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RECENT ADVANCES IN THE DIAGNOSIS, TREATMENT, AND CLINICAL MANAGEMENT OF DEEP VEIN THROMBOSIS: A COMPREHENSIVE REVIEW

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ABSTRACT

A frequent disorder called deep vein thrombosis (DVT) can have fatal consequences such pulmonary embolism, postphlebitic syndrome, and embolism. Over time, the method for diagnosing DVT has changed. These days, a safe and practical method for investigating suspected lower-extremity thrombosis combines compression ultrasound imaging, D-dimer test, & pretest probability into an algorithm strategy. Diagnostic imaging is not necessary to exclude proximal DVT in patients with low pretest likelihood & negative result of D-dimer test. Anticoagulation therapy is the cornerstone of treatment for DVT; thrombolysis and inferior vena cava filter implantation are saved for extreme circumstances. The majority of DVT patients can be managed outpatient with the use of low-molecular-weight heparin. Whether the original event was caused by a transitory risk factor or was idiopathic determines how long anticoagulant medication should be administered. More investigation is needed to identify the best predictors of recurrent DVT in order to identify the patients who will benefit from continued anticoagulant medication.

KEYWORDS: Vitamin K-antagonists (VKAs), direct oral anticoagulants (DOACs), warfarin, deep vein thrombosis (DVT), & anticoagulants.

INTRODUCTION

Venous thromboembolism (VTE) is a subtype of deep venous thrombosis (DVT), which is the most prevalent cause of mortality & morbidity globally. One case of VTE is occur for every 1000 persons annually.[1,2] About two thirds of these cases are thought to be caused by DVT.[3] pulmonary embolism (PE) results up to one-third of instances of DVT, a feared consequence that is the primary trigger of death.[4] the emergence of post-thrombotic syndrome, which occurs two years after DVT and affects up to 50% of patients & includes variety of symptom such legs discomfort, edema, & in serious conditions; venous ulceration, is largely responsible for DVT morbidity.[5,6]

The cornerstone of the treatment of DVT is anticoagulants, which aims to stop the condition from progressing to PE and from thrombosis reoccurring. In patients having DVT who are not taking anticoagulants, the thirty-day mortality rate is higher than 3%, & the risks of death increase tenfold in patients with PE.[7] Direct oral anticoagulants (DOACs) introduction have necessitated a comparison between the previously established vitamin K-antagonists (VKAs) and these newer medications in the treatment of deep vein thrombosis. This matter has been the subject of several recent clinical investigations, which have shown that the efficacy & safety profiles of the two medication classes are comparable. Physicians are now better equipped to integrate patient- & disease-specific factors for DVT management because more alternative therapeutic medications are available.

The estimated yearly DVT incidence in the general population is 67 per 100,000.[8,9] Acute pulmonary embolism patients have a mortality rate of 1% to 8% even with appropriate management.[10,11] Long-term sequelae include and chronic thromboembolic pulmonary hypertension (4%)[12] and postphlebitic syndrome (40%).[13] Anticoagulant medication lowers the chance of recurrent thrombosis, but it also raises the risk of significant bleeding. Prior to 1995, all patients suffering from DVT were imaged, & if the results were negative, the tests were repeated a week later.[14] Since only 10% to 25% of individuals with suspected DVT were discovered to have the condition and most serial test

results were negative, this technique was ineffective.[15,16] New approaches to the diagnosis & management of suspected DVT were developed throughout the last ten years.

Pathogenesis

First described in 1856, Virchow's Triad suggests three variables that are involved in the origin of thrombosis. Venous stasis, hypercoagulability, & vascular injury. The most significant of these elements is venous stasis, although it doesn't seem to be enough to induce thrombus formation on its own. Nonetheless, the chance of a clot forming is significantly increased when vein stagnation and vascular damage or hypercoagulability coexist. The elements of Virchow's Triad are essentially connected to the clinical conditions that are most strongly linked to DVT; these includes trauma, surgery, extended immobility, cancer, CHF, pregnancy, obesity, varicose veins, advanced age, & DVT history.[17]

In areas where the flow of blood is restricted or physically changed, such as the pockets adjacent to valves in the deep veins of the legs, venous thrombosis usually occurs. Despite the fact that valves help to promote blood flow through the venous circulation, venous stasis and hypoxia can also happen there. Venous clots tendencies to develop in the sinus adjacent to venous valve as demonstrated by several postmortem studies.[3] Hematocrit rises in tandem with a decrease in oxygen tension when the flow of the blood decreases. Antithrombotic protein, like endothelial protein C receptor (EPCR) along with thrombomodulin, which are expressed primarily on venous valve, might be downregulated in the ensuing hypercoagulable microenvironment.[18] Important anticoagulant proteins are inhibited by hypoxia, which also stimulates the synthesis of several procoagulants. P-selectin is one of these; it's adhesive proteins that attracts immune cells to the endothelium via tissue factor.[19] There is disagreement if tissue factors are expressed by the cells of the extravascular tissue or on the endothelium in this process. Tissue factors are widely acknowledged as the primary factor in thrombus formation. P-selectin and tissue factors appear to be necessary for the development of thrombus.[19,20]

Venous thrombi consist of two parts: an exterior red cell dense fibrin clot encircling inner platelet rich white thrombi that forms what-called lines of Zahn. The outer scaffold, which is composed of complexes of histone proteins and fibrin, may have an important role in thrombi sensitivities to thrombolysis and tissue plasminogen activator (TPA).[21] The likelihood of the development of thrombus rises with procoagulants to anticoagulant ratio. The proportion of endothelial cell surface to blood volume influences the quantity of proteins. Procoagulants benefit from a reduced ratio of blood volume to cell surface (i.e., big vessels). Prothrombin, von Willebrand factor, factor VII, and factor VIII appear to have a significant impact on the likelihood of coagulation.[22] Prothrombin dampens a natural anticoagulant process by inhibiting activated protein C's anticoagulant qualities in addition to stimulating thrombin production. Three such mechanisms include the heparin-antithrombin pipeline, the pathway of tissue factors inhibitor, & the pathway of protein C anticoagulant (that involves thrombomodulin, protein S, protein C, & EPCR). An elevated risk of thrombus formation is linked to defects in these pathways. Less is known about the function of the tissue factor inhibitor pathway in humans.[20,22,&23]

Numerous familial variations also increase the levels of von Willebrand factor, factor VII, VIII, IX, & prothrombin, that predisposes to the formation of thrombus. Protein C cannot inhibit active factor Va in factor V Leiden, which affects up to 5% of Caucasians and raises the risk of thrombosis seven times.[20] Moreover, obesity, oral contraceptives, aging, & cancers are risk factors for the development of clots. Compression is a common side effect of veins cancer that exacerbates stasis. Furthermore, it causes procoagulants to be shed onto membrane particles, such as tissue factor, which encourages thrombosis.[24]

Oral contraceptives use & obesity convey separate risks for thrombus formation. They work in concert to increase thrombus risks.[25] Lastly, increasing age is associated with an increased risks of thrombosis. A variety of aging-related factors are being observed, though the exact cause is still unknown. These include an increase in the prevalence of obesity, an increase in diseases along with comorbid ailments, prolonged immobility, and an increase in procoagulants without an equal increase in anticoagulants, such as protein C.[20] When considered together, thrombus formations are dynamics, multifactorial processes which depends upon a delicate equilibrium between biochemical and physical stimuli.

Diagnosis

DVT frequently presents clinically in an ambiguous manner. Therefore, for an accurate diagnosis, confirmatory studies comprising imaging and D-dimer tests, appraisal of pre-test clinical likelihood, and increasing incorporation of clinical symptoms are required.

Deep Vein Thrombosis Signs and Symptoms

Leg discomfort, edema, erythema, and enlarged superficial veins are among the symptoms and indicators of DVT in the legs or pelvis. Similar arm-specific symptoms are present in arm DVT. Asymptomatic DVTs can also exist. Lymphedema, cellulitis, chronic venous insufficiency, hematoma, and, in the case of leg DVT, a ruptured Baker cyst are among the differential diagnosis for the condition.[26]

Clinical Gestalt or Impression prior to testing

Based on clinical examination, the gestalt likelihood of deep vein thrombosis represents an unstructured

assessment for the possibility of deep vein thrombosis. If the pre-tests chance is determined through a medical professional with expertise, it can be useful.[27,28] Validated clinical decision principles, however, offer more dependability.[29]

Clinical Decision Rule-Based Prior Probability Testing

The Wells guideline for DVT guides investigations and aids in calculating the prior testing probability of DVT in primary care & outpatients who have suspected deep vein thrombosis.[30] According to the Wells rule, clinical signs and risk factors of deep vein thrombosis are assigned points. This results in a total score that ranges from -2 to 9 points, classifying individuals as either "unlikely" (≤ 1 score) or "likely" (≥ 2 scores) to have deep vein thrombosis.[31] Given that both groups need investigations, a possible limitation is the requirement for doctors to subjectively assess the likelihood or unlikability of an alternative (non-DVT) diagnosis. Image studies are essential for inpatients having suspected deep vein thrombosis because D-dimer test is often produces false-positive result and clinical decision guidelines have not been established.

D-Dimer Test

The majority of DVT patients (sensitivity: 94–96%), as well as elderly individuals and those having chronic kidney failure, malignancy, sepsis, inflammation, trauma, recent surgery, pregnancy, & severe burns (specificity: 42–52%), have elevated D-dimer level.[32,33] Consequently, a positive D-dimer tests necessitates image study to confirm its presence, whereas negative D-dimer test will aid to rule out DVT, especially if the clinical probabilities are minimal. D-dimer testing is not advised as indicator for subclinical disease recurrences or to track response for anticoagulants, but it can be used to estimate the likelihood of recurrent venous thromboembolism upon stopping anticoagulants.[34]

Imaging

The first-line DVT imaging technique is venous ultrasonography (VUS). It is predicated on power imaging and B-mode, either alone or in conjunction with Color-Doppler US. The diagnosis criteria for DVT include aberrant spectral and Color-Doppler flow, direct thrombus image with vein enlargement, & cross-sectional vein incompressibility. VUS can be carried out by extended imaging of the inferior vena cava, iliac and femoral veins, and calf veins (whole-leg VUS or complete VUS), or by focusing exclusively on the popliteal and common femoral veins [2-point/2-region compression venous ultrasonography (CUS) or limited CUS]. There are disagreements regarding whether to investigate the problematic leg exclusively or both.[35,36]

When DVT is clinically suspected, VUS has a total specificity of 93.8% and an accuracy of 94.2% for proximal & 63.5% for isolated distal DVT. Color-Doppler US in combination improves sensitivity but decreases specificity.[37] In those who have a single normal complete VUS, anticoagulation could be safely deferred when DVT has been identified (without PE symptoms). The same holds true for restricted CUS, given that it can be replicated and incorporated into a diagnostic plan that also considers clinical probability & D-dimer evaluation.[38] According to randomized trials, however both approaches are said to be comparable.[39,40] Complete VUS can offer up to 42% alternate diagnoses, which could help to explain the patient's symptom. When combined with restricted CUS, point-of-care ultrasound (POC) administered by emergency physicians has demonstrated excellent results (96.1% sensitivity, 96.8% specificity)[41] and could be helpful in situations where vascular laboratories are not always open.[42] When individuals who have suspected recurrent deep vein thrombosis compare tests findings with baseline image study after stopping anticoagulants, the diagnosis of recurrence can be confidently ruled out.[43] The most reliable US criterion is a 2- or 4-mm increment venous diameter over two measurements in the popliteal and femoral vein following complete compression.

Investigating for Underlying Risk Factors

The probability of recurrent DVT is determined by the risk factors for DVT (table 1).[44] Up to 10% of individuals with unprovoked VTE may have occult malignancy, which needs to be evaluated.[45] Nevertheless, it is not advised to have a thorough cancer screening using tumor markers or body computed tomography unless there are indications of a potential cancer.[46] Screening for hereditary thrombophilia can help evaluate whether a family member needs long-term preventive anticoagulation and can also help identify a tendency to the development of VTE. Tests for thrombophilia is not recommended on regular basis, though. Because factor V Leiden and prothrombin gene mutation, the most frequent forms of thrombophilia, are not reliable indicators of recurrent VTE, care must be used when choosing who to test. The results will not alter the course of treatment for the majority of VTE patients.[47] Patients with spontaneous VTE under 50 years of age, those with a significant family history of VTE, and those with recurring venous or artery thrombosis may want to think about getting tested for thrombophilia.[48,49]

Table 1: Risk factors for venous thromboembolism.

VTE risk factor category	Examples
Transient	• Major: surgery with general anaesthesia > 30 minutes, confined to bed in hospital ≥ 3 days with an acute illness, or caesarean section • Minor: surgery with general anaesthesia < 30 minutes, admission to hospital < 3 days with an acute illness, oestrogen therapy, pregnancy, confined to bed out of hospital for ≥ 3 days with an acute illness, leg injury with reduced mobility
Permanent/persistent	• Active cancer • Chronic inflammation (eg, inflammatory bowel disease) • Chronic autoimmune disease • Chronic infections
Unprovoked	• No transient or permanent/persistent factors
Non-environmental	• Male • Hereditary thrombophilia (eg, protein C deficiency, protein S deficiency, antithrombin deficiency, factor V Leiden mutation, prothrombin gene mutation) • Older age

* Environmental (or acquired) risk factors for venous thromboembolism (VTE) may be transient or persistent. A transient risk factor is one that resolves after it has provoked the VTE. Resolution of the transient risk factor should be confirmed before stopping anticoagulation therapy. A permanent/persistent risk factor is one that is still present after it provokes the VTE. A VTE that occurs without transient or permanent/persistent risk factors is considered unprovoked. Non-environmental (or intrinsic) risk factors do not influence whether a VTE is considered provoked or unprovoked but may influence the risk of recurrence. ◆

Patients with VTE caused by serious trauma or surgery should not undergo thrombophilia testing due to the low probability of recurring VTE. When patients experience arterial or venous thrombosis in the presence of hemolytic anemia, thrombocytopenia, livedo reticularis, or cognitive dysfunction without a stroke, testing for the antiphospholipid syndrome, an acquired thrombophilia, is recommended.[50] It is advised that patients without cirrhosis or cancer undergo testing for the Janus kinase 2 (JAK2) V617F mutation if they have abdominal (portal or hepatic vein) thromboembolism because they might have an underlying myeloproliferative disease.[51] Screening for paroxysmal nocturnal hemoglobinuria should be taken into consideration when DVT develops in the context of pancytopenia or hemolytic anemia, particularly if the thrombosis is in an atypical position (e.g., cerebral sinuses or splanchnic veins).[52,53]

MANAGEMENT

Anticoagulation

The cornerstone of VTE treatment is anticoagulants, that attempts to decrease the possibility of PTS (after DVT) & long-term thromboembolic pulmonary hypertension (following pulmonary embolism), as well as death, thrombus extension, and recurrence. "Initial" refers to the first week following a VTE diagnosis; "long term" refers to the first three months following diagnosis; and "extended" refers to the treatment with no set stop date (table 2).[54] Anticoagulants are contraindicated in cases of clinically severe bleeding. Some relative contraindications include endocarditis, uncontrolled hypertension, known hemorrhage disorders, recent trauma, severe thrombocytopenia, severe bleeding (e.g., gastrointestinal hemorrhage within two weeks, cerebral hemorrhage within three months), and hemorrhage disorders. Age over 65, a history of bleeding, cancer, cancer with metastases, liver and renal failure, thrombocytopenia, a history of diabetes, stroke, antiplatelet therapy, anemia, inadequate anticoagulants control (for vitamin K antagonists), complications as well as reduced functional capacity, recent surgery, recurrent fall, and alcohol misuse are risks factors for bleeding. If one or more of these conditions are met, the likelihood of hemorrhage could be classified as low, intermediate, & high.[54] Non-steroidal anti-inflammatory drug use must be stopped wherever feasible for extended periods of time. However, patients with superimposed superficial phlebitis or an inflamed leg may benefit from brief (1–2 week) courses of treatment. Aspirin should not be used more than 100 mg per day by people who need it for cardiovascular prophylaxis; contrary, it ought to be avoided when on anticoagulant medication.[55] If DVT is suspected, starting anticoagulation while awaiting test result is sense if the suspicions are "likely." For patients who are more susceptible to bleed or if DVT is suspected but not confirmed, delaying the start of anticoagulation is permissible as long as the results are available in less than a day.[54]

Table 2: Anticoagulants for venous thromboembolism (VTE).

Agent and VTE treatment dose	Phase		
	Initial	Long term	Extended
Unfractionated heparin 80 IU/kg intravenous bolus, then 18 IU/kg per hour intravenous infusion, target aPTT is hospital-specific	•		
Enoxaparin 1.5 mg/kg subcutaneous daily, or 1.0 mg/kg subcutaneous twice daily	•	• (cancer)	• (cancer)
Dalteparin 100 IU/kg subcutaneous twice daily, or for patients with cancer 200 IU/kg subcutaneous daily (maximum 18 000 IU/day) for 30 days, 150 IU/kg thereafter	•	• (cancer)	• (cancer)
Nadroparin 86 anti-Xa IU/kg body weight subcutaneous twice daily	•		
Apixaban 10 mg oral twice daily for 7 days, then 5 mg twice daily. For extended treatment, decrease to 2.5 mg twice daily	•	•	•
Rivaroxaban 15 mg oral twice daily for 21 days, then 20 mg daily. For extended treatment, decrease to 10 mg daily	•	•	•
Dabigatran* 150 mg oral twice daily. Decrease to 110 mg twice daily if age > 75 years or CrCl 30–49 mL/min		•	•
Warfarin* once daily, oral administration; target INR 2.0–3.0		•	•
Aspirin† 100 mg daily (after anticoagulation ceased)			•

aPTT = activated partial thromboplastin time; CrCl = creatinine clearance; INR = international normalised ratio. * Initial parenteral anticoagulation (unfractionated heparin or low molecular weight heparin) is required for dabigatran for a minimum of 5 days, and for warfarin until the INR is 2.0–3.0. † For patients with first unprovoked VTE who cannot access or tolerate ongoing anticoagulation but require reduction of thrombosis risk. ◆

Anticoagulant Agents

Initial intravenous management was given through the randomized phase 3 clinical trials of dabigatran & edoxaban, so options for treating VTE initially encompass a DOAC (rivaroxaban or apixaban), initial intravenous anticoagulants accompanied by a DOAC (edoxaban or dabigatran), or initial intravenous anticoagulants overlapping via warfarin and continued over at least 5 days till the international normalized ratio (INR) exceeds 2 on two occasions separated by one-day period. The DOACs, which includes; edoxaban, rivaroxaban, & apixaban (the factor Xa inhibitors) as well as dabigatran (the direct thrombin inhibitor), are safer and equally effective as warfarin (INR, 2.0–3.0) when treating VTE, while betrixaban has not been studied in relation to treating VTE and is only recommended for prophylaxis of VTE in hospitalized patients.[56,57] The Pharmaceutical Benefits Scheme has approved dabigatran, rivaroxaban, and apixaban as three DOACs for the treatment of VTE. Although the DOACs are categorized as a group, each has a distinct chemical structure, and as such, they ought to be regarded as independent anticoagulants (table 3) (58-61). With the increased risks for significant hemorrhage of roughly 1%, warfarin is linked to a slightly greater risk of hemorrhage than DOACs and need regular coagulation monitoring.[54,56,&62]

Table 3: Efficacy of direct oral anticoagulants versus warfarin (international normalized ratio, 2.0–3.0) for symptomatic venous thromboembolism (VTE).

	RE-COVER[40]	EINSTEIN-DVT[41]	AMPLIFY[42]	Hokusai-VTE[43]
Treatment	Dabigatran* (*n* = 1274) v warfarin* (*n* = 1265)	Rivaroxaban* (*n* = 1731) v warfarin* (*n* = 1718)	Apixaban (*n* = 2691) v warfarin* (*n* = 2704)	Edoxaban* (*n* = 4118) v warfarin* (*n* = 4122)
Index event	▪ DVT 69% ▪ PE 21% ▪ PE + DVT 10%	▪ DVT 99% ▪ PE 1%	▪ DVT 65% ▪ PE 25% ▪ PE + DVT 9%	▪ DVT 60% ▪ PE 40%
Outcomes	**HR (95% CI)**	**HR (95% CI)**	**RR (95% CI)**	**HR (95% CI)**
Primary efficacy†	1.10 (0.65–1.84)		0.84 (0.60–1.18)‡	0.89 (0.70–1.13)‡
Recurrent VTE		0.68 (0.44–1.04)‡		
Major bleeding	0.82 (0.45–1.48)	0.65 (0.33–1.30)	0.31 (0.17–0.55)‡	0.84 (0.59–1.21)
All deaths	0.98 (0.53–1.79)	0.67 (0.44–1.02)	0.79 (0.53–1.19)	

AMPLIFY = Apixaban for the Initial Management of Pulmonary Embolism and Deep Vein Thrombosis as First-line Therapy; DVT = deep vein thrombosis; EINSTEIN-DVT = Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients with Acute Symptomatic Deep Vein Thrombosis without Symptomatic Pulmonary Embolism; Hokusai-VTE = Edoxaban versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism; HR = hazard ratio; RE-COVER = Efficacy and Safety of Dabigatran Compared with Warfarin for 6-month Treatment of Acute Symptomatic Venous Thromboembolism; RR = relative risk. * Initial parenteral anticoagulation (heparin or low molecular weight heparin) was administered. † Recurrent symptomatic VTE or VTE-related death. ‡ $P < 0.05$. ◆

Selection of Anticoagulants

Medical concerns including safety, effectiveness, renal and hepatic functions, & co-occurring prescriptions would all be taken into account while choosing anticoagulants. Practical considerations involving patient preference, cost, ease of use, & availability would also be made. When treating VTE in a patient with simple symptoms, DOACs are the best first-line anticoagulant because they have less drug–drug interactions, are superior to vitamin K antagonists (table 4)[63], and can reverse anticoagulation in an emergency (e.g., urgent surgery, life-threatening bleeding).[64] Exanet Alfa was recently approved in Europe and the US to reverse the anticoagulant effect in patients receiving rivaroxaban or apixaban, but it is not yet approved in Australia.[65] Pregnant women should not take DOAC treatment, and patients with severe renal impairment (CrCl < 30 mL/min for dabigatran, apixaban, and rivaroxaban 15 mg and 20 mg tablets; or CrCl < 25 mL/min for apixaban; or CrCl < 15 mL/min for rivaroxaban 10 mg tablets), severe hepatic impairment (Child-Pugh score C), mechanical heart valve, & concurrent administration of medications which are potent CYP3A4 & P-glycoprotein inhibitors should not receive DOAC treatment.[66,67] Alternatives to DOAC therapy include low molecular weight heparin (LMWH), intravenous unfractionated heparin, & warfarin.

Table 4: Key factors that influence the choice of anticoagulant for venous thromboembolism (VTE).

Anticoagulant	Indications	Routine monitoring	Daily injections	Adverse effects	Contraindications†	Reversal agent	Cost
Dabigatran	▪ DVT ▪ PE	No	No	Bleeding,‡ dyspepsia	CrCl < 30 mL/min, severe hepatic impairment, pregnancy, breastfeeding	Idarucizumab	$$$
Rivaroxaban	▪ DVT ▪ PE	No	No	Bleeding‡	CrCl < 30 mL/min, severe hepatic impairment, pregnancy, breastfeeding		$$$
Apixaban	▪ DVT ▪ PE	No	No	Bleeding‡	CrCl < 25 mL/min, severe hepatic impairment, pregnancy, breastfeeding		$$$
Enoxaparin	▪ DVT ▪ PE ▪ Cancer-associated VTE	No	Yes	Bleeding	Heparin-induced thrombocytopenia within previous 100 days		$$$
Dalteparin	▪ DVT ▪ PE	No	Yes	Bleeding	Heparin-induced thrombocytopenia		$$$
Warfarin	▪ DVT ▪ PE	Yes	No	Bleeding, intracranial haemorrhage, not safe in pregnancy	Intracranial haemorrhage, skin necrosis, pregnancy, breastfeeding	Vitamin K, prothrombin complex concentrate	$
Unfractionated heparin	▪ DVT ▪ PE ▪ Cancer-associated VTE	Yes	Yes		Heparin-induced thrombocytopenia	Protamine	$

CrCl = creatinine clearance; DVT = deep vein thrombosis; PE = pulmonary embolism. * Patients with acute VTE should be evaluated for treatment with a direct oral anticoagulant (DOAC). In patients who are eligible for treatment with a DOAC, there is no evidence to recommend one agent over another because the DOACs have not been compared directly. The choice of DOAC is guided by considering renal function, whether initial parenteral anticoagulation (with dabigatran) is cumbersome, and whether once per day or twice per day dosing is preferred. † Active bleeding and known hypersensitivity are contraindications for all anticoagulants. ‡ Including upper gastrointestinal tract bleeding. ◆

The Duration of Anticoagulants

The length of anticoagulants for deep vein thrombosis is based on the likelihood of a recur that is ascertained wether the it was caused by an unprovoked or persistent risk factor. If a temporary, permanent, or permanent environmental risks factors are found, a DVT may be deemed provoked; if not, it may be deemed unprovoked (table 1).[44] The probability of recurrent VTE is determined by risk factors for VTE. For instance, stopping anticoagulation after 3-6 months of treatment for VTE patients is linked to one-year hazard of occurrences approximately 1-3 percent if the initial VTE arose in the presence of significant transient risks factors, approximately ten % if the occurrences are unprovoked, & even higher than ten % whenever the event arises in patients who are actively undergoing cancer treatment.[44] Although prothrombin gene mutations and factor V Leiden are weak predictors of the recurrence of the disease in thrombophilia patients, less common factors like inherited protein C, protein S, and antithrombin deficiencies as well as the antiphospholipid antibodies syndrome have more reliable indicators of VTE recurrence, and the THANZ guideline recommend extended anticoagulants management for these patients.[48] When treating distal DVT brought on by a significant temporary risk factor which is no longer present, six weeks of anticoagulant are advised. For the treatment of unprovoked isolated distal DVT, proximal DVT caused by trauma or surgery, unprovoked DVT when bleeding risk is high, and proximal DVT caused by a non-surgical transitory risks factors, three months of anticoagulation is advised. For spontaneous proximal DVT, anticoagulation for at least three months is recommended, followed by a reassessment of the risk-benefit ratio. For thrombosis caused by active malignancy, anticoagulation for at least six months is advised.

If risk factors like active malignancy continue, or if the bleeding risk is modest and the DVT is unprovoked proximal, extended anticoagulation is advised.[62] Patients on extended anticoagulants would be checked on at least once annually to assess the unique risks of bleeding & thrombosis, keep an eye out for any side effects from the medication, and look for any changes that might have an impact on the anticoagulant's half-life, such as renal impairment. For prolonged and long-term use of anticoagulants medication, DOACs were preferable over warfarin, assuming there were no contraindications. However, where INR monitoring is practicable & the expense of acquiring DOACs is a concern, warfarin is an acceptable substitute. Extended therapy with modest doses of apixaban (2.5 mg two time per day) or rivaroxaban (10 mg single daily dose) after long-term VTE treatment reduces the risk of VTE recurrence more effectively than placebo or aspirin, accordingly, without raising the probability of significant haemorrhage.[68,69]

Vena Cava Inferior Filter

Under certain clinical conditions, the installation of an inferior vena cava (IVC) filters would be taken into consideration. IVC filter implantation decreased the incidence of a future pulmonary embolism in 2055 patients suffering from acute proximal DVT who were not prescribed anticoagulation by 50% as compared to individuals without a filter.[70] On the other hand, IVC filters come with special dangers such filter thrombosis (which occurs in around 2% of instances), immigration, & penetration of the IVC wall, which are linked to 70% greater risks of later DVT in comparison to those not having IVC filter insertion. In a cohort analysis of individuals with VTE & an anticoagulation contraindication, patients who underwent IVC filter implantation had a significantly higher 30-day death rate than those who did not.[71] Only patients who have a complete opposition to anticoagulants or certain patients who experience recurrent PE while on anticoagulants & have a large amount of residual DVT should be evaluated for IVC filters.[62] The need for an IVC filter is not indicated by a massive pulmonary embolism.[70,72] After 21 days of placement, or whenever it's appropriate to resume anticoagulants, the IVC filter should be taken out.

Thrombolysis

In catheter-directed thrombolysis, thrombolytics (usually recombinant tissue plasminogen activator, or tPA) is infused immediately into the deep vein thrombosis using percutaneous catheter insertion. In those suffering from acute proximal leg thrombosis, a randomized trial comparing anticoagulants plus tPA to anticoagulants alone revealed no decrease in the risk of PTS as well as higher bleeding rates with dual treatment.[73] Individuals at low bleeding risk who have recently (within a week) developed significant DVT, usually iliofemoral, or who have phlegmasia cerulea dolens might continue to benefit via catheter-directed thrombolysis. These patients were not well represented in this research.[74] There haven't been any randomized trials using thrombolysis to treat arm DVT, contrary to leg DVT.[75]

Surgical Thrombus Removal

The use of surgery to remove DVT has not been demonstrated. Venous thrombectomy, according to some, would be considered only for patients who have imminent venous gangrene despite receiving optimal anticoagulation & meeting all other requirements, such as having iliofemoral DVT, catheter-directed thrombolysis unavailable, symptoms lasting less than seven days, good functional status, a life expectancy of more than a year, and access to the necessary resources & expertise's.[54]

Compressions Stockings

According to available data, early uses of elastic compressions stocking might aid prevent PTS & residual vein blockage. In those suffering from acute proximal thrombosis, compressions stocking worn for a minimum

of half a year till the Villalta score dropped to four or less on two consecutive readings, as opposed to two years, were non-inferior for preventing PTS.[76] Within a predetermined sub-study of the IDEAL DVT study, there was a reduction in residual vein obstruction & post-treatment symptom (PTS) when acute leg compression was applied within 24 hours of thrombus diagnosis as opposed to no compressions.[77]

Secondary prevention of venous thromboembolism

For individuals who have finished anticoagulation therapy in an initial unprovoked deep vein thrombosis or pulmonary embolism & for whom continued anticoagulants is either inappropriate or inaccessible, taking 100 mg of aspirin per day is a viable way to reduce the risk of recurrent VTE.[78] New approaches to secondary prevention have been investigated since the advent of DOACs. After 6–12 months of anticoagulants management, extended anticoagulants using low dose apixaban 2.5 mg two time daily for another year had been more successful compared to a placebo in decreasing recurrent VTE or death from whatever reason in patients with VTE.[68] Extended anticoagulation with rivaroxaban was not associated with a substantial rise in hemorrhage rate (major bleeding 0.5% with rivaroxaban 20 mg, 0.4% with rivaroxaban 10 mg, and 0.3% with aspirin 100 mg daily); instead, it was more effective than aspirin in reducing recurrent VTE in another similar population.[69]

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