Pharmacotherapy of Thrombo-embolic disorders

Intended Learning Objectives:

1. Define thromboembolic disorders
2. Identify risk factors, signs and symptoms of Venous thromboembolism.
3. Describe the processes of thrombosis & fibrinolysis, including the role of the vascular endothelium, platelets, coagulation cascade, and thrombolytic proteins.
4. Determine a patient’s relative risk (low, moderate, high, or very high) of developing venous thrombosis.
5. Potential advantages of the low-molecular-weight heparins and fondaparinux over unfractionated heparin.
6. Role of new oral anticoagulants (NOACs) in VTE.
7. Formulate an appropriate prevention strategy for a patient at risk for deep vein thrombosis.
8. Formulate an appropriate treatment plan for a patient who develops a deep vein thrombosis or pulmonary embolism,

Thrombo-embolic disorders is the combination of thrombus and its main complication embolism. **Thrombus** is the formation of a blood clot inside a blood vessel, obstructing the flow of blood through the circulatory system. A clot that breaks free and begin to travel around the body is known as an **embolus**. Thrombo-embolic disorders are classified into venous thrombo-embolism (VTE) and arterial thrombo-embolism (ATE).
Venous thrombo-embolism:

- VTE is manifested as deep vein thrombosis (DVT) and pulmonary embolism (PE) resulting from thrombus formation in the venous circulation.
- It is often provoked by prolonged immobility and vascular injury and is most frequently seen in patients who have been hospitalized for a serious medical illness, trauma, or major surgery. VTE can also occur with little or no provocation in patients who have an underlying hypercoagulable disorder.
- While VTE may initially cause few or no symptoms, the first overt manifestation of the disease may be sudden death.
- Death from PE can occur within minutes, before effective treatment can be given.
- Long-term complications of VTE include Post-Thrombotic Syndrome (PTS) (after DVT) and Chronic Thrombo-embolic Pulmonary Hypertension (CTPH) (after PE) and recurrent thromboembolic events.
- The treatment of VTE is fraught with substantial risks since antithrombotic drugs require precise dosing, close monitoring as well as ongoing patient education.

Arterial thrombo-embolism:

- Arterial thrombosis is the formation of a thrombus within an artery. In most cases, arterial thrombosis follows rupture of an atheroma, and is therefore referred to atherothrombosis.
- Arterial thrombosis can embolize and is the major cause of arterial embolism, potentially causing infarction of almost any organ in the body as brain (stroke), heart (myocardial infarction), limbs (peripheral arterial occlusion), eye (central retinal artery occlusion).
**Virchow’s triad**

The main causes of thrombosis are given by Virchow’s triad which lists hypercoagulability, endothelial cell injury and disturbed blood flow.

**Pathophysiology:**
Thrombogenesis

- With vascular injury, a dynamic interplay between **thrombogenic** (activating) and **antithrombotic** (inhibiting) forces result in the local formation of a hemostatic plug that seals the vessel wall and prevents further blood loss.

- A disruption of this delicate system of checks and balances may lead to inappropriate clot formation within the blood vessel that can obstruct blood flow or embolize to a distant vascular bed.

- The clotting cascade is a stepwise series of enzymatic reactions that result in the formation of a fibrin mesh. Clotting factors circulate in the blood in inactive forms. Once a precursor is activated by specific stimuli, it activates the next precursor in the sequence. The final steps in the cascade are the conversion of prothrombin to thrombin and fibrinogen to fibrin.

- **Thrombin** plays a key role in the coagulation cascade; it is responsible not only for the production of fibrin, but also for the conversion of factors V and VIII, creating a positive feedback loop that greatly accelerates the entire cascade. Thrombin also enhances platelet aggregation.

- A number of tempering mechanisms control coagulation. The intact endothelium adjacent to the damaged tissue actively secretes several antithrombotic substances including heparan sulfate, thrombomodulin, protein C, and protein S.

- Activated protein C inhibits factor Va and VIIIa activity. Antithrombin and heparin cofactor II (HCII) are circulating proteins that inhibit thrombin and factor Xa. Heparan sulfate exponentially accelerates antithrombin and HCII activity. Tissue factor pathway inhibitor (TFPI) inhibits the extrinsic coagulation pathway.

- When these self-regulatory mechanisms are intact, the formation of the fibrin clot is limited to the zone of tissue injury. However, disruptions in the system often result in inappropriate clot formation.
Fibrinolysis:

- The fibrinolytic protein **plasmin** degrades the fibrin mesh into soluble end products collectively known as fibrin split products or fibrin degradation products.
- The fibrinolytic system is also under the control of a series of stimulatory and inhibitory substances. **Tissue plasminogen activator (t-PA)** and **urokinase plasminogen activator (u-PA)** convert plasminogen to plasmin.
- **Plasminogen activator inhibitor-1 (PAI-1)** inhibits the plasminogen activators and **α₂-antiplasmin** inhibits plasmin activity.
- Aberrations in the fibrinolytic system have also been linked to hypercoagulability.

1. Venous Thromboembolism:

**Signs & Symptoms of VTE**

- The symptoms of DVT or PE are non-specific and it is extremely difficult to differentiate VTE from other disorders.

**Common symptoms of DVT:**

- Unilateral calf or thigh pain, leg swelling, or redness.
- In up to half of the cases, this may not result in local symptoms or signs, and the onset of PE may be the first evidence of presence of VTE.
- PTS is long term complication of DVT caused by damage to the venous valves, producing chronic lower extremity swelling, pain, tenderness, skin discoloration and ulceration.
Common symptoms of PE:

- In the majority of cases, PE is suspected due to dyspnea and pleuritic chest pain either alone or in combination.
- Patients with massive PE may experience syncope associated with findings of hemodynamic collapse (severe hypotension & right ventricular failure followed by death)
- Acute sub-massive PE, involving only segmental or sub-segmental pulmonary arteries may have minimal or no symptoms.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Example</th>
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<tbody>
<tr>
<td>Age</td>
<td>Risk doubles with each decade after age 50</td>
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<tr>
<td>Prior history of VTE</td>
<td>Strongest known risk factor for DVT and PE</td>
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<tr>
<td>Venous stasis</td>
<td>Major medical illness (e.g., congestive heart failure)</td>
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<td></td>
<td>Major surgery (e.g., general anesthesia for greater than 30 minutes)</td>
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<td>Paralysis (e.g., due to stroke or spinal cord injury)</td>
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<td>Polycythemia vera</td>
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<td>Obesity</td>
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<td>Varicose veins</td>
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<tr>
<td>Vascular injury</td>
<td>Major orthopedic surgery (e.g., knee and hip replacement)</td>
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<td></td>
<td>Trauma (esp. fractures of the pelvis, hip, or leg)</td>
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<td>Indwelling venous catheters</td>
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<td>Hypercoagulable</td>
<td>Malignancy, diagnosed or occult</td>
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<td>states</td>
<td>Activated protein C resistance/factor V Leiden</td>
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<td></td>
<td>Prothrombin (20210A) gene mutation</td>
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<td></td>
<td>Protein C deficiency</td>
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<td>Protein S deficiency</td>
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<td></td>
<td>Antithrombin deficiency</td>
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<td></td>
<td>Factor VIII excess (greater than 90th percentile)</td>
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<td>Factor XI excess (greater than 90th percentile)</td>
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<tr>
<td></td>
<td>Antiphospholipid antibodies</td>
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<td></td>
<td>Dysfibrinogenemia</td>
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<tr>
<td></td>
<td>PAI-1 excess</td>
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<tr>
<td>Drug therapy</td>
<td>Pregnancy/postpartum</td>
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<td></td>
<td>Estrogen-containing oral contraceptive pills</td>
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<td></td>
<td>Estrogen replacement therapy</td>
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<td></td>
<td>SERMs</td>
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<tr>
<td></td>
<td>HIT</td>
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</table>
**Diagnosis:**

*Given that VTE can be debilitating or fatal, it is important to treat it quickly and aggressively. On the other hand, because major bleeding induced by antithrombotic drugs can be equally harmful, it is important to avoid treatment when the diagnosis is not reasonably certain.*

1. **Pretest Probability of PE & DVT (Modified Geneva & Wells score)**

The clinical examination for DVT is often unreliable, therefore, clinical decision rules (pretest probability scores) based on patient’s age, symptoms and risk factors have been developed to stratify patient into low, moderate or high clinical probability. This approach helps to improve the effectiveness of diagnosing DVT and to limit the need for additional testing.

2. **D-dimer**: is a degradation product of a cross-linked fibrin blood clot that is typically elevated in patients with acute VTE, but also by a variety of non-thrombotic disorders including recent major surgery, hemorrhage, trauma, pregnancy, or cancer.

3. **Imaging tests**

   **For DVT:**

   - **Duplex ultrasound** (is the most commonly used test to diagnosis DVT. It is a non-invasive test that can measure the rate and direction of blood flow and visualize clot formation in proximal veins of the legs. It cannot reliably detect small blood clots in distal veins. Coupled with a careful clinical assessment, it can rule in or out (include or exclude) the diagnosis in the majority of cases.
   - **Venography** is the gold standard for the diagnosis of DVT. However, it is an invasive test that involves injection of radiopaque contrast dye into a foot vein. It is expensive and can cause anaphylaxis and nephrotoxicity.
For PE:

- **Ventilation-perfusion (V/Q) lung scans**: measures the distribution of blood and air flow in the lungs. When there is a large mismatch between blood and air flow in one area of the lung, there is a high probability that the patient has a PE.

- **Pulmonary angiography** is the gold standard for the diagnosis of PE. However, it is an invasive test that involves injection of radiopaque contrast dye into the pulmonary artery. The test is expensive and associated with a significant risk of mortality.

- **Computerized tomographic pulmonary angiography (CTPA)** currently are the most widely used and evaluated tests for the diagnosis.

**Pharmacotherapy of VTE:**

Drugs used in prophylaxis & treatment of VTE are classified into:

1. **Parenteral anticoagulants:**
   - **Unfractionated Heparin (UHF) (iv & sc)**
     - UHF blocks coagulation by binding with antithrombin enhancing many folds its catalytic inhibitory effect on factor IIa (thrombin) & factor Xa.
     - UHF is a heterogeneous mixture of negatively charged sulfated mucopolysaccharide with Mwt ranging from 3000Da to 30000Da.
     - UFH binds non-selectively to a number of plasma & cellular protein reducing its anticoagulant effect.
     - UFH is cleared by zero-order enzymatic degradation (dose-dependent) & first-order renal elimination (dose-independent).
     - When administrated in fixed dose, the anticoagulant response to UFH shows inter-patient and intra-patient variability.
     - Protein binding and saturable elimination kinetics explain the wide variation in anticoagulant effect of UFH.
     - When given sc, the bioavailability of UFH ranges from 30 to 70% depending on the dose given, delayed onset of action and higher doses are required.
     - For the treatment of VTE, UFH is given by iv infusion following an initial bolus dose.
- Side effects include: bleeding, HIT (heparin-induced thrombocytopenia), osteoporosis.

These cooperate with bodies anti-thrombin
- Make it work more efficiently
- Which inactivates factors II and X

**Mechanism of Action**

UFH
- Inactivates Xa and IIa in 1:1 proportion

LMWH
- Inactivates Xa preferentially
  - 4:1 compared to IIa

Fondaparinux
- Only inactivates Xa

- **Low Molecular Weight Heparin (LMWH) (sc only)**
  Enoxaparin (*Clexane*®), Tinzaparin (*Innohep*®), Dalteparin (*Fragmin*®).
  - The LMWHs are smaller heparin fragments obtained by chemical or enzymatic depolymerization of UFH.
  - Due to their smaller chain length, LMWHs have relatively greater activity against factor Xa and inhibit thrombin to a lesser degree.
  - They exhibit less binding to plasma and cellular proteins, resulting in a more predictable anticoagulant response.
  - Consequently, routine monitoring of anticoagulation activity and dose adjustments are not required in the majority of patients.
  - On the contrary, monitoring is important in obese (BMI > 50 kg/m²), weight < 50 kg, renal impairment CrCl < 30 ml/min & pregnant women.
- LMWHs have longer plasma half-lives, allowing once- or twice-daily administration, improved subcutaneous bioavailability (> 90%), and dose-independent renal clearance.
- In addition, they are also associated with a lower incidence of bleeding, HIT and osteopenia.
- Advantages of LMWHs over UFH:
  - Greater bioavailability
  - Predictability and dose-dependent plasma level
  - Lower risk of bleeding
  - Lower risk of HIT
  - Lower risk of heparin induced osteoporosis
  - No need for blood monitoring
  - Can be safely administrated in outpatients, cancer & pregnancy.
  - Longer duration of anticoagulant effect enabling once or twice daily administration

- **Fondaparinux (Arixtra®) (sc only).**
  - Fondaparinux, the first agent in this class, is an indirect inhibitor of factor Xa, and exerts its anticoagulant activity by accelerating AT & has no effect on thrombin (factor IIa).
  - Predictable and linear dose-response relationship, rapid onset of activity, and long half-life.
  - Factor Xa inhibitors do not require routine coagulation monitoring or dose adjustments.
  - Fondaparinux has a half-life of 17 to 21 hours, permitting once-daily administration, but the anticoagulant effects of fondaparinux will persist for 2 to 4 days after stopping the drug.
  - Fondaparinux is as safe and effective
  - Fondaparinux is as safe and effective and can be used in patients with a history of HIT who require anticoagulation therapy.
  - Effective as IV UFH for the treatment of PE and SC LMWH for DVT treatment.
  - Is contraindicated in patients with severe renal impairment (CrCl less than 30 mL/minute).
As with other anticoagulants, the major side effect associated with fondaparinux is bleeding. Fondaparinux should be used with caution in elderly patients because their risk of bleeding is higher.

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2. **Oral anticoagulants:**
   - **Vitamin K Antagonist (VKA):**
     - Warfarin is FDA-approved for the prevention and treatment of VTE, as well as the prevention of thromboembolic complications in patients with myocardial infarction, atrial fibrillation, and heart valve replacement.
     - While very effective, warfarin has a narrow therapeutic index, requiring frequent dose adjustments and careful patient monitoring.
     - Warfarin exerts its anticoagulant effect by inhibiting the production of the vitamin K–dependent coagulation factors II (prothrombin), VII, IX, and X, as well as the anticoagulant proteins C and S and its full antithrombotic activity is delayed for 7 to 15 days.
It is extensively bound to albumin (98-99%) & metabolized in the liver via several isoenzymes including cytochrome P-450 (CYP)1A2, 2C9, 2C19, 2C18, and 3A4.

Hepatic metabolism of warfarin varies greatly among patients, leading to very large inter-patient differences in dose requirements and genetic variations in these isoenzymes result in a significantly lower warfarin dose requirement to achieve a therapeutic response.

Warfarin does not follow linear kinetics. Small dose adjustments can lead to large changes in anticoagulant response.

The dose of warfarin is determined by each patient’s individual response to therapy and the desired intensity of anticoagulation.

In addition to hepatic metabolism, warfarin dose requirements are influenced by diet, drug-drug interactions, and health status.

Therefore, the dose of warfarin must be determined by frequent clinical and laboratory monitoring.

The initial dose of warfarin must be overlapped with UFH or LMWHs.

Patients who are younger (less than 55 years of age) and otherwise healthy can safely use higher warfarin initiation doses (e.g., 7.5 or 10 mg).

A more conservative initiation dose (e.g., 5 mg or less) should be given to elderly.

The typical maintenance dose of warfarin for most patients will be between 25 and 55 mg per week, although some patients require higher or lower doses.

Adjustments in the maintenance warfarin dose should be determined on the total weekly dose and by reducing or increasing the weekly dose by 5% to 25%.

When adjusting the maintenance dose, wait at least 7 days to ensure that a steady state has been attained on the new dose before checking the INR again.

Side effect include mainly GI bleeding, intra-cranial bleeding.
• New/Novel/Non-vitamin K Oral Anticoagulants (NOACs)
  o Direct Thrombin inhibitor (DTI) (Factor IIa inhibitor): Dabigatran (Pradaxa®)
  o Factor Xa Inhibitors: Rivaroxaban (Xarelto®), Apixaban (Eliquis®) Edoxaban (Savaysa® or Lixiana®).

NOACs:

Pharmacodynamics:

• NOACs inhibit only a single target either factor Xa in case of rivaroxaban, apixaban & edoxaban or thrombin (factor IIa) in case of dabigatran.
• They have a rapid onset of action (peak plasma within 1-4 hours) and half-lives of about 12 hours (once or twice daily administration), they have also a rapid offset of action.
• NOACs produce a more predictable anticoagulant response, therefore given in fixed doses without routine monitoring.

Pharmacokinetics:

• NOACs are excreted in at least in part via the kidneys. The extent of renal clearance varies depending on the agent: 80% of dabigatran is excreted unchanged by the kidney and 50%, 33% and 27% of edoxaban, rivaroxaban and apixaban respectively.
• Because of their renal clearance, NOACs should be used with caution in patients with a CrCl < 30 ml/min and shouldn’t be used in patients with CrCl < 15 ml/min.
• All NOACs require some degree of hepatic metabolism, consequently they should be avoided in patient with liver dysfunction as evidence by increased PT/INR and reduced serum albumin at baseline.
• Potent inducers of CYP3A4, as phenytoin & carbamazepine may reduce plasma level of apixaban & rivaroxaban but will not affect the level of dabigatran & edoxaban.
• There are no dietary restrictions, except that rivaroxaban should be administrated with meal to maximize its absorption.

Adverse effects & Limitations

• There are no specific antidotes for the NOACs, but these are under development.
• Dabigatran may be not the best choice in patients with a history of coronary artery disease because of its higher risk of MI compared with warfarin.
• Dyspepsia have reported in patients treated with dabigatran.

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Thrombin</th>
<th>Factor Xa</th>
<th>Factor Xa</th>
<th>Factor Xa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>VKORC1</td>
<td>Thrombin</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
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<tr>
<td>Prolong</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>100</td>
<td>7</td>
<td>80</td>
<td>69</td>
<td>62</td>
</tr>
<tr>
<td>Dosing</td>
<td>OD</td>
<td>BID</td>
<td>OD (BID)</td>
<td>BID</td>
<td>OD</td>
</tr>
<tr>
<td>Time-to-peak effect</td>
<td>4-6 d</td>
<td>1-3 h</td>
<td>2-4 h</td>
<td>1-2 h</td>
<td>1-2 h</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>40</td>
<td>14-17</td>
<td>7-11</td>
<td>6-14</td>
<td>5-11</td>
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<tr>
<td>Renal clearance as unchanged drug (%)</td>
<td>None</td>
<td>80</td>
<td>33</td>
<td>27</td>
<td>50</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Interactions</td>
<td>Multiple</td>
<td>P-gp</td>
<td>3A4 P-gp</td>
<td>3A4 P-gp</td>
<td>P-gp</td>
</tr>
</tbody>
</table>

Except for apixaban, the rate of gastrointestinal bleeding with the NOACs is higher than that of warfarin, particularly in the elderly.

**Pharmacotherapy of VTE:**

A. **Prevention of VTE:**

• Given that VTE is often clinically silent and potentially fatal (high morbidity & mortality), prevention strategies have the greatest potential to improve patient outcomes.
• To rely on the early diagnosis and treatment of VTE is unacceptable because many patients will die before treatment can be initiated.
• **The goal** of an effective **VTE prophylaxis program** is to **identify** all patient at risk, **determine** each patient’s level of risk and **implement** regimens that provide sufficient protection for the level of each risk.
## Risk Classification and Consensus Guidelines for VTE Prevention

<table>
<thead>
<tr>
<th>Level of Risk</th>
<th>Calf Vein Thrombosis (%)</th>
<th>Symptomatic PE (%)</th>
<th>Fatal PE (%)</th>
<th>Prevention Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Minor surgery, age less than 40 years, and no clinical risk factors</td>
<td>2</td>
<td>0.2</td>
<td>0.002</td>
<td>Ambulation</td>
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<tr>
<td><strong>Moderate</strong></td>
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<tr>
<td>Major or minor surgery, age 40-60 years, and no clinical risk factors</td>
<td>10-20</td>
<td>1-2</td>
<td>0.1-0.4</td>
<td>Enoxaparin 40 mg SC every 24 hours, Tinzaparin 3500 units SC every 24 hours</td>
</tr>
<tr>
<td>Major surgery, age less than 40 years, and no clinical risk factors</td>
<td></td>
<td></td>
<td></td>
<td>IPC, Graduated compression stockings</td>
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<tr>
<td>Minor surgery, with clinical risk factor(s)</td>
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<tr>
<td>Acutely ill (e.g., myocardial infarction, ischemic stroke, heart failure exacerbation), and no clinical risk factors</td>
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<tr>
<td><strong>High</strong></td>
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</tr>
<tr>
<td>Major surgery, age greater than 60 years, and no clinical risk factors</td>
<td>20-40</td>
<td>2-4</td>
<td>0.4-1</td>
<td>UFH 5000 units SC every 8 hours, Dalteparin 5000 units SC every 24 hours</td>
</tr>
<tr>
<td>Major surgery, age 40-60 years, with clinical risk factor(s)</td>
<td></td>
<td></td>
<td></td>
<td>Enoxaparin 40 mg SC every 24 hours, Fondaparinux 2.5 mg SC every 24 hours, Tinzaparin 25,000 units SC every 24 hours</td>
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<tr>
<td>Acutely ill (e.g., myocardial infarction, ischemic stroke, heart failure exacerbation), with clinical risk factor(s)</td>
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<td></td>
<td>IPC</td>
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<tr>
<td><strong>Highest</strong></td>
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<tr>
<td>Major lower extremity orthopedic surgery</td>
<td>40-80</td>
<td>4-10</td>
<td>0.2-5</td>
<td>Adjusted dose UFH SC every 8 hours, aPTT greater than 36 seconds, Desirudin 15 mg SC every 12 hours</td>
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<tr>
<td>Hip fracture</td>
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<tr>
<td>Multiple trauma</td>
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<tr>
<td>Major surgery, age greater than 40 years, and prior history of VTE</td>
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<td></td>
<td>Enoxaparin 30 mg SC every 12 hours, Fondaparinux 2.5 mg SC every 24 hours, Tinzaparin 75,000 units SC every 24 hours, Warfarin (target INR = 2-3)</td>
</tr>
<tr>
<td>Major surgery, age greater than 40 years, and malignancy</td>
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<tr>
<td>Major surgery, age greater than 40 years, and hypercoagulable state</td>
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<tr>
<td>Spinal cord injury or stroke with limb paralysis</td>
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</table>

aPTT, activated partial thromboplastin time; INR, International Normalized Ratio; IPC, intermittent pneumatic compression; PE, pulmonary embolism; SC, subcutaneous; UFH, unfractionated heparin; VTE, venous thromboembolism.
- Low-dose UFH (5000 units every 8 or 12 hours) sc has been shown to reduce the risk of VTE by 55% to 70% both in patients with moderate to high level of risks.
- The LMWHs and fondaparinux provide a higher degree of protection against VTE in most high-risk & in very-high-risk populations.
- Warfarin appears to be as effective as the LMWHs for the prevention of symptomatic VTE events in the highest-risk populations. When used to prevent VTE, the dose of warfarin must be adjusted to maintain an International Normalized Ratio (INR) between 2 and 3.
- Oral administration and low drug cost give warfarin some advantages over the LMWHs and fondaparinux.
- However, warfarin does not achieve its full antithrombotic effect for several days, requires frequent monitoring and periodic dosage adjustments, and carries a substantial risk of major bleeding.
- Warfarin should only be used when a systematic patient monitoring system is available. If TTR is below 65%, discontinue warfarin & switch to LMWHs or fondaparinux.

**Time in Therapeutic Range of INR of 2.0 to 3.0:**

1. **Percent of Visits in Range (Traditional Method)**
   This looks at how many visits had INR results in range, and divides by the total number of visits. If the patient has had 8 visits, and 6 had readings within their therapeutic range, then the patient is considered in range 75% of the time.

2. **Percent of Days in Range (Rosendaal Method)**
   This is the most complex of the calculations, as it looks at the amount of time between visits to determine how long the patient might have been within their therapeutic range. If a patient has a therapeutic range of 2.0 - 3.0, and on May 1st tested at 2.5, then tested 3.5 on May 31st, then we can determine how many days were in range. Since there were 30 days between tests, you assume that the patient slowly moved from 2.5 to 3.5 over those 30 days, so around May 15th, the patient was probably over 3.0, and therefore was out of range. Therefore, we estimate that 15 days were in range, and 15 days were out of range (within the 30-day time period), which means the patient is within range 50% of the time.

Patient who are well controlled on warfarin (TTR of 65% or more) should not consider any priority for switching.
NOACs in orthopedic thromboprophylaxis:

- **Rivaroxaban** (10 mg once daily), **Dabigatran** (220 mg once daily) & **Apixaban** (2.5 mg twice daily) are currently licensed in orthopedic thromboprophylaxis (Total Hip Arthroplasty THA & Total Knee Arthroplasty TKA) in USA & EU.

- Compared with **enoxaparin**, the risk of symptomatic VTE was **lower with rivaroxaban** but **similar with dabigatran and apixaban**.

- Compared with **enoxaparin**, clinically significant bleeding was **higher with rivaroxaban** but **similar with dabigatran and lower with apixaban**.

**Case scenario**

KK is a 69-year-old obese female who fell and fractured her right hip. She is hospitalized and will undergo surgery to repair her fractured right hip.

**PMH:** Hypertension × 12 years; dyslipidemia × 10 years; obesity ×20 years; degenerative joint disease × 5 years; recurrent urinary tract infections. Smoke one-half pack per day for 25 years; occasional alcohol use. The patient has Medicare, but due to her fixed income, has difficulty paying for medications, leading to occasional periods of non-compliance.

**Current Meds:** Metoprolol 100 mg by mouth twice daily, Hydrochlorothiazide 25 mg by mouth daily, Vytorin 10/40 (ezetimibe 10 mg/simvastatin 40 mg) by mouth daily, Salsalate 750 mg by mouth twice daily (NSAID: salicylates), Trimethoprim-sulfamethoxazole SS tablets by mouth twice daily for 7 days (last treatment was 1 month ago), Shark cartilage 3 tablets by mouth daily, Enteric-coated aspirin 81 mg by mouth daily, Ginseng 2 tablets by mouth daily

**Allergies:** No known drug allergies

**PE:** VS: blood pressure 145/90 mm Hg; heart rate, 72; respiratory rate,16; temperature, 37.4°C (99.3°F); weight 280 lb. (127.3 kg); body mass index (BMI) 40 kg/m²

**Labs:** Within normal limits; estimated glomerular filtration rate =74 mL/minute

- Which risk factor(s) predispose KK to VTE?
- What is KK’s estimated risk for developing VTE?
- Given KK’s presentation and history, create an appropriate VTE prophylaxis plan including the pharmacologic agent, dose, route and frequency of administration, duration of therapy, monitoring parameters, and patient education.
B. Treatment of VTE:

Clinical therapeutic outcomes:

- The goal of VTE treatment is to prevent short and long-term complications of the disease.
- In the short-term (few days to 6 months), the aim of therapy is to prevent propagation or local extension of the clot, embolization and death.
- In the long-term (more than 6 months), the aim of therapy is to prevent complications, such as PTS, CTPH and recurrent VTE.

A. Conventional regimen for treatment of VET:

1. Initial therapy (2 overlapped steps):
   - Starts with a rapidly-acting parenteral anticoagulant, as UFH or LMWHs overlapped with VKA. (why?)
   - The parenteral anticoagulant is given for at least 5 days and is stopped when the anticoagulant response with VKA is therapeutic as evidenced by INR between 2 & 3.
   - Once UFH commences, check aPTT at 6-hour interval and adjust to maintained at 1.5-2.5 times the institutional therapeutic range.
   - LMWHs do not require aPTT monitoring.
   - Platelets count must be checked daily while on UFH or LMWHs
   - Stop UHF or LMWHs after 5 days overlap with warfarin (minimally), when INR stable between 2-3 for 2 days.
   - Achieving a therapeutic aPTT (1.5-2.5 times control value) in the first 24 hours after initiating UFH is critical because this has been shown to lower the risk of recurrent VTE.
   - Weight-based dosing regimen are more likely to exceed the therapeutic threshold in the first 24 hours.
   - Another approach is 5000-unit bolus dose iv followed by iv infusion at rate of 1000 to 1200 unit/hour.
Doses of UFH, LMWHs & fondaparinux in acute VTE:

2. **Long-term therapy**
   - Once therapeutic INR is established, VKA is then continued as monotherapy for a minimum 3 months.
   - At this point, the decision to stop or continue treatment depends on the balance between the risk of recurrence if warfarin is stopped and the risk of bleeding if it is continued.
   - Patients with VTE in the setting of a transient and reversible risk factors such as surgery, long air travel, have a low risk of recurrence if anticoagulant therapy is stopped at 3 months provided they are fully mobile (grade 1B, AT10, 2016).

3. **Extended therapy:**
   - In contrast those with ongoing risk factors, such as active cancer, patients with **unprovoked VTE**, are often prescribed extended anticoagulant therapy as long as the bleeding risk is not excessive (6-12 months).
   - **If anticoagulant therapy is stopped in patients with unprovoked VTE, the risk of recurrence is at least 10% at 1 year and 30% at 5 years.**
B. NOACs indications in acute VTE:

- Because of their rapid onset of action, and lack of routine monitoring of anticoagulant effect, hence simplifying the VTE treatment, NOACs have the potential to enable **all-oral regimen** which can replace parenteral anticoagulant and warfarin for initial, long-term and extended VTE treatment. *(AT10, 2016, Grade 2B, ACCP; ESC 2014, Grade 1B)*.

- Apixaban: 10mg twice daily for 7 days then 5mg twice daily for at least 3 months
- Rivaroxaban: 15mg twice daily for 3 weeks than 20mg once daily thereafter for 3 months
- In case of dabigatran (150mg twice daily) & edoxaban (60mg once daily), they must be preceded by 5 days parenteral anticoagulant & continued for 3 months.
- NOACs are also recommended for extended therapy in case where INR monitoring is impractical, patient has a poor anticoagulant control on warfarin (TTR< 65%), and likelihood of drug interaction between warfarin and other concomitant drugs or food.

Treatment of VTE in special population:

- **In cancer patients:** In patient with DVT or PE and cancer (cancer-associated thrombosis), as long term anticoagulant therapy, LMWHs are preferred over VKA *(Grade 2B, AT10, 2016)*.
- **In pregnant women:** VKA is contraindicated in pregnancy due to teratogenic effect in the first trimester and risk of fetal intracranial bleeding in the third trimester. LMWHs is the drug of choice for VTE during pregnancy.

**Thrombolytics**

- Candidates for thrombolytic therapy are patients with acute massive embolism who are hemodynamically unstable (SBP < 90 mm Hg) and
at low risk of bleeding & in case of threatened limb loss (grade 2B, AT10, 2016).

- Thrombolytic therapy may be systemic or catheter-directed.