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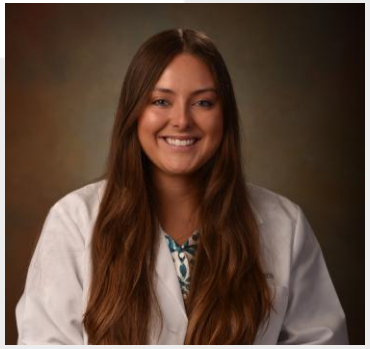
The Great Load Debate: Transitioning from Parenteral Anticoagulation to Direct Oral Anticoagulants in the Treatment Phase of Deep Vein Thrombosis & Pulmonary Embolism

A presentation for HealthTrust Members
March 25, 2026



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Objectives

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Recall	Recall the pharmacologic rationale for lead-in dosing with direct oral anticoagulants (DOACs) in the treatment of acute venous thromboembolism (VTE).
Identify	Identify parental and oral pharmacological therapies for VTE treatment.
Recognize	Recognize evidence-based principles and patient-specific factors to recommend appropriate treatment strategies when transitioning from DOACs in the management of deep vein thrombosis (DVT) and pulmonary embolism (PE).

Abbreviations

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- **AFib** – Atrial Fibrillation
- **DVT** – Deep Vein Thrombosis
- **PE** – Pulmonary Embolism
- **VTE** – Venous Thromboembolism
- **DOAC** – Direct Oral Anticoagulant
- **UFH** – Unfractionated Heparin
- **LMWH** – Low Molecular Weight Heparin
- **CRNMB** – Clinically Relevant Nonmajor Bleeding
- **ATIII** – Antithrombin III
- **BID** – Twice Daily
- **CI** – Confidence Interval
- **CTPA** – Computed Tomography Pulmonary Angiography
- **HR** – Hazard Ratio
- **INR** – International Normalized Ratio
- **IV** – Intravenous
- **MOA** – Mechanism of Action
- **PO** – By Mouth (Oral)
- **RV** – Right Ventricle
- **SubQ** – Subcutaneous
- **TF** – Tissue Factor
- **TFPI** – Tissue Factor Pathway Inhibitor
- **VKORC1** – Vitamin K Epoxide Reductase Complex 1
- **VKA** – Vitamin K Antagonist
- **V/Q** – Ventilation-Perfusion

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Venous Thromboembolism Overview

'Always happens after a long flight.'

Source: fity.club/lists/2025/deep-vein-thrombosis-memes

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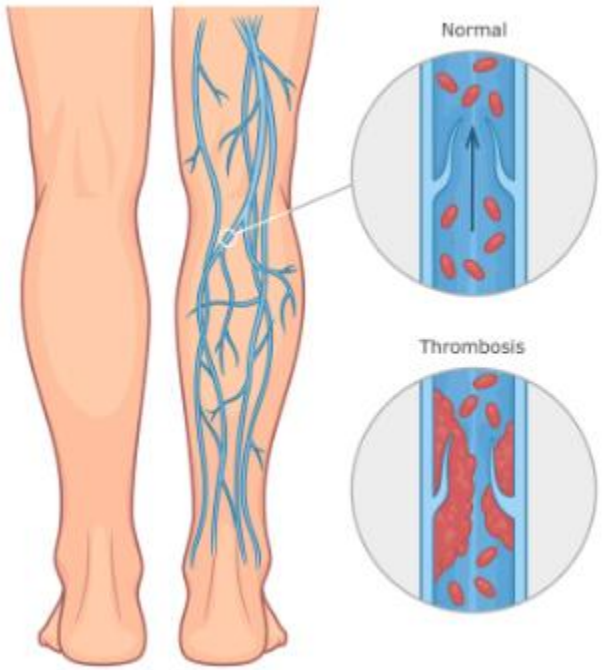
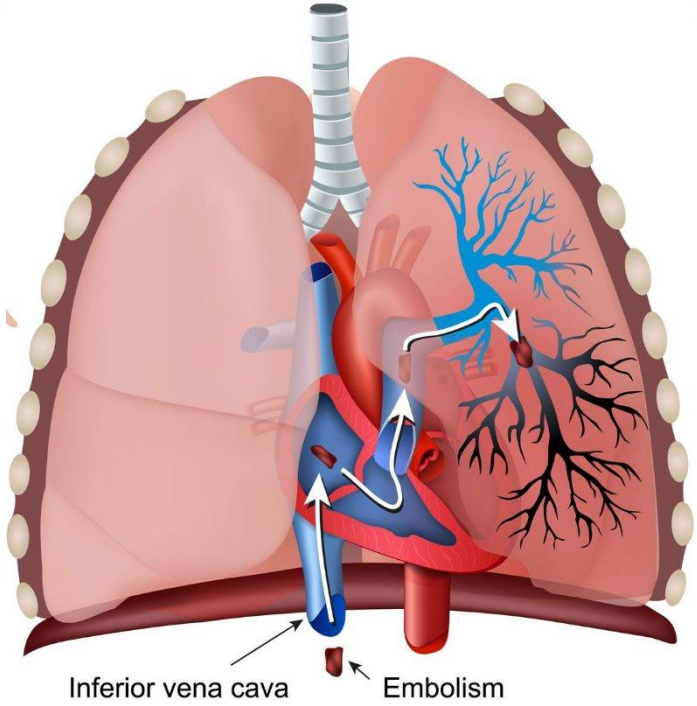
Venous Thromboembolism

Deep Vein Thrombosis



VS

Pulmonary Embolism



Sources: cartoondealer.com//#256425653;
stock.adobe.com/es/images/deep-vein-thrombosis

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Epidemiology & Prevalence

Up to 900,000 people in the United States are affected by VTE events each year.

An estimated 60,000 - 100,000 Americans die of VTE events each year.

One third (~33%) of people with a VTE will have a recurrence within 10 years.

Source: Ortel TL, et al. *Blood Adv*. 2020

Risk Factors

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Major Transient	Minor Transient	Persistent
• Surgery with general anesthesia > 30 minutes • Hospitalization for acute medical illness > 72 hours while confined to hospital bed • Cesarean section • Lower limb fracture	• Surgery with general anesthesia < 30 minutes • Hospitalization for acute medical illness <72 hours • Out-of-hospital acute medical illness >72 hours while confined to bed • Estrogen therapy (hormone replacement or contraceptive) • Peripartum period • Trauma with decreased mobility >72 hours	• Active cancer with or without ongoing treatment • Autoimmune disease (e.g., rheumatoid arthritis, systemic lupus erythematous) • Inflammatory bowel disease • Chronic immobility

Source: Creager MA, et al. *Circulation*. 2026 Feb.

Provoked vs. Unprovoked VTE

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Provoked VTE	Unprovoked VTE
• Occurs in the presence of an identifiable risk factor • Transient provoking factors are temporary conditions that increase VTE risk only while the factor is present or shortly thereafter • Persistent provoking factors are ongoing or long-term conditions that confer a sustained or potentially indefinite risk of VTE.	• Occurs in the absence of an identifiable triggering factor. • Patients may have underlying non-environmental risk factors, such as sex or ethnicity

Source: National Blood Clot Alliance. *Stop the Clot*.

Precipitating Factors

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Precipitating Factors
VTE provoked by a major transient risk factor (present within the 3 months before VTE diagnosis)
VTE provoked by a minor transient risk factor (present within the 2 months before VTE diagnosis)
VTE provoked by a persistent risk factor
Unprovoked VTE

Source: Ortel TL, et al. *Blood Adv*. 2020

Clinical Presentation

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Signs and Symptoms	
DVT	**PE**
• Asymptomatic • Pain/tenderness • Erythema • Acute swelling • Pallor- Phlegmasia Alba • Cyanosis-Phlegmasia Cerulea	• Dyspnea • Chest pain • Cough • Syncope • Fever • Diaphoresis • Severe cases may involve hemodynamic instability and signs of right ventricular strain

Source: National Blood Clot Alliance. *Stop the Clot*.

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VTE Diagnosis

Diagnosis of DVT/PE

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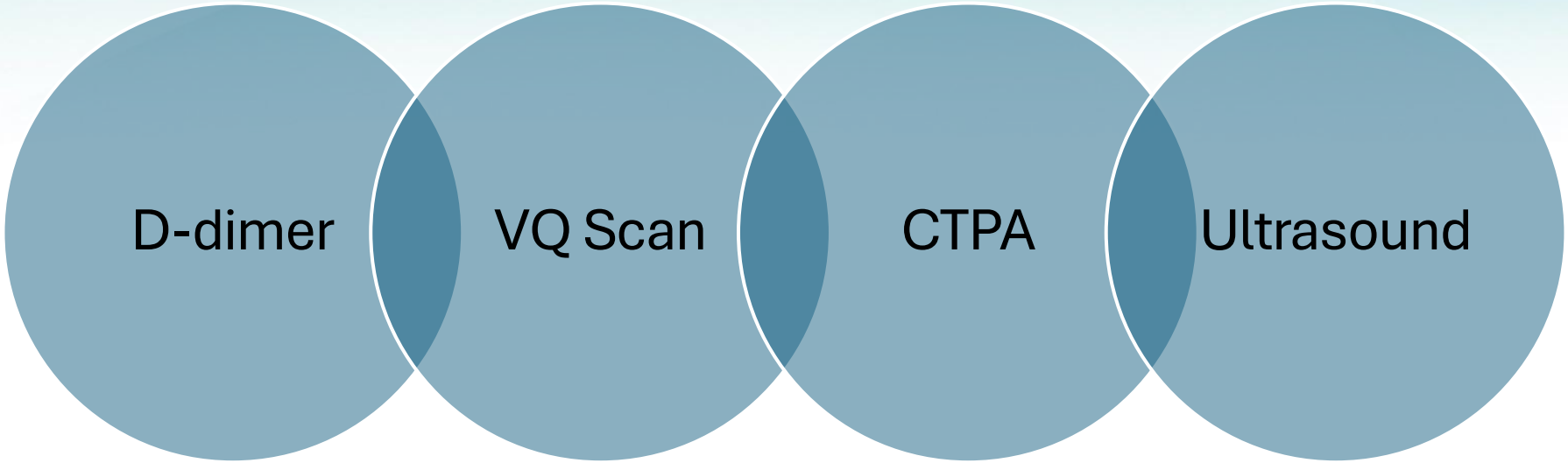

- VTE diagnosis begins with estimating **clinical probability** using validated tools (e.g., Wells Criteria, Pulmonary Embolism Rule-Out Criteria test).
- Patients are categorized as:
  - Low probability
  - Intermediate probability
  - High probability

Source: Lim W, et al. *Blood Adv*. 2018 Nov.

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Wells Criteria

- Physical findings suggestive of DVT (unilateral leg swelling, calf or thigh tenderness) **(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 4 weeks **(1.5 points)**
- Prior history of DVT or PE **(1.5 points)**
- Prescence of hemoptysis **(1 point)**
- Prescence of malignancy **(1 point)**

Standard Wells Scoring:

- Low: < 2
- Moderate: 2-6
- High: > 6

Modified Wells Scoring:

- PE likely: > 4
- PE unlikely: ≤ 4

Source: Lim W, et al. *Blood Adv*. 2018 Nov.

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PERC Test

- When all criteria are met, the likelihood of PE is **low** and **no further testing is required**
  - Age < 50 years of age
  - Heart rate < 100 bpm
  - Oxygen saturation ≥ 95% on room air
  - No hemoptysis
  - No estrogen use
  - No prior DVT or PE
  - No unilateral leg swelling
  - No surgery/trauma requiring hospitalization within the previous 4 weeks

Source: Lim W, et al. *Blood Adv*. 2018 Nov.

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Risk Categories

Low Probability

- Negative D-dimer: VTE ruled out
- Positive D-dimer: Proceed to imaging

Intermediate Probability

- Start with D-dimer

High Probability

- Skip D-dimer
- Go directly to diagnostic imaging
  - CTPA preferred; V/Q scan if CTPA not feasible

Source: Lim W, et al. *Blood Adv*. 2018 Nov.

D-dimer

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- D-dimer is elevated during acute thrombosis because coagulation and fibrinolysis occur simultaneously.
- High negative predictive value
- Low positive predictive value
- Test specificity decreases with age (≈10% specificity in patients > 80 years).
- Age-adjusted D-dimer thresholds improve diagnostic performance in patients >50 years:
  - Formula: Age × 10 ng/mL
  - Example: Age 75 → cutoff 750 ng/mL
- Using age-adjusted cutoffs increases the number of patients ruled out for PE without increasing false negatives.

Source: Lim W, et al. *Blood Adv*. 2018 Nov.

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VQ Scan

- A ventilation-perfusion (VQ) scan is a diagnostic test using radioisotopes to evaluate lung perfusion and ventilation.
- VQ scanning is an established diagnostic test for PE, primarily used when CTPA is contraindicated, inconclusive, or additional testing is needed.
- Often used in patients with
  - Severe renal failure
  - Contrast allergy or prior contrast-induced anaphylaxis
- Normal scan → effectively excludes PE
- Results reported as low , normal, intermediate, and high probability

Source: Lim W, et al. *Blood Adv*. 2018 Nov.

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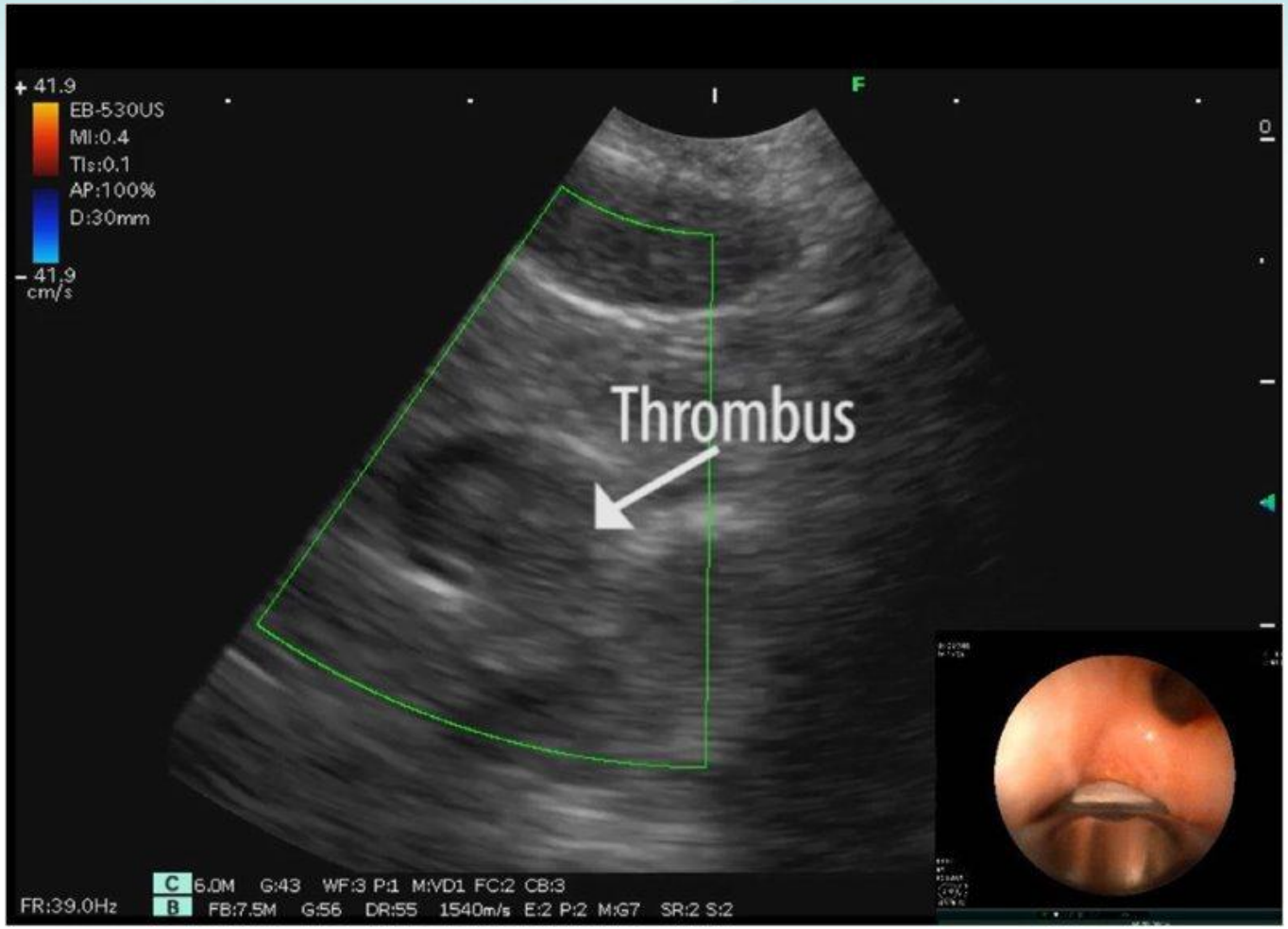
CTPA

- Computed Tomography Pulmonary Angiography (CTPA) is the diagnostic test of choice for suspected PE
- Diagnostic Accuracy
  - Sensitivity: 83%
  - Specificity: 96%
- CTPA can assess right ventricular (RV) enlargement and dysfunction.

Source: Lim W, et al. *Blood Adv*. 2018 Nov.



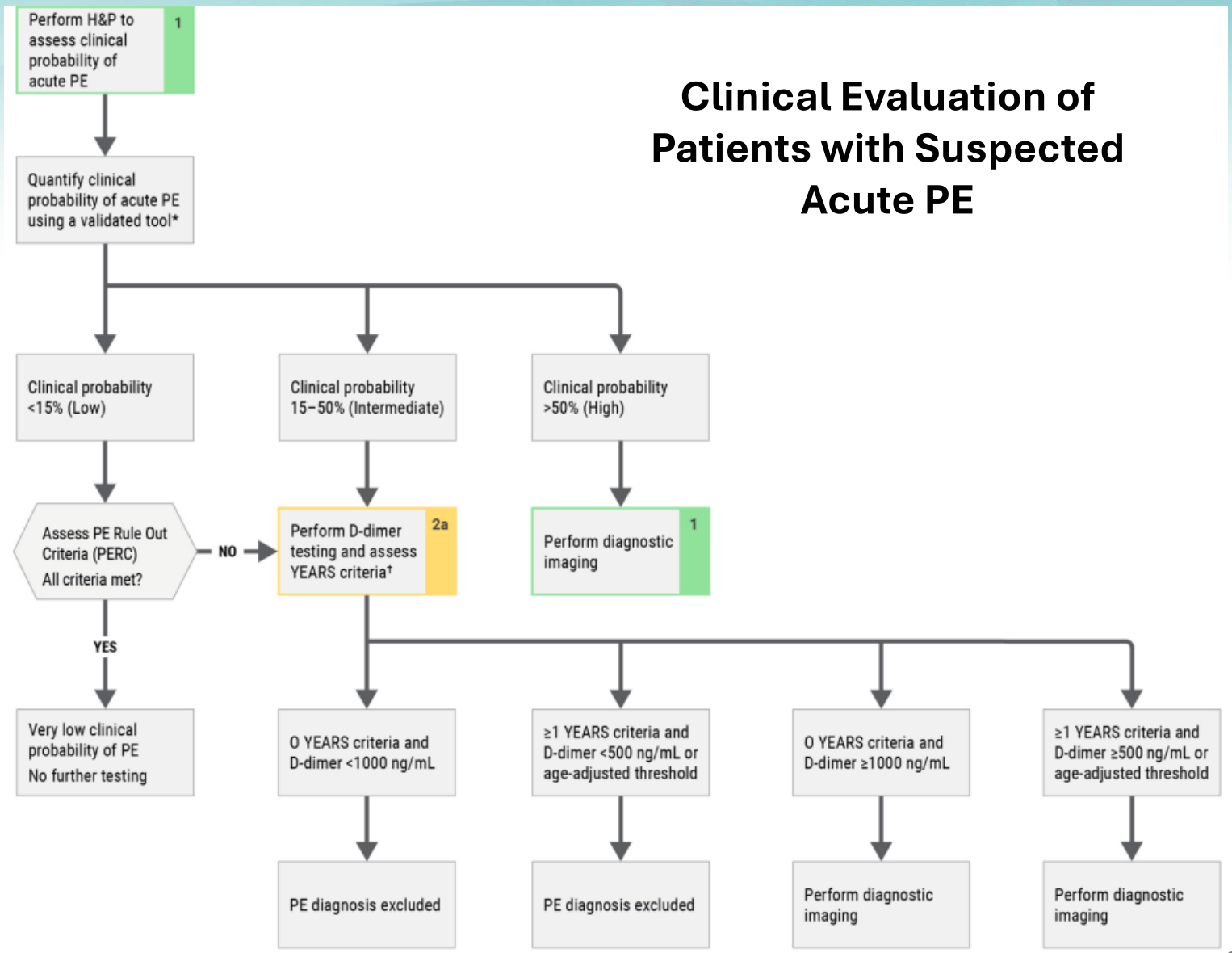
https://cardiovascularultrasound.biomedcentral.com/articles/10.1186/s12947-020-00208-z/figures/1

Ultrasound

- Compression ultrasonography is the primary imaging modality for diagnosis of suspected lower extremity DVT.
- Ultrasound evaluates vein compressibility, with noncompressible veins indicating possible thrombus presence.

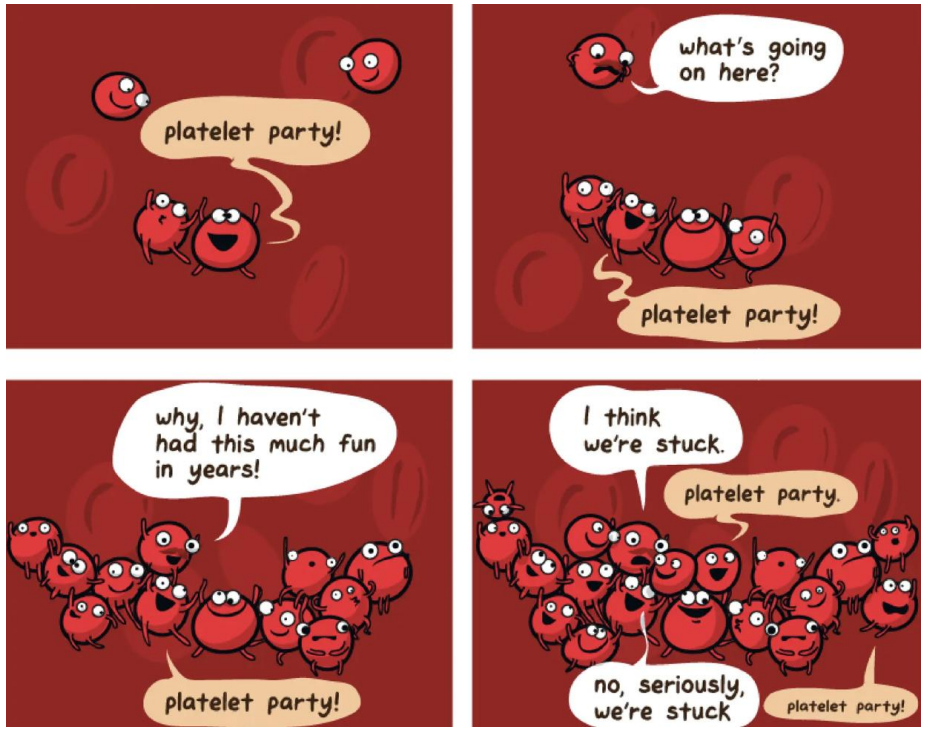
Source: Lim W, et al. *Blood Adv*. 2018 Nov.

PE Diagnosis Algorithm



Source: Creager MA, et al. *Circulation*. 2026 Feb.

Clot Formation



Source: www.theawkwardyeti.com

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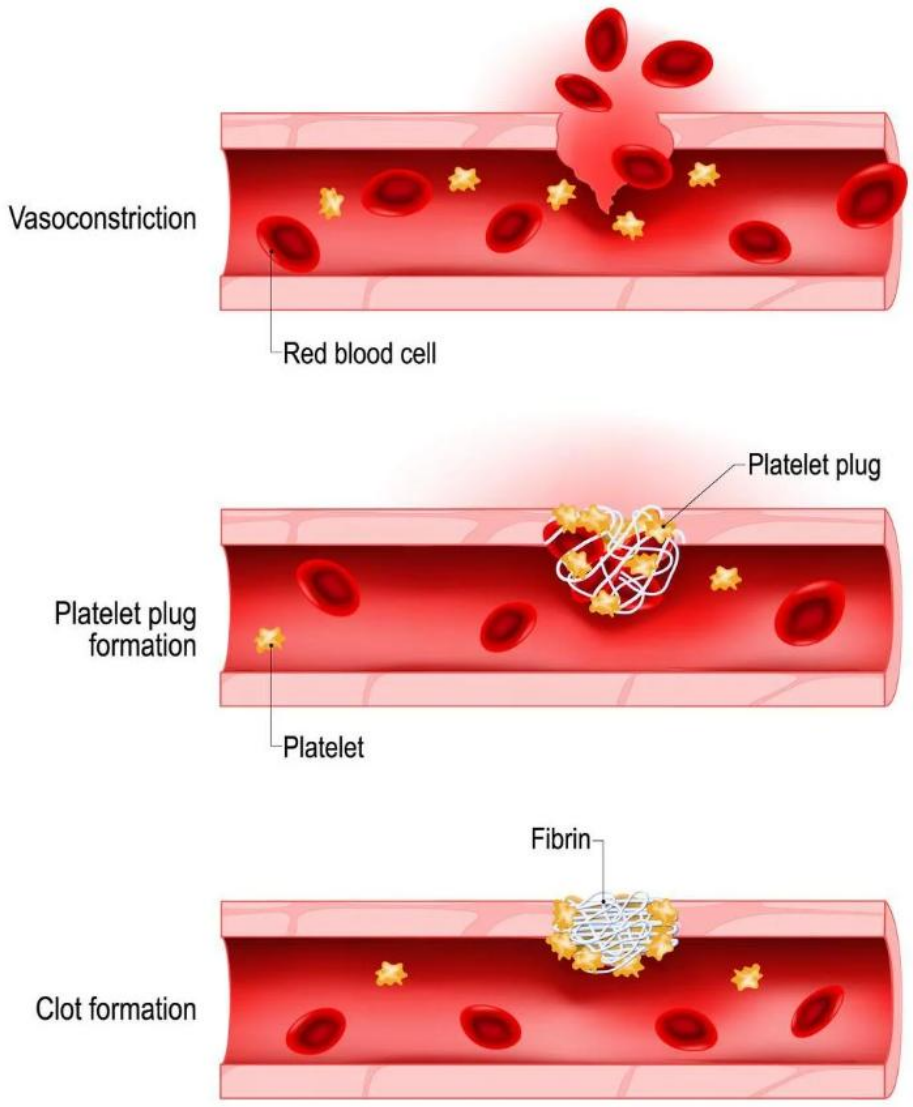
Pathophysiology: Hemostasis



- Process of the blood clot formation at the site of the vessel injury
- Arrest or cessation of hemorrhaging during blood vessel injury

Source: National Blood Clot Alliance. *Stop the Clot*.

Phases of Clot Formation

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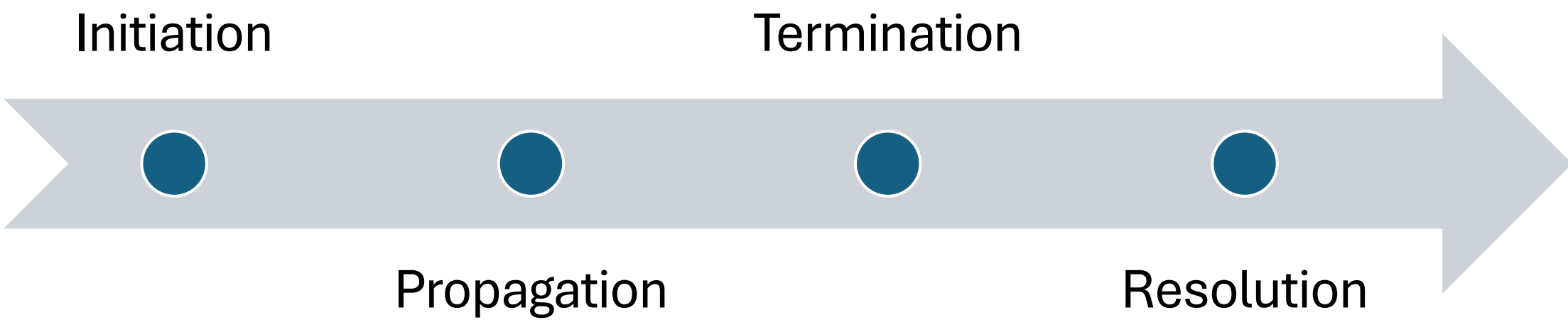

Source: National Blood Clot Alliance. *Stop the Clot*.

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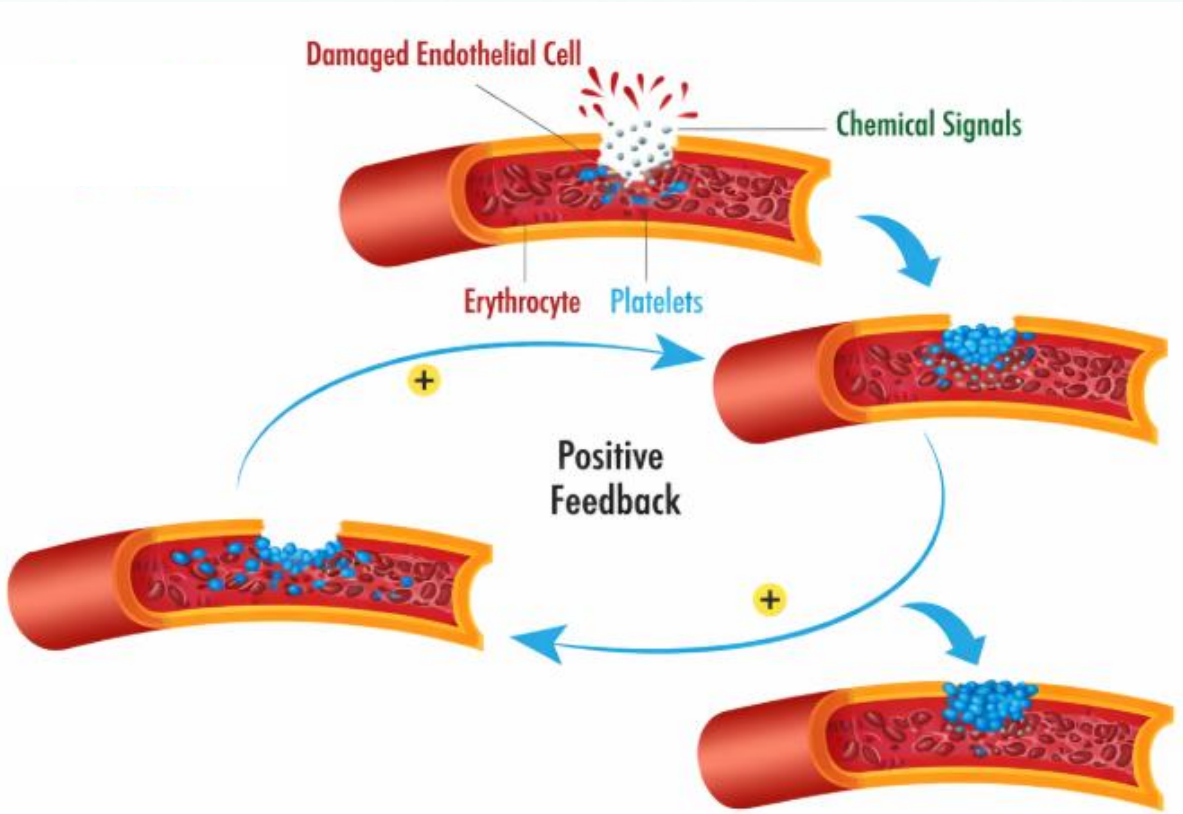
Initiation

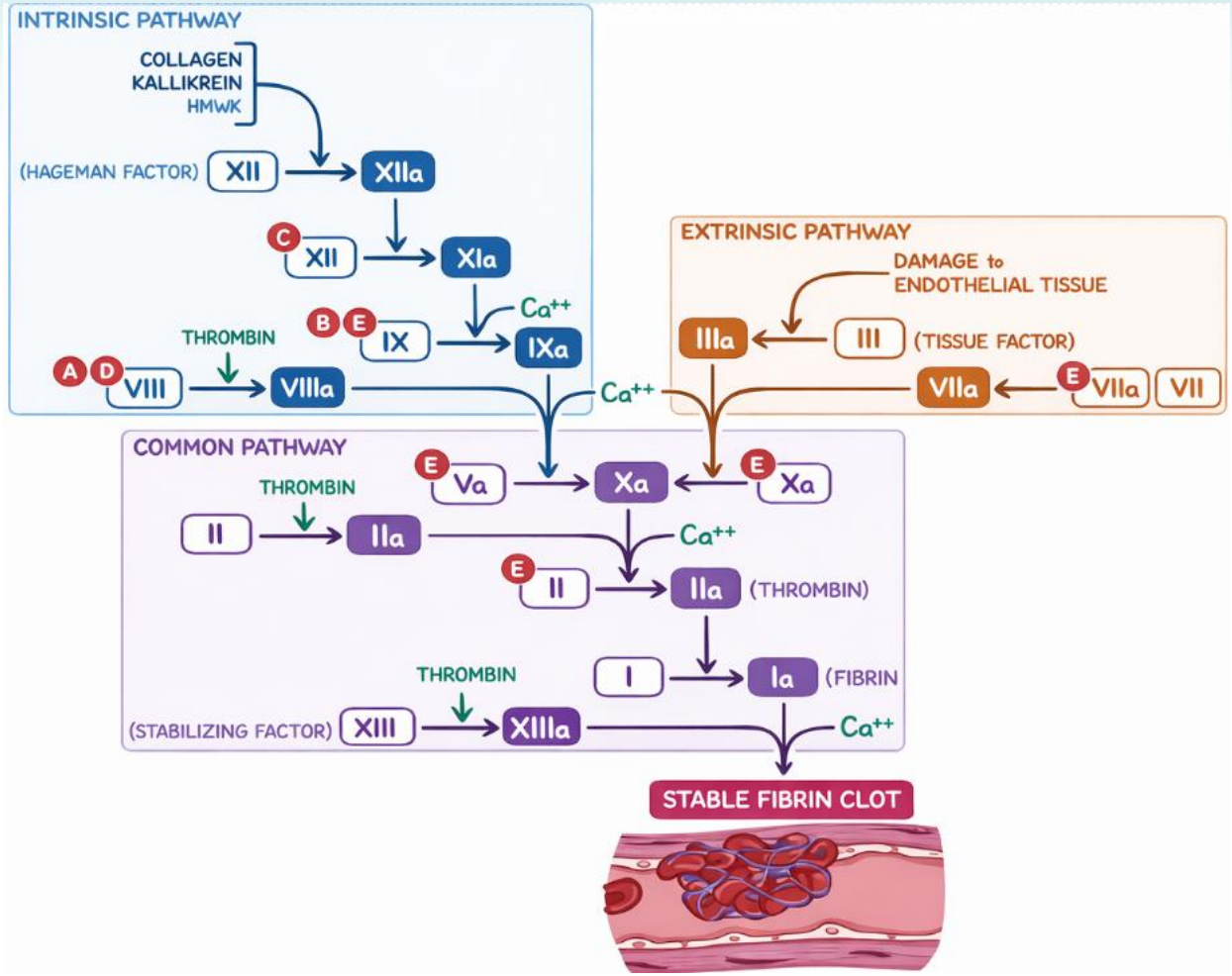
- **Endothelial injury** exposes subendothelial proteins, initiating platelet activation.
- **Platelets adhere** to exposed collagen and von Willebrand factor at the injury site.
- **Thrombin production** further activates platelets and amplifies the coagulation response.
- **Activated platelets release mediators** that recruit additional platelets.
- **Platelet aggregation forms a temporary platelet plug**, providing initial hemostasis before fibrin stabilizes the clot.



Source: National Blood Clot Alliance. *Stop the Clot.*

Propagation

- **Vessel injury activates the intrinsic and extrinsic pathways**, leading to formation of factor Xa.
- **Factor Xa triggers the common pathway**, producing large amounts of thrombin.
- **Thrombin converts fibrinogen to fibrin**, creating a fibrin mesh over the platelet plug.
- **Fibrin cross-linking stabilizes the clot**, strengthening hemostasis and preventing further bleeding.
- The coagulation system is highly coordinated, with overlapping pathways that regulate clot formation but **can lead to thrombosis or bleeding if dysregulated**.



Source: National Blood Clot Alliance. *Stop the Clot*.

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Termination & Resolution

Multiple physiologic mechanisms regulate coagulation to prevent uncontrolled thrombus formation

→

Normal blood flow dilutes and removes activated clotting factors, limiting excessive clot propagation

→

Hepatic clearance and natural anticoagulant proteins regulate coagulation activity within circulation

↓

The fibrinolytic system degrades fibrin and dissolves clots once hemostasis is achieved

→

Disruption in any of these regulatory systems increases the risk of pathologic thrombosis

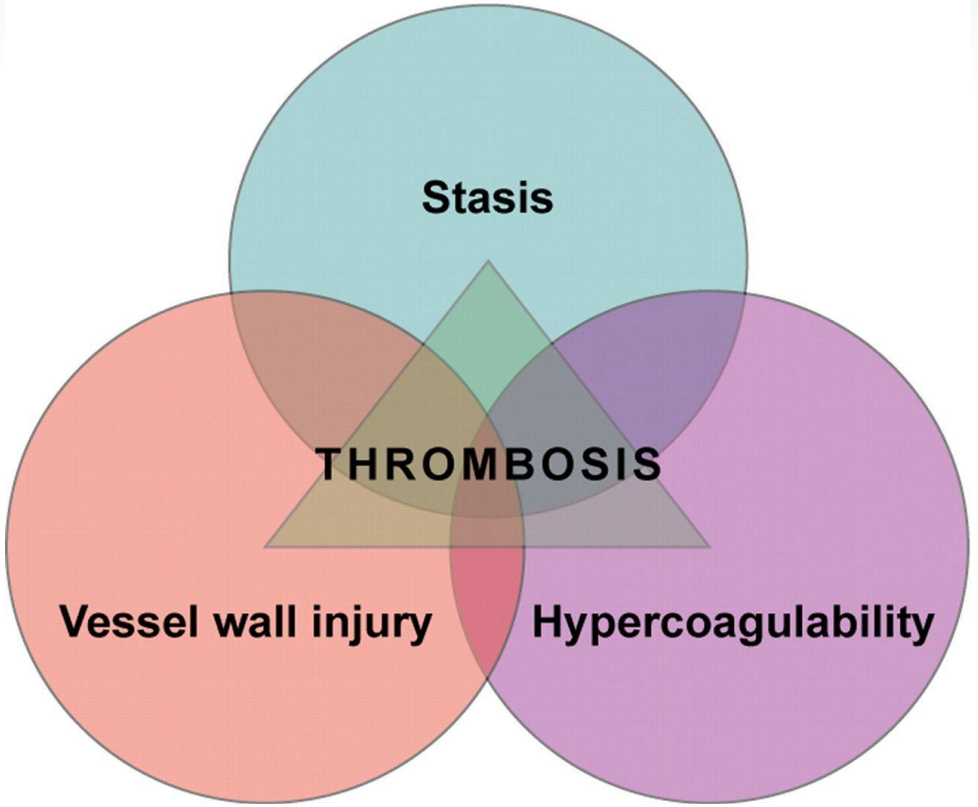
→

Key endogenous anticoagulant proteins:

- Protein C and Protein S
- Antithrombin
- Tissue Factor Pathway Inhibitor (TFPI)

Source: National Blood Clot Alliance. *Stop the Clot*.

Pathophysiology: Virchow's Triad



Source: National Blood Clot Alliance. *Stop the Clot*.

Vessel Wall Injury

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The first component of Virchow's Triad involves injury or dysfunction of the vessel wall, particularly the endothelium.

Healthy endothelial cells provide an antithrombotic surface, preventing platelet adhesion and inappropriate clot formation.

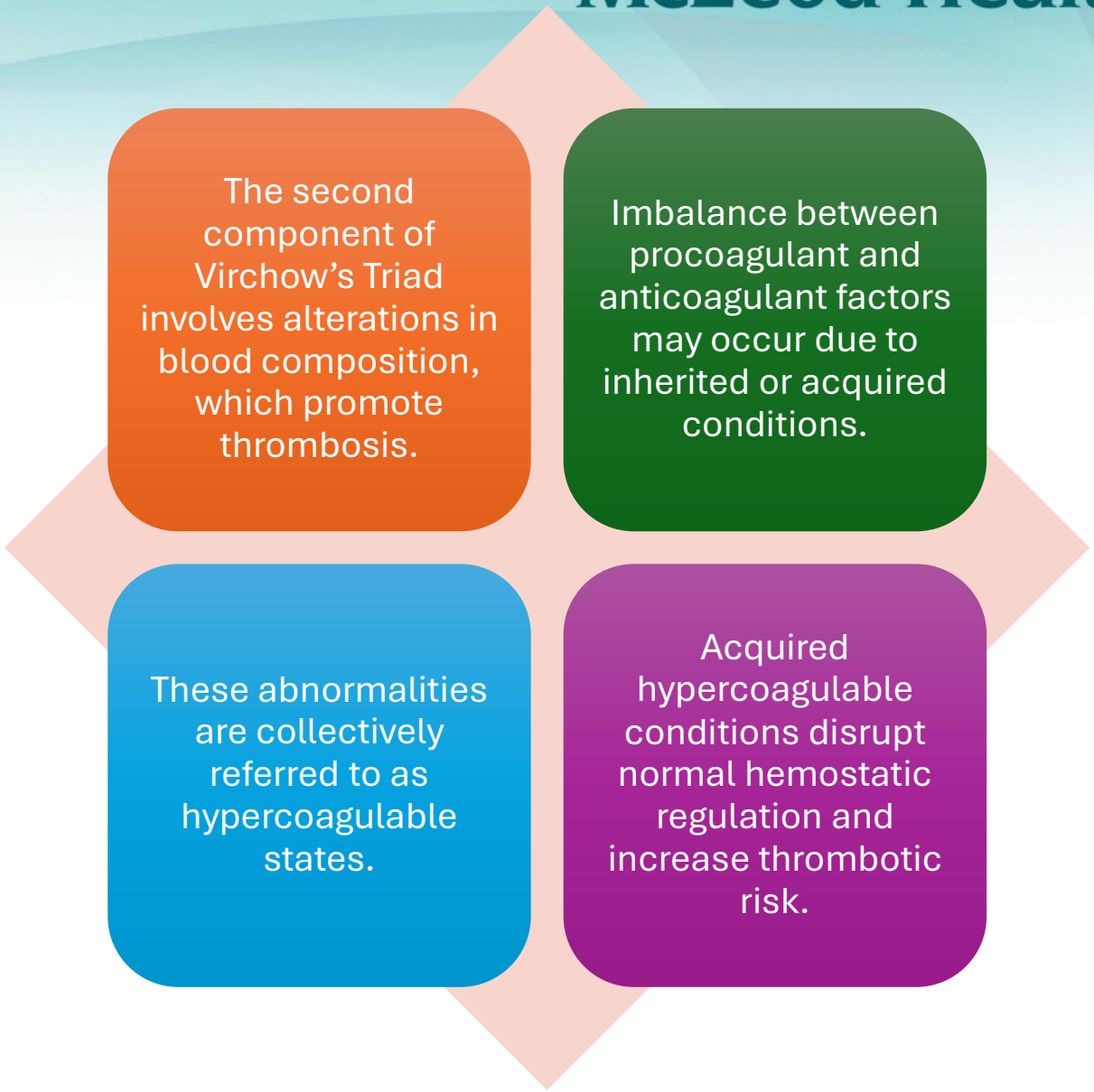
Damage to the endothelium exposes procoagulant factors, including tissue factor, which initiates the coagulation cascade at the site of injury.

Endothelial injury may result from direct trauma, inflammation, infection, or vascular disease.

Structural changes to the vessel wall, such as scarring following a prior DVT, can promote abnormal blood flow and persistent thrombotic risk.

Source: National Blood Clot Alliance. *Stop the Clot*.

Hypercoagulability



Source: National Blood Clot Alliance. *Stop the Clot.*

Stasis

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The third component of Virchow's Triad is stasis, or reduced blood flow within the vessel.

Normal venous return relies on contraction of surrounding skeletal and smooth muscles, which help propel blood back toward the heart.

Immobility or reduced activity decreases this pumping mechanism, resulting in slower venous circulation.

Sluggish blood flow - particularly in the lower extremities - promotes accumulation of clotting factors and increases the likelihood of coagulation.

Source: National Blood Clot Alliance. *Stop the Clot*.

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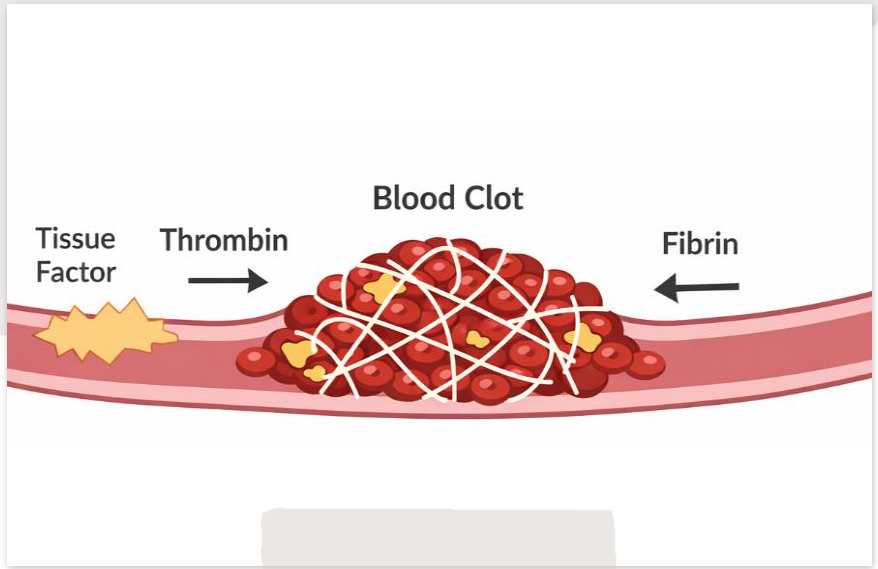
Clot Formation in the Acute Phase



- Virchow's triad (venous stasis, endothelial injury, hypercoagulability) disrupts normal anticoagulant balance and initiates clot formation.
- Tissue factor exposure activates the coagulation cascade, generating small amounts of thrombin.
- Thrombin amplification activates additional clotting factors and platelets, producing a rapid thrombin burst.
- Fibrin formation creates a mesh that traps red blood cells and platelets, forming a fibrin-rich ("red") venous thrombus that can propagate.
- Early in VTE, clot formation exceeds breakdown, making the thrombus unstable and at highest risk for extension or embolization.
- Anticoagulation prevents new thrombin generation, stabilizing the clot and allowing natural fibrinolysis to gradually resolve it.

Source: National Blood Clot Alliance. *Stop the Clot*.

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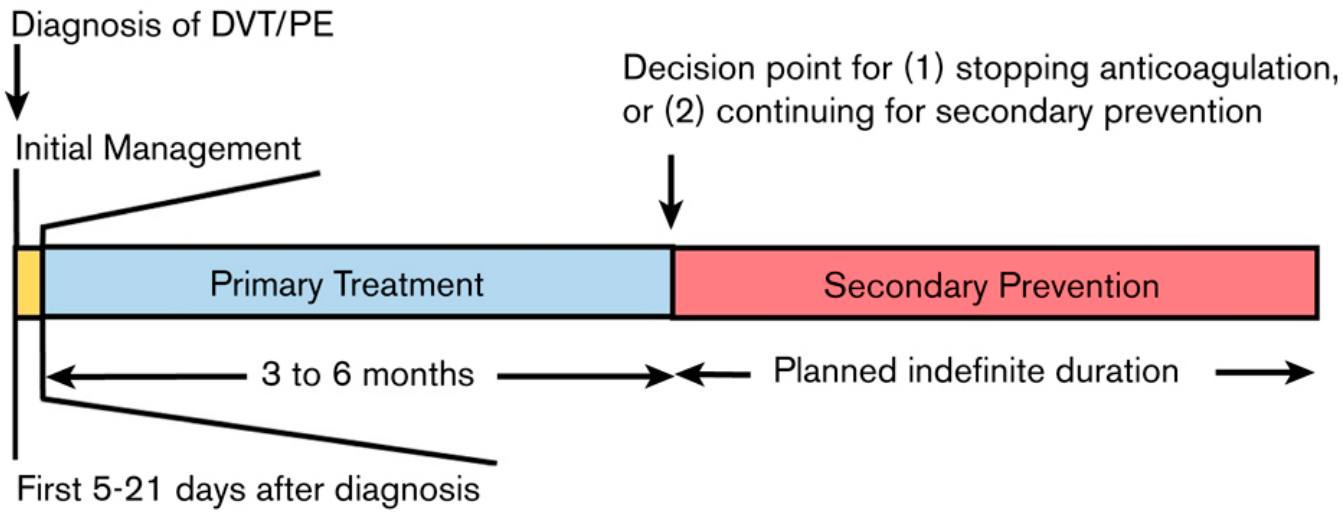
VTE Management Recommendations

Acute Management



Source: Ortel TL, et al. *Blood Adv*. 2020 Oct.

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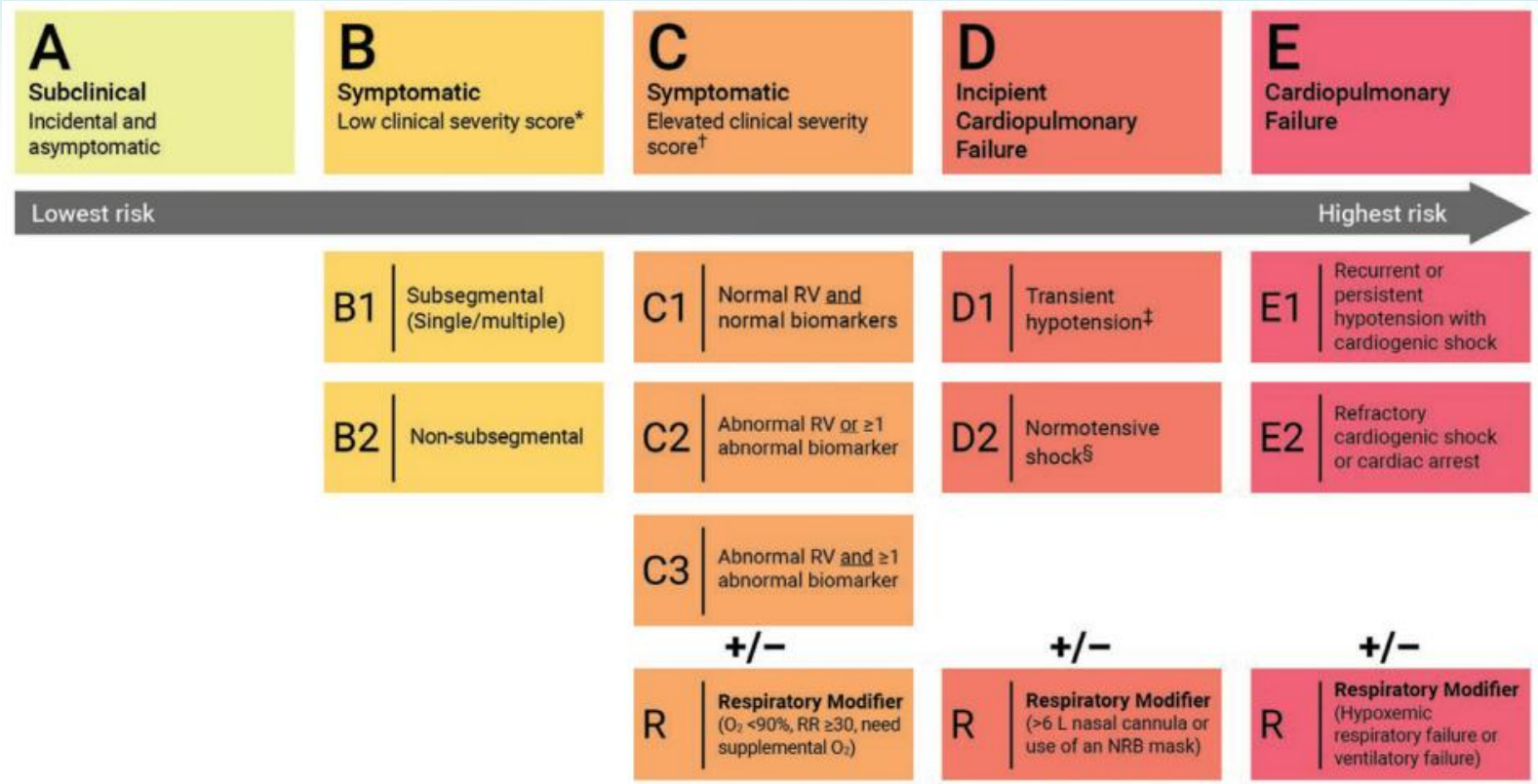
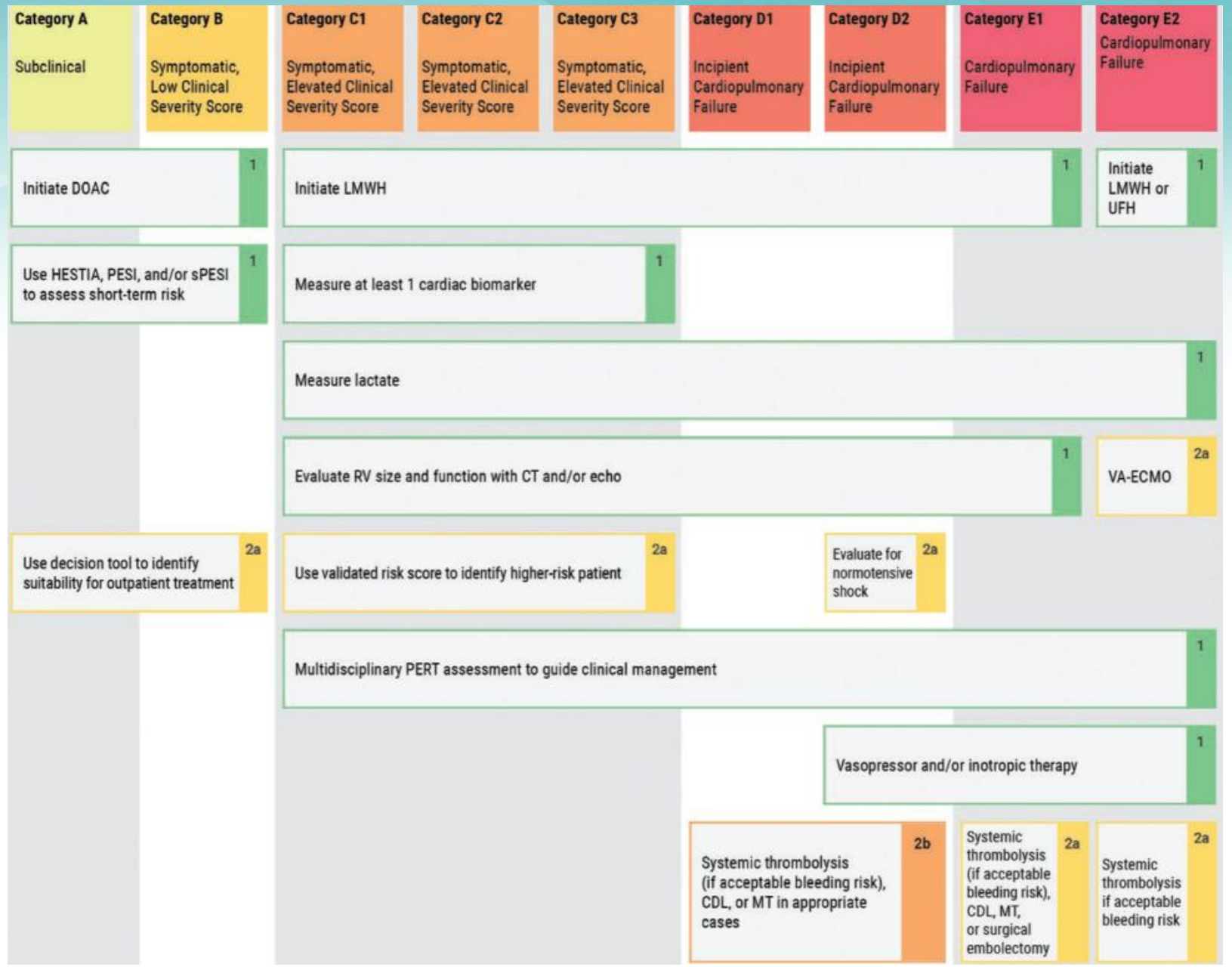
AHA/ACC 2026 Acute PE Clinical Categories



Source: Creager MA, et al. *Circulation*. 2026 Feb.

ACC/AHA 2026 Acute PE Management



Source: Creager MA, et al. *Circulation*. 2026 Feb.

2026 ACC/AHA Guidelines

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Class I Recommendation

• **Anticoagulation is recommended in all patients with acute PE without absolute contraindications**
• **Low-molecular-weight heparin (LMWH) preferred over unfractionated heparin (UFH)**
  ○ Associated with: lower recurrent VTE rates, reduced major bleeding, more predictable pharmacokinetics
  ○ UFH may still be preferred in select patients: hemodynamic instability, anticipated procedures/thrombolysis, severe renal impairment

• **Direct oral anticoagulants (DOACs) preferred over vitamin K antagonists**
• Recommended in patients eligible for oral therapy and without contraindications
• Advantages include:
  ○ Comparable or improved efficacy
  ○ Lower major bleeding risk
  ○ Fixed dosing without routine monitoring

Source: Creager MA, et al. *Circulation*. 2026 Feb.

Treatment

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Oral Agents	Parental Agents

• **Vitamin K Antagonists**
  ○ Warfarin
• **Direct Oral Anticoagulants**
  ○ Dabigatran
  ○ Apixaban
  ○ Rivaroxaban
  ○ Edoxaban
	• **Unfractionated Heparin**
	• **Low Molecular Weight Heparin**
	  ○ Enoxaparin
	  ○ Dalteparin
	• **Fondaparinux**
	• **Argatroban**

Source: National Blood Clot Alliance. *Stop the Clot*.

AMPLIFY & EINSTEIN trial

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Characteristic	AMPLIFY Trial (Apixaban)	EINSTEIN Trial (Rivaroxaban)
Study Design	Randomized, double-blind, noninferiority	Randomized, open-label, noninferiority
Population	Acute symptomatic DVT and/or PE	Acute symptomatic proximal DVT
Intervent		days → 20 mg
Compara		n (INR 2–3)
Parenteral in Requi		
Primary Eff Outcon		c VTE erior)
Major Blee		; NS)
Conclusions	bleeding and CRNMB occurred in 4.3% of the patients in the apixaban group, vs 9.7% of those in the conventional-therapy group (P<0.001).	n 2.1% with standard therapy (HR 0.68; P<0.001 for noninferiority). • Clinically relevant bleeding occurred in 8.1% in both groups.

Main Takeaway – these landmark trials established oral-only treatment strategies for acute VTE, supporting the use of intensified oral lead-in dosing with apixaban and rivaroxaban without the need for initial parenteral anticoagulation.

Sources: Agnelli G, et al. N Engl J Med. 2013
Bauersachs R, Berkowitz SD, et al. N Engl J Med. 2010

HOKUDSAI-VTE & RE-COVER

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Characteristic	HOKUDSAI-VTE Trial	RE-COVER Trial
Study Design	Randomized, double-blind, noninferiority	Randomized, open-label, noninferiority
Population	Acute symptomatic DVT and/or PE	Symptomatic DVT and/or PE
Interven		daily*
Compar		–3)
Parenteral Requir		
Primary Ef Outcor		atic VTE nferior)
Major Ble		nilar)
Conclusions	Dabigatran has similar effects on VTE recurrence and a lower risk of bleeding compared with warfarin for the treatment of acute VTE.	owing initial heparin therapy was noninferior to warfarin for the treatment of VTE and was associated with significantly less bleeding, including in patients with severe PE

Main Takeaway – these landmark trials demonstrated efficacy only after initial parenteral anticoagulation, which is why dabigatran and edoxaban require a parenteral lead-in prior to oral therapy initiation in acute VTE treatment.

Sources: Büller HR, et al. *N Engl J Med*. 2013
Schulman S, et al. *Circulation*. 2014

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Anticoagulation Mechanism of Action

Class	Medications	Target/Mechanism	Effect
Vitamin K antagonists	Warfarin	Inhibit VKORC1 → ↓ Factors II, VII, IX, X	Prevent fibrin formation
Heparins	Heparin, Enoxaparin	Potentiate at III → inhibit IIa, Xa	Rapid anticoagulation
Direct thrombin inhibitors	Dabigatran, Argatroban	Block thrombin active site	Prevent fibrinogen → fibrin
Direct factor Xa inhibitors	Rivaroxaban, Apixaban	Inhibit factor Xa	↓ Thrombin generation
Synthetic pentasaccharides	Fondaparinux	Activate AT III → inhibit Xa	Selective Xa inhibition

Sources: Lexicomp Online. Argatroban. Lexicomp Online. Enoxaparin. Lexicomp Online. Heparin.
Lexicomp Online. Rivaroxaban. Lexicomp Online. Fondaparinux. Lexicomp Online. Warfarin.
Lexicomp Online. Apixaban. Lexicomp Online. Dabigatran.

Anticoagulant Selection Based on Clot Activity

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Phase	Clot Activity	Treatment Goal	Pharmacologic Strategy
Acute propagation (0 – 48 hours)	Active thrombin burst, fibrin deposition, embolization risk highest	Stop clot growth immediately	UFH/LMWH or DOAC loading doses
Stabilization (Days 3 – 21)	Clot organizing; thrombin generation declining	Maintain strong anticoagulation	DOAC treatment dosing or transition from parenteral
Resolution (Weeks – Months)	Endogenous fibrinolysis + recanalization	Prevent recurrence	Maintenance dosing
Secondary prevention (> 3 months)	Residual clot remodeling	Prevent new thrombosis	Reduced-dose DOAC or continued therapy if indicated

Heparin/LMWH

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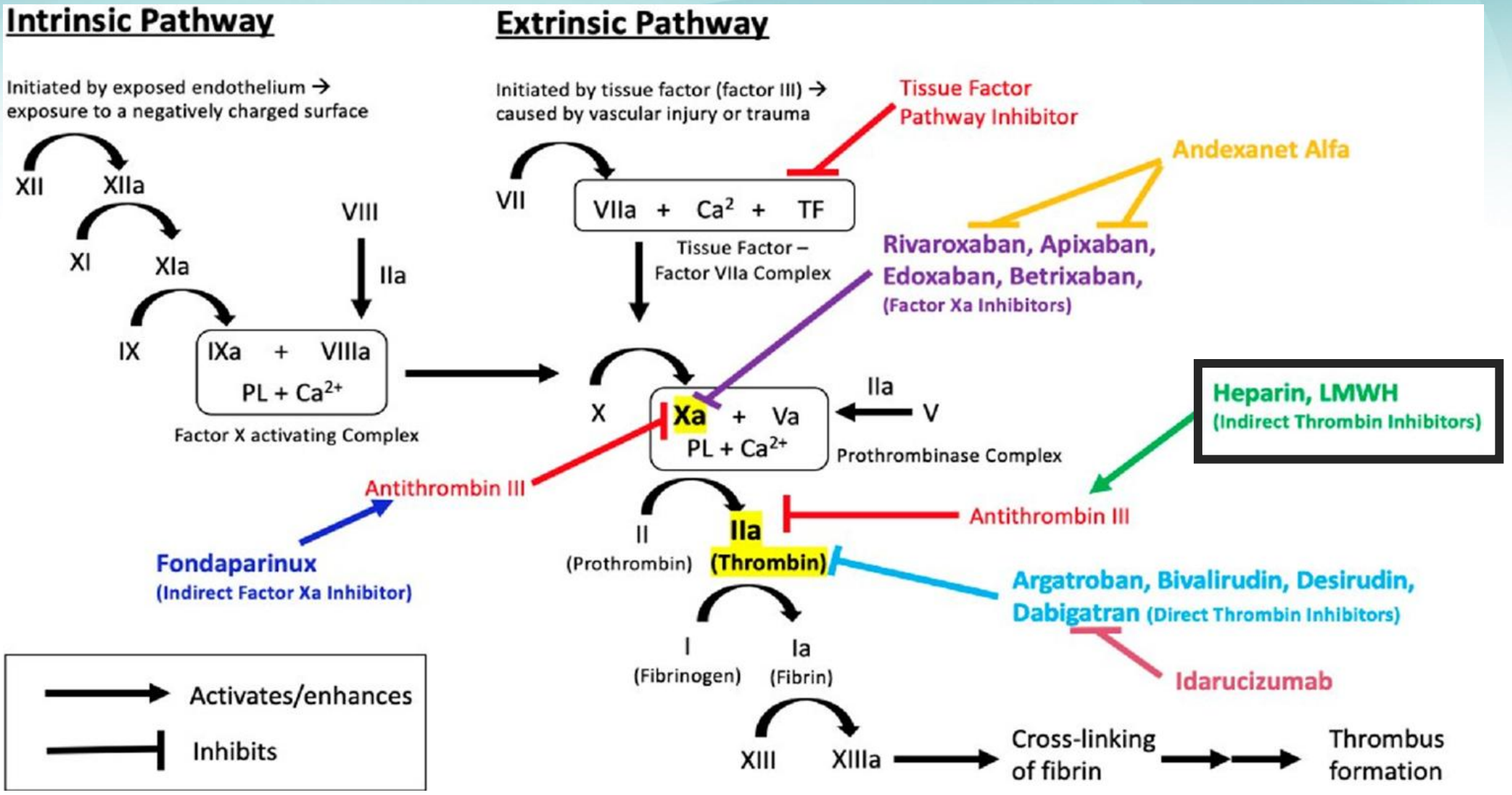

Source: Kustos SA, et al. Medicines (Basel). 2019 Oct

Heparin/LMWH

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Therapy	Target in Coagulation	Effect on Acute Clot Biology	Onset of Anticoagulant Effect	Acute Treatment (Labeled Dosing)	Why Load or Lead-In Exists	Typical Treatment Duration Role
UFH (IV Heparin)	Antithrombin-mediated inhibition of Xa + IIa (thrombin)	Immediately suppresses thrombin generation → stops clot propagation	Immediate (minutes)	Weight-based bolus + infusion per institutional nomogram	Rapid anticoagulation needed while clot actively propagates; easily titratable/reversible	Initial stabilization phase; preferred when procedures expected and severe renal impairment
LMWH (enoxaparin)	Antithrombin-mediated inhibition (anti-Xa >> IIa)	Rapidly decreases new thrombin formation → stabilizes fibrin clot	3 – 5 hours	1 mg/kg SubQ q12h OR 1.5 mg/kg daily	Provides immediate anticoagulation during highest thrombin activity	Acute treatment or bridge therapy

Sources: Lexicomp Online. Heparin.
Lexicomp Online. Enoxaparin.

DOACs

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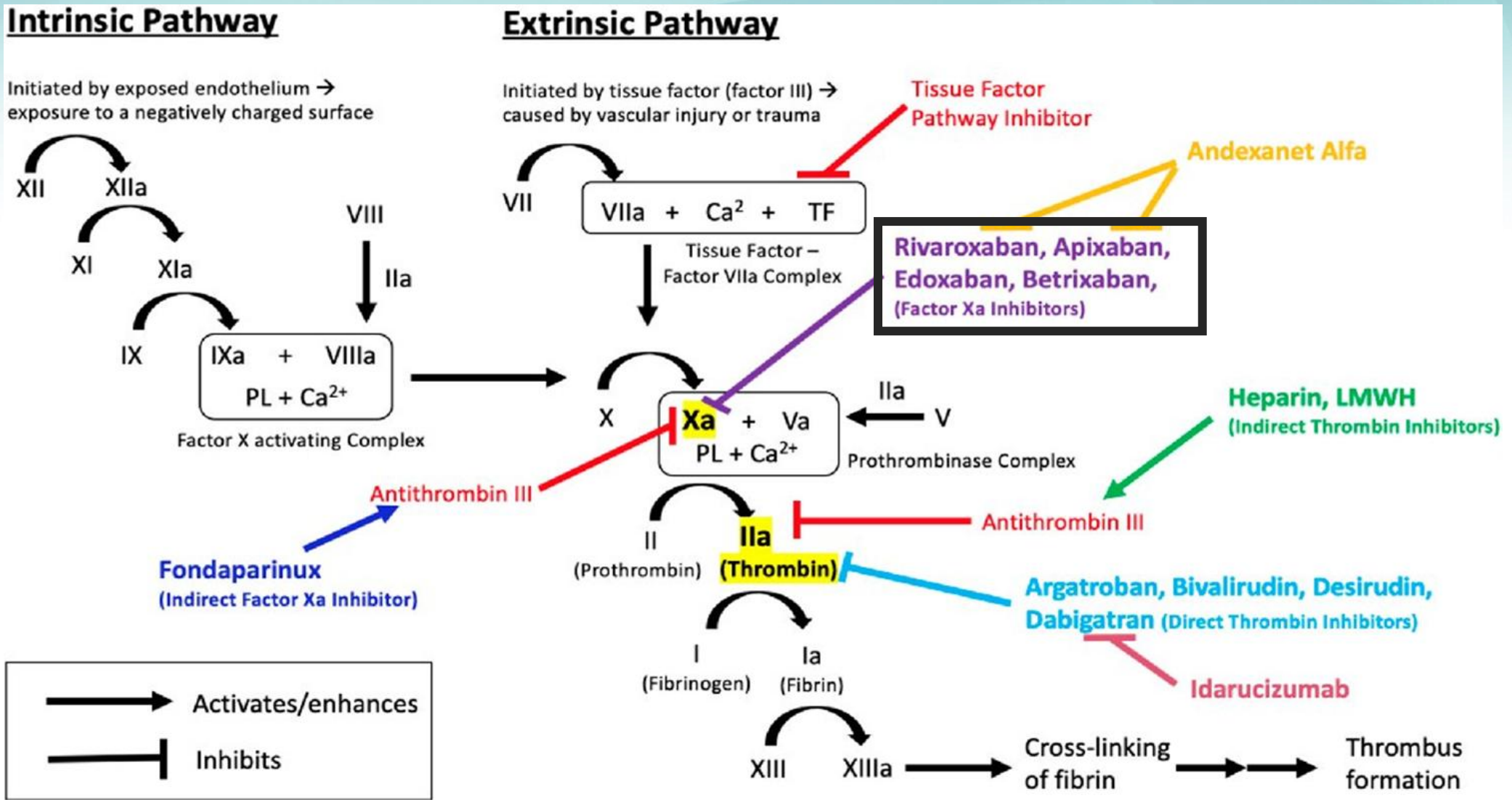

Source: Kustos SA, et al. Medicines (Basel). 2019 Oct

DOACS

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Therapy	Target in Coagulation Cascade	Effect on Acute Clot	Onset of Anticoagulant Effect	Acute Treatment (Labeled Dosing)	Why Load or Lead-In Exists
Apixaban	Direct Factor Xa inhibitor	Blocks thrombin generation at cascade bottleneck → prevents fibrin expansion	3 – 4 hours	10 mg PO BID x 7 days	Extended high-intensity phase covers prolonged early hypercoagulability and replaces need for parenteral therapy during highest recurrence risk
Rivaroxaban			2 – 4 hours	15 mg PO BID x 21 days (with food)	
Edoxaban			1-2 hours	Start with parenteral overlap then: 60 mg PO daily (30 mg if CrCl 15 – 50mL/min, ≤60 kg, or P-gp inhibitors)	Requires 5-10 days parenteral anticoagulation first (never tested as monotherapy in acute unstable VTE and FDA labeling follows trial design)
Dabigatran			Fasting state: 1 hour; delayed 2 hours by food	Start with parenteral overlap then: 150 mg PO BID	

Sources: Lexicomp Online. Apixaban. Lexicomp Online. Edoxaban. Lexicomp Online. Rivaroxaban. Lexicomp Online. Dabigatran.

Warfarin

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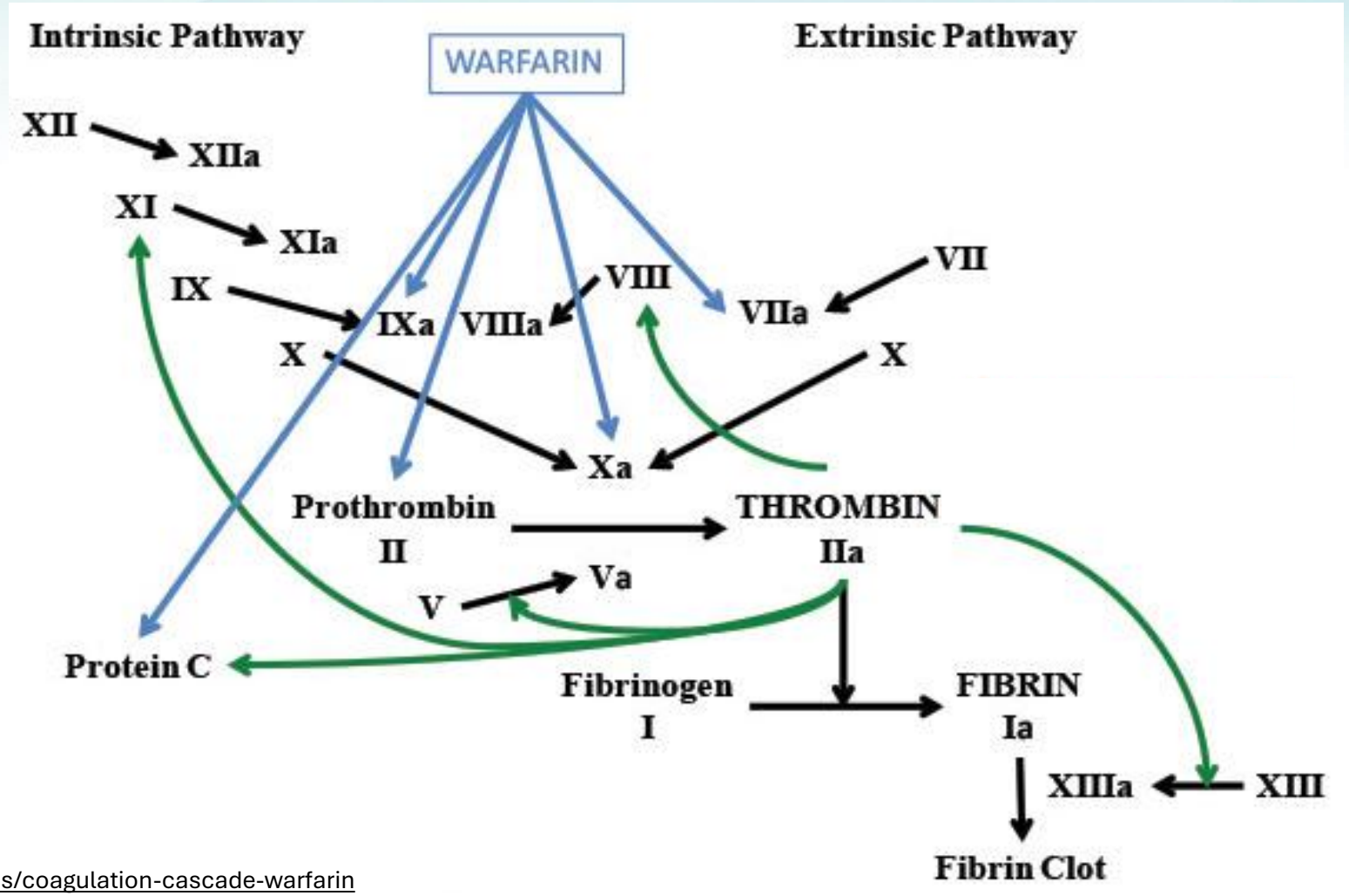

Source: animalia-life.club/qa/pictures/coagulation-cascade-warfarin

Warfarin

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Therapy	Target in Coagulation Cascade	Effect on Acute Clot	Onset of Anticoagulant Effect	Acute Treatment (Labeled Dosing)	Why Lead-In
Warfarin	Inhibits vitamin K epoxide reductase → ↓ synthesis of **II, VII, IX, X**	Prevents production of new clotting factors; does NOT inhibit existing thrombin	Delayed (3 – 5 days)	Start with parenteral overlap	Existing clotting factors remain active initially → risk of propagation if unbridged

Source: Lexicomp Online. Warfarin.

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Bleeding Risk

Bleeding Risk Stratification

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Bleeding risk stratification should play a central role in guiding anticoagulation for acute VTE.

Incorporating validated risk assessment tools allows for individualized anticoagulant intensity and transition strategies.

Tailoring therapy based on patient-specific risk helps balance thrombotic protection with bleeding safety, especially during the early high-risk phase.

Source: Creager MA, et al. *Circulation*. 2026 Feb.

Bleeding Risk

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Prediction Models for Quantifying Bleeding Risk			
Prediction Model	Parameters	Points	Categories of bleeding risk
Improve VTE Bleed (For use in acutely ill hospitalized patients)	• ≥ 85 years old • 40 – 84 years old • Male • eGFR 30-59 ml/min/m2 • eGFR ≤ 30 ml/min/m2 • Liver failure (INR ≥ 1.5) • Platelets < 50k/cm3 • Admission to ICU or CCU • Central venous catheter • Active gastric or duodenal ulcer • Prior bleeding w/in last 3 months • Rheumatic disease • Active malignancy	3.5 1.5 1 1 2.5 2.5 4 2.5 2 4.5 4 2 2	< 7: Not at increased risk of bleeding ≥ 7: Increased risk of bleeding
VTE-Bleed	• Active cancer • Male patient with uncontrolled hypertension • Anemia • History of bleeding • Age ≥ 60 years • Renal dysfunction (CrCl 30-60 mL/min)	1.5 2 1 1.5 1.5 1.5	0-1: low bleeding risk ≥ 2: high bleeding risk

Source: Creager MA, et al. *Circulation*. 2026 Feb.

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Literature Review

Clinical Question:
If a patient already receives several days of parenteral anticoagulant, do they still need the FULL duration of oral lead-in with DOACs?

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Study #1

Rethinking lead-in strategies: evaluation of full vs. reduced dose factor Xa inhibitors in acute VTE

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Source: Jolakoski N, et al. *J Thromb Thrombolysis*. 2025 Dec.

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Background

Venous thromboembolism (VTE), including deep vein thrombosis(DVT) and pulmonary embolism (PE), is associated with significant morbidity and mortality.

The highest risk of VTE recurrence occurs within the first week after diagnosis, with continued elevated risk during the first month.

Mortality risk is also significantly increased during the initial 30 days following a VTE event.

Early anticoagulation intensity is critical during the initial treatment phase.

Source: Jolakoski N, et al. *J Thromb Thrombolysis*. 2025 Dec.

Purpose

To evaluate whether reducing the oral factor Xa (FXa) inhibitor lead-in duration after therapeutic parenteral anticoagulation affects:

- VTE recurrence
- Bleeding outcomes

Source: Jolakoski N, et al. *J Thromb Thrombolysis*. 2025 Dec.

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Study Design

- Multicenter, retrospective, observational cohort study
- Conducted across 29 hospitals in the United States
- Evaluated full vs. reduced FXa inhibitor lead-in dosing
- Included patients treated with apixaban or rivaroxaban following parenteral anticoagulation for VTE
- Study period: January 2017 – March 2024

Source: Jolakoski N, et al. *J Thromb Thrombolysis*. 2025 Dec.

Methods

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Parenteral anticoagulation:

- ≥ 24 hours of therapeutic heparin, enoxaparin, fondaparinux, bivalirudin, or argatroban prior to FXa inhibitor initiation

Full lead-in dosing:

- Apixaban: 13 – 14 doses of 10 mg (6.5 - 7 days)
- Rivaroxaban: 39 – 42 doses of 15 mg (19.5 – 21 days)

Reduced lead-in dosing:

- Receipt of at least 7 or 21 days of sequential parenteral anticoagulation and lead-in dosing of apixaban or rivaroxaban
- Two doses of apixaban or rivaroxaban lead-in dosing were substituted for each 24-hour period of therapeutic parenteral anticoagulation

Source: Jolakoski N, et al. *J Thromb Thrombolysis*. 2025 Dec.

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Inclusion vs Exclusion Criteria

Inclusion	Exclusion
• Hospital admission for a new diagnosis of DVT or PE • Receipt of ≥ 24 hours of therapeutic parenteral anticoagulation • Treatment with apixaban or rivaroxaban for VTE	• Lead-in dose reduction not aligned with parenteral anticoagulation duration • Active bleeding at index admission or prior to anticoagulation • Mechanical heart valve or moderate/severe mitral stenosis • Antiphospholipid antibody syndrome • Severe or decompensated liver disease • Pregnancy or incarceration • 1 hour overlap between parenteral anticoagulation and FXa inhibitor initiation • Therapeutic anticoagulation prior to admission • Use of contraindicated interacting medications

Source: Jolakoski N, et al. *J Thromb Thrombolysis*. 2025 Dec.

Baseline Characteristics

- Patients in the reduced lead-in group were older, more frequently admitted to the ICU, and received significantly longer parenteral anticoagulation prior to DOAC transition (192 vs 44 hours, $p<0.01$)
- Apixaban was the most commonly used agent in both groups.

Source: Jolakoski N, et al. *J Thromb Thrombolysis*. 2025 Dec.

Primary Outcome

Time to recurrent VTE

- Measured from index admission through 6 months
- Follow-up continued until:
  - Anticoagulant discontinuation
  - Anticoagulant switch
  - Completion of 6-month follow-up

Recurrent VTE defined using CHEST and ASH diagnostic criteria

Recurrent PE: confirmed by CT pulmonary angiography or pulmonary angiography

Recurrent DVT:

- New non-compressible venous segment, or
- Significant thrombus diameter increase in a previously abnormal segment on compression ultrasound or venography

Source: Jolakoski N, et al. *J Thromb Thrombolysis*. 2025 Dec.

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Secondary Outcomes

Major bleeding (ISTH definition)

Clinically relevant non-major bleeding

Re-hospitalization for:

- VTE-related events
- Anticoagulant-related complications

Hospital length of stay

All-cause mortality within 6 months

Source: Jolakoski N, et al. *J Thromb Thrombolysis*. 2025 Dec.

Bleeding Definitions

- **Major bleeding (ISTH criteria):**
  - Fatal bleeding
  - Symptomatic bleeding in a critical organ or space (e.g., intracranial, retroperitoneal, pericardial)
  - Hemoglobin decrease ≥ 2 g/dL
  - Transfusion of ≥ 2 units of whole blood or red blood cells
- **CRNMB:**
  - Bleeding not meeting major criteria but requiring:
    - Medical intervention
    - Higher level of care
    - Face-to-face clinical evaluation

Source: Jolakoski N, et al. *J Thromb Thrombolysis*. 2025 Dec.

Statistical Analysis

Baseline characteristics were summarized using frequencies/percentages for categorical variables and means ± SD or medians (IQR) for continuous variables, with group comparisons performed using Chi-square, Student's t-test, or Mann–Whitney U tests based on data distribution.

Primary outcome (time to recurrent VTE) was analyzed using Kaplan–Meier survival curves, with differences between groups compared using the log-rank test; patients were censored at recurrence, death, or 6 months.

Multivariable Cox proportional hazards regression was used to adjust for potential confounders, including variables that were clinically relevant or associated with outcomes in univariable analysis ($p < 0.1$).

Sensitivity analysis with 1:1 propensity score matching (caliper 0.1 SD) was performed to balance baseline characteristics between groups, and statistical significance was defined as $p < 0.05$.

Source: Jolakoski N, et al. *J Thromb Thrombolysis*. 2025 Dec.

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Sample Size

- Sample size based on prior retrospective data comparing full vs. reduced FXa inhibitor lead-in dosing
- Assumed 3% absolute difference in recurrent VTE:
  - 2% in full lead-in group
  - 5% in reduced lead-in group
- Required 1,424 patients to achieve:
  - 80% power
  - $\alpha = 0.05$
- Allocation ratio: 3:1 (full : reduced lead-in)
  - 1,068 patients in full lead-in group
  - 356 patients in reduced lead-in group

Source: Jolakoski N, et al. *J Thromb Thrombolysis*. 2025 Dec.

Results

Primary Outcome	Safety and Secondary Outcomes

• **Recurrent VTE**
  • No significant difference:
  ○ HR 0.53 (95% CI 0.20 -1.37)
  ○ p = 0.19
• **Recurrence rates:**
  ○ Full lead-in: 2.7%
  ○ Reduced lead-in: 1.4%
	• Rates of major bleeding and clinically relevant nonmajor bleeding were similar between groups
	• **No significant difference:**
	  ○ HR 0.69 (95% CI 0.31–1.56)
	  ○ p = 0.45

Source: Jolakoski N, et al. *J Thromb Thrombolysis*. 2025 Dec.

Strengths vs Limitations

Strengths	Limitations
• Large, multicenter study • Clinically relevant outcomes • Adequately powered sample size • Propensity score matching performed	• Retrospective observational design • Patients receiving reduced lead in were generally sicker • Medication adherence unknown

Source: Jolakoski N, et al. *J Thromb Thrombolysis*. 2025 Dec.

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Author's Conclusions

These findings support a potential alternative strategy for a common real-world clinical scenario.

However, prospective studies are needed to confirm safety and determine optimal lead-in duration relative to prior heparin exposure.

A reduced DOAC lead-in duration was not associated with increased VTE recurrence or major bleeding when transitioning from parenteral anticoagulation to oral factor Xa inhibitors.

Source: Jolakoski N, et al. *J Thromb Thrombolysis*. 2025 Dec.

Conclusion

A reduced apixaban or rivaroxaban lead-in following therapeutic parenteral anticoagulation was not associated with increased VTE recurrence or bleeding, suggesting a shorter lead-in may be reasonable in selected patients

Prospective, randomized controlled trials are needed before routine practice changes can be recommended.

Source: Jolakoski N, et al. *J Thromb Thrombolysis*. 2025 Dec.

Study #2

Reduced versus full apixaban lead-in dosing following parenteral treatment of acute venous thromboembolism

Daniella Veloria [a,*], Benjamin Wang [a], Ran Ran [b], David Ha [c], Robert Diep [d], Calvin Diep [a]

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[b] *Department of Emergency & Critical Care Medicine, Oregon Health & Science University, Portland, OR, United States*
[c] *Division of Infectious Diseases and Geographic Medicine, Stanford University, United States*
[d] *Division of Hematology, Stanford University, Palo Alto, CA, United States*

Source: Veloria D, et al. *Thrombosis Update*. 2025

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Background

The risk of recurrent venous thromboembolism (VTE) is highest during the first 4 weeks after the initial event.

In hospitalized patients, clinicians often start parenteral anticoagulation (e.g., heparin) before transitioning to apixaban due to illness severity, procedures, or bleeding concerns.

There is limited guidance on how to manage apixaban lead-in dosing when patients have already received >24 hours of parenteral anticoagulation.

Source: Veloria D, et al. *Thrombosis Update*. 2025

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Purpose

To compare the safety and effectiveness
of using a reduced apixaban lead-in vs. full lead-in dosing
in hospitalized patients that received >24 h of parenteral anticoagulation
for the treatment of VTE

Source: Veloria D, et al. *Thrombosis Update*. 2025

Methods

Design: Single-center, retrospective cohort study

Setting: Stanford Health Care, a 613-bed academic medical center

Study period: January 1, 2017 – December 31, 2023

Study groups:

- Full lead-in cohort: Apixaban 10 mg BID for ≥ 6 days
- Reduced lead-in cohort: Apixaban 10 mg BID for < 6 days
- Lead-in duration was determined by the treating clinical team.

Source: Veloria D, et al. *Thrombosis Update*. 2025

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Inclusion vs. Exclusion Criteria

Inclusion	Exclusion
• ≥18 years old • Hospitalized for ≥7 days • Received >24 hours of parenteral anticoagulation • Transitioned to apixaban • Had an ICD-9 or ICD-10 diagnosis code for VTE	• Antiphospholipid syndrome • Chronic thromboembolic pulmonary hypertension • Heparin-induced thrombocytopenia (HIT) • Pregnancy • Incarceration • Death within 48 hours of admission

Source: Veloria D, et al. *Thrombosis Update*. 2025

Outcomes

- **Primary outcome:**
  - Recurrent VTE within 30 days (new DVT and/or PE confirmed by imaging)
- **Secondary outcomes:**
  - Major bleeding
  - Clinically relevant non-major bleeding (CRNMB)
  - Defined using International Society on Thrombosis and Haemostasis (ISTH) criteria

Source: Veloria D, et al. *Thrombosis Update*. 2025

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Statistical Analysis

Significance level: **p < 0.05 (two-tailed)**

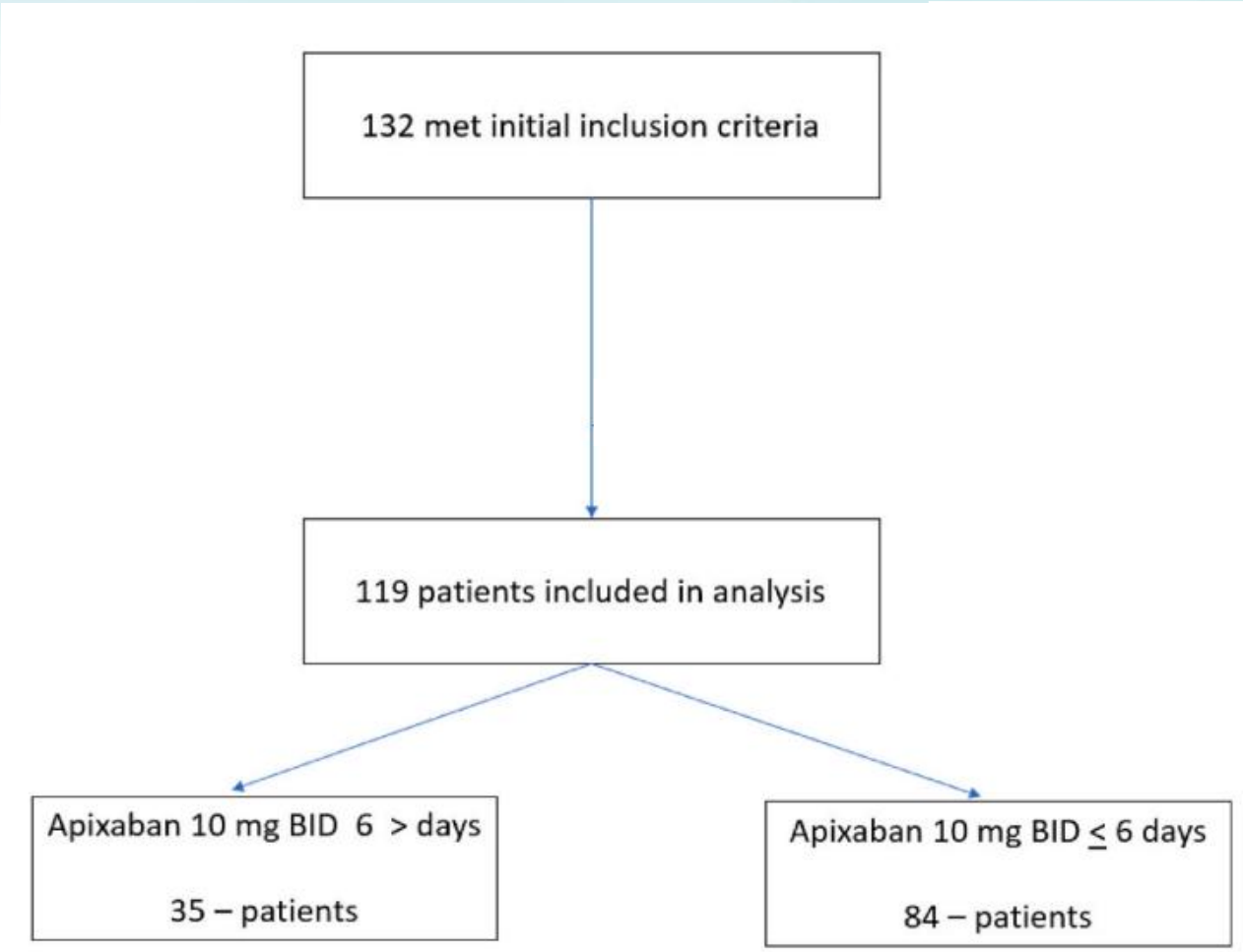
Tests used:

- **Student t-test** → parametric continuous variables
- **Mann–Whitney U test** → nonparametric continuous variables
- **Chi-square or Fisher exact test** → categorical variables

Source: Veloria D, et al. *Thrombosis Update*. 2025

Study Population

- **Total patients:** 119
  - **Full lead-in:** 35 patients
  - **Reduced lead-in:** 84 patients



Source: Veloria D, et al. *Thrombosis Update*. 2025

Results

Patients receiving reduced apixaban lead-in dosing:

- More likely to have active cancer or be receiving chemotherapy (46% vs 23%, p = 0.02)
- Higher bleeding risk, with more patients having a VTE-BLEED score >2 (88% vs 60%, p < 0.01) and a higher median VTE-BLEED score (4.5 vs 3, p = 0.01).
- Received longer parenteral anticoagulation before transitioning to apixaban (median 6.7 vs 2 days, p < 0.01)
- Among reduced lead-in patients, 82% received no apixaban 10 mg BID lead-in dosing.

Type of parenteral anticoagulant used was similar between groups.

Source: Veloria D, et al. *Thrombosis Update*. 2025

Results

Outcomes			
Outcome	Full Lead-In (n=35)	Reduced Lead-In (n=84)	p-value
VTE recurrence, within 30 days, n (%) DVT PE	 1 (3%) 0 (0%)	 1 (1%) 1(1%)	1.00
Bleeding events within 30 days, n (%) Major bleeding Clinically relevant non-major bleeding	 1 (3%) 0 (0%)	 5 (6%) 2 (2%)	0.57

Source: Veloria D, et al. *Thrombosis Update*. 2025

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Author's Conclusions

Reduced apixaban lead-in dosing was frequently used in patients with **higher bleeding risk**, including those with **a VTE-BLEED score ≥ 2**.

Use of a reduced lead-in strategy **did not increase recurrent VTE or bleeding events** compared with full lead-in dosing.

Due to study limitations (e.g., retrospective design and small sample size), **prospective clinical trials are needed** to confirm the safety and effectiveness of this approach.

Source: Veloria D, et al. *Thrombosis Update*. 2025

Strengths vs Limitations

Strengths	Limitations
• Addresses a real-world clinical question • Included hospitalized patients receiving >24 h of parenteral anticoagulation, reflecting common inpatient practice • Used objective clinical outcomes (recurrent VTE and ISTH-defined bleeding events)	• Single-center, retrospective cohort design • Small overall sample size • Treatment strategy determined by clinicians • Baseline groups not well balanced • 30-day follow-up only • Possible underreporting of outcomes if patients received care outside the Stanford system

Source: Veloria D, et al. *Thrombosis Update*. 2025

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Conclusion

This study suggests that reducing or omitting apixaban lead-in dosing after adequate therapeutic parenteral anticoagulation may be a reasonable strategy without increased short-term VTE recurrence or bleeding.

However, given the retrospective design, small sample size, and confounding by indication, findings should be considered hypothesis-generating.

Prospective randomized studies are needed before routine deviation from labeled dosing or guideline recommendations can be endorsed.

Source: Veloria D, et al. *Thrombosis Update*. 2025

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Maintenance Therapy – 2026 ACC/AHA Guidelines

- In patients with acute PE who are eligible for oral anticoagulation, DOACs are recommended over vitamin K antagonists (VKAs), unless contraindicated, to prevent recurrent VTE and reduce major bleeding
- After the initial 3 to 6 months of treatment, patients transitioning to extended therapy can often be managed with reduced-dose apixaban or rivaroxaban. This approach helps maintain protection against recurrent VTE while lowering bleeding risk.

Source: Creager MA, et al. *Circulation*. 2026 Feb.

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Maintenance - 2026 ACC/AHA Guidelines

PE Type	Recurrence Risk	Treatment Duration
Transient provoked	Low after trigger resolves	3 - 6 months → STOP • Continuing therapy increases bleeding risk without added benefit.
Persistent provoked	Ongoing	Extended therapy • Continuing anticoagulation beyond 3 - 6 months is reasonable for those with persistent risk factors
Unprovoked	High	Extended/indefinite therapy • DOACs preferred over warfarin (VKA) unless contraindicated.

Source: Creager MA, et al. *Circulation*. 2026 Feb.

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Acute VTE Is a Time-Dependent Prothrombotic State

- Highest risk of thrombosis extension and recurrence occurs within the first days to weeks after diagnosis
- Active thrombin generation drives clot propagation during the acute phase
- Early anticoagulation intensity is critical to stabilize clot and prevent embolization
- **Anticoagulants Do NOT Dissolve Clots**
  - Primary role is to inhibit new thrombin generation
  - Prevent clot expansion while endogenous fibrinolysis gradually resolves thrombus
  - Treatment strategy must match underlying clot biology across phases of VTE

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Why Lead-In Strategies Exist

Early VTE characterized by persistent hypercoagulability

Higher-intensity anticoagulation during initial treatment phase compensates for:

- Ongoing thrombin burst
- Elevated recurrence risk

Trial design shaped current FDA-labeled dosing:

- Apixaban/Rivaroxaban → oral loading replaces parenteral lead-in
- Dabigatran/Edoxaban → require initial parenteral anticoagulation

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Clinical Considerations

- Reduced lead-in may be reasonable when:
  - ≥ 24 - 72 hours therapeutic parenteral anticoagulation already administered
  - Bleeding risk outweighs recurrence risk
  - Patient clinically stable with improving clot burden
- Requires individualized risk-benefit assessment

Assessment Question #1

Which statement best describes the rationale for intensified lead-in dosing with DOACs during the acute phase of VTE treatment?

a. To prevent heparin-induced thrombocytopenia
b. To target the early hypercoagulable phase and reduce recurrent VTE risk
c. To achieve faster renal clearance of DOACs
d. To minimize gastrointestinal absorption variability

Assessment Question #1: Correct Response

Which statement best describes the rationale for intensified lead-in dosing with DOACs during the acute phase of VTE treatment?

a. To prevent heparin-induced thrombocytopenia

b. To target the early hypercoagulable phase and reduce recurrent VTE risk

c. To achieve faster renal clearance of DOACs

d. To minimize gastrointestinal absorption variability

Assessment Question #2

Which of the following accurately differentiates rivaroxaban and dabigatran in the initial treatment of acute VTE?

a. Both require at least 5 days of parenteral anticoagulation before initiation
b. Rivaroxaban is started immediately with a lead-in phase; dabigatran requires prior parenteral therapy
c. Dabigatran includes a lead-in dosing phase similar to apixaban
d. Both agents are contraindicated in patients with renal impairment

Assessment Question #2: Correct Response

Which of the following accurately differentiates rivaroxaban and dabigatran in the initial treatment of acute VTE?

a. Both require at least 5 days of parenteral anticoagulation before initiation

b. Rivaroxaban is started immediately with a lead-in phase; dabigatran requires prior parenteral therapy

c. Dabigatran includes a lead-in dosing phase similar to apixaban

d. Both agents are contraindicated in patients with renal impairment

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Assessment Question #3

A 68-year-old male with an acute pulmonary embolism received 48 hours of heparin infusion, with therapeutic PTTs, and the provider asks for recommendations transitioning to a DOAC. He has a PMH significant for uncontrolled hypertension, alcohol consumption (>10 drinks per week), and admits to taking ibuprofen 800mg once daily for arthritis pain. The patient has normal renal function with a VTE-BLEED score of 2.5. Which of the following regimens would you utilize for your patient?

a. Start apixaban 10 mg twice daily for 7 days, then 5 mg twice daily
b. Start apixaban 5 mg twice daily immediately
c. Start dabigatran 150 mg twice daily immediately
d. Start apixaban 10 mg twice daily for 5 days, then 5 mg twice daily

Assessment Question #3: Correct Response

A 68-year-old male with an acute pulmonary embolism received 48 hours of heparin infusion, with therapeutic PTTs, and the provider asks for recommendations transitioning to a DOAC. He has a PMH significant for uncontrolled hypertension, alcohol consumption (>10 drinks per week), and admits to taking ibuprofen 800mg once daily for arthritis pain. The patient has normal renal function with a VTE-BLEED score of 2.5. Which of the following regimens would you utilize for your patient?

a. Start apixaban 10 mg twice daily for 7 days, then 5 mg twice daily
b. Start apixaban 5 mg twice daily immediately
c. Start dabigatran 150 mg twice daily immediately
d. Start apixaban 10 mg twice daily for 5 days, then 5 mg twice daily

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Thank you!!

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