VTE

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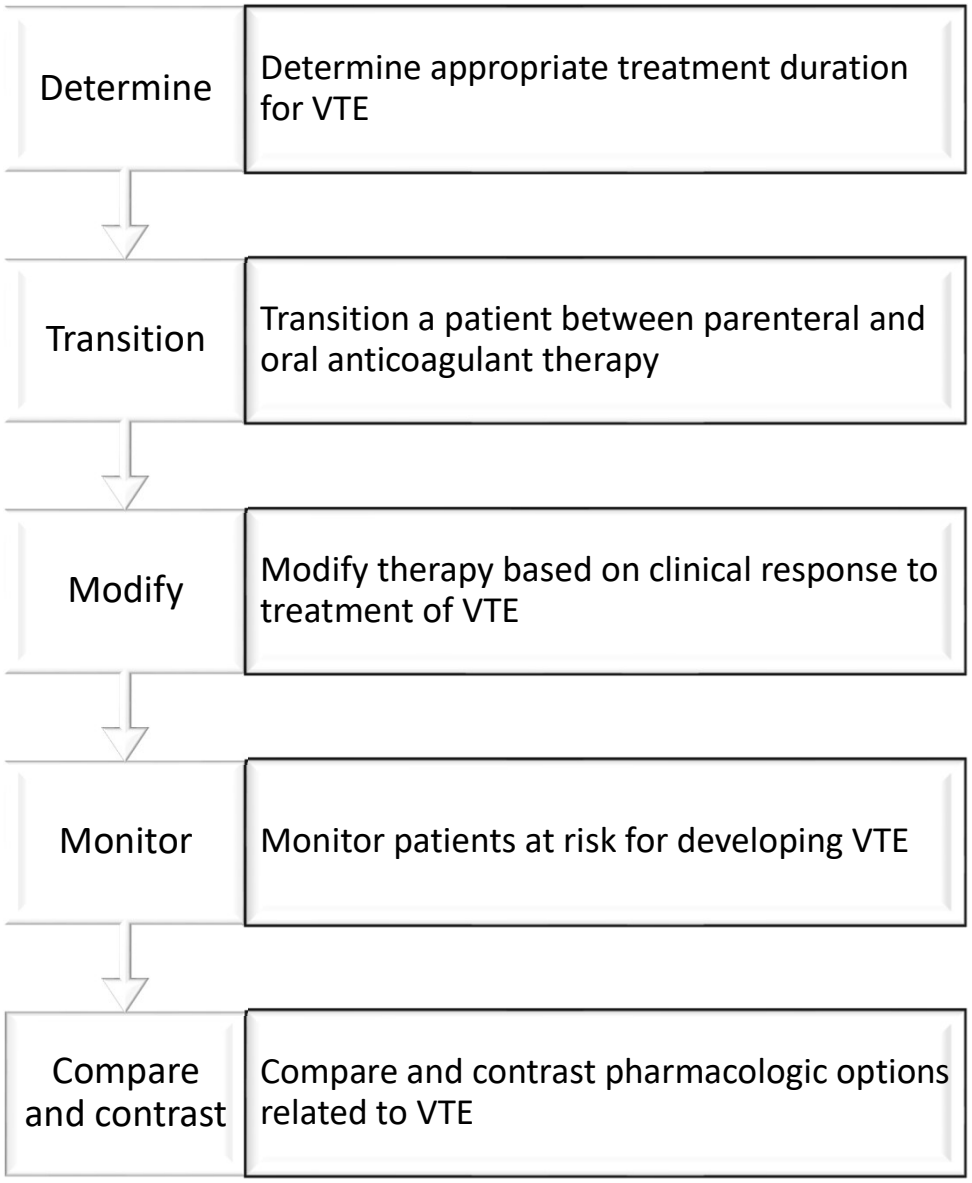
Pharmacotherapy I

Learning Objectives



Definition
VTE

Venous …of or pertaining to the venous system

Thrombo-…related to a blood clot

Embolism…mobilized

Background

One of the most common cardiovascular disorders in the U.S.

Involves

- Deep Vein Thrombosis (DVT)
  - Pulmonary embolism (PE)

Results from

- Thrombus formation +/- embolization
- In venous circulation

Represents a range

- Silent thrombosis →symptomatic pulmonary embolism

Background

Considered most common preventable cause of death in hospitalized patients

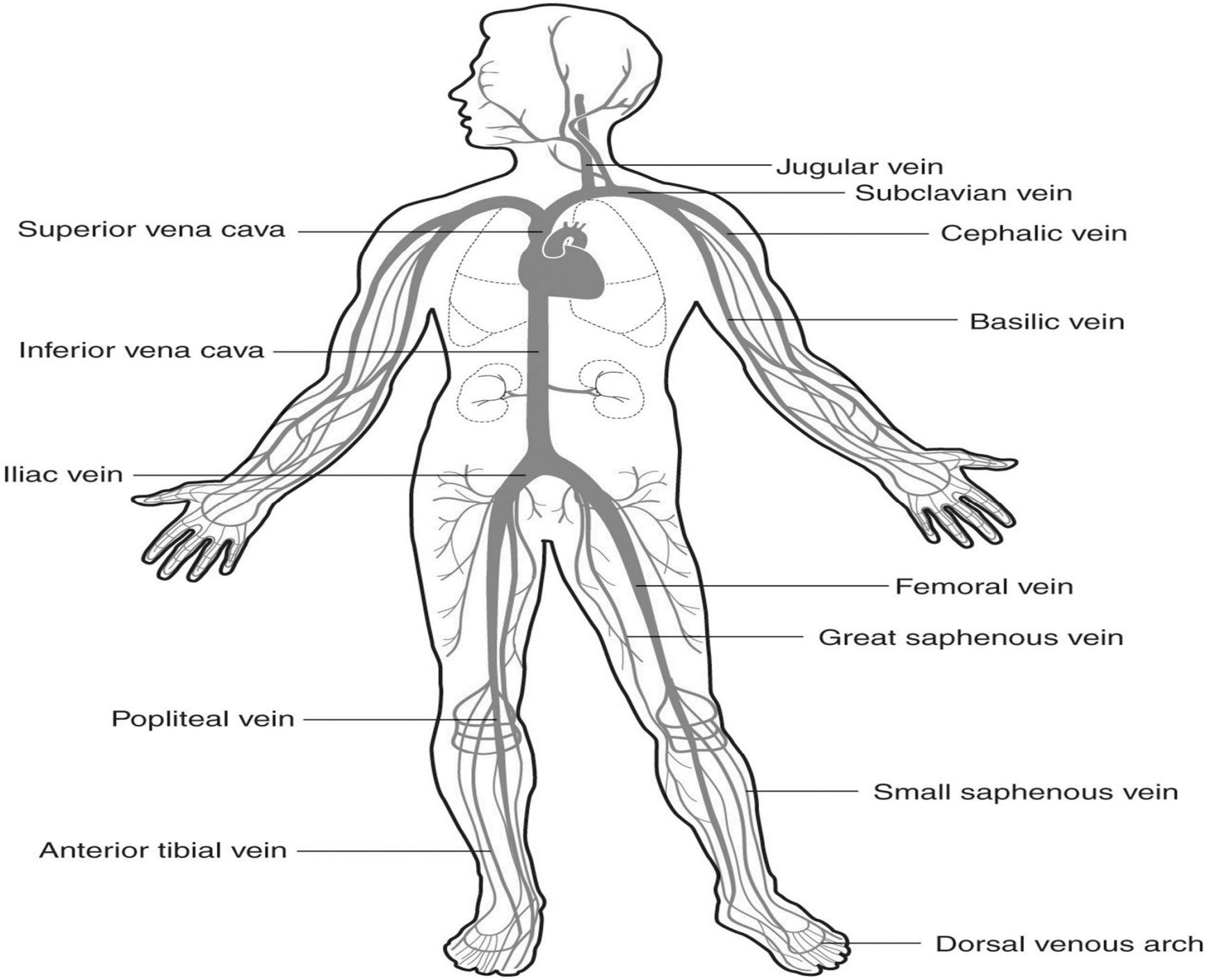
Associated with substantial healthcare costs

- $1 billion annually

Complications can be severe

- Up to and including sudden death

Recognition and rapid diagnosis is critical



Epidemiology

True incidence unknown

>50% do not have symptoms or are undiagnosed

Roughly 2 million develop VTE per year

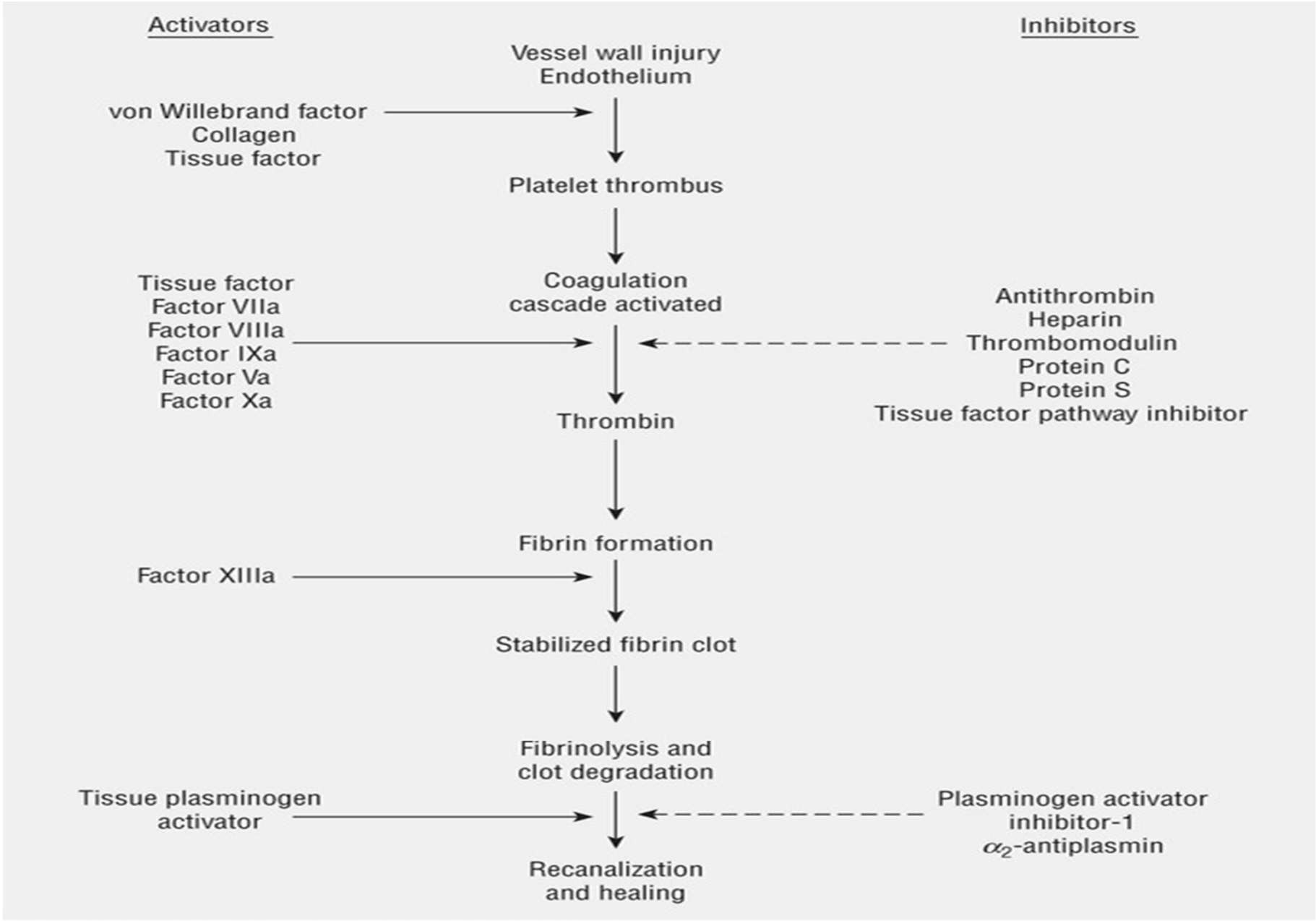
Higher incidence in those over 80 years old

Highest risk populations

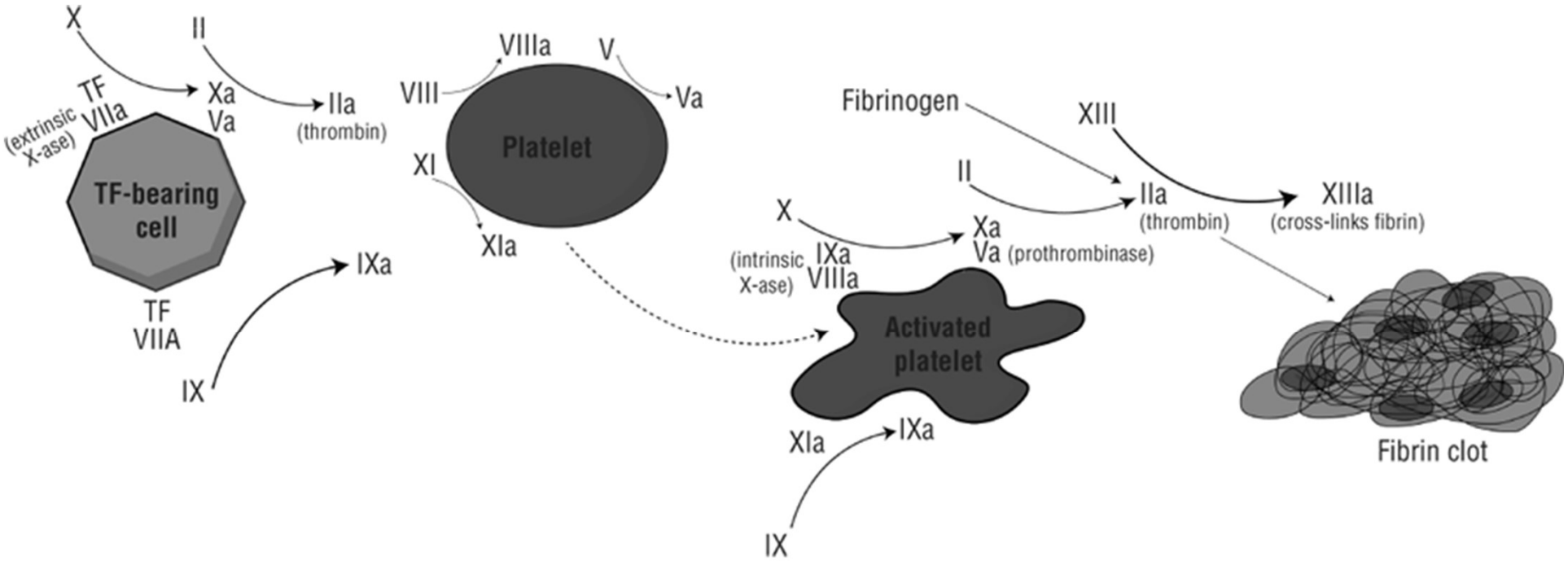
- Multiple trauma
- Orthopedic surgery of lower extremities
- History of VTE
- Metastatic cancer

Risk Factors

- Age
- Prior VTE History
- Blood Stasis
- Vascular Injury
- Hypercoagulable States
- Drug Therapy



Cellular coagulation cascade model.



Source: J.T. DiPiro, R.L. Talbert, G.C. Yee, G.R. Matzke, B.G. Wells, L.M. Posey: Pharmacotherapy: A Pathophysiologic Approach, 10th Edition, www.accesspharmacy.com

Clotting Cascade

Initiation

- Tissue Factor (TF) bearing cells exposed after vessel injury or captured by activated platelets → starts clotting cascade
- Factor Xa and Va combine to generate small amount of IIa

Amplification

- IIa produced in initiation phase → activates factor V and VIII → large scale **thrombin generation**

Propogation

- "Burst" of thrombin generation as well **as factor Xa**
- **Thrombin → converts fibrinogen to fibrin →** meshwork to surround platelets and stabilize clot
- Clot formation ends when expanding mesh of fibrin/platelets "paves" over initiation site and additional activated factors are unable to diffuse through overlying layers of clot

Regulation of Thrombosis

Intact self-regulatory mechanisms ensure clot is limited to zone of vessel injury

Any disruption may lead to hypercoagulability

Activated Protein C (aPC)

- Uses protein S as cofactor
- Inactivates factors Va and VIIIa (inhibits IIa generation in initiation and amplification phases)
  - Factor V Leiden → Va resistant to degradation

Antithrombin

- Inhibits factors:
  - IIa → inhibits amplification phase and fibrin formation
  - Xa →inhibits activation of thrombin in initiation phase

Regulation of Thrombosis

Tissue factor pathway inhibitor

- Regulates TF/VIIa induced coagulation by terminating the initiation phase

Heparan sulfate

- Accelerates antithrombin activity
- Inhibits factor IIa

Plasmin

- Plasminogen is activated to plasmin
  - Activated by action of thrombin, tissue-type plasminogen activator (t-PA) and/or urokinase-type plasminogen activator (u-PA)
- Fibrinolysis → dissolution of formed blood clot into soluble end products (e.g. D-dimer)

Inherited Hypercoagulability Disorders

Factor V Leiden

- Factor V resistant to degradation by aPC
- Most common inherited hypercoagulability disorder (up to 7% of Caucasians)
- 3x higher risk of VTE

Prothrombin G20210A Mutation

- Increased circulating prothrombin – elevated thrombin
- 2nd most frequent hypercoagulability disorder (up to 4% of Caucasians)
- 3x higher risk of VTE

Some patients may have multiple inherited coagulation disorders

Acquired Hypercoagulability Disorders

Malignancy

- Secretion of procoagulant substances
- May also cause reduced levels of protein C, protein S, and antithrombin
- Cancer cells use thrombotic mechanisms to recruit a blood supply

Antiphospholipid antibodies

- Antibodies prolong phospholipid-based clotting assays
- Up to 5% of normal healthy population
- Much more common in patients with autoimmune disorders
  - Systemic lupus erythematosus, inflammatory bowel disease

Estrogen use

Clinical Presentation DVD

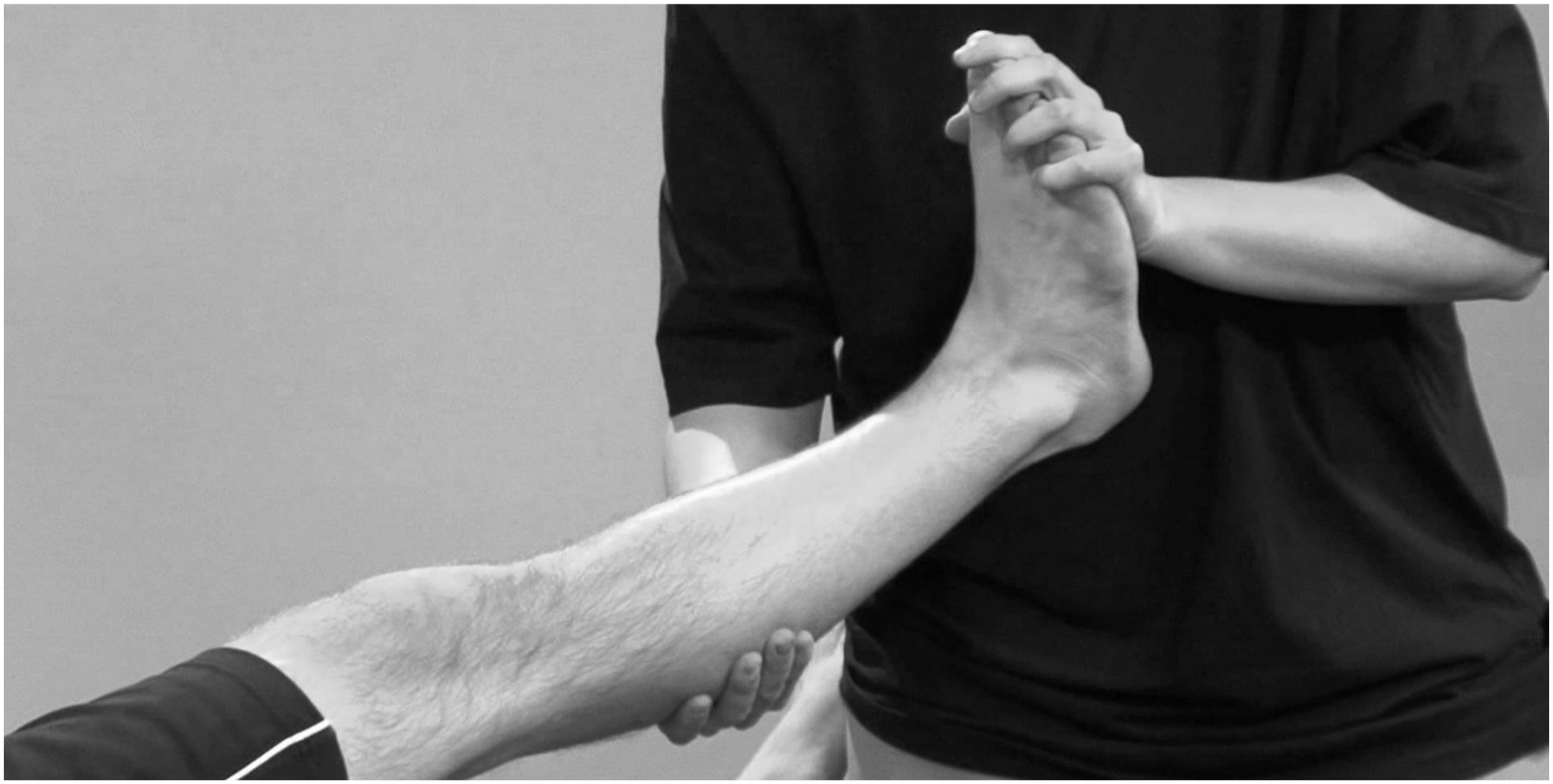
Symptoms

- Usually in the legs
  - Unilateral
  - Leg swelling
  - Pain
  - Warmth
  - Skin discoloration

Signs

- Dilated superficial veins
- “Palpable cord” in affected leg
- Homan’s sign→ pain in back of knee upon dorsiflexion of foot
- Unilateral leg edema
- Erythema
- Tenderness

Homan’s Sign



Clinical Presentation PE

Symptoms

- Cough +/- blood
- Chest pain
- Chest tightness
- Shortness of breath
- Palpitation
- Dizziness

Signs

- Tachypnea
- Tachycardia
- Diaphoresis
- Distended neck veins
- Decreased O2-sat
- Hemoptysis

Clinical Presentation PE

Laboratory Tests

- D-dimer – elevated

Diagnostic Tests

- **CT – most common**
- **Pulmonary angiography (GOLD standard)**
  - Most accurate and reliable method for diagnosis
  - Expensive, invasive procedures involving contrast dye
  - Risk for nephrotoxicity, and VTE

Venous ultrasound (Doppler)

Ventilation-Perfusion Scan (V/Q Scan)

D-dimer

Highly sensitive

Not specific for VTE

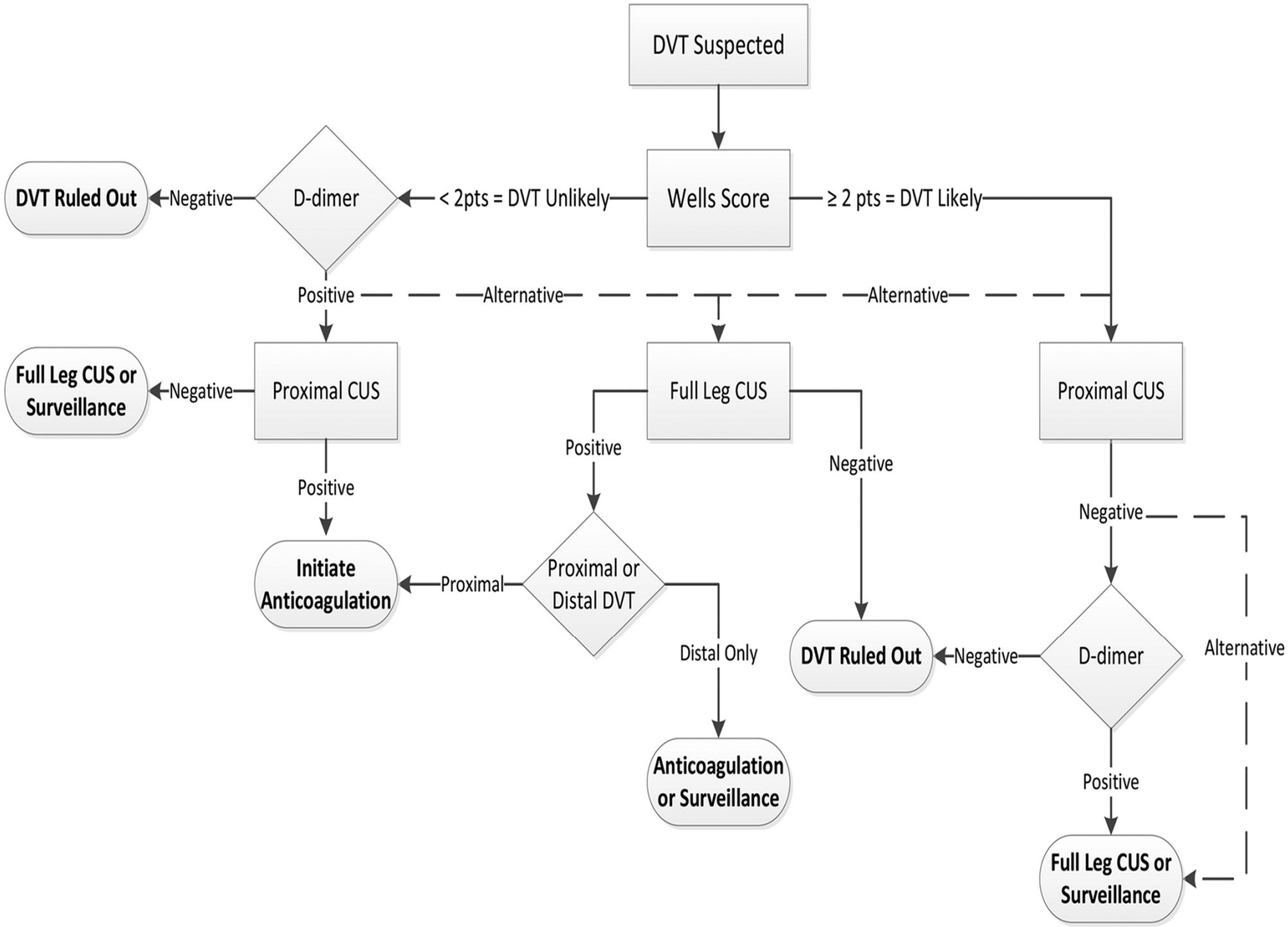
- Elevation with recent surgery/trauma, cancer, pregnancy, increasing age and cancer

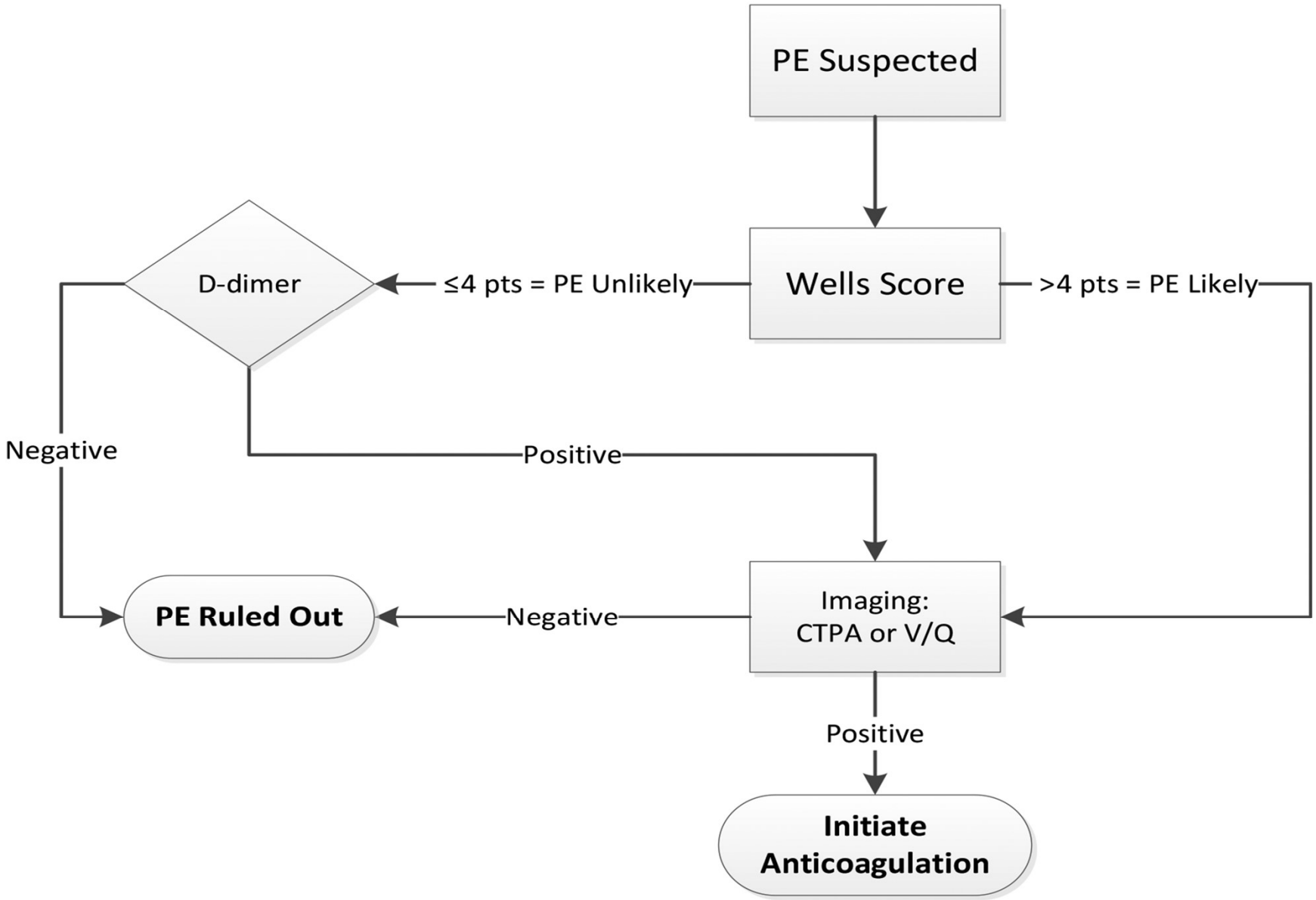
Initial risk stratification

- If negative, can rule out VTE < 500ng/ml
- If positive, does not diagnose VTE
- Advanced age is known to elevate D-dimer levels, and a proposed strategy involves multiplying patient age by 10 to obtain an age-adjusted D-dimer threshold

Diagnostic Approach (fig 19—6/7 dipiro)

- Does patient have risk factors?
- What are the symptoms?
- What are the signs?
- What is the clinical probability of VTE?
- What do laboratory tests show?



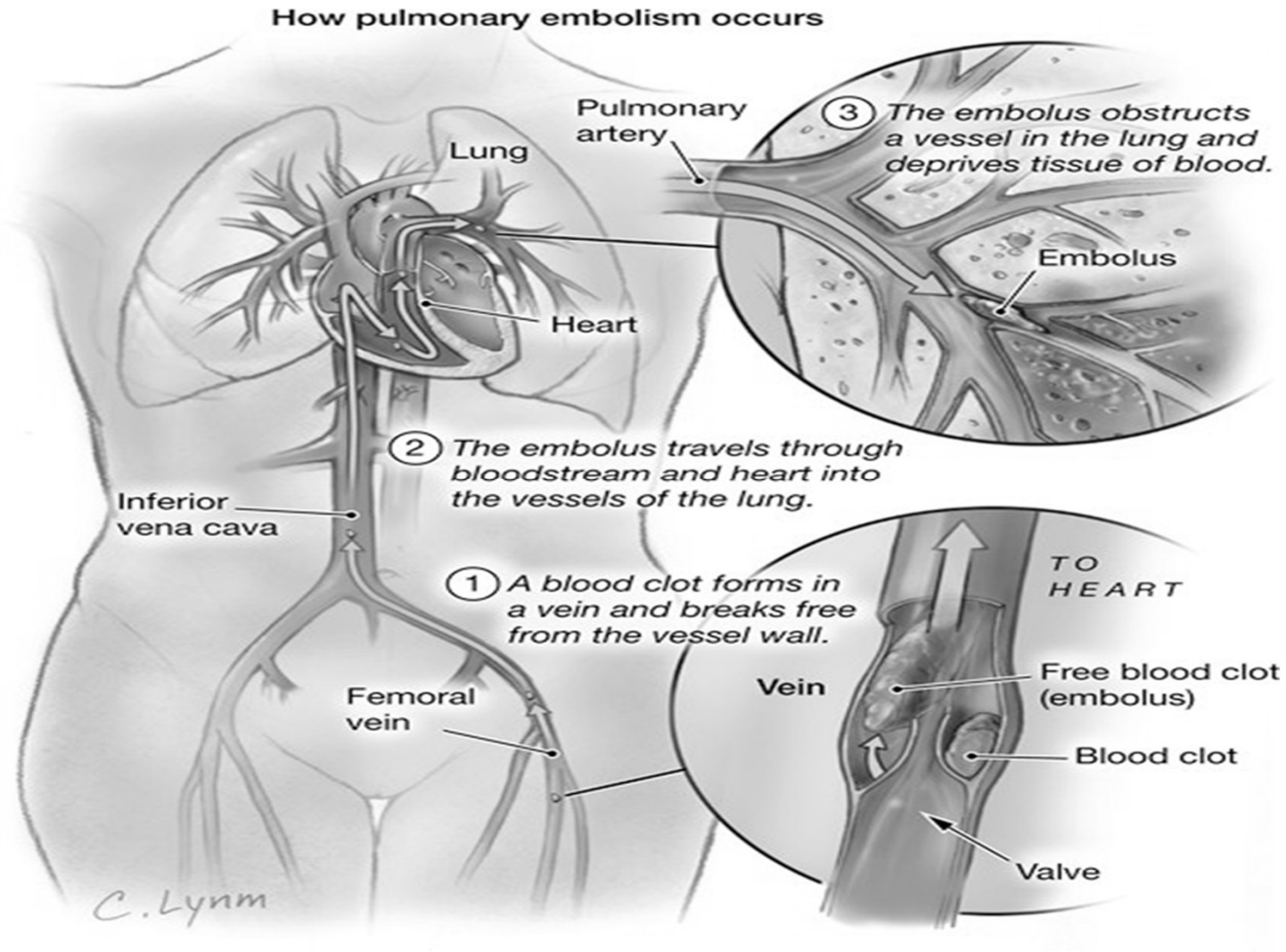


Clinical Model/Wells Criteria for Evaluating the Pretest Probability of Deep Vein Thrombosis[a]

Clinical Characteristic	Score
Active cancer (cancer treatment within previous 6 months or currently on palliative treatment)	+1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	+1
Recently bedridden for 3 days or more, or major surgery within the previous 12 weeks requiring general or regional anesthesia	+1
Localized tenderness along the distribution of the deep venous system	+1
Entire leg swollen	+1
Calf swelling at least 3 cm larger than that on the asymptomatic side (measured 10 cm below tibial tuberosity)	+1
Pitting edema confined to the symptomatic leg	+1
Collateral superficial veins (nonvaricose)	+1
Previously documented deep vein thrombosis	+1
Alternative diagnosis at least as likely as deep vein thrombosis	−2

[a]Clinical probability of deep vein thrombosis: low, less than 0; moderate, 1–2; high, greater than 3. In patients with symptoms in both legs, the more symptomatic leg is used.

PE


How pulmonary embolism occurs
Pulmonary artery
Lung
Heart
3 The embolus obstructs a vessel in the lung and deprives tissue of blood.
Embolus
2 The embolus travels through bloodstream and heart into the vessels of the lung.
Inferior vena cava
1 A blood clot forms in a vein and breaks free from the vessel wall.
TO HEART
Vein
Free blood clot (embolus)
Blood clot
Femoral vein
Valve
C. Lynn

Clinical Model/Wells Criteria for Evaluating the Pretest Probability of Pulmonary Embolism[a]	
Clinical Characteristic	**Score**
Cancer	+1
Hemoptysis	+1
Previous PE or DVT	+1.5
Heart rate greater than 100 beats/min	+1.5
Recent surgery or immobilization	+1.5
Clinical signs of DVT	+3
Alternative diagnosis less likely than PE	+3

[a]Clinical probability of PE: low, 0–1; moderate, 2–6; high, 7 or greater.

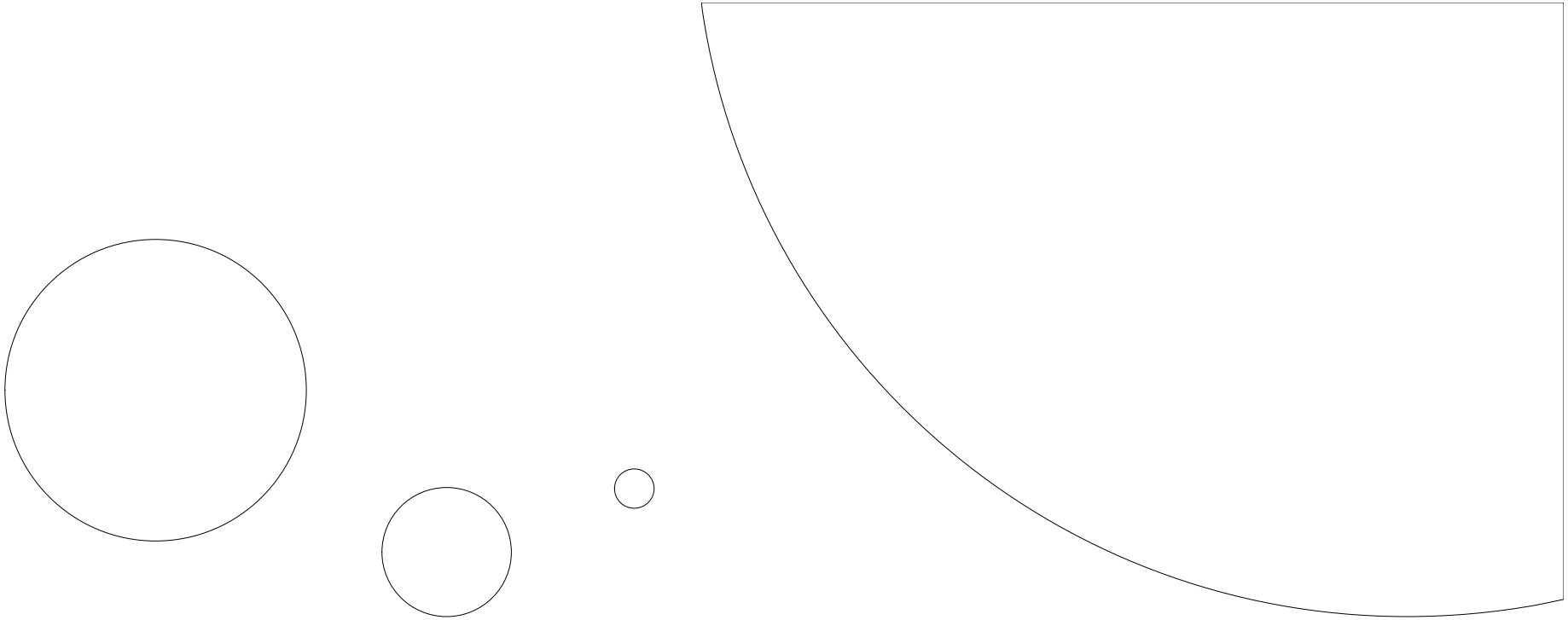
Padua Prediction score

Hospitalized and critically ill patients

Prospectively validated

High Risk = Score 4 or greater

- 11% VTE rate at 90 days if not prophylaxed



Prevention

Prevention

Underutilized

American College of Chest Physicians

- Hospitals need formal, active strategy for prevention

Document risk assessment and prevention strategy within 24 hrs of admission

- High prevalence of VTE in hospitalized patients
- Mortality/morbidity; long term complications
- Favorable risk/benefit
- Cost-effective

Prevention

goals

Prevent formation of DVT or PE in those at risk

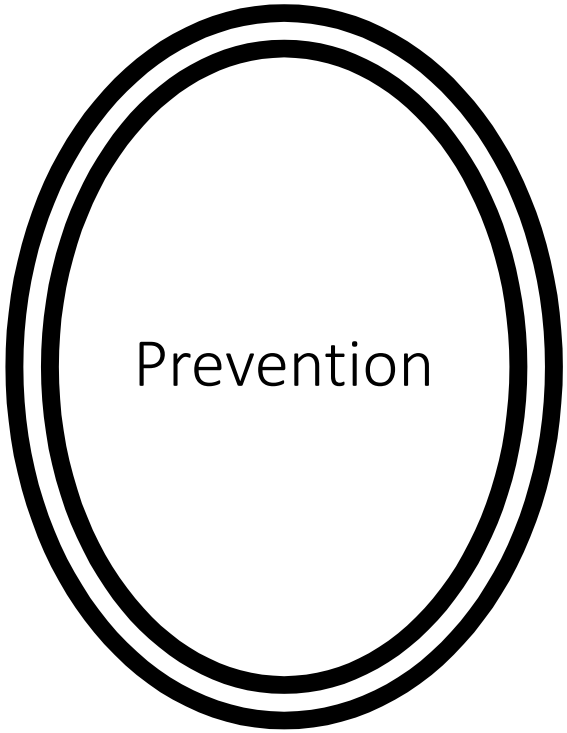
Prevent mortality and reduce morbidity

Minimize adverse drug reactions, cost, LOS

Two models

Non-pharmacologic

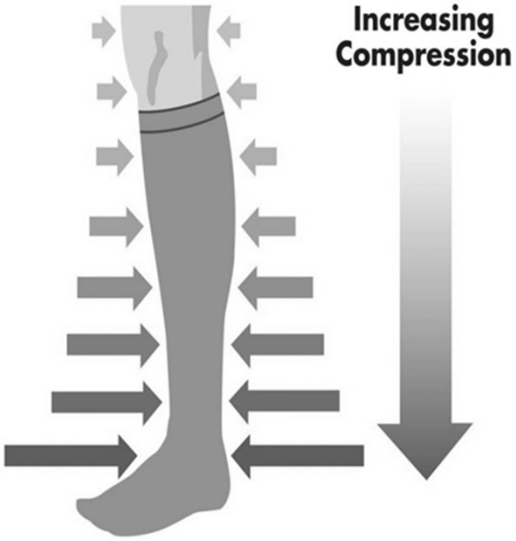
pharmacologic



Non-pharmacologic (mechanical)

- Graduated compression stockings (GCS)
- Intermittent pneumatic compression devices (IPCD)
- Inferior vena cava filters (IVCF)

Graduated Compression Stockings GCS



Medically ill

- Limited evidence

Orthopedic, cardiac, gynecologic, and neuro- surgery

- Reduce VTE by ~65%

Increase venous velocity

Can be uncomfortable/cause skin reactions

Graduated Compression Stockings

Support	Pressure	Use
Light Support	8 – 15 mmHg	minor ankle & leg swelling, pregnancy, leg fatigue
Mild Support	15 – 20 mmHg	mild ankle & leg swelling, leg fatigue, travel
Moderate Support	20 – 30 mmHg	moderate ankle & leg swelling, venous stasis ulcerations, VTE prevention
Firm Support	30 – 40 mmHg	severe ankle & leg swelling, venous stasis ulcerations, VTE prevention, post-thrombotic syndrome

Adapted From: Dager WE, ed. Anticoagulation Therapy: A Point of Care Guide

Inferior vena cava filters "IVCF"

Filter implanted into inferior vena cava to catch emboli

Decrease risk of PE (short term)

Anticoagulation continued unless contraindicated

Begin/consider anticoagulation once contraindication has resolved

Filter NOT intended to be permanent

- Filter migration
- Increased incidence of DVT

Prevention

- Pharmacologic (anticoagulant)
  - UFH
  - LMWH
  - Fondaparinux
  - Warfarin
  - DOACs

Unfractionated Heparin

Heterogeneous mixture of glycosaminoglycans

- Variable chain lengths
- Variable pharmacokinetic/dynamic properties
- Small chains cleared less rapidly
- Small chains cannot bind antithrombin and thrombin at the same time

Mechanism of action

- **UFH pentasaccharide binds to antithrombin antithrombin becomes more potent**
- **inactivation of Xa and IIa**
- **Inactivation prevents growth of thrombus**

Prophylaxis

- **Heparin 5000 units SQ BID – TID**

Treatment

- **Weight based dosing**
- **Bolus: 80 units/kg IV**
- **Infusion: 18 units/kg/hr IV**

Preferred for patients with significant renal impairment

UFH

Monitoring

- Efficacy
  - Treatment dose
  - aPTT baseline and 6 hrs after dose changes
  - “Therapeutic” aPTT = 1.5-2.5 baseline (baseline = 25-30)
  - Adjust rate based on current aPTT
  - Low aPTT →increase rate +/- bolus
  - High aPTT →decrease rate +/- hold infusion
- Safety
  - Bleeding, CBC (Hgb, Hct, Plt)

Contraindications

- Severe thrombocytopenia
- Inability to monitor treatment (IV)
- Active bleeding, except disseminated intravascular coagulation
- History of heparin induced thrombocytopenia (HIT)

Warnings

- Hypersensitivity
- Bleeding
- Hyperkalemia (due to inhibition of aldosterone production)
- Osteoporosis (with prolonged use > 6 months)
- Thrombocytopenia

Low Molecular Weight Heparin

Derived from UFH by depolymerization

Reduced inhibitory activity against thrombin

- Due to smaller size of particles compared to UFH

Retains anti-Xa activity

Dosing

- Prophylaxis – fixed dose
- Treatment – weight based dose

Agents: **enoxaparin**, dalteparin, tinzaparin

Low Molecular Weight Heparin

Enoxaparin (Lovenox)

- Prophylaxis: 40mg SC daily; 30mg SC Q12H
- Treatment: 1mg/kg SC Q12H; 1.5mg/kg SC daily
- CrCl < 30ml/min:
  - Prophylaxis dose = 30mg SC daily
  - Treatment dose = 1mg/kg SC daily

Dalteparin (Fragmin) and Tinzaparin (Innohep)

- Dosed in units of anti-Xa activity
- Weight based dosing similar to enoxaparin

Low Molecular Weight Heparin

More predictable absorption compared to UFH

Reduced need for laboratory monitoring

- Able to be used in outpatient setting if needed
  - SC administration
- **<u>Anti-Xa levels for monitoring → not routine</u>**

Often used as a “bridge” while patients are starting warfarin therapy

Low Molecular Weight Heparin

Contraindications

- Major bleeding
- Hypersensitivity to heparin, LMWH, pork products
- History of HIT

Warnings:

- Bleeding
- Hyperkalemia (suppression of aldosterone production)
- Thrombocytopenia
- HIT → happens less often than with UFH
- There **IS** cross sensitivity between LMWH and UFH

Heparin/LMWH Reversal

Protamine IV

- Forms a salt with heparin to inactivate
- 1mg per 100 units of heparin given in last 2-2.5 hrs
  - Max 50mg
- Onset 5 min
- Duration 2 hours

Works best with UFH

- Difficulty binding short chains in LMWH
- May give 1mg protamine/1mg enoxaparin given in last 8 hours

Indications:

- Accidental overdoses
- Unclear instructions, drug interactions, concomitant illnesses, etc.
- Emergent surgeries
- Bleeding/trauma

HAT/HIT

Thrombocytopenia → heparin

HAT: heparin associated thrombocytopenia

- Benign; non-immune mediated
- Days 2-4 of therapy

HIT: heparin induced thrombocytopenia

- Life threatening; immune mediated
- Days 5-10 of therapy

Monitor platelets at baseline at Q48-72H during days 4-14 of therapy

HIT

Thrombocytopenia = platelets < 150,000/mm^3

Platelets generally drop 30-50% between days 5-10 of therapy

- Total platelet count may still be > 150,000/mm^3

4 Ts

- Thrombocytopenia (drop by 30-50% or more)
- Timing of platelet count fall (days 5-10 of tx)
- Thrombosis (new VTE or skin necrosis)
- Thrombocytopenia causes (none other present)

Suspected HIT

If high suspicion, discontinue heparin/LMWH

- Do not wait until confirmatory test comes back

Hypercoagulable state

- Use of alternate non-heparin anticoagulant
  - Argatroban
  - Fondaparinux
  - Bivalirudin

Patient cannot receive heparin or LMWH in future

- Recurrence of HIT → happens faster upon subsequent exposure

Heparin-Induced Thrombocytopenia Management

D/C all sources of heparin, do not re-challenge

Initiate anticoagulation with DTI immediately

unless C/I (lepirudin, argatroban) and regardless of thrombosis presence

Initiate warfarin once PLT > 150,000 /mL
Otherwise high risk for venous limb gangrene and warfarin induced skin necrosis

- Reverse warfarin if already started

Avoid PLT transfusion unless actively bleeding

Fondaparinux (Arixtra)

Synthetic analog of antithrombin binding pentasaccharide found in heparin and LMWH

- Increased affinity for antithrombin, Increased specificity, Increased half life

Factor Xa inhibitor

Dosing

- Prophylaxis: 2.5mg SC daily
- Treatment: < 50kg = 5mg SC daily; 50-100kg = 7.5kg/day; > 100kg = 10mg SC daily

Contraindications

- Hypersensitivity
- CrCl < 30 ml/min
- Body weight < 50 kg (prophylaxis) – clearance significantly reduced
- Major bleeding
- Bacterial endocarditis
- Thrombocytopenia related to fondaparinux antibody

Warnings

- Bleeding
- Thrombocytopenia
  - Very rarely presents similarly to HIT
  - OK to use in patients with history of HIT

Use with caution in patients with CrCl 30-50 ml/min

Argatroban

Direct Thrombin Inhibitor

Useful for treatment of HIT

Monitored via aPTT

Dose:

- Continuous infusion → 1-2mcg/kg/hr
- Titrate to maintain aPTT 1.5-2.5 baseline

Increase INR to some extent

Metabolized via CYP3A4 in liver

Contraindications

- Hypersensitivity

Warnings

- Bleeding
- Use in hepatic impairment – requires dosage reduction

Alteplase (Activase)

Fibrinolytic approved for use in PE

Promotes conversion of plasminogen to plasmin → dissolution of clot

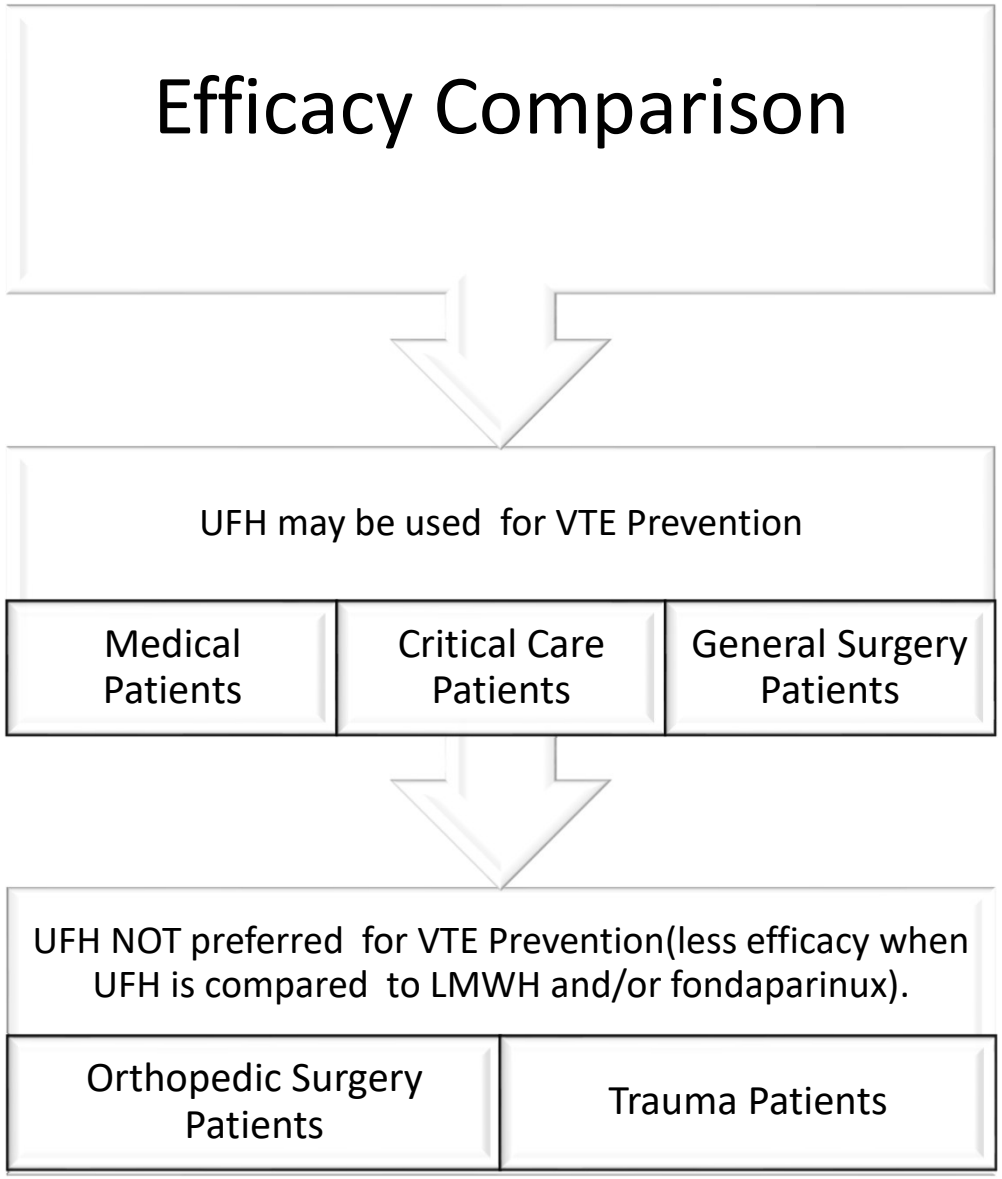
Dose:

- 100mg IV over 2 hours
  - Give 10mg as bolus
  - Give remaining 90mg over 2 hours
- Dose is different than stroke indication!

Contraindications

- Active internal bleeding
- History of recent stroke (within 2 months)
- Intracranial or intraspinal surgery
- Serious head trauma
- Known bleeding diathesis
- Uncontrolled severe hypertension

Parenteral Pharmacological options



VTE Prophylaxis Dosing

Anticoagulant	Patient Population	Dose	Renal Impairment
Unfractionated Heparin (UFH)		5000 units SubQ every 8 – 12 hours	No dosage adjustment required.
Low Molecular Weight Heparins (LMWH) Enoxaparin (Lovenox®)	Medical Abdominal Surgery Trauma Knee Replacement Hip Replacement	40 mg SubQ every 24 hours 40 mg SubQ every 24 hours 30 mg SubQ every 12 hours 30 mg SubQ every 12 hours 30 mg SubQ every 12 hours (post-op) **OR** 40 mg every 24 hours (pre-op)	Avoid use in ESRD and HD patients. **CrCl < 30 mL/min**: 30 mg SubQ every 24 hours
Factor Xa Inhibitors Fondaparinux (Arixtra®)		2.5 mg SubQ every 24 hours	**CrCl 30-50 mL/min**: use caution; may need dose adjustment **CrCl < 30 mL/min**: C/I

Oral pharmacological options

Warfarin

- Dose to INR goal of 2 – 3 (or "dose-adjusted")

Rivaroxaban (XARELTO)

- Prevention of VTE after total hip or knee replacement
- Dose: 10 mg PO once daily, initiate 6-10 hours after surgery
- **Renal dose:**
- CrCL >30 ML/MIN 10 mg once a day
  - CAUTION : CrCL 30-50 ml/min
- <30 ml/min: do not use

Oral pharmacological options

(Dabigatran) (PRADAXA)

- Indication: VTE prevention (HIP replacement)
- **Renal Function (mL/min) Dose:**
  - ≥ 30 110 mg once daily (1 to 4 hours after surgery and hemostasis; if not initiated on day of surgery, then initiate 220 mg once daily) up to 35 days suggested
- < 30 Do not use; not studied

Dose (Apixaban) (ELIQUIS)

- Indication: : VTE prevention (HIP replacement)
- Renal Function dose
- **CrCL ≥30**
- 2.5 mg twice daily (35 days: hip)
  - 2.5 mg twice daily (12 days: knee)
  - **CrCl < 30 Excluded from trial**

Use of DOACS

Advantages of New Anticoagulants	Disadvantages of New Anticoagulants
Few drug interactions	Increased cost
No interactions with diet	Contraindications exist with renal and/or liver disease
No routine monitoring needed	Long term safety/efficacy unknown
Rapid onset time	Antidotes/reversal agents not widely available
	No routine monitoring: compliance? peri-procedural use?

VTE risk and Suggested Prevention

Risk Level	VTE Risk	Suggested Prevention
Low Risk Minor surgery (fully ambulatory) Medical illness (fully ambulatory)	< 10%	Early, aggressive ambulation +/- Mechanical prevention
Moderate Risk Most general surgery patients Medical illness (limited mobility/bed rest) Critical care patients	10 to 40%	UFH LMWH Fondaparinux* Mechanical prevention (as a substitute or in addition to pharmacologic)**
High Risk Orthopedic surgery Major trauma	40 to 80%	LMWH Fondaparinux* Warfarin (INR 2-3) – ortho only Rivaroxaban /apixaban /dabigatran – ortho only
		Mechanical prevention (as a substitute or in addition to pharmacologic)**

*Insufficient evidence with fondaparinux for VTE prevention in critical care, trauma patients.

**Mechanical prevention recommended for: patients with high bleeding risk (in place of anticoagulation) OR patients at high VTE risk (in combination with anticoagulation)

Signs/symptoms of bleeding

Bruising	Epistaxis	Hematuria	GI hemorrhage (hematemesis, melena, hematochezia
Bleeding gums	Hemoptysis	Headaches, dizziness, weakness	Hypotension
	Joint swelling/pain	Hematuria	

Managing Bleeding Events

Minor Bleeding

- Reduce or hold anticoagulation
- Mechanical compression

Major Bleeding

- Hold anticoagulation +/- reversal
- Life saving therapies – IV fluids, vasopressors, packed red blood cells
- Consider hemostatic therapies/blood products
- Consider surgical procedures if necessary

Acute VTE Treatment

Presentation

Presentation of DVT?

- Unilateral swelling, warmth, pain
- Palpable “cord” in affected leg
- (+) Homan’s sign

Presentation of PE?

- Cough, chest pain, SOB, dizziness, (+/-) hemoptysis
- Tachypnea, tachycardia, diaphoresis
- Possible cyanosis, hypotension, hypoxia if severe

Presentation

Verify clinical suspicion with d-dimer and diagnostic testing

- Venous compression ultrasound (Doppler)
- Chest CT scan
- Ventilation-Perfusion (V/Q) Scan

If confirmed, is patient candidate for fibrinolytic therapy?

- Life-threatening PE (cyanosis, hypoxia, hypotension)
- Limb-threatening DVT (very rare)

Life-Threatening PE

PE with s/s of shock

- Hypotension (SBP < 90mmHg)
- Poor O2 saturation

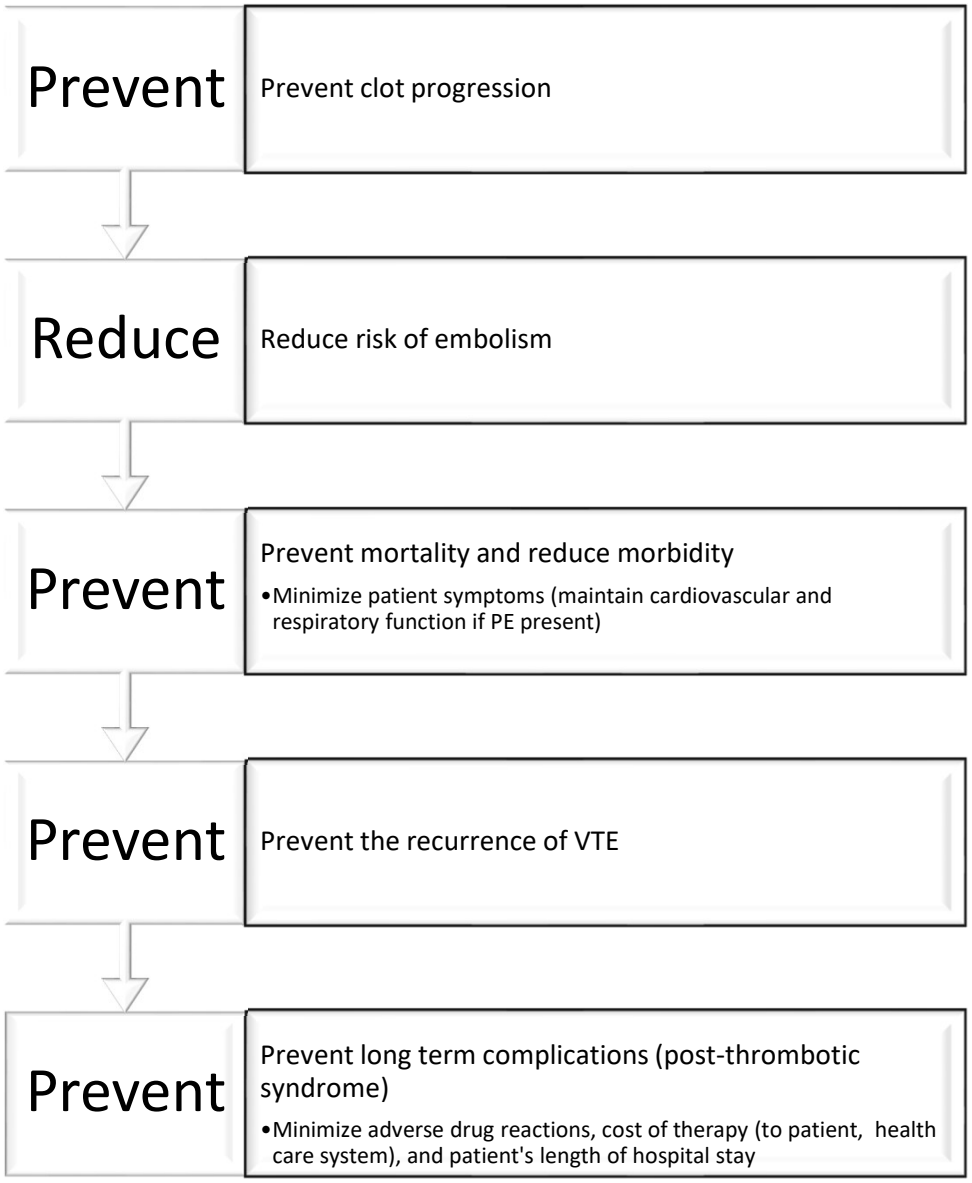
Consider fibrinolytic therapy

- Alteplase

If high bleeding risk or fibrinolytic therapy unsuccessful → thrombectomy

- Full dose anticoagulation required during procedure

VTE Therapeutic Goals



Duration of VTE Treatment

Determined by asking the following questions:

Did VTE develop in setting of a **transient, reversible risk factor or surgery**?

- Examples of **major risk factors**: surgery, hospitalization, or plaster cast immobilization, all within 1 month of VTE diagnosis.
- Examples of **minor risk factors**: estrogen therapy, pregnancy, prolonged travel (>8 h), or above major factors when they have occurred 1 to 3 months before VTE diagnosis.

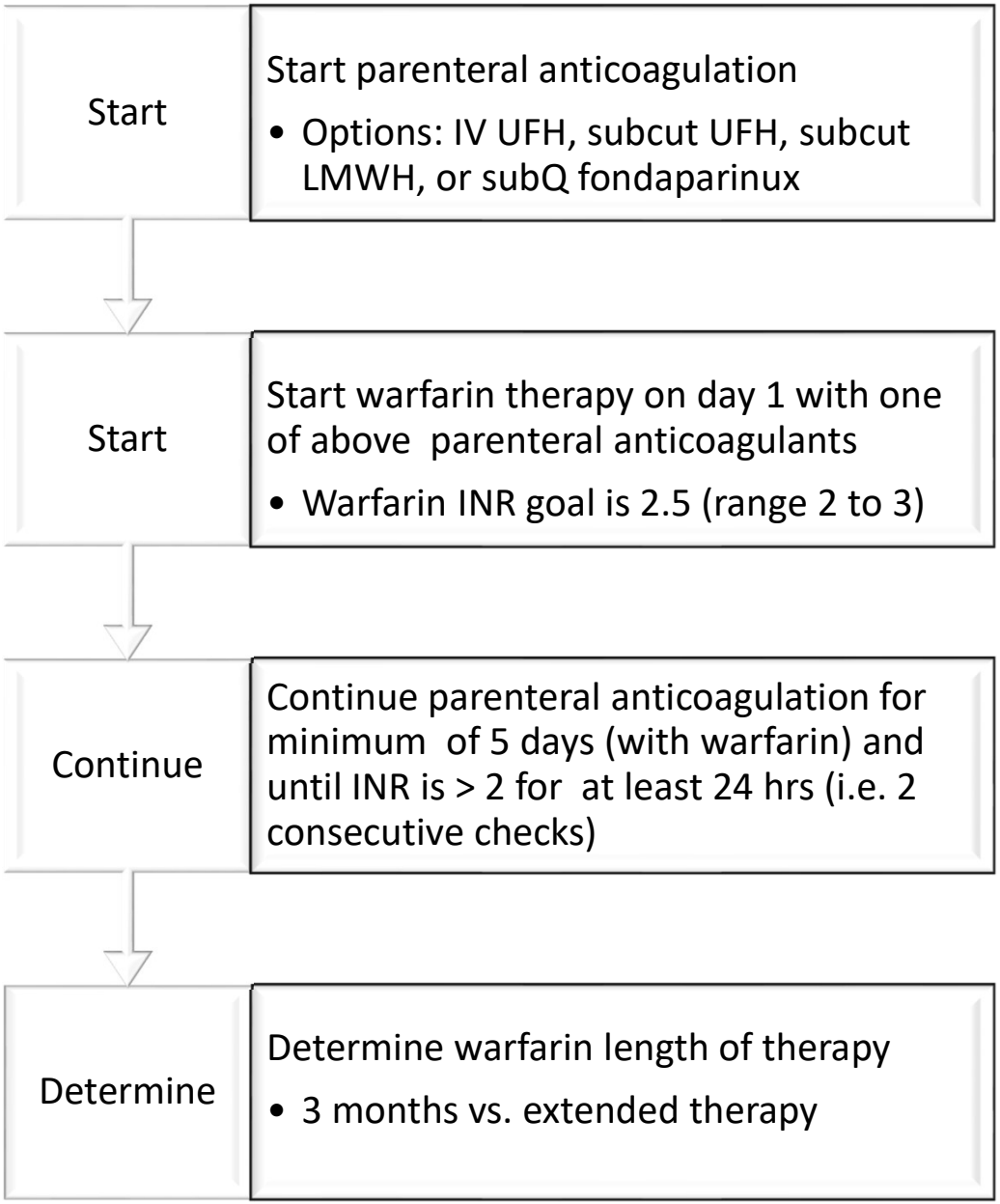
Was VTE **unprovoked** (no cause can be identified)?

Does the patient have **active cancer**?

Is this the **first VTE episode** or is **VTE recurrent**?

What is the **risk of bleeding** for the patient?

VTE Treatment Steps



Overlap of Parenteral Anticoagulants and Warfarin

Protein C (anticoagulant) -half-life:8-10 hours

Factor II -half-life: 60-100 hours

Protein C declines before warfarin's full antithrombotic effects are realized

- Causes brief hypercoagulable state
- Overlap parenteral anticoagulant with warfarin for at least 5 days – even if INR is therapeutic prior to day 5
- Remember: elevated INR in first 24-48 hours is due to factor VII depletion (half-life 6-8 hours)

Initial Warfarin Dosing

Usually start with 5 mg

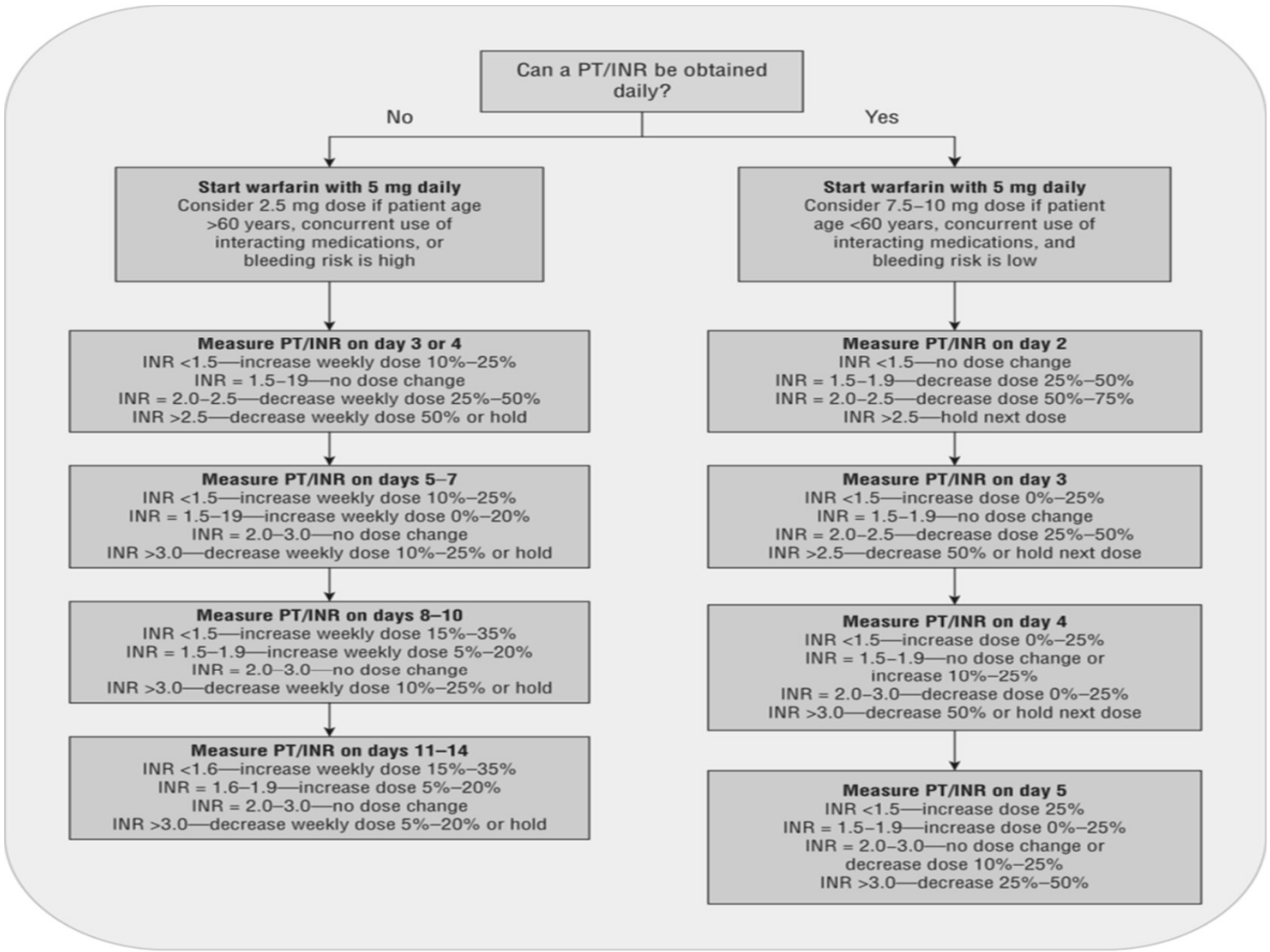
Dose daily based on INR (while hospitalized)

Patients who may require **> 5 mg** per day

- Young (< 55 years of age)
- Male gender
- African American ethnicity
- Body weight >90 kg
- Vitamin K intake > 400 mcg per day

Patients who may require **< 5 mg** per day

- Elderly
- Malnourished
- Heart failure
- Liver disease
- Concomitant significant interacting medications



Initiation of warfarin therapy. INR, international normalized ratio; PT, prothrombin time.

Parenteral Pharmacological Options
VTE Treatment Dosing

Anticoagulant	Dose	Renal Impairment
Unfractionated Heparin (UFH)	**IV Infusion (wt based)**: 80 units/kg IV bolus (max 10,000); Then 18 units/kg/hr continuous infusion (max 2,300) **SubQ**: 333 units/kg SubQ x 1 dose; Then 250 units/kg SubQ Q12 hrs	No dosage adjustment required.
Low Molecular Weight Heparins (LMWH) Enoxaparin (Lovenox®)	1 mg/kg SubQ Q12 hrs **or** 1.5 mg/kg SubQ Q24 hrs	Avoid use in ESRD and HD patients. **CrCl < 30 mL/min:** 1 mg/kg SubQ Q24 hrs
Factor Xa Inhibitors Fondaparinux (Arixtra®)	**<50 kg**: 5 mg SubQ Q24 hrs **50–100 kg**: 7.5 mg SubQ Q24 hrs **>100 kg**: 10 mg SubQ Q24 hrs	**CrCl 30–50 mL/min**: use caution; may need dose adjustment **CrCl < 30 mL/min**: C/I

Indication	Initial Loading Dose	Initial Infusion Rate
VTE (DVT/PE)	80 units/kg bolus	18 units/kg/hr

aPTT (sec)	UFH Dose adjustment
< 37	80 units/kg bolus, then increase infusion by 4 units/kg/hr
37-47	40 units/kg bolus, then increase infusion by 2 units/kg/hr
48-71 (therapeutic)	No change
72-93	Decrease infusion by 2 units/kg/hr
> 93	Hold infusion for 1 hr, then decrease by 3 units/kg/hr

CHEST 2016;149(2):315–352.

Weight-Based IV Heparin dosing using a Heparin Nomogram

- Actual Body weight used for calculation
- Adjusted or maximum dose may be used for obese patients

Thrombolytics

in pts with PE and hemodynamic instability Can be used

High bleeding risk-careful pt selection needed

Streptokinase, urokinase, alteplase are FDA approved for PE treatment

All are equally efficacious, t-PA has shortest infusion time

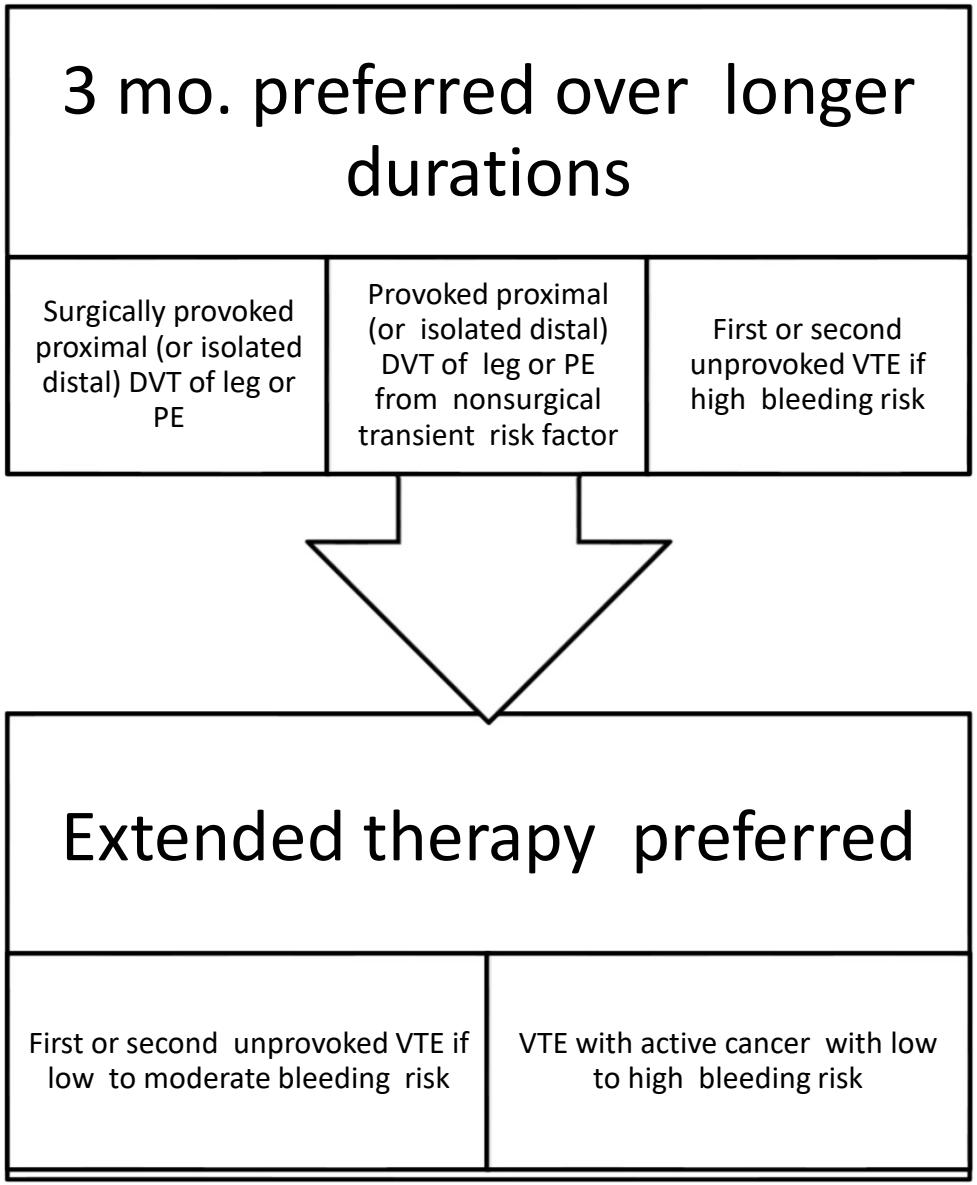
Alteplasedose: 100 mg IV over 2h

Parenteral anticoagulation resumed near end or immediately following infusion

Fig. 19–8

Fig. 19–9

AC Duration


3 mo. preferred over longer durations
Surgically provoked proximal (or isolated distal) DVT of leg or PE
Provoked proximal (or isolated distal) DVT of leg or PE from nonsurgical transient risk factor
First or second unprovoked VTE if high bleeding risk
Extended therapy preferred
First or second unprovoked VTE if low to moderate bleeding risk
VTE with active cancer with low to high bleeding risk

Candidate for Outpatient Treatment

Candidates include patients

- without hemodynamic compromise (stable vitals)
- with low bleeding risk, not actively bleeding
- with normal renal function
- without recent surgery or trauma
- without other acute conditions (requiring hospitalization)

Reduces healthcare costs, improves patient satisfaction

Systemic Thrombolytics for PE

Acute PE with hypotension and without high bleeding risk

- Systemic thrombolytics recommended

Acute PE without hypotension

- Systemic thrombolytics NOT recommended

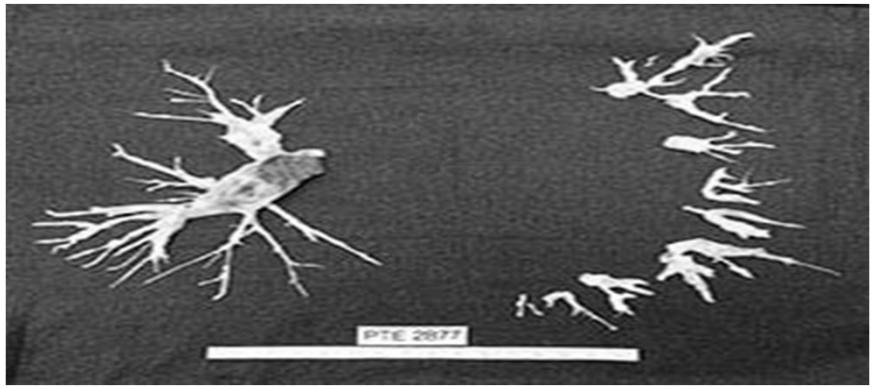
Acute PE with deterioration after AC therapy is started with low bleeding risk and without hypotension

- Systemic thrombolytics recommended

Pulmonary Thrombo-endarterectomy for CTEPH

Preferred if experienced surgeons available

Blockages removed by PTE from a patient's pulmonary arteries.



Recurrent VTE while on AC

If on VKA therapy and in range or DOACS

- Switch to LMWH temporarily (at least 1 mo)

If on long-term LMWH

- Increase dose by 25 to 33%

VTE Treatment Steps

changes with use of DOACs

Start oral anticoagulation

Determine **oral anticoagulation** length of therapy

3 months vs. extended therapy

VTE Treatment Steps

changes with use of DOACs

Dabigatran (Pradaxa)

- Dabigatran 150 mg orally twice daily
- After 5 to 10 days of initial therapy with a parenteral anticoagulant

Rivaroxaban (Xarelto)

- Rivaroxaban 15 mg PO twice daily with food for 3 weeks followed by 20 mg PO once daily with food for 3-12 months
- (no initial parenteral anticoagulation) vs. therapeutic enoxaparin followed by warfarin (INR 2-3)

Apixaban (Eliquis)

- Apixaban 10 mg orally twice daily x 7 days. Then 5 mg twice daily (AMPLIFY)
- Reduction in risk for recurrence (after 6 mo.) 2.5 mg twice daily (AMPLIFY-EX)

Endoxaban (Savaysa)

- Edoxaban 60 mg orally once daily
- After 5 to 10 days of initial therapy with a parenteral anticoagulant
- HOKUSAI-VTE

Engl J Med 2013; 369:799-808

Summary of Rivaroxaban dosing by indication

Indication	Renal Function (mL/min)	Dose
Atrial fibrillation	> 50	20 mg once daily with evening meal
	50 – 15	15 mg once daily with evening meal
	< 15	Do not use
VTE prevention (hip and knee replacement)	≥ 30	10 mg once daily (use with caution if CrCl is 30–50 mL/min)
	< 30	Do not use
VTE treatment	≥ 30	15 mg twice daily with food x 3 weeks , then 20 mg once daily with food
	< 30	Do not use
Reduction in risk of recurrent VTE	≥ 30	20 mg once daily with food
	< 30	Do not use

Summary

- VTE is a disorder that can have life-threatening consequences.
- Patients presenting with life-threatening or limb-threatening VTE may require fibrinolytic therapy to dissolve the clot.
- Treatment of VTE involves anticoagulation with parenteral and/or oral agents.
- HIT is a major complication of therapy with UFH and is also possible with LMWH.
- Treatment of HIT involves discontinuation of heparin and initiation of non-heparin anticoagulant (argatroban)
- Bleeding is an important side effect of anticoagulation.