Introduction

Pulmonary embolism (PE) and deep vein thrombosis (DVT) together constitute venous thromboembolism (VTE). VTE affects about 1-2 per 1,000 individuals per year [1, 2]. PE is a potentially lethal complication of VTE with a mortality rate of >15% in the first 3 months after diagnosis [3, 4]. According to Virchow’s triad, VTE results from stasis, changes in blood coagulability and alterations in the vessel wall (Figure 1) [5-8]. These changes, as well as hypercoagulable states, may be inherited and/or acquired and may act in concert (Table 1). Thus, VTE results from multiple interactions between acquired and inherited risk factors [9-11]. For familial thrombophilia – clustering of VTE in families – five major genetic risk factors have been identified: deficiencies of protein S, protein C, and antithrombin, factor V Leiden Gln506 (rs6025) and prothrombin G20210A (rs1799963) [12, 13]. The list of new susceptibility loci for VTE is, however, growing fast (Table 1) [14]. Family history is the sum of the interactions of familial genetic and environmental causes [15-18]. However, family history is not a binary trait [17,
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18]. The risk is dependent on the number of affected relatives [17, 18]. A large number of acquired risk factors for VTE have been identified and include age, previous episode of VTE, immobilization, surgery, trauma, pregnancy, puerperium, lupus anticoagulant, cardiolipin antibodies, malignant disease, hormone replacement therapy (HRT), and oral contraceptives [1, 2, 9-11]. The list of known acquired risk factors has also grown in recent years. Socioeconomic factors are associated with an increased risk not only of atherosclerosis, but also for VTE [19, 20]. Infections have also been linked to an increased VTE risk, probably due to inflammation [21-23], though endotoxins have specific effects in severe infections. Inflammation may also explain the increased risk of VTE in patients with autoimmune and immune-mediated disorders, which this article will review (Table 1).

It has long been known that certain autoimmune disorders, such as systemic lupus erythematosus (SLE) [24-26], inflammatory bowel disease (IBD) [27,

![Virchow's triad](image)

Figure 1. Virchow’s triad and some of the extensive inflammatory changes that may contribute to the development of venous thromboembolism. PAI-1=plasminogen activator inhibitor 1, EPCR=endothelial protein C receptor.

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<thead>
<tr>
<th>Table 1. Inherited and acquired risk factors for hypercoagulable states.</th>
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<td>Cystathione beta-synthase deficiency (CBS)</td>
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<td>Factor V Leiden Gln506 (rs6025) * (F5)</td>
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<td>Prothrombin G20210A (rs1799963) (F2)</td>
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<td>Protein C deficiency (PROC)</td>
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<td>ABO blood group (ABO)</td>
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<td><strong>Emerging susceptibility loci for VTE</strong></td>
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<td>Coagulation factor XI (F11)</td>
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<td>Fibrinogen gamma chain (FGG)</td>
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<td>Glycoprotein VI (GP6)</td>
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<td>Human immunodeficiency virus type 1 enhancer binding protein 1 (HIVEP1)</td>
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<td>Syntaxin binding protein 5 (STXB5)</td>
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<td>Tandem C2 domains, nuclear (TC2N)</td>
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<td>Family history of VTE (sum of the effects of and interactions between familial genetic and environmental factors)</td>
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*The major genetic cause of activated protein C (APC) resistance.
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Autoimmune and immune-mediated disorders linked to an increased risk of VTE. The list of autoimmune and immune-mediated disorders linked to an increased risk of VTE has grown longer and longer, and now also includes rheumatoid arthritis (RA) [30], celiac disease [31], hyperthyroidism [32], and Wegener’s granulomatosis [33]. However, two recent reports have linked a large number of autoimmune disorders/immune-mediated disease to an increased risk of PE and VTE [34, 35]. Inflammation is a common feature of these disorders. The epidemiological and experimental evidence and clinical implications of the association between autoimmune/immune-mediated disorders and VTE will be discussed.

Inflammation, hypercoagulability and autoimmune/immune-mediated disorders

Inflammation is a common feature of many autoimmune and immune-mediated disorders [36]. Comparative studies indicate that coagulation and innate immunity have a common evolutionary origin [37, 38]. It is therefore not surprising that the immune system and coagulations system are linked, with many molecular components being important for both systems [23, 39-42]. Inflammatory pathways and coagulation are integrated by extensive crosstalk and a tendency to function in concert [23, 39-42]. They comprise a large number of cellular and molecular factors, which interact in a very complex manner [23, 39-42]. Some of the central features of the hypercoagulability induced by inflammation are cytokine induction of tissue factor (TF) expression, endothelial dysfunction, inhibition of the protein C system and inhibition of fibrinolysis (increased plasminogen activator inhibitor 1 levels) (Figure 1) [23, 39-42]. Other important players that contribute to inflammation-induced hypercoagulability are platelets, microparticles (MP), neutrophils, thrombin and protease-activated receptors, fibrinogen, α1-antitrypsin, heparin proteoglycans and the contact system (Factor XII and the kallikrein-kinin system) [23, 39-42].

Especially interesting are the effects of inflammation on the protein C system. Genetic defects affecting the protein C system (deficiencies in protein S and protein C, and the factor V Leiden Gln506 (rs6025) mutation associated with activated resistance to protein C) are the most common inherited risk factors for venous thrombosis [5, 12]. Complete lack of protein C or protein S results in a fatal microvascular thrombotic disease (purpura fulminans) in the neonatal period [5]. This indicates that the protein C system is vitally important to keep the blood in a fluid state [5].

Protein C pathway

The anticoagulant protein C system regulates the activity of the coagulation factors VIIIa and Va, cofactors in the activation of factor X and prothrombin, respectively [5]. Protein C is activated on the endothelium by the thrombin-thrombomodulin-EPCR (endothelial protein C receptor) complex [5]. Activated protein C (APC)-mediated cleavage of factors VIIIa and Va occurs on negatively-charged phospholipid membranes and involves protein cofactors, protein S and factor V [5]. APC also has anti-inflammatory and anti-apoptotic activities that involve binding of APC to EPCR and cleavage of protease-activated receptor-1 (PAR-1) [43, 44]. Thus, inhibition of the protein C system may augment the inflammatory response.

Tumor necrosis factor (TNF)-α and other inflammatory mediators can down-regulate EPCR and thrombomodulin (TM), while interleukin (IL)-6 can depress levels of protein S in experimental animals [43, 44]. Neutrophils may also decrease TM activity through cleavage of TM by elastase or oxidation of methionine on TM by reactive oxygen species [43, 44].

Another link between the protein C system and the complement pathway is the high-affinity interaction between the anticoagulant vitamin K-dependent protein S and the complement regulator C4b-binding protein (C4BP) [45]. Free protein S is a cofactor for APC in the inactivation of factor Va and factor VIIIa [5]. Approximately 70% of total protein S circulates in complex with C4BP; the remainder is free [45]. The free form is mainly responsible for the anticoagulant activity of protein S. The high-affinity binding of protein S to C4BP may direct C4BP to negatively-charged phospholipid membranes, thereby localizing complement regulatory activity to the membrane [45]. In inherited protein S deficiency, the tight binding of protein S to C4BP results in a pronounced and selective fall in the concentration of free protein S; the concentration of protein S in complex with C4BP is less affected [46]. C4BP is an acute-phase protein.
During inflammation, levels of C4BP molecules lacking the protein S binding site (β chain) are selectively increased. This guarantees that free protein S levels during inflammation are normal [47]. However, an acquired decrease in protein S levels due to antiphospholipid antibodies against protein S has been reported in SLE patients [48-50] and may contribute to an increased risk of thrombosis. Non-phospholipid autoantibodies against protein S have also been reported to be associated with venous thrombosis [51, 52].

**Antiphospholipid antibodies, autoimmunity and VTE**

Antiphospholipid antibodies target phospholipid-protein complexes [53-57] and have been reported to be risk factors for venous thrombosis [58-59]. These phospholipid-dependent autoantibodies include anticardiolipin antibodies, lupus anticoagulant and anti-β2 glycoprotein I antibodies. Primary antiphospholipid syndrome is an acquired condition that is characterized by venous or arterial thromboembolism, miscarriage and the presence of antiphospholipid antibodies [53-57]. Antibodies should be measurable on at least two occasions 12 weeks apart. However, absence of gold standards and marked heterogeneity in the autoantibodies make interpretation of laboratory results difficult [60]. Though antiphospholipid antibodies are a necessary feature of primary antiphospholipid syndrome, they are also common among patients with other autoimmune disorders. High prevalences of antiphospholipid antibodies have been observed in patients with SLE (33%) [61], primary systemic vasculitis (17%) [62], immune thrombocytopenic purpura (ITP) (25%) [63], thyroid disease (24%) [64], autoimmune hemolytic anemia (12%) [65] and RA (16%) [66]. Antiphospholipid antibodies may therefore be an important risk factor for thrombosis in several autoimmune disorders.

**SLE and VTE**

SLE is an autoimmune disease with a diverse array of clinical manifestations. Its incidence peaks between the age of 15 and 40 years, and it is more common in females than in males. There is strong evidence for an association between SLE and an increased risk of VTE [67, 68]. VTE occurs with a higher frequency in SLE patients compared to the general population. Moreover, SLE is also associated with premature atherosclerosis. Antiphospholipid antibodies are important risk factors for VTE among SLE patients [67, 68]. However, it not all SLE patients who develop thrombosis have antiphospholipid antibodies [61]. Other mechanisms such as inflammation, acquired protein S deficiency [48-50] and microparticles may also contribute to the thrombotic risk among SLE patients [42].

Thrombosis has been reported in about 10-26% of patients with SLE [69-75]. In one study, the risk of VTE was highest during the first 30 days after diagnosis of SLE [74]. However, in another study the risk of thrombosis remained elevated throughout the course of the disease [75]. In a large Swedish study of the risk of PE in patients hospitalized with 33 different autoimmune disorders, the risk for SLE was particularly high during the first year after diagnosis of an autoimmune disorder (Table 2), as compared to the general population [35]. In an English study of patients hospitalized with SLE, the risk of VTE was 3.7 times higher compared to a reference group of inpatients (Table 2) [34].

**IBD and VTE**

Numerous case reports and case series have described VTE in patients IBD [76-79]. A large number of studies have confirmed that the risk of VTE is increased in patients with IBD [76-86]. One study also found increased mortality from PE in IBD patients [87]. Only one study failed to show an association between VTE and IBD [88], but this study lacked a formal control group. Thus, there is strong clinical and epidemiological evidence for an increased risk of VTE among IBD patients. In a large Swedish study, the risk of PE in patients hospitalized with ulcerative colitis or Crohn’s disease was particularly high during the first year after diagnosis (Table 2), as compared to the general population [35]. A higher risk of VTE with increased disease activity (8.4 times increased compared to controls) was reported in an English study by Grainge et al [85]. Hospitalized IBD patients are at higher risk of VTE than ambulatory IBD patients, particularly in the context of active disease, and should be the focus of strategies aimed at preventing VTE among IBD patients [89].

In human and experimental murine IBD there is support for downregulation of EPCR and TM.
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TM and EPCR expression was reduced in IBD, suggesting downregulation of the protein C pathway. Moreover, recombinant APC has potent anti-inflammatory effects, downregulating cytokine-dependent cell adhesion molecule expression and chemokine production and inhibiting leukocyte adhesion. In murine colitis, administration of APC was effective in reducing weight loss, disease activity index and histological colitis scores, and inhibiting leukocyte adhesion [90]. In another study, Yoshida et al showed that elevated APC levels protected against thrombosis in a murine colitis model [91]. Thus, increasing protein C pathway activity may reduce both inflammation and the risk of thrombosis in patients with IBD [90, 91].

RA and VTE

The link between RA and VTE has not been as well studied as the ones for SLE and IBD. RA does not appear to be an additional risk factor

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<td>Ramagopalan et al[34]**</td>
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<tr>
<td>All</td>
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*Reference group: general population; **Reference group: inpatients. SIR=standardized incidence ratio, nd=not determined. Values shown in bold were significant at the 95% level.
for VTE after total knee arthroplasty [92]. However, in a large US study, DVT was diagnosed in 79,000 of 4,818,000 (1.64%) patients with RA who did not undergo joint surgery, compared with 7,681,000 of 891,055,000 patients (0.86%) who did not have RA or undergo joint surgery (relative risk (RR) = 1.90) [93]. The RR of VTE (PE and/or DVT) in these patients was 1.99. In other studies from England [34], Sweden [35] and Denmark [94] based on hospitalized patients; RA was a risk factor for VTE (Table 2). In the Danish study, the risk of VTE was high in patients with juvenile RA (RR 3.0) [94]. Thus, it appears that RA is a risk factor for VTE in hospitalized medical patients. A heightened awareness of the risk of VTE would be appropriate for hospitalized patients with RA.

Epidemiological link between autoimmunity and VTE

There is accumulating clinical, epidemiological and experimental data that an increased risk of VTE may not be limited to autoimmune conditions like Behçet’s syndrome, SLE and IBD. The inflammation associated with many autoimmune/immune-mediated disorders may increase the risk of VTE in a number of autoimmune disorders. In a study from England, Ramagopalan et al investigated the risk of VTE among patients hospitalized for 23 immune-mediated disorders (Table 2) [34]. The reference group was hospitalized patients with other diagnoses, mainly minor medical conditions [34]. The authors found that all 23 autoimmune disorders they studied were associated with an increased risk of VTE (Table 2). They found that the risk of VTE was increased both during and after the first 90 days after diagnosis. In a large Swedish study by Zöller et al, risk of PE in patients hospitalized with 33 different autoimmune/immune-mediated disorders was investigated (Table 2) [35]. The reference group was the general population adjusted for age, sex, time period and 10 different comorbidities, and the risk of PE over time was determined. For all 33 studied autoimmune disorders, the risk of PE was very high during the first year after hospitalization (Table 2) [35]. The overall risk of PE was 6.4 times higher compared to the normal population during the first year after diagnosis. Risk of PE was especially high in patients with autoimmune disorders such as immune thrombocytopenic purpura (standardized incidence ratio (SIR=11), polyarteritis nodosa (SIR=13), polymyositis/dermatomyositis (SIR=16), IBD (SIR=10) and SLE (SIR=10) (Table 2) [35] and the overall risk during whole follow up time was increased for 30 of the 33 autoimmune disorders. However, the overall risk during whole follow up time was much lower than that during the first year. The higher initial risk is most likely due to a combination of severe inflammation related to high disease activity and immobilization. Other possible factors are treatment effects (corticosteroids may affect the coagulation system) and the possibility that those patients with VTE predisposition (thrombophilia) may develop PE during the first year after diagnosis. For instance, among patients taking oral contraceptives, the risk of VTE is highest during the first year of treatment [95].

Though designs of the Swedish and English studies are somewhat different, the risk estimates for the different autoimmune disorders assessed in both studies are correlated. The correlation between the 1-year follow up PE risks in the Swedish study and the VTE risks in the English study (first versus third column in Table 2) is significant (Pearson’s coefficient 0.675; p=0.001). Correlating the overall risk for the whole follow-up period in the Swedish study (second column in Table 2) with the risk estimates from English study gives a Pearson’s coefficient of 0.643 (p=0.002). A limitation of both the English and Swedish studies is that they included only hospitalized patients, and not outpatients [34, 35]. Hospitalized patients are likely to have not only higher disease activity but also more comorbidities. Thus, the risk of VTE in outpatients with autoimmune diseases may be much lower. A Danish study of autoimmune skin disorders and connective tissue disorders based on both inpatients and outpatients by Johannesdottir et al tried to correct for comorbidities by adjusting for prescribed medicines [94]. Autoimmune skin disorders were not found to be risk factors for VTE (RR 1.0) [94]. However, autoimmune connective tissue disorders were associated with an increased risk of VTE (2.3-fold increased risk within 90 days) [94]. Further studies of outpatients with autoimmune diseases may therefore be warranted.

Is inflammation a link between VTE and atherosclerosis?

Several studies have found associations between VTE and atherosclerosis and its different
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thromboembolic manifestations, including myocardial infarction (MI) and coronary heart disease [96-100]. After the discovery of APC resistance by Dahlbäck et al [101] and the finding that factor V Leiden Gln506 (rs6025) [102, 103], the mutation that causes APC resistance in the majority of cases [104], is associated with premature MI [105], a large number of studies on this topic have been published. However, association studies of hemostatic factors and MI and CHD have produced varying results [106]. Meta-analysis data suggest that factor V Leiden Gln506 (rs6025) and the prothrombin G20210A (rs1799963), important risk factors for VTE, are only weak risk factors for CHD (RR 1.17 and 1.31, respectively) [106]. Moreover, in a nationwide Swedish family study, family history of VTE was not a strong risk factor for CHD and myocardial infarction [107]. In another nationwide Swedish family study, family history of VTE was not a strong risk factor for ischemic stroke [108]. These results argue against the existence of common shared disease-causing mutations for CHD and ischemic stroke and VTE in the Swedish population. During recent years it has become clear that systemic inflammation can increase atherogenesis [109]. It is therefore interesting that 27 of 32 immune-mediated diseases investigated in a nationwide Swedish study were associated with an increased risk of CHD during the first year after hospitalization [110]. Thus, most immune-mediated diseases are linked both to VTE and CHD [34, 35, 110], which further confirms that inflammation is a link between VTE and atherosclerosis [111].

Treatment of inflammation and risk of VTE

Treating inflammation in autoimmune and immune-mediated diseases is probably the most important way of preventing VTE, and is of course mandatory for many autoimmune/immune-mediated disorders in order to reduce morbidity and mortality. Inflammatory pathways and coagulation are integrated by extensive crosstalk and tend to function in concert [39-42]; inflammation promotes a number of procoagulant changes in the coagulation and anticoagulation systems, as discussed above. Moreover, higher inflammatory disease activity has been linked to higher VTE risk [35, 85, 89]. It is therefore a reasonable hypothesis that efficient treatment of the inflammation associated with autoimmune disorders will reduce the risk of PE and VTE. In mouse models of colitis, treatment with APC reduced inflammation and protected against thrombosis [90, 91].

A recent study found no difference in thrombotic risk between RA patients treated with anti-TNF therapy and those treated with non-biological disease-modifying antirheumatic drugs, suggesting that these newer agents are safe from a thrombotic perspective [112]. A special topic is the possible induction of procoagulant hemostatic changes by glucocorticoids [113]. Whether glucocorticoid use contributes to a hypercoagulable state, and thereby increases the thrombotic risk, is controversial [114]. A systematic review showed that the effects of glucocorticoids differ according to the clinical situation in which there is given, most likely as a result of their disease-modifying properties. The authors conclude that clinical outcome studies are needed to assess the risk-benefit of glucocorticoid use regarding thrombotic complications [114].

Prophylactic treatment with low-molecular weight heparin?

Three large well-controlled studies (MEDENOX, PREVENT and ARTEMIS) showed a consistent 50% reduction in VTE events in acutely ill medical patients treated with low-molecular weight heparin (LMWH) [115-117]. However, LMWH has failed to reduce mortality in acutely ill medical patients [118]. A systematic review concluded that heparin prophylaxis had no significant effect on mortality, but might reduce PE risk [119]. However, heparin also increased the risk of bleeding risk [119]. Benefits and risks did not differ according to the type of heparin used.

As randomized trials focused on autoimmune and immune-mediated diseases are lacking, decisions regarding prophylactic treatment in hospitalized patients have to be based on general published guidelines [120]. According to the Evidence-Based Clinical Practice Guidelines of the American College of Chest Physicians, decisions regarding prophylaxis in nonsurgical patients should be made after consideration of risk factors for both thrombosis and bleeding, clinical context, and patients’ values and preferences [120]. For acutely ill hospitalized medical patients at increased risk of thrombosis, these guidelines recommend anticoagulant thromboprophylaxis with LMWH, low-dose unfraction-
ated heparin or fondaparinux, and advise against extended thromboprophylaxis beyond the period of patient immobilization or acute hospitalization [120]. For patients at low risk of thrombosis, they advise against the use of pharmacologic prophylaxis or mechanical prophylaxis [120]. For thrombosis-prone hospitalized patients who are bleeding or are at high risk of major bleeding, they suggest mechanical thromboprophylaxis [120].

Conclusions

The immune and coagulation systems are tightly linked. Accumulating epidemiological, clinical and experimental evidence shows that an increased risk of VTE is a feature of most autoimmune disorders and immune-mediated diseases. Mechanisms involved in this association include inflammation and antiphospholipid autoantibodies. Active untreated autoimmune disorders should be considered as hypercoagulable disorders and not only inflammatory disorders. Further studies are needed to evaluate potential thrombotic mechanisms and clinical risk factors, and prophylactic strategies.

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Address correspondence to: Dr. Bengt Zöller, Center for Primary Health Care Research, Lund University/Region Skåne, Clinical Research Centre, Floor 11, Building 28, Jan Waldenströms gata 35, Skåne University Hospital, 205 02, Malmö, Sweden Tel: +46 70-6691476; Fax: +46 40-391370; E-mail: bengt.zoller@med.lu.se

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