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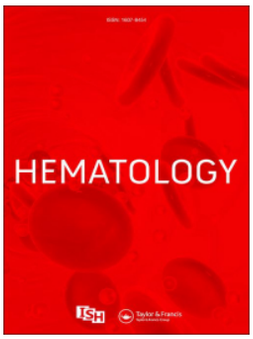

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Inflammation in deep vein thrombosis: a therapeutic target?

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ABSTRACT

Deep vein thrombosis is a common disease associated with a variety of complications including post-thrombotic syndrome as a late complication. It is now clear that in addition to classical deep vein thrombosis triggers such as blood flow disturbance, hypercoagulability, and vessel wall changes, inflammation has a key role in the pathophysiology of deep vein thrombosis, and there is a close relationship between inflammation and coagulation. As attested by changes in several plasma biomarkers, inflammation may have a significant role in the development of post-thrombotic syndrome. Here, we review the link between inflammation and deep vein thrombosis and thus the potential value of anti-inflammatory and/or anticoagulant drugs in the treatment of deep vein thrombosis and the prevention of post-thrombotic syndrome.

KEYWORDS

Deep vein thrombosis; inflammation; post-thrombotic syndrome; DOAC; heparin; neutrophil extracellular traps (NETs); P-selectin; CRP

Introduction

Deep vein thrombosis (DVT) is a relatively common disease associated with both early and late complications. Pulmonary embolism is a severe early complication of DVT, with a high mortality rate. Incident venous thromboembolism (VTE, i.e. DVT and pulmonary embolism) affects about 400,000 people a year [1], and 20–50% of these patients will develop a late complication, post-thrombotic syndrome (PTS), within two years [2]. PTS is a chronic disease, the signs and symptoms of which include leg swelling, skin changes, pain, and chronic ulceration [3–5]. Hence, PTS has a major impact on quality of life – particularly for patients with severe PTS [2].

Treatment with anticoagulants has considerably improved the acute-phase outcomes for patients with DVT [6] by preventing thrombus extension, pulmonary embolism, and the recurrence of DVT. The successive development of several drug classes, the most recent being the direct oral anticoagulants (DOACs), has clearly improved the treated patients' quality of life [7], but their use is associated with a significant bleeding risk. Moreover, there are still unmet therapeutic needs – particularly with regard to the occurrence of PTS. The acute phase of thrombosis and its clinical management can have a major impact on the occurrence of this late complication of DVT. In particular, thrombus resolution and vessel wall scarring have a pivotal role in the pathogenesis of PTS [8].

Better knowledge of the pathophysiology of DVT is therefore critical for the development of new therapeutic approaches. It is now clear that in addition to Virchow's triad (blood flow disturbance, hypercoagulability, and vessel wall changes), inflammation has a key role in triggering DVT. Several inflammation-related clinical settings such as sepsis, systemic infections, cancer, trauma, and surgery are associated with an increased risk of VTE. Inflammation might also be involved in the pathophysiology of PTS and particularly in the fibrotic vein injury, incomplete recanalization, and valve incompetence that contribute to pressure increases in the venous system following DVT [8].

Coagulation activation and inflammation are intimately related because several cellular and plasma-related factors are involved in both processes. Indeed, monocytes can display inducible tissue factor and constitute a major source of pro-inflammatory cytokines. Platelets contain polyphosphates, which act as pro-inflammatory mediators and contact system activators [9]. It was recently shown that polymorphonuclear neutrophils can produce neutrophil extracellular traps (NETs), and that the latter are highly prothrombotic [10].

Here, we review the link between inflammation and DVT and thus the potential value of anti-inflammatory and/or anticoagulant drugs in the treatment of DVT and the prevention of PTS.

Involvement of inflammation in the pathophysiology of DVT and PTS

In VTE, an inflammatory response is involved in thrombus formation, thrombus organization, and the vein recanalization process.

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Thrombus formation and organization

The endothelium is a key factor in the pathophysiology of DVT. Under resting conditions, the endothelium exerts an antithrombotic effect via the surface expression of several anticoagulant system components such as the protein C system receptors (thrombomodulin (TM) and endothelial cell protein C receptor), tissue factor pathway inhibitor, and glycosaminoglycans. Moreover, the endothelium has anticoagulant properties and acts as a physical barrier by preventing contact between the blood and the procoagulant subendothelium. However, endothelium activation leads to a shift from an anticoagulant phenotype to a procoagulant phenotype. Several agonists including pro-inflammatory cytokines like tumor necrosis factor-alpha can activate the endothelium [11]. Upon activation, endothelial cells express several adhesion molecules; these include E- and P-selectins involved in leukocyte rolling, and ICAM-1 and VCAM-1 leading to firm adhesion and transendothelial leukocyte migration. The adhesion of leukocytes and platelets appears to be essential for thrombosis initiation and propagation [12], and several ligands, such as Mac-1 on leukocytes, and GP1b alpha on platelets, are involved in the recruitment of cell to the site of injury – as evidenced by a delay in thrombosis in mice lacking Mac-1 or expressing Mac-1 with a mutation in GPIb alpha-binding site [13].

In murine models of inferior vena cava thrombosis, neutrophil infiltration occurs within a few hours [14,15]. Monocytes and macrophages then extravasate over the course of the following days. This leukocyte infiltration is promoted by the very early exposure of P-selectin – probably from the pool of P-selectin present in the membrane of the endothelial cells' Weibel-Palade bodies and platelet alpha granules. E-selectin is upregulated later, and requires mRNA synthesis [15]. The involvement of these selectins in thrombus formation has been evidenced by several means, including the generation of knock-out mice for P-selectin, E-selectin or both [16], the application of an antibody against the P-selectin receptor (PSGL-1) [17], and treatment with a small-molecule inhibitor [18]. Soluble P-selectin (sP-selectin) circulates in the plasma, and most of the soluble form originates from proteolysis of the transmembrane protein. Interestingly, it was recently shown that sP-selectin dimers can also promote immunothrombosis [19]. Similarly, soluble ICAM-1 (sICAM-1) is also found in plasma and reflects the level of endothelial and leukocyte activation.

Leukocyte infiltration into the vessel wall is associated with cytokine and chemokine production, which in turn promotes inflammation, endothelial cell activation, and coagulation. In fact, pro-inflammatory cytokines can elicit tissue factor (TF) production on the endothelium and monocytes, and thus thrombosis [20]. It has also been reported that TF can be transferred to platelets in a P-selectin-/PSGL-1 dependent manner [21], and that fibrin deposition is promoted when leukocytes bind to adherent platelets through P-selectin [22]. Moreover, P-selectin and PSLG-1 are involved in the formation of prothrombotic microparticles [23]. Intense crosstalk between coagulation and inflammation is likely to amplify these events. Indeed, coagulation activation leads to the production of thrombin, FXa, and TF-FVIIa, all of which have pro-inflammatory properties. Via the activation of protease-activated receptors (PARs), these activated coagulation factors can lead to endothelial stress [24], cytokine production, exposure of adhesion molecules on the activated endothelium, and thus inflammation.

As mentioned above, leukocytes (including neutrophils) are rapidly attracted to and retained at the site of thrombosis. The concept of 'immunothrombosis' – an interaction between the innate immune system and coagulation activation – has recently emerged [10]. In particular, it has been shown that neutrophils can promote thrombosis by releasing NETs. These structures are mainly composed of decondensed DNA, citrullinated histones, and neutrophil enzymes, particularly neutrophil elastase and myeloperoxidase (MPO). The citrullination of H3 and H4 histones (giving H3Cit and H4Cit, respectively) is followed by chromatin decondensation [25].

The process of NET formation (also referred to as NETosis) can be promote by several stimuli – notably by circulating pathogens. In this context, NETs contribute to clot formation and thus immobilization of the pathogen. However, other NETosis triggers include cytokines [26] and activated platelets [27]. In addition to their involvement in combatting infections, NETs can contribute to platelet activation and thrombus formation in a non-infectious context [12,28]. *In vitro*, the perfusion of NETs with platelet suspended in plasma resulted in platelet activation and thrombus formation [28]. In a baboon model of iliac vein thrombosis, histologic analysis of the thrombus revealed (i) the presence of NETs, and (ii) colocalization between NETs and fibrin strings. This was also observed in a mouse model of DVT induced by flow restriction in the inferior vena cava [29]. In humans, several studies have reported the presence of NETs in venous thrombi. Indeed, histologic analysis of venous thrombi from 11 patients revealed the presence of neutrophil and H3Cit. These NETs were particularly present in the growing part of the thrombus but less so in the organized part [30]. Given that NETs are resistant to fibrinolysis, they might contribute to the impairment of thrombus resolution in the pathophysiology of PTS. Interestingly, NETs are degraded by DNAses [31] and dismantled by heparins; the latter can neutralize the harmful effects of histones released when the NET breaks up [28]. Moreover,

NETosis is inhibited by aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) [32].

Lastly, it was recently reported that inorganic polyphosphate, a pro-inflammatory mediator present in platelet dense granules [9], can trigger coagulation via the contact system – again emphasizing the strong, reciprocal relationship between coagulation and inflammation. Indeed, polyphosphates released during platelet activation may then be bound on the activated platelet surface; this prompts the formation of membrane-associated inorganic polyphosphate nanoparticles able to efficiently activate factor XII [33]. It has also recently been shown that polyphosphates can contribute to the inflammatory reaction through various mechanisms – particularly by dampening the complement classical pathway [34]. Furthermore, inorganic polyphosphates amplify the inflammatory properties of both histone 4 and high mobility group box 1 displayed on endothelial cells [35]. Lastly, inorganic polyphosphates also reportedly activate the NF-κB pathway, with the upregulation of ICAM and VCAM expression and greater adhesion of monocytes to the endothelium [36].

Thrombus resolution and vessel scarring

Several mechanisms including fibrinolysis and matrix remodeling are involved in thrombus resolution and wound healing. The nature and time course of thrombus resolution may have a major impact on the occurrence of PTS because incomplete recanalization is associated with more severe PTS [37,38].

Inflammation, particularly through leukocyte recruitment in the thrombus and vessel wall, also has an important role in thrombus resolution. In addition to the polymorphonuclear neutrophils' above-mentioned role in thrombus formation via NETosis, these cells are involved in thrombus resolution and vessel wound healing. Polymorphonuclear neutrophils promote fibrinolysis through urokinase release and vessel repair through the production of collagenase and matrix metalloproteases-9 (MMP-9), both of which are involved in tissue remodeling [39]. In a murine model of stasis DVT induced in mice lacking CXCR2 (the main receptor for CXC chemokines in mice) [40], the thrombi were seen to be disorganized, with diminished leukocyte infiltration, i.e. fewer polymorphonuclear neutrophils involved in the early step of the thrombus formation but also fewer monocytes involved later on. Interestingly, thrombus resolution was also impaired.

Concerning MMPs, the macrophage-derived MMP9 [41] is particularly involved in thrombus resolution. In a murine model of thrombus resolution, MMP-9 expression was found to be significantly elevated in the thrombus and in the vessel wall in the days following DVT [42–44] Interestingly, MMP9 inactivation did not impact thrombus formation but did have a significant effect on thrombus resolution and the recovery of vessel wall elasticity, with greater wall compliance observed in MMP9 knock-out mice. Inactivation of MMP9 also resulted in greater macrophage infiltration into the thrombus and a relative reduction in the stiffness of collagen and elastin fibers during thrombus resolution – making MMP9 a potentially valuable therapeutic target [45]. Although MMP2 is also involved in thrombus resolution, it is expressed later than MMP9 [44,46,47]. Inflammation therefore has a significant impact on post-DVT vessel scarring, vessel recanalization, fibrosis, compliance, and, lastly, valve damage which is another major factor in the pathophysiology of PTS. Histologic analysis has shown that monocyte infiltration is also associated with valve damage [48]. Lastly, the increased venous pressures observed in PTS probably favor leukocyte infiltration into the vessel wall and contribute to the maintenance of a local pro-inflammatory environment in the damaged vessel.

Inflammation-related biomarkers of DVT

Given the role of inflammation in thrombus formation, organization and degradation, researchers have looked for biomarkers of inflammation with a view to better understanding the pathophysiology of DVT and to predict the occurrence and outcome of DVT. A large number of inflammation-related factors – including both conventional biomarkers (such as CRP, sP-selectin, sICAM, IL6 and other cytokines) and more specific markers (MMPs and NETs) – have therefore been evaluated as indicators of thrombus resolution and/or predictive markers for PTS. The hypothesis was that the type, intensity and duration of the inflammatory response during the acute phase of DVT influences the thrombus resolution rate and thus the development of PTS.

Cytokines and soluble adhesion molecules

The most extensively studied conventional biomarkers of inflammation include CRP and IL6. Plasma levels of CRP and IL6 are strongly linked, since CRP gene transcription depends significantly on IL6 levels [49]. In a prospective longitudinal study of 44 patients, CRP and sP-selectin levels were measured at different times during DVT and compared with data from 88 age – and sex-matched healthy controls [49]. At diagnosis, CRP levels were higher in the patients than in the controls [50]. Although the patients' CRP levels fell markedly over time, this difference was still significant at 1 month (but not at months 3 and 12). In the same cohort of patients, sP-selectin levels were significantly higher at DVT onset than in controls and then decreased rapidly within the first month. Elevated plasma sP-selectin and CRP levels upon diagnosis of DVT were also observed by Mosevoll *et al.* [51] and for sP-selectin by Vandy

et al. [52]. A similar pattern (with elevated CRP, IL6 and sICAM1 upon diagnosis) was reported in a prospective study of over 600 patients [53]. Levels of CRP and IL6 were also elevated in a small, prospective study of 73 patients with suspected DVT. Phlebography confirmed the diagnosis in 44 patients, whereas the 30 with negative phlebography results then served as controls [54]. CRP levels peaked between days 2 and 3 post-DVT, and then declined progressively. However, levels were still higher than in controls at the end of the follow-up (day 5). As expected, IL6 release occurred slightly earlier, the levels were the highest upon admission but then fell progressively to day 5, when they were still higher than in controls. Although elevated levels of inflammatory endothelial-derived proteins (such as P-selectin and von Willebrand factor) are observed during acute-phase DVT, levels of soluble thrombomodulin (sTM), considered to be a good indicator of endothelial activation, are significantly low (relative to control values) in patients at DVT onset [55]. This might be due to consumption during the acute-phase DVT of sTM, which has clear anticoagulant properties via the activation of the protein C system.

Taken as a whole, these results show that the acute DVT-related inflammatory reaction starts early and then lasts for at least 1 month, as evidenced by the presence of certain inflammatory biomarkers. One of the main difference between the above-described studies relates to the nature of the control group, i.e. healthy controls vs. patients initially suspected to have DVT; these two approaches have clear differences [51].

Cytokines and soluble adhesion molecules have also been evaluated as markers of thrombus resolution. Interestingly, Jezovnik *et al*.'s [56] study of 49 patients with idiopathic DVT found that plasma IL-6 and P-selectin levels are predictive of the vein recanalization rate 4–6 months after the acute event. Similarly, elevated IL6 and CRP levels upon diagnosis of DVT have been linked to venous outflow resistance 90 days after the acute phase; this may in part reflect persistent outflow obstruction [57]. Many researchers have sought to evaluate the relationship between inflammation and occurrence of PTS. Some studies have found that high FVIII levels (also an acute phase protein) are associated with the occurrence of PTS, [58] whereas other studies have not observed this association [59]. The same is true for other markers of inflammation (e.g. CRP); a significant association between PTS and the CRP level measured 1 year after the index DVT was observed in one study [59], whereas no associations between PTS and CRP or IL6 levels at baseline [4,60] or after 90 days [57] or 18 months of follow-up [60] were observed in other studies. Similarly, Rabinovich *et al*. reported that patients with and without PTS did not differ significantly with regard to CRP or IL6 levels [53]. However, a significant association was observed between high plasma sICAM-1 levels and the occurrence of PTS, as previously observed by Shbaklo et al. [61]. Further studies are needed to confirm or refute sICAM-1's putative value as a predictive biomarker of PTS. Indeed, marked inter-study differences in design (particularly the time interval between the acute episode and the biomarker measurement) make it hard to compare the literature data, and so probably explain the discrepancies between these results.

Matrix metalloproteases

Given the MMPs' role in thrombus resolution, plasma levels of these enzymes have been investigated as predictive markers of the incidence of PTS. Although serum levels of MMP9 are higher in patients with DVT than in healthy controls [62], this was not the case for MMP9 or MMP2 when the control group was composed of patients with an unconfirmed diagnosis [51]. In the same study, MMP8 was the only MMP tested to differ significantly as a function of the diagnosis. Moreover, patients with PTS had higher levels of MMP-8. A similar association between plasma levels of MMP-1 and PTS was reported in the same study. Further studies are needed to determine whether MMPs are indeed predictive biomarkers of PTS.

Markers of NETosis

There are few specific biomarkers of NETosis. Indeed, many researchers refer to NETosis when they have measured cell-free DNA or circulating MPO levels [63]; in fact, the former may merely reflect cellular necrosis or apoptosis, and the latter may merely reflect neutrophil degranulation. Similarly, elevated levels of circulating nucleosomes and neutrophil elastase-α1-antitrypsin complexes have been linked to a 3-fold greater risk of DVT [64] but are not specific for NETs. Levels of the NET component H3Cit [65] have been studied, particularly in the context of VTE associated with cancer [66]. Indeed, patients with elevated H3Cit levels experienced a significantly higher cumulative incidence of VTE than patients with lower levels. The proportion of MPO/H3Cit-positive neutrophils – a specific marker of NETosis – detected by flow cytometry, was also significantly higher in patients with DVT than in controls [67]. However, an association between NETosis-specific biomarkers and PTS has not been reported.

Pharmacological prevention of PTS by targeting inflammation

Given (i) the interrelation between coagulation and inflammation during DVT and (ii) the acute-phase reaction's impact on thrombus formation, organization and resolution, it is reasonable to consider inflammation as a potential target in the treatment of DVT. Inhibition of

the inflammation that occurs within hours or days of DVT may also be associated with much longer-term effects – particularly on the occurrence of PTS. Indeed, the importance of the early post-DVT period is emphasized by the finding that the intensity of anticoagulation during the first three months, but not thereafter, influences the occurrence of PTS [68]. Accordingly, several anti-inflammatory drugs have been tested for their ability to reduce the occurrence of PTS.

Anti-inflammatory drugs

Interestingly, the use of non-aspirin NSAIDs, one of the main classes of anti-inflammatory drug, was associated with a 1.8- to 2-fold increase in the risk of VTE [69,70]. However, these results must be interpreted with caution; in particular, one cannot rule out the possibility that the NSAIDs in these studies were prescribed for the treatment of underlying illnesses associated with a higher risk of VTE. Moreover, NSAID treatment was not associated with the occurrence of PTS.

Statins have pleiotropic effects, including antithrombotic and anti-inflammatory activities [71], and so have also been considered as an adjuvant treatment for DVT. Statin treatment was indeed reported to reduce the occurrence of DVT, [72] although these results are subject to debate in the literature [73]. Statins have also shown anti-inflammatory effects in rodent models of thrombosis, as evidenced by reductions in (i) the levels of several inflammatory biomarkers (including cytokines, sP-selectin), (ii) neutrophil and macrophage infiltrations, and (iii) levels of H3Cit within the thrombi [74] or the vessel wall [75]. Moreover, the observation of accelerated thrombus resolution and less DVT-induced vein wall scarring suggested that statins protect against the onset of PTS [74]. Lastly, a clinical trial assessed the adjunction of rosuvastatin to the low-molecular-weight heparin (LMWH) bemiparin; after 3 months of follow-up, the CRP level and incidence of PTS were significantly lower in the patients receiving the adjunct statin treatment [76]. However, these preliminary results must be confirmed in large clinical trials.

The pivotal role of P-selectin in the pathophysiology of venous thrombosis has prompted researchers to evaluate different ways of inhibiting this pathway [18,77,78]. Indeed, P-Selectin/PSGL-1 inhibition strategy has been assessed in a primate model of iliofemoral DVT, albeit with inconclusive results. Although the antibody was as efficacious as the LMWH enoxaparin in treating the animals, this effect was not associated with a relative decrease in inflammation or better vein re-opening [79]. However, the use of anti-PSGL-1 antibody should not be associated with an increase in the bleeding risk although this remains to be demonstrated. Similarly, inhibiting the interaction between P-selectin and PSGL-1 with specific aptamers appeared to reduce the harmful consequences of DVT on vein wall fibrosis, vein recanalization, and valve competency – suggesting that this approach had countered the development of PTS [78]. However, the inhibition of P-selectin has not yet been tested in large-scale clinical trials.

The impact of anticoagulant use during acute-phase thrombosis on inflammation

The use of anticoagulants with anti-inflammatory activities or that target pro-inflammatory coagulation proteins may also have an impact on DVT-related inflammation and the subsequent occurrence of PTS.

Heparins reportedly have anti-inflammatory properties mediated by several mechanisms (for a review, see [80,81]), and act to reduce the involvement of several important components, such as histones, L and P-selectin, Mac-1, and PECAM-1, in the inflammatory reaction. For example, heparins limit neutrophil migration into tissues. Low-molecular-weight heparins and unfractionated heparin (UFH) are also able to dismantle NETs [28], protect the endothelial glycocalyx, [82] and limit NFkB activation in LPS-activated monocytes, resulting in a relative decrease in pro-inflammatory cytokine production [83]. These effects were observed at pharmacologically relevant doses (0.1–1 IU/mL). Lastly, heparins also impair inflammation through their ability to inhibit FXa and thrombin, and it has been clearly shown that both of the latter have pleiotropic, PAR-mediated pro-inflammatory effects [84]. Indeed, thrombin and FXa have many activating effects on endothelial cells – resulting in adhesion molecule exposure, cytokine production, and increased endothelial permeability. With regard to coagulation, both UFH and LMWH increase plasma levels of tissue factor pathway inhibitor [85], which limits TF-FVIIa's protease activity and half-life, and thus reduces PAR-dependent pro-inflammatory effects. The structure–function relationship underlying the heparins' anti-inflammatory activity has not been characterized. In a cell-based model, both UFH and LMWH had similar levels of activity [83]. However, in a murine *in vivo* model of thrombosis, only LMWH (and not UFH) decreased inflammation independently of the compounds' respective anticoagulant activities [86]. Interestingly, the fact that non-anticoagulant heparins have anti-inflammatory effects [87–89] suggest that antithrombin binding is not crucial for the mediation of these effects. In a mouse model of renal ischemia-reperfusion, administration of pentasaccharide (the smallest heparin derivative) was associated with a better outcome and a lower inflammatory response [90]. Even a modified form which cannot bind antithrombin still has anti-inflammatory activity [91].

With regard to PTS, the impact of heparin treatment during the early phase of thrombosis was evaluated in the prospective HOME-LITE study of 3 months of treatment with the LMWH tinzaparin vs. long-term treatment with warfarin. The occurrence of PTS was significantly lower in the patients treated with tinzaparin [92]. Although several studies found that recanalization [93–96] was better after long-term treatment with an LMWH (relative to vitamin K antagonists (VKAs)), Daskalopoulos *et al*. [96] did not evidence a clinical reduction in PTS when comparing the two treatments.

Given that recurrent DVT is a major risk factor for PTS [5], correct anticoagulation treatment is a real challenge. Indeed, a relationship between the quality of VKA treatment and the development of PTS has been observed in various studies [3,97,98]. Interestingly, a significant increase in the incidence of PTS was observed in patients with subtherapeutic anticoagulation (defined as more than 20% [3] or more than 50% [97] of their international normalized ratio (INR) values below 2). However, Galanaud *et al*. found that the degree of INR control for patients treated with VKA was not predictive of PTS [4].

Although no specific anti-inflammatory effects have been reported for DOACs, the latter target two coagulation factors that both have pro-inflammatory properties. Hence, one can reasonably expect dabigatran (an oral direct thrombin inhibitor) to have anti-inflammatory effects. Similarly, use of an oral direct FXa inhibitor results in limited FXa availability and secondary thrombin production – both of which might help to reduce the inflammation associated with DVT. Recent studies of the effect of rivaroxaban (an oral FXa direct inhibitor) on PTS led to conflicting results. A significant reduction in the incidence of PTS was reported in 61 patients treated for 6 months with rivaroxaban, when compared with 39 patients having received overlapping, conventional treatment with LMWH (for 5–7 days) and VKA [99]. Interestingly, the patients receiving rivaroxaban in this study also exhibited significantly lower levels of fibrinogen, an inflammatory marker. In contrast, a post-hoc analysis of the Einstein DVT study data on PTS was performed for 335 patients (162 patients receiving rivaroxaban and 174 receiving enoxaparin/VKA) only revealed a non-significant trend in the risk of PTS [100]. These findings (obtained in small patient populations) need to be strengthened in a large randomized trial. Moreover, it would be of great value to compare DOACs with LMWH, since heparins are reported to have numerous direct anti-inflammatory effects in addition to those mediated by thrombin and FXa inhibition.

Conclusion

It has now been clearly established that inflammatory processes are involved in the pathophysiology of DVT and may have a significant role in the development of PTS. Changes in several plasma biomarkers attest to this inflammatory process, but none has showed clear clinical value for PTS prediction. The close relationship between inflammation and coagulation means that any therapeutic approach that targets both pathways is of potential value. Whereas several anti-inflammatory drugs have been evaluated, the lack of well-designed, large-scale, clinical trials means that no firm conclusions can yet be drawn. Anticoagulants such as LMWH, which both have anticoagulant and direct anti-inflammatory potential, might be good candidates for large-scale clinical evaluation. When considering physiological coagulation inhibitors, sTM, which has already been successfully compared with LMWH in the prevention of DVT in orthopedic surgery [101], has many anti-inflammatory properties and might be worth investigating further [102].

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References

[1] Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and Stroke Statistics-2017 Update: a report from the American Heart Association. Circulation. 2017;135(10):e146–e603.
[2] Kahn SR, Comerota AJ, Cushman M, et al. The post-thrombotic syndrome: evidence-based prevention, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. Circulation. 2014;130(18):1636–1661.
[3] Chitsike RS, Rodger MA, Kovacs MJ, et al. Risk of post-thrombotic syndrome after subtherapeutic warfarin anticoagulation for a first unprovoked deep vein thrombosis: results from the REVERSE study. J. Thromb. Haemost. JTH. 2012;10(10):2039–2044.
[4] Galanaud JP, Holcroft CA, Rodger MA, et al. Predictors of post-thrombotic syndrome in a population with a first deep vein thrombosis and no primary venous insufficiency. J. Thromb. Haemost. JTH. 2013;11(3):474–480.
[5] Stain M, Schönauer V, Minar E, et al. The post-thrombotic syndrome: risk factors and impact on the course of

thrombotic disease. J. Thromb. Haemost. JTH. 2005;3 (12):2671–2676.
[6] Barritt DW, Jordan SC. Anticoagulant drugs in the treatment of pulmonary embolism. A controlled trial. Lancet Lond. Engl. 1960;275(7138):1309–1312.
[7] Hillis CM, Crowther MA. Acute phase treatment of VTE: anticoagulation, including non-vitamin K antagonist oral anticoagulants. Thromb. Haemost. 2015;113 (6):1193–1202.
[8] ten Cate-Hoek AJ, Henke PK, Wakefield TW. The post thrombotic syndrome: Ignore it and it will come back to bite you. Blood Rev. 2016;30(2):131–137.
[9] Hassanian SM, Avan A, Ardeshirylajimi A. Inorganic polyphosphate: a key modulator of inflammation. J. Thromb. Haemost. JTH. 2017;15(2):213–218.
[10] Brinkmann V. Neutrophil extracellular traps in the second decade. J. Innate Immun. 2018;10(5–6):414–421.
[11] Pober JS. Activation and injury of endothelial cells by cytokines. Pathol. Biol. (Paris). 1998;46(3):159–163.
[12] von Brühl M-L, Stark K, Steinhart A, et al. Monocytes, neutrophils, and platelets cooperate to initiate and propagate venous thrombosis in mice in vivo. J. Exp. Med. 2012;209(4):819–835.
[13] Wang Y, Gao H, Shi C, et al. Leukocyte integrin Mac-1 regulates thrombosis via interaction with platelet GPIbα. Nat. Commun. 2017;8:15559.
[14] Saha P, Humphries J, Modarai B, et al. Leukocytes and the natural history of deep vein thrombosis: current concepts and future directions. Arterioscler. Thromb. Vasc. Biol. 2011;31(3):506–512.
[15] Wakefield TW, Henke PK. The role of inflammation in early and late venous thrombosis: are there clinical implications? Semin. Vasc. Surg. 2005;18 (3):118–129.
[16] Myers D, Farris D, Hawley A, et al. Selectins influence thrombosis in a mouse model of experimental deep venous thrombosis. J. Surg. Res. 2002;108(2):212–221.
[17] Myers DD, Schaub R, Wrobleski SK, et al. P-selectin antagonism causes dose-dependent venous thrombosis inhibition. Thromb. Haemost. 2001;85(3):423–429.
[18] Bedard PW, Clerin V, Sushkova N, et al. Characterization of the novel P-selectin inhibitor PSI-697 [2-(4-chlorobenzyl)-3-hydroxy-7,8,9,10-tetrahydrobenzo[h] quinoline-4-carboxylic acid] in vitro and in rodent models of vascular inflammation and thrombosis. J. Pharmacol. Exp. Ther. 2008;324(2):497–506.
[19] Panicker SR, Mehta-D'souza P, Zhang N, et al. Circulating soluble P-selectin must dimerize to promote inflammation and coagulation in mice. Blood. 2017;130(2):181–191.
[20] Wakefield TW, Greenfield LJ, Rolfe MW, et al. Inflammatory and procoagulant mediator interactions in an experimental baboon model of venous thrombosis. Thromb. Haemost. 1993;69(2):164–172.
[21] Lefer AM, Campbell B, Scalia R, et al. Synergism between platelets and neutrophils in provoking cardiac dysfunction after ischemia and reperfusion: role of selectins. Circulation. 1998;98(13):1322–1328.
[22] Palabrica T, Lobb R, Furie BC, et al. Leukocyte accumulation promoting fibrin deposition is mediated in vivo by P-selectin on adherent platelets. Nature. 1992;359 (6398):848–851.
[23] Hrachovinová I, Cambien B, Hafezi-Moghadam A, et al. Interaction of P-selectin and PSGL-1 generates microparticles that correct hemostasis in a mouse model of hemophilia A. Nat. Med. 2003;9(8):1020–1025.
[24] Kremers BMM, Ten Cate H, Spronk HMH. Pleiotropic effects of the hemostatic system. J. Thromb. Haemost. JTH. 2018;16(8):1464–1473.
[25] Martinod K, Demers M, Fuchs TA, et al. Neutrophil histone modification by peptidylarginine deiminase 4 is critical for deep vein thrombosis in mice. Proc. Natl. Acad. Sci. U. S. A. 2013;110(21):8674–8679.
[26] Gupta AK, Hasler P, Holzgreve W, et al. Induction of neutrophil extracellular DNA lattices by placental microparticles and IL-8 and their presence in preeclampsia. Hum. Immunol. 2005;66(11):1146–1154.
[27] Clark SR, Ma AC, Tavener SA, et al. Platelet TLR4 activates neutrophil extracellular traps to ensnare bacteria in septic blood. Nat. Med. 2007;13(4):463–469.
[28] Fuchs TA, Brill A, Duerschmied D, et al. Extracellular DNA traps promote thrombosis. Proc. Natl. Acad. Sci. U. S. A. 2010;107(36):15880–15885.
[29] Brill A, Fuchs TA, Savchenko AS, et al. Neutrophil extracellular traps promote deep vein thrombosis in mice. J. Thromb. Haemost. JTH. 2012;10(1):136–144.
[30] Savchenko AS, Martinod K, Seidman MA, et al. Neutrophil extracellular traps form predominantly during the organizing stage of human venous thromboembolism development. J. Thromb. Haemost. JTH. 2014;12(6):860–870.
[31] Jiménez-Alcázar M, Rangaswamy C, Panda R, et al. Host DNases prevent vascular occlusion by neutrophil extracellular traps. Science. 2017;358(6367):1202–1206.
[32] Lapponi MJ, Carestia A, Landoni VI, et al. Regulation of neutrophil extracellular trap formation by anti-inflammatory drugs. J. Pharmacol. Exp. Ther. 2013;345 (3):430–437.
[33] Verhoef JJF, Barendrecht AD, Nickel KF, et al. Polyphosphate nanoparticles on the platelet surface trigger contact system activation. Blood. 2017;129 (12):1707–1717.
[34] Wijeyewickrema LC, Lameignere E, Hor L, et al. Polyphosphate is a novel cofactor for regulation of complement by a serpin, C1 inhibitor. Blood. 2016;128(13):1766–1776.
[35] Dinarvand P, Hassanian SM, Qureshi SH, et al. Polyphosphate amplifies proinflammatory responses of nuclear proteins through interaction with receptor for advanced glycation end products and P2Y1 purinergic receptor. Blood. 2014;123(6):935–945.
[36] Bae J-S, Lee W, Rezaie AR. Polyphosphate elicits proinflammatory responses that are counteracted by activated protein C in both cellular and animal models. J. Thromb. Haemost. JTH. 2012;10(6):1145–1151.
[37] Johnson BF, Manzo RA, Bergelin RO, et al. Relationship between changes in the deep venous system and the development of the postthrombotic syndrome after an acute episode of lower limb deep vein thrombosis: a one- to six-year follow-up. J. Vasc. Surg. 1995;21 (2):307–313. discussion 313.
[38] Yamaki T, Nozaki M. Patterns of venous insufficiency after an acute deep vein thrombosis. J. Am. Coll. Surg. 2005;201(2):231–238.
[39] Raffetto JD, Khalil RA. Matrix metalloproteinases in venous tissue remodeling and varicose vein formation. Curr. Vasc. Pharmacol. 2008;6(3):158–172.
[40] Henke PK, Varga A, De S, et al. Deep vein thrombosis resolution is modulated by monocyte CXCR2-mediated activity in a mouse model. Arterioscler. Thromb. Vasc. Biol. 2004;24(6):1130–1137.
[41] Lepidi S, Kenagy RD, Raines EW, et al. MMP9 production by human monocyte-derived macrophages is

decreased on polymerized type I collagen. J. Vasc. Surg. 2001;34(6):1111–1118.
[42] Nosaka M, Ishida Y, Kimura A, et al. Absence of IFN-γ accelerates thrombus resolution through enhanced MMP-9 and VEGF expression in mice. J. Clin. Invest. 2011;121(7):2911–2920.
[43] Nguyen KP, McGilvray KC, Puttlitz CM, et al. Matrix metalloproteinase 9 (MMP-9) regulates vein wall biomechanics in murine thrombus resolution. PloS One. 2015;10(9):e0139145.
[44] Henke PK, Varma MR, Moaveni DK, et al. Fibrotic injury after experimental deep vein thrombosis is determined by the mechanism of thrombogenesis. Thromb. Haemost. 2007;98(5):1045–1055.
[45] Deatrick KB, Obi A, Luke CE, et al. Matrix metalloproteinase-9 deletion is associated with decreased mid-term vein wall fibrosis in experimental stasis DVT. Thromb. Res. 2013;132(3):360–366.
[46] Deatrick KB, Luke CE, Elfline MA, et al. The effect of matrix metalloproteinase 2 and matrix metalloproteinase 2/9 deletion in experimental post-thrombotic vein wall remodeling. J. Vasc. Surg. 2013;58(5):1375–1384.e2.
[47] Dahi S, Lee JG, Lovett DH, et al. Differential transcriptional activation of matrix metalloproteinase-2 and membrane type-1 matrix metalloproteinase by experimental deep venous thrombosis and thrombin. J. Vasc. Surg. 2005;42(3):539–545.
[48] Ono T, Bergan JJ, Schmid-Schönbein GW, et al. Monocyte infiltration into venous valves. J. Vasc. Surg. 1998;27(1):158–166.
[49] Li SP, Goldman ND. Regulation of human C-reactive protein gene expression by two synergistic IL-6 responsive elements. *Biochemistry (Mosc.)*. 1996;35 (28):9060–9068.
[50] Gremmel T, Ay C, Seidinger D, et al. Soluble p-selectin, D-dimer, and high-sensitivity C-reactive protein after acute deep vein thrombosis of the lower limb. J. Vasc. Surg. 2011;54(6 Suppl):48S–55S.
[51] Mosevoll KA, Lindås R, Tvedt THA, et al. Altered plasma levels of cytokines, soluble adhesion molecules and matrix metalloproteases in venous thrombosis. Thromb. Res. 2015;136(1):30–39.
[52] Vandy FC, Stabler C, Eliassen AM, et al. Soluble P-selectin for the diagnosis of lower extremity deep venous thrombosis. J. Vasc. Surg. Venous Lymphat. Disord. 2013;1(2):117–125.
[53] Rabinovich A, Cohen JM, Cushman M, et al. Inflammation markers and their trajectories after deep vein thrombosis in relation to risk of post-thrombotic syndrome. J. Thromb. Haemost. JTH. 2015;13 (3):398–408.
[54] Roumen-Klappe EM, den Heijer M, van Uum SHM, et al. Inflammatory response in the acute phase of deep vein thrombosis. J. Vasc. Surg. 2002;35(4):701–706.
[55] Bombeli T, Jutzi M, De Conno E, et al. In patients with deep-vein thrombosis elevated levels of factor VIII correlate only with von Willebrand factor but not other endothelial cell-derived coagulation and fibrinolysis proteins. Blood Coagul. Fibrinolysis Int. J. Haemost. Thromb. 2002;13(7):577–581.
[56] Jezovnik MK, Poredos P. Factors influencing the recanalisation rate of deep venous thrombosis. Int. Angiol. J. Int. Union Angiol. 2012;31(2):169–175.
[57] Roumen-Klappe EM, Janssen MCH, Van Rossum J, et al. Inflammation in deep vein thrombosis and the development of post-thrombotic syndrome: a prospective study. J. Thromb. Haemost. JTH. 2009;7 (4):582–587.
[58] Roberts LN, Patel RK, Goss DE, et al. Relationship between development of post-thrombotic syndrome and serial ultrasound, D-dimer, and factor VIII activity after a first deep venous thrombosis. J. Vasc. Surg. Venous Lymphat. Disord. 2016;4(1):28–35.
[59] Bouman AC, Smits JJM, Ten Cate H, et al. Markers of coagulation, fibrinolysis and inflammation in relation to post-thrombotic syndrome. J. Thromb. Haemost. JTH. 2012;10(8):1532–1538.
[60] de Franciscis S, Gallelli L, Amato B, et al. Plasma MMP and TIMP evaluation in patients with deep venous thrombosis: could they have a predictive role in the development of post-thrombotic syndrome? Int. Wound J. 2016;13(6):1237–1245.
[61] Shbaklo H, Holcroft CA, Kahn SR. Levels of inflammatory markers and the development of the post-thrombotic syndrome. Thromb. Haemost. 2009;101(3):505–512.
[62] Deatrick KB, Elfline M, Baker N, et al. Postthrombotic vein wall remodeling: preliminary observations. J. Vasc. Surg. 2011;53(1):139–146.
[63] Diaz JA, Fuchs TA, Jackson TO, et al. Plasma DNA is elevated in patients with deep vein thrombosis. J. Vasc. Surg. Venous Lymphat. Disord. 2013;1(4):341–348.
[64] van Montfoort ML, Stephan F, Lauw MN, et al. Circulating nucleosomes and neutrophil activation as risk factors for deep vein thrombosis. Arterioscler. Thromb. Vasc. Biol. 2013;33(1):147–151.
[65] Thålin C, Daleskog M, Göransson SP, et al. Validation of an enzyme-linked immunosorbent assay for the quantification of citrullinated histone H3 as a marker for neutrophil extracellular traps in human plasma. Immunol. Res. 2017;65(3):706–712.
[66] Mauracher L-M, Posch F, Martinod K, et al. Citrullinated histone H3, a biomarker of neutrophil extracellular trap formation, predicts the risk of venous thromboembolism in cancer patients. J. Thromb. Haemost. JTH. 2018;16(3):508–518.
[67] Lee KH, Cavanaugh L, Leung H, et al. Quantification of NETs-associated markers by flow cytometry and serum assays in patients with thrombosis and sepsis. Int. J. Lab. Hematol. 2018;40(4):392–399.
[68] Kahn SR, Kearon C, Julian JA, et al. Predictors of the post-thrombotic syndrome during long-term treatment of proximal deep vein thrombosis. J. Thromb. Haemost. JTH. 2005;3(4):718–723.
[69] Schmidt M, Christiansen CF, Horváth-Puhó E, et al. Non-steroidal anti-inflammatory drug use and risk of venous thromboembolism. J. Thromb. Haemost. JTH. 2011;9(7):1326–1333.
[70] Ungprasert P, Srivali N, Wijarnpreecha K, et al. Non-steroidal anti-inflammatory drugs and risk of venous thromboembolism: a systematic review and meta-analysis. Rheumatol. Oxf. Engl. 2015;54(4):736–742.
[71] Satoh M, Takahashi Y, Tabuchi T, et al. Cellular and molecular mechanisms of statins: an update on pleiotropic effects. Clin. Sci. Lond. Engl. 1979. 2015;129 (2):93–105.
[72] Glynn RJ, Danielson E, Fonseca FAH, et al. A randomized trial of rosuvastatin in the prevention of venous thromboembolism. N. Engl. J. Med. 2009;360 (18):1851–1861.

[73] Rahimi K, Bhala N, Kamphuisen P, et al. Effect of statins on venous thromboembolic events: a meta-analysis of published and unpublished evidence from randomised controlled trials. PLoS Med. 2012;9(9):e1001310.
[74] Kessinger CW, Kim JW, Henke PK, et al. Statins improve the resolution of established murine venous thrombosis: reductions in thrombus burden and vein wall scarring. PloS One. 2015;10(2):e0116621.
[75] Feng Y, Lei B, Zhang F, et al. Anti-inflammatory effects of simvastatin during the resolution phase of experimentally formed venous thrombi. J. Investig. Med. Off. Publ. Am. Fed. Clin. Res. 2017;65(6):999–1007.
[76] San Norberto EM, Gastambide MV, Taylor JH, et al. Effects of rosuvastatin as an adjuvant treatment for deep vein thrombosis. VASA Z. Gefasskrankheiten. 2016;45(2):133–140.
[77] Meier TR, Myers DD, Wrobleski SK, et al. Prophylactic P-selectin inhibition with PSI-421 promotes resolution of venous thrombosis without anticoagulation. Thromb. Haemost. 2008;99(2):343–351.
[78] Diaz JA, Wrobleski SK, Alvarado CM, et al. P-selectin inhibition therapeutically promotes thrombus resolution and prevents vein wall fibrosis better than enoxaparin and an inhibitor to von Willebrand factor. Arterioscler. Thromb. Vasc. Biol. 2015;35(4):829–837.
[79] Ramacciotti E, Myers DD, Wrobleski SK, et al. P-selectin/PSGL-1 inhibitors versus enoxaparin in the resolution of venous thrombosis: a meta-analysis. Thromb. Res. 2010;125(4):e138–e142.
[80] Poterucha TJ, Libby P, Goldhaber SZ. More than an anticoagulant: Do heparins have direct anti-inflammatory effects? Thromb. Haemost. 2017;117(3):437–444.
[81] Mastrolia SA, Mazor M, Holcberg G, et al. The physiologic anticoagulant and anti-inflammatory role of heparins and their utility in the prevention of pregnancy complications. Thromb. Haemost. 2015;113(6):1236–1246.
[82] Lipowsky HH, Lescanic A. Inhibition of inflammation induced shedding of the endothelial glycocalyx with low molecular weight heparin. Microvasc. Res. 2017;112:72–78.
[83] Hochart H, Jenkins PV, Smith OP, et al. Low-molecular weight and unfractionated heparins induce a downregulation of inflammation: decreased levels of proinflammatory cytokines and nuclear factor-kappaB in LPS-stimulated human monocytes. Br. J. Haematol. 2006;133(1):62–67.
[84] Esmon CT. Targeting factor Xa and thrombin: impact on coagulation and beyond. Thromb. Haemost. 2014;111(4):625–633.
[85] Lupu C, Poulsen E, Roquefeuil S, et al. Cellular effects of heparin on the production and release of tissue factor pathway inhibitor in human endothelial cells in culture. Arterioscler. Thromb. Vasc. Biol. 1999;19(9):2251–2262.
[86] Downing LJ, Strieter RM, Kadell AM, et al. Low-dose low-molecular-weight heparin is anti-inflammatory during venous thrombosis. J. Vasc. Surg. 1998;28(5):848–854.
[87] Gao Y, Li N, Fei R, et al. P-Selectin-mediated acute inflammation can be blocked by chemically modified heparin, RO-heparin. Mol Cells. 2005;19(3):350–355.
[88] Rao NV, Argyle B, Xu X, et al. Low anticoagulant heparin targets multiple sites of inflammation, suppresses heparin-induced thrombocytopenia, and inhibits interaction of RAGE with its ligands. Am. J. Physiol. Cell Physiol. 2010;299(1):C97–C110.
[89] Gonzales JN, Kim K, Zemskova MA, et al. Low anticoagulant heparin blocks thrombin-induced endothelial permeability in a PAR-dependent manner. Vascul. Pharmacol. 2014;62(2):63–71.
[90] Frank RD, Schabbauer G, Holscher T, et al. The synthetic pentasaccharide fondaparinux reduces coagulation, inflammation and neutrophil accumulation in kidney ischemia-reperfusion injury. J. Thromb. Haemost. JTH. 2005;3(3):531–540.
[91] Frank RD, Holscher T, Schabbauer G, et al. A non-anticoagulant synthetic pentasaccharide reduces inflammation in a murine model of kidney ischemia-reperfusion injury. Thromb. Haemost. 2006;96(6):802–806.
[92] Hull RD, Pineo GF, Brant R, et al. Home therapy of venous thrombosis with long-term LMWH versus usual care: patient satisfaction and post-thrombotic syndrome. Am. J. Med. 2009;122(8):762–769.e3.
[93] Gonzalez-Fajardo JA, Arreba E, Castrodeza J, et al. Venographic comparison of subcutaneous low-molecular weight heparin with oral anticoagulant therapy in the long-term treatment of deep venous thrombosis. J. Vasc. Surg. 1999;30(2):283–292.
[94] López-Beret P, Orgaz A, Fontcuberta J, et al. Low molecular weight heparin versus oral anticoagulants in the long-term treatment of deep venous thrombosis. J. Vasc. Surg. 2001;33(1):77–90.
[95] Romera A, Cairols MA, Vila-Coll R, et al. A randomised open-label trial comparing long-term sub-cutaneous low-molecular-weight heparin compared with oral-anticoagulant therapy in the treatment of deep venous thrombosis. Eur. J. Vasc. Endovasc. Surg. Off. J. Eur. Soc. Vasc. Surg. 2009;37(3):349–356.
[96] Daskalopoulos ME, Daskalopoulou SS, Tzortzis E, et al. Long-term treatment of deep venous thrombosis with a low molecular weight heparin (tinzaparin): a prospective randomized trial. Eur. J. Vasc. Endovasc. Surg. Off. J. Eur. Soc. Vasc. Surg. 2005;29(6):638–650.
[97] van Dongen CJJ, Prandoni P, Frulla M, et al. Relation between quality of anticoagulant treatment and the development of the postthrombotic syndrome. J. Thromb. Haemost. JTH. 2005;3(5):939–942.
[98] Ziegler S, Schillinger M, Maca TH, et al. Post-thrombotic syndrome after primary event of deep venous thrombosis 10 to 20 years ago. Thromb. Res. 2001;101(2):23–33.
[99] Jeraj L, Jezovnik MK, Poredos P. Rivaroxaban versus warfarin in the prevention of post-thrombotic syndrome. Thromb. Res. 2017;157:46–48.
[100] Cheung YW, Middeldorp S, Prins MH, et al. Post-thrombotic syndrome in patients treated with rivaroxaban or enoxaparin/vitamin K antagonists for acute deep-vein thrombosis. A post-hoc analysis. Thromb. Haemost. 2016;116(4):733–738.
[101] Kearon C, Comp P, Douketis J, et al. Dose-response study of recombinant human soluble thrombomodulin (ART-123) in the prevention of venous thromboembolism after total hip replacement. J. Thromb. Haemost. JTH. 2005;3(5):962–968.
[102] Loghmani H, Conway EM. Exploring traditional and nontraditional roles for thrombomodulin. Blood. 2018;132(2):148–158.