Hypercoagulable state/Thrombosis
(DVT/Pulmonary Embolism)

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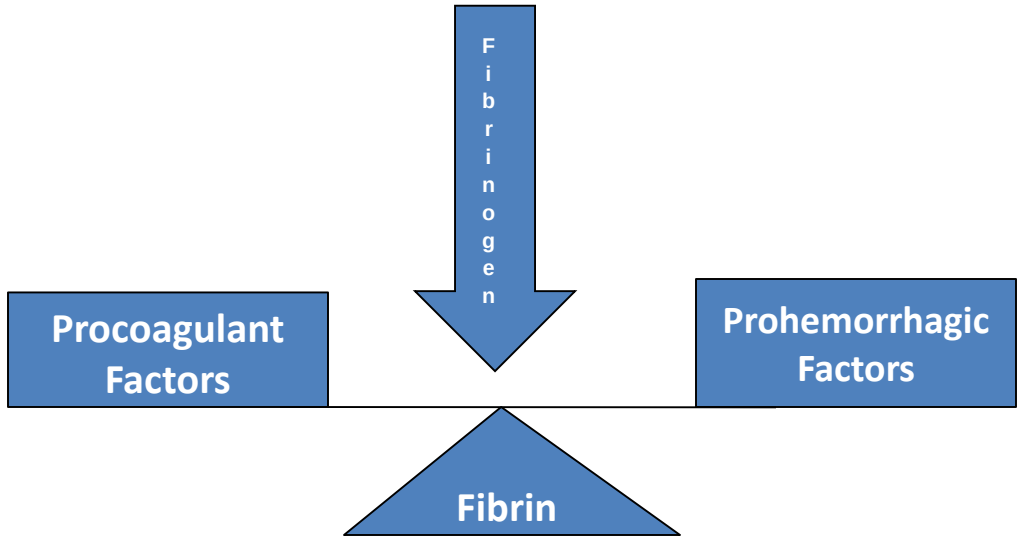
Objectives of presentation

- Definition
- Physiology of Hemostatic system
- Etiology of thrombosis (venous)
- Inherited thrombotic conditions
- Acquired thrombotic condition
- Clinical manifestations and diagnosis of thrombosis
- Treatment of thrombosis

Hypercoagulable state (Thrombophilia)

- Definition: Hypercoagulable state/Thrombophilia is characterized by clinical tendency to thrombosis or molecular abnormalities of hemostasis that predisposes to thromboembolic disease.
- Alteration in the hemostatic balance between blood fluidity and clot formation due to genetic or acquired disorders, which shift the balance toward excessive clot formation that lead to thrombosis.

Balance of Hemostasis



- Balance of bleeding and clotting
- *Imbalance in one direction can lead to:

Hypocoagulable state → bleeding OR

Hypercoagulable state → thrombosis

Synonyms:

- Hypercoagulable state
- Prothrombotic state
- Thrombophilia
- Thrombogenic state

- Inherited Thrombophilia

  Inherited thrombophilia is a genetic/inherited tendency to venous thromboembolism.
- Acquired thrombophilia

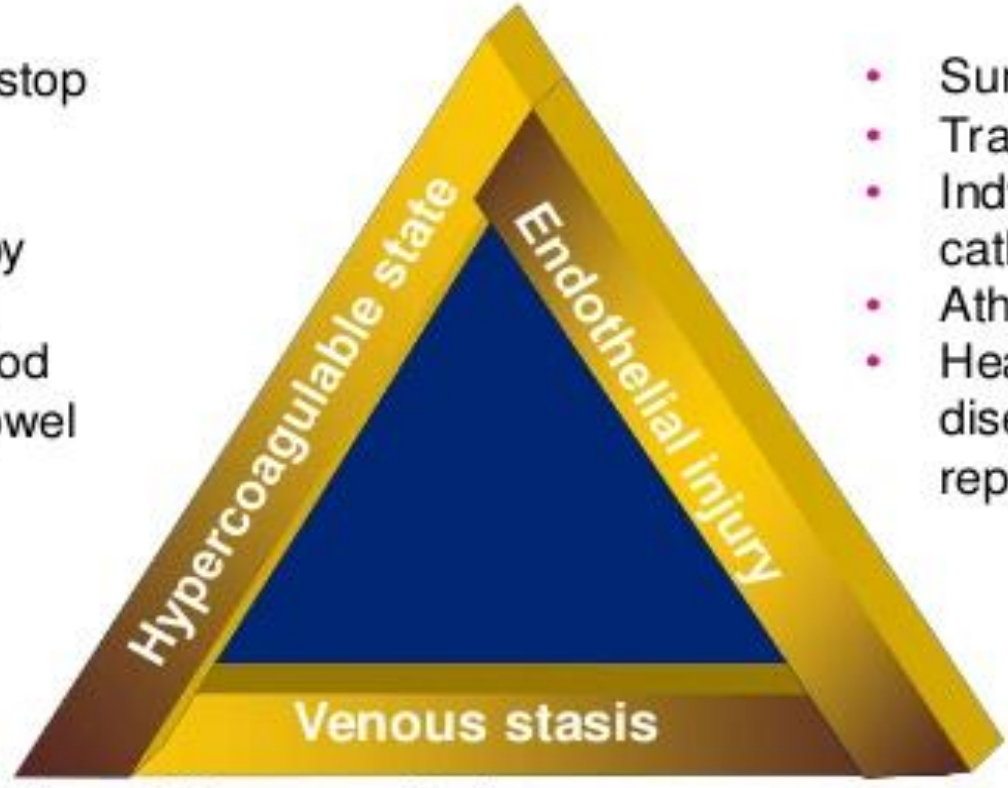
Virchow's Triad

Rudolf Virchow, 1821-1902

- **Virchow's triad**
  - **Alterations in blood flow (i.e., stasis)**
    - **Disrupted laminar flow allows greater interaction between platelets and endothelial surface**
    - **Prevents dilution of locally activated clotting factors**
    - **Prevents inflow of clotting factor inhibitors**
    - **Promotes endothelial cell damage and activation**
  - **Vascular endothelial injury**
    - **Causes exposure of sub-endothelium and release of tissue factor, thereby activating coagulation cascade**
  - **Alterations in constituents of blood (i.e., hypercoagulability)**
    - **Acquired vs inherited coagulopathies**
    - **Predisposing factors for thrombus formation**

Virchow's triad

- Acute phase postop
- Cancer
- Thrombophilia
- Estrogen therapy
- Pregnancy and postpartum period
- Inflammatory bowel disease



- Surgery
- Trauma
- Indwelling catheter
- Atherosclerosis
- Heart valve disease or replacement

- Immobility or paralysis
- Heart failure
- Venous insufficiency or varicose veins
- Venous obstruction from tumour, obesity or pregnancy

Virchow R, ed. *Gesammelte Abhandlungun zur Wissenschaftichen Medicin.* Von Meidinger Sohn, Frankfurt, 1856.

Venous Thromboembolism (VTE) is a Major Source of Mortality and Morbidity

- 350,000 to 650,000 cases of VTE per year in USA
- 100,000 to > 200,000 deaths per year
- About half are hospital related
- The annual death rate due to VTE is
  - More than HIV, RTAs, Breast Ca *combined*

- VTE causes ~10% of hospital deaths
  - PE among top causes of preventable hospital related deaths
- Huge costs and morbidity (recurrence, post-thrombotic syndrome, chronic PAH, anticoagulation)

Surgeon General's Call to Action to Prevent DVT and PE 2008 DHHS

Causes of venous thrombo-embolism

The causes of venous thrombo-embolism (VTE) can be divided into two groups:

- Inherited conditions
- Acquired conditions

and are often multiple in a given patient.

Prothrombotic states

- **Inherited risk factors**
  - Factor V Leiden
  - Prothrombin gene mutation 20210A
  - Protein S deficiency
  - Protein C deficiency
  - Antithrombin deficiency
  - Hyperhomocysteinemia
- As a group, the inherited thrombophilias have a prevalence of around 10-50%
- Total incidence of an inherited thrombophilia in subjects with DVT range from 24 – 50%

Factor V Leiden

- Discovered in Leiden, the Netherlands (1993) amongst a group of subjects with unexplained VTE

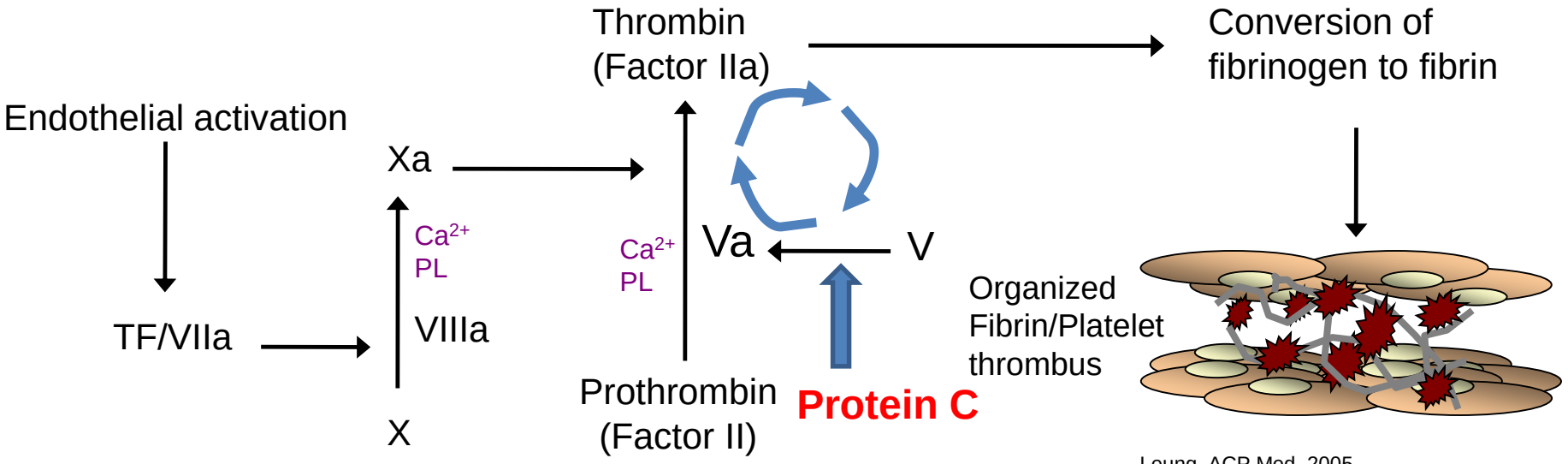
Mutant Leiden gene product is not susceptible to cleavage by APC

- The presence of point mutation **G-->A of nucleotide 1691** of Factor V gene (Leiden mutation) is responsible for the resistance of factor Va to activated protein C degradation (APC-resistance) and is associated with an increased risk for thrombosis.

Leung. ACP Med, 2005.

Factor V Leiden

- Factor V Leiden (=Factor V mutation → **activated protein C resistance**)
  - Most common form of inherited thrombophilia (~50% of cases)



Leung. ACP Med, 2005..

Protein C & S deficiency

- Protein C and S
  - Inhibit activated cofactors Va and VIIIa, respectively

- Protein C & S deficiency:
  - Inherited or acquired
  - Heterozygous or homozygous,
  - Clinical expression of hypercoagulability variable, and does not necessarily correspond with absolute concentration of Protein C

  Protein C levels can be low in vitamin K deficiency, DIC (consumed), liver disease, etc

- **Acquired Protein S deficiency may be induced by OCPs, pregnancy, or nephrotic syndrome**

Leung. ACP Med, 2005..

Prothrombin gene mutation

- Normal prothrombin (Factor II) circulates as Vitamin K-dependent cofactor with ½ life of 3-5 days
- Mutation discovered in 1996 as a transition (G→A) at nucleotide 20210, resulting in elevated plasma levels of Factor II
  - Heterozygotes have a 30% higher plasma prothrombin level compared to normals
- Prothrombin G20210A mutation is the 2nd most common prothrombotic mutation (↓ thrombin inactivation)

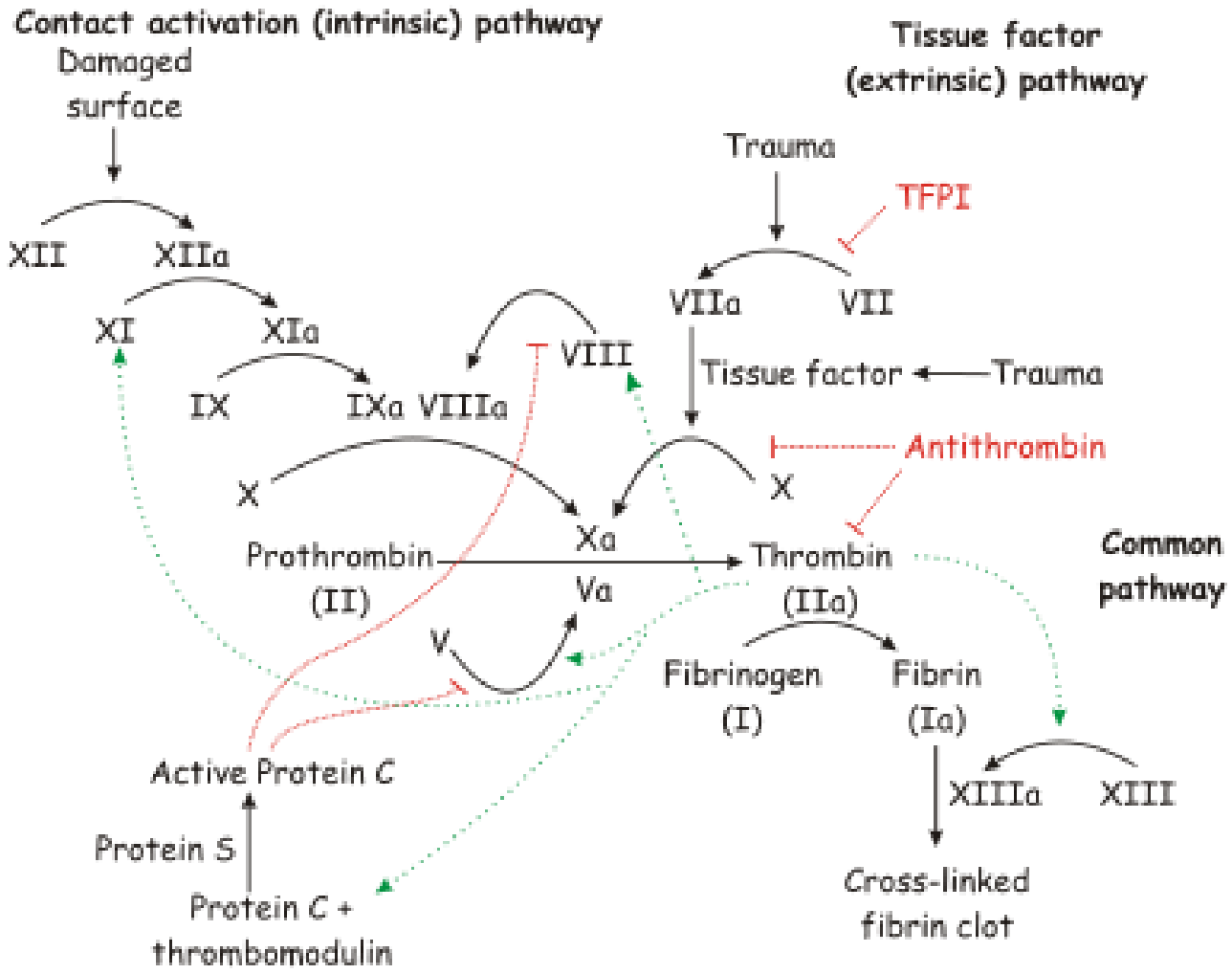
Antithrombin (AT) deficiency

- AT is a potent inhibitor of thrombin and other serine proteases of the coagulation cascade (e.g., FXa, FIXa)

- AT deficiency typically occurs in a AD inheritance pattern, thereby affecting both sexes equally
- Overall incidence of AT deficiency is low
- Females with AT deficiency are at particularly high-risk for VTE during pregnancy
  - DVT occurred in 18% of pts with AT deficiency, and in 33% in the postpartum period

Hyperhomocysteinemia

- Homocysteinuria or severe hyperhcomocysteinemia is a rare autosomal recessive disorder characterized by developmental delay, osteoporosis, ocular abnormalities, VTE, and severe premature CAD
- Less marked elevations of homoysteine are more common, occurring in 5-7% of the population, and are associated with a number of clinical factors
  - **Vitamin deficiencies** (i.e., folate, Vit B6, and/or Vit B12)
- Homocysteine has primary atherogenic and prothrombotic properties
- Meta-analyses of case-control studies have found an odds ratio of 2.5-3 for VTE in pts with homocysteine levels > 2 standard deviations above the mean value of control groups


Contact activation (intrinsic) pathway
Damaged surface
XII
XIIa
XI
XIa
IX
IXa VIIIa
VIII
X
Xa
Va
Prothrombin (II)
Thrombin (IIa)
V
Active Protein C
Protein S
Protein C + thrombomodulin
Tissue factor (extrinsic) pathway
Trauma
TFPI
VIIa
VII
Tissue factor
Trauma
Antithrombin
X
Common pathway
Fibrinogen (I)
Fibrin (Ia)
XIIIa
XIII
Cross-linked fibrin clot

Combined effect of inherited thrombophilias on tendency for VTE

- ✓ Pooled analysis of 2310 cases and 3204 controls amongst 8 case-control studies (from UK, Denmark, France, Italy, Sweden, Brazil) evaluating the risks in patients with FVL and/or prothrombin 20210A
- ✓ Of patients with VTE,
  - ✓ 23% were heterozygous for prothrombin gene mutation
  - ✓ 12% were heterozygous for Factor V Leiden
  - ✓ 2.2% were double heterozygotes

Inherited hypercoagulable state	Odds Ratio for VTE
Prothrombin gene mutation 20210A heterozygotes	3.8
Factor V Leiden mutation heterozygotes	4.9
Combined Prothrombin and Factor V Leiden heterozygotes	20.0

An odds ratio (OR) is a measure of association between an exposure and an outcome.

Emmerich et al. Thromb Haemost. 2001; 86(3):809.

- Fifty percent of thrombotic events in patients with inherited thrombophilia are associated with the additional presence of an acquired risk factor (eg, surgery, prolonged bed rest, pregnancy, oral contraceptive, etc).
- Some patients have more than one form of inherited thrombophilia or more than one form of acquired thrombophilia and appear to be at even greater risk for thrombosis.

Acquired prothrombotic States

Acquired risk factors

- **Prior thrombotic event or family H/O VTE**
- Recent major surgery
  - Especially orthopedic (hip & knee replacement)
- Immobilization
- Heart failure
- Cancer
- Trauma
- Presence of a central venous catheter
- Obesity & older age (>60)

Bauer and Leung. UpToDate. Accessed online 7/08.

Acquired risk factors (cont.)

- Pregnancy
- Oral contraceptive or hormone replacement therapy
- Antiphospholipid antibody syndrome
- Myeloproliferative disorders
  - Polycythemia vera or essential thrombocythemia
- Heparin induced thrombocytopenia & thrombosis (HIT)
- Hyperviscosity syndromes
  - Multiple myeloma or Waldenstrom's macroglobulinemia

(and many more conditions)

Bauer and Leung. UpToDate. Accessed online 7/08.

Antiphospholipid Syndrome

- Antiphospholipid syndrome (APS) is an autoimmune multisystem disorder, either primary or secondary, characterized by venous, arterial, or small vessel thromboembolic events
- And/or recurrent abortions in the presence of persistent antiphospholipid antibodies (aPL). aPLs are a heterogeneous group of autoantibodies which are directed against phospholipid-binding proteins.

Antiphospholipid Syndrome

Clinical manifestations

- Deep vein thrombosis (31.4%)
- Pulmonary embolism (23.8%)
- Stroke (14.9%)
- Transient ischemic attack (11.9%)
- Early spontaneous abortions (67.1%)
- Stillbirths (62.5%)
- Skin rash
- Livido reticularis
- Thrombocytopenia

Antiphospholipid Syndrome

Type of antibodies

- Anticardiolipin antibodies
- Anti-b*eta* 2 glycoprotein
- Lupus anticoagulant (initially found in patients with SLE (usually prolonged APTT and/or PT).

Antiphospholipid Syndrome

Diagnostic criteria

- Clinical

  Thrombosis (venous, arterial, small vessel)

  And/or recurrent abortions

- Laboratory

  Any one of the antibodies positive

  (should be done twice, 12 weeks apart)

Malignancy (cancer)

- Risk for thrombosis is multi-factorial.
- Predominantly venous thrombosis - stasis, tumor invasion of vessels, chemotherapy damage of endothelium, superimposed on acquired or primary defects in hemostasis.
- Increased production of tissue factor by tumors found in many patients which can activate FX directly.

Thrombosis manifestations

Clinical presentation:

Venous – superficial vein or deep veins

-Deep vein thrombosis

swollen, painful extremity

-Pulmonary embolus

Arterial – coronary, carotid and femoral

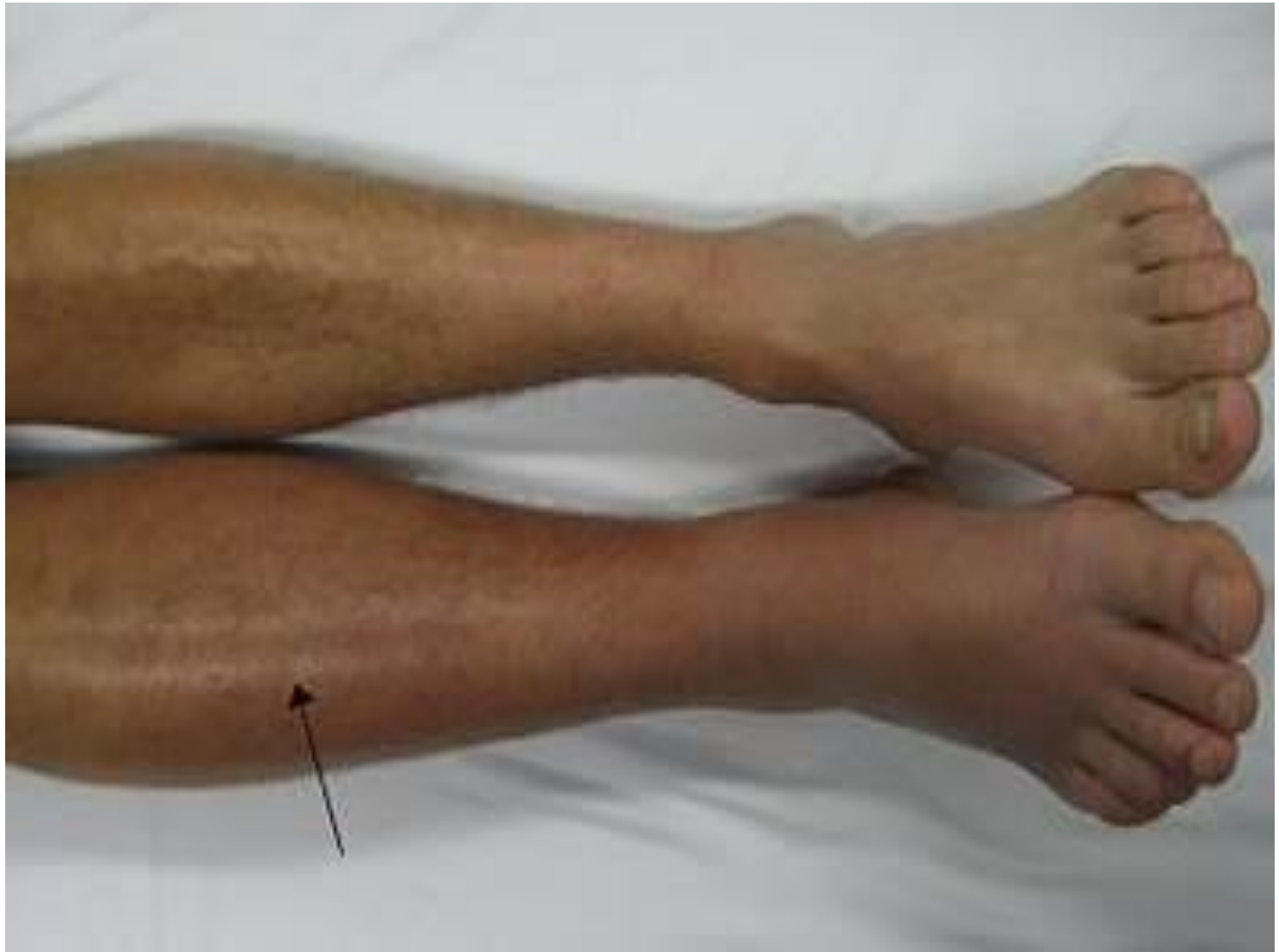
- Acute MI, Angina
- CVA, TIA
- Claudication

Thrombosis manifestations

Clinical presentation: DVT

- Lower limb most common site
- Can happen in upper limb, abdominal veins, cerebral veins & sinuses
- Symptoms & signs depend on the site
    - Limb swelling
    - Pain
    - Redness
    - Skin changes

A right-sided acute deep vein thrombosis. The leg is swollen and red due to venous outflow obstruction.



Thrombosis Manifestations

Clinical presentation: Pulmonary embolism (PE)

- Shortness of breath that may occur suddenly.
- Sudden, sharp chest pain that may become worse with deep breathing or coughing (can be pleuritic type).
- Palpitation (tachycardia).
- Rapid breathing (tachypnea).
- Sweating & anxiety.
- Hemoptysis or pink, foamy sputum.
- Dizziness and fainting (low BP).
- **PE with low BP (<90 mmHg systolic) is called massive PE.**

Diagnosis of Thrombosis

- DVT and pulmonary embolism are the two manifestations of the same disease… VTE
  - 90% of cases of acute PE are due to emboli originating from the proximal veins of the lower extremities; proximal DVTs are clinically most significant due to high morbidity and mortality
- Consider the differential diagnosis of DVT
  - Cellulitis, superficial thrombophlebitis, popliteal (Baker) cyst, muscle pulls/tears, chronic venous insufficiency
  - Consider pre-test probability of VTE before proceeding further for diagnostic evaluation
  - Among those with suspected to have DVT or PE, a minority (17-32%) actually have the disease

Wells Prediction Rule (criteria) for Diagnosing DVT:
Clinical Evaluation Table for Predicting Pretest Probability of Lower Limb DVT

Clinical feature	Score
Active cancer (treatment ongoing or within previous 6 months or palliative)	**1**
Paralysis, paresis, or recent plaster immobilization of the lower extremities	**1**
Recently bedridden for more than 3 days or major surgery, within 4 weeks	**1**
Localized tenderness along the distribution of the deep venous system	**1**
Entire leg swollen	**1**
Calf swelling by more than 3 cm when compared with the asymptomatic leg (measured 10 cm below tibial tuberosity)	**1**
Pitting edema (greater in the symptomatic leg)	**1**
Collateral superficial veins (non-varicose)	**1**
Alternative diagnosis as likely or greater than that of deep-vein thrombosis	**–2**

Modified Wells Prediction Rule (criteria) for Diagnosing Pulmonary Embolism: Clinical Evaluation Table for Predicting Pretest Probability of PE

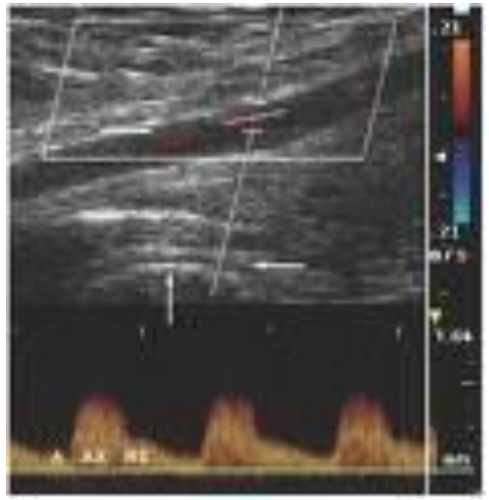
Clinical Characteristic	Score
Previous pulmonary embolism or deep vein thrombosis	+ 1.5
Heart rate >100 beats per minute	+ 1.5
Recent surgery or immobilization (within the last 30 days)	+ 1.5
Clinical signs of deep vein thrombosis	+ 3
Alternative diagnosis less likely than pulmonary embolism	+ 3
Hemoptysis	+ 1
Cancer (treated within the last 6 month)	+ 1

Modified Wells Prediction Rule (criteria) for Diagnosing Pulmonary Embolism: Clinical Evaluation Table for Predicting Pretest Probability of PE

Clinical Probability of Pulmonary Embolism	Score
Low	0-1
Intermediate	2-6
High	≥6

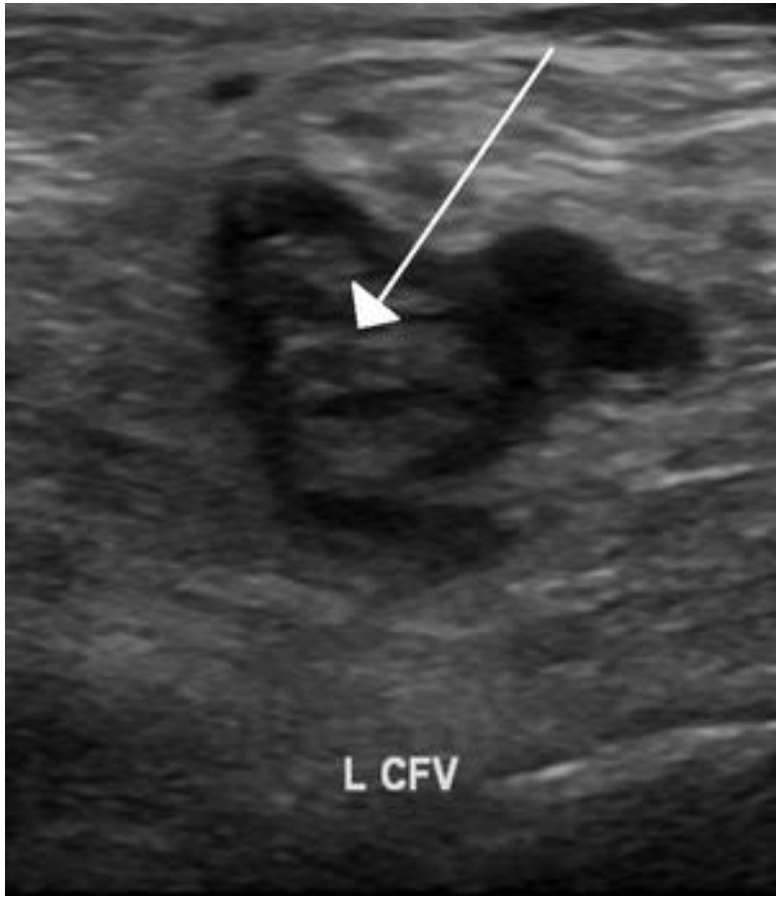
Diagnosis of Thrombosis

- **Clinical examination** (non-specific)
  - Physical findings may include a palpable cord over the calf, ipsilateral edema, warmth, and/or superficial venous dilatation
- **Contrast venography**
- Non-invasive testing
  - Impedance plethysmography
  - **Compression ultrasonography**
    - Recommended in moderate to high pre-test probability
  - D-dimer
    - Useful in low pre-test probability to exclude diagnosis of VTE
    - Sensitivity and negative predictive value are high (~99%)
  - Magnetic resonance venography
  - Computed tomography
  - Echocardiography, ventilation-perfusion (V/Q) scanning, and pulmonary angiography



Grant and Leung. UpToDate. Accessed online 7/08.

An ultrasound image demonstrating a blood clot in the left common femoral vein.



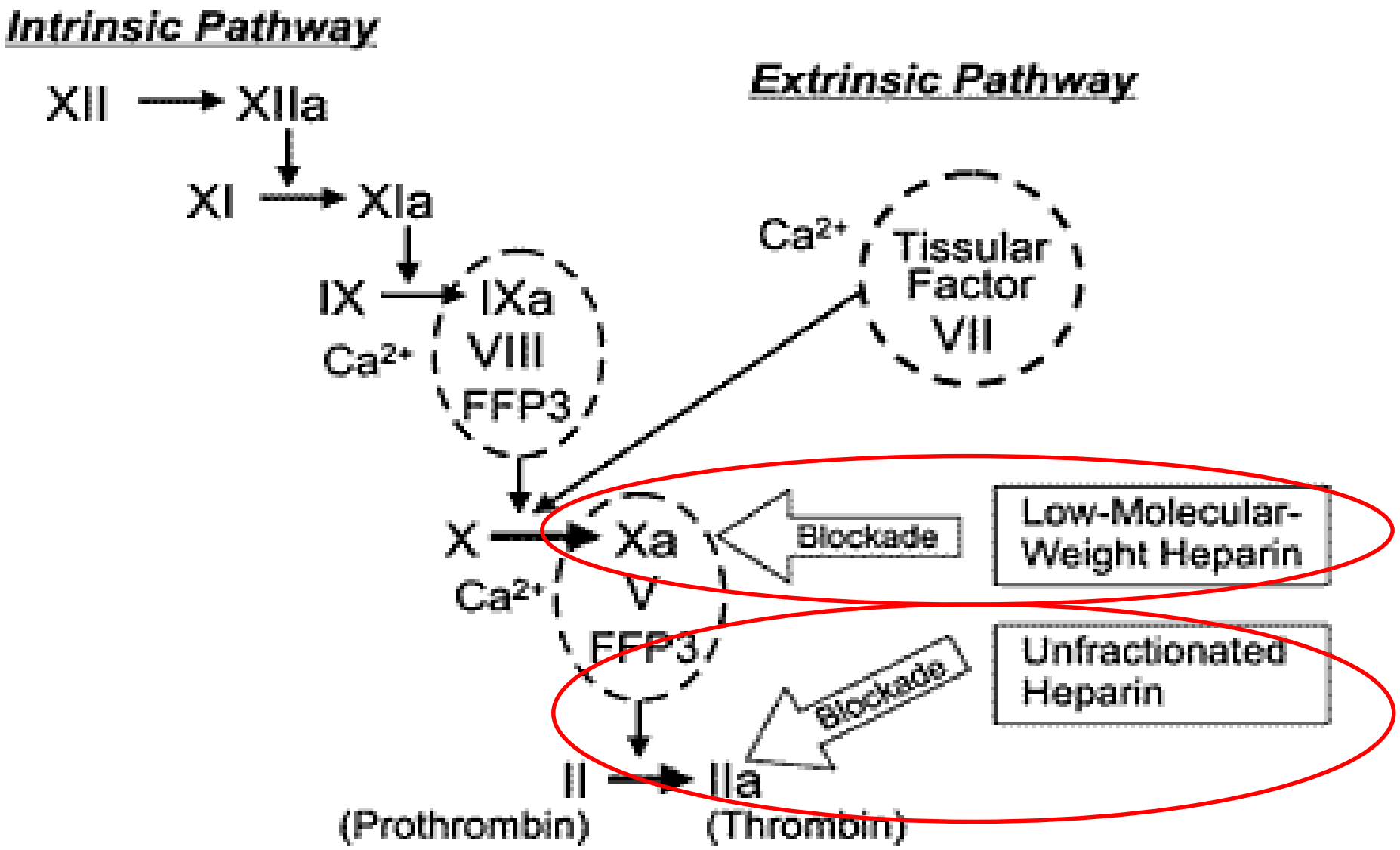
Treatment of Venous Thromboembolism (VTE)

- Anticoagulation
  - Unfractionated (UFH) and low-molecular weight heparin (LMWH, ie, enoxaparin, tinzaparin, dalteparin, etc)
    - Enable antithrombin to accelerate many-fold its inactivation of thrombin
    - LMWH should be avoided in CKD; contraindicated in Stage-V CKD
  - Vitamin K antagonists (warfarin)
    - Heparin + warfarin is more effective than warfarin alone; all cases of VTE should be "bridged" with heparin
  - Factor Xa inhibitors (fonduparinux)
  - Hirudins (lepirudin, bivalirudin)
  - **Direct oral Anticoagulants (DOACs)**
- Thrombolysis (Usually reserved for massive PE)
  - Tissue plasminogen activators (t-PA, u-PA, urokinase, alteplase)
- Thrombectomy (arterial)

Treatment of VTE

Conventional Anticoagulation

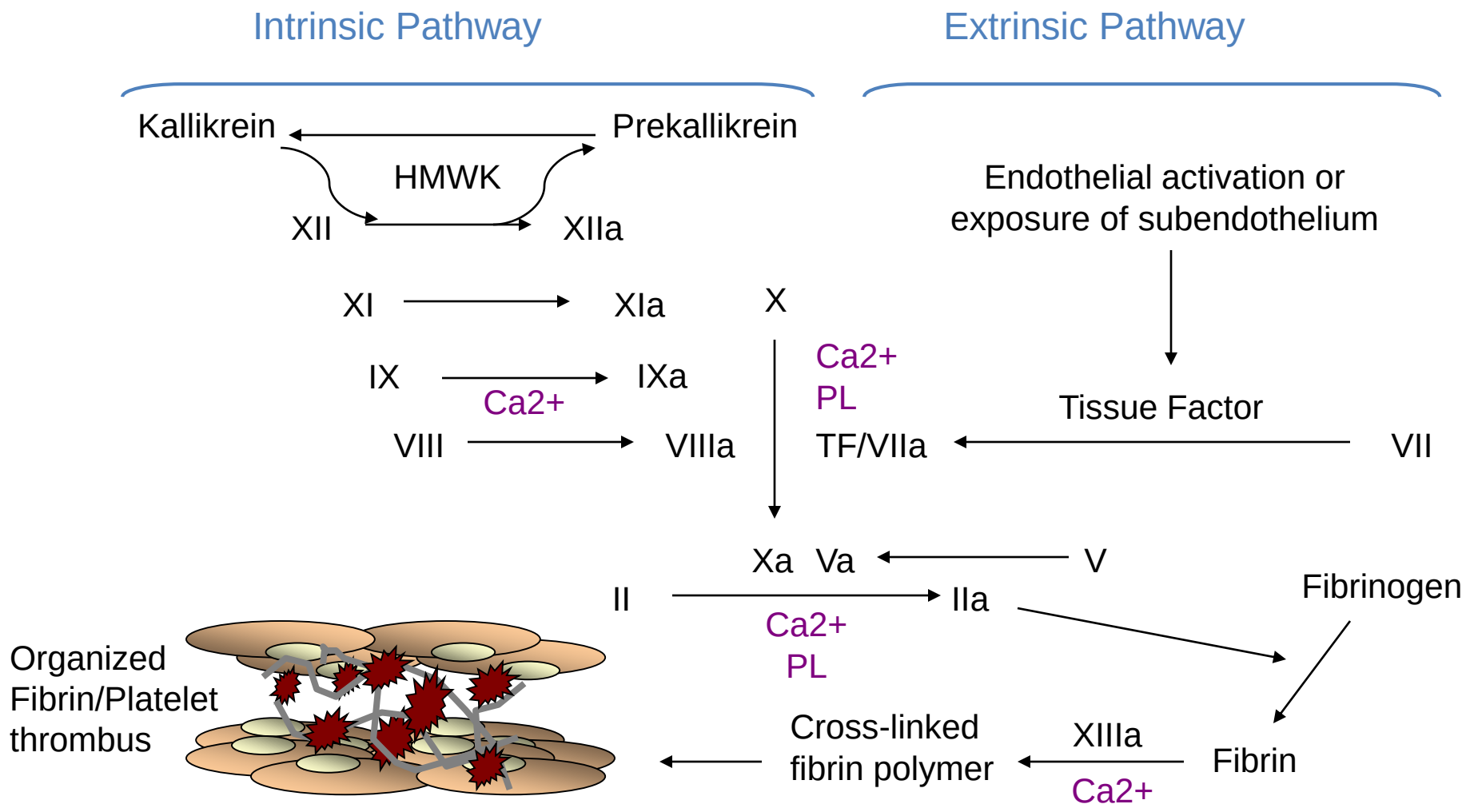
- Treatment usually started with heparin (immediate action)
- Warfarin can be started at the same time
- Warfarin takes time to work & may increase the tendency to further thrombosis initially (reduces level of Protein C & S)
- Around 4 days of warfarin & heparin overlap needed
- Heparin can be stopped when INR reaches therapeutic levels (2-3)
- LMWH (SC) in stable cases of VTE but UFH (IV) needed in hemodynamically unstable patients or pts who need procedures


Intrinsic Pathway
Extrinsic Pathway
XII
XIIa
XI
XIa
IX
IXa
VIII
FFP3
Ca2+
Ca2+
Tissular
Factor
VII
X
Xa
V
FFP3
Ca2+
Blockade
Low-Molecular-
Weight Heparin
Blockade
Unfractionated
Heparin
II
(Prothrombin)
IIa
(Thrombin)

Warfarin-mechanism of action

- Warfarin inhibits vitamin-K dependent coagulation factors (II, VII, XI and X)

Sites of Vitamin-K antagonism



Warfarin Treatment & Monitoring

- No fixed dose of warfarin, every patient needs a different dose (loading dose + maintenance)
- Monitor INR (International normalized ratio)
- Therapeutic INR 2-3 in most cases
- Initially heparin is a must as warfarin slow to act and initially pro-thrombotic
- Treatment continued for 3-6 months mostly but longer or life long AC may be needed in recurrent cases of VTE

Warfarin Treatment & Monitoring

- In patients starting warfarin therapy for initiation of oral anticoagulation, doses between 5 and 10 mg for the first 2-3 days are recommended for most individuals and subsequent dosing based on the INR response

- A loading dose (*ie,* > 10 mg) of warfarin is not recommended

Warfarin Treatment & Monitoring

- A starting dose of < 5 mg might be appropriate in elderly patients; in patients with impaired nutrition, liver disease, or congestive heart failure (CHF); and in patients who are at high risk of bleeding e.g have had recent major surgery

Warfarin tablet colors & strengths

How to Remember Warfarin Color & Strengths

Treatment & Monitoring

Fluctuations in INR may occur because of any one or more of the following conditions:

- Patient non-compliance
- Changes in vitamin K intake (diet)
- Effect(s) of concomitant drug(s) use
- Changes in warfarin metabolism & vitamin K dependent coagulation factor synthesis or metabolism
- Inaccuracy in INR testing

Current indications of warfarin

- Prosthetic (metallic) heart valves
- High risk antiphospholipid syndrome
- Thrombosis in patients with end stage renal failure
- Failure of other anticoagulants (eg., thrombosis developing while taking other anticoagulants like DOACs)

Overdose & Anti-dotes

- For heparin…protamine sulphate

- For warfarin…vitamin K but may take time (many hours) to act
- An actively bleeding patient on warfarin may also need fresh frozen plasma (FFP) or prothrombin complex

Direct oral anticoagulants (DOACs)

- **Direct thrombin inhibitors (DTI)**

  Dabigatran (Pradaxa, Boehringer)

- **Factor X inhibitors**

  Rivaroxaban (Xarelto, Bayer/Janssen)

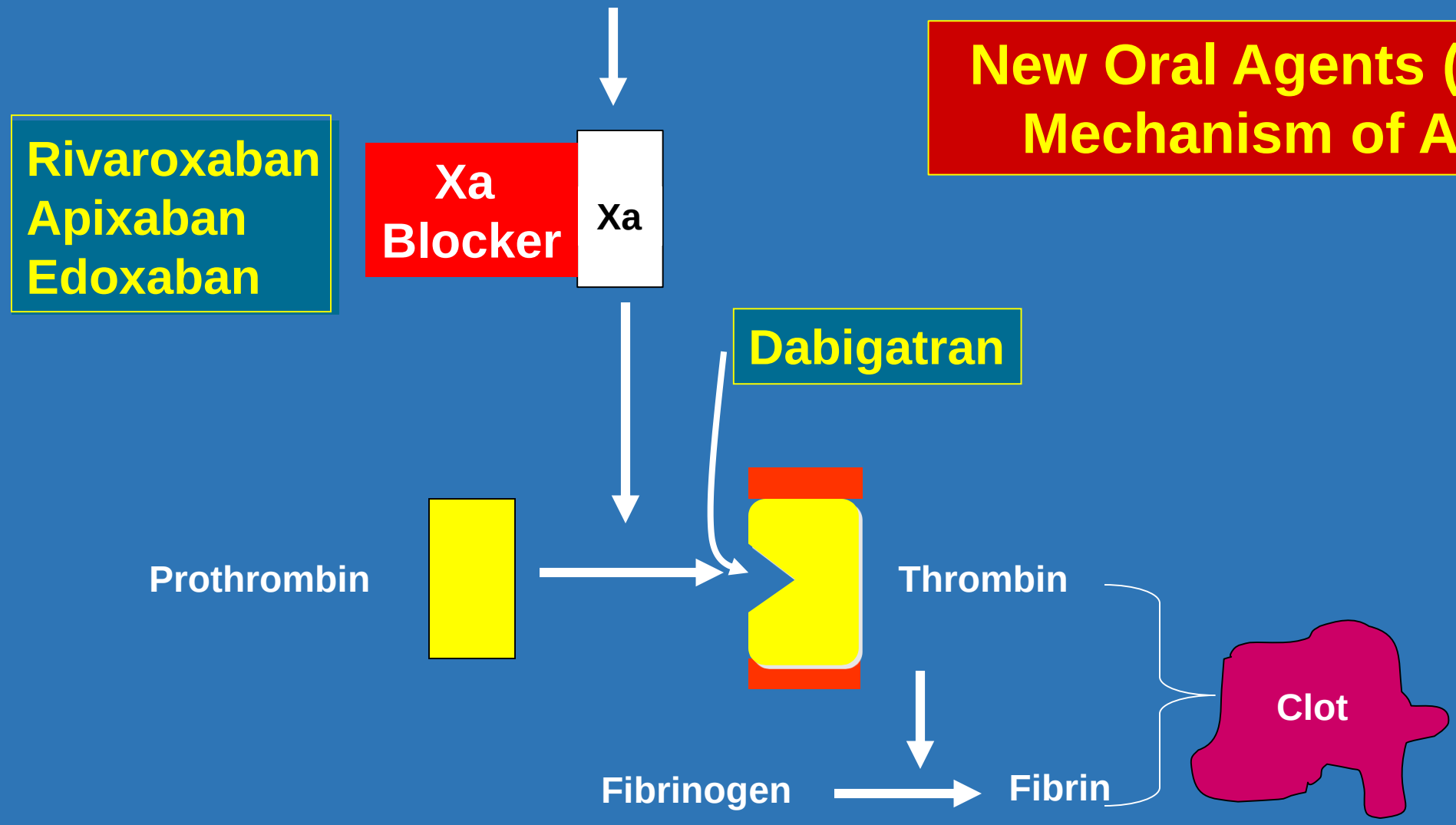
  Apixaban (Eliquis, Pfizer/BMS)

  Edoxaban (Savaysa, Daichii Sankyo)

  Betrixaban (Bevyxxa, Portola)

Extended Thromboprophylaxis with Betrixaban in Acutely Ill Medical Patients. Cohen AT, et al; APEX Investigators. N Engl J Med. 2016 Aug 11;375(6):534-44

New Oral Agents (DOAC) Mechanism of Action



DOACs- indications

- Treatment of venous thromboembolism (VTE)
- VTE prevention in atrial fibrillation
- Prophylaxis in orthopedic surgery
- Treatment of VTE in cancer patients
- VTE prophylaxis in cancer patients

Advantages of Direct Oral Anticoagulants

Advantage	Clinical implications
• Rapid onset of action • Predictable anticoagulant effect	• No need for bridging • No need for routine coagulation monitoring
• Low potential of food interactions • Low potential for drug interactions • Specific coagulation enzyme target • Prophylactic dose	• No dietary precautions • Few drug restrictions • Low risk of off-target adverse effects • Smaller doses can be used as prophylaxis?

Disadvantages of Direct Oral Anticoagulants

- More expensive
- Reversal (was) a problem (Antidote available now)
- Not suitable for AC for prosthetic heart valves
- Higher failure rate in APS
- Can not be used in end stage renal failure (apixaban)

Warfarin still treatment of choice for longer term AC

- Patients with prosthetic heart valves
- Patients with end stage renal failure
- Antiphospholipid syndrome (high risk)

Some Important Facts about DOACs

- The risk of bleeding with the DOACs, and particularly intracranial bleeding, is less when compared with warfarin
- GI bleeding seems to be higher with DOACs (dabigatran, rivaroxaban, and edoxaban) compared with warfarin
- Based on indirect comparisons, the risk of bleeding may be lower with apixaban than with other DOACs

Chai-Adisaksopha, C, et al*Blood*. 2014; 124: 2450–2458.
Castellucci, L.A., et al *JAMA*. 2014;312: 1122–1135.

Anticoagulation Duration for VTE:

- The minimum duration of anticoagulant therapy for DVT or PE is usually 3 months.
- A decision to treat patients for longer than 3 months, which we refer to as **“extended anticoagulant therapy,”** (eg, 6, 12, or 24 months) may depend on an ongoing risk factor for VTE (like immobilization, active cancer, etc)
- Patients with recurrent thrombosis, extensive thrombosis, and unprovoked thrombosis may be considered for extended anticoagulant therapy (indefinite or life long).
- Initial parenteral anticoagulation (e.g., heparin) for VTE is given before dabigatran and edoxaban, is not needed before rivaroxaban and apixaban.

Kearon C. et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest. 2016 Feb;149(2):315-352.

Assessment for bleeding risk

- Always assess for bleeding risk in all patients starting on anticoagulant therapy.

Kearon C. et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest. 2016 Feb;149(2):315-352.

Anticoagulant Prophylaxis

- Patients at high risk of thrombosis should be considered for anticoagulant prophylaxis
- All hospitalized patients should be considered for prophylactic anticoagulation

Kearon C. et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest. 2016 Feb;149(2):315-352.

How to assess for risk of thrombosis?

By using risk assessment scoring by clinically validated models

The Padua Prediction Score (Risk Assessment Model)

Risk Factor	Points
Active cancer	3
Previous VTE (with exclusion of superficial VT	3
Reduced mobility	3
Already known thrombophilic condition	3
Recent trauma (≤ 1 mon) and/or surgery	2
Elderly (age ≥ 70 y)	1
Heart and/or respiratory failure	1
Acute MI or ischemic stroke	1
Acute infection and/or rheumatologic disorder	1
Obesity (BMI ≥ 30)	1
Ongoing hormonal treatment	1

Patients with ≥ 4 or more points are considered to be at high risk for developing VTE

Barbar S, et al. (2010) A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. J Thromb Haemost**8**:2450–2457

Caprini Prediction Score (Risk Assessment Model)

Used for surgical patients and can also be used for medical patients as it contains more risk factors for the patients and more detailed but more difficult to use

Caprini Risk Assessment Model (RAM)

Deep Vein Thrombosis (DVT)

Prophylaxis Orders

(For use in Elective General Surgery Patients)

Thrombosis Risk Factor Assessment (Choose all that apply)

BIRTHDATE

NAME

CPI No.

SEX M F VISIT No. _____

Each Risk Factor Represents 1 Point

- ❑ Age 41-60 years
- ❑ Swollen legs (current)
- ❑ Varicose veins
- ❑ Obesity (BMI >25)
- ❑ Minor surgery planned
- ❑ Sepsis (<1 month)
- ❑ Acute myocardial infarction
- ❑ Congestive heart failure (<1 month)
- ❑ Medical patient currently at bed rest
- ❑ History of inflammatory bowel disease
- ❑ History of prior major surgery (<1 month)
- ❑ Abnormal pulmonary function (COPD)
- ❑ Serious Lung disease including pneumonia (<1 month)
- ❑ Oral contraceptives or hormone replacement therapy
- ❑ Pregnancy or postpartum (<1 month)
- ❑ History of unexplained stillborn infant, recurrent spontaneous abortion (≥ 3), premature birth with toxemia or growth-restricted infant
- ❑ Other risk factors_____

Subtotal:

Each Risk Factor Represents 2 Points

- ❑ Age 61-74 years
- ❑ Arthroscopic surgery
- ❑ Malignancy (present or previous)
- ❑ Laparoscopic surgery (>45 minutes)
- ❑ Patient confined to bed (>72 hours)
- ❑ Immobilizing plaster cast (<1 month)
- ❑ Central venous access
- ❑ Major surgery (>45 minutes)

Subtotal:

Each Risk Factor Represents 3 Points

- ❑ Age 75 years or older
- ❑ History of DVT/PE
- ❑ Positive Factor V Leiden
- ❑ Elevated serum homocysteine
- ❑ Heparin-induced thrombocytopenia (HIT) (Do not use heparin or any low molecular weight heparin)
- ❑ Elevated anticardiolipin antibodies
- ❑ Other congenital or acquired thrombophilia

If yes: Type_____

- ❑ **Family History of thrombosis***
- ❑ Positive Prothrombin 20210A
- ❑ Positive Lupus anticoagulant

Subtotal:

*** most frequently missed risk factor**

Each Risk Factor Represents 5 Points

- ❑ Stroke (<1 month)
- ❑ Elective major lower extremity arthroplasty
- ❑ Hip, pelvis or leg fracture (<1 month)
- ❑ Acute spinal cord injury (paralysis) (<1 month)
- ❑ Multiple trauma (<1 month)

Subtotal:

TOTAL RISK FACTOR SCORE:

Anticoagulant Prophylaxis Methods

- Mechanical methods
  - Graduated compression stockings (or elastic stockings or anti-embolism stockings)
  - Intermittent pneumatic compression
  - Venous foot pump.

- Pharmacologic methods

  Low molecular weight heparin (40 mg/day)

  Unfractionated heparin (5000 units BD or TDS)

  Rivaroxaban (10 mg daily)

  Apixaban (2.5 mg daily)

Management of Bleeding (clinically significant)

- Reduction in Hb >2 g/dL or requiring RBC transfusion >2 units
- Stop DOAC therapy
- Give oral charcoal if DOAC ingested <2 hours ago
- Maintain adequate hydration to aid drug clearance
- Local hemostatic measures, mechanical compression
- Transfusion support: RBC transfusion as per Hb level
- Consider platelet transfusion if an antiplatelet or if platelets < 50 x 10^9/L
- Consider radiological and surgical interventions to identify and treat source of bleeding

Management of life threatening bleeding

- Bleeding in critical area or organ, loss of Hb > 5 g/dL, hypotension not responding to resuscitation
- Get advice of hematologist!
- a) FEIBA (factor eight inhibitor bypass activity) 25-100 International Units/kg, repeat at 12 hours (probably beneficial)
- b) Prothrombin complex (Promathrombinex-VF) 25-30 International Units/kg (If not administered earlier)
- c) Recombinant Factor VII (rVlla) 90 microgram/kg every 2-3 hours (possibly beneficial)
- d) Tranexamic acid 15-30 mg/kg for mucosal bleeds

Reversal of Direct Thrombin inhibitors (Dabigatron)

Idarucizumab

- Idarucizumab is a humanized monoclonal antibody fragment that binds dabigatran with 350-fold higher affinity than that of dabigatran for thrombin.
- In addition to binding dabigatran, idarucizumab also binds the active glucuronide metabolites of dabigatran to form essentially irreversible 1:1 stoichiometric complexes.
- Idarucizumab and idarucizumab-dabigatran complexes are cleared by the kidneys, as is dabigatran.
- After intravenous infusion, the half-life of idarucizumab is about 45 min in subjects with normal renal function.

Reversal of Factor-X Inhibitors

Andexanet alfa

Andexanet alfa is a recombinant human FXa variant with the active-site serine residue replaced with alanine to eliminate catalytic activity and with the membrane-binding domain deleted to prevent incorporation into the prothrombinase complex.

Andexanet serves as a decoy for the oral FXa inhibitors because it binds them with affinities similar to those of native FXa. Because andexanet also binds tissue factor pathway inhibitor (TFPI) to form a non-productive andexanet–TFPI complex, it reduces TFPI activity.

Thank you