VENOUS THROMBOEMBOLISM: FOCUS ON RISK STRATIFICATION AND ANTICOAGULATION

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- Identify risk factors for the development of venous thromboembolism (VTE) and utilize validated scoring tools to evaluate pretest probability in patients with suspected VTE
- Recognize clinical characteristics, signs and symptoms, laboratory abnormalities, and radiographic findings in patients with deep venous thrombosis and/or pulmonary embolism
- Apply standardized definitions for massive, low and high risk submissive pulmonary embolism to select appropriate anticoagulant or thrombolytic therapy
- Design a patient-specific anticoagulant pharmacotherapeutic plan to manage the initial treatment phase in patients with VTE
- Determine an appropriate duration of anticoagulation for patients with VTE

EPIDEMIOLOGY

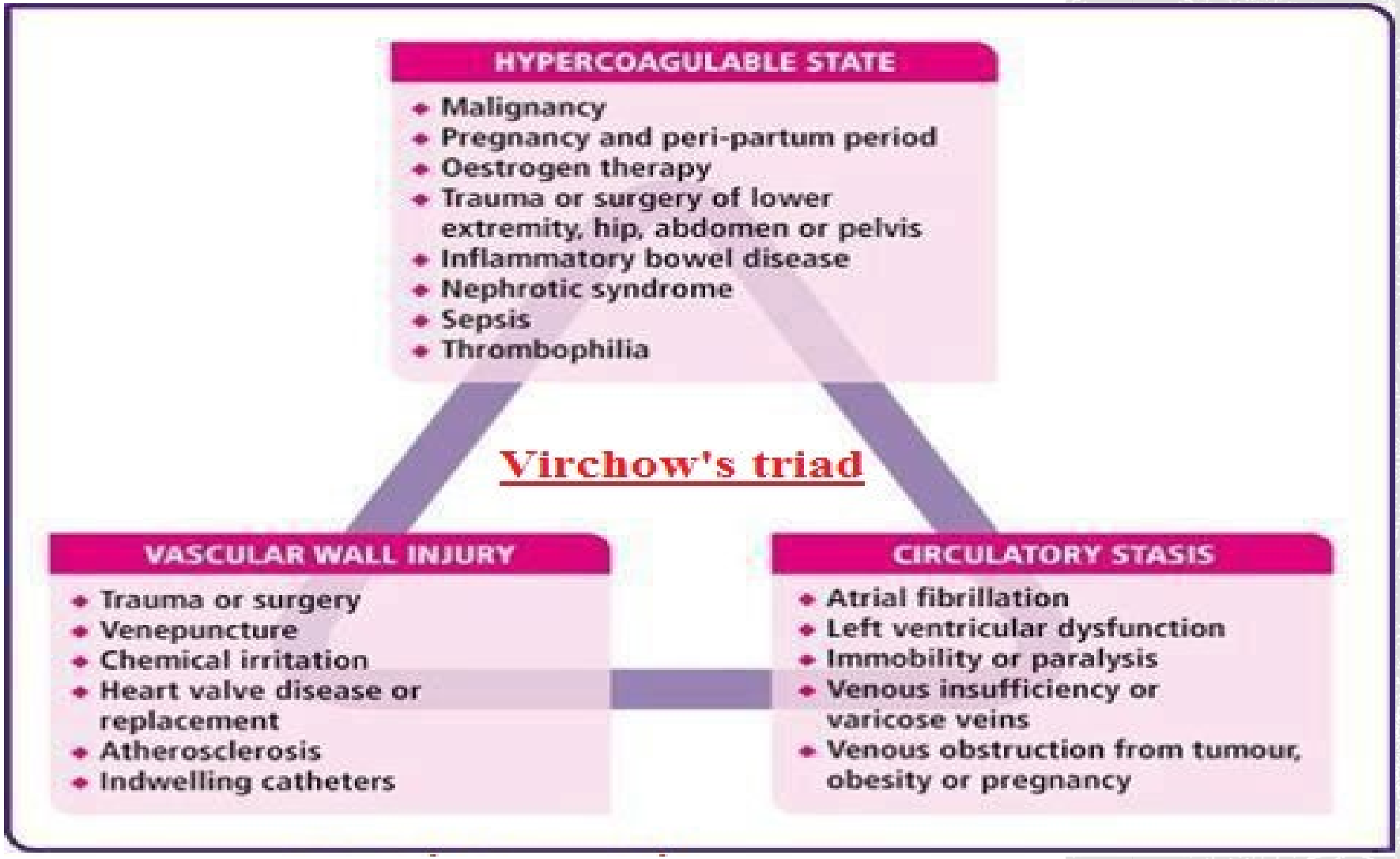
- Venous thromboembolism (VTE) which includes deep venous thrombosis (DVT) and pulmonary embolism (PE) occurs in 1-2 individuals per 1,000 each year (~300,000 – 600,000 events in the U.S. annually)
- Approximately one-third of all patients with a new diagnosis of VTE have PE with or without DVT, and it is estimated that up to one-quarter of all patients with PE present with sudden death
- Risk of recurrent VTE varies depending on the presence or absence of transient vs. persistent provoking risk factors
  - For patients with unprovoked VTE, risk of recurrence ~10% by 2 years, and > 30% by 10 years
- Occurrence of long-term complications:
  - Post thrombotic syndrome (PTS) after DVT 20-50% (5% of cases classified as severe)
  - Chronic thromboembolic pulmonary hypertension (CTPH) develops in ~5% of patients with PE

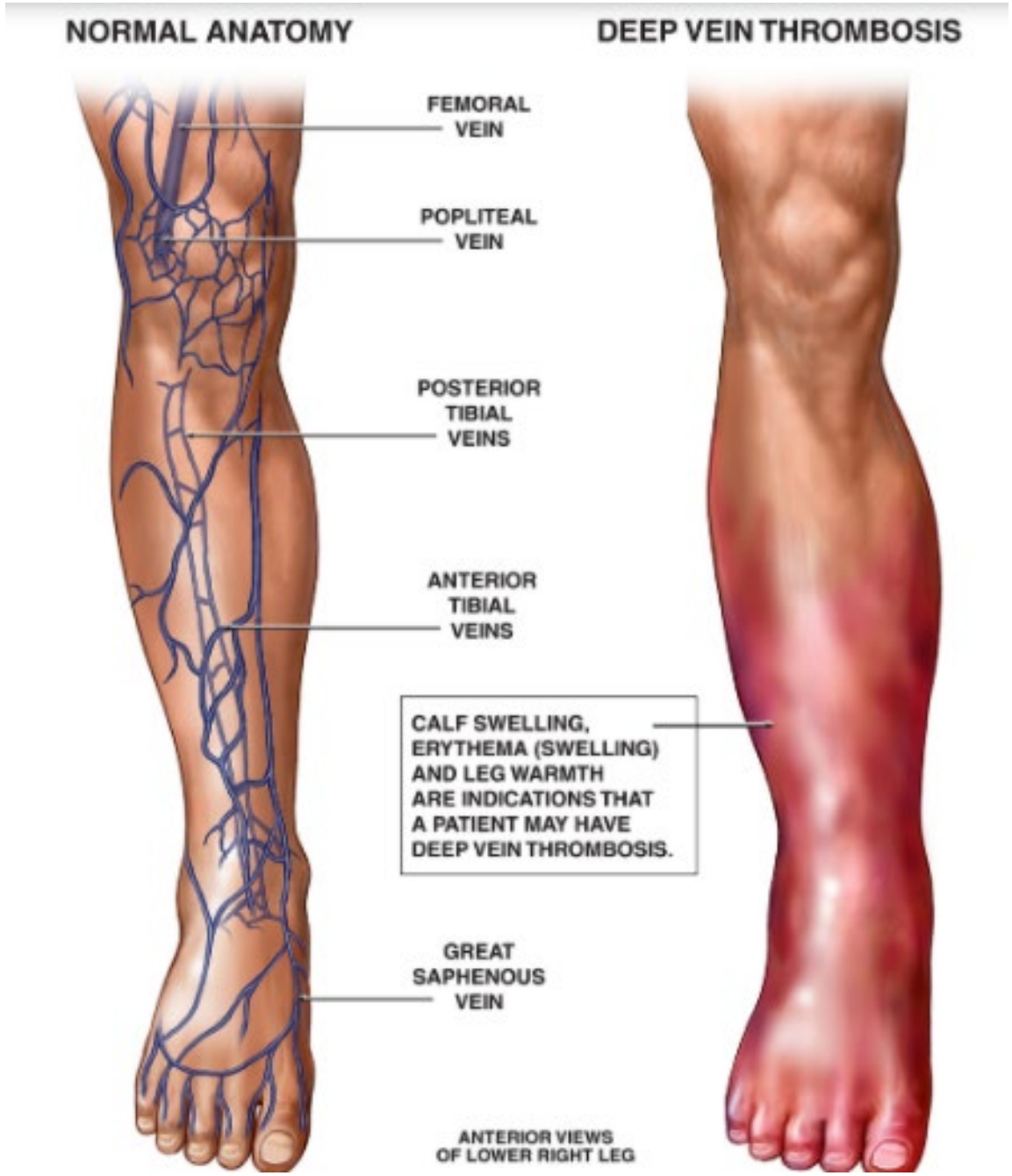
Ortel TL, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. Blood Adv. 2020 Oct 13;4(19):4693-4738.

RISK FACTORS

- Acquired Risk Factors:
  - Malignancy
  - Trauma
  - Surgery, especially orthopedic or prolonged procedures
  - Immobilization (hospitalization, injury)
  - Obesity
  - Pregnancy
  - Inflammatory bowel disease
  - Medications, especially oral contraceptives/estrogen
  - Nephrotic syndrome
  - Sepsis
  - Antiphospholipid antibody syndrome
  - COVID19
  - Heparin-induced thrombocytopenia

- Hereditary/Inherited Coagulopathies:
  - Factor V Leiden mutation
  - Prothrombin G20210A mutation
  - Protein C or S deficiency
  - Antithrombin deficiency
  - Hyperhomocysteinemia


HYPERCOAGULABLE STATE
Malignancy
Pregnancy and peri-partum period
Oestrogen therapy
Trauma or surgery of lower extremity, hip, abdomen or pelvis
Inflammatory bowel disease
Nephrotic syndrome
Sepsis
Thrombophilia
Virchow's triad
VASCULAR WALL INJURY
Trauma or surgery
Venepuncture
Chemical irritation
Heart valve disease or replacement
Atherosclerosis
Indwelling catheters
CIRCULATORY STASIS
Atrial fibrillation
Left ventricular dysfunction
Immobility or paralysis
Venous insufficiency or varicose veins
Venous obstruction from tumour, obesity or pregnancy



CLINICAL PRESENTATION: DEEP VENOUS THROMBOSIS

- Patients with DVT present with leg swelling, pain, warmth, and erythema
- Suspect DVT when symptoms are unilateral
- Assess for evidence of pulmonary embolism (dyspnea, pleuritic chest pain)
- Assess clinical pretest probability before ordering additional laboratory tests such as D-dimer or compression ultrasound

NOTE: proximal deep veins include popliteal, femoral, or iliac

PREDICTION TOOL: WELL'S CRITERIA DVT

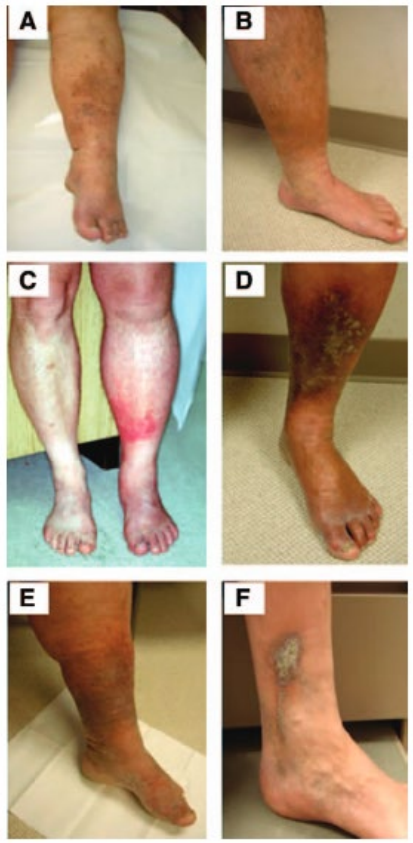
Active cancer Treatment or palliation within 6 months	No 0	Yes +1
Bedridden recently >3 days or major surgery within 12 weeks	No 0	Yes +1
Calf swelling >3 cm compared to the other leg Measured 10 cm below tibial tuberosity	No 0	Yes +1
Collateral (nonvaricose) superficial veins present	No 0	Yes +1
Entire leg swollen	No 0	Yes +1
Localized tenderness along the deep venous system	No 0	Yes +1
Pitting edema, confined to symptomatic leg	No 0	Yes +1
Paralysis, paresis, or recent plaster immobilization of the lower extremity	No 0	Yes +1
Previously documented DVT	No 0	Yes +1
Alternative diagnosis to DVT as likely or more likely	No 0	Yes -2

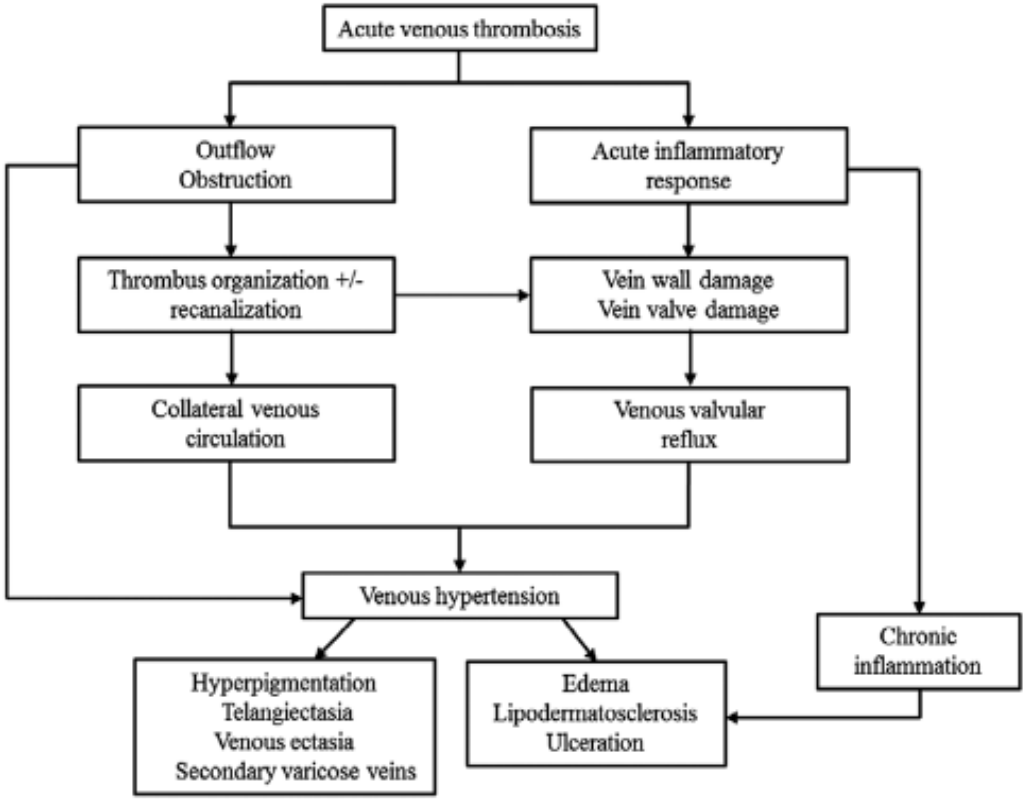
Wells' Score	Risk group	Prevalence of DVT
≤0	Low/unlikely	5%
1-2	Moderate	17%
≥3	High/likely	17-53%

Wells PS, et al. JAMA 2006 Jan 11;295(2):199-207.
Silveira PC, et al. JAMA Intern Med. 2015 Jul;175(7):1112-7.

COMPLICATIONS OF DVT: POST THROMBOTIC SYNDROME (PTS)

- 20-50% of patients with DVT develop PTS within a few months to a few years and 5 – 10 % of cases are severe





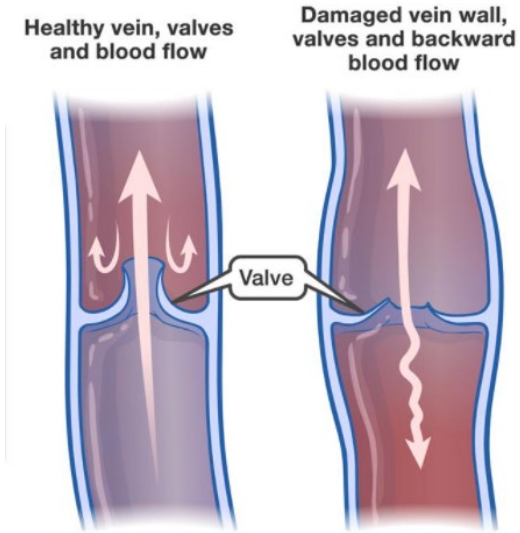


Table 2. Clinical Characteristics of PTS

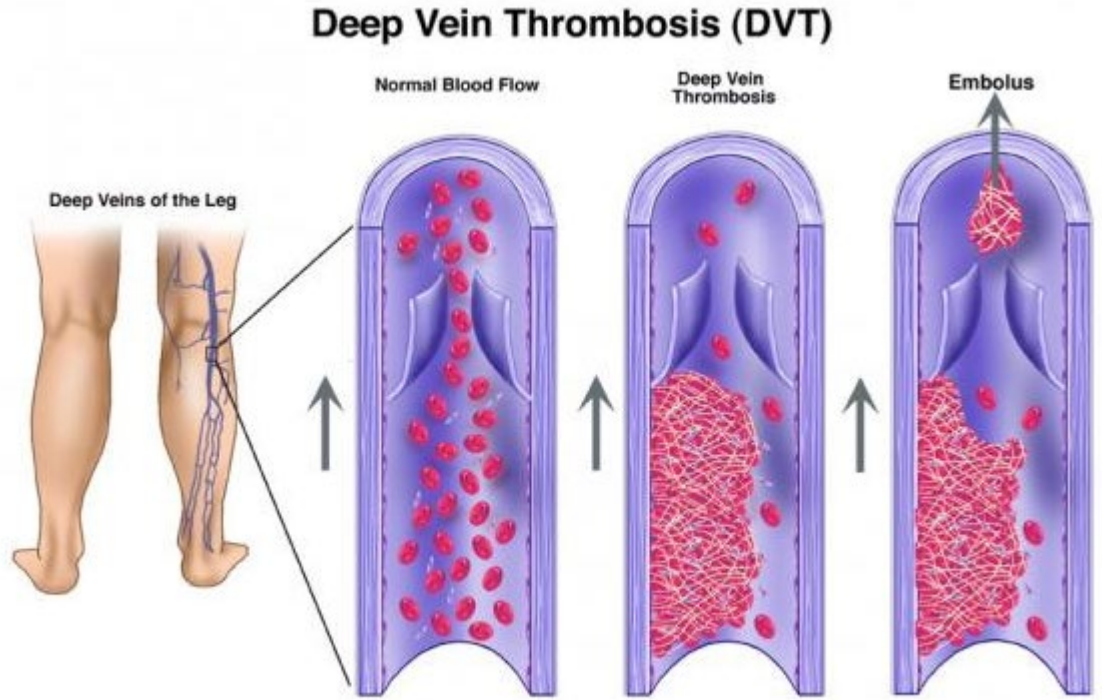
Symptoms	Clinical Signs
Pain	Edema
Sensation of swelling	Telangiectasia
Cramps	Venous dilatation/ectasia
Heaviness	Varicose veins
Fatigue	Redness
Itching	Cyanosis
Pruritis	Hyperpigmentation
Paresthesia	Eczema
Bursting pain	Pain during calf compression
Venous claudication	Lipodermatosclerosis
	Atrophie blanche
	Open or healed ulcers

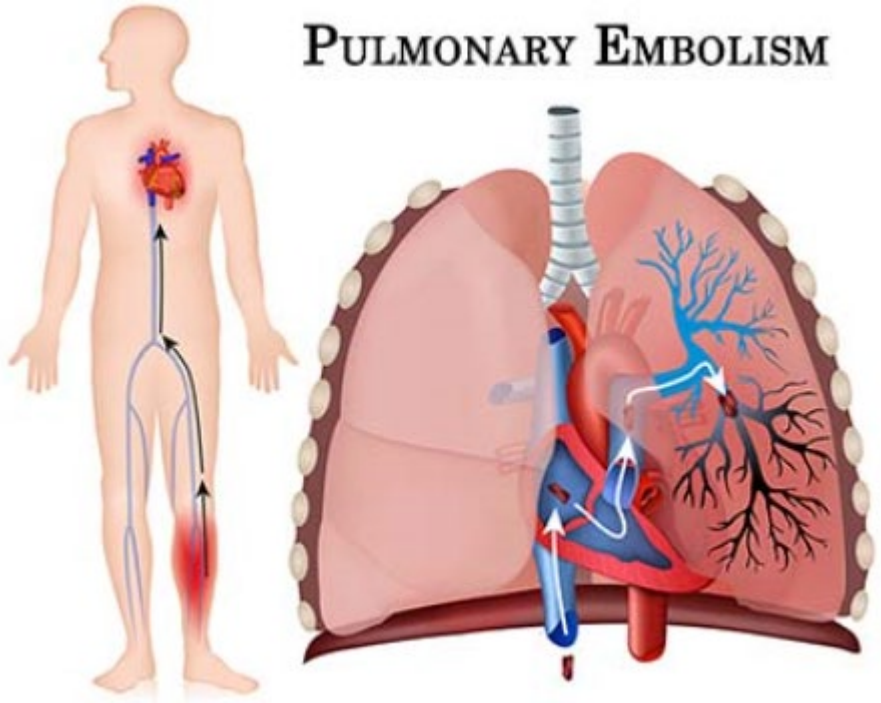
PTS indicates postthrombotic syndrome.

Kahn SR, et al. Circulation. 2014 Oct 28;130(18):1636-61.

COMPLICATIONS OF DVT: EMBOLIZATION

- Reminder: anticoagulants do not actively lyse or dissolve the blood clot or prevent it from embolizing, these agents prevent new clots from forming and the existing clot from extending





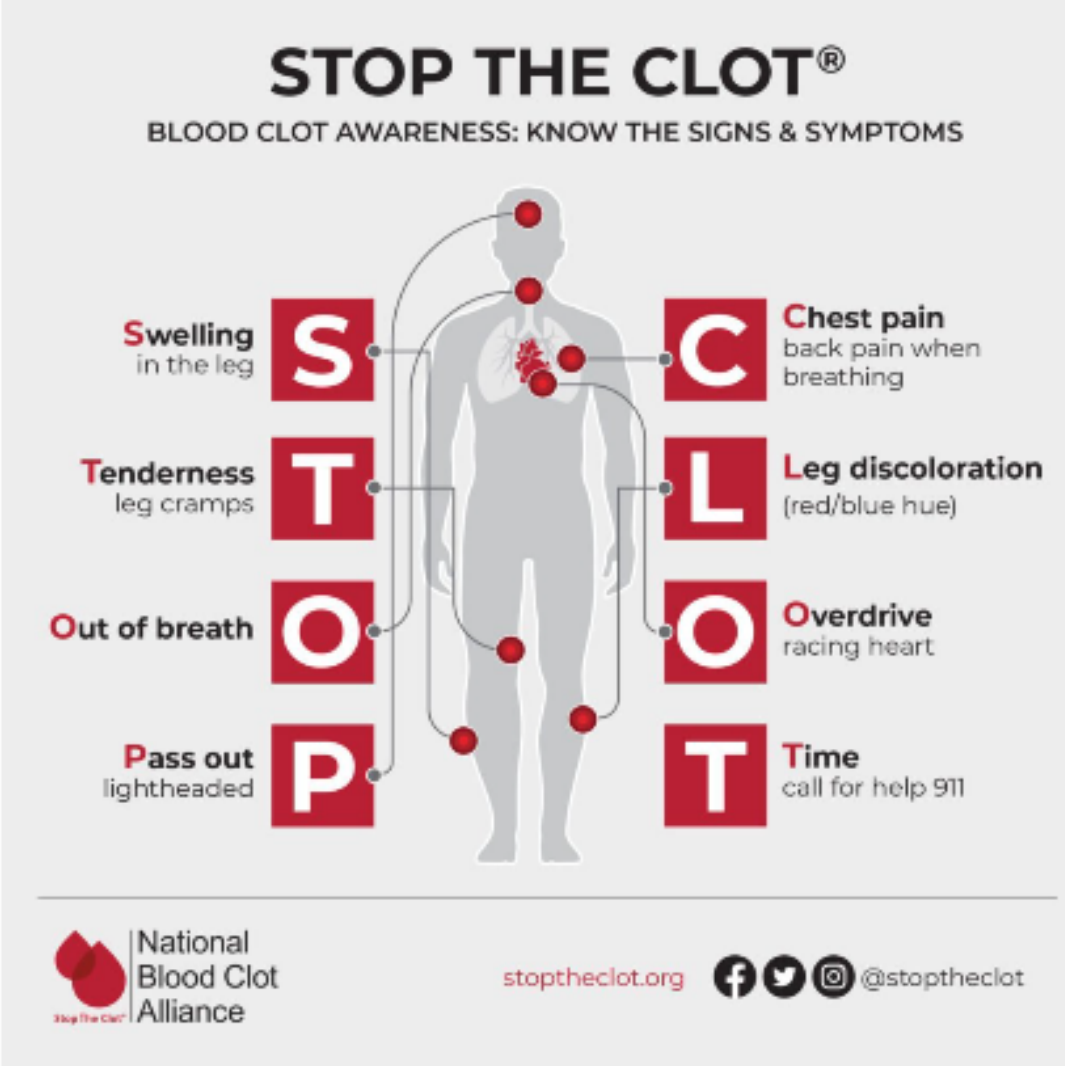
Pulmonary embolism (PE) occurs when clot break off from vein walls, most commonly from lower extremity DVT, and travels through the heart to the pulmonary arteries where it becomes lodged, blocking circulation to this area of lung tissue

Kahn SR, et al. Circulation. 2014 Oct 28;130(18):1636-61.

CLINICAL PRESENTATION: PULMONARY EMBOLISM

Signs and symptoms of PE:

- Shortness of breath
- Pleuritic chest pain
- Tachycardia
- Hemoptysis
- Low grade fever
- Tachypnea
- Dyspnea
- Diaphoresis
- Evidence of DVT
- Syncope
- Hypotension



Link MS, et al. Circulation. 2015 Nov 3;132(18 Suppl 2):S444-64

PREDICTION TOOLS FOR PULMONARY EMBOLISM

Pulmonary Embolism Wells Score

Share

Select Criteria:

- [ ] Symptoms of DVT (3 points)
- [ ] No alternative diagnosis better explains the illness (3 points)
- [ ] Tachycardia with pulse > 100 (1.5 points)
- [ ] Immobilization (>= 3 days) or surgery in the previous four weeks (1.5 points)
- [ ] Prior history of DVT or pulmonary embolism (1.5 points)
- [ ] Presence of hemoptysis (1 point)
- [ ] Presence of malignancy (1 point)

Results:

Total Criteria Point Count: 0

Reset Form

Pulmonary Embolism Risk Score Interpretation

Score > 6: High probability
Score >= 2 and <= 6: Moderate probability
Score < 2: Low Probability

Wells PS, et al. Ann Intern Med. 2001 Jul 17;135(2):98-107
Van Belle A, et al. JAMA. Jan 11 2006;295(2):172-179.

PERC Criteria

Box 1. Pulmonary Embolism Rule-out Criteria[a]

- Age ≥50
- Heart Rate ≥100 beats/min
- Sao_2 on room air < 95%
- Unilateral leg swelling
- Hemoptysis
- Recent surgery or trauma in the past 4 weeks
- Prior PE or DVT
- Hormone use

[a]If patient meets any of these criteria, further testing should be considered.

DVT = deep venous thrombosis; PE = pulmonary embolism.

Kline JA, et al. Prospective multicenter evaluation of the pulmonary embolism rule-out criteria. J Thromb Haemost 2008;6:772-80.

- D-dimer: small protein fragment, a cross-linked fibrin degradation product found in blood after a blood clot is degraded by fibrinolysis
- D-dimer has high sensitivity (96%) and low specificity (83%)
  - D-dimer is non-specific and is elevated in many other conditions: malignancy, sepsis, recent surgery, trauma, pregnancy, renal failure, COVID-19
- **Reference range**:
  - Negative D-dimer/normal level: < 500 ng/mL
  - Positive D-dimer level: > 500 ng/mL → not diagnostic for VTE
- **Age-adjusted D-dimer**: D-dimer values rise with age, further limiting sensitivity in older patients.
  - Higher D-dimer cutoff in older patients improves diagnostic utility and specificity
  - Only use for low to intermediate risk, DO NOT use for patients with high pretest probability when proceeding to imaging regardless of D-dimer is appropriate
  - Age-adjusted D-dimer = age [years] x 10 ng/mL for patients > 50 years

KNOWLEDGE CHECK:

- 67/M presents with right lower extremity redness without clearly demarcated borders and pain throughout the erythematous area. Calf is warm, appears minimally swollen > 3 cm compared to other leg, and some pitting edema noted along with a small break in the skin and small amount of purulent drainage.
- PMH: hypertension, BPH
- No recent surgery. He does admit to recent short trip to Cincinnati to watch a football game

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≤0	Low/unlikely	5%
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	Active cancer Treatment or palliation within 6 months	No 0	Yes +1
	Bedridden recently >3 days or major surgery within 12 weeks	No 0	Yes +1
→	Calf swelling >3 cm compared to the other leg Measured 10 cm below tibial tuberosity	No 0	Yes +1
	Collateral (nonvaricose) superficial veins present	No 0	Yes +1
	Entire leg swollen	No 0	Yes +1
	Localized tenderness along the deep venous system	No 0	Yes +1
→	Pitting edema, confined to symptomatic leg	No 0	Yes +1
	Paralysis, paresis, or recent plaster immobilization of the lower extremity	No 0	Yes +1
	Previously documented DVT	No 0	Yes +1
→	Alternative diagnosis to DVT as likely or more likely	No 0	Yes -2

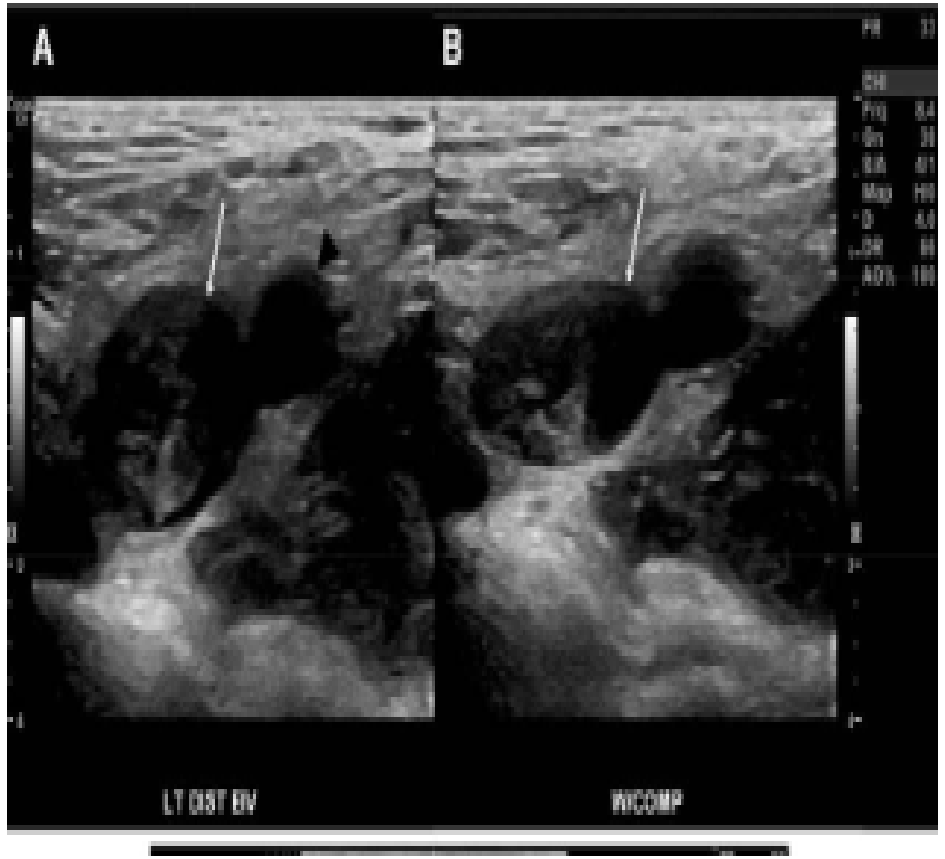
1 + 1 -2 = 0 Wells Score = Low risk DVT

KNOWLEDGE CHECK: CASE CONTINUED

- 67/M presents with right lower extremity redness without clearly demarcated borders and pain throughout the erythematous area. Calf is warm, appears minimally swollen > 3 cm compared to other leg, and some pitting edema noted along with a small break in the skin and small amount of purulent drainage.
- PMH: hypertension, BPH
- No recent surgery. He does admit to recent short trip to Cincinnati to watch a football game.
- D-dimer = 590 ng/mL
- Cut-off of "positive" D-dimer is > 500 ng/mL, age-adjusted D-dimer cutoff for this patient who is 67 years old = 10 ng/mL x age (65 years) = 650 ng/mL
  - D-dimer of 590 ng/mL is not above the age-adjusted cutoff of 650 ng/mL AND patient had low risk on pretest probability (Wells Score) AND patient has a more likely diagnosis of cellulitis → lower extremity ultrasound will likely be painful and based on clinical picture is not clinically indicated

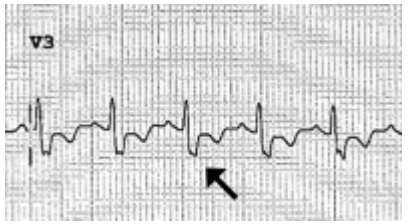
VTE IMAGING: ULTRASOUND FOR DVT

- Venous ultrasound is the standard imaging test for suspected DVT
- Compression duplex ultrasound (CDUS) is the preferred venous ultrasound test for the diagnosis of acute DVT
  - Compression at 2 cm intervals along femoral, popliteal, peroneal, posterior tibial veins
  - Loss of compressibility of the vein is a reliable indicator of the presence of thrombus within the vein and acutely thrombosed veins are commonly dilated with diameter greater than adjacent artery

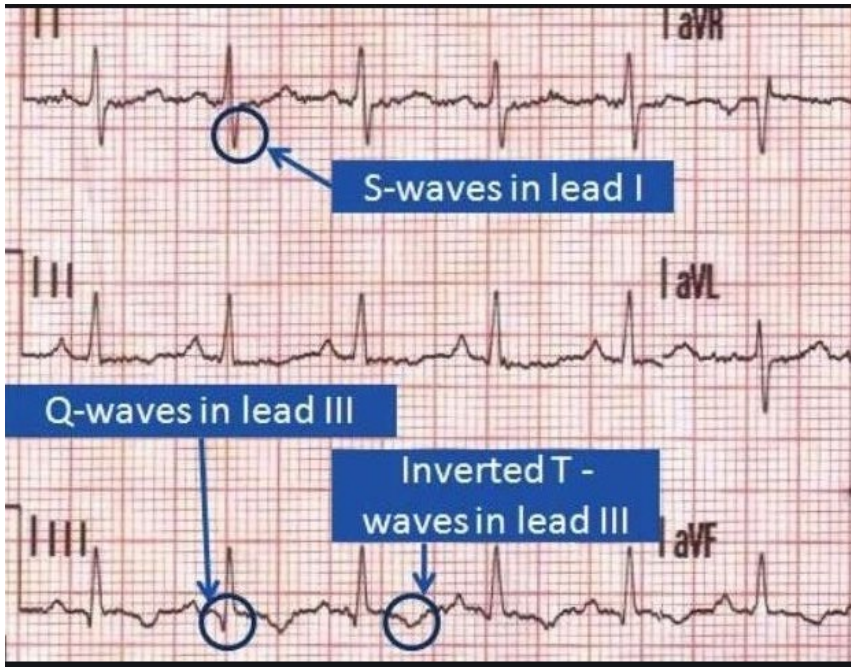


ECG CHANGES ASSOCIATED WITH PE

- Abrupt increase in pulmonary vascular resistance (due to mechanical obstruction and vasoconstriction secondary to inflammatory mediators and hypoxia) leads to right ventricular dilation and alterations in contractile properties
  - Sinus tachycardia
  - New right bundle branch block
  - T-wave inversions (precordial leads V1-V4)
  - S1Q3T3 (indicates right heart strain)

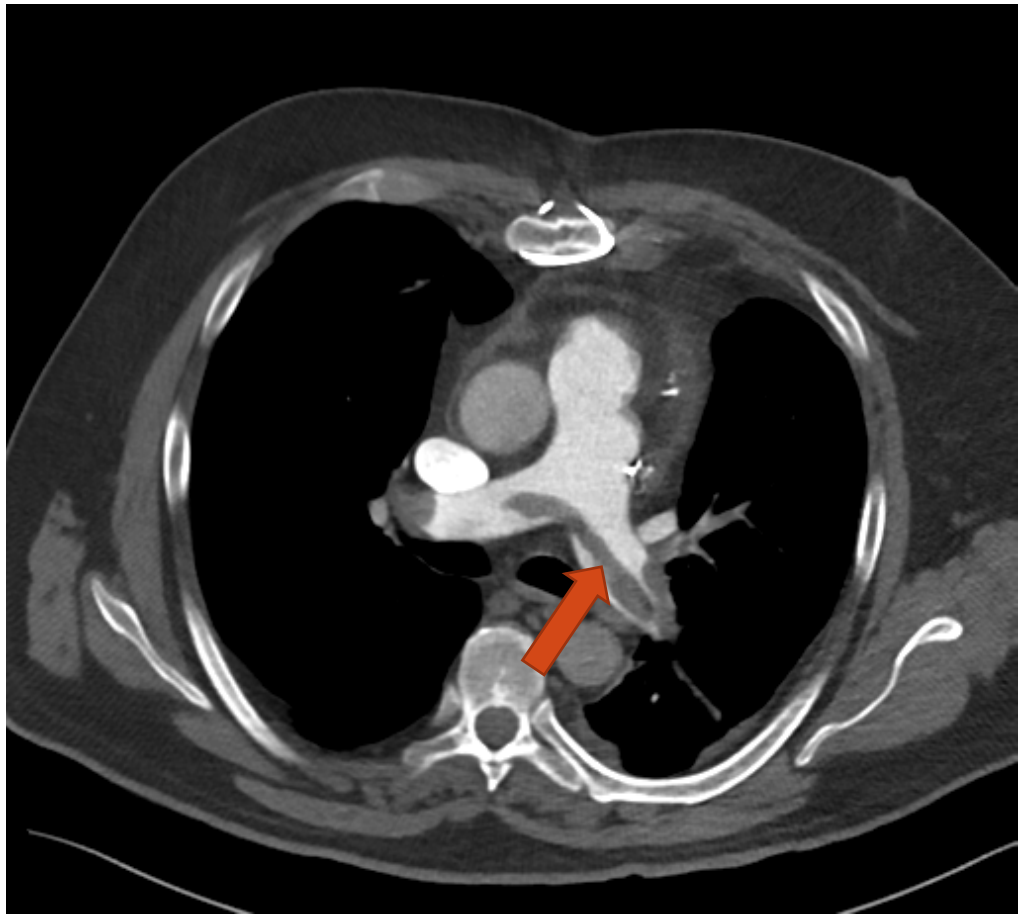


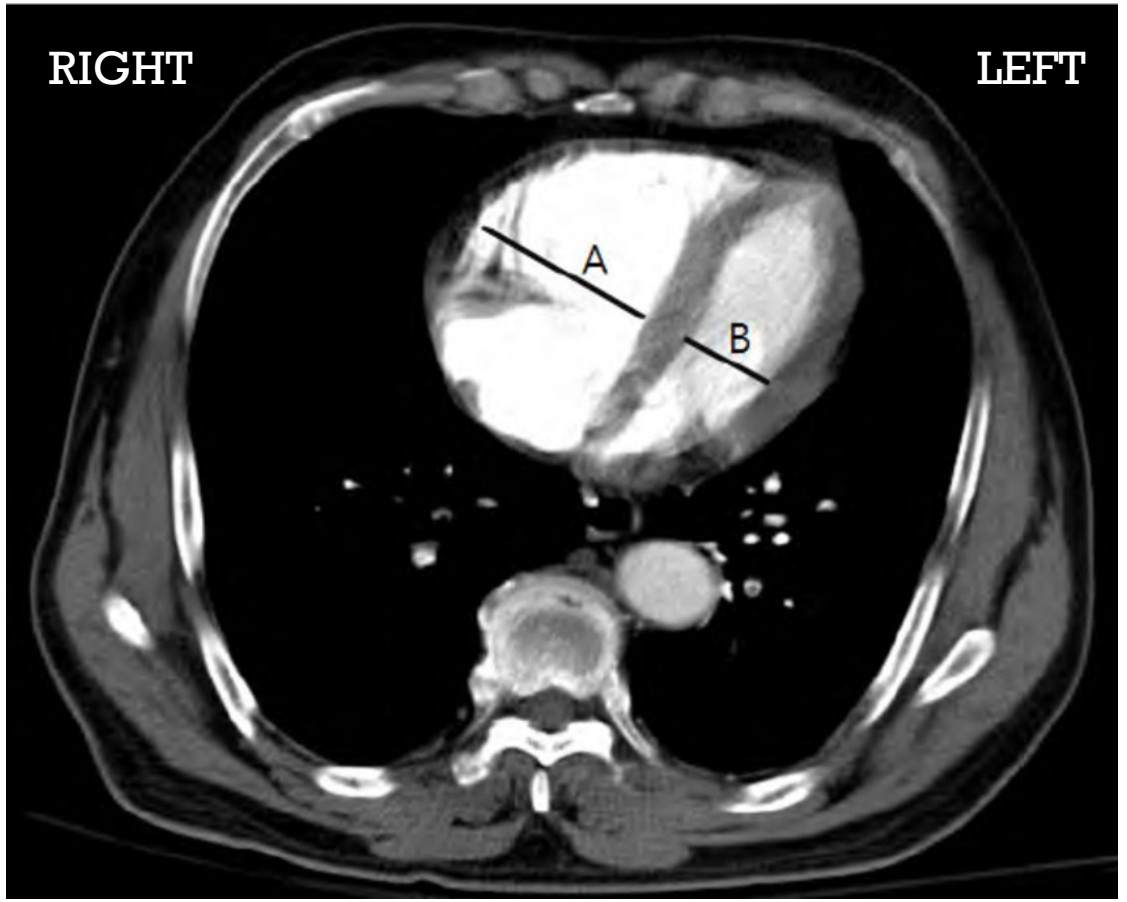
Right bundle branch block



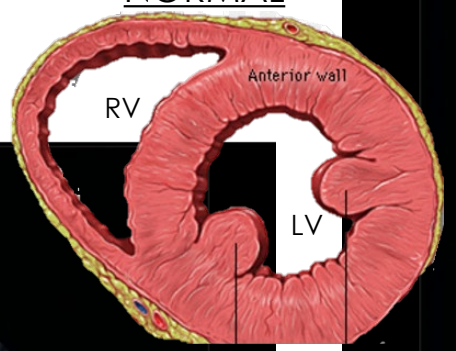
Digby, et al. The value of electrocardiographic abnormalities in the prognosis of pulmonary embolism: a consensus paper. Ann Noninvasive Electrocardiol. 2015 May;20(3):207-23.

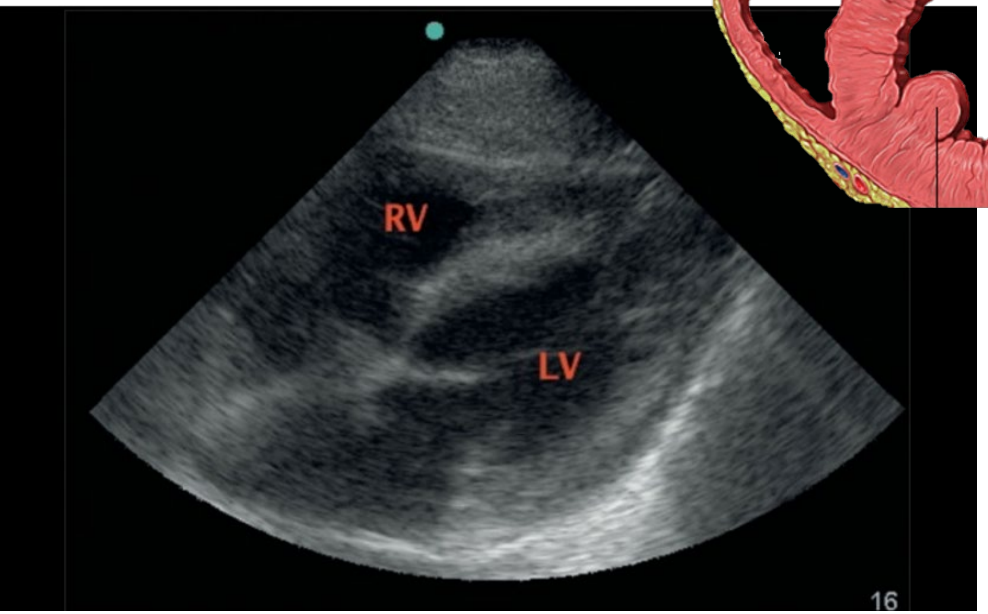
CT-ANGIOTRAM: IMAGING IN ACUTE PULMONARY EMBOLISM



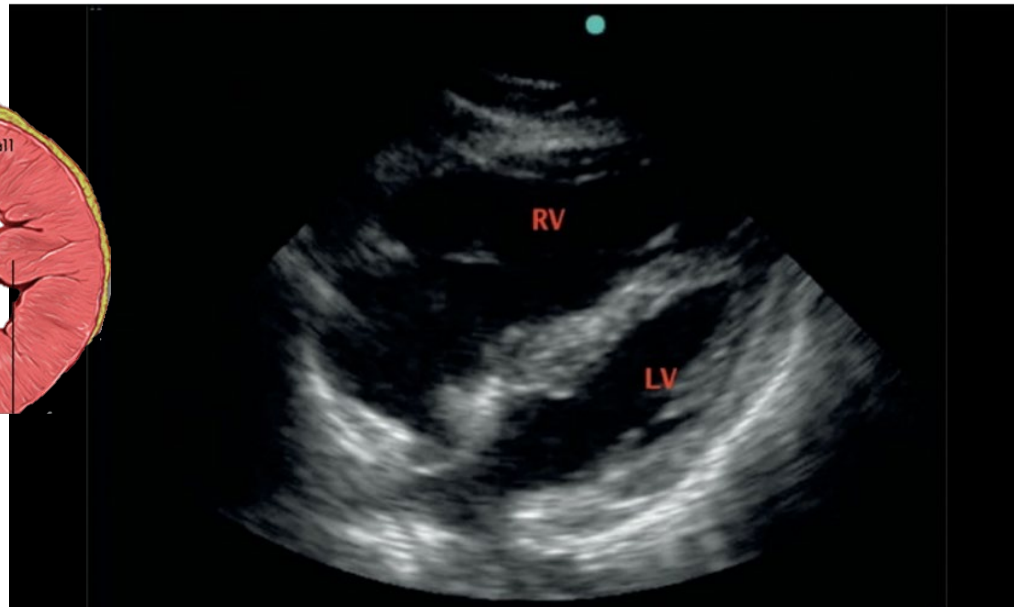


RIGHT VENTRICULAR STRAIN ON BEDSIDE ECHO



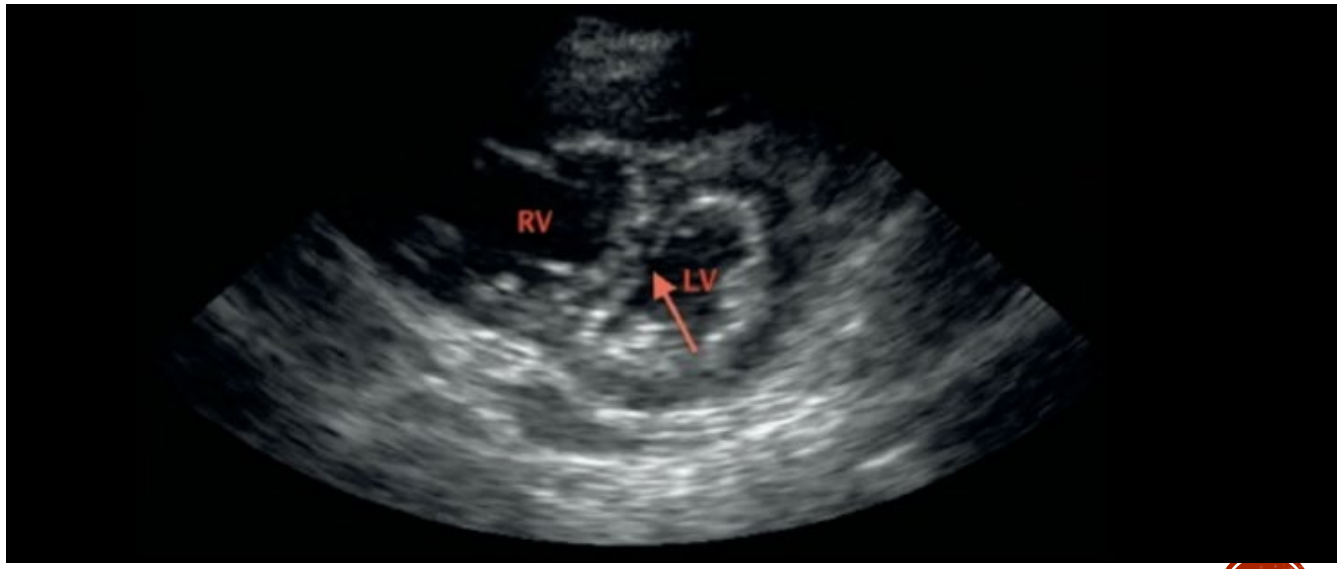


Subxiphoid view: Normal size right ventricle



Subxiphoid view: enlarged right ventricle

Parasternal view: D-shaped left ventricle secondary to right ventricular bowing into left ventricle



Echocardiographic signs of RV dysfunction secondary to pulmonary embolism:

- RV dilatation > 1:1
- Right ventricular systolic dysfunction
- McConnell's sign: mid RV wall hypokinesis with apical sparing

PATHOPHYSIOLOGY OF HEMODYNAMICALLY SIGNIFICANT PULMONARY EMBOLISM

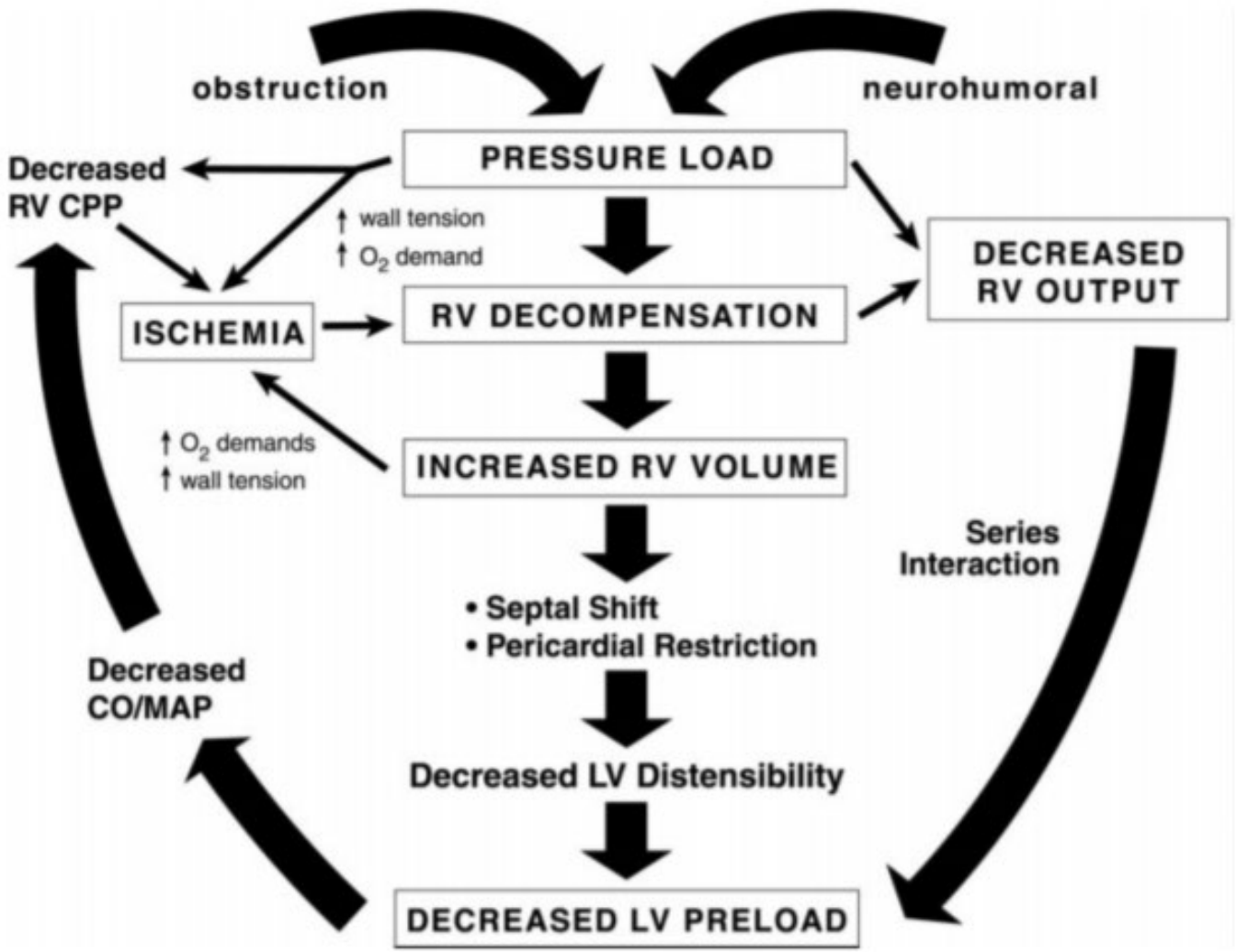


FIGURE 4. Pathophysiologic cycle of MPE.

Wood KE. Crit Care Clin. 2011 Oct;27(4):885-906, vi-vii

PULMONARY EMBOLISM PATHOPHYSIOLOGY

- Pulmonary embolism causes anatomical obstruction of pulmonary vasculature leading to increased pulmonary vascular resistance and eventual right ventricular strain, and decrease in cardiac output
  - Platelet aggregation leads to production of platelet-derived vasoconstrictors (thromboxane A2) which also increase pulmonary vascular resistance
  - Dilation of the right ventricle shifts interventricular septum into the left ventricle, decreasing left ventricular preload
  - RV compromise is also the result of oxygen demand outweighing oxygen supply creating ischemia
  - Hypoxemia may be present, however, PaO2 has been reported to be normal in approximately 30% of patients with PE

Wood KE. Crit Care Clin. 2011 Oct;27(4):885-906, vi-vii

"The Golden Hour"

PE presenting with shock = 3-7 fold increase in mortality, with a majority of deaths occurring within 1-hour of presentation

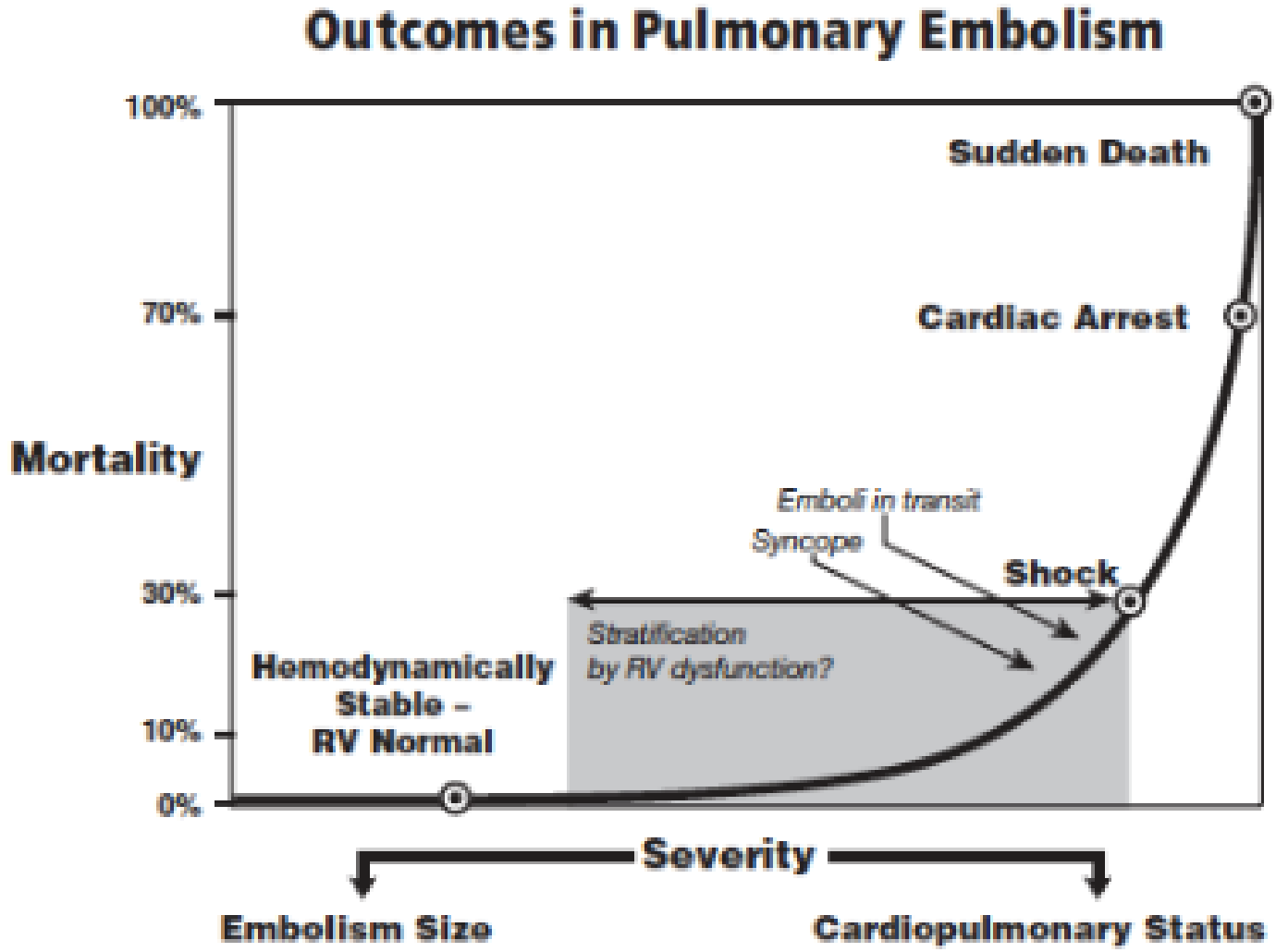


Fig. 1. Outcomes in PE. (*From* Wood KE. Major pulmonary embolism: review of a pathophysiologic approach to the golden hour of hemodynamically significant pulmonary embolism. Chest 2002;121;877–905; with permission.)

PULMONARY EMBOLISM SEVERITY INDEX (PESI) SCORE

Predictors	Points
Age (years)	1 point per year
Male sex	+ 10 points
COMORBIDITIES	
Cancer	+ 30 points
Heart failure	+ 10 points
Chronic lung disease	+ 10 points
CLINICAL FINDINGS	
Pulse ≥ 110 beats/min	+ 20 points
SBP < 100 mmHg	+ 30 points
RR > 30 breaths/min	+ 20 points
Temp < 36°C	+ 20 points
Altered mental status	+ 60 points
SaO2 < 90 %	+ 20 points

Class	Score	30-day mortality
I	≤ 65	1.1%
II	66 – 85	3.1%
III	86 – 105	6.5%
IV	106 – 125	10.4%
V	> 125	24.5%

Aujeskey et al. Derivation and Validation of a Prognostic Model for Pulmonary Embolism . Am J Crit Care Med. 2005. Vol 172:1041-1046.

SIMPLIFIED PESI SCORE

Criteria	Points
Age ≥ 80 years	+1
History of cancer	+1
History of chronic cardiopulmonary disease	+1
Heart rate ≥ 110 bpm	+1
Systolic BP < 100 mmHg	+1
O2 saturation < 90%	+1

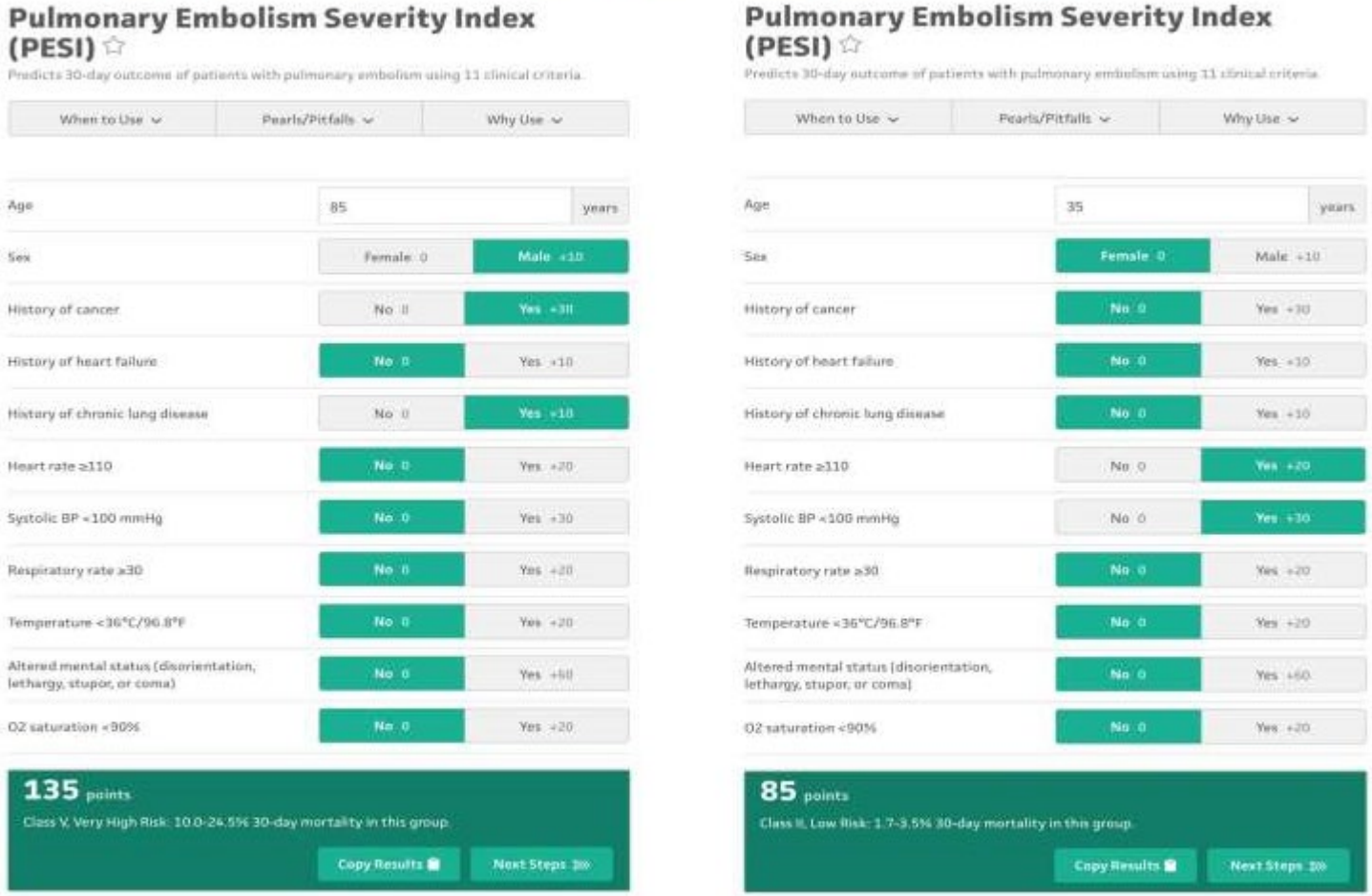
Score	Risk Group	Interpretation
0 points	Low	30-day mortality risk 1%
≥ 1 point	High	30-day mortality risk appx 10% (95% CI 8.5 – 13.2%)

Jimenez D, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med. 2010 Aug 9;170(15):1383-9.

RISK STRATIFICATION PE PEARLS

- Note the PESI and the sPESI are designed to predict all-cause 30-day mortality NOT the short-term risk acutely when a patient is being evaluated for the risk of deterioration/cardiovascular collapse in the hospital
- Example where high-risk patient may incorrectly receive a "low" risk category by PESI score

Examples of how the PESI score fails in acute prognosis of PE



PESI score fails because it was designed to detect 30-day all-cause mortality (not short-term PE-related mortality).

- **Left panel**: PESI may categorize elderly patients with comorbidities as "very high risk" - even if they have a tiny pulmonary embolism and have no acute physiologic abnormality at all.
- **Right panel**: PESI may categorize young patients without comorbidities as "low risk" - even if they have hemodynamic instability.

DEFINITIONS: MASSIVE AND SUBMASSIVE PULMONARY EMBOLISM

- Massive pulmonary embolism: **hemodynamic instability**
  - Hypotension defined as a systolic blood pressure < 90 mmHg or a drop in systolic blood pressure ≥ 40 mmHg from baseline
  - Hypotension that requires vasopressors or inotropic agents and is not explained by other causes such as sepsis, arrhythmia, left ventricular dysfunction from acute myocardial ischemia or infarction, hypovolemia
- Submassive pulmonary embolism: does not meet definition for massive PE (patient is hemodynamically stable), but with evidence of **right ventricular strain** on imaging (CT or echo) **and/or elevated cardiac biomarkers** (troponin/BNP)
  - Submassive-low risk PE: RV dilation/strain OR elevated cardiac biomarkers (troponin/BNP)
  - Submassive-high risk PE: RV dilation strain AND elevated cardiac biomarkers (troponin/BNP)

OTHER OMINOUS SIGNS: PATIENTS WITH PE AT HIGHER RISK FOR DETERIORATION

- In addition to evaluating for hemodynamic instability (hypotension), RV strain, and/or elevated cardiac biomarkers → look for other ominous signs
- Use clinical judgment to identify patients who are at high risk for hemodynamic collapse but who do not "yet" meet objective criteria for high risk submassive pulmonary embolism:
  - Presentation with syncope or near-syncope
  - Recent onset and accelerating symptoms
  - General appearance: sense of impending doom, diaphoresis, cool extremities, confusion
  - Bradycardia – may represent impending PEA/asystolic cardiac arrest
  - Persistent tachycardia: shock index (HR/SBP > 1) suggests poor hemodynamic reserve
  - Elevated lactate
  - Relative or absolute hypotension unresponsive to fluids
  - Tachypnea (even at rest or with very minimal exertion); persistent hypoxemia

RISK STRATIFICATION IN PULMONARY EMBOLISM

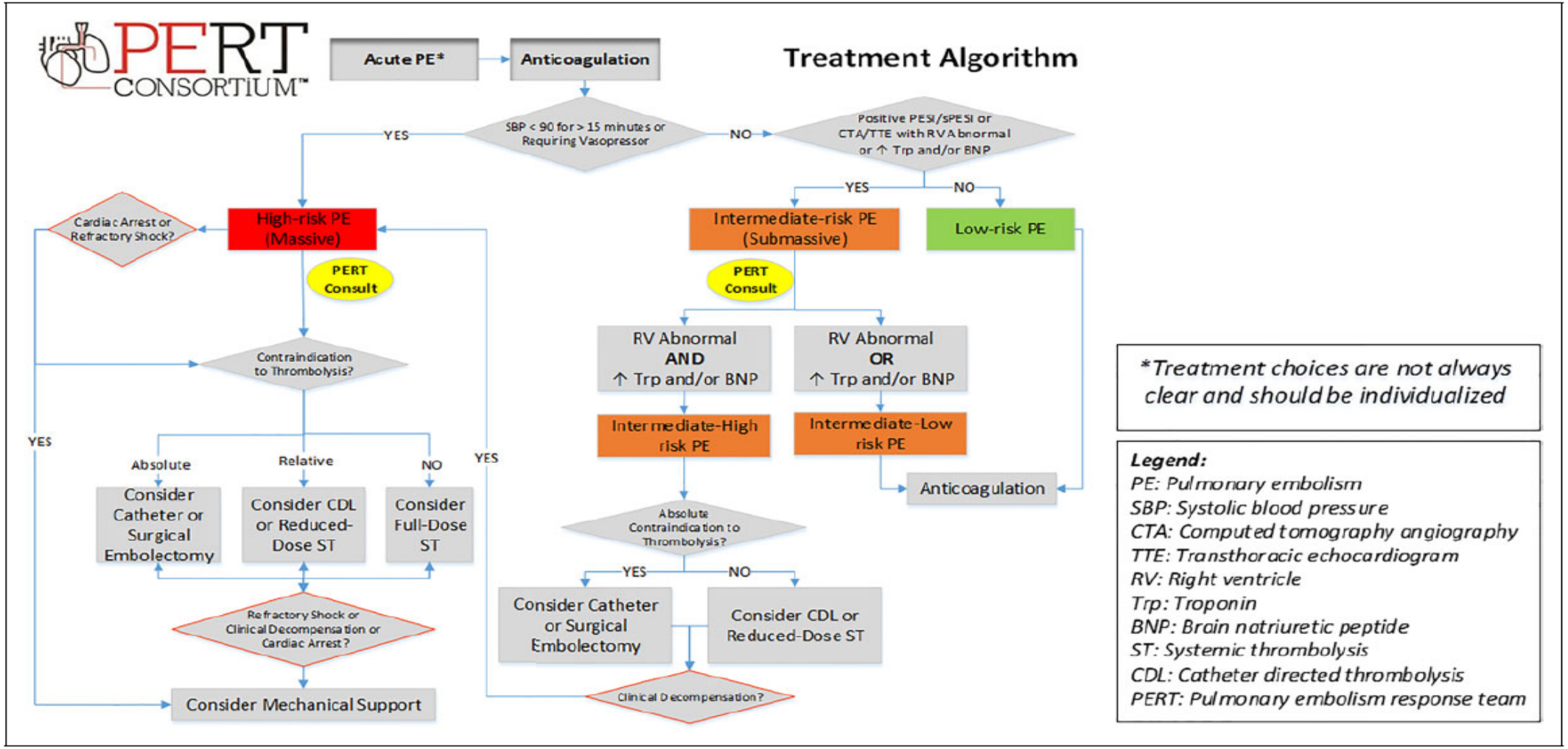


Figure 3. Pulmonary embolism treatment algorithm.

Rivera-Lebron B, et al. Diagnosis, Treatment and Follow Up of Acute Pulmonary Embolism; Consensus Practice from the PERT Consortium. Clin and Applied Thrombosis/Hemostasis. 2019;25:1-16.

TREATMENT PRINCIPLES: DVT

- Isolated distal DVT (i.e. calf DVT) without severe symptoms or risk factors for extension* → recommend serial imaging (repeat ultrasound once weekly for 2 weeks) and *only anticoagulate if* evidence of any propagation, even if extension remains confined to distal veins)
- Acute proximal DVT → anticoagulation alone over intervention (mechanical or thrombolytic)
  - DOACs over warfarin for treatment of VTE
  - Warfarin over DOACs in confirmed antiphospholipid antibody syndrome
  - If contraindication to anticoagulation → IVC filter placement

* D-dimer positive, extensive thrombosis > 5 cm in length, involves multiple veins, > 7 mm in diameter, thrombosis close to proximal vein, no reversible provoking factor, active cancer, history of VTE, inpatient, COVID-19, highly symptomatic, patient preference to avoid serial imaging

Stevens SM, et al. Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report. Chest. 2021 Dec;160(6):e545-e608.

TREATMENT PRINCIPLES: PULMONARY EMBOLISM

- Subsegmental PE (no involvement of more proximal pulmonary arteries) and no proximal DVT, AND low risk for recurrent VTE* → clinical surveillance over anticoagulation
- Acute PE without hypotension → anticoagulation alone
  - Low risk patients suitable for treatment at home (PESI < 85 or sPESI = 0)
  - If oral therapy, DOAC preferred over warfarin due to lower risk of bleeding, especially intracranial
  - If deterioration, switch to thrombolytic
- Acute PE with hypotension (SBP < 90 mmHg) → systemic thrombolytic (or catheter-directed thrombus removal if high bleeding risk or shock likely to cause death before systemic thrombolysis can take effect)

* Hospitalized or have reduced mobility for another reason, active cancer particularly if metastatic or being treated with chemotherapy, no reversible risk factor for VTE such as recent surgery, pregnancy

Stevens SM, et al. Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report. Chest. 2021 Dec;160(6):e545-e608.

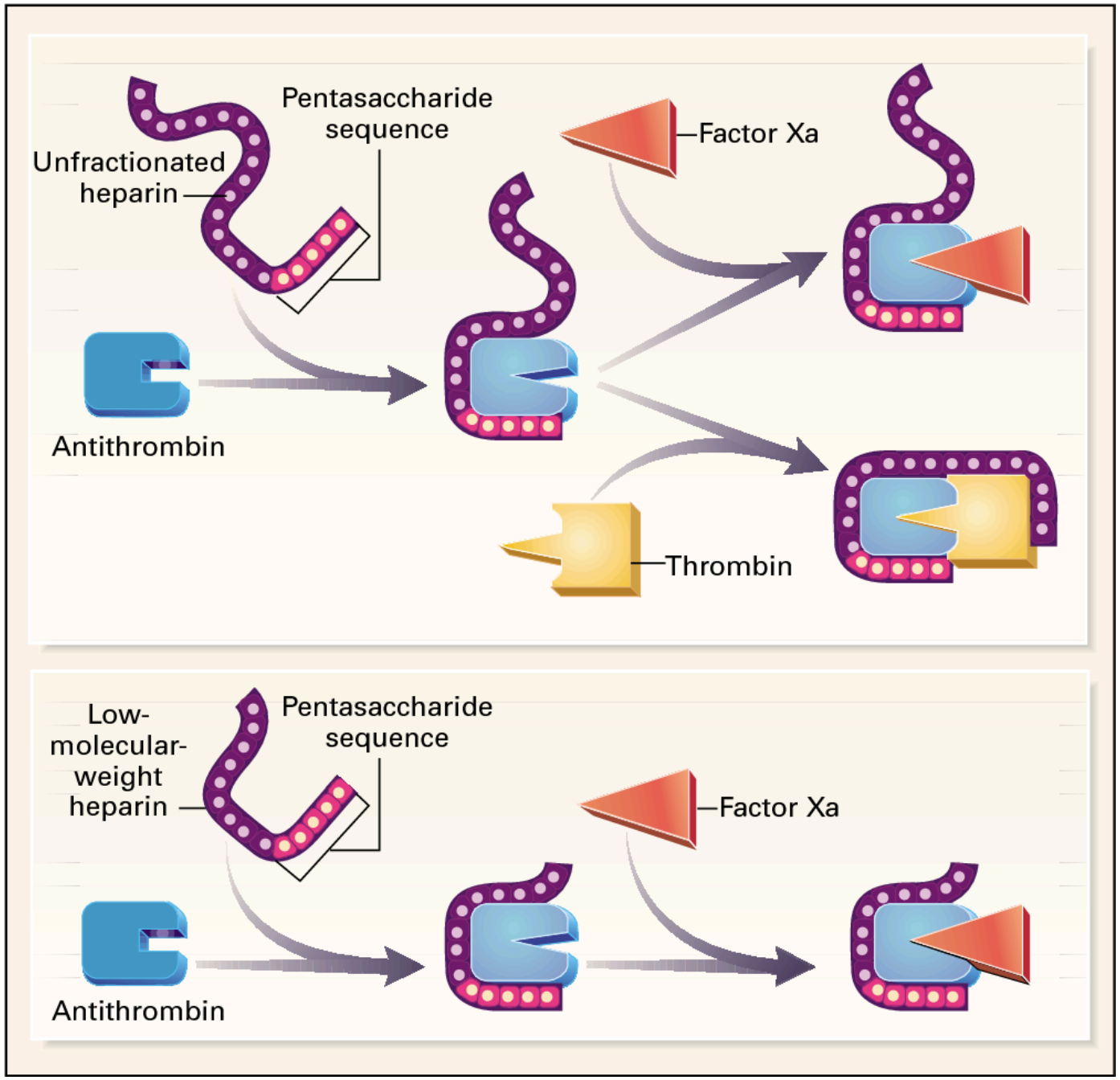
PARENTERAL TREATMENT OPTIONS: NON-MASSIVE PE

For patients with hospital admission for VTE treatment, parenteral anticoagulants are commonly used because of their fast onset of action and predictable duration; these characteristics are ideal if anticoagulation needs to be suspended for a procedure or bleeding event

	Dose	Considerations
Enoxaparin (Lovenox)	1 mg/kg SC BID CrCL < 30 mL/min: 1 mg/kg SC once daily	Anti-Xa measurements can be monitored in patients with stable renal function with CrCL near 30 mL/min, pregnancy, or obesity
Heparin	80 units/kg IV followed by 18 units/kg/hr titrated to therapeutic aPTT 74 – 99 seconds (MCHS)	Preferred if patient likely to receive systemic thrombolytic due to supporting clinical trials and shorter half-life
Fondaparinux (Arixtra)	< 50 kg: 5 mg once daily 50 – 100 kg: 7.5 mg once daily > 100 kg: 10 mg once daily	Dose adjustment for renal failure (caution CrCL < 50 mL/min and consider 50% dose; contraindicated CrCL < 30 mL/min); long half-life: 17 – 21 hours

PHARMACOKINETIC COMPARISON UFH VS. LMWH

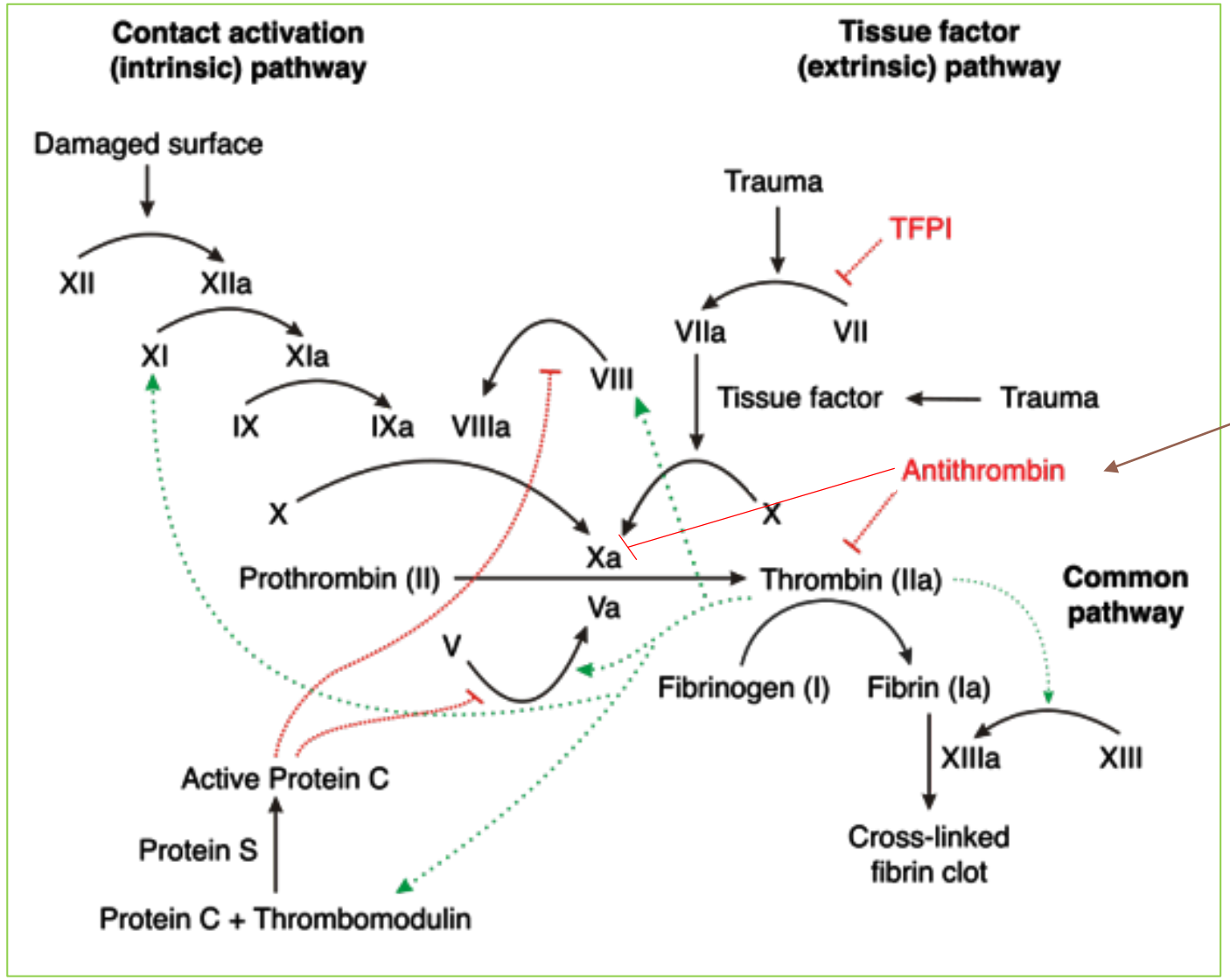
	Heparin	Enoxaparin
Onset	IV: Immediate SC: ~20 – 30 minutes (absorption 30-70%; erratic)	Peak: 3 – 5 hours
Duration/Half-life	Dose-dependent = mean 1.5 hours	4.5 – 7 hours
Elimination/ Metabolism	Depolymerization and desulfation via reticuloendothelial system primarily in liver and spleen	Hepatic metabolism; **renal elimination**
Hold before surgery/procedure	6 hours	12 hours
Dose adjustment in renal failure	No	Yes



MECHANISM OF HEPARIN PRODUCTS:

HEPARIN: NEGATIVELY CHARGED CARBOHYDRATE CHAINS WITH MOLECULAR WEIGHT 3,000 – 30,000 DA. BINDS ANTITHROMBIN III TO INHIBIT 1:1 FACTOR IIA (THROMBIN) AND FACTOR XA

LMWH: AVERAGE MOLECULAR WEIGHT 4500 DA; MOSTLY INHIBITS FACTOR XA



UFH and LMWH bind to antithrombin III enhancing the inhibition of factors

Heparin inhibits Factor IIa (thrombin) and Factor Xa (1:1)

Enoxaparin inhibits Factor Xa

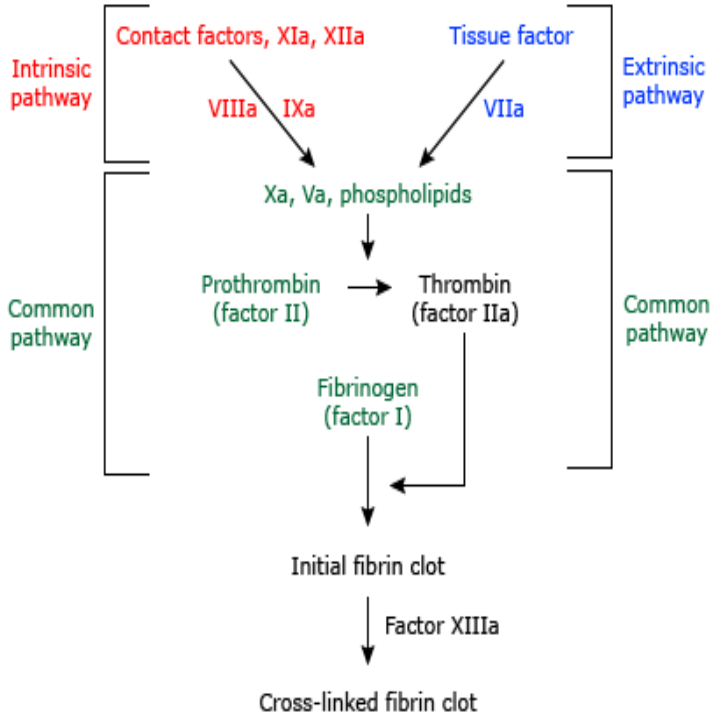
Note: heparin products can only inhibit free floating thrombin; therefore does not have fibrinolytic activity and cannot break down existing thrombi, but does effectively prevent clot propagation and development of new clots

Comparison of aPTT and anti-Xa

Activated partial thromboplastin time (aPTT)	Anti-Factor Xa
Measures the time it takes plasma to clot when exposed to substances that activate contact factors, which assess the intrinsic and common pathways of coagulation	More direct, pharmacokinetic measure of plasma heparin concentrations. Functional, chromogenic assay
Less than 50% of the variability in the aPTT can be explained by heparin plasma concentrations*	Independent of thomboplastin reagents, insensitive to underlying biologic variables
Goal is variable depending on reagents and instrumentation in different laboratories (aPTT that corresponds to anti-Xa concentration of 0.3 – 0.7 UI/mL can range from 1.6 up to 6 times the control)	Standard range: goal anti-Xa level for therapeutic unfractionated heparin = 0.3 – 0.7 IU/mL Note: recent oral Fxa inhibitor ingestion increases baseline anti-Xa level; use aPTT levels to monitor heparin until effect of DOAC subsides

*Factors that may prolong aPTT: DIC, leukemia, contact clotting factor deficiency, liver disease, medications (warfarin, DOACs, oritavancin), nutritional deficits, polycythemia, hemophilia-associated inhibitors, lupus anticoagulant (antiphospholipid antibody syndrome), recent pregnancy or miscarriage, **COVID-19**

Intrinsic, extrinsic, and common coagulation pathways



ENOXAPARIN: ANTI-XA MONITORING

MONITORING ANTI-Xa LEVELS

- INDICATIONS FOR MONITORING ANTI-Xa LEVELS:
  - Pregnancy
  - Obesity (> 20% above ideal body weight)
  - Low body weight (female: < 45 kg, male: < 57 kg)
  - Chronic renal insufficiency: CrCL < 30 mL/min

- Anti-Xa Level Reference Ranges (FOR ENOXAPARIN DOSING ONLY)
  - Obtain level after day 2 and drawn 4 hours after a dose of enoxaparin

Indication	Reference Range
Venous thromboembolism prophylaxis	0.1 – 0.4 units/mL
Therapeutic/treatment dosing (BID dosing)	0.5 – 1 units/mL*
Therapeutic/treatment dosing (once daily dosing)	1 – 2 units/mL

- Peak Anti-Xa Level Dosing Adjustment Nomogram for Treatment Dosing:

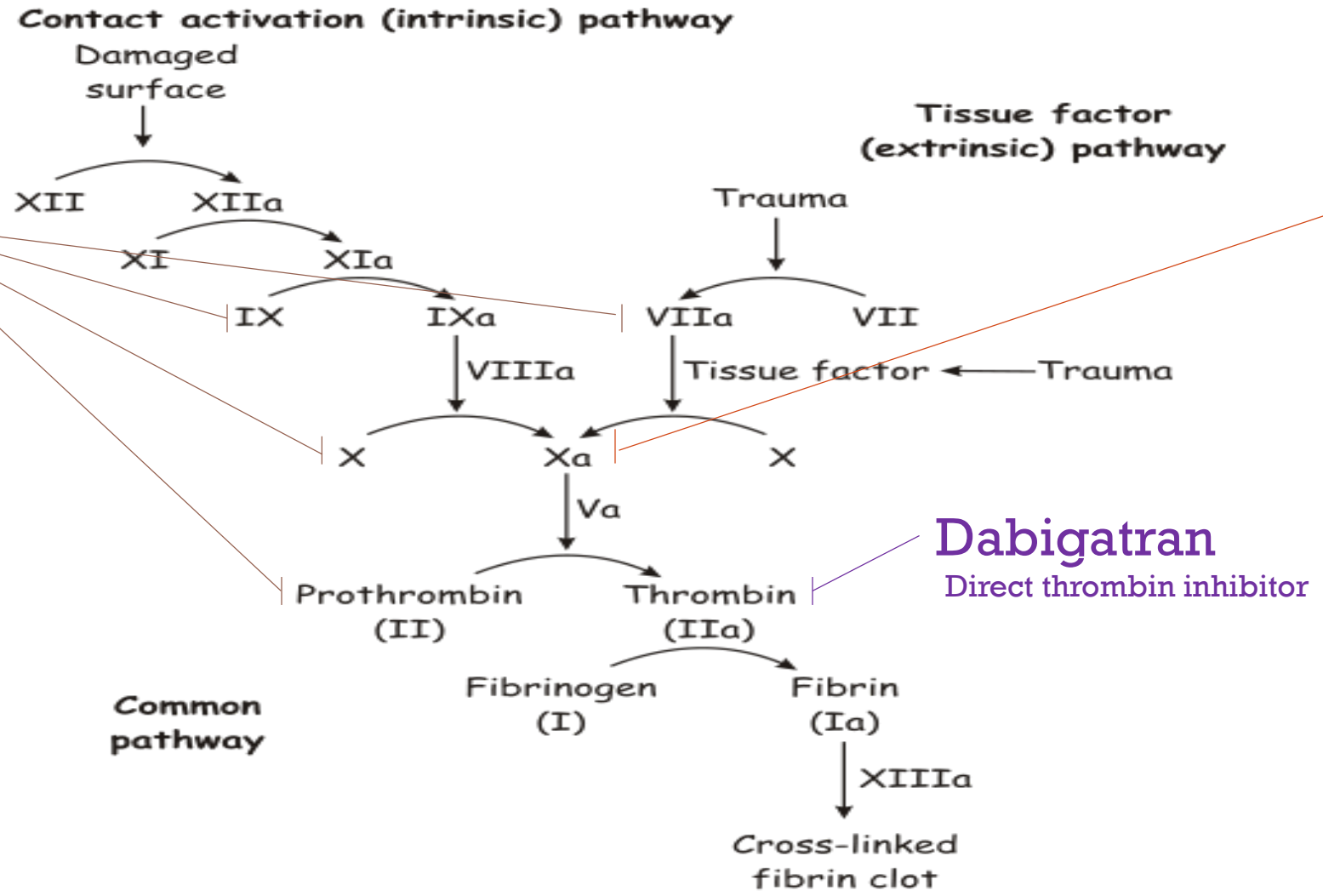
Anti-Factor Xa Level (IU/mL)	Hold Next Dose	Change Enoxaparin Dosage By	Repeat Anti-Factor Xa
Less than 0.35	No	Increase dose by 25%	4 hours after next dose
0.35 – 0.49	No	Increase dose by 10%	4 hours after next dose
0.5 – 1	No	At goal, no change	
1.1 – 1.5	No	Decrease dose by 20%	4 hours after next dose
> 1.6	Hold for 3 hours	Decrease dose by 30%	4 hours after next dose

Reminder: goal aPTT for UFH and LMWH are not the same
Goal anti-Xa for unfractionated heparin IV therapeutic dose) = 0.3 – 0.7 units/mL

DOACS: VENOUS THROMBOEMBOLISM DOSING

	VTE Treatment Dose	Renal Dose Adjustment	PK/PD/Comments
Apixaban (Eliquis)	10 mg BID x 7 days followed by 5 mg BID Reduced-intensity (after 6 months full dose): 2.5 mg BID	No renal adjustment in package label for VTE indication	Onset: 3 – 4 hours Excretion: 27% renal elimination as unchanged drug Half-life: ~ 12 hours
Rivaroxaban (Xarelto)	15 mg BID x 21 days followed by 20 mg daily with food Reduced-intensity (after 6 months full dose): 10 mg daily	CrCL < 30 mL/min: avoid	Bioavailability: 80 – 100% (with food); 66% (fasting) Excretion: 36% renal elimination as unchanged drug Half-life: 5 – 9 hours (elderly 11 – 13 hours)
Dabigatran (Pradaxa)	150 mg BID after 5 – 10 days initial therapy with parenteral anticoagulant	CrCL < 30 mL/min: avoid	DO NOT open capsules, do not administer by feeding tubes Bioavailability: 3 – 7% Half-life: 12 – 17 hours
Edoxaban (Savaysa)	60 mg daily after 5 – 10 days initial therapy with parenteral anticoagulant *Body weight ≤ 60 kg: 30 mg daily*	CrCL > 95 mL/min: avoid use CrCL 15 – 50 mL/min: 30 mg daily CrCL < 15 mL/min: avoid use	Onset: 1 – 2 hours Half-life: 10 – 14 hours Excretion: renal ~50% of total clearance

MECHANISM OF ORAL ANTICOAGULANTS



Warfarin

Block formation of vitamin-K dependent clotting factors 2, 7, 9, 10

Rivaroxaban
Apixaban
Edoxaban

Factor Xa Inhibitors

Dabigatran

Direct thrombin inhibitor

APIXABAN (ELIQUIS)

- Mechanism: factor Xa inhibitor
  Dose: VTE initial treatment: **apixaban 10 mg BID x 7 days followed by 5 mg PO BID**
- Dose VTE indefinite (reduced-intensity dosing): after at least 6 months of therapeutic dose: **apixaban 2.5 mg PO BID**
- Renal dose adjustment: no renal adjustment in package label for any degree of renal dysfunction including hemodialysis (14% dialyzable in 4 hours)
- Hepatic impairment: avoid use if Child-Pugh C
- Peak concentration: 3 – 4 hours after a dose
- Half-life: 12 hours
- Renal clearance: 27%
- Reversal: severe, life-threatening bleed: andexanet-alfa (Andexxa); some hospital protocols use prothrombin complex concentrate (PCC)

Lexi-Comp, Inc. (Lexi-Drugs™). Lexi-Comp, Inc.; March 2021

APIXABAN (ELIQUIS) DOSING

First 7 days

10 mg twice daily

AM: Two 5 mg tablets

PM: Two 5 mg tablets

After 7 days

5 mg twice daily

AM: One 5 mg tablet

PM: One 5 mg tablet

A LOW DOSE:

After at least 6 months of treatment for DVT or PE

2.5 mg twice daily

AM: One 2.5 mg tablet

PM: One 2.5 mg tablet

Available as a starter pack:
all 5 mg tablets #74
30-day supply

RIVAROXABAN (XARELTO)

- Mechanism: Factor Xa inhibitor
- Dose: VTE initial treatment: **15 mg PO BID with food for 21 days followed by 20 mg PO once daily with food**
- Dose indefinite anticoagulation (reduced intensity following ≥ 6 months of therapeutic dose): **10 PO once daily**
- Renal dose adjustment:
  - CrCL ≥ 30 mL/min: no dosage adjustment necessary
  - CrCL < 15 - 30 ml/min or hemodialysis: avoid use
- Hepatic impairment: avoid use if Child-Pugh B or C
- Peak concentration: 2 – 4 hours
- Half-life: 5 – 9 hours (elderly 11 – 13 hours)
- Renal clearance: 35%
- Reversal: severe, life-threatening bleed: andexanet alfa (Andexxa); some hospital protocols use prothrombin complex concentrate (PCC)

Lexi-Comp, Inc. (Lexi-Drugs™). Lexi-Comp, Inc.; March 2021

RIVAROXABAN (XARELTO) DOSING

First 21 days

One 15-mg tablet
Start with: **twice a day with food**

Tablets shown not actual size

On day 22

One 20-mg tablet
Switch to: **once a day with food**

Starter pack contains total # 51 (15 mg tabs #42 plus 20 mg tabs #9) for 30-day supply

EDOXABAN (SAVAYSA)

- Mechanism: Factor Xa inhibitor
- Dose: VTE: after at least 5 days of initial parenteral anticoatulation the transition to edoxaban:
  - Weight > 60 kg: **60 mg PO daily**
  - Weight ≤ 60 kg: 30 mg PO daily
- Renal dose adjustment:
  - NOTE DO NOT USE IF CRCL > 95 mL/min since proven to be less effective
  - CrCL 15 – 50 mL/min: 30 mg PO daily
  - CrCL < 15 mL/min or dialysis: avoid use
- Hepatic: Avoid use moderate/severe hepatic impairment
- Peak: 1 – 2 hours
- Excretion: 50% renal
  Half-life: 10 – 14 hours
- Reversal: Severe, life-threatening bleed: andexanet alfa (Andexxa); some hospital protocols use prothrombin complex concentrate (PCC)

Lexi-Comp, Inc. (Lexi-Drugs™). Lexi-Comp, Inc.; March

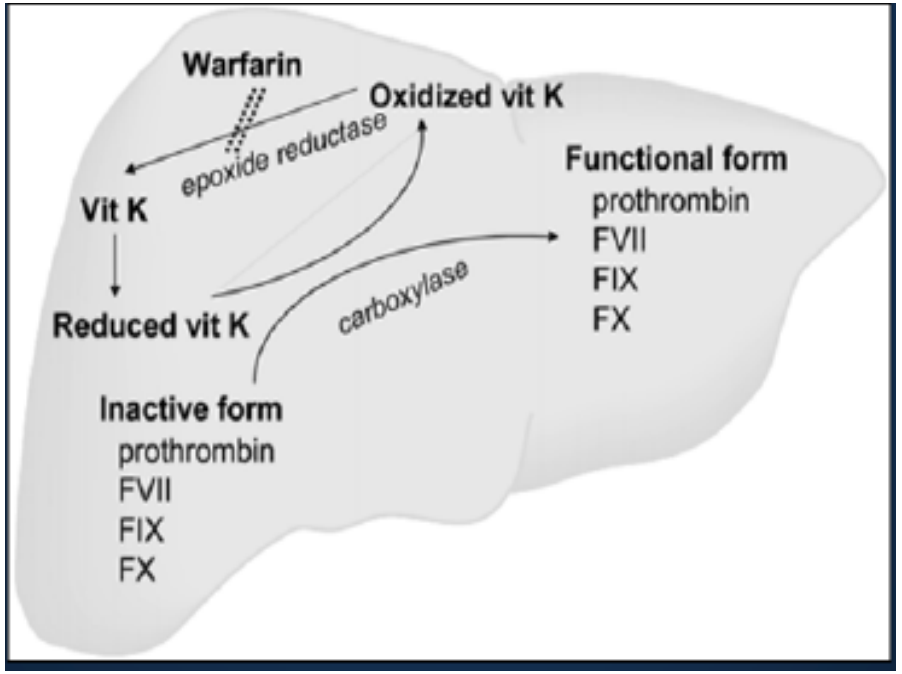
DABIGATRAN (PRADAXA)

- Mechanism: direct thrombin inhibitor
- Dose: VTE after at least 5 days of initial therapy with a parenteral anticoagulant, transition to **dabigatran 150 mg PO BID**
- Renal dose adjustment:
  - CrCL ≤ 30 ml/min or dialysis: avoid use
- Bioavailability: 3 – 7%: do not chew, break or open capsules (increase bioavailability by 75%)
- Peak concentration: 1 – 2 hours
- Half-life: 12 – 17 hours
- Renal clearance: 80%
- Reversal: idarucizumab (Praxbind) IV; if refractory bleeding consider re-dosing and/or hemodialysis

Lexi-Comp, Inc. (Lexi-Drugs™). Lexi-Comp, Inc.; March 2019

WARFARIN (COUMADIN)

- Mechanism: vitamin K antagonist
  - Deplete vitamin K reserves to reduce the synthesis of vitamin K dependent clotting factors II, VII, IX, X (as well as protein C and S)
- Dosing
  - Typical starting dose: 5 mg daily
    - Titrated based on INR levels requires overlap with therapeutic dosing parenteral bridge for minimum of 5 days
- Contraindicated in pregnancy; teratogenic including fetal CNS abnormalities
- Diet restrictions: keep vitamin K intake consistent (green leafy vegetables)
- Reversal: Vitamin K; severe, life-threatening bleed: prothrombin complex concentrate (Kcentra)



WARFARIN (COUMADIN)

- Why does warfarin require bridge/overlap with therapeutic parenteral agent for at least 5 days with initiation?
  - Warfarin blocks the formation of new vitamin-K dependent clotting factors but does not inhibit existing/circulating factors (prothrombin has long half-life 42-72 hours) and warfarin is not clinically effective until circulating levels of prothrombin are reduced (3-5 half-lives = at least 5 days)
- Renal dose adjustment: none
- Time to peak: onset of anticoagulant effect 24 – 72 hours; full therapeutic effect 5 – 7 days
- Hepatic metabolism: primarily CYP2C9
- Protein binding: 99%
- Half-life warfarin: 20 – 60 hours

	Effect	Half-life
Factor II (Prothrombin)	Clotting factor	42 – 72 hours
Factor X	Clotting factor	27 – 48 hours
Factor IX	Clotting factor	21 – 30 hours
Factor VII	Clotting factor	4 – 6 hours
Protein S	Anticoagulant	48 hours
Protein C	Anticoagulant	8 hours

Lexi-Comp, Inc. (Lexi-Drugs™). Lexi-Comp, Inc.; March 2021

WARFARIN MAJOR DRUG INTERACTIONS

Interacting Medication	Mechanism of interaction	Recommended Warfarin dose reduction
Amiodarone	Block metabolism of warfarin at CYP2CP	Reduce dose of warfarin 25 – 50%
Fluconazole	CYP2C9 and CYP3A4	25 – 50% of usual dose
Metronidazole	CYP2C9 and CYP3A4	Reduce up to 50% of usual dose
Sulfamethoxazole/ trimethoprim (Bactrim)	CYP2C9 and displacement of warfarin from protein	Reduce up to 50% of usual dose
Fluoroquinolones	CYP 1A2 and CYP3A4	Reduce dose 25% of usual dose or monitor more closely
NSAIDs	Inhibit platelet function, additive risk of bleeding while receiving anticoagulant	Recommended to avoid NSAIDS while on warfarin unless benefit outweighs risk
Rifampin	Induces CYP2C9	Increase warfarin dose during interaction
Phenobarbital	Induces CYP2C9	May need to increase warfarin dose

Lexi-Comp, Inc. (Lexi-Drugs™). Lexi-Comp, Inc.; March 2021

DOACS IN OBESITY

- In 2016 the International Society on Thrombosis and Haemostasis published guidance that suggested not using DOACs in patients with extreme obesity (BMI ≥ 40 kg/m2 or weight > 120 kg)
  - Concern due to lack of clinical evidence regarding efficacy and safety of DOACs in obesity
  - Pharmacokinetic and pharmacodynamic evaluations demonstrated alterations in obesity including lower peak plasma levels

- After review of current evidence, ISTH published updated communication in 2021:
  - "For treatment of VTE, we suggest that standard doses of rivaroxaban or apixaban are among appropriate anticoagulant options regardless of high BMI and weight. VKA, weight-based LMWH, and fondaparinux are also options"

	Phase 3 Studies Comparing DOACs with VKA in VTE		Phase 4 Studies Comparing DOAC with VKA in VTE (Including Retrospective and Prospective Studies and Meta-analyses)	
	BMI >35 or BW >120 kg	BMI >40	BMI >35 or BW >120 kg	BMI >40
Apixaban	X	X	Similar outcomes[6]	Similar outcomes[7,8]
Dabigatran	X	X	X	X
Edoxaban	X	X	X	X
Rivaroxaban	Similar outcomes[7]	X	Similar outcomes[8,10-10]	Similar outcomes[8,9]
Pooled DOAC	Similar outcomes[11]	X	Similar outcomes [12-16]	Similar outcomes[11]

Note: Similar outcome = DOAC compared with LMWH/VKA; X = no available data.

Abbreviations: BMI, body mass index, expressed in kg/m^2; BW, body weight; DOAC, direct oral anticoagulant; LMWH, low molecular weight heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Martin KA, et al.. J Thromb Haemost. 2021 Aug;19(8):1874-1882.

DOACS: CLINICALLY SIGNIFICANT DRUG INTERACTIONS

	Drug Interaction	Effect of DOAC	Recommendations
Dabigatran	P-gp inhibitors	Increase in concentration	Reduce dose or avoid depending on renal function
	P-gp inducers	Significant reduction in concentration	Avoid use
	Antacids	Moderate reduction in concentration	No dose adjustments required; consider spacing regiments by 2 h
Apixaban	Strong CYP3A4 inhibitor+P-gp inhibitor	Significant increase in concentration	Reduce dose or avoid use
	Moderate CYP3A4 inhibitor+P-gp inhibitor	Moderate increase in concentration	No dose adjustments required; use with caution Avoid use in patient with severe renal insufficiency
	Strong CYP3A4 inducer or P-gp inducer	Significant reduction concentration	Avoid use
Rivaroxaban	Strong CYP3A4 inhibitor+P-gp inhibitor	Significant increase in concentration	Avoid use
	Moderate CYP3A4 inhibitor+P-gp inhibitor	Moderate increase in concentration	No precaution necessary Avoid use in patient with severe renal insufficiency
	Strong CYP3A4 inducer or P-gp inducer	Significant reduction concentration	Avoid use

Drug Interaction	Examples
Strong CYP3A4 inhibitors + combined P-gp inhibitor	Itraconazole, ketoconazole, ritonavir
Moderate CYP3A4 inhibitor + combined P-gp inhibitor	Clarithromycin, diltiazem
Strong CYP3A4 inducer + combined P-gp inducer	Carbamazepine, rifampin, St. John's wort
Strong CYP3A4 inducers	Phenytoin
P-gp inhibitors	Amiodarone, clarithromycin, cyclosporine, dronedarone, erythromycin, ketoconazole, nifedipine, quinidine, ranolazine, ticagrelor, tolvaptan, verapamil
P-gp inducers	Rifampin

Chen A, et al. Direct Oral Anticoagulation Use: A Practical Guide to Common Clinical Challenges. J Am Heart Assoc. 2020 Jul 7;9(13):e017559.

SWITCHING BETWEEN ANTICOAGULANTS

From	To	Action
VKA	DOAC	Stop VKA and start DOAC once INR is <2 or lower INR limit of therapeutic range Measurement of INR before and after DOAC initiation is warranted as DOAC may falsely elevated INRs
Dabigatran	VKA	CrCl >50 mL/min: start VKA and stop dabigatran 3 d later CrCl 31 to 50 mL/min: start VKA and stop dabigatran 2 d later CrCl 15 to 30 mL/min: start VKA and stop dabigatran 1 d later
Rivaroxaban Apixaban	VKA	Start VKA and stop DOAC 3 d later OR for continuous anticoagulation: Stop DOAC and start LMWH and VKA at the time DOAC would have been due, then stop LMWH when INR is within therapeutic range
Edoxaban	VKA	Start VKA and stop DOAC 3 d later OR for continuous anticoagulation: Patients taking 60 mg: reduce edoxaban to 30 mg and start warfarin concomitantly. Stop edoxaban when INR >2 Patients taking 30 mg: reduce edoxaban to 15 mg and start warfarin concomitantly. Stop edoxaban when INR ≥2
Betrixaban	VKA	Start VKA and stop DOAC when INR > lower limit of therapeutic range
DOAC	DOAC	Stop current DOAC regimen and begin the new DOAC agent at the time next dose of DOAC is due
DOAC	Parental anticoagulant*	Stop DOAC and start parenteral anticoagulant at the same time that the next dose of DOAC would have been given
Parenteral anticoagulant*	DOAC	Intravenous: Start DOAC 0 to 2 h after stopping UFH Subcutaneous: Stop LMWH and start DOAC at the same time that the next dose of LMWH would have been given

CrCl indicates Cockcroft-Gault creatinine clearance; DOAC, direct oral anticoagulant; INR, International Normalized Ratio; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; and VKA, vitamin K antagonist.

*Parenteral anticoagulant: LMWH or UFH.

VTE IN CANCER: EVIDENCE FOR DOACS

- Patients with cancer are at a higher risk of VTE than the general population AND also a higher risk for bleeding which makes anticoagulation selection challenging
- Historically, LMWH *had been* the preferred agent for long-term anticoagulation in cancer-related VTE over warfarin due to evidence of superiority in prevention of recurrent VTE and lacking evidence for DOACs
- Growing evidence to support DOACs to treat and prevent recurrent cancer-related VTE as more convenient, non-parenteral alternative to LMWH
  - Edoxaban: NEJM 2018: 1046 patients with cancer-related VTE → edoxaban non-inferior to LMWH for prevention of recurrent VTE 11.3% vs 7.9%, p = 0.09); but higher bleeding with edoxaban 6.9% vs 4%, p = 0.04
  - Rivaroxaban: J Clin Oncol 2018 (SELECT-D): 672 patients with cancer-related VTE → rivaroxaban non-inferior to LMWH for prevention of recurrent VTE 11% vs 4% (HR 1.83; CI 9-19%); but higher clinically relevant major bleeding with rivaroxaban 13% vs 4%, HR 3.76 (CI 1.63-8.69)
  - Apixaban: NEJM 2020: 1,155 patients with cancer-related VTE → apixaban non-inferior to LMWH for prevention of recurrent VTE 7.9% vs 5.6%; p < 0.001 and no difference in major bleeding (3.8% vs. 4%, HR 0.82, p = 0.6)

Raskob, et al. NEJM 2018;378:615-24… Young, et al. J Clin Oncol 2018;36:2017-23 Agnelli, et al. NEJM 2020;382:1599-1607

VTE IN CANCER: NATIONAL GUIDELINES

- Guideline recommendations:
  - CHEST Guidelines 2021: DOACs over enoxaparin in cancer-related VTE (apixaban associated with less bleeding in GI malignancy)
  - ASH Guidelines 2021: initial (first week) treatment of cancer-related VTE with LMWH or DOAC (rivaroxaban or apixaban); followed by 3 – 6 months of DOAC (apixaban, rivaroxaban, or edoxaban) over LMWH → followed by long term DOAC in patients with active cancer
  - ASCO Guidelines 2019: initial treatment of cancer-related VTE with LMWH for initial 5 – 10 days, then option for rivaroxaban

- Duration of anticoagulation is long-term in patients with active cancer (cancer diagnosed within the previous 6 months, regionally advanced or metastatic, or for which treatment administered within 6 months)

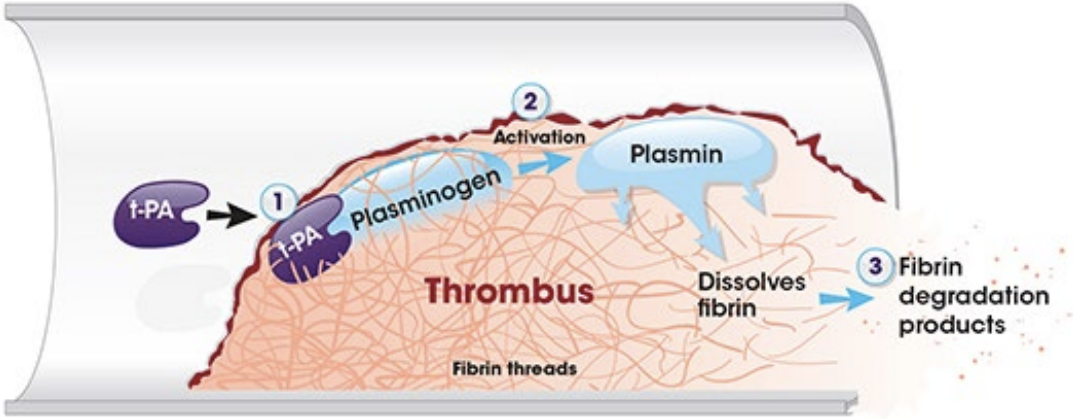
Lyman GH, Blood Adv. 2021 Feb 23;5(4):927-974. Stevens SM, et al. Chest. 2021 Dec;160(6):e545-e608. Key NS, et al. J Clin Oncol. 2020 Feb 10;38(5):496-520.

MASSIVE PULMONARY EMBOLISM: SYSTEMIC THROMBOLYTIC THERAPY: BASICS

- Systemic thrombolytic therapy accelerates resolution of PE → more rapid lowering of pulmonary artery pressure, increased arterial oxygenation, and resolution of perfusion defects on imaging
- Thrombolytic therapy increases risk of bleeding
- Patient selection is key and involves careful risk stratification to assess an individual patient's risk of dying from acute PE (and/or development of long-term pulmonary hypertension) and risk of bleeding

TREATMENT OF MASSIVE PE

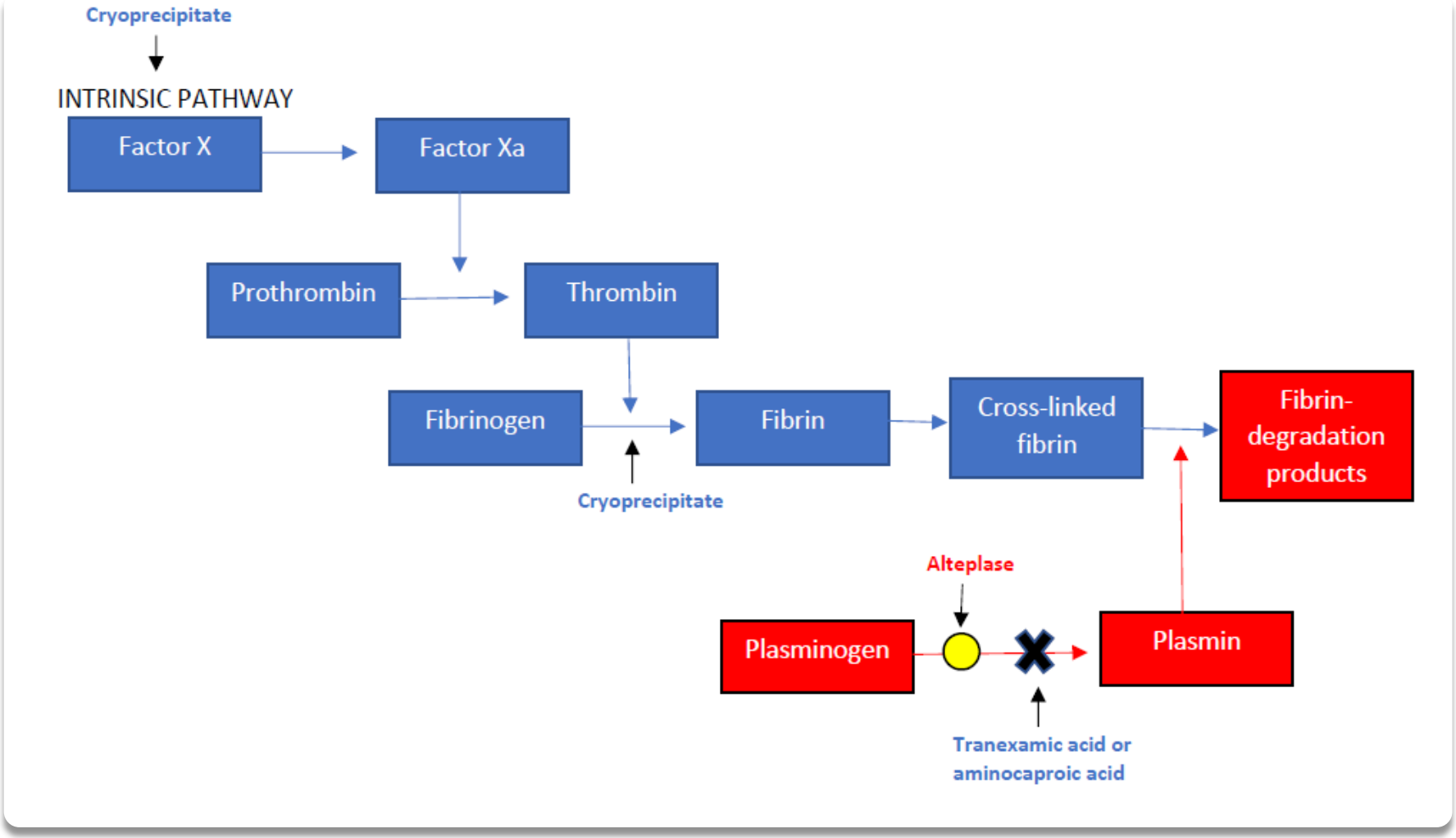
- **Dosing for Massive Pulmonary Embolism**:
  - FDA approved dosing: 100 mg IV administered over 2 hours peripherally
  - *If tPA administered; hold heparin during infusion of tPA. Obtain aptt 1 hour after completion of tPA and resume heparin when aptt less than upper limit of therapeutic range without heparin bolus dose*
- **FDA-approved for acute massive PE**
- **Mechanism:** inhibits fibrinolysis by binding to fibrin in a thrombus and converts entrapped plasminogen to plasmin



1 Recombinant t-PA (alteplase) binds to fibrin in thrombus 2 converts entrapped plasminogen to plasmin that 3 initiates local fibrinolysis.

Activase (Alteplase) Package Insert. South San Francisco, CA: Genentech, Inc; 2015.

ALTEPLASE: MECHANISM OF ACTION



Half-life: 5 minutes

Duration: > 50% in plasma cleared in 5 minutes after infusion stopped, 80% cleared in 10 minutes; fibrinolytic activity for up to 1 hour

Note: consumptive coagulopathy may persist for ~ 24 hours (the degree to which is patient specific). Hypofibrinogenemia (fibrinogen < 150 mg/dL) is a risk factor for sICH

CLINICAL EVIDENCE: SYSTEMIC TPA SUBMASSIVE PE

- PEITHO study: 1,005 patients randomized to tenecteplase vs placebo for "intermediate risk PE" (submassive PE); all-cause mortality or hemodynamic decompensation at 7 days 2.6% vs. 5.6% (p = 0.02; NNT 33)
- Reduction in risk for hemodynamic decompensation (1.6% vs 5%; p = 0.002), but not mortality (1.2% vs 1.8%; p = 0.42)
- Bleeding:
  - Major extracranial 6.3% vs 1.2% p < 0.001, NNH 20; hemorrhagic stroke 2% vs 0.2%, p = 0.003
  - Note: higher incidence of bleeding in age ≥ 75 years

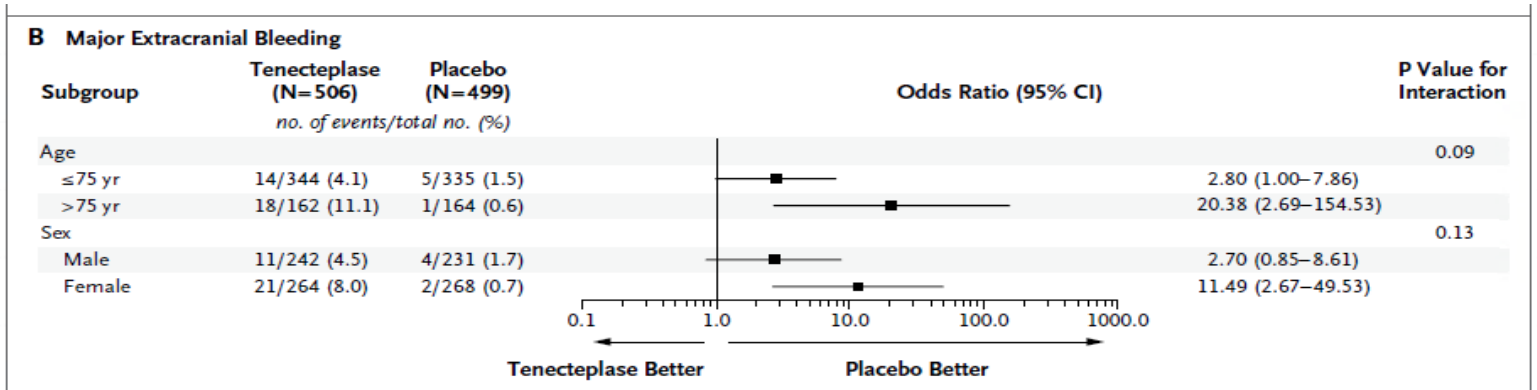


Figure 1. Efficacy and Safety Outcomes in Prespecified Subgroups.
Panel A shows the primary efficacy outcome (death or hemodynamic decompensation), and Panel B shows a safety outcome (major extracranial bleeding), both within 7 days after randomization.

Meyer, et al. NEJM 2014;370:1402-11.

TPA IN CARDIAC ARREST: ACLS 2020 GUIDELINES

- Confirmed pulmonary embolism as the precipitant of cardiac arrest → thrombolysis, surgical embolectomy, and mechanical embolectomy are reasonable emergency treatment options
  - "The risk of major bleeding in patients receiving thrombolysis and CPR is relatively low"
- Suspected pulmonary embolism as cause of cardiac arrest → thrombolysis may be considered
  - "PE is difficult to diagnose in the intra-arrest setting, and when ROSC is not obtained and PE is strongly suspected, the evidence supports consideration of thrombolysis"

Dose of alteplase during cardiac arrest:

Alteplase 50 mg IV bolus with an option for repeat bolus in 15 minutes if no ROSC (alternative single weight-based dose 0.6 mg/kg IV bolus (max 50 mg))

Note: thrombolysis is NOT contraindicated when chest compressions have been provided or continued

TPA FOR PE

- Contraindications differ depending on clinical scenario
- The severity of the PE must be considered to determine whether the bleeding risk is significant enough to withhold a thrombolytic
- Remember mortality in submassive PE = 3 – 15% and 65% for PE causing cardiac arrest

Table 3. Contraindications to Systemic Thrombolysis in PE

	Massive PE Causing Cardiac Arrest	Massive (high risk) PE	Submassive (intermediate risk) PE
Absolute contraindications	• None	• Active internal bleeding • Recent intracranial bleeding	• Structural intracranial disease • Previous intracranial hemorrhage • Ischemic stroke within 3 mo • Active internal bleeding • Recent brain or spinal surgery • Recent head trauma with fracture or brain injury • Bleeding diathesis
Relative contraindications	• Active internal bleeding • Recent intracranial bleeding	• Structural intracranial disease • Previous intracranial hemorrhage • Ischemic stroke within 3 mo • Recent brain or spinal surgery • Recent head trauma with fracture or brain injury • Bleeding diathesis	• SBP > 180 mm Hg • Diastolic blood pressure > 110 mm Hg • Recent bleeding (non-intracranial) • Recent surgery • Recent invasive procedure • Ischemic stroke > 3 mo previously • Anticoagulated • Traumatic CPR • Pericarditis or pericardial fluid • Diabetic retinopathy • Pregnancy • Age > 75 • Low body weight < 65 kg • Female sex • African American

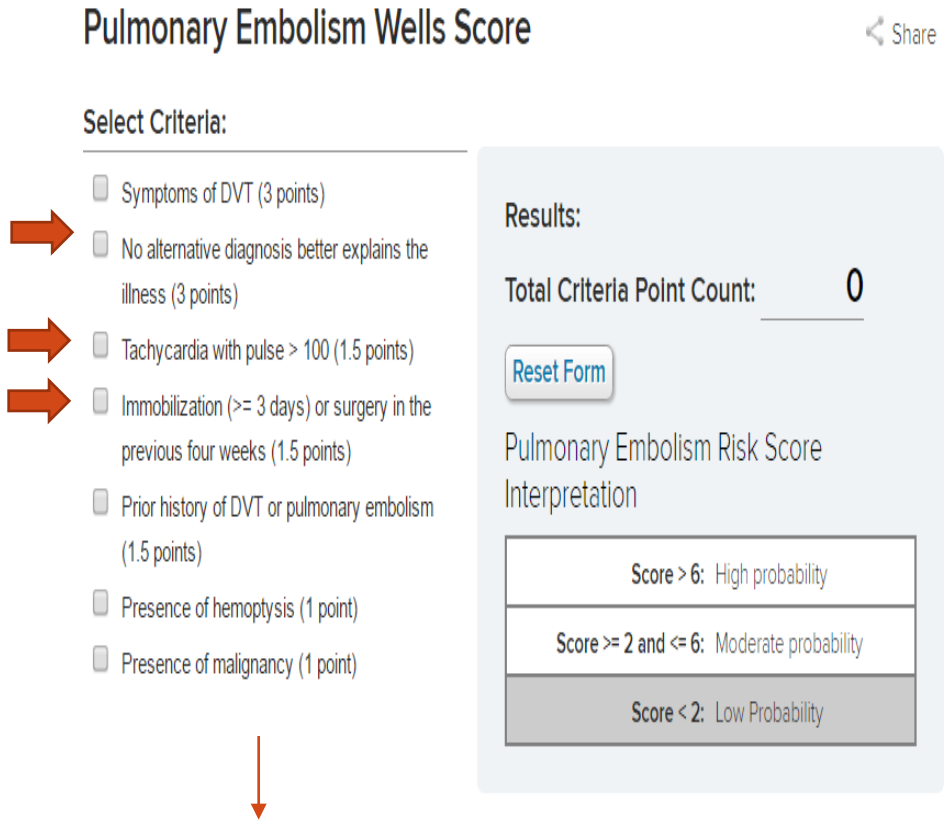
CPR = cardiopulmonary resuscitation.

Information from: Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest 2016;149:315-52; and Fengler BT, Brady WJ. Fibrinolytic therapy in pulmonary embolism: an evidence-based treatment algorithm. Am J Emerg Med 2009;27:84-95.

REVIEW CASE

- 59-year-old male patient with recent history of prolonged hospitalization due to COVID-19, who had recovered from his respiratory symptoms over the past 3 weeks but now presents to the hospital with sudden onset chest tightness, shortness of breath, and near syncopal episode upon standing
- PMH: HTN and DM2
- He appears pale and diaphoretic while sitting at rest
- Vital signs: HR 108 bpm BP: 100/82 RR: 24 O2 sat 94% Tmax 98 F
- BMP and CBC WNL
- INITIATE parenteral anticoagulation even before confirmation of diagnosis due to high likelihood of pulmonary embolism in this case

Use a validated tool to predict if PE is the most likely explanation for this patient's symptoms:



Wells score = 6: high probability of PE → warrants CT angiogram for confirmation of diagnosis

PERC Criteria

Box 1. Pulmonary Embolism Rule-out Criteria[a]

- Age ≥50
- Heart Rate ≥100 beats/min
- Sao_2 on room air < 95%
- Unilateral leg swelling
- Hemoptysis
- Recent surgery or trauma in the past 4 weeks
- Prior PE or DVT
- Hormone use

[a]If patient meets any of these criteria, further testing should be considered.

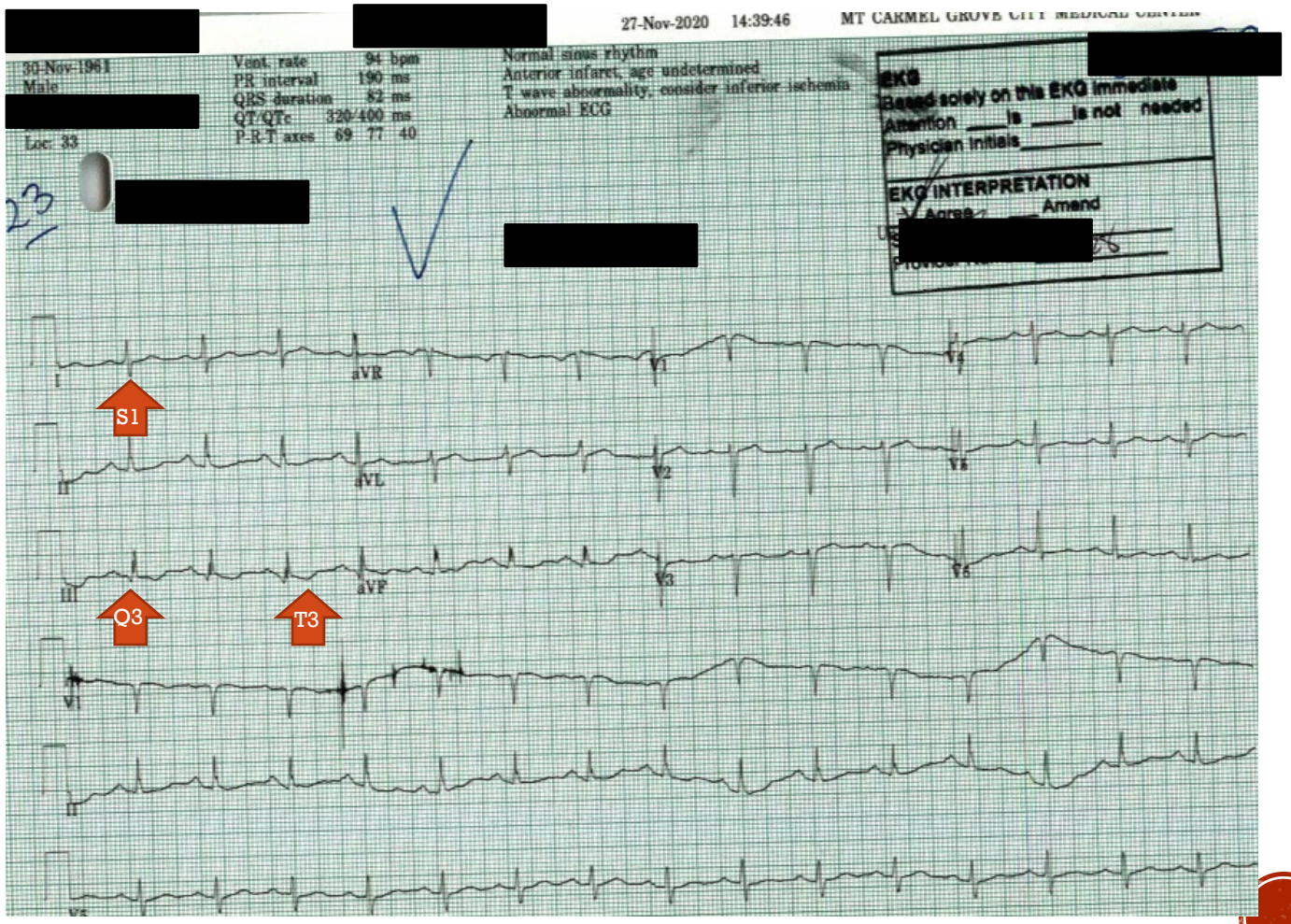
DVT = deep venous thrombosis; PE = pulmonary embolism.

Meets 3 PERC criteria → warrants further testing to evaluate for PE

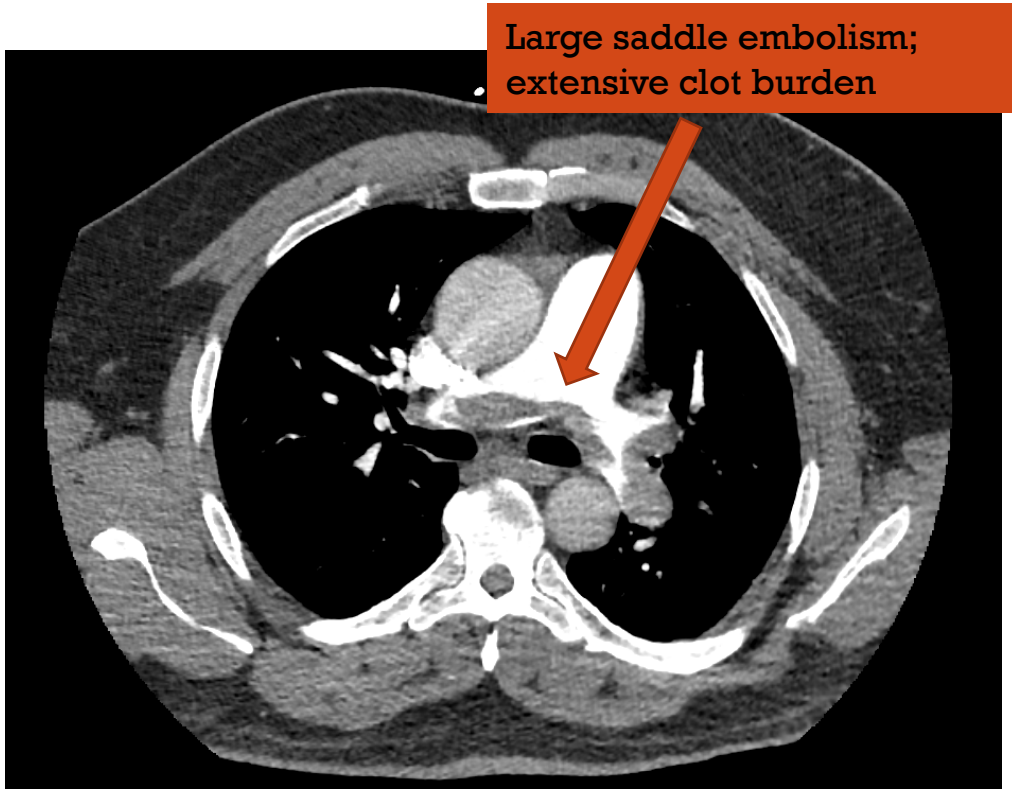
REVIEW CASE

- High sensitivity Troponin: < 20 ng/mL
- BNP: 641 picogram/mL
- ECG with non-specific findings suggestive of right heart strain
- Mild sinus tachycardia
- S1Q3T3 sign
  - S waves in lead I
  - Q waves in lead 3
  - Inverted t waves in lead 3

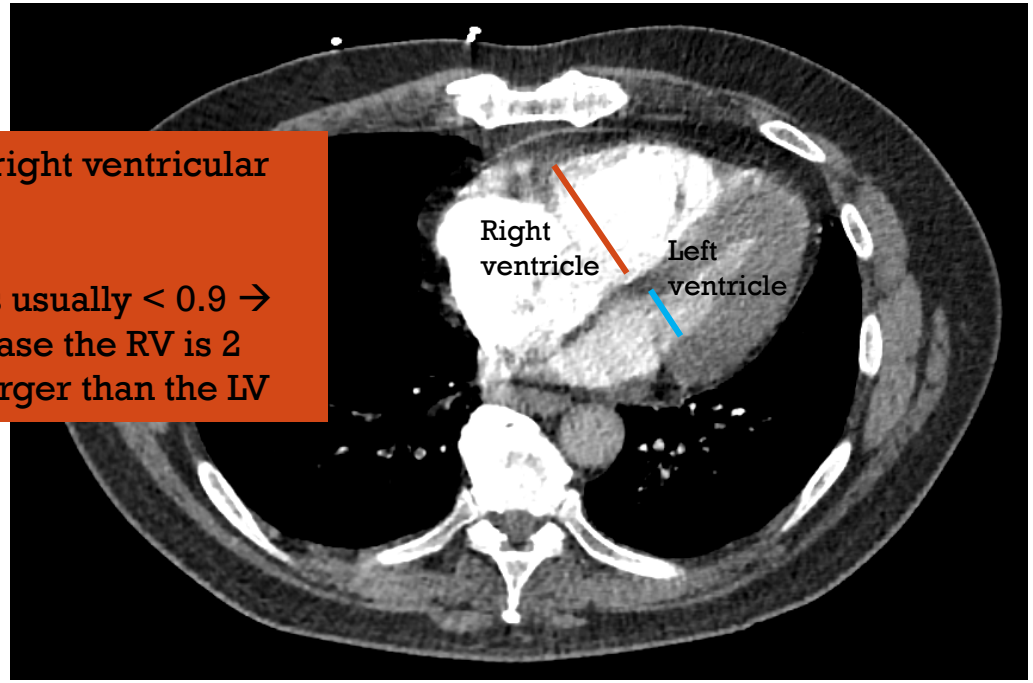
- Note: even if no ECG changes are evident, based on this patient's presentation, CTA is warranted to evaluate for PE based on Well's or PERC score



REVIEW CASE



Clinicians do not need to wait for echocardiogram to evaluate for right heart strain; it can be observed on CTA of the chest



Severe right ventricular strain

RV:LV is usually < 0.9 → in this case the RV is 2 times larger than the LV

RISK STRATIFICATION IN PULMONARY EMBOLISM

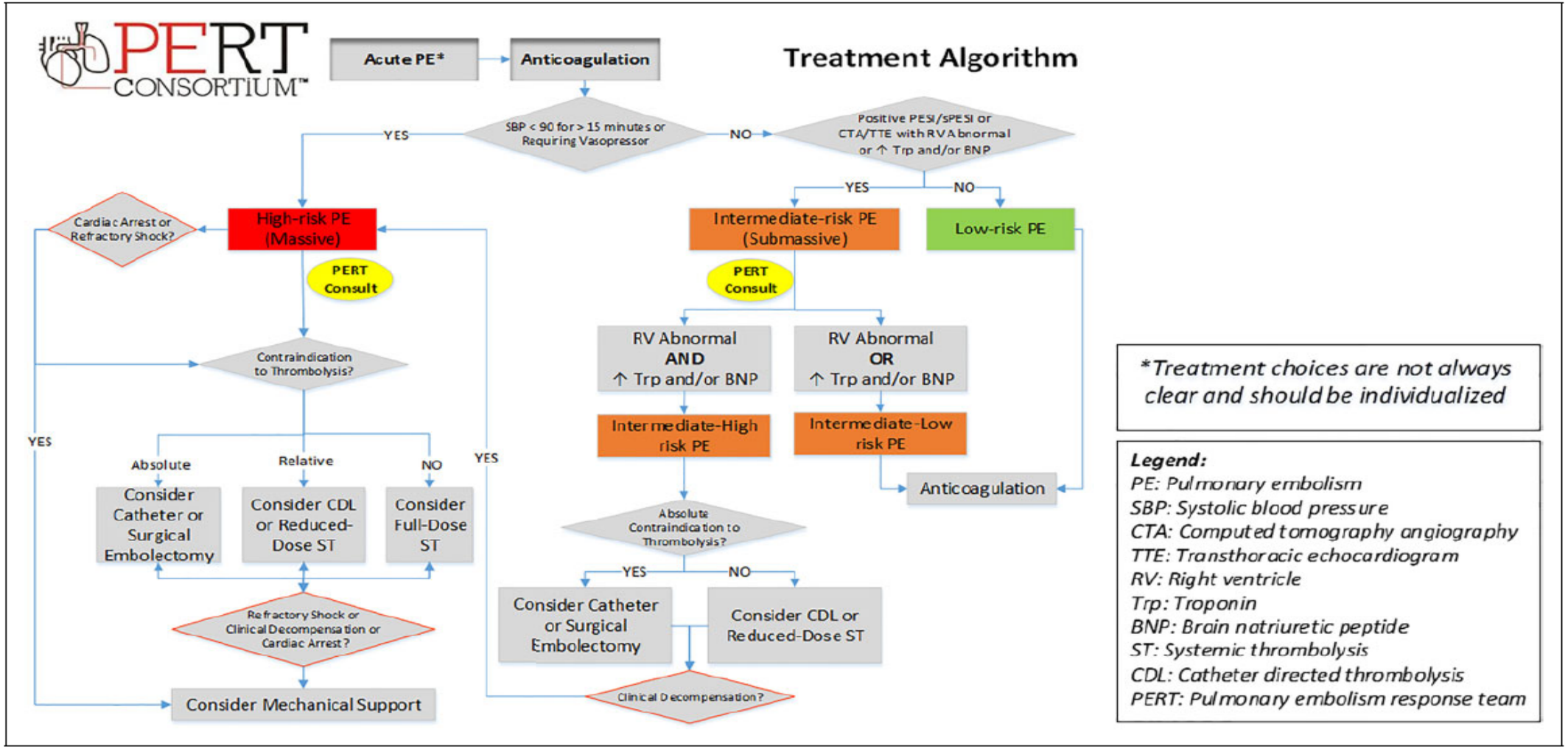


Figure 3. Pulmonary embolism treatment algorithm.

Rivera-Lebron B, et al. Diagnosis, Treatment and Follow Up of Acute Pulmonary Embolism; Consensus Practice from the PERT Consortium. Clin and Applied Thrombosis/Hemostasis. 2019;25:1-16.

REVIEW CASE

- How would you classify this patient's pulmonary embolism?

Submassive Pulmonary Embolism

Not massive even if the radiologist describes this very large clot as "massive" → the clinical definition of massive pulmonary embolism is based upon hemodynamic stability (this patient is NOT hypotensive or requiring vasopressors)

- Submassive PE is further subdivided into low risk and high risk for deterioration:
  - Submassive low risk = RV strain but no elevated cardiac biomarkers
  - Submassive high risk = RV strain AND elevated cardiac biomarkers (troponin or BNP)
    - Note: RV strain and elevated cardiac biomarkers appropriate to consult specialist to evaluate for potential systemic or catheter-directed thrombolysis
    - Note the presence of several ominous signs:
      - Presentation with near syncopal episode
      - Tachypnea and hypoxia at rest
      - General appearance: pale and diaphoretic
      - Very large clot burden and severe right ventricular strain

REVIEW CASE

- The patient received a heparin IV bolus of 80 units/kg x 1 followed by IV heparin at a continuous rate of 18 units/kg/hr (patient is 100 kg → 1800 units/hr) and plan to monitor aPTT every 6 hours until therapeutic
- Vital signs: HR: 130 RR: 24 BP: 85/49 O_2 sat: 95% on 2 L NC

- What would you do now?
  - The patient is becoming hemodynamically unstable; previous SBP was 131 mmHg and is now 85 mmHg (a decrease of > 40 mmHg AND < 90 mmHg) → this alone meets the criteria for MASSIVE pulmonary embolism
  - Systemic tPA should now be administered after assessing for any contraindications
  - Hold heparin infusion, start Alteplase 100 mg IV over 2 hours, when alteplase infusion complete, check aPTT and resume heparin without bolus when aPTT < 80 – 99 seconds

REVIEW CASE

- While the team is preparing to start the alteplase infusion the patient becomes unresponsive and loses palpable pulse → chest compressions initiated and CODE BLUE called → ACLS is in progress, initial rhythm PEA

- Considering the known etiology of cardiac arrest in this patient is obstructive shock secondary to massive pulmonary embolism → alteplase should be administered as an IV bolus during the resuscitation efforts

- The dose of alteplase during cardiac arrest is 50 mg IV push → if patient does not achieve return of spontaneous circulation in 15 minutes with active chest compressions, repeat dose of alteplase 50 mg IV push may be administered

DURATION OF TREATMENT VTE (NON-CANCER): 2021 CHEST GUIDELINE RECOMMENDATIONS

- **Treatment phase**:
  - In patients with acute VTE who do not have a contraindication → minimum 3-month treatment phase of anticoagulation with preferred DOAC followed by assessment for extended-phase therapy

- **Extended phase therapy**:
  - If VTE in the setting of transient risk factor (i.e. "provoked") → no extended-phase anticoagulation
    - Major transient "VTE-provoking" risk factor = surgery with general anesthesia > 30 min, confinement in bed in hospital ≥ 3 days with acute illness, cesarean section
    - Minor transient "VTE-provoking" risk factor = surgery with general anesthesia < 30 min, admission to hospital < 3 days, estrogen therapy, pregnancy or peripartum, confinement to bed out of hospital ≥ 3 days with acute illness, leg injury associated with reduced mobility
  - If VTE in absence of transient provocation (i.e. "unprovoked" or persistent risk factor) → offer extended-phase anticoagulation with DOAC preferred over warfarin
    - Reduced dose apixaban 2.5 mg PO BID or reduced dose rivaroxaban 10 mg PO daily
  - Extended phase therapy does not have a predefined stop date; but should be reevaluated at least annually

EVIDENCE FOR "EXTENDED-PHASE" ANTICOAGULATION FOR UNPROVOKED VTE

Outcome

Recurrent VTE

Forest Plot

Study or Subgroup	Indefinite (Extended) Events	Total	Time-limited Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.1.1 100% Unprovoked						
AUREC-FVIII 2009	7	17	2	17	4.9%	3.50 [0.85, 14.49]
Farraj 2004	3	32	7	32	5.5%	0.43 [0.12, 1.51]
LAFIT 1999	1	79	17	83	3.3%	0.06 [0.01, 0.45]
PADIS-DVT 2019	14	50	17	54	8.5%	0.89 [0.49, 1.61]
PADIS-PE 2015	28	184	39	187	9.2%	0.73 [0.47, 1 13]
PREVENT 2003	14	255	37	253	8.5%	0.38 [0.21, 0.68]
WODIT-DVT 2001	21	134	21	133	8.7%	0.99 [0.57, 1.73]
Subtotal (95% CI)		**751**		**759**	**48.6%**	**0.68 [0.41, 1.11]**
Total events	88		140			
Heterogeneity: Tau² = 0.25; χ^2 = 17.67, *df* = 6 (*P* = .007); I² = 66%						
Test for overall effect: *z* = 1.53 (*P* = .12)						
1.1.2 < 100% Unprovoked						
AMPLIFY-EXT 2013	14	840	73	829	8.7%	0.19 [0.11, 0.33]
DACUS 2008	17	88	25	92	8.7%	0.71 [0.41, 1.22]
DURAC 1997	2	116	23	111	4.9%	0.08 [0.02, 0.34]
EINSTEIN-EXT 2010	8	602	42	594	7.8%	0.19 [0.09, 0.40]
Levine 1995	7	109	12	105	7.1%	0.56 [0.23, 1.37]
RESONATE 2013	3	681	37	662	5.9%	0.08 [0.02, 0.25]
WODIT-PE 2003	15	165	18	161	8.3%	0.81 [0.42, 1.56]
Subtotal (95% CI)		**2,601**		**2,554**	**51.4%**	**0.29 [0.15, 0.56]**
Total events	66		230			
Heterogeneity: Tau² = 0.62; χ^2 = 31.46, *df* = 6 (*P* < .0001); I² = 81%						
Test for overall effect: *z* = 3.67 (*P* = .0002)						
Total (95% CI)		**3,352**		**3,313**	**100.0%**	**0.43 [0.28, 0.67]**
Total events	154		370			
Heterogeneity: Tau² = 0.50; χ^2 = 62.11, *df* = 13 (*P* < .00001); I² = 79%						
Test for overall effect: *z* = 3.72 (*P* = .0002)						
Test for subgroup differences: χ^2 = 4.13, *df* = 1 (*P* = .04), I² = 75.8%						

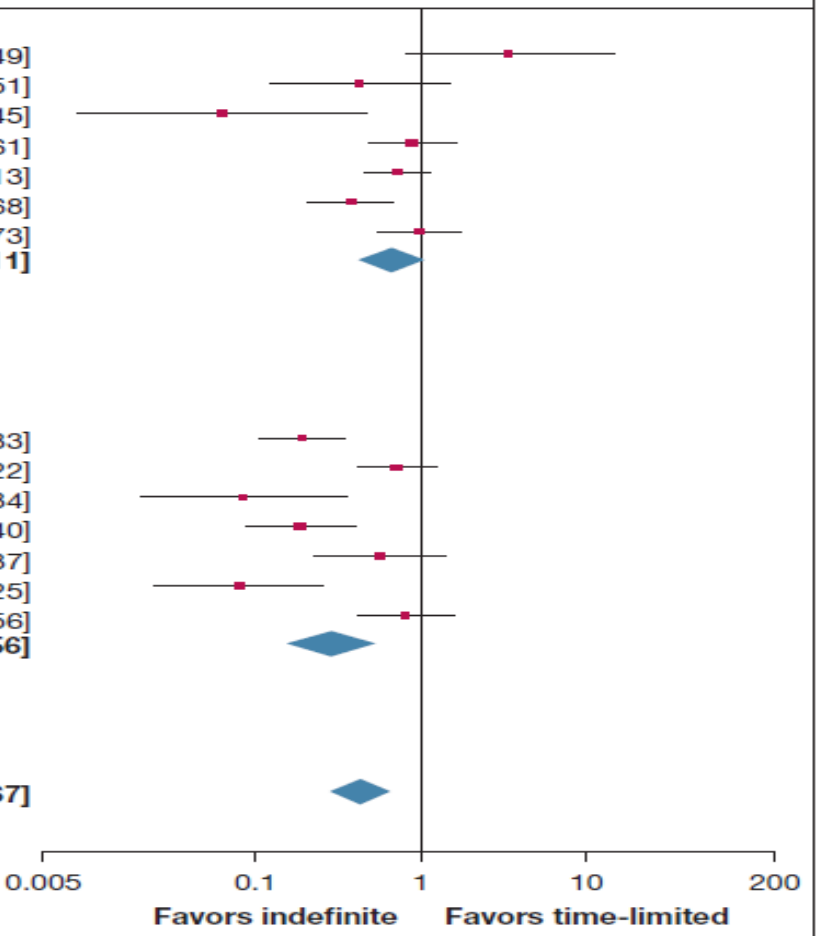
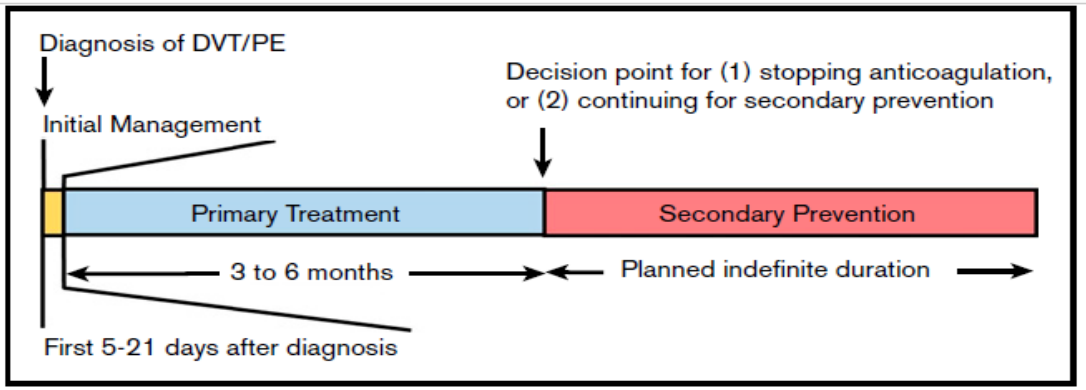


Figure 6 – *Forest plot of pooled estimates: extended-phase anticoagulation (indefinite period) vs time-limited anticoagulation for prevention of subsequent provoked or unprovoked VTE. IV = inverse-variance. (Review Manager [RevMan], version 5.3 [Cochrane Collaboration], was used to construct the forest plot.)*

DURATION OF TREATMENT VTE (NON-CANCER): ASH 2020 GUIDELINES



- Primary treatment (minimal length of time for treatment of the initial VTE):
  - Whether provoked or unprovoked ASH guideline panel suggests shorter course 3 – 6 months over longer course (6 – 12 months)
    - A longer initial course (6 – 12 months) could be justified in selected patients with chronic risk factor for which some improvement is expected over time (i.e. improved mobility with rehabilitation)
- Secondary prevention (following completion of primary treatment for initial VTE)
  - Provoked by transient risk factor (unless history of unprovoked VTE) →
    - Typically do not require anticoagulation after completion of primary treatment even if patient has a history of previous VTE provoked by transient risk factor
  - Unprovoked VTE or provoked by chronic risk factor →
    - Indefinite anticoagulation (standard dose or lower-dose DOAC* or warfarin with INR goal 2 – 3) is probably appropriate for the majority of patients unless patient has a high risk for bleeding complications

*Note: patients with a higher risk of recurrence were excluded from studies of extended duration low dose DOACs (active cancer, recurrent unprovoked VTE, another indication for therapeutic dose anticoagulation)

DETERMINING BLEEDING RISK: HAS-BLED SCORE

Criteria	Points
Hypertension	+1
Abnormal Renal or Liver Function (1 point each) disease (SCr > 2.26 mg/dL or dialysis) Liver disease (Cirrhosis, bilirubin > 2x ULN with AST/ALT/AP > 3x ULN)	+ 1 or 2
Stroke history	+1
Bleeding history	+1
Labile INR (unstable INR, time in therapeutic range < 60%)	+1
Elderly age > 65 years	+1
Drugs or Alcohol (1 point each) Medication usage predisposing to bleeding (ASA, other antiplatelets, NSAIDs) Alcohol use (≥ 8 drinks/week)	+1 or 2

- Validated scoring tools exist but there is NOT an absolute cut-off to withhold or withdraw anticoagulation
- Bleeding risk assessment tools are used to establish appropriate monitoring plan and to attempt to eliminate modifiable risk factors for bleeding

HAS-BLED Score	Bleeds per 100 patient years	% bleeding in one validation study
0	1.13	0.9%
1	1.02	3.4%
2	1.88	4.1%
3	3.72	5.8%
4	8.70	8.9%
5	12.5	9.1%
≥ 6	--	> 10%

PATIENT-SPECIFIC DECISION MAKING BEYOND "LIFELONG" ANTICOAGULATION

Follow-up D-dimer 1 month after completion of 3- 6 months initial anticoagulation and continue if D-dimer remains elevated

- Persistently elevated D-dimer level (> 250 – 500 mcg/L) is associated with recurrent VTE (HR 2.59; CI 1.9 -3.52)

Ultra-sound guided determination of duration of anticoagulation after initial 3 months of anticoagulation for DVT

- Meta-analysis demonstrated residual vein thrombosis is an independent risk factor associated with recurrent VTE (HR 1.32, CI 1.06-1.65)
- Individual randomized trials demonstrate only modest benefit and this strategy is not routinely recommended

Donadini MP, et al. Thromb Haemost. 2014 Jan;111(1):172-9
Prandoni P, et al. Ann Intern Med. 2009 May 5;150(9):577-85.
Douketis J, et al.. Ann Intern Med. 2010 Oct 19;153(8):523-31.

PATIENT-SPECIFIC DECISION MAKING BEYOND "LIFELONG" ANTICOAGULATION

- Prognostic indicators (HERDOO2, Vienna, DASH) all include D-dimer but differ in regard to additional clinical characteristics
- HERDOO2 rule demonstrated that women with first unprovoked VTE and 0-1 criteria (low-risk) could safely discontinue anticoagulant therapy after 5 – 12 months of initial therapy
  - Recurrent VTE occurred 3% in low-risk group per patient year during follow-up (17 episodes during 564 patient years of follow-up) vs 8.1% in high-risk (when only 1.6% of high-risk patients had recurrent VTE if continued on anticoagulation)

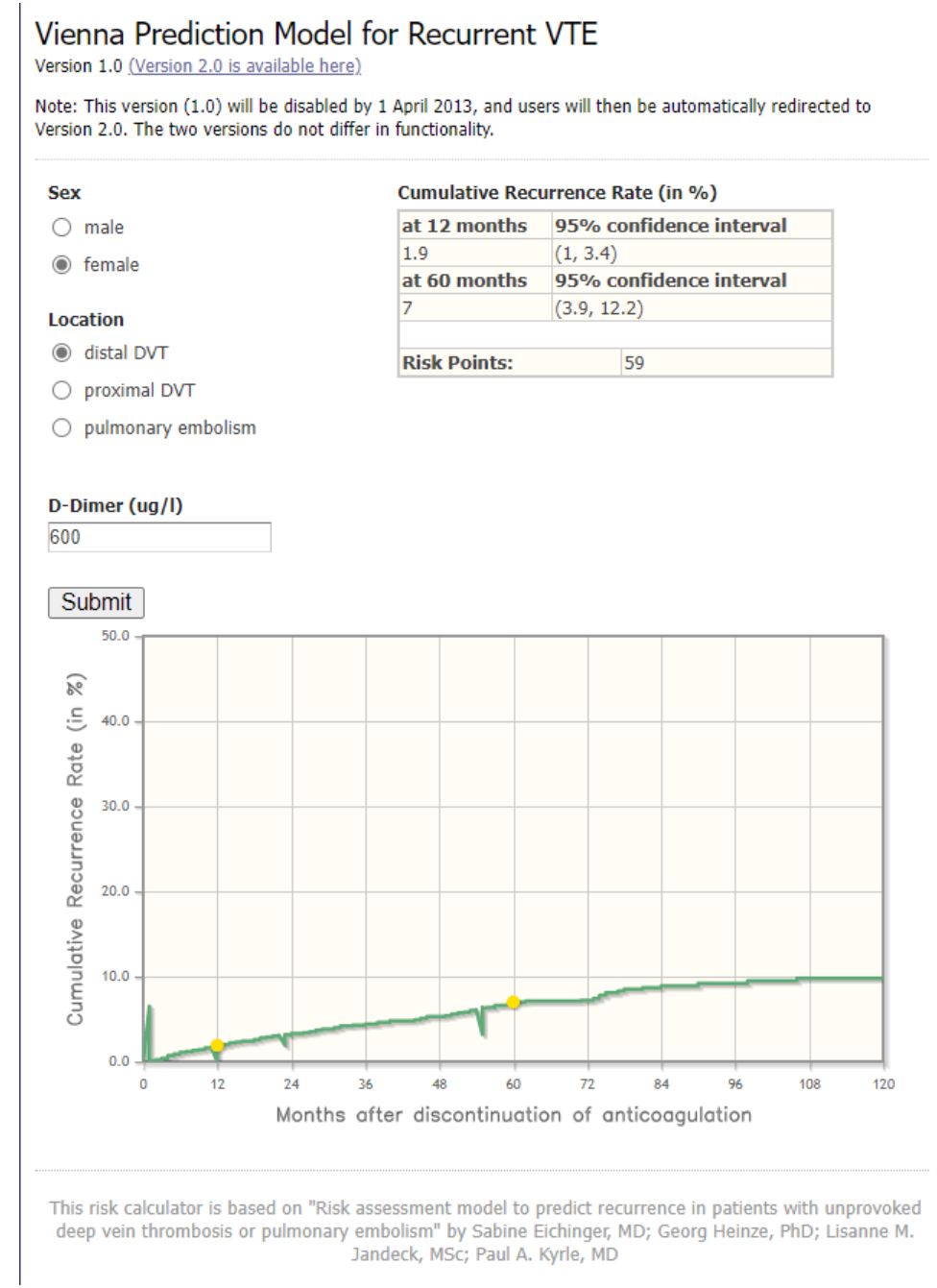
	Predictor	Scoring
H	Hyperpigmentation	1 point total, if any one of these criteria is present
E	Edema	
R	Redness of either leg	
D	D-dimer ≥ 250 µg/L while anticoagulated	1
O	Obesity with BMI ≥ 30 kg/m^2	1
O	Older age, ie, ≥ 65 years	1

Decision Making:		
Women:	0-1	Discontinue anticoagulation
	≥2	Continue anticoagulation
All men		Continue long-term anticoagulation

Rodger MA, et al. BMJ. 2017 Mar 17;356:j1065.

PATIENT-SPECIFIC DECISION MAKING BEYOND "LIFELONG" ANTICOAGULATION

- Vienna Prediction Model: gender, location of thrombotic event (distal DVT, proximal DVT, PE), and D-dimer level 3 weeks after discontinuation of anticoagulants
- Risk-Calculator (meduniwien.ac.at)
- Shows promise based on strong development methodology and some external validation but not recommended by any national guideline for routine use



Ensor J,et al. BMJ Open. 2016 May 6;6(5):e011190.
Ortel TL, et al. Blood Adv. 2020 Oct 13;4(19):4693-4738.

DASH Prediction Score for Recurrent VTE ☆

Predicts likelihood of recurrence of first VTE.

INSTRUCTIONS

Do NOT use in patients with active hemorrhage or signs/symptoms of VTE.

When to Use ⌄ | Pearls/Pitfalls ⌄ | Why Use ⌄

D-dimer abnormal Measured ~1 month after stopping anticoagulation	**No 0**	Yes +2
Age ≤50 years	**No 0**	Yes +1
Male patient	**No 0**	Yes +1
Hormone use at VTE onset (if female) If male patient, select "No"	**No 0**	Yes -2

DASH Score	Annual Recurrence Rate
-2	1.8%*
-1	1.0%
0	2.4%
1	3.9%
2	6.3%
3	10.8%
4	19.9%

*A very small sample had DASH Score of -2 in the derivation study.

Tosetto A, et al. J Thromb Hemost. 2012 Jul;10(6):1019-25.
Tosetto A, et al. J Thromb Haemost. 2017; 15(10):1963-1970.

PATIENT-SPECIFIC DECISION MAKING BEYOND "LIFELONG" ANTICOAGULATION

SUMMARY OF MAIN POINTS

- When evaluating patients for suspected VTE use validated pretest probability score such as Wells criteria
- Differentiate between massive and submassive pulmonary embolism by the presence of hypotension
- Massive pulmonary embolism should be treated with thrombolytic therapy (tPA) immediately in the absence of contraindication due to high risk of cardiovascular collapse and death
- Submassive pulmonary embolism if evidence of right ventricular strain
  - High risk submassive PE (RV strain + elevated cardiac markers) → evaluate for potential thrombolytic
  - Low risk submasive PE → treated with anticoagulation alone but monitor closely
- VTE oral anticoagulation preference = DOAC due to lower risk of bleeding vs. warfarin
- Cancer-associated VTE → DOACs now an option, apixaban may be preferred due to lower risk of bleeding, continued as long as cancer is active
- Duration of non-cancer associated VTE full dose anticoagulation at least 3 months
  - If provoked by transient risk factor may stop anticoagulation after 3 months
  - Unprovoked VTE or provoked by chronic risk factor continue extended anticoagulation therapy
  - Ongoing risk:benefit assessment in patients who are candidates for lifelong therapy

REFERENCES

- Stevens SM, Woller SC, Kreuziger LB, et al. Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report. Chest. 2021 Dec;160(6):e545-e608.
- Ortel TL, Neumann I, Ageno W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. Blood Adv. 2020 Oct 13;4(19):4693-4738.
- Kahn SR, Comerota AJ, Cushman M, et al. The postthrombotic syndrome: evidence-based prevention, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. Circulation. 2014 Oct 28;130(18):1636-61.
- Wells PS, Owen C, Doucette S, et al. Does this patient have a deep vein thrombosis. JAMA. 2006 Jan 11;295(2):199-207.
- Silveira PC, et al. Performance of Wells Score for Deep Venous Thrombosis in the Inpatient Setting. JAMA Intern Med. 2015 Jul;175(7):1112-7.
- Chen A, Stecker E, Warden BA. Direct Oral Anticoagulation Use: A Practical Guide to Common Clinical Challenges. J Am Heart Assoc. 2020 Jul 7;9(13):e017559.
- Panchal AR, Bartos JA, Cabanas JG, et al. Part 3: Adult Basic and Advanced Life Support: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2020 Oct 20;142(16_suppl_2):S366-S468.
- Key NS, Khorana AA, Kuderer NM, et al. Venous Thromboembolism Prophylaxis and Treatment in Patients with Cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol. 2020 Feb 10;38(5):496-520.
- Lyman GH, Carrier M, Ay C, et al. American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer. Blood Adv. 2021 Feb 23;5(4):927-974.
- Eddy M, et al. External validation of the YEARS diagnostic algorithm for suspected pulmonary embolism. J Thromb Haemost. 2020 Dec;18(12):3289-3295.
- Martin KA, Beyer-Westerndorm J, Davidson BL, et al. Use of direct oral anticoagulants in patients with obesity for treatment and prevention of venous thromboembolism: Updated communication from the ISTH SSC Subcommittee on Control of Anticoagulation. J Thromb Haemost. 2021 Aug;19(8):1874-1882.
- Rivera-Lebron B, et al. Diagnosis, Treatment and Follow Up of Acute Pulmonary Embolism; Consensus Practice from the PERT Consortium. Clin and Applied Thrombosis/Hemostasis. 2019;25:1-16.

REFERENCES

- Jimenez D, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med. 2010 Aug 9;170(15):1383-9.
- Donadini MP, Ageno W, Antonucci E, et al. Prognostic significance of residual venous obstruction in patients with treated unprovoked deep vein thrombosis: a patient-level meta-analysis. Thromb Haemost. 2014 Jan;111(1):172-9.
- Prandoni P, Prins MH, Lensing AWA, et al. Residual thrombosis on ultrasonography to guide the duration of anticoagulation in patients with deep venous thrombosis: a randomized trial. Ann Intern Med. 2009 May 5;150(9):577-85.
- Rodger MA, Le Gal G, Anderson DR, et al. Validating the HERDOO2 rule to guide treatment duration for women with unprovoked venous thrombosis: multinational prospective cohort management study. BMJ. 2017 Mar 17;356:j1065.
- Ensor J, Riley RD, Moore D, et al. Systematic review of prognostic models for recurrent venous thromboembolism (VTE) post-treatment of first unprovoked VTE. BMJ Open. 2016 May 6;6(5):e011190.
- Douketis J, Tosetto A, Marcucci M, et al. Patient-level meta-analysis: effect of measurement timing, threshold, and patient age on ability of D-dimer testing to assess recurrence risk after unprovoked venous thromboembolism. Ann Intern Med. 2010 Oct 19;153(8):523-31.
- Pisters R, Lane DA, Nieuwlaat R, et al. A Novel User-Friendly Score (Has-Bled) To Assess 1-Year Risk of Major Bleeding in Patients with Atrial Fibrillation: The Euro Heart Survey. Chest. 2010;138(5):1093-1100.
- Lip GY, Frison L, Halperin JL, et al. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score. J Am Coll Cardiol. 2011 Jan 11;57(2):173-80.
- Tosetto A, Iorio A, Marcucci M, et al. Predicting disease recurrence in patients with previous unprovoked venous thromboembolism: a proposed prediction score (DASH). J Thromb Hemost. 2012 Jul;10(6):1019-25.
- Tosetto A, Testa S, Martinelli I, et al. External validation of the DASH prediction rule: a retrospective cohort study. J Thromb Haemost. 2017; 15(10):1963-1970.