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# ANTI - COAGULANT MANAGEMENT OF VENOUS THROMBOEMBOLISM: MECHANISMS, SELECTING THERAPIES AND STRATEGIES FOR OPTIMIZING OUTCOMES

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**ABSTRACT**

Thromboembolism is a vascular disorder, which is characterised by the obstruction of blood vessels (arteries or veins) due to formation of blood clot (thrombus) inside the blood vessels, that may even lead to formation of embolus (movement of blood clot from one place to another place). Based on type and location of blood clot formation, they are classified into venous thromboembolism (arise of clot formation inside the vein) and arterial thromboembolism (arise of clot formation inside the artery). Venous thromboembolism is a disorder where the blood clot blocks the flow of blood through veins. The VTE can lead to two different kinds of blood clotting conditions: deep vein thrombosis and pulmonary embolism. When a vein is blocked, the blockage leads to inflammation and cannot get enough oxygen and nutrients. This can-do serious damage to the veins, tissues, and organs. Arterial thromboembolism is a tissue death of arteries occurs when the blood clot breaks off and blocks an artery that brings oxygen-rich blood from the heart to rest of the body. This causes ischemia, stroke, or heart attack. Sometimes infarction (myocardial infarction) – tissue death due to inadequate blood supply. The mainstay of thromboembolism management is the anticoagulation therapy as it is considered as the first line therapy and drug of choice for both treatment and prophylaxis. Anticoagulant drugs, ranging from different preparation of heparin, direct oral anticoagulants, and vitamin k antagonists. These work mainly by inhibiting important factors and enzymes in the coagulation cascade by preventing the thrombus propagation and embolization. The choice and duration of anticoagulation depend on the individual patient's risk factors, bleeding risk and preferences; such treatment reduces the risk of recurrence.

## INTRODUCTION

Venous thromboembolism (VTE) is a chronic illness that collectively encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE). Venous thromboembolism (VTE) is the third leading cardiovascular diagnosis after a heart attack and stroke [1]. VTE occurs when a blood clot (thrombus) starts in a vein, it is when a thrombus or blood clot form in a deep vein usually in the lower extremities like leg, thigh or pelvis termed as deep vein thrombosis, because of something called Virchow's triad [2]. The Virchow's triad consists of three characteristics include: endothelial injury (which means damage of the vein), venous stasis (blood remains stationary) and hypercoagulation (condition where blood clots easily), at these conditions the patient possess high risk for forming a thrombus [3].

The blood clot can even break off and travel (embolize) through the body into the lungs, which is called a pulmonary embolism [2-4]. The risk of VTE is highest after a major surgery or major injury, this is because blood clot can develop in veins damaged by surgery or injury due to lack of movement. VTE can restrict or block blood flow and oxygen, which damage the body's tissue or organs [1]. This can be especially serious in the case of pulmonary embolism, where the embolus blocks blood flow to the lungs, leading to cause of sudden chest pain, shortness of breath and even cause of death [2-4]. In terms of treatment, the patient is put on an anticoagulant, these help the blood clot from getting any bigger and will prevent the formation of new clots. For some patients a precipitating cause of their VTE event can be identified, these are considered to have "provoked" VTE. For many other patients, no precipitating event is identifiable. These patients are often categorized as having "unprovoked" or "idiopathic" [5] VTE. This is gradually developing disorder which is often underdiagnosed but can have a serious consequence. Nevertheless, it is a preventable medical condition if diagnosed accurately and early.

**Venous thromboembolism:** The disease venous thromboembolism (VTE) process starts often in one of the large veins of the leg with the formation of a blood clot (thrombus). This can be due to vessel wall injuries, a pathological increase in the coagulability of the blood or circulation deficits such as venous stasis. The resulting blood clot consists mostly of red blood cells (RBC's), which are held loosely together by strands of fibrin. The clot can either remain localized or may lead into a considerable risk of clot breaking away and travelling with the bloodstream, through the heart and into the lungs. That is where the fragment of clot eventually blocks a pulmonary artery, which is a life-threatening outcome [2,3]. Deep vein thrombosis and pulmonary embolism are the two most important manifestation of venous thromboembolism (VTE) [1].

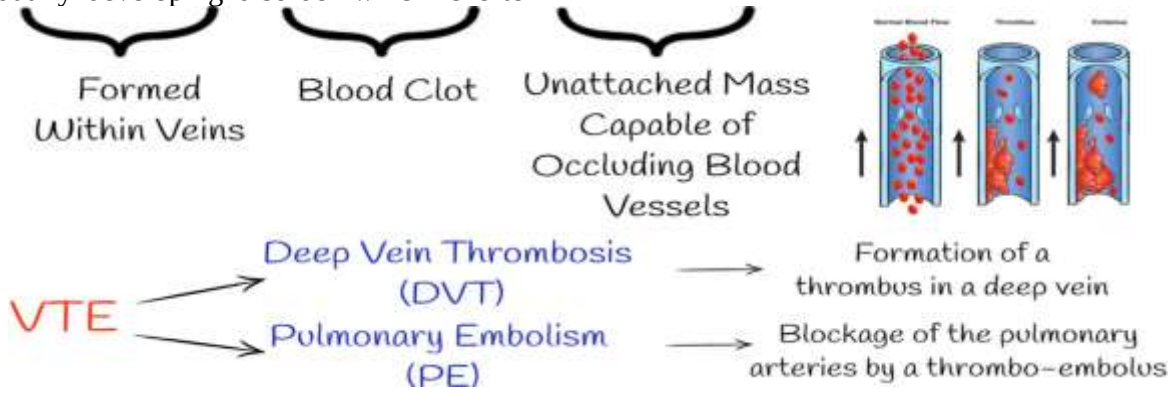


**Figure 1: Understanding of venous thromboembolism (VTE)**

**Deep vein thrombosis (DVT)**: A DVT occurs when a blood clot, or thrombus forms in one or more of the deep veins in the body, which impedes(block) the return of the venous flow. This causes increased pressure within the vein's legs, thigh or pelvis (specifically the popliteal and femoral veins) [2]. In some cases, DVT can occur in other areas, such as the arms. The formation of a clot can damage valves and walls of veins. If clot remains in the veins for a long period of time, this can result in long-term consequences known as post-thrombotic syndrome (PTS). PTS impacts up to 50% of DVT patients with life debilitating symptoms such as severe pain, swelling and discoloration of the affected limb.

**Pulmonary embolism (PE):** A PE is a serious and potentially life-threatening cardiovascular condition characterized by the obstruction of one or more pulmonary arteries by a thrombus (blood clot), that has typically originated elsewhere in the body, most commonly from the deep veins of the lower extremities. The affected area of the lung is no longer available for the oxygenation of blood, causing increased stress on the heart and decreased

oxygen levels in the body [3]. As a manifestation of venous thromboembolism (VTE), PE represents a significant global health burden, contributing to substantial morbidity and mortality, if not promptly recognized and managed [1].

**Pathophysiology**

**Vasoconstriction -** within the few minutes of damage or trauma to the blood vessels, vascular spasm, which leads to vasoconstriction at the site of disrupted endothelial lining [6].

**Platelet adhesion –** the extracellular matrix becomes exposed to the blood components, these extracellular matrix releases cytokines and inflammatory markers that leads to adhesion of the platelets. It is the complex process mediated by interactions between various receptors and proteins including tyrosine kinase receptors, glycoproteins receptors and other G-protein receptors [6].

**Platelet activation and aggregation –** the platelets that have adhered, release their cytoplasmic granules (ADP, serotonin and other activation factors). They also undergo transformation, P2Y1 receptors help in the conformational changes in platelets. Thus, the platelets are activated, adhered to each other and damage the endothelial surface leading to the formation of a primary platelet plug [6].

**Extrinsic pathway –** the tissue factor binds to factor VII. The factor VII (VIIa) further activates factor X and factor IX. Then factor VIII (factor VIIa), leads to the activation of factor Xa. This factor Xa binds to factor Va and calcium to generate prothrombinase complex that cleaves the prothrombin into thrombin [7].

**Intrinsic pathway –** with the thrombin production, there occurs conversion of factor XI to activated factor XIa. Factor XIa with activated factor VII and tissue factors convert factor IX to activated factor IXa. The activated IX combines with activated (factor VIIIa) and activated factor Xa and then the activated factor Xa binds to activated factor Va and converts prothrombin to thrombin [7].

**Fibrin clot formation –** This is the final step in the coagulation cascade involve the conversion of fibrinogen to fibrin, these fibrin monomers forms to fibrin polymer mesh and result in a cross-linked fibrin clot [7].

**Complications:** A VTE can lead to several significant complications:

- Anticoagulant related risk - the studies shows that the risk of bleed is higher with warfarin that with direct oral anticoagulants or due to concomitant use of other medications (e.g. antiplatelets) that independently increase the risk of bleeding.
- Patient related risks - age, recent surgery, underlying medical conditions (deep vein thrombosis, pulmonary embolism, recurrent VTE, anemia, cancer, renal failure, diabetes, and thrombocytopenia), coagulopathy.

**Diagnosis and tests:** To confirm that patient have a venous thromboembolism (VTE)disease, initially diagnosing requires combination of medical history, risk factors, physical examination, and diagnostic tests by taking the preliminary blood test to look for markers of blood clotting through image testing, to locate the blockage in order to rule out the possible condition. Hence, based on the specific medical history different tests are used to diagnose deep vein thrombosis (DVT) and pulmonary embolism (PE) [4,7,8].

**Biomarkers**

**D-dimer test**- It is a blood test that measures the presence of protein fragments. D-dimer is a protein formed in our body when a blood clot dissolves or breaks. The prime use of the test is to assess the possibility of blood clotting disorders, like deep vein thrombosis (DVT), pulmonary embolism (PE), and other disseminated intravascular coagulation [9].

**P-selectin**- It is a protein expressed on the surface of activated platelets and endothelial cells. This protein involves in the elevated inflammation and blood clot formation in venous thromboembolism (VTE) patients and P-selectin serves as a potential biomarker for its early marker for the disease [9].

**Image studies**

**Ultrasound**-This method is usually preferred as the first choice for visualizing the veins and the flow of blood through them with the help of sound waves. It is the widely accepted diagnostic tool used for the detection of clot or blockages in the veins. Hence this protocol involves in evaluating venous

thromboembolism (VTE), including deep vein thrombosis (DVT) [9].

**Venography**-It is a diagnostic imaging technique, where a contrast agent is injected into a peripheral vein allowing x-rays to visualize the venous system to detect blood clots and provides information about the severity and extent of venous thromboembolism (VTE) [9].

**CT pulmonary angiography-** It is a non-invasive imagining technique used to detect pulmonary embolism (PE). The computed technology (CT) scan, provides 3-D imaging of the blood clots within the veins and arteries of the lungs. This method is considered as the standard test for PE [9].

**Pulmonary angiogram–**It is a procedure that uses x-rays and a special dye to visualize the arteries in the lungs and to diagnose conditions like pulmonary embolism. The procedure typically involves inserting a thin, flexible tube (catheter) into a vein, usually the arm. This method is preferred when other tests are inconclusive to detect blood clots in the pulmonary artery [9].

**TREATMENT:** Venous thromboembolism (VTE) is a commonly found medical condition with high morbidity and mortality. The VTE is effectively treated with anticoagulant therapy often called as "blood thinners" [4,8]. These medications are used to prevent the thrombus extension and reduce the risk of recurrent VTE. It is important to identify if a VTE is provoked or unprovoked as it is crucial in deciding how to manage the treatments choice and duration of anticoagulation depend on the individual patient's risk factors, bleeding risk and preferences. Therapy for venous thromboembolism typically involves a multiple stage approach with initial rapid anticoagulation, primary treatment and followed by extended therapy. The anticoagulants are broadly classified into oral and parenteral choices include: Heparin or LMWH (low molecular weight heparin), vitamin k antagonists or DOACs (direct oral anticoagulants) [10,11].

**Parenteral anticoagulants**- The therapy involves administration of medication to thin the blood through injection or infusion via intravenously or subcutaneously. This type of therapy used for acute situations like treating or preventing venous thromboembolism (VTE). Parenteral anticoagulants are categorized into unfractionated heparin (UFH), low molecular weight heparin (LMWH), fondaparinux [10].

**Oral anticoagulants**- The therapy involves medications taken by mouth to reduce the risk of blood clots by preventing thromboembolic events. These medications are used in conditions like venous thromboembolism (VTE), that includes both deep vein thrombosis (DVT) and pulmonary embolism (PE). Oral anticoagulants are broadly categorized into vitamin k antagonist (warfarin) and direct oral anticoagulants [10].

**Anticoagulant choices**

**HEPARIN or unfractionated heparin (UFH) -** It is the most powerful and instantaneously acting anticoagulant. It acts indirectly by activating plasma antithrombin III then the heparin antithrombin III complex binds to the clotting factors of the intrinsic and common pathways (Xa, IIa, IXa,XIa, XIIa and XIII) and inactivates them except the factor VIIa in the extrinsic pathway. At low concentration of heparin, factor Xa mediated conversion of prothrombin to thrombin is selectively affected. The anticoagulation action is exerted mainly by inhibition of factor Xa as well as thrombin (IIa) mediated conversion of fibrinogen to fibrin [10,11]

**Low molecular weight heparins (LMWH) -** Heparins has been fractionated into LMW forms, these LMWH selectively inhibit factor Xa with little effect on IIa. They act only by inducing conformational change in antithrombin III and not by providing an interaction of antithrombin III with thrombin. As a result, LMW heparins have smaller effect on PPT (partial thromboplastin time) and whole blood clotting time than unfractionated heparin (UFH) [10-12].

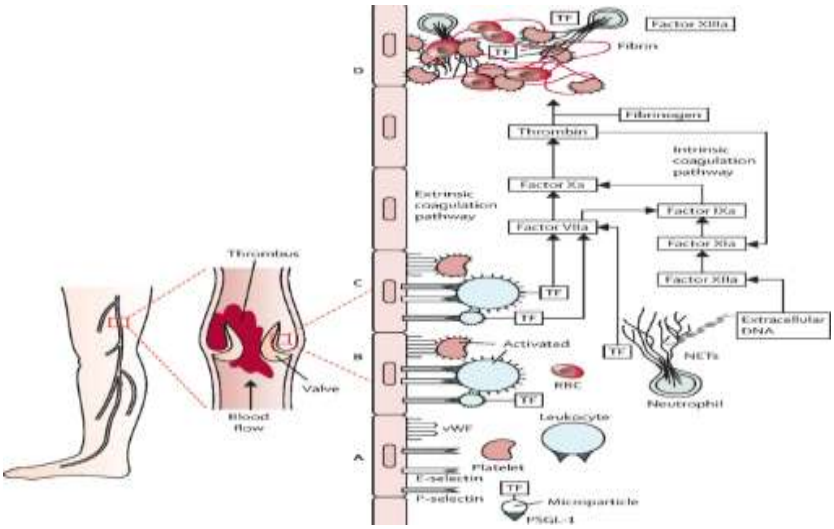


**Figure 2: Pathophysiological mechanism of clot formation**

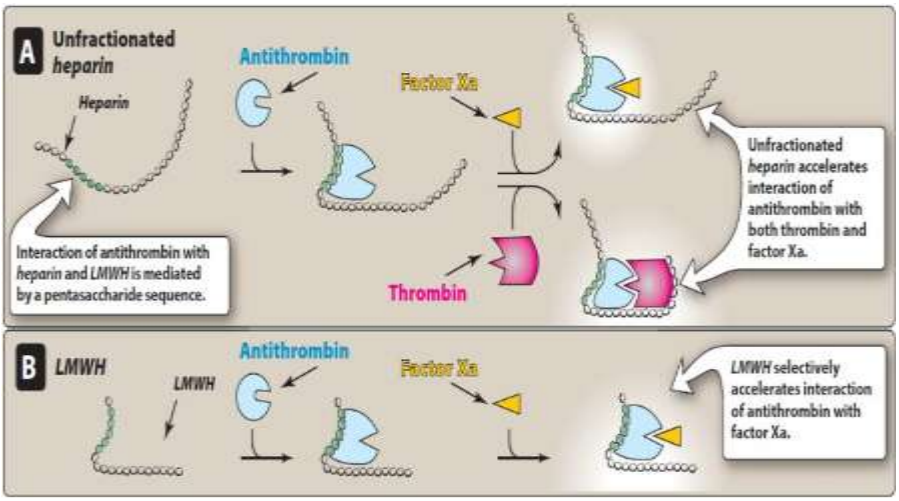


**Figure 3: Heparin and low molecular weight heparin (LMWH) – mediated inactivation of thrombin or factor Xa**

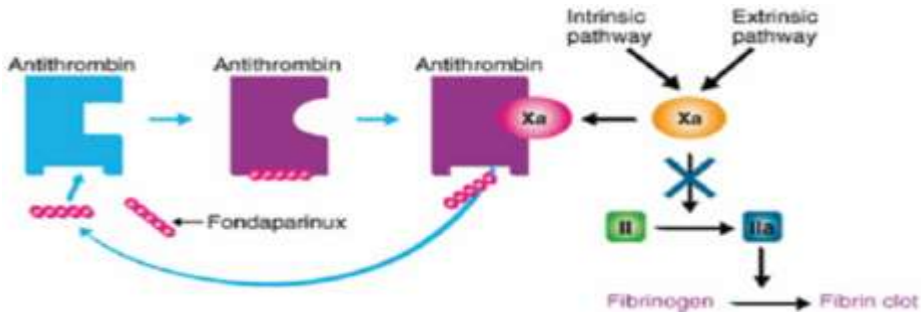


**Figure 4 Mechanism of selective inhibitor of factor Xa**

**Fondaparinux:** It is a synthetic anticoagulant which is a selective Xa inhibitor. Fondaparinux selectively binds to antithrombin III to neutralize factor Xa. The neutralization of factor Xa interrupts the blood coagulation cascade and thus inhibits thrombin (factor IIa) formation and thrombus development [12].

**Vitamin K antagonist (warfarin)**- warfarin is a drug that act indirectly by interfering with the synthesis of vitamin k dependent clotting factors (II, VII, IX and X) in liver and as well

as the regulatory factors such as protein c and protein s, that are needed for the formation of clot. The warfarin competitively inhibits an enzyme called vitamin k epoxide reductase complex 1, which is essential for activating vitamin K in the body, and interfere with the regeneration of the active hydroquinone form of vitamin, thus inhibition of these enzymes in the body depletes the functional vitamin k available in the body and ultimately impairs the synthesis of clotting factors and blood clotting process [11-12].

**Direct oral anticoagulants (DOAC's)** – This refers to those oral anticoagulants that specifically inhibit factor IIa (thrombin) or Xa. These are categorized into-

**Direct thrombin inhibitors**-drugs bivalirudin, argatroban, and dabigatran, these act by inhibiting the conversion of fibrinogen to fibrin by binding directly to thrombin.

**Direct factor Xa inhibitors**- drugs include rivaroxaban, apixaban, edoxaban etc. involves in inhibiting the conversion of prothrombin to thrombin by binding directly to factor Xa [12].

**Phases and duration of anticoagulants**

The treatment for VTE typically in three phases: the initiation, primary treatment and the extended or secondary phase. Anticoagulation therapy options include unfractionated heparin (UFH), low molecular weight heparin (LWMH), fondaparinux, vitamin K antagonist (VKAs) i.e. warfarin, and direct oral anticoagulants (DOAC's).

**Initiation phase -** The goal of the initiation is to slow down the thrombus formation to prevent new thrombus forming and allowing to maintain venous blood flow. This can be achieved through either oral anticoagulation, with apixaban or rivaroxaban or through parenteral medication (unfractionated heparin, low molecular weight heparin) quickly after diagnosis for 5-12 days [10].

**Treatment phase**- The treatment phase can last between 3-6 months, depending on the thrombus burden, symptoms, and patient clinical scenario. DOACs are the mainstay treatment in this phase. If the patients using apixaban or rivaroxaban as an oral strategy, these DOACs can typically used with a dose reduction. The aim of this phase is to prevent the recurrence of VTE [10].

**Extended phase** –This includes anticoagulation beyond the treatment phase of 3-6 months. Patient preference as well as risk scores can assist with the process for extended phase anticoagulation. In patients with unprovoked VTE, extended phase treatment should be considered. Both DCOAs and warfarin are viable options for extended phase anticoagulation [10]. Inpatient treatment of VTE begins with parenteral agents, preferably LMWH. Unfractionated heparin is preferred over LMWH if patient is hemodynamically unstable, has severe renal insufficiency, high risk bleeding. Outpatient is treated with LMWH for phase 1 and then DOAC or warfarin for phase 2 and extended phase.

**Specific consideration**–Deciding on which anticoagulant to use depend on the indication, patient underlying condition and preference. Heparin, LWMH, fondaparinux and the DOACs (rivaroxaban and apixaban) are the only agents approved by the Food and Drug Administration (FDA), recommended for the acute treatment phase, while the DOAC's and warfarin are anticoagulation options for the long-term and extended treatment phases. The LMWHs can be used for the patients with cancer and during pregnancy.

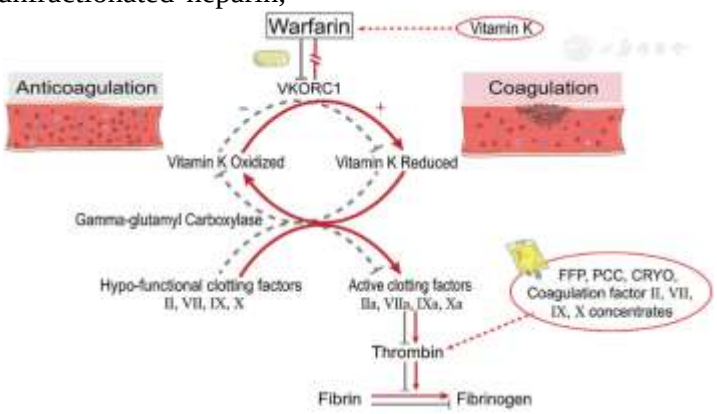

**Figure 5: Mechanism of action of warfarin**

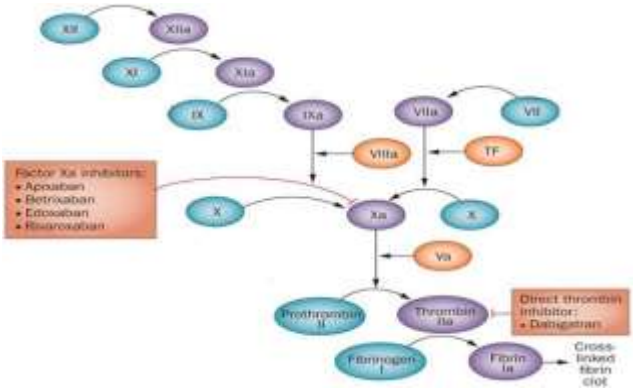


**Figure 6: Oral anticoagulants inhibiting factor IIa and Xa**

**Table 1: Anticoagulant agents for patients with venous thromboembolism by treatment phases**

| Patient | Initial phase (first one week after diagnosis) | Treatment phase (3-6 months) | Extended phase (beyond 3-6 months) |
|---|---|---|---|
| Most patients | UFH, LMWH, fondaparinux or DOACs (rivaroxaban or apixaban) | DOACs (rivaroxaban, apixaban, dabigatran, or edoxaban) or VKA (warfarin) | Use same anticoagulant used in the treatment phase. If first or second VTE is unprovoked DVT of leg or PE with low or moderate bleeding risk |
| Renal failure or liver failure with coagulopathy | UFH | VKA (warfarin) | Warfarin |
| Hemodynamically unstable patients | UFH or LMWH | Not applicable | Not applicable |
| Pregnancy or cancer patients | UFH or LMWH | LMWH | LMWH |
| Recurrent VTE | Not applicable | If on a non LMWH anticoagulant convert to LMWH. If on LMWH, increase the dose. | If on a non LMWH anticoagulant convert to LMWH. If on LMWH, increase the dose. |
| Need for reversal agent | UFH, LMWH (partially reversible) | Warfarin<br><br>Dabigatran | Warfarin<br><br>Dabigatran |

*DOAC = direct oral anticoagulants, DVT = deep vein thrombosis, PE = pulmonary embolism, LMWH = low molecular weight heparin, VKA = vitamin k antagonist, UFH = unfractionated heparin, VTE = venous thromboembolism.*

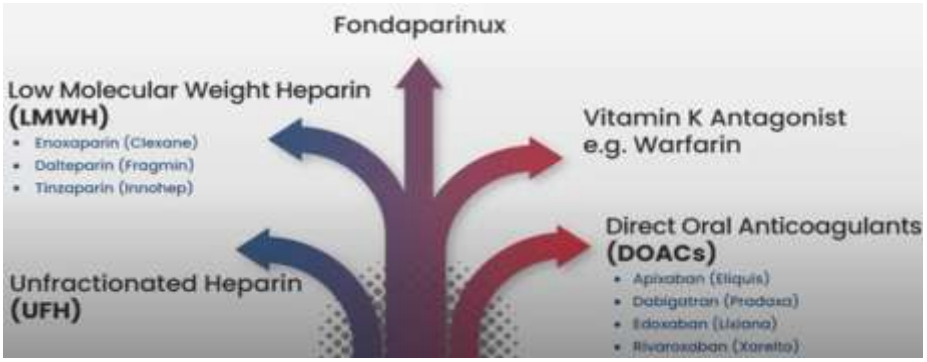


**Figure 7: List of anticoagulation agents**

**Prevention:** Preventing VTE is a critical aspect of patient care, particularly in high-risk individuals. Strategies include;

- Pharmacological prophylaxis, using anticoagulants like low-molecular weight heparin (LMWH), unfractionated heparin (UFH), direct oral anticoagulants at a lower dose to prevent clot formation.
- Early ambulation of patients out of bed to move as soon as a safely possible after surgery or illness.
- Elastic compression stockings.
- Intermittent pneumatic compression (IPC) devices, that inflate and deflate around the legs to promote blood flow.
- Lifestyle modifications
    - Staying active and exercising regularly
    - Maintain a healthy weight
    - Staying hydrated
    - Moving legs and taking breaks during long periods of sitting (e.g. during travelling) [13].

**Conflicts of interest:** None

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