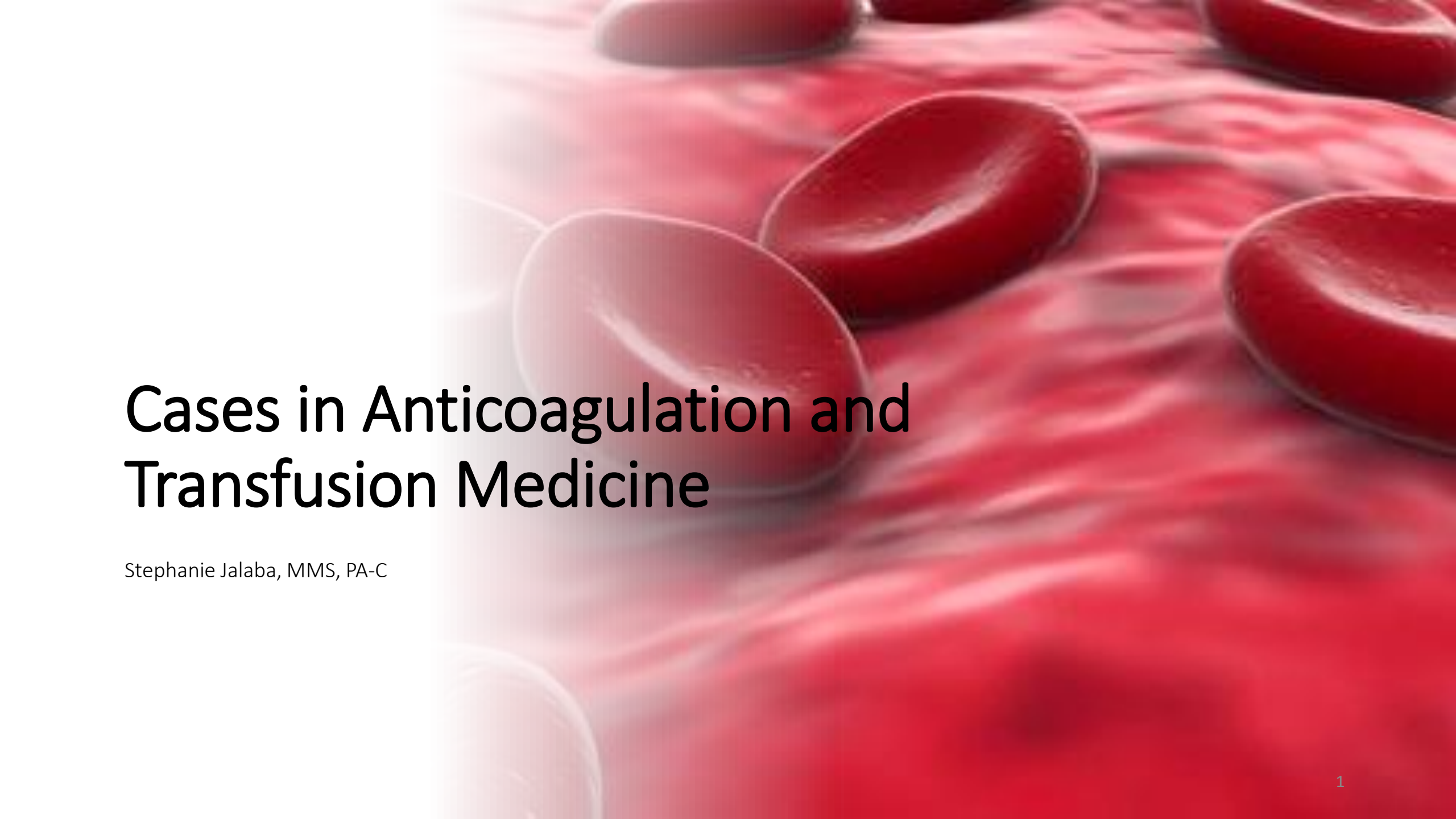


Cases in Anticoagulation and Transfusion Medicine

Stephanie Jalaba, MMS, PA-C

DISCLOSURES

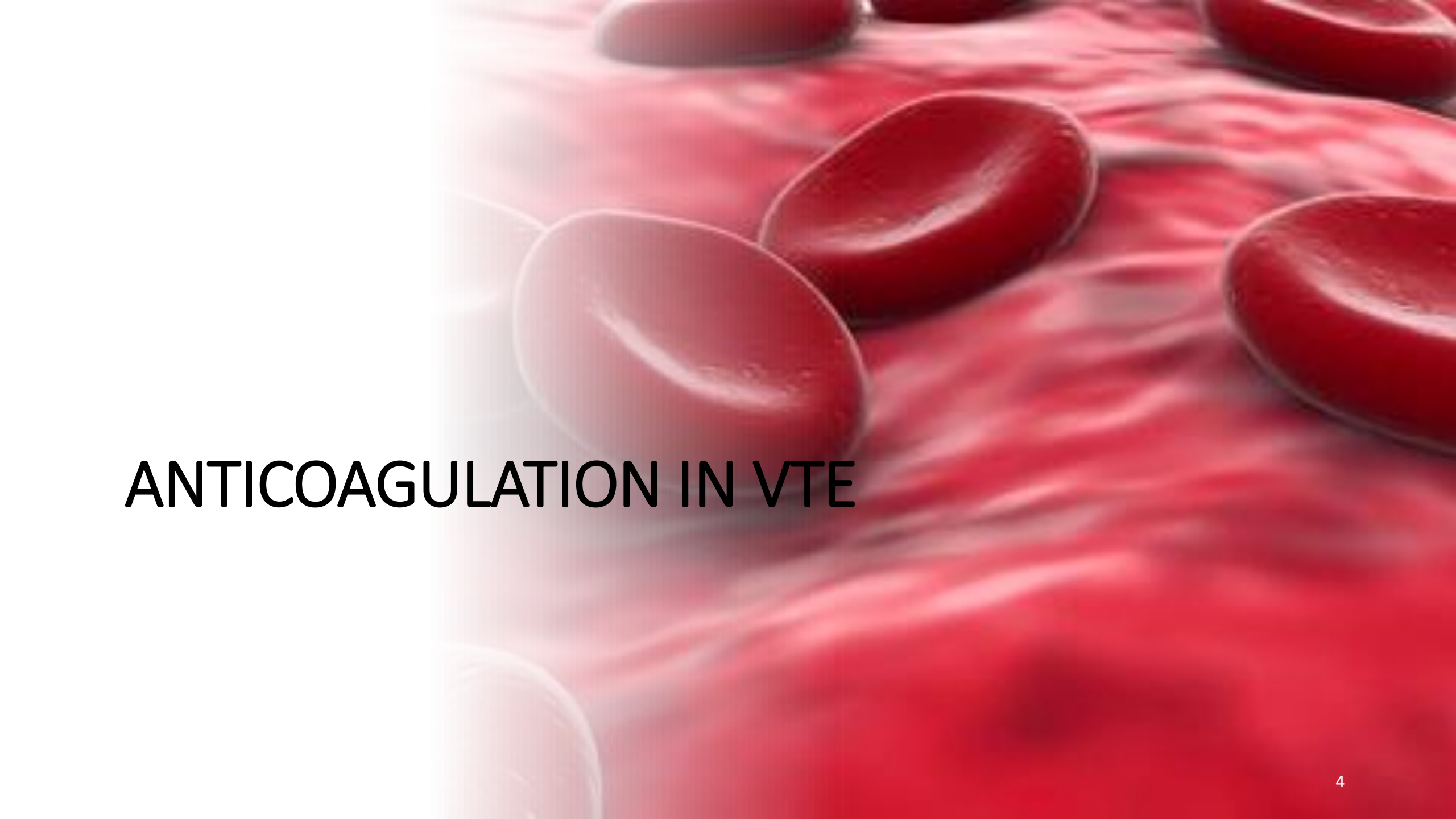
- I have no financial disclosures to share.
- This presentation does discuss off-label use of 4-factor prothrombin complex concentrate.

LEARNING OBJECTIVES:

At the conclusion of this session, the participant should be able to:

1. Describe different options for anticoagulation including the latest guideline updates for treatment of VTE.
2. Review options for anticoagulation reversal.
3. Demonstrate knowledge of the current transfusion guidelines and appropriate transfusion methods.
4. Distinguish transfusion reactions and discuss appropriate work-up.

ANTICOAGULATION IN VTE

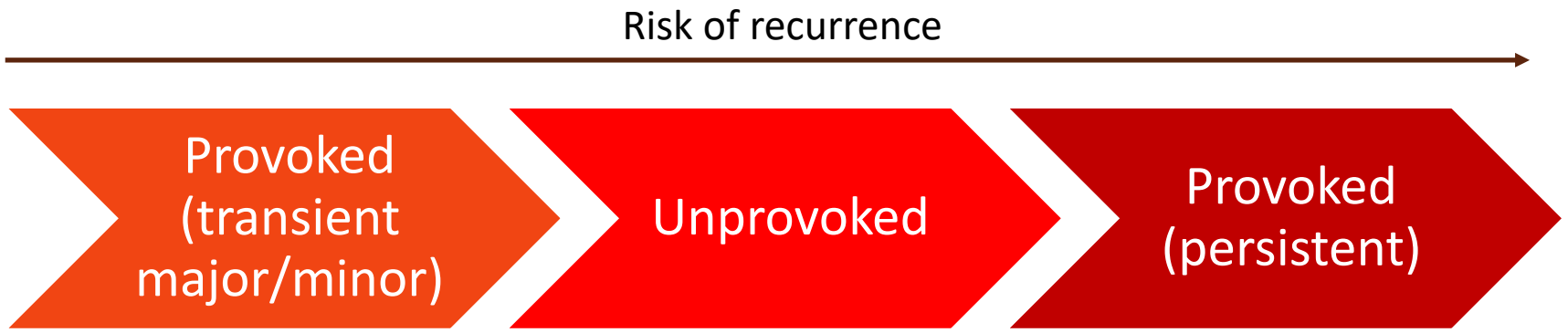


Treating VTE

- Risk stratification
- DOAC vs. parenteral vs. VKA
- Provoked vs. unprovoked
- Risk factors
  - Transient vs. persistent
- Primary vs. secondary treatment

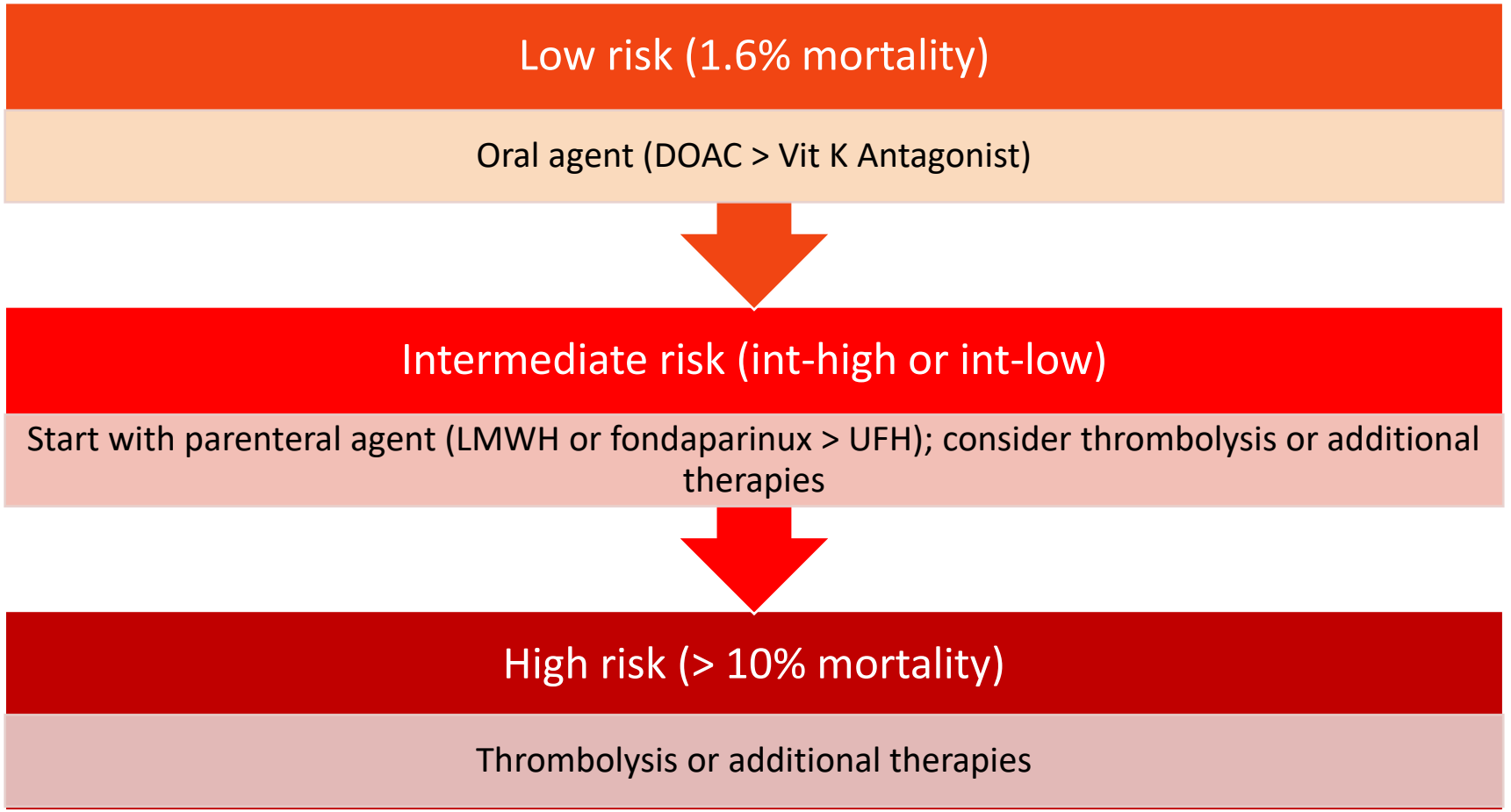
Initial considerations

Additional considerations



2019 ESC Guidelines for DX & Tx of Acute PE[1]

Risk stratify based on PESI (or sPESI) score



Anticoagulant	Mechanism of Action	FDA Approved Usage
Rivaroxaban	Factor Xa inhibitor	• Nonvalvular atrial fibrillation • DVT or PE • Postoperative thromboprophylaxis of DVT with THA or TKA • VTE prophylaxis during/after hospitalization • At risk for recurrent DVT/PE after initial 6-month treatment • Risk reduction for major thrombotic vascular events and cardiovascular events in CAD
Apixaban	Factor Xa inhibitor	• DVT/PE • Nonvalvular atrial fibrillation • Postoperative thromboprophylaxis following hip or knee replacement
Edoxaban	Factor Xa inhibitor	• Nonvalvular atrial fibrillation • DVT/PE following 5-10 days of therapy with parenteral anticoagulant
Betrixaban	Factor Xa inhibitor	• VTE prophylaxis in hospitalized adults who are at risk
Dabigatran	Direct thrombin inhibitor	• DVT /PE following 5-10 days of therapy with parenteral anticoagulant • Nonvalvular atrial fibrillation • Thromboprophylaxis in hip replacement • Risk reduction of recurrence in those previously treated for DVT/PE

**This list does not include the limitations of these medications.

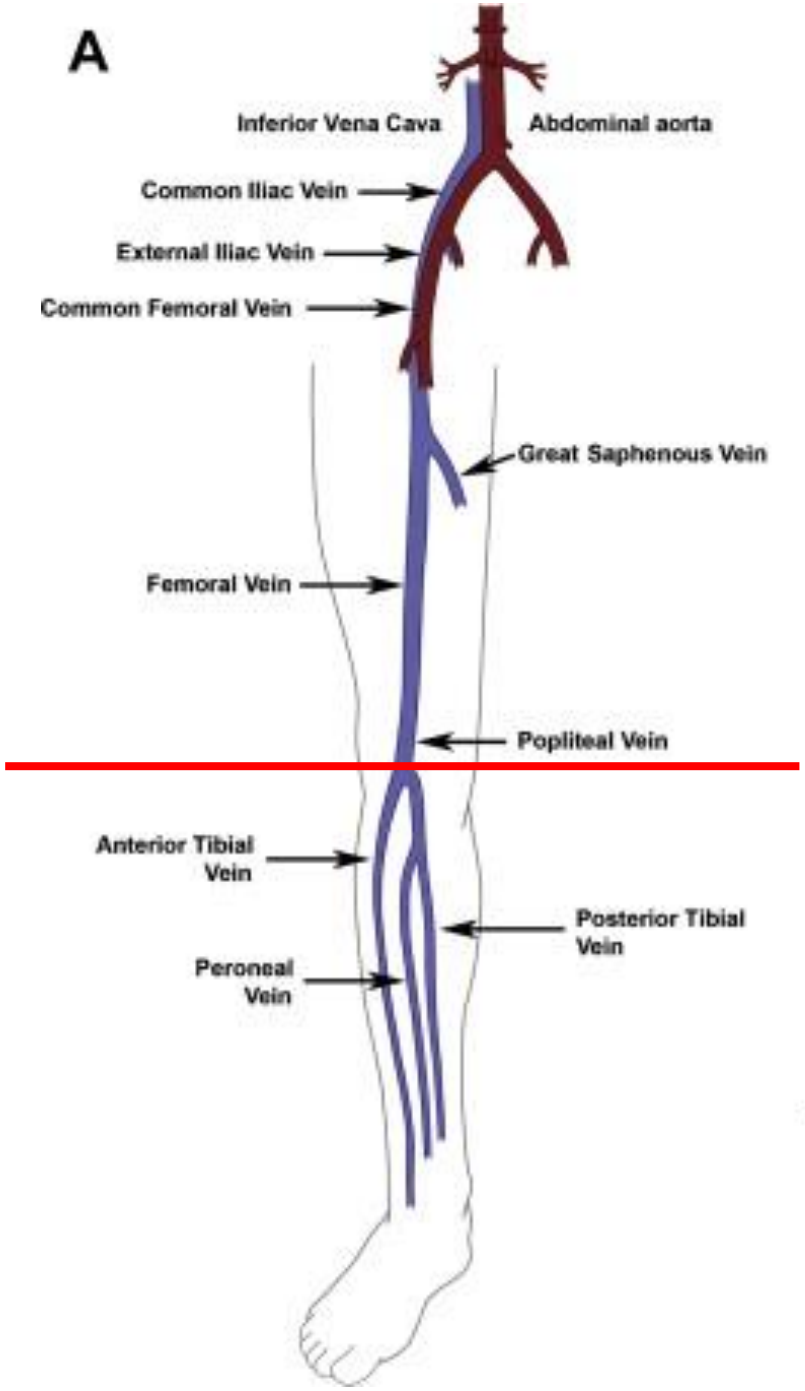
Case #1

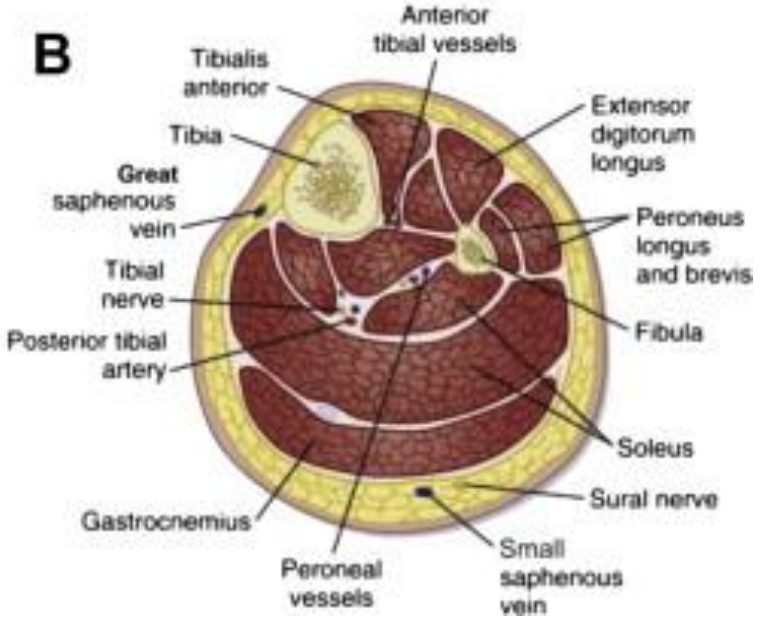
- A 42-year-old healthy female who returned from a 14-day trip to Greece 2 weeks ago presents to the ED with LLE edema and pain in her lower leg/ankle, which began 5 days ago. She denies SOB, CP, or hemoptysis.
- **VS**: T 37.6 C, HR 82, BP 124/86, RR 16, SpO2 98%
- **PE**: Unilateral L leg edema below the level of the knee with mild overlying circumferential erythema and tenderness to palpation
- **US venous duplex LLE:** acute non-occlusive DVT in the peroneal vein

Needleman, Laurence, MD. Published November 1, 2014. Radiology Clinics of North America. Volume 2, Issue 56.

proximal

distal



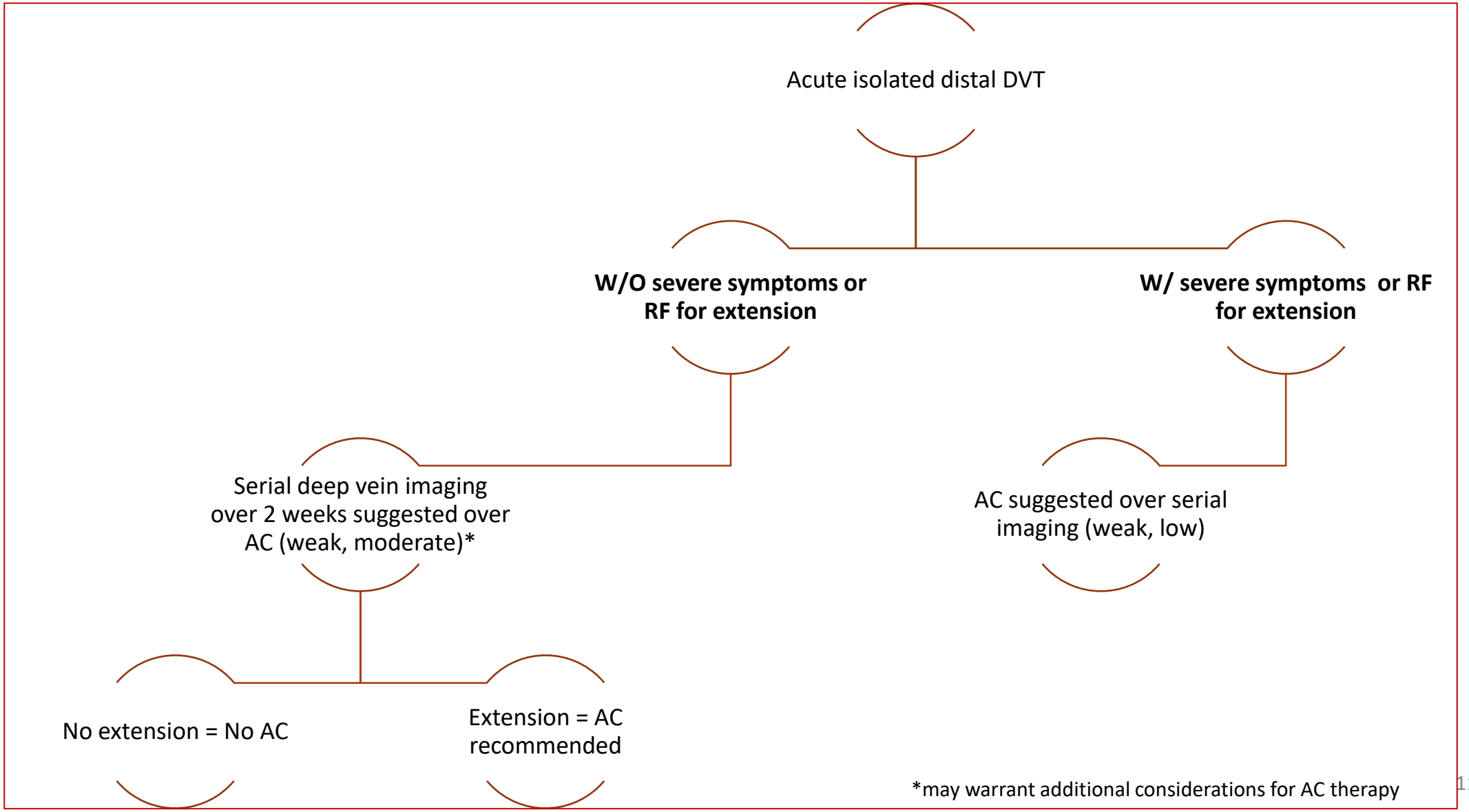


Case #1

How would you manage this patient?

1. Serial ultrasound imaging for 2 weeks
2. Anticoagulant therapy x 3 months
3. IVC Filter
4. Full dose aspirin

Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline [2]



Case #2

- A 56-year-old female with HTN, DM2, and breast CA currently on chemotherapy presents to the ED with pleuritic chest pain and shortness of breath x1 day.
- **VS:** HR 86; BP 126/86; RR 18; SpO2 96% ; T 37.5 C
- **ECG**: Normal sinus rhythm
- **Troponin T:** <0.01 x2
- **CT Angiogram Chest:** acute PE without evidence of RV enlargement or strain

Case #2

Which initial anticoagulant would you choose for this patient?

1. None, high risk for bleed due to cancer.
2. IV unfractionated heparin (UFH)
3. Edoxaban
4. Rivaroxaban

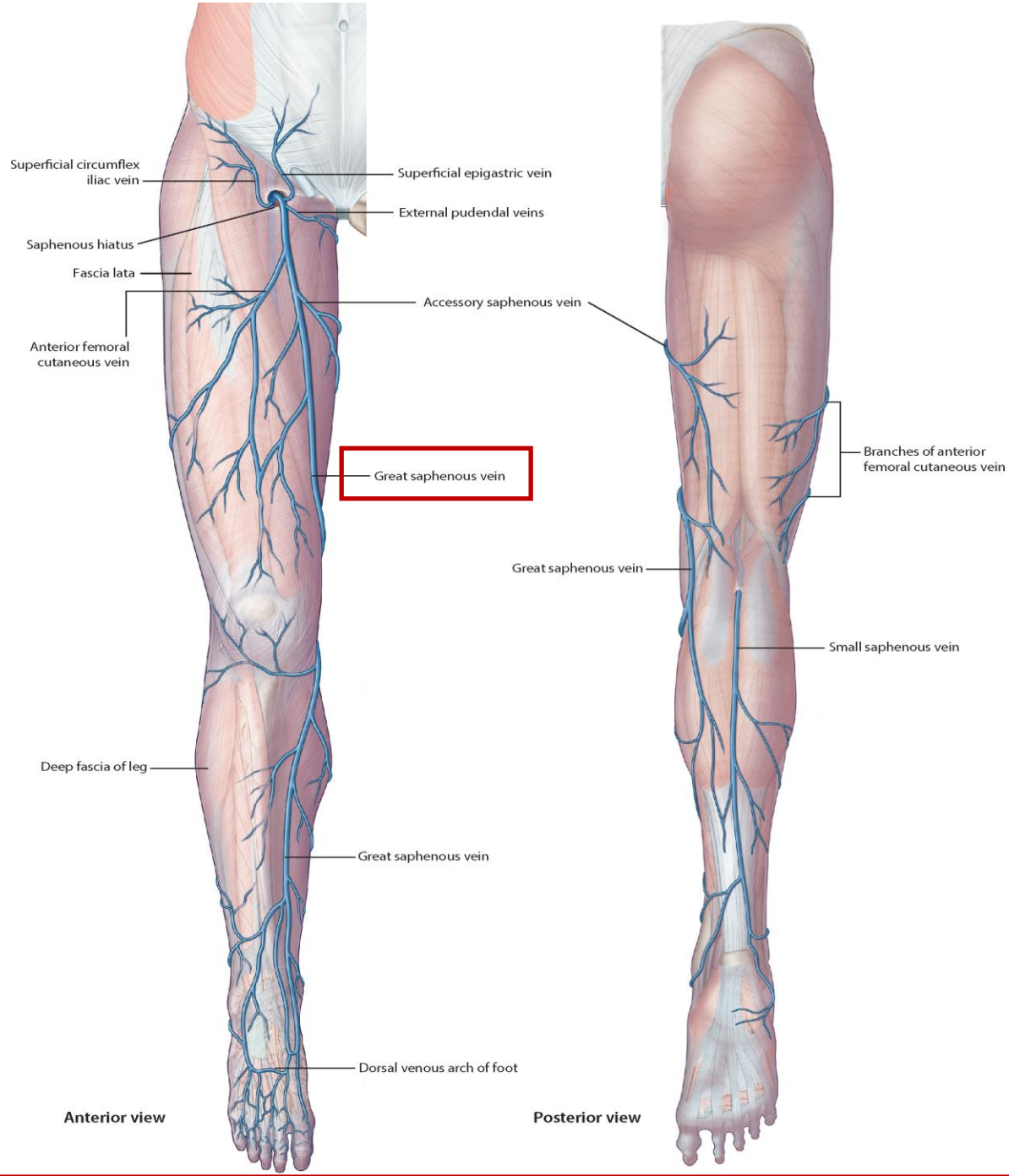
Acute VTE in Malignancy

- **Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline [2]**
  - Oral Xa inhibitor (apixaban, edoxaban, rivaroxaban) recommended OVER LMWH for initiation AND treatment phases
  - Consider apixaban or LMWH in luminal GI malignancies*

Case #3

- A 37-year-old female is admitted with endocarditis 2/2 IV drug use. She is on HD #4. She mentions that the medial aspect of her left knee is very tender to touch, and she has noticed some overlying erythema develop there and into the medial thigh. On exam, a palpable cord is noted extending from just below the knee to the upper medial thigh. She notes a family history of VTE upon further questioning.

- **US duplex LLE:** superficial thrombosis of the great saphenous vein, 8 cm segment, about 6 cm from the sapheno-femoral junction (SFJ)



Drake, Richard L., FAAA; Vogl, A. Wayne, PhD, FAAA; Mitchell, Adam W.M., MBBS, FRCS, FRCR. Published December 31, 2020. Gray's Atlas of Anatomy. Pages 293-384.

Case #3

How would you treat this patient's SVT?

1. Symptomatic treatment, elevation, warm compress
2. ASA 325mg daily x 45 days
3. Fondaparinux 2.5mg daily x 45 days
4. Rivaroxaban 20mg daily x 3 months

Factors that Favor AC Therapy in SVT [2]

- Extensive SVT
- Involvement above the knee/close to saphenofemoral junction
- Severe symptoms
- Involvement of the greater saphenous vein (feeds to deep system)
- Hx of VTE or SVT
- Active cancer
- Recent surgery

CHEST Guideline Update [2]

SVT of the lower limb at increased risk of clot progression to DVT or PE

Anticoagulation with fondaparinux 2.5mg daily (suggested over other AC such as prophylactic or therapeutic LMWH) for 45 days (weak, low certainty);
low dose rivaroxaban alternative (10mg daily x 45 days)*

Thrombosis Canada (2019) [4]

FIGURE 1: APPROACH TO MANAGEMENT OF SVT

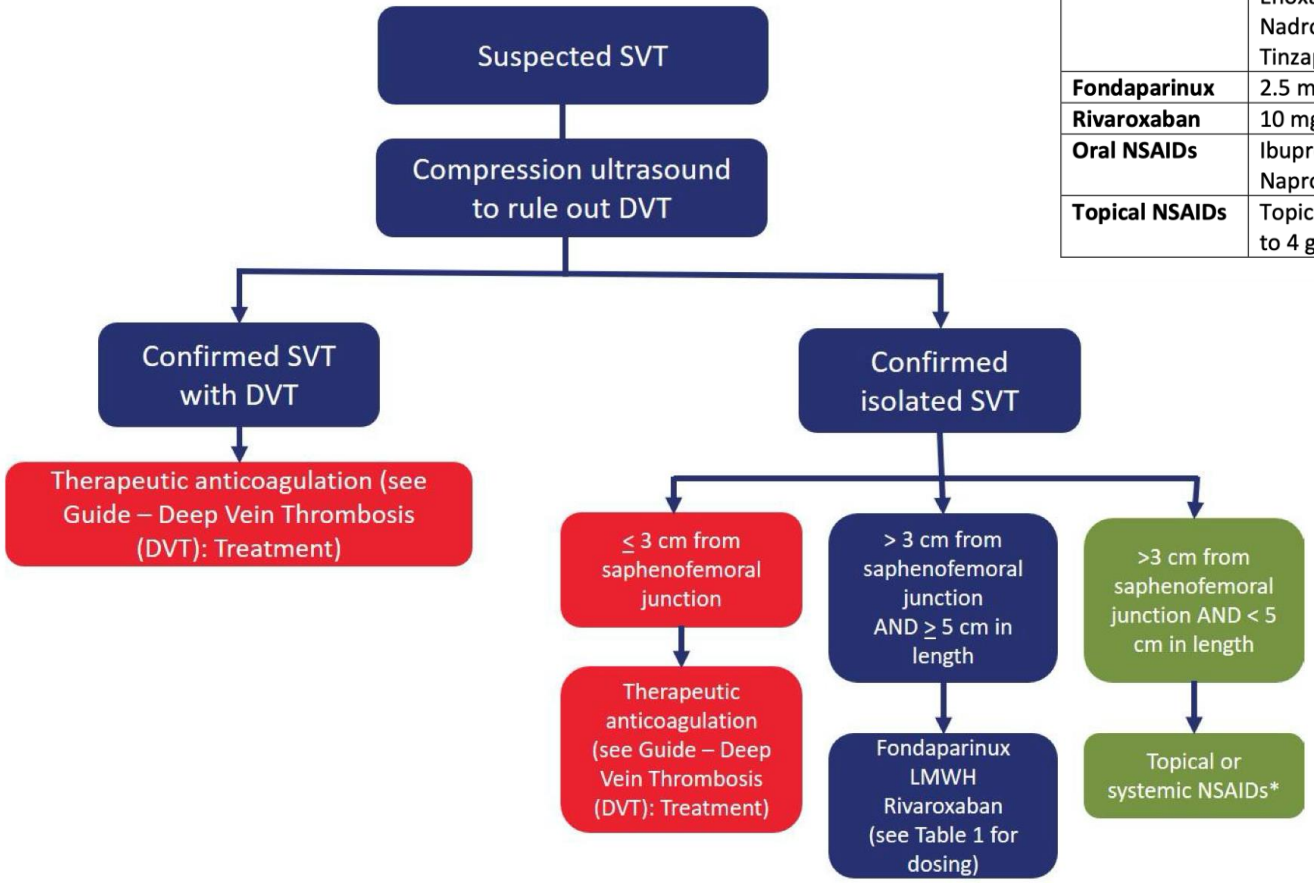


Table 1: Treatment Options for SVT >3cm from SFJ and ≥5 cm in Length

Drug Class	Suggested dosing	Duration of treatment
LMWH	Dalteparin 5,000-10,000 units SC daily Enoxaparin 40-80 mg SC daily Nadroparin 2,850-5,700 units SC daily Tinzaparin 4,500-10,000 units SC daily	45 days
Fondaparinux	2.5 mg SC daily	45 days
Rivaroxaban	10 mg PO daily	45 days
Oral NSAIDs	Ibuprofen 400 mg PO TID Naproxen 500 mg PO BID	7-14 days
Topical NSAIDs	Topical diclofenac [Voltaren Emugel®] apply 2 to 4 g to affected area 3 or 4 times daily	7-14 days

* Prophylactic/intermediate dosing anticoagulation is reasonable for severe symptoms or with risk factors. If not treating or if using topical NSAIDs, monitor for extension with serial U/S

Case #4

- A 72-year-old male with COPD, poorly controlled Type 2 Diabetes, HLD, HTN, and a history of GI bleeds (last one 5 years ago) presents to the ED with progressively worsening shortness of breath x 4 days. He denies increased cough or sputum production and has no recent ill contacts.
- Vitals: HR 102, BP 116/80, RR 22 br/min, SpO2 88%, T 98.8 F
- CXR is (-)
- Viral PCR swabs (-)
- **CTA**: multiple acute pulmonary emboli seen in the right pulmonary artery involving lobar and segmental branches; no evidence of RV strain

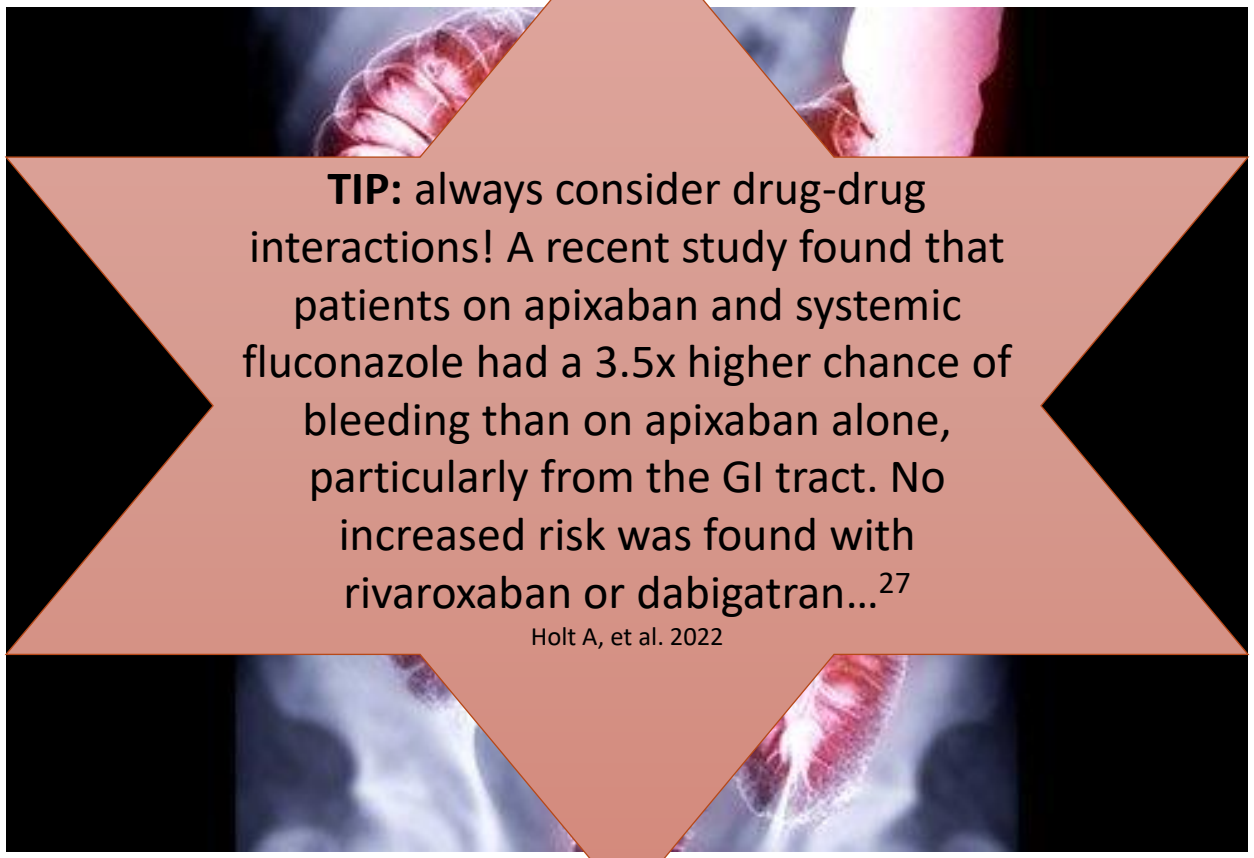
Case #4

You discuss the risks and benefits of certain anticoagulation modalities given his history of GI bleeds. He decides he would like to try a DOAC. Which would you choose for him?

1. Rivaroxaban
2. Apixaban
3. Dabigatran
4. Edoxaban

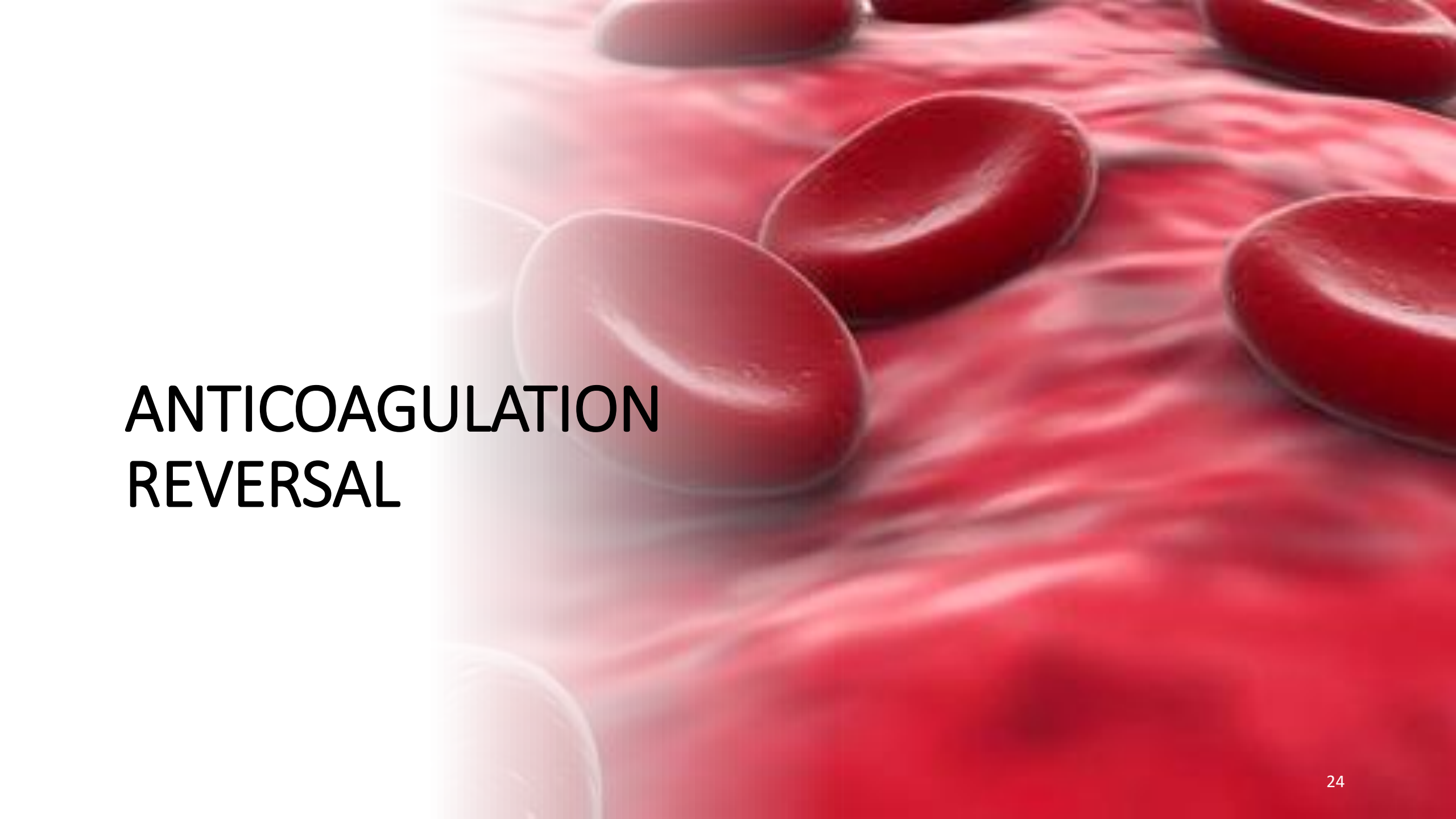
DOACs and GI Bleeding [5-12]

- There is variability among DOACs, with **apixaban** typically showing the safest GI bleed profile.
- Warfarin vs. DOACs?



https://www.emedicinehealth.com/gastrointestinal_bleeding/article_em.htm

ANTICOAGULATION REVERSAL



Case #5

- A 42-year-old male with a recent DVT on **warfarin** presents to the ED. He is found to have an acute abdomen due to a perforated diverticulum. He requires emergent surgery. His INR is 3.5.

https://blog.makersacademy.com/keeping-my-hand-off-the-panic-button-75a3bc67da55

Case #5

What is the most appropriate reversal agent for this patient?

1. Fresh Frozen Plasma (FFP)
2. IV Vitamin K + FFP
3. Cryoprecipitate
4. IV Vitamin K + 4-Factor Prothrombin Complex Concentrate (4F-PCC)

Prothrombin Complex Concentrates (PCC)

- **4-Factor PCC FDA Approved Indication:** Urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonist therapy in adult patients with acute major bleeding or need for urgent surgery/invasive procedure

- Co-administration with vitamin K

- Not studied in patients with thromboembolic events in last 3 mo.

3-Factor	4-Factor
II, IX, X	II, IX, X
	VII
	Protein C&S

4F-PCC Dosing

- Warfarin Reversal

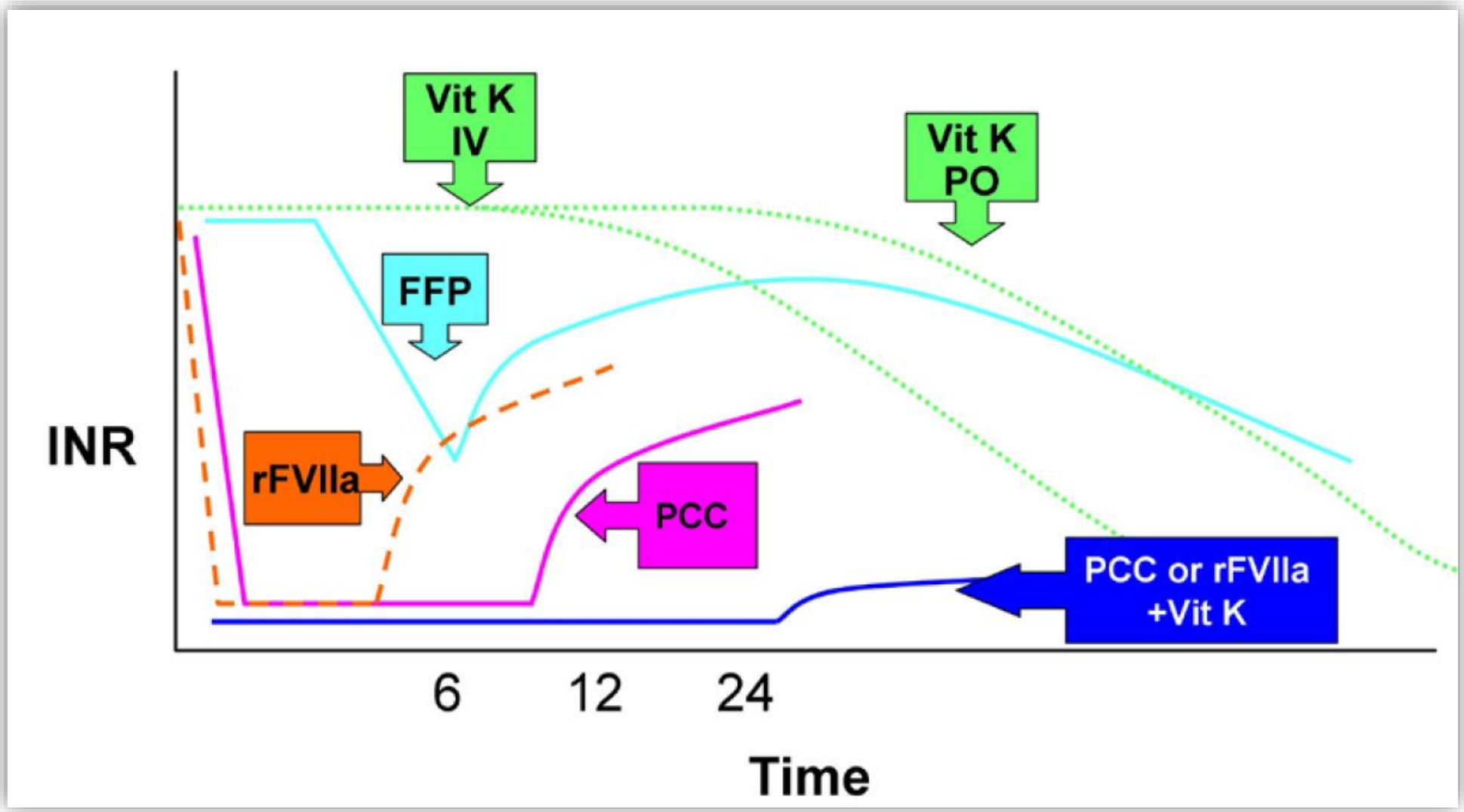
Baseline INR	Kcentra dose (units of factor IX/kg)	Maxi (units
2 - <4	25	Do not exceed
4 - 6	35	Do not exceed
> 6	50	Do not exceed 5

Update: Published March 2022, the PROPER3 trial found that fixed vs. variable dosing had similar outcomes in achieving effective hemostasis and lowering INR, and time to treatment was **shorter** with fixed dosing. [28]

Abdoellakhan RA, et al. 2022.

- DOAC reversal (OFF-LABEL)
  - 50 units/kg
- Max dose (warfarin or DOAC) = Do not exceed 5000 units

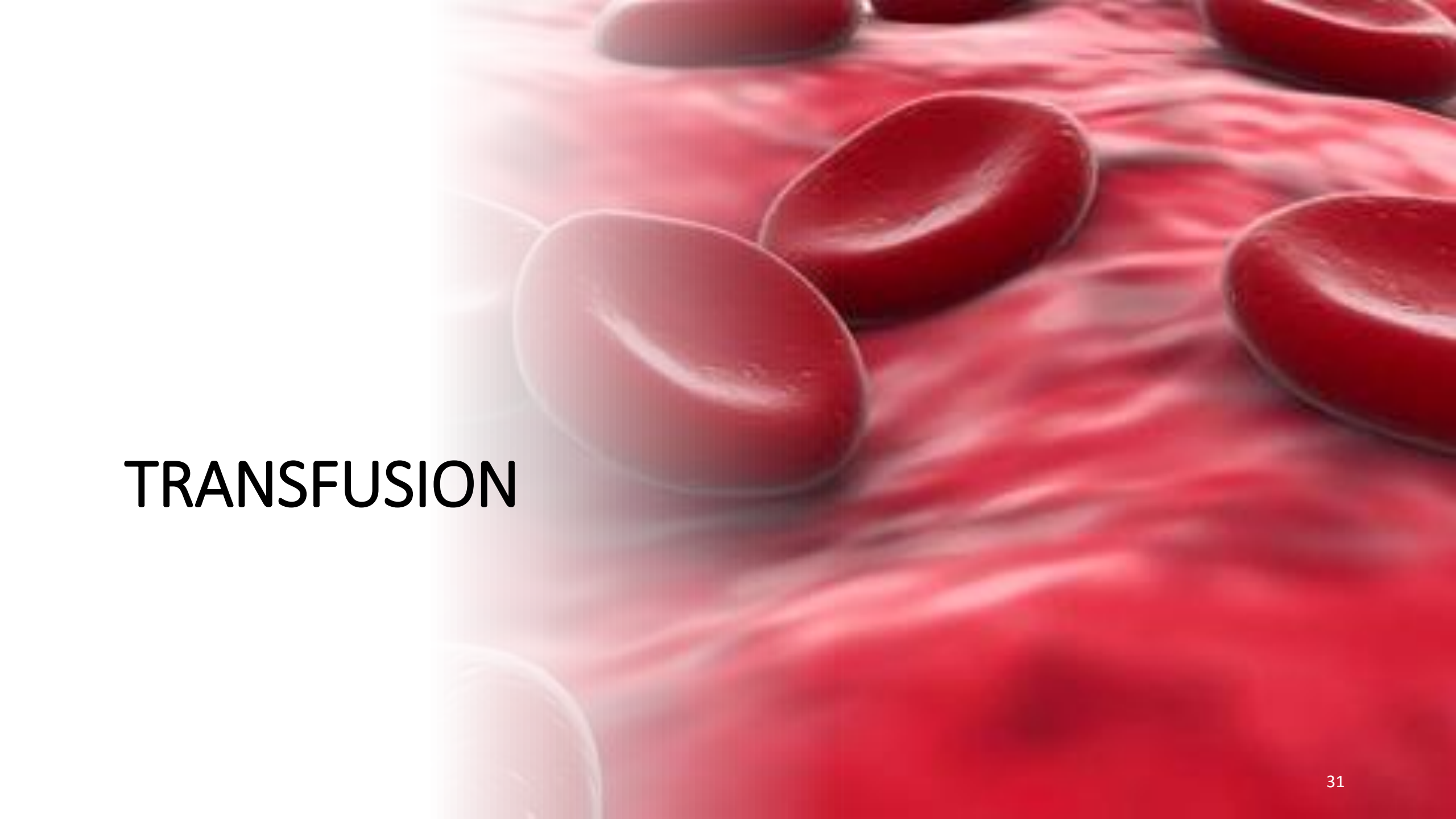
Reversal Agent Onset of Action



Targeted Anticoagulation Reversal

Anticoagulant	Reversal Agent
Unfractionated heparin	Protamine sulfate
Low molecular weight heparin	Protamine sulfate
Warfarin	4F-PCC Vitamin K
Dabigatran	Idarucizumab
Rivaroxaban Apixaban (edoxaban and betrixaban off-label)	Andexanet alfa

TRANSFUSION



Case #6

- A 70-year-old female who is on chemotherapy for lung cancer presents with a hemoglobin of 6.2 g/dL. She is hemodynamically stable and asymptomatic. There are no signs of active bleeding. She has no history of cardiac disease.

Case #6

How many units of PRBCs would you transfuse?

1. None
2. 1 u PRBCS
3. 2 u PRBCs
4. 3 u PRBCs

Thresholds for PRBC Transfusion[15-17]

Indication	Threshold*
Stable, asymptomatic hospitalized/ICU adult	Transfuse < 7g/dL
Stable asymptomatic CAD	Transfuse < 8g/dL; consider more liberal approach based on patient
ACS	Transfuse < 8g/dL; consider if between 8-10g/dL
Orthopedic surgery, asymptomatic	Transfuse < 8g/dL
Cardiac Surgery	Transfuse < 7.5-8g/dL may be safe in cardiac surgery
Acute blood loss	No threshold designated

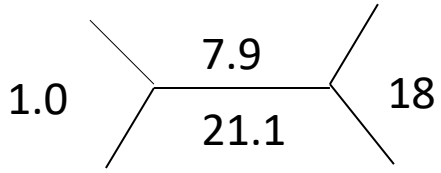
Always consider the individual patient's circumstances!

*sources may vary, cross-referencing multiple guidelines encouraged

Case #7

- A 68-year-old male who is on chemotherapy for pancreatic cancer presents septic in the setting of cholangitis.

- His CBC:



Case #7

Would you transfuse him platelets, and if so, how many units?

1. No transfusion
2. 1 unit of platelets
3. 2 units of platelets
4. 3 units of platelets

Relative Thresholds for Prophylactic Platelet Transfusion [18-22]

Threshold*	Indication
10,000/µL	Stable, non-bleeding patient; malignancy
20,000-30,000/µL	Risk factors for bleeding; Central venous catheter insertion (20,000) - Fever, sepsis, DIC or other conditions leading to increased platelet consumption
50,000/µL	Most bleeding; Most major surgical procedures; Endoscopy; Lumbar Puncture; Concurrent therapeutic anticoagulation
100,000/µL	Neurosurgical/ophthalmologic procedures; CNS bleeding

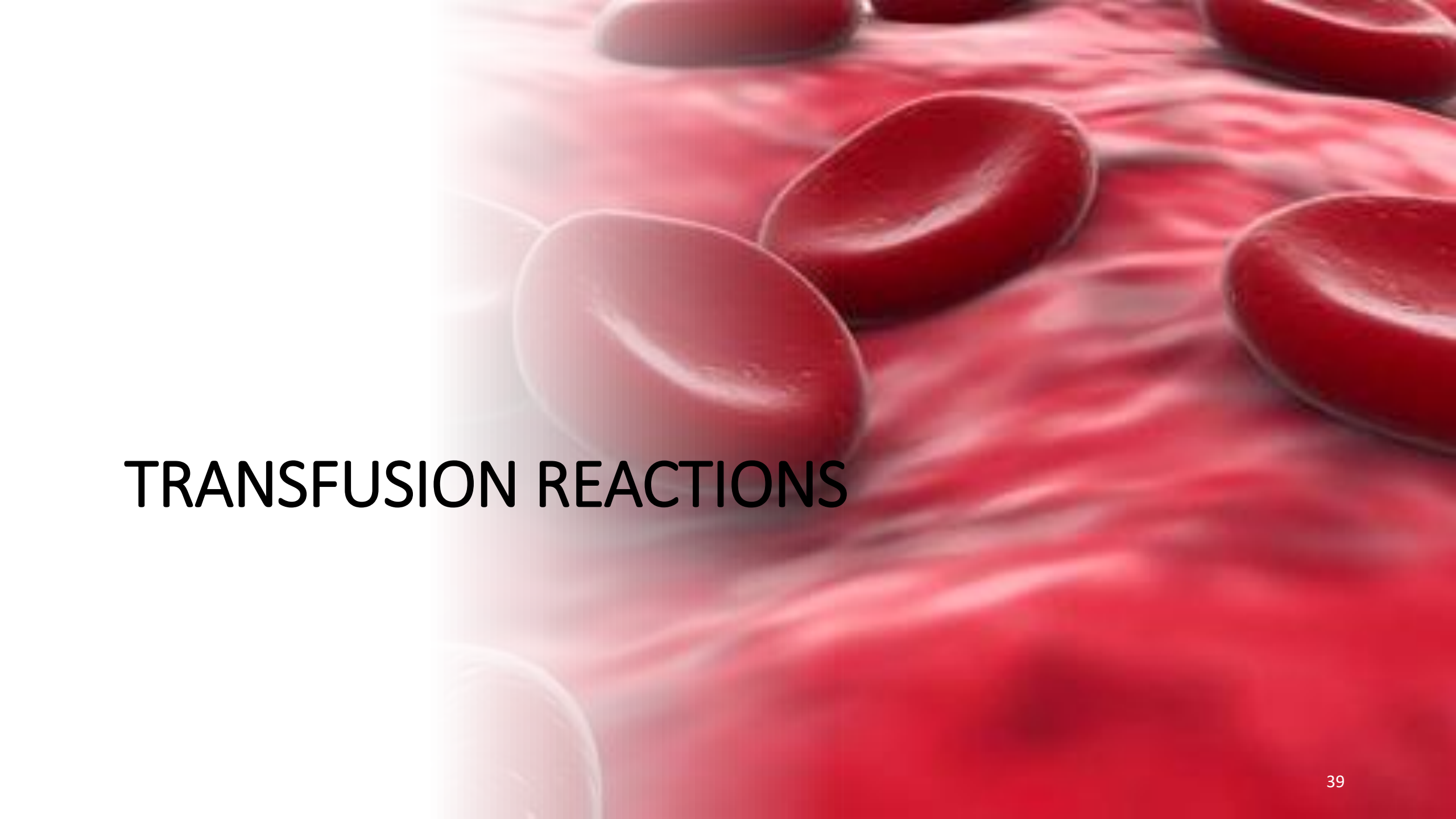
*relative thresholds, evidence may vary between sources

Patient Blood Management Programs

- Optimizing care of patients who may need transfusion and helping curb the blood supply shortage in 3 ways:
  - Optimize hematopoiesis
  - Minimizing blood loss and bleeding
  - Optimizing tolerance/treatment of anemia

- PBM piloted in an 8-year program[26]
  - Cost savings: $7 million
  - Shortened LOS by 15%
  - 22% reduction in allogenic units transfused
  - Adverse events reduced

- High Value Academic Practice Alliance has established a “blueprint” for hospitals to use



TRANSFUSION REACTIONS

Case #8

- A 73-year-old female with a history of iron deficiency anemia is receiving 1U PRBCs for a hemoglobin of 6.2 g/dL. About 30 minutes into the transfusion, she develops a fever of 38.4 C and rigors. Her temperature continues to increase over the next 20-30 minutes though the transfusion was stopped.

Case #8

What should the next course of action be?

1. Stop the transfusion, give antipyretic, submit a transfusion workup, and attempt to rule out hemolytic or bacterial cause.
2. Stop the transfusion, give demerol, and rule out hemolysis.
3. Continue the transfusion and administer antipyretic.
4. Call the blood bank for a new unit of PRBCs and give antipyretics and antibiotics in the meantime.

Transfusion Reactions

Immunologic reactions:

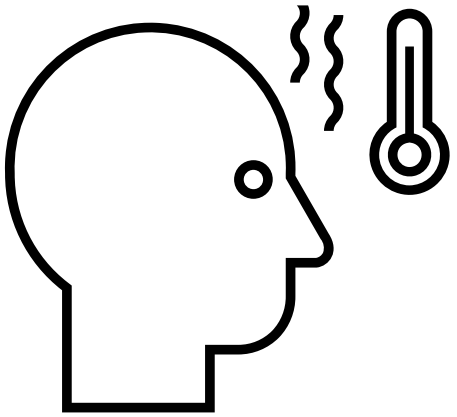
- Febrile (nonhemolytic) reactions
- Allergic reactions
- Hemolytic transfusion reactions
- Transfusion-related acute lung injury (TRALI)
- Urticaria
- Anaphylaxis

Non-immunologic reactions:

- Iron overload
- Transfusion-associated circulatory overload (TACO)
- Transfusion-associated sepsis

Fevers in Transfusion

- Fever =
  - Underlying medical condition
  - Febrile (nonhemolytic) reaction
  - Hemolytic transfusion reaction
  - Transfusion associate lung injury (TRALI)



Febrile (nonhemolytic) Transfusion Reaction

- Fever
  - Fever (38 °C) and/or ≥ 1°C increase in pre-transfusion temp during or within 4 hours of transfusion completion and/or chills/rigors
  - May be accompanied by nausea, HA
- Consider:
  - Underlying medical condition, bacterial contamination, hemolytic reaction
- Premedication?
  - Antipyretics
  - Diphenhydramine
- 0.1 – 1 %

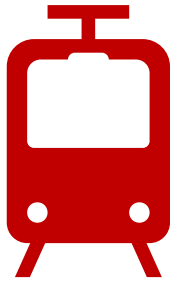
Febrile Hemolytic Transfusion Reaction

- **Clinical presentation:**
  - Fever, chills
  - Hemoglobinuria/Dark urine
  - Severe hypotension
  - Severe flank pain
  - Pain at infusion site
  - Chest tightness
  - DIC (oozing from IV site)
  - N/V/D

TRALI

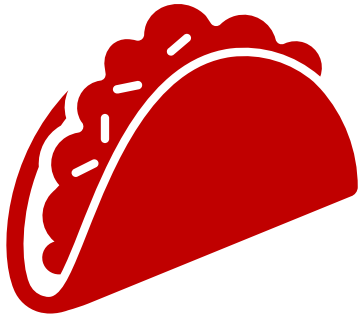
- Reaction between patient's WBC and donor's antibodies
- Neutrophils cause acute lung injury
- Onset of acute lung injury within 6 hours of transfusion cessation, radiographic evidence of bilateral infiltrates, hypoxemia, no evidence of left atrial hypertension, no evidence of ALI prior

- 0.01 – 1.12%, likely under-reported



TACO

- Pulmonary edema due to volume excess or circulatory overload (hydrostatic)
- Large volume of product over short period of time
- At least 3 within 6 hours of transfusion: acute respiratory distress, evidence of positive fluid balance, elevated BNP, radiographic pulmonary edema, evidence of L heart failure, elevated CVP



- 1-8%, but probably under-reported

In Summary…

- Treatment of VTE requires consideration of multiple aspects
  - Risk factors, provocation, location, etc.
- DOACs increasingly supported over other forms of AC
- Consider the timing of onset, effects of reversal agents when deciding which is best for your patient
- Transfuse wisely
  - Base on specific indications
  - Be on the lookout for transfusion reactions
- Consult your local hematologist/transfusion medicine specialist

Questions?

Email: jalabast@msu.edu

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