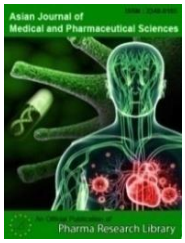

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A Review on Novel Therapeutic Approaches for Prevention and Treatment of Deep Vein Thrombosis

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A B S T R A C T

Venous thromboembolism includes pulmonary embolism (PE), which is potentially fatal and causes chronic thromboembolic pulmonary hypertension, and deep vein thrombosis, which causes leg swelling and postthrombotic syndrome. In addition, VTE may develop in a splanchnic vein and in other atypical locations. Currently, cancer-associated thrombosis is highlighted due to the increased prevalence of cancer. Inadequate anticoagulation (inadequate dosage, poor compliance, discontinuation for an anticipated procedure, malabsorption) is the most common cause of recurrent Venous thromboembolism during therapy. However, recurrent Venous thromboembolism should be confirmed by radiologic testing and should be examined for other etiologies, such as malignancy, May-Thurner syndrome, inherited thrombotic disorders, or antiphospholipid antibody syndrome. Treatment options for initial failure include increasing the dose or administration frequency of the anticoagulants or alternate agents. Idarucizumab is an engineered antibody fragment with a structure similar to that of thrombin; it binds to dabigatran. Andexanet alfa is a modified, recombinant human factor Xa protein that binds to factor Xa inhibitors and low molecular weight heparin but is catalytically inactive. Novel antithrombotic agents, with more specific activity on the coagulation cascade, more predictable pharmacodynamics and pharmacokinetics, simpler dosing regimens, and few or no laboratory monitoring requirements, have been developed to overcome limitations associated with some of the nonspecific traditional anticoagulants. Unfractionated heparin and low molecular weight heparin are currently the recommended options for initial anticoagulation in patients with acute thromboembolism. Warfarin is the most commonly used agent for chronic anticoagulation.

Keywords: Venous thromboembolism, pulmonary embolism, pulmonary hypertension, malabsorption, pharmacodynamics and pharmacokinetics, anticoagulation.

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

A deep-vein thrombosis (DVT) is a blood clot that forms within the deep veins, usually of the leg, but can occur in the arms and the mesenteric and cerebral veins. Deep-vein thrombosis is a common and important disease. It is part of the venous thromboembolism disorders, representing the third most common cause of death from cardiovascular disease after heart attacks and stroke. Even in patients who do not get pulmonary emboli, recurrent thrombosis and "post-thrombotic syndrome" are major causes of morbidity. Deep vein thrombosis (DVT) is an obstructive disease with

hindering venous reflux mechanism. DVT usually involves the lower limb venous system, with clot formation originating in a deep calf vein and propagating proximally. It is a common venous thromboembolic (VTE) disorder with an incidence of 1.6 per 1000 annually. The rate of particular site involvement depends on the anatomical location as follows, distal veins 40%, popliteal 16%, femoral 20%, common femoral 20%, and iliac veins 4%.

A deep-vein thrombosis (DVT) is a blood clot that forms within the deep veins, usually of the leg, but can occur in the arms and the mesenteric and cerebral veins. Deep-vein thrombosis is a common and important disease. It is part of the venous thromboembolism disorders, representing the third most common cause of death from cardiovascular disease after heart attacks and stroke. Even in patients who do not get pulmonary emboli, recurrent thrombosis and "post-thrombotic syndrome" are major causes of morbidity[1-3].

Venous thromboembolism (VTE), that consists of the interrelated diseases of pulmonary embolism and deep-vein thrombosis (DVT), is among the top five most common vascular diseases in most countries[1]. The lifetime risk of VTE is estimated to be 8% overall among US adults[2]. Approximately 20% of individuals die within 1 year of a VTE diagnosis, sometimes from VTE but often from conditions that provoked the event.

VTE is preventable, and the risk of VTE is a marker of adverse conditions at the levels of the individual, society and health systems. At the individual level, obesity and lack of physical exercise increase the risk of VTE. These factors are often caused by adverse societal conditions, such as a lack of access to high-quality nutrition or safe places to exercise. At the health systems level, opportunities are missed to provide effective preventive measures during hospitalization or after selected interventions, or in individuals with a personal or family history of VTE. The pathophysiology of VTE is also distinct among vascular diseases because several established risk factors for atherosclerotic cardiovascular disease, such as hyperlipidaemia, hypertension and diabetes mellitus, are not associated with the risk of VTE independently of established VTE risk factors, such as age and obesity.

The risk of VTE is multifactorial. In epidemiological studies, VTE is often defined as provoked or unprovoked. Provoked events occur after triggering factors in the previous 3 months, such as immobilization, trauma, surgery, cancer or hospitalization, whereas unprovoked events occur in the absence of these conditions. Although the classification of provoked and unprovoked can be useful both epidemiologically and clinically, it is controversial. For instance, some studies might classify pregnancy and hormone-related VTE as provoked. Given that VTE is multifactorial, it can be challenging (or impossible) to identify a single characteristic that led to VTE or to consider as unprovoked an array of smaller thrombotic challenges that led to a VTE event. The 2019 European Society of Cardiology/European Respiratory Society guidelines for the diagnosis and management of acute pulmonary embolism avoided the terminology of 'provoked' and 'unprovoked', instead focusing on the estimated long-term risk of VTE recurrence.

VTE is treated with anticoagulant therapy. VTE treatment is divided into three phases: initial stabilization (days to weeks), primary treatment (3–6 months) and secondary prevention (after completion of primary treatment). The designation of provoked versus unprovoked VTE also guides treatment duration, particularly whether or not to use secondary prevention strategies, which are recommended for individuals with unprovoked VTE and can include surveillance, anticoagulation therapy during high-risk periods or continued anticoagulation therapy[21]. However, the distinction between provoked and unprovoked is inconsistently applied in clinical practice and is often not reflective of management decisions. People with incurable cancer and VTE (a provoked event) are offered indefinite anticoagulation therapy, and women with hormone-associated VTE (an unprovoked event) are offered a finite course of treatment.This inconsistency in VTE management is further confused because minor triggers, such as travel or minor orthopaedic injuries, are often thought of as provoking factors clinically but not in epidemiological studies. The lack of unified definitions and practice recommendations leads to heterogeneity in treatment patterns, prevention and, potentially, outcomes[4-9].

2. Etiology

Risk Factors

Following are the risk factors that are considered causes of deep venous thrombosis:

- Reduced blood flow: Immobility (bed rest, general anesthesia, operations, stroke, long flight.
- Increased venous pressure: Mechanical compression or functional impairment leading to reduced flow in the veins (neoplasm, pregnancy, stenosis, or congenital anomaly which increases outflow resistance).
- Mechanical injury to the vein: Trauma, surgery, peripherally inserted venous catheters, previous DVT, intravenous drug abuse.
- Increased blood viscosity: Polycythaemia rubra vera, thrombocytosis, dehydration.
- Anatomic variations in venous anatomy can contribute to thrombosis.

Increased Risk of Coagulation

- **Genetic deficiencies:** Anticoagulation proteins C and S, antithrombin III deficiency, factor V Leiden mutation
- **Acquired:** Cancer, sepsis, myocardial infarction, heart failure, vasculitis, systemic lupus erythematosus, lupus anticoagulant, Inflammatory bowel disease, nephrotic syndrome, burns, oral estrogens, smoking, hypertension, diabetes

Constitutional Factors

Obesity, pregnancy, the advanced age of older than 60, surgery, critical care admission, dehydration, and cancer are the established causalities of DVT and VTE. Obesity is associated with a hypercoagulability status via two mechanisms, 1. increased fibrinogen levels that may even surpass twofold the normal value, and 2. slower venous circulation flow in the infra diaphragmatic and especially in the lower limbs. Both factors, associated with disorders in several coagulation factors, favor the appearance of venous thrombosis, thrombophlebitis, and thromboembolic events, and mostly fatal pulmonary thromboembolisms (PE), which are the primary cause of mortality in obese patients[10].

Potential risk factors of deep vein thrombosis might be categorized according to the transient, persistent or unprovoked criteria. Accordingly, transient risk factors are as follows; 1. surgery with general anesthetics, 2. hospitalization, 3. cesarean section, 4. hormone replacement therapy, 5. pregnancy and peripartum period, 6. lower extremity injury with limited mobility for more than 72 hours.

It should be noted that general anesthesia for longer than 30 minutes and hospitalization for longer than 72 hours is considered the transient risk factors of DVT. However, active cancers and specific medical conditions that increase the risk of venous thromboembolism are categorized as persistent risk factors. Systemic lupus erythematosus and inflammatory bowel disease are among the predisposing medical conditions. Any further etiological risk factors not categorized among either transient or persistent subgroups should be labeled as unprovoked venous thromboembolism. For instance, a recent cohort study, including 500 participants evaluating the association of blood lipid levels and lower extremity DVT (LEDVT), demonstrated that higher total cholesterol levels, high-density lipoprotein (HDL-C), and apolipoprotein A1 (ApoA1) were associated with a decreased risk of lower extremity DVT (LEDVT). However, higher triglyceride levels (TG) were associated with a greater risk of LEDVT.

Triggering risk factors

Inflammation

High levels of biomarkers of chronic inflammation, such as serum C-reactive protein and serum albumin, have been consistently associated with a greater risk of VTE. Genetic studies that identified coagulation-related gene variants linked to the risk of VTE have also highlighted a role of inflammatory pathways in VTE. However, the most compelling data linking inflammation to the risk of VTE come from randomized, controlled, clinical trials of statins. In addition to their anti-hyperlipidaemic properties, statins are also potent anti-inflammatory agents and might also improve the coagulation profile. In the JUPITER trial, rosuvastatin therapy reduced the risk of VTE compared with placebo. Importantly, blood lipid levels are not associated with the risk of VTE, suggesting that the role of statins in reducing the risk of VTE is via their anti-inflammatory effects.

Hormonal states

Oral contraceptive use, hormone replacement therapy, and pregnancy

The risk of VTE is elevated in women receiving oestrogen-based contraceptives, hormone replacement therapy or infertility treatment, as well as during pregnancy. In a cohort study of ~1.2 million women from four national registries, women taking combined (oestrogen and progestogen) oral contraceptives or progestin-only oral contraceptives were at approximately sixfold and threefold increased risk, respectively, of VTE compared with women who did not take oral contraceptives. Although the prevalence of exposure to oral contraceptives and the magnitude of the association with VTE is relatively large, owing to the overall low incidence of VTE in this age group, 2,000 women would need to shift from combined oral contraceptives to progestin-only contraceptives to prevent one VTE annually. Oestrogen therapy intensity seems to be important, with the highest risk of VTE in those individuals receiving continuous oestrogen therapy and a lower risk with increasing break periods in the therapy cycle[65]. Exposure to high-intensity exogenous hormones in the context of fertility treatments (for example, to simulate egg development and in vitro fertilization) can lead to ovarian hyperstimulation syndrome. Up to 10% of women with severe ovarian hyperstimulation syndrome develop VTE. Users of hormone replacement therapy have an increased risk of VTE, similar to that observed with oral contraceptives; however, the increased absolute baseline risk of VTE in this older patient population might change the risk–benefit ratio of hormone replacement therapy in this setting. Research in transgender women might also provide additional insights into the role of sex hormones in the risk of VTE.

VTE complicates ~1.2 in 1,000 pregnancies and accounts for approximately 9% of pregnancy-associated deaths in the USA. Pregnancy is a procoagulant state and is also associated with greatly elevated steroid hormone levels, mechanical venous obstruction and venous stasis, which increase the risk of VTE before delivery and during the puerperium.

Testosterone

Endogenous testosterone levels are not associated with VTE risk. However, exogenous testosterone therapy might increase the risk of VTE. Hypothesized mechanisms include elevated haematocrit levels (which can increase blood viscosity), platelet accumulation and elevated thromboxane A_2 production by platelets and increased concentrations in the blood, all of which can increase the risk of VTE. The three largest studies on this topic have all relied on administrative databases. One study that used a case–crossover design determined that testosterone therapy is associated with a doubling in VTE risk. Another study using a cohort design found a 70% greater risk with testosterone therapy. A third study found no significant association[82]. Although the available data for VTE risk and testosterone therapy are not entirely conclusive, these findings, together with those suggesting that testosterone therapy is associated with increased risk of atherosclerotic

disease, suggest that caution should be used when prescribing exogenous testosterone. Research among transgender men might also provide novel insights into the role of testosterone in the risk of VTE.

Epidemiology

Incidence and prevalence: Deep-vein thrombosis and pulmonary emboli are common and often "silent" and thus go undiagnosed or are only picked up at autopsy. Therefore, the incidence and prevalence are often underestimated. It is thought the annual incidence of DVT is 80 cases per 100,000, with a prevalence of lower limb DVT of 1 case per 1000 population. Annually in the United States, more than 200,000 people develop venous thrombosis; of those, 50,000 cases are complicated by pulmonary embolism[11-15].

Age: Deep-vein thrombosis is rare in children, and the risk increases with age, most occurring in the over-40 age group.

Gender: There is no consensus about whether there is a sex bias in the incidence of DVT.

Ethnicity**:** There is evidence from the United States that there is an increased incidence of DVT and an increased risk of complications in African Americans and white people compared to Hispanics and Asians. The incidence of VTE in Europe and the USA is estimated to be ~1–2 per 1,000 person-years[1], but varies widely by age, sex, race and medical conditions. In Asia, the rates of VTE are thought to be lower than in Europe and the USA. For instance, the incidence of VTE in South Korea was estimated to be 0.2 per 1,000 person-years. Fewer data exist for South America and Oceania. A study from Buenos Aires, Argentina, found a VTE incidence of 0.7 per 1,000 person-years, and a study from Perth, Australia, found a VTE incidence of 0.8 per 1,000 person-years. Very little is known about VTE incidence in Africa.

The most robust data on VTE incidence come from the USA and Europe. An American Heart Association report from 2021 estimated that approximately 1,220,000 total cases of VTE occur in the USA annually. This estimate was based on previously unpublished data from the National Inpatient Sample, and showed ~370,000 cases of pulmonary embolism and ~857,000 cases of DVT in 2016 and assumed 30% of DVTs were treated in the outpatient setting. A modelling study estimated that the annual VTE incidence in six countries in Europe (total population 310.4 million) was 296,000 cases of pulmonary embolism and ~466,000 cases of DVT.

Pathophysiology

According to Virchow's triad, the following are the main pathophysiological mechanisms involved in DVT:

- Damage to the vessel wall
- Blood flow turbulence
- Hypercoagulability

Thrombosis is a protective mechanism that prevents the loss of blood and seals off damaged blood vessels. Fibrinolysis counteracts or stabilizes thrombosis. The triggers of venous thrombosis are frequently multifactorial, with the different parts of the triad of Virchow contributing in varying degrees in each patient, but all result in early thrombus interaction with the endothelium. This stimulates local cytokine production and causes leukocyte adhesion to the endothelium, promoting venous thrombosis. Depending on the relative balance between the coagulation and thrombolytic pathways, thrombus propagation occurs. DVT is commonest in the lower limb below the knee and starts at low-flow sites, such as the soleal sinuses, behind venous valve pockets.

3. Diagnosis

The clinical presentation of acute lower extremity DVT varies with the anatomic distribution, extent, and degree of occlusion of the thrombus. Symptoms may range from absence to massive swelling and cyanosis with impending venous gangrene. Three patterns of thrombosis are usually recognized: isolated calf vein (distal), femoropopliteal, and iliofemoral thrombosis, and symptoms tend to be more severe as thrombosis extends more proximally. However, up to 50% of patients with acute DVT may lack specific signs or symptoms.[5][6] Postoperative patients are, in particular, more likely to have small, asymptomatic, distal, non-occlusive thrombi. When present, signs and symptoms of acute lower extremity DVT may include pain, edema, erythema, tenderness, fever, prominent superficial veins, pain with passive dorsiflexion of the foot (Homan's sign), and peripheral cyanosis. Phlegmasia cerulea dolens, characterized by the triad of massive swelling, cyanosis, and pain, is the most severe form of acute lower extremity DVT and results from complete thrombosis of an extremity's venous outflow.

In advanced cases, it is marked by severe venous hypertension with collateral and microvascular thrombosis, leading to venous gangrene. Venous gangrene is particularly associated with warfarin-mediated protein C depletion in patients with cancer or heparin-induced thrombocytopenia.

Obtaining the diagnosis of DVT only based on clinical signs and symptoms is notoriously inaccurate. The signs and symptoms of DVT are generally non-specific. They may be associated and misdiagnosed with other lower extremity disorders[16-22]. Accordingly, lymphedema, superficial venous thrombosis, and cellulitis should be excluded. However, the most common presenting symptoms with inconsistent sensitivity and specificity are calf pain and swelling. The former index has a sensitivity of 75% to 91% and a specificity of 3% to 87%, and the latter might have a sensitivity of up to 97% and a specificity of up to 88%.

History

- Pain (50% of patients)
- Redness
- Swelling (70% of patients)

Physical Examination

- Limb edema may be unilateral or bilateral if the thrombus extends to pelvic veins.
- Red and hot skin with dilated veins
- Tenderness

The following veins are categorized as deep veins according to the Clinical-Etiology-Anatomy-Pathophysiology (CEAP) classification; 1. inferior vena cava, 2. common iliac, 3. internal and external iliac, 4. pelvic veins, including a. gonadal, and b. broad ligament veins, 5. common femoral, 6. deep femoral vein, 7. femoral, 8. popliteal, 9. paired crural veins of anterior and posterior tibial and peroneal, 10. muscular veins of gastrocnemial, and soleal. [31]

As per the National Institute for Clinical Excellence (NICE) guidelines following investigations are done:

- D-dimers (very sensitive but not very specific)
- Coagulation profile
- Proximal leg vein ultrasound, which, when positive, indicates that the patient should be treated as having a DVT

Deciding how to investigate is determined by the risk of DVT. The first step is to assess the clinical probability of a DVT using the Wells scoring system.

- The clinical probability is low for patients with a score of 0 to 1, but for those with two or above, the clinical probability is high.
- If a patient scores 2 or above, either a proximal leg vein ultrasound scan should be done within 4 hours, and if the result is negative, a D-dimer test should be done. If imaging is not possible within 4 hours, a D-dimer test should be undertaken, and an interim 24-hour dose of a parenteral anticoagulant should be given. A proximal leg vein ultrasound scan should be carried out within 24 hours of being requested.
- In the case of a positive D-dimer test and a negative proximal leg vein ultrasound scan, the proximal leg vein ultrasound scan should be repeated 6 to 8 days later for all patients.
- If the patient does not score 2 on the DVT Wells score, but the D-dimer test is positive, the patient should have a proximal leg vein ultrasound scan within 4 hours, or if this is not possible, the patient should receive an interim 24-hour dose of a parenteral anticoagulant. A proximal leg vein ultrasound scan should be carried out within 24 hours of being requested.

- In all patients diagnosed with DVT, treat as if there is a positive proximal leg vein ultrasound scan.

Clinical decision rules such as the Pulmonary Embolism Rule-Out Criteria (PERC) and the Wells Criteria should be employed with the patient presenting with a possible DVT. Risk stratification is crucial in deciding diagnostic and management options. Patients who meet PERC criteria may need no further testing, whereas those who do not meet PERC criteria and are low probability based on the Wells criteria may be candidates for rule-out with a D-dimer. The D-dimer test is sensitive but not specific and should be used selectively in a low-probability patient who does not have other confounding diagnoses that could produce a false positive test. The test also should be used with caution, perhaps with different cut-off values in the elderly.

Imaging modalities available to evaluate for DVT include diagnostic ultrasound, vascular studies, CT venograms, and point-of-care ultrasound (POCUS). The POCUS exam is described below.

Rapid diagnosis or rule-out by the emergency provider can expedite necessary treatment and reduce the length of stay, and it is particularly useful when access to 24-hour ultrasound is unavailable. There is evidence that emergency practitioners can perform a two-point compression exam at the two highest probability sites for identifying a DVT: femoral and popliteal veins. However, recent literature suggests a two-region approach where clinicians do serial compression testing may significantly improve diagnostic sensitivity without greatly increasing diagnostic time. This point-of-care ultrasound exam should be used with other clinical decision rules and is perhaps most useful in those patients with high and low pre-test probability.

With the patient supine in the frog-leg position, apply approximately 20 to 30 degrees of reverse Trendelenburg to increase venous distention. Place the high-frequency linear transducer (5 to 10 MHz) in the transverse plane at the anatomical location of the inguinal ligament. Just distal to the inguinal ligament, the common femoral vein can be visualized. Apply direct pressure to the vein. The complete collapse of the vein indicates there is no presence of a DVT. Continue distally along the femoral vein to where the greater saphenous vein and deep femoral vein deviate from the common femoral vein. Complete compression of all venous structures at these levels rules out a proximal DVT.
Next, proceed to the popliteal region. Laterally rotate the leg, flex the knee, and place the high-frequency transducer transversely in the popliteal fossa. The popliteal vein typically resides just anterior to the popliteal artery. Apply a compressive force once again and observe for complete compression. Compress the areas just proximal and distal to the popliteal fossa as well to complete the two-region technique.

Prevention

VTE is divided epidemiologically and clinically into provoked and unprovoked events. As described in the Introduction, the terminology is confusing and used inconsistently. Provoked events are those associated with conditions such as cancer, surgery, hospitalization and/or immobility, whereas unprovoked events are those associated with no identifiable trigger but include pregnancy and hormone-associated VTE. Approximately half of all VTE events are associated with a defined trigger and are, therefore, potentially preventable through interventions of finite duration. Unprovoked VTE can theoretically be prevented by healthy lifestyle choices, and even by off-target effects of cardiovascular disease therapies such as statins. However, this strategy might lack

a holistic and patient-centred approach to VTE prevention. One alternative approach is to view VTE risk as a temporally layered set of risk factors[23-27].

Primordial prevention

Primordial prevention refers to preventing disease in otherwise healthy people by preventing the development of risk factors for the disease. Not all risk factors are amenable to primordial prevention (such as age, sex and genetics). However, interventions that improve health have the potential to reduce the risk of VTE, although they might not have been studied specifically for VTE prevention. Ideal levels of physical activity and dietary interventions (see relevant sections) can result in less obesity and fewer hospitalizations, which could reduce the risk of VTE[222]. Preventing individuals from starting to smoke could reduce the risk of VTE by reducing the incidence of and hospitalizations for respiratory diseases, cardiovascular diseases and certain cancers. Equitable lifestyle interventions (by age, sex, race and socioeconomic status) to improve diet and physical activity and prevent smoking in the general population improve health without having to add VTE risk reduction into the equation. Even for static risk factors, such as genetic factors, primordial prevention matters. Healthy lifestyle choices can attenuate the increased risk of VTE associated with adverse genetic variants. Other opportunities for primordial prevention include a focus on gynaecological and obstetric health in younger women by selecting lower risk methods of contraception, such as cyclic oral contraceptives and intrauterine devices.

Primary prevention

Primary prevention of VTE reduces VTE by specific interventions in those individuals at risk of VTE. The most common intervention is pharmacological prophylaxis with low doses of anticoagulation drugs. The two most discussed opportunities for primary prevention of VTE relate to hospitalization and cancer. Given the large number of VTE events attributable to hospitalization and the finite risk period, hospital-associated VTE risk has become a key target of VTE prevention measures to reduce health-care-associated complications. Whereas guidelines exist for the prevention of VTE during the hospital stay, there is limited clarity on how long prophylaxis should be continued after discharge, except for certain orthopaedic procedures for which guidelines are well established. A similar consensus on primary prevention of VTE is evolving for patients with cancer, although the best strategy to prevent VTE in these patients is not known because the risk of VTE varies over time. Primary prevention with anticoagulation therapy increases the risk of bleeding, and the risk–benefit balance is not established in many populations at risk of VTE.

Another intriguing pharmacological intervention for the primary prevention of VTE is the use of statins. The JUPITER trial[62], which recruited individuals with elevated plasma C-reactive protein levels and normal blood lipid levels, demonstrated that an off-target benefit for rosuvastatin therapy was a reduction in VTE risk. Whether statins can be used in individuals with increased risk of VTE to reduce VTE events has not been tested.

Secondary prevention

Secondary prevention refers to the prevention of recurrent VTE events in individuals with a history of VTE. Traditionally, the strategy for secondary prevention of VTE is anticoagulation therapy. This approach reflects VTE being considered in clinical medicine as an event rather than a lifelong disease. Of note, in clinical practice, one of the strongest risk factors for VTE is a history of VTE. Even individuals with provoked VTE events often have multiple VTE recurrences throughout their life.

Although imperfect guidelines exist for who should be offered secondary VTE prevention with anticoagulation therapy, even, and perhaps especially, individuals who are not receiving anticoagulation therapy for secondary prevention are at risk of VTE recurrence with further provoking events such as pregnancy, hormone therapy, bone fracture, hospitalization and surgery. In women, VTE provoked by exogenous hormone therapy or pregnancy warrants secondary prevention with anticoagulation therapy with subsequent pregnancy or hormone use. For hospitalized people, previous VTE is one of the most consistent risk factors for hospital-acquired VTE. The bottom line is that although the decision to offer anticoagulation therapy for secondary prevention of VTE is made once in the 3–6 months after the initial event, decisions on how best to prevent recurrent VTE during periods of VTE risk should be made throughout the life course. Although there are intriguing findings for non-antithrombotic agents for the secondary prevention of VTE, none are currently recommended for use in clinical practice.

Management and Treatment

Activity Guidelines

A DVT may make it harder for you to get around at first because of leg pain and swelling. But you'll be able to slowly return to your normal activities. If your legs feel swollen or heavy, lie in bed with your heels propped up about 5 to 6 inches. This helps improve circulation and decreases swelling.

The main goals of treatment are to:

- Keep the clot from getting bigger and involving other veins.
- Prevent the clot from breaking off in your vein and moving to your lungs.
- Lessen the risk of another blood clot.
- Prevent long-term complications from the blood clot (like chronic venous insufficiency).
- Important information about medications
- Take your medications exactly as healthcare provider tells you to.
- Have blood tests your provider requests and keep all scheduled laboratory appointments.
- Don't stop or start taking any medication

DVT treatments

Anti coagulants

This type of medication makes it harder for your blood to clot. Anticoagulants also stop clots from getting bigger and

prevent blood clots from moving. Anticoagulants don't destroy or "melt" blood clots[28-30].

Compression Stockings

These stockings are tight at the ankle and become looser as they go away from your ankle. This causes gentle pressure (compression) on your leg. Some people need to wear these for two years or more. Several clinical studies have shown that compression stockings improve the symptoms of leg pain and swelling by at least 50% as long as they're worn daily from morning to evening (they don't have to be worn overnight). After surgery, your providers may put in device on calves to put pressure on them. These machines squeeze and release the fabric-covered devices around your calves while you're lying in bed. These devices help prevent a DVT if you're in the hospital, but they aren't prescribed outside of the hospital. In addition, unlike compression stockings that you can wear safely when a leg DVT is present, you shouldn't use these devices for DVT prevention if you have a DVT.

DVT Treatment Procedures

When you can't take medications to thin your blood or you have blood clots while taking blood thinners without missing doses, a surgeon may have to do a procedure to put in an inferior. The procedure is done under local anesthesia. The surgeon inserts the IVC filter through a catheter into a large vein in your groin or neck, and then into your vena cava (the largest vein in your body). While an IVC filter helps prevent a pulmonary embolism, it doesn't keep more blood clots from forming in veins.

Treatment

Treatment of DVT aims to prevent pulmonary embolism, reduce morbidity, and prevent or minimize the risk of developing post-thrombotic syndrome. The cornerstone of treatment is anticoagulation. NICE guidelines only recommend treating proximal DVT (not distal) and those with pulmonary emboli. In each patient, the risks of anticoagulation need to be weighed against the benefits.

Treatment for DVT should be addressed mainly according to the underlying causality of DVT as follows:

- The preferred anticoagulant to address DVT in cancer-associated thromboembolism is low molecular weight heparin and factor Xa inhibitors, including rivaroxaban. However, in the following circumstances, the higher levels of anticoagulation should be considered; 1. recently diagnosed cancer, 2. extensive VTE circumstances, and 3. cancer treatment-related adverse effects, including vomiting.
- In circumstances where once-daily oral therapy is the preferred management, the following options are viable; 1. rivaroxaban, 2. edoxaban, and 3. vitamin-K antagonist (VKA)
- In the context of liver disease, DVT should be managed with low-molecular-weight heparin. Direct oral anticoagulants (DOACs) are contraindicated in raised INR levels.
- In patients with renal disease suppressed creatinine clearance to less than 30 ml/min, VKAs are recommended. DOACs and LMWH should be avoided in patients with end-stage renal disease.
- In patients with a remarkable past medical history of coronary artery disease, the following alternatives are recommended; 1. VKA, 2.rivaroxaban, 3.apixaban, and 4. edoxaban[

The following guidelines address the required duration of treatment:

1. Low-molecular-weight heparin or fondaparinux for five days or until INR is greater than 2 for 24 hours (unfractionated heparin for patients with renal failure and increased risk of bleeding)
2. Vitamin K antagonists for three months
3. In patients with cancer, consider anticoagulation for six months with low-molecular-weight heparin.
4. In patients with unprovoked DVT, consider vitamin K antagonists beyond three months.
5. Rivaroxaban is an oral factor Xa inhibitor which has recently been approved by the FDA and NICE and is attractive because there is no need for regular INR monitoring.
6. If the platelet count drops to less than 75,000, switch from heparin to fondaparinux, which is not associated heparin-induced thrombocytopenia.

Thrombolysis: The indications for the use of thrombolytics include:

1. Symptomatic iliofemoral DVT
2. Symptoms of less than 14 days duration
3. Good functional status
4. A life expectancy of 1 year or more
5. Low risk of bleeding

The use of thrombolytic therapy can result in an intracranial bleed, and hence, careful patient selection is vital. Recently endovascular interventions like catheter-directed extraction, stenting, or mechanical thrombectomy have been tried with moderate success.

- Compression hosiery: Below-knee graduated compression stockings with an ankle pressure greater than 23 mm Hg for two years if there are no contraindications
- Inferior vena cava filters: If anticoagulation is contraindicated or if emboli are occurring despite adequate anticoagulation

Newer Drugs

Rivaroxaban, apixaban, dabigatran, edoxaban, and betrixaban are relatively newer factor Xa inhibitors approved for prophylaxis of deep vein thrombosis. The duration of DVT treatment is 3 to 6 months, but recurrent episodes may require at least 12 months of treatment. Patients with cancer need long-term treatment.

Inferior vena cava filters are not recommended in acute DVT. There are both permanent and temporary inferior vena cava filters available. These devices may decrease the rate of recurrent DVT but do not affect survival. Today, only patients with contraindications to anticoagulation with an increased risk of bleeding should have these filters inserted[31-36].

Complications

The following are the two major complications of DVT:

- Pulmonary emboli (paradoxical emboli if an atrial-septal defect is present)

- Post-thrombotic syndrome
- Bleeding from the use of anticoagulants

4. Conclusion

VTE is an underappreciated source of morbidity and mortality worldwide. In the developed Western world, an estimated 8% of people will develop VTE in their lifetime. However, global estimates of VTE incidence and burden are limited owing to the lack of VTE surveillance systems. VTE risk factors are multifactorial including acute triggers, subacute triggers and basal and acquired risk factors. Although the breadth of VTE risk factors make it difficult to determine who will develop VTE, it also yields many pathways amenable to targeting for VTE prevention. As with most conditions, the greatest potential to reduce the societal burden of VTE would be through primordial prevention to prevent the development of risk factors for VTE (such as obesity and common acute triggers). For individuals at risk of VTE or who have previous VTE, primary and secondary prevention are essential to reducing the burden of VTE. Differences related to race, ethnicity and socioeconomic status exist in VTE incidence and outcomes, and approaches to VTE prevention that improve health equity should be prioritized[37-43].

In the future, risk factors need to be considered to improve the VTE treatment guidelines. First, studies examining whether lower doses of anticoagulants can maintain their therapeutic effects while reducing bleeding side effects are a worldwide issue. These studies are necessary, particularly for VTE patients with a high risk of bleeding[44-45]. Second, the diagnosis of asymptomatic incidental VTE is increasing due to a changing medical environment, and updated treatment guidelines are urgently required. The current recommendations are based not only on insufficient evidence, but also mostly on Western data. Therefore, recommendations need to be amended based on Korean data in the future.

5. References

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