Venous thromboembolism

Thrombosis is the process involved in the formation of **a fibrin blood clot**. Both platelets and a series of coagulant proteins (clotting factors) contribute to clot formation. An **embolus** is a small part of a clot that breaks off and travels to another part of the vascular system. Damage is caused when the embolus becomes trapped in a small vessel, causing occlusion and leading to **ischemia** or **infarction** of the surrounding tissue.

Venous thromboembolism (VTE) refers to a blood clot that starts in a vein. There are two types:

1-**Deep vein thrombosis (DVT)** is a clot in a deep vein, usually in the leg. DVT sometimes affects the arm or other veins.

2-**Pulmonary embolism (PE)** occurs when a DVT clot breaks free from a vein wall, travels to the lungs and then blocks some or all of the blood supply. Blood clots originating in the thigh are more likely to break off and travel to the lungs than blood clots in the lower leg or other parts of the body.

Epidemiology

VTE is the third most common cause of vascular death (after myocardial infarction and stroke). Incidence of VTE doubles in each decade of life after age 50 years. About 90% of the instances of DVT involve the legs, about 5% involve the upper extremities (axillary, subclavian, or jugular veins), and the remaining 5% involve other veins of the body (e.g., internal iliac, renal, ovarian). About 50% of the cases of VTE are associated with hospitalization, which emphasizes the importance of using appropriate prophylaxis to prevent VTE in high-risk patients.

Etiology of Thromboembolism

VTE risk factors can be categorized in to: stasis in blood flow, vascular endothelial injury, and inherited or acquired changes in blood constituents resulting in hypercoagulation states. Most patients who develop VTE have more than one, and often multiple, risk factors. Venous injury is thought to predispose to thrombosis by exposing blood to subendothelial tissue factor and to collagen, which binds von Willebrand's factor. Vascular injury occurs with trauma (especially fractures of the pelvis, hip, or leg), orthopedic surgery (eg, knee and hip replacement), or venous catheters.

A balance between naturally occurring coagulation and fibrinolytic factors and their inhibitors serves to maintain blood fluidity and hemostasis. Inherited or acquired changes in this balance can predispose to thrombosis. The most

important inherited biochemical disorders associated with VTE are defects of the naturally occurring inhibitors of coagulation (i.e., deficiencies of antithrombin, protein C, or protein S and resistance to activated protein C). Acquired hypercoagulable states include estrogen therapy (three-fold increase in VTE, highest during the first 6 months), lupus erythematosus, and malignancy. Stasis can result from vessel obstruction, prolonged immobility, or increased blood viscosity resulting from medical illness (eg, heart failure), surgery, paralysis (eg, stroke), polycythemia vera, obesity, or varicose veins. Venous stasis is thought to predispose to thrombosis by causing local hypoxia, which attracts inflammatory cells and causes endothelial dysfunction, leading to an increase in the local concentration of clotting factors and tissue factor and an increase in interactions between circulating cells and the venous endothelium.

Clinical Presentation:

Many patients never develop symptoms from the acute event. More than 90% of asymptomatic postoperative DVT resolves without causing symptoms. DVT mainly affects the large veins in the lower leg and thigh, almost always on one side of the body at a time. The clot can block blood flow and cause:

1-Leg pain or tenderness of the thigh or calf.

2-Leg swelling (edema).

3-Skin that feels warm to the touch.

4-Reddish discoloration or red streaks.

PE, or pulmonary embolism, can be fatal and occurs when the DVT breaks free from a vein wall and blocks some or all of the blood supply to the lungs, causing: Cough, chest pain or tightness, shortness of breath, palpitations, hemoptysis, dizziness, or lightheadedness.

Post thrombotic syndrome (PTS), a long-term complication of DVT caused by damage to the venous valves, may also result in chronic lower extremity swelling, pain, tenderness, skin discoloration, and, in the most severe cases, ulceration.

Diagnosis of Deep Venous Thrombosis

The clinical features of DVT, such as swelling, redness, and tenderness are nonspecific, and the diagnosis should always be confirmed by objective tests.

Venography: which involves the injection of a radiocontrast agent into a vein, is the reference standard for the diagnosis of DVT. However, it is expensive and technically difficult to perform, can be painful, and requires injection of

radiographic contrast, which can cause allergic reactions or renal impairment. For these reasons, venography is now rarely performed.

Duplex ultrasonography: it is the most commonly used test to diagnose DVT. It is a noninvasive test (Does not carry the adverse effects of venography) 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 most cases. Repeat testing may be necessary if the first test is negative and the patient is still symptomatic (Negative test result does not exclude DVT, particularly in calf veins).

dimer Blood Testing: D-dimer is a fibrin clot degradation product. Elevated d-dimer blood levels occur in acute thrombosis but also with other conditions (eg, recent surgery or trauma, pregnancy, cancer). Therefore, a negative test can help exclude VTE, but a positive test is not conclusive evidence of the diagnosis.

Diagnosis of Pulmonary Embolism

The clinical features of PE, like those of DVT, are nonspecific, and PE is diagnosed in only about 20% of those in whom it is suspected.

A computed tomography (CT) scan is the most commonly used test to diagnose PE. A Pulmonary angiography is the gold standard for diagnosis of PE. However, it is an invasive and expensive with significant risk.

Prevention of Venous Thromboembolism

The most effective way to reduce mortality and morbidity from VTE is to use primary prophylaxis in patients at risk for VTE, particularly during hospitalization. Prophylaxis is achieved by reducing blood coagulability or by preventing venous stasis.

Nonpharmacologic Therapy

Nonpharmacologic methods improve venous blood flow by mechanical means and include early ambulation, graduated compression stockings, intermittent pneumatic compression (IPC) devices, and inferior vena cava filters.

Ambulation as soon as possible following surgery lowers the incidence of VTE in low-risk patients. Walking increases venous blood flow and promotes the flow of natural antithrombotic factors into the lower extremities. All hospitalized patients should be encouraged to ambulate as early as possible, and as frequently as possible.

Graduated compression stockings (GCS)

GCS are specialized hosiery that provide graduated pressure on the lower legs and feet to help prevent thrombosis. Compared with anticoagulant drugs, GCS are relatively inexpensive and safe; however, they are less effective and not recommended in moderate to higher risk patients. They offer an alternate choice in low- to moderate-risk patients when pharmacologic interventions are contraindicated (patients who are at high risk for bleeding and in those who are unable to tolerate any bleeding (e.g., neurosurgical patients). When combined with pharmacologic interventions, GCS have an additive effect. However, some patients are unable to wear compression stockings because of the size or shape of their legs, and some patients may find them hot, confining, and uncomfortable. Wearing GCS after a DVT reduces the risk of PTS by as much as 50%.

Intermittent pneumatic compression (IPC) devices

IPC devices increase the velocity of blood flow in the lower extremities. These devices sequentially inflate a series of cuffs wrapped around the patient's legs from the ankles to the thighs and then deflate in 1- to 2-minute cycles. IPC is more effective than graduated stockings alone, particularly after major orthopedic surgery. Although IPC is safe to use in patients who have contraindications to pharmacologic therapies, it does have a few drawbacks: it is more expensive than GCS, it is a relatively cumbersome technique, some patients may have difficulty sleeping while using it, and some patients find the devices hot, sticky, and uncomfortable. To be effective, IPC needs to be used throughout the day. In practice, this is difficult to achieve, and special efforts should be made to ensure the devices are worn and operational for most of the day.

Inferior vena cava (IVC) filters

IVC filter provide short-term protection against PE in very high-risk patients by preventing the embolization of a thrombus formed in the lower extremities into the pulmonary circulation. To further reduce the long-term risk of VTE in association with IVC filters, pharmacologic prophylaxis is necessary in patients with IVC filters in place, and warfarin therapy should begin as soon as the patient is able to tolerate it. If used, Removable filters are preferred, which can be removed once pharmacologic prophylaxis can be safely administered or once the patient is no longer at risk for VTE.

Pharmacologic prophylactic therapy

Anticoagulants reduce coagulability and can also be used for the prevention of VTE, including subcutaneous heparin (at a dose of 5000 U 2 hours before surgery

and 5000 U every 8 or 12 hours after surgery), low-molecular-weight-heparin (LMWH: dalteparin and enoxaparin) (enoxaparin 40 mg subcutaneously (SC) daily), and fondaparinux, as well as oral vitamin K antagonists [The dose of warfarin, must be adjusted to maintain an international normalized ratio (INR) between 2 and 3], and direct acting oral anticoagulants [Dabigatran (oral direct thrombin inhibitor) and apixaban and rivaroxaban (oral factor Xa inhibitors)].

Optimal VTE prophylaxis duration following surgery is not well established. For general surgical procedures once, patients are able to ambulate regularly and other risk factors are no longer present, prophylaxis can be discontinued. Because of relatively high VTE incidence in the month following hospital discharge among patients undergoing lower extremity orthopedic procedures, extended prophylaxis appears to be beneficial. Most clinical trials support the use of antithrombotic prophylaxis for 21 to 35 days following total hip replacement and hip fracture repair surgeries.

Treatment of venous thromboembolism (VTE)

Nonpharmacologic therapy

- Encourage patients to ambulate as much as symptoms permit.
- Ambulation in conjunction with graduated compression stockings results in faster reduction in pain and swelling than strict bedrest with no increase in embolization rate.
- Inferior vena cava filters should only be used when anticoagulants are contraindicated due to active bleeding.
- Elimination of the obstructing thrombus via thrombolysis or thrombectomy may be warranted in life- or limb-threatening DVT.

Pharmacologic Therapy

Anticoagulation is the primary treatment for VTE; DVT and PE are treated similarly. Anticoagulation is the mainstay of therapy for acute DVT of the leg and PE. The main objectives of anticoagulant therapy are to prevent extension of DVT, early PE, and later recurrences of VTE. The anticoagulant drugs used to treat VTE are the same as those used for VTE prevention; however, there are important differences in the approach to VTE treatment in terms of the doses used and duration of therapy. The acute treatment phase of VTE is typically accomplished by administering a fast-acting parenteral or a direct acting oral anticoagulant).

The long-term and extended phase treatments of VTE are usually accomplished using oral anticoagulant agents such as warfarin, or one of the direct acting oral anticoagulant (apixaban, dabigatran, and rivaroxaban). In certain populations,

such as patients with cancer and women who are pregnant, the LMWHs are the preferred agents during long-term and extended treatment phases due to better safety or efficacy. In the absence of contraindications, the treatment of VTE should initially include a rapid-acting injectable anticoagulant (eg, UFH, LMWH, fondaparinux) or a rapidly acting DOAC (dabigatran, rivaroxaban, apixaban, or edoxaban). In patients with acute DVT of the leg or PE, a DOAC is suggested over warfarin therapy. If warfarin is used for oral anticoagulation, it should be initiated on the same day as the parenteral anticoagulant, and the parenteral agent should be overlapped for a minimum of 5 days and until the INR is greater than or equal to 2 for at least 24 hours.

Therapy duration:

Anticoagulation therapy should be continued for a minimum of 3 months. life-threatening PE, the long-term risks of anticoagulant use (bleeding) must be weighed against the risk of repeated thrombosis after completing a minimum of 3 months of anticoagulation therapy. In patients with DVT of the leg or PE who are treated with warfarin, a therapeutic INR range of 2-3 (target INR of 2.5) is recommended for all treatment durations.

Pregnancy

Anticoagulation therapy is commonly used for the prevention and treatment of VTE during pregnancy. UFH and LMWH do not cross the placenta and are preferred during pregnancy. LMWHs are preferred because they have a lower risk of osteoporosis and of heparin-induced thrombocytopenia. Low molecular weight heparins are eliminated more rapidly in pregnancy, requiring alteration of the dosage regimen. Warfarin is absolutely contraindicated in early (i.e., first-trimester) pregnancy because of the risk of teratogenicity, and it is often avoided during the entire pregnancy because of the risk of fetal bleeding.

Drugs used in the treatment of VTE

Unfractionated Heparin

Unfractionated heparin binds to antithrombin, provoking a conformation change that makes it much more potent in inhibiting the activity of factors IXa, Xa, XIIa, and IIa. This prevents thrombus growth and propagation allowing endogenous thrombolytic systems to lyse the clot. Because some patients fail to achieve an adequate response, IV UFH has largely been replaced by LMWH or fondaparinux. UFH continues to have a role in patients with CrCl less than 30 mL/min (0.5 mL/s). UFH can be administered via the intravenous (IV) or subcutaneous (SC) route. When rapid anticoagulation is required, UFH should be administered IV and an initial bolus dose should be given .For the treatment

of VTE, UFH is generally given as a continuous IV infusion .Due to significant variability in interpatient response and changes in patient response over time, UFH requires close monitoring and periodic dose adjustment. The activated partial thromboplastin time (aPTT) is the most widely used test in clinical practice to monitor UFH.

Bleeding is the primary adverse effect associated with anticoagulant drugs. The most common bleeding sites include the gastrointestinal (GI) tract, urinary tract, and soft tissues. Critical areas include intracranial, pericardial, and intraocular sites, and adrenal glands. Symptoms of bleeding include severe headache, joint pain, chest pain, abdominal pain, swelling, tarry stools, hematuria, or the passing of bright red blood through the rectum. Minor bleeding occurs frequently (eg, epistaxis, gingival bleeding, prolonged bleeding from cuts, bruising from minor trauma). If major bleeding occurs, discontinue UFH immediately and give IV protamine sulfate. Long-term UFH has been reported to cause alopecia, priapism, hyperkalemia, and osteoporosis. Heparin-induced thrombocytopenia (HIT) is a serious immune-mediated problem that requires immediate intervention (Discontinue heparin and initiate alternative anticoagulation with a parenteral direct thrombin inhibitor).

Low-Molecular-Weight Heparin

Advantages of LMWHs over UFH include: predictable anticoagulation dose response, improved SC bioavailability, dose-independent clearance, Longer biologic half-life, lower incidence of thrombocytopenia, and less need for routine laboratory monitoring. LMWHs can be easily administered in the outpatient setting, thus enabling the treatment of VTE at home. Because LMWH anticoagulant response is predictable when given SC, routine laboratory monitoring is unnecessary. Prior to initiating therapy, obtain a baseline complete blood cell count (CBC) with platelet count and serum creatinine. Check the CBC every 5 to 10 days during the first 2 weeks of LMWH therapy and every 2 to 4 weeks thereafter to monitor for occult bleeding. Measuring anti–factor Xa activity is the most widely used method to monitor LMWH; routine measurement is unnecessary in stable and uncomplicated patients. As with other anticoagulants, bleeding is the most common adverse effect of LMWH therapy, but major bleeding may be less common than with UFH. If major bleeding occurs, administer protamine sulfate IV, although it cannot neutralize the anticoagulant effect completely. Thrombocytopenia can occur with LMWHs, but the incidence of HIT is three times lower than with UFH.

Warfarin

Act by suppressing the production of clotting factors, warfarin prevents initial formation and propagation of thrombi. Warfarin has no effect on circulating coagulation factors that have been previously formed, and its therapeutic

antithrombotic activity is delayed for 5 to 7 days. This delay is related to half-lives of the clotting factors. Warfarin inhibiting production of the vitamin K–dependent coagulation factors as well as the anticoagulant proteins C and S. Reductions in the concentration of natural anticoagulants before the clotting factors are depleted can lead to a paradoxical hypercoagulable state during the first few days of warfarin therapy. It is for this reason that patients with acute thrombosis should receive a fast-acting anticoagulant (heparin, LMWH, or fondaparinux) while transitioning to warfarin therapy. In patients with acute VTE, a rapid-acting anticoagulant (UFH, LMWH, or fondaparinux) should be overlapped with warfarin for a minimum of 5 days and until the INR is greater than 2 and stable. Warfarin requires frequent laboratory monitoring to ensure optimal outcomes and minimize complications. Monitor warfarin therapy by the INR; for most indications, the target INR is 2.5, with an acceptable range of 2 to 3. Hemorrhagic complications ranging from mild to severe and life-threatening can occur at anybody site. The GI tract and nose are the most frequent sites of bleeding. Intracranial hemorrhage is the most serious complication and often results in permanent disability and death. Non-hemorrhagic adverse effects of warfarin include the rare "purple toe" syndrome and skin necrosis. Because of the large number of food–drug and drug–drug interactions with warfarin, close monitoring and additional INR determinations may be indicated whenever other medications are initiated, or discontinued, or an alteration in consumption of vitamin K–containing foods is noted.

Target-specific oral anticoagulants

These currently include two categories, direct thrombin (factor IIa) inhibitor (DTI) (dabigatran) and direct Xa inhibitors (rivaroxaban, apixaban, and edoxaban). As compared to warfarin, these oral anticoagulants have a more rapid onset, shorter half-life, wider therapeutic window, and more predictable pharmacokinetics. These features allow for sole oral therapy without the need for an overlapping parenteral agent (with the exception of edoxaban for VTE), no need for titration or dose adjustments in patients with normal renal function, and no need for routine monitoring. Compared to warfarin, the target-specific anticoagulants have a lower risk of intracranial hemorrhage. Issues of concern include the lack of antidotes, and risk of thrombosis due to missed doses).

Parenteral DTIs

Several injectable DTIs are available including lepirudin, bivalirudin, argatroban, and desirudin. Parenteral DTIs are considered the drugs of choice for the treatment of VTE in patients with a diagnosis or history of HIT.

Parenteral Xa inhibitor (Fondaparinux)

Fondaparinux is a safe and effective alternative to LMWH for treatment of DVT or PE. It is approved for prevention of VTE following orthopedic (hip fracture, hip and knee replacement) or abdominal surgery and for the treatment of DVT and PE (in conjunction with warfarin). Patients receiving fondaparinux do not require routine coagulation testing.

Thrombolytics

Thrombolytic agents are proteolytic enzymes that enhance conversion of plasminogen to plasmin, which subsequently degrades the fibrin matrix. The role of thrombolysis in the treatment of VTE is controversial. Compared with anticoagulants, thrombolytics restore venous patency more quickly; however, the bleeding risk associated with their use is significantly higher. Given the relative lack of data to support their routine use, thrombolytics should be reserved for select high-risk circumstances. Candidates for thrombolytic therapy are patients with acute massive embolism who are hemodynamically unstable (SBP less than 90 mm Hg) and at low risk for bleeding.