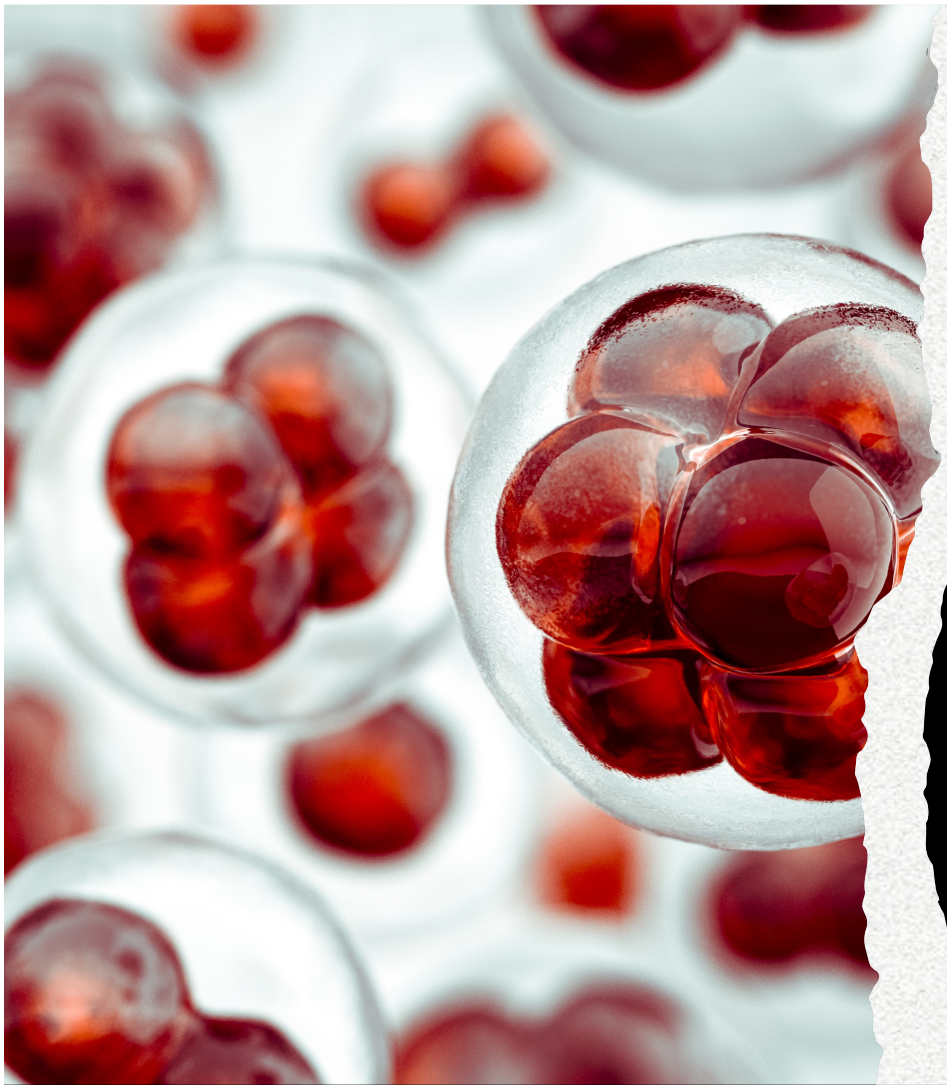


Cases in Anticoagulation and Transfusion Medicine

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.

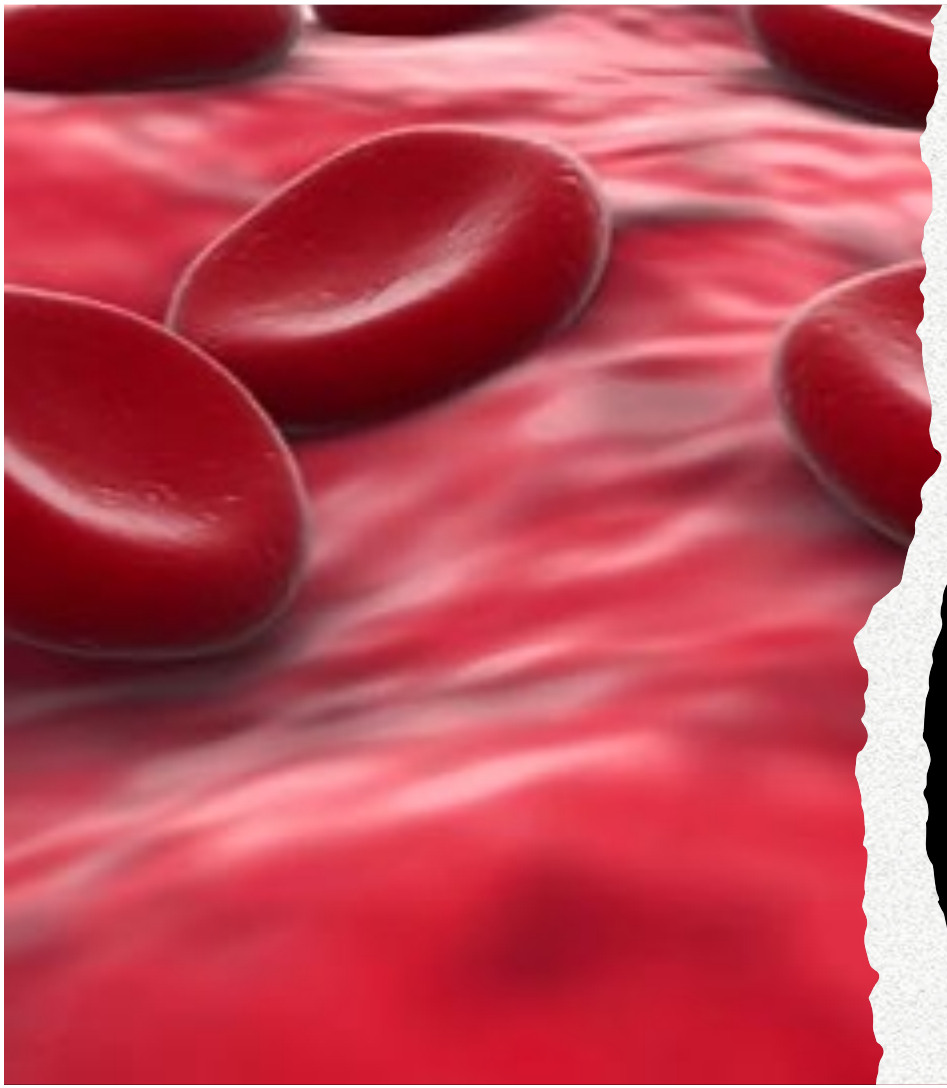
LEARNING OBJECTIVES:

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

1. Explore different options for anticoagulation, including the latest guideline updates for treatment of VTE.

2. Discuss a patient-centered approach to choosing the appropriate anticoagulation method.

3. Analyze options for anticoagulation reversal.



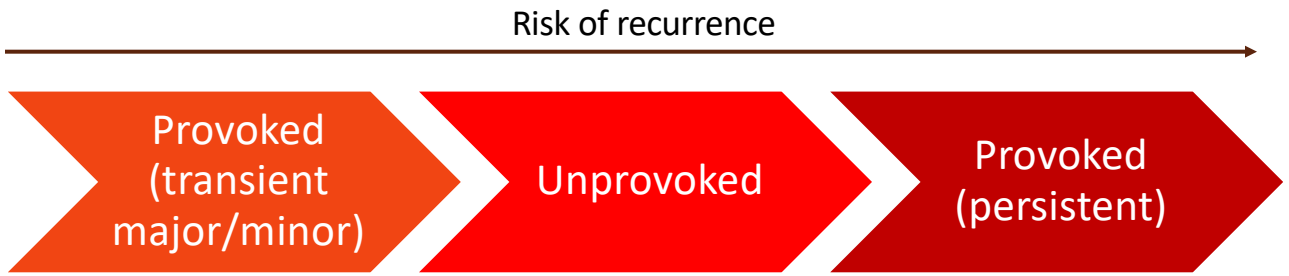
ANTICOAGULATION IN VTE

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



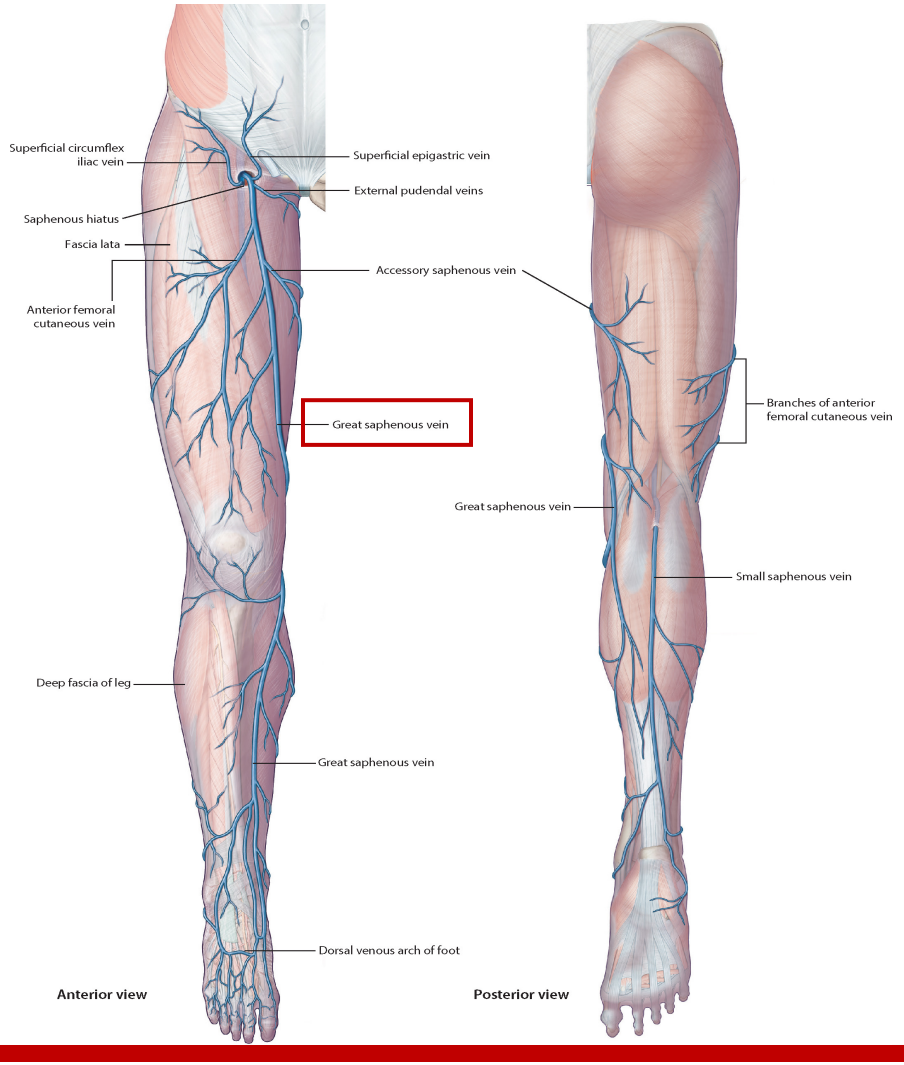
Anticoagulant	Mechanism of Action	FDA Approved Usage
Rivaroxaban	Factor Xa inhibitor	• Nonvalvular atrial fibrillation • DVT or PE • Postoperative thromboprophylaxis of DVT with THA or TKA • VTE prophylaxis during/after hospitalization • At risk for recurrent DVT/PE after initial 6-month treatment • 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 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.

- **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.

How would you treat this patient's SVT?

0

Symptomatic treatment, elevation, warm compress

0%

ASA 325mg daily x 45 days

0%

Fondaparinux 2.5mg daily x 45 days

0%

Rivaroxaban 20mg daily x 3 months

0%

Case #1

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

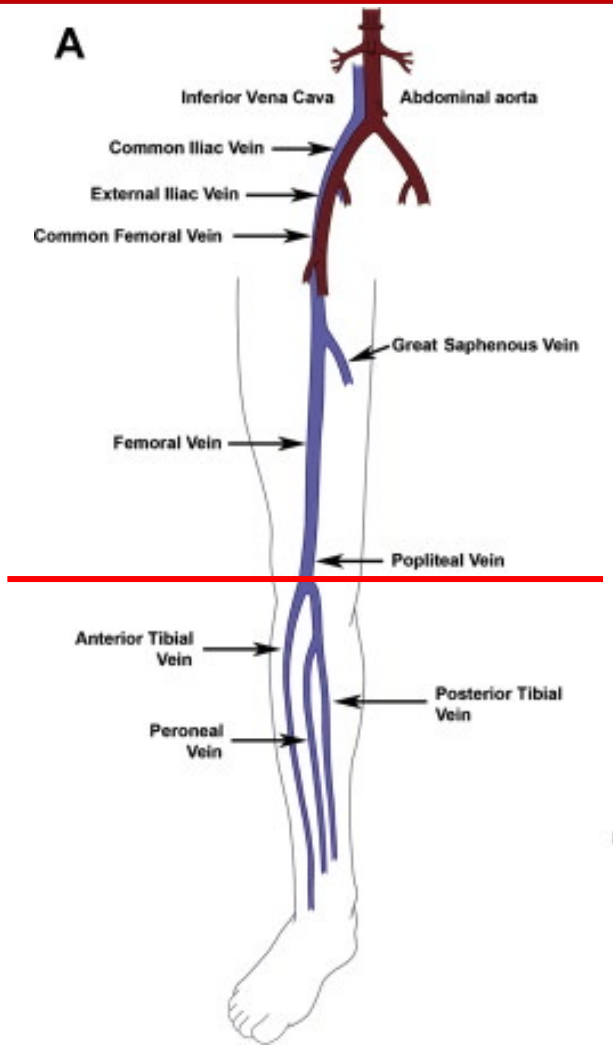
CHEST Guideline Update [2]

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)*

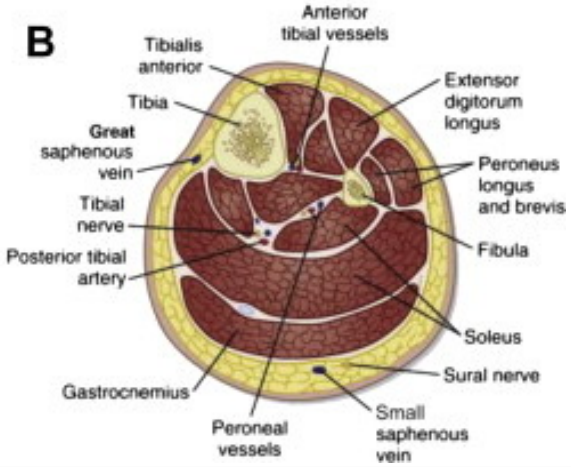
Case #2

- A 22-year-old female with obesity and tobacco use presents with pain in her left lower extremity. She has felt tightness in her calf and noticed the area looks quite swollen. She denies any history of VTE, recent travel, shortness of breath, hemoptysis, or chest pain. She notes that the only recent change to her medical history is that she recently started oral contraceptive pills.
- **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 posterior tibial vein



proximal

distal



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

How would you manage this patient?

0

Serial ultrasound imaging for 2 weeks

0%

Anticoagulant therapy x 3 months

0%

IVC Filter

0%

Full dose aspirin

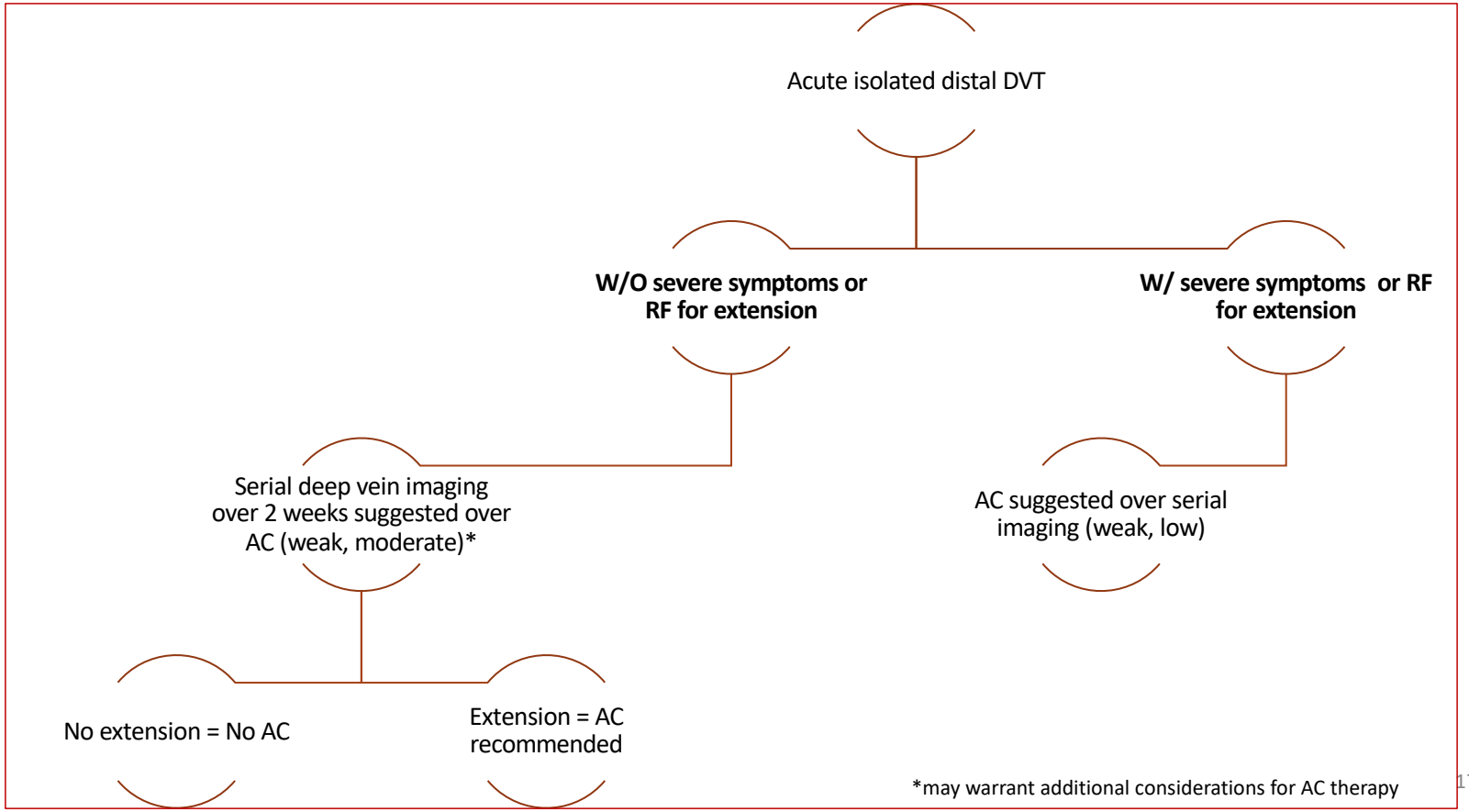
0%

Case #2

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]



DVT Propagation

- 25% of isolated calf DVTs will extend into more proximal deep veins
- Estimated that 50% of those will embolize, resulting in PE
- Complication and mortality rates much higher from PE than DVT…

Risk Factors for DVT

- Acquired vs. Inherited
- Over 50% of patients with DVT have >1 acquired risk factor
- Inherited risk factor + acquired risk factor → increases risk for DVT by an odds ratio up to >80
  - Odds ratio dependent on underlying risk
- Estimated first-time VTE risk is an annual incidence of 0.1%
- >1 million per year in the United States

Risk Factors for DVT

Acquired

- Surgeries
- Trauma
- Immobilization
- Older age (60+ rate rises to 1%)
- Pregnancy
- Smoking
- Obesity
- Long travel?
- Prior VTE…10-year recurrence rate after first DVT of 25%
- Malignancy
- Antiphospholipid antibody syndrome
- Chronic medical conditions – CKD, heart failure, HTN, polycythemia vera, IBD, PCOS, DM, etc…
- Sepsis or acute illness
- Drugs – OCPs, HRT, steroids, tamoxifen, testosterone, heparin, IV drug use, etc…

Inherited

- Factor V Leiden mutation
- Prothrombin gene mutation
- Protein C deficiency
- Protein S deficiency
- Antithrombin deficiency
- Dysfibrinogenemia
- Factor XII deficiency
- Hyperhomocysteinemia
- Non-O blood group

Relative Risk of VTE

Table 1
Selected conditions and associated relative risks for venous thromboembolism

Condition	Approximate Relative Risk
Antithrombin deficiency	25
Protein C or S deficiency	10
Factor V Leiden mutation	Heterozygous: 5; homozygous: 50
Prothrombin gene mutation	2.5
Major surgery or trauma	5–200
History of VTE	50
Antiphospholipid antibodies	2–10
Cancer	5
Medical illness with hospitalization	5
Age >50	5
Age >70	10
Pregnancy	7
Estrogen	OCPs: 5; hormone replacement: 2
Estrogen chemotherapy	Tamoxifen: 5; raloxifene: 3
Obesity	1–3
Hyperhomocysteinemia	3
Elevated factors VIII, IX or X (>90th percentile)	2.2–3

Data from Bates SM, Ginsberg JS. Clinical practice. Treatment of deep-vein thrombosis. N Engl J Med 2004;351(3):268–77.

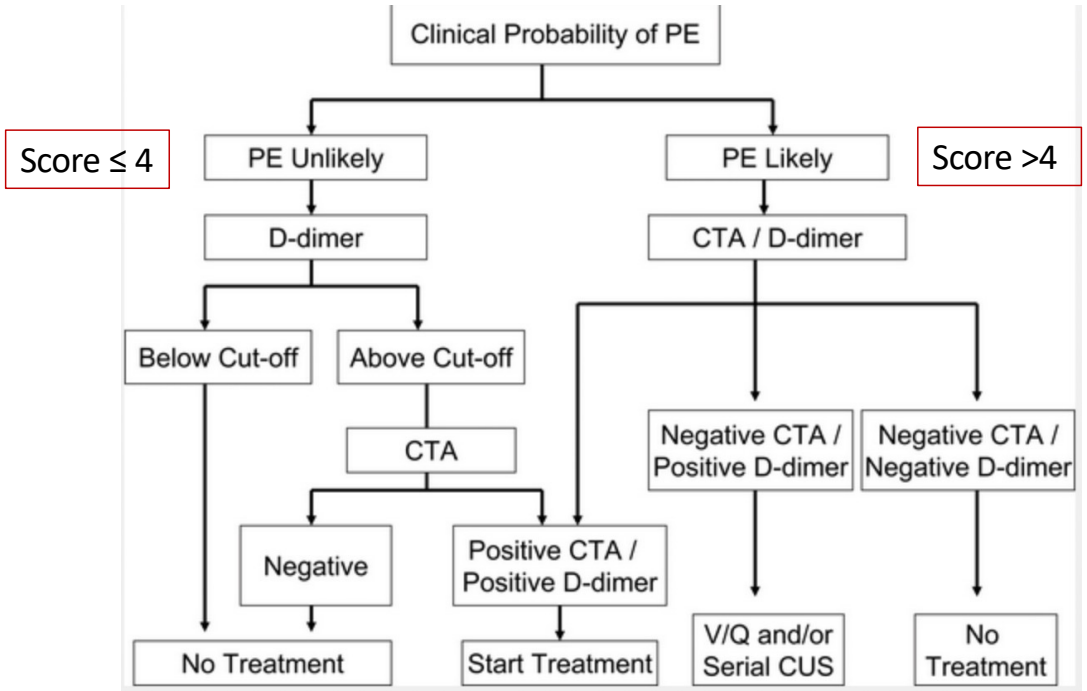
Risk Stratification

- Wells scoring system for DVT + D-dimer testing/duplex ultrasound
- D-dimer – sensitive (94% on ELISA) but not specific
- Duplex ultrasound – specificity 94%, sensitivity 90%
  - Bedside ultrasound performed by physicians – variability from study to study, sensitivity ranging from 66-100%

Case #3

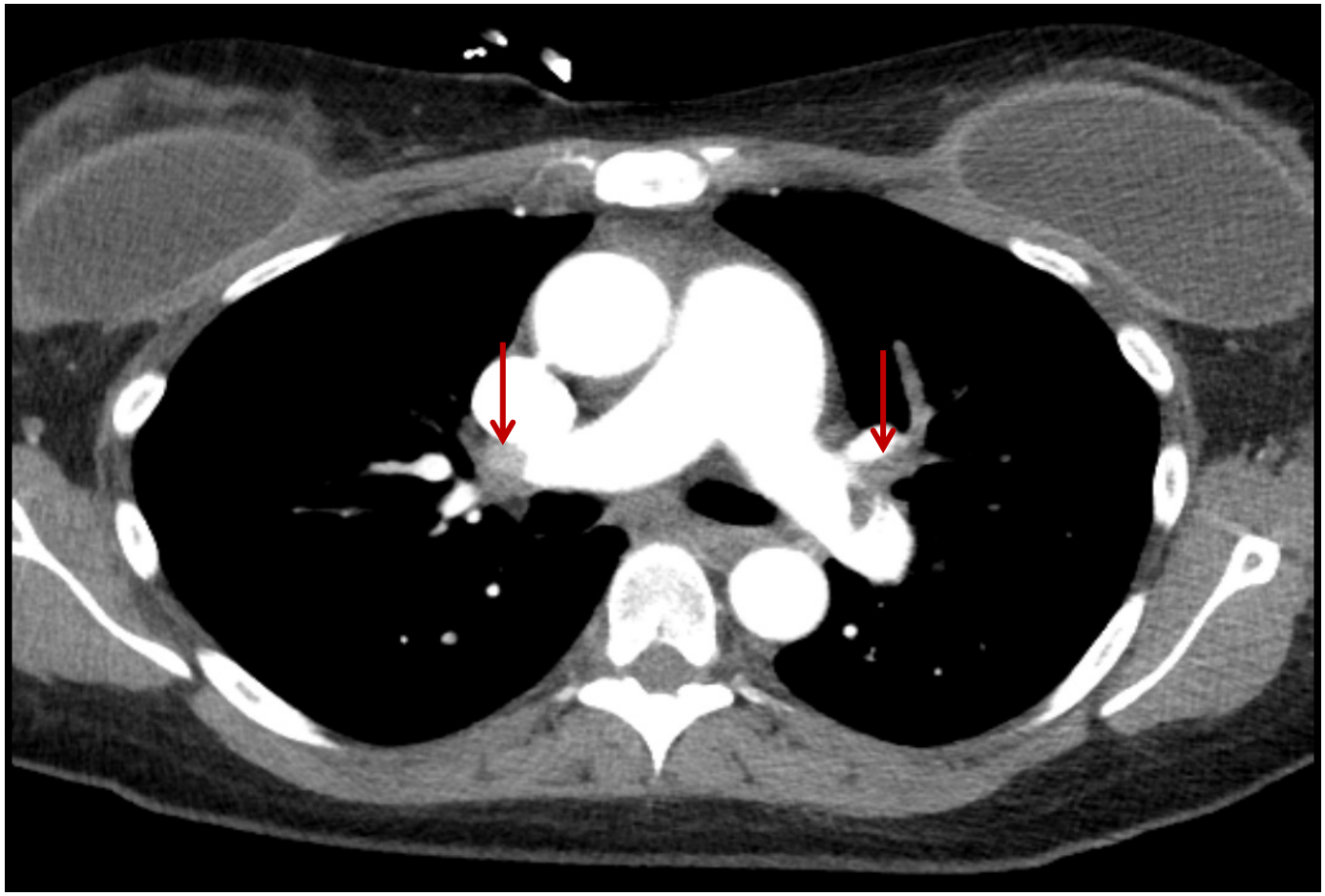
- A 72-year-old male with HTN, DM type 2, COPD, and lung cancer (on active chemotherapy) presents with chest pain and shortness of breath x 2 days.
- **VS:** HR 110; BP 126/86; RR 18; SpO2 96% ; T 37.5 C
- **ECG**: Sinus tachycardia without ST-T wave changes
- **CXR:** No acute cardiopulmonary abnormalities
- **Troponin T:** <0.01 x2
- **CT Angiogram Chest:** …

Wells Criteria for PE



Our patient:

- Malignancy +1
- HR > 100 +1.5
- PE is #1 dx or equally likely +3
- Score = 5.5



CT Angiogram Chest:
Multiple acute pulmonary emboli involving all lobar and segmental branches, with features of pulmonary artery hypertension and right ventricular strain.

Which initial anticoagulant would you choose for this patient?

0

None, high risk for bleed due to cancer

0%

IV unfractionated heparin (UFH)

0%

Edoxaban

0%

Rivaroxaban

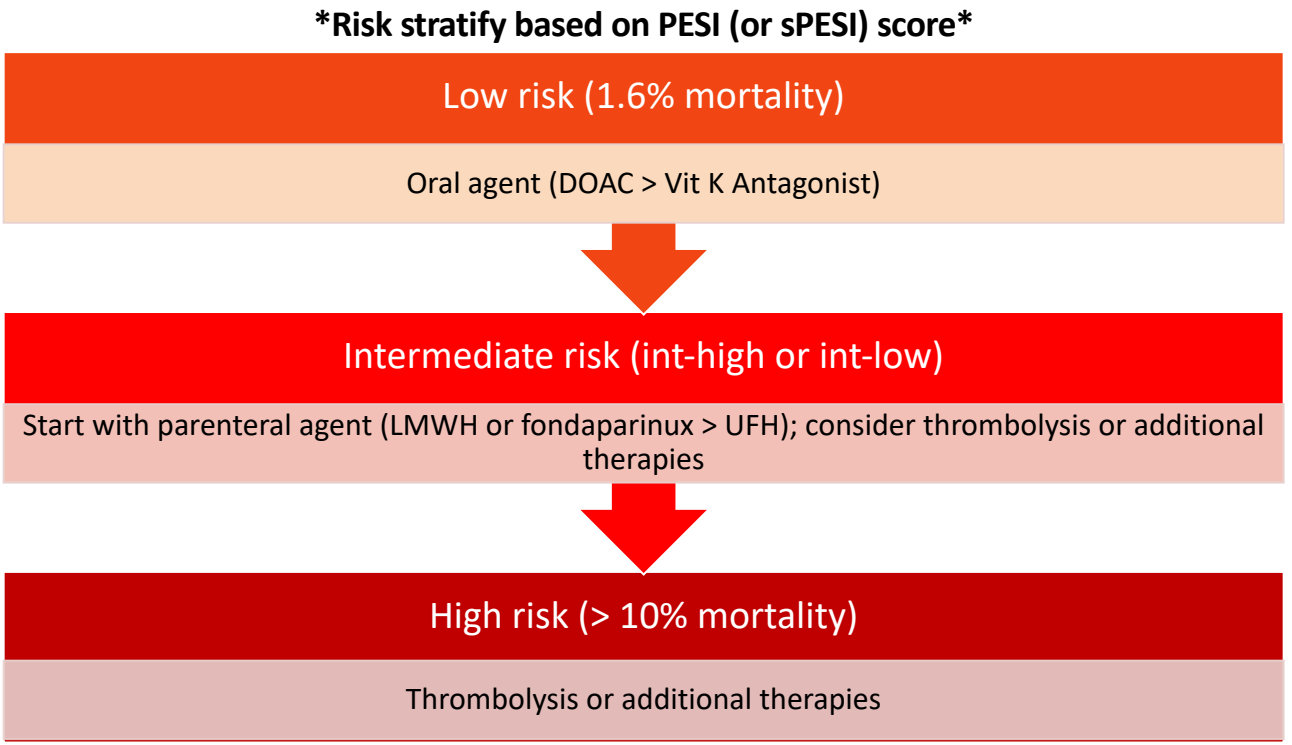
0%

Case #3

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

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



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 #4

- A 68-year-old female with HTN, HLD, osteoporosis, and ulcerative colitis with a history of severe GI bleeds (last one 5 years ago) presents to the ED with progressively worsening shortness of breath x 4 days. She denies increased cough or sputum production and has no recent ill contacts.
- **Vitals:** HR 100, BP 96/70, RR 22 br/min, SpO2 86%, T 98.8 F
- **CXR:** no acute cardiopulmonary abnormalities
- **Viral PCR swabs:** negative
- **Age-adjusted D-dimer**: 882 µg/L
- **CTA**: multiple acute pulmonary emboli seen in the right pulmonary artery involving lobar and segmental branches; no evidence of RV strain

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?

0

Rivaroxaban

0%

Apixaban

0%

Dabigatran

0%

Edoxaban

0%

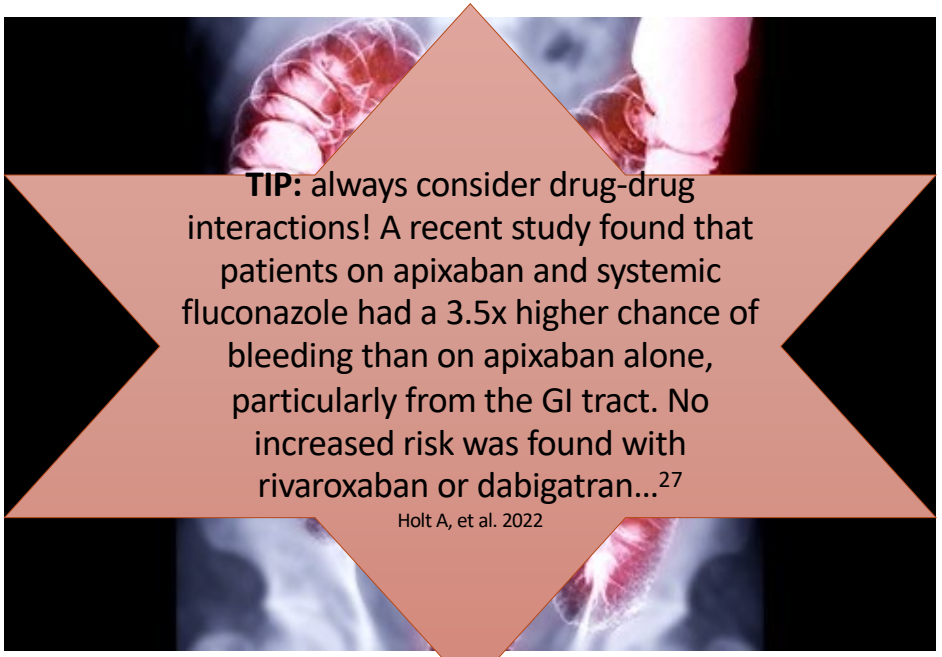
Case #4

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?

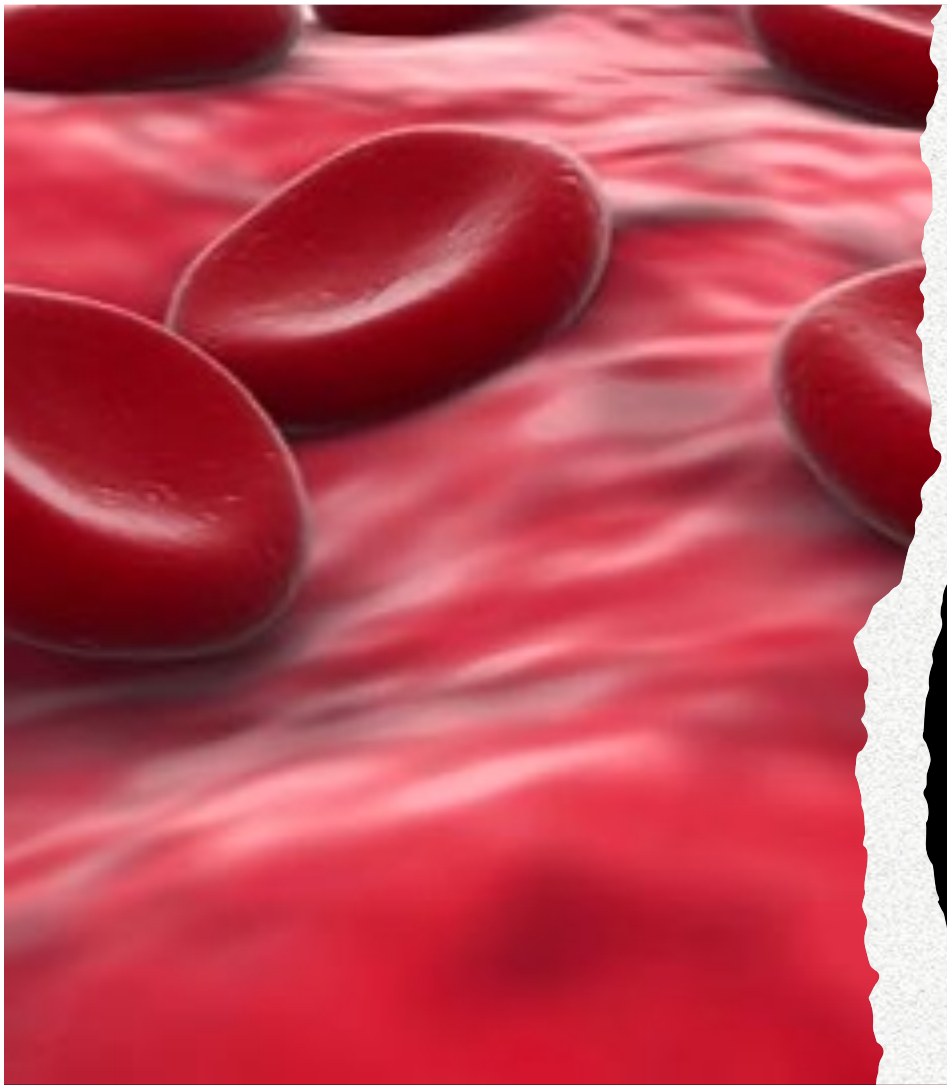
1. Rivaroxaban
2. Apixaban
3. Dabigatran
4. Edoxaban

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 52-year-old male with a history of Factor V Leiden mutation and recurrent DVTs on **warfarin** presents to the ED. He is found to have a perforated gastric ulcer and requires emergent abdominal surgery. His INR is 4.5.

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

Which reversal agent will offer the best results for this patient?

0

Fresh Frozen Plasma (FFP)

0%

IV Vitamin K + FFP

0%

Cryoprecipitate

0%

IV Vitamin K + 4-Factor Prothrombin Complex Concentrate (4F-PCC)

0%

Case #5

Which reversal agent will offer the best results 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)

- **<u>4-Factor PCC FDA Approved Indication:</u>** 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

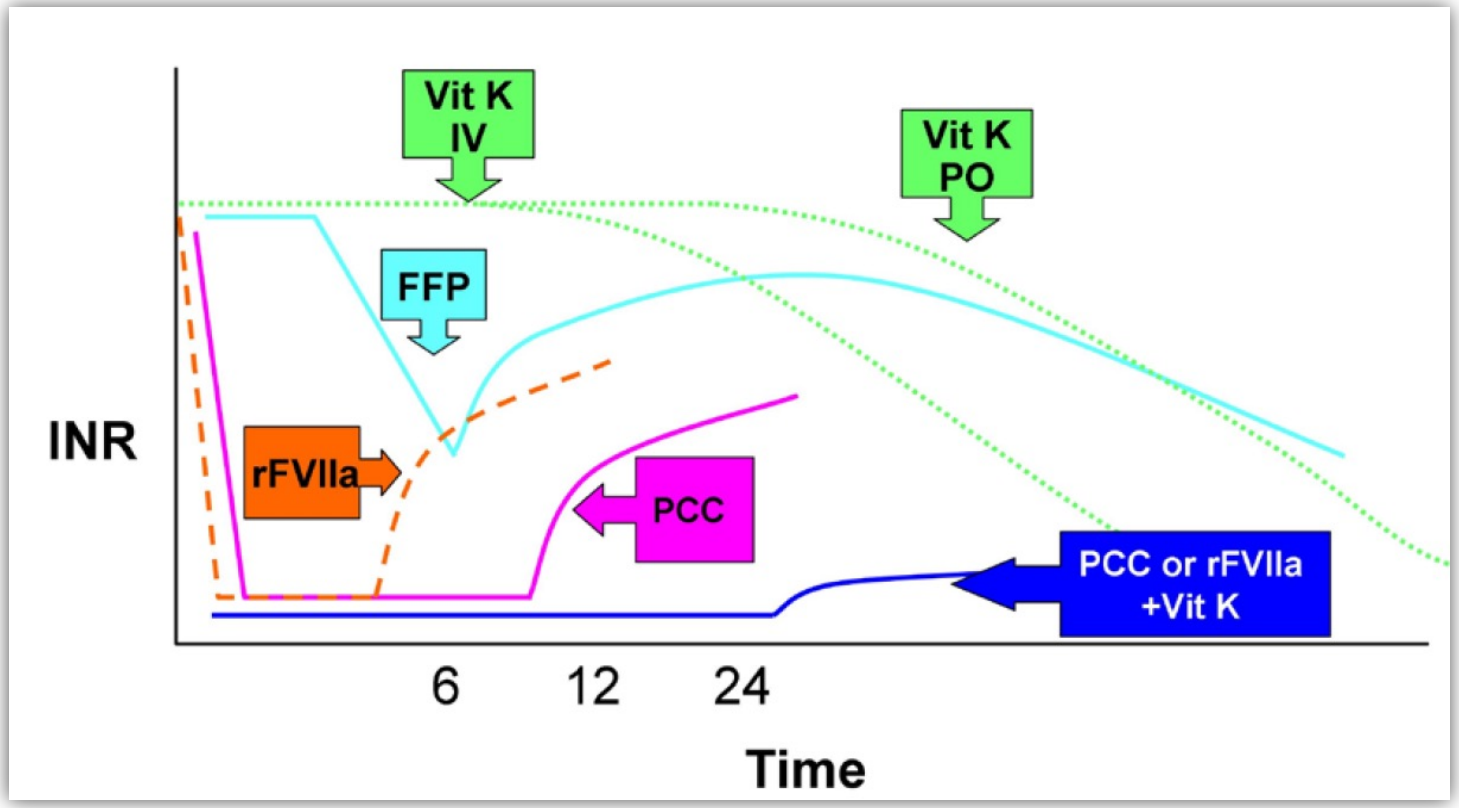
- Warfarin Reversal

Baseline INR	Kcentra dose (units of factor IX/kg)	Max (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.

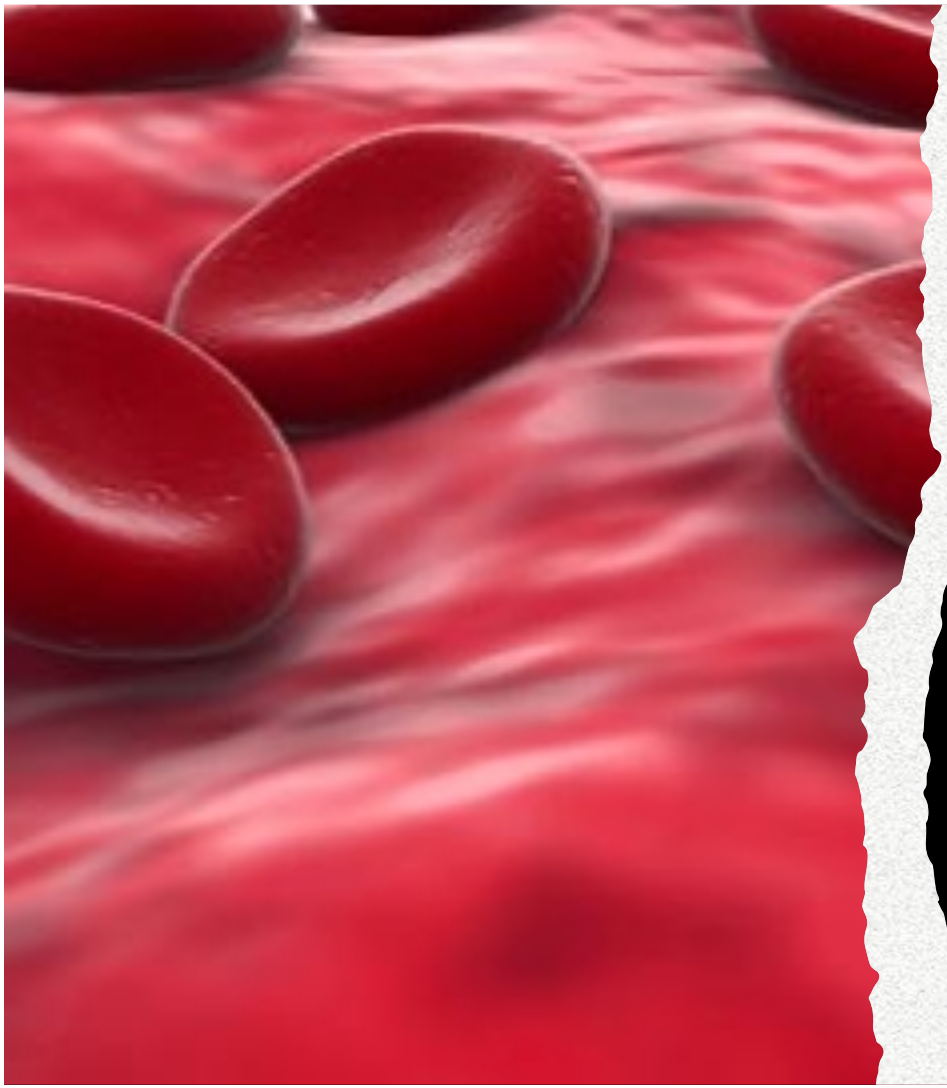
- DOAC reversal (OFF-LABEL)
  - 50 units/kg
- Max dose (warfarin or DOAC) = Do not exceed 5000 units

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 63-year-old male presents with chest pain and shortness of breath and is found to be in ACS. He also has a history of myelofibrosis with chronic anemia, leukopenia, and thrombocytopenia. He is transfusion dependent for his anemia.

- His current hemoglobin is 6.2 g/dL.

How many units of PRBCs would you transfuse?

0

None 0%

1 u PRBCS 0%

2 u PRBCs 0%

3 u PRBCs 0%

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

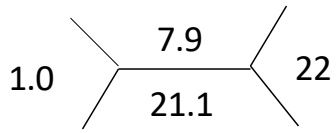
Always consider the individual patient's circumstances!

*sources may vary, cross-referencing multiple guidelines encouraged

Case #7

- A 54-year-old male who is on chemotherapy for pancreatic cancer presents septic and altered. After initial impression, it seems he needs a neurologic workup for source of infection. Lumbar puncture is planned…

- His CBC:



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

0

No transfusion

0%

1 unit of platelets

0%

3 units of platelets

0%

4 units of platelets

0%

Case #7

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

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

You have transfused platelets, and the neuro PA is calling you to see when she can come perform the LP. How soon can you check a post-transfusion platelet count that is reliable?

0

In 10 minutes — 0%

In 30 minutes — 0%

In 60 minutes — 0%

In 120 minutes — 0%

Platelet Transfusion

You have transfused platelets, and the neuro PA is calling you to see when she can come perform the LP. How soon can you check a post-transfusion platelet count that is reliable?

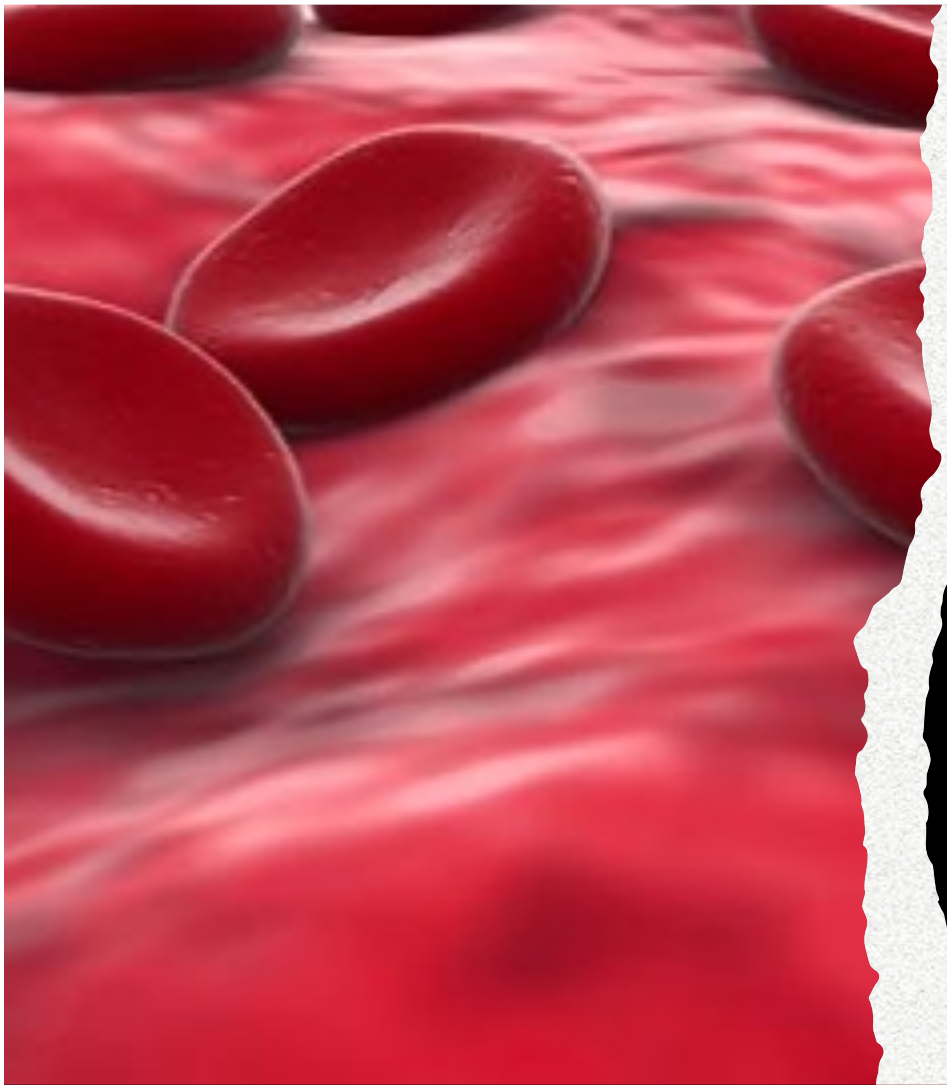
1. In 10 minutes
2. In 30 minutes
3. In 60 minutes
4. In 120 minutes

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 54-year-old female with a history of iron deficiency anemia 2/2 crohns disease is receiving 1U PRBCs for a hemoglobin of 6.0 g/dL. About 30 minutes into the transfusion, she develops a fever of 38.6 C and rigors. Her temperature continues to increase over the next 20-30 minutes even though the transfusion was stopped.

The nurse calls you to inform you of what has happened. What should the next course of action be?

0

Stop the transfusion, give antipyretic, submit a transfusion workup, and attempt to rule out hemolytic or bacterial cause.

0%

Stop the transfusion, give demerol, and rule out hemolysis.

0%

Continue the transfusion and administer antipyretic.

0%

Call the blood bank for a new unit of PRBCs and give antipyretics and antibiotics in the meantime.

0%

Case #8

The nurse calls you to inform you of what has happened. 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:

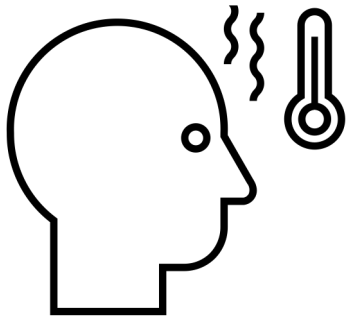
- Febrile (nonhemolytic) reactions
- Allergic reactions
- Hemolytic transfusion reactions
- Transfusion-related acute lung injury (TRALI)
- Urticaria
- Anaphylaxis

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

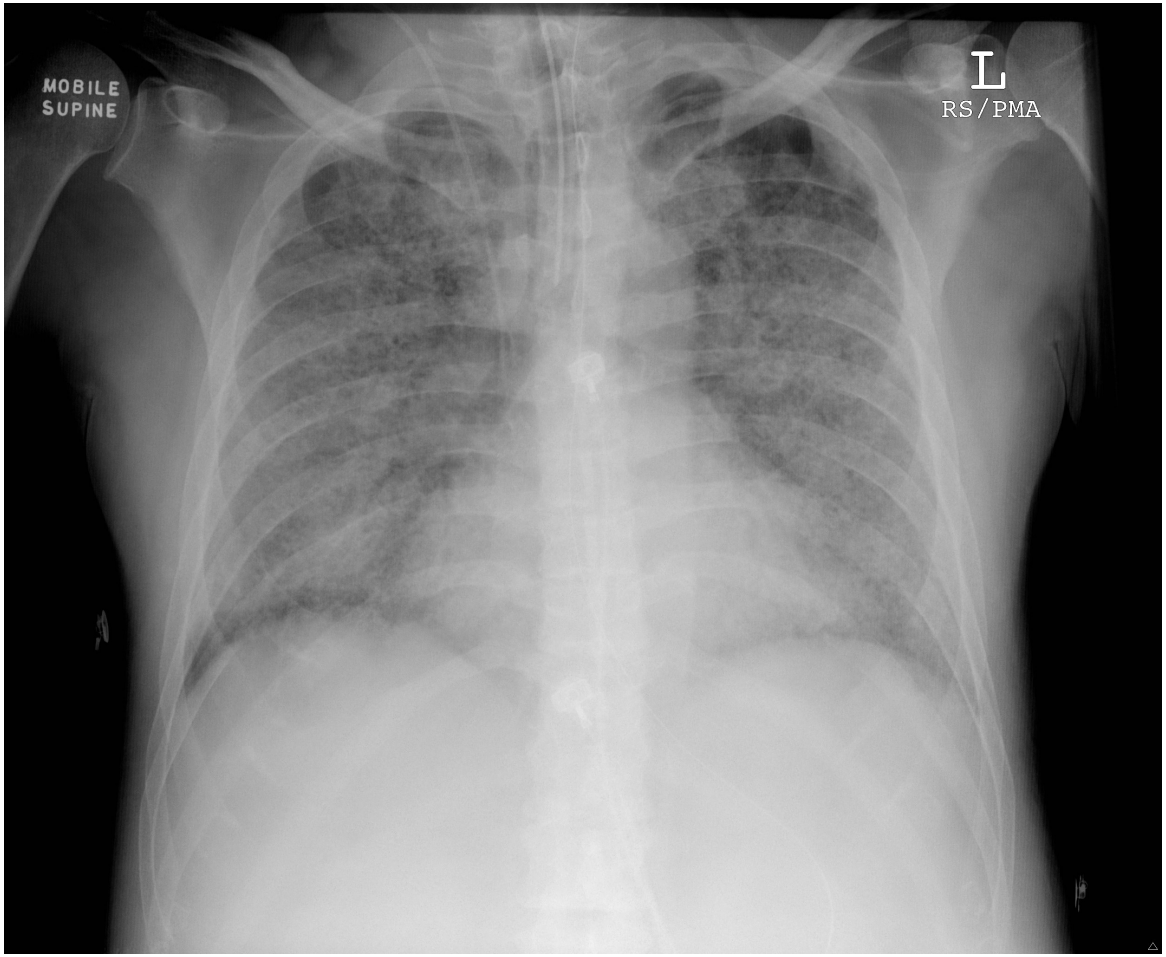
- Fever
  - Fever (38 °C) and/or ≥ 1°C increase in pre-transfusion temp during or within 4 hours of transfusion completion and/or chills/rigors
  - May be accompanied by nausea, HA
- Consider:
  - Underlying medical condition, bacterial contamination, hemolytic reaction
- Premedication?
  - Antipyretics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

Case #9

- A 45-year-old male who is post-liver transplant for cirrhosis from hepatitis B is admitted to the ICU. He is 5 days post-op and has not been extubated due to complications following his surgery. He had an intra-operative CVA and declining respiratory status with the development of mild ARDS. In addition, his hemoglobin has started to drop. He was transfused one unit of PRBCs with no complication, but during his second unit, which was 4 hours after the first, he develops worsening respiratory status. The transfusion is stopped and a CXR is obtained…



Case courtesy of Craig Hacking, Radiopaedia.org, rID: 66478

What do you suspect is the cause of the patient's worsening respiratory status?

0

Worsening ARDS

0%

Transfusion associated lung injury (TRALI)

0%

Transfusion related circulatory overload (TACO)

0%

I’m not sure…I need more information

0%

Case #9

What do you suspect is the cause of the patient's worsening respiratory status?

1. Worsening ARDS
2. Transfusion associated lung injury (TRALI)
3. Transfusion related circulatory overload (TACO)
4. I'm not sure…I need more information

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

TRALI

- Now recognized as one of the leading causes of transfusion morbidity and mortality
- New definition:
  - ~~Possible TRALI~~
  - TRALI type I: without ARDS risk factor
  - TRALI type II: with ARDS risk factor or mild preexisting ARDS
    - *ARDS risk factors or mild ARDS do NOT exclude the possibility of TRALI
- Still a clinical diagnosis
- Hemovigilance reporting mechanism recommended for any pulmonary complications following transfusion
  - Universal reporting form underway…

Table 2. New consensus TRALI definition

TRALI Type I—Patients who have no risk factors for ARDS and meet the following criteria:

a. i. Acute onset

ii. Hypoxemia (P/F≤300 [*] or SpO_2 < 90% on room air)

iii. Clear evidence of bilateral pulmonary edema on imaging (e.g., chest radiograph, chest CT, or ultrasound)

iv. No evidence of LAH [†] or, if LAH is present, it is judged to not be the main contributor to the hypoxemia

b. Onset during or within 6 hr of transfusion [‡]

c. No temporal relationship to an alternative risk factor for ARDS

TRALI Type II—Patients who have risk factors for ARDS (but who have not been diagnosed with ARDS) or who have existing mild ARDS (P/F of 200-300), but whose respiratory status deteriorates [§] and is judged to be due to transfusion based on:

a. Findings as described in categories *a and b* of TRALI Type I, and

b. Stable respiratory status in the 12 hr before transfusion

* If altitude is higher than 1000 m, the correction factor should be calculated as follows: [(P/F) × (barometric pressure/760)].

† Use objective evaluation when LAH is suspected (imaging, e.g., echocardiography, or invasive measurement using, e.g., pulmonary artery catheter).

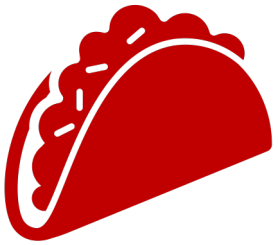
‡ Onset of pulmonary symptoms (e.g., hypoxemia—lower P/F ratio or SpO_2) should be within 6 hours of end of transfusion. The additional findings needed to diagnose TRALI (pulmonary edema on a lung imaging study and determination of lack of substantial LAH) would ideally be available at the same time but could be documented up to 24 hours after TRALI onset.

§ Use P/F ratio deterioration along with other respiratory parameters and clinical judgment to determine progression from mild to moderate or severe ARDS. See conversion table in Appendix S2 to convert nasal O_2 supplementation to FiO_2.

Adapted from Vlaar et al. A consensus redefinition of transfusion-related acute lung injury. Transfusion. 2019 Jul;59(7):2465-2476.doi: 10.1111/trf.15311. Epub 2019 Apr 1

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

Case #9

- CVP has remained consistent
- BNP is elevated, but not more than 2 days prior
- Cardiac output remains stable

- TRALI is more likely than TACO in this scenario

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?

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