Hypercoagulable state (Thrombosis/DVT)

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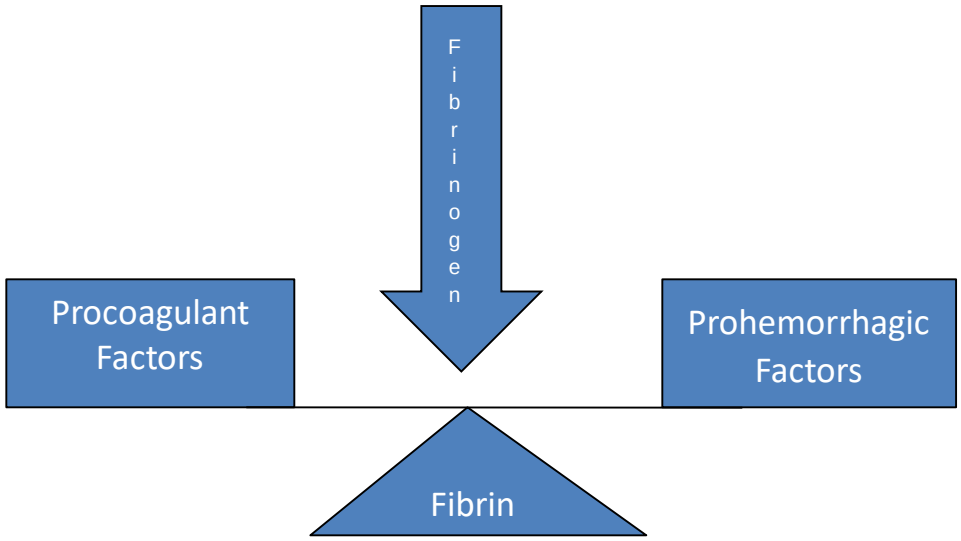
Hypercoagulable state (Thrombophilia)

- Definition: Alteration in the hemostatic balance between blood fluidity and clot formation due to genetic or acquired disorders which shift the balance toward excessive platelet aggregation and thrombin generation (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
- Thrombogenic state

- Inherited Thrombophilia

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

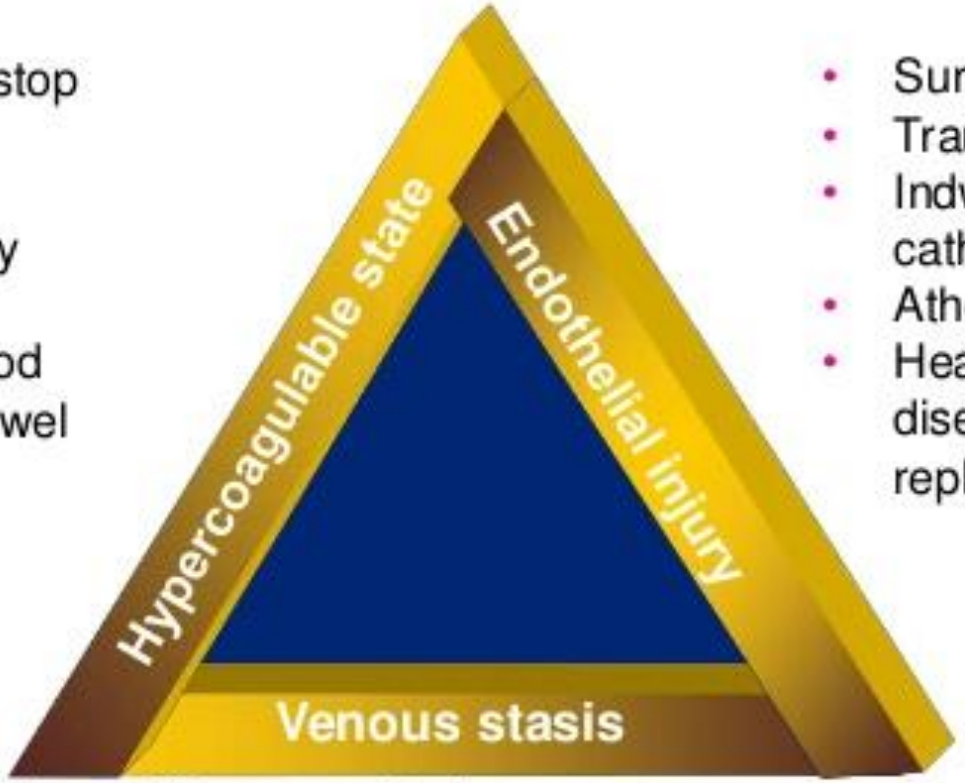
Virchow's Triad

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.

Antithrombotic functions of endothelium

- Prostacyclin (PGI2)
- Nitrous oxide (NO2)
- Thrombomodulin
- Heparans (proteoglycans)
- Tissue factor pathway inhibitors (TFPI)
- Plasminogen activator inhibitors (PAI-1)

Prothrombotic states

- Vascular (Endothelial dysfunction)
- Platelets (↑ activity and/or numbers)
- Coagulation factors (↑)
- Natural anticoagulants (↓ and/or dysfunction)
- Fibrinolytic system (↓)
- Pathological conditions

(e.g.: cancer, CCF, antiphospholipid syndrome, Contraceptive pills, etc.)

Causes of venous thrombo-embolism

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

- Hereditary
- Acquired

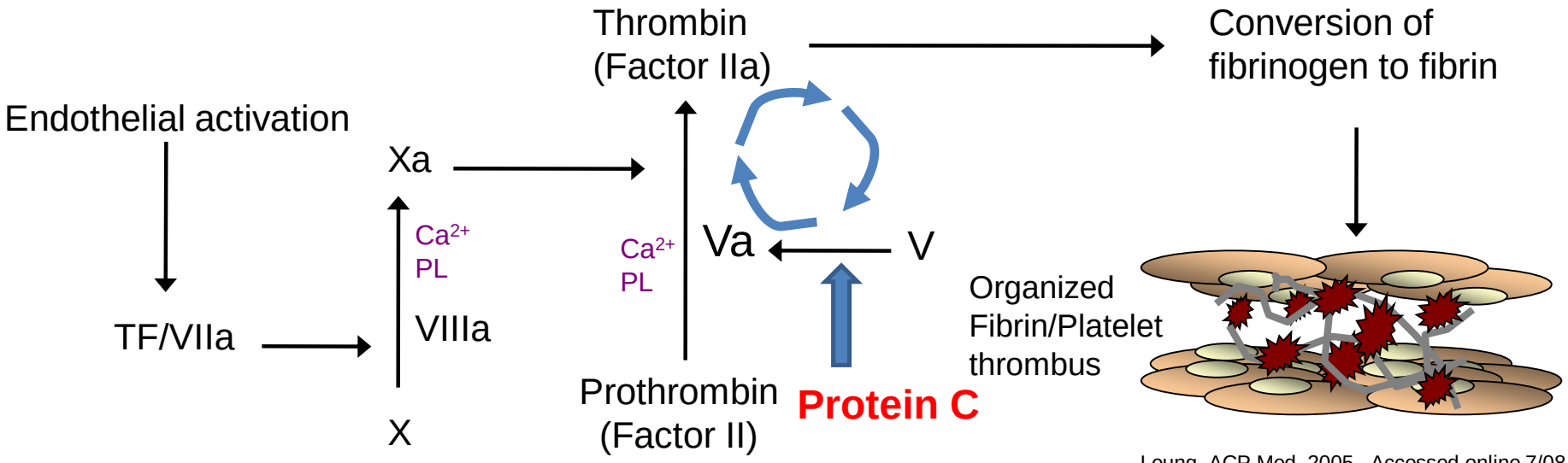
and are often multiple in a given patient.

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

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



Leung. ACP Med, 2005. Accessed online 7/08.

Factor V Leiden

- Activated Protein C (APC) resistance
  - 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**
- Dual prothrombotic state of Factor V Leiden
  - Increased coagulation
    - FV Leiden → ↑ thrombin generation, (↓ anticoagulation)
      ↓ inactivation of factor FVIIIa

(also ↓ PAI inactivation → ↓ fibrinolysis)

Leung. ACP Med, 2005.

Protein C & S deficiency

- Protein C and S
  - Inhibit activated cofactors Va and VIIIa, respectively
- Protein C is consumed and levels are low in vitamin K deficiency, DIC , liver disease, etc

- Protein C & S deficiency ;
  - Heterozygous or homozygous,
  - Congenital or acquired
  - Clinical expression of hypercoagulability variable, and do not necessarily correspond with absolute concentration of Protein C
- **Acquired Protein S deficiency may be induced by OCPs, pregnancy, or nephrotic syndrome**

Leung. ACP Med, 2005..

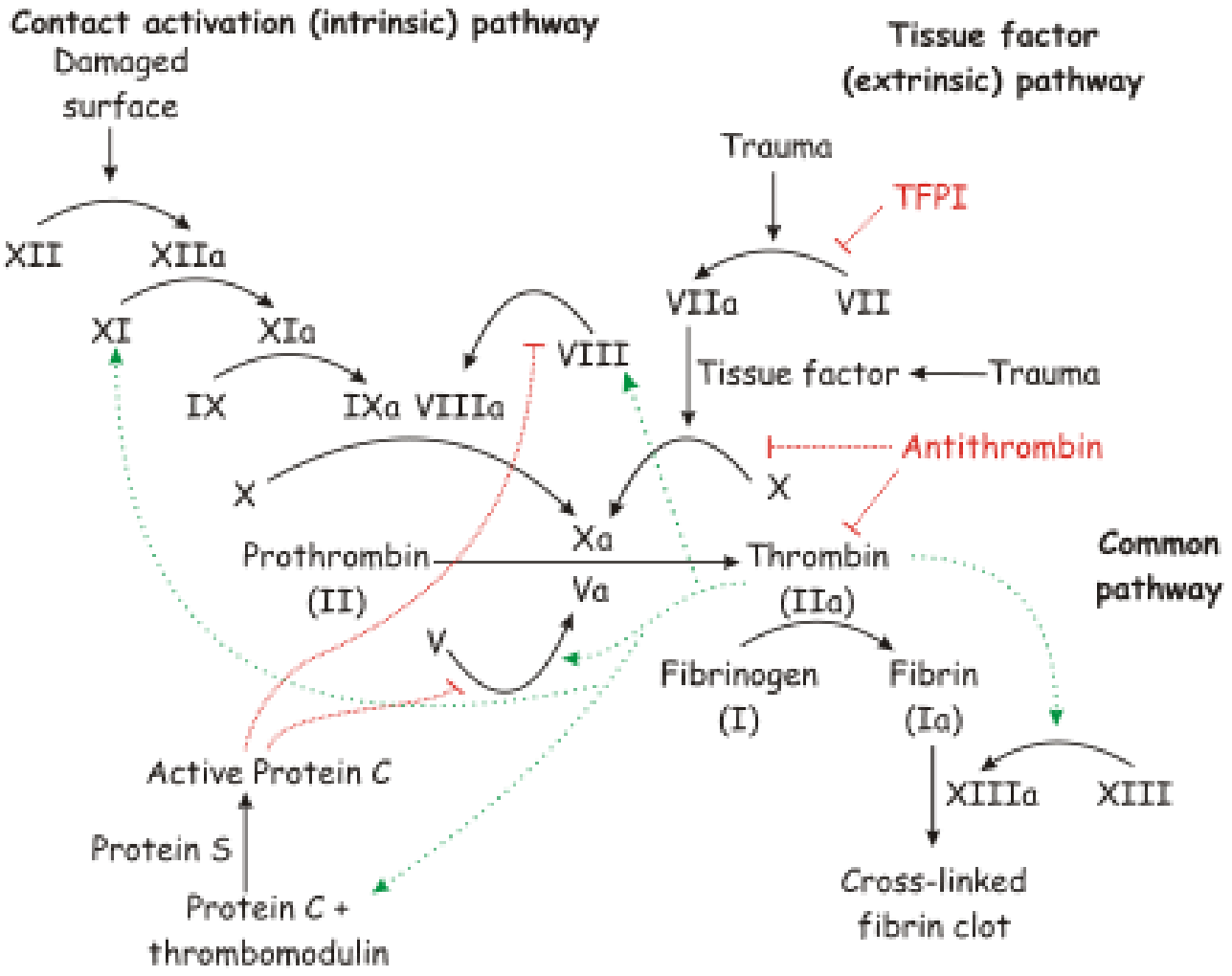
Prothrombin gene mutation

- Normal prothrombin (Factor II) circulates as Vitamin K-dependent cofactor w/ 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


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

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).
- 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
- Malignancy
- 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

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

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

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

- Risk for thrombosis is multi-factorial.
- Predominantly venous thrombosis - stasis, tumor invasion of vessels, chemotherapy effects superimposed on acquired or primary defects in hemostasis.
- Increased production of tissue factor by tumours 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

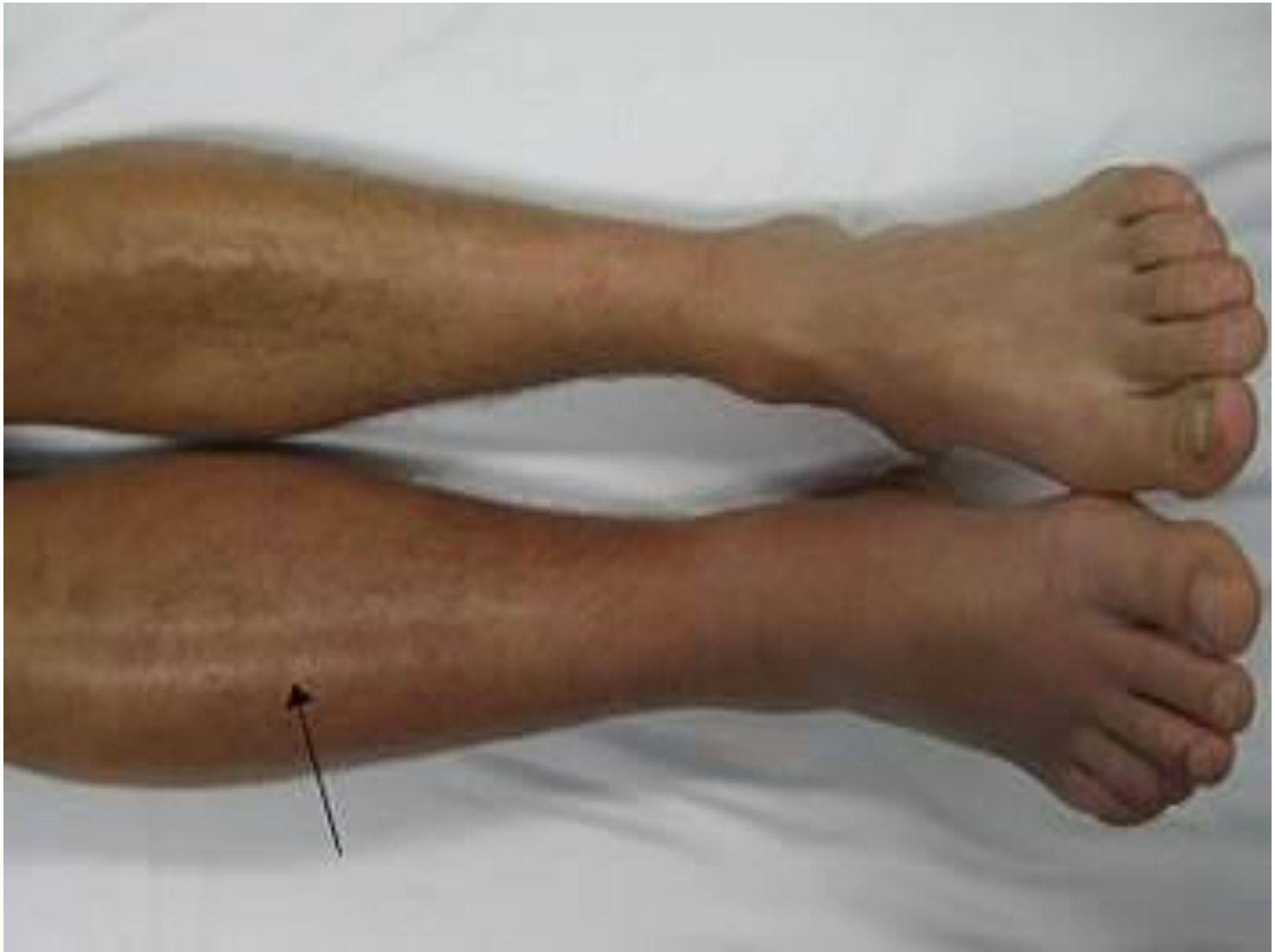
- Acute MI, Angina
- CVA, TIA
- Claudication

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) is called massive PE.**

Diagnosis of Thrombosis

- DVT and pulmonary embolism are the two most common manifestations of the same disease: VTE
  - 90% of cases of acute PE are due to emboli emanating 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
  - Popliteal (Baker) cyst, superficial thrombophlebitis, muscle pulls/tears, chronic venous insufficiency, cellulitis
  - Consider pre-test probability for VTE before proceeding further in diagnostic evaluation
    - Among those with suspected of DVT of the LE, a minority (17-32%) actually have the disease

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

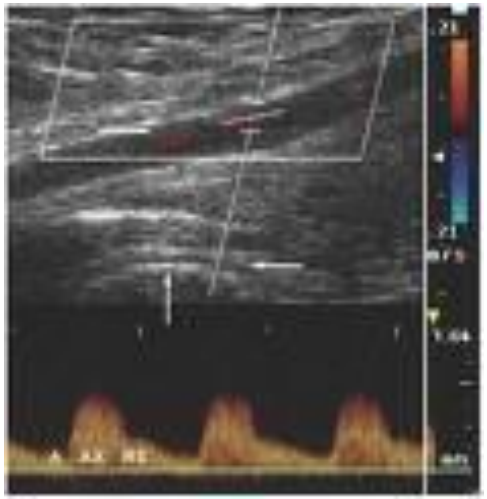
Clinical Characteristic	**Score**
Previous pulmonary embolism or deep vein thrombosis	+ 1.5
Heart rate >100 beats per minute	+ 1.5
Recent surgery or immobilization (within the last 30 d)	+ 1.5
Clinical signs of deep vein thrombosis	+ 3
Alternative diagnosis less likely than pulmonary embolism	+ 3
Hemoptysis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

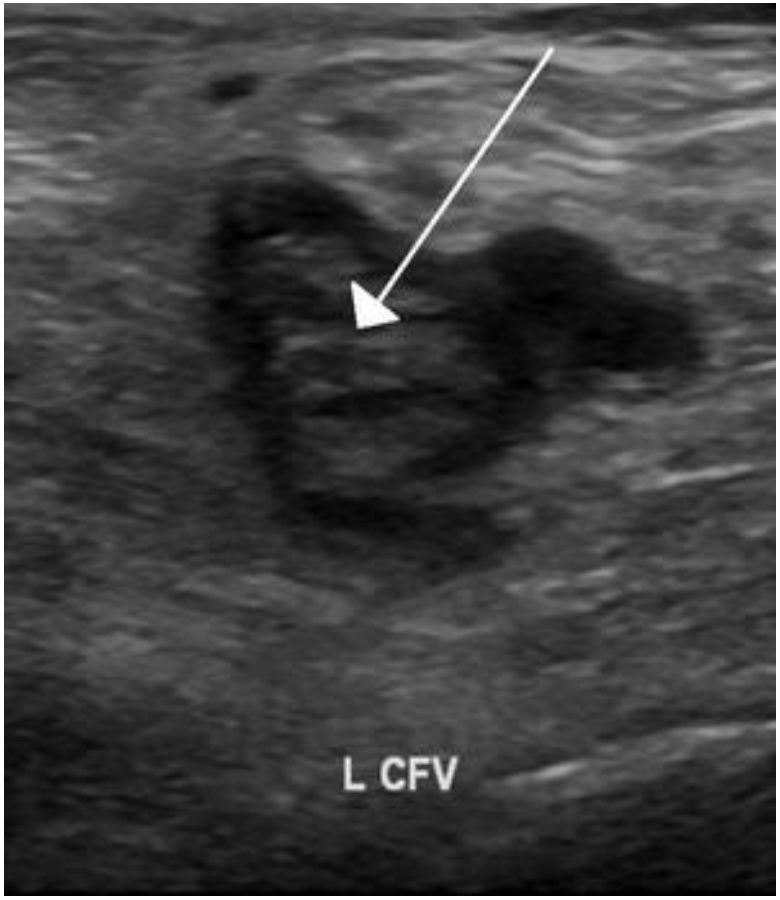
Diagnosis of Thrombosis

- 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.



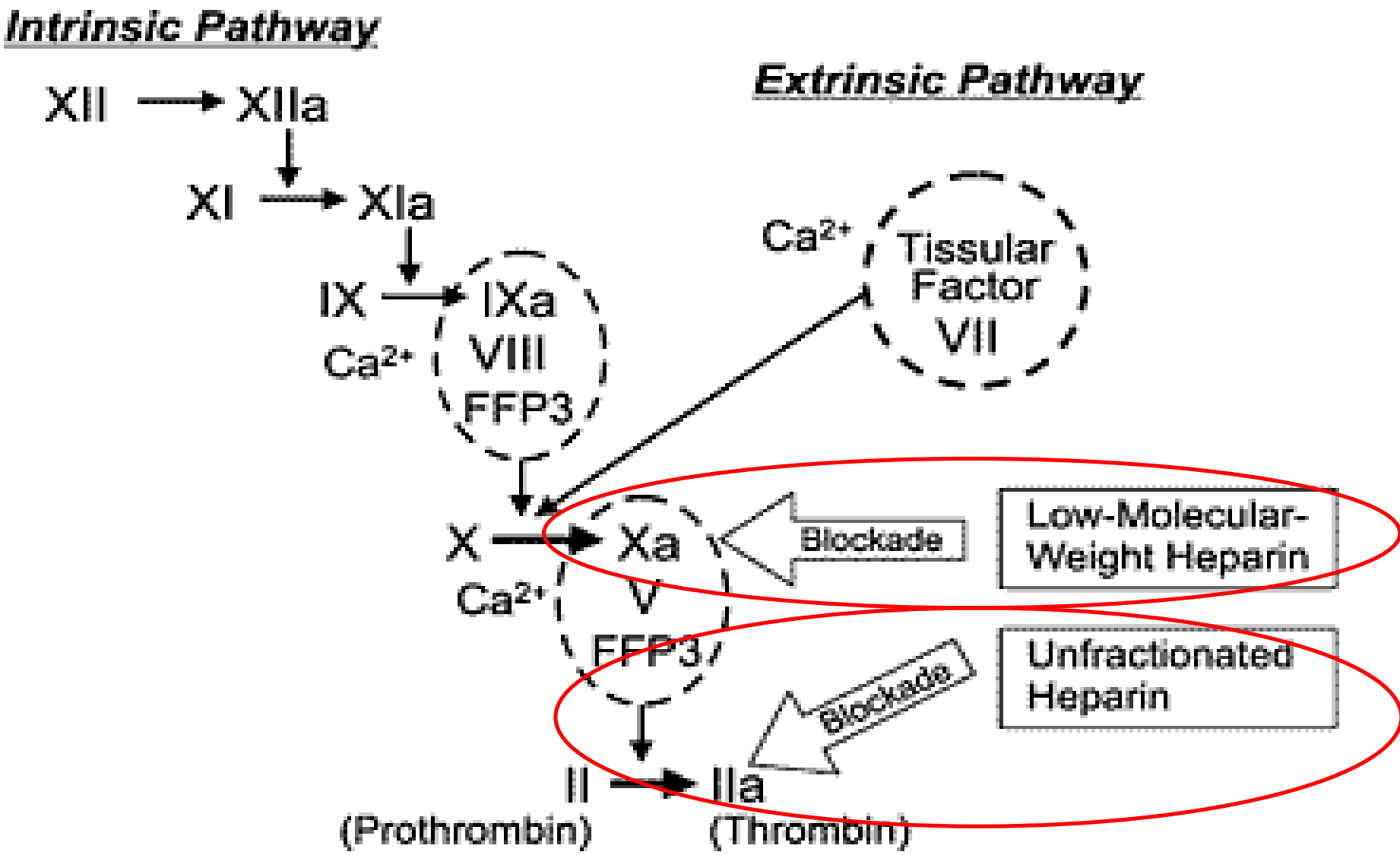
Treatment of VTE

- 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

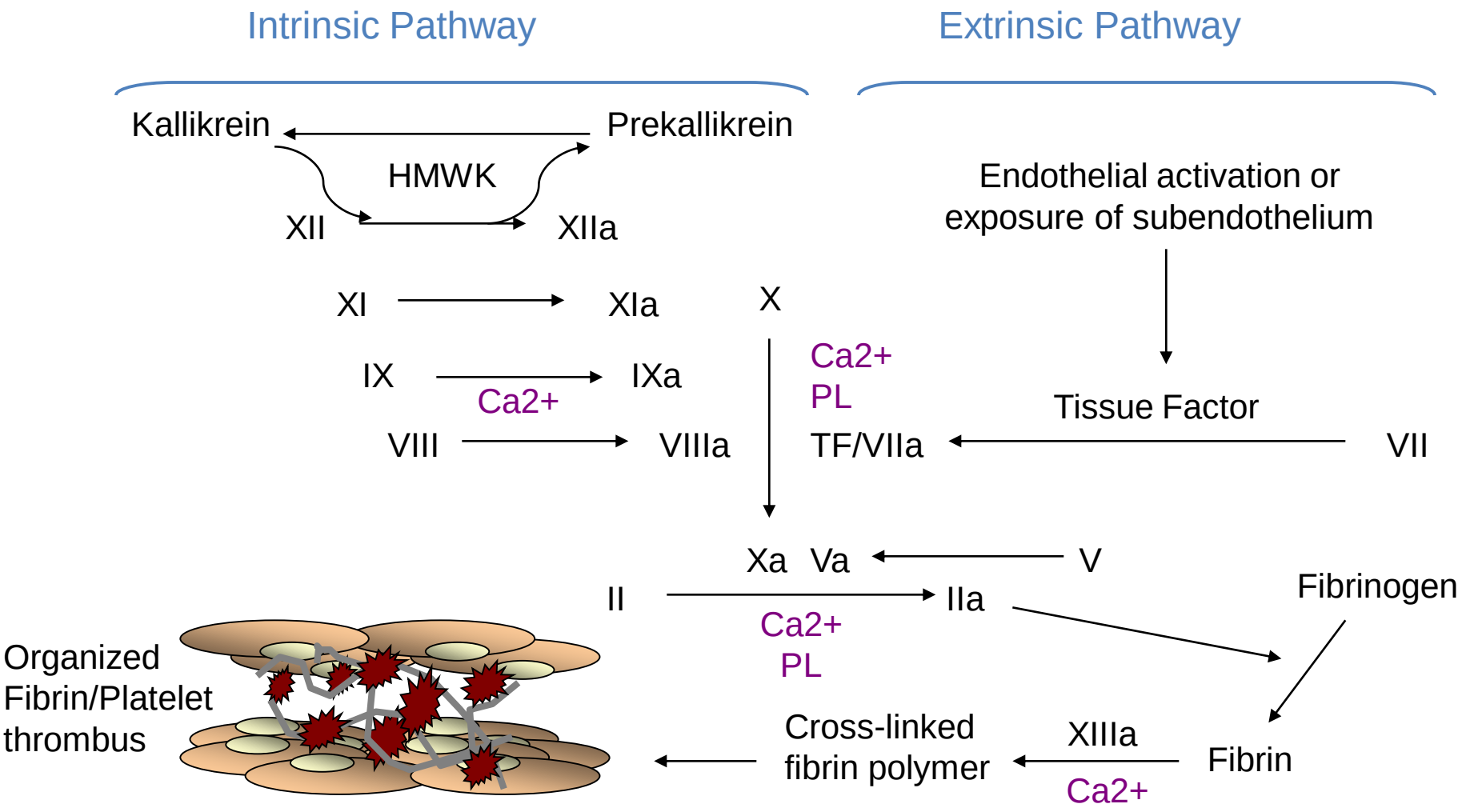
- Treatment always started with heparin (immediate action)
- Warfarin can be started at the same time
- Warfarin takes time to work & may increase the tendency to further thrombosis initially (reduces level of Protein C & S)
- Around 4 days of warfarin & heparin overlap needed
- Heparin can be stopped when INR reaches therapeutic levels (2-3)
- LMWH (SC) in stable cases of VTE but UNH (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)
- 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 3-12 months mostly but longer or life long AC may be needed in recurrent cases of VTE

Treatment & Monitoring

- In patients starting warfarin therapy for initiation of oral anticoagulation, doses between 5 and 10 mg for the first 1 or 2 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

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
- Changes in vitamin K dependent coagulation factor synthesis or metabolism
- Inaccuracy in INR testing

Overdose & Anti-dotes

- For heparin…protamine sulphate

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

Direct oral anticoagulants (DOACs)

- **Direct thrombin inhibitors (DTI)**

  Dabigatran (Pradaxa, Boehringer)

- **Factor X inhibitors**

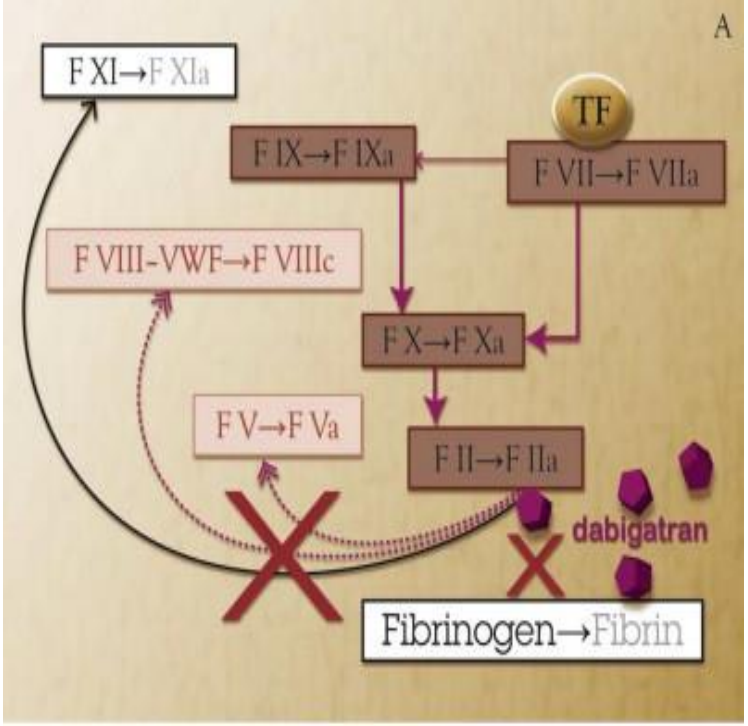
  Rivaroxaban (Xarelto, Bayer/Janssen)

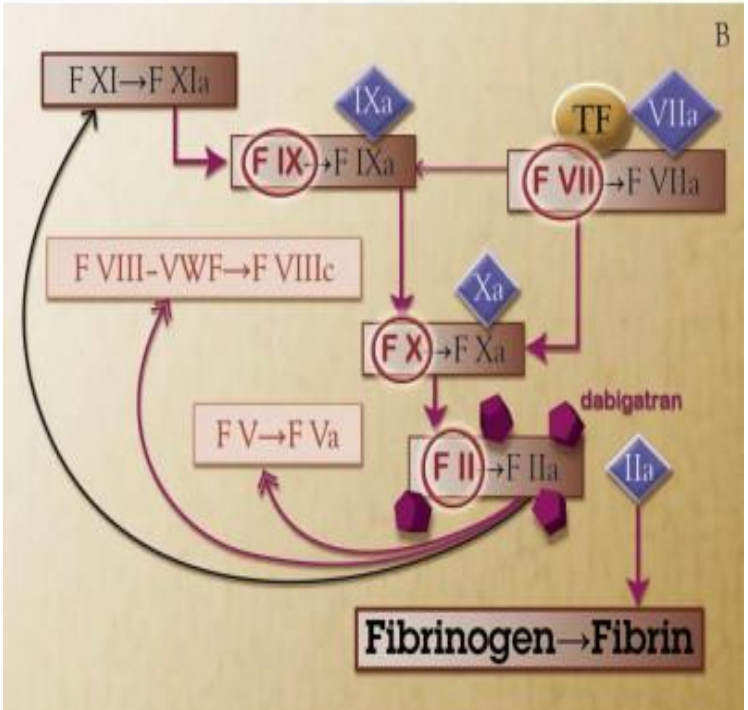
  Apixaban (Eliquis, Pfizer/BMS)

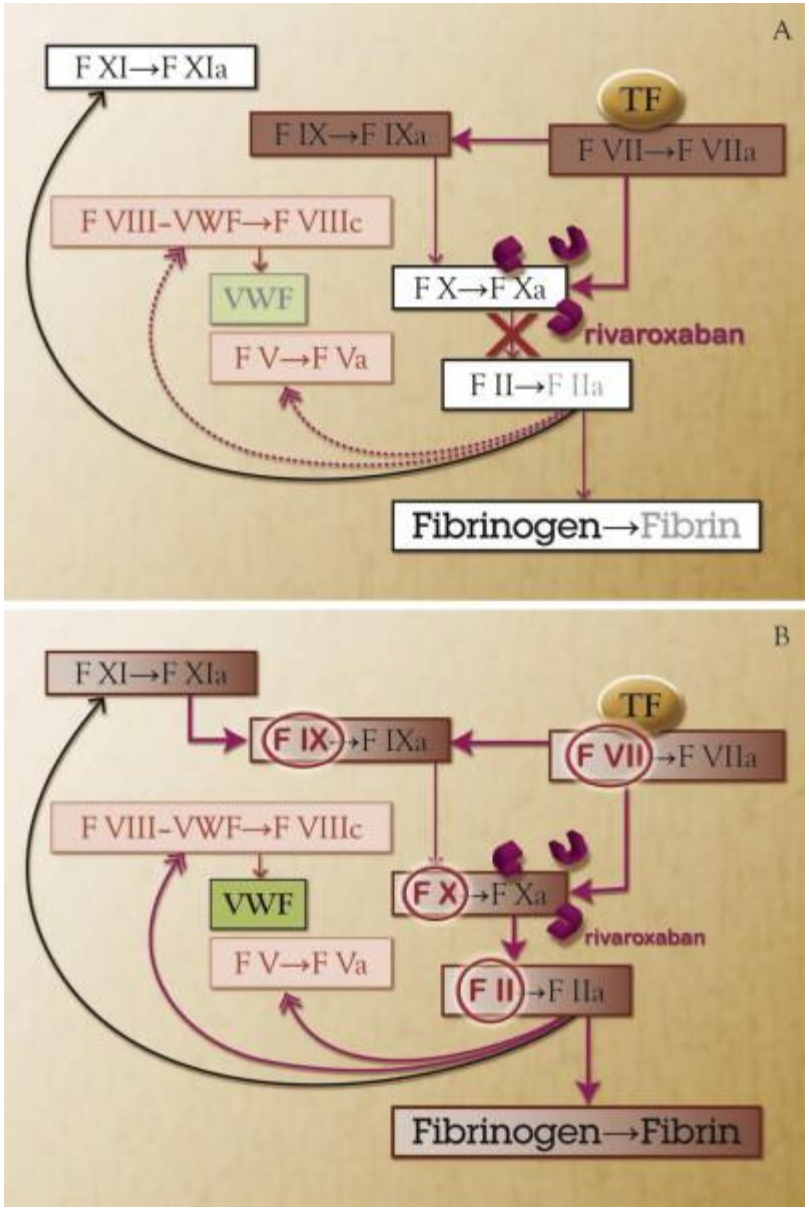
  Edoxaban (Savaysa, Daichii Sankyo)

  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


A
F XI→F XIa
TF
F IX→F IXa
F VII→F VIIa
F VIII-VWF→F VIIIc
F X→F Xa
F V→F Va
F II→F IIa
dabigatran
Fibrinogen→Fibrin


B
F XI→F XIa
IXa
TF
VIIa
F IX→F IXa
F VII→F VIIa
F VIII-VWF→F VIIIc
Xa
F X→F Xa
dabigatran
F V→F Va
F II→F IIa
IIa
Fibrinogen→Fibrin


A
F XI→F XIa
TF
F IX→F IXa
F VII→F VIIa
F VIII-VWF→F VIIIc
VWF
F X→F Xa
rivaroxaban
F V→F Va
F II→F IIa
Fibrinogen→Fibrin
B
F XI→F XIa
TF
F IX→F IXa
F VII→F VIIa
F VIII-VWF→F VIIIc
VWF
F X→F Xa
rivaroxaban
F V→F Va
F II→F IIa
Fibrinogen→Fibrin

DOACs- indications

- Treatment of venous thromboembolism
- TE 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 (Cost of drug/year $3000)
- Reversal a problem (Antidote available now)
- Can not be used in end stage renal failure
- Not suitable for AC for prosthetic valves

Warfarin still Tx of choice for longer term AC

- End stage renal failure
- Prosthetic valves
- Antiphospholipid syndrome?

Some Important Facts about DOACs

- The risk of bleeding with the NOACs, and particularly intracranial bleeding, is less with the NOACs than with VKA therapy
- Based on patients with atrial fibrillation, GI bleeding may be higher with dabigatran, rivaroxaban, and edoxaban than with VKA therapy, although this has not been seen in patients with VTE
- Based on indirect comparisons, the risk of bleeding may be lower with apixaban than with the other NOACs
- Despite the lack of specific reversal agents for the NOACs, the risk that a major bleed will be fatal appears to be no higher for the NOACs than for VKA therapy.

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

Anticoagulants in VTE: Current Recommendation *Statements & Remarks*:

- The minimum duration of anticoagulant therapy for DVT or PE is usually 3 months; this period of treatment is referred to as **"long-term therapy."**
- Treatment longer than 3 months but for a limited period **"longer time-limited period"** (eg, 6, 12, or 24 months).
- A decision to treat patients for longer than 3 months, which we refer to as **"extended anticoagulant therapy,"** usually implies that anticoagulant therapy will be continued indefinitely.
- Initial parenteral anticoagulation is given before dabigatran and edoxaban, is not given before rivaroxaban and apixaban, and is overlapped with VKA therapy.

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

Anticoagulants in VTE: Current Recommendation *Statements & Remarks*:

- In patients with a first VTE that is an unprovoked proximal DVT of the leg or PE and who have a (i) low or moderate bleeding risk, we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 2B), and (ii) high bleeding risk, we recommend 3 months of anticoagulant therapy over extended therapy (no scheduled stop date) (Grade 1B).
- Patient sex and D-dimer level measured a month after stopping anticoagulant therapy may influence the decision to stop or extend anticoagulant therapy. In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (eg, annually).

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

Reversal of DTI (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.