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COMPREHENSIVE INVESTIGATION OF THROMBOPHILIA MARKERS IN THE PATHOGENESIS AND RECURRENCE OF VENOUS THROMBOEMBOLISM: A REVIEW

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Abstract

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a significant cause of preventable morbidity and mortality worldwide. It arises primarily due to a combination of factors described by Virchow's triad: venous stasis, endothelial injury, and hypercoagulability. VTE can affect individuals of all ages but is particularly common in hospitalized, surgical, and immobile patients. Several risk factors contribute to its development, including cancer, trauma, pregnancy, hormone therapy, genetic predisposition, and prolonged immobilization. Timely and accurate diagnosis is essential and typically involves a combination of clinical assessment, D-dimer testing, and imaging techniques such as Doppler ultrasound for DVT or CT pulmonary angiography for PE. Management focuses on anticoagulant therapy, with direct oral anticoagulants (DOACs) now widely preferred due to their safety and ease of use compared to traditional therapies like warfarin. Preventive strategies, including pharmacologic prophylaxis and mechanical methods, are crucial in high-risk populations. Despite advances in treatment and prevention, challenges such as bleeding complications and underdiagnosis persist. This report reviews the latest literature on the epidemiology, pathophysiology, diagnosis, treatment, and prevention of VTE, emphasizing the need for continued research and awareness to improve patient outcomes and reduce the global health burden of this condition.

INTRODUCTION

Thrombophilia, prothrombotic state or hypercoagulability, is a coagulopathy of the blood wherein there is an abnormality that makes the patient susceptible to developing an excess thrombosis, especially venous thrombosis. It may be inherited or acquired and is most commonly encountered in the context of venous thromboembolism (VTE), i.e., deep vein thrombosis (DVT) and pulmonary embolism (PE). Thrombophilia is present in about half of patients with unprovoked thrombosis, and it is more frequent in patients with history of VTE (1).

The word "thrombophilia" typically refers to those conditions with venous thrombosis risk. Although arterial thrombosis is a risky situation, thrombophilia is typically more concerned with venous phenomena. Thrombophilia is something that we need to take note of as it can be helpful in prevention and treatment of VTE, the leading reason for morbidity and mortality throughout the globe.

Thrombin-activatable fibrinolysis inhibitor (TAFI) is a proenzyme that, trigger activation by thrombin, plasmin, or the thrombin-thrombomodulin complex, is a very effective inhibitor of the fibrinolytic system. It inhibits the formation of plasmin, thereby inhibiting fibrin clot lysis. Elevated plasma concentrations of TAFI have been shown to be involved in an enhanced risk of thrombotic disease by inhibiting clot lysis (2).

In addition to TAFI and factor VIII, additional markers have been reported with uncertain relevance in thrombophilia. These consist of α2-antiplasmin, lipoprotein(a), and the PAI-1 4G/5G polymorphism. No evidence is available to implicate high α2-antiplasmin levels with an enhanced risk of thrombosis. Although theoretically able to cause inhibition of fibrinolysis, recent data indicate that lipoprotein(a) is not likely to raise thrombotic risk significantly. There is early evidence to imply a possible relationship between the PAI-1 4G/5G polymorphism and thromboembolism in certain circumstances, but this needs to be clarified(2).

VTE pathogenesis is multifactorial and is based on Virchow's triad: stasis of blood flow, endothelial injury, and hypercoagulability. The triad was originally proposed by Rudolf Virchow in the mid-19th century and is still a cornerstone of thrombosis formation in VTE. Thrombophilia impacts the hypercoagulable condition by deranging the balance between procoagulant and anticoagulant factors. Stasis of blood can result in clot formation, usually occurring in immobile or patients with diseases that decelerate the blood flow. Damage to the lining of blood vessels, for example, through trauma, surgery, or other illnesses, can start clotting and is endothelial damage. Hypercoagulability, a disbalance of the coagulation system, in most instances induced by thrombophilia, may augment the risk of coagulation (3).

Inherited thrombophilia's are hereditary disorders that make a person susceptible to the formation of venous thrombosis. They are antithrombin, protein C, and protein S deficiency, factor V Leiden mutation, and prothrombin G20210A mutation. Antithrombin is a natural anticoagulant that effectively inhibits certain enzymes of the coagulation cascade. Antithrombin deficiency makes a person more prone to clotting. Protein S and protein C are also components of the body's natural anticoagulant pathways, and either a deficiency in one of these proteins can cause an elevated chance of thrombosis. Factor V Leiden is an inherited thrombophilia that is quite common in which a mutation in the factor V gene renders protein C inactivation, resulting in heightened clotting. Prothrombin G20210A mutation enhances the synthesis of prothrombin, a clotting factor, thus increasing the risk of thrombosis(3).

Acquired thrombophilias are conditions that arise over time and are not genetic. They include antiphospholipid syndrome, cancer, pregnancy, and the intake of hormonal contraceptives. Antiphospholipid syndrome is an autoimmune condition that helps in the formation of antibodies that enhance the chances of clotting. Some cancers have the potential to increase thrombosis risk through the production of procoagulant substances. Pregnancy heightens the risk of VTE because of expanded blood volume and venous stasis. Taking estrogen-containing contraceptives is also likely to elevate the risk of VTE.(4)

Venous thromboembolism is a serious condition within the medical environment, particularly in hospitalized or bedridden patients, due to the potential for it to cause life-threatening complications. VTE has two major presentations: deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT is the occurrence of blood clots in the deep veins, usually in the legs. DVT may be asymptomatic or present with leg swelling, pain, and redness. DVT is serious because it may result in pulmonary embolism if the clot dislodges and migrates to the lungs.(5)

Antithrombin, protein C, and protein S deficiency are established risk factors for VTE. Factor V Leiden and prothrombin G20210A mutation are prevalent reasons for inherited thrombophilia. Increased factor VIII is associated with the chance of VTE, especially following orthopedic surgery. TAFI and hyperhomocysteinemia are markers of unclear significance in the screening for thrombophilia.(6)

Diagnosis of VTE is usually made with imaging studies like ultrasound for DVT and CT scans for PE. Treatment consists of anticoagulation therapy to avoid further clotting and, in severe conditions, thrombolytic therapy to break up the clots that are

present. In patients with recurrent VTE, long-term anticoagulation is frequently advised to prevent future events. Thrombophilia studies are done in VTE patients, especially those who are young, have multiple events, present with thrombosis at non-typical sites, or have a positive familial history of the condition. These tests are carried out to screen for individuals who are at increased risk and for whom management will be adjusted. (7)

Venous thromboembolism is the second most frequent CVS disorder after myocardial infarction and more so than stroke. The prevalence of VTE is age-dependent: about 1 per 100,000 per year in children, 1 per 1,000 per year in adults, and much higher in older age. The prevalence of thrombophilia also depends on the type and group. Factor V Leiden is present in approximately 5% of Northern Europeans and in some 10% of patients with thrombosis. Risk factors for VTE are immobility, surgery (especially orthopedic), cancer, pregnancy, and hormonal contraceptive use. Genetic conditions such as factor V Leiden gene mutation or prothrombin gene mutation also predispose a person to VTE. There have been recent studies indicating a correlation between non-O blood groups (A, B, and AB) and an increased risk of VTE. The correlation is believed to be the result of increased levels of von Willebrand factor and factor VIII in non-O blood group individuals, which can enhance clotting tendency.(8)

Thrombophilia and venous thromboembolism are serious clinical conditions that need early diagnosis and treatment to avoid severe complications. Knowledge of the pathogenesis and risk factors for VTE is important in creating successful prevention and treatment measures. Significant progress has been made through the advances in genetics and molecular biology in discovering many of the risk factors, but more research needs to be conducted to enhance the outcomes in patients suffering from these conditions.

MAIN BODY

1.Introduction to thrombophilia and venous thromboembolism

Thrombophilia, or hypercoagulability or prothrombotic state, is defined as an abnormality of blood coagulation predisposing to thrombosis (blood clotting in blood vessels). Such abnormalities may be inherited or acquired and are detected in a high percentage of patients with unprovoked thrombotic events. The incidence of thrombophilia is highly variable based on the type and population. Inherited thrombophilias, including antithrombin deficiency and protein C deficiency, are uncommon, occurring in less than 1% of the local population. They are more frequent in patients with venous thrombosis, in 0.5–7.5% and 2.5–6% of cases, respectively. More frequent types such as factor V Leiden occur in approximately 5% of Northern Europeans and 10% of patients with thrombosis. Thrombophilia prevalence in Caucasians is roughly 10-7,000 per 100,000 persons across the globe(9).

Venous thromboembolism includes deep vein thrombosis and pulmonary thromboembolism, which are conditions of the development of blood clots in the deep veins and the possibility of breaking loose and migrating to the lungs, respectively. The pathogenesis of VTE is a multifaceted interaction between factors referred to as Virchow's triad: stasis of blood flow, endothelial damage, and hypercoagulability. Thrombophilia affects the hypercoagulable state by deranging the procoagulant-anticoagulant balance. For example, factor V Leiden and prothrombin G20210A mutations predispose to clot formation by augmenting the procoagulant activity of factor V and prothrombin, respectively. Furthermore, diseases such as antiphospholipid syndrome may result in an autoimmune-mediated hypercoagulable state(10).

1.2 Pathophysiology of venous thromboembolism

Venous thromboembolism (VTE) includes deep vein thrombosis (DVT) and pulmonary embolism (PE), which are conditions with blood clots in the deep veins and their ability to dislodge and become lodged in the lungs, respectively. The pathogenesis of VTE is through the interaction of numerous factors that together constitute Virchow's triad: changes in blood flow (stasis), endothelial damage, and hypercoagulability.

1.2.1. Components of Virchow's Triad

The components of virchows triad are Venous stasis, vascular injury, and hypercoagulability. Venous stasis takes place when blood circulation is slowed down or

blocked, resulting in higher viscosity of blood and microthrombi formation. Stasis can be caused by prolonged immobility, surgery, or external compression of veins. Stasis itself may not be enough to initiate thrombus formation, but when the stasis is combined with other factors, it greatly enhances the tendency for clot formation.

Hypercoagulability is an imbalance in the coagulation system, usually caused by a genetic mutation (e.g., factor V Leiden) or acquired condition (e.g., antiphospholipid syndrome), resulting in a heightened risk of blood to clot.Hypercoagulability is a consequence of elevated levels of procoagulant factors or low levels of anticoagulant proteins, e.g., antithrombin(11).

The pathophysiologic process of VTE occurs through the following steps:

The processing of the coagulation cascade is brought about by tissue factor expression on injured endothelial, resulting in the activation of factor VII and subsequent activation of factor X. Activated platelets and coagulation factors amplifies the coagulant signal, resulting in thrombin generation and fibrin clot formation. Cross-linking stabilizes the fibrin clot to form a mature thrombus. Understanding the pathophysiology of VTE is crucial in the prevention and management of these diseases. Anticoagulation therapy is commonly used to cure and prevent the recurrence of VTE by correcting the hypercoagulable state (12).

Figure 2.1: Pathophysiology of venous thromboembolism

2. Thrombophilia markers

Inherited thrombophilia markers are genetic mutations such as Factor V Leiden and prothrombin G20210A mutation. Factor V Leiden is the one of the common inherited thrombophilia due to a mutation that makes factor V resistant to activated protein C and hence liable to thrombosis. Prothrombin G20210A mutation results in elevated levels of prothrombin, thus increased tendency to thrombosis. Lack of naturally occurring anticoagulants such as antithrombin, protein C, and protein S are also key inherited markers(13).

Acquired markers of thrombophilia usually include antiphospholipid syndrome, which is typified by the occurrence of antiphospholipid antibodies like lupus anticoagulant, anti-cardiolipin, and anti-β2-glycoprotein-1 antibodies. The antibodies may interfere with standard blood clotting processes, predisposing to abnormal blood coagulation. Thrombophilia testing is typically a mixture of genetic and serologic testing. Activated protein C resistance testing is performed to test if activated protein C is able to prevent the formation of blood clots effectively, typically for Factor V Leiden. Antithrombin activity, protein C and S activity, and antiphospholipid antibodies are some other tests(14). Thrombophilia screening is generally recommended in VTE patients, particularly if they are young, have a history of recurrence, or have a positive family history for the condition[4]. Testing also does not always determine recurrence or reduce risk in unselected symptomatic VTE patients. In clinical practice, the presence of thrombophilia markers helps individualize treatment measures, such as anticoagulation therapy, to minimize future thrombosis[4]. The American Society of Hematology offers thrombophilia testing and treatment guidelines based on evidence-based management with the goal of optimizing patient outcomes(15).

In most cases, thrombophilia markers are very important in diagnosis as well as treating patients who are at risk of thrombotic complications, and therefore allowing appropriate interventions to be made in a bid to curb abnormal blood clotting complications.

2.1. Genetic markers

Genetic thrombophilia markers are specific mutations or gene changes that increase a person's risk of forming blood clots. Genetic marker identification is helpful in identifying people with inherited thrombophilia, which has a high risk of venous thromboembolism (VTE) and deep vein thrombosis, and pulmonary embolism. Inherited thrombophilia is a hypercoagulable condition of increased sensitivity to blood coagulation because of gene mutations in the coagulation cascade.(16).

One of the common genetic markers for thrombophilia include Factor V Leiden, prothrombin G20210A mutation, methylene tetrahydrofolate reductase mutations, and plasminogen activator inhibitor-1 (PAI-1) polymorphisms. The most prevalent inherited marker of thrombophilia is Factor V Leiden, due to a point mutation at position G1691A of the factor V gene. The mutation makes factor V resistant to activated protein C and hence thrombosis-susceptible. The mutation G20210A in the prothrombin gene leads to elevated prothrombin levels and hence elevated susceptibility to thrombosis. Mutations in MTHFR, the C677T and A1298C mutations, are associated with hyperhomocysteinemia, a condition that is connected with a high chances of thrombosis. The 4G/5G polymorphism of PAI-1 affects the expression of PAI-1, an inhibitor of fibrinolysis, or the dissolution of blood clots(17).

The clinical relevance of these genetic markers is that they can guide risk assessment and management practices. Genetic markers help to determine the risk of an individual experiencing thrombotic events, particularly in the case of recurrent thrombosis or family history. For instance, women with thrombophilic markers are at higher risk of pregnancy-related complications such as multiple miscarriages and intra -uterine fetal growth restriction. Genetic marker data may direct the use of anticoagulant therapy to prevent recurrent thrombotic events in at-risk patients (18).

In clinical practice, one needs to be aware of the genetic markers of thrombophilia in order to individualize the management in order to prevent thrombotic events. According to the National Blood Clot Alliance, it is essential to have genetic testing in

thrombophilia risk assessment because it is an autosomal dominant disorder and a single copy of the faulty gene will be enough to predispose patients. Additionally, it has been proven that inherited thrombophilic factors are most commonly found in early venous thromboembolism and hence genetic assessment is essential in recurrent thrombotic event patients (19).

In conclusion, genetic thrombophilia markers play a crucial role in the diagnosis and treatment of thrombotic predisposed patients. Detection of the markers by clinicians can trigger specific interventions to prevent complications of blood over-coagulation, with the ultimate goal of enhancing patient outcomes.

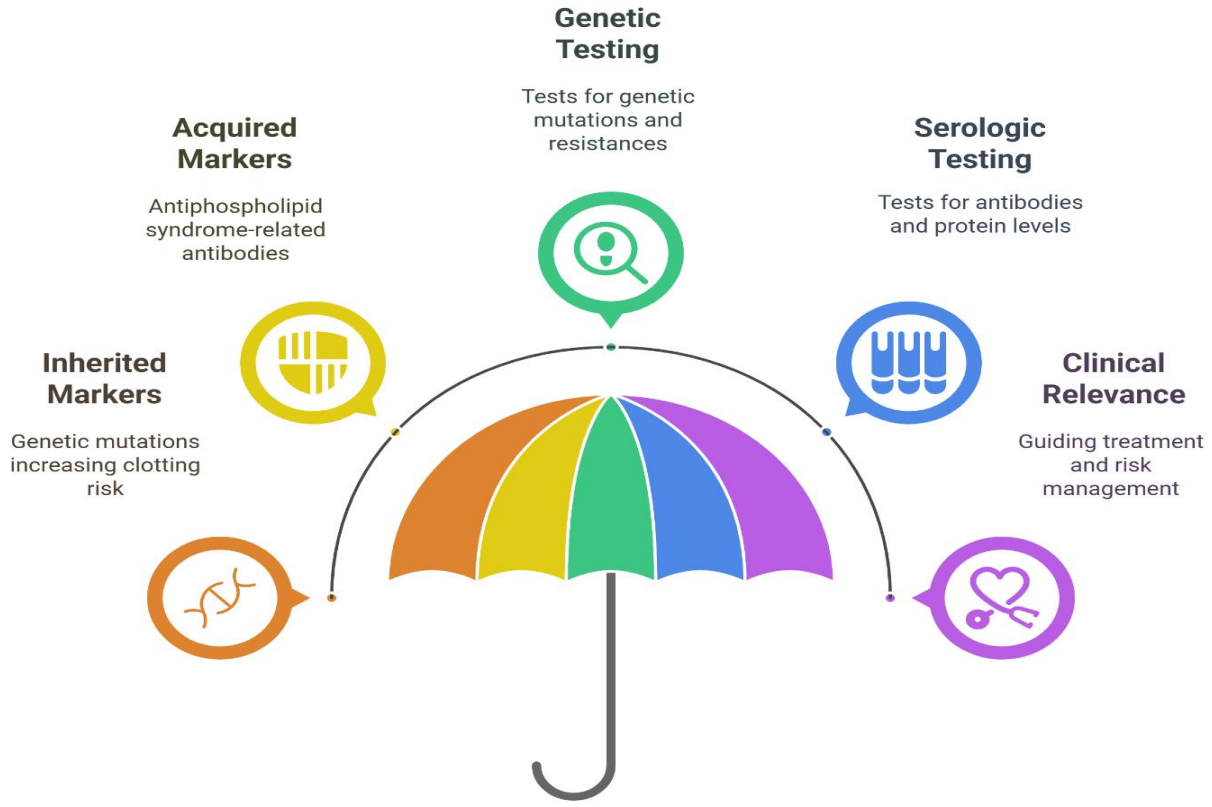

Figure 2.2: Understanding of thrombophilia markers

3. Clinical presentation of venous thromboembolism

Venous thromboembolism (VTE) is a life-threatening illness characterized by the formation of blood clots in the veins and leads to two serious clinical syndromes: deep vein thrombosis (DVT) and pulmonary embolism (PE). These syndromes are potentially fatal and require prompt treatment.

DVT is where a blood clot forms in a deep vein, typically in the legs, thighs, or pelvis. Symptoms of DVT include pain or tenderness in the limb, swelling, heat, and redness of the skin. The pain will initially occur in the calf or thigh and worsen with walking or standing. DVT might not be accompanied by overt symptoms in some instances, and thus one should remain vigilant for risk factors like immobilization for more than 3 days, recent surgery, or previous history of blood clots(18).

Diagnosis of VTE is a combination of physical examination, imaging tests, and medical history taking. Ultrasound of the affected limb is the most applied diagnostic test in the context of DVT, while in PE, computed tomography pulmonary angiogram (CTPA) is the most utilized one. Laboratory investigations consist of D-dimer levels to look for the evidence of clotting activity.(19)Complications of VTE are severe and consist of post-thrombotic syndrome and chronic thromboembolic pulmonary

hypertension. Early diagnosis and prompt medical intervention are necessary to prevent complications and improve patient outcomes.(20)

Finally, clinical presentation of VTE is diverse and can range from non-severe symptoms of DVT to potentially life-threatening PE. Familiarity with these symptoms and early medical intervention in case of their presentation is essential for effective management and prevention of life-threatening complications.

3.1. Deep vein thrombosis

Deep vein thrombosis is a serious medical condition that happens when a blood clot develops in a deep vein, most commonly in the legs, thighs, or pelvis. DVT can lead to significant health problems and, if severe, can lead to death when the clot breaks loose and travels to the lungs, resulting in a pulmonary embolism (PE).

Symptoms of DVT are variable but most typically include swelling of the involved limb, pain or tenderness, warmth, and skin discoloration, which can be red or blue. Pain typically starts in the calf or thigh and is exacerbated by walking or standing. A few individuals do not have apparent symptoms, so it is crucial to identify risk factors such as prolonged immobility, recent surgery, or a previous history of blood clots.(21)

Risk factors for DVT include obesity, age over 40 years, pregnancy, certain drugs like birth control pills, and pacemaker or central venous catheterization. Physical inactivity is also a risk factor. DVT can occur suddenly, and if there are symptoms, medical help should be obtained immediately.

Diagnosis of DVT is through imaging investigations such as ultrasound and laboratory investigations such as the D-dimer test. Treatment is typically with anticoagulant medication to inhibit further clotting and can also include the use of compression stockings to improve circulation and reduce swelling. Surgery or insertion of an inferior vena cava (IVC) filter is necessary in severe cases. Complications of DVT can include post-thrombotic syndrome, which presents as chronic pain, swelling, and discoloration of the leg skin. Preventive measures such as frequent movement in prolonged immobilization and use of compression stockings can be used to prevent the occurrence of DVT (22).

DVT is a potentially life-threatening condition that warrants a doctor's visit if symptoms are present. One should know the symptoms and risk factors to allow early diagnosis and treatment to avoid severe complications.

3.2. Pulmonary embolism

Pulmonary embolism (PE) is a medical emergency in which an artery within the lung becomes blocked by a blood clot, usually from deep vein thrombosis (DVT) of the leg. PE has the potential to cause serious illness and can be fatal if left untreated. The presentation of PE is very variable based on the size of the clot and the extent of pulmonary disturbance but typically includes acute onset dizziness due to an acute reduction in blood pressure.(22,23)

Diagnosis of PE involves clinical assessment, imaging scan, and laboratory testing. The desired test for diagnosing the existence of PE is a computed tomography pulmonary angiogram (CTPA). Blood tests such as the D-dimer test can also be employed to detect clotting activity but are not definitive on their own. There may also be symptoms of DVT, i.e., swelling, redness, and pain, in the affected leg, that may betray the diagnosis in some cases.(24)

Briefly, pulmonary embolism is an illness that should be taken seriously and treated right away with medical assistance if there are symptoms. It is necessary to know the symptoms and risk factors for early detection and proper management to prevent serious complications. While PE is fatal, it can be cured with appropriate medical intervention, emphasizing the necessity of seeking emergency medical treatment if there are symptoms.(24).

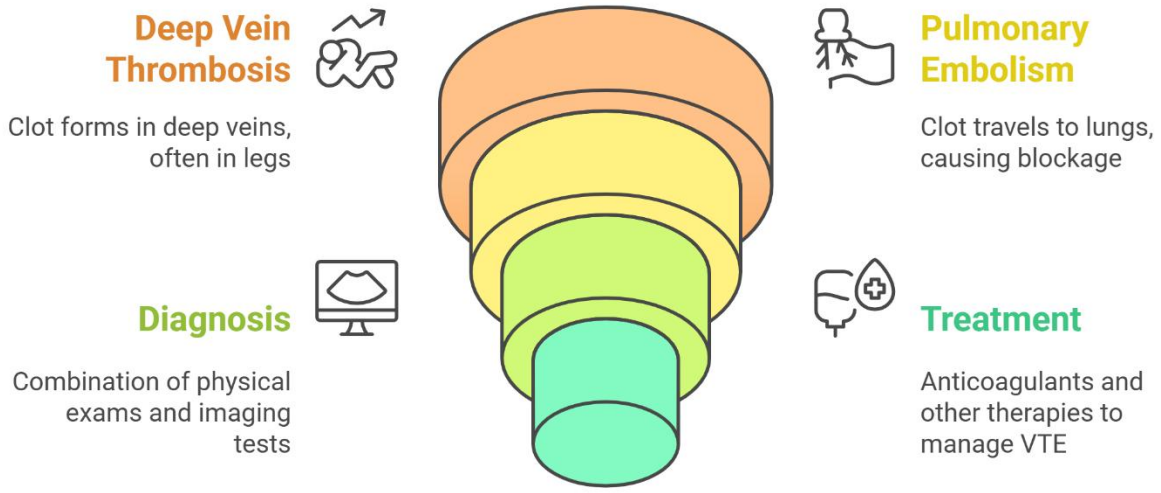

Figure 2.3: Progression and management of venous thromboembolism

4.. Laboratory tests for thrombophilia markers

Laboratory tests for thrombophilia markers are extremely crucial in the identification of an individual with a high risk of forming blood clots, known as thrombophilia. Thrombophilia can be inherited or acquired and is associated with an increased risk of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE). American Society of Hematology (ASH) guidelines point out the significance of screening for hereditary thrombophilias in young VTE patients with recurrent cases or those with a history of disease in the family.

A full thrombophilia screen typically consists of a battery of tests to diagnose inherited and acquired thrombophilic conditions. Inherited thrombophilias are assessed by tests for deficiency of the naturally occurring anticoagulants such as antithrombin, protein C, and protein S, and genetic mutations such as Factor V Leiden and prothrombin G20210A mutation. Acquired thrombophilias, such as antiphospholipid syndrome (APS), are tested by lupus anticoagulant, anticardiolipin antibodies, and anti-β2-glycoprotein-1 antibodies tests.(25). Turnaround time for the tests would vary, typically taking weeks to days to get fulfilled, based on the complexity and the need for send-away tests. It is to be remembered that proper results are not possible if the patient is undergoing anticoagulant treatment as it interferes with the tests.(26)

The diagnosis of thrombophilia involves assessment of the plasmatic anticoagulant mechanisms to determine deficiency of antithrombin, protein C, and protein S. Genetic testing for mutations like Factor V Leiden and prothrombin G20210A is also required, as these are the most common hereditary causes of thrombophilia. If thrombosis occurs in atypical locations, additional genetic tests may be recommended to rule out other conditions like myeloproliferative neoplasms (MPN).(27)

Finally, laboratory analysis for thrombophilia markers plays a critical role in the recognition of high-risk VTE patients. The tests direct management, such as anticoagulant treatment, in an attempt to prevent recurrent thrombosis. It is imperative that health workers are familiar with proper utilization and interpretation of such tests for ideal patient care.

5. Treatment and management

In high-risk PE, with hemodynamically unstable patients, stronger interventions are appropriate. Systemic thrombolysis is typically used to rapidly dissolve the clot and restore blood to the lung. But the technique carries the hazard of major bleeding, including intracranial hemorrhage, and is generally reserved for deteriorating patients with poor presentation or patients in whom other therapy fails.

Catheter-directed thrombolysis and surgical pulmonary embolectomy (SPE) are other treatments for reperfusion in contraindication to systemic thrombolysis or failure of other therapy. SPE is a process in which the clot is removed from the pulmonary arteries and preserved in life-threatening cases when other techniques are unavailable (28).

In addition to these treatments, supportive care is crucial in the management of PE. These include cardiopulmonary support by oxygenation and, if necessary, inotropic support to maintain blood pressure and avoid hypoxemia. In critical presentations, extracorporeal membrane oxygenation (ECMO) can be used as a bridging tool for the heart and lungs until the patient recovers.(12)

Long-term care is a situation of continuous anticoagulation to avoid reoccurrence and follow-up for the potentiality of complications such as chronic thromboembolic pulmonary hypertension. Vena cava filters are put in patients where there are anticoagulant contraindications to block clots from reaching the lung. Treatment in general for PE is a combined effort, undertaken by emergency physicians, cardiologists, pulmonologists, and surgeons to attain the best possible outcomes.

5.1 Anticoagulant therapy

Anticoagulant therapy is the cornerstone of therapy for pulmonary embolism (PE), aiming to avoid extension of existing clots and reduce the risk of recurrent venous thromboembolism (VTE). The primary aim of anticoagulation is to allow the body's natural mechanisms to lyse existing clots with time without allowing new clot formation. Initial treatment of patients with PE is generally anticoagulation for at least three months, which can be extended based on individual risk factors and clinical status.(28) Low Molecular Weight Heparin is typically given first, especially in patients requiring catheter-directed therapy or cancer-associated thrombosis, since it has a reliable anticoagulant effect.(29) Additionally, cancer-related thrombosis patients are usually necessitated with LMWH due to proven efficacy in avoidance of recurrent embolism among these patients.(30)

anticoagulation therapy is central in the management of PE, and DOACs are suited for most patients due to ease of use and excellent safety profile. Prolongation of anticoagulation is nevertheless subject to risk factors as well as the presentation of the patient and therefore requires personalized consideration to avoid reoccurrence as well as adverse events.

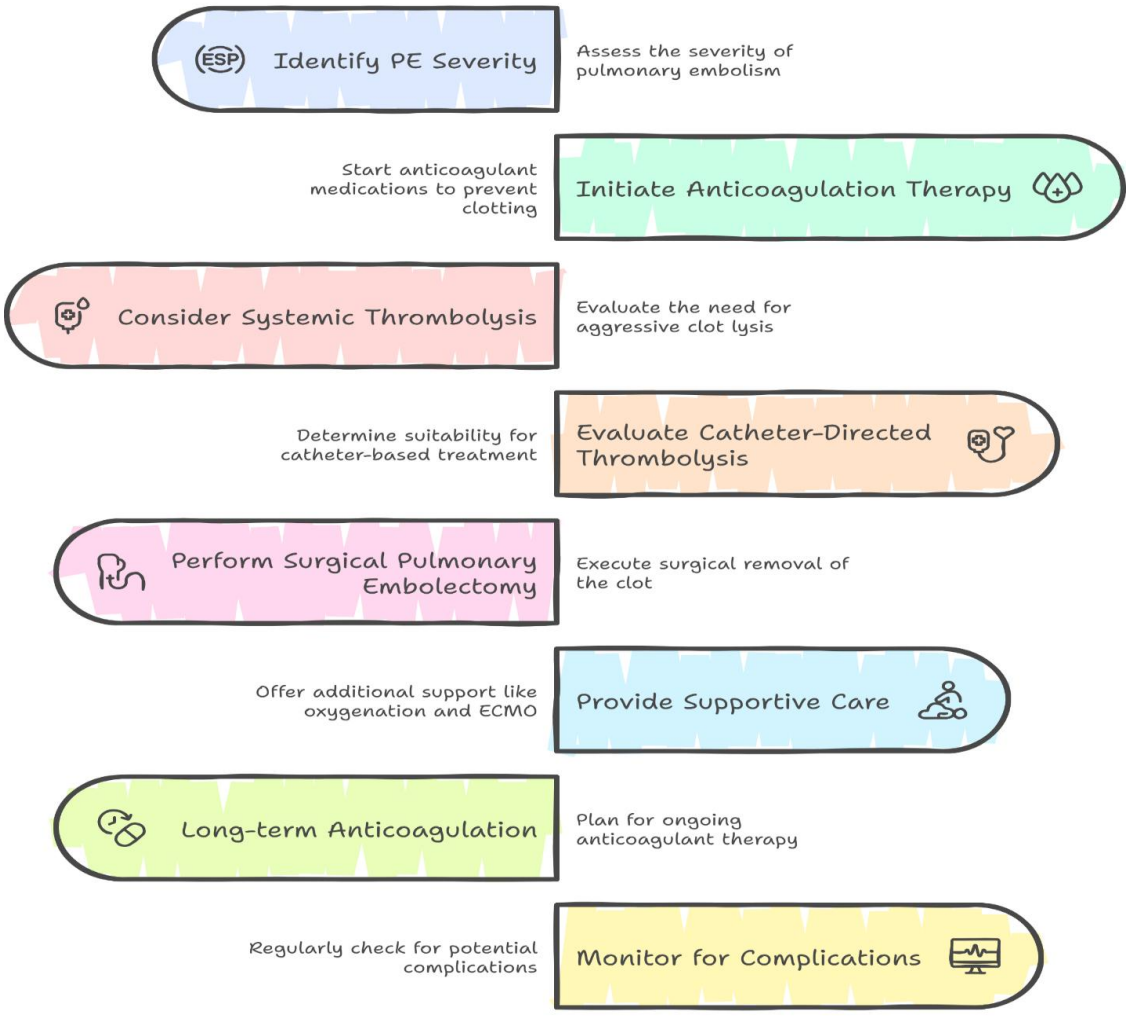

Figure 2.4: Treatment and management of pulmonary embolism

6. Recurrence risk assessment

Assessment of recurrence risk in venous thromboembolism (VTE) patients is valuable for guiding treatment decisions and preventing future thrombosis. Recurrence risk also varies substantially depending on whether the initial VTE was provoked or unprovoked. Unprovoked VTE, which occurs in the absence of a clear-cut transient risk factor like surgery or trauma, has a much chance of recurrence compared with provoked VTE. It has been made sure by researches that unprovoked VTE patients are at greater risk for recurrence annually because the hazard ratio is around 2.3 compared to provoked VTE patients. (31)

A number of clinical and laboratory variables are employed for estimation of recurrence risk. These are male sex, proximal deep vein thrombosis, and pulmonary embolism, and these are also at higher risk of recurrence. For instance, the hazard ratio for male versus female patients is 1.90, and proximal deep vein thrombosis and pulmonary embolism are 2.08 and 2.60, respectively, versus distal thrombosis. Elevated levels of D-dimer, a protein produced by blood clots, also have higher risk of recurrence with a hazard ratio of 1.27 for every doubling of D-dimer. (32)

Risk estimation of recurrence VTE is an assessment of a clinical variable and a laboratory marker for identifying who is at the highest risk of experiencing future thrombotic occurrences. This is the personalized strategy for maximizing therapy and reducing risk for recurrence in order to have a healthier patient.

6.1 Predictive models

Recurrent VTE prediction models have been built to allow high- and low-risk patients, with a propensity for subsequent thrombosis, to be identified. The models are invaluable to inform therapeutic management, including how long to give anticoagulant therapy, and also improve patient outcome at the cost of prevention of chronic anticoagulation complications.

A notably significant model for prediction is the Vienna Prediction Model, which, in large trials, has been found to adequately predict patients who are at low VTE risk for recurrence. This model based on parameters like sex, original site of the thrombosis, and the level of D-dimer would offer an approximation of recurrence risk. By the identification of low-risk patients, the Vienna Prediction Model allows for the discontinuation of anticoagulant therapy in these patients, thereby removing its associated bleeding complications and improving quality of life.(34)

Besides these models, machine learning approaches have also been employed to develop predictive models for VTE recurrence, particularly in cancer patients. These models use electronic health records to identify predictors like primary pulmonary embolism, deep vein thrombosis, metastasis, and laboratory markers like hemoglobin and serum creatinine levels. These predictive indicators have tremendous potential to improve the clinical management of high-risk patients by identifying individuals requiring more aggressive monitoring and treatment.(35)

Overall, predictive models for VTE recurrence are helpful clinical tools that allow clinicians to tailor treatment strategies according to patient risk. No single model should be applied to all patients, but collectively they assist in rendering a more tailored approach to VTE management, balancing the need to prevent recurrence against the harms of long-term anticoagulation.

7. Emerging therapies and future directions

Future treatments and directions in the management of venous thromboembolism (VTE) are geared toward optimizing the effectiveness of treatment, reducing complications, and enhancing patient outcome. Emerging advances include the development of new thrombolytic therapy aimed at inhibitors of fibrinolysis such as alpha2-antiplasmin and plasminogen activator inhibitor-1. These treatments are intended to safely lyse venous thrombi without appreciably increasing risks of bleeding, offering a possible substitute for traditional anticoagulants and fibrinolytic agents, which are hampered by partial lysis of the thrombus and rethrombosis.(36)

The venous thromboembolism therapeutic market is projected to grow significantly based on the increasing use of new oral anticoagulants (NOACs) like dabigatran, rivaroxaban, and apixaban. The NOACs are many advantages compared to traditional anticoagulants like warfarin due to less blood monitoring required, less drug interactions, and more improved safety profiles. The market size is estimated to reach $3.7 billion by 2025, signifying increasing needs for the NOACs for prevention and therapy of VTE.(37)

Mechanical thrombectomy equipment is also gaining popularity with the potential to cure VTE. The equipment enables the mechanical removal of the blood clots, offering an effective and quick method of treatment for patients who report severe VTE. Traditionally used in the treatment of arterial conditions like stroke, their utilization in venous thrombectomy is now gaining momentum, presenting new hope in the management of acute VTE.(38)

In general, novel VTE therapies are focused on improving safety, efficacy, and patient outcomes. From novel thrombolytic agents to advanced nanotechnology and mechanical thrombectomy devices, these technologies hold promise for revolutionizing the near future management of VTE.(39, 40).

Conclusion

Inherited and acquired thrombophilia plays a major part in the pathogenesis and recurrence of venous thromboembolism (VTE). Having knowledge about various thrombophilia markers such as genetic defects involving factor V Leiden and prothrombin G20210A and also acquired ones involving antiphospholipid syndrome is highly important in management and prevention of VTE. The detection of these markers' aids in the customization of

treatment modalities, including anticoagulation therapy, to prevent the recurrence of thrombotic events. Progress in genetics and molecular biology continues to enhance our knowledge of thrombophilia, facilitating improved risk assessment and individualized management strategies for patients. More research is necessary to elucidate the contribution of less well-characterized markers, including TAFI and increased factor VIII, to the risk of thrombosis. Finally, early diagnosis and proper management of thrombophilia are necessary to avoid severe complications related to VTE.

Limitations for patients

Venous thromboembolism can have significant long-term consequences that limit a patient's quality of life, physical functioning, and overall well-being. While acute episodes of deep vein thrombosis (DVT) or pulmonary embolism (PE) may be successfully treated, many individuals continue to face complications that affect their future health and lifestyle. Some of the key limitations include:

Some patients require extended or lifelong anticoagulant therapy to prevent recurrence, which comes with a risk of bleeding complications. This also imposes lifestyle limitations, such as avoiding high-risk physical activities and regular monitoring of blood parameters.

Experiencing a life-threatening event like a PE can lead to anxiety, depression, and post-traumatic stress. Fear of recurrence and the burden of chronic disease management may affect mental health and social functioning.

Physical limitations or the need for frequent medical follow-up can hinder return to work, career progression, and participation in social or recreational activities, particularly in younger or working-age patients.

Long-term treatment, hospitalizations, follow-up care, and reduced ability to work can result in significant economic hardship for patients and their families. (41)

Future Recommendation

To improve outcomes and quality of life for patients with venous thromboembolism (VTE), several key recommendations should be considered for future clinical practice and research. First, personalized treatment approaches based on individual risk profiles—including genetic factors, comorbidities, and bleeding risks—should be further developed to guide the duration and type of anticoagulation therapy. The development of safer anticoagulants with lower bleeding risks and fewer drug interactions is also essential.

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