Epidemiology and pathophysiology of venous thromboembolism: similarities with atherothrombosis and the role of inflammation

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Summary
Venous thromboembolism (VTE) is a multifactorial disease. Major provoking factors (e.g. surgery, cancer, major trauma, and immobilisation) are identified in 50–60% of patients, while the remaining cases are classified as unprovoked. However, minor predisposing conditions may be detectable in these patients, possibly concurring to the pathophysiology of the disease, especially when co-existing. In recent years, the role of chronic inflammatory disorders, infectious diseases and traditional cardiovascular risk factors has been extensively investigated. Inflammation, with its underlying prothrombotic state, could be the potential link between these risk factors, as well as the explanation for the reported association between arterial and venous thromboembolic events.

Keywords
Venous thromboembolism, etiopathogenesis, inflammation, atherothrombosis

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Introduction
The classical paradigm of the pathophysiology of venous thromboembolism (VTE) was summarised two centuries ago by the German pathologist Virchow, who described venous stasis, hypercoagulability, and endothelial damage as the major determinants of venous thrombosis (1). There are several conditions (e.g. surgery, cancer, major trauma, and immobilisation) that can induce one or more of the alterations described in the famous triad and that are clearly and independently associated with the risk of VTE. These conditions, considered as major provoking factors, can be identified in about 50% to 60% of patients with VTE (2). In the remaining patients, VTE events are classified as idiopathic or unprovoked based on current definitions (2). However, VTE is best understood as a multicausal disease resulting from the complex interaction between congenital and acquired risk factors, many of which individually determine minor effects on one or more elements of the Virchow’s triad. Although these minor risk factors are usually insufficient to cause VTE when isolated, they may determine the occurrence of the disease when co-existent (3). As a consequence, investigation on the role of these minor risk factors, which include traditional cardiovascular risk factors and inflammatory disorders, has gained increasing interest.

Epidemiology of venous thromboembolism and traditional risk factors
VTE, with an annual incidence of about 100 new cases per 100,000 persons (4–7), is the third most common vascular disorder in Western countries, after myocardial infarction and stroke (8, 9). In addition, pulmonary embolism (PE) is a leading cause of in-hospital mortality, accounting for 5 to 10% of hospital deaths (10–11). Similar to other cardiovascular diseases, the annual incidence of VTE in the general population is clearly dependent on aging, ranging from 60 cases per 100,000 persons in individuals aged between 50 and 60 years, up to 300 cases per 100,000 persons in individuals aged 70 to 80 years (12). This finding is not surprising from a pathophysiologic standpoint, due to the higher prevalence of major risk factors for VTE in older subjects (e.g. cancer, hospitalisation, and reduced mobility) (13) and to the modifications of the vascular wall (mainly endothelial dysfunction) and of the coagulation cascade associated with aging (14, 15).

In addition, and similar to other cardiovascular diseases, the epidemiology of VTE differs among ethnicities. For example, the annual incidence of VTE in the north-American population of African origin has been reported to be about 318 cases per 100,000 persons (16); in the European Union this incidence, mostly calculated in Caucasians, was about 245 per 100,000 (17), whereas in Asian countries it was much lower, with about 51–70 cases per 100,000 persons per year (18). This variation is partially attributed to differences in the prevalence of VTE risk factors associated with
the environment, such as obesity, or more likely, to the different prevalence of genetic predisposing factors, such as Factor V Leiden or Factor II G20210A mutations. In the same way, higher levels of factor VIII and von Willebrand factor and lower levels of protein C may be responsible for the increased risk in the Afro-American populations (19, 20).

Independently from age and ethnicity, a number of disease related risk factors have a substantial effect on the risk of VTE. Surgical procedures, in particular major orthopaedic surgery, neurosurgery, and cancer surgery, are associated with an overall incidence of symptomatic VTE events up to 10% in the absence of prophylactic strategies (21, 22). In patients with major trauma this incidence ranges from 1% to about 8% (23), with PE being the third leading cause of death in trauma patients surviving beyond 72 hours after trauma, and accounting for 6.5% of all deaths (24, 25). Immobilisation is another independent risk factor, resulting in up to five-fold increased risk of VTE when compared to normal mobility (26). In addition, acute medical diseases leading to immobilisation, such as heart failure, acute respiratory failure, acute infection or inflammatory disorders, are also associated with an increased risk of VTE (27). Finally, there is a well-known association between cancer and VTE, with 10 to 20% of VTE patients having concomitant overt malignancies and 4 to 10% of VTE patients having occult cancer at the time of VTE diagnosis (28). Overall, cancer increases the risk of VTE by about seven-fold, with this risk being highest in the presence of metastases and during chemotherapy (29–30).

The role of minor risk factors for VTE

Both from a research and a clinical standpoint, there is a clear need to better explain those 40 to 50% of VTE events that remain labelled as idiopathic or unprovoked, after excluding the presence of major risk factors (13, 31). Ameliorating the understanding of the mechanisms of the disease may have important clinical implications, in particular with regards to secondary prevention strategies (32). To address this key issue, it is important to recall the concept of VTE as a multicausal disease. The susceptibility to VTE is potentially explained by the clustering of several inherited and mild environmental risk factors, which act in an additive way until reaching a certain threshold.

With regards to minor inherited risk factors, in recent years, a long series of new candidate gene polymorphisms have been described to be possibly associated with VTE in addition to the well-known genetic conditions such as Factor V Leiden or prothrombin G20210A mutations or protein C, S or antithrombin deficiencies (33). Among these genetic conditions, only some have been consistently associated with VTE, including single nucleotide polymorphism within FGG gene (encoding for the fibrinogen polypeptide gamma), Factor XI gene and KNG1 gene (encoding high-molecular-weight kininogen)(34). Besides those polymorphisms, some rare mutations have been recently described to be associated with VTE, including prothrombin Yukuhashi (35), Factor IX Padua (36) and FV Nara (37). Moreover, a somatic mutation (the acquired gain-of-function mutation (V617F) within the JAK2 gene) was found to be highly prevalent among patients diagnosed with splanchnic vein thrombosis (38, 39) and to have a significant role in its development (40, 41), even in the absence of known myeloproliferative neoplasms (MPNs).

In addition to genetic risk factors, several environmental factors, including infectious diseases (42), minor trauma (43), endocrine disorders (44, 45), coeliac disease (46), chronic inflammatory disorders (47), and cardiovascular risk factors (48) have been found to be associated with VTE. All these conditions have the potential to affect the coagulation system through different mechanisms. For example, among endocrine disorders, a tendency towards a hypercoagulable state has been shown for overt hyperthyroidism (49), probably mediated by an increase of factor VIII level and von Willebrand factor (vWF) antigen level and activity (50, 51); this association has been recently confirmed in a large population based case-control study (52). High levels of factor VIII, factor IX, and vWF have also been found in Cushing syndrome (53).

In addition, a glucocorticoid-induced increase in PAI-1 levels has been described, which is positively correlated with midnight serum cortisol concentration in patients with Cushing syndrome (54). Finally, the effects of pheochromocytoma, hyperprolactinaemia and hyperaldosteronism on the coagulation system have been reported, even if the available evidence is less robust (55).

For many other minor risk factors, inflammation appears to be the most likely common link.

The role of inflammation in the pathophysiology of arterial and venous thrombosis

Traditionally, arterial and venous thrombosis have been considered as two different disease entities. Arterial thrombi, which consist mainly of platelets (white thrombi), tend to occur at sites of atherosclerotic plaque rupture where shear stress is high (56, 57). Conversely, venous thrombi, which are mainly composed of red blood cells and fibrin (red thrombi), tend to occur at sites where blood flow and shear rates are low (56, 57). Nonetheless, recent data suggest that atherothrombosis and VTE might share similar etiologic pathways and, in particular, the underlying inflammatory status.

Inflammation is a protective tissue response to different types of injuries (such as trauma or infection), which involves mainly blood vessels and leukocytes, together with several mediators (58). Since the twentieth century, atherosclerosis has been recognised as a chronic inflammatory disease (59). Inflammatory processes may have a role not only in the initiation and evolution of the atheroma, but also in the progression to acute thrombotic complications (60). The first step in atherosclerosis is arterial endothelium dysfunction which is triggered by several stimuli (such as high levels of low-density lipoprotein cholesterol or free radicals produced by cigarette smoking, diabetes mellitus and hypertension) (59). The inflammatory response leads to an increased endothelial permeability and adhesion of leukocytes (59). Moreover, proinflammatory cytokines within the atheroma direct the migration of
leukocytes into the intima and promote the replication of macrophages, which express scavenger receptors and perform phagocytosis of modified lipoproteins (60). During the evolution of the atherosclerotic lesion, leukocytes produce cytokines that stimulate the migration and replication of smooth-muscle cells, which, in response to the inflammatory stimulation, express enzymes that can degrade elastin and collagen. When the rupture of an atherosclerotic plaque occurs, the highly thrombogenic tissue factor and collagen contained in the atheroma are exposed to the circulating blood (60). The rapid thrombus formation is mainly due to the adhesion and activation of platelets, while the coagulation cascade plays only a minor role in arterial thrombosis (61).

The pathophysiology of VTE is traditionally attributed to the three elements of the Virchow’s triad: endothelial injury, venous stasis and hypercoagulability (1). More recently, a mechanistic view of VTE risk factors has been proposed, which is an extended version of the Virchow’s triad (62).

Decreased blood flow and stasis, especially near venous valves, may provoke hypoxia and oxidative stress. An intact endothelium expresses several anticoagulants, such as thrombomodulin, tissue factor pathway inhibitor and endothelial protein C receptor (63). Conversely, the venous endothelium, activated from the oxidative stress, expresses adhesion receptors with recruitment of leukocytes and platelets (62, 64). The exposure of tissue factor initiates the extrinsic pathway, while products released from damaged granulocytes activate factor XII and initiate the intrinsic pathway of coagulation (62). Therefore, activation of the coagulation system is the main step in venous thrombosis, while the role of the endothelium activation, as well as the role of platelets, still require to be better elucidated. Evidence suggest that platelets also play a role in VTE, although less important than in arterial thrombosis. However, the involvement of platelets in the formation of venous thrombi appears at a later stage, since the initial core is platelet-free, while subsequent layers contain some platelets (65). Indeed, activated platelets may catalyse both extrinsic and intrinsic thrombin generation (62).

The evidence of a correlation between inflammation and coagulation derives from basic science as well as clinical epidemiological studies. Inflammatory processes may have an influence on three key elements of coagulation: initiation and propagation of coagulation activation; downregulation of physiological anticoagulant pathways; inhibition of fibrin removal (66).

Tissue factor is the pivotal initiator of inflammation-induced thrombin generation. In severe sepsis, circulating mononuclear cells, triggered by pro-inflammatory cytokines (mainly interleukin [IL]-6), express abundant tissue factor at their surface, leading to systemic activation of coagulation (67). In fact, the complex tissue factor-factor VIIa converts factor X to Xa, which therefore generates thrombin (factor IIa). Thrombin, in turn, converts fibrinogen into fibrin.

During inflammation-induced activation of coagulation, the three major anticoagulant pathways (antithrombin, protein C system and tissue factor pathway inhibitor) are impaired (66). In severe inflammatory response, antithrombin levels are decreased because of consumption, impaired synthesis and degradation by neutrophil elastase (68). Protein C levels are low not only as a result of impaired synthesis and degradation by neutrophil elastase, but also because proinflammatory cytokines (mainly tumour necrosis factor [TNF]-α and IL-1β) downregulate thrombomodulin, a cofactor in protein C activation (69). The endogenous concentrations of tissue factor pathway inhibitor, the main inhibitor of the complex tissue factor-factor VIIa, during inflammation are insufficient to have a downstream effect on the activated coagulation cascade (66).

During inflammation, the release of plasminogen activators is increased with subsequent plasmin generation. However, a study performed in healthy volunteers showed that TNF, after early activation of fibrin removal, induces a rapid inhibition of fibrinolysis mediated by a delayed increase in plasminogen activator inhibitor-1 (70). The inhibition of fibrinolysis might be particularly evident in situations characterised by excessive release of TNF, such as septicemia where a tendency towards microvascular thrombosis has been reported (66).

These findings suggest that inflammation might shift the haemostatic balance towards a prothrombotic state. Inflammation can play a role in VTE associated with classical risk factors, such as cancer or trauma. Tumour cells activate the clotting system through the release of procoagulant substances (such as tissue factor) or through the release of inflammatory cytokines (such as TNF and IL-1) which, in turn, enhance the prothrombotic process (71). The procoagulopathy reported after severe trauma is mainly due to the release of proinflammatory cytokines, the development of disseminated intravascular coagulation and the dysregulation of tissue factor and thrombin (72). Inflammation can also play a role in unprovoked VTE, in the presence of non-major provoking factors such as inflammatory and infectious diseases and, possibly, traditional cardiovascular risk factors.

Inflammatory and infectious diseases as risk factors for venous thromboembolism

Several studies have identified inflammatory and infectious diseases as risk factors for VTE and reported a stronger association when the time between the exposure and the outcome was short (e.g. recent diagnosis of inflammatory or infectious disease or active auto-immune disorder).

Inflammatory bowel diseases (IBD), among other inflammatory and infectious diseases, are known to carry the greatest risk. A systematic review reported that patients with Crohn’s disease or ulcerative colitis have a two- to four-fold increased risk of first VTE (47). Grainge et al. showed that the risk is very high during IBD flare-ups (hazard ratio [HR] 8.4, 95% confidence interval [CI] 5.5–12.8), remains high during the chronic phase (HR 6.5, 95% CI 4.6–9.2), and also persists during remission (HR 2.1, 95% CI 1.6–2.9) (73). Moreover, IBD carries a 2.5-fold increased risk of recurrent VTE (RR 2.5, 95% CI 1.4–4.2, p = 0.001) (74).

Recently, rheumatoid arthritis (RA) has also been correlated with the development of VTE. Bacani et al. reported a higher than three-fold increased incidence of VTE in patients with a first
diagnosis of RA compared to non-RA subjects (HR 3.6, 95% CI 1.5–8.6), and a cumulative 10-year incidence of 6.7% vs 2.8% (p=0.005) (75). Chung et al. showed a slightly higher risk of developing deep-vein thrombosis (DVT) (HR 3.36, 95% CI 2.79–4.03) than PE (HR 2.07, 95% CI 1.55–2.76), when compared to matched controls (76).

In patients with chronic inflammatory diseases, such as IBD or RA, the underlying mechanism for the increased risk of VTE has been hypothesised to be related to the activation of innate and acquired immunity, especially activated leukocytes (62).

In patients with coeliac disease (CD) the predisposition to VTE seems to be related to a state of hypercoagulability, due to hyperhomocysteinaemia, elevated levels of thrombin-activatable fibrinolysis inhibitor and reduced levels of vitamin K–dependent anticoagulant proteins (protein S and C) (77). However, clinical studies found contrasting results. Ludvigsson et al. reported an increased risk of VTE in patients diagnosed with CD in adulthood compared to matched controls (0.102 vs 0.065 per 100 person-years, HR 1.86, 95% CI 1.54–2.24) (46). Conversely, Johannesdot-tir et al. found no association between CD and VTE, after adjusting for VTE risk factors, such as medication use and several co-morbidities (odds ratio [OR] 1.0, 95% CI 0.8–1.4) (78). These results suggest that the role of CD as risk factor for VTE is still not clear and that CD patients should also be considered according to their dietary pattern, since a gluten-free diet might prevent the inflammatory response triggered by gluten ingestion (77).

An association between other systemic autoimmune disorders and VTE has been suggested. For instance, Zöller et al. described a markedly increased risk for PE in the first year after hospital admission for several autoimmune diseases (incidence ratio 6.38, 95% CI 6.19–6.57), including rheumatologic, hematologic and neurologic diseases (79). Moreover, an association between psoriasis and VTE has been described (80) as well as for atopic disease (81).

The role of infections has been reported in studies assessing predisposing factors for VTE in hospitalised patients (82, 83). Furthermore, Smeeht et al. reported that community acute infections carry approximately a two-fold transient increase in the risk of VTE (42), with this risk being raised especially in the first two weeks after an acute urinary tract infection (incidence ratio for DVT 2.10, 95% CI 1.56–2.82, and for PE 2.11, 95% CI 1.38–3.23) or an acute systemic respiratory tract infection (incidence ratio for DVT 1.91, 95% CI 1.49–2.44), then gradually decreasing over months. Community-acquired bacteremia has also been reported to raise the risk of VTE, especially within 90 days of admission (OR 1.9, 95% CI 1.4–2.7 compared to hospitalised controls and OR 23.4, 95% CI 12.9–42.6 compared to population controls) (84). Among the causative pathogens, Gram-positive infections were associated with a greater increase of VTE risk (OR 2.5, 95% CI 1.6–4.1) than Gram-negative infections (OR 1.2, 95% CI 0.7–2.1), mainly due to Staphylococcus aureus (OR 7.2, 95% CI 2.7–19.2) (84).

The influenza virus has been shown to stimulate a prothrombotic state, in a mouse model, through increased thrombin generation (85). This finding has been supported by a 26% reduction in the risk of VTE with influenza vaccination in a case-control study of VTE patients matched with controls without venous or arterial thrombotic disease (86). However, more direct evidences are needed to confirm the role of influenza virus.

Other agents have been reported to be associated with VTE (e.g. *Chlamydia pneumoniae*, cytomegalovirus, or HIV), but their role is not clearly established (47).

### Cardiovascular risk factors and the development of venous thromboembolism

Several studies suggested that established cardiovascular risk factors are significantly associated with VTE. A meta-analysis of 21 case-control and cohort studies reported an increased risk for VTE in patients with obesity (OR 2.33, 95% CI 1.68–3.24), hypertension (OR 1.51, 95% CI 1.23–1.85) and diabetes mellitus (OR 1.42, 95% CI 1.12–1.77) when compared to control subjects (48). Furthermore, high-density lipoprotein (HDL) cholesterol levels were significantly lower and triglycerides levels significantly higher in VTE patients, suggesting that also dyslipidaemia may contribute to the development of VTE (48). Despite conflicting results coming from previous small studies, smoking has been recently associated with a 50% increase in the risk of developing VTE (HR 1.52, 95% CI 1.15–2.01) (87). This association has been reported for current smokers (OR 1.43, 95% CI 1.28–1.60) as well as former smokers (OR 1.23, 95% CI 1.09–1.38), and VTE risk was particularly high in young people smoking 20 or more pack-years (OR 4.30, 95% CI 2.59–7.14) (88). Male sex, a well-known risk factor for arterial thrombotic events, was independently associated with the development of first VTE (HR 1.24, 95% CI 1.08–1.42) (87) and was also reported to be correlated with VTE recurrence and therefore included in several prediction rules (89–91).

Other minor risk factors, traditionally linked to atherothrombosis, were found to be slightly associated with VTE, including diet (Western dietary pattern; red and processed meat intake; trans fatty acid intake; diet low in vegetables) (92, 93) and reduced physical activity (94). Conversely, some cardiovascular protective factors acting, at least in part, on inflammation, have been found to be associated with a lower incidence of VTE, such as vitamin E, vitamin B6 and fibre intake (92), moderate coffee consumption (95) and moderate alcohol consumption (96).

The metabolic syndrome, a combination of visceral obesity, hypertension, hyperglycaemia, dyslipidaemia with high triglycerides or low HDL cholesterol (97, 98), was recently linked to VTE. We described a higher prevalence of this condition in patients with idiopathic DVT compared to control subjects (50.5% vs 34.6%, OR 1.94, 95% CI 1.04–3.63) (99). Moreover, a recently published meta-analysis showed that metabolic syndrome is also more common in patients with VTE provoked by major thrombotic risk factors than in controls (35.1% vs 14.9%, OR 2.01, 95% CI 1.06–3.82) (100).

These findings were confirmed by a number of case-control studies (101), but not entirely by the results of two prospective cohort studies. Both in the Tromsø (102) and in the LITE...
Venous Thromboembolism

Risk of arterial thrombotic events after venous thromboembolism

The presence of common risk factors may suggest the possibility that patients with VTE are at increased risk of atherothrombosis and vice versa.

In a case-control study by Prandoni et al. (113), patients with unprovoked DVT were more likely to have symptomatic carotid plaques (47.1%) than patients with secondary thrombosis (27.4%) or age- and sex-matched controls (32.0%), with ORs of 2.3 (95% CI 1.4–3.7) and 1.8 (95% CI 1.1–2.9), respectively. In another case-control study, Hong et al. (114) found an increased prevalence of coronary arteries calcification, a different marker of systemic atherosclerosis, in patients with idiopathic VTE than in matched hospital controls without VTE (51.7% vs 28.1%), corresponding to an OR of 4.3 (95% CI 1.9–10.1).

In addition, several studies demonstrated that the long-term incidence of arterial thrombotic events after VTE is not negligible, suggesting that, in high cardiovascular risk patients, VTE might be the first symptomatic event.

In a meta-analysis by Becattini et al., the incidence of arterial cardiovascular events (acute myocardial infarction and ischaemic stroke) after VTE was 0.74 per 100 patient-years (95% CI 0.59–0.89) (115). The risk was almost two-fold higher after unprovoked VTE, when compared to the general population (incidence rate ratio [IRR] 1.87, 95% CI 1.32–2.65) and to provoked VTE (IRR 1.86, 95% CI 1.19–2.89). Data from a Danish registry, showed that the excess risk for arterial cardiovascular events was more evident during the first year of follow-up (relative risk [RR] 1.88, 95% CI 1.66–2.12 after DVT and 2.73, 95% CI 2.36–3.16 after PE, when compared to the respective control cohorts), but remained increased for up to 20 years (RR 1.26, 95% CI 1.20–1.31, and 1.31, 95% CI 1.23–1.39, respectively) (116). Moreover, a recently published study reported a statistically significant interaction of age and sex with the risk of subsequent cardiovascular events (117). In this study, the association between VTE and the development of subsequent arterial thrombotic diseases was demonstrated for women of all ages (HR 3.28, 95% CI 1.69–6.35, for women < 65 years and HR 1.55, 95% CI, 1.11–2.18, for women ≥ 65 years) and for men < 65 years (HR 2.06, 95% CI, 1.32–3.20), while no association was found in men aged ≥ 65 years.

Conversely, the presence of atherosclerosis has not been correlated with an increased risk of future VTE. Several prospective studies, investigating whether markers of subclinical atherosclerosis (increased carotid intima-media thickness or presence of carotid plaque at ultrasound) may predict the subsequent development of VTE, failed to find such an association (118–120). Interestingly, in two of these studies an association between atherosclerosis and VTE was found in the crude statistical analysis, but disappeared after adjustment for various potential confounders, such as age, sex, and ethnicity (118, 119). Therefore, it is unlikely that atherosclerosis directly increases the risk of VTE, but the hypothesis that VTE and atherosclerosis share some risk factors has been reinforced (56).

Conclusion

VTE is a multifactorial disease. Apart from major congenital and acquired risk factors, minor risk factors are currently known to contribute to the pathophysiology of the disease, especially if combined.

An association between inflammation and coagulation has also been reported. Inflammatory and infectious diseases are correlated with an increased risk for VTE and also well-established risk factors such as age, sex, and ethnicity have been associated with an increased risk of VTE. The presence of common risk factors may suggest the possibility that patients with VTE are at increased risk of atherothrombosis and vice versa.

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factors for atherothrombosis, such as obesity, have been associated with venous thrombosis. Again, inflammation appears to be the most plausible common link between the two conditions. Since patients with VTE are at increased risk of subsequent arterial thrombotic events, it may be advisable to carefully assess the presence of cardiovascular risk factors, given that these risk factors are often modifiable with appropriate lifestyle changes. This evaluation is particularly important in patients with unprovoked VTE who still represent a considerable proportion of the VTE population. Future research and experimental studies are needed to confirm whether interventions on traditional cardiovascular risk factors, while preventing arterial thrombotic events, may also reduce the risk of recurrent VTE.

Conflicts of interest
None declared.

References
39. Venous Thromboembolism


