Clinical Overview of Deep Vein Thrombosis

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ABSTRACT.

Deep vein thrombosis (DVT) is a common but preventable condition in hospitalized patients with potential acute fatal complications and disabling chronic morbidity. The risk factors are linked with the identified underlying pathogenic mechanism as described by Virchow's triad of stasis, hypercoagulability and vascular injury. Prompt and accurate diagnosis and treatment is crucial to prevent the potential complications. The validated diagnostic algorithm involves clinical suspicion, validated clinical prediction rule, D-dimer and Doppler ultrasonography which is the gold standard for diagnosis. The mainstay of treatment of DVT is anticoagulation unless when there is increased risk of bleeding. The standard anticoagulants in use include low molecular weight heparin, unfractionated heparin, warfarin and the newly introduced direct oral anticoagulants (DOAs). DVT prophylaxis is important to prevent DVT and methods of prophylaxis include mechanical methods and anticoagulants either alone or in combination depending on the risk factor(s) in a particular patient.

KEY WORDS: *Deep vein thrombosis, Thromboprophylaxis, Wells score, Pulmonary embolism, Anticoagulant.*

INTRODUCTION

Venous thromboembolism (VTE) is a global health concern with substantial morbidity and mortality. It is often asymptomatic and underdiagnosed, leading to long-term complications and reduced survival.[(1)] VTE refers to all forms of thrombosis in the venous circulation and manifests clinically as deep vein thrombosis (DVT) and pulmonary embolism (PE). Both conditions are related aspects of the same dynamic disease process, VTE, and have the same risk factors and treatment but also require a coordinated approach to make the timely diagnosis .[2]

Deep vein thrombosis is the formation of thrombus in the deep veins. Although deep vein thrombosis develops most commonly in the lower limbs, the deep veins of the arms, the splanchnic veins, and the cerebral veins can be affected.[1]

Deep vein thrombosis (DVT) is a common problem in ambulatory and hospitalized patients. Untreated DVT may lead to potentially acute fatal complication such as pulmonary embolism (PE) and long-term complications of post-thrombotic syndrome and pulmonary hypertension.[3,4] Prevention is the most effective strategy to reduce the burden of this disease and there is evidences that appropriate use of anticoagulants and mechanical prophylaxis can reduce the incidence of DVT among hospitalized patients.[5,6,7] However unjustified anticoagulation may be associated with the risk for bleeding in misdiagnosed patients. Correct diagnosis and prompt treatment are therefore essential in the overall management of DVT.[3,4] This article provides an overview of the pathology, diagnosis, treatment and prophylaxis of DVT.

EPIDEMIOLOGY

The true incidence of VTE is difficult to estimate because of the often silent nature of the condition. The global ENDORSE study- a multinational cross-sectional survey of 68,183 patients in acute hospital beds across 32 countries, showed that 51.8% of hospitalized patients[surgical (64.4%) , and medical (41.5%)] were at risk for developing VTE according to ACCP guidelines.[8] A systematic review of whole population studies indicates a weighted mean incidence of first deep vein thrombosis (DVT) of approximately 0.5 per 1,000 person - years, with a similar incidence in men and women.[9] DVT is rare in children below the age of 15 years but its frequency increases with age with an incidence of 2-3 per 10,000 people aged 30-49 years; rising to 20 per 10,000 in the 70-79-year age group.[9]

The approximate risk for DVT in patients undergoing general surgery procedures without prophylaxis range from 15% to 40% and fatal PE from 0.2% to 0.9%.[9] The risk for DVT and PE in patients undergoing gynaecological surgeries are comparable to those seen after general surgical procedures.[9] Patients undergoing hip and knee replacement surgeries, hip fracture surgeries and those with major trauma without DVT prophylaxis have DVT risk of 40%-60% while spinal cord injured patients have approximated DVT risk of 60%-80%.[10]

Pathogenesis and classification of DVT

Rudolph Virchow in 1856 described three main mechanisms responsible for the formation of thrombus in the deep veins : (1) venous stasis , (2) hypercoagulability and (3) vascular

injury.[3,8,,11,12] These three factors are interrelated and favor clot formation by disrupting the balance of the opposing coagulative and fibrinolytic systems.

Venous stasis can occur as a result of anything that slows or obstructs the flow of venous blood. This contributes to thrombogenesis by allowing activated coagulation factors to accumulate. Disorder of stasis occurs in prolong immobility and bed rest, limb cast application, spinal cord injury , after major surgeries and in patients with debilitating diseases like myocardial infarction, cerebrovascular accident and congestive cardiac failure.

A hypercoagulable state can occur due to a biochemical imbalance between circulating factors or changes in blood coagulation pathway, shifting balance toward coagulation. Both acquired and hereditary diseases predispose to hypercoagulability. Acquired risk factors include malignancy, chemotherapy, oral contraceptive and hormone replacement therapy, pregnancy and postpartum period. Inherited thrombophilia like protein C deficiency, protein S deficiency and antithrombin III deficiency also lead to increased blood viscosity.

Although the normal endothelium is nonthrombogenic, damage or injury to the endothelium can trigger the activation of platelets and coagulation. Endothelia injury may result from trauma, surgery and invasive procedures. The aetiology of venous thrombosis is frequently multifactorial, with components of the Virchow triad assuming variable importance in individual patients but when combined, these mechanisms can greatly enhance the risk for DVT.[3,8,11,12]

DVT in the lower extremity can be classified as (a) proximal (the popliteal vein or thigh veins are involved) or (b) distal (the calf veins are involved). Approximately 25% to 50% of proximal DVTs cause pulmonary emboli while a distal DVT will propagate upward to a proximal location in 20% to 30% of cases. The proximal DVTs are more likely to be associated with pulmonary embolism, a higher death rate, and a higher rate of post-thrombotic syndrome than the distal DVTs.[3]

RISK FACTORS

There are several well-recognized risk factors for DVT and an understanding of these risk factors is necessary in order to maximize the prevention of the disease in high risk individuals and patients. There has been an increasing recognition that all DVT risk factors reflect one of the three underlying pathophysiologic processes of: (1) venous stasis, (2) hypercoagulability, (3) vascular injury and that VTE does not usually develop in their absence. The risk of developing DVT increases in proportion to the number of predisposing factors.[13,14] The predictive values of these factors are not equal and indications for prophylaxis should be based on both the strength of individual risk factors and the cumulative weight of all risk factors.[13] Table 1 outlines some of the clinical risk factors for development of DVT .

Surgery

The risk of thrombosis in surgical patients depend on the type of surgery, the site and extent of surgical trauma, duration and nature of the operative procedure , the length of time that the patient remains immobilized preoperatively and postoperatively and additional risk factors inherent in the patient. Procedures associated with high risk of DVT include major lower limb and pelvic orthopaedic surgeries, major general and vascular surgeries, neurosurgeries, surgeries for gynaecological malignancy and major urological surgeries. Advanced age, presence of other medical comorbidities, obesity, previous history of DVT or cancer increase the risk of postoperative DVT.[13,14,15]

Trauma

Following trauma patients are at increased risk of developing DVT. The incidence of DVT after trauma is influenced by factors, including patient demographics, the nature, site and severity of injury, and the method of detection. The risk of venography confirmed DVT in major trauma patients without prophylaxis according to Geerts et al[16] was 58%.[16] Identified risk factors for DVT in trauma patients are spine and spinal cord injury, higher injury severity score, age above 40 years, lower extremity fractures, pelvic fractures, head injury, severe chest injuries and requirement for mechanical ventilatory support.[17,18]

Age

Age is a very important risk factor for venous thrombosis, but the underlying mechanism is not clearly understood. Patients $\leq$40 years of age are at significantly higher risk of DVT compared with younger patients, and the risk approximately doubles with each subsequent decade.[13] Venous dilation occurs in the elderly particularly when they are confined to bed, and this combined with their greatly reduced mobility, may result in venous stasis.[19] The incidence of DVT is low in children[13] and young patients with venous thrombosis usually have strong predisposing factors, such as multiple trauma, leg fractures, or indwelling central venous lines.[20,21]

Malignancy

Cancer is a major risk factor for deep vein thrombosis. A population-based, case-control study by Heit et al[22], showed a fourfold increase (odds ratio [OR] 4.05; 95% CI, 1.938.52) in the risk of thrombosis for patients with malignant neoplasm compared with patients with no malignant neoplasm. This risk is multiplied further in advanced cancer, when chemotherapy is given and cancer surgery.[13,19,22,23]

Previous history of DVT

A previous episode of VTE is a strong risk factor for recurrence particularly when exposed to high-risk conditions (eg, major surgery, prolonged immobility, or serious illness). An epidemiologic study of 1272 medical outpatients in France (the Sirius study) [24] on the most important risk factor for a new VTE and a report on risk factors in surgical patients by Flordal et al[25] both demonstrated that previous VTE was also an independent risk factor for VTE in this population. The increased risk of thrombosis in patients with previous episode of venous thrombosis may be caused by venous stasis, which occurs as a consequence of valve damage, or by venous obstruction or alterations in the blood (either recognized for example deficiency of antithrombin III, protein C, protein S, plasminogen or possibly heparin cofactor II or unrecognized), which predisposed the patient to the initial episode.[19]

Acute medical illness

Although DVT is most commonly associated with surgery or trauma, by far the greatest proportion (70%) of symptomatic cases of VTE events and fatal PE occur in patients hospitalized for acute medical illnesses such as myocardial infarction (MI), malignancy, ischaemic stroke, pneumonia, and congestive heart failure.[26,27]

Hospitalized Patients
Hospitalized patients are at risk of DVT from immobilization, cancer, surgery, infections and other pathological conditions. Absolute risk factors for DVT according to a surveillance study for general medical patients was 10%-20%, general surgery 15%-40%, major gynaecological patients 15%-40% and orthopaedic patients undergoing major knee and hip surgeries 40%-60%.[27] Many of these events may not be clinically apparent. It is therefore important to administer DVT prophylaxis according to established guidelines in hospitalized patients to prevent complications of DVT.

Immobilization
Immobilization increases the risk of DVT due to venous stasis and resultant pooling of blood in the intramuscular sinuses of the calf. Relevant settings of immobility include bedrest, plaster casts on the legs and paresis of the legs due to neurological conditions, preoperative and postoperative immobility. Whereas prolonged bed rest or immobility alone does not provide adequate reason for prescribing prophylactic anticoagulant therapy, prolonged immobility combined with other major risk factors increases the likelihood of VTE.[13,14,19]

Obesity
Obesity is defined as a body mass index (BMI) above 30 kg/M^2. The association between obesity and DVT is still under investigation. A number of studies have reported association between obesity and post-operative DVT. Obesity has been shown to double the risk of venous thrombosis in both men and women.[28,29,30,31] Obesity is reported to be associated with impaired fibrinolytic activity and in addition postoperative mobilization is more likely to be delayed in obese patient than their non- obese counterparts.[19] However other studies[32,33,34] have reported that obesity is not an independent risk factor for DVT.

Oral Contraceptives
Most oral contraceptives combine estrogen and progestin. There is evidence that the risk of VTE is higher among users of oral estrogen-containing contraceptives than nonusers,[35,36,37] however the absolute risk is low with absolute risk of VTE of less than 1/10,000 patients/y and increased to only 3 to 4/10,000 patients/y during the time oral contraceptives were used.[38] The risk of DVT with oral contraceptive use is somewhat small in young fit patients but may be significant in patients with additional risk factors.[28]

Hereditary Risk Factors
In addition to acquired risk factors, several distinct inherited abnormalities in the coagulation system have been found to be associated with increased risk for DVT.[39] These conditions are often referred to as "thrombophilias", " thrombophilic disorders" or "hypercoagulable syndromes". There is a more than 2-fold increase in VTE incidence among those with family history.[14]The two most common genetic risk factors for VTE are factor V Leiden and the prothrombin gene mutation. Others are protein C and protein S deficiency, antithrombin deficiency and Hyperhomocysteinemia. Although the genetic risk factors increase the likelihood of an initial VTE, their predictive value is poor. Risk for deep vein thrombosis can increase when patients with thrombophilia are exposed to other risk conditions such as surgery , trauma or immobilization.[15,23,31]

Table 1.Risk Factors for Venous Thromboembolosm.

Stasis
• Surgery , trauma, immobility, paresis • Increasing age • Pregnancy and postpartum • Heart or respiratory failure • Obesity
Vessel injury
• Previous deep vein thrombosis • Smoking • Varicose veins • Central venous catheterization
Hypercoagulability
• Increasing age • Malignancy or cancer therapy • Oestrogen therapy (contraception or hormone rep replacement) • Acute medical illness • Nephrotic syndrome • Myeloproliferative disorders • Paroxysmal nocturnal haemoglobinuria • Inherited or acquired thrombophilia

Diagnosis
Accurate diagnosis of DVT and prompt treatment is crucial to ~~prevent potentially fatal pulmonary embolism and~~ unnecessary anticoagulation in the absence of DVT should be avoided due to risk of bleeding. Pain, calf swelling, tenderness and discolorations due to venous stasis are the most common clinical signs and symptoms of acute DVT but these are nonspecific and unreliable to make definitive diagnosis of DVT.[7,23] Other clinical conditions like infection, heamatoma and acute joint/muscle injuries may present in the same way. Additionally studies have shown that only 20%-40% of patients with clinically suspected DVT have confirmed diagnosis of DVT underscoring the importance of accurate diagnostic strategies .[15,40] Because the clinical diagnosis of DVT is nonspecific and insensitive, confirmation with objective investigation is essential. Now it has been established that diagnostic work-up of suspected DVT based on algorithms combining clinical prediction rules with D-dimer testing, then followed by imaging procedures(ultrasonography), if necessary is non-invasive and has been confirmed to be safe, reliable reproducible and cost effective.[7,41,42,43,44.]

Clinical prediction rules
These are evidence based diagnostic tools for DVT that combine standardized multiple clinical variables(e.g., patient characteristics, history, symptoms, signs from clinical examination) in order to estimate the pretest probability for DVT to occur and also guide interpretation of subsequent

diagnostic test. Several validated clinical prediction models in use include but are not limited to Khan score,[45] St. Andre hospital score,[46] Padua prediction score,[47] Wells score.[48,49,50] The best validated and most commonly used prediction score is Wells score either in its dichotomized (unlikely ≤2points, or likely ≥2points) or tripartite (low risk ≤0 , intermediate =1 or 2points, high≥=3 points) set-up and can be applied to both outpatient and inpatient(table2).[7,48,49,50,51]

Table 2. The Wells score

Clinical variable	Point
Active cancer (treatment on-going or within previous 6 months or palliative)	+1
Paralysis, paresis or recent plaster immobilization of the lower extremities	+1
Recently bedridden for 3 days or more, or major surgery within the previous	+1
12 weeks requiring general or regional anaesthesia	+1
Localized tenderness along the distribution of the deep venous system	+1
Entire leg swelling	+1
Calf swelling at least 3cm larger than that on the asymptomatic leg (measured 10cm below the tibial tuberosity)	+1
Pitting edema confined to the symptomatic leg collateral superficial veins (non varicose)	+1
Previously documented DVT	+1
Alternative diagnosis at least as likely as DVT	+1
Three level wells score	
Low	+2
Intermediate	
High	<1
Two-level wells score	1-2
Unlikely	>2
Likely	
The American Academy of Family Physicians (AAFP)/American College of Physicians (ACP) clinical	≤1
	≥2

practice guideline recommended for diagnosis of DVT in patients with clinical suspicion of DVT are as follows:[52]
Recommendation 1: Validated clinical prediction rules (e.g., Wells score) should be used to estimate pretest probability of venous thromboembolism (VTE), both deep venous thrombosis (DVT) and pulmonary embolism, and for the basis of interpretation of subsequent tests.
Recommendation 2: In appropriately selected patients with low pretest probability of DVT or pulmonary emobolism, obtaining a high-sensitivity D-dimer is a reasonable option, and if negative indicates a low likelihood of VTE.

Recommendation 3: Ultrasound is recommended for patients with intermediate to high pretest probability of DVT in the lower extremities.

Recommendation 4: Patients with intermediate or high pretest probability of pulmonary emobolism require diagnostic imaging studies (ventilationperfusion (V/Q) scan, multidetector helical computer axial tomography (CT), and pulmonary angiography).

In events of clinical suspicion of DVT, after thorough history and complete physical examination is done. The first step is to determine the clinical pretest probability of DVT using validated clinical prediction score such as Wells score (table1). If the score is =1 (DVT unlikely) D-dimer assay is obtained. A negative D-dimer assay excludes the possibility of venous thrombosis (DVT). If D-dimer assay is positive, a venous ultrasound is indicated. Positive venous ultrasonography confirms the diagnosis of DVT and negative venous ultrasound scan excludes the diagnosis of DVT.[3]

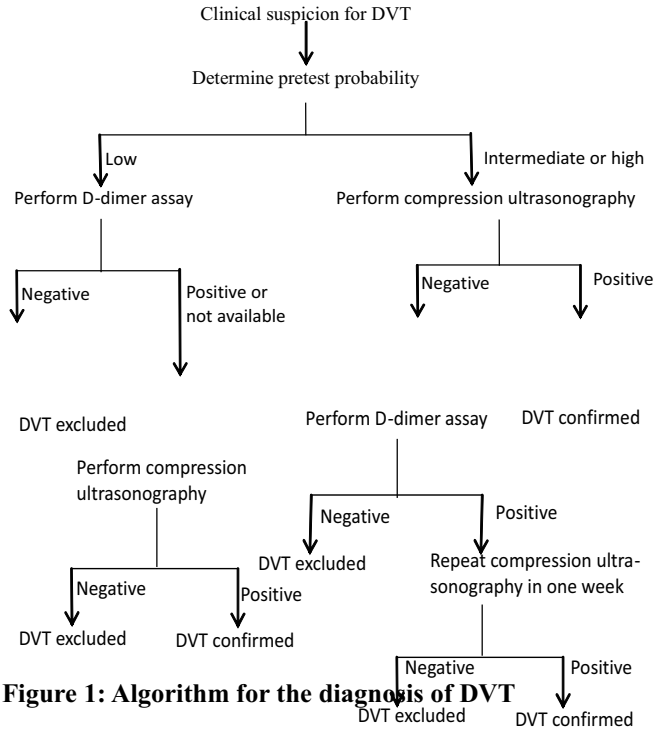

Figure 1: Algorithm for the diagnosis of DVT

If the pretest probability is moderate to high (score =2), venous

ultrasound is done. If the ultrasound is positive, DVT is diagnosed and treated. If the ultrasound is negative then D-dimer assay is done. A negative D-dimer assay excludes the diagnosis of DVT while a positive D-dimer test is an indication for further follow up studies(repeat ultrasound in 6 to 8 days or do venography).[3]

D-dimer Assay.

D-dimer is a degradation products of circulating cross-linked fibrin formed following degradation of fibrin clot by plasmin during activation of the coagulation system and so plasma levels are raised in events of thrombus formation .[3,23,42] It reflects global activation of blood coagulation and fibrinolysis. It has been studied extensively as an adjuvant test in the diagnosis of DVT. However, the D-dimer level can also be elevated in other non-thrombotic conditions like infection, in the immediate postoperative state or with clinical conditions such as disseminated intravascular coagulation, trauma, and malignancy.[3,23,42]

All currently available D-dimer assay (ELISA Latex agglutination assay, Red blood cell whole blood agglutination assay (simpliRED)) are highly sensitive for DVT but variable. ELISA method is most sensitive with a negative predictive value of about 95%.[3,23] Specificity is also variable and poor, with whole blood agglutination being the most specific (68%).[23] It is also noteworthy that patients with DVT may have false-negative D-dimer results, such as after treatment with low molecular weight heparin, or patients with DVT symptoms longer than 23 weeks.[3,42] Thus D-dimer assay cannot be used as a stand-alone test to rule-in or rule- out DVT.[3,42,53]

Imaging studies.

Because the clinical signs and symptoms of DVT are non-specific and not always reliable, the diagnosis depends heavily on the use of objective tests.

Venous ultrasonography is now the imaging test of choice to diagnose DVT in patient stratified as DVT likely or with a low/moderate probability and a positive D-dimer test .[3,15,54,55,56]

It is safe, noninvasive, easily accessible, reliable, relatively inexpensive and cost- effective and has replaced invasive venography as the gold standard.[57,58]

Two distinct ultrasound approaches used to confirm or exclude DVT in symptomatic patients are: (1)

Serial, 2-point/2-region compression venous ultrasonography (CUS) or limited (CUS)compression ultrasonography of the proximal veins, based on the belief that thrombosis of the distal veins (ie, distal to the popliteal vein) are not dangerous unless they extend proximally, or (2) complete compression ultrasonography of the deep veins of the entire lower extremity, including the calves (whole-leg VUS or complete VUS) .[42,59] When compression ultrasound is complemented by Doppler color flow evaluation

("duplex" sonography), the sensitivity for thrombosis detection is about 96%, with a high negative predictive value (99%).[60] DVT diagnostic criteria are lack of compressibility of a venous segment , direct thrombus imaging with vein enlargement, and abnormal spectral and color-Doppler flow.

A single normal ultrasound of the deep vein of the entire lower limb (whole-leg VUS) can safely exclude DVT this is not the case with limited CUS because it does not investigate the distal veins and repeat testing within one week is mandatory to identify proximal extension of undetected distal DVT.

Two randomized studies that compared limited CUS and whole- leg VUS in symptomatic out-patient with suspected DVT failed to record statistically significant differences between the two ultrasound approaches,[61,62] whole-leg VUS is the preferred venous ultrasound test for the diagnosis of acute DVT according to the recommendations of a consensus conference.[63]

In patients with unlikely pretest probability for DVT and normal D-dimer levels, Ultrasound can be safely avoided. However if CUS is performed, all patients with normal baseline findings need to undergo either a repeat CUS within one week, unless they are at low pretest probability, or have normal D-dimer results. If WLUS is chosen, no further testing is required in patients with normal baseline findings.[42]

The other advantages of venous ultrasound are its ability to diagnose other pathologies (Baker's cysts, superficial or intramuscular hematomas, lymphadenopathy, femoral aneurysm, superficial thrombophlebitis, and abscess), and the fact that there is no risk of exposure to irradiation, while its major limitation is its reduced ability to diagnose distal thrombus.

CONTRAST VENOGRAPHY[3,23,55]

Contrast venography has long been considered the standard criterion test for diagnosing DVT. However, it is not recommended in the initial evaluation because of the invasiveness, technical difficulties, and risks (e.g., hematoma, pain, vessel damage, allergic reaction to contrast media). It should be reserved either for patients with negative non-invasive tests and high clinical probability or for those in whom non-invasive tests are equivocal or non-feasible.

Other imaging procedures are occasionally used to diagnose DVT, including impedance plethysmography, computed tomography (CT), and magnetic resonance imaging (MRI).[3,23,55]

Plethysmography is based on measurement of the rate of change in impedance between two electrodes on the calf when a venous occlusion cuff is deflated. . The test is not specific for thrombotic obstruction to venous outflow. Thus, false positive results may be obtained in patients with preexisting venous disease, heart failure, or peripheral artery disease. Impedance plethysmography is rarely used except in population studies of patients at increased risk of DVT.

Plethysmography measures electrical impedance to detect calf blood volume changes induced by inflation of a thigh cuff. Blood volume change is reduced by obstruction of the popliteal or more proximal veins. The test is not specific for thrombotic obstruction to venous outflow. Thus, false positive results may be obtained during pregnancy if a patient is positioned incorrectly, if the vein is compressed by an extravascular mass, or if venous outflow is impaired by increased central venous pressure. The reported sensitivities and specificities for the diagnosis of symptomatic proximal venous thrombosis range from as low as 65% to as high as 95%. [68,69] The test may also not detect large, non-occlusive proximal vein thrombi and fails to detect most thrombi within the calf. Because venous reflux is easily recognized with Doppler US or duplex scanning, these modalities are preferred over impedance plethysmography.

Computerised tomography may be used to diagnose venous thrombosis in pelvic and abdominal veins, to determine the

cause of leg swelling, or to evaluate a soft tissue mass, but it is rarely used to diagnose DVT. It involves the injection of contrast medium, exposes the patient to radiation, may be difficult to interpret when artefact and insufficient venous filling are present, and is more expensive than ultrasonography and of limited availability.

Magnetic resonance imaging is non -invasive and without the risk of exposure to irradiation. It has been studied for DVT diagnosis and appears to have sensitivity and specificity equivalent to that of ultrasonography. However, MRI is expensive, it may not be available in emergency room settings, and it is impractical for critically ill patients

Treatment

Prompt diagnosis and treatment of DVT with appropriate anticoagulant is most crucial. The goal of the therapy for lower-extremity DVT is to prevent the extension of thrombus and pulmonary embolism in the short-term and to prevent recurrent events in the long-term.

Based on extensive research evaluating the risk of recurrent DVT, guidelines have been established for the duration of anticoagulation therapy. Guideline recommendations for anticoagulation are divided into phases: initial phase (first week after diagnosis), long-term phase (second week to three months), and extended phase (beyond three months).[7, 55, 64]

Anticoagulation (AC) is the primary approach to therapy during all three phases of VTE treatment (initial phase, long term phase and extended phase), however in patients with contraindications to anticoagulation, placement of a vena cava filter can be considered in patients at risk for PE.[3,65]

The anticoagulant therapy for DVT has evolved from inpatient administration of intravenous unfractionated heparin (UFH) to therapy with low molecular weight heparin (LMWH), warfarin and non-Vitamin-K antagonist oral anticoagulants (NOACs)/ Direct oral anticoagulants (DOAs).

Firm evidences demonstrate that LMWH is superior to unfractionated heparin for the initial treatment of DVT, particularly for reducing mortality and reducing the risk for major bleeding during initial therapy.[8,66,67] However, unfractionated heparin is preferred in patients with severe renal insufficiency, high bleeding risk, hemodynamic instability, or morbid obesity.

The efficacy and safety of NOACs/DOAs versus warfarin or parenteral anticoagulation plus warfarin in the treatment of acute VTE have been evaluated and NOACs has been found to be as effective as the conventional treatment in reducing recurrence VTE , PE risk and major bleeding were significantly lower in the NOACs group.[64,68,69] Non-Vitamin-K antagonist oral anticoagulants (NOACs)offer a convenient and attractive approach to the treatment of VTE for a number of reasons;they can be taken orally and in some cases do not require bridging, they do not require routine laboratory monitoring and have fewer drugdrug interactions than oral VKA.[64,70] Dabigatran and edoxaban require initial treatment with low molecular weight heparin (LMWH) for 5-10 days before their commencement , whereas rivaroxaban and apixaban do not.[64,71] However NOACs/DOAs should be avoided in pregnant or breastfeeding women or in those with significant renal dysfunction.

Anticoagulation in non-cancer and non-pregnant patients.[7]

The three phases of Deep vein thrombosis treatment are; Figure 2

Initial treatment (5-21 days following diagnosis); during this period, patients receive either parenteral therapy and are transited to vitamin K antagonists (VKA) or use high-dose direct oral anticoagulants (DOACs).

Long-term treatment (for 3-6 months); patients are treated with VKA or DOACs.

Initial and long-term treatments are mandatory for all DVT patients.

Extended treatment (beyond first 3-6 months) is based on benefit/risk balance of continued anticoagulation. Extended anticoagulation is recommended for patients with an unprovoked VTE and low risk of bleeding.

Dabigatran 150mg bid preceded by LMWH for 5-10 days

Edoxaban 60mg od (30mg od if CI Creat 50-30<ml/min or concomitant potent P-P inhibitors) preceded by LMWH for 5-10 days

Rivaroxaban 15mg bid for 21 days Rivaroxaban 20mg od: Rivaroxaban 10mg or 20mg od beyond 6 months

VKA to achieve INR 2-3 preceded by LMWH for 5-10 days

Figure 2: Deep vein thrombosis treatment phases.

Anticoagulation agents and Dosing

In the initial phase of anticoagulation, a decision must be made between using the vitamin K antagonist warfarin or a direct-acting oral anticoagulant. If warfarin, dabigatran (Pradaxa), or edoxaban (Savaysa) is selected, concomitant parenteral anticoagulation is required for at least five days.

Conventional anticoagulation.

In the standard treatment of DVT the initial phase of anticoagulation is started with parenteral anticoagulants, either unfractionated or low-molecular-weight heparin, followed by long-term vitamin K antagonists (Wafarin). Guidelines from the American College of Chest Physicians (ACCP), recommend immediate anticoagulation with subcutaneous low molecular weight heparins for at least five days, with simultaneously oral anticoagulants such as warfarin for at least three months.[72]

LMWH (Enoxaparin or tinzaparin) or fondaparinux may be used as initial therapy in conjunction with warfarin for at least the first 5 days and until the international normalized ratio

(INR) reaches at least 2.0 or above for two consecutive days while Warfarin is continued for three months.

Tinzaparin dose is 175 IU/kg once daily
Enoxaparin dose is 1 mg/kg twice daily
Fondaparinux dose is 7.5 mg daily (5 mg if <50 kg; 10 mg if >100 kg)
Warfarin 5mg daily
LMWH may also be used as monotherapy for the full duration of treatment; this is the preferred long-term treatment for active cancer patients and those with DVT in pregnancy.

NOACs/DOACs (Non-vitamin K antagonist Oral Anticoagulants/Direct Oral Anticoagulants).
Guidelines from NICE, ACCP and European Society of Cardiology(ESC) recommends direct oral anticoagulants (DOACs), including the direct thrombin inhibitor dabigatran and the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban, as first line treatment for both DVT and PE.[73,74] The advantages of these anticoagulant agents over vitamin K antagonists (VKAs), include a rapid onset of action like the LMWH and can replace these parenteral agents, predictable pharmacokinetic profile, which allow for simplified drug administration in a standardized dose, fewer clinically related drug interactions and they can be administered once or twice daily without need for laboratory monitoring and dose adjustment.

Rivaroxaban acts by direct inhibition of factor Xa and achieves maximum plasma levels approximately 3 hours after oral ingestion. Once at steady state, the terminal half-life is 4 to 9 hours (up to 12 hours in patients 75 years old).The recommended dose of rivaroxaban is 15 mg twice daily for the first 21 days followed by 20 mg once daily for continued treatment
and prevention of recurrence. For patients continuing on long-term treatment beyond 6 months, consideration can be given to reducing the dose to 10 mg PO daily.
Rivaroxaban has very few significant drug-drug interactions, and food does not affect absorption from the gastrointestinal tract; the oral bioavailability is more than 80%.[7,55,64,75]

Apixaban is a direct inhibitor of factor Xa . It has more than 50% bioavailability and reaches peak plasma concentration in 3 to 4 hours after oral administration. Apixaban is dosed at 10 mg PO twice daily for the first 7 days, followed by 5 mg PO twice daily for the duration of treatment. For patients continuing on long-term treatment beyond 6 months, consideration can be given to reducing the dose to 2.5 mg PO daily.[7,55,64,75]

Edoxaban is a direct oral inhibitor of factor Xa that is capable of inhibiting free and bound factor Xa. Edoxaban is administered at 60 mg once daily after 5-10 days of initial parenteral anticoagulation (usually a LMWH) for the duration of treatment.[7,55,64,75]

Dabigatran is an oral anticoagulant that works through direct inhibition of clotting factor IIa (thrombin). Dabigatran requires a 5-10 day initial treatment period with a parenteral anticoagulant (usually a LMWH). Dabigatran is dosed at 150 mg PO twice daily for the duration of treatment. Dose reduction has not been studied with this drug.[7,55,64,75]

Thrombolysis.
NICE guidelines and other studies suggest thrombolysis can be considered in massive proximal lower extremity thrombosis or iliofemoral thrombosis associated with severe symptoms or limb-threatening ischemia for less than 14 days. Treatment modalities include systemic thrombolysis, catheter-directed thrombolysis, and surgical thrombectomy.[71,76,77] Selection of patients must be guided by a multidisciplinary approach, with inputs from a vascular surgeon and interventional radiologist, and must consider patient preferences

Non-pharmacological therapy for DVT.
Inferior Vena Cava (IVC) Filters for Deep Vein **ThrombosisTreatment.**
The use of vena cava filters in treatment of VTE is controversial and evidence for safety and effectiveness is lacking.An inferior vena cava filter is rarely indicated. However in some high risk patients; If there is an absolute contraindication to therapeutic anticoagulation, complications from anticoagulation, or failure of anticoagulation in a patient with acute proximal DVT, an inferior vena cava filter may be indicated. Possible complications from inferior vena cava filter placement include thrombosis and arteriovenous fistula.[7,55]

Compression
Graduated compression stocking traditionally has been an integral part of the treatment of acute DVT because of proven evidence of reduction of the incidence and severity of post thrombotic syndrome. [23,80,81,82] More recent trials and meta-analysis have however shown no benefit of graduated compression stocking in preventing the occurrence of post phlebitis syndrome in patients diagnosed with DVT.[83,84,85] Stockings should therefore no longer be prescribed routinely but only used selectively in patients to treat symptoms (swelling, pain).
Absolute contra-indications for compression stocking in DVT are advanced peripheral arterial occlusive disease, decompensated heart failure, septic phlebitis and phlegmasiacaeruleadolens (DVT leading to severe swelling of the whole leg). Relative contra-indications are suppurative dermatoses, intolerance of compression stocking fabric, advanced neuropathy and chronic arthritis.

Duration of treatment
The risk of VTE recurrence is greatest in the first year after the event and remains elevated indefinitely compared with the general population. According to data from a randomized trials, the risk of early recurrence (on anticoagulant treatment) is about 1-2%.[78] Lifetime recurrence rates for DVT ranges from 21% to 30%, depending on the population. If anticoagulants are stopped before active treatment is completed, the risk of recurrent VTE is higher than if treatment

was stopped after its completion[2,3] Long-term anticoagulation reduces the risk of recurrent VTE but results in more bleeding events.

The duration of treatment should be individualized and based on estimated risks of recurrent thrombosis and risk of bleeding. If there are no contraindications, current guidelines recommend anticoagulation for a minimum of three months for PE and proximal DVT if a reversible provoking factor is identified as the cause of VTE(surgery, ceasation of hormonal therapy).[55,79]

Extended anticoagulation therapy is recommended in patients with a first VTE that is an unprovoked proximal DVT of the leg or PE with a low to moderate bleeding risk. [79] Patients with permanent risk factors or patients with recurrent DVT or PE require lifelong secondary prevention.[79]

PROPHYLAXIS

Venous thromboembolism (VTE) is a common complication during and after hospitalization for acute medical illness or surgery. The risk of VTE in hospitalized medical and surgical patients based on ACCP guidelines was 51% in the multinational cross-section ENDORSE study.[8] Surveillance studies have found that the absolute risk of DVT without thromboprophylaxis, in hospitalized patients is approximately 10 to 40% among general medical patients or general surgical patients and 40 to 60% following major orthopedic surgery (Table 3).[27] Approximately 70-80% of such thrombi are clinically silent or asymptomatic and are detected when medical patients undergo objective screening for DVT. Pulmonary embolism from DVT accounts for 5-10% of deaths in hospitalized patients; making VTE the most common preventable cause of in-hospital death.[8] It is difficult to determine which at risk patient will develop DVT and PE. Thromboprophylaxis is therefore the most appropriate measure in the hospitalized patients to prevent the mortality and morbidity from DVT.

Table 3: Approximate Risks of DVT in Hospitalized Patients.

Patients Group	DVT Prevalence (%)
Medical patients	10-20
General surgery	15-40
Major gynecologic surgery	15-40
Major urologic surgery	15-40
Neurosurgery	15-40
Stroke	20-50
Hip or knee arthroplasty, HFS	40-60
Major trauma	40-80
SCI	60-80
Critical care patients	10-80

Risk assessment for thromboprophylaxis and bleeding.

Risk assessment is an important tool for preventing VTE and it should also include bleeding risk assessment.

The risk of VTE in hospitalized patients is determined by both patient characteristics and the clinical settings and this can be stratified based on age of the patient, presence or absence of other risk factors for DVT and the type of trauma or surgery. Those at low risk do not need specific therapy apart from early mobilization, whereas those at moderate or higher risk should receive thromboprophylaxis (Table 4).[10] Example of risk assessment model for individual patients as the basis of prescribing thromboprophylaxis for medical patient is Paudal risk assessment model (Table 5a and 5b).[47]

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines 8th edition recommended implementation of group-specific thromboprophylaxis routinely for all patients who belong to each of the major target group, for example medical patents, patients undergoing major surgery or trauma (Table 6).[86]

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Table 4 Levels of Thromboembolism Risk and Recommended Thromboprophylaxis in Patients.

Levels of Risk	Approximate DVT Risk without Thromboprophylaxis %	Suggested thrombo prophylaxis options
Low risk	< 10	No specific thromboprophylaxis
Minor surgery in mobile patients		Early and "aggressive" ambulation
Moderate risk	10 40	
Most general, open gynecologic or urologic surgery patients		LMWH (at recommended doses),
Medical patients, bed rest or sick		LDUH bid or tid, fondaparinux
Moderate VTE risk plus high bleeding risk		Mechanical thromboprophylaxis
High risk	40 - 80	LMWH (at recommended doses),
Hip or knee arthroplasty, HFS		fondaparinux oral vitamin K antagonist
Major trauma, SCI		(INR 2.3)
High VTE risk plus high bleeding risk		Mechanical thromboprophylaxis

Table 5a Padua Risk Assessment score for Medical Patients

Risk Factor	Points
Active cancer	3
Previous VTE (with the exclusion of superficial vein thrombosis)	3
Reduced mobility	3
Already known thrombophilic condition	3
Recent (> 1 mo) trauma and /or surgery	2
Elderly age(>70 y)	
Heart and /or respiratory failure	1
Acute myocardial infarction or ischemic stroke	1
Acute infection and /or rheumatologic disorder	1
Obesity (BMI >30)	1
Ongoing hormonal treatment	

- For patients with risk of bleeding, non-pharmacological means of thromboprophylaxis is recommended, these include AES, IPC and patients with stroke are not recommended to use AES in the acute phases of stroke.
- LMWH has proven to be safe in medical patients who do not have a significant bleeding risk
- UFH is safer for patients with renal insufficiency CrCl<30mL/min)

Table 5b VTE Prophylaxis Recommendations Based on Risk Score

Points	Risk	Recommendation
<4	Low VTE Risk	VTE prophylaxis not needed
>4	High VTE Risk and Low Bleed Risk	Pharmacologic Prophylaxis
	High VTE Risk and High Bleed Risk	Mechanical Prophylaxis

Table 6 Degree of Thromboemolism Risk in Surgical Patients without Prophylaxis

Risk level	Calf DVT	Proximal DVT	Clinical PE	Fatal PE
Low risk Minor surgery in patients aged <40 y with no additional risk factors	2%	0.4%	0.2%	<0.01%
Moderate risk Minor surgery in patients with additional risk factors Surgery in patients aged 40-60 y with no additional risk factors	10%-20%	2%-4%	1%-2%	0.1%-0,4%
High risk Surgery in patients >60 y or with additional risk factors (eg. Prior VTE, cancer	20%-40%	4%-8%	2%-4%	0.4%-1.0%
Highest risk Surgery in patients with multiple risk factors (age>40 y, cancer, prior VTE) Hip or knee arthroplasty, hip fracture surgery	40%-80%	10%-20%	4%-10%	0.2%-5%

Methods of Prophylaxis:

Thromboprophylaxis methods in use include general measures, mechanical and pharmacological agents.

General Measures: [87]

Early mobilization and leg exercises are encouraged in patients recently immobilized. Immobility has been demonstrated to increase the risk of DVT tenfold [88] and prolonged bed rest has not been found to be of any significant benefit for many medical conditions.[89]

Adequate hydration should also be ensured in immobilised patients because haemoconcentration increases blood viscosity and reduces blood flow, especially in the deep veins of the leg in immobile patients.

Both mechanical and pharmacologic agents can be used for thromboprophylaxis. Mechanical methods serve to prevent venous stagnation in the lower limbs by promoting venous outflow, whereas pharmacologic methods act by attenuating coagulation.

Mechanical methods of thromboprophylaxis

Early and frequent full ambulation may not be immediately feasible in hospitalized patients or after surgery and many hospital associated symptomatic thromboembolic events occur after ambulation is initiated. Mobilization alone does not and cannot provide adequate thromboprophylaxis in hospitalized patients.

Mechanical thromboprophylactic method includes graduated compression stockings (GCS) with graduated pressure (highest at the ankle and lower proximally) to prevent venous stasis due to pressure difference. Intermittent pneumatic compression (IPC) involves alternate inflation and deflation of cuffs, while venous foot pump (VFP) entails intermittent plantar compression and serves to prevent venous stagnation in the lower limbs by increasing mean blood flow velocity in leg veins and reducing venous stasis. The mechanical methods do not cause bleeding hence they can be used for patients in which anticoagulants are contraindicated. Including patients with active or recent gastrointestinal bleeding, patients with hemorrhagic stroke and those with hemostatic defects.

All the three mechanical methods of thromboprophylaxis have been shown to reduce the risk of DVT in a number of patient groups, however they have been studied much less extensively than anticoagulant-based approaches and are generally less efficacious than anticoagulant thromboprophylaxis.[86,90]

Chemical prophylaxis

Established anticoagulants in use include warfarin (Coumadin), unfractionated heparin, low-molecular weight heparin, fondaparinux, and the Non-vitamin K antagonist Oral Anticoagulants (dabigatran, rivaroxaban, apixaban, and edoxaban). Aspirin has been considered as possible low risk measure for preventing DVT and its use advocated by the Scottish Intercollegiate Guidelines,[90] and other studies[91,92] however the guidelines from the American College of Chest Physicians,[86] the Institute for Clinical Systems Improvement,[93] and other studies[94,95] caution against relying on aspirin for prevention of DVT because of the risk of increased bleeding and its failure to significantly reduce the rate of recurrence of venous thromboembolism.

DVT PROPHYLACTIC GUIDELINES

Early and frequent ambulation of hospitalized patients at risk for VTE is an important principle of patient care.

Mechanical prophylaxis is recommended primarily in patients at high risk for bleeding or as an adjunct to anticoagulant-based thromboprophylaxis. It should be worn continuously during the period of immobility to the return of full ambulation. It is contraindicated in critical limb ischaemia.

Dabigatran, rivaroxaban, apixaban or LMWH were all recommended as first line chemoprophylaxis for thromboembolism in patients with hip/knee joint re-placement surgery.[28, 87, 96] The ACCP guidelines[98], recommended dabigatran in patients with a history of ischemic stroke or TIA and atrial fibrillation, including paroxysmal atrial fibrillation. However, dabigatran is contraindicated in patients with severe renal impairment. UFH is the preferred anticoagulant for VTE prophylaxis in patients with renal impairment and LMWHs in all other patient populations with no contraindications.

The duration of thromboprophylaxis depends on the level of risk of VTE. Standard thromboprophylaxis of 7 to 14 days is usually commenced until the patient is ambulating. Recent studies have found that activation of coagulation persists for at least 30 days after THR and that extended thromboprophylaxis through the 4 weeks after hospital discharge is beneficial for certain high risk situations such as in patients undergoing surgery for cancer or total hip replacement, total knee replacement and hip fracture treatment.[13,86,97] However patients admitted with acute medical illness thromboprophylaxis should be continued until discharge for the majority of the patients

CONCLUSION

DVT is a preventable common clinical condition in hospitalized patients with potential fatal acute complication of pulmonary embolism and disabling morbidity. Clinical symptoms and signs are unreliable for diagnosis. The validated diagnostic pathway involves clinical suspicion, pretest probability, D-dimer assay, and venous ultrasound as the gold standard. Diagnosis should be prompt and anticoagulant is the mainstay of treatment unless contraindicated. Prevention of DVT and its potential complications can be achieved by reduced immobilization, early ambulation, rehydration and combination of anticoagulants and mechanical methods in high risk patients.

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