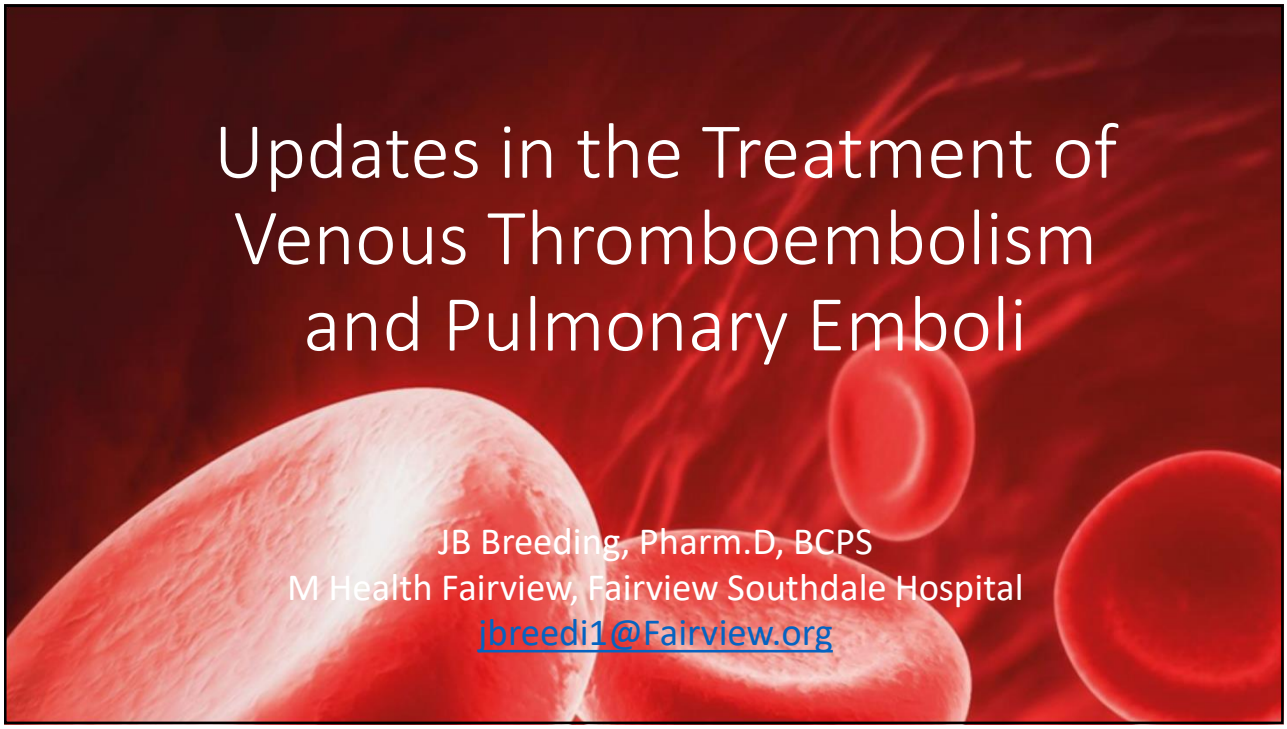

Updates in the Treatment of Venous Thromboembolism and Pulmonary Emboli

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Learning Outcomes

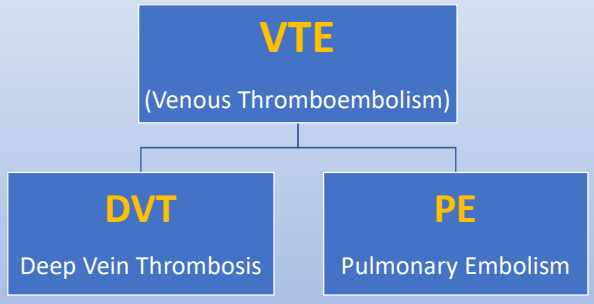
- Indicate an improved understanding of pharmacologic therapies that are indicated for the treatment of VTE/PE, as well as the reversal therapies available for antithrombotic-induced hemorrhage.
- Describe the major requirements mandated by the Joint Commission Anticoagulation National Patient Safety Goals (03.05.01)
- List at least one site-based action that can be implemented to help improve the care of VTE patients.

The Basics

Acronyms

- CDT= catheter directed therapy
- DVT= Deep vein thrombosis
- HR= Heart Rate
- IVC= Inferior Vena Cava
- LE= Lower Extremity
- Lytic = Thrombolytic
- PE = Pulmonary embolism
- PTS= Post Thrombotic Syndrome
- RV= Right Ventricle
- UE= Upper Extremity
- VTE= Venous thromboembolism

What is "VTE"?



VTE Incidence[1]

- Approximately 547,596 acute VTE hospitalizations in the US per year[2,3]. Of those VTE hospitalizations:
  - ✓ 64% had DVT
  - ✓ 51% had PE
  - ✓ 14% had both DVT and PE on admission
- 70-120 cases per 100,000 persons per year in the US[3]
- 10-30% of persons die within 1 month of diagnosis (Beckman et al 2010)
- 33% experience another VTE within 10 years (Beckman et al 2010)

1. Tripp LM /Breeding JB "Pharmacologic Management and Mobilization of Pts with VTE"
2. MMWR Morb Mortal Wkly Rep. 2012 Jun 8;61(22):401-43
3. Cohen et al
4. Beckman et al. *Am J Prev Med*. 2010;38:S495-S501

DVT & PE Statistics

- **DVT**
  - 50% risk of PE if proximal LE DVT is not treated[1]
  - 20-25% risk of PE if isolated distal LE DVT is not treated[1]
  - Up to 50% develop PTS, even with anticoagulant use[2,3]
- **PE**
  - ~ 1 in 5 persons with acute PE die almost immediately[4]
  - 40% of persons with acute PE die within 3 months[4]
  - 1% of hospitalized patients die of acute PE[5]
  - 10% of hospital deaths are PE-related[6]
  - Survivors of PE may have significant cardiopulmonary morbidity

1. Geerts WH et al. *Chest*. 2001;119(1 suppl):132S-175S
2. Kahn SR et al. *Lancet*. 2014;383:880-888.
3. Streiff MB et al. *MMWR Morb Mortal Wkly Rep*. 2014;63:190-193.
4. Galson SK. US Department of Health and Human Services; 2008.
5. Stein PD et al. Chest Journal. 1995:108(4):978-981
6. Lindblad B. et al. British Medical Journal. 1991:302(6778):709-711

VTE Signs and Symptoms

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Lower Extremity DVT

- Pitting Edema
- Achy tenderness and pain in leg
- Erythema
- Warmth
- Swelling of the leg
- Prominent superficial veins

Upper Extremity DVT

- Tenderness and pain in arm/shoulder/neck
- Erythema/Warmth
- Swelling of arm/hand
- Extremity cyanosis
- UE DVT due to venous compression (e.g. Thoracic outlet syndrome) can also present with arm/hand atrophy/weakness

Pulmonary Embolism

- Shortness of breath
- Chest pain: Usually worse with breathing / coughing
- Tachypnea
- Tachycardia/palpitations
- Sweating
- Anxiety
- Hemoptysis or pink, foamy mucus
- Fainting
- Signs/symptoms of shock

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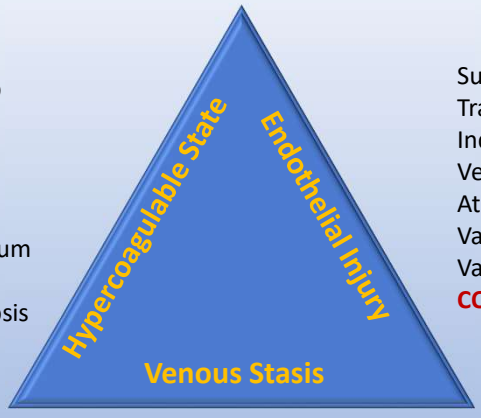
VTE Risk Factors: Virchow's Triad[1]

Previous VTE
Acute phase post op
Age > 55-60
Cancer
Thrombophilia
Estrogen therapy
Pregnancy/postpartum
Inflammatory Bowel
Severe infection/sepsis
COVID



Surgery
Trauma
Indwelling catheter
Venipuncture
Atherosclerosis
Valvular Heart Disease
Valve Replacement
COVID

Immobility (bed rest, long car/plane trips, fractures)
Heart Failure
AFib
Venous Insufficiency/obstruction (tumor, obesity, pregnancy)
COVID

1. Virchow R. ed. *Gesammelte Abhandlungun zur Wissenschaftichen Medicin.* Von Meidinger Sohn, Frankfurt, 1856

Chronic Conditions Secondary to VTE

DVT	PE

Post Thrombotic Syndrome (PTS)

A clot remains in the leg's vein obstructing blood flow leading to venous hypertension, damage to the vein and compromised flow

- Chronic limb edema
- Thickened, coarse, and brownish skin along distal leg
- Venous stasis ulceration

Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

- Reduced oxygenation and pulmonary hypertension as a result of PE

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Pulmonary Embolism Categories

	Minor/ Non-Massive ("low risk")	Submassive ("intermediate Risk")	Massive ("high risk")
BPs	Normal (SBP > 90)	Normal (SBP > 90)	**HYPOTENSION** (inotrope/ pressor support)
RV Dysfunction (troponin, BNP, echo)	Not present	**Present**	**Present**
HR	Normal	Normal	**Bradycardia w/signs and symptoms of shock**

Why do the PE Categories Matter?

- The ICOPER trial in 1999 discovered a large difference in mortality between the 3 groups:

  ✓ Massive PE = 58% mortality at 3 months
  ✓ Submassive PE = 21% mortality at 3 months
  ✓Minor PE = 0% mortality at 3 months

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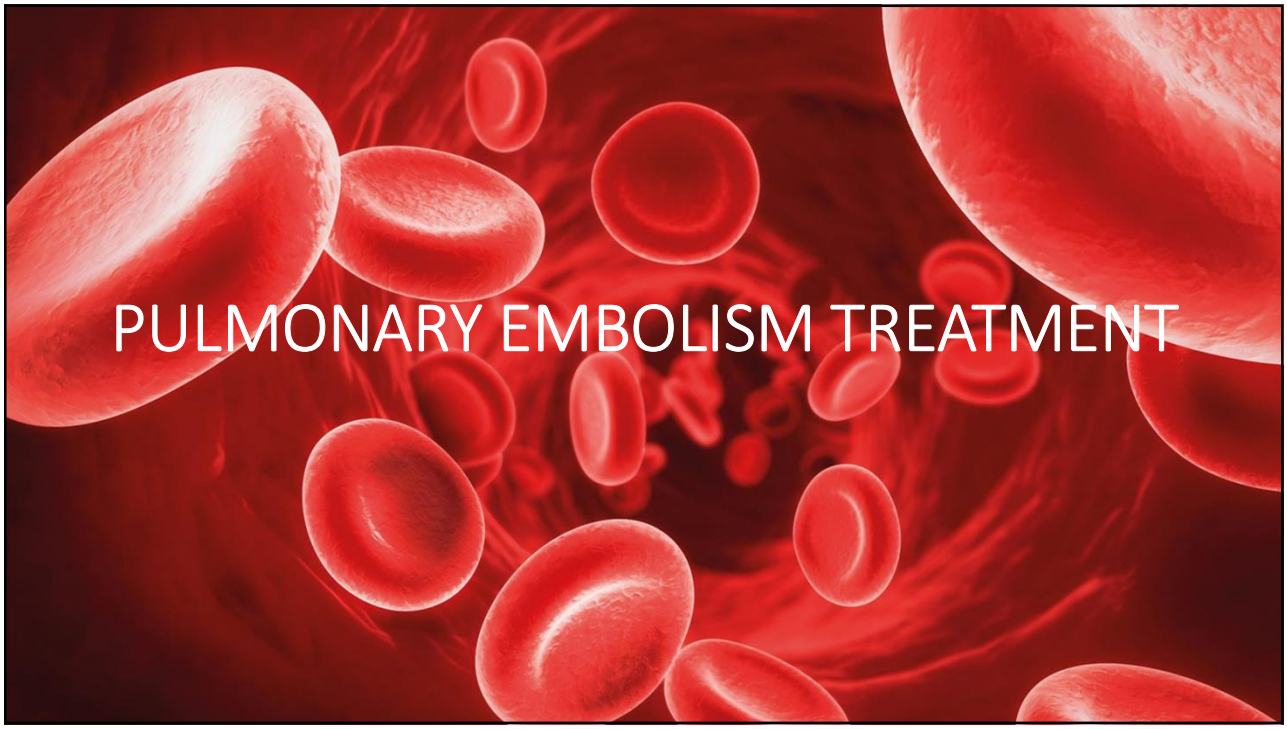
1. Goldhaber SZ. "ICOPER Trial". Lancet 1999 Apr 24;353(9162):1386-9



Anticoagulation for VTE Treatment

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Parenteral (IV/SQ)

- Argatroban drip *(uncommon)*
- Bivalirudin drip *(uncommon)*
- Enoxaparin SQ (Lovenox®)
- Fondaparinux SQ (Arixtra®)
- Heparin drip

Oral

- Apixaban (Eliquis®)
- Dabigatran (Pradaxa®)
- Edoxaban (Savaysa®)
- Rivaroxaban (Xarelto®)
- Warfarin (Coumadin®, Jantoven®)

  Warfarin must be given with a parenteral anticoagulant x 4-7 days

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Anticoagulant Mechanisms

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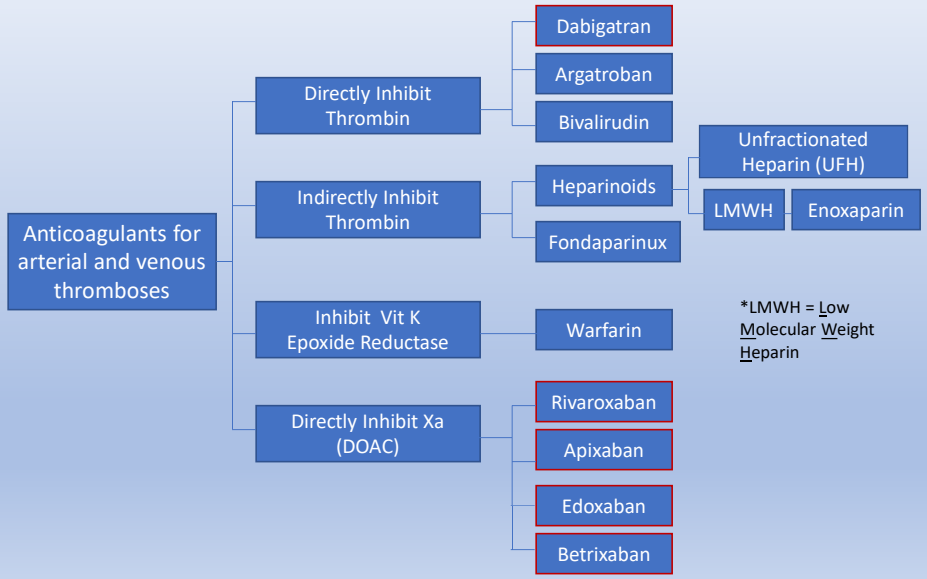

*LMWH = Low Molecular Weight Heparin

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Oral DOACs Used for VTE Treatment

	Apixaban *(Eliquis®)*	Dabigatran *(Pradaxa®)*	Edoxaban *(Savaysa®)*	Rivaroxaban *(Xarelto®)*
Treatment of DVT/PE	**10 mg PO BID x 7 days then 5 mg PO BID**	**150 mg BID*** **start dabigatran after 5-10 days of IV/SQ anticoagulation*	**CrCl > 50: 60 mg daily** *(after 5-10 days of IV/SQ anticoagulation)* IF CrCl 15-50, or wt ≤ 60 kg: **30 mg daily**	**15 mg PO BID x 3 weeks Then 20 mg daily** *(take with food)*
		Do NOT use if: CrCl ≤ 30 or HD	**Do NOT use if:** CrCl < 15	**Do NOT use if:** CrCl < 15
Prevention of DVT/PE Recurrence	**2.5 mg PO BID**	CrCl> 30: **150 mg BID** *CrCl ≤ 30: **Do NOT use**	NA	**10 mg daily*** with or without food *CrCl < 15: **Do NOT use**

DOACs vs. Warfarin

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	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban	Warfarin
Onset	1-2 hrs after dose	2-4 hrs after dose	3-4 hrs after dose	1-2 hrs after dose	3-4 hrs after dose	4-5 days
Duration	48 hours	24-48 hours	24-48 hours	24 hours	19-27 hours	4-5 days
Bridging Needed?	**NO BRIDGING NECESSARY! Do NOT "bridge" with a parenteral anticoagulant.**					Bridging Required for acute VTE

Intravenous/Subcutaneous Anticoagulants

	Argatroban Drip	Bivalirudin Drip	Fondaparinux SQ injection	Enoxaparin SQ injection	Heparin Drip
Onset	Immediate	Immediate	3-4 hrs after 1st dose	2-4 hrs after 1st dose	IV drip= Immediate SQ = 20-30 min
DVT/PE Treatment Dose	0.5-2 mcg/kg/min	0.02-0.15 mcg/kg/hour	5-10 mg SQ Q24H Avoid if CrCL < 30	1 mg/kg SQ Q12 Avoid in acute renal failure	80 unit/kg bolus, then 18 units/kg/hr Goal AXA 0.3-0.7 IU/mL
DVT Prophylaxis	NA	NA	2.5 mg SQ Q24H	40 mg SQ Q24H	5000 units SQ Q8-12H
Safe to use in patients with HIT* and/or heparin allergy?	YES			NO	

*HIT= heparin induced thrombocytopenia

Alteplase (tPA) for VTE

Found to be most beneficial for patients with submassive/massive PE with RV dysfxn[1]

Thrombolytic	Dose
Alteplase (tPA)	<u>Systemic</u> • For massive PE: 100 mg IV over 2 hours[1] • For submassive PE: 50 mg IV over 2 hours[2] • For DVT: systemic thrombolysis not typically used for DVT! <u>Catheter Directed Thrombolysis (CDT)</u> • For PE: ~ 1 mg/hour x 12-15 hours (10-20 mg over 15 hours) • For DVT: 0.5-1 mg/hour x 12 hours

1. Chatterjee S. et al JAMA. 2014 Jun;311(23):2414-21
2. Goldhaber SZ et al. Lancet 1993; *341*: 507–511.
3. Sharifi M. et al "MOPETT" Trial *The American Journal of Cardiology*. 2012. 111(2):273-7.

Ultrasound Thrombolysis (EKOS) for PE

- The EKOS catheter has multiple microscopic holes all along the catheter and is fitted with ultrasound
- The EKOS catheter allows the provider to use ultrasound with catheter directed thrombolysis
- The acoustic pulses delivered via the catheter are theorized to:
  - Enhance the thrombolytic process by accelerating the contact of TPA with plasminogen within the thrombus
  - Improved clot removal and enhanced clinical improvement vs standard catheter-directed drug therapy or thrombectomy.[2, 3]

1. Kucher N et al. *Circulation* 2014;129:479-86.
2. Lin, P et al., Vasc. 17(Suppl. 3), 2009, S137-S147.
3. Lin, P et al., Persp in Vasc Surg & Endo Ther, 2010, 22(3):152-163

How EKOS Works

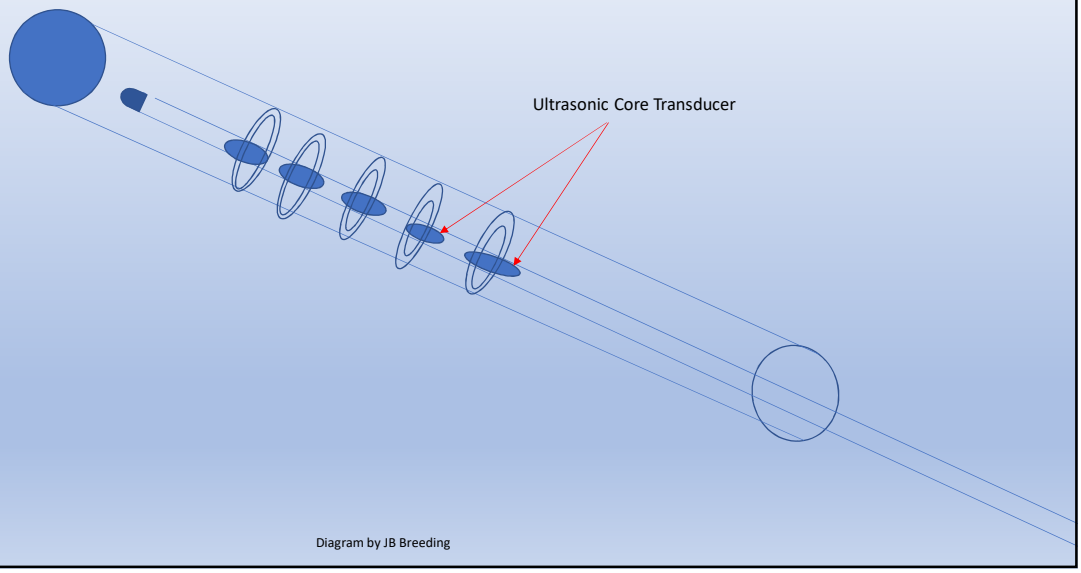
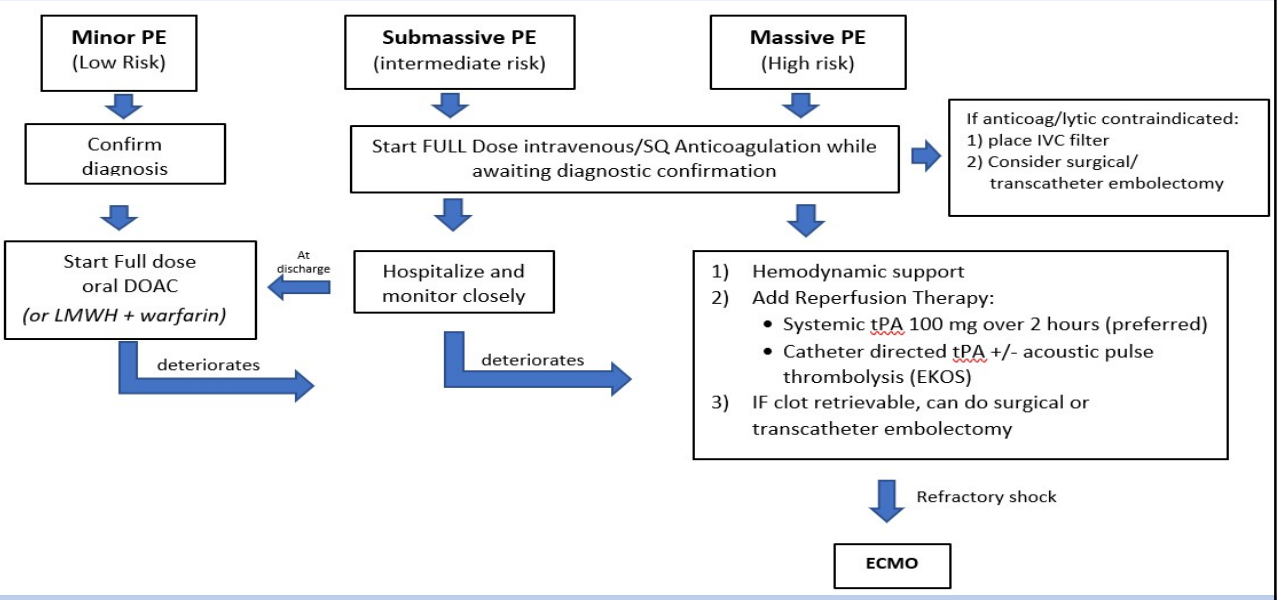
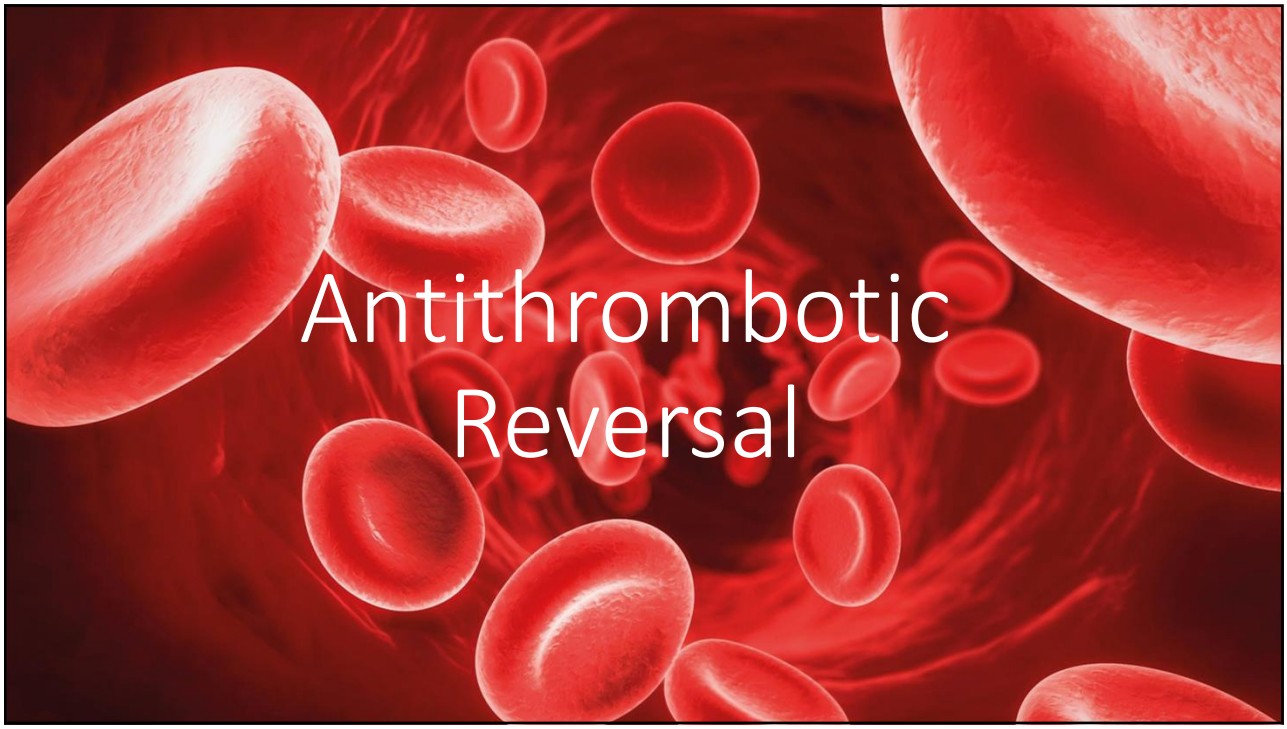


Diagram by JB Breeding

Pulmonary Embolism Treatment Algorithm





Anticoagulation Reversal

Anticoagulant	Reversal
Argatroban, Bivalirudin	• No reversal agent available, use supportive measures • Could consider factor VII or prothrombotics (tranexamic acid, aminocaproic acid) in a life-threatening bleed
Apixaban, Betrixaban Edoxaban, Rivaroxaban	• Prothrombin complex concentrate (PCC, Kcentra®) • For life threatening hemorrhage can consider Andexxa® instead *(if on formulary at your hospital)*
Dabigatran	• Idarucizumab (Praxbind®)
Heparin, Enoxaparin	• Protamine (reverses heparin 100%/enoxaparin 30%)
Fondaparinux	• No reversal agent available • Could consider PCC (or Andexanet if on formulary)
Warfarin	• Vitamin K intravenous/oral • Prothrombin complex concentrate (PCC, Kcentra®) • Fresh Frozen Plasma

Thrombolytic (tPA, alteplase) Reversal

- No antidote available to reverse alteplase or tenecteplase
- Treatment of thrombolytic hemorrhage includes:
  - ✓Cryoprecipitate
  - ✓Consider platelets, FFP and PRBCs as needed
  - ✓Can also consider administering prothrombotics (tranexamic acid, aminocaproic acid)

Improving the Antithrombotic Reversal Process

- ✓Create a policy dedicated to antithrombotic reversal
- ✓Create an antithrombotic reversal order set in your electronic medical record
  - All dosages should be PREFILLED
  - Medications should be set to STAT priority
  - The set should be retrievable by the anticoagulant you are trying to reverse!
- ✓Teach all disciplines (providers, nursing, pharmacy) about reversal
- ✓Make sure your pharmacy staff are crystal clear on what antidotes should be kept in stock and where they are located

WHAT'S CHANGED IN THE LAST FEW YEARS?

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What's Changed in the Last 3-5 Years?

1. **Heparin is falling out of favor**
   - Concern for HIT (drastically increases cost and LOS)

Risk for HIT[1]

Heparin > Enoxaparin > Fondaparinux/DOACs
(2.6%) (0.2%) (0%)

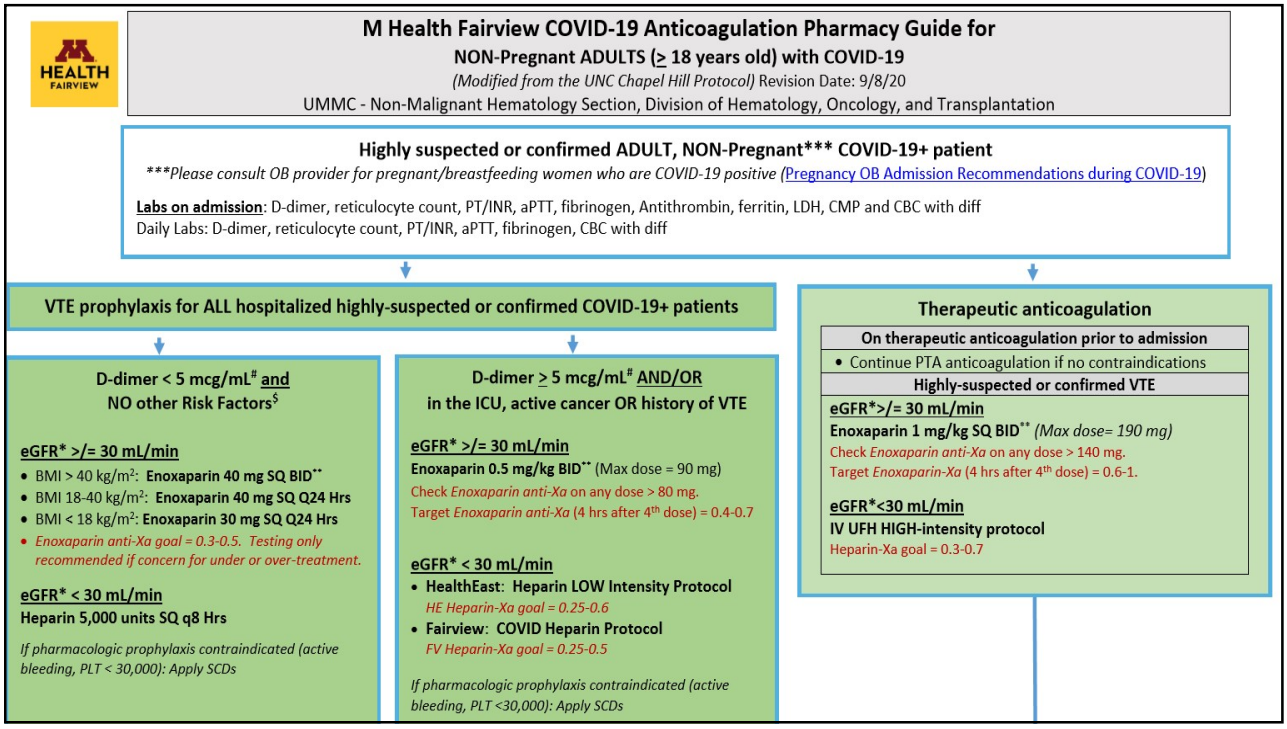
   - Also, heparin exposes staff (RN, lab) far more to COVID positive patients vs other therapies (lab draws, pump programming + boluses, etc.)
   - Use enoxaparin instead of heparin where possible!

1. Martel, N. et al. *Blood* (2005) 106 (8): 2710–2715.

What's Changed in the Last 3-5 Years?

2. **COVID is associated with an INCREASE in the risk for VTE[1]**.
   - 18.4% of hospitalized patients who are COVID positive will develop VTE[1]
   - Unless contraindicated, all hospitalized COVID positive patients should receive VTE prophylaxis with LMWH or fondaparinux[2,3]
   - Critically ill COVID positive patients and those with a positive VTE history MAY require higher prophylaxis dosing?

1. Kunutsor SK. et al. Thrombosis Research 2020; 196:27-30.
2. Moores LK. et al. CHEST 2020; 158(3):1143-1163.
3. Spyropoulos AC et al. J Thromb Haemost. 2020;18:1859-65.



Post-hospitalization VTE prophylaxis

Discharging provider to weigh risk vs benefits of anticoagulation at the time of discharge.

- **Consider one of the following for 30 days and until the patient is mobile:**
  - Apixaban (Eliquis) 2.5 mg BID
  - Rivaroxaban (Xarelto) 10 mg once daily
- **All patients to be educated about the symptoms of DVT** (swelling, pain, redness, warmth) and PE (SOB, CP, tachycardia, cough/hemoptysis).

Post-hospitalization VTE management:

- Follow standard for full anticoagulation treatment

#5 mcg/mL represents 10 times the upper limit of normal

$ Risk factors = Critically ill/in ICU, active cancer or history of thromboembolism

*eGFR and Creatinine Clearance can be used interchangeably to estimate renal function

**BID is encouraged to LIMIT the number of times a nurse needs to enter the COVID positive patient's room. Pharmacists should help standardize administration times whenever possible.

Questions regarding this protocol may be directed to: Dr. Surbhi Shah (shahx090@umn.edu) or Dr. Mark Reding (redin002@umn.edu)

What's Changed in the Last 3-5 Years?

3. **Inferior vena cava (IVC) filters are typically only indicated for prevention of pulmonary embolism if:**
   - The patient has an contraindication to anticoagulation
   - The patient has had multiple PEs, despite being on full anticoagulation (anticoagulation failure)
   - **IVC filters can cause harm** (*the filter can migrate, break, cause IVC stenosis and may increase the risk of further DVT*)
   - For a great overview of all IVC guidelines:
     DeYoung E et al. Semin Intervent Radiol 2016;33:65–70

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1. Ray CE et al. J Vasc Interv Radiol 2006;17(10):1595–1604
2. Charles HW et al. J Vasc Interv Radiol 2009;20(8):1046–105

What's Changed in the Last 5 Years?

4. **Direct Oral Anticoagulants (DOACs) are now the drugs of choice for adult patients with low risk/stable VTE/PE. Even in patients:**
   - With renal failure (use apixaban)
   - Who are obese

   Avoid DOACs in:
   - *Pregnancy*
   - *Patients w/ significant valvular heart disease*
   - *Patients likely needing imminent reversal (e.g. ventricular assist device, on transplant wait list)*

What's Changed in the Last 3-5 Years?

5. **Many hospitals now have access to apixaban/rivaroxaban specific anti-Xa levels. Consider for:**
   - Extremely over/underweight patients
   - Significant renal dysfunction
   - Treatment failure
   - Assessing patient compliance
   - Apixaban/Rivaroxaban hemorrhage reversal protocols

What's Changed in the Last 3-5 Years?

6. **Factor Xa recombinant (ANDEXXA®) is now commercially available for severe factor Xa inhibitor-induced hemorrhage**
   - **Pros**:
     - Has FDA approval for DOAC reversal
     - Immediately reverses all oral DOACs
   - **Cons**:
     - $$$
     - Approximately 4 hours after administration, endogenous DOAC levels can rebound
     - Andexxa also negates: heparin, enoxaparin and fondaparinux!
     - Many hospitals do not have Andexxa® on formulary

What's Changed in the Last 3-5 Years?

7. **In late 2019, Joint Commission announced greatly expanded anticoagulation "National Patient Safety Goals"[1] for 2020.** Hospitals must review these goals and prepare!

Joint Commission 2020 Anticoagulation NPSGs[1]

EP	Requirement
1	The [hospital/organization] uses approved protocols and evidence-based practice guidelines for the initiation and maintenance of anticoagulant therapy that addresses: • Medication selection; • Dosing (including adjustments for age and renal or liver function) • Drug-drug and drug-food interactions • other risk factors as applicable.
2 (NEW)	The [hospital/organization] uses approved protocols and evidence-based practice guidelines for **REVERSAL** of anticoagulation and management of bleeding events related to each anticoagulant medication.
3 (NEW)	The hospital uses approved protocols and evidence-based practice guidelines for **PERIOPERATIVE** management of all patients on oral anticoagulants. Note: *Perioperative management may address the use of bridging medications, timing for stopping an anticoagulant, and timing and dosing for restarting an anticoagulant.*

1. https://www.jointcommission.org/-/media/tjc/documents/standards/national-patient-safety-goals/2020/npsg_chapter_hap_jul2020.pdf

Joint Commission 2020 Anticoagulation NPSGs[1]

EP	Requirement
4	The [hospital/organization] has a written policy addressing the need for baseline and ongoing laboratory tests to monitor and adjust anticoagulant therapy.
5	The [hospital/organization] addresses anticoagulation safety practices through the following: - Establishing a process to identify, respond to, and report adverse drug events, including adverse drug event outcomes - Evaluating anticoagulation safety practices, taking actions to improve safety practices, and measuring the effectiveness of those actions in a time frame determined by the organization

1. https://www.jointcommission.org/-/media/tjc/documents/standards/national-patient-safety-goals/2020/npsg_chapter_hap_jul2020.pdf

Joint Commission 2020 Anticoagulation NPSGs[1]

EP	Requirement
6	The [hospital/organization] provides education to patients and families specific to the anticoagulant medication prescribed, including the following: • Adherence to medication dose and schedule • Importance of follow-up appointments and laboratory testing (if applicable) • Potential drug-drug and drug-food interactions • The potential for adverse drug reactions
7	The [hospital/organization] uses only oral unit-dose products, prefilled syringes, or premixed infusion bags when these types of products are available.
8	When heparin is administered intravenously and continuously, the [hospital/organization] uses programmable pumps to provide consistent and accurate dosing.

1. https://www.jointcommission.org/-/media/tjc/documents/standards/national-patient-safety-goals/2020/npsg_chapter_hap_jul2020.pdf

In addition to NPSG, there was also a DOAC "*Sentinel Event Alert*" released in July, 2019

Why does this alert matter?

This JC alert recommended 6 ACTIONS for hospitals to perform!

Joint Commission DOAC Sentinel Event Alert[1]

Actions recommended by JC
Create **name awareness** for the various kinds of DOACs — particularly among pharmacists, ER clinicians and providers
For each type of anticoagulant, use evidence-based protocols and practice guidelines for: • drug initiation and maintenance • reversal of anticoagulation and management of bleeding events • perioperative management
For reversal of anticoagulation and management of bleeding events, address: • Variations in presentation severity (e.g., location and severity of bleeding, indication for reversal) • Appropriate reversal agents (e.g., drug discontinuation, use of concentrated clotting therapy)
Hospitals and critical access hospitals should stock blood products and any antidotes appropriate for use with each type of anticoagulant.

1. **Joint Commission Sentinel Event Alert published in Issue 61, on July 30, 2019**
   https://www.jointcommission.org/resources/patient-safety-topics/sentinel-event/sentinel-event-alert-newsletters/sentinel-event-alert-61-managing-the-risks-of-direct-oral-anticoagulants/

Joint Commission DOAC Sentinel Event Alert

Actions recommended by JC
For perioperative management, address: • Use of bridging meds • Timing for stopping/restarting an anticoagulant • The patient's bleeding risk and renal function, as well as the half-life of the medication.
Have a written policy on the need for baseline and ongoing laboratory tests to monitor and adjust anticoagulant therapy. For patients on a DOAC, follow evidence-based practice guidelines for baseline and ongoing laboratory tests to ensure that patients are monitored and dosed appropriately
Include the particular DOAC's indications for use on the patient's prescription, in the instructions for the patient, and in the electronic medical record (EMR).
Evaluate anticoagulation safety practices, and take actions to improve safety practices and measure the effectiveness of those actions in a time frame determined by the organization

1. **Joint Commission Sentinel Event Alert published in Issue 61, on July 30, 2019**
   https://www.jointcommission.org/resources/patient-safety-topics/sentinel-event/sentinel-event-alert-newsletters/sentinel-event-alert-61-managing-the-risks-of-direct-oral-anticoagulants/

Joint Commission DOAC Sentinel Event Alert

Actions recommended by JC
Provide education to patients and families specific to the DOAC medication prescribed, including: • Adherence to medication dose and schedule. • Importance of follow-up appointments and laboratory testing • Potential drug-drug and drug-herb/supplement interactions. • Potential for adverse drug reactions and knowledge of how adverse reactions present. • When to contact the doctor or visit the emergency department.

1. *Joint Commission Sentinel Event Alert published in Issue 61, on July 30, 2019*