REVIEW ARTICLE

UPI JOURNAL OF CHEMICAL AND LIFE SCIENCES (UPI-JCLS)

ISSN: 2581-4648 (An International online Peer Reviewed Open Access Journal)

www.uniquepubinternational.com Published by Unique Pub International (UPI)

DIAGNOSIS AND TREATMENT OF VENOUS THROMBOEMBOLISM

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Received: 04 Jan 2025 Revised: 26 Jan 2025 Accepted: 15 Feb 2025

Abstract

Venous thromboembolism (VTE), which includes pulmonary embolism and deep vein thrombosis, is a condition characterized by abnormal blood clot formation in the pulmonary arteries and the deep venous vasculature. It is often serious and sometimes even fatal if not promptly and appropriately treated. Moreover, the later consequences of VTE may result in reduced quality of life. The treatment of VTE depends on various factors, including the type, cause, and patient comorbidities. Furthermore, bleeding may occur as a side effect of VTE treatment.In populations, but recent studies have shown an increase in the incidence of VTE in Asia. A variety of treatment options are currently available owing to the introduction of direct oral anticoagulants. The current VTE treatment recommendation is based on evidence from previous studies, but it should be applied with careful consideration of the racial, genetic, and social characteristics in the Korean population.

Keywords: Venous thromboembolism ,Modeling ,Thrombosis ,Hemo-dynamics ,Deep vein thrombosis ,Pulmonary embolism , Body mass index , Diagnosis .ointment, Wound healing, Anti inflammatory, Tissue repair, Skin regeneration, Extract, Topical herbal treatment.

INTRODUCTION

Venous thromboembolism (VTE) includes deep vein thrombosis (DVT) and/or pulmonary embolism (PE), affecting approximately 1 in 1000 individuals annually. Timely diagnosis and treatment are crucial, as untreated PE has a mortality rate of around 30%, and nearly 30% of untreated DVTs can lead to severe leg swelling or ulceration. With prompt intervention, the death rate due to PE or treatment-related complications drops to less than 1%. Additionally, accurately ruling out VTE helps avoid unnecessary anticoagulation therapy and its associated risks. The goal of VTE diagnosis is to quickly identify patients who require treatment while minimizing the number of diagnostic tests for those without VTE. Over the past few decades, advancements in diagnostic approaches have reduced the need for imaging tests in suspected VTE cases while ensuring few patients who need treatment are overlooked. The diagnostic process for VTE can be divided into several stages-initially, the patient's history and physical examination guide the clinician's suspicion of VTE; next, screening tests to exclude VTE may be performed; and finally, patients in whom VTE remains uncertain undergo definitive imaging. This review outlines current diagnostic strategies for VTE, focusing on areas that need further enhancement [1, 2]

EPIDEMIOLOGY OF VTE

A recent study indicated that the annual incidence of VTE in the USA was 123 per 100,000 individuals. Another report estimated the annual incidence of VTE in European countries to be 131 per 100,000 individuals, with the incidence increasing with age. While data on the incidence of VTE across different racial groups remains limited, it is believed that the rates are higher in White and African-American populations and lower in Asian and Native American populations [3].

CLINICAL CHALLENGES OF VENOUS THROMBOEMBOLISM

Epidemiology and Associated Complications

Hemostasis is a collection of interrelated processes that preserve blood circulation within the body, primarily through the clotting response to blood vessel injury. Venous thrombosis arises from disruptions in these hemostatic Mechanisms, including impaired venous return and dysfunction of endothelial cells. Coagulation of venous blood is initiated by stagnant flow, interactions with extracellular proteins, and elevated concentrations of blood factors, which trigger a complex series of mechanical and biochemical responses. Due to pathological conditions or changes in blood flow, venous thrombosis can develop without any direct vascular injury, leading to severe complications. Typically, this abnormal thrombosis occurs in the deep venous system, driven by a combination of reduced flow, increased blood coagulability, and vessel wall dysfunction-elements that constitute Virchow's triad [2, 4].

RISK FACTORS

Several risk factors contribute to a patient's likelihood of developing VTE, including both genetic predispositions and acquired factors linked to lifestyle and medical history. Numerous elements can elevate the risk of DVT formation, such as advancing age, high BMI, prolonged immobility (e.g., during hospitalization), stasis in a deep vein resulting from injury or surgery, pregnancy, cancer, congestive heart failure, chronic obstructive pulmonary disease, previous VTE episodes, or a family history of blood clots[9].

- Age
- Family history
- Sex
- Pregnancy
- Surgery
- Hormone based medicines

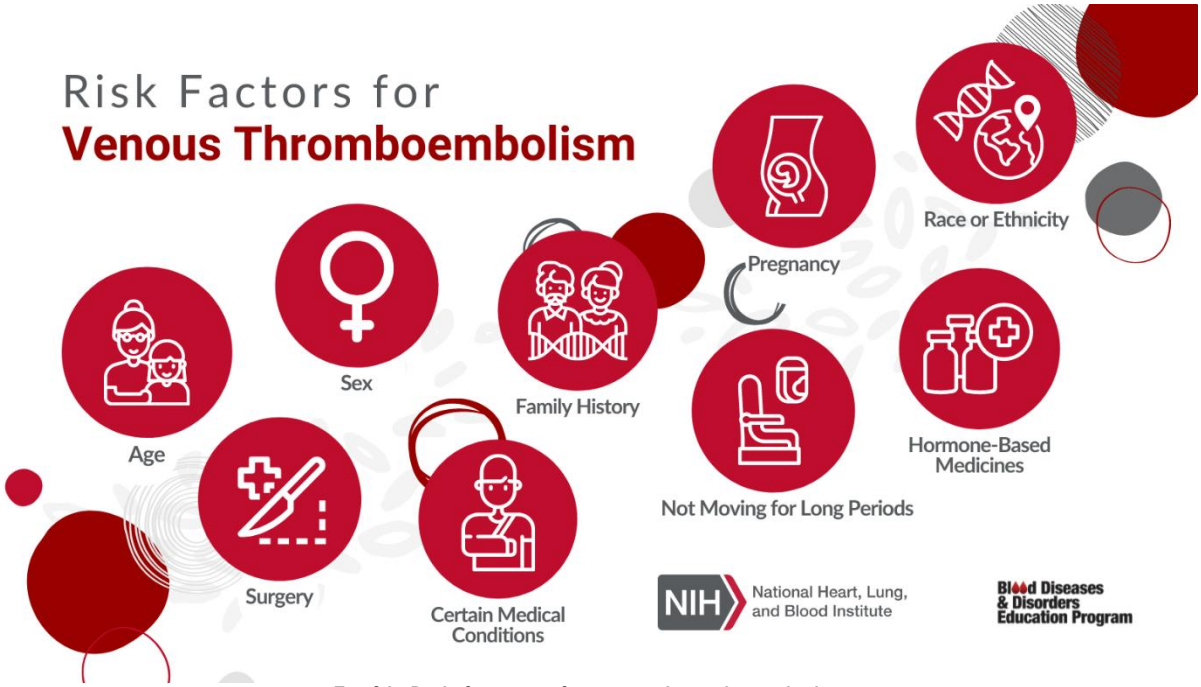

Fig 01: Risk factors of venous thromboembolism

TREATMENT OF DEEP VEIN THROMBOSIS

Treatment of proximal deep vein thrombosis (DVT): Proximal lower extremity DVT occurs when a clot forms in the popliteal, femoral, or iliac veins. The clinical presentation varies based on the location, extent, and degree of blockage, ranging from no symptoms to significant swelling and tissue death (gangrene). Anticoagulant therapy is recommended for all patients with proximal DVT. However, in cases of active bleeding, low platelet counts (＜50,000×10^9/L), or a history of intracranial hemorrhage, an inferior vena cava (IVC) filter is preferred. For patients with provoked proximal DVT, a course of anticoagulant therapy for 3 months is generally recommended. For those with unprovoked proximal DVT, extended anticoagulant therapy (at least 3 months, and possibly indefinitely) is advised. In patients with a high risk of bleeding, 3 months of anticoagulant treatment is suggested. Treatment options for proximal DVT include vitamin K antagonists (VKA), low-molecular-weight heparin (LMWH), or direct oral anticoagulants (DOACs). The choice among these treatments is typically based on the clinician's judgment, considering factors such as bleeding risks, comorbid conditions, patient preferences, cost, and convenience. Thrombolytic therapy is generally not recommended, except for patients with massive iliofemoral or femoral DVT who have a high risk of developing limb gangrene [10].

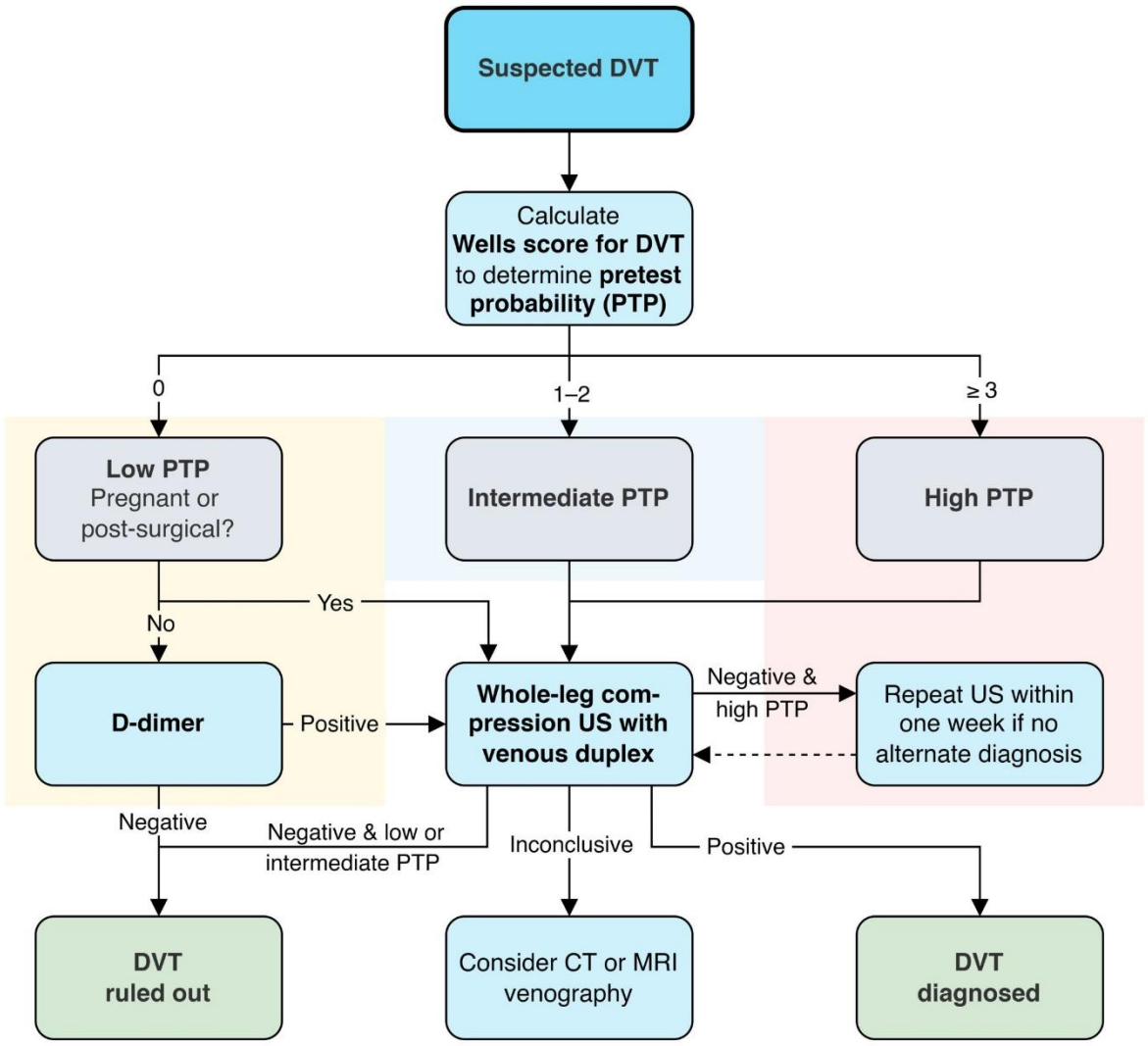

Fig 02:Treatment of deep vein thrombosis

Treatment of cancer-associated venous thrombo embolism

Incidental pulmonary embolism (PE) is often detected during enhanced chest CT scans. Although the embolic burden in incidental PE is typically lower than in symptomatic PE, anticoagulation should be started if the embolism involves areas proximal to the subsegmental vasculature. In the case of incidental subsegmental PE (SSPE), the evidence is mixed, as mentioned in Section 4.2.3. Some researchers recommend observation without anticoagulant treatment for these cases [5].

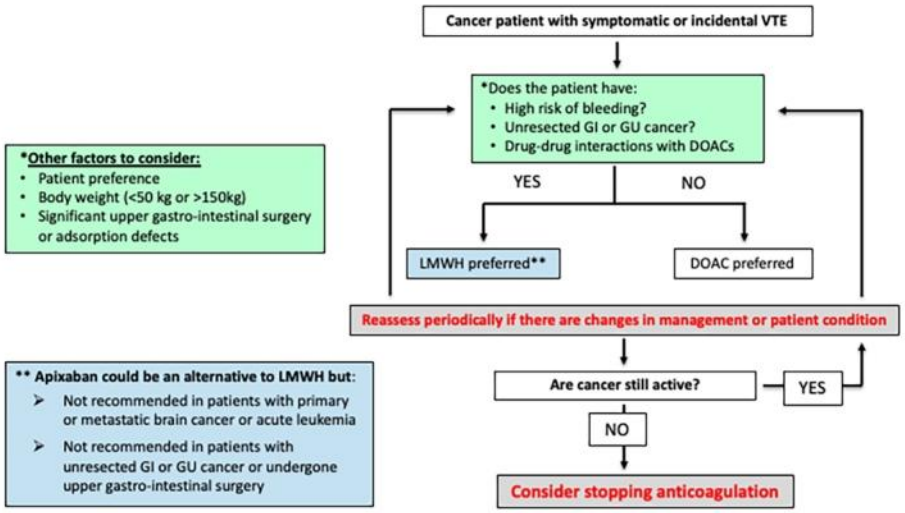

Fig 03: Treatment of cancer-associated venous thrombo embolism

TREATMENT OF VENOUS THROMBOSIS OF OTHER SITES

Treatment of superficial venous thrombophlebitis

Although superficial thrombophlebitis is typically considered a benign and self-limiting condition, there is growing awareness that many individuals with this disorder may have concurrent deep vein thrombosis (DVT) or pulmonary embolism (PE), or are at a substantial risk of developing venous thromboembolism (VTE). The management of superficial thrombophlebitis remains a subject of debate. Nevertheless, treatment strategies should focus on alleviating symptoms, preventing the extension of the thrombosis, and minimizing the risk of PE. A randomized controlled trial demonstrated that anticoagulation with unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and vitamin K antagonists (VKA) were more effective than compression therapy alone in preventing the extension of superficial thrombophlebitis [6,7].

Treatment of catheter-related venous thrombosis

Thrombotic complications related to catheter use are frequently seen in cancer patients, leading to significant patient discomfort, catheter malfunction, and potential infections. There are no large, prospective, randomized studies focused on treatments for catheter-related thrombosis. When symptomatic catheter-related thrombosis occurs, it is typically treated with anticoagulation therapy alone, usually without the need for catheter removal. The optimal duration for anticoagulation in catheter-related thrombosis has not been extensively studied in clinical trials. According to the American College of Chest Physicians (ACCP) guidelines, anticoagulation is recommended for 3 months if the thrombosis is symptomatic. Recently, direct oral anticoagulants (DOACs) have been suggested for use in cancer patients with catheter-related thrombosis. Various reviews offer strategies for preventing catheter-related thrombosis [8].

Treatment of splanchnic vein thrombosis

Splanchnic vein thrombosis (SVT) represents the most common type of thrombosis in atypical locations, accounting for approximately 4% of all thrombotic events. SVT includes thrombosis in the portal, mesenteric, hepatic, and splenic veins. Doppler ultrasonography is the primary diagnostic tool for portal and hepatic vein thrombosis, while CT angiography is preferred for identifying mesenteric vein thrombosis. The most prevalent acquired risk factors for SVT include abdominal cancers (particularly hepatobiliary, gastrointestinal, and pancreatic), liver cirrhosis, and myeloproliferative neoplasms (MPNs). Therefore, in patients with non-cirrhotic, non-malignant SVT, screening for MPNs (e.g., JAK2 mutation analysis) and paroxysmal nocturnal hemoglobinuria is advised, even for those with normal complete blood counts. Although no high-quality randomized controlled trials have been published, several guidelines and reviews provide recommendations for managing SVT.

VENOUS THROMBOEMBOLISM ASSOCIATED WITH PREGNANCY

Although the absolute risk of venous thromboembolism (VTE) during pregnancy is low (0.6–1.2 per 1,000 deliveries), it remains a significant concern, as it is one of the leading causes of maternal morbidity and mortality. Pulmonary embolism (PE) is especially critical among VTE cases, as it is a primary cause of maternal death. For pregnant women suspected of having PE, computed tomography pulmonary angiography (CTPA) or ventilation-perfusion scanning often becomes necessary, given the limited diagnostic sensitivity and specificity of D-dimer testing. A recently published pregnancy-adapted YEARS algorithm for diagnosing suspected PE can safely rule out PE; a prospective study demonstrated that 32–65% of patients avoided unnecessary CTPA, with the highest efficiency during the first trimester.

Pregnant women diagnosed with acute VTE should receive anticoagulation therapy. Vitamin K antagonists (VKA) are contraindicated due to the risk of foetal malformations, and the safety of direct oral anticoagulants (DOACs) is not well-established, with concerns raised regarding foetal safety in some studies. Low-molecular-weight heparin (LMWH) is preferred over unfractionated heparin (UFH) due to its greater convenience [7].

VENOUS THROMBO EMBOLISM IN CHILDREN

Cause and risk factors of venous thrombo embolism in children:

Venous thrombosis in children is uncommon and is typically linked to multiple underlying medical conditions. The occurrence of symptomatic VTE in neonates is 0.51 per 10,000, and in children, it ranges from 0.07 to 0.14 per 10,000. According to the Canadian registry, 96% of deep vein thrombosis (DVT) and pulmonary embolism (PE) cases are associated with medical conditions, including cancer, congenital heart defects, or trauma. The most significant and frequent risk factor for VTE is the presence of a central venous catheter (CVC), which is found in 33–48% of pediatric VTE cases. In neonates, this risk factor is as high as 94%. In contrast, inherited thrombophilia was found in only 8.8% of the cohort. Factor V Leiden and prothrombin gene mutations are more common in Caucasian patients but less frequent in individuals of Asian descent. The incidence of protein C deficiency is 0.2–0.5% in the general population, but it is higher, at 2–5%, in those with VTE. Measurement of protein S deficiency is complex, and its incidence is believed to be as low as 0.9%. The prevalence of hereditary antithrombin III deficiency is estimated to range from 0.03 to 0.8%[9].

8.2 Diagnostic Tests for Inherited Thrombophilia in Children:

A comprehensive panel of tests for thrombophilia should include factor V Leiden mutations, prothrombin 20210 mutations, deficiencies in antithrombin, protein C, and protein S, homocysteine levels, factor VIII levels, lipoprotein levels, and detection of antiphospholipid antibodies. The developmental state of the hemostatic system in children, along with naturally lower levels of coagulant and anticoagulant proteins and other factors such as drug use, infections, or inflammation, must be considered. Typically, thrombophilia tests do not influence decisions regarding the initiation or duration of acute treatment, except in specific cases, such as those with purpura fulminans due to severe protein C or S deficiency or those affected by VKA-induced skin necrosis. Testing is generally reserved for patients with unprovoked, spontaneous, or recurrent thrombotic events, which are rare in children and adolescents, as it can help identify inherited thrombophilia and inform management. Up to half of VTE events in atypical sites, such as the cerebral or splanchnic veins, or those resulting in strokes, are associated with inherited thrombophilia, and these patients may benefit from testing. As such, testing after the first instance of CVC-related VTE, unless there is a strong family history (such as a first-degree relative with VTE under the age of 40), is generally not recommended [10].

TREATMENT OF VENOUS THROMBOEMBOLISM IN CHILDREN

Treatment recommendations for pediatric VTE are largely derived from adult studies, as there is limited evidence in children. The treatment options for VTE in pediatric patients include anticoagulation, thrombolysis, surgery, and observation. The potential benefits must be carefully balanced against the risks, especially in premature neonates and critically ill children who are at higher risk of bleeding. For acute anticoagulation, unfractionated heparin (UFH) or low molecular weight heparin (LMWH) are the options, with LMWH being more commonly used due to its ease of dosing and reduced need for monitoring. After the acute phase of anticoagulation with UFH or LMWH, patients may continue with LMWH or transition to vitamin K antagonists (VKAs). When starting a patient on VKA, UFH or LMWH should be continued until the international normalized ratio (INR) reaches the therapeutic range and remains there for 2 consecutive days, which usually takes 5 to 7 days [10].

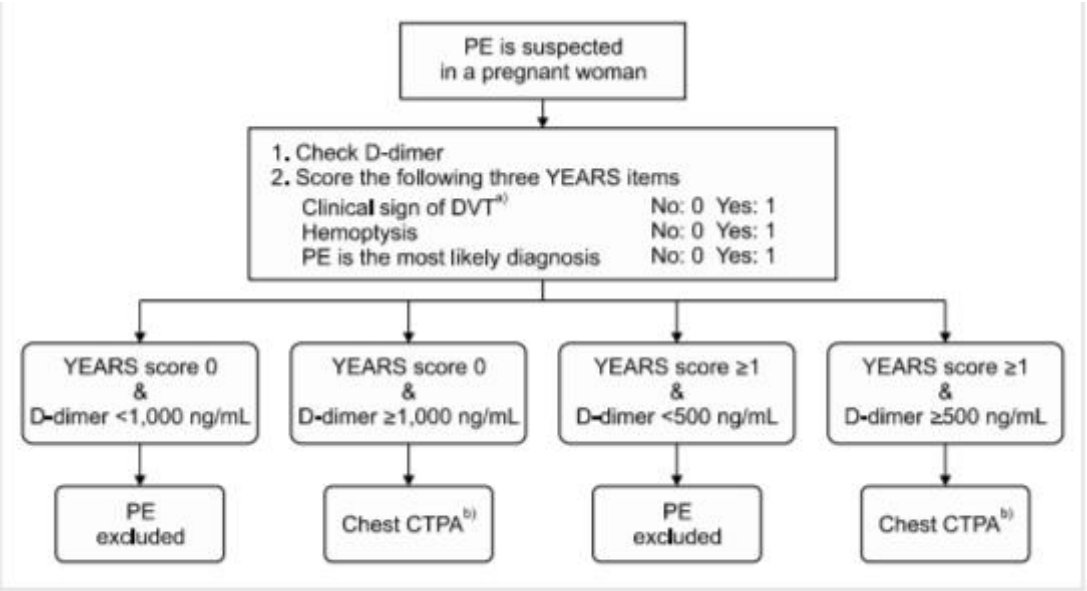

Fig 04: Treatment of venous thromboembolism in children

ANTICOAGULATION THERAPY WITH DOACS FOR VTE

The primary treatment for VTE is anticoagulation therapy. Delayed initiation of anticoagulation or failure to provide timely therapeutic anticoagulation can lead to worse outcomes. Therefore, having anticoagulants that act quickly and exhibit a predictable dose-response relationship is essential for effective acute treatment of VTE. In this regard, direct oral anticoagulants (DOACs) demonstrate a favorable pharmacodynamic profile and a consistent dose-response curve, although they cannot be assessed with standard coagulation tests. Two main treatment strategies have been developed for DOACs in VTE management. The first is a single-drug approach, which involves an initial high-dose regimen of DOACs followed by a maintenance dose without the use of parenteral anticoagulants. The second, the sequential approach, starts with heparin or fondaparinux for 5 to 10 days, followed by a maintenance dose of DOACs. Apixaban and rivaroxaban follow the single-drug approach, while dabigatran and edoxaban are administered according to the sequential approach [11].

ANTICOAGULATION THERAPY FOR CANCER-ASSOCIATED VTE AND DOACS

Cancer is a significant risk factor for venous thromboembolism (VTE), with cancer patients experiencing a seven-fold higher incidence of VTE compared to those without cancer. The incidence of VTE in cancer patients has been rising over time. Those with active cancer are at an especially higher risk for recurrent VTE and bleeding, complicating the ability to find an optimal risk-benefit balance with anticoagulation therapy. As such, managing cancer-associated VTE has become a significant challenge for clinicians. Before the era of direct oral anticoagulants (DOACs), clinical trials like the CLOT and CATCH trials compared low-molecular-weight heparin (LMWH) to warfarin for the treatment of cancer-associated VTE. These trials showed that LMWH was more effective in reducing the recurrence of VTE than warfarin. Based on these findings, various VTE guidelines recommended LMWH as the preferred anticoagulant over warfarin[12].
12. Treatment after an initial failure of anticoagulation:

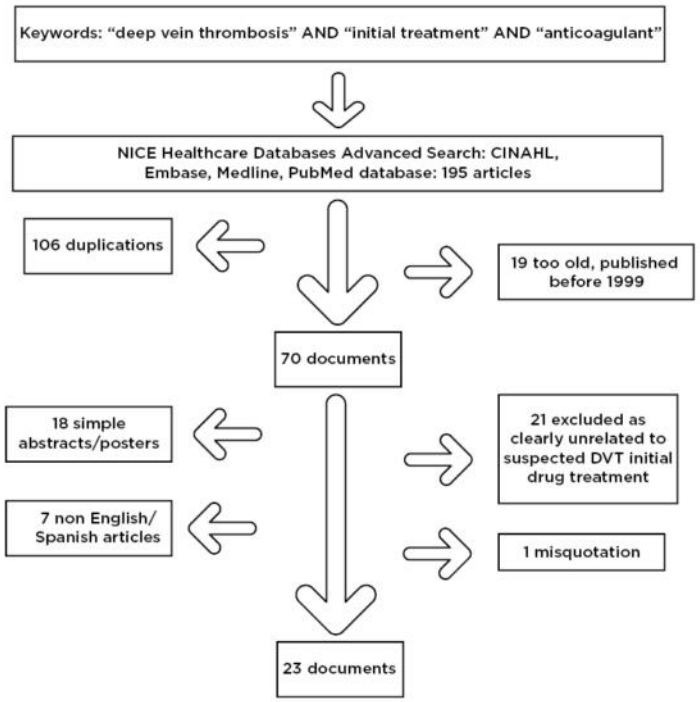

Fig 05: Treatment of an initial anticoagulation

REVERSAL OF ANTICOAGULATION

In patients with VTE, anticoagulation reversal is necessary in cases of bleeding, invasive procedures or surgery, or over-anticoagulation. The decision to reverse anticoagulation should be based on the individual patient's situation, weighing the benefits and risks. Below are key pharmacokinetic characteristics and available or potential antidotes for anticoagulants. Oral or intravenous vitamin K is used to reverse severe (INR >8) or moderate INR prolongation in the presence of bleeding or a significant bleeding risk. Fresh frozen plasma is frequently utilized due to its cost-effectiveness and ease of use. Protamine sulfate is an approved antidote for unfractionated heparin (UFH) reversal, and it should be infused slowly, typically at 1 mg per 80–100 units of UFH for neutralization. Although low molecular weight heparin (LMWH) has a stronger effect on factor Xa than thrombin, protamine sulfate may still be considered for LMWH reversal, at a dose of 1 mg per 100 units of LMWH [13,17].

DIAGNOSIS OF CLINICALLY RELEVANT ISOLATED DISTAL DVT (BELOW KNEE)

A negative proximal ultrasound rules out a significant proximal DVT but does not eliminate the possibility of an isolated distal DVT (IDDVT). IDDVT refers to thrombus located in any vein below the popliteal vein in the lower extremity. Since up to 10% of patients with IDDVT may progress to proximal DVT or pulmonary embolism (PE), a follow-up proximal ultrasound might be necessary even after an initially negative result. While it may seem appealing to perform imaging of the distal veins to avoid the need for repeated ultrasounds, it's essential to recognize the limitations of whole-leg ultrasonography. Imaging of the distal veins is more technically challenging compared to the proximal veins, and there is a higher chance of false positives. Proximal vein compression typically takes just a few minutes, whereas whole-leg ultrasound is more complex and time-consuming. Additionally, many healthcare facilities do not routinely use whole-leg ultrasounds[14,15,16].

CONCLUSION

Recent advances in the treatment of venous thromboembolism (VTE) have been largely influenced by the introduction of direct oral anticoagulants (DOACs), which have replaced traditional therapies like warfarin and heparin in most cases due to their lower risk of bleeding and ease of use. However, to further improve treatment guidelines for VTE in Korea, two factors must be addressed. First, research is needed to determine whether lower doses of anticoagulants can maintain their effectiveness while reducing bleeding risks, particularly for high-risk Korean patients. Second, the increasing diagnosis of asymptomatic incidental VTE due to evolving medical practices highlights the need for updated treatment guidelines, as current recommendations, largely based on Western data, may not fully reflect the specific needs of the Korean population.

AUTHOR CONTRIBUTIONS
All authors are contributed equally

FINANCIAL SUPPORT
None

DECLARATION OF COMPETING INTEREST
The Authors have no Conflicts of Interest to Declare.

ACKNOWLEDGEMENTS:
None

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