INTERNATIONAL JOURNAL IN PHARMACEUTICAL SCIENCES

Journal Homepage: https://www.ijpsjournal.com

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Review Article

A Review On Modern Approaches Towards Anticoagulant Therapy Of Venous Thromboembolism

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ARTICLE INFO

Received: 13 Dec 2023
Accepted: 16 Dec 2023
Published: 19 Dec 2023

Keywords:
venous thromboembolism, deep vein thrombosis, pulmonary embolism, anticoagulation, secondary prevention.

DOI:
10.5281/zenodo.10396652

ABSTRACT

A common and possibly fatal condition is venous thromboembolism (VTE), a disease entity that includes pulmonary embolism (PE) and deep vein thrombosis (DVT). Currently, there are several medicines that may be used to effectively treat acute viral transmission disease and prevent its recurrence. The subcutaneous administration of fondaparinux or low molecular weight heparin (LMWH), followed by a vitamin K antagonist (VKA), was the accepted protocol of therapy for a number of years. For the treatment of VTE, the so-called direct oral anticoagulants (DOAC) were just recently brought into clinical practice. In comparison to VKA, DOAC appears to have a better risk-benefit profile. Moreover, because DOAC are taken at set dosages and don't require periodic monitoring, they greatly simplify the management of VTE. Therapeutic anticoagulation should be administered to patients with objectively confirmed DVT or PE for a minimum of three months. Each patient should have their requirements assessed individually, with the decision to continue therapy mostly based on risk factors identified by the thrombotic event's features and patient-related variables. Treatment of VTE is more difficult in some patient groups than in the general population (e.g., elderly patients, cancer patients, and pregnant women), and special considerations must be made for these patients. An overview of the current approaches to treating acute VTE and secondary prophylaxis is the goal of this study. Specifically, issues pertaining to the start of VTE therapy, the length of anticoagulation, and certain patient populations will be covered.

INTRODUCTION

After myocardial infarction and stroke, venous thromboembolism (VTE) is the third most common cardiovascular illness. About one instance of VTE is thought to occur for every 1000 person-years. Leg deep vein thrombosis (DVT) is

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

the most common location of VTE. Pulmonary embolism (PE), a potentially fatal consequence of deep vein thrombosis (DVT), arises when a thrombus becomes embolized inside the pulmonary arteries. In this study, we'll refer to both DVT and PE by the term VTE, which was coined for both. For a number of years, the subcutaneous administration of fondaparinux or low molecular weight heparin (LMWH) was the standard of care for treating acute VTE. Over time, oral vitamin K antagonist (VKA) ingestion was added. When it comes to preventing recurrent VTE , this regimen is quite successful. However, because of a limited therapeutic range and a very high prevalence of bleeding problems, VKA therapy need continuous monitoring. Furthermore, because VKA has a delayed beginning of effect, parenteral anticoagulation in the form of subcutaneous injections of LMWH or fondaparinux is necessary for the immediate therapy of VTE. For the acute and long-term therapy of VTE, a novel family of medications known as direct oral anticoagulants (DOAC) has just entered clinical practice. Large-scale clinical studies have demonstrated that, when compared to the conventional LMWH/VKA combination, DOAC are both safe and efficacious in treating VTE. The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have previously approved dabigatran, apixaban, and rivaroxaban for the treatment of VTE. Edoxaban is presently pending clearance in Europe after receiving permission in the USA and Japan. Because DOAC are administered at a set dosage and do not require frequent monitoring, they greatly simplify the management of VTE. Furthermore, DOAC were linked to a noticeably decreased incidence of bleeding problems in meta-analyses. We provide an overview of the current state-of-the-art for the treatment of PE and DVT in this review. Additionally, we want to offer information for clinical decision-making concerning the many treatment modalities that are accessible for distinct patient groups and their very unique needs [1-15].

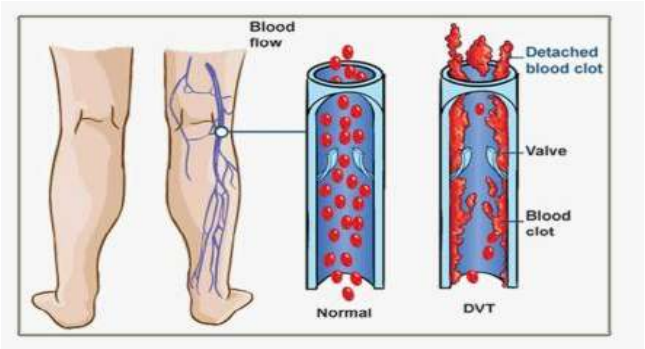

Fig no:1 Deep Vein Thrombosis

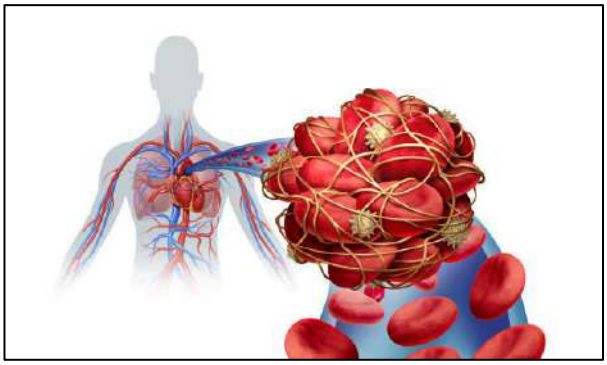

Fig no:2 Pulmonary Embolism

BACKGROUND

Venous thromboembolism (VTE), encompassing conditions like deep vein thrombosis (DVT) and pulmonary embolism (PE), represents a substantial healthcare burden that often goes under-recognized [53,54]. Despite the use of anticoagulant therapy, the early phase of VTE is associated with high mortality rates and a significant risk of recurrence . Furthermore, VTE can lead to severe long-term complications, including chronic pulmonary hypertension and post-thrombotic syndrome. Managing these complications requires substantial healthcare resources and is linked to considerable morbidity . VTE is a notable cause of preventable mortality for both medical and surgical patients. Beyond early mortality related to PE, VTE associated with hospitalization is a primary contributor to lost disability-adjusted life years globally, spanning low-, middle-, and high-income countries. While anticoagulant therapy has demonstrated efficacy in

reducing the risk of postoperative VTE in Western populations, routine VTE prophylaxis is not consistently administered in Asian countries .

The disease burden linked with VTE is substantial, with an incidence of approximately 100 cases per 100,000 patient-years in Western countries . Although the incidence of VTE has been on the rise in Asia in recent years, it remains lower than that observed in Western countries [55]. This review provides a summary of the epidemiology, risk stratification, diagnosis, and treatment considerations in the management of VTE in Asia.

Epidemiology

While Asian populations share major acquired risk factors for venous thromboembolism (VTE) with Western populations, studies conducted in Asia consistently report lower rates of VTE compared to Caucasians (Table 1) [53,55,56,57]. These findings are consistent with data from Asian patients in Western countries as well [58,59]. Several factors may contribute to the observed lower rates of VTE in Asian populations relative to Western populations. Firstly, the estimates might be lower than the actual numbers due to limited availability of epidemiological data in Asia and the often asymptomatic nature of VTE. Secondly, historical differences in incidence rates may reflect underdiagnosis in Asian patients stemming from low awareness of thrombotic diseases, low clinical suspicion due to perceived low incidence rates, and restricted access to healthcare resources [60,61]. Additionally, low autopsy rates, influenced by cultural and religious practices, may partly contribute to the perceived lower incidence rate of VTE in Asia [61]. Autopsy studies have shown high rates of asymptomatic thrombosis, and data indicate that the incidence of pulmonary embolism (PE) in Asian countries is comparable to that in Western countries [54, 62, 63]. Lastly, the lower rates of VTE in Asian populations may be linked to the lower prevalence of certain risk factors, such as obesity and mutations in prothrombin or factor V Leiden genes [64,65]. Consequently, these data suggest that the rate of VTE in Asia may be underestimated, particularly as thrombi in Asian patients may not always progress to symptomatic thrombosis [66].

Table 1:Estimated incidence of VTE from studies in Western and Asian populations

WESTERN COUNTRIES			
Incidence	**UK**	**Norway**	**US (age-adjusted)**
VTE	75	143	117
DVT	40	93	48
PE	34	50	69

ASIAN COUNTRIES				
Taiwan	**Hong Kong**	**Japan**	**Korean (age adjusted)**	**Singapore**
16	17	NR	14	57
NR	NR	12	5	NR
NR	NR	6	7	15

Risk factors

Heritable risk factors stem from genetic abnormalities affecting components of the coagulation pathway, resulting in hereditary thrombophilia. These abnormalities include mutations in factor V and prothrombin, as well as deficiencies of protein S, protein C, and antithrombin [64]. Notably, factor V Leiden and prothrombin G20210A polymorphisms are specific to Caucasians, whereas the prevalence of deficiencies in protein S, protein C, and antithrombin in Asian populations tends to be higher than in Caucasians (Table 2) [67,68].

Table 2: Ethnic differences in the distribution of inherited thrombophilias

	Healthy subjects Western	**Asian**	**Patients with VTE Western**	**Asian**
Factor V Leiden mutation	4.8%	0%–0.2%	18.8%	0%
Prothrombin G20210A mutation	2.7%	0%–0.2%	7.1%	0%

Protein S deficiency	0.03%–0.13%	0.06%–6.4%	2.3%	10.7%–17.8%
Protein C deficiency	0.2%–0.4%	0.3%–4.0%	3.7%	8.9%–10.7%

While the major inherited risk factors for venous thromboembolism (VTE) differ between Asian and Western populations, the major acquired risk factors in Asians are similar to those observed in Western populations [70]. Transient and reversible risk factors, such as surgery, trauma, prolonged bed rest, immobility, and pregnancy, coexist with irreversible risk factors like malignancy and paralysis due to nerve damage. Malignancy is the most common acquired risk factor for VTE in Asians, with 16% to 40% of VTE cases being cancer-associated [71–72]. Other prevalent acquired risk factors for VTE in Asians include surgery, immobility, obesity, advanced age, and the use of oral contraceptives [70-73]. VTE remains a serious complication after high-risk surgeries, even with preventive measures in place. Symptomatic deep vein thrombosis (DVT) and pulmonary embolism (PE) rates with low-molecular-weight heparin (LMWH) after orthopedic surgery are reported to be 0.8% and 0.35%, respectively . While Asian patients are often perceived to have a lower risk of symptomatic VTE following surgery than Western populations, regular prophylaxis for Asian patients at high risk for VTE is not universally administered [74]. Studies involving Asian patients undergoing major surgery, however, have indicated that the incidence of postoperative DVT is comparable to that reported in Western populations [70,75]. For instance, the Assessment of the Incidence of Deep Vein Thrombosis in Asia (AIDA) study, conducted in 19 centers across Asia, revealed a DVT rate of 41% in patients undergoing total hip or knee arthroplasty or hip fracture surgery who did not receive thromboprophylaxis [76]. A meta-analysis of 22 studies in Asian patients undergoing orthopedic procedures demonstrated similar overall DVT rates detected by venography but a lower rate of symptomatic and proximal DVT compared to Western populations [77]. The Epidemiologic International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting (ENDORSE) study, a multinational cross-sectional survey, indicated that surgical patients at risk for VTE in Asian countries should receive appropriate VTE prophylaxis .

Diagnostic tests:-

D-dimer, a breakdown product of cross-linked fibrin, is typically elevated in venous thromboembolism (VTE) but can also be increased in conditions such as infection, malignancy, pregnancy, surgery, trauma, and stroke [79]. The utility of D-dimer testing, given its moderate specificity, lies in its role as a negative predictor in patients with suspected deep vein thrombosis (DVT) or pulmonary embolism (PE), particularly when used in conjunction with clinical pretest probability, a strategy applicable to both Asian and Western populations [78, 80-82]. This approach streamlines the diagnostic process . While D-dimer testing alone may not be accurate enough to detect DVT after total knee arthroplasty in Asian patients , it has proven useful in excluding DVT in hospitalized Japanese patients with acute medical diseases. Among 42 hospitalized patients with acute medical diseases where plasma D-dimer was measured, the sensitivity and negative predictive value of D-dimer reached 100%, while the positive predictive value (31.6%) and specificity (13.3%) were low [81,82].Commercially available D-dimer assays include latex agglutination, whole blood agglutination, and enzyme-linked immunosorbent assays [83]. The Taiwan Society of Cardiology guidelines recommend using D-dimer enzyme-linked immunofluorescence,

enzyme-linked immunosorbent, and latex quantitative assays over whole blood, latex semiquantitative, and latex qualitative assays due to their higher sensitivity. Moreover, as the specificity of D-dimer assay tends to decrease with age, age-adjusted cutoffs (age × 10 μg/L above 50 years) are suggested to enhance the specificity of D-dimer testing [84]. Due to challenges in standardizing different available assays, those employed in diagnostic processes should exhibit equivalent sensitivity and specificity to those used in clinical trials, ensuring comparability of results obtained with various methods. In both Asian and Western populations, compression ultrasound (CUS) and multidetector computed tomographic angiography (CTA) have emerged as the preferred methods for effectively imaging the vasculature with high sensitivity and specificity in patients with suspected deep vein thrombosis (DVT) and pulmonary embolism (PE), respectively [85,86]. The sensitivity and specificity of CUS for DVT (proximal and distal) are 90.3% and 97.8%, respectively. For CTA in detecting PE, the sensitivity and specificity are reported to be 83.0% and 96.0%, respectively [87,88].

Considerations before Initiation of Treatment

Hemodynamically unstable pulmonary embolism

Patients with suspected PE who are hemodynamically unstable and exhibit shock or hypotension face a heightened risk of short-term mortality [16]. If PE is confirmed, these patients should be considered for thrombolysis, and in exceptional cases, surgical or catheter embolectomy may be considered, especially if the risk of bleeding is not high [16,17]. Additionally, in cases of hypotension or shock, unfractioned heparin (UFH) is recommended for initial anticoagulation, as opposed to LMWH, fondaparinux, or a DOAC, in accordance with the current guidelines of the European Society of Cardiology (ESC) [18]. The Pulmonary Embolism Severity Index (PESI) score and its simplified version can aid in distinguishing between patients requiring hospitalization and those who could potentially be treated in an ambulatory setting [19,22] .

High bleeding risk

As per the current American College of Chest Physicians (ACCP) guidelines, patients with acute proximal DVT or PE may have an inferior vena cava filter placed if anticoagulation is not feasible due to an exceptionally high bleeding risk [23]. However, the guidelines lack specific details on the definition of "bleeding risk." To assess bleeding risk, clinical scores like the RIETE score and the HEMORR2HAGES score, which are prospectively validated, can be considered, although their utility and applicability in routine clinical practice are yet to be fully established [24,25]. It's crucial to note that permanent vena cava filters are associated with long-term complications, including filter thrombosis and migration. Temporary filters require removal within a few days, while retrievable filters can be left in place for extended periods [25].

Impaired renal function

Low molecular weight heparin (LMWH) and fondaparinux are primarily excreted through the kidneys, whereas unfractionated heparin (UFH) is mainly eliminated by the reticuloendothelial system, and vitamin K antagonists (VKA) are metabolized by CYP2C9 and the liver's vitamin K epoxide reductase [26]. In individuals with a creatinine clearance below 30 mL/min, caution is advised due to the potential accumulation of LMWH and, especially, fondaparinux, leading to a risk of over-anticoagulation. Monitoring of LMWH and fondaparinux can be achieved by measuring peak anti-factor Xa activity, typically assessed 4 hours after administration. However, precise therapeutic ranges are not well-established. For LMWH administered twice daily, an effective therapeutic anticoagulation is suggested with a

peak anti-factor Xa activity ranging from 0.6 to 1.0 IU/mL [27, 28]. The therapeutic range for once-daily dosing is less defined but is proposed to be between 1.0 and 2.0 IU/mL [28]. Renal function plays a crucial role in considering anticoagulation with Direct Oral Anticoagulants (DOACs). In the Hokusai-VTE trial, which investigated edoxaban, patients with a glomerular filtration rate (GFR) between 30 and 50 mg/dL were administered a reduced dose (30 mg instead of 60 mg once daily), demonstrating safety. Those with a GFR below 30 mg/dL were excluded from the study [11]. In major controlled trials leading to the approval of rivaroxaban, dabigatran, and apixaban, individuals with a GFR below 30 mg/dL (rivaroxaban and dabigatran) or below 25 mg/dL (apixaban) were excluded [10, 29–31]. Rivaroxaban includes a dose reduction guideline in its package insert for patients with a GFR between 15 and 30 mg/dL. Nevertheless, we do not recommend the use of any DOAC in patients with a GFR below 30 mg/dL (or below 25 mg/dL for apixaban) due to insufficient clinical data.

Selecting appropriate therapies and anticoagulants for venous thromboembolism.

General principle of anticoagulation

Medical anticoagulation encompasses three periods: acute (the first 5–21 days), long-term (3–6 months), and extended. In the acute phase, anticoagulants are initiated via parenteral heparin lead-in or with a higher dose of oral anticoagulants. Long-term treatment typically lasts 3 months for postoperative VTE due to low recurrence risk but extends to 6 months for unprovoked VTE. Extended treatment may be considered for cases with a high risk of VTE recurrence. For the management of venous thromboembolism (VTE), heparin and vitamin K antagonists (VKA) have been extensively employed over an extended period, although direct oral anticoagulants (DOACs) are rapidly supplanting them due to their user-friendly nature. Nevertheless, in specific scenarios or for individuals with prolonged usage of older anticoagulants, heparin and VKA may still be applicable [32]. Low-molecular-weight heparin (LMWH) is frequently utilized, particularly in cases of catheter-associated thrombosis (CAT). In comparison to unfractionated heparin (UFH), LMWH is more likely to exhibit a predictable dose-response relationship. It possesses a lengthier half-life, allowing for subcutaneous administration once or twice daily, and carries a reduced risk of heparin-induced thrombocytopenia and osteoporosis. Due to its predominant renal excretion, caution is advised in patients with severe renal impairment. Conversely, UFH has a shorter half-life and can be advantageous in situations where an immediate anticoagulant effect is required for prompt conversion. VKA is absorbed in the gastrointestinal tract and metabolized in the liver. It exerts moderate anticoagulant effects by inhibiting vitamin K approximately 48 to 72 hours after initiation. During the initial days of VKA administration, there is an elevated risk of thrombosis and skin necrosis as natural anticoagulants, protein C and protein S, may decrease. Hence, heparin administration alongside VKA is recommended during this period. The efficacy of VKA is influenced by factors such as liver function, concurrent medications, and dietary intake, necessitating careful monitoring. Dabigatran functions by directly inhibiting factor IIa, while rivaroxaban, apixaban, and edoxaban act by inhibiting factor Xa. Numerous large-scale phase 3 studies have compared direct oral anticoagulant (DOAC) therapies with vitamin K antagonists (VKA), affirming that DOACs are noninferior in terms of both antithrombotic efficacy and bleeding [33-36]. Consequently, DOACs have supplanted VKA in the treatment of venous thromboembolism (VTE). The primary absorption sites for rivaroxaban, dabigatran, and edoxaban are the

stomach and proximal small intestine. Thus, caution is warranted in patients with a history of total gastrectomy, as these drugs may not be efficiently absorbed. In contrast to other DOACs, apixaban is predominantly absorbed in the distal small intestine and ascending colon, making it suitable for use in patients who have undergone gastrectomy. However, it should be avoided in those with prior resection of the ascending colon [37]. Dabigatran is formulated as a capsule, and its bioavailability increases rapidly when the capsule is opened and the contents are ingested alone. It is crucial to note that opening, crushing, or chewing dabigatran capsules is strictly prohibited. For DOACs in cancer-associated thrombosis (CAT), refer to the section 'Treatment of cancer-associated venous thromboembolism'.

TREATMENT OF VENOUS THROMBOEMBOLISM

Treatment of deep vein thrombosis

Treatment of proximal deep vein thrombosis:

Proximal lower extremity deep vein thrombosis (DVT) occurs when a blood clot is situated in the popliteal, femoral, or iliac veins. Clinical symptoms can vary based on the location, extent, and degree of blockage, ranging from no noticeable symptoms to significant edema and potential gangrene. Anticoagulant therapy is recommended for all patients diagnosed with proximal DVT [38]. In cases of active bleeding, low platelet counts (<50,000×10 /L), or a history of intracerebral hemorrhage, an inferior vena cava (IVC) filter is a preferred option. For provoked proximal DVT, guidelines recommend a duration of 3 months of anticoagulant therapy [38]. Unprovoked proximal DVT may necessitate extended anticoagulant therapy (at least 3 months, potentially indefinite), while individuals at high risk of bleeding may be managed with a 3-month course of anticoagulation [38]. Treatment options for proximal DVT encompass vitamin K antagonists (VKA), low-molecular-weight heparin (LMWH), or direct oral anticoagulants (DOACs). The choice among these agents is typically influenced by clinician expertise, bleeding risks, patient comorbidities, preferences, cost considerations, and convenience. Thrombolytic therapy is generally not recommended, except in cases of massive iliofemoral or femoral DVT where there is a high risk of limb gangrene [38].

Treatment of isolated distal deep vein thrombosis:

Isolated distal deep vein thrombosis (DVT) is diagnosed when a blood clot forms below the popliteal vein without extending to the proximal veins. The decision on whether to treat isolated DVT is a subject of controversy, as studies have shown discordant 3-month recurrent venous thromboembolism (VTE) risks between untreated and treated groups [39-42]. However, the absolute risk of VTE recurrence in isolated distal DVT is generally reported to be lower than that in proximal DVT or pulmonary embolism (PE). Notably, unlike proximal DVT and PE, there is a lack of high-level evidence supporting guidelines for the management of isolated DVT. A meta-analysis of 24 studies involving 4,072 patients indicated that anticoagulation reduced the VTE recurrence rate compared to no anticoagulant treatment (odds ratio [OR], 0.50; 95% confidence interval [CI], 0.31–0.79), without a significant increase in the rate of major bleeding (OR, 0.64; 95% CI, 0.15–2.73) [43]. In contrast, based on evidence from a randomized placebo-controlled prospective trial [44], asymptomatic patients without high-risk features for VTE recurrence or extension (such as immobilization, active cancer, unprovoked VTE), and with a high risk of bleeding, may undergo surveillance with serial screening for DVT of the lower leg without anticoagulation. However, if patients are acutely symptomatic, exhibit high-risk features for recurrence and extension, and do not have a bleeding risk, anticoagulation is recommended [38]. As an alternative to anticoagulants, aspirin is

sometimes used due to the less aggressive nature of isolated distal DVT, although this approach lacks robust evidence [45]. After the decision to initiate anticoagulation, the choice of drugs and the duration may follow treatment strategies for proximal DVT of the lower extremities.

Treatment of pulmonary embolism

Treatment of hemodynamically unstable pulmonary embolism:

Patients experiencing life-threatening pulmonary embolism (PE) might necessitate supplementary interventions beyond anticoagulation, such as systemic thrombolysis, catheter-directed therapy, or embolectomy. A comprehensive analysis revealed that the application of thrombolytics correlated with a decreased overall mortality rate. This decline in mortality appears to be primarily attributed to studies involving patients with hemodynamic instability [89]. Anticoagulation initiation is recommended once the patient achieves stability, without encountering bleeding complications subsequent to thrombolysis.

Treatment of hemodynamically stable pulmonary embolism:

The primary treatment approach for confirmed pulmonary embolism (PE) is anticoagulation, and it should be administered to all patients suspected of having the disease, provided there is no active bleeding, even before the confirmation of PE diagnosis. Notably, the landscape of anticoagulation for PE has undergone significant changes in recent years with the introduction of Direct Oral Anticoagulants (DOACs). Large randomized clinical trials have demonstrated that DOACs exhibit comparable efficacy and safety to traditional anticoagulants in individuals with acute PE [90,91]. Although the direct comparison of different DOACs in terms of risk reduction for recurrent Venous Thromboembolism (VTE) hasn't been conducted, indirect comparisons suggest a similar effectiveness across all DOACs. Typically, the recommended duration of treatment for PE is six months, but it can vary, ranging from three months in patients with transient risk factors to an indefinite duration in those with ongoing major risk factors such as cancer or recurrent unprovoked PE.

Treatment of subsegmental pulmonary embolism:

Subsegmental pulmonary embolism (SSPE) is diagnosed when pulmonary embolism does not affect the proximal pulmonary arteries. The management of asymptomatic SSPE patients poses a challenge due to the lack of robust support from high-quality randomized clinical trials. Computed tomographic (CT) angiography, the diagnostic tool for SSPE, can yield false-positive results, particularly in cases with a single subsegmental involvement in one image and normal D-dimer levels. Furthermore, the question of whether SSPE could progress or recur without anticoagulation remains a topic of debate [92,93]. For patients with SSPE, it is recommended to undergo bilateral Doppler ultrasonography of the lower extremities and assess high-risk deep vein thrombosis (DVT) sites [94], such as upper extremities with indwelling central venous catheters. Asymptomatic patients without co-existing DVT, high-risk features for recurrent or progressive venous thromboembolism (VTE), and who are at high risk of bleeding may be considered for surveillance with serial screening for DVT of the lower leg without anticoagulation [95]. However, if patients exhibit symptoms, have co-existing DVT and/or high-risk features, and have no bleeding risk, anticoagulation is recommended rather than surveillance alone. The choice of anticoagulant drugs and the duration of treatment may follow the strategies recommended for PE in larger pulmonary arteries when deciding on anticoagulation.

Incidental pulmonary embolism:

Incidental pulmonary embolism (PE) is commonly detected in enhanced chest CT scans. While the

embolic burden in incidental PE is typically lower than that in symptomatic PE, anticoagulation is recommended if it affects a location proximal to the subsegmental vasculature [96]. However, in incidental subsegmental pulmonary embolism (SSPE), conflicting data exist . Some researchers propose observation without anticoagulant use for this particular group.

Treatment of cancer-associated venous thromboembolism :

Cancer-associated thrombosis (CAT) is a common complication of cancer, linked to elevated morbidity and mortality rates. Following the confirmation of CAT, physicians should contemplate anticoagulant therapy, regardless of the presence of thrombosis-related symptoms. However, factors such as limited life expectancy in advanced cancer, heightened bleeding risks—especially in severe thrombocytopenia—or thrombotic symptoms unlikely to improve may hinder the initiation of anticoagulation. Traditionally, low-molecular-weight heparin (LMWH) was the standard treatment for CAT, endorsed for its effectiveness against thrombosis recurrence and improved safety profile compared to vitamin K antagonists (VKA), as per major clinical trials comparing LMWH with VKA. More recently, direct oral anticoagulants (DOACs) have emerged as potential alternatives to LMWH due to their convenient administration and predictable pharmacokinetics. However, the evidence supporting their use in CAT remains inconclusive, given that only a small fraction of the study populations in these trials had CAT. Recent studies, including a Korean phase IV study with rivaroxaban and two phase III trials comparing DOACs to LMWH in CAT patients, reported comparable efficacies with a slightly increased bleeding risk for DOACs. As a result, the latest guidelines have incorporated rivaroxaban and edoxaban as options for venous thromboembolism (VTE) treatment. A meticulous selection of treatment candidates and the implementation of appropriate anticoagulant strategies are crucial for effective CAT management. For information on anticoagulation in patients with CAT and thrombocytopenia [97-101].

Treatment of venous thrombosis of other sites:

Treatment of superficial venous thrombophlebitis:

While superficial thrombophlebitis is commonly considered harmless and self-limiting, there is a growing acknowledgment that a considerable number of individuals with this condition may either have concurrent deep vein thrombosis (DVT) or pulmonary embolism (PE) or be at a significant risk of developing venous thromboembolism (VTE) [102]. The management of superficial thrombophlebitis remains a topic of debate. Nevertheless, treatment approaches should encompass relief of symptoms, restriction of thrombosis expansion, and a decrease in the risk of PE. Results from a randomized controlled trial indicated that anticoagulation with unfractionated heparin (UFH), low molecular weight heparin (LMWH), and vitamin K antagonists (VKA) was more effective than compression therapy alone in reducing the extension of superficial thrombophlebitis [103,104]. The SURPRISE study proposed the feasibility of using an oral anticoagulant (rivaroxaban) in individuals with superficial thrombophlebitis [105]. Current guidelines suggest treating superficial thrombophlebitis with a length of at least 5 cm with prophylactic doses of fondaparinux or LMWH for 45 days. However, guidelines specify that patients with less extensive superficial thrombophlebitis do not require anticoagulant treatment .

Treatment of catheter-related venous thrombosis:

Catheter-related thrombosis is a frequent occurrence in cancer patients, resulting in patient discomfort, catheter malfunction, and the risk of

infection. Notably, there is a lack of extensive, prospective, randomized trials examining treatments for thrombotic complications associated with catheter use [106]. When catheter-related thrombosis presents with symptoms, anticoagulation is typically employed as a standalone treatment, often without the need for catheter removal. The ideal duration of anticoagulation for catheter-related thrombosis remains unexplored in clinical trials. According to guidelines from the American College of Chest Physicians (ACCP), anticoagulation is recommended for three months if the catheter has been removed and for the entire duration that the catheter is in place if it exceeds three months . Recently, direct oral anticoagulants (DOACs) have been reported as potential options for managing catheter-related thrombosis in cancer patients [107,108]. Numerous reviews discussing strategies to prevent catheter-related thrombosis are available [109,110].

Treatment of splanchnic vein thrombosis:

Splanchnic vein thrombosis (SVT) stands out as the most prevalent form of thrombosis occurring in uncommon sites, constituting about 4% of all thrombotic events. SVT involves thrombosis in the portal, mesenteric, hepatic, and splenic veins [111]. Doppler ultrasonography serves as the primary diagnostic tool for portal and hepatic vein thrombosis, while CT angiography is the preferred modality for identifying mesenteric vein thrombosis [112].The primary acquired risk factors for SVT include abdominal cancers, particularly hepatobiliary, gastrointestinal, and pancreatic, along with liver cirrhosis and myeloproliferative neoplasms (MPNs). Consequently, in non-cirrhotic, non-malignant SVT cases, screening for MPNs (e.g., JAK2 mutation analysis) and paroxysmal nocturnal hemoglobinuria is advised, even in patients with normal complete blood cell counts [113]. Though no high-quality randomized controlled trials have been reported, various guidelines and reviews have proposed management strategies for SVTs [114-116]. Anticoagulation is recommended over surveillance for acute, symptomatic, extensive SVTs, and for patients planning liver transplantation. The presence of esophageal or fundic varices, especially in cirrhotic patients, is not a contraindication for anticoagulation, but appropriate prophylactic treatment (e.g., β-blockers, endoscopic ligation) should precede anticoagulation. Currently, there is no available data on the use of direct oral anticoagulants (DOACs) for SVT treatment. For SVTs, unfractionated heparin (UFH), low molecular weight heparin (LMWH), and heparin transition to vitamin K antagonists (VKA) are recommended. A minimum of 3 months of anticoagulation is advised for all SVT patients. Those with transient risk factors (such as surgery or infections) may discontinue treatment after 3 months, while patients with cirrhosis, active cancer, MPNs, and other thrombophilic conditions should undergo extended anticoagulation, carefully considering its risks and benefits. Gastrointestinal bleeding should be monitored before or during anticoagulation and should be effectively controlled in every scenario.

VENOUS THROMBOEMBOLISM IN PREGNANT WOMEN:

Pregnancy is linked to a twofold increased risk of venous thromboembolism (VTE) [117], with fatal pulmonary embolism (PE) being the leading cause of death among pregnant women in Western countries [118]. In managing acute VTE during pregnancy, low molecular weight heparins (LMWHs) are the preferred treatment. LMWHs are favored because they do not pass through the placenta, and they have been extensively used in a large number of patients. According to the current guidelines from the American College of Chest Physicians (ACCP), weight-adjusted therapeutic doses of LMWH should be administered for VTE

treatment during pregnancy, continuing for at least 6 weeks after delivery (a minimum of 3 months of therapy). It is recommended to discontinue LMWH 24 hours prior to a planned delivery [119]. In contrast, vitamin K antagonists (VKAs) should not be administered to pregnant women as they cross the placenta, and their intake is associated with embryopathy , particularly in the first trimester. Direct oral anticoagulants (DOACs) have not been studied in pregnant women, and as a result, they are contraindicated .

Venous thromboembolism in children

Risk and causes of venous thromboembolism in children:

Venous thrombosis in children is a rare occurrence, and it is typically associated with multifactorial medical conditions [57]. The incidence of symptomatic venous thromboembolism (VTE) in neonates is reported to be 0.51 per 10,000, and in children, it ranges from 0.07 to 0.14 per 10,000 [59]. According to the Canadian registry, 96% of deep vein thrombosis (DVT) and pulmonary embolism (PE) cases in children are linked to underlying medical conditions such as cancer, congenital heart disease, or trauma. A notable and common risk factor for VTE is the presence of a central venous catheter (CVC), observed in 33–48% of VTE cases in children and as high as 94% in neonates .In contrast, inherited thrombophilia is reported in only 8.8% of the cohort . Factor V Leiden and prothrombin gene mutations are more frequent in Caucasian patients but less so in individuals of Asian ethnicity. The incidence of protein C deficiency is 0.2–0.5% in the general population but higher, ranging from 2% to 5%, in individuals with VTE . Measuring protein S is particularly challenging, and the incidence of deficiency is believed to be as low as 0.9% . The prevalence of hereditary antithrombin III deficiency is estimated to be between 0.03% and 0.8% [67].

Treatment of venous thromboembolism in children:

Treatment recommendations for pediatric VTE rely on adult studies due to limited evidence in children. Options encompass anticoagulation, thrombolysis, surgery, and observation. Premature neonates and critically ill children, prone to bleeding, require careful risk-benefit assessment. Acute anticoagulation choices include UFH or LMWH, with LMWH being favored for its dosing simplicity and reduced monitoring need. After an initial period, patients may continue LMWH or transition to VKA, with VKA administration maintained until the INR reaches the therapeutic range for two consecutive days. Anticoagulation (LMWH or VKA) is advised over no anticoagulation for symptomatic DVT or PE in children. Duration recommendations include ≤3 months for provoked events and 6 to 12 months for unprovoked ones; those with recurrent thrombosis or antiphospholipid antibody syndrome may need indefinite anticoagulation. Therapeutic UFH is titrated to achieve an aPTT range, while LMWH requires monitoring with a target anti-Xa activity range. VKA monitoring targets an INR of 2.5 (range, 2.0–3.0), except for those with prosthetic cardiac valves following adult guidelines. CVC-related thrombi may be treated without removal if the catheter functions; nonfunctioning or unnecessary catheters should be removed after 3 to 5 days of therapeutic anticoagulation. The recommended anticoagulant duration is 6 weeks to 3 months. Thrombolytic therapy is reserved for life- or limb-threatening situations. Thrombectomy, IVC filter insertion, or anticoagulation alone is suggested for symptomatic DVT or PE in children. While DOACs offer potential benefits, their routine use in children is not yet recommended, awaiting further study results [123-126].

MONITORING AND DRUG-DRUG INTERACTION OF DOACS :

Direct oral anticoagulants (DOACs) offer the advantage of fixed doses without the need for routine monitoring in the majority of patients, distinguishing them from vitamin K antagonists (VKA). However, emerging data suggest that measuring DOAC concentrations could be beneficial in specific critical situations [46]. Proper monitoring of DOACs can aid decision-making regarding invasive procedures or the use of expensive reversal agents. Traditional laboratory tests, such as thrombin time and activated partial thromboplastin time (aPTT), can reflect dabigatran activity but may yield imperfect and often false-negative results, particularly for aPTT [47,48]. Prothrombin time and/or aPTT are frequently prolonged after the use of Xa inhibitors, but the degree of prolongation does not correlate with DOAC levels, and results vary with the reagents used [49]. Chromogenic assays for anti-Xa are reliable and relatively cost-effective with proper calibration [50]. Liquid chromatography/tandem mass spectrometry is considered the gold standard method for monitoring DOACs, although it is not practical for routine clinical laboratory use [51]. The future development of DOAC-specific tests with good reliability, faster turnaround time, and affordable costs is essential for more accurate DOAC monitoring and clinical benefits. Drug-drug interactions involving DOACs can occur through pharmacokinetic or pharmacodynamic mechanisms [93]. DOACs are pharmacokinetically influenced by cytochrome CYP3A and P-glycoprotein to varying degrees. Therefore, the concomitant administration of commonly used drugs can impact DOAC activity. Some classes of drugs, such as antiplatelet compounds, nonsteroidal anti-inflammatory drugs, and selective serotonin or noradrenaline reuptake inhibitors, can augment the pharmacodynamics of DOACs [52]. Careful scrutiny of other medications is necessary, and prescription adjustments should be made by a professional pharmacist, especially in elderly individuals with polypharmacy or cancer patients undergoing active treatment, considering potential drug-drug interactions.

CONCLUSION & DISSCUSION

Venous thromboembolism poses a frequent and potentially life-threatening risk. Various agents are currently available for effectively treating acute VTE and preventing its recurrence. Direct oral anticoagulants (DOACs) appear to offer a more favorable risk-benefit profile compared to vitamin K antagonists (VKAs). Tailoring patient-specific treatment approaches based on individual characteristics and lab results is crucial. Clinical decision-making should be guided by existing guidelines, risk assessment scores, and data from randomized controlled trials. Special attention is needed to determine if extended anticoagulation is necessary for secondary VTE prophylaxis. Certain patient groups, such as pregnant women, cancer patients, and the elderly, present unique challenges in VTE treatment, requiring expert consideration of additional factors to determine appropriate regimens.

ACKNOWLEDGEMENTS:

This review is about modern approaches towards treatment of venous thromboembolism.

The author is thankful to Principal, professor's, guide and Staff of Library for providing facilities and books for this review.

ABBREVIATIONS:-

AF Atrial fibrillation

CTA Computed tomographic angiography

CUS Compression ultrasound DVT Deep vein thrombosis

VTE Venous thromboembolism

VKA Vitamin K antagonist

UFH Unfractionated heparin

RV Right ventricular

PK Pharmacokinetic
PD Pharmacodynamic
NOAC Non-vitamin K antagonist oral anticoagulant
LMWH Low-molecular-weight heparin
INR International normalized ratio
DVT Deep vein thrombosis
SVT Sphlanchic vein thrombosis
ACCP American College of Chest Physicians
CAT Cancer associated thrombosis.

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HOW TO CITE: Anurag Milind Sanghave , Anjali Mali, Gajanan Sanap, A Review On Modern Approaches Towards Anticoagulant Therapy Of Venous Thromboembolism, Int. J. in Pharm. Sci., 2023, Vol 1, Issue 12, 453-473. https://doi.org/10.5281/zenodo.10396652