
Pharmacotherapy of Venous Thromboembolism (VTE)

Tessema Tsehay (B.Pharm., M.Pharm., RPh.)

Contents

- Definition
- Pathophysiology
- Clinical presentations
- Diagnosis
- Desired outcome
- Treatment
- Evaluation of Therapeutic outcomes

Definition

- VTE is a potentially fatal disorder and a significant health problem in the aging society.
- VTE results from **clot formation in the venous circulation** and is manifested as
 - deep vein thrombosis (DVT)
 - a thrombus composed of cellular material (red and white blood cells, platelets) bound together with fibrin strands. and
 - pulmonary embolism (PE)
 - a thrombus that arises from the systemic circulation and **lodges in the pulmonary artery** or one of its branches, causing complete or partial obstruction of pulmonary blood flow.

Cont...

- It most frequently occurs in patients
 - who sustain multiple trauma
 - undergo major surgery
 - are immobile for a lengthy period of time or
 - have a hypercoagulable disorder
- Death from PE can occur **within minutes** after the onset of symptoms, before effective treatment can be given.

Pathophysiology

- **The coagulation cascade**
 - The arrest of bleeding following vascular injury (hemostasis) is an amazingly complex process that is essential to life.
 - is a stepwise series of enzymatic reactions that results in the formation of **a fibrin mesh**
 - It can be triggered through either the **intrinsic** or **extrinsic** pathways.

Cont...

- Vascular injury also exposes the sub-endothelium, causing **adherence, activation, and aggregation of platelets**.
- The intrinsic and extrinsic pathways meet at a **common point** with the activation of factor X.
- With its partner, factor Va, factor Xa converts prothrombin (II) to thrombin (IIa), which then cleaves fibrinogen, forming fibrin monomers.
- Factor XIII covalently bonds fibrin strands together.

Cont...

- The fibrinolytic protein plasmin ultimately degrades the fibrin mesh into soluble end products known as fibrin split products or **fibrin degradation products**.
- Three primary components, **Virchow's triad**, play a role in the development of a pathogenic thrombus
 - venous stasis
 - vascular injury and
 - hypercoagulability

Cont...

- **Venous stasis**

- is slowed blood flow in the deep veins of the legs resulting from

- damage to venous valves
 - vessel obstruction
 - prolonged periods of immobility or
 - increased blood viscosity

Cont...

- Conditions associated with **venous stasis** include
 - major medical illness (e.g., HF, MI)
 - major surgery
 - paralysis (e.g., stroke, spinal cord injury)
 - polycythemia vera
 - obesity
 - varicose veins

Cont...

- **Vascular injury**

- may result from major

- orthopedic surgery (e.g., knee and hip replacement)
 - trauma (especially fractures of the pelvis, hip or leg)
 - indwelling venous catheters

Cont...

- **Hypercoagulable states** include
 - Malignancy
 - activated protein C resistance
 - deficiency of protein C, protein S or antithrombin
 - factor VIII or XI excess
 - antiphospholipid antibodies
 - Estrogens and SERMs have been linked to venous thrombosis,
 - perhaps due in part to increased serum clotting factor concentrations.

Cont...

- Although a thrombus can form in any part of the venous circulation, the majority of thrombi begin in the **lower extremities**.
- Once formed, a venous thrombus may:
 - remain asymptomatic
 - lyse spontaneously
 - Obstruct the venous circulation
 - propagate into more proximal veins
 - Embolize or act in any combination of these ways.
- Even asymptomatic patients may experience long-term consequences, such as the **postthrombotic syndrome** and **recurrent VTE**.

Coagulation factors

Factor^a	Synonym	Biologic Half-life (h)	Blood Product Source
I	Fibrinogen	100–150	Cryoprecipitate (200–300 mg/bag)
II	Prothrombin	50–80	FFP, PCC
V	Proaccelerin	12–36	FFP
VII	Proconvertin	4–6	Recombinant VIIa, FFP, PCC
VIII	Antihemophilic factor	12–15	FFP, factor concentrates, cryoprecipitate
IX	Christmas factor	18–30	FFP, PCC, factor concentrates
X	Stuart-Power factor	25–60	FFP, PCC
XI	Plasma thromboplastin antecedent	40–80	FFP
XII	Hageman factor	50–70	Not associated with bleeding diathesis
XIII	Fibrin-stabilizing factor	150	FFP, cryoprecipitate, factor concentrate
VWF	von Willebrand factor	8–12	FFP, cryoprecipitate, factor concentrate

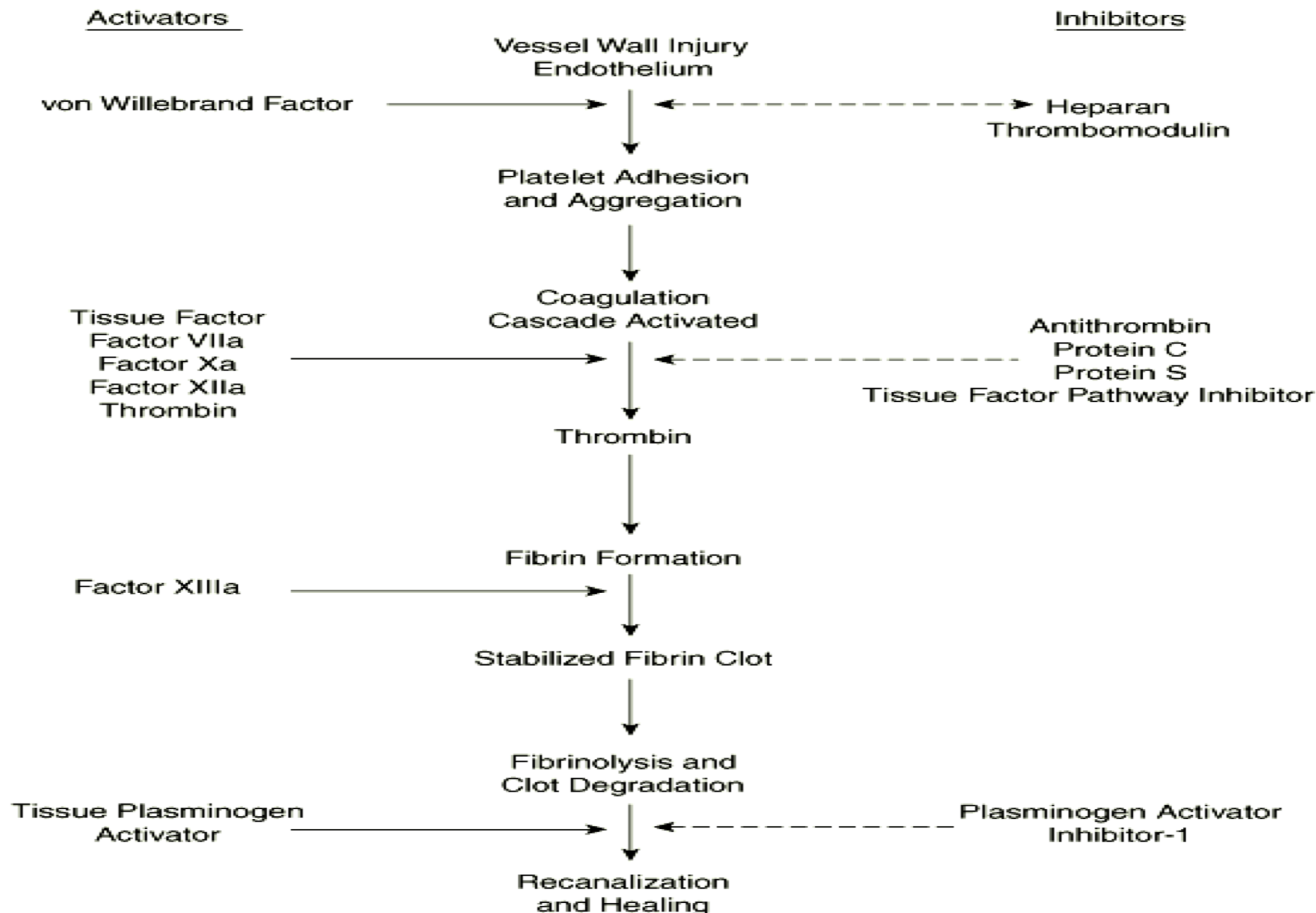
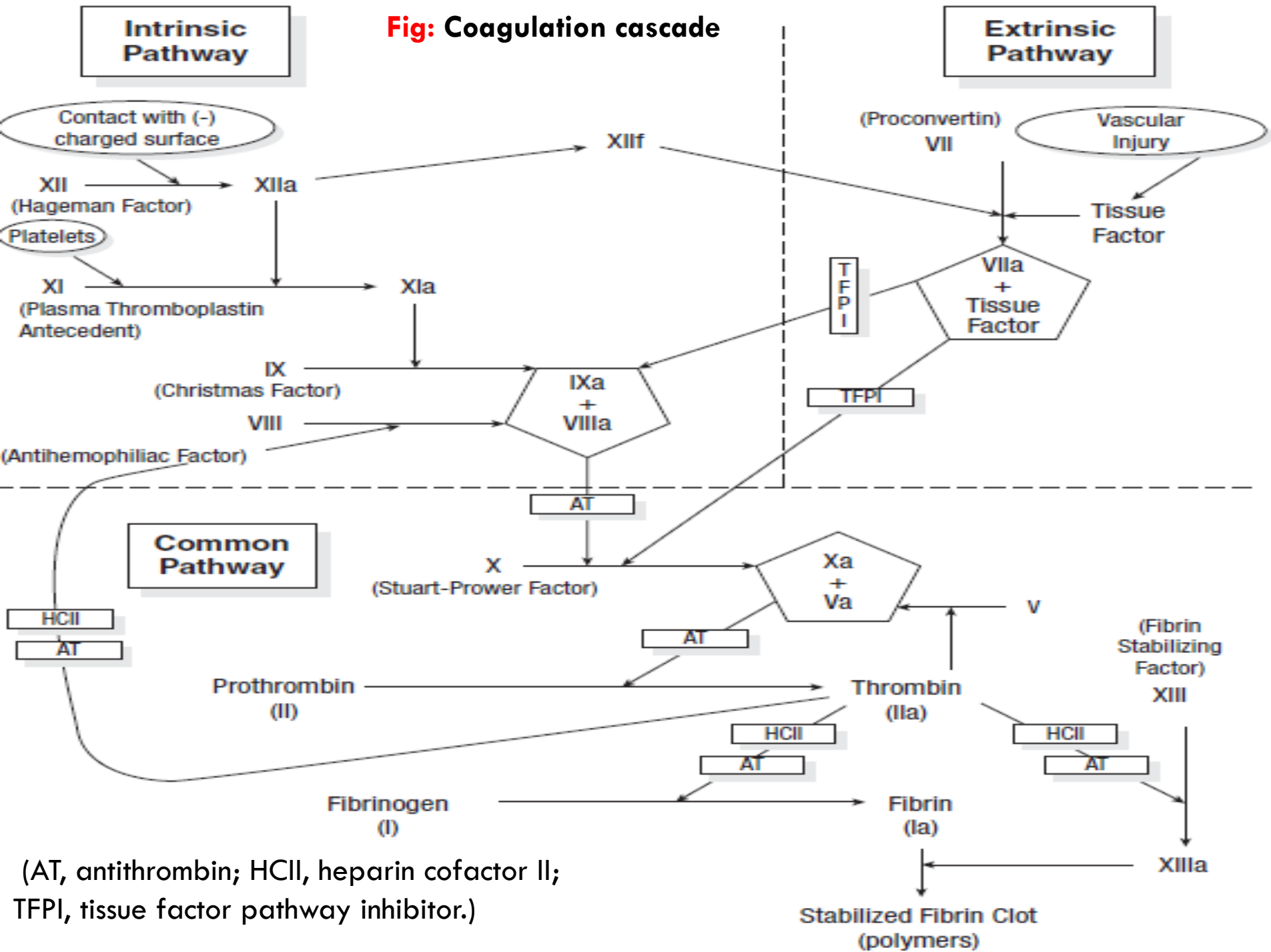


Fig: Coagulation cascade



Clinical Presentations

- Most patients with VTE **never develop symptoms from the acute event.**
- > 50% of patient population with VTE have clinically silent disease
- Symptoms of **DVT** include
 - unilateral leg swelling
 - pain, tenderness
 - erythema and
 - warmth



Cont...

- Physical signs may include
 - **Palpable cord:** The patient's superficial veins may be dilated and a "*palpable cord*" may be felt in the affected leg
 - **Positive Homans' sign:** The patient may experience pain in back of the knee when the examiner dorsiflexes the foot of the affected leg
- **Postthrombotic syndrome** (a long-term complication of DVT caused by damage to venous valves) may produce
 - chronic lower extremity swelling, pain, tenderness, skin discoloration and ulceration

Cont...

- Symptoms of **PE** include
 - dyspnea, tachypnea, pleuritic chest pain, tachycardia, palpitations, cough, diaphoresis, and hemoptysis.
 - Cardiovascular collapse, characterized by cyanosis, shock and oliguria is a life threatening sign

Diagnosis

- Assessment of the patient's status should focus on the search for **risk factors** e.g.,
 - increased age
 - major surgery
 - previous VTE
 - trauma
 - Malignancy
 - hypercoagulable states and
 - drug therapy
- Signs and symptoms of DVT are **nonspecific**
 - **objective tests** are required to confirm or exclude the diagnosis.

Cont...

Imaging studies

- **Radiographic contrast studies:** most accurate and reliable
 - **Contrast venography** allows visualization of the entire venous system in the lower extremity and abdomen
 - **Pulmonary angiography** allows visualization of the pulmonary arteries
 - **Multiple X-ray films:** finding of a persistent intraluminal filling defect

Cont...

- Because contrast studies are **expensive, invasive, and technically difficult** to perform and evaluate, the following noninvasive tests are used frequently for the initial evaluation of patients with suspected VTE
 - **ultrasonography**
 - **computed tomography scans**
 - **ventilation-perfusion scan**

Cont...

Laboratory test

- **D-dimer**
 - is a byproduct of thrombin generation
 - substantially elevated in patients with acute thrombosis
 - elevated levels can result from a variety of other conditions (a positive test cannot confirm the diagnosis)
 - e.g., recent surgery or trauma, pregnancy and cancer
 - negative test can help exclude the diagnosis of VTE
- Patients may have an **elevated ESR** and **WBC count**.

Desired Outcome

- The objectives of treating VTE are
 - to prevent the development of PE and the postthrombotic syndrome
 - to reduce morbidity and mortality from the acute event and
 - to minimize adverse effects and cost of treatment

Treatment

Unfractionated Heparin (UFH)

- UFH binds to **antithrombin**, provoking a conformational change
 - The UFH-antithrombin complex is 100 to 1,000 times more potent as an anticoagulant than antithrombin alone
 - Antithrombin inhibits the activity of **factors IXa, Xa, XIIa, and thrombin (IIa)**
 - It also inhibits thrombin-induced activation of factors V and VIII

Cont...

- UFH
 - **prevents** the **growth** and **propagation** of a formed thrombus and
 - allows the patient's own thrombolytic system to degrade the clot
- **Contraindications** to heparin therapy include
 - hypersensitivity to the drug
 - active bleeding
 - Hemophilia
 - severe liver disease with elevated prothrombin time (PT)
 - severe thrombocytopenia
 - malignant hypertension and
 - inability to meticulously supervise and monitor treatment

Cont...

- UFH must be given parenterally, preferably by the **IV** or **subcutaneous** (SC) route.
 - IV administration is needed when rapid anticoagulation is required.
 - A weight-based IV bolus dose followed by a continuous **IV infusion** is preferred
- Intramuscular administration is discouraged
 - because absorption is erratic and it may cause large hematomas.

Cont...

- The **activated partial thromboplastin time (aPTT)** should be measured
 - prior to initiation of therapy then no sooner than 6 hours after beginning the infusion or after a dose change.
 - The traditional therapeutic range is **1.5 to 2.5 times** the mean normal control value (plasma heparin concentration of 0.3 to 0.7 units/mL)
 - aPTT is usually between **20-35 seconds** though it varies based on reagent

Cont...

- The **dose** of heparin should be **adjusted** promptly based on
 - patient's response and
 - institution-specific therapeutic range
- Once the target aPTT is achieved,
 - **daily monitoring** is indicated for minor dosing adjustments

Cont...

- **Bleeding** is the primary adverse effect associated with UFH.
 - The most common bleeding sites are
 - GI tract, urinary tract and soft tissues
 - Critical areas include
 - intracranial, pericardial and intraocular sites as well as the adrenal glands

Cont...

- **Symptoms of bleeding** may include
 - severe headache, joint pain, chest pain, abdominal pain
 - swelling
 - tarry stools
 - Hematuria or the passing of bright red blood through the rectum
- If **major bleeding** occurs,
 - UFH should be discontinued immediately and
 - IV **protamine sulfate** should be given by **slow IV infusion over 10 minutes**
 - 1mg/100 units of UFH administered in the previous 4 hours;
maximum 50 mg

Cont...

- **Thrombocytopenia** (platelet count $<150,000/\text{mm}^3$) is common and two distinct types can occur:
 - **Heparin-associated thrombocytopenia (Type I)**
 - is a benign, transient and mild phenomenon that usually occurs **within the first few days** of treatment.
 - Platelet counts rarely drop below $100,000/\text{mm}^3$ and recover with continued therapy.

Cont...

- **Heparin-induced thrombocytopenia (HIT) (Type II)**
 - Less common and more serious
 - is a serious **immune-mediated** problem that requires immediate intervention.
 - For patients receiving therapeutic UFH doses,
 - a baseline platelet count should be obtained before therapy is initiated and
 - then every-other-day for 14 days or until therapy is stopped, whichever occurs first.

Cont...

- HIT should be suspected if a patient develops a thromboembolic event (e.g., DVT, PE, stroke, myocardial infarction, limb artery occlusion) during or soon after receiving UFH.
- The platelet count invariably drops by more than 50% from baseline and is typically less than 150,000/mm³

Cont...

- Platelet counts typically begin to fall
 - after 5 to 10 days of UFH therapy but
 - may drop sooner if the patient has received UFH in the past 3 months.
- Laboratory testing to detect **heparin antibodies** (PF-4) must be performed to confirm the diagnosis of HIT.
- All sources of heparin (including heparin flushes) should be discontinued immediately and an alternative anticoagulant should be initiated.

Cont...

- Anticoagulants that rapidly inhibit thrombin activity and are **devoid of** significant cross-reactivity with heparin antibodies are **the drugs of choice**.
- The direct thrombin inhibitors **lepirudin** and **argatroban** are FDA approved for this use

Cont...

- Hypersensitivity reactions involving chills, fever, urticaria, and rarely bronchospasm, nausea, vomiting, and shock have been reported in patients with HIT.
- Long-term UFH has been reported to cause alopecia, priapism, hyperkalemia and osteoporosis.

Weight-Based^a Dosing for Unfractionated Heparin Administered by Continuous IV Infusion

Indication

Deep venous thrombosis/pulmonary embolism

Initial Loading Dose

80–100 units/kg

Maximum = 10,000
units

Initial Infusion Rate

17–20 units/kg/hour

Maximum = 2,300
units/hour

Maintenance Infusion Rate

Activated Partial Thromboplastin Time (seconds)

<37 (or >12 seconds below institution-specific therapeutic range)

37–47 (or 1–12 seconds below institution-specific therapeutic range)

48–71 (within institution-specific therapeutic range)

72–93 (or 1–22 seconds above institution-specific therapeutic range)

>93 (or >22 seconds above institution-specific therapeutic range)

Dose Adjustment

80 units/kg bolus then increase infusion by 4 units/kg/hour

40 units/kg bolus then increase infusion by 2 units/kg/hour

No change

Decrease infusion by 2 units/kg/hour

Hold infusion for 1 hour then decrease by 3 units/kg/hour

^aUse actual body weight for all calculations. Adjusted body weight may be used for obese patients (>130% of ideal body weight).

Low-molecular-weight Heparins

- **LMWHs** are fragments of UFH with approximately one-third the molecular weight of UFH.
- Like UFH, the LMWHs
 - enhance and accelerate the activity of **antithrombin** and prevent the growth and propagation of formed thrombi.
- Advantages of LMWHs over UFH include:
 - more predictable anticoagulation dose response
 - improved SC bioavailability
 - dose-independent clearance
 - longer biologic half-life
 - lower incidence of thrombocytopenia and
 - less need for routine laboratory monitoring

Cont...

- The peak anticoagulant effect is seen in **3 to 5 hours** after SC dosing.
- The recommended doses (based on actual body weight) for treatment of DVT with or without PE are:
 - **Enoxaparin** (Lovenox)
 - 1 mg/kg every 12 hours or 1.5 mg/kg every 24 hours
 - **Dalteparin** (Fragmin)
 - 100 units/kg every 12 hours or 200 units/kg every 24 hours
 - **Tinzaparin** (Innohep)
 - 175 units/kg every 24 hours

Cont...

- Because the LMWHs achieve **predictable anticoagulant response** when given subcutaneously, routine laboratory monitoring is unnecessary to guide dosing.
 - The PT and aPTT are minimally affected by LMWH.
 - Prior to the initiation of therapy, a baseline PT/INR, aPTT, CBC with platelet count and SCr should be obtained.
 - Periodic monitoring of the CBC and platelet counts and occult fecal blood is recommended during therapy

Cont...

- As with UFH, **bleeding** is the most common adverse effect of the LMWHs, but major bleeding may be less common than with UFH.
- Minor bleeding occurs frequently, particularly at the site of injection.
- If major bleeding occurs, **protamine sulfate** should be administered IV, although it cannot neutralize the anticoagulant effect completely.

Cont...

- The recommended dose of protamine sulfate is
 - 1 mg per 1 mg of enoxaparin or
 - 1 mg per 100 antifactor Xa units of dalteparin or tinzaparin administered in the previous 8 hours.
- If the LMWH dose was given in the previous 8 to 12 hours,
 - the protamine sulfate dose is 0.5 mg per 100 antifactor Xa units.
 - Protamine sulfate is not recommended if the LMWH was given more than 12 hours earlier.

Fondaparinux

- Fondaparinux sodium (Arixtra) is a **selective inhibitor of factor Xa**.
- Similar to UFH and the LMWHs, it binds to **antithrombin**, greatly accelerating its activity.
- However, it has no direct effect on thrombin activity at therapeutic plasma concentrations.

Cont...

- It is approved for
 - prevention of VTE in patients undergoing orthopedic (hip fracture, hip and knee replacement) surgery and
 - for treatment of VTE
- For VTE prevention, the dose is
 - 2.5 mg subcutaneously once daily starting 6 to 8 hours after surgery.
- For treatment of DVT and PE, the usual dose is
 - 7.5 mg subcutaneously once daily.

Cont...

- A CBC should be measured at baseline and periodically thereafter to detect **occult bleeding**.
- Signs and symptoms of bleeding should be monitored daily.
- Patients receiving fondaparinux do not require routine coagulation testing.

Direct Thrombin Inhibitors

- These agents interact directly with thrombin and do not require anti-thrombin to have antithrombotic activity.
- They are capable of inhibiting both circulating and clot-bound thrombin, which is a potential advantage over UFH and the LMWHs.
- They also **do not induce immune-mediated thrombocytopenia** and are widely used for the treatment of HIT

Cont...

Lepirudin (Refludan)

- is indicated for anticoagulation in patients with HIT and associated thrombosis to prevent further thromboembolic complications.
- The recommended dose is
 - 0.4 mg/kg as an IV bolus over 15 to 20 seconds, followed by
 - a 0.15-mg/kg/hour continuous IV infusion for 2 to 10 days or longer if clinically needed.
- After obtaining a baseline aPTT, an aPTT should be obtained at least 4 hours after starting the infusion and then at least daily thereafter.

Cont...

- The dose should be titrated to achieve an aPTT 1.5 to 2.5 times control.
- Dose adjustment is required in patients with impaired renal function.
- Many patients develop **antibodies** to lepirudin, which **may increase its anticoagulant effect**;
 - close monitoring of aPTT is necessary during prolonged therapy.
- Because fatal anaphylaxis has been reported in patients who developed antibodies,
 - patients should not be treated with lepirudin more than once.

Cont...

Bivalirudin (Angiomax)

- has several indications:
 - used as an anticoagulant in patients with unstable angina undergoing PCI
 - with provisional use of glycoprotein IIb/IIIa inhibitor for use as an anticoagulant in patients undergoing PCI
 - for patients with (or at risk of) HIT undergoing PCI.

Cont...

- For PCI, the recommended dose is an IV bolus of
 - 0.75 mg/kg followed by a continuous infusion of
 - 1.75 mg/kg/hour for the duration of the PCI procedure.
- Bivalirudin is intended for use with aspirin 300 to 325 mg/day.
- The **activated clotting time** is used to monitor the anticoagulant effect of bivalirudin.

Cont...

- **Argatroban** has two indications:
 - prevention or treatment of thrombosis in patients with HIT and as an anticoagulant in patients with HIT, or at risk of HIT, who are undergoing PCI.
 - The recommended dose for the treatment of HIT is 2 mcg/kg/min by continuous IV infusion.
 - The first aPTT should be obtained 2 hours after initiation.
 - The dose can be adjusted as clinically indicated (maximum 10 mcg/kg/min) until the aPTT is **1.5 to 3 times control**

Cont...

- **Desirudin (Iprivask)**

- is approved for prevention of DVT in patients undergoing elective hip replacement surgery
- The recommended dose is 15 mg subcutaneously every 12 hours beginning 5 to 15 minutes prior to surgery and for up to 12 days thereafter.
- Daily aPTT monitoring is recommended.

Cont...

- Contraindications are similar to those of other antithrombotic drugs, and **hemorrhage** is the most common and serious adverse effect.
- For all agents in this class, a CBC should be obtained at baseline and periodically thereafter to detect potential bleeding.
- There are **no known agents** that reverse the activity of direct thrombin inhibitors.

Warfarin

- Warfarin inhibits the enzymes responsible for the cyclic inter conversion of vitamin K in the liver.
- Reduced vitamin K is a cofactor required for the carboxylation of
 - the vitamin K–dependent coagulation proteins prothrombin (II); factors VII, IX, and X; and the endogenous anticoagulant proteins C and S.

Cont...

- By reducing the supply of vitamin K available to serve as a cofactor in the production of these proteins, warfarin indirectly slows their rate of synthesis.
- By suppressing the production of clotting factors, warfarin prevents the initial formation and propagation of thrombi.
- Warfarin has no direct effect on previously circulating clotting factors or previously formed thrombi.

Cont...

- The time required to achieve its anticoagulant effect depends on the **elimination half-lives of the coagulation proteins.**
- Because prothrombin has a **2-3 day half-life**,
 - warfarin's full antithrombotic effect is not achieved for 8 to 15 days after initiation of therapy

Cont...

- Warfarin should begin concurrently with UFH or LMWH therapy.
- For patients with acute VTE, heparin and warfarin therapy should be over-lapped
 - for at least **4 to 5 days**, regardless of whether the target INR has been achieved earlier.
 - The UFH or LMWH can then be discontinued once the INR is within the desired range for **2 consecutive days**.

Cont...

- The usual initial dose is **5 to 10 mg**.
 - In older patients (**age >60 years**) and those taking potentially **interacting medications**, a starting dose of **2.5 mg** should be considered
- Warfarin therapy is monitored by the INR (target: 2 to 3 for DVT or PE).
 - After an acute thromboembolic event, the INR should be measured minimally **every 3 days** during the first week of therapy.

Cont...

- In general, dose changes should not be made more frequently than every 3 days.
- Doses should be adjusted by calculating the weekly dose and reducing or increasing it by **5% to 25%**.
- The effect of a small dose change may not become evident for 5 to 7 days.
- Once the patient's dose response is established, an INR should be determined every 7 to 14 days until it stabilizes and then every 4 weeks thereafter.

Cont...

- If the initial thrombotic event was associated with hospitalization
 - only **3 months** of oral anticoagulation is warranted.
- For VTE associated within 6 weeks of starting estrogen therapy
 - 3 months is reasonable but some experts prefer 6 months of treatment.

Cont...

- Patients with unprovoked (idiopathic) VTE have a high recurrence rate and
 - should be considered for **indefinite** oral anticoagulation if possible, but should receive at least 6 to 12 months of therapy.
- For patients with recurrent VTE events or one of the thrombophilias known to impart a high lifetime risk of thrombosis
 - **indefinite** or lifelong anticoagulation should be considered

Cont...

- **Bleeding risk**

- Hemorrhagic complications ranging from mild to severe and life-threatening can occur at any body site.
- The **GI tract** is the most frequent site of bleeding.
- Bruising on the arms and legs is common, but a painful hematoma may necessitate **temporary discontinuation of therapy**.
- **Intracranial hemorrhage** is the most serious complication and often results in permanent disability and death.

Cont...

- Patients with a mildly elevated INR (3.5 to 5) and no signs or symptoms of bleeding can usually be managed by
 - either reducing the dose or holding one or two warfarin doses.
- If **rapid reduction of an elevated INR** is required,
 - oral or IV administration of **vitamin K1 (phytonadione)** can be given.
 - Oral administration is preferable in the absence of major bleeding.
 - The IV route produces the most rapid reversal of anticoagulation, but it has been associated with **anaphylactoid reactions**.

Cont...

- If the INR is 5 to 9,
 - warfarin doses may be withheld or may be combined with oral phytonadione 1 to 5 mg.
- If the INR is greater than 9,
 - a 5-mg oral dose of phytonadione is recommended.
 - Low vitamin K doses reduce the INR consistently within 24 hours without making the patient refractory to warfarin.
 - In the event of serious or life-threatening bleeding, IV vitamin K should be administered together with fresh-frozen plasma, clotting factor concentrates, or recombinant factor VII.

Cont...

- Non-hemorrhagic adverse effects include the rare “purple toe syndrome” and skin necrosis.
- Absolute contraindications to warfarin include
 - active bleeding
 - hemorrhagic tendencies
 - Pregnancy and
 - a history of warfarin-induced skin necrosis.

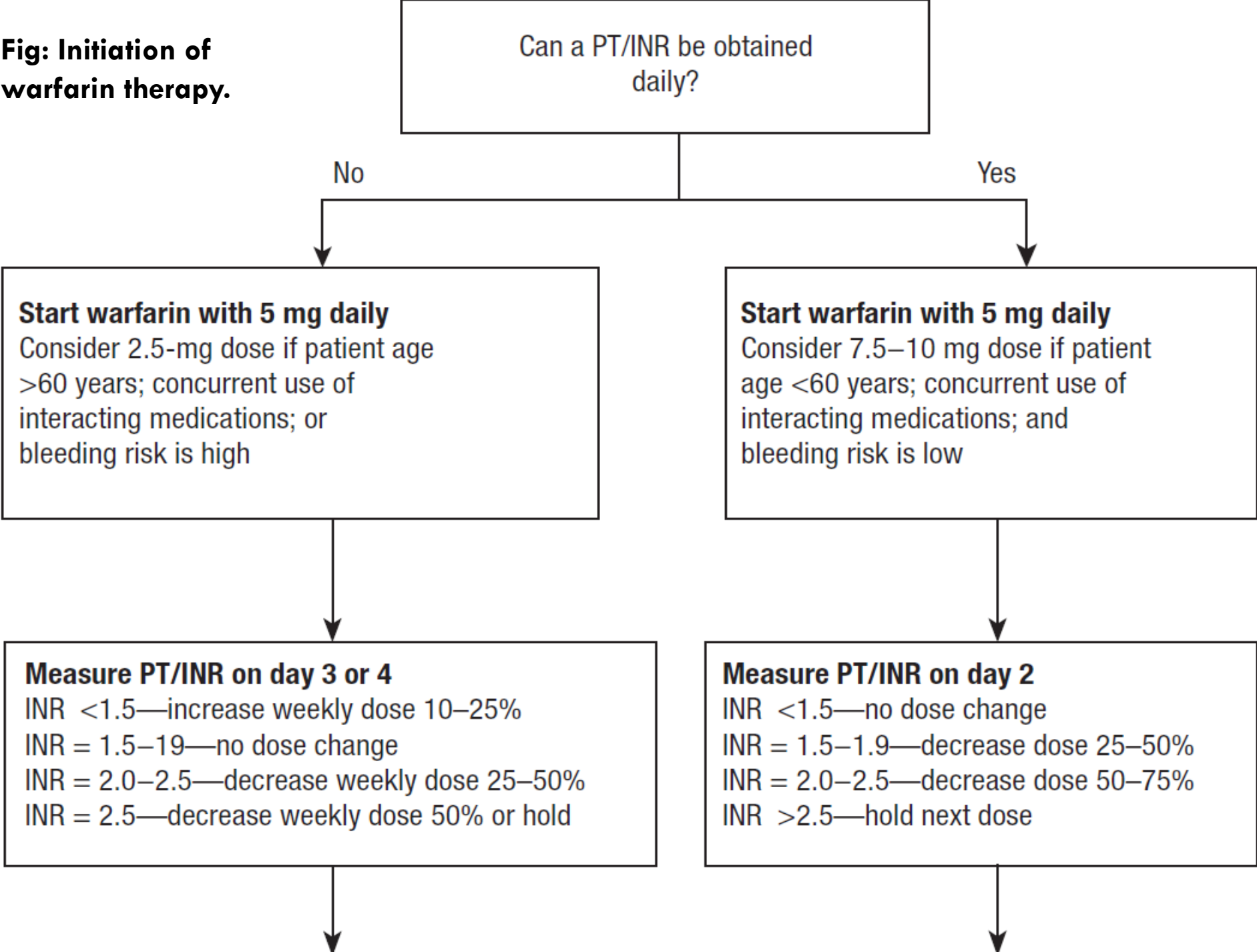
Cont...

- It should be used with great caution in patients with
 - a history of GI bleeding
 - recent neurosurgery
 - alcoholic liver disease
 - severe renal impairment, or inability to keep follow-up appointments for monitoring.

Cont...

- Because of the large number of food–drug and drug–drug interactions with warfarin, **close monitoring** and **additional INR determinations** may be indicated whenever
 - other medications are initiated or discontinued or
 - an alteration in consumption of vitamin K–containing foods is noted.

Fig: Initiation of warfarin therapy.



↓

Measure PT/INR on days 5–7

INR <1.5—increase weekly dose 10–25%
INR = 1.5–1.9—increase weekly dose 0–20%
INR = 2.0–3.0—no dose change
INR >3.0—decrease weekly dose 10–25%
or hold

↓

Measure PT/INR on days 8–10

INR <1.5—increase weekly dose 15–35%
INR = 1.5–1.9—increase weekly dose 5–20%
INR = 2.0–3.0—no dose change
INR >3.0—decrease weekly dose 10–25%
or hold

↓

Measure PT/INR on days 11–14

INR <1.6—increase weekly dose 15–35%
INR = 1.6–1.9—increase dose 5–20%
INR = 2.0–3.0—no dose change
INR >3.0—decrease weekly dose 5–20%
or hold

↓

Measure PT/INR on day 3

INR <1.5—increase dose 0–25%
INR = 1.5–1.9—no dose change
INR = 2.0–2.5—decrease dose 25–50%
INR = 2.5—decrease 50% or hold
next dose

↓

Measure PT/INR on day 4

INR <1.5—increase dose 0–25%
INR = 1.5–1.9—no dose change or
increase 10–25%
INR = 2.0–3.0—decrease dose 0–25%
INR >3.0—decrease 50% or hold
next dose

↓

Measure PT/INR on day 5

INR <1.5—increase dose 25%
INR = 1.5–1.9—increase dose 0–25%
INR = 2.0–3.0—no dose change or
decrease dose 10–25%
INR >3.0—decrease 25–50%

Is the patient experiencing signs or symptoms of bleeding? *OR*
Is rapid reversal of excessive anticoagulation required?

Yes

No

**Fig: Management
of an elevated
INR in patients
taking warfarin.**

Determine the site and severity of
bleeding.

Administer vitamin K 10 mg via slow
IV infusion, along with fresh-frozen
plasma, rFVII, or prothrombin complex
as needed. Check INR in 12 hours
and repeat vitamin K infusion as
needed until INR normalized or within
therapeutic range.

What is the INR
value?

Above therapeutic
range but <5.0

5.0–9.0

>9.0

Omit next 1–2 doses of
warfarin. Check INR in 3–7 days.
Restart warfarin at reduced dose.

Does the patient have risk
factors for bleeding?

Yes

No

Omit next 1–3 doses of
warfarin
and
administer vitamin K
2.5 mg orally. Check INR
every 24–48 hours.
Restart at reduced dose.

Are conditions present that
increase the patient's risk of
thromboembolic
complications?

Yes

No

Omit next 1–3 doses of
warfarin. Consider
administering vitamin K 2.5 mg orally if
INR >8.0. Avoid using higher doses
(5–10 mg) of vitamin K. Check INR every
24–48 hours. Restart at reduced
dose once therapeutic.

Omit next 1–3 doses of
warfarin
and
administer vitamin K 2.5–5 mg
orally and check INR every
24–48 hours. Restart at reduced
dose once therapeutic.

Omit next 1–3 doses of
warfarin
and
Administer vitamin K
5–10 mg orally.
Check INR in 12–24 hours.
If INR still elevated
above 9, repeat
administration of
vitamin K.
Check INR every 24 hours.
Restart warfarin at
reduced dose once
therapeutic.

Cont...

- Conditions that increase the risk of **thromboembolic complications** include
 - history of hypercoagulability disorders
 - (e.g., protein C or S deficiency, presence of antiphospholipid antibodies, antithrombin deficiency, activated protein C resistance),
 - arterial or venous thrombosis within the previous month
 - thromboembolism associated with malignancy and
 - mechanical mitral valve in conjunction with atrial fibrillation
 - previous stroke
 - poor ventricular function or
 - coexisting mechanical aortic valve.

Thrombolysis And Thrombectomy

- Thrombolytic agents are proteolytic enzymes
 - that enhance the conversion of plasminogen to plasmin, which subsequently degrades the fibrin matrix.
- In the management of PE, thrombolytics
 - restore pulmonary artery patency more rapidly when compared to UFH alone,
 - but this early benefit does not improve long-term patient outcomes.

Cont...

- Thrombolytic therapy has not been shown to improve morbidity or mortality and is associated with a **substantial risk of hemorrhage**.
- For these reasons, thrombolytics should be reserved for patients with PE who are most likely to benefit
 - those who present with shock
 - Hypotension
 - right ventricular strain or
 - massive DVT with limb gangrene

Cont...

- Three thrombolytic agents and regimens are available for treatment of DVT and/or PE:
- **Streptokinase** (Streptase):
 - 250,000 units IV over 30 minutes followed by a continuous IV infusion of 100,000 units/hour for 24 hours (PE) or 24 to 72 hours (DVT).

Cont...

- **Urokinase (Abbokinase):**
 - For PE, 4,400 international units/kg IV over 10 minutes followed by 4,400 international units/kg/hour for 12 to 24 hours.
- **Alteplase (Activase):**
 - For PE, 100 mg by IV infusion over 2 hours.

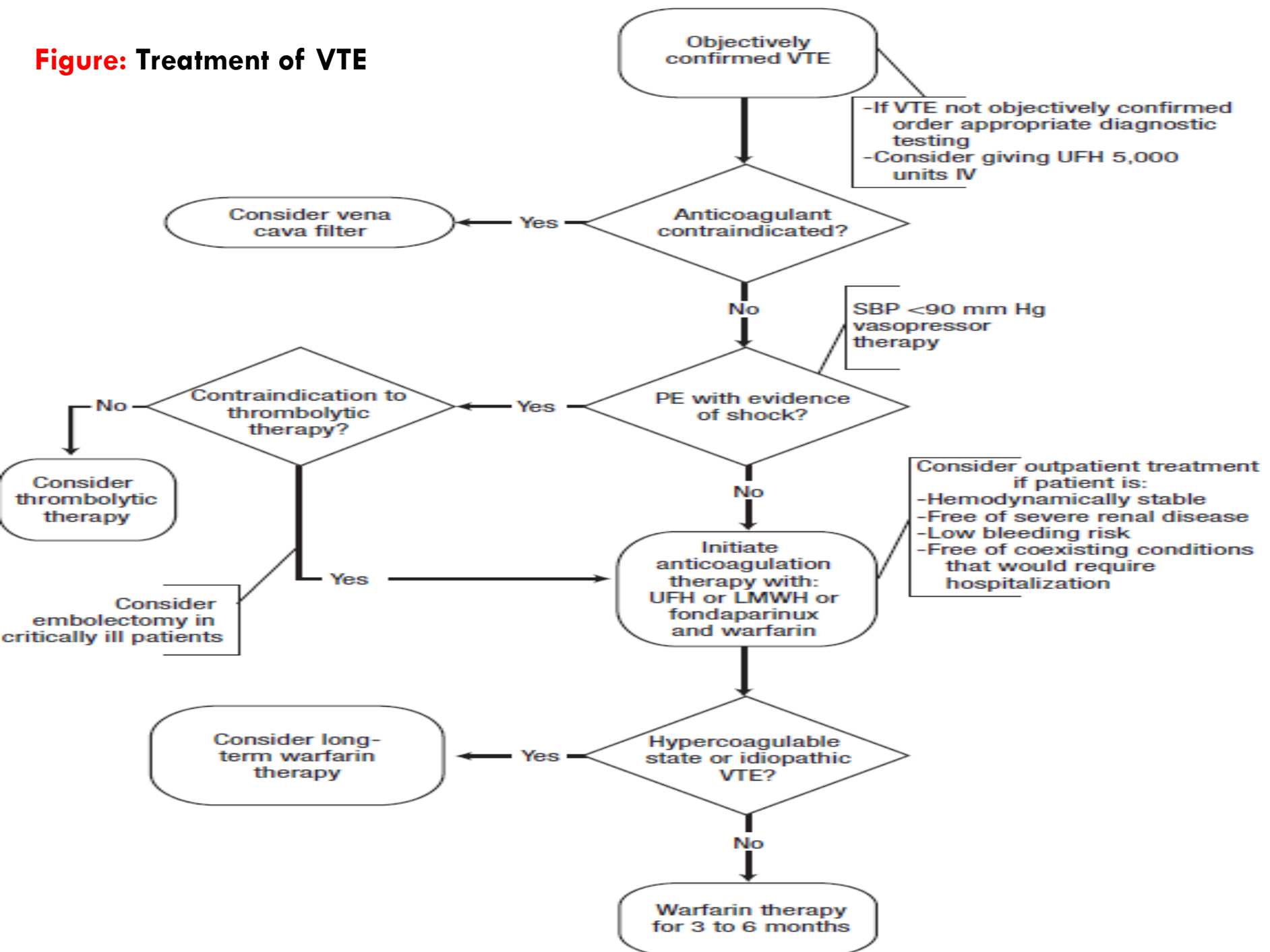
Cont...

- **UFH should not be used** during thrombolytic therapy.
- The aPTT should be measured after the completion of thrombolytic therapy.
 - If the aPTT at that time is <2.5 times control, a UFH infusion should be started and adjusted to maintain the aPTT in the therapeutic range.
 - If the post-treatment aPTT is >2.5 times control, it should be re-measured every 2 to 4 hours and
 - a UFH infusion started when the aPTT is <2.5 times control.

Cont...

- Venous **thrombectomy** may be performed to remove a **massive obstructive thrombus** in a patient with significant iliofemoral venous thrombosis,
 - particularly if the patient is either not a candidate for or has not responded to thrombolysis.
 - Full-dose anticoagulation therapy is essential during the entire operative and postoperative period.
 - These patients need indefinite oral anticoagulation therapy targeted to an INR of 2.5 (range 2.0 to 3.0).

Figure: Treatment of VTE



Consensus Guidelines for Venous Thromboembolism Treatment

	Recommendation	Grade ^a
Acute anticoagulation	Acute treatment of DVT or PE should be with LMWH, fondaparinux, intravenous UFH, or adjusted-dose subcutaneous UFH	1A
	The dose of UFH should be sufficient to prolong the aPTT to a range that corresponds to a plasma heparin level of 0.2 to 0.4 international units/mL by protamine titration or an anti-Xa level of 0.3 to 0.6 international units/mL	1C+
	LMWH and fondaparinux are preferred over UFH	2B
Duration of acute treatment	An LMWH is preferred in patients with cancer	1A
	Treatment with UFH, LMWH, or fondaparinux should be overlapped with warfarin for at least 5 days and can be stopped when the INR is >2.0; most patients should have warfarin started at the same time as UFH, LMWH, or fondaparinux	1A
	Patients with cancer should be treated with an LMWH for at least 6 months	1A
	A longer period of heparin therapy (approximately 10 days) is recommended for massive PE or severe iliofemoral thrombosis	1C
Long-term anticoagulation	Oral anticoagulation therapy (target INR 2.5, range: 2.0 to 3.0) should be continued for at least 3 months; if oral anticoagulation therapy is contraindicated (e.g., pregnancy), a treatment dose of LMWH or adjusted-dose UFH should be used	1A
	Patients with an idiopathic VTE, an inherited disorder of hypercoagulability, or antiphospholipid antibodies should be treated indefinitely (at least 2.5 years)	1A
	Patients with continuing risk factors (e.g., malignancy, immobility) should be treated for <i>at least</i> 12 months	1C

Prevention Of VTE

- Non-pharmacologic methods improve venous blood flow by mechanical means and include
 - early ambulation
 - electrical stimulation of calf muscles during prolonged surgery
 - graduated compression stockings (GCS)
 - intermittent pneumatic compression (IPC) devices and
 - inferior vena cava filters (IVF)

Cont...

- Pharmacologic techniques counteract the propensity for thrombosis formation by dampening the coagulation cascade.
- Appropriately selected therapy can dramatically reduce the incidence of VTE after
 - hip or knee replacement
 - general surgery
 - myocardial infarction and
 - ischemic stroke.

Cont...

- The LMWHs and fondaparinux provide superior protection against VTE compared with **low-dose** UFH.
- Even so, UFH is a highly effective, cost-conscious choice for many patients, provided that it is given in the appropriate dose.
- **Adjusted-dose SC** UFH with doses adjusted to maintain the aPTT at high-normal is more effective than low-dose UFH in
 - the highest risk patients (hip and knee replacement surgery).

Cont...

- There is no evidence that one LMWH is superior to another for the prevention of VTE.
- Warfarin is commonly used for VTE prevention after **orthopedic** surgeries of the lower extremities,
 - but evidence is equivocal regarding its relative effectiveness compared to LMWH for preventing clinically important VTE events in the highest risk populations.

Cont...

- Prophylaxis should be **continued throughout the period of risk.**
- For general surgical procedures and medical conditions,
 - prophylaxis can be discontinued once the patient is able to ambulate regularly and other risk factors are no longer present.
- Most clinical trials support the use of antithrombotic therapy for
 - **21 to 35 days** after total hip replacement and hip fracture repair surgeries.

Level of Risk**Low**

Minor surgery, age <40 years, and no clinical risk factors

Moderate

Major or minor surgery, age 40–60 years, and no clinical risk factors

Major surgery, age <40 years and no clinical risk factors

Minor surgery, with clinical risk factor(s)

Acutely ill (e.g., MI, ischemic stroke, CHF exacerbation), and no clinical risk factors

High

Major surgery, age >60 years, and no clinical risk factors

Major surgery, age 40–60 years, with clinical risk factor(s)

Acutely ill (e.g., MI, ischemic stroke, CHF exacerbation), with risk factor(s)

Highest

Major lower extremity orthopedic surgery

Hip fracture

Multiple trauma

Major surgery, age >40 years, and prior history of VTE

Major surgery, age >40 years, and malignancy

Major surgery, age >40 years, and hypercoagulable state

Spinal cord injury or stroke with limb paralysis

Prevention Strategies

Ambulation

UFH 5,000 units SC q 12 h

Dalteparin 2,500 units SC q 24 h

Enoxaparin 40 mg SC q 24 h

Tinzaparin 3,500 units SC q 24 h

IPC

Graduated compression stockings

UFH 5,000 units SC q 8 h

Dalteparin 5,000 units SC q 24 h

Enoxaparin 40 mg SC q 24 h

Fondaparinux 2.5 mg SC q 24 h

Tinzaparin 75 units/kg SC q 24 h

IPC

Adjusted dose UFH SC q 8 h (aPTT >36 seconds)

Dalteparin 5,000 units SC q 24 h

Desirudin 15 mg SC q 12 h

Enoxaparin 30 mg SC q 12 h

Fondaparinux 2.5 mg SC q 24 h

Tinzaparin 75 units/kg SC q 24 h

Warfarin (INR = 2.0–3.0)

IPC with UFH 5,000 units SC q 8 h

Evaluation of Therapeutic Outcomes

- Patients should be monitored for
 - resolution of symptoms
 - the development of recurrent thrombosis and
 - symptoms of the postthrombotic syndrome
 - adverse effects from the treatments
 - Hemoglobin, hematocrit, and blood pressure should be monitored carefully to detect bleeding from anticoagulant therapy.

Cont...

- Coagulation tests (aPTT, PT, INR) should be performed
 - prior to initiating therapy to establish the patient's baseline values and guide later anticoagulation.
- Outpatients taking warfarin should be questioned about
 - medication adherence and symptoms related to bleeding and thromboembolic complications.
- Any changes in concurrent medications should be carefully explored.

Case Study#1

Mr. Jones develops an objectively confirmed deep vein thrombosis (DVT) while receiving unfractionated heparin (UFH) for venous thromboembolism (VTE) prophylaxis for the past 7 days. The patient's platelet count has dropped by 50% and is less than 100,000; therefore, heparin-induced thrombocytopenia is strongly suspected. Mr. Jones is 5 foot 11 inches tall and weighs 100 kg. Which of the following strategies would be the most appropriate in the initial management for Mr. Jones?

- A. Stop heparin and start warfarin 5mg orally every day
- B. Stop heparin and start enoxaparin 100 mg SC q 12 h
- C. Stop heparin and start argatroban 200 mcg/min via intravenous infusion
- D. Stop heparin therapy and wait for results of laboratory tests to confirm diagnosis before making a treatment decision

Case #2

Ms. Smith is a 67-year-old female who has had recurrent DVT and has been taking warfarin for the past 3 years. Her last six INR values have been within her goal range. Today, the patient's INR is 1.2. Which of the following would be the most likely explanation?

- A. Ms. Smith inadvertently took an extra dose of warfarin last night.
- B. Ms. Smith drank tomato and carrot juice for breakfast this morning.
- C. Ms. Smith ate spinach and basil pesto fettuccini for dinner last night.
- D. Ms. Smith finished a 10-day course of sulfamethoxazole/trimethoprim (SMZ/TMP) for a urinary tract infection yesterday.

