Fibrin formed as a result of fibrinogen polymerization is the main protein component of a clot in a test tube and intravascular thrombi in vivo. Fibrin clot structure characterized by fiber diameter and pore size differs between healthy persons and those with thromboembolic diseases, in part due to the quality and quantity of fibrinogen and the magnitude of thrombin generation. A key measure of plasma clot structure is its permeability, reflected by the Darcy constant ($K_s$). Reduced $K_s$ is a typical feature of the prothrombotic fibrin clot phenotype, which is associated with faster formation of denser fibrin mesh, relatively resistant to lysis. Low $K_s$ has been reported in patients with prior or acute myocardial infarction (MI), stroke, or venous thromboembolism (encompassing deep vein thrombosis [DVT] and pulmonary embolism [PE]), as well as in those with prothrombotic conditions (eg, in several thrombophilic states) and in the presence of cardiovascular risk factors (eg, obesity). Antithrombotic and anticoagulant agents, along with statins, have been shown to increase $K_s$. Growing evidence indicates associations between the properties of plasma fibrin clots and morphology of intravascular thrombi in patients with MI. Recently, reduced $K_s$ has been shown to predict recurrent thromboembolic episodes in patients with a history of stroke, PE, DVT, and their serious complications, including postthrombotic syndrome and thromboembolic pulmonary hypertension. We discuss the current evidence for the significance of clot density measured in vitro as a prognostic marker in a number of clinical conditions associated with elevated thromboembolic risk.
Abbreviations: A, cross-sectional area; Abs, absorbance; L, clot length; Q, volume of the fluid; Δp, differential pressure.

Mechanical properties of fibrin  The structure of fibrin and its resistance to mechanical deformation and/or enzymatic degradation are essential for fibrin functions and depend on fibers’ architecture and their individual properties. At the level of the individual fibrin monomers, the coiled-coil connectors, folded globular nodules, and αC regions largely contribute to the fibrin clot mechanics. Fibrin networks have 1.5- to 3-fold lower extensibilities than individual fibers, thus clot degradation after extension is limited to the branch points rather than single fibers. Fibrin fibers are composed of thousands of twisted protofibrils arranged side by side with a periodicity of 22.5 nm. Extremely durable cross-linked fibrin fibers can be strained over 6 times their length and they have the largest extensibilities among fiber proteins.

Assessment of fibrin properties  The architecture of a fibrin clot can be characterized by the fiber diameter and the size of the pores in the fibrin network. Fibrin porosity is typically estimated using a clot permeability under different hydrostatic pressures in a few assays of varying reagents and their concentrations. Clot permeability is calculated based on the volume of a buffer flowing through a fibrin gel in a given time period using the Darcy constant: \( K_s = \frac{Q}{A \times \eta \times \Delta p} \), where \( Q \) is the volume (in ml) of liquid passed through in time \( t \), \( \eta \) is the viscosity of the fluid (in poise), \( L \) is the length of the gel (in cm), \( A \) is a cross-sectional area (in cm²), and \( p \) is the applied pressure (in dyne/cm²) (FIGURE 1A).

Clot compaction is a measure of fibrin density, thus indirectly clot permeability. After clot formation, samples are centrifuged at 6000 to 8000 x g for usually 60 seconds and the volume of the supernatant evacuated from tubes is assessed as a difference in tube weight. Finally, clot compaction is expressed as a volume of the supernatant divided by the initial plasma volume used to form the clot. A normal clot compaction is about 60% to 70% using this technique. Less compact clots (usually about 40%) are associated with impaired clot lysis due to impaired transport of proteolytic enzymes through the fibrin network.

Fibrin formation in purified systems as well as in plasma are assessed by turbidimetry. The parameters used are the lag phase that reflects the time to the start of lateral fibril aggregation, the maximum absorbance of the growing clot that reflects an average fibrin fiber size and the number of protofibrils per fiber, and the rate of absorbance increase (FIGURE 1B).

The most commonly used imaging techniques for visualization of fibrin clot structure include scanning or transmission electron microscopy, along with confocal microscopy. Scanning electron microscopy allows a measurement of the fiber diameter, pore size, and branching angles. However, this technique requires a clot fixation with glutaraldehyde solution followed by its dehydration. Physiologically, fibrinogen undergoes many posttranslational modifications, thus purified models compared with plasma-based models can mimic the in vivo situation. Fibrin clot formed from a citrated plasma is characterized by 2 to 4 times thicker fibers and larger pores compared with a clot formed from purified fibrinogen at similar protein levels. Fibrinogen is known as the main determinant of fibrin clot structure; however, variation in its levels explained only 18% of the variation in \( K_s \) and 48% of the variation in maximum absorbance in turbidimetry.
At low concentrations of fibrinogen, clots are composed of thicker fibers, while clots formed at higher concentrations of fibrinogen are composed of thinner fibers. Clot structure also depends on the conditions during fibrinogen polymerization. Increased thrombin concentrations in a dose-dependent manner result in faster formation of thinner fibrin fibers with smaller pores. Thus, higher thrombin generation is directly associated with lower clot permeability. Elevated FXIII activity has also been shown to affect clot structure by increasing its stability. Generally, fibrin clots are composed of thinner fibers and smaller pores and are more compact and less permeable, while those with thicker fibers are more permeable and susceptible for fibrinolysis.

In 1977, Carr et al estimated for the first time the clot permeability by measuring the buffer flow through a fibrin gel. Currently, several methods and models are used to determine fibrin porosity, including those in which clotting is initiated by thrombin or tissue factor in platelet-poor or platelet-rich plasma, using manual or semiautomated techniques. In 2012, the Factor XIII and Fibrinogen Subcommittee of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis published the first recommended protocol for $K_s$ measurement. Regardless of the assay used, $K_s$ measurement requires much hands-on experience to obtain reproducible results (variability around 10% or less) and universal standards to ensure acceptable between-laboratory variability.

This review will focus on reduced fibrin clot permeability, which represents the so-called prothrombotic fibrin clot phenotype in patients with thromboembolic disorders, in particular on myocardial infarction (MI), stroke, and venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT). Clinical conditions associated with reduced fibrin clot permeability are shown in Figure 2.

**Fibrin clot phenotype in myocardial infarction**

Acute coronary artery thrombus formation associated mostly with atherosclerotic plaque rupture results in a blood flow cessation in an infarct-related artery area, leading to ST-segment elevation MI (STEMI). Scanning electron microscopy of intracoronary thrombi from patients with STEMI showed that thrombus composition evolves over time during the acute phase of MI and fibrin content increased from 31% to 78%. Fibrin, erythrocyte, platelet, and white blood cell content in the thrombi were estimated at 49.1%, 24.2%, 11.6%, and 3.7%, respectively.

In patients with acute MI before percutaneous coronary intervention (PCI), fibrinogen, P-selectin, and plasminogen activator...
inhibitor 1 (PAI-1) were positively correlated with thrombus fibrin content.\textsuperscript{25} Diminished clot permeability in 40 patients with acute MI was related to the degree of oxidative stress and inflammation.\textsuperscript{27} Different oxidative modifications of fibrinogen molecule were associated with various changes in the clot structure and function.\textsuperscript{28-31} Serum F2-isoprostanates produced upon nonenzymatic arachidonic acid peroxidation, as well as platelet activation reflected by the concentrations of β-thromboglobulin, have been shown to correlate with Ks in patients with acute MI.\textsuperscript{29} Zalewski et al\textsuperscript{30} showed for the first time that fibrin content in the intracoronary thrombi obtained from patients with acute MI was inversely correlated with Ks, and the latter variable independently predicted fibrin content in the whole thrombus. This indicates that plasma clot features affect thrombi formed in the vessels, which supports the value of plasma clot analysis in the prediction of in vivo thrombus composition.

The presence and amount of the proteins within a plasma clot also influence clot properties.\textsuperscript{31} Using a shotgun proteomic method to investigate time-dependent protein composition of clots prepared ex vivo from citrated plasma obtained from patients with acute MI, 62 proteins were identified in all 8 samples grouping into several distinct functional clusters (eg, cholesterol transporter activity, immunoglobulin binding, and peptidase regulatory activity).\textsuperscript{32} The protein signatures of clots differed significantly depending on time after acute coronary syndrome, showing 30% greater variability in protein composition of the plasma clots generated 2 months after the onset of acute MI.\textsuperscript{32} Differences involving proteins of potential influence on within-clot fibrinolysis (ie, α,-antiplasmin) may at least in part explain time-dependent changes in the clot structure in patients with acute MI.\textsuperscript{32} Before PCI, fibrinogen, P-selectin, and PAI-1 levels were positively correlated with thrombus fibrin content, while after PCI, von Willebrand factor antigen, soluble CD40 ligand, and myeloperoxidase were associated with thrombus fibrin content.\textsuperscript{25} After adjustment for fibrinogen and the onset-to-thrombectomy time, circulating von Willebrand factor antigen was the independent predictor of fibrin-rich intracoronary thrombi.\textsuperscript{25}

Reduced clot permeability by about 30% has been reported for the first time in men with a history of premature MI.\textsuperscript{25} Thus, thrombotic disorders can be attributed to more compact and less permeable fibrin structure.\textsuperscript{24} MI in the past has also been linked with the prothrombotic fibrin clot phenotype in young patients.\textsuperscript{25} Interestingly, first-degree male relatives of patients with premature coronary artery disease had less permeable clots than controls.\textsuperscript{33} Reduced clot permeability by 21% and 18%, respectively, characterized also patients with in-stent thrombosis\textsuperscript{34} and patients with a history of the no-reflow phenomenon,\textsuperscript{35} defined as the absence of a complete myocardial perfusion despite successful opening of the blocked coronary artery. A small prospective study demonstrated an increased risk of arterial thrombotic events associated with reduced Ks and prolonged lysis time in patients on long-term hemodialysis.\textsuperscript{28}

Altered fibrin clot structure and function observed in MI is largely determined by factors associated with increased oxidative stress and thrombin generation, along with prothrombotic actions of platelet-derived proteins (eg, platelet factor 4 or β-thromboglobulin).\textsuperscript{11,26,28,29} Hyperglycemia, observed in up to 50% of the patients with acute MI, impaired clot susceptibility to lysis but had no effect on Ks.\textsuperscript{40} On the other hand, patients with type 2 diabetes presented impaired clot structure, including its reduced Ks, associated with prolonged duration of diabetes.\textsuperscript{41} This observation underlines the role of prothrombotic memory in the pathogenesis and risk assessment of thrombotic events.\textsuperscript{42} Interestingly, cellular fibronectin, a marker of vascular injury, was increased and associated with altered fibrin clot properties in patients with type 2 diabetes and concomitant cardiovascular disease but not in patients without cardiovascular disease, suggesting a direct link between blood vessel damage and prothrombotic clot phenotype.\textsuperscript{42}

Increased oxidative stress, platelet activation, and thrombin generation play a key role in the pathogenesis of MI. Growing evidence indicates that clots formed in the presence of oxidants and high thrombin concentrations are compact, composed of thin fibers, and have reduced Ks.\textsuperscript{30,43,44} Thus, fibrin clot porosity is a promising prognostic marker in patients with MI.

Fibrin clot phenotype in stroke Precerebral or cerebral artery occlusions constitute a major percentage of all acute strokes. Thrombi retrieved from the cerebral arteries of patients with acute ischemic stroke contained fibrin and platelet deposits, together with erythrocyte components.\textsuperscript{45} Fibrin content in thrombi obtained from 50 patients with acute middle cerebral artery ischemic stroke was 61%, and fibrin-rich thrombus occurred most commonly among these patients.\textsuperscript{46} Acute ischemic stroke within the first 72 hours of symptom onset was associated with reduced Ks by 30% as compared with healthy controls.\textsuperscript{47} Fibrin properties showed an association with stroke severity but not with mortality during long-term follow-up.\textsuperscript{48} Fibrin clot compaction correlated with neurological deficit both on admission and at discharge of patients admitted for acute ischemic stroke.\textsuperscript{47} Formation of denser fibrin clots displaying impaired lysability and pattern of their changes induced by thrombolysis may affect clinical outcome in patients with acute ischemic stroke.\textsuperscript{13} We have reported recently that in stroke patients eligible for recombinant tissue plasminogen activator (rtPA) treatment, fibrin networks assessed 24 hours since thrombolysis were 37% less compact and lysed 21% more rapidly compared with the pretreatment
The prothrombotic fibrin clot phenotype, including more compact plasma clots generated in vitro with an increased fiber diameter and density, was characterized by abnormal plasma fibrin clot properties. The first report showing prothrombotic clot abnormalities was published for patients with cryptogenic stroke and evidenced more compact plasma clots generated in vitro with a large contribution of activated factor XI which was found in about 15% of patients.

Patients who survived ischemic stroke have also been characterized by abnormal plasma fibrin clot properties. The first report showing prothrombotic clot abnormalities was published for patients with cryptogenic stroke and evidenced more compact plasma clots generated in vitro with an increased fiber diameter and density.

Reduced Ks observed within the first 24 hours since the onset of stroke symptoms in nonthrombolysed patients remained unaltered after 60 days from the event, suggesting that the prothrombotic clot phenotype is a persistent feature of patients suffering from ischemic stroke.

The worse prognosis is observed in patients with atrial fibrillation (AF) who experienced acute cerebrovascular stroke. Since 15% of ischemic strokes occur in patients with AF and they are mostly caused by thrombotic material formed within the left atrium, precisely in 90% in its appendage, the prothrombotic fibrin clot phenotype might also increase the risk of cerebral infarction. It has been shown that formation of compact plasma fibrin clots resistant to lysis is observed in patients with different types of AF, and those unfavorable fibrin properties can at least in part determine the efficacy and safety of anticoagulation with vitamin K antagonists. Interestingly, patients with lower Ks (<6.8×10⁻⁹ cm²) had increased risk of ischemic stroke or transient ischemic attack (hazard ratio [HR], 6.55; 95% confidence interval [CI], 2.17–19.82) and major bleeds (HR, 10.65; 95% CI, 3.52–32.22), while patients with elevated Ks (≥6.8×10⁻⁹ cm²) had an increased rate of minor bleeding compared with the remainder (11.63% per year vs 3.55% per year). Interestingly, in 160 patients with AF, prothrombotic fibrin clot properties were determined by PAI-1 and N-terminal pro-B-type natriuretic peptide associated with long-term prognosis.

Prothrombotic blood alterations could be also involved in the left atrial appendage thrombus formation in patients without documented AF and are associated with increased risk of stroke or transient ischemic attack. Ks reduced by 1 unit was shown to be associated with 5-fold higher odds of recurrent left atrial appendage thrombus during follow-up, which suggests that clot features persist over time and might have a prognostic value. Fibrin clot features could be involved in an increased stroke risk also in specific patient populations, including those with acquired thrombophilia. We found that plasma fibrin clots from patients with antiphospholipid syndrome, who experienced stroke and/or MI at least 5 months earlier, were less permeable and were lysed faster compared with those with VTE alone. This study showed for the first time that antiphospholipid syndrome is associated with the prothrombotic plasma fibrin clot phenotype, with even worse characteristics in patients following arterial thrombosis, largely stroke.

Overall, ischemic stroke is linked with prothrombotic alterations in fibrin structure and function, indicating common mechanisms leading to cerebrovascular and coronary thromboembolic episodes.

**Fibrin clot phenotype in venous thromboembolism**

The pathogenesis of VTE, encompassing DVT and PE, is multifactorial with about 50% of patients suffering from unprovoked (formerly idiopathic) episodes. Thrombotic material removed from the pulmonary arteries in acute PE showed that the main component of the thrombus is fibrin. Interestingly, thrombi located in the distal arteries were richer in fibrin and contained fewer erythrocytes than those from the proximal arteries. Martinez et al showed that clot structure and functional properties, including clot formation, lysis, and viscoelastic properties, differentiated patients with acute DVT from those with PE, suggesting that lower fiber density and faster lysis in patients with PE may affect embolization. Less compact fibrin structure associated with faster clot lysis seems to characterize patients who experienced PE, regardless of the presence of concomitant DVT. It might be speculated that higher Ks combined with shorter lysis time, found in patients with PE compared with DVT, contributes to clot fragmentation and the subsequent embolization. Recently published computational model simulations describing interactions between main clot components under shear flow suggest that blood clots with higher clot shell permeability are more prone to embolization under increasing shear rate.

It has been reported that some environmental factors affect fibrin clot structure in patients with DVT. Long-term exposure to particulate matter with a diameter of less than 10 μm (PM₁₀) has been associated with a denser fibrin network with Ks, decreased by 22% in 103 patients with DVT but not in controls, suggesting an increased risk of recurrent episodes in patients predisposed to venous thrombosis.

Siudut et al showed that cerebral venous sinus thrombosis (CVST), which is a rare form of VTE, can be associated with the formation of more compact plasma fibrin clots and resistance to fibrinolysis. Ks was 12% lower in 50 patients with CVST (mean [SD] age, 38.9 [9.8] years) after the event unrelated to trauma or malignancy following anticoagulation withdrawal, as compared with controls. Importantly, recurrent CVST during follow-up was associated with 21% higher baseline fibrinogen levels and 20% lower Ks, which suggest a predictive value of this fibrin clot structure measure (Figure 3).
Recent data indeed indicate that plasma clot characteristics might identify patients at high risk of recurrent VTE. In 2017, we observed that recurrent PE, diagnosed during follow-up in 23 patients (5% per year) following the first-ever provoked or unprovoked PE, is associated with formation of denser fibrin networks, as evidenced by reduced $K_s$ (HR, 1.82; 95% CI, 1.01–3.13; figure 3).65

Postthrombotic syndrome is a common complication of DVT that has been found to be associated with $K_s$ reduced by 11.7% when assessed 3 months after the index DVT.66 Recurrent VTE occurred also more commonly in patients with postthrombotic syndrome, who were characterized by lower $K_s$ and prolonged clot lysis time (CLT).66

Very recently, we have published convincing evidence for the predictive value of the prothrombotic clot phenotype in patients with DVT. Among 320 consecutive patients after the first-ever DVT, recurrences were observed in 25% of the patients (6.6% per year) during a median follow-up of 44 months. Recurrent DVT was associated with denser fibrin networks (12% lower $K_s$), and reduced $K_s$ was an independent predictor of recurrences.67 The risk of recurrent DVT increased 15-fold (95% CI, 7.5–33.5) in patients with low $K_s$ (≤7.3 × 10$^{-9}$ cm$^2$) combined with prolonged CLT (>96 min).67 Interestingly, fibrin properties analyzed as single measures were less effective as DVT predictors when compared with the combined analysis of $K_s$ and CLT (figure 3).67

This work encourages efforts to develop user-friendly assays to test clot properties in practice to improve identification of patients with VTE at risk of recurrent episodes following anticoagulation cessation. The prothrombotic clot phenotype could be a factor which renders the patient suitable for long-term anticoagulation, now easier to achieve with new oral anticoagulants available worldwide.

Patients with residual vein obstruction, detected in up to 50% of patients following DVT, were also characterized by 14% lower $K_s$ related to elevated lipoprotein(a) and overrepresentation of its smaller isoforms.68

Chronic thromboembolic pulmonary hypertension (CTEPH), a severe PE complication, is associated with changes in fibrinogen molecule structure and/or function followed by altered properties of the clot formed from modified protein.69 This might result in the development of CTEPH by prolonged fibrin clot presence within the pulmonary arteries and remodeling of the thrombi into fibrotic layer. Patients with CTEPH have a relatively high incidence of inherited dysfibrinogenemias in which abnormal fibrin clot phenotype occurs,70,71 suggesting that clot properties may lead to identification of patients at risk of this complication and might be helpful in determining the efficacy of therapy.72

Looking at genetic thrombophilias attributed to VTE, fibrin abnormalities have also been reported. The prothrombin G20210A mutation in patients after VTE has been shown to be linked with unfavorable fibrin clot characteristics, including 12% lower $K_s$ compared with noncarriers.73 Rivaroxaban treatment improved fibrin clot properties in carriers and noncarriers of the prothrombin G20210A mutation, but anticoagulant therapy cannot abolish more prothrombotic fibrin clot phenotype observed in prothrombin mutation carriers following VTE.73 Factor V (FV) Leiden mutation is observed in 3% to 15% of the white population and in 15% to 30% of patients with VTE.74 In thrombosis-free heterozygous carriers of FV Leiden mutation, $K_s$ was slightly reduced compared with noncarriers.74

**FIGURE 3** Relative differences in plasma fibrin clot permeability ($\Delta K_s$) measured after 3 to 6 months since the index event between patients who experienced recurrent venous thromboembolic (VTE) episodes, including cerebral venous sinus thrombosis (CVST), deep vein thrombosis (DVT), and pulmonary embolism (PE) during a few years’ follow-up versus those free of such events in the respective studies.64,65,67 $K_s$ for patients without recurrent VTE is marked on the top of the vertical line.
Among modifiable VTE risk factors, oral contraceptives have been shown to unfavorably alter plasma clot characteristics. Discontinuation of oral contraceptives was associated with shortened lysis time and increased Kₗ.

It is known that obesity is associated with an increased risk of thromboembolic events. Interestingly, in 29 obese patients studied before and after 3-month low-fat diet, which resulted in the reduction of body weight and the levels of total cholesterol, low-density lipoprotein cholesterol, triglycerides, and PAI-1, was also associated with increased clot potential to lysis, while Kₓ remained unchanged.

Taken together, there is evidence that a number of thrombosis risk factors, both genetically determined and acquired, are associated with denser plasma clot structure, which might contribute to their effects reaching beyond the impact of increased thrombin generation.

### Antithrombotic agents and fibrin clots

Growing evidence indicates a strong impact of several antithrombotic, cholesterol-lowering, or antihypertensive agents on fibrin clot structure (Table 1). Administration of low-dose aspirin was shown to be associated with improved clot properties largely through fibrinogen acetylation. Fibrinogen is acetylated at several lysine residues, which also are involved in the FXIII-mediated cross linking of fibrin. In vivo, aspirin concentration of 37.5, 320, and 640 mg/d increased Kₗ by 44%, 31%, and 21%, respectively, and treatment with low-dose aspirin led to formation of thicker fibrin fibers with larger pores. Similar effects of low-dose aspirin were seen in patients with coronary artery disease and in those with VTE. Moreover, 1 week after aspirin withdrawal, Kₓ returned to the baseline value.

The impact of several other antithrombotic drugs on fibrin clot structure and function was determined by the influence on clotting factors and/or reduced thrombin generation. Direct and indirect thrombin inhibitors, including argatroban, bivalirudin, and danaparoid, have been shown to increase Kₓ at therapeutic concentrations in vitro models to a similar extent. Direct thrombin and factor Xa inhibitors added in vitro to normal plasma also increased Kₓ by 36% to 91% at therapeutic plasma concentration. In the same model, warfarin at plasma concentration adjusted to obtain the therapeutic range (international normalized ratio, 2–3) resulted in an Kₓ increase of about 35%. Warfarin and acenocoumarol as vitamin K antagonists have been shown to increase Kₓ in patients with AF as early as after 3 days of treatment, reaching the plateau value after 7 days. Those favorable changes in clot structure were strictly associated with diminished activities of vitamin K-dependent clotting factors and lower protein C activity, resulting in lower thrombin generation. Rivaroxaban, a non–vitamin K antagonist oral anticoagulant and direct Xa inhibitor, at 2 to 6 hours after intake improved Kₓ by 37% in patients with previous VTE. Interestingly, after 20 to 25 hours since rivaroxaban intake, clot permeability returned to the baseline value.

Statins also produce fibrin modulatory effects. Atorvastatin, beside its role as a cholesterol-lowering agent, has also antithrombotic properties in VTE patients, observed as favorable alterations in fibrin clot phenotype, in particular Kₓ reduced by 23% after statin use for 3 days. Furthermore, anticoagulant effects of statins have been related to a decreased tissue factor expression followed by reduced thrombin generation, attenuation of procoagulant reactions catalyzed by thrombin, such as fibrinogen cleavage, FV and FXIII activation, and enhanced endothelial thrombomodulin expression, resulting in increased protein C activation and inactivation of activated FV. A 3-month simvastatin treatment increased Kₓ in patients without history of cardiovascular events and low density lipoprotein cholesterol of less than 3.4 mmol/L. Beneficial effects of simvastatin treatment on Kₓ (an increase of 16%), irrespective of cholesterol reduction, were also seen in patients with chronic obstructive pulmonary disease. These findings provide evidence that fibrin clot modulation contributes to antithrombotic effects of statins, which explains at least in part a reduced VTE risk in statin users observed in several studies.

### Practical implications

There are several limitations to assess fibrin clot properties in clinical practice. The availability of fibrin measures is limited to a few specialized laboratories. Due to

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### Table 1: Medications reported to alter fibrin clot permeability

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mode of action: suggested change in</th>
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<tbody>
<tr>
<td>Metformin</td>
<td>Glycation of fibrinogen and plasminogen; inflammatory state</td>
</tr>
<tr>
<td>Insulin</td>
<td>Glycation of fibrinogen and plasminogen; inflammatory state</td>
</tr>
<tr>
<td>Statins (simvastatin and atorvastatin)</td>
<td>Thrombin generation; inflammatory state</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Acetylation of fibrinogen</td>
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<tr>
<td>Angiotensin converting enzyme inhibitors</td>
<td>Fibrinolysis</td>
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<tr>
<td>Vitamin K antagonists (warfarin, acenocoumarol)</td>
<td>Thrombin generation via vitamin K-dependent factors</td>
</tr>
<tr>
<td>Non–vitamin K antagonist oral anticoagulants (rivaroxaban, apixaban, dabigatran)</td>
<td>Thrombin generation by activated factor X or thrombin inhibition</td>
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<tr>
<td>Heparins</td>
<td>Thrombin generation by activated factor X inhibition</td>
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high between-laboratory variability of the methods describing fibrin clot structure and function, the standardization of assays is highly required. A well-trained technical staff with great hands-on experience can support this process; however, still an automatization of manual methods is needed to reduce operator-related bias. 22 Recently, we have developed a semi-automated device controlled by software to assess $K_s$ quickly and precisely after clot washing. 23 Even though the clot preparation has to be conducted manually, our device allows for an analysis of additional parameters describing clot structure and kinetics of buffer permeation through the fibrin mesh. 24 Such devices are needed to implement $K_s$ measurements in clinical practice.

Concluding remarks  Fibrin clot structure and function is involved in the pathogenesis and prognosis of thromboembolic events. Fibrin clots composed of compact, highly branched networks with thin fibers are resistant to lysis, and such properties have been reported in patients with several diseases with increased risk of thromboembolism. Recent data indicate that the prothrombotic fibrin phenotype assessed in plasma samples might be used as a prognostic marker in VTE and ischemic stroke related to AF. Further research is needed to better understand the role of fibrin properties in thromboembolism and implement these measures in clinical practice.

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