Mason General Hospital Pharmacy and Therapeutics Committee

Summary:

- This is a recommendation to the P&T committee on the factors of ANDEXXA's (andexanet alfa) value as a formulary agent in contrast to Kcentra (4-Factor Prothrombin Complex Concentrate [4F-PCC]). It is not recommended to have ANDEXXA added onto Mason General Hospital's formulary at this present moment due to cost, lack of superior evidence, and the 4F-PCC's off-label indication to reverse bleeding frrom newer anticoagulation drugs.

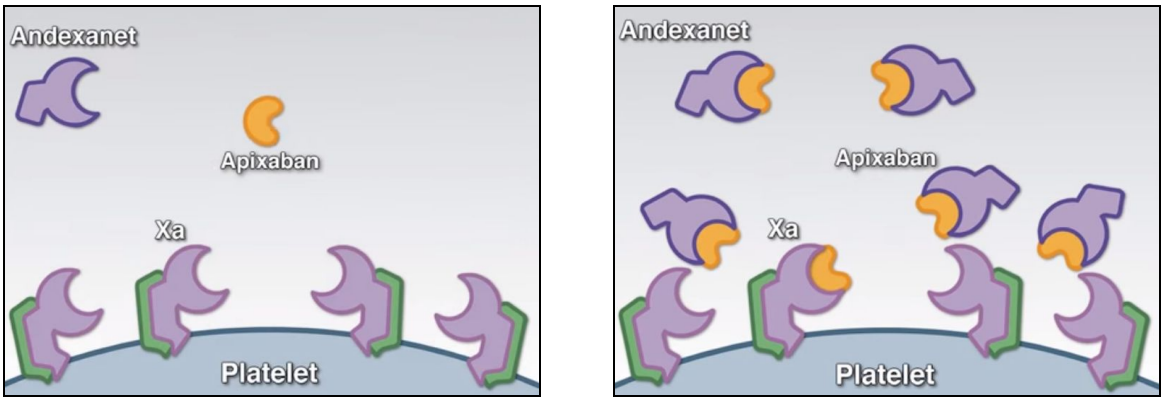
Background:

- In 2016 there were approximately 117,000 hospital admissions in the U.S. and nearly 2,000 deaths attributable to factor Xa (fXa) inhibitor-related bleeding. The cost to manage patients with these severe life-threatening bleeds can exceed up to $100,000.[1] Although there is a current alternative (eg. 4F-PCC) to treat the incident of major bleeding caused by direct oral anticoagulants (DOACs), 4F-PCC does not have FDA's review and approval to support this.[2]

  ANDEXXA (andexanet alfa) was given an accelerated approved by the FDA and is currently indicated for the reversal of two DOACs currently in the market: Xarelto (rivaroxaban) and Eliquis (apixaban)**.** ANDEXXA may have continued approval contingent of indicated reversals upon further review.

  - **Indication[3]:** Reversal treatment for patients who are on rivaroxaban and apixaban upon a life-threatening or uncontrolled bleeding incident.

  - **Pharmacology[3]**: ANDEXXA is a modified, recombinant human fXa molecule and an inactivated-zhzo that can as a decoy to bind and sequester direct and indirect fXa inhibitors. ANDEXXA retains high affinity to the fXa inhibitors yet remains catalytically inactive.



Figures above depicts ANDEXXA's mechanism of action against apixaban[(4)]

- **Administration**[3]:
  i. Administer ANDEXXA intravenously, using a 0.2 or 0.22 micron in-line polyethersulfone or equivalent low protein-binding filter.
  ii. Start the bolus at a target rate of approximately 30 mg/minute.
  iii. Within 2 minutes following the bolus dose, administer the continuous IV infusion for up to 120 minutes.

- **Reconstitution and Stability**[3]:
  Upon reconstitution, the parenteral drug product should be inspected visually for particulate matter and discoloration prior to administration.
  - The reconstituted solution contains coagulation fXa (recombinant), inactivated-zhzo at a concentration of 10 mg/mL.
  - Reconstituted ANDEXXA in vials is stable at room temperature for up to 8 hours, or may be stored for up to 24 hours at 2°C to 8°C.
  - Reconstituted ANDEXXA in IV bags is stable at room temperature for up to 8 hours, or may be stored for up to 16 hours at 2°C to 8°C.

Efficacy Results (ANNEXA-4; Phase 3 Clinical Trial)
In ANDEXXA's phase 3 clinical trial **(For patient eligibility criteria, refer to Appendix 1)**[5], the study measured the median anti-factor Xa activity from baseline and multiple times after the bolus administration.

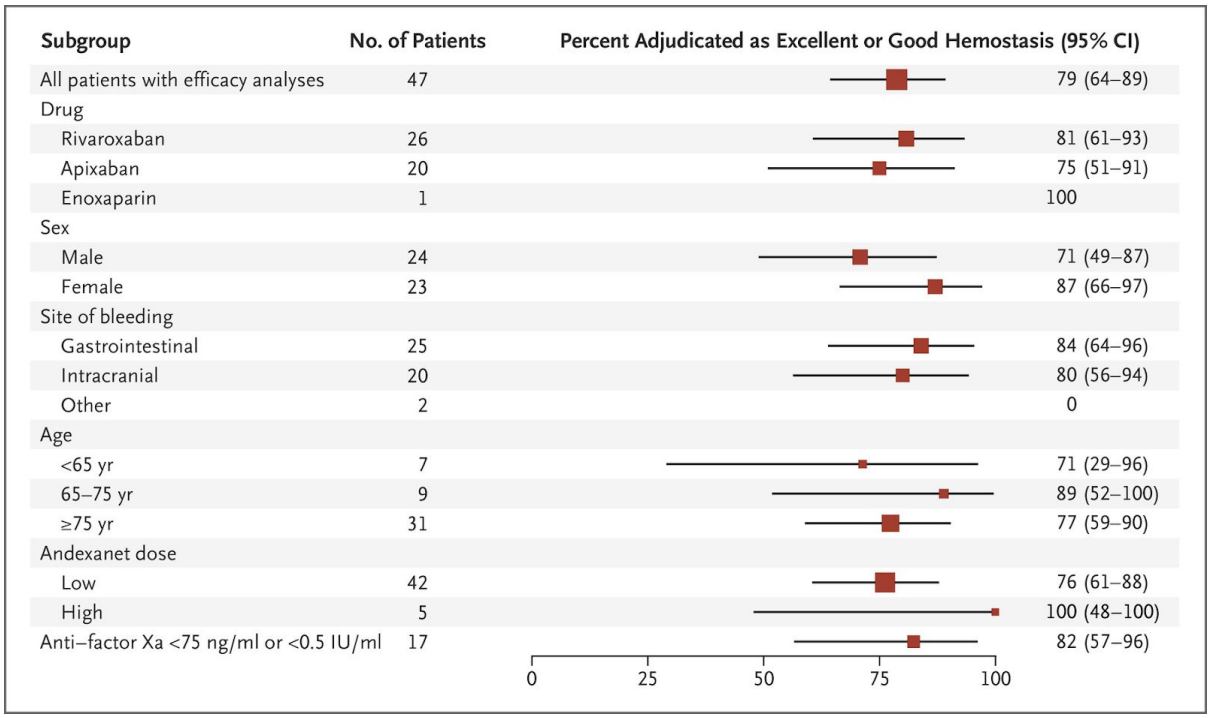
	Median Baseline	Median After Bolus	Median @ 2 Hr Infusion	Median 4 Hrs after Infusion
Rivaroxaban	*277.0 ng/mL*	**16.8 ng/mL**	**30.6 ng/mL**	**177.7 ng/mL**
Apixaban	*149.7 ng/mL*	**10.3 ng/mL**	**12.5 ng/mL**	**103.0 ng/mL**

Rivaroxaban:
- Median Baseline - Median After Bolus = **-89%** (-58 to -94, 95% CI)
- Median Baseline - Median @ 2 Hrs Infusion = **-86%** (-55 to 93, 95% CI)
- Median Baseline - Median 4 Hrs after Infusion = **-39%** (-27 to -45, 95% CI)

Apixaban:
- Median Baseline - Median After Bolus = **-93%** (-87 to -94, 95% CI)
- Median Baseline - Median @ 2 Hrs Infusion = **-92%** (-85 to -94, 95% CI)
- Median Baseline - Median 4 Hrs after Infusion = **-30%** (-23 to -46, 95% CI)

The primary outcome of the trial focused on the proportion of the patients with excellent or good hemostasis after 12 hours from the ANDEXXA bolus administration **(Appendix 2)**. Out of the 47 patients that were in the efficacy population, 6 were determined to in the criteria of good

hemostasis and 31 as excellent hemostasis. The figure below provides further details of those 47 patients:



Comparative Effectiveness:

- ANDEXXA → Indicated: apixaban, rivaroxaban (FDA approved)
- Kcentra → Indicated: warfarin (FDA approved)
    - [off-label: Life-threatening bleeding associated with non-vitamin K antagonist anticoagulants][16]
- Praxbind → Indicated: dabigatran (FDA approved)
- Ciraparantag → Indicated: edoxaban, enoxaparin, dabigatran, rivaroxaban, apixaban, enoxaparin (tentative) -- currently in phase 2 trials[6]

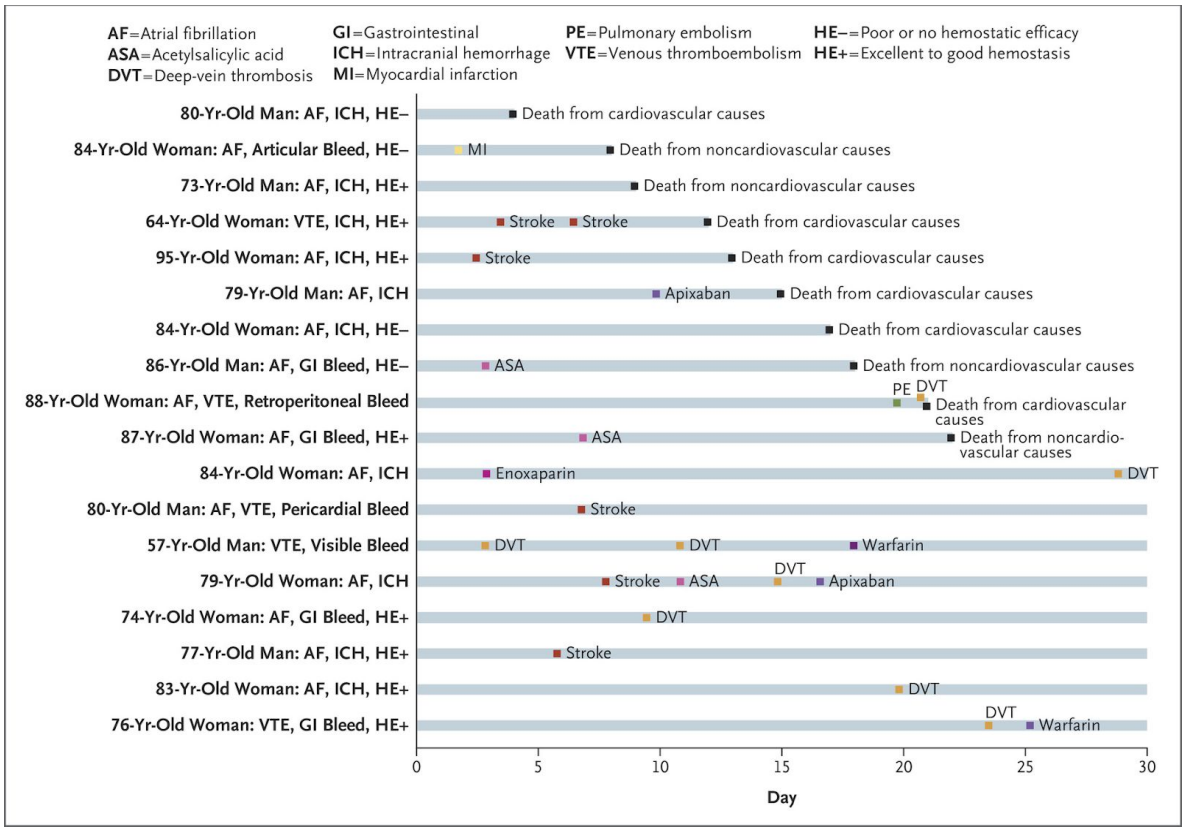
Safety:

The black box label on ANDEXXA warns for possible thromboembolic risks, ischemic risks, cardiac arrest, and sudden deaths.[3] No contraindications are indicated but there is a lack of studies pertaining to patients being treated by ANDEXXA during pregnancy, lactation, and childhood. There are no significant drug-drug interactions reported. Adverse events which have appeared are local infusion site reactions, urinary tract infections, pneumonia, acute respiratory failure, and antibody development in addition to the black box warnings.[3,7]

In the ongoing phase 3 trial, 33/185 patients experienced an event explained in the black box warning within 30 days after the exposure of ANDEXXA. For 86 patients who were

re-anticoagulated prior to a thrombotic event, 11 patients experienced one of the event warnings mentioned on the black box label.[3]

The figure underneath details thrombotic events or death during the 30-day study period after receiving ANDEXXA, 12 patients of which had experienced thrombotic events[5]:



Safety has yet to be evaluated among patients given ANDEXXA after experiencing thromboembolic events or disseminated intravascular coagulation within two weeks prior to their life-threatening bleeding event. Safety also has not been evaluated in patients who received PCC, recombinant factor VIIa, or whole blood products within seven days prior to the bleeding event.[3] Safety should be evaluated at a personal level with patient to pursue further treatment.

Limitations:

- Not tested on patients with inherited/acquired hypercoagulable conditions

- It is on clinicians to balance risk of bleeding against risk of thromboembolism in order to decide to restart anticoagulation after using ANDEXXA.[5]

- Cannot offer random control trial study due to impracticability and otherwise with additional randomization parameters, the treatment of ANDEXXA can be hindered.[8]

Cost: $27,500 per gram[1]

fXa Inhibitor	IV Bolus	IV Infusion
All patients receiving apixaban and those patients who received rivaroxaban >7 hours ago	400 mg at a target rate of 30 mg/min	480 mg @ 4 mg/min for 120 minutes
Patients who received enoxaparin, edoxaban, or a dose of rivaroxaban within ≤ 7 hours or at an unknown time* Patients who are believed to have received a fXa inhibitor but it is uncertain which one *if there is a delay between medical presentation and start of andexanet of more than 7 hours, the patient should receive the dose for rivaroxaban >7 hours ago	800 mg at a target rate of 30 mg/min	960 mg @ 8 mg/min for 120 minutes

- These ANDEXXA doses were selected because their use was associated with a rapid reversal of anti–factor Xa activity of 80% or more in previous studies[5]

Comparative analysis of Kcentra vs ANDEXXA

- Kcentra = $847.26 / vial (approximately 500 units available in each Vial)[17]
- 50 units/kg IV based upon **Appendix 3**

Reversing Rivaroxaban (Xarelto) >7 hours ago	
Kcentra (4F-PCC)	**ANDEXXA (andexanet alfa)**
50 units/kg IV * 80-100 kg	**400 mg bolus + 480 mg infusion**
(4000 units or 5000 units) * $847.26 / 500 units (vial)	**880 mg * $27,500 / 1000 mg**
$6778.08 for 80 kg patient, or $8472.60 for 100 kg patient	**$24200.00 for any weight of patient**

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Recommendation:
Upon further exterior review of the clinical trials, one meta-analysis overview on 18 studies suggests the risk of bleeding in patients who take fXa inhibitors are generally lower than patients who are prescribed vitamin K antagonist (VKAs, eg. warfarin).[9] Albeit, there are many factors which may influence the actual probability of bleeding, the statistical analyses and meta-regression trended fXa inhibitors to have lower chances of bleeding altogether.[10] The clinical severity of hemorrhage also seems to be reduced with rivaroxaban versus VKA according to another study.[11]

In the incident that Mason General Hospital (MGH) comes across a patient with major bleeding and has been taking rivaroxaban or apixaban, there are independent studies shown to have restore thrombin generation and reverse the DOACs anticoagulation effects.[10,12,13] Additionally, the American College of Cardiology published a consensus report on management of bleeding in patients on oral anticoagulants and outlined the possible use of 4F-PCC including rivaroxaban and apixaban (Appendix 3).[14]

Therefore, the recommendation to supplement ANDEXXA as part of the current MGH formulary is presently unnecessary. The formulary review of ANDEXXA should be revisited when a substantial discovery of increasing MGH's demographic are being admitted with medication history of prescribed DOACs. It should also help to be aware if the patient population are increasingly susceptible to internal bleeding after comprehensively understanding the patient's' risk and comorbidities.

Appendix

1) Eligibility/Inclusion/Exclusion of ANNEXA-4 (Phase 3 Clinical Trial)[5]

Eligibility: Ages > 18 years, Sex M or F, No healthy volunteers

Inclusion Criteria for Phase 3 Clinical Trial**:**

1. Acute major bleeding episode requiring urgent reversal of anticoagulation; defined by at least one of the following:
    - Acute bleeding that is potentially life-threatening, OR
    - Acute bleeding associated with a rapid decrease in hemoglobin level by ≥2 g/dL, OR
    - Acute bleeding associated with a hemoglobin level of ≤8 g/dL if no baseline hemoglobin is available, OR
    - Acute bleeding in a critical area or organ such as intraspinal, pericardial, or intracranial.
2. If bleeding is intracranial or intraspinal, the patient must have undergone a head CT or MRI scan demonstrating the bleeding.
3. Patient received or is believed to have received one of the following within 18 hours prior to andexanet administration: apixaban, rivaroxaban, edoxaban or enoxaparin.
4. For patients with intracranial bleeding, there must be a reasonable expectation that andexanet treatment will commence within 2 hours of the baseline imaging evaluation.

Exclusion Criteria for Phase 3 Clinical Trial**:**

1. The patient is scheduled to undergo surgery in less than 12 hours, with the exception of minimally invasive surgery/procedures.
2. A patient with an intracerebral hemorrhage has any of the following:
    - Glasgow coma score < 7, OR
    - Intracerebral hematoma > 60 mL as assessed by CT or MRI
3. Patients with visible, musculoskeletal or intra-articular bleeding as their qualifying bleed.
4. Expected survival of less than 1 month
5. Recent history (within 2 weeks) of a diagnosed thrombotic event (TE) as follows: venous thromboembolism, myocardial infarction, disseminated intravascular coagulation (DIC), cerebral vascular accident, transient ischemic attack, unstable angina pectoris hospitalization or severe peripheral vascular disease within 2 weeks prior to screening.
6. Severe sepsis or septic shock at the time of screening.
7. Pregnant or a lactating female.

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8. Patient has received any of the following drugs or blood products within 7 days of screening:
    - Vitamin K antagonist (VKA)
    - Dabigatran
    - Prothrombin Complex Concentrate products (PCC) or recombinant factor VIIa (rfVIIa)
    - Whole blood, plasma fractions
9. Treated with an investigational drug <30 days prior to screening
10. Planned administration of PCC, fresh frozen plasma (FFP) or rfVIIa from screening until within 12 hours after the end of the andexanet infusion.

2) Hemostasis Criteria for Excellent, Good, and Poor/None[15]

Bleed Type	Excellent (effective)	Good (effective)	Poor/none (not effective)
Visible	Cessation of bleeding ≤ 1 hour after end of infusion and no plasma, coagulation factor or blood products (excludes pRBCs).[1]	Cessation of bleeding between > 1 and ≤ 4 hours after end of infusion and ≤ 2 units plasma, coagulation factor or blood products (excludes pRBCs).[4]	Cessation of bleeding > 4 hours after end of the infusion and /or >2 units plasma, coagulation factor or blood products (excludes pRBCs).[5]
Muscular/skeletal	pain relief or no increase in swelling or unequivocal improvement in objective signs of bleeding ≤1 hour after the end of infusion; and the condition has not deteriorated during the 12-hour period	pain relief or no increase in swelling or unequivocal improvement in objective signs of bleeding >1 and ≤4 hours after end of infusion; and the condition has not deteriorated during the 12-hour period	No improvement by 4 hours after end of infusion and/or condition has deteriorated during the 12-hour period
Intracerebral hematoma	≤20% increase in hematoma volume compared to baseline on a repeat CT or MRI scan performed 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 or MRI scan at +12-hour time point	>35% increase in hematoma volume on a CT or MRI compared to baseline on a repeat CT or MRI scan at +12-hour time point
Subarachnoid bleed	≤20% increase in maximum thickness using the most dense area on the follow-up vs baseline at both the 1 and 12 hour post infusion time points	>20% but <35% increase in maximum thickness using the most dense area on the follow-up at +12h vs baseline	>35% increase in maximum thickness using the most dense area on the +12h vs at baseline
Subdural hematoma	≤20% increase in maximum thickness at both the 1 and 12 hour post infusion assessments compared to baseline	>20% but < 35% increase in maximum thickness at +12h compared to baseline	>35% increase in maximum thickness at +12h compared to baseline
Pericardial	No increase in the size of pericardial effusion on repeat echocardiogram done within 12 hours of the end of infusion	<10% increase in the size of pericardial effusion on repeat echocardiogram done within 12 hours of the end of infusion	10% or more increase in the size of pericardial effusion on repeat echocardiogram done within 12 hours of the end of infusion
Intra-spinal	No increase in hematoma size on repeat CT or MRI scan done within 12 hours of the end of infusion	<10% increase in hematoma size on repeat CT or MRI scan done within 12 hours of the end of infusion	10% or more increase in hematoma size on repeat CT or MRI scan done within 12 hours of the end of infusion
GI, Urinary or non-visible bleeding not described above	≤10% decrease in both corrected hemoglobin/hematocrit at 12 hours[2,3] compared to baseline	>10 % to ≤20% decrease in both corrected hemoglobin/hematocrit at 12 hours compared to baseline[2,3]	>20% decrease in both corrected hemoglobin/hematocrit[2,3]

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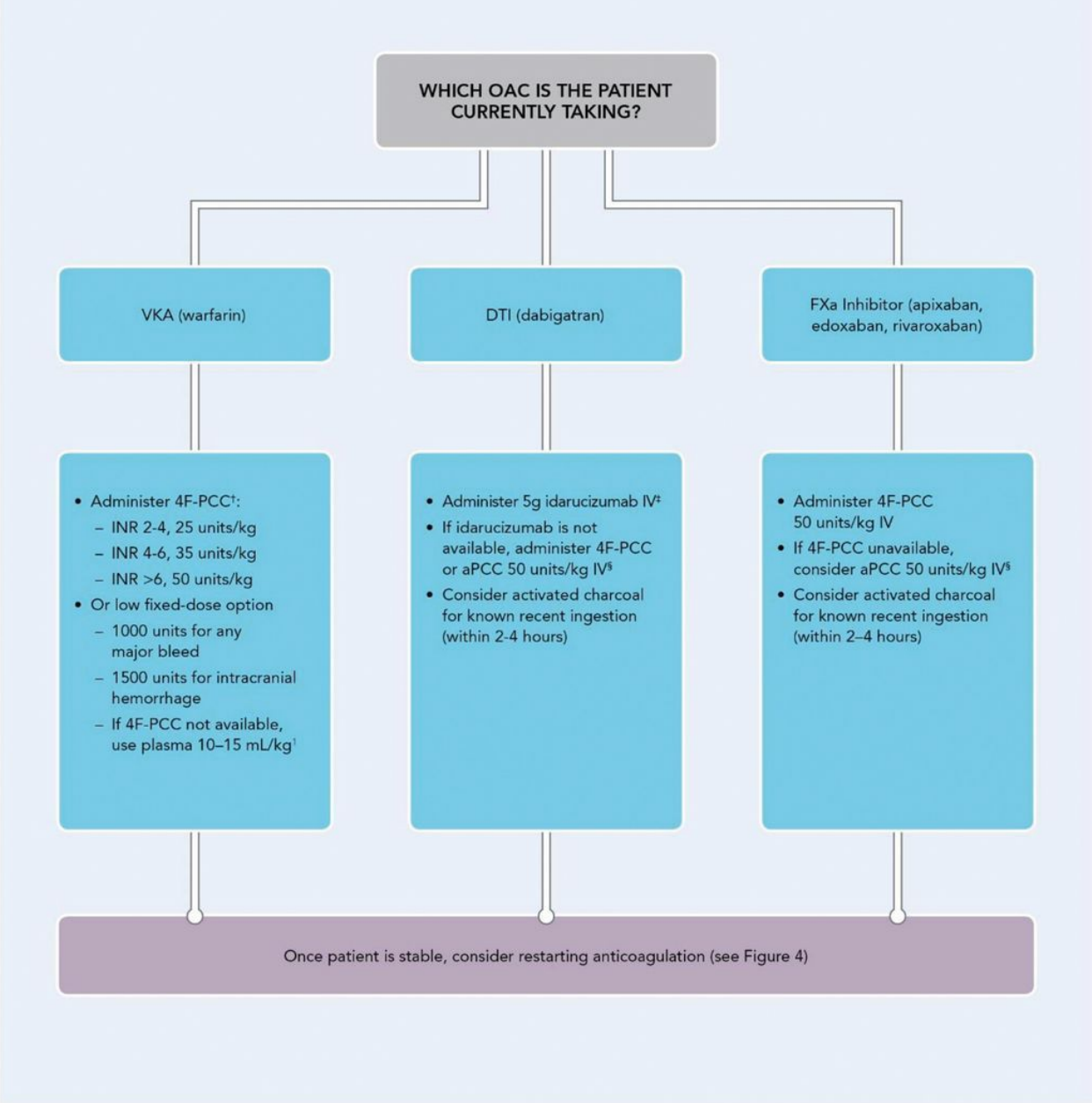
3) Journal of American College of Cardiology flowchart for reversing oral anticoagulants[14]



4F-PCC = four-factor prothrombin complex concentrate; aPCC = activated prothrombin complex concentrate; DOAC = direct oral anticoagulant; DTI = direct thrombin inhibitor; FXa = Factor Xa; INR = international normalized ratio; IV = intravenous; OAC = oral anticoagulant, including DOACs and VKAs; PCCs = prothrombin complex concentrates; VitK = vitamin K; VKA = Vitamin K antagonist.

*Reversal agents include repletion strategies such as PCCs, plasma, VitK, and specific reversal agents for DOACs (e.g., idarucizumab for dabigatran).

† When PCCs are used to reverse VKAs, VitK should also always be given (see Figure 2 for dosing guidance).

‡ If bleeding persists after reversal and there is laboratory evidence of a persistent dabigatran effect, or if there is concern for a persistent anticoagulant effect before a second invasive procedure, a second dose of idarucizumab may be reasonable.

§ Refer to prescribing information for max units.

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