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Risk of venous thromboembolism in autoimmune diseases: A comprehensive review

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ABSTRACT

Autoimmune diseases have specific pathophysiologic mechanisms leading to an increased risk of arterial and venous thrombosis. The risk of venous thromboembolism (VTE) varies according to the type and stage of the disease, and to concomitant treatments. In this review, we revise the most common autoimmune disease such as antiphospholipid syndrome, inflammatory myositis, polymyositis and dermatomyositis, rheumatoid arthritis, sarcoidosis, Sjogren syndrome, autoimmune haemolytic anaemia, systemic lupus erythematosus, systemic sclerosis, vasculitis and inflammatory bowel disease. We also provide an overview of pathophysiology responsible for the risk of VTE in each autoimmune disorder, and report current indications to anticoagulant treatment for primary and secondary prevention of VTE.

1. Introduction

Autoimmune diseases have specific pathophysiologic mechanisms potentially leading to an increased risk of arterial and venous thrombosis. [1,2] The risk of venous thromboembolism (VTE) varies according to the type and stage of the disease, and may be influenced by concomitant treatments [3]. One of the main contributing mechanisms is represented by the systemic inflammation that is a typical feature of autoimmune diseases; inflammation may contribute to a hypercoagulable state associated with endothelial dysfunction leading to thrombosis. [1] Other key elements of the hypercoagulability are platelet activation, microparticles release, and neutrophils tissue factor (TF) expression, inhibition of the protein C system, and impaired fibrinolysis. [3,4]

Whether specific antithrombotic therapeutic regimens such as long-term anticoagulation may be effective and safe in this clinical scenario is not always well established.

The aim of this narrative review is to report available evidence on the incidence of VTE in specific autoimmune diseases, such as antiphospholipid syndrome, rheumatoid arthritis, inflammatory myositis, polymyositis/dermatomyositis, sarcoidosis, Sjogren syndrome, autoimmune haemolytic anaemia, systemic lupus erythematosus (SLE), systemic sclerosis, vasculitis, inflammatory bowel disease and to provide practical advice on antithrombotic treatments to clinicians.

2. Autoimmune diseases and risk of venous thromboembolism

2.1. Antiphospholipid syndrome

Patients with antiphospholipid syndrome (APS) suffer from thrombotic vascular venous and/or arterial events and obstetric complications [5,6]. They present with circulating antiphospholipid antibodies (aPLs) targeting cell membrane phospholipids namely cardiolipin (aCL) and/or their associated proteins such as β2-glycoprotein (aβ_2GPI). According to the revised Sapporo criteria [6,7], APS diagnosis requires at least one clinical and one laboratory feature.

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In addition, some 'non-criteria' symptoms and clinical manifestations may be present in APS patients, such as neurological disorders [8] or dermatological [6] signs. APS may also be primary (isolated) or secondary when it is associated with other autoimmune diseases, typically the SLE [9].

Even if the thrombogenic activity of aPLs is well documented, their presence alone seems not be enough to activate the procoagulant cascade leading to VTE. The "two hit hypothesis" has been therefore formulated to summarize the pathogenetic events associated with thrombosis onset [10]. The first hit is represented by circulating aPLs, that would represent a sort of predisposition of patient to develop thrombosis. Patients may have circulating aPLs from the birth, or may be induced (usually in a transient manner) by some acute events, such myocardial infartcion, trauma, surgery, infection or inflammation disorder (these representing the second hit) [10].

Several mechanisms are involved in thrombosis induced by aPLs (Fig. 1). Several studies suggest that aPLs have a pro-thrombotic effect inhibiting the anticoagulant protein C/S pathway [11]. Furthermore, aPLs promote thrombosis influencing the activity of endothelial cells, platelets and white blood cells such as neutrophils and monocytes and complement pathways **[10]**.

Upon the binding with aPLs, endothelial cells and neutrophils release the TF, pro-inflammatory cytokines such as interleukin (IL)-6, IL-8, IL-1B, tumor necrosis factor (TNF) α. In endothelial cells, aPLs also induce the overexpression of adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1) and *E*-selectin promoting clotting adhesion **[10]**. Furthermore, aPLs may induce the formation of neutrophil extracellular traps, which have pro-thrombotic functions activating platelets and clotting factors. Finally, aPLs promote complement activation pathways inducing C5 to bind endothelial cells increasing cell adhesion [10].

APS prevalence in patients with unprovoked VTE is higher than in normal population. Thus, in a cross-sectional study including 524 patients with VTE, the prevalence of APS was 9% [12].

On the other side, the Euro-phospholipid project [13,14] that included 1000 APS patients who were followed for 10 years showed that a history of VTE was present in 38.9% [13]. In addition, during follow-up, VTE was the most frequent thrombotic event (4.3% DVT and 3.5% PE) despite antithrombotic treatment in most patients [14].

The risk of thrombosis seems to vary according to aPL profile. The highest risk of VTE is reported in patients who turn triple positive for aPL (aCL, aβ_2GPI and LAC) [15–17].

In secondary APS, the presence of aPL increases the VTE risk as shown by a large metanalysis including 45 studies of patients with SLE; the subgroup of patients positive to aPL had an increased absolute risk of VTE compared to negative ones [18].

2.2. *Inflammatory myositis, polymyositis and dermatomyositis*

Inflammatory myositis, polymyositis (PM) and dermatomyositis (DM), are systemic autoimmune diseases characterized by chronic muscle weakness associated with activation of the inflammatory response and inflammatory cells infiltrates into the skeletal muscle. [19] The prevalence of DM and PM is 21.5/100000, higher in women and older individuals [20].

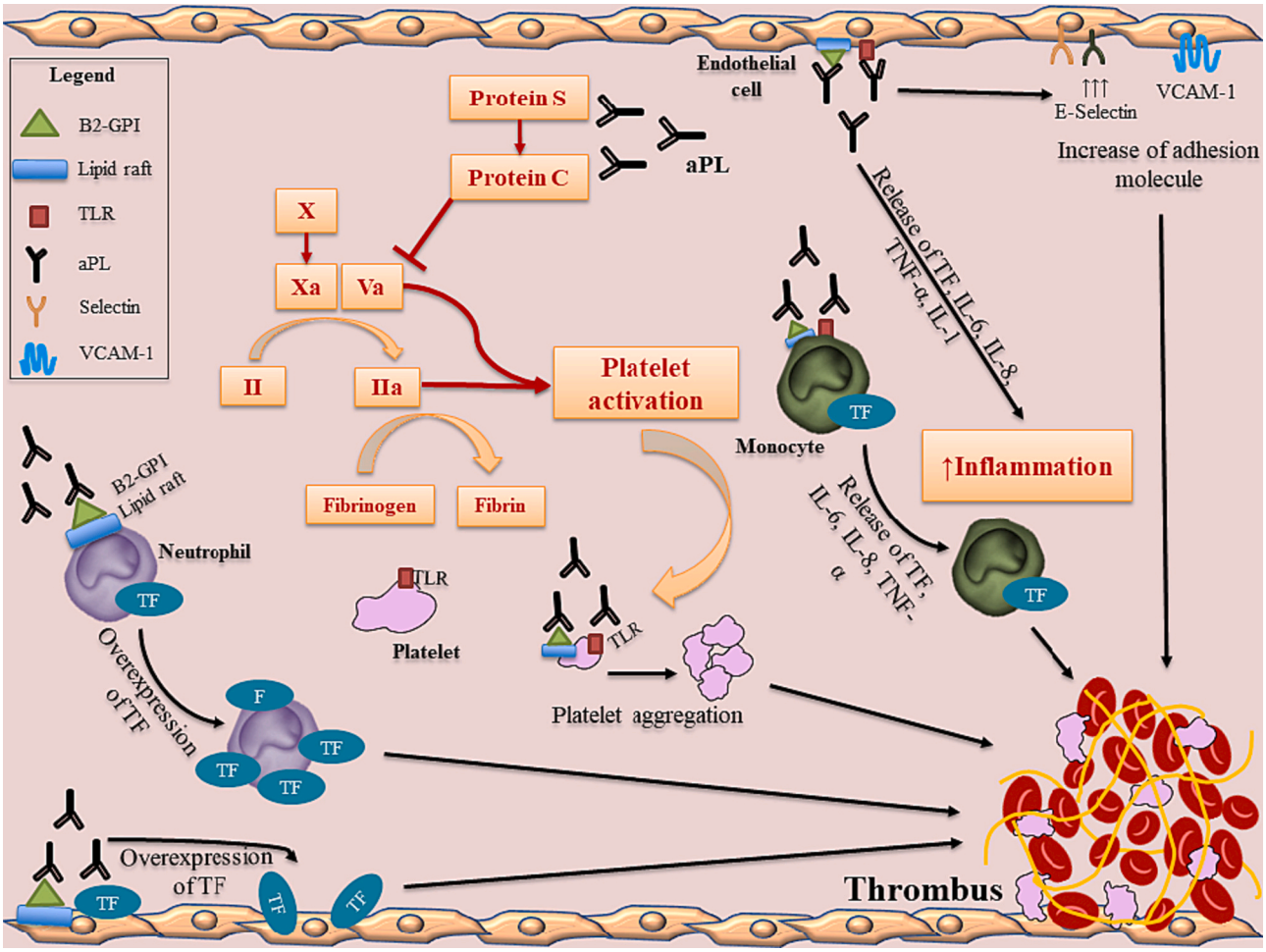

Fig. 1. Mechanisms favouring venous thromboembolism in patients with antiphospholipid syndrome.
aPL: antiphosholipid antibodies, B2-GPI: β2-glycoprotein I, IL: interleukin, TF: tissue factor, TNF: tumor necrosis factor, VCAM-1: vascular cell adhesion molecule-1.

Inflammatory myopathies carry an increased risk of both cardiovascular events, such as ischaemic heart disease and cerebrovascular accidents, and VTE [21].

A metanalysis including 9045 patients affected by PM or DM showed an overall risk of VTE Odds Ratio (OR) of 4.31; in particular, PM-associated OR of VTE was estimated at 6.87, and the DM-associated risk at OR of 8.67. The OR for DVT or PE was similar 4.86 and 4.74, respectively, irrespective of the type of inflammatory myositis [22].

Interestingly, the risk of developing a first VTE episode in patients suffering from inflammatory myositis increases with age, and is highest in the first year after the diagnosis (Hazard Ratio [HR] 26.6) [23].

The most common hypothesis on the mechanism that leads to development of VTE in inflammatory myositis is the abnormal activation of inflammation that may provoke a procoagulant mismatch increasing the procoagulants factors and inhibiting fibrinolysis [22]. However, inflammation degree of PM or DM seems to be lower than other autoimmune diseases, as showed by lower levels of erythrocyte sedimentation rate or C reactive protein (CRP) [23]. The underlying mechanisms behind this increased VTE risk remain unclear.

2.3. Rheumatoid Arthritis

Rheumatoid Arthritis (RA) is a chronic inflammatory disease characterized by a symmetric polyarthritis that can result in severe functional disabilities. RA is commonly associated with extra articular manifestation such as vasculitis, neuropathy and lung involvement [24]. The disease has a worldwide prevalence of about 5 per 1000 adults and women are two to three times more likely to be affected than men. It can occur at any age but the peak incidence is in the sixth decade [25]. While the association between RA and cardiovascular disease (CVD) has been well documented [26], its association with VTE is less studied. The risk of VTE depends on the activity of the disease with a cumulative incidence of 2.18% [27]. The OR of RA patients for developing VTE was estimated at 2.23 when compared to age-, sex- and other comorbidity-matched populations [27].

It has been thought that hypercoagulability may be induced by active systemic inflammation and production of cytokines such as TNF-alfa and IL-1 [28]. These inflammatory molecules can lead to endothelial dysfunction, down-regulation of protein C and inhibition of fibrinolysis [29] [30].

2.4. Sarcoidosis

Sarcoidosis is an inflammatory disease characterized by the presence of noncaseating granulomas affecting lungs, liver, skin and eyes [31]. Women, non-smokers, African Americans or people from European descent are more likely to develop the disease. Mortality is estimated at about 2–4% of cases, mainly related to lung fibrosis and respiratory failure [32]. Although clinical remission occurs in half of the subjects, the remaining patients develop a chronic disease.

In a recent meta-analysis, the risk adjusted for age and sex appeared to be higher among patients with sarcoidosis with HR of 3.04 for VTE, 3.14 for DVT and 4.29 for PE [33]. As patients with sarcoidosis frequently undergo thoracic imaging, the Authors performed a sensitivity analysis including only VTE events that occurred at least 6 months after the diagnosis [33]. In this subset, HR was slightly lower for both VTE (2.73), DVT (3.00) and PE (3.58) [33].

Regarding VTE risk, sarcoidosis shares with other autoimmune diseases many features, in particular local and systemic chronic inflammation which determine an increased production of cytokines [34]. Another possible explanation could rely on the observation that patients with sarcoidosis had an intensified activity of TF and plasma factor VII in their bronchoalveolar lavage fluid sample compared to normal individuals [35].

2.5. Sjogren syndrome

Sjögren's syndrome (SS) is a chronic inflammatory disorder characterized by lymphocytic infiltration of exocrine glands. This phenomenon leads is responsible for the clinical presentation of the disease that is characterized by the dryness of the oral cavity and eyes because of the impairment of salivary and lacrimal glands [36]. In addition to these common glandular dysfunctions known as “sicca complex” - the hallmark of SS -, there are other extraglandular manifestations, which can occur in about one-fourth of patients including arthritis, lung disease (interstitial pneumonia), vasculitis and neuropathy [37].

It has been investigated, as well as in other autoimmune diseases, an association between SS and the development of VTE.

In a meta-analysis including 235,301 patients with SS, it emerged that the pooled RR of VTE was 2.05 [38]. Patients with primary SS seem to have lower risk of PE than secondary SS patients (adjusted HR 3.21 and 5.06, respectively) [39]. Furthermore, a general population-based study found a 7-fold greater risk of VTE in the first year after the diagnosis than in matched controls, showing the highest thrombotic risk at SS onset [40].

The coexistence of additional thrombotic factors (e.g., advanced age, hospitalization) may further increase the risk of VTE [2,39].

The link between SS and VTE could be explained by chronic inflammation [34]: it activates blood coagulation and impairs the fibrinolytic process causing a prothrombotic state [41].

The hypercoagulability induced by endothelial dysfunction and TF expression increases the inflammatory response, which may drive also arterial and microvascular thrombosis [42].

A role in causing the activation of coagulation cascade could be played by aPL antibodies [43], found in up to one-third of patients with primary SS, which could explain the association with both venous and arterial thrombosis.

Also the presence of Ro/SSA and La/SSB autoantibodies in SS patients may favour thrombosis; the SS subgroup with the highest risk was the one with SSA/SSB double positivity (HR 3.1), compared to SSA/SSB single-positive (HR 1.7) and also to SSA/SSB negative patients (HR 1.6) [44].

2.6. Autoimmune haemolytic anaemia

Autoimmune haemolytic anaemia (AIHA) represents a rare disease caused by the production of antibodies against red blood cells surface antigens, which leads to their premature peripheral destruction, with an estimated incidence in the adult population of around 1–3 cases per 100,000 person per year, especially among 60–70 years old people [45]. These polyclonal immunoglobulins can react at different temperatures: in two-thirds of cases at body temperature (warm AIHA, the most common subtype) or at colder temperatures (cold-reactive subtype or mixed subtype).

The thrombotic risk in AIHA seems to be underestimated: in 1967, Allgood et al. [46] showed in their cohort of 47 patients that VTE represented the most cause of death. Other studies have demonstrated a high risk of VTE in AIHA patients, especially in the 90 days following the onset of the disease [47,48]. According to a metanalysis including 13,036 patients [49], VTE risk in AIHA patients is 2.6-fold higher than in non-AIHA patients.

In particular, a retrospective cohort study of 48 patients with warm AIHA [50], showed no differences in VTE frequency between primary and secondary AIHA (23.7% vs. 19.2%; $p = 0.5$). Of note, in multivariable analysis, only the leukocyte count and total bilirubin levels, but not haemoglobin serum levels and C-reactive protein, are associated with VTE [50].

Pathophysiological mechanisms of thrombosis in AIHA patients need to be clarified, but they seem to be related to the damage of red blood cell membrane and to the consequent release of phosphatidylserine [51], which causes the initiation and propagation of coagulation

cascade.

Microparticles [52] derived from haemolyzed red blood cell and platelets seem to be also implicated in this process, determining endothelial injuries and the exposure of tissue factor [53], which leads to blood coagulation. Strategies to identify patients at higher risk of VTE are needed.

2.7. Systemic lupus erythematosus (SLE)

SLE is a chronic, heterogeneous and multiorgan autoimmune disease with variable clinical features. [54,55] The prevalence of SLE is highest in women regardless of age or ethnic origin and there is also a wide geographical variation. White people have the highest incidence and prevalence of SLE worldwide. [56] The clinical manifestations include arthralgias, nonerosive polyarthritis, malar rash, hematologic anomalies (anaemia, leukopenia, thrombocytopenia), neurologic disorders, serositis, renal and cardiovascular involvement. [57] Regarding the latter, patients with SLE have an increased risk of cardiovascular complications, including VTE. [18,58,59]. It should also be noted that around 40% of patients with SLE have aPL, but <40% of them will develop thrombotic events. [60] In a large meta-analysis which involved 25 studies, a cumulative VTE incidence of 7.29% was reported. [27] A recent metanalysis found that patient with SLE had a statistically significantly increased risk of VTE than general population (relative risk [RR] 4.38), with the risk of VTE being particularly high in younger (<40 years) patients with SLE versus those aged 41–64 years [18]. Furthermore, in the subgroup analysis an higher absolute risk of VTE was estimated in patients with SLE with aPLs and APS versus patients with SLE without aPLs/APS. [18] Although data about the risk of VTE in patients with SLE are consistent over the years, the risk of recurrent VTE is unclear.

2.8. Systemic sclerosis

Systemic Sclerosis (SSc) is an immune-mediated rheumatic disease that is characterized by diffuse obliterative microangiopathy and fibrosis. The prevalence of SSc in Europe is estimated to be 7.2–33.9 per 100,000 individuals [61] with a 5- and 10-year survival rates of 83–84% and 65–73%, respectively [62–64]. The leading causes of death in these patients are the cardio-respiratory manifestations, accounting for 65% of all deaths [64,65]. The clinical manifestations include skin fibrosis, interstitial pneumonia, esophageal dysmotility, renal failure, myocardial and pericardial involvement, SA block, synovitis [66]. In 2014, a large meta–analysis, analysed VTE rates for SSc ($N = 24{,}145$) reporting a cumulative incidence of VTEs in this population of 3.13% with an OR of 2.98. [27] Patients whit SSc may have increased damage to the blood vessel wall as suggested by the vasculopathy and vascular injury that are predominant features of the disease [67]. Moreover, this damage determines the release of thrombin and subsequent initiation of the coagulation cascade [68]. In addition, among the features of SSc there is also endothelial dysfunction which is a well-established risk factor for VTE [69].

2.9. Vasculitis

Systemic vasculitis is a group of chronic, autoimmune disorders in which the inflammation system is pathologically activated on the blood vessel walls. The most common classification of vasculitis is based on the size of the vessel predominantly affected in large-vessel, medium-vessel, small-vessel, alongside with variable vessel vasculitis. [70] Vasculitis carry a heavy inflammatory burden which is supposed to increase the risk of VTE.

2.9.1. Large- vessel vasculitis

This group includes the Takayasu arteritis and giant-cell arteritis (GCA, formerly called Horton Arteritis), the first one affecting younger patient (<50 years old), and the latter being the most common vasculitis in the elderly. Although Takayasu arteritis carries an increased risk of arterial thromboembolism, there is no evidence of an associated increased risk in VTE in this patient population. A meta-analysis showed that patients affected by GCA had an increased risk of VTE (pooled RR 2.26) [71].

2.9.2. Medium-vessel vasculitis

Kawasaki disease mostly affects young patients with typical coronary involvement, but there is no strong evidence supporting an increased risk of VTE. Conversely, there is evidence on the association between another medium-vessel vasculitis, Panarteritis Nodosa (PAN) and VTE risk.

PAN is reported to increase the risk of VTE with a pooled RR of 3.00 [71] and even though this evidence comes from a metanalysis of observational studies the underlying mechanisms behind this risk are still not clear.

2.9.3. Small-vessel vasculitis

Small vessel vasculitis can be divided into two groups, based on the etiology behind the inflammatory activation: the ones associated with Anti-Neutrophils Cytoplasmic Antibodies (ANCA) and the immune complexes associated. In the ANCA-associated group, a strong association with an increased risk of VTE has been proven. A meta-analysis showed a pooled incidence of 12.4% of VTE in patients affected by ANCA-associated vasculitis, of which 63.4% were DVT and 26.3% were PE [72]. Moreover, the presence of Mieloperoxidase-ANCA proved to be the strongest factor associated with a first episode or a recurrence of VTE.

Another vasculitis associated with an increased risk of VTE is the Granulomatosis with Poliangiitis (GPA, previously known as Wegener's Granulomatosis), with a pooled RR of 3.94 reported in the metanalysis from Unprasert [71] and a HR of 2.90 in a population study from Marozoff et al., which an even higher risk in the first year from the diagnosis [73].

A work from Moiseev et al. showed how patients affected with eosinophilic granulomatosis with polyangiitis are exposed to an increased risk of VTE, with an estimated incidence of 9.8% [74]. Similarly, patients affected with Microscopic Polyangiitis suffer from an increased risk of VTE (HR 3.24) mostly driven by the risk of PE (HR 4.71). [75]

Although the rationale of continuously activated inflammation system in course of immune-complex associated vasculitis leading to an increased risk of VTE, the evidence on this field is still lacking.

2.9.4. Variable-vessel vasculitis

Superficial vein thrombosis and DVT are the most common vascular manifestations of Behçet's Syndrome (BS), affecting up to 40% of patients and being one of the earliest manifestations of this disease. However, the precise prevalence of VTE in this disease is still lacking. Thrombosis can affect either superior or inferior limbs and atypical sites can be characteristic of vascular BS, with an high incidence of complications, such as post-thrombotic syndrome. [76] The risk of a first VTE episode and of recurrences drops when a proper immunosuppressive treatment, such as azathioprine and cyclosporine in association with low-dose corticosteroids, is started, while the effectiveness of the anticoagulant treatment is still debated [77]. Indeed, In BS patients with DVT anticoagulation therapy seems to not reduce the risk of DVT recurrence [78], probably due to the predominant role of systemic inflammation in the pathogenesis of VTE in patients with BS [77,79].

Due to the very low prevalence of Cogan's Syndrome no data were found on the risk of VTE in this group of patients.

2.10. Inflammatory bowel disease

The evidence of inflammatory bowel disease (IBD) as risk factor for

developing VTE is largely accepted and supported by numerous studies. According to data derived from two large meta-analyses, the risk of VTE seems to be 2.5-fold higher in the IBD patients as compared with controls [80,81].

The incidence rate ratios (IRR) were 4.7 for DVT and 2.9 for PE in Crohn's disease and 2.8 for DVT and 3.6 for PE in ulcerative colitis resulting both in an increase of DVT and PE risk compared to population control group [82]. Grainge et al., enrolled 13,756 patients with IBD and 71,672 matched controls: 139 patients and 165 controls developed VTE ($p < 0{\cdot}0001$). They found that this risk (absolute risk of 2.6 per 1000 person-years) was higher at the time of a flare, defined as the period 120 days after a new corticosteroid prescription, with an absolute risk of 9.0 per 1000 person-years [83].

In a population-based nationwide study of 49,799 patients with IBD (14,211 Crohn's disease, 35,229 ulcerative colitis) and 477,504 subjects from the general population, the risk of VTE was elevated in patients with IBD [HR 2.0 for total events, HR 1.6 for unprovoked events]. Among those ≤20 years old, HRs for DVT and PE were 6.0 and 6.4, respectively [84]. Interestingly, both Crohn's disease and ulcerative colitis are associated with higher risk of any VTE (HR 2.2 and 1.9, respectively) and also unprovoked VTE (HR 2.0 and HR 1.5, respectively) [84].

Two more recent studies on Asian populations, despite the lower incidence of VTE in this population in comparison to the Western countries' one, confirmed these results, concluding that East Asian patients with IBD have a two-fold risk of developing VTE compared to general population [85,86].

Despite DVT of the lower limbs and PE are the most common clinical presentations, also unusual sites of thrombosis, have been described [87]. IBD are also identified as a risk factors for thrombosis recurrence in patients with previous unprovoked VTE [88]. Novacek et al. first compared the risk of recurrent VTE in IBD and non-IBD patients with unprovoked first VTE: the probability of recurrence after 5 years was 33.4% and 21.% in patients with and without IBD, respectively [89].

Similar VTE recurrence rate (30%) was observed in a single cohort of IBD patients with a history of VTE, that also showed a relationship between disease activity and the occurrence of VTE [90].

The pathogenesis of VTE (Fig. 2) in IBD is multifactorial and partially clarified. Acquired risk factors for thrombosis, which are more frequent in IBD patients compared with the general population, only partially explain the increased risk for VTE [91–93]. Many studies have focused on the local and systemic inflammatory state, the coagulation cascade, endothelial activation and VTE in patients with IBD. In particular, a reduction in fibrinolysis activators, an increase of coagulation factors and a high level of inflammatory cytokines have been shown especially during an IBD flare [91–93]. Indeed, IBD are characterized by an increased inflammation of intestinal mucosa, involved in subclinical microthrombi of enteric vessel leading to coagulation abnormalities such as an increased serum levels of V, VII, VIII, X, XI, XII coagulation factors and fibrinogen and a reduction of serum levels of XIII coagulation factor (Fig. 2) [91,92,94].

Additionally, abnormalities of platelets, such as thrombocytosis, due to high serum levels of IL-6 and thrombopoietin in IBD, and increased activation and aggregation, have been described. [95] Indeed, platelet activation leads to high serum levels of soluble form of CD40L (sCD40L) and a high surface expression of CD40L and a high production of microparticles with TF overexpressed on surface (Fig. 2) [91].

Inflammation of enteric mucosa leads to an increase of CRP, TNF-α and IL-1. These cytokines promote, on one hand, the overexpression of TF on leukocytes inducing the activation of intrinsic coagulation pathway, on the other hand, they promote fibrinolytic abnormalities reducing serum levels of tissue plasminogen activator (tPA) and increasing plasminogen activator inhibitor 1 (PAI-1) and thrombin-activatable fibrinolysis inhibitor (TAFI) [91,92,94].

Furthermore, chronic inflammation of enteric mucosa in IBD patients leads to endothelial injury and impaired oxidative stress status: indeed, nitric oxygen (NO) production seems to be impaired in IBD endothelium due to NO synthase 2 (NOS2) deficient transcription and due to higher

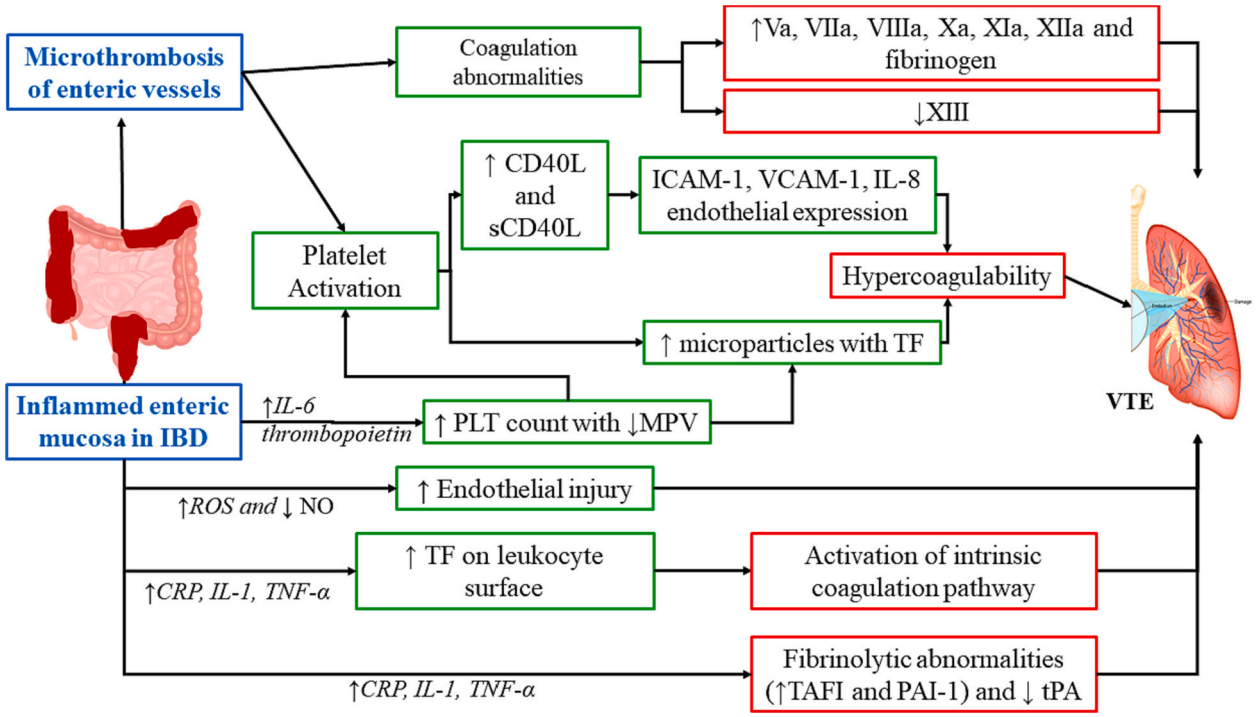

Fig. 2. Mechanisms favouring venous thromboembolism in patients with inflammatory bowel disease.
CRP: C reactive protein, IBD: inflammatory bowel disease, ICAM- 1: intercellular adhesion molecule-1, IL: interleukin, MPV: mean platelet volume, NO: nitric oxide, PAI-1: plasminogen activator inhibitor 1, PLT: platelet, ROS: reactive oxygen species, TAFI: thrombin-activatable fibrinolysis inhibitor, TF: tissue factor, TNF: tumor necrosis factor, tPA: tissue plasminogen activator, VCAM-1: vascular cell adhesion molecule-1, VTE: venous thromboembolism.

induction of nitric oxide species (NOS) competitor arginase by inflammatory citokynes such as IL-2 and TNF-α [91]. Finally, an increased production of reactive oxygen species (ROS) has been described in IBD enteric endothelium with a higher oxidative stress and accumulation of vWF multimers [91]. In this context, gut-derived lipopolysaccharides (LPS), associated with inflammatory and oxidative stress and platelet activation [96,97], may play a role in VTE occurrence in patients with IBD [98]. A summary of acknowledgment mechanism of VTE in patients with IBD is shown in Fig. 2.

Of note, although several studies found high serum levels of aPL in IBD patients [91] with and without previous VTE [99,100], their role in the genesis of VTE in patients with IBD is still a source of debate and their clinical and pathophysiological significance is still unclear [101].

3. Anticoagulation in patients with autoimmune disease

Anticoagulation represents a backbone of DVT and PE treatment but strategies of primary and secondary prophylaxis in patients with autoimmune disease are still undefined in many cases. According to the European guidelines, autoimmune diseases have a 2- to 9-fold increased risk of developing an episode of VTE [102]. Due to intermediate risk for long-term VTE recurrence (3–8% per year), indefinite anticoagulation therapy might be considered if not contraindicated [102]. However, clinical trials investigating the optimal duration and type of oral anticoagulants in patients with autoimmune disease are lacking [103].

In particular, APS is associated with high risk of developing recurrent VTE and for this reason, after a first VTE event, long-term anticoagulation with vitamin K antagonists (VKAs) and INR range 2.0–3.0 is recommended [104]. On the other hand, the use of direct oral anticoagulants (DOACs) is not routinely recommended and should be considered for patients with VTE who refuse VKAs therapy, for those with poor quality anticoagulation with VKAs or with known allergy to or serious adverse events with VKAs after careful evaluation and shared informed decision with patients [104]. Anticoagulation in aPL carriers without a thrombotic event is not recommended, while low-dose aspirin may be considered in high-risk profile such as patients with overlap of SLE of triple positivity to aPL [105]. In patients with SLE, primary thromboprophylaxis with anticoagulants is not recommended [106,107], while long-term secondary prophylaxis should be considered according to risk-benefit imbalance.

In patients with IBD the highest VTE risk is reported during illness flare and hospitalization with an increased risk of VTE of 3-fold higher than patients with cancer [108]. For this reason, The Canadian Association of Gastroenterology and the American College of Chest Physicians recommend a thromboprophylaxis with low molecular weight heparin (LMWH), unfractionated heparin (UFH) or fondaparinux in hospitalized IBD patients [109] but not in IBD outpatients without previous VTE [109,110]. Of note, the Canadian guidelines suggest at least 3 months of therapy in patients with IBD and VTE during illness flare, without indefinite anticoagulation. However, for IBD patients who are diagnosed with their first episode of VTE during clinical remission and in the absence of another provoking factor, they suggest indefinite anticoagulant therapy with periodic review of risk-benefit profile [109].

In patients with AIHA there are no study investigating primary and secondary prophylaxis with anticoagulants to prevent VTE, however, small cohort studies suggest a potential role of thromboprophylaxis during illness flare in in- and outpatients with AIHA [111].

In patients with vasculitis, data about indefinite anticoagulation are lacking. In patients with ANCA-associated vasculitis, the optimal duration of anticoagulation is unknown for patients who experience VTE [112]. If VTE occurs during illness flare and no other risk factors are present, VTE could be considered as provoked event with a transient risk factor. Thus, short-term instead of lifelong anticoagulation may be considered [112].

There is lack of evidence on which anticoagulant has the best efficacy-safety profile for the treatment of VTE in SSc. Patients suffering from SSc are also commonly affected by Pulmonary Arterial Hypertension, for which an anticoagulant treatment could be indicated, but started but there is no sufficient evidence to recommend VKA therapy on this basis [113].

RA, especially during illness flare, and its treatment, such as Janus kinase inhibitors (JAKi), may be associated with an increased risk of VTE. In patients with high risk of VTE, a thromboprophylaxis with mechanical or medical treatment (heparin, warfarin, and DOACs) may be considered [114],

Focusing on DOACs, it should be noted that there is no clear contraindication on its use in autoimmune disease without aPL positivity [102] and long-term anticoagulation with DOACs on unprovoked VTE in moderate-severe risk patients could be considered due to an higher adherence to DOACs and better quality of life compared to VKAs [115]. Considering the increased risk of gastrointestinal bleeding in patients taking DOACs, their use in patients with IBD should be carefully considered (probably preferring apixaban for its lower impact on bleeding at this site). However, a strong evidence supporting their use is lacking. Furthermore, trials on DOACs are ongoing to study the effect of these drugs on the prognosis of SSc associated Pulmonary Artery Hypertension. [116]

No data are available on the primary and secondary thromboprophylaxis in patients with Inflammatory myositis, PM and DM, SS and sarcoidosis.

4. Conclusions

In conclusion, autoimmune/inflammatory diseases are associated with a variable risk of VTE (Table 1). The mechanisms underlying this association are mostly unknown, but they seem to be related to the increased activation of proinflammatory pathways which are closely linked to the coagulation and platelet activation. Further studies are needed to clarify the disease-specific pathophysiological pathways. Strategies to stratify the risk of VTE in patients with autoimmune disease are yet to be established and the beneficial effect of anticoagulation

Table 1
Incidence of venous thromboembolism according to different autoimmune disorder.

Autoimmune disorder	VTE	Reference
Antiphospholipid syndrome	Recurrence VTE: ~14–17% after 1 year	[117,118]
Inflammatory myositis, Polymyositis and Dermatomyositis	Cumulative incidence: 4.03% 16.20 per 1000 Patients-year SIR 3.36	[2,23,27,119]
Rheumatoid arthritis	Cumulative incidence: 2.18% SIR 1.91	[27,119]
Sarcoidosis	SIR 1.54	[119]
Sjogren Syndrome	Cumulative incidence: 2.18% SIR 2.19	[27,119]
Autoimmune haemolytic anaemia	SIR 3.44	[119]
Systemic lupus erythematosus	Cumulative incidence: 7.29% 8.04 per 1000 Patients-year SIR 2.20	[2,18,27,119]
Systemic sclerosis	Cumulative incidence: 3.13% SIR 1.61	[27,119]
Vasculitis	Cumulative incidence: 7.97%	[27,119]
Inflammatory bowel disease	2.6–9.0 per 1000 person-years SIR Chron disease 1.63 SIR ulcerative colitis 1.97	[83,119]

SIR: standardised incidence ratio, VTE; venous thromboembolism.

treatment is proven so far only in some specific diseases, but the optimal anticoagulation intensity and duration is still unclear in some cases.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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References

[1] Tamaki H, Khasnis A. Venous thromboembolism in systemic autoimmune diseases: a narrative review with emphasis on primary systemic vasculitides. Vasc Med 2015;20:369–76.
[2] Ramagopalan SV, Wotton CJ, Handel AE, Yeates D, Goldacre MJ. Risk of venous thromboembolism in people admitted to hospital with selected immune-mediated diseases: record-linkage study. BMC Med 2011;9:1.
[3] Zoller B, Li X, Sundquist J, Sundquist K. Autoimmune diseases and venous thromboembolism: a review of the literature. Am J Cardiovasc Dis 2012;2:171–83.
[4] Borjas Howard J, Ruiz-Sada P, de Leeuw K, Lopez-Jimenez L, Font C, Marchena PJ, et al. I. Registro Informatizado de Enfermedad TromboEmbolica, Risk of recurrent venous thromboembolism in patients with autoimmune diseases: data from the Registro Informatizado de Enfermedad TromboEmbolica (RIETE) registry. Br J Haematol 2021;194:195–9.
[5] Garcia D, Erkan D. Diagnosis and Management of the Antiphospholipid Syndrome. N Engl J Med 2018;378:2010–21.
[6] Pignatelli P, Ettorre E, Menichelli D, Pani A, Violi F, Pastori D. Seronegative antiphospholipid syndrome: refining the value of "non-criteria" antibodies for diagnosis and clinical management. Haematologica 2020;105:562–72.
[7] Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006;4:295–306.
[8] Bucci T, Menichelli D, Pignatelli P, Triggiani M, Violi F, Pastori D. Relationship of antiphospholipid antibodies to risk of dementia: a systematic review. J Alzheimers Dis 2019;69:561–76.
[9] Willis R, Gonzalez EB, Brasier AR. The journey of antiphospholipid antibodies from cellular activation to antiphospholipid syndrome. Curr Rheumatol Rep 2015;17:16.
[10] Capozzi A, Manganelli V, Riitano G, Caissutti D, Longo A, Garofalo T, et al. Advances in the pathophysiology of thrombosis in antiphospholipid syndrome: Molecular mechanisms and signaling through lipid rafts. J Clin Med 2023;12.
[11] Farmer-Boatwright MK, Roubey RA. Venous thrombosis in the antiphospholipid syndrome. Arterioscler Thromb Vasc Biol 2009;29:321–5.
[12] Miranda S, Park J, Le Gal G, Piran S, Kherani S, Rodger MA, et al. Prevalence of confirmed antiphospholipid syndrome in 18-50 years unselected patients with first unprovoked venous thromboembolism. J Thromb Haemost 2020;18:926–30.
[13] Cervera R, Boffa MC, Khamashta MA, Hughes GR. The euro-phospholipid project: epidemiology of the antiphospholipid syndrome in Europe. Lupus 2009;18:889–93.
[14] Cervera R, Serrano R, Pons-Estel GJ, Ceberio-Hualde L, Shoenfeld Y, de Ramon E, et al. Morbidity and mortality in the antiphospholipid syndrome during a 10-year period: a multicentre prospective study of 1000 patients. Ann Rheum Dis 2015;74:1011–8.
[15] Galli M, Luciani D, Bertolini G, Barbui T. Lupus anticoagulants are stronger risk factors for thrombosis than anticardiolipin antibodies in the antiphospholipid syndrome: a systematic review of the literature. Blood 2003;101:1827–32.
[16] Pengo V, Biasiolo A, Pegoraro C, Cucchini U, Noventa F, Iliceto S. Antibody profiles for the diagnosis of antiphospholipid syndrome. Thromb Haemost 2005;93:1147–52.
[17] Galli M, Luciani D, Bertolini G, Barbui T. Anti-beta 2-glycoprotein I, antiprothrombin antibodies, and the risk of thrombosis in the antiphospholipid syndrome. Blood 2003;102:2717–23.
[18] Bello N, Meyers KJ, Workman J, Marcano Belisario J, Cervera R. Systematic literature review and Meta-analysis of venous thromboembolism events in systemic lupus erythematosus. Rheumatol Ther 2023;10:7–34.
[19] Dalakas MC, Hohlfeld R. Polymyositis and dermatomyositis. Lancet 2003;362:971–82.
[20] Bernatsky S, Joseph L, Pineau CA, Belisle P, Boivin JF, Banerjee D, et al. Estimating the prevalence of polymyositis and dermatomyositis from administrative data: age, sex and regional differences. Ann Rheum Dis 2009;68:1192–6.
[21] Xiong A, Hu Z, Zhou S, Qiang Y, Song Z, Chen H, et al. Cardiovascular events in adult polymyositis and dermatomyositis: a meta-analysis of observational studies. Rheumatology 2021;61:2728–39.
[22] Li Y, Wang P, Li L, Wang F, Liu Y. Increased risk of venous thromboembolism associated with polymyositis and dermatomyositis: a meta-analysis. Ther Clin Risk Manag 2018;14:157–65.
[23] Antovic A, Notarnicola A, Svensson J, Lundberg IE, Holmqvist M. Venous thromboembolic events in idiopathic inflammatory myopathy: occurrence and relation to disease onset. Arthritis Care Res (Hoboken) 2018;70:1849–55.
[24] Gravallese EM, Firestein GS. Rheumatoid arthritis - common origins, divergent mechanisms. N Engl J Med 2023;388:529–42.
[25] Myasoedova E, Crowson CS, Kremers HM, Therneau TM, Gabriel SE. Is the incidence of rheumatoid arthritis rising?: results from Olmsted County, Minnesota, 1955-2007. Arthritis Rheum 2010;62:1576–82.
[26] Gabriel SE. Cardiovascular morbidity and mortality in rheumatoid arthritis. Am J Med 2008;121:S9–14.
[27] Lee JJ, Pope JE. A meta-analysis of the risk of venous thromboembolism in inflammatory rheumatic diseases. Arthritis Res Ther 2014;16:435.
[28] van der Poll T, Buller HR, ten Cate H, Wortel CH, Bauer KA, van Deventer SJ, et al. Activation of coagulation after administration of tumor necrosis factor to normal subjects. N Engl J Med 1990;322:1622–7.
[29] Khan F, Galarraga B, Belch JJ. The role of endothelial function and its assessment in rheumatoid arthritis. Nat Rev Rheumatol 2010;6:253–61.
[30] Borensztajn KS, von der Thusen JH, Spek CA. The role of coagulation in chronic inflammatory disorders: a jack of all trades. Curr Pharm Des 2011;17:9–16.
[31] Judson MA, Boan AD, Lackland DT. The clinical course of sarcoidosis: presentation, diagnosis, and treatment in a large white and black cohort in the United States. Sarcoidosis Vasc Diffuse Lung Dis 2012;29:119–27.
[32] Newman LS, Rose CS, Maier LA. Sarcoidosis. N Engl J Med 1997;336:1224–34.
[33] Ungprasert P, Crowson CS, Matteson EL. Association of sarcoidosis with increased risk of VTE: a population-based study, 1976 to 2013. Chest 2017;151:425–30.
[34] Xu J, Lupu F, Esmon CT. Inflammation, innate immunity and blood coagulation. Hamostaseologie 2010;30:5–6 [8-9].
[35] Chapman HA, Allen CL, Stone OL. Abnormalities in pathways of alveolar fibrin turnover among patients with interstitial lung disease. Am Rev Respir Dis 1986;133:437–43.
[36] Venables PJ. Sjogren's syndrome. Best Pract Res Clin Rheumatol 2004;18:313–29.
[37] Asmussen K, Andersen V, Bendixen G, Schiodt M, Oxholm P. A new model for classification of disease manifestations in primary Sjogren's syndrome: evaluation in a retrospective long-term study. J Intern Med 1996;239:475–82.
[38] Ungprasert P, Srivali N, Kittanamongkolchai W. Risk of venous thromboembolism in patients with Sjogren's syndrome: a systematic review and meta-analysis. Clin Exp Rheumatol 2015;33:746–50.
[39] Chung WS, Lin CL, Sung FC, Hsu WH, Chen YF, Kao CH. Increased risks of deep vein thrombosis and pulmonary embolism in Sjogren syndrome: a nationwide cohort study. J Rheumatol 2014;41:909–15.
[40] Avina-Zubieta JA, Jansz M, Sayre EC, Choi HK. The risk of deep venous thrombosis and pulmonary embolism in primary Sjogren syndrome: a general population-based study. J Rheumatol 2017;44:1184–9.
[41] Silvarino R, Danza A, Merola V, Berez A, Mendez E, Espinosa G, et al. Venous thromboembolic disease in systemic autoimmune diseases: an association to keep in mind. Autoimmun Rev 2012;12:289–94.
[42] Bartoloni E, Shoenfeld Y, Gerli R. Inflammatory and autoimmune mechanisms in the induction of atherosclerotic damage in systemic rheumatic diseases: two faces of the same coin. Arthritis Care Res (Hoboken) 2011;63:178–83.
[43] Fauchais AL, Lambert M, Launay D, Michon-Pasturel U, Queyrel V, Nguyen N, et al. Antiphospholipid antibodies in primary Sjogren's syndrome: prevalence and clinical significance in a series of 74 patients. Lupus 2004;13:245–8.
[44] Mofors J, Holmqvist M, Westermark L, Bjork A, Kvarnstrom M, Forsblad-d'Elia H, et al. Concomitant Ro/SSA and La/SSB antibodies are biomarkers for the risk of venous thromboembolism and cerebral infarction in primary Sjogren's syndrome. J Intern Med 2019;286:458–68.
[45] Bass GF, Tuscano ET, Tuscano JM. Diagnosis and classification of autoimmune hemolytic anemia. Autoimmun Rev 2014;13:560–4.
[46] Allgood JW, Chaplin Jr H. Idiopathic acquired autoimmune hemolytic anemia. A review of forty-seven cases treated from 1955 through 1965. Am J Med 1967;43:254–73.
[47] Lecouffe-Desprets M, Neel A, Graveleau J, Leux C, Perrin F, Visomblain B, et al. Venous thromboembolism related to warm autoimmune hemolytic anemia: a case-control study. Autoimmun Rev 2015;14:1023–8.
[48] Hendrick AM. Auto-immune haemolytic anaemia–a high-risk disorder for thromboembolism? Hematology 2003;8:53–6.
[49] Ungprasert P, Tanratana P, Srivali N. Autoimmune hemolytic anemia and venous thromboembolism: a systematic review and meta-analysis. Thromb Res 2015;136:1013–7.
[50] Audia S, Bach B, Samson M, Lakomy D, Bour JB, Burlet B, et al. Venous thromboembolic events during warm autoimmune hemolytic anemia. PloS One 2018;13:e0207218.

[51] Ruf W, Rehemtulla A, Morrissey JH, Edgington TS. Phospholipid-independent and -dependent interactions required for tissue factor receptor and cofactor function. J Biol Chem 1991;266:16256.
[52] Camus SM, De Moraes JA, Bonnin P, Abbyad P, Le Jeune S, Lionnet F, et al. Circulating cell membrane microparticles transfer heme to endothelial cells and trigger vasoocclusions in sickle cell disease. Blood 2015;125:3805–14.
[53] Bach R, Gentry R, Nemerson Y. Factor VII binding to tissue factor in reconstituted phospholipid vesicles: induction of cooperativity by phosphatidylserine. Biochemistry 1986;25:4007–20.
[54] Dorner T, Furie R. Novel paradigms in systemic lupus erythematosus. Lancet 2019;393:2344–58.
[55] Bazzan M, Vaccarino A, Marletto F. Systemic lupus erythematosus and thrombosis. Thromb J 2015;13:16.
[56] Rees F, Doherty M, Grainge MJ, Lanyon P, Zhang W. The worldwide incidence and prevalence of systemic lupus erythematosus: a systematic review of epidemiological studies. Rheumatology (Oxford) 2017;56:1945–61.
[57] Zucchi D, Elefante E, Schiliro D, Signorini V, Trentin F, Bortoluzzi A, et al. One year in review 2022: systemic lupus erythematosus. Clin Exp Rheumatol 2022;40:4–14.
[58] Yusuf HR, Hooper WC, Grosse SD, Parker CS, Boulet SL, Ortel TL. Risk of venous thromboembolism occurrence among adults with selected autoimmune diseases: a study among a U.S. cohort of commercial insurance enrollees. Thromb Res 2015;135:50–7.
[59] Kaiser R, Cleveland CM, Criswell LA. Risk and protective factors for thrombosis in systemic lupus erythematosus: results from a large, multi-ethnic cohort. Ann Rheum Dis 2009;68:238–41.
[60] Pons-Estel GJ, Andreoli L, Scanzi F, Cervera R, Tincani A. The antiphospholipid syndrome in patients with systemic lupus erythematosus. J Autoimmun 2017;76:10–20.
[61] Bergamasco A, Hartmann N, Wallace L, Verpillat P. Epidemiology of systemic sclerosis and systemic sclerosis-associated interstitial lung disease. Clin Epidemiol 2019;11:257–73.
[62] Alamanos Y, Tsifetaki N, Voulgari PV, Siozos C, Tsamandouraki K, Alexiou GA, et al. Epidemiology of systemic sclerosis in Northwest Greece 1981 to 2002. Semin Arthritis Rheum 2005;34:714–20.
[63] Arias-Nunez MC, Llorca J, Vazquez-Rodriguez TR, Gomez-Acebo I, Miranda-Filloy JA, Martin J, et al. Systemic sclerosis in northwestern Spain: a 19-year epidemiologic study. Medicine (Baltimore) 2008;87:272–80.
[64] Czirjak L, Kumanovics G, Varju C, Nagy Z, Pakozdi A, Szekanecz Z, et al. Survival and causes of death in 366 Hungarian patients with systemic sclerosis. Ann Rheum Dis 2008;67:59–63.
[65] Gaultier JB, Hot A, Cathebras P, Grange C, Ninet J, Rousset H. Systemic sclerosis in men. Rev Med Interne 2008;29:181–6.
[66] Denton CP, Khanna D. Systemic sclerosis. Lancet 2017;390:1685–99.
[67] Kahaleh MB, LeRoy EC. Autoimmunity and vascular involvement in systemic sclerosis (SSc). Autoimmunity 1999;31:195–214.
[68] Ludwicka-Bradley A, Silver RM, Bogatkevich GS. Coagulation and autoimmunity in scleroderma interstitial lung disease. Semin Arthritis Rheum 2011;41:212–22.
[69] Fleming JN, Nash RA, Mahoney Jr WM, Schwartz SM. Is scleroderma a vasculopathy? Curr Rheumatol Rep 2009;11:103–10.
[70] Mahr A, de Menthon M. Classification and classification criteria for vasculitis: achievements, limitations and prospects. Curr Opin Rheumatol 2015;27:1–9.
[71] Ungprasert P, Koster MJ, Thongprayoon C, Warrington KJ. Risk of venous thromboembolism among patients with vasculitis: a systematic review and meta-analysis. Clin Rheumatol 2016;35:2741–7.
[72] Hansrivijit P, Trongtorsak A, Gadhiya KP, Lnu K, Dimech CT, Thongprayoon C, et al. Incidence and risk factors of venous thromboembolism in ANCA-associated vasculitis: a metaanalysis and metaregression. Clin Rheumatol 2021;40:2843–53.
[73] Marozoff S, Mai A, Dehghan N, Sayre EC, Choi HK, Avina-Zubieta JA. Increased risk of venous thromboembolism in patients with granulomatosis with polyangiitis: a population-based study. PloS One 2022;17:e0270142.
[74] Moiseev S, Kronbichler A, Makarov E, Bulanov N, Crnogorac M, Direskeneli H, et al. Association of venous thromboembolic events with skin, pulmonary and kidney involvement in ANCA-associated vasculitis: a multinational study. Rheumatology (Oxford) 2021;60:4654–61.
[75] Ahn JK, Hwang J, Choi CB, Seo GH. Risk of acute myocardial infarction, stroke, and venous thromboembolism among patients with anti-neutrophil cytoplasmic antibody-associated vasculitis in South Korea: a nationwide population-based study. Joint Bone Spine 2023;90:105498.
[76] Toledo-Samaniego N, Oblitas CM, Penaloza-Martinez E, Del-Toro-Cervera J, Alvarez-Sala-Walther LA, Demelo-Rodriguez P, et al. Arterial and venous involvement in Behcet's syndrome: a narrative review. J Thromb Thrombolysis 2022;54:162–71.
[77] Emmi G, Bettiol A, Silvestri E, Di Scala G, Becatti M, Fiorillo C, et al. Vascular Behcet's syndrome: an update. Intern Emerg Med 2019;14:645–52.
[78] Ahn JK, Lee YS, Jeon CH, Koh EM, Cha HS. Treatment of venous thrombosis associated with Behcet's disease: immunosuppressive therapy alone versus immunosuppressive therapy plus anticoagulation. Clin Rheumatol 2008;27:201–5.
[79] Hatemi G, Christensen R, Bang D, Bodaghi B, Celik AF, Fortune F, et al. 2018 update of the EULAR recommendations for the management of Behcet's syndrome. Ann Rheum Dis 2018;77:808–18.
[80] Fumery M, Xiaocang C, Dauchet L, Gower-Rousseau C, Peyrin-Biroulet L, Colombel JF. Thromboembolic events and cardiovascular mortality in inflammatory bowel diseases: a meta-analysis of observational studies. J Crohns Colitis 2014;8:469–79.
[81] Yuhara H, Steinmaus C, Corley D, Koike J, Igarashi M, Suzuki T, et al. Meta-analysis: the risk of venous thromboembolism in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2013;37:953–62.
[82] Bernstein CN, Blanchard JF, Houston DS, Wajda A. The incidence of deep venous thrombosis and pulmonary embolism among patients with inflammatory bowel disease: a population-based cohort study. Thromb Haemost 2001;85:430–4.
[83] Grainge MJ, West J, Card TR. Venous thromboembolism during active disease and remission in inflammatory bowel disease: a cohort study. Lancet 2010;375:657–63.
[84] Kappelman MD, Horvath-Puho E, Sandler RS, Rubin DT, Ullman TA, Pedersen L, et al. Thromboembolic risk among Danish children and adults with inflammatory bowel diseases: a population-based nationwide study. Gut 2011;60:937–43.
[85] Weng MT, Park SH, Matsuoka K, Tung CC, Lee JY, Chang CH, et al. Incidence and risk factor analysis of thromboembolic events in east Asian patients with inflammatory bowel disease, a multinational collaborative study. Inflamm Bowel Dis 2018;24:1791–800.
[86] Heo CM, Kim TJ, Kim ER, Hong SN, Chang DK, Yang M, et al. Risk of venous thromboembolism in Asian patients with inflammatory bowel disease: a nationwide cohort study. Sci Rep 2021;11:2025.
[87] Papay P, Miehsler W, Tilg H, Petritsch W, Reinisch W, Mayer A, et al. Clinical presentation of venous thromboembolism in inflammatory bowel disease. J Crohns Colitis 2013;7:723–9.
[88] Stadnicki A, Stadnicka I. Venous and arterial thromboembolism in patients with inflammatory bowel diseases. World J Gastroenterol 2021;27:6757–74.
[89] Novacek G, Weltermann A, Sobala A, Tilg H, Petritsch W, Reinisch W, et al. Inflammatory bowel disease is a risk factor for recurrent venous thromboembolism. Gastroenterology 2010;139. 779–87, 787.e1.
[90] Bollen L, Vande Casteele N, Ballet V, van Assche G, Ferrante M, Vermeire S, et al. Thromboembolism as an important complication of inflammatory bowel disease. Eur J Gastroenterol Hepatol 2016;28:1–7.
[91] Giannotta M, Tapete G, Emmi G, Silvestri E, Milla M. Thrombosis in inflammatory bowel diseases: what's the link? Thromb J 2015;13:14.
[92] Cheng K, Faye AS. Venous thromboembolism in inflammatory bowel disease. World J Gastroenterol 2020;26:1231–41.
[93] Papa A, Gerardi V, Marzo M, Felice C, Rapaccini GL, Gasbarrini A. Venous thromboembolism in patients with inflammatory bowel disease: focus on prevention and treatment. World J Gastroenterol 2014;20:3173–9.
[94] Danese S, Sans M, Fiocchi C. Inflammatory bowel disease: the role of environmental factors. Autoimmun Rev 2004;3:394–400.
[95] Danese S, Papa A, Saibeni S, Repici A, Malesci A, Vecchi M. Inflammation and coagulation in inflammatory bowel disease: the clot thickens. Am J Gastroenterol 2007;102:174–86.
[96] Pastori D, Carnevale R, Menichelli D, Nocella C, Bartimoccia S, Novo M, et al. Is there an interplay between adherence to Mediterranean diet, antioxidant status, and vascular disease in atrial fibrillation patients? Antioxid Redox Signal 2016;25:751–5.
[97] Carnevale R, Pastori D, Nocella C, Cammisotto V, Baratta F, Del Ben M, et al. Low-grade endotoxemia, gut permeability and platelet activation in patients with impaired fasting glucose. Nutr Metab Cardiovasc Dis 2017;27:890–5.
[98] Caradonna L, Amati L, Magrone T, Pellegrino NM, Jirillo E, Caccavo D. Enteric bacteria, lipopolysaccharides and related cytokines in inflammatory bowel disease: biological and clinical significance. J Endotoxin Res 2000;6:205–14.
[99] Magro F, Soares JB, Fernandes D. Venous thrombosis and prothrombotic factors in inflammatory bowel disease. World J Gastroenterol 2014;20:4857–72.
[100] Koutroubakis IE, Petinaki E, Anagnostopoulou E, Kritikos H, Mouzas IA, Kouroumalis EA, et al. Anti-cardiolipin and anti-beta2-glycoprotein I antibodies in patients with inflammatory bowel disease. Dig Dis Sci 1998;43:2507–12.
[101] Saibeni S, Vecchi M, Valsecchi C, Faioni EM, Razzari C, de Franchis R. Reduced free protein S levels in patients with inflammatory bowel disease: prevalence, clinical relevance, and role of anti-protein S antibodies. Dig Dis Sci 2001;46:637–43.
[102] Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, et al. 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J 2020;41:543–603.
[103] Yamashita Y, Morimoto T, Kimura T. Optimal duration of anticoagulation therapy for venous thromboembolism in autoimmune diseases. Eur J Intern Med 2022;95:102–3.
[104] Pastori D, Menichelli D, Cammisotto V, Pignatelli P. Use of direct Oral anticoagulants in patients with antiphospholipid syndrome: a systematic review and comparison of the international guidelines. Front Cardiovasc Med 2021;8:715878.
[105] Tektonidou MG, Andreoli L, Limper M, Amoura Z, Cervera R, Costedoat-Chalumeau N, et al. EULAR recommendations for the management of antiphospholipid syndrome in adults. Ann Rheum Dis 2019;78:1296–304.
[106] Fanouriakis A, Kostopoulou M, Alunno A, Aringer M, Bajema I, Boletis JN, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. Ann Rheum Dis 2019;78:736–45.
[107] Yuan W, Guan F. Thrombosis and anticoagulation therapy in systemic lupus erythematosus. Autoimmune Dis 2022;2022. 3208037.
[108] Murthy SK, Robertson McCurdy AB, Carrier M, McCurdy JD. Venous thromboembolic events in inflammatory bowel diseases: a review of current evidence and guidance on risk in the post-hospitalization setting. Thromb Res 2020;194:26–32.
[109] Nguyen GC, Bernstein CN, Bitton A, Chan AK, Griffiths AM, Leontiadis GI, et al. Consensus statements on the risk, prevention, and treatment of venous

thromboembolism in inflammatory bowel disease: Canadian Association of Gastroenterology. Gastroenterology 2014;146:835–48 [e6].
[110] Eikelboom JW, Hirsh J, Spencer FA, Baglin TP, Weitz JI. Antiplatelet drugs: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141: e89S–119S.
[111] Solari D, Alberio L, Ribi C, Grandoni F, Stalder G. Autoimmune hemolytic anemia and pulmonary embolism: an association to consider. TH Open 2021;5:e8–13.
[112] Chung SA, Langford CA, Maz M, Abril A, Gorelik M, Guyatt G, et al. 2021 American College of Rheumatology/Vasculitis Foundation guideline for the management of antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheumatol 2021;73:1366–83.
[113] Johnson SR, Granton JT, Tomlinson GA, Grosbein HA, Le T, Lee P, et al. Warfarin in systemic sclerosis-associated and idiopathic pulmonary arterial hypertension. A Bayesian approach to evaluating treatment for uncommon disease. J Rheumatol 2012;39:276–85.
[114] Omair MA, Alkhelb SA, Ezzat SE, Boudal AM, Bedaiwi MK, Almaghlouth I. Venous thromboembolism in rheumatoid arthritis: the added effect of disease activity to traditional risk factors. Open Access Rheumatol 2022;14:231–42.
[115] Weitz JI, Prandoni P, Verhamme P. Anticoagulation for patients with venous thromboembolism: when is extended treatment required? TH Open 2020;4: e446–56.
[116] Calderone A, Stevens W, Prior D, Nandurkar H, Gabbay E, Proudman SM, et al. Multicentre randomised placebo-controlled trial of oral anticoagulation with apixaban in systemic sclerosis-related pulmonary arterial hypertension: the SPHInX study protocol. BMJ Open 2016;6:e011028.
[117] Lim W. Prevention of thrombosis in antiphospholipid syndrome. Hematology Am Soc Hematol Educ Program 2016;2016:707–13.
[118] Garcia D, Akl EA, Carr R, Kearon C. Antiphospholipid antibodies and the risk of recurrence after a first episode of venous thromboembolism: a systematic review. Blood 2013;122:817–24.
[119] Zoller B, Li X, Sundquist J, Sundquist K. Risk of pulmonary embolism in patients with autoimmune disorders: a nationwide follow-up study from Sweden. Lancet 2012;379:244–9.