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REVIEW

Venous Thromboembolism: Review of Clinical Challenges, Biology, Assessment, Treatment, and Modeling

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Abstract

Venous thromboembolism (VTE) is a massive clinical challenge, annually affecting millions of patients globally. VTE is a particularly consequential pathology, as incidence is correlated with extremely common risk factors, and a large cohort of patients experience recurrent VTE after initial intervention. Altered hemodynamics, hypercoagulability, and damaged vascular tissue cause deep-vein thrombosis and pulmonary embolism, the two permutations of VTE. Venous valves have been identified as likely locations for initial blood clot formation, but the exact pathway by which thrombosis occurs in this environment is not entirely clear. Several risk factors are known to increase the likelihood of VTE, particularly those that increase inflammation and coagulability, increase venous resistance, and damage the endothelial lining. While these risk factors are useful as predictive tools, VTE diagnosis prior to presentation of outward symptoms is difficult, chiefly due to challenges in successfully imaging deep-vein thrombi. Clinically, VTE can be managed by anticoagulants or mechanical intervention. Recently, direct oral anticoagulants and catheter-directed thrombolysis have emerged as leading tools in resolution of venous thrombosis. While a satisfactory VTE model has yet to be developed, recent strides have been made in advancing in silico models of venous hemodynamics, hemorheology, fluid–structure interaction, and clot growth. These models are often guided by imaging-informed boundary conditions or inspired by benchtop animal models. These gaps in knowledge are critical targets to address necessary improvements in prediction and diagnosis, clinical management, and VTE experimental and computational models.

Keywords Venous thromboembolism · Modeling · Thrombosis · Hemodynamics · Modeling

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Clinical Challenges of Venous Thromboembolism

Epidemiology and Associated Complications

Hemostasis is a collection of complementary processes that maintain blood flow within the body, chiefly acting through the clotting response to vascular damage. Venous thrombosis is a result of perturbed hemostatic pathways, poor venous return, and endothelial cell dysfunction. Coagulation of venous blood is triggered by flow stagnation, exposure to extracellular proteins, and high concentrations of blood factors [1–3], resulting in a complex web of interacting mechanical stimuli and biochemical reactions. Due to pathological conditions or altered blood flow, venous thrombosis can occur in the absence of any vascular injury and result in serious complications. Typically, this pathological thrombosis occurs in the deep venous system due to a combination of reduced flow or stasis, increased blood coagulability, and vessel wall dysfunction that form the components of Virchow's triad [4]. Deep vein thrombosis (DVT) is most common in the leg and pelvic veins and is classified as either proximal DVT (iliac, popliteal, femoral, and deep femoral veins) or distal DVT (peroneal, posterior, and anterior tibial veins) [5–7]. Once the thrombus has formed, it can detach and be transported to the heart via the inferior vena cava. Consequently, the embolus enters the narrow pulmonary circuit and occludes the pulmonary arteries, causing a pulmonary embolism (PE).

Venous thromboembolism (VTE), a collective term to describe DVT with or without PE, is a major public health problem, with high mortality and recurrence rates, with an annual incidence in the United States of up to 900,000 individuals and prevalence increasing exponentially for elderly patients of both sexes [8–11]. At least half of DVT cases can progress to a PE within three months with serious outcomes [12], including death. The risk of early death among DVT patients with PE is 18-fold higher than among patients that present with DVT alone [13]. However, this risk gradually decreases over time in those treated; after three months, the survival rate among patients with PE is similar to survival among patients with only DVT [8, 14]. The signs and symptoms of DVT include pain and asymmetrical swelling in the affected limb. The onset of PE is accompanied by a new set of symptoms: from shortness of breath and pleuritic chest pain to sudden collapse or death. Depending on the degree of occlusion, a PE can increase pulmonary vascular pressure, eventually leading to right-heart failure. This results in a lower cardiac output and decreased blood pressure. Extended residence of mature pulmonary emboli in the lungs leads to chronic thromboembolic pulmonary hypertension (CTEPH), affecting ~ 2% of untreated PE patients [15]. The vascular remodeling of CTEPH patients following PE events can cause significant pulmonary hypertension leading to potential right-heart failure and death. CTEPH presents substantial challenges in both clinical diagnosis and management [16]. About 20% to 50% of patients develop a chronic complication after DVT, known as post-thrombotic syndrome (PTS) [17]. This develops when a thrombus damages the valves in the veins, causing valvular dysfunction and insufficient venous drainage. These veins become engorged with blood, dilating, and raising the venous pressure in the superficial and deep venous systems (venous hypertension), ultimately leading to skin changes, swelling, hyperpigmentation, and potentially ulceration.

Risk Factors

Several risk factors determine a patient's susceptibility to VTE, including genetics and acquired risk factors due to lifestyle and medical history (Table 1). There is a plethora of factors that may increase the risk of DVT formation, including age, elevated BMI, extended periods of bed rest such as during a hospital stay, stagnation in a deep vein due to injury or surgery, pregnancy, cancer, congestive heart failure, chronic obstructive pulmonary disease, prior VTE, or familial history of blood clots [18–20].

Biological Mechanisms of Venous Thromboembolism

Hemostasis and Thrombosis Processes

Thrombosis is a complex process that is reactive to biochemical and mechanical stimulation. The self-amplifying pathways of the coagulation cascade act in concert with the production of physiological anticoagulants that limit coagulation, comprising an elegant and balanced mechanism for maintaining hemostasis. Some of the key actors of hemostasis that are relevant to VTE are tissue factor (TF), platelets, thrombin, and plasmin. Virchow's Triad outlines the three primary etiologic determinants that lead to venous thrombus (VT) formation, namely injury to the vessel wall, blood hypercoagulability, and altered hemodynamics. These factors must be considered when constructing models of VTE [23]. Conventionally, VTE has been understood to be a function of valve incompetence and flow stagnation [24, 25], leading to the formation of "red clots" composed primarily of erythrocytes and fibrin [26]. An overview of coagulation can be found in Monroe et al. [27], while subsequent interactions between coagulation factors and platelet derived

Table 1 Summary of the most common risk factors of common venous thromboembolism [8, 9, 18–22]

Acquired transient	Acquired non-transient	Genetic
Surgery	Antiphospholipid syndrome	Antithrombin deficiency
Abdominal/thoracic	Prior VTE	Protein C deficiency
Knee/hip replacement	Cancer	Protein S deficiency
Major traumatic injury	Aging	Factor V Leiden (APC resistance)
Hospitalization	Obesity	Prothrombin G2021 OA
Acute infection/inflammatory disorder	Smoking	Dysfibrinogenemia
Oral contraceptives/hormone therapy	Chronic inflammatory disorder	Private thrombophilias
Pregnancy	Congestive heart failure	
Myocardial infarction	Chronic obstructive pulmonary disease (COPD)	
Stroke	Varicose veins	
Bed rest (>3-4 days)		
Long-distance travel	Varicose veins	
Nephrotic syndrome		

Risk factors can be separated into transient acquired conditions (left), non-transient acquired conditions (center), and genetic conditions (right)

microparticles are discussed in Sims et al., Gilbert et al., Hickey et al., Bennett et al., and Müller et al. [28–32].

While initially thought to be functionally irrelevant in VTE compared to the dominant role in the arterial system, platelets are now hypothesized to be part of early VT development, as well as directing later inflammatory cell actions [33–35]. In vitro static and dynamic flow experiments suggested that genetic deletion of von Willebrand factor (vWF) was associated with significantly reduced venous thrombus size, which was not restored with recombinant factor VIII [36]. This indicates that the release of platelet contents and vWF-mediated tethering is required to stabilize the clot prior to fibrin cross-linking. Once the platelet plug has formed, localized release of coagulation proteins and transport of platelets and coagulation factors from the freestream permit thrombus assembly. Thereafter, the extrinsic [37–40] and intrinsic [41] pathways coalesce to form a thrombus. These pathways converge to the common pathway, by which thrombin cleaves fibrinogen to form fibrin monomers that will cross-link to form a fibrin mesh.

Physiological Anticoagulant and Fibrinolytic Mechanisms

Endogenous anticoagulant processes are essential to restricting coagulation to localized sites of injury. Antithrombin (AT) and activated protein C (APC) are two of these physiological anticoagulants. AT is a liver-derived serine protease inhibitor that serves as the main circulating anticoagulant, capturing any thrombin that escapes vessel wall anticoagulant mechanisms, such as the protein C system. Thrombin production leads to the activation of Protein C, a physiological anticoagulant that works cooperatively with endothelial thrombomodulin to prevent transport and activity of thrombin beyond areas of vascular injury [37]. Physiologic clot formation is balanced by a contained process of clot lysis, which in addition to the physiological anticoagulants, prevents thrombus formation from expanding beyond the site of vessel injury. The central fibrinolytic enzyme is plasmin, a serine protease generated by the proteolytic cleavage of the proenzyme, plasminogen with primary substrates that include fibrin, fibrinogen, and other coagulation factors. Plasminogen activation provides localized proteolytic activity [42]. The major endogenous plasminogen activators (PA) are t-PA and urokinase PA (uPA). Thrombin promotes t-PA release from endothelial cells and the production of plasminogen activator inhibitor-1 (PAI-1) from endothelial cells [43, 44]. Plasmin digestion of fibrin yields D-dimer [45], a waste product that can be utilized as a marker for risk of recurrent VTE following treatment [46, 47].

Fibrinolysis is also mediated by a biochemical system of checks and balances, primarily by two plasmin inhibitors. First, α2-antiplasmin(α2-AP) is released by endothelial cells and the liver and forms a complex with plasmin, inactivating excess plasmin. The second fibrinolytic inhibitor is PAI-1, which is the primary inhibitor of plasminogen activators [48] and released by the liver and platelets during acute phase responses.

Endothelium and Thrombogenicity

Endothelial cells exhibit key regulatory behaviors that modulate vascular tension, express adhesion molecules and cytokines, and influence hemostasis by the secretion of procoagulant and anticoagulant factors [49]. The vascular endothelium produces adenosine, nitric oxide (NO), and

PGI2 and maintains a vasodilatory and local fibrinolytic state in which coagulation, platelet adhesion and activation, and leukocyte activation are suppressed. The endothelial surface normally expresses an antithrombotic phenotype, outlined in a thorough review by Wolberg *et al* [4].

Activation of the endothelium by cytokines, thrombin, and multiple other factors leads to the endothelium switching from an antithrombotic to a prothrombotic phenotype [50]. The antithrombotic phenotype is maintained by high levels of the antithrombotic proteins thrombomodulin, endothelial protein C receptor (EPCR), and TFPI, and low levels of prothrombotic proteins vWF, P-selectin, and intracellular adhesion molecule (ICAM)− 1 and production of nitric oxide. This phenotypic shift is due to multiple changes, including shedding of cell surface proteins, the exposure of the extracellular matrix, release of tissue factor, and cessation of NO expression. Endothelial release of platelet-activating factor (PAF) and endothelin-1 promotes vasoconstriction and platelet aggregation [51]. vWF, TF, PAI-1, and factor V production are subsequently increased, permitting platelet adhesion and local transport of agonists.

Experimental Venous Thrombus Resolution of Human and Murine DVT

Murine models of VT typically focus on the inferior vena cava (IVC), with various mechanisms such as ligation, stenosis, electrolytic, or chemical injury implemented to induce thrombus growth. Much discussion has occurred in the literature to examine the strengths and weaknesses of these various models [52]. Experimental venous thrombus resolution within animal models has historically been characterized by imaging and histology, with appearances similar to that in humans [53]. An unavoidable contrast between human and animal models is that humans are bipedal, providing increased hydrostatic pressure due to increased pressure from gravity. Importantly, the gap in knowledge concerning how fluid dynamics within the venous circulation affects VT has precluded progress in understanding the thrombogenic effects of arterial flows.

Inflammatory Response and VTE

Decades of in vivo studies conducted within murine models have shed light on the pathway of VTE progression. Leucocytes are important contributors to thrombosis, recanalization, and organization [54, 55]. Thrombus resolution resembles wound healing and involves profibrotic growth factors, collagen deposition, matrix metalloproteinase (MMP) expression, and activation [56, 57]. As the thrombus resolves, many pro-inflammatory factors are released into the local environment, including interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) [58]. The cellular sources of these different mediators are likely leukocytes and smooth muscle-like cells that have been incorporated into the interlapping zone of the thrombus and the adjacent vein wall. Leukocytes invade the thrombus in a specific sequence, suggesting their importance in normal thrombus resolution [55].

Polymorphonuclear leukocytes (PMN) are essential for early thrombus clearance by promoting fibrinolysis and collagenolysis [43, 45, 59, 60]. The shift between prothrombotic and prothrombolytic activities is likely determined by the timing of PMN influx and the amount of peripheral blood flow surrounding the thrombus. In a rat model of VT due to flow stasis, neutropenia was associated with larger thrombi, increased thrombus fibrotic maturity, and significantly lower intra-thrombus levels of uPA and MMP-9 [60]. Conversely, in a dynamic flow venous thrombus model, PMNs may promote thrombosis, partly due to neutrophil extracellular traps (NETs), extracellular fragments of DNA-containing histones and antimicrobial proteins [35, 61]. The NETs provide a scaffold for thrombus formation and are pro-inflammatory and prothrombotic [62].

Experimental Post-Thrombotic Vein Wall Injury

Venous endothelial injury may contribute to fibrosis of the venous wall, as well as the predisposition to recurrent thrombosis. An in vitro rat model of VT demonstrated that reduced expression of homeostatic endothelial genes such as NO and TM relative to control subjects was correlated with a loss of vWF and cell luminal staining [63]. This result suggests an increased capacity for platelet capture and subsequent thrombus initiation. Other investigations of the fibrinolytic system have found that prolonged venous stagnation is associated with decreased plasminogen activators, likely related to loss of endothelium, as well as early vein wall dysfunction [64, 65].

Recurrent DVT is a strong risk factor for PTS [66]. A recently published murine model suggests the vein wall is primed for fibrosis by recurrent VT, with increased levels of transforming growth factor-beta (TGF-β), interleukin-6 (IL-6), and MMPs in the secondary, or recurrent, post-thrombotic venous walls [67]. This study also delineated the melding and incorporation of the primary thrombus into the venous wall, contributing to the thickness, increased size, and mass of the post-thrombotic vein. Recurrent VT has also been visualized by FDG-PET and suggests a critical early role of PMNs in this process. Using real-time imaging to characterize different stages of VT maturity may allow better determination of thrombus characteristics [68].

Anatomic and Structural Factors in DVT

DVT typically starts within the venous valve sinus, the empty, bulbous area surrounding the inner leaflets of venous valves. These leaflets and valvular cusps physically thicken with aging, reducing compliance and valve closure and resulting in poor washout of the sinus and a loss of oscillatory flow patterns [69, 70]. At these high-risk locations, thrombus initiation and subsequent propagation are permitted by impaired oscillatory shear stress and loss of antithrombotic endothelial surface phenotype. Further, the hypoxemic micro-environment in the valve sinus due to poor replenishment of oxygen-rich blood may also drive changes in the endothelial phenotype, thereby promoting a procoagulant state. Other factors such as the valve geometry and shear flows mediate VT in vitro—namely, as a TF, platelet, and glycoprotein VI-dependent process [71].

Pharmacological Intervention

Anticoagulation therapy aims to prevent the occurrence of VTE (primary thromboprophylaxis) and also the recurrence of VTE (secondary thromboprophylaxis). Primary prevention is commonly used in hospitalized patients especially after invasive surgery, lower limb injuries, and bedridden patients with severe medical conditions, which increase the risk of clot formation.

To treat fresh VTE (secondary thromboprophylaxis) patient-specific treatment plans with a tailored dosage and duration are guided by balancing the risks and benefits of different anticoagulant drugs. Some anticoagulants such as unfractionated heparin have unpredictable pharmacokinetics and so require monitoring (anti-FXa assay in the case of unfractionated heparin infusion), others such as low molecular weight heparin have predictable pharmacokinetics and rarely need monitoring. The clinical practice guideline recommendations for anticoagulation therapy are divided into 2 phases: initial first three months, and extended or sometimes indefinite (beyond three months) if there is a high risk of recurrence [72–75].

Heparins and Fondaparinux

Antithrombin (previously known as antithrombin III) is a physiological inhibitor of certain activated coagulation factors. Its action is potentiated over 1000-fold by naturally produced heparins and the synthetic compound fondaparinux [76–79]. Heparins are highly sulfated glycosaminoglycans (GaGs) available in the forms of unfractionated heparin (UFH) and LMWH. The long structure of UFH allows for an inhibitory interaction with thrombin (Fig. 1) and Factor

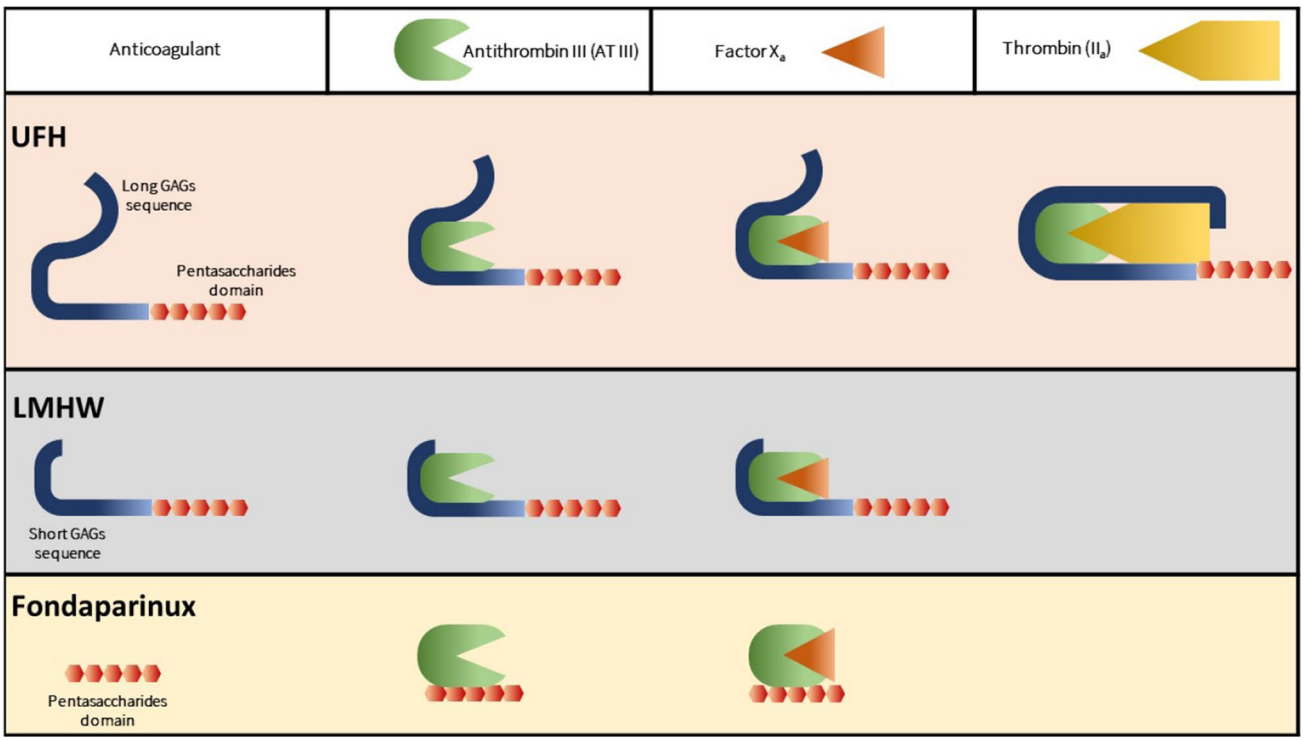

Fig. 1 Mechanism of action of unfractionated heparin (UFH), low molecular weight heparin (LMWH), and fondaparinux (Adapted with permission from Weitz [77])

Xa [77]. LMWH and fondaparinux mainly inhibit Factor Xa and are preferred due to their reliable pharmacokinetics [73, 80–83]. Complications of heparin therapies include hemorrhage, elevated liver enzymes, and osteopenia with long-term use of unfractionated heparin. Heparin-induced thrombocytopenia (HIT) is one of the most severe complications, in which an immune response-driven increase in platelet activation that can lead to extensive thrombosis [84–87]. HIT can be detected in patients by a serotonin release assay in parallel with platelet counts.

The production of Vitamin-K-dependent coagulation factors II, VII, IX, X, and the anticoagulant proteins C, S, and Z are targeted by vitamin K antagonists such as warfarin. Warfarin has been available for over 60 years and used widely in secondary thromboprophylaxis [73, 83], but much less frequently used since the arrival of direct oral anticoagulants (DOACs) as they have predictable pharmacokinetics and so do not usually require monitoring and have lower rates of intracranial bleeding than warfarin [88]. (Fig. 2). DOACs can be separated into direct inhibitors of factor Xa (apixaban, edoxaban, and rivaroxaban) and direct inhibitors of thrombin (dabigatran). Thus far, DOACs have exhibited vast improvements in treating acute VTE and extended treatment in VTE recurrence, as well as an equal risk of hemorrhage [72, 73, 88, 89]. However, their use is not recommended for patients with renal or hepatic failure due to reduced clearance rates [73, 88–91]. Overall, DOACs have proven effective with a wide range of indications for use and have become the primary oral anticoagulant treatment for VTE [92].

Mechanical Interventions

Graduated Compression Stockings and Sequential Compression Devices

Non-anticoagulant VTE prophylaxis includes graduated compression stockings (GCS) and intermittent pneumatic compression devices. GCS have gained widespread acceptance despite a lack of evidence showing efficacy in modern studies [94]. Sequential compression (SC) devices involve a cyclic application of forces applied by pneumatic manipulation of a sleeve placed around the lower limb, primarily used for bedridden patients with or without underlying compression stockings. In contrast to GCS, they have been shown to be highly efficacious in reducing risk of VTE. The inflation of these sleeves simulates walking, imitating the muscle pump mechanism, and driving venous return [95].. Recent technological advances have highlighted the efficacy of improved, wearable SC devices when used in conjunction

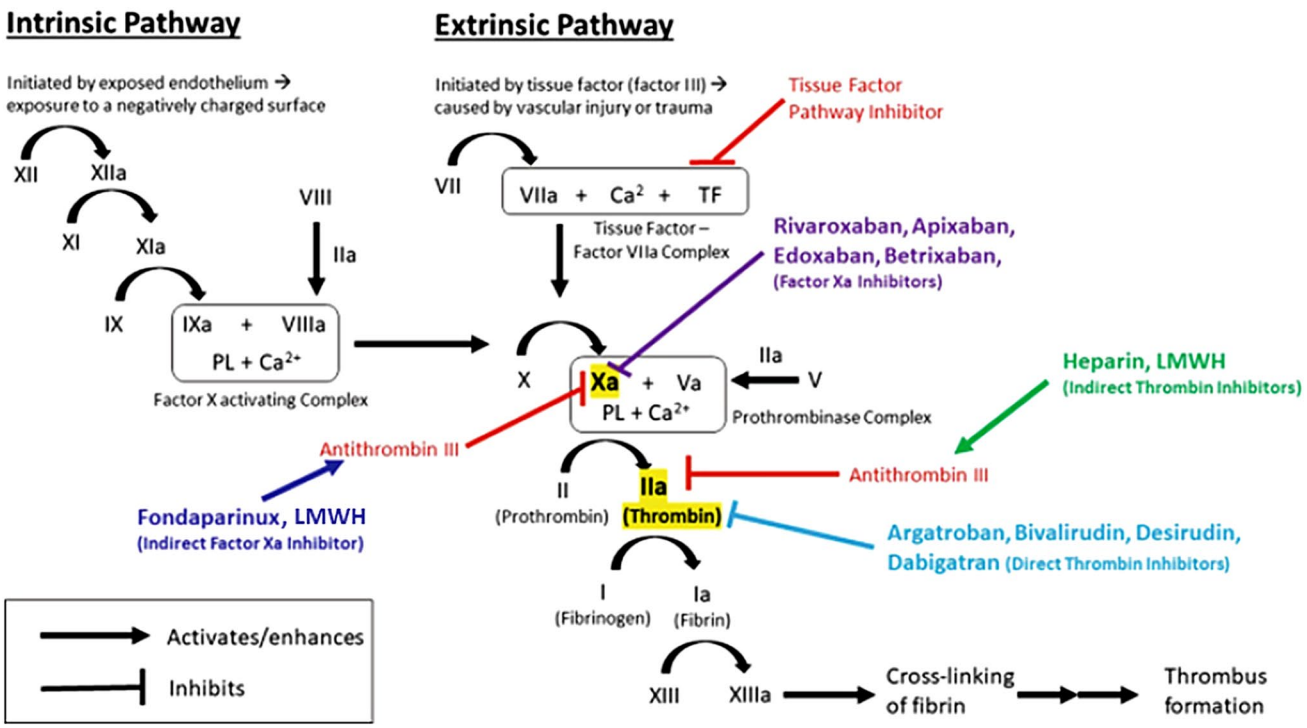

Fig. 2 Relevant targets of direct oral anticoagulants (DOACs), Heparins, and Fondaparinux in the coagulation cascade. DOACs can be further parsed into direct thrombin inhibitors or inhibitors of Factor Xa. *LMWH* lower molecular weight heparin. *PL* phospholipids. Adapted with permission from Fasinu et al. [93].

with support stockings, stressing the need for patient compliance [96].

Effects of Graduated Compression Stockings on Hemodynamics

The development of GCS has been largely guided by the intent to prevent blood stagnation in valvular sinuses. Therefore, evaluations of compression devices are usually conducted by monitoring blood flow parameters, such as peak velocity and augmentation of blood output. A Doppler ultrasound study of MCS-altered flow found that compression increased venous blood flux in the resting condition [97]. However, when a study was conducted with modern duplex ultrasound techniques, no increase in resting flow velocity was observed when MCS was worn [98, 99]. Pulsed Doppler ultrasound and MRI scanning demonstrated that grade 1 GCS decreased deep venous volume by 59%, reducing the level of pulsatility and increasing the time-averaged blood velocity in the popliteal veins [94]. This study was limited in that anatomical MRI and acquisition of velocity waveforms by Doppler ultrasound were not performed simultaneously. Additionally, velocity fields were obtained from the downstream popliteal and great saphenous veins rather than the deep calf veins due to the lack of ultrasound penetration [94]. However, the GAPS study showed that GCS had no clinical benefit in surgical patients already receiving LMWH [100].

Inferior Vena Cava Filters

Inferior vena cava (IVC) filters are devices capable of mechanically trapping emboli that have dislodged from the lower venous system [101]. These filters are implanted in patients with acute DVT of the lower extremities to prevent emboli from reaching the pulmonary circulation and causing PE. The structure of the filters consists of an umbrella-shaped or cylindrical-shaped device with legs anchored to the wall of the vessel using small hooks. The IVC filter is implanted percutaneously in the right femoral vein, right jugular vein, or another peripheral or central venous access point. The filter is placed in the inferior vena cava at either the infrarenal (below the level of the hepatic veins) or suprarenal portion. The latter position is less common and is preferred in pregnant patients due to the infrarenal compression as the fetus develops [102]. Potential complications associated with the IVC filter are insertion issues, infection, filter migration, tilting, fracture, and retrieval failure [103–105]. The various modes of failure or device-associated complications have been defined under a standard naming convention by the Society of Interventional Radiology [106].

The long-term efficacy and safety of the procedure are suboptimal [107, 108]. The PREPIC study is one of the first randomized studies that have weighed the benefits of permanent IVC filter implantation against anticoagulation alone, as determine by the prevention of PE in short- and long-term groups [109]. The early results showed that placement of a permanent IVC filter was correlated with an increased likelihood of DVT and a decreased likelihood of PE with no difference in mortality rate (DVT and PE combined) between the two groups. The authors recommended IVC filters only in a select group of patients at high risk of fatal PE. After a longitudinal study with a final follow-up at 8 years post-implantation [110], the results of the initial observation were confirmed, with IVC filters demonstrating an association with fewer symptomatic PEs and an increase in recurring DVTs. The same group has evaluated the benefit of retrieval IVC filters supplemented with anticoagulants for 3 months against anticoagulation alone in hospitalized patients with severe acute PE [111]. The results showed that the placement of an IVC filter did not reduce recurrent PE in patients with PE and DVT who had no contraindication to anticoagulant therapy.

Currently the use of IVC filters is discouraged internationally [72, 73, 102, 112, 113]: (i) The use is only recommended in patients with acute PE and absolute contraindications to anticoagulant therapy. A summary of major clinical practice guidelines for IVC filter indications can be found in the literature [103].

Systemic and Catheter-Directed Thrombolytic Therapy

Residual venous thrombosis in proximal DVT patients is a strong predictor of PTS and recurrent VTE [87, 114]. Two primary methods exist for the removal of venous thrombi: chemically induced thrombolysis and surgical thrombus removal. The goal of thrombolytic therapy is to restore vein patency, improve blood flow, preserve venous valvular function, and relieve or eliminate the symptoms. One of the advantages of fibrinolytic agents over anticoagulant drugs is that preexisting clots are actively broken down, while anticoagulants prevent the further growth of preexisting clots and further clot formation, relying on endogenous thrombolytic agents to dissolve a thrombus. Thrombolytics upregulate these endogenous factors and increase clot dissolution, typically through fibrinolysis. Thrombolytics can either be administered via an intravenous catheter upstream of the clot location or a much lower dose of thrombolytic can be used via a percutaneous catheter terminally placed directly contacting the thrombus. Percutaneous thrombolytic treatment is known as a catheter-directed technique (CDT), and it is used to improve the efficacy of the treatment and reduce the required dose of lysis drugs. CDT can be used in conjunction with targeted low-power ultrasound at a high

frequency to accelerate the thrombolytic process without imbuing mechanical force on the thrombus.

Thrombolytic drugs consist of agents that stimulate the fibrinolytic cascade, typically analogs of tissue plasminogen activator (t-PA) or urokinase, which convert plasminogen into plasmin. Plasmin also degrades fibrinogen, factors V, VII, II, and XII so patients receiving thrombolysis need monitoring for bleeding. Fibrinolytic drugs are divided into first generation (streptokinase and urokinase), second generation (alteplase), and third generation (Tenecteplase). Second- and third-generation thrombolytic drugs were developed with recombinant DNA to create recombinant tissue plasminogen activator (rtPA). rtPA is formulated with a higher affinity for bound plasminogen present on linked fibrin within the clot, rather than circulating plasminogen, reducing the occurrence of hemorrhage associated with first-generation agents.

For patients with PE, systemic thrombolytic therapy is only used in those with a high risk of dying. These are classified as "massive" or "high risk" PE and are associated with systemic hypotension (systolic blood pressure < 90 mmHg), cardiogenic shock, or respiratory failure. In selected patients with "sub-massive" or "intermediate risk" PE, small doses of lytics may be considered if there is clinical deterioration despite the use of conventional anticoagulants [113, 115].

For patients with DVT, a meta-analysis study has shown that thrombolytic therapy reduces the incidence of PTS and increases vein patency compared to a similar course of conventional anticoagulant therapy [116]. However, due to bleeding risks, thrombolytic drugs are only considered for a small selection of patients with DVT, including those with extended iliofemoral DVT who are young (<60 years) with a high risk of PTS and have no risk factors for bleeding. Catheter-directed thrombolytic therapy is preferred over systemic thrombolysis in patients with extensive DVT in the lower extremities (Phlegmasia cerulea dolens). Long-term outcomes of a randomized trial reported that CDT (without ultrasound) reduced the incidence of PTS in iliofemoral DVT patients compared to anticoagulation therapy and elastic compression stockings alone [117, 118]. However, the use of systemic, catheter-directed, and localized infusion of thrombolytics for patients with VTE has been associated with an increased risk of major hemorrhage and stroke [118–121]. A recent clinical study has shown that catheter-directed thrombolytic therapy supplemented by anticoagulation therapy does not reduce the incidence of PTS [121].

Percutaneous Mechanical Thrombolysis

Percutaneous mechanical thrombolysis, also known as mechanical thrombectomy (MT), is an endovascular procedure, which directs pressure pulses through a guided catheter capable of navigating through the venous vessel until the occlusion is reached. The catheter is placed within the thrombosed vein segment in the case of DVT, or in the pulmonary arteries in the case of PE. The MT systems are divided into groups based on the method of clot removal: rotational, suction, and rheolytic thrombectomy. More advanced systems also allow the use of a combined approach: pharmaco-mechanical thrombectomy (PMT) which uses a catheter to inject thrombolytics directly into the thrombus. Without catheter removal, the same device is employed and mechanically removes the partially dissolved clot by either fragmentation or aspiration. Table 2 describes the most used catheter-based techniques of thrombectomy for VTE treatment. As a thrombolytic therapy, PMT aims to restore blood flow to the vessel, gives immediate relief to the patient, restores venous patency, and reduces the risk of PE and other long-term complications. Good clinical trials assessing the utility of these methods are overdue.

Review of Modeling Strategies

Modeling VTE presents unique challenges due to the chronic nature of the disease and incomplete understanding of the underlying biology. As a result, a computational approach to help predict clinical incidence is lacking. Despite the underdeveloped nature of this field of modeling, it remains a potentially attractive avenue for a few predictive methods. Anticoagulation strategies, VTE recurrence, embolization, post-thrombotic syndrome prediction, and fundamental

Table 2 Catheter-based thrombus removal techniques for VTE treatment [122, 123]

Category	Technique	Description
CDT	Catheter-directed thrombolysis	Multi-hole catheter infuses thrombolytic agent locally. An angioplasty balloon may be used to increase the exposed area.
	Catheter-directed thrombolysis ultrasound assisted	Low-energy ultrasound is used to assist penetration of thrombolytic into the clot.
MT	Rotational thrombectomy	Fragmentation of the thrombus using a rotational catheter.
	Rheolytic thrombectomy	High-pressure saline jet that dislodges and aspirates thrombus.
	Suction thrombectomy	Negative pressure is applied with an aspiration syringe.
PCDT	Combination of CDT and MT techniques	

mechanisms of DVT formation are all areas in which clinically relevant understanding could be improved by the development of related computational models. The validation of these models has, thus, far proven difficult due to imaging challenges and the lack of an acute inciting event. This review explores a few considerations critical to a fully functional predictive model of VTE and some of the difficulties facing the implementation of these features.

Modeling Venous Hemodynamics and VTE

From a computational perspective, the venous hemodynamics, blood rheology, biochemistry, fluid–structure interactions (FSI) of the venous circulation, and the growth, detachment, and transport of the venous thrombus to emboli are challenging to represent in silico. Although these pillars are present in both arterial and venous flow, they are applicable in different regards and act through different mechanisms due to the stark contrasts in flow regimes. The lower shear forces of the venous system, as well as higher vascular compliance, results in the activation of different biochemical pathways within the coagulation cascade that must be accounted for in developing high-fidelity computational models [50, 124].

Venous Hemodynamics

Blood flow enters the venous return tract at the capillary bed, experiencing high compliance, and reduced flow speed relative to arteries. This increased resistance of the capillaries dampens the pulsatility imbued from the cardiac rhythm, creating a hypotensive (15 mmHg) environment that can be considered practically a continuous flow. Venous pressure is insufficient to overcome hydrostatic pressure, necessitating other pumping mechanisms, such as respiration in the upper extremities, and muscle pump action in the lower extremities, particularly below the knee. The large venous sinusoids in these muscles act as bellows, and the contraction of the calf muscles drives the flow upwards. Calf muscle contractions can produce a pressure of more than 200 mmHg, sufficient to expel blood from the sinusoids to the deep veins of the thighs. The banded muscle fibers, or fascia, surrounding these deep veins perform a similar function by driving flow upwards through the pelvis to the heart. Additionally, venous valves in large veins act in concert with the muscle pump to prevent retrograde flow (Fig. 3). The leaflets and valve cusps are structured so that blood is directed toward the heart, and the contents of superficial veins accumulate in the deep veins. Without these valves, a standing blood column from the heart to the ankle could form, unable to overcome the force of gravity [125, 126].

Rheology

Blood is a two-phase suspension of solids (primarily erythrocytes, but also white cells and platelets) that are immersed in plasma, a water-based mixture of diluted proteins (e.g., fibrinogen, albumin, cholesterol, prothrombin, etc.) with

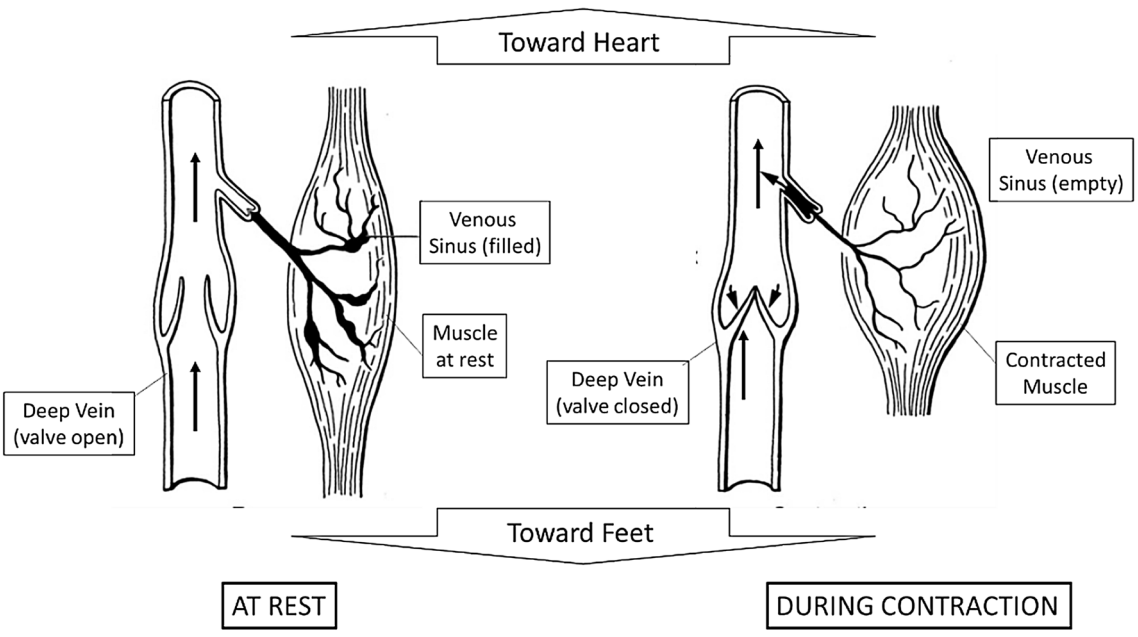

Fig. 3 Schematic illustration of the joint action of the calf muscle pumping and venous valves. Adapted from Maggisano et al. [127], figure property of Dr. Robert Maggisano

free ions (e.g., sodium, calcium, etc.). In most cases, blood can be modeled as a homogeneous mixture, a continuum in which red blood cells are responsible for the viscoelastic response, while plasma can be considered a Newtonian fluid. The fact that blood is a suspension is more evident in microcirculations where the diameter of the vessels is less than 100 μm. The Fåhræus-Lindqvist effect is the result of the scale of blood vessels approaching that of the plasma skimming layer, driving hemodynamics in arterioles, venules, and capillaries. The consequential migration of erythrocytes from the vessel wall (cell-free layer) results in a change in hematocrit and, thus, apparent viscosity as the plasma skimming layer becomes a considerable portion of the total vessel diameter. This plasma skimming layer has a significant impact on platelet adhesion. The presence of red blood cells in the vessel center drives platelets to the near wall region in a phenomenon known as platelet margination, or axial flow. Reduced hematocrit may consequently result in impaired hemostasis, due to a lower platelet population in the near wall region. Capillaries can be thinner than the diameter of a red blood cell, causing bending and a "train" of cells delineated by pockets of plasma [128]. This phenomenon is also evident at diverging bifurcations, with the fraction of red blood cell volume increasing to the high-flow branch. The mathematical considerations of hemodynamics specific to this event are discussed in a recent review [23] and are beyond the scope of this discussion. Excellent reviews of the challenges relevant to deriving the macroscopic constitutive laws for blood are available [129, 130].

Rheological modeling of whole blood is challenging due to the unique mechanical properties of red blood cells stemming from the viscoelastic membrane [131, 132]. Whole blood behaves in a non-Newtonian shear-thinning manner, while red blood cells exhibit rouleaux formation, tank treading motion, and extreme membrane deformability that confound conventional strategies of rheology [133–136]. These complexities are particularly apparent when multiscale models are considered, as linking the fidelity of molecular models to computationally efficient continuum models has proven quite challenging [137–139]. While recent advances have been made in using continuum models to predict the hemodynamics of microcirculations [140], unaddressed challenges arise when channel diameters approach the length scales of red blood cells, as in capillary flow where red blood cells travel in a single file separated by plasma. The hemodynamics at this scale are much more akin to a multiphase particle suspension than a homogenous fluid, and cannot, as of yet, be accurately compared to continuum models.

Models of Blood Viscosity

Several non-Newtonian fluid models have been proposed to describe how the effective viscosity decreases with the local shear rate. Besides the power-law model [141], a popular model is the Carreau-Yasuda formulation, where the effective viscosity is described as a function of viscosity at low and high shear rates and experimentally derived constants. Alternatively, the Casson model accounts for the yield stress of blood, incorporating constants that are dependent on hematocrit, temperature, and other physiological conditions [142]. These models are computationally inexpensive and are useful in simulating clinically relevant conditions [143–146]. While the microstructure of blood plays a vital role in determining macroscopic properties such as viscoelasticity and thixotropy, most rheological models are decoupled from the physiological microstructure [147–149]. Recent models have incorporated rouleaux breakage as a function of local shear rate and have compared favorably with numerous experimental studies [150–155]. Additional models considering hematological microstructure and the Fåhræus–Lindqvist effect have proven promising but are computationally expensive [156–161]. A thorough review of innovative strategies in the field of blood rheology has been published by Beris et al. [137], which details several recent attempts at multiscale modeling. Clinical data show that rheological traits (plasma viscosity, red blood cell concentration, distribution, and aggregation capacity) are often different for patients suffering from VTE [162–164] and that the altered rheology is also present in patients with persistent risk factors [165]. As these physiological factors are known to directly affect blood viscosity [166], patient-specific parameters might play an important role in selecting an appropriate rheological model for hemodynamics relevant to VTE.

Fluid–Structure Interaction (FSI)

Modeling the interactions between blood flow, valves, and the vessel wall in the venous circulatory system is central to understanding the flow-mediated mechanisms of VTE. To date, FSI modeling of cardiac valves, including modeling contact between the leaflets during closure and their interactions with the perivalvular apparatus, continues to be very challenging [167, 168]. FSI models can be either one-way or two-way coupled. Typically, one-way (weakly coupled) models consider only the effect of fluid motion on the deformation of the solid, while two-way (strongly coupled) models also consider the dynamic interactions between the fluid and the solid due to the changing flow field as a result of the motion of the solid. Strong coupling refers to monolithic FSI where the fluid and solid equations of motion are solved together (typically in finite element modeling using arbitrary Lagrangian–Eulerian method). Conversely, weak coupling refers to a staggered FSI where the fluid and solid equations of motion are solved separately while iterating to satisfy kinematic and dynamic boundary conditions at the

interface. Due to the high degree of valve motion, two-way FSI coupling is the current standard to accurately capture local velocity fields and the leaflets' stresses and strains [169–171]. An alternative, without coupling, is to calculate only the fluid flow, with the movement of solid boundaries prescribed from medical images [172]. Although the pressures on the venous valves are much lower than in the left heart, compliant vessels and limited availability of the tissue's biomechanical characteristics resulted in fewer studies performing FSI in veins. Cardiac valves experience dramatically different hemodynamic conditions than venous valves and are structurally and compositionally different, leading to different mechanical properties. Despite this, the similarities between the two valve types are strong enough that strategies applied to modeling cardiac valve motion might be adapted to venous valve behavior.

Significant advances were made in modeling cardiac valves in health and disease, and a recent review discusses these methods in detail [173]. While these methods could be applied to modeling venous valves, the unique physiological mechanisms that promote VTE genesis and growth in the valve sinuses (Fig. 4) need to be considered [69]. The blood flow and its interactions with the valve tissue that drives VT formation have yet to be fully characterized. A loss of hemodynamic modulation of the endothelial antithrombotic phenotype in the valve sinus could play a decisive role in determining the thrombogenic potential of a venous valve and cause potential disagreement between the model and experiment [50, 174]. In the sinus, blood circulation conditions differ from the lumen and depend on mobility. Lack of muscular activity reduces oscillatory flow in the valve sinus, resulting in flow stasis and increased residence time, a measure of the time spent by blood in each region of interest, ultimately leading to loss of oscillatory-shear-dependent transcriptional and antithrombotic phenotypes in perivalvular endothelial cells [50]. A recent review discusses genetic

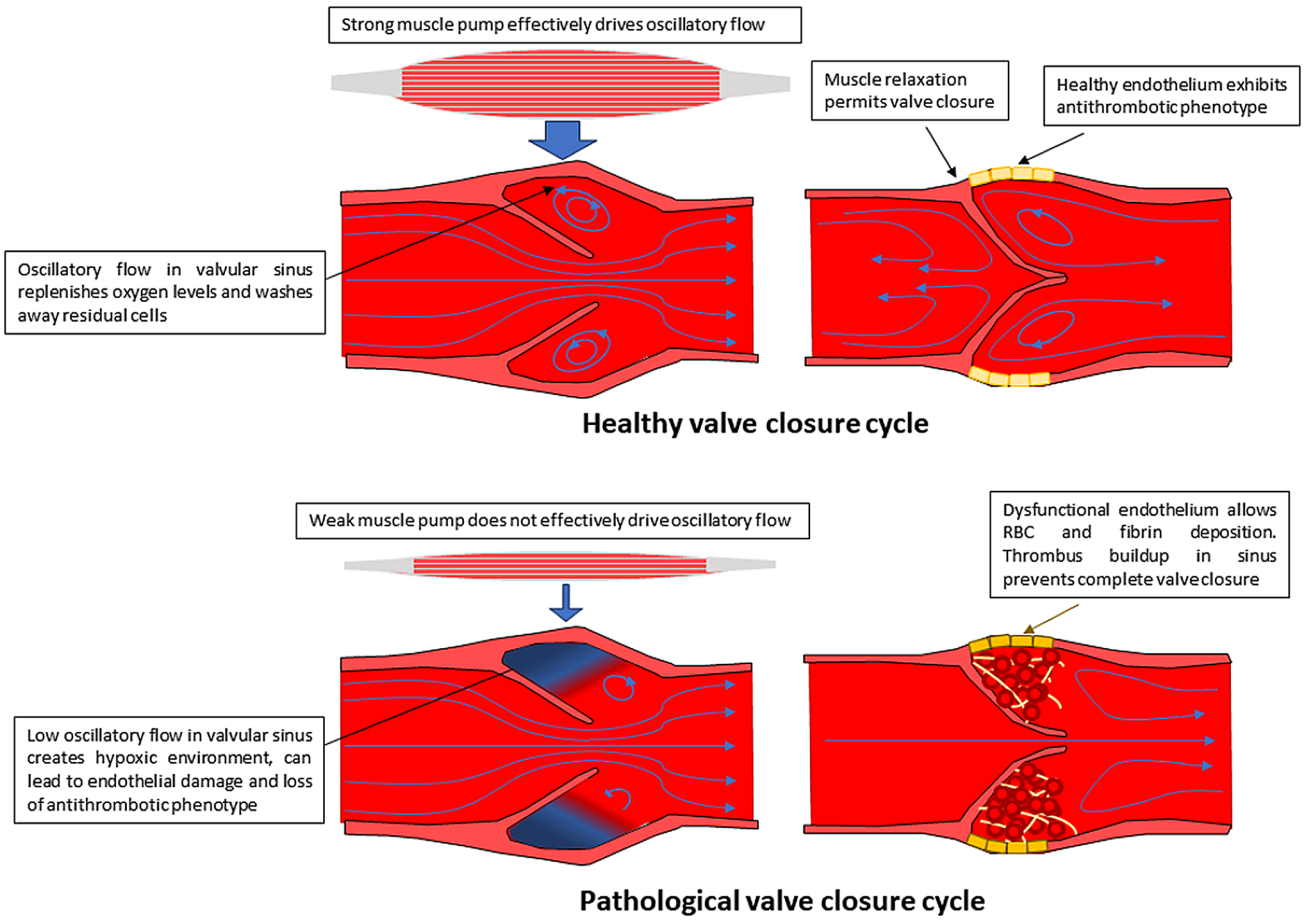

Fig. 4 Schematic of a venous valve and the related blood flow structure. The inwards-facing surfaces of the vessel are covered by endothelial cells with antithrombotic properties that depend on the oscillatory mechanical stimulus of blood flow [50]. Top left: valve is open and blood flows from the lower extremities to the right heart. Top right: valve is closed and prevents reflux. Bottom left: Weakened flow prevents oxygen-rich blood from reaching sinus endothelium. Bottom right: Damaged endothelium allow thrombus formation and further valvular incompetency.

sources of variability in hemostatic and antithrombotic function of endothelial cells [175]. Transient increase in pressure during valve closure induces additional stress and vessel stretching. While oscillatory shear is pivotal in maintaining cell function, the role of hemodynamic stresses and vessel stretching within the sinus during each closing cycle remains poorly understood. Further, it is unclear how prolonged stasis in the valve sinus during sleep does not trigger DVT, suggesting that DVT genesis involves more than one factor from Virchow's triad [174].

Impaired venous valves contribute to chronic venous insufficiency (CVI). Venous valve mechanics leading to failure remains poorly explored in this area, although it is established that valve failure and incontinence are at least partly responsible for blood reflux. CVI is caused by a combination of venous hypertension, valve incompetence, or residual chronic venous obstruction, and might be either primitive or associated with PTS [50, 66].

Most computational venous flow studies assume rigid walls for computational simplicity; however, the compliance and mechanical behavior of the venous tissue are likely critical in modeling venous hemodynamics and thromboembolism. This practice is evident in the literature, demonstrated in investigations of the efficacy of vena cava filters [176], the performance of arteriovenous grafts [177], and the influence of hemodynamics on the structure of thromboemboli and the lines of Zahn [178]. This assumption was also used in a study to assess the transport and capture of rigid spherical emboli in the presence of a filter [179]. Khodaee et al. [180] and Wang et al. [181] both used MRI-based computational fluid dynamics (CFD) to study the effect of compression stocking on the hemodynamics of the peroneal veins of 10 volunteers. These studies reported an increase in wall shear stress due to the reduction of the vessel's cross-sectional area after static compression; a recent review of the computational methods relevant to compression therapy is available [182].

Although more computationally demanding, accounting for the deformability of a patient-specific venous wall, derived from image data, and embolus would lead to more realistic transport and capture prediction. The first successful study of 3D FSI of venous valve dynamics [183] replicated the general characteristics of leaflet dynamics, albeit using some simplifying approximations (Newtonian fluid, linear rheology of valve and vein, simplified geometry). Another exciting FSI simulation in a bi-leaflet venous valve model was performed by Simão et al. [184] (Fig. 5), assuming blood as a non-Newtonian fluid and a compliant venous wall that can collapse under external forces. This model setup reproduces the experimentally observed reduction in filling

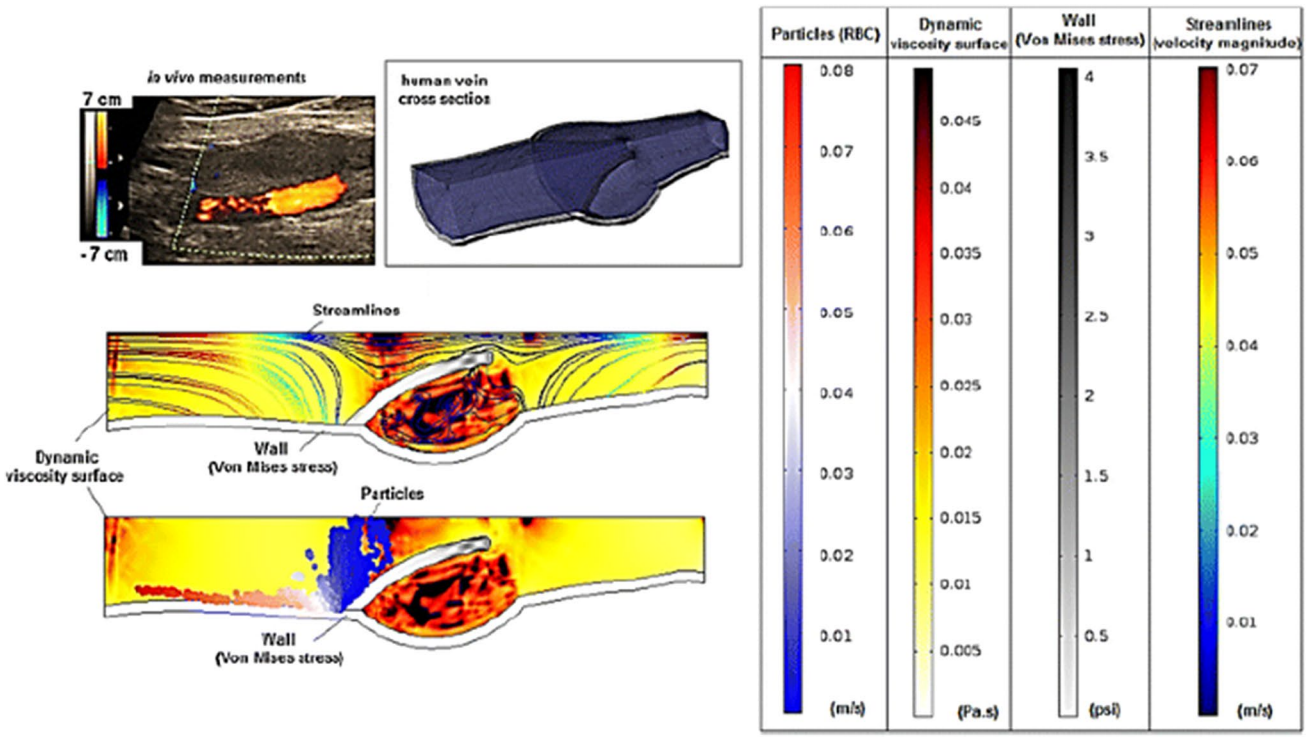

Fig. 5 Use of in vivo flow visualization to validate FSI modeling. Top left: in vivo Doppler ultrasound images and mesh reconstruction of venous valve geometry. Bottom left: FSI simulation of leaflet stress and surrounding fluid flow during valve opening. Right: Extracted values of flow velocity and leaflet stresses. Particle and streamline velocity correspond to the measured velocity in the Doppler ultrasound images. Extracted with permission from Simão et al. [184].

time in an altered valve and produces blood flow values comparable to in vivo measurements [184]. Venous valve sequential pairing was studied in silico [185], demonstrating that the optimal configuration, assessed using residence time and wall shear stress, is 4 cm spacing and 90° orientation between the two successive valves, promoting helical flow along the longitudinal venous axis and is consistent with experimental observations [185, 186]. Other FSI studies include exploring the dynamics of free emboli around flexible venous valves [187], and analyzing the leaflet stress distribution that was found to be the highest near the valve-vein junction [188].

Very few of the above FSI studies considered the biochemistry of the blood in the computational domain to simulate DVT. A biochemically intensive study [189] analyzed thrombin generation due to the recirculation region caused by an open valve and the presence of prothrombotic surface reactions in the downstream area. However, this study assumed a two-dimensional computational domain and excluded FSI in their model. In the coagulation model, prothrombin is one of the twenty-two biochemical species transported and interacts via a cascading biokinetic pattern triggered by the surface tissue factor. In all the studies cited above, with a singular exception [189], the risk of clotting is assessed very crudely, typically by tracking massless particle accumulation. An integrative computational simulation of VTE incorporating patient-specific vasculature, complex blood rheology, FSI, and realistic clot formation, evolution, and detachment model with physiologically relevant biochemical species description [190–193] is still on the horizon, although a reliable modeling framework to meet this objective is now emerging [194].

VTE Growth, Detachment, and Transport

Computational models of the later stages of clot maturation, namely the plateau in clot growth, retraction and stiffening, and detachment and transport, are relatively new and, as such, not fully developed. Clearly, it is not possible to model time scales (days, weeks) covering a thromboembolic event, whereas existing predictive thrombosis models simulate events that occur between milliseconds and minutes. While compromises are made in this regard, some recent work demonstrates promising capabilities for predicting biochemical and hemodynamics-based thromboembolism [144, 190, 195, 196]. An attractive proposition is to predict the likelihood of VTE occurrence using machine learning and patient populations with comorbidities to create predictive indices for VTE, identifying at-risk patients in need of screening [195]. While many computational models of thrombosis focus on arterial circulation and intra-device conditions, a recent numerical study investigated the role of an initial layer of platelets in clot growth under venous conditions [196]. A 3D model within an idealized venous capillary was seeded with physiological platelet counts and clotting agonist concentrations. A reduced-order equation for thrombin generation due to venous injury and subsequent clot growth was developed and shown to reasonably agree with experimental results for up to 1 hour of simulation time [196].Other models have leveraged macroscopic measurements of the clot's mechanical properties in conjunction with continuum models to simulate growth and the subsequent effects of occlusion on vascular flow [190]. An interesting focus within this study was evaluating thrombus development from a state where fibrin imparted the mechanical strength to a collagen-infiltrated clot. This study also recognized the link between the mechanical stimulation of a growing thrombus and the upregulation or downregulation of factors within the coagulation or fibrinolytic cascade. Studies focused on the prediction of embolus behavior are very limited. While analogs have been modeled in idealized scenarios, the emboli are modeled as already detached from the vascular wall. Using patient-specific geometries and inserting devices [144] to predict thrombus transport and device performance makes these models more clinically relevant but unsatisfying regarding the actual embolization process. Ultimately, there does not yet exist a well-verified model for embolization and subsequent transport that considers the local hemodynamic and biochemical environment or the multiscale-multiphysics interactions involving the clot, vessel wall, or valvular structures.

Computational models have also provided valuable insight into the effects of external compression on flow in the venous system. Based on a theoretical framework for flow in collapsible tubes [197], early numerical simulations predicted the hemodynamic impact of various compression conditions [197, 198]. These models are, however, limited in the necessary adherence to the tube law, a pressure/volume relationship that limits model application to highly idealized geometries, unlike the branching, twisting, and irregular surfaces of vessels.

Imaging techniques, such as CT and MRI, have been commonly used to provide anatomical and flow information for subject-specific modeling of arterial hemodynamics, and a large body of literature exists in this area [199–202]. However, image-based modeling of venous flow, especially in the deep veins, is lacking owing to challenges in obtaining accurate in vivo anatomical and flow data in the deep veins. Despite this lack of established practices, recent advances in MR imaging leading to improvements in in vivo resolution and image fidelity, combining MRI and CFD to examine hemodynamics in patient-specific veins of interest has recently become possible. Image-based computational modeling has become an established tool in studying arterial hemodynamics. It offers the potential to provide data that cannot be

measured by flow visualization alone, like WSS and its related derivatives. However, this technique has not yet become commonplace in studying deep veins, and corresponding CFD models are scarce. The first reported study developed a CFD model of deep and superficial veins in the calf based on MR images and pulsed Doppler-based flow measurements [94]. The model determined that graduated compression stockings (GCS) effectively raised venous wall shear stress in subjects in the prone position, especially in the deep vessels. Further evidence of this effect was established in a later study [181], where in vivo blood velocities in the deep calf veins were acquired using phase-contrast MR velocity mapping, overlaid with simultaneously acquired anatomical data. Patient-specific CFD simulations of the peroneal veins (Fig. 6) in ten healthy volunteers showed an increase in time-averaged wall shear stress (TAWSS) of 398% after compression (median 98%), but the variance between individuals was extremely high. Given the vital role of wall shear stress in regulating the biological functions of endothelial cells and in thrombogenesis, it is crucial to establish a standardized quantitative analysis of WSS in the deep venous system. Doing so may help unravel the mechanism by which MCS provide their clinical benefit and provide inspiration for developing novel methods of modulating VTE.

Summary

While major advances have been made in the clinical management of VTE, gaps remain in knowledge within multiple disciplines that demand urgent attention. Notably, computational models of VTE have not yet matured to the point where predictive capabilities are clinically useful. Fundamentally, the mechanism by which VTE initiates is less well defined when compared to thrombosis in the arterial compartments. The limited understanding of the fundamental biology leading to deep venous thrombosis and embolization, patient variance in hemostatic milieu, venous insufficiency, the effect of lifestyle, and limitations of the timescale of computational models are considerable difficulties in implementing a successful model. While both benchtop models and clinical trials have highlighted a litany of risk factors and anatomical conditions that promote the formation of thrombosis within the venous circulation, the dominant biochemical pathway has yet to be clearly defined. While stagnant flow clearly leads to endothelial hypoxia and loss of antithrombotic phenotype, the sequence by which this promotes an initial layer of platelet activation and deposition does not clearly follow the shear-mediated mechanisms of platelet capture in the arterial environment. Clarifying these initial molecular changes may lead to the discovery of novel drug targets. These improvements would be welcomed, as modern anticoagulants are still associated with bleeding and other complications. Some advances highlighted here have

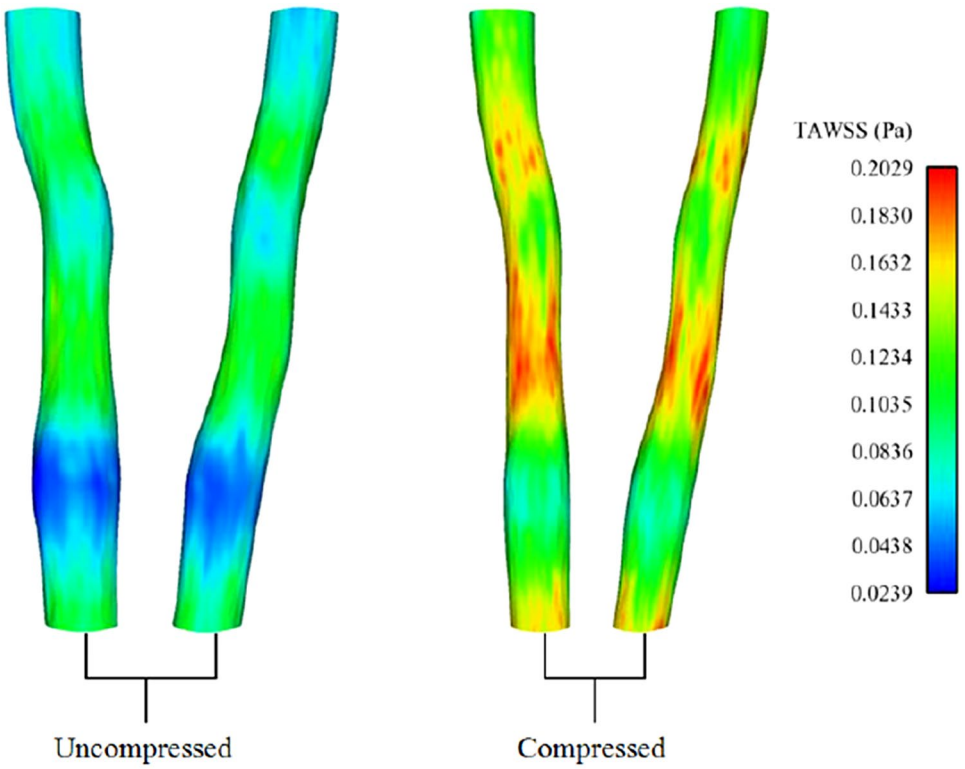

Fig. 6 Representative time-averaged wall shear stress maps in the peroneal vein obtained from MRI-based CFD simulations before (left) and after (right) compression. Extracted with permission from Wang et al. [181]

made incremental progress toward a functional model, but further work is needed. Specifically, experimental investigation of the biology behind deep venous thrombosis and embolization is needed for a deeper understanding of the processes being modeled and experimental validation. Imaging modalities must be leveraged to obtain anatomical and mechanical data on venous valve behavior in patients with chronic venous insufficiency. Currently used risk factors should be employed in parallel with patient-specific imaging to assess the likelihood of imminent primary or recurring VT formation, rather than relying on general population-based long-term risk profiles.

Despite the limitations of current techniques within the field, many sources of optimism remain. Improved therapeutic drugs and the advancement of surgical techniques may increase survival rates of VTE patients and reduce the incidence of PTS, recurrent or development of DVT. Further advances in the work discussed may be useful for predictive purposes, but significant strides must be made prior to the clinical implementation of computational models.

Declarations

Conflict of interest JCC has received research funding from Grifols Biopharma and holds a patent (17/146,912) related to use of antithrombin for improving chemoprophylaxis and mitigating the incidence of venous thromboembolism after traumatic injury. All other authors have no competing interests or conflicts related to this manuscript.

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