

Review

# Individualised Risk Assessments for Recurrent Venous Thromboembolism: New Frontiers in the Era of Direct Oral Anticoagulants

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**Abstract:** Venous thromboembolism (VTE) is a leading cause of morbidity and mortality and is associated with high recurrence rates. The introduction of direct oral anticoagulants (DOACs) in the 2010s has changed the landscape of VTE management. DOACs have become the preferred anticoagulant therapy for their ease of use, predictable pharmacokinetics, and improved safety profile. Increasingly, guidelines have recommended long term anticoagulation for some indications such as following first unprovoked major VTE, although an objective individualised risk assessment for VTE recurrence remains elusive. The balance of preventing VTE recurrence needs to be weighed against the not insignificant bleeding risk, which is cumulative with prolonged use. Hence, there is a need for an individualised, targeted approach for assessing the risk of VTE recurrence, especially in those patients in whom the balance between benefit and risk of long-term anticoagulation is not clear. Clinical factors alone do not provide the level of discrimination required on an individual level. Laboratory data from global coagulation assays and biomarkers may provide enhanced risk assessment ability and are an active area of research. A review of the prediction models and biomarkers for assessing VTE recurrence risk is provided, with an emphasis on contemporary developments in the era of DOACs and global coagulation assays.

**Keywords:** venous thromboembolism; recurrent venous thromboembolism; clinical prediction models; global coagulation assays



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## 1. Introduction

Venous thromboembolism (VTE) is defined as thrombosis of the venous system and includes deep vein thrombosis (DVT) and pulmonary embolism (PE). The incidence of VTE is approximately 1 to 1.8 per 1000 person-years, similar to incidence rates for stroke, and rises exponentially with increasing age [1,2]. Worldwide, VTE is the leading cause of hospital-related disability-adjusted life years (DALYs) lost [3], and was estimated to cost AUD 117,000 per patient in 2008 [4].

One of the major challenges in managing VTE remains estimating the risk of VTE recurrence after withdrawal of anticoagulation. Identification of these at-risk individuals has historically relied on the presence of persistent or transient risk factors (see Table 1). Persistent risk factors are intrinsic to the individual and include known inherited and non-inherited thrombophilia [5], male gender [6], obesity [7], and the presence of malignancy [8]. Transient risk factors may include surgery, injuries, and long-distance flights, which temporarily increase the risk of VTE [9]. For those without an identifiable provoking factor, the estimated risk of recurrence approaches 30% at five years, and the risk is highest during the first year after anticoagulation cessation at around 10% [9,10]. On the other hand, the presence of strong transient risk factors such as surgery or physical injury is

associated with the lowest risk of recurrence [9,11]. The long-term recurrence risk is intermediate following events provoked by minor transient risk factors including long-haul flights, hormonal therapy, and non-surgical transient immobility [11,12].

**Table 1.** Risk factors for recurrent venous thromboembolism (VTE) after stopping anticoagulants [13].

Risk Factors	Risk Ratio
Strong transient risk factor, e.g., surgery and injury vs unprovoked	0.2 [9,11]
Minor transient risk factor vs unprovoked	0.5 [9,11]
Malignancy vs unprovoked	1.5–3 [8,14]
Obesity	1.5–2.5 [7,15]
History of recurrent VTE ( $\geq 2$ episodes)	1.5 [16]
Male	1.75 [6,9]
Abnormal D-dimer after unprovoked VTE	1.5–2.5 [17]
Hereditary thrombophilia	1.2–2.0 [5,18]
Malignancy vs unprovoked	1.5–3 [8,14]

Evaluating the individual risk of VTE recurrence is important when deciding if long-term anticoagulation is justified and needs to be carefully balanced against the risk of major bleeding. Whilst long-term anticoagulation is clearly recommended for patients with recurrent unprovoked VTE, the optimal duration for patients with VTE not meeting this criterion is less clear. For example, the need for anticoagulation after the first episode of unprovoked major VTE is unclear, although a number of clinical trials have shown benefits in continuing anticoagulation with the risk of VTE reduced by 80% [19–21]. However, given that 70% of patients with their first episode of VTE do not have a recurrence during the first five years, it would mean that these patients have potentially received unnecessary anticoagulation treatment. Hence, most guidelines agree that in this situation of “clinical equipoise”, a personalised approach balancing the benefits of reduced VTE recurrence against the risks of major bleeding is required [22–24].

The introduction of direct oral anticoagulants (DOACs) has seen sizable shifts in the anticoagulation prescribing practices around the world [25–28]. Many VTE guidelines now suggest DOACs as the preferred anticoagulation therapy [22,23] due to their non-inferior efficacy compared with vitamin K antagonists (VKAs), improved safety, and ease of administration. Major bleeding events associated with DOACs have consistently been shown to be fewer compared to VKAs. A meta-analysis of randomised controlled trials involving DOACs for extended anticoagulation following VTE found an incidence of major bleeding of 0.48 per 100 patient years compared to 2.89 per 100 patient years for VKAs [21]. Real-life registry data in atrial fibrillation patients have also confirmed reduced bleeding on DOACs compared to VKAs [29,30]. There is also evidence that major bleeding associated with DOACs leads to reduced case-fatality rate (7.57% DOACs vs 11.04% VKAs) [31]. For all these reasons, DOACs have risen in popularity and VKA use has fallen as a consequence.

Surveys of prescribing activity since the introduction of DOACs have revealed an increase in total anticoagulation use [26,27]. This can partly be explained by the fact that ease of DOAC administration and relative long-term safety compared to VKAs have provided an attractive option for long-term anticoagulation in non-valvular atrial fibrillation as well as secondary VTE thromboprophylaxis [32]. Real-world data of major bleeding on long-term DOAC therapy following VTE are scarce. In the non-interventional XALIA [33] study, in which patients treated with rivaroxaban after DVT were followed for a median 239 days, the annualised major bleeding rate was 1.2%. In the Dresden NOAC registry [34], 575 VTE patients on rivaroxaban for a median of 274 days had a major bleeding rate of 4.1 per 100 patient-years. The age of this cohort was markedly higher than in XALIA (68 vs 59 years) and EINSTEIN [35] (68 vs. 57 years), which could explain the increased bleeding observed. More data are required in the long-term VTE setting, especially in those taking reduced dose DOACs. However, the cumulative clinically significant bleeding risk is not insignificant in VTE patients receiving long-term DOAC therapy, especially

in older individuals who are at greater risk of both developing VTE and major bleeding. Adequately defining individuals at low risk for VTE recurrence should be a priority to minimise unnecessary over-medication as well as to reduce major bleeding complications.

An individualised, targeted approach for assessing VTE recurrence risk would be ideal, especially in those patients in whom the balance between benefit and risk is not clear. Clinical factors alone do not provide the level of discrimination required on an individual level, and single biomarkers alone may not be strong enough in their discriminatory power. Increasing evidence has suggested that global coagulation assays may better reflect the overall prothrombotic phenotype of an individual and could be a promising additional tool in the quest for truly individualised risk assessments for recurrent VTE [36]. This review aims to provide an overview of the current clinical risk prediction models and biomarkers for assessing VTE recurrence risk, with an emphasis on recent developments in the era of DOACs and future potential biomarkers, e.g., global coagulation assays.

## 2. Risk Factors and Clinical Risk Prediction Models

Risk factors for VTE recurrence have been well documented, and their estimated magnitudes are displayed in Table 1. It should be noted, however, that several risk factors may co-exist in the same individual, and that the combined effect of multiple risk factors together have not been clearly defined. In addition, factors such as age, malignancy and comorbidities such as renal failure are concurrent risks for thrombosis and bleeding, making the risk–benefit assessment of long-term anticoagulation challenging. Existing models for predicting bleeding risk such as the HAS-BLED or RIETE score do not account for this complexity, and in addition, have been formulated in the warfarin era prior to the introduction of DOACs. The HAS-BLED [37] score for instance allocates one point for labile INRs, which would be of no relevance to patients receiving DOACs.

Clinical prediction models have been developed to aid in the identification of low-risk individuals in whom anticoagulation can be ceased. For the purposes of this review, we will be concentrating on the HERDOO2, DASH and Vienna prediction models, which are widely known, validated, and combine clinical parameters with laboratory biomarkers. Details of these models are displayed in Table 2. These models have been validated in separate studies and are elaborated below. In both the derivation and validation studies, patients were anticoagulated with VKAs except in the HERDOO2 validation study [38], which included a small number of patients treated with rivaroxaban.

**Table 2.** Clinical prediction models for recurrent VTE.

Model	Inclusion Criteria	Variables	Findings
HERDOO2 [39]	1st unprovoked major VTE Included provoked by: <ul style="list-style-type: none"> <li>hormonal therapy</li> <li>long-haul flight,</li> <li>immobility &lt;3 days</li> </ul>	<ul style="list-style-type: none"> <li>Gender</li> <li>Age <math>\geq</math> 65 years</li> <li>D-dimer <math>\geq</math> 250 <math>\mu</math>g/L on anticoagulation</li> <li>BMI <math>\geq</math> 30 kg/m<sup>2</sup></li> <li>Features of post-thrombotic syndrome (hyperpigmentation, oedema, redness)</li> </ul>	Annualised recurrence risk: <ul style="list-style-type: none"> <li>Females 0 or 1 factors—1.6%</li> <li>Females <math>\geq</math> 2 factors—14.1%</li> <li>Males—no low-risk group identified</li> </ul>
DASH [40]	1st unprovoked major VTE Included provoked by: <ul style="list-style-type: none"> <li>Oral hormonal therapy, e.g., OCP/HRT</li> </ul>	<ul style="list-style-type: none"> <li>Abnormal post-anticoagulation D-dimer (3–5 weeks post-anticoagulation cessation) (+2)</li> <li>Age <math>\leq</math> 50 years (+1)</li> <li>Male (+1)</li> <li>Oral hormone use (–2)</li> </ul>	Annualised recurrence risk: <ul style="list-style-type: none"> <li>Score <math>\leq</math> 1—3.1%</li> <li>Score &gt; 1—9.3%</li> </ul>
Vienna [41]	1st unprovoked VTE Included isolated distal DVT Excluded events provoked by hormonal therapy	<ul style="list-style-type: none"> <li>Gender</li> <li>VTE location: distal DVT, proximal DVT, PE</li> <li>D-dimer value (3 weeks post-anticoagulation cessation)</li> </ul>	Nomogram with continuous variables Annualised recurrence risk: <ul style="list-style-type: none"> <li>Lowest quartile risk score—1.9%</li> </ul>

Table 2. Cont.

Model	Inclusion Criteria	Variables	Findings
Updated Vienna [42]	1st unprovoked VTE Included isolated distal DVT Excluded events provoked by hormonal therapy	<ul style="list-style-type: none"> <li>• Gender</li> <li>• VTE location: distal DVT, proximal DVT, PE</li> <li>• D-dimer value—taken at 3 weeks, 3 months, 9 months, and 15 months after anticoagulation cessation</li> </ul>	Nomograms with continuous variables

The HERDOO2 rule has been prospectively validated in a study of 2785 patients, following a first unprovoked or minimally provoked VTE and followed up for a mean 11.6 months [38]. In this study, the HERDOO2 rule was able to distinguish females at low risk of recurrence (3% per patient year, 95% CI 1.8–4.8%) while high risk females had a similar recurrence risk to men (8.1% per patient year 95% CI 5.2–11.9%). Hence, the HERDOO2 may be useful in defining a low-risk group in women but is not subtle enough to identify a similar low risk group in men.

The DASH model was validated in a retrospective study of 827 patients [43] after the first episode of unprovoked major VTE (hormonally related events were included), with a median follow-up of 25.2 months. Those with DASH score of 1 or below had an annualised recurrence rate of 3.5% (95% CI 2.5–4.7%) and could represent a lower risk population where long-term anticoagulation can be ceased. However, the model was found to be less useful in elderly patients, where the recurrence rate in patients aged >65 years was found to be >5% regardless of their DASH score, which in part may be due to the increasing D-dimer with age.

The Vienna Prediction Model (VPM) is the only model to have been prospectively validated in a randomised controlled trial. Geersing et al. [44] used the VPM to guide treatment for 883 patients with unprovoked VTE. During 24 months of follow-up, there were no differences in the rates of recurrent major VTE between the two arms (10.4% in the intervention (model-assisted treatment recommendation) group; 11.3% in the control (at clinician discretion) group;  $p = 0.67$ ). This was despite the model showing good discriminatory performance and being able to identify 47% of subjects as belonging to the low-risk group. The lack of difference seen between the intervention and control arms could have been explained by the fact that a significant number of patients in the study did not comply with the treatment recommendations of the VPM, and distal DVTs were not included in the definition of recurrent events. Nonetheless, given the good discriminatory performance, the use of a standardised model such as VPM may help to facilitate and standardise clinical judgment. Similarly, Tristchler et al. [45] prospectively applied the updated VPM to 156 elderly patients (>65 years old) after acute unprovoked VTE (subjects with prior VTE history were not excluded). In this cohort, the updated VPM was not able to discriminate VTE recurrence risk between low and high-risk patients (13% vs. 10%;  $p = 0.77$  at 12 months). Compared to the updated VPM derivation study, however, the average age was significantly higher (74 vs. 53 years) and the participants had higher D-dimer levels (1022 vs. 356 ng/mL).

It is clear that although each of the discussed clinical prediction models show promise and merit, and in most cases can identify a low-risk population, they each have significant deficiencies, limiting applicability in clinical practice and consequently have not led to recommendations in guidelines [22]. Some of these limiting factors include differing definitions of unprovoked VTE as well as the use of D-dimers as biomarkers, which is confounded by increasing age, and contributes to the poor performance of these risk models in older populations [38,43,45,46]. However, defining a low VTE-recurrence risk group in elderly patients is clinically important, because they concurrently have a high risk of bleeding and clotting. Similarly, some models are not subtle enough to determine a low-risk group in men, which would subject a significant number of VTE patients to

indefinite anticoagulation. Finally, all the model derivation and validation studies have been conducted prior to the widespread use of DOACs, and therefore direct application in the current era where anticoagulation use is convenient and potentially safer, is not fully understood. Nevertheless, these models were the first to combine clinical and laboratory markers, and remain the basis of how we can further individualise VTE treatment in the future.

### 3. Biomarkers

Clinical factors alone do not account for the entirety of VTE recurrence risk, and certain biological factors detectable as biomarkers may also contribute. In this section, some well-studied biomarkers associated with increased VTE recurrence risk are discussed.

#### 3.1. D-Dimer

Perhaps the most well-studied biomarker is the D-dimer, which is a by-product of the lysis of cross-linked fibrin [47], and high levels following the withdrawal of anticoagulation after unprovoked major VTE have been repeatedly associated with increased risk of recurrent VTE [48–51]. A meta-analysis of 1818 patients [17] following unprovoked major VTE found the hazard ratio for recurrent VTE in those with abnormal D-dimers vs normal D-dimers to be 2.59 (95%CI 1.9–3.52). The evidence for D-dimer testing, however, in other VTE cohorts such as provoked VTE and distal DVT are conflicting and sparse [51,52]. In an analysis of 1655 VTE patients [53] from the RIETE registry, abnormal D-dimers after anticoagulation cessation was associated with a significantly increased risk for VTE recurrence (hazard ratio (HR) 1.74, 95% CI 1.51–3.63) in those with minimally provoked VTE but not surgically provoked VTE. In our centre, we performed a retrospective analysis of 173 VTE patients [54] and found that in those with IDDDVT, an abnormal post-anticoagulation cessation D-dimer was significantly associated with an increased risk of recurrent VTE (HR 10.48,  $p = 0.003$ ). Of the recurrent events, 30% were major VTE, suggesting that VTE recurrence following isolated distal DVTs may not be entirely low risk events. Travel-provoked VTE was also found to be associated with abnormal D-dimers in our cohort.

Although D-dimer tests can potentially identify higher risk populations, its applicability into clinical practice is not without challenges. One of the issues is that D-dimers are non-specific and increase naturally with age, during pregnancy, and can be attributed to malignancy or inflammation [47]. Similarly, post-anticoagulation cessation D-dimers may lack discriminatory ability in males [55], although this finding has been demonstrated in only one study so far. Age-adjustment of the D-dimer in the diagnostic setting has been a proven strategy to minimise false positives in elderly patients suspected for DVT and PE [56,57], however, a similar strategy has not been well studied to risk stratify for VTE recurrence. In the DULCIS study [49], altered D-dimer cut-off values according to patient age (single threshold of 70 years), gender, and type of D-dimer assay were adopted instead of the manufacturer's recommended threshold values. The resulting performance, however, was not improved in those patients aged over 70 years old with negative D-dimers, in whom 8.9% developed recurrent major VTE compared with 2.1% in those younger than 70 years old, during two years of follow-up. The authors of the study concluded that more research is required before age-adjustment of the D-dimer can be employed in the post-anticoagulant, VTE recurrence risk assessment setting.

A lack of standardisation of D-dimer methods may affect the interpretation of results and affect predictive model performance in the clinical setting. Various different D-dimer assays have been used across studies including quantitative latex immunoturbidimetric, enzyme-linked immunofluorescence assay (ELFA), chemiluminescent enzyme immuno-metric assays, and various point-of-care (POC) tests. These differences may partly explain conflicting results and differing abnormal D-dimer thresholds across populations [52,55]. Quantitative tests using ELFAs and latex immunoturbidimetric technology have been shown to have higher negative predictive value with higher sensitivity (>95%) and lower

specificity (50%) compared to POC tests (83% sensitivity and 71% specificity for DVT) [58]. An understanding of the performance qualities of local D-dimer assays in use would be crucial before adopting it into clinical practice.

Legnani et al. [59] found rates of abnormal D-dimers to be significantly higher after cessation of DOAC therapy compared to matched subjects who had received VKAs (18.8% vs. 11.8%,  $p = 0.02$ ). This finding has not yet been replicated in other studies, and it remains to be seen if there may be any effect on the utility of D-dimers as a predictor of recurrent VTE.

### 3.2. Factor VIII

There is some evidence that high levels of factor VIII are associated with VTE recurrence following a first unprovoked event [60,61], although this association has not been consistently reported [5,62]. Persistently elevated factor VIII over time has been found to be a feature following VTE and can be independent of an acute phase reaction [60,61]. In a study of 2242 patients [63], following a first VTE (provoked and unprovoked), incorporating the factor VIII (measured three months post-anticoagulation cessation) into the DASH predictive model led to improvement of the model performance, including in patients assumed to have low risk of recurrence. Differing methods for quantifying factor VIII may also limit direct comparisons between studies and cohorts. The optimal timing of factor VIII measurement, however, requires further studies.

### 3.3. P-Selectin

P-selectin is a cell-adhesion molecule normally found in the alpha granules of platelets and expressed on the surface of activated endothelial cells [64]. P-selectin mediates the adhesion of leukocytes and platelets and has been found in mouse models to be important in the process of venous thrombosis formation [65]. Soluble P-selectin (sP-selectin) has been detected in the circulation of patients following VTE [66], and has been implicated as a risk factor for VTE recurrence [67,68]. sP-selectin has been found to be an independent predictor of VTE occurrence in patients with malignancy (11.9% in those with sP-selectin above the 75th percentile, and 3.7% below the 75th percentile) [69].

### 3.4. C-Reactive Protein (CRP)

Elevated CRP is a marker of inflammation and has been associated with increased risk of arterial thromboses [70]. CRP has also been studied in venous thrombosis. The HUNT2 study found CRP in the highest quintile was associated with a 1.6-fold odds ratio of subsequently developing venous thrombosis [71]. In patients following cancer-associated thrombosis, high CRP  $>4.5\text{mg/L}$  at 21 days after stopping anticoagulation could predict VTE recurrence, and in this cohort, 66% of patients could safely stop anticoagulation based on the 21-day CRP value [72].

### 3.5. Microparticles

Microparticles are small membrane vesicles measuring between 100 and 1000 nm in diameter that are released by cells in response to cell activation or apoptosis. Microparticles can display membrane phospholipids and tissue factor and can promote thrombin and fibrin formation via the tissue factor-dependent pathway [73]. Tissue factor positive microparticles have been found to be elevated in patients with recurrent DVT compared to normal individuals [74] and in patients following acute PE [75]. However, a study by Ay et al. did not find any association between microparticles and patients with a history of recurrent VTE [76]. Considerable heterogeneity of methods to enumerate microparticles has limited our ability to make direct comparisons between studies. The International Society of Thrombosis and Haemostasis (ISTH) has sought to standardise enumeration procedures across different platforms [77,78].

Individual biomarkers may be insufficiently able to discriminate VTE recurrence risk on their own, and therefore may be better utilised as part of a multivariate clinical

prediction model in conjunction with clinical factors and other biomarkers. This approach has been most well studied for D-dimer but has also been explored for factor VIII [63]. Individual biomarkers often interrogate specific components of the coagulation system, and do not provide a global view of the complex interplay between the various components that contribute to pathological thrombosis. Hence, a comprehensive assessment of the various components of the coagulation system, as well as incorporating clinical information remains the future of individualised VTE risk assessments.

#### 4. Future Directions and the Role of Global Coagulation Assays

One of the challenges with predicting VTE recurrence is the lack of a single reliable biomarker. Assays which can capture the interplay of multiple factors in the coagulation system may better reflect the *in vivo* conditions in an individual. Currently available clotting assays such as the prothrombin and active partial thromboplastin time only capture the start of the clotting process until the beginning of thrombin formation, leaving the majority of the coagulation and fibrinolytic process unexamined. Hence, assays evaluating the final product of the coagulation cascade (e.g., thrombin and fibrin) have been an active area of investigation and may provide a better assessment of the unique prothrombotic signature in each individual.

##### 4.1. Thrombin Generation and VTE Recurrence

Thrombin has been recognised as a central component of the clotting system, with multiple functions including fibrin conversion, thrombomodulin activation, and thrombin activatable fibrinolysis inhibitor (TAFI) activation at high thrombin levels [79]. Advances in technique [80] have made thrombin generation assays more reliable and less labour-intensive, paving the way for clinical application. Several commercial thrombin generation assays are available. One of the most well-studied and widely available assays is the calibrated automated thrombogram (CAT), in which tissue factor and phospholipids are added to the test system and the generated thrombin is determined by its interaction with a fluorogenic substrate, detected by continuous measurement. The result is a thrombin generation curve from which several parameters can be determined: lag time (time until thrombin burst), peak thrombin (maximum level of thrombin generated), endogenous thrombin potential (ETP area under thrombin generation curve), time to peak thrombin, and velocity index (rate of thrombin generated).

Several studies have found positive associations between increased thrombin generation parameters and VTE recurrence [41,81–84]. Eichinger et al. followed 861 patients after the first unprovoked VTE, and using the Dade Behring ETP assay, found high ETP to be independently associated with increased risk of VTE recurrence (HR 1.6, 95% CI 1.0–2.4) even after adjustment for D-dimers [41]. Tripodi [82] et al., found ETP and peak thrombin as measured by the CAT to be associated with VTE recurrence following unprovoked VTE, and that addition of thrombomodulin into the test system resulted in more significant findings (HR for high peak thrombin of 4.57 in the presence of thrombomodulin, 2.65 in the absence of thrombomodulin). Addition of thrombomodulin to the test system is thought to better replicate *in vivo* conditions, because thrombomodulin is required to fully activate the protein C anticoagulant system. However, the optimal concentration of thrombomodulin may differ for each test system with a lack of standardisation across studies. Previous groups have determined their own *in-house* optimal concentrations of thrombomodulin needed to distinguish a population with prothrombotic phenotype [82,84,85]. Of note, several studies have investigated the use of an ETP-based activated protein C (APC) resistance test in the presence of thrombomodulin [86] in the setting of women using hormonal contraceptives [87]. This assay was able to detect APC resistance independently of the factor V Leiden mutation, suggesting that it may have a role in predicting hypercoagulability and VTE recurrence and warrants further investigation.

There have been two studies that have found no association between thrombin generation and VTE recurrence [85,88], however both studies had significant methodological

issues. In the earlier study [85], due to insufficient plasma volume collected, CAT was performed on plasma diluted 1:4 with a buffer. Additionally, a much higher concentration of tissue factor (15 pM) was used to initiate coagulation and may have reduced the sensitivity of the test to hypercoagulability. In the latter study [88], blood samples were collected up to 25 months following anticoagulation cessation, which also diverges from other published studies.

#### 4.2. Viscoelastic Tests and VTE Recurrence

Viscoelastic testing employs mechanical rotation to detect the kinetics of thrombus formation and lysis and is performed on whole blood (citrate or native), thus in theory is better reflecting of *in vivo* haemostasis, taking into account plasma clotting factors, platelets, leucocytes and red cells [89,90]. The two most commonly available commercial viscoelastic testing devices are thromboelastography (TEG<sup>®</sup>, Haemonetics, Braintree, MA, USA) and rotational thromboelastometry (ROTEM<sup>®</sup>, Haemoview Diagnostics, Brisbane, Australia). In the TEG<sup>®</sup> device, whole blood is placed in a cup with calcium and an activator (e.g., Kaolin) and warmed to 37 °C. The cup is then rotated around a pin, and, as the clot forms, fibrin strands increase the torsion around the pin, and decrease as fibrinolysis breaks down the fibrin strands. These changes in torque are then displayed graphically. In the ROTEM<sup>®</sup>, the pin itself oscillates within the cup, which remains stationary. Results from ROTEM<sup>®</sup> and TEG<sup>®</sup> are not interchangeable [91], and differences in blood used [92] (native whole blood vs citrated) as well as activators also introduce differences into results [93].

Viscoelastic testing has gained popularity and is widely used in guiding resuscitation during massive haemorrhages, especially in the settings of trauma-induced coagulopathy and post-partum haemorrhage [94–96]. However, although the evidence of assessing thrombotic risk is limited, growing research points to the ability of viscoelastic testing to detect a hypercoagulable state and an increased propensity to develop thrombosis. This has been found in cancer [97], trauma [98], and in the peri-operative setting [99]. Specifically, in VTE, TEG<sup>®</sup> was unable to detect a difference between 19 patients following cerebral venous thrombosis and sex- and age-matched controls [100]. In a study of portal vein thrombosis, ROTEM<sup>®</sup> detected no significant differences between cirrhotic patients who had developed portal vein thrombosis and those who had not [101]. To the best of our knowledge, there have not been any studies examining the association of a hypercoagulable state, as detected by viscoelastic testing with VTE recurrence. With current viscoelastic technology, the limitation of whole blood samples means large scale batch testing on stored samples is not feasible, and the current body of evidence examining VTE recurrence has focused on those assays which can utilize stored frozen plasma samples, such as the CAT.

#### 4.3. Fibrin Generation, Fibrinolysis and VTE Recurrence

Abnormal fibrin clot structures such as reduced clot permeability, increased fibrin fibre density, and resistance to fibrinolysis have been linked to increased venous and arterial thromboembolism [102,103]. A complex system governs fibrinolysis and its regulatory mechanisms, and hypofibrinolysis has been postulated as a possible risk factor for VTE recurrence. However, studies interrogating individual components of the fibrinolytic pathway (plasminogen activator inhibitor-1 (PAI-1), tissue plasminogen activator (tPA), TAFI) have so far led to conflicting findings [104–108].

There have been efforts to develop assays to reflect the overall plasma fibrinolytic potential and the interplay of multiple parts of the fibrinolytic pathway. In the clot lysis time (CLT) test, plasma is activated with tissue factor, phospholipid, and calcium, and placed in a 96-well microtitre plate with exogenous tPA. The resulting changes in turbidity are detected by light absorbance at 405 nm, and the clot lysis time is defined by the time to 50% maximal turbidity to the time to half maximal lysis [109]. Meltzer [110] et al. have found that the CLT reflects levels of all fibrinolytic factors except t-PA, and after adjustment for acute-phase proteins TAFI and PAI-1 remained associated with thrombosis. Several studies have convincingly demonstrated that, compared to controls, subjects with VTE

have evidence of hypofibrinolysis demonstrated by prolonged CLT [111–113]. Evidence linking CLT and VTE recurrence have been conflicting however [108,112,114–116], and may be due to heterogeneous study designs, inclusion criteria and assay methodologies.

The overall haemostatic potential (OHP) assay is a variant of the CLT and was devised by Blomback et al. in 1999 [117] and modified for laboratory use in 2001 [118]. Two parallel fibrin aggregation curves are made by running two samples in parallel: one with a small amount of thrombin or tissue factor to trigger fibrin generation (OCP), and the second curve by the addition of tPA resulting in fibrinolysis (OHP). The difference in the two curves results in the overall fibrinolytic potential (OFP), and is calculated using  $((\text{OCP}-\text{OHP})/\text{OCP} \times 100\%)$ . The advantage of the OHP assay over CLT is the ability to interrogate both fibrin generation and lysis in one system. The most recent modification [119] of the OHP assay is also able to incorporate information about the speed of fibrin generation and lysis. This new assay is better able to correlate with changes in PAI-1 levels compared to the previously derived OFP [119]. Although there is limited evidence available suggesting that OHP can detect persistent hypercoagulable states and hypofibrinolysis following DVT and PE [120,121], there have been no studies exploring the link between increased OHP and VTE recurrence to our knowledge.

#### 4.4. Limitations of Global Coagulation Assays

Research supporting the use of global coagulation assays as a predictor of VTE recurrence is promising but in its infancy. Standardisation of methodologies remains a major barrier to the reproducibility of results and must be improved before there can be widespread adoption in clinical practice. The ISTH has made recommendations to standardise thrombin generation measurements in haemophilia using CAT [122] as well as the CLT [123], in order to facilitate translation of results across different laboratories. New automated analysers such as the ST-Genesia analyser (Diagnostica Stago, France) have been commercialised, which will be crucial to facilitate mass throughput testing and ensure standardisation in clinical practice. Additionally, most research into global coagulation assays have been conducted in the bleeding disorder population and prior to the widespread adoption of DOACs, and further refinement is required in these areas.

A major practical issue limiting the widespread adoption of global coagulation assays, and indeed, most biomarkers, into clinical practice is the influence of concurrent anticoagulation therapy. Thrombin generation assays are affected by all anticoagulants and have been investigated as tools to monitor anticoagulant therapy [124–126]. Concurrent anticoagulants limit the ability of global assays and biomarkers to uncover the underlying hypercoagulable state. Consequently, the majority of studies examining biomarkers and global coagulation assays have been conducted on non-anticoagulated patients, usually around four weeks following anticoagulation cessation. However, the risk of VTE recurrence following anticoagulation cessation can be as high as 0.5–1.5% within the first month [17,127]. Hence, the decision to withhold anticoagulation to facilitate D-dimers or global coagulation testing, for instance, must be made cautiously in a patient in high clinical risk category of VTE recurrence.

Despite these limitations, global coagulation assays may more accurately reflect the balance between prothrombotic and bleeding states on an individual level and could become crucial diagnostic tools in the quest for individualised VTE recurrence risk assessment in the future.

## 5. Conclusions

Assessing the risk of VTE recurrence remains challenging and imperfect in the current era of DOACs, especially in the elderly, males, and those at a concurrent high risk of bleeding. Novel biomarkers and global coagulation assays may hold promise in improving the ability to risk-stratify patients following VTE and identify those low-risk individuals who can safely stop anticoagulation treatments. Future efforts should focus on developing new validated clinical prediction models and potentially incorporating multiple biomarkers

and global coagulation assays that examine different parts of the coagulation system, which together may provide a more holistic picture of an individual's prothrombotic state.

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