex concentrate is effective for warfarin reversal. *Am J Emerg Med*. 2020; 38:806-809.
6. Schwebach AA, Waybright RA, Johnson TJ. Fixed-Dose Four-Factor Prothrombin Complex Concentrate for Vitamin K Antagonist Reversal: Does One Dose Fit All. *Pharmacotherapy*. 2019; 39:599-608.
7. Levy JH, Douketis J, Steiner T et al. Prothrombin Complex Concentrates for Perioperative Vitamin K Antagonist and Non-vitamin K Anticoagulant Reversal. *Anesthesiology*. 2018; 129:1171-1184.
8. Cuker A, Burnett A, Triller D et al. Reversal of direct oral anticoagulants: Guidance from the Anticoagulation Forum. *Am J Hematol*. 2019; 94:697-709.
9. Hornor MA, Duane TM, Ehlers AP et al. American College of Surgeons' Guidelines for the Perioperative Management of Antithrombotic Medication. *J Am Coll Surg*. 2018; 227:521-536.e1.
10. Greenberg SM, Ziai WC, Cordonnier C, et al. 2022 Guideline for the Management of Patients With Spontaneous Intracerebral Hemorrhage: A Guideline From the American Heart Association/American Stroke Association. *Stroke*. 2022;53(7):e282-e361.
11. Erdoes G, Koster A, Ortmann E, et al. A European consensus statement on the use of four-factor prothrombin complex concentrate for cardiac and non-cardiac surgical patients. *Anaesthesia.* 2021;76:381-92.
12. Witt DM, Nieuwlaat R, Clark NP et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. *Blood Adv*. 2018; 2:3257-3291.
13. Kozek-Langenecker SA, Ahmed AB, Afshari A et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology: First update 2016. *Eur J Anaesthesiol.* 2017; 34:332-395.
14. Ageno W, Gallus AS, Wittkowsky A et al. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012; 141(2 Suppl):e44S-88S.
15. Baugh CW, Levine M, Cornutt D, et al. Anticoagulant Reversal Strategies in the Emergency Department Setting: Recommendations of a Multidisciplinary Expert Panel. *Ann Emerg Med*. 2020;76(4):470-485. doi:10.1016/j.annemergmed.2019.09.001
16. Khorsand N, Beyer-Westendorf J, Sarode R, Schulman S, Meijer K. Definition of haemostatic effectiveness in interventions used to treat major bleeding: Communication from the ISTH SSC Subcommittee on Control of Anticoagulation. *J Thromb Haemost*. 2021;19(4):1112-1115. doi:10.1111/jth.15222
17. Majeed A, Agren A, Holmstrom M, et al. Management of rivaroxaban or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study. *Blood*. 2017;130:1706-12.
18. 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;118:842-51.
19. Kim C, Cottingham L, Eberwein K, Komyathy K, Ratliff PD. Comparison of Hemostatic Outcomes in Patients Receiving Fixed-Dose vs. Weight-Based 4-Factor Prothrombin Complex Concentrate. J Emerg Med. 2020;59(1):25-32. doi:10.1016/j.jemermed.2020.04.049
20. Ammar AA, Ammar MA, Owusu KA, et al. Andexanet Alfa Versus 4-Factor Prothrombin Complex Concentrate for Reversal of Factor Xa Inhibitors in Intracranial Hemorrhage. *Neurocrit Care.* 2021;35(1):255-261.
21. Parsels KA, Seabury RW, Zyck S, et al. Andexanet alfa effectiveness and safety versus four-factor prothrombin complex concentrate in intracranial hemorrhage while on apixaban or rivaroxaban: A single-center, retrospective, matched cohort analysis. *Am J Emerg Med*. 2022;55:16-19
22. Barra ME, Das AS, Hayes BD, et al. Evaluation of andexanet alfa and four-factor prothrombin complex concentrate for reversal of rivaroxaban- and apixaban-associated intracranial hemorrhages. *J Thromb Haemost*. 2020;18(7):1637-1647.
23. Vestal ML, Hodulik K, Mando-Vandrick J, et al. Andexanet alfa and four-factor prothrombin complex concentrate for the reversal of apixaban and rivaroxaban in patients diagnosed with intracranial hemorrhage. *J Thromb Thrombolysis*, 2022;53(1):167-175
24. Gish RG, Stravitz RT. Correction of Coagulopathy of Liver Disease Prior to Procedures. *Gastroenterol Hepatol (N Y)*. 2021;17(1 Suppl 1):16-23.
25. O'Leary JG, Greenberg CS, Patton HM, Caldwell SH. AGA Clinical Practice Update: Coagulation in Cirrhosis. *Gastroenterology*. 2019;157(1):34-43.e1. doi:10.1053/j.gastro.2019.03.070
26. Nanchal R, Subramanian R, Karvellas CJ, et al. Guidelines for the Management of Adult Acute and Acute-on-Chronic Liver Failure in the ICU: Cardiovascular, Endocrine, Hematologic, Pulmonary and Renal Considerations: Executive Summary. *Crit Care Med*. 2020;48(3):415-419. doi:10.1097/CCM.0000000000004193
27. Kwon JO, MacLaren R. Comparison of Fresh-Frozen Plasma, Four-Factor Prothrombin Complex Concentrates, and Recombinant Factor VIIa to Facilitate Procedures in Critically Ill Patients with Coagulopathy from Liver Disease: A Retrospective Cohort Study. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*. 2016;36(10):1047-1054. doi:10.1002/phar.1827
28. Drebes A, de Vos M, Gill S, et al. Prothrombin Complex Concentrates for Coagulopathy in Liver Disease: Single-Center, Clinical Experience in 105 Patients. *Hepatology Communications*. 2019;3(4):513-524. doi:10.1002/hep4.1293
29. Douketis JD, Spyropoulos AC, Murad MH, et al. Perioperative Management of Antithrombotic Therapy. *Chest*. 2022;162(5):e207-e243. doi:10.1016/j.chest.2022.07.025
30. Doherty JU, Gluckman TJ, Hucker WJ, et al. 2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation. *Journal of the American College of Cardiology*. 2017;69(7):871-898. doi:10.1016/j.jacc.2016.11.024
31. National Patient Safety Goals Effective January 2023. The Joint Commission.https://www.jointcommission.org/-/media/tjc/documents/standards/national-patient-safety-goals/2023/npsg_chapter_hap_jan2023.pdf. Accessed April 4, 2023.

# Thank You!

MIN SUN (MINNY) JEONG, PHARMD

PGY2 MEDICATION-USE SAFETY & POLICY PHARMACY RESIDENT

ERNEST MARIO SCHOOL OF PHARMACY, RUTGERS UNIVERSITY

ROBERT WOOD JOHNSON UNIVERSITY HOSPITAL – NEW BRUNSWICK

minny.jeong@rutgers.edu