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Chapter

# Anticoagulation in Thrombophilia

*Iris Bararu Bojan, Stefan Dobreanu, Oana Viola Badulescu, Maria Cristina Vladeanu, Andrei Bojan, Carmen Elena Plesoianu and Manuela Ciocoiu*

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## Abstract

Thrombophilia is a condition of hypercoagulability, which is defined as an abnormality of blood clotting, disturbing the balance between procoagulants and anticoagulants in favor of the former, thus increasing the risk of thrombosis. It can be classified into different categories, such as genetic/administered; primary/secondary; permanent/transient; low risk/high risk. Venous thromboembolism is the main and most common complication of a hypercoagulable condition, with an enormous impact on any national health system. The pathophysiological mechanisms involved are at various stages of research, some of which are far from being fully elucidated. Treatment of thrombophilia differs—while most conditions do not require anticoagulation as primary prophylaxis, secondary prophylaxis may require transient or permanent anticoagulation. Treatment options include parenteral unfractionated heparin, low molecular weight heparin (LMWH), fondaparinux or orally administered vitamin K antagonists, and direct oral anticoagulants (DOAC), such as rivaroxaban, apixaban, dabigatran, with increasing indications as data accumulate from recent and ongoing studies and trials.

**Keywords:** thrombophilia, hypercoagulability, thromboembolism, anticoagulation, prophylaxis

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## 1. Introduction

Clotting is a physiological property of the body to form clots and thus minimize blood loss at the site of injury. Normal blood flow is kept in balance by factors that promote clotting and by antithrombotic factors. A hypercoagulable state, which may be complicated by the development of thromboembolism, is a consequence of hyperactivity of clotting promoters or anticoagulant deficiency. But the interaction between the two facets is much more complex than this, as thrombosis can be influenced by the qualitative and quantitative properties of factors, for example, their secretion, accumulation, or degradation [1].

What Virchow described in 1856 as the triad of conditions that must be met to develop venous thrombosis is accepted nowadays as hypercoagulability, vascular stasis and vascular trauma underlie the pathophysiological mechanism that explains this situation. Arterial thrombosis, on the other hand, results from the rupture of

an atherosclerotic plaque, which pierces the vascular endothelium, resulting in the formation of platelet-rich thrombus around it [1].

Thrombophilia is a hypercoagulable or prothrombotic state, which is defined as an abnormality of blood clotting, thus increasing the risk of thrombosis. It can be classified into different categories, depending on its mechanism of action, how it occurs, whether it is an acquired or an inborn disease. [Genetic vs. acquired; primary vs. secondary; permanent vs. transient; low risk vs. high risk].

The known possible causes of thrombophilia are listed in **Table 1** [3].

Type 1 or major thrombophilias are a group of rare diseases that include antithrombin deficiency, protein C deficiency, or protein S deficiency, which together occur in less than 1% of the population but account for up to 7% of patients with thrombosis [4].

Type 2 thrombophilias or minor thrombophilias are much more common, the most important example being the factor V Leiden mutation, which can be identified in 5% of the European-born population and 30–50% of patients referred for thrombophilia testing.

The prothrombin mutation affects 1–4% of the general population but is found in up to 15% of patients tested for thrombophilia. Both types of mutations are much more common in Caucasians and almost never found in patients of Asian or African descent [4].

Hereditary thrombophilias are those in which a genetic mutation inherited from one or both parents leads to a condition in which the function of certain proteins of the clotting system is impaired. The condition can be expressed as a deficiency or loss

| **Primary (genetic)** | **Secondary (acquired)** |
|---|---|
| Factor V mutation (G1691A mutation; factor V Leiden) | Prolonged bed rest or immobilization |
| Prothrombin mutation (G20210A) | Myocardial infarction |
| 5,10-Methylene tetrahydrofolate reductase (hyperhomocysteinemia) | Atrial fibrillation |
| Increased levels of factor VIII, IX, XI, or fibrinogen | Tissue injury (surgery, fracture, burn) |
| Antithrombin III deficiency | Cancer |
| Protein C deficiency | Prosthetic cardiac valves |
| Protein S deficiency | Disseminated intravascular coagulation |
| Fibrinolysis defect | Heparin-induced thrombocytopenia |
| Homozygous homocystinuria (deficiency of cystathionine B-synthase) | Antiphospholipid syndrome |
| | Cardiomyopathy |
| | Nephrotic syndrome |
| | Hyperestrogenic states (pregnancy and postpartum) |
| | Oral contraceptive use |
| | Sickle cell anemia |
| | Smoking |
| | Infection (Covid 19) |

**Table 1.**
*Thrombophilia causes, Robbins and Cotran pathologic basis of disease (ninth edition.) [2].*

of function, best exemplified by mutations in the antithrombin, protein C, or protein S genes, or as a gain of function, such as mutations in factor V Leiden and prothrombin 20,210 A/G. Other conditions, although less common, are the presence of abnormal levels of clotting factors, elevated homocysteine, or defects in the fibrinolytic pathway. Nowadays, we have reached a point where gene factors can be identified in up to 30% of patients with thrombophilia [5, 6].

Acquired thrombophilia is a hypercoagulable status composed of the association of a divergent group of clinical conditions, which include malignancy, pregnancy, prolonged bed rest, postoperative, nephrotic syndrome, or lifestyle risk factors, such as smoking or obesity. But the most important example is an antiphospholipid syndrome which is also included in the guidelines and should be tested for each time thrombophilia is suspected [5].

Although hypercoagulability disorders are classified as either inherited or acquired, thrombosis develops due to the interaction of both genetic and environmental factors, which has led to the development of the multiple-hit hypothesis, thus providing a possible explanation for the differences observed between subjects carrying the same gene mutation [6].

In an article by R H Thomas, the CALMSHAPES mnemonic was proposed to more easily recall the different etiologies of the hypercoagulable state, which are as follows:.

- Protein C deficiency
- Antiphospholipid syndrome
- Factor V Leiden mutation
- Malignancy

| Syndrome | % in the general population | % in patients with venous thromboembolism | Relative risk of thromboembolism |
|---|---|---|---|
| Factor V Leiden (G1691A) | 0.05–4.8 | 18.8 | 4 |
| Factor V Leiden (A1691A) | 0.02 | 1.5 | 80 |
| Prothrombin G20210A | 0.06–2.7 | 7.1 | 2.8 |
| Low protein C levels | 0.2–0.4 | 3.7 | 6.5 |
| Low protein S levels | 0.16–0.1 | 2.3 | 5.0 |
| Low antithrombin levels | 0.02 | 1.9 | 20 |
| Hyperhomocysteinemia | 5–7 | 10 | 2.95 |
| High factor VIII levels | 11 | 25 | 4.8 |
| High factor IX levels | 10 | 20 | 2.8 |
| High factor XI levels | 10 | 19 | 2.2 |
| Lipoprotein (a) | 7 | 20 | 3.2 |
| Antiphospholipid antibody | 0–7 | 5–15 | 5.5 |

**Table 2.**
*Prevalence of different thrombophilias and the risk of developing venous thromboembolism [3].*

- Protein S deficiency
- Hyperhomocysteinemia
- Antithrombin III deficiency
- Prothrombin G2021A mutation
- Factor eight excesses
- Sticky platelet syndrome [6]

Venous thromboembolism is the main and most common complication of a hypercoagulable condition, with a huge impact on any national health system. Available data from the United States estimates that venous thromboembolism is responsible for more than half a million hospitalizations annually, with an estimated cost of treatment per patient of more than $56,000, totaling an estimated $5–$20 billion. The different mechanisms of occurrence of a hypercoagulable state have different penetration in the general population, with different risk rates for complications, such as venous thromboembolism, as shown in **Table 2**.

## 2. Pathophysiology

### 2.1 Factor V Leiden

Factor V Leiden is an autosomal dominant transmissible gene abnormality that shows incomplete penetrance; therefore, the disease will not be developed by all carriers of the mutation. In terms of pathophysiological mechanism, factor V Leiden is also known as factor V Arg506Gln and as factor V R506Q, due to a single mutation of the factor V gene in which guanine replaces arginine at nucleotide 1691. Consequently, just one amino acid change, replacing arginine with glutamine, suppresses the binding site to the activated proteolytic protein C of factors V and Va [7, 8]. With the malformed binding site, the natural anticoagulant protein C can no longer bind and cleave factor V and Va to inactivate it, therefore factor V concentration increases and disrupts the pro−/anticoagulant balance, leading to an increased risk of thrombosis [7]. The result of the so-called activated protein C resistance phenotype is blamed in up to 95% of cases as a consequence of a factor V mutation, which has resulted in a 7-fold increase in the relative risk of developing deep vein thrombosis in patients [8].

### 2.2 Prothrombin G20210A

Prothrombin G20210A is a specific genetic mutation of nucleotide 20210A of the second factor of the coagulation cascade (factor II—prothrombin) and consists of a change of guanine to adenine, with a higher concentration of prothrombin found in mutation carriers [9]. Although several attempts have been made to explain why this happens, the exact mechanism of how the mutation leads to increased protein production, thereby increasing the overall risk of thrombosis, is not yet fully understood [10]. Caucasians have a higher risk of developing this condition, but the risk of thrombosis is minimal for heterozygotes in whom no other risk factors are identified.

However, in the presence of other secondary risk factors, such as prolonged bed rest or pregnancy, the risk is greatly increased. Homozygous carriers face an increased risk of thrombosis by 2 to 3 folds [11].

### 2.3 Protein C

Protein C and its activated form are vitamin K-dependent zymogens with an important role in the regulation of anticoagulation by inactivating coagulation factors Va and VIIIa [12].

Protein C deficiency is a rare abnormality that alters the activity of protein C, a consequence of which is the loss of activated protein C function and, consequently, its inability to control coagulation [13].

Mutations in the PROC gene are responsible for the development of congenital protein C deficiency and are transmitted in an autosomal dominant manner, affecting heterozygous carriers much less than homozygous carriers. To date, more than 160 PROC mutations have been identified, which can affect protein C concentration (type I) or result in the production of an altered protein with reduced activity and ineffective anticoagulant function (type II) [13].

Protein C is activated by interactions with thrombin after the latter has attached to thrombomodulin expressed on the endothelial cell surface. Activated protein C then proceeds to reduce clotting by cleaving and inactivating clotting factors Va and VIIIa. Low concentrations or structural alterations of protein C disturb the coagulation balance, favoring the development of a hypercoagulable state [13].

### 2.4 Protein S

Protein S is a vitamin K-dependent glycoprotein synthesized by the liver with an important role in coagulation, where it acts as a cofactor for protein C to inactivate coagulation factors Va and VIIIa and also as a cofactor for tissue factor pathway inhibitory protein, leading to inactivation of factor Xa and tissue factor/factor VII. In the human body, protein S exists in two forms—one free and one bound to the complementary protein C4b [13, 14].

Protein S deficiency is an unusual condition caused by quantitative or qualitative abnormalities following point mutations in the PROS1 gene. Mutations are transmitted in an autosomal dominant manner with incomplete penetrance. Homozygous individuals have a higher risk of thrombosis than heterozygous individuals, of whom only an estimated 50% develop venous thromboembolism, the other half remaining asymptomatic. More than 200 genetic mutations have been identified, causing a range of defects, which can be classified into three types—type I is characterized by low levels of total S protein and free S protein, type II total S protein concentrations are normal but with low activity, while type III has normal levels of total S protein but low levels of free S protein [13].

A quantitative or qualitative deficiency of protein S will have great implications in the regulation of coagulation, as the natural anticoagulant mechanisms will be less effective in inactivating coagulation factors Va, VIIIa, and VIIa, thus favoring a thrombosis-prone state.

### 2.5 Antiphospholipid syndrome

Antiphospholipid syndrome is an autoimmune-generated hypercoagulable state caused by the presence of antiphospholipid antibodies and is the most common cause

of acquired thrombophilia. It is characterized by the presence of at least one of three antiphospholipid antibodies, which are lupus anticoagulant, anticardiolipin antibodies, or antibeta2 glycoprotein antibodies, in addition to one or more clinical manifestations of thrombosis [15, 16].

The condition can be classified into a primary antiphospholipid syndrome, which occurs without a concurrent autoimmune disease, and a secondary antiphospholipid syndrome, in the presence of another autoimmune condition, the most prominent example being systemic lupus erythematosus [15].

Two profile risks for thrombosis have been identified in terms of the type and titer of antibodies present:

A high-risk profile involves one of the following: Thromboembolism risk profile:

- the presence of lupus anticoagulant at 2 different measurements taken at least 12 weeks apart;
- any combination of 2 of the 3 defining antibodies;
- identification of all 3 antiphospholipid antibodies;
- the persistence of high antiphospholipid antibody titers;

A low-risk profile requires transient isolation of anticardiolipin antibodies or antibeta2 glycoprotein antibodies at low-to-medium titers [16].

The mechanisms involved in the generation of hypercoagulability require further investigation, as the few proposed mechanisms cannot exclusively explain this condition. Antiphospholipid antibodies are thought to interfere with platelet and endothelial cell membranes, proteins in the coagulation cascade or inhibit protein C.

The types, isotypes, and titers of antibodies found to correlate directly with the risk of thrombosis risk increases with higher titers, the presence of IgG antibodies, or the identification of lupus anticoagulant [15].

### 2.6 Malignancy

Thromboembolic complications in cancer patients are the second leading cause of mortality, presenting in various forms from venous or arterial thrombosis to disseminated intravascular coagulation. Venous thromboembolism is a significant cause of morbidity and mortality, with pulmonary embolism being three times more common than in a person who has developed venous thrombosis but does not have cancer [17, 18].

Other rarer thrombotic complications are also seen more frequently in patients with cancer, such as disseminated intravascular coagulation and thrombotic microangiopathy. Disseminated intravascular coagulation is a condition in which the coagulation cascade is activated systemically, resulting on the one hand in the formation of fibrin deposits that move to different organs blocking microcirculation, and on the other hand consuming clotting factors and platelets, which can lead to life-threatening bleeding [17, 19].

It has long been observed that patients with cancer and thromboembolic disease are strongly associated, but despite this, the mechanisms leading to the hypercoagulable state are numerous, complex, and not yet fully understood. Tumor-specific factors are also thought to play a role, because of the variable risk of thrombosis for different cancers. Returning to Virchow's triad, all three conditions for thrombosis can occur

simultaneously in a cancer patient, the best example being venous stasis following venous compression by a tumor [17, 18].

Various cancer therapies can also contribute to a prothrombotic state, with many reports suggesting an association between chemotherapy and arterial thrombosis. The most implicated agents are platinum-based therapeutics (cisplatin) and those that interfere with vascular endothelial growth factor, either to inhibit it directly (bevacizumab) or to inhibit its receptor tyrosine kinase (sorafenib) [20].

### 2.7 Pregnancy

The hypercoagulable state observed during pregnancy is the result of physiological, hormonal, and physical changes that affect women during pregnancy and in the peri- and post-natal periods.

As a result of hormonal changes, levels of certain clotting factors are increased, such as those of factors VII, VIII, X, von Willebrand factor, and fibrinogen. Meanwhile, during the second and third trimesters, resistance to activated protein C has been observed, as well as decreased activity of protein S. The number of studies has also reported decreased activity of the fibrinolytic pathway, due to an increase in its inhibitors, such as plasminogen activator inhibitor 1 and 2 and activable fibrinolytic inhibitor. All of these changes contribute to a tilting of the coagulation balance toward a prothrombotic state [21, 22].

Physical changes that promote thrombosis include prolonged bed rest in the peripartum period and mechanical compression of the pelvic veins by the gravid uterus, leading to decreased venous return from the lower extremities, consecutive stasis, and the development of venous thrombosis [21].

### 2.8 Heparin-induced thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is a condition mediated by the immune system through the development of heparin-dependent antibodies that have activated platelets, thereby increasing the risk of both venous and arterial thrombosis [15, 23].

IgG antibodies are directed against the antigenic complex formed by the binding of platelet factor 4 to heparin on the surface of platelets. This, in turn, activates surrounding platelets, leading to thrombin generation and the procoagulant state with the characteristic clinical manifestations of thrombocytopenia and thrombosis [23].

The diagnosis is confirmed by a decrease in platelets below 150,000/mL or by 50% from baseline in the presence of IgG HIT antibodies. The condition usually develops between 5 and 14 days after the start of heparin treatment, but may also develop within the first 24 hours in the case of previously administered heparin treatment. The risk is higher in surgical patients, especially following orthopedic and cardiac surgery, and is related to the period of exposure to heparin. Although heparin-induced thrombocytopenia is usually the result of treatment with unfractionated heparin, the occurrence of this condition has also been observed after administration of LMWH due to cross-reactivity between the two classes [15].

### 2.9 SARS-CoV-2

COVID-19 infection with severe acute respiratory syndrome coronavirus 2 has been shown to lead to a prothrombotic state, with variably reported incidences ranging from 11 to 70%, conditional on case severity and other predisposing factors.

The pathogen is thought to injure the vascular endothelium by attaching spike protein to the angiotensin-converting enzyme 2 receptors, thereby altering the properties of the endothelium into a thrombogenic surface, favoring platelet adhesion, hypercoagulability, and the development of micro or macrothrombosis at this level [11, 24].

## 3. Anticoagulation

Anticoagulant drugs are the first line of treatment for the prevention and treatment of thrombosis. This includes unfractionated heparin, low molecular weight heparin, fondaparinux, vitamin K antagonists (warfarin), and direct oral anticoagulants, which have a better safety profile than warfarin and have been shown to be equally effective, gradually replacing older agents [25].

The use of anticoagulants for primary prophylaxis has selected indications, such as for transient risk factors (prolonged hospitalization, postoperative status, certain orthopedic conditions) or may be considered for patients with high-risk hereditary thrombophilia, although for the latter there are not a large number of studies to support this indication [11, 26].

A patient who has developed a deep vein thrombosis and/or pulmonary embolism, whether provoked or unprovoked, should begin treatment with a direct oral anticoagulant for 3–6 months, according to the 2020 guidelines developed by the American Society of Hematology. It is also recommended that patients who have developed an unprovoked episode of deep vein thrombosis and/or pulmonary embolism or in whom a chronic risk factor can be identified should continue to receive secondary prophylaxis with either a standard or low-dose direct oral anticoagulant [10, 27].

For the purpose of secondary prophylaxis of various low-risk thrombophilias, the most recent studies recommend the use of direct oral anticoagulants instead of vitamin K antagonists, as the former possess a similar efficacy profile but with a better safety profile in terms of minor or major bleeding events. In high-risk thrombophilia, there is little data available to support the use of direct oral anticoagulants. A recent study testing the use of Rivaroxaban for secondary prophylaxis of high-risk antiphospholipid syndrome showed no additional benefit over traditional treatment, but an increased risk of bleeding [28, 29].

### 3.1 Factor V Leiden

In patients carrying the factor V Leiden mutation, no benefit of long-term anticoagulation has been shown in asymptomatic patients with no history of thrombosis. Although, short-term anticoagulation may be beneficial when other transient risk factors are identified. It is also recommended that women with or without a history of venous thromboembolism refrain from using estrogen-containing contraception and hormone replacement therapy [30].

Following an unprovoked venous thromboembolism event, the evidence favors long-term anticoagulation over short-term anticoagulation as secondary prophylaxis, although the duration has not been established but may be extended indefinitely if the risk of bleeding permits [31].

As a therapeutic agent, any direct oral anticoagulant can be used, as this is in line with the latest guidelines for the management of thromboembolism and the conclusion of several studies [29].

### 3.2 Prothrombin mutations

Carriers of heterozygous mutations, in the absence of other risk factors, do not require anticoagulation as primary prophylaxis [32].

After a first episode of deep vein thrombosis and/or pulmonary embolism associated with a reversible risk factor, it is recommended that the patient undergo anticoagulation therapy for at least 3 months, which may continue throughout life in case of recurrence [10, 32].

The initial treatment of venous thromboembolism is direct oral anticoagulation, although not all patient groups are suitable for this therapy, such as patients with antiphospholipid syndrome or extreme bodyweight. LMWH should be given before dabigatran and edoxaban [10, 32].

If treatment with direct oral anticoagulants is not possible, it is recommended to start warfarin therapy concomitantly with LMWH or fondaparinux for at least 5 days, monitoring INR, which should be in the range of 2.0–3.0 [33].

### 3.3 Factors C and S

The conclusion from the analysis of patients with factor C and S deficiency is limited by the lack of sufficient data to make specific recommendations, but it is safe to approach these patients from the point of view of venous thromboembolism management [10, 29].

Treatment of the first episode of venous thromboembolism should consist of unfractionated or LMWH for at least 5 days followed by vitamin k antagonists or DOAC for at least 3–6 months. In the presence of other clotting disorders or risk factors for thrombosis, or if the first episode was life-threatening or occurred in multiple sites, anticoagulation may be prolonged indefinitely [13].

### 3.4 Antiphospholipid syndrome

Primary prophylaxis with anticoagulant medication has not been shown to be beneficial for asymptomatic patients with no other risk factors, regardless of risk profile. Instead, some authors suggest daily administration of a low dose of aspirin, but this measure is not widely accepted. If other risk factors for thrombosis are associated, such as hospitalization, surgery, or concomitant autoimmune disease, prophylaxis is recommended, on a case-by-case basis [16, 34].

Secondary prophylaxis is recommended for patients with definite antiphospholipid syndrome and consists of lifelong vitamin K antagonist medication with a target INR of 2–3. In case of relapse or episodes of arterial thrombosis, the target INR should be >3. Combination with aspirin is not supported by data and is subject to controversy [16, 35].

The use of DOAC in patients with the definite antiphospholipid syndrome is not recommended, following the results of several studies that found direct oral anticoagulation to have a lower efficacy and safety profile than traditional vitamin K antagonist therapy [36].

### 3.5 Malignant conditions

Primary thromboprophylaxis of ambulatory cancer patients should be decided according to the individual risk of bleeding, the type of cancer, or the stage of the disease [37]. For hospitalized patients without acute venous thromboembolism or a

history of venous thromboembolism, the American Society of Hematology recommends thromboprophylaxis with low molecular weight heparin, but only for the duration of the hospital stay. If during hospitalization a patient has undergone surgery or if a patient is receiving outpatient systemic chemotherapy and is at high risk of thrombosis, continued administration of LMWH has been shown to be beneficial. Oral anticoagulation, in the form of vitamin K antagonists or DOAC, is not included in current guidelines because there is insufficient data on its efficacy [38].

For a patient with active cancer who develops venous thromboembolism, initial treatment can be with either LMWH or DOAC, the latter being the medication of choice. It is recommended to continue treatment for at least 3–6 months, which may be extended as a secondary prophylactic measure in patients with active cancer and/or recurrence of venous thromboembolism. Direct oral anticoagulation remains the first choice of treatment in this case as well [38].

In a cancer patient with visceral or splanchnic venous thrombosis, according to the guidelines, treatment should consist of short-term anticoagulation (3–6 months) or clinical observation [38].

### 3.6 Pregnancy

Despite the prothrombotic status of physiological changes occurring during pregnancy, prophylactic anticoagulation of asymptomatic patients with no history of venous thromboembolism should be judged on a case-by-case basis [21, 39].

Anticoagulation for a venous thromboembolism event should be with LMWH if occurring before the 36th week of pregnancy and should be switched to unfractionated heparin afterward to minimize complications of epidural anesthesia. Vitamin K antagonists are not recommended after the first trimester as they are known to cause "warfarin embryopathy." Direct oral anticoagulation is also not approved for administration during pregnancy [21, 40].

Following an episode of venous thromboembolism, anticoagulation should be continued for 3–6 months, or 4–6 weeks postpartum, with either low molecular dose heparin or unfractionated heparin [21].

Patients with antiphospholipid syndrome and a history of thrombotic complications during previous pregnancies may benefit from prophylactic anticoagulation during pregnancy and for an additional 6 weeks postpartum [34].

### 3.7 SARS-CoV-2

Anticoagulation management of patients with Covid-19 depends on the severity of the disease. The administration of unfractionated heparin to patients hospitalized in an uncritical state has been observed to reduce the need for intensive care maneuvers, such as specific organ support or intubation, and also reduces the death rate. On the other hand, the condition of critically ill patients has not been improved by heparin treatment, and heparin treatment actually increases the rate of complications and is subsequently not recommended.[41].

After discharge, patients with high thrombotic risk and a low bleeding risk could benefit from low-dose rivaroxaban treatment for an optimal duration to be determined [41].

## 4. Discussion/conclusion

A hypercoagulable state increases the patient's risk of developing arterial or venous thrombosis with subsequent complications. Venous thromboembolism is much more common, places a greater financial burden on health systems and therefore more data are available for its management.

Venous thromboembolism is now considered a multifaceted condition, usually resulting from the interaction of inherited and acquired risk factors, with different penetration in the general population and also with distinct risk profiles.

In terms of treatment, primary anticoagulant prophylaxis is recommended only for selected cases, while most patients require no treatment other than minimization of modifiable risk factors.

For the treatment of a first thrombotic event, secondary prophylaxis or relapse, anticoagulation is recommended. Although most episodes of a first thrombosis episode, especially when transient risk factors are identified, require short-term anticoagulation (3–6 months), there are cases where long-term (>6 months) or even indefinite anticoagulation may be given.

When choosing appropriate therapy, a large number of factors must be weighed, such as patient education, preference, and compliance for certain drugs, their availability for long-term follow-up, the financial burden of some therapies, or quality of life, for example when choosing between parenteral and oral treatment.

For patients with venous thromboembolism, the modern approved and guideline-supported treatment is DOAC, with superior efficacy and safety, and quality of life profiles compared to traditional vitamin K antagonist therapy. However, a limitation of DOAC is for the treatment of patients with high-risk antiphospholipid syndrome, where, in a recent study, DOAC showed no efficacy benefit but a higher risk compared to warfarin treatment.

Even though DOAC is finding an increasing number of indications, further research is needed to fully understand what is the best drug choice for each patient, for each condition, for the dose needed, for the duration of treatment, and for follow-up.

In conclusion, hypercoagulable conditions develop as a result of numerous individual or coexisting genetic or acquired risk factors that may be present and induce a higher risk for the patient to develop thrombotic complications. To prevent them, asymptomatic patients may have to undergo anticoagulant treatment in selected cases. For initial treatment and prevention of relapses, the modern and most recommended treatment is with direct anticoagulants, except for patients with high-risk antiphospholipid syndrome.

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## Author details

Iris Bararu Bojan, Stefan Dobreanu*, Oana Viola Badulescu, Maria Cristina Vladeanu, Andrei Bojan, Carmen Elena Plesoianu and Manuela Ciocoiu
Department of Internal Medicine, University of Medicine and Pharmacy "Grigore T. Popa" Iasi, Romania

*Address all correspondence to: stefan.dobreanu@yahoo.com

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