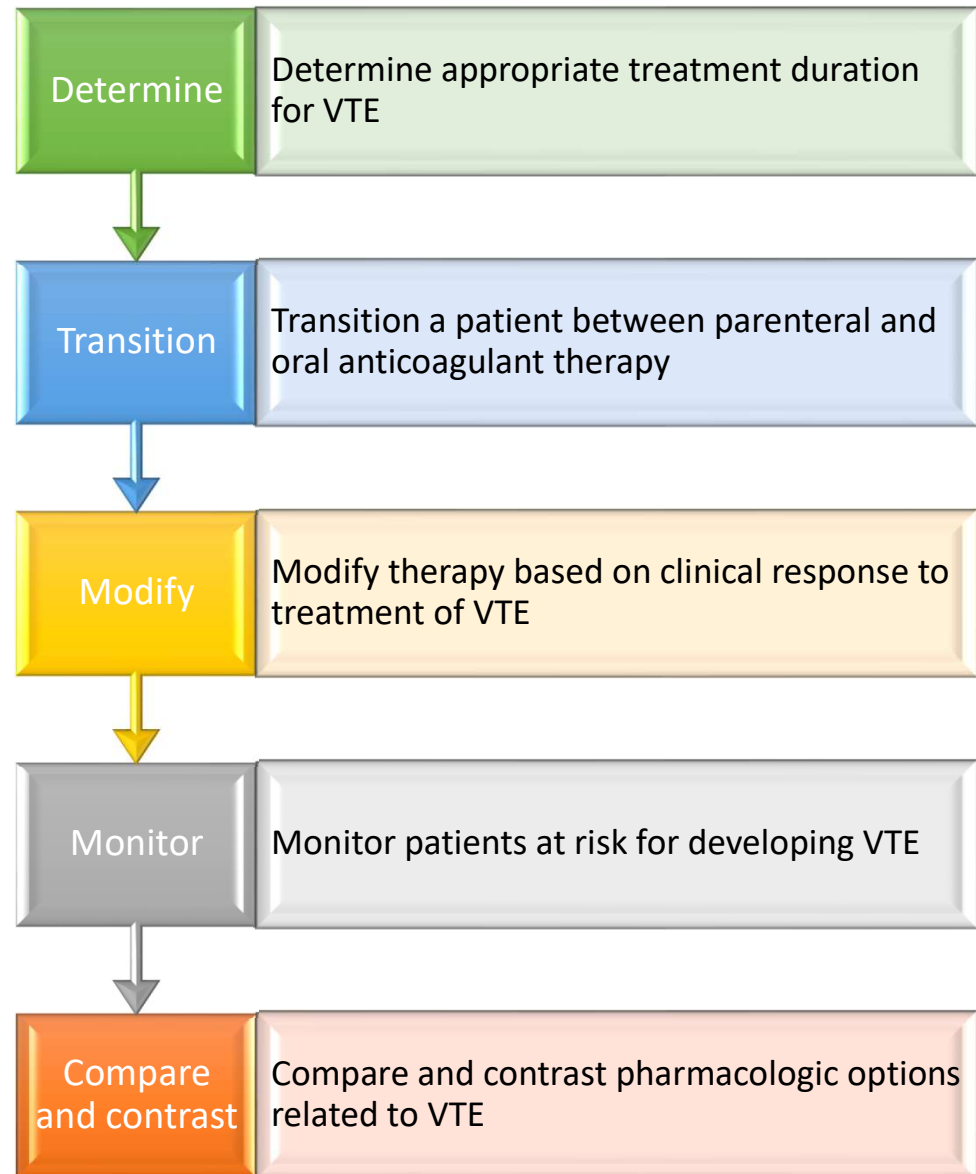


VTE

Dr. Abdallah ABUKHALIL  
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

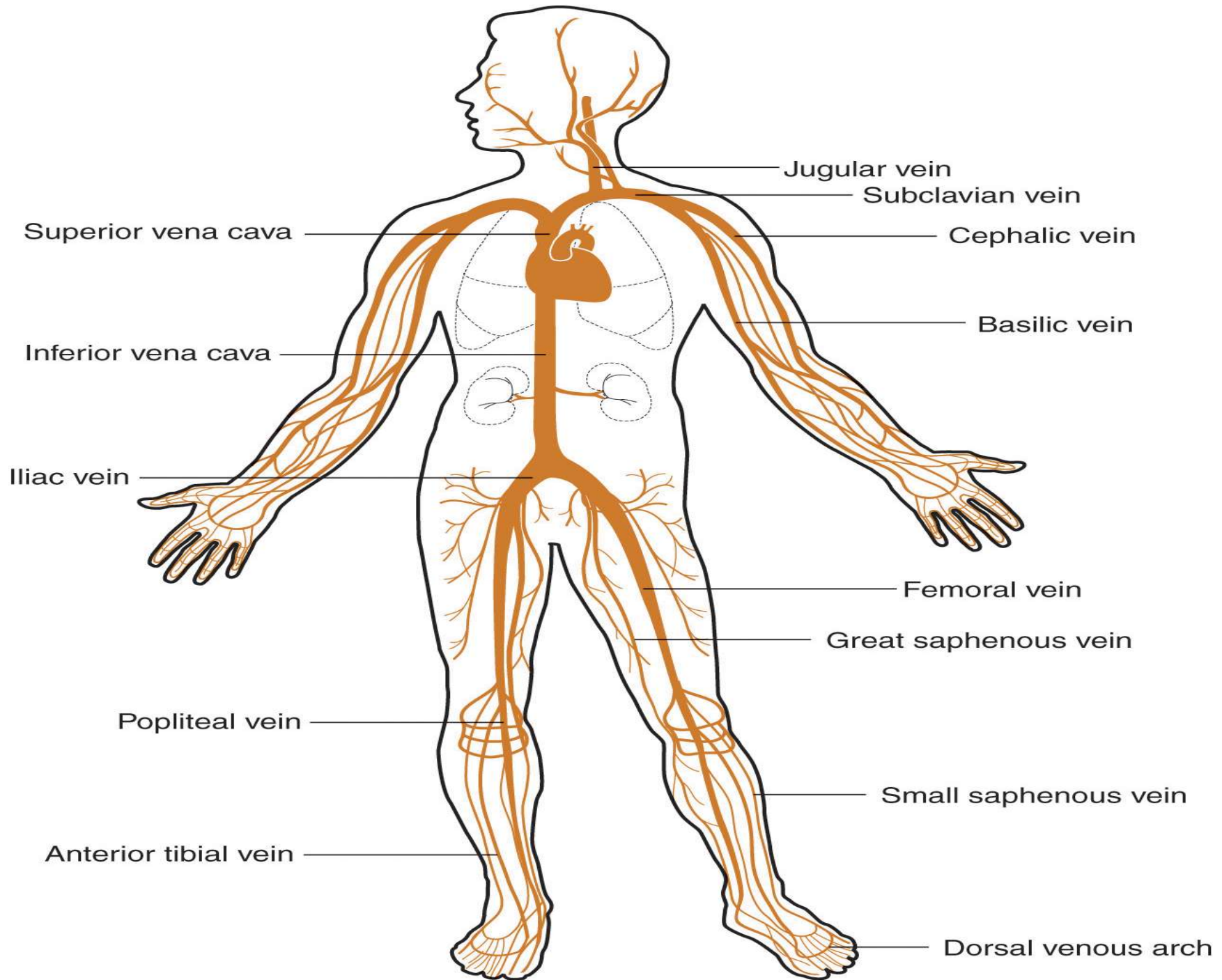
Associated with substantial healthcare costs

- \$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

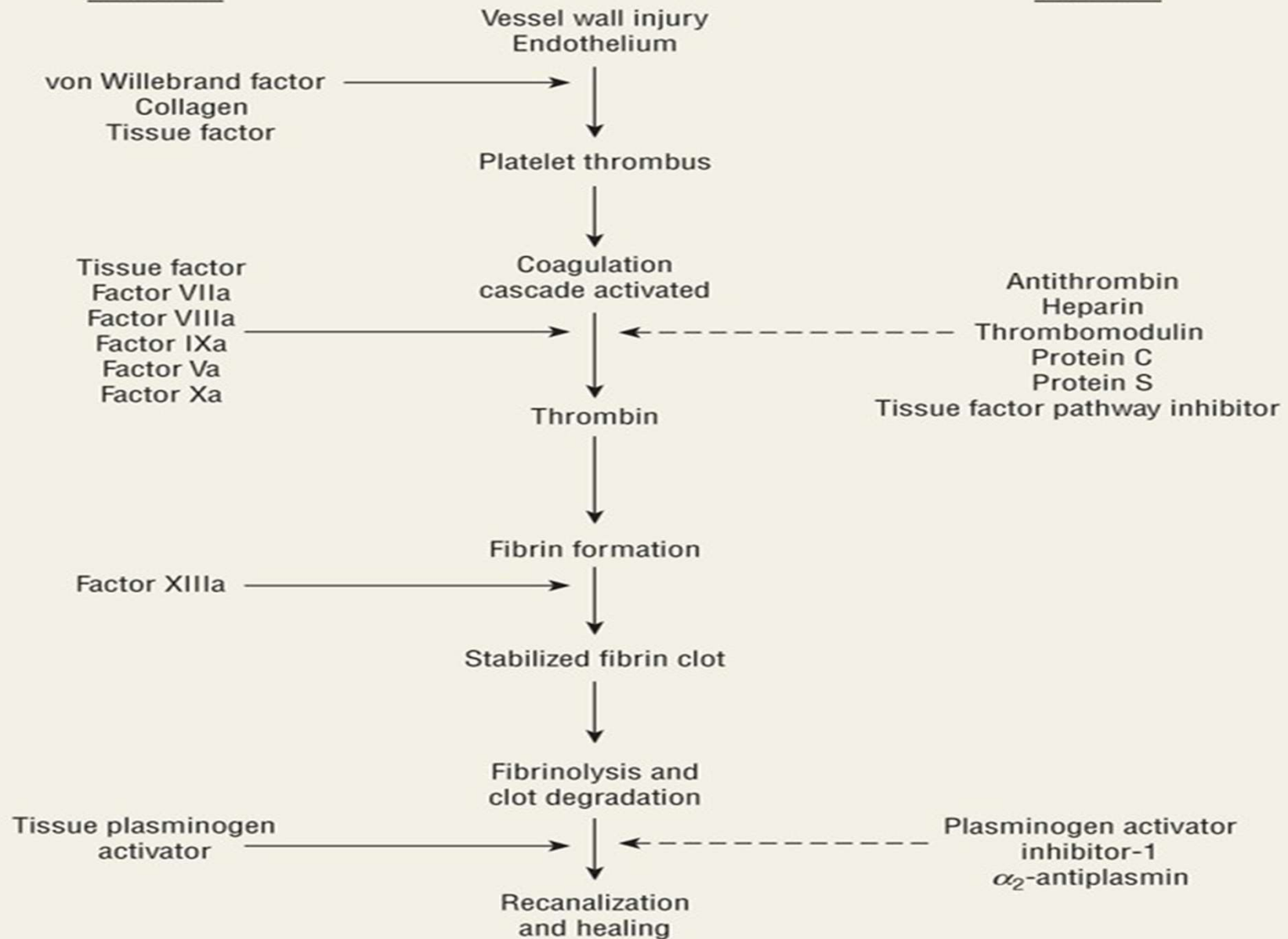
Hypercoagulable States

Drug Therapy



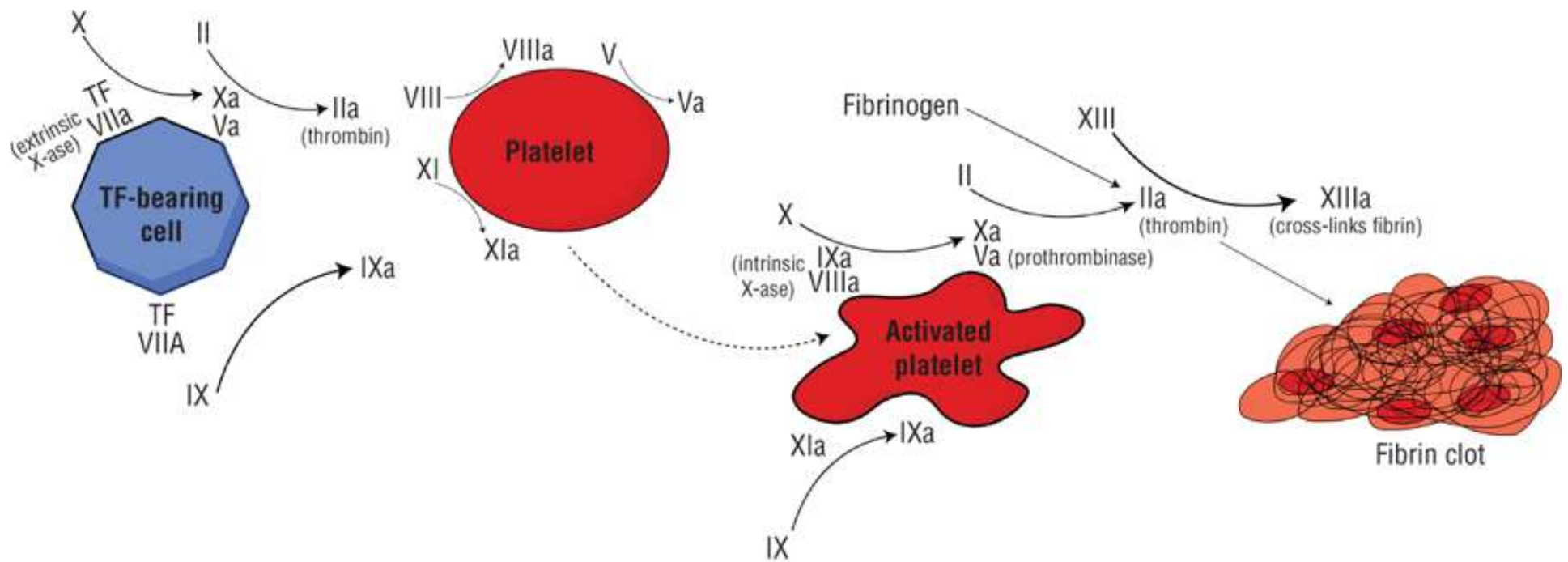
Activators

Inhibitors



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 Copyright © McGraw-Hill Education. All rights reserved.

# 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 Copyright © McGraw-Hill Education. All rights reserved.

# 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**

## Propagation

- “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
- 2<sup>nd</sup> 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 O<sub>2</sub>-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  $< 500\text{ng/ml}$
- 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)

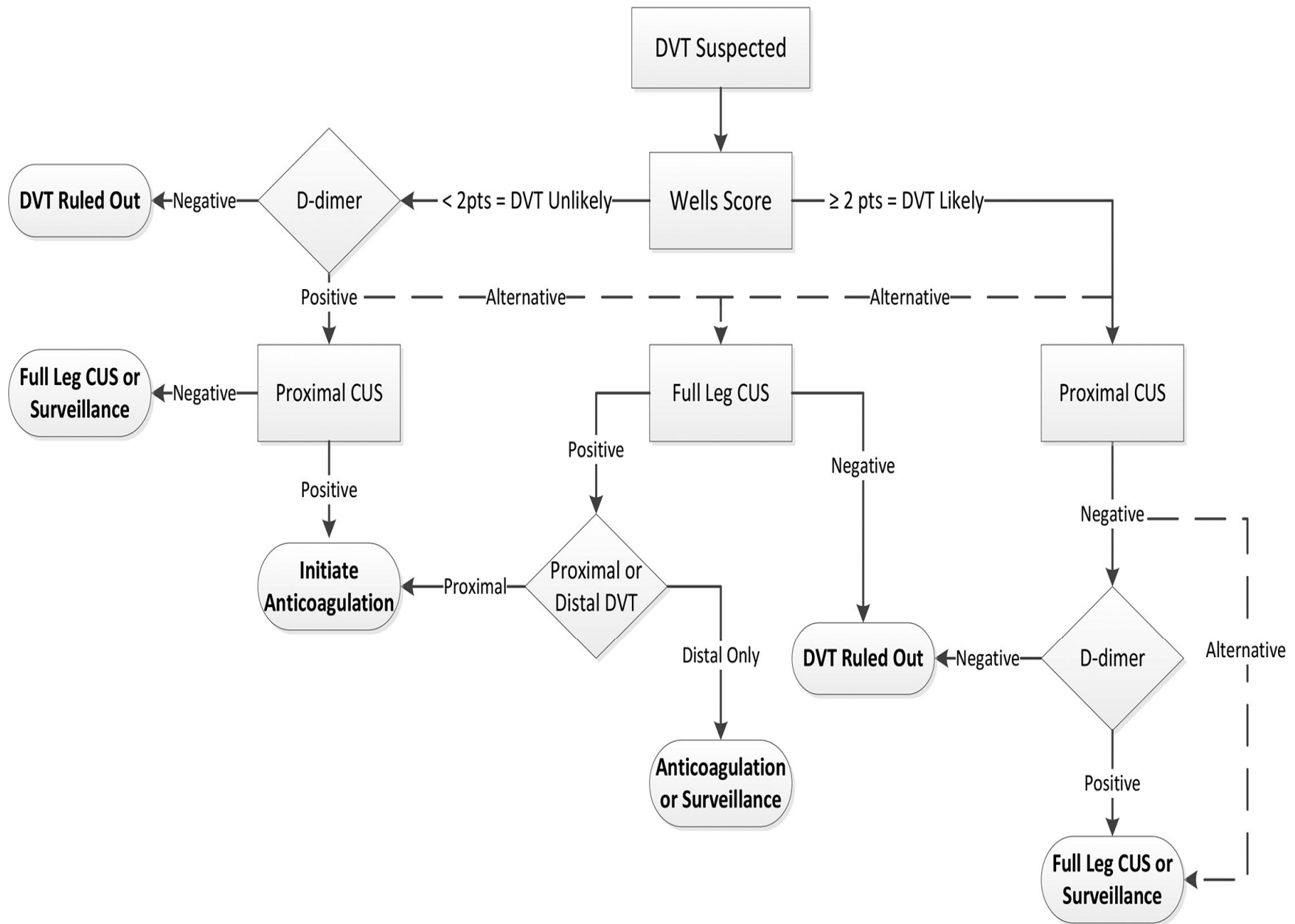
Does patient have risk factors?

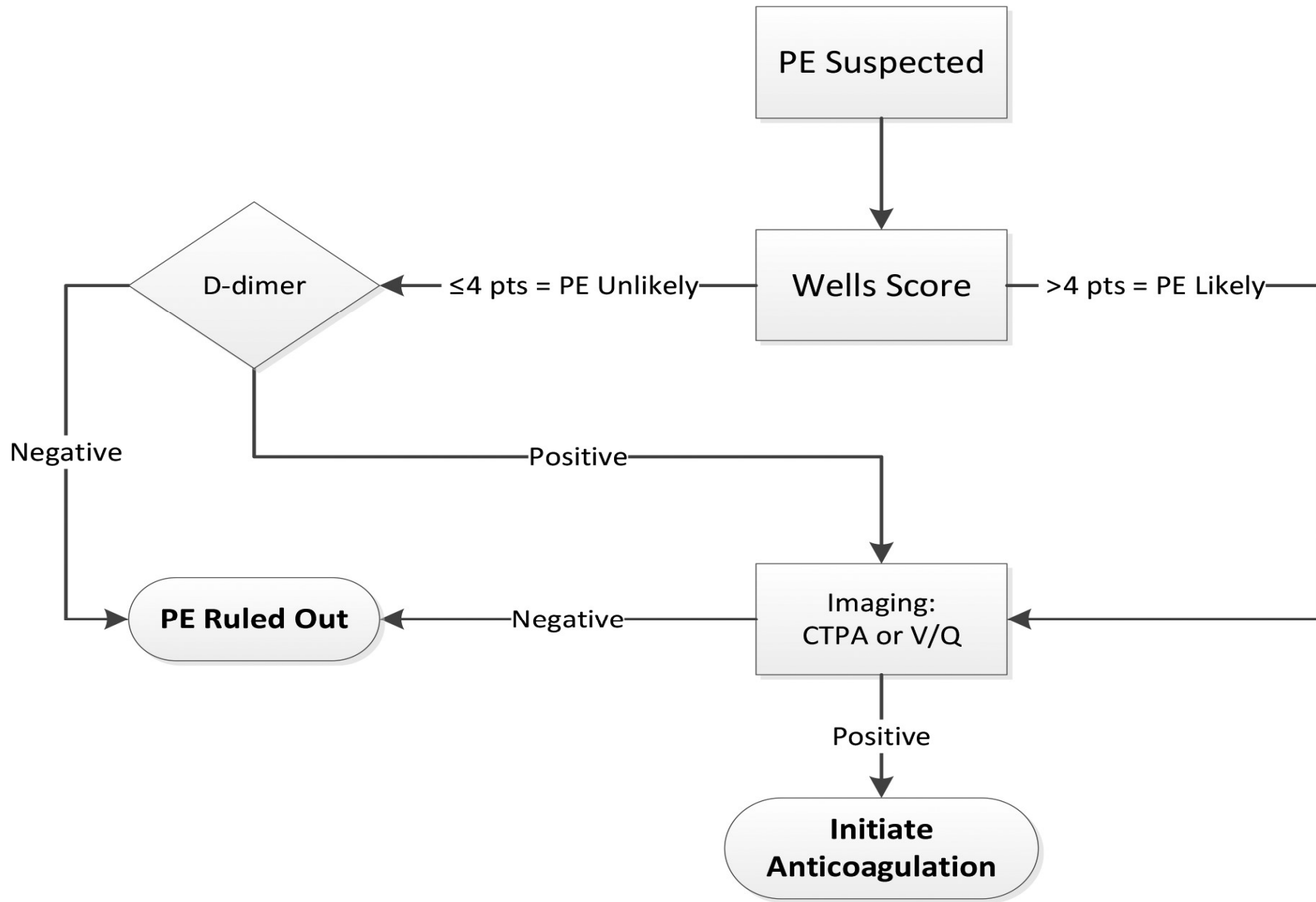
What are the symptoms?

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<sup>a</sup>

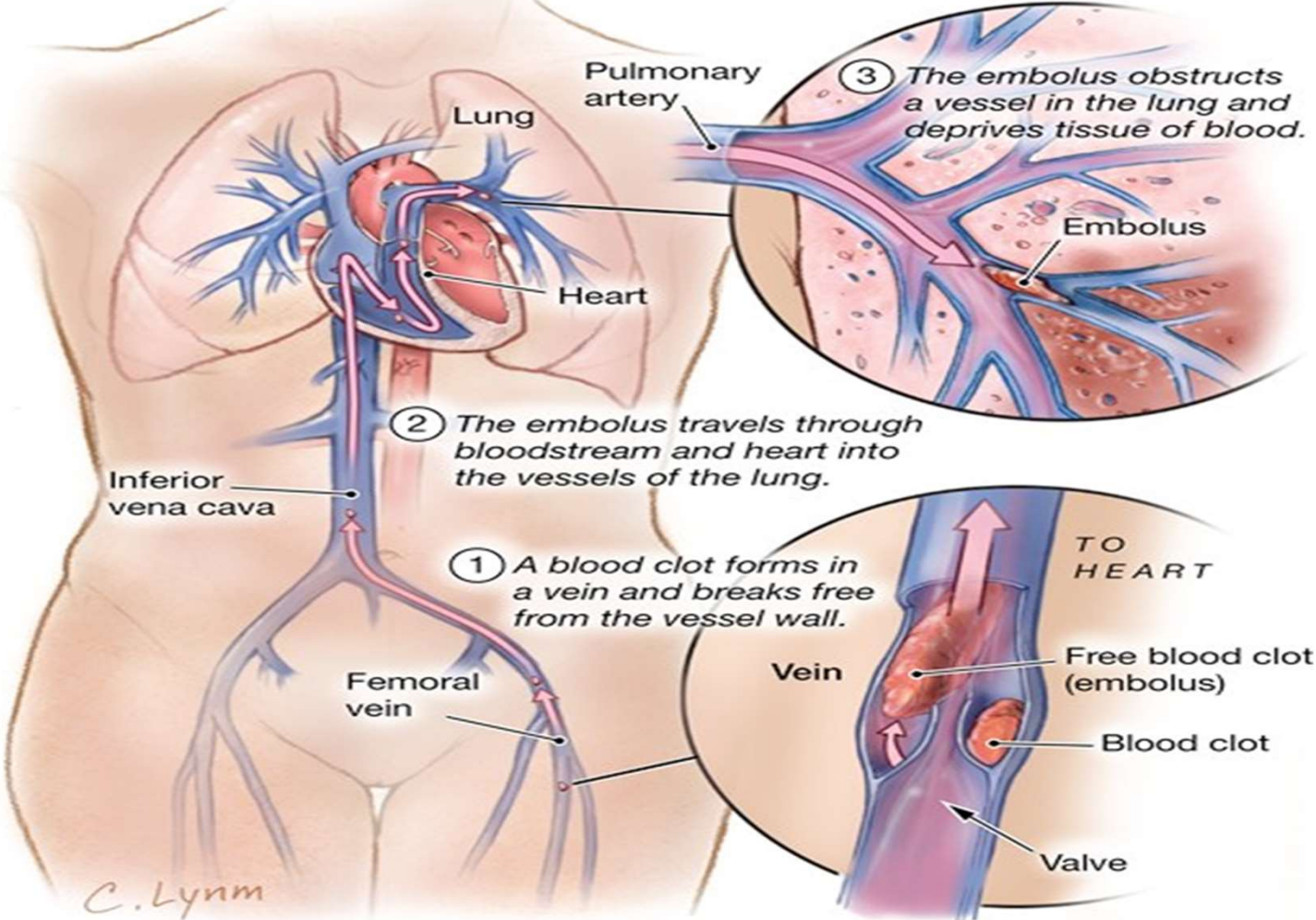
Clinical Characteristic	Score
Active cancer (cancer treatment within previous 6 months or currently on palliative treatment)	+1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	+1
Recently bedridden for 3 days or more, or major surgery within the previous 12 weeks requiring 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

<sup>a</sup>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



## Clinical Model/Wells Criteria for Evaluating the Pretest Probability of Pulmonary Embolism<sup>a</sup>

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

<sup>a</sup>Clinical probability of PE: low, 0-1; moderate, 2-6; high, 7 or greater.

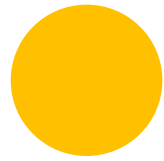
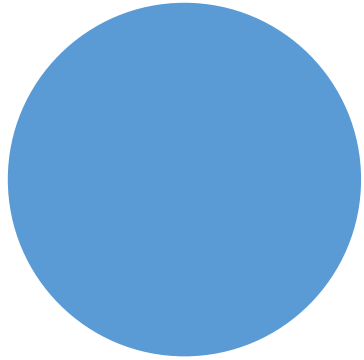
Padua  
Prediction  
score

Hospitalized and  
critically ill patients

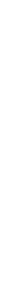
Prospectively  
validated

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

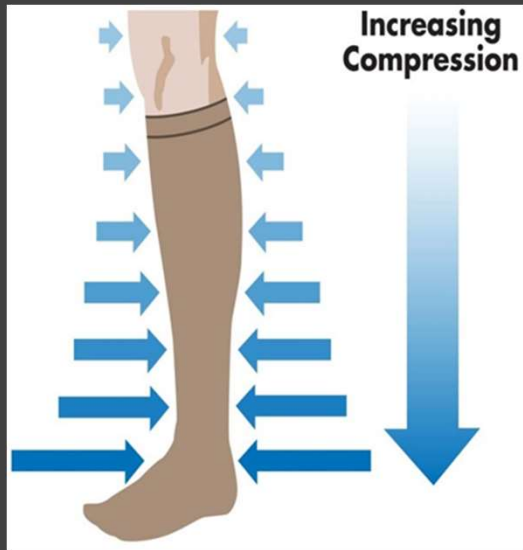


Prevention

## 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
- **Anti-Xa levels for monitoring → not routine**

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/LM WH 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<sup>3</sup>

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

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

## 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 = 7.5mg/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

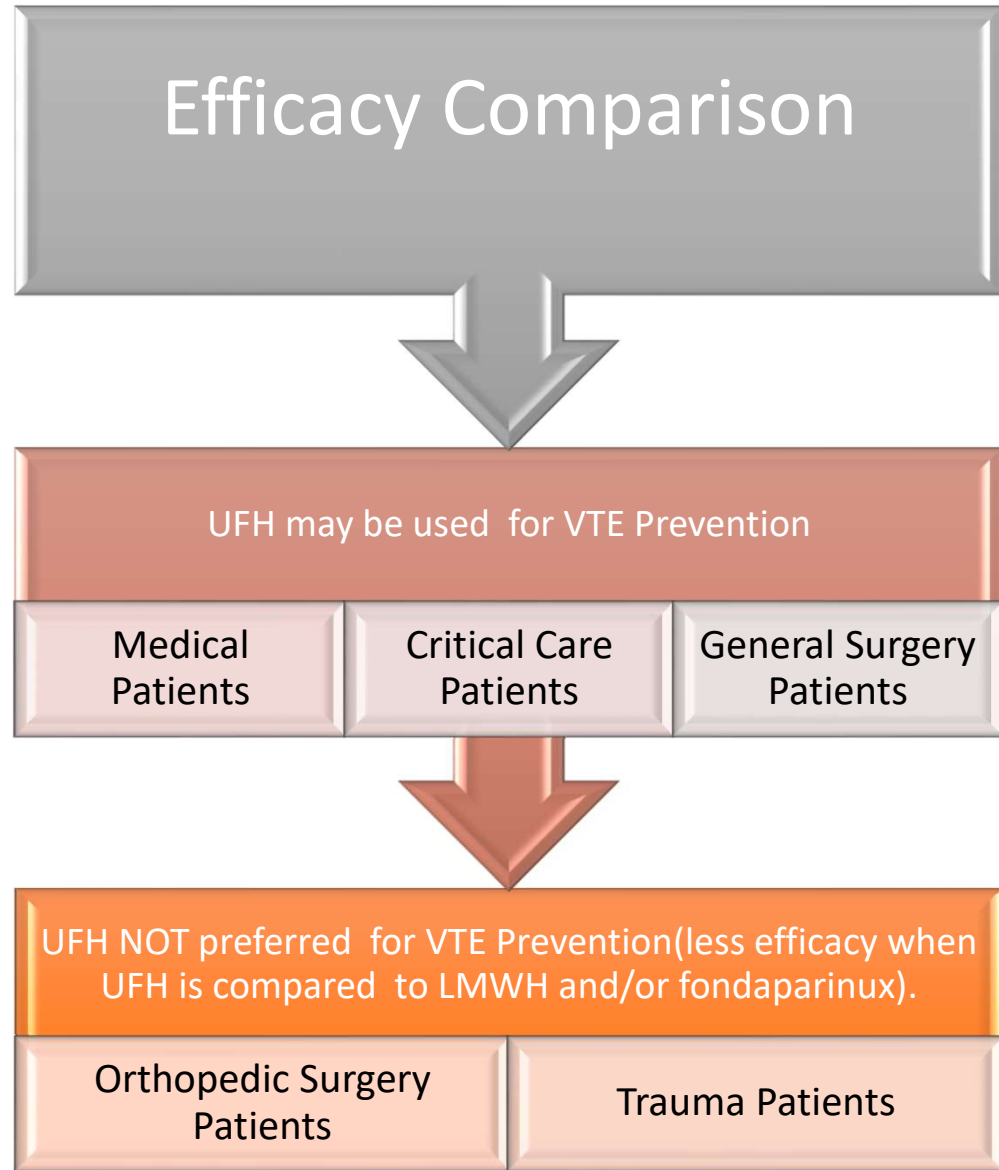
Dose:

- 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)	<b>Avoid use in ESRD and HD patients.</b>  <u>CrCl &lt; 30 mL/min:</u> 30 mg SubQ every 24 hours
Factor Xa Inhibitors  Fondaparinux (Arixtra®)		2.5 mg SubQ every 24 hours	<u>CrCl 30-50 mL/min:</u> use caution; may need dose adjustment  <u>CrCl &lt; 30 mL/min:</u> 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:**
  - $\geq 30$  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  $\geq 30$**
- 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
<b>Low Risk</b> Minor surgery (fully ambulatory) Medical illness (fully ambulatory)	< 10%	Early, aggressive ambulation +/- Mechanical prevention
<b>Moderate Risk</b> 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)**
<b>High Risk</b> 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



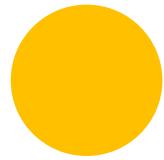
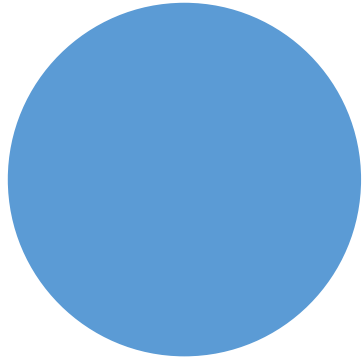
## Managing Bleeding Events

### 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

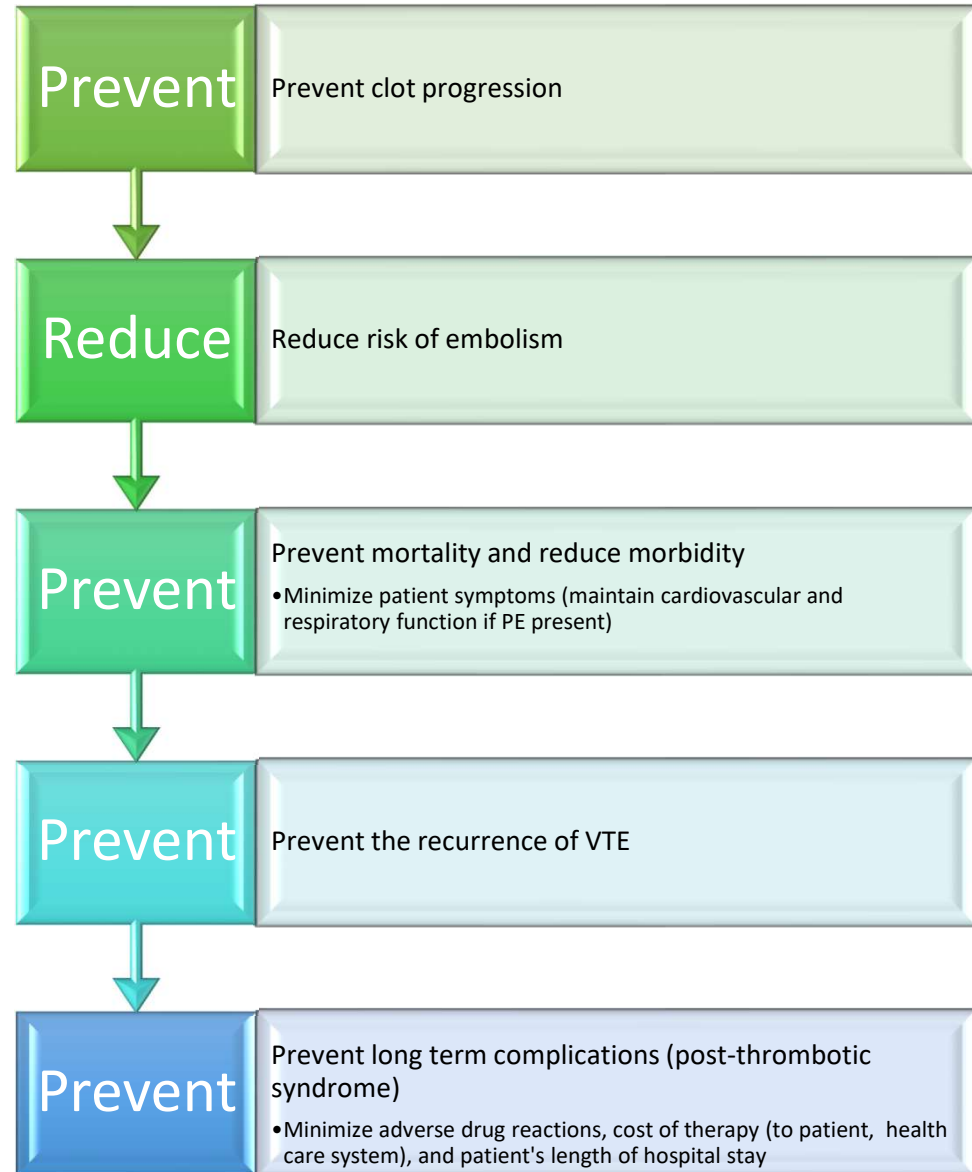
Consider fibrinolytic therapy

- 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.

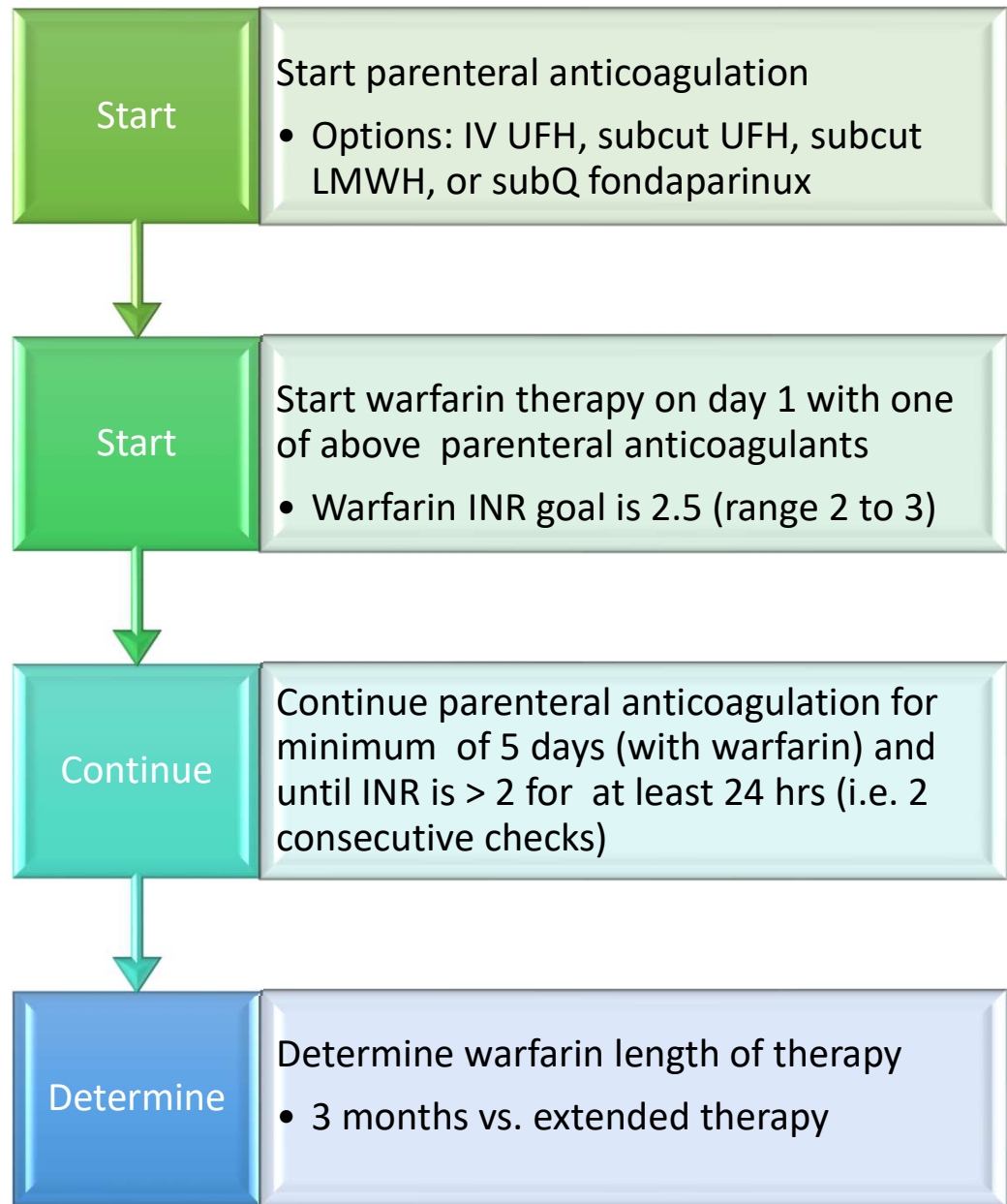
Was VTE **unprovoked** (no cause can be identified)?

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

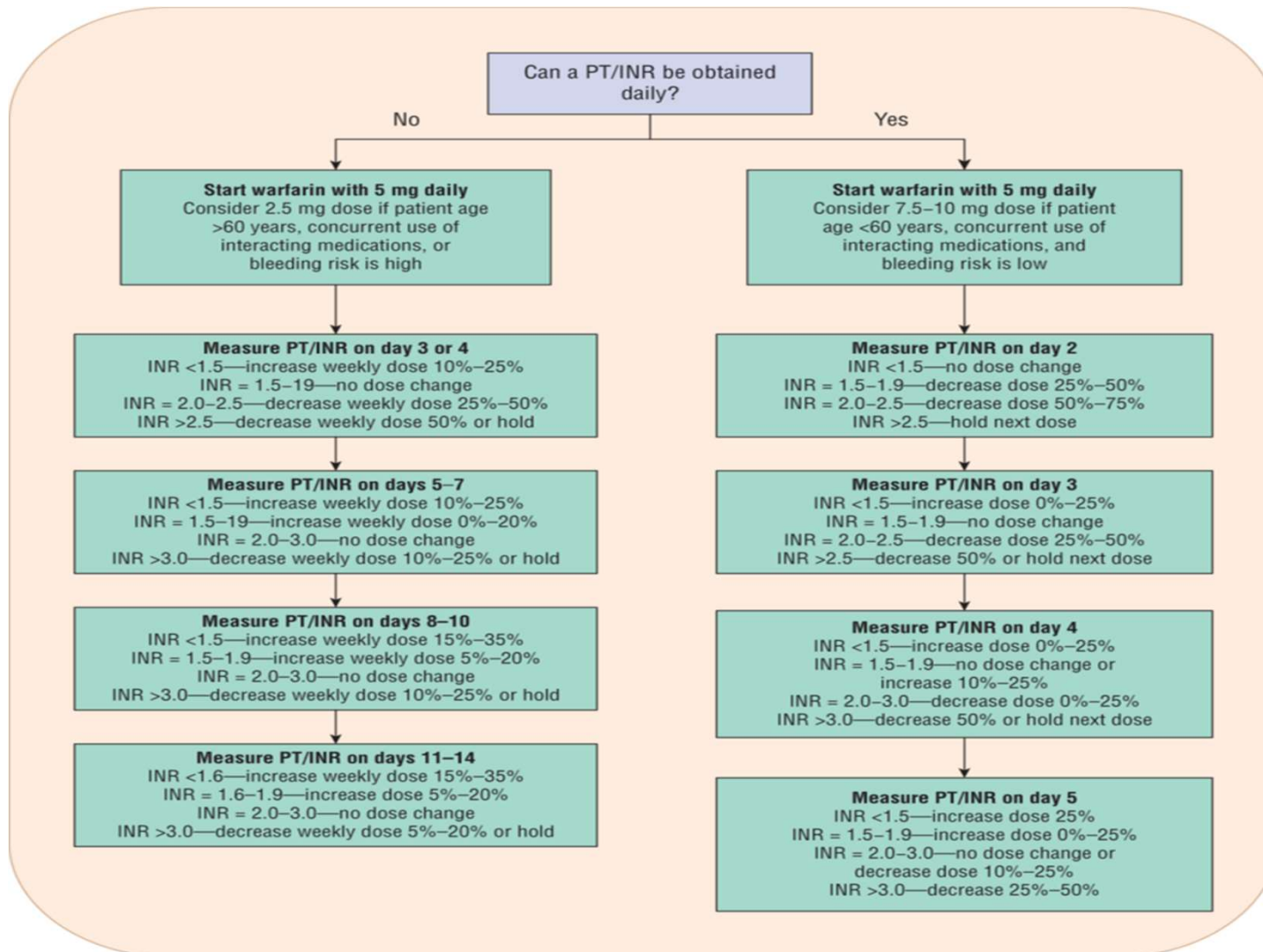
Dose daily based on INR (while hospitalized)

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



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 Copyright © McGraw-Hill Education. All rights reserved.

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

# Parenteral Pharmacological Options

## VTE Treatment Dosing

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

Indication	Initial Loading Dose	Initial Infusion Rate
VTE (DVT/PE)	80 units/kg bolus	18 units/kg/hr
<b>aPTT (sec)</b>		
<b>UFH Dose adjustment</b>		
< 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	

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## 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

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in pts with PE and hemodynamic instability Can be used

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High bleeding risk-careful pt selection needed

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Streptokinase, urokinase, alteplase are FDA approved for PE treatment

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

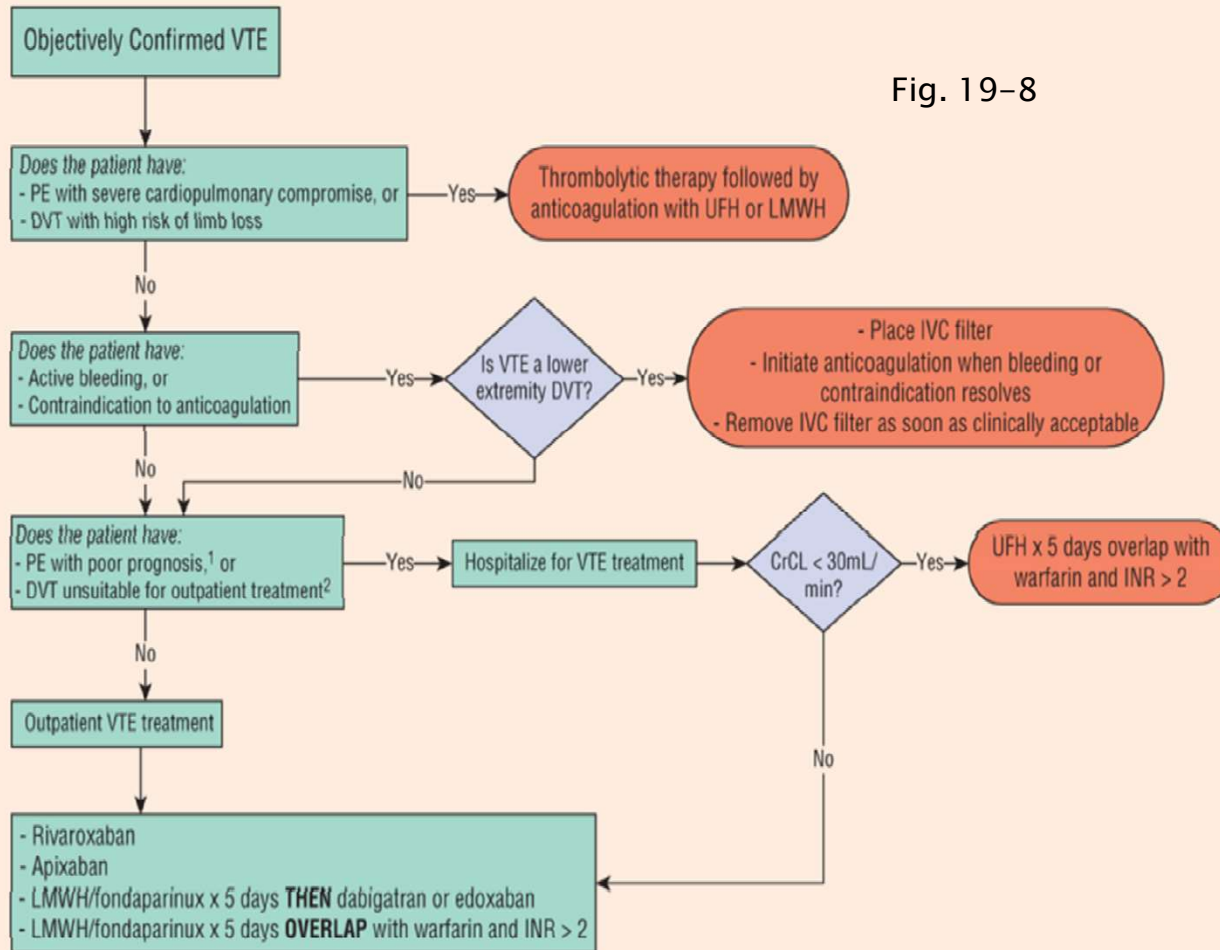
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Alteplasedose: 100 mg IV over 2h

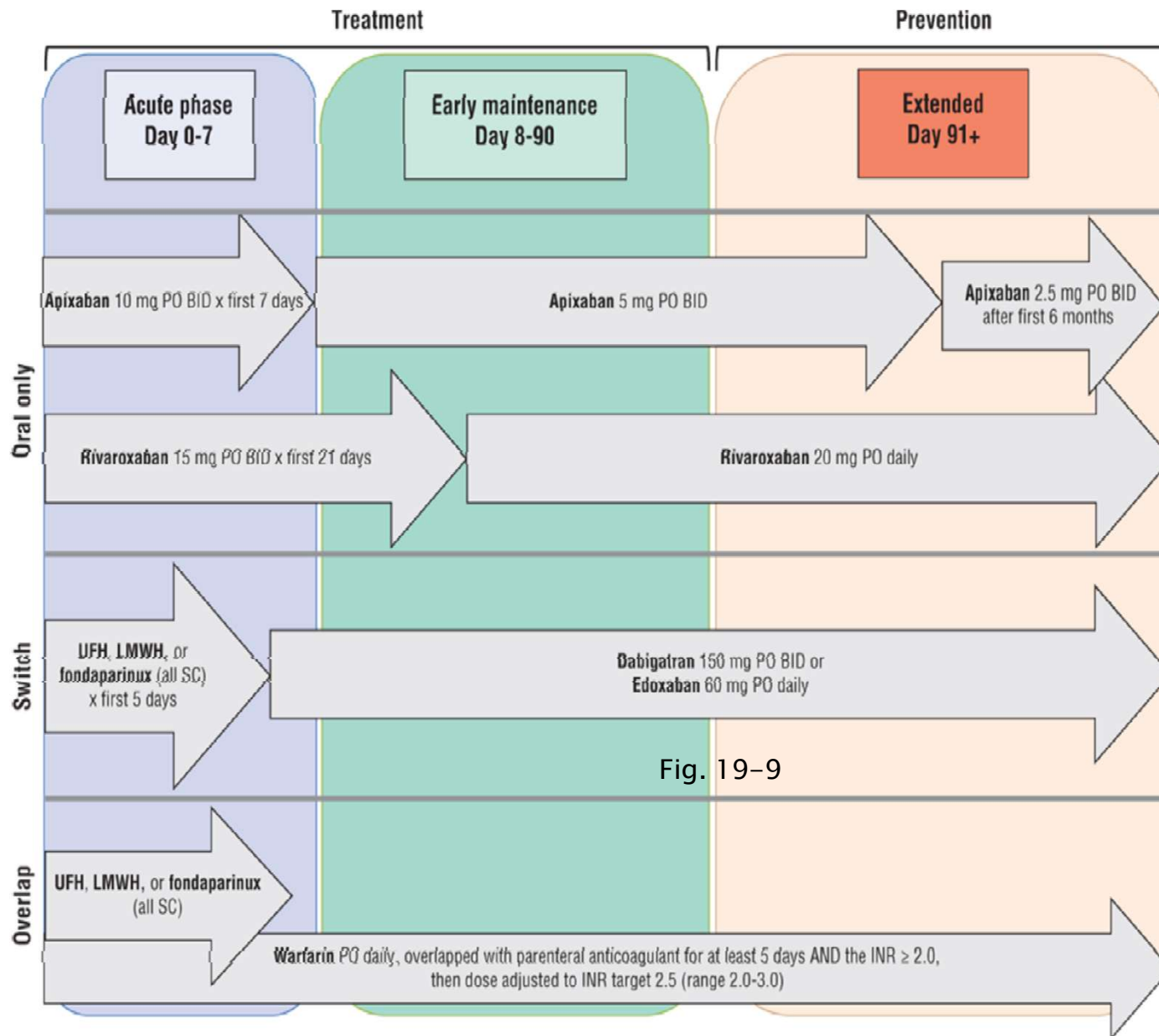
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Parenteral anticoagulation resumed near end or immediately following infusion

Fig. 19-8



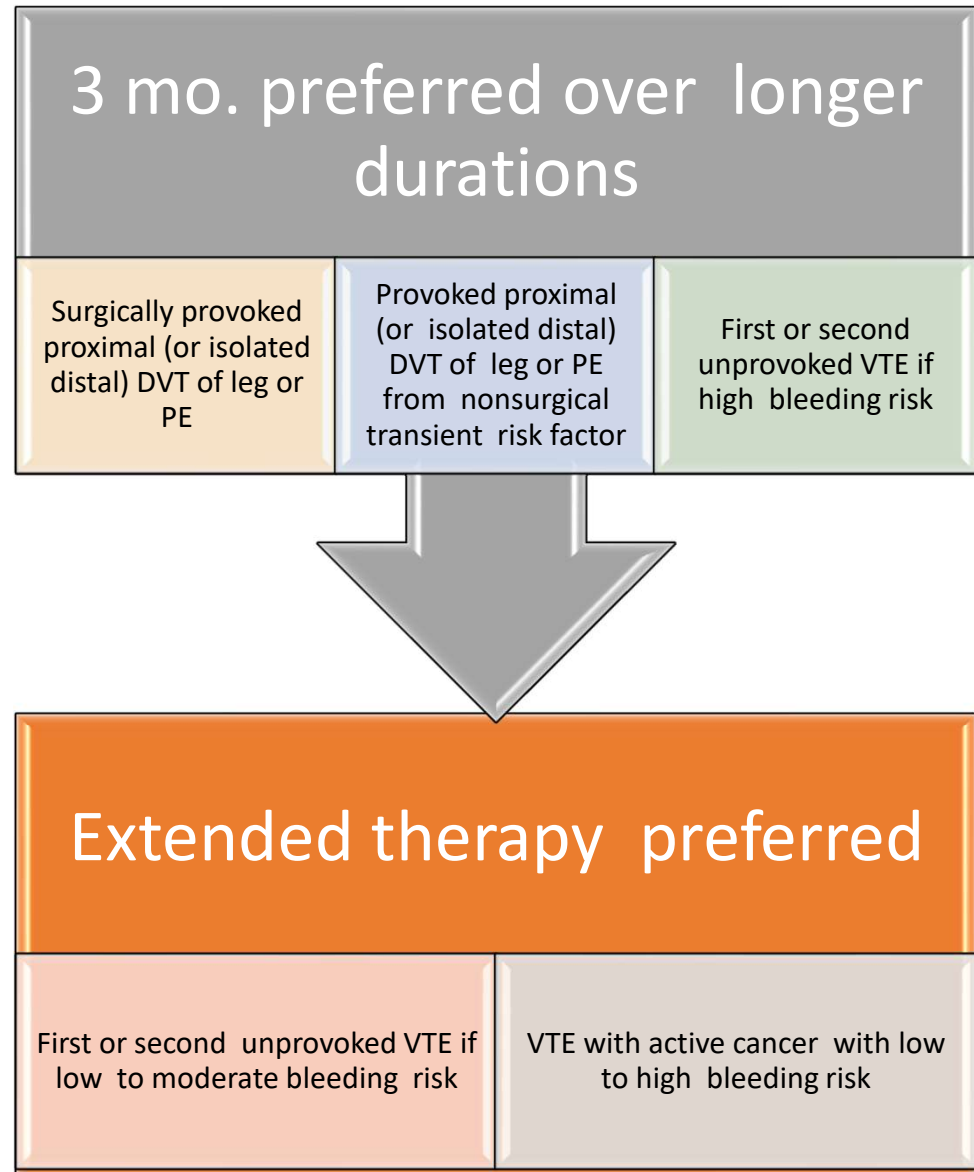
<sup>1</sup>-Severe symptoms, renal impairment, inability to obtain or administer appropriate initial anticoagulant therapy, or high bleeding risk.  
<sup>2</sup>-PESI score  $\geq 86$  points: age (1 pt for each year); male sex (10pts); cancer (30pts); heart failure (10pts); COPD (10pts); heart rate  $> 110$  bpm (20pts); respiratory rate  $> 30$  bpm (20pts); temperature  $< 36^{\circ}\text{C}$  (20pts); altered mental status (60pts);  $\text{O}_2$  sat  $< 90\%$  (20pts).



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 Copyright © McGraw-Hill Education. All rights reserved.



# AC Duration



**TABLE 6 ] Factors That May Influence Which Anticoagulant Is Chosen for Initial and Long-Term Treatment of VTE**

Factor	Preferred Anticoagulant	Qualifying Remarks
Cancer	LMWH	More so if: just diagnosed, extensive VTE, metastatic cancer, very symptomatic; vomiting; on cancer chemotherapy.
Parenteral therapy to be avoided	Rivaroxaban; apixaban	VKA, dabigatran, and edoxaban require initial parenteral therapy.
Once daily oral therapy preferred	Rivaroxaban; edoxaban; VKA	
Liver disease and coagulopathy	LMWH	NOACs contraindicated if INR raised because of liver disease; VKA difficult to control and INR may not reflect antithrombotic effect.
Renal disease and creatinine clearance <30 mL/min	VKA	NOACs and LMWH contraindicated with severe renal impairment. Dosing of NOACs with levels of renal impairment differ with the NOAC and among jurisdictions.
Coronary artery disease	VKA, rivaroxaban, apixaban, edoxaban	Coronary artery events appear to occur more often with dabigatran than with VKA. This has not been seen with the other NOACs, and they have demonstrated efficacy for coronary artery disease. Antiplatelet therapy should be avoided if possible in patients on anticoagulants because of increased bleeding.
Dyspepsia or history of GI bleeding	VKA, apixaban	Dabigatran increased dyspepsia. Dabigatran, rivaroxaban, and edoxaban may be associated with more GI bleeding than VKA.
Poor compliance	VKA	INR monitoring can help to detect problems. However, some patients may be more compliant with a NOAC because it is less complex.
Thrombolytic therapy use	UFH infusion	Greater experience with its use in patients treated with thrombolytic therapy
Reversal agent needed	VKA, UFH	
Pregnancy or pregnancy risk	LMWH	Potential for other agents to cross the placenta
Cost, coverage, licensing	Varies among regions and with individual circumstances	

## 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

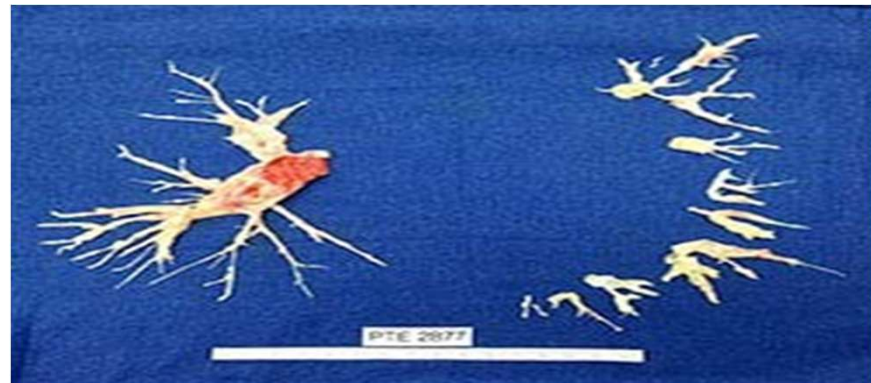
# Pulmonary Thrombo- endarterectomy for CTEPH



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



## 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)	$\geq 30$	10 mg once daily (use with caution if CrCl is 30–50 mL/min)
	< 30	Do not use
VTE treatment	$\geq 30$	15 mg <u>twice</u> daily with food x 3 weeks , then 20 mg once daily with food
	< 30	Do not use
Reduction in risk of recurrent VTE	$\geq 30$	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.