**Thrombotic events in autoimmune rheumatological diseases**

# **Abstract**

Active inflammation is a prothrombotic state characterized by the activation of procoagulant mechanisms and endothelial cells. In fact, the correlation between antiphospholipid antibodies in systemic lupus erythematosus and the predisposition to venous and arterial thrombosis is known. It thus appears that thrombotic events are associated with disease activity and/or inflammation in many of the inflammatory rheumatic diseases. The present study is a review where we look for main pathogenetic features and clinical aspects of thrombosis in autoimmune rheumatic diseases, systemic lupus erythematosus, rheumatoid arthritis, vasculitis, Sjogren's syndrome and dermatomyositis/polymyositis, highlighting also the appropriate therapeutic approaches in each case. It therefore appears that autoimmune rheumatological diseases are associated with an increased thrombotic risk and predisposition to arterial and venous thrombosis, greater than the general population.

Key words: thrombosis, thrombotic events, arterial and venous thrombosis, autoimmune diseases, rheumatological, systematic erythematosus lupus, rheumatoid arthritis, vasculitis, Sjögren's syndrome (pSS)

### **INTRODUCTION**

### **Mechanisms linking inflammation and venous thrombosis.**

### Thrombosis is a multifactorial disease resulting from the confluence of inherited, acquired, and environmental risk factors. These factors may contribute to a part of Virchow's triad, which is used to explain the pathophysiology of venous thrombosis. This triad consists of impaired blood flow (stasis), hypercoagulability of blood components, and damage to the inner wall of blood vessels (endothelial damage). 1 Inflammation is a key feature of systemic autoimmune diseases. Many studies have been conducted to establish the relationship between inflammation and the hypercoagulable state or between inflammation and endothelial dysfunction.

### There are three main natural anticoagulation mechanisms, including the tissue factor inhibitor (TFPI), the heparin-antithrombin III pathway, and the protein C anticoagulant pathway. 2

### These mechanisms exert a strong anticoagulant effect during physiological conditions. However, inflammation can disrupt this balance and induce a predisposing state for thrombosis through several different mechanisms.

### **Tissue factor (TF)**

### Tissue factor (TF) is a glycoprotein found inside cells that express tissue factor (stromal fibroblasts and leukocytes) and is responsible for initiating the extrinsic coagulation pathway. It is expressed in cells such as monocytes, endothelial cells and arterial smooth muscle cells. Exposed TF forms a complex with factor VIIa on a phospholipid surface and further activates the coagulation pathway. TFPI (tissue factor inhibitor) specifically inhibits factor VIIa complex and TF (TF-FVIIa).

###  **Fibrinolysis**

### Another important pathway linking inflammation and coagulation is the fibrinolytic system. Plasminogen is converted to plasmin by tissue-type plasminogen activator (t-PA) or urokinase-type plasminogen activator (u-PA), both of which are regulated by plasminogen activator inhibitor-1 (PAI-1). Plasmin degrades fibrin into soluble fibrin degradation products (FDP). This process is regulated by α2-antiplasminogen. Thrombin activates thrombin-activatable inhibitor of fibrinolysis, which inhibits fibrinolysis. 3

### **Tumor necrosis factor (TNF-α)**

### Active inflammation is a prothrombotic state characterized by upregulation of tumor necrosis factor α (TNF-α) and endothelial cell activation. Upregulation of TNF-α is thought to increase serum tissue factor, a natural procoagulant mechanism. Also, endothelial cell activation promotes platelet activation, which is important for thrombus formation. 4 In patients with rheumatoid arthritis and ankylosing spondylitis, inhibition of TNF-α decreased PAI-1 and decreased the PAI-1/t-PA ratio. This means that TNF-α is probably involved in inhibiting the fibrinolytic system among patients with chronic rheumatic diseases.

### TNF-α receptor (TNFR) subtypes may play an important role in thrombogenesis. TNFR1 is ubiquitously expressed, but TNFR2 is predominantly expressed in immune and endothelial cells. In a mouse study, the time to complete thrombotic arterial occlusion followed by vessel wall injury was accelerated in TNFR1-deficient mice but not in TNFR2-deficient or TNFR1/TNFR2-deficient mice when TNF-α was administered. This suggests that a TNF-α-induced hypercoagulable state requires the presence of TNFR2. 5

### As mentioned there is an association between TNF-α inhibitors and thrombosis. TNF-α is an inflammatory cytokine involved in the pathogenesis of various inflammatory conditions. Although the exact relationship between TNF-α and thrombosis has not been fully elucidated, there are reports indicating that TNF-α inhibitors may increase the risk of thrombosis in some patients. In addition, the lupus-like syndrome associated with TNF-α inhibitors is reported as an emerging pathological condition. This syndrome shares some symptoms with SLE. Patients receiving TNF-α inhibitors have reported the development of autoantibodies, such as antinuclear antibodies, anti-double-stranded DNA antibodies, and antiphospholipid antibodies. In addition, clinical cases of thrombosis associated with the use of TNF-α inhibitors and the presence of antiphospholipid antibodies have been reported.

**The main rheumatological diseases where we will look for the existence of thrombotic phenomena are:**

##  **Systemic lupus erythematosus (SLE)**

Systemic lupus erythematosus (SLE) is an autoimmune inflammatory disease in which pathogenic autoantibodies and immune complexes are formed that cause multiple organ and tissue damage. The global incidence rate of SLE ranges from 1.5 to 11 per 100,000 person-years, while the prevalence ranges from 13 to 7,713.5 per 100,000 person-years. 6

Smoking, age, disease activity, the presence of lupus anticoagulant and the dose of glucocorticoids during the therapeutic approach are risk factors for the occurrence of venous thromboembolic disease (VTED) in patients with SLE, while diabetes mellitus, hypertension, dyslipidemia, nephrotic syndrome, and chronic tissue damage are more associated with arterial thrombosis. 7 In a prospective study involving 219 patients lasting five years, 16% experienced a thrombotic event during the study period. 3.5% had arterial thrombosis and 12.5% had STD. 8

Arterial and venous thrombosis are a well-known clinic manifestation in patients with SLE.The prevalence ranges >10% and it may even exceed 50% in patients with additional factors risk of thrombosis. 9

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##  **The antiphospholipid syndrome (APS)**

Antiphospholipid syndrome is the most common form of acquired thrombophilia and is caused by autoantibodies directed against plasma proteins that bind to negatively charged phospholipid surfaces. These are anti-cardiolipin (ACA), lupus anticoagulant (LAC) and anti-β2-glycoprotein I (anti-ß2-GPI) and lupus anticoagulant (LA). 10 Thrombosis can be located in arteries, veins or small vessels but more frequent are deep vein thrombosis of the lower extremities and thrombosis of intracranial vessels 

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**Diagnostic criteria**

Diagnostic criteria require the presence of one or more of the following antibodies: lupus anticoagulant (LA), anti-β2-glycoprotein IgG or IgM, and anti-cardiolipin IgG or IgM. Antibodies should remain positive on two or more measurements at least 12 weeks apart. In addition, the presence of at least one clinical criterion is required, i.e. confirmed thrombosis or obstetric complication, which include three or more spontaneous abortions at a gestational age of less than 10 weeks, one or more fetal deaths at a gestational age of more than 10 weeks, premature birth <34th week of gestation due in eclampsia, pre-eclampsia and other placental disorders. 11

###  **Therapeutic approach**

The therapeutic approach is shown in the table below in established venous thrombosis. After venous thrombosis, i.e. for secondary prevention, vitamin K antagonists (e.g. Sintrom) are the drug of choice, aiming for an INR of 2-3. Treatment should be initiated at the first episode of venous thrombosis. Prophylactic low-dose aspirin is recommended in: asymptomatic with positive antiphospholipid antibodies, in SLE patients without a history of thrombosis, and in non-pregnant women with a history of obstetric APS, provided that in each case there is an increased thrombotic risk. Newer anticoagulants are still being studied for APS. In patients with a history of obstetric APS, a combination of low-dose aspirin and prophylactic heparin is recommended during pregnancy. In cases with recurrent obstetric complications, options include increasing heparin to a therapeutic dose, adding hydroxychloroquine, or adding low-dose cortisone for the first 3 months. 12



Εικόνα 1 Recommendations for the management of antithrombotic prophylaxis and therapy in the antiphospholipid syndrome.2019 EULAR; 2020 BSH; 16th International Congress on Antiphospholipid Antibodies Task Force Report on Antiphospholipid Syndrome Treatment Trends).

## **Rheumatoid arthritis**

## Rheumatoid arthritis (RA) is one of the most common chronic inflammatory diseases and its prevalence is influenced by both gender and age. The prevalence of RA is estimated between 0.5% and 1.0% in developed countries. The etiology of RA is unknown and the pathogenesis is complex, involving genetic, environmental and immunological factors. Inflammation and autoimmunity cause tissue damage (cartilage destruction, bone erosion) and systemic inflammatory response. More generally, it leads to continued functional decline and disability due to the changes in the cartilage, bones and joints. Treatments that target inflammation can prevent damage or disease progression, and physical function can improve without further sequelae. As an inflammatory disease, it promotes a hypercoagulable state that increases the risk of deep vein thrombosis (DVT) and pulmonary embolism (PE). Similarly, the mortality associated with RA is due to an increased risk of thrombotic disease and more generally of thrombotic events, including cardiovascular events and venous thromboembolism (VTE). 13

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## **Vasculitis**

###  **Behçet's syndrome (BS)**

### Behçet's syndrome (BS) is a systemic inflammatory vasculitis of unknown etiology. Despite considerable clinical polymorphism, it is particularly characterized by an association of recurrent oral and genital ulcers and ocular inflammation. Skin and joint manifestations are often reported. Involvement of the central nervous system, gastrointestinal tract, and blood vessels is less common but contributes to disease severity. BS is generally characterized by recurrent acute inflammatory attacks with a tendency to be more active and severe during the first five years of progression. 14 The pathogenesis of thrombosis in Behçet syndrome (BS) is not widely studied but nevertheless the systemic inflammatory reaction seems to play an important role as a generalized disturbance of immune CD4+ lymphocytes, monocytes, neutrophils and the increased production of pro-inflammatory cytokines associated with Th1 cells response, promote thrombotic events in BS. 15 At the same time, endothelial dysfunction, resulting from immune and inflammatory factors, appears to be a characteristic of BS and plays an important role in the manifestation of thrombotic manifestations.

## Thrombosis is the most common vascular manifestation in patients with BS, its prevalence ranging from 14% to 39%, and venous involvement is characteristically more common, accounting for 75% of all vascular complications, while arterial involvement is present in 1 to 7 % of patients with BS. 15

### **ANCA vasculitis**

## Vasculitis associated with ANCA autoantibodies are systemic necrotizing vasculitis with a preference for small vessels and include Wegener's granulomatosis, Churg-Strauss vasculitis, and microscopic polyangiitis. ANCA vasculitis is accompanied by cANCA against proteinase-3 (PR3) or pANCA against myeloperoxidase (MPO) which have a high specificity for these vasculitis. 15 They concern people of both sexes with a greater incidence at the ages of 65-75. The most frequently affected organs are the upper and lower respiratory tract, kidneys, skin, eyes and peripheral nerves. They are characterized by a high rate of recurrence even after achieving complete remission. The prognosis is mainly determined by the age of the patient and the presence or absence of renal involvement. 16

## Evidence has emerged to support an increased incidence of venous thrombotic events in ANCA vasculitis with an increased incidence of thromboembolism. 15 At the same time, arterial events have also been observed with cardiovascular events. Both endothelial cell dysfunction via the interaction between neutrophils (activated by TNFα and ANCA) and endothelial cells is implicated in this, with subsequent massive oxidative stress ultimately leading to atherothrombotic complications.

### **Large vessel vasculitis (LVV)**

## Large vessel vasculitis (LVV) commonly includes giant cell arteritis (GCA) and Takayasu arteritis (TA). The histopathological features of these two entities are similar, while they differ substantially in the age range of affected patients, since TA usually affects young women and GCA predominates in the elderly.

## Most interestingly, one of the possible vascular complications is the development of aneurysms as a consequence of inflammatory damage. Remodeling of the vascular wall begins in the extra layer, with an infiltrate consisting mainly of Th1/Th17 lymphocytes activated by resident dendritic cells and macrophages that produce proinflammatory cytokines such as IL1β and IL6. Macrophages of the outer and middle layers are responsible for the production of growth factors, such as platelet-derived growth factor and VEGF, which cause intimal hyperplasia. 15

## **Polymyositis and Dermatomyositis (PM/DM)**

Polymyositis and dermatomyositis (PM/DM) are the main inflammatory myositis in adults, characterized by chronic muscle inflammation/weakness. PM/DM, known as inflammatory myositis idiopathic, is a chronic inflammatory disorder that affects the muscles, skin, joints, esophagus, lungs, and heart. The prognosis of PM/DM is extremely poor, with a mortality rate as high as 50%–61%. Patients with PM/DM have a reduced quality of life and are at increased risk for several comorbidities, such as osteoporosis and cardiovascular disease.

In recent years, the risk of venous thromboembolism associated with PM/DM has attracted attention. VTE appears to be associated with disease activity in many of the inflammatory rheumatic diseases, including PM/DM, i.e. in the acute phase of the disease where the inflammatory background is most pronounced and most thrombotic events are observed. 17

## **Sjögren's syndrome (pSS)**

Sjögren's syndrome (pSS) is an inflammatory autoimmune disease characterized by lymphocytic infiltration of the exocrine glands and subsequent gland dysfunction, with characteristic periepithelial lymphocytic infiltration mainly by T and B lymphocytes of the exocrine glands. Dysfunction of the lacrimal and salivary glands causes dry eyes and dry mouth, respectively, and is the hallmark of pSS. pSS occurs both in isolation and as a secondary entity in the context of other established autoimmune diseases, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) or systemic sclerosis (SSc). 18

#  **Method**

Purpose of Review

The aim of this review is to search for the clinical aspects of thrombosis in autoimmune rheumatic diseases, highlighting the possible pathogenic mechanisms, frequency of thrombotic events and the appropriate therapeutic approaches in each case.

 Search Strategy

We performed a literature search of English-language publications related to thrombotic phenomena in patients with inflammatory arthritis, vasculitis such as Behçet's, ANCA or giant cell, Sjögren's syndrome, inflammatory myositis and dermatomyositis. The PubMed database was searched from 2000 to April 2023. All studies that included thrombosis in the context of autoimmune rheumatic diseases were collected. The terms were used as keywords in English “thrombosis OR (thrombotic events) AND (autoimmune diseases)”, “thrombosis AND (rheumatological diseases)”, “(arterial and venous thrombosis) AND (rheumatological diseases)”, “ thrombosis AND (systematic erythematosus disease)”, “thrombosis AND lupus”, “thrombosis AND (rheumatoid arthritis)”, “thrombosis AND (Sjogren syndrome)”, “thrombosis AND polymyositis”, “dermatomyositis AND thrombosis”,” PE AND (systematic erythematosus disease)”, “PE AND lupus”, “PE AND (rheumatoid arthritis)” , “PE AND (Sjogren syndrome)” , “PE AND polymyositis” , “PE AND dermatomyositis” , “VTE AND (systematic erythematosus disease)”, “VTE AND lupus”, “VTE AND (rheumatoid arthritis)” , “VTE AND (Sjogren syndrome)”, “VTE AND polymyositis” , “VTE AND dermatomyositis”, “DVT AND (systematic erythematosus disease”, “DVT AND lupus” , “DVT AND (rheumatoid arthritis)”, “DVT AND (Sjogren syndrome)”, “DVT AND polymyositis’, ‘DVT AND dermatomyositis”, “thrombosis in vasculitis”, ‘thrombosis AND vasculitis’, “Behçet".

## Inclusion criteria

##  Inclusion criteria included articles published in English regarding thrombotic phenomena in adult patients with the aforementioned rheumatological diseases. Exclusion criteria included articles dealing with pregnancy-related thrombotic phenomena and postoperative outcomes. Articles published in the English language were selected, with particular emphasis on review articles, clinical patient studies and published patient series with a review of the relevant literature. After reviewing the abstracts of a significant number of articles, the most representative ones were selected.

##  Description of studies

## Data from each study were extracted by one investigator. The following information was systematically extracted: first author, year of publication, country where the study took place, total number of patients included (cases and controls), total number of thrombotic events observed in each rheumatological disease examined, and total number of control patient population where available. Some studies included multiple patient populations with various rheumatic diseases. Therefore, data for each disease were extracted from these articles and analyzed separately.

# **Results**

##  **Systemic lupus erythematosus (SLE)**

### Thrombosis in SLE

Arterial and venous thrombosis are a well-known clinical entity in SLE, with a prevalence of >10%. This prevalence may even exceed 50% in high-risk patients. 9 A 30-year study of patients with SLE found that 20% of patients experienced thrombotic events during disease progression (20.3% 49 thrombotic events, relative risk 9.6 (95% CI 4.1-27.4, p<0.0001)). 19 The incidence of thrombosis tends to increase in the first year. Possible reasons for this early higher incidence of thrombosis could be high levels of disease activity and circulating immune complexes, cytotoxic antibodies, or a more general inflammatory state. In a 10-year prospective study of patients with SLE, the most common causes of death found were active SLE (26.5%), thrombosis (26.5%), and infection (25%), with thrombosis second most frequently. 5-year follow-up period of the disease. (20) The study by Bello et al. showed that patients with SLE have a statistically significantly increased risk of deep vein thrombosis compared to the general population (RR 4.38). In fact, VTE cases concern younger patients than the general population, and the frequency of episodes is even higher in positive antiphospholipid antibodies. (APLAs) 21

### Thrombosis risk factors in SLE

Below are risk factors for thrombosis in SLE, antiphospholipid antibodies, inflammatory disease activity, and other thrombophilic factors.

### Antiphospholipid antibodies (APLAs)

30% of SLE cases have positive antiphospholipid antibodies. 7 Antiphospholipid antibodies (APLAs) bind to plasma proteins with affinity for surface phospholipids. The most important recognized antigens are β2-glycoprotein and prothrombin. Anti-cardiolipin antibodies (ACA), lupus anticoagulant (LAC), and anti-β2-glycoprotein I (anti-ß2-GPI) have been confirmed to increase the risk of thrombosis from the very first studies in SLE. 22 In Bello's study, the incidence of thromboembolic events in SLE patients with positive antiphospholipid antibodies was estimated to be 0.13 (n/N, 95% CI 0.07–0.21) and in SLE patients without positive APLAs was 0. .07 (n/N, 95% CI 0.04– 0.10). 22 Antiphospholipid antibodies may be transiently positive. 50% of patients with SLE show positive antiphospholipid antibodies. To be considered significant, they should be persistently positive on at least two occasions, 12 weeks apart. Not all patients with APLA develop thrombosis which could be explained by different phospholipids or different binding proteins. Several hypotheses have been proposed to explain the pathogenic effects of these autoantibodies and their role in the development of thrombosis. They attach to the negatively charged surface of phospholipids which can cause platelet activation, interfere with coagulation inhibitors such as protein C, inhibit antithrombin and fibrinolysis, and then initiate thrombus formation. In fact, they are related to both arterial and venous thrombosis. However, about 40% of adults with SLE who are not positive for antiphospholipid antibodies may develop thrombosis, which means that other clotting factors, such as homocysteine levels, protein C and S, anti-neutrophil antibodies (ANCA) , and neutrophil intracellular traps (NETs) play an important role in the manifestation of thrombosis. 20

The prevalence of lupus anticoagulant (LAC) and anticardiolipin antibody (ACA) titers for SLE is 28 and 42%, respectively. Of the above patients, 42% of lupus anticoagulant-positive patients and 40% of anti-cardiolipin antibody-positive subjects had a history of thrombosis. In contrast, the prevalence of thrombosis in patients without anticardiolipin antibodies or lupus anticoagulant is only 10–18%. 20

### Inflammatory disease activity - coagulation activation

Inflammation has been shown to induce the expression of tissue factors, an important step in the initiation of coagulation. So vasculitis mediated by immune complexes and chronic destruction of the vessels is caused. Consequently, inflammation of the endothelial cells leads to thrombosis. 20The deposition of immune complexes on the vascular endothelium can lead to increased surface factor expression, increased thrombocyte, and activation of plasminogen inhibitor I. Thus, activation of the coagulation pathway is consequential. If vessel damage is present, vasoconstriction occurs as a critical initial response, causing a reduction in vessel diameter and slowing the flow of a blood, which is the hemodynamic basis for subsequent hypercoagulable processes. Circulating blood cells and endothelial cells lining blood vessels generally do not express TF and are exposed to the blood after vascular injury. (promoter of the extrinsic coagulation pathway) At the same time, when the endothelium is damaged, the underlying collagen is exposed to circulating platelets, which activate the intrinsic coagulation pathway. Circulating platelets adhere directly to collagen via glycoprotein (GP) Ia/IIa surface receptors. This adhesion is further enhanced by von Willebrand factor (vWF) released by vascular endothelial cells and platelets. These interactions also activate platelets. Activated platelets release ADP, serotonin, platelet-activating factor (PAF), vWF, and thromboxane A2 (TXA2) into the plasma, which then activates additional platelets. Fibrinogen binds to GP IIb/IIIa, which contributes to the aggregation of adjacent platelets, increasing the risk of thrombosis. 7

### NETs

Activated neutrophils may release Neutrophil Extracellular Traps (NETs) during a distinct form of cell death, termed NETosis. NETs are rich in bioactive molecules that promote thrombosis (including atherothrombosis), inflammation and fibrosis. Thus, although neutrophils may not be present in chronic inflammatory lesions, their remnants may enhance the inflammatory response beyond their short lifetime in tissues.23 Neutrophils can cause pathological venous and arterial thrombosis or “immunothrombosis” by releasing NETs, which are networks of chromatin fibers released during neutrophil necrosis. NETs include histones, antimicrobial peptides, and oxidative enzymes such as neutrophil elastase and myeloperoxidase (MPO). 7 NETs trap erythrocytes and platelets and bind fibrinogen, fibronectin, von Willebrand factor, and tissue factor, promoting thrombus formation and stabilization. (23) Therefore, intervening NETs could be a potential target for anticoagulant therapy.

### Anti-endothelial cell antibodies (AECA) and anti-neutrophil antibodies (ANCA)

AECAs are antibodies, parts of immunoglobulin A, G or M and bind to antigens through the F (ab) domain. AECA is a heterogeneous group of autoantibodies that can react with different antigenic structures associated with endothelial cells, such as heparin-like compounds, DNA and DNA-histone complexes, ribosomal proteins PO and L6, elongation factor 1a, fibronectin and β2. -glycoprotein I, thereby promoting the production of tissue factor (TF) and leading to vascular damage. The presence of AECA has been associated with renal involvement, vascular lesions, pulmonary hypertension, anticardiolipin antibodies, and thrombosis in lupus. 7

Antineutrophil cytoplasmic autoantibodies (ANCA) are a class of autoantibodies responsible for causing systemic vascular inflammation by binding to target antigens on neutrophils. Several studies have shown that ANCA can activate neutrophils that adhere to the endothelium of blood vessels and release reactive oxygen species (ROS), nitric oxide, inflammatory cytokines (TNF-α, IL-1β, IL-8 and IL-12) . , toxic substances (serine proteases) and NETs, which result in vascular endothelial injury in small blood vessels and thus activate the coagulation pathway. 7,16



Figure 1When endothelial cells are destroyed by autoantibodies (ANCA, AECA, APL) and neutrophil extracellular traps, collagen and TF are exposed in the circulating blood, activating the coagulation cascade. Circulating platelets adhere directly to collagen via glycoprotein Ia/IIa surface receptors. This adhesion is further enhanced by the release of von Willebrand factor (vWF) from damaged vascular endothelium and activated platelets. These interactions further activate platelets, ultimately leading to increased platelet aggregation and thrombosis. 2022 Jun 27. doi: 10.1155/2022/3208037

### Protein C and S

 Protein C, protein S, and antithrombin deficiencies are rare but carry a higher risk of venous thrombosis. 20 Disorders of the protein C pathway in SLE have received much attention in recent years. Antithrombomodulin antibodies interfere with activated protein C (APC) and antiphospholipid antibodies (APLA) interfere with the protein C pathway, leading to an increased risk of thrombosis.24 Lupus anticoagulant also increases APC resistance. Activated protein C (APC-R) resistance is defined as a reduced anticoagulant response in the protein C pathway. Hereditary APC-R caused by the factor V Leiden mutation is strongly associated with an increased risk of venous thrombosis (VTE). Although APC resistance increases the risk of venous thrombosis, it remains unclear whether it increases the risk of arterial thrombosis.7

### Homocysteine levels

Plasma homocysteine level is an independent risk factor for atherosclerosis, arterial thrombosis and possibly venous thrombosis. Elevated plasma homocysteine levels may occur as a result of vitamin B12 or B6 or folate deficiency, chronic renal failure, hypothyroidism, certain malignancies, medications, and inherited enzyme abnormalities. The prothrombotic activities may be attributed either to a direct toxic effect on the endothelium or to indirect effects. Hyperhomocysteinemia is detected in approximately 15% of lupus patients. The prevalence of hyperhomocysteinemia is significantly higher in SLE patients with thrombosis. Elevated homocysteine levels are demonstrated in 27.3% of SLE patients with thrombosis compared with 16.9% of those without thrombosis.20

### Treatment strategies for thrombosis in SLE

In recent decades, the treatment of SLE has shifted from the use of hydroxychloroquine (HCQ), glucocorticosteroids and conventional immunosuppressive drugs to biologic agents, among which belimumab is the first and only biologic agent approved for the treatment of SLE to date. Due to the application of biological agents, the prognosis of patients with SLE has improved significantly. However, as patient survival has increased, the incidence of complications such as thrombosis has increased.7 Treatment strategies focus primarily on controlling disease activity while minimizing the accumulation of damage associated with active disease and drug-related adverse effects. Anticoagulants are used to treat thrombotic episodes. Concomitant initiation of heparin (either intravenous or subcutaneous) is recommended, and oral anticoagulants are indicated to be started at the same time. 20 Heparin administration is usually continued for 3-5 days to achieve the corresponding therapeutic INR range. If intravenous heparin is used, the APTT is used to monitor the response to establish effective heparinization. However, the APTT may be prolonged in the presence of lupus anticoagulant (LAC) in the blood. Duration of treatment can be determined by the presence of APLA, site of thrombosis, recurrence, and presence of precipitating factors. Derksen's study concluded that the probability of no recurrence in patients taking oral anticoagulants at eight years was 100%, whereas in patients who discontinued anticoagulants, the recurrence rate was 50% at 2 years and 78% at 8 years of follow-up. 7

## **The antiphospholipid syndrome (APS)**

###  Incidence of thrombosis

The exact incidence of antiphospholipid syndrome in the general population is not known. The prevalence of the syndrome is 40-50 cases per 100,000 people. The presence of antiphospholipid antibodies in the general population varies between 1-5%. However, only a minority of individuals with positive antiphospholipid antibodies will develop clinical manifestations of the syndrome. The clinical significance of the presence of antiphospholipid antibodies in the younger population, who have not developed vascular manifestations, is not known.

 In systemic lupus erythematosus, antiphospholipid antibodies (aPL) are frequently detected, with at least one antiphospholipid antibody (aPL) test positive in more than 30% of patients.25

### Thrombotic manifestations

 Venous thrombosis is more common than arterial thrombosis. Arterial thrombosis mainly involves the CNS with manifestations of cerebrovascular events. Thrombosis can occur in any organ, be deep or superficial, affect the upper or lower limbs, the lungs or be located in unusual places (intra-abdominal, etc.).

Thrombotic episodes in antiphospholipid syndrome are recurrent, and recurrences usually have the same distribution as the initial episode. So patients with venous thrombosisthrombosis have recurrences from the venous system, while patients with arterial thrombosis have recurrences from the arterial circulation system. The heterogeneity in the clinical expression of the syndrome is due to a combination of vaso-occlusive events, characterized by pulmonary embolism, cerebrovascular strokes and deep vein thrombosis, even events from different organs were observed in the same patient, with the time window between the events varying from weeks to months or even years.26

### Therapeutic approach

The therapeutic approach is based on coumarins, where they remain the basis of treatment and secondary prevention. The benefit emerges in patients where the drop in INR leads to recurrence of symptoms or recurrence of thrombosis. In pregnancy, the official therapeutic strategy requires the administration of heparin and aspirin. Current evidence and guidelines condemn the use of DOACs in patients with APS. On the other hand, in APS patients with VTE and single or double autoantibody positivity, DOACs may be considered on an individual basis. Although current evidence is insufficient to make recommendations, if the choice of anticoagulant falls within a DOAC, dabigatran may be preferred over the other anti-factor Xa DOAC.27

## **Rheumatoid Arthritis (RA)**

### Risk of VTE in rheumatoid arthritis

A Swedish prospective nationwide follow-up study showed that Swedish patients with RA had an increased risk of deep vein thrombosis (VTE), which was consistently elevated for the first 10 years after diagnosis. The incidence rate of pulmonary embolism (PE) appears to be 6.38 within the first year after diagnosis and 1.53 within the first 1–5 years of follow-up, decreasing to 1.15 after 5 years. In fact, the risk of thromboembolism was found to be significantly increased in hospitalized RA patients compared to healthy controls (relative risk = 2.25) and appears to be independent of classic risk factors for venous thromboembolic disease.28

### Pathophysiological mechanisms

RA results in the generation of autoreactive T and B cells leading to immunosuppression. The presence of autoantibodies against citrullinated peptides and against immunoglobulin G (rheumatoid factor) leads to the formation of immune complexes and abundant complement activation. A key inflammatory cascade is the overproduction of TNF and interleukin (IL)-6. Cataracts create excess fibrin, and the typical disease processes are due to the interaction of fibrin thrombi with the endothelial cells of the vessels. The etiology of thrombotic propensity in RA is still unclear due to various mechanisms and causative factors.13

The factors responsible for the thrombotic tendency of rheumatoid arthritis are presented below.

1.1.2.1 Endothelial damage

 Recent studies have shown that the disruption of endothelial function in the early stages of the disease due to inflammation leads to endothelial cell activation, altered endothelial permeability and increased leukocyte and platelet adhesion, which predisposes to thrombosis. Endothelial dysfunction is associated with inflammation, as endothelial-derived coagulation factors von Willebrand Factor and PAI-1 are increased, and may play an important role in both the course of RA and thrombosis.29 During the inflammation process, monocytes express transcellular adhesion molecules, which are induced by proinflammatory cytokines such as IL-1β, TNF-α, and C-reactive protein (CRP). Endothelial dysfunction not only leads to venous thrombosis, it also promotes atherosclerosis and predisposes to arterial clots.30 Endothelial dysfunction not only leads to venous thrombosis, but also affects arteries by accelerating atherosclerosis and promoting arterial thrombosis as well. 13

1.1.2.2 Hypercoagulability and inhibition of fibrinolysis

Inflammation modulates thrombotic responses by reducing anticoagulants and suppressing fibrinolysis.30 Natural anticoagulants reduce the thrombotic response but may be suppressed by inflammatory mediators. A transmembrane glycoprotein synthesized by vascular endothelial cells and distributed on the endothelial cell surface is thrombomodulin that binds to thrombin and activates protein C. Prothrombotic activities are thought to exert a toxic effect on the endothelium and lead to decreased expression of thrombomodulin. Therefore, the protein C pathway is considered a major target. TNF-α factor specifically decreases thrombomodulin and the endothelial cell protein C receptor, both of which are needed for optimal activation of protein C. Therefore, activated protein C and thus protein S, the other natural anticoagulant, are reduced. increasing the risk of VTE.13

 Thrombin-activated fibrinolysis inhibitor (TAFI) is a proenzyme that activates the fibrinolytic system after activation by factors such as thrombin/plasmin and thrombomodulin. TAFI has been found to be elevated in RA patients compared to controls, particularly in patients with active inflammation. Therefore, a higher TAFI titer may cause a hypercoagulable state leading to VTE.29

1.1.2.3 Viscosity and vascular stasis

Plasma hyperviscosity, which occurs during active joint disease (acute inflammation), is a major predisposing factor for VTE. Similarly, impaired venous blood flow and stasis caused by immobility during critically active disease also predispose to VTE.13 In addition, coagulation factor VIII, fibrinogen, and von Willebrand factor are significantly elevated in inflammatory rheumatic diseases and are known to increase plasma viscosity, which is a risk factor for thrombosis.29

Therefore, plasma hyperviscosity and venous stasis in RA patients during acute inflammation are important factors influencing formation of Virchow's triad, leading to thrombus formation.13 At the same time, the immobilization of the patient caused by joint disease further predisposes to deep vein thrombosis.29

1.1.2.4 Antiphospholipid antibodies

The presence of positive antiphospholipid antibodies (aPL) in patients with RA does not correlate with thrombosis or other clinical features of antiphospholipid syndrome (APS). Lupus anticoagulant is poorly described in patients with RA and VTE and the literature is limited, but should be considered as it is a strong risk factor for VTE. 13 In a review published in 2006 by Olech and Merrill, the prevalence of aPL antibodies in patients with rheumatoid arthritis was 22% in samples of no more than 200 patients, with some studies showing some association, but further investigation is needed. 29

1.1.3 Treatment of VTE in a patient with RA

The first goal of treatment in patients with RA is to relieve pain and reduce inflammation. The most effective drugs are nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. 13

Glucocorticoids (GC) are the mainstay of RA treatment. Efforts have been made to limit their use as bridging therapy or during flare-ups. Their chronic use is still significant but is decreasing over time. Their use increases the risk of VTE 2-3-fold in different patient populations while further increasing endothelial injury by decreasing nitric oxide levels and increasing adhesion molecule expression. 29

1.1.3.1 Pharmacological prophylaxis for VTE

Although patients with RA have a higher rate of spontaneous VTE compared to the general population, long-term systemic prophylactic anticoagulation is not recommended. However, patients with rheumatoid arthritis are often exposed to risk conditions for VTE that may require prophylactic anticoagulation. Patients with RA are often referred for total knee or hip replacement. This perioperative situation is generally accepted as a high-risk situation for VTE. However, RA patients undergoing surgery have an increased risk, similar to that of the general population.

Surgery had the same risk of postoperative VTE (about 1.9%). The situation is different in the hospitalized patient. Awareness of the risk of VTE and anticoagulation prophylaxis should be strongly considered in these cases, even if there are still no specific recommendations in patients with RA for the administration of prophylactic anticoagulation. 13

1.1.3.2 Therapeutic approach for VTE in RA setting

The main treatment of VTE is anticoagulation. In patients with suspected or confirmed VTE, anticoagulation should be started as soon as possible and before the results of diagnostic tests. The risk of VTE recurrence decreases rapidly once anticoagulation is started. Anticoagulation is preferably initiated using LMWH or fondaparinux. Current guidelines recommend that after the first episode, patients need anticoagulation for 3 months. NOACs are used primarily as first-line therapy as there is no need to perform laboratory testing of their efficacy. It is worth noting that NOACs have never been specifically evaluated in patients with RA, therefore further studies are needed. 13

## Vasculitis

### Behçet's syndrome (BS)

Pathogenesis of Behçet's thrombosis

1. Immunological principle

The pathophysiology of thrombosis in Behçet syndrome (BS) is not widely established, but the systemic inflammatory response appears to play an important role. However, it must be emphasized that inflammation and hemostasis are closely related and that the immune system plays a role in the thrombotic process. A generalized disruption of CD4+ lymphocytes, monocytes and neutrophils and overproduction of Th1 cell-associated pro-inflammatory cytokines, such as interferon-gamma (IFNγ), tumor necrosis factor (TNF)α, interleukin (IL)1, IL6, IL8 and IL12, have been observed in BS. Th17 cells together with their cytokines, IL17A, IL22, TNFa, also appear to be involved in the inflammatory process, as well as IL21 which can promote Th1 and Th17 differentiation and suppression of Treg(T regulatory) cells. All these prothrombotic factors promote thrombotic events in BS. 15

1. Coagulating mechanism

 In BS, the coagulation system can promote inflammation and thrombosis through multiple factors such as tissue factor (TF), thrombin and protein C with accompanying fibrinolysis disorder. Endothelial dysfunction, resulting from immune and inflammatory factors, appears to be a hallmark of of BS and plays a key role in the occurrence of thrombotic events. Decreased production of nitric oxide (NO), an important marker of endothelial dysfunction, was observed in some patients with active BS. In addition, high levels of other markers of endothelial damage, such as circulating von Willebrand factor and thrombomodulin were found in patients with active BS. Increased levels of endothelial growth factor (VEGF), which is a marker of angiogenesis, and certain adhesion molecules such as intercellular adhesion molecule-1 and E-selectin, produced by activated endothelial cells, have also been reported in BS patients.15

1. Venous thrombosis in Behçet's syndrome

Thrombosis is the most common vascular event in patients with BS, its prevalence ranging from 14% to 39%, and venous involvement is characteristically more common, accounting for 75% of all vascular complications. Venous thrombosis occurs more often in men with active disease in the early years, sometimes early after the occurrence of the disease, and tends to recur. Deep vein thrombosis (DVT) and superficial venous thrombosis of the lower extremities are the typical manifestations, but thrombosis can occur anywhere in the venous system and involve atypical sites such as the hepatic veins, superior and inferior vena cava, and sinus veins brain.15 Indeed, the prevalence of Budd-Chiari syndrome as a result of occlusion of the main hepatic veins, the inferior vena cava, or both has an occurrence rate of 3.2% in Behçet's patients. Inferior vena cava thrombosis is often involved in association with hepatic vein thrombosis.31

1. Arterial involvement in Behçet's syndrome

Arterial involvement is present in 1 to 7% of patients. The most characteristic arterial manifestations in patients with BS are aneurysms while arterial thrombosis is less frequent. These complications may remain asymptomatic or lead to life-threatening events such as acute myocardial infarction, stroke, mesenteric thrombosis, intermittent claudication, or gangrene of the lower extremities. Arterial occlusions and venous thrombi sometimes coexist in the same patient and may be associated with aneurysms. Thus, the coexistence of thrombosis and aneurysms is a peculiar feature of BS.15

1. Treatment

Currently, the management of vascular thrombosis in patients with BS relies on immunosuppressive therapy to reduce vessel wall inflammation. Anti-inflammatory treatments are capable of promoting the rapid and effective regression of vascular lesions, preventing the expansion of thrombosis and its recurrence. European League Against Rheumatism (EULAR) recommendations suggest immunosuppressive therapy with agents such as corticosteroids (CS), azathioprine (AZA), cyclophosphamide (CYC) or cyclosporine A (CsA). AZA and CsA in combination with low-dose CS are usually the first choice in the treatment of DVT and superficial venous thrombosis. CYC is the recommended treatment in BS patients with arterial involvement. Usually, anticoagulants alone are not recommended in patients with BS. In fact, it is only for CNS venous thrombosis that some recommend anticoagulation, with or without corticosteroids. As a general approach in daily practice, life-threatening conditions such as pulmonary artery aneurysms and Budd-Chiari syndrome are treated with more aggressive medical treatments, including cycles of cyclophosphamide and glucocorticoids.32

### ANCA vasculitis

Pathogenesis of thrombosis in ANCA vasculitis

Endothelial dysfunction

Endothelial cell dysfunction is characteristic and is likely caused by the interaction between neutrophils (activated by TNFα and ANCA) and endothelial cells, with subsequent massive oxidative stress ultimately leading to atherothrombotic complications. Activation of circulating factors such as factor VIII further drives the coagulation cascade. The cleavage of prothrombin to thrombin by factor Xa is a critical step leading to the conversion of fibrinogen to fibrin, which forms the bulk of the clot. Clot formation is usually followed by fibrinolysis, driven by the conversion of plasminogen to plasmin by the enzyme tissue plasminogen activator (tPA) in the presence of fibrin, which means increased thrombotic activity.33

Activation of neutrophils

An additional mechanism of neutrophil activation has been described, termed NETosis. Neutrophils are capable of releasing extracellular nucleic acids associated with histones and granule proteins capable of trapping bacterial agents. These neutrophil extracellular traps (NETs) have also been implicated in thrombotic events and appear to be a potential bridge between autoimmunity and coagulation. In particular, ANCA-primed neutrophils degranulate and release NETs, which in turn contain MPO and PR3, which act as autoantigens, thus creating a self-reinforcing process. 33,15

Venous thrombosis in ANCA-associated vasculitis

In recent years, evidence has emerged to support an increased incidence of venous thrombotic events in ANCA vasculitis. They were found to have an increased incidence of venous thromboembolism, especially during active disease, which was confirmed by subsequent studies.15

Arterial involvement in ANCA-associated vasculitis

An increased incidence of arterial events in ANCA vasculitis has been reported in the literature. An increased risk of acute myocardial infarction was observed in a Swedish study, particularly in men aged >50 years at the time of diagnosis. Interestingly, this population had an increased risk of acute coronary events in both the early (within 5 years of diagnosis) and the late (after 10 years of diagnosis) phase of the disease, suggesting that not only acute but also chronic inflammation may be involved in this process.

Immunothrombosis in the context of COVID-19 and ANCA vasculitis

In the context of the ongoing coronavirus disease 2019 (COVID-19) pandemic, thrombotic events occurring as a consequence of endotheliitis have been associated with neutrophil activation resulting in the formation of NETs. The literature studies ANCA vasculitis diagnosed shortly after the COVID disease. 33

Treatment

There are no recommendations for antiplatelet/anticoagulant administration in ANCA thrombosis.

### Vasculitis of large vessels

Venous thrombosis in large vessel vasculitis

Venous thrombosis has been poorly investigated. In temporal arteritis (GCA) the incidence rate of venous involvement is estimated to be 13.3/1000/year for VTE and 8.5/1000/year for DVT. In a retrospective study of 909 patients, an increased risk of VTE (both DVT and PE) has been observed particularly in the first year after diagnosis. Also in this population the risk was higher in the first year after diagnosis, suggesting a possible role of inflammation in the pathogenesis of vascular events. 15

Arterial thrombosis in large vessel vasculitis

A recent prospective study evaluating almost 3500 patients with GCA has reported an increased risk of thrombosis, especially in the first month after diagnosis. 15

Treatment

A recently published comprehensive meta-analysis clearly showed that the use of antiplatelet/anticoagulant therapy is not effective for primary prophylaxis, whereas it could be beneficial as combination therapy with corticosteroids in established disease, without an increased risk of bleeding.15

### Polyarteritis nodosa (PAN)

Polyarteritis nodosa (PAN) is a multisystem necrotizing vasculitis of medium-sized arteries, not associated with glomerulonephritis or ANCA positivity. Results regarding thrombotic events in PAN are conflicting. A study in 285 patients with PAN has reported a much lower incidence of VTE compared with ANCA vasculitis, while a more recent Swedish population-based study has suggested an increased risk of thrombotic events. 34

### Henoch-Schönlein purpura

Henoch-Schönlein purpura (HSP) is a systemic vasculitis of the small vessels that mainly affects children. There are insufficient reports of thrombotic events.35

###  Kawasaki disease

Kawasaki disease is a systemic vasculitis and represents the most common cause of acquired heart disease in childhood. Sometimes, despite appropriate treatment, coronary aneurysms occur, which could lead to vascular occlusion and consequently myocardial infarction. 34

### Retroperitoneal fibrosis

Retroperitoneal fibrosis (RPF) is a rare fibro-inflammatory disorder characterized by the presence of a retroperitoneal mass, which could be primary or secondary, mainly in neoplastic or infectious diseases. Venous thrombosis can be a symptom due to compression of vessels in circular structures in the iliac or inferior vena cava. 15

## Dermatomyositis/Polymyositis (PM/DM)

The meta-analysis of Li et al. demonstrated that inflammatory myositis is associated with an increased risk of VTE. In fact, an increased risk of VTE was found to be associated not only with polymyositis (PM), but also with dermatomyositis (DM). Systemic inflammation associated with PM/DM can induce a hypercoagulable state by activating the coagulation machinery, reducing natural anticoagulants and suppressing fibrinolysis, which leads to thrombus formation. The findings of course, eh are limited because they are based on relatively small samples. A significant association between PM/DM and VTE risk was observed in Caucasians. This relationship cannot be assessed among other populations, such as Asians and Africans, due to a lack of relevant publications on VTE risk. More future studies are needed to ascertain whether this association is also significant among other populations of different origins. 17

A prospective study conducted in the British Columbia population showed, among 752 cases with inflammatory myopathies, an increased risk of VTE, DVT and PE in PM and similarly in DM (Incidence Rate 8.14 (4.62 to 13.99), 6 .16 (2.50 to 13.92) and 9.42 (4.59 to 18.70), respectively) and especially in the first year after the diagnosis of the disease the highest rates of thrombosis were observed. There are plausible mechanisms that explain the increased risk of VTE events. Inflammatory arthritic conditions can affect venous stasis by reducing mobility. Inflammation modulates thrombotic responses by increasing the expression of procoagulant factors such as tissue factor, downregulating natural anticoagulants such as proteins C and S, and suppressing fibrinolysis, all of which lead to a hypercoagulable state. In addition, inflammation can affect the function of the endothelium in both arteries and veins and lead to vessel wall damage. 37

## Sjögren's syndrome (pSS)

**Risk of thrombosis in pSS**

The study by Zubieta et al, 2018 confirmed the relationship of pSS in 1175 patients and the increased risk of venous thrombosis and specifically for PE, DVT, and VTE compared with the general population of British Columbia, Canada with rates of PE, DVT, and VTE in SjS cases respectively 4.07 (95% CI, 2.04–8.09), 2.80 (95% CI, 1.27–6.17), and 2.92 (95% CI, 1.66–5.16).18

In another study conducted by the medical school of Hannover, Germany, the risk of cardiac events and vascular events was studied in 312 patients diagnosed with pSS. Initially, it was found that 1/10 (28/312 ie 9%) of the patients experienced at least one episode of either myocardial ischemia, cerebrovascular stroke or peripheral arterial disease. It was found that pSS patients with thrombotic complications with CNS symptoms were younger than expected compared to the average age of onset in the German population, and indeed of all ischemic events, 21% of these cases had obvious symptoms of ischemic stroke. (i.e. from 9% of all pSS patients) involving CNS involvement compared to 6/28 (21.4%) vs. 23/284 (8.1%), p = 0.021) In addition, almost one fifth of pSS patients (specifically 61/312 cases (19.6%)) were affected by cardiac events as the risk of myocardial ischemia was significantly higher. 38

**Mechanism**

 The most likely mechanism is that inflammation caused by lymphocytic infiltration contributes to the development of VTE because it activates procoagulant mechanisms, reduces the activity of natural anticoagulant mechanisms, and impairs the fibrinolytic system. This is also consistent with the fact that the risk was found to be higher during the period when the disease is most active and the inflammation less controlled, i.e. immediately after diagnosis. 18

At the same time, the increased concentration of autoantibodies has been implicated for a higher risk of cerebral infarction and venous thromboembolism in patients with pSS who carry higher titers of anti-SSA/Ro and anti-SSB/La antibodies. We observed a higher prevalence of anti-SSB/La positivity in pSS patients with MI (p = 0.017). Nevertheless, the association of thrombotic phenomena with pSS is suggestive, as the association with atrial fibrillation or other risk factors was not sought. Knowledge about risk factors may help clinicians identify patients with pSS who are at risk for CVD.38

#  **Discussion**

Patients with inflammatory rheumatic diseases have an increased risk of developing mainly venous but also arterial thrombosis. Regarding SLE, arterial and venous thrombosis are a well-known clinical entity in SLE, with a prevalence of >10% and indeed the risk of thrombosis is increased among patients with higher titers of lupus anticoagulant, anticardiolipin antibodies and antiphospholipid antibodies. Inflammatory disease activity, and activation of NETs by neutrophils further promote thrombosis. In the antiphospholipid syndrome, venous thrombosis is more frequent than arterial thrombosis. Arterial thrombosis mainly involves the CNS with manifestations of cerebrovascular events. Thrombosis can occur in any organ, be deep or superficial, affect the upper or lower limbs, the lungs or be located in unusual places (intra-abdominal, etc.).20,9,22,24

Regarding the increased risk of thromboembolism in patients with SLE and ANCA-associated vasculitis, their risk appears to be significantly higher compared to the other disease populations. The reasons that ANCA vasculitis is associated with a greater likelihood of thromboembolism is due either to the vasculitis itself through injury to the vessel, or to greater local edema and vascular narrowing in the context of vascular inflammation. Regarding the increased risk in SLE, again it is likely a multifactorial issue, excluding renal involvement (such as nephrotic syndrome, which may increase hypercoagulability due to an imbalance in the excretion of antithrombotic factors), an increased concentration of antiphospholipid antibodies, and an overall inflammatory state such as and in all other auto-inflammatory diseases.

 In rheumatoid arthritis it appears to predispose to an increased risk of deep vein thrombosis and pulmonary embolism due to impaired endothelial function in the early stages of the disease due to a proinflammatory state, increased viscosity, vascular stasis and impaired fibrinolysis, while arterial thrombosis has not been observed.29,13

Regarding Sjögren's syndrome, high rates of both venous thrombotic events were found compared to the general population, with twice the frequency of PE, DVT, and VTE in Sjögren's patients than the general population, as well as arterial thrombotic events, i.e. strokes, myocardial ischemia and peripheral arterial disease. 38,18

Dermatomyositis/polymyositis presents a high risk for deep vein thrombosis and pulmonary embolism especially in the first year after the diagnosis of the disease.37

The meta-analysis by Lee et al showed a significantly increased risk of deep vein thrombosis in inflammatory rheumatic diseases, especially in the first year of disease onset.4However, the true rates of deep vein thrombosis in rheumatic diseases, and in the reviewed studies, may be underestimated. Patient-reported symptoms may be vague and may even be misattributed to the rheumatologic disorder.

The reasons that lead to the increased thrombotic risk is the increased inflammatory activity of rheumatic diseases. Inflammation has been shown to induce the expression of tissue factors, an important step in the initiation of coagulation. So vasculitis mediated by immune complexes and chronic destruction of the vessels is caused. 20 At the same time, the activation of NETs (neutrophis extracellular traps), rich in bioactive molecules, promote thrombosis (including atherothrombosis), inflammation and fibrosis. Thus, although neutrophils may not be present in chronic inflammatory lesions, their remnants may enhance the inflammatory response beyond their short lifetime in tissues. (23) In particular, with regard to inflammatory joint diseases, the immobilization caused by the inflammation and the need for surgical treatment, such as arthroplasty, increases the risk of deep vein thrombosis.13

Thrombotic phenomena in patients with autoimmune rheumatological diseases is a field under investigation. The study by Ramagopalan et al. looked for the risk of venous thromboembolism in people admitted to hospital with a history of autoimmune rheumatic diseases, using the full National Hospital for England statistical episode data set from 1999 to 2008. Compared with controls, patients with various autoimmune rheumatic conditions showed statistically higher rates of thromboembolism. Specifically, rates pooled were, systemic lupus erythematosus (SLE) 3.71 [95% confidence interval (CI); 3.43–4.02, P<0.001], Sjögren's syndrome 2.02 [95% CI · 1.80–2.26, P<0.001], 1%CI97ma –2.23, P<0.001], rheumatoid arthritis (RA) 1.75 [95% CI; 1.70–1.80, P <0.001], the nodular poly arteritis 3.53 [95% CI; 2.76–4.44, P<0.0001, P<0.001] and ankylosing spondylitis 1.93 [95% CI; 1.74–2.14, P<0 .0001]). 39

The Swedish study by Zöller et al examined the risk of pulmonary embolism in patients with autoimmune diseases from Sweden. The MigMed2 database containing information on all registered residents of Sweden from 1964–2008 was used. The results showed that among rheumatological diseases, especially polyarteritis nodosa (SIR 13.26, 95% CI; 9.33–18.29), polymyositis/dermatomyositis (SIR 16.44, 95% CI; 11.57–22 .69) and SLE (SIR 13.4% , 23.29% , 23.29% CI) were associated with a higher risk of pulmonary embolism.34

A particularly increased risk of thrombosis in autoimmune rheumatological diseases is observed in the present study, especially in deep vein thrombosis and especially in the first year of the onset of the disease where the inflammatory activity is particularly intense. However, further studies and more extensive studies are needed so that the corresponding guidelines for the prevention and treatment of thrombotic events in rheumatological diseases can exist.

# Conclusions

Patients with inflammatory rheumatic diseases have an increased risk of developing venous and arterial thrombosis. Arterial and venous thrombosis are common clinical entities in systemic lupus erythematosus (SLE), with an increased risk of thrombosis in patients with higher titers of lupus anticoagulant, anticardiolipin antibodies, and antiphospholipid antibodies. Rheumatoid arthritis appears to predispose to an increased risk of deep vein thrombosis and pulmonary embolism while venous thrombosis predominates in Sjögren's syndrome. Additionally, in dermatomyositis/polymyositis there is a high risk of deep vein thrombosis and pulmonary embolism. These phenomena are observed in the first year of the onset of the disease where the inflammatory process is more intense. However, further studies and more extensive studies are needed so that the corresponding guidelines for the prevention and treatment of thrombotic events in rheumatological diseases can exist.

In this study, we looked for the risk of thrombotic events in patients with autoimmune rheumatological diseases, which is increased and mainly in the first year of diagnosis of the disease with high rates of deep vein thrombosis but also of other venous and arterial thrombosis.

# **Bibliography**

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| 1. | Khasnis et al. Venous thromboembolism in systemic autoimmune diseases: A narrative review with emphasis on primary systemic vasculitides. Vascular Medicine. 2015;: Volume 20, Issue 4, Pages 369-376. |
| 2. | CT E. The interactions between inflammation and coagulation. Br J Haematol. 2005;: 131: 417–430. |
| 3. | Rijken DC et al. New insights into the molecular mechanisms of the fibrinolytic system.. J Thromb Haemost. 2009;: 7: 4–13. |
| 4. | Lee JJ et al. A meta-analysis of the risk of venoust hromboembolism in inflammatory rheumatic diseases. Arthritis Research & Therapy. 2014;: 1-8.doi:10.1186/s13075-014-0435-y. |
| 5. | Pircher J et al. Prothrombotic effects of tumor necrosis factor alpha in vivo are amplified by the absence of TNF-alpha receptor subtype 1 and require TNF-alpha receptor subtype 2.. Arthritis Res Ther. 2012;: 14: R225. |
| 6. | Barber M. et al. Global epidemiology of systemic lupus erythematosus. Nature Reviews Rheumatology.. 2021;: ;17:515–532. doi: 10.1038/s41584-021-00668-1.. |
| 7. | Yuan W GF. Thrombosis and Anticoagulation Therapy in Systemic Lupus Erythematosus. Autoimmune. 2022;: doi: 10.1155/2022/3208037. PMID: 35795725; PMCID: PMC9252713. |
| 8. | Klein A et al. Hematological Manifestations among rheumatic diseases. Acta Haematologica. 2020;: 144(4), 403–412. doi:10.1159/000511759. |
| 9. | A. Afeltra et al. “Thrombosis systemic lupus erythematosus; congenital and acquired risk factors. Arthritis Care and Research. 2005;: vol. 53, no. 3, pp. 452–459. |
| 10. | Βριτσάλη Ε. ΑΧ. Η παθογένεια του αντιφωσφολιπιδικού συνδρόμου. Ελληνική Ρευματολογία. 2006;: 17(3):212-226. |
| 11. | Miyakis Sea. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (ΑPS). Journal of thrombosis and haemostasis : JTH. 2006;: 4(2):295-306.. |
| 12. | Tektonidou MG et al. EULAR recommendations for the management of antiphospholipid syndrome in adults. 2019. |
| 13. | Chahinez Ketfi et al. Risk of Venous Thromboembolism in Rheumatoid Arthritis. Joint Bone Spine. 2020;: 1-29, doi:https://doi.org/10.1016/j.jbspin.2020.10512. |
| 14. | Z Tazi Mezalek et al. Les complications vasculaires de la maladie de Behçet [Vascular manifestations of Behcet's disease]. Rev Med Interne. 2023;: 44(2):72-78. French. doi: 10.1016/j.revmed.2022.11.011. Epub 2022 Dec 21. PMID: 36564248. |
| 15. | Giacomo Emmi et al. Thrombosis in vasculitis: from pathogenesis to treatment. Thrombosis Journal. 2015;: 13:15 DOI 10.1186/s12959-015-0047-z. |
| 16. | Xiao H. HP et al. Overview of the pathogenesis of ANCA-associated vasculitis. Kidney Disease. 2016;: 1:205–215. doi: 10.1159/000442323. |
| 17. | Yanqing Li PWLLFWYL. Increased risk of venous thromboembolism associated with polymyositis and dermatomyositis:a meta-analysis. herapeutics and Clinical Risk Management. 2018;: 14 157–16. |
| 18. | Aviña-Zubieta et al. The Risk of Deep Venous Thrombosis and Pulmonary Embolism in Primary Sjögren Syndrome: A General Population-based Study. J Rheumatol. 2017;: 44(8):1184-1189. doi: 10.3899/jrheum.160185. Epub 2017 Mar 15. PMIPMID: 28298559; PMCID: PMC5587200. |
| 19. | Juanita Romero-Díaz et al. Thrombosis in systemic lupus erythematosus and other autoimmune diseases of recent onset. The Journal of Rheumatology. 2009;: 36 (1) 68-75; DOI: https://doi.org/10.3899/jrheum.071244. |
| 20. | Al-Homood et al. Thrombosis in Systemic Lupus Erythematosus: A Review Article. ISRN Rheumatology. 2012;: 1-6. |
| 21. | Natalia Bello et al. Systematic Literature Review and Meta-analysis of Venous Thromboembolism Events in Systemic Lupus Erythematosus. Rheumatol Ther. 2023;: 10(1): 7–34. doi: 10.1007/s40744-022-00513-1. |
| 22. | Santoro et al. Antiphospholipid antibodies:anticardiolipin and the lupus anticoagulant in systemic lupuserythematosus (SLE) and in non-SLE disorders. Prevalence and clinical significance. Annals of Internal Medicine. 1990;: Vol.112, no9, 682-698. |
| 23. | Eleni Frangou et al. An emerging role of neutrophils and NETosis in chronic inflammation and fibrosis in systemic lupus erythematosus (SLE) and ANCA-associated vasculitides (AAV): Implications for the pathogenesis and treatment. Autoimmunity Reviews. 2019;: Volume 18, Issue 8, Pages 751-760. |
| 24. | Urbanus R. et al. Antiphospholipid antibodies and the protein C pathway. Lupus. 2010;: Vol 19, pages 394-399 doi: 10.1177/0961203309360841. |
| 25. | Ruiz-Irastorza et al. "Antiphospholipid Syndrome." Lancet. 2010;: 376(9751):1498-509. |
| 26. | Cervera R et al. Morbidity and mortality in the antiphospholipid syndrome during a 5-year period: a multicenter prospective study of 1000 patients.. Ann Rheum Dis. 2009;: 68:1428–32. |
| 27. | Marco Capecchi et al. Anticoagulant Therapy in Patients with Antiphospholipid Syndrome. Journal of Clinical medicine. 2022;: 11(23): 6984. doi: 10.3390/jcm11236984. |
| 28. | Marie E. Holmqvist MNJEÄMSWJLTHJJA. Risk of Venous Thromboembolism in Patients With Rheumatoid Arthritis and Association With Disease Duration and Hospitalization. American Medical Association. 2012;: Vol 308, No. 13 pg.1350-1356, doi:10.1001/2012.jama.11741. |
| 29. | Omair MA ASESBABMAI. Venous Thromboembolism in Rheumatoid Arthritis: The Added Effect of Disease Activity to Traditional Risk Factors. Open Access Rheumatol. 2022;: 14:231-242https://doi.org/10.2147/OARRR.S284757. |
| 30. | Eric A. Fox SRK. The relationship between inflammation and venous thrombosis. Thromb Haemost. 2005;: 94(02): 362-365. |
| 31. | I Ben Ghorbel REMLMKMMMHH. Budd-Chiari syndrome associated with Behçet's disease. Gastroenterol Clin Biol. 2008 ;: 32(3):316-20. doi: 10.1016/j.gcb.2007.12.022. Epub 2008 Apr 9. |
| 32. | Alibaz-Oner F DH. Advances in the Treatment of Behcet's Disease. Curr Rheumatol. 2021 ;: 3(6):47. doi: 10.1007/s11926-021-01011-z. PMID: 34014377; PMCID: PMC8136102. |
| 33. | Misra DP TKGAZO. Mechanisms of thrombosis in ANCA-associated vasculitis. Clin Rheumatol.. 2021;: 40(12):4807-4815. doi: 10.1007/s10067-021-05790-9. Epub 2021 Jun 9. PMID: 34109491; PMCID: PMC8189705. |
| 34. | Zoller B LXSJSK. Risk of pulmonary embolism inpatients with autoimmune disorders: a nationwide follow-up study from Sweden. Lancet. 2012;: 379:244–9. |
| 35. | Li L ZJZYJH. Thrombosis warning in children suffering from henoch-schonlein purpura. Indian J Dermatol.. 2013;: 58:409. |
| 36. | Sanchez-Manubens J BRAJ. Diagnosis and classification of Kawasaki disease. J Autoimmun.. 2014;: 48–49:113–7. |
| 37. | Carruthers EC CHSEAZJ. Risk of deep venous thrombosis and pulmonary embolism in individuals with polymyositis and dermatomyositis: a general population-based study.. Αnn Rheum Dis.. 2016 ;: 75(1):110-6. doi: 10.1136/annrheumdis. |
| 38. | Zippel CL BSKEKFSTSTHSJAWTSKED. Premature stroke and cardiovascular risk in primary Sjögren's syndrome. Front Cardiovasc Med.. 2022 ;: 14;9:1048684. doi: 10.3389/fcvm.2022.1048684. PMID: 36588566; PMCID: PMC9794609. |
| 39. | Ramagopalan SV WCHAea. Risk of venous thromboembolism in people admitted to hospital with selected immune-mediated diseases: record-linkage study.. BMC Med. 2011. |
| 40. | Santoro PELaSA. Antiphospholipid antibodies:anticardiolipin and the lupus anticoagulant in systemic lupus erythematosus (SLE) and in non-SLE disorders. Prevalence and clinical significance. Annalsof InternalMedicine. 1990;: vol.112, no. 9, pp. 682–698. |
| 41. | Ruiz-Irastorza G CMRAIea. Evidence based recommendations for the prevention and long-term management of thrombosis in antiphospholipid antibody-positive patients: report of a task force at the 13th International Congress on antiphospholipid antibodies.. 2011; 20(2). |