

# Management of Patients With Unprovoked Venous Thromboembolism: An Evidence-Based and Practical Approach

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## Opinion statement

The management of patients with unprovoked venous thromboembolism is a common and challenging clinical problem. Although the initial antithrombotic management is well-established, there is uncertainty about the optimal long-term anticoagulant management, specifically whether patients should receive a short (i.e., 3- to 6-month) duration of anticoagulant therapy or indefinite anticoagulation. Factors that may be considered to estimate patients' risk for recurrent thromboembolism include the mode of initial clinical presentation, as deep vein thrombosis or pulmonary embolism, patient sex, antecedent hormonal therapy use, thrombophilia, D-dimer levels, and residual vein occlusion in patients with deep vein thrombosis. Many of these factors have been integrated into clinical prediction guides which stratify patients with unprovoked venous thromboembolism according to their risk for disease recurrence and, thereby, can assist clinicians in decisions about the duration of anticoagulation. The objective of this review is to consider the evidence relating to the clinical significance of purported risk factors and provide a practical case-based approach to guide decisions on duration of anticoagulation for patients with unprovoked venous thromboembolism.

## Introduction

The management of patients with venous thromboembolism (VTE) should reflect the biphasic, acute and chronic, nature of this disease [1•]. In the acute phase, the overall treatment aim is to reduce symptoms related to deep vein thrombosis (DVT) and pulmonary embolism (PE) and to prevent thrombus extension and (additional) embolization, the latter of which can increase mortality [2–4]. This can be done with prompt initiation of anticoagulant therapy [5••]. The initial phase of anticoagulation aims also to prevent extension of asymptomatic DVT, which occurs in 20 % of patients presenting with symptomatic PE alone, and to prevent recurrent PE, which is present but silent in up to 50 % of patients presenting with DVT alone [6]. Minimizing the risk for DVT progression or recurrent PE is important to mitigate the risk that patients will develop the post-thrombotic syndrome [7] and chronic thromboembolic pulmonary hypertension [8], and to prevent recurrent VTE that is fatal.

After this initial treatment, the aim of anticoagulant therapy is to minimize the risk for disease recurrence since the occurrence of a first VTE markedly increases the risk for further VTE [6,9]. Vitamin K antagonist therapy, typically with warfarin, is highly effective in reducing the risk for recurrent VTE [10,11]. Although this clinical benefit is not maintained after treatment discontinuation, regardless of its duration [11,12,13••], the benefit of continued anticoagulation needs to be balanced against the risk for anticoagulant-related bleeding [14]. Given the effectiveness of anticoagulants to prevent recurrent VTE (as summarized in Table 1), the challenge facing the clinician is to identify which patients would derive a net clinical benefit from indefinite anticoagulant therapy and those in whom avoidance of long-term anticoagulation is preferable.

It is widely accepted that three months of anticoagulation is sufficient for most patients with a first VTE that occurs in association with a major transient risk factor such as surgery, lower limb fracture or other trauma, pregnancy, and immobilization [5••,15••]. For these patients, the risk of recurrent VTE after three months of anticoagulation is lower compared with a shorter duration of treatment but there is no therapeutic advantage to longer treatment duration [13••]. Such patients have a good prognosis, with a 1–3 % person-year risk for recurrent VTE [15••]. Patients who develop

VTE in association with a weak risk factor, such as estrogen use or long-distance travel, appear to have a slightly higher risk for recurrence [15••] but three months of anticoagulation also is sufficient in such patients. Finally, patients who develop VTE in association with active cancer warrant consideration for indefinite anticoagulation [5••].

In contrast, there is uncertainty about optimal management for patients with unprovoked VTE, who comprise approximately 50 % of all patients with a first VTE. In such patients who have received three months of anticoagulation, the risk for recurrent VTE is 5–15 % per year after anticoagulation is stopped [15••,16•], or up to 30–35 % after five years [16•,17••, 18], and this recurrence risk is not affected by whether patients receive an additional 3–9 months of anticoagulation [13••]. Stated differently, patients with unprovoked VTE who are destined to develop disease recurrence will do so irrespective of the duration of anticoagulation. When considered against a 1–3 % annual risk for anticoagulant-related bleeding [14], the net therapeutic benefit would seem to favor administering indefinite anticoagulation in all patients with unprovoked VTE. However, rather than subject all such patients to the risks and costs of indefinite anticoagulation, the challenge for the clinician is to identify patients who are most likely to develop recurrent VTE, in whom indefinite anticoagulation can be justified, and those patients with an acceptably low risk for recurrence in whom anticoagulation can be stopped.

Against this background, the objectives of this review are: 1) to summarize, risk factors and clinical prediction guides (CPGs) that can be used to estimate patients' risk for recurrence after a first unprovoked VTE; and 2) to suggest a management strategy to help guide decisions of whether to recommend 3–6 months or indefinite anticoagulation in such patients. Three representative case vignettes will be considered to help illustrate the suggested clinical approach:

- 58 year old man, otherwise well, with a first unprovoked PE (D-dimer not available);
- 35 year old woman, otherwise well, with a first PE occurring during oral contraceptive use;
- 82 year old woman, with co-morbidities, and a first unprovoked DVT (D-dimer available)

**Table 1. Pharmacologic treatment options**

Drug [ref] <sup>‡</sup>	Standard dosage and timing Acute phase treatment	Long-term and extended* treatment	Comments
Unfractionated heparin (UFH) [5••,95]	80 U/kg bolus i.v., then 18 U/kg/h (or 5,000 U i.v. then 1000 U/h), adjusting infusion velocity to reach a PTT target 1.5-2.5 times normal	-	When thrombolytic therapy is planned, UFH is recommended over LMWH or fondaparinux for the acute phase treatment.
Low-molecular-weight heparin (LMWH) [5••,95,96]	Enoxaparin: 1 mg/kg s.c. twice a day Enoxaparin: 1.5 mg/kg s.c. once daily Tinzaparin: 175 U/kg s.c. once daily Dalteparin: 200 U/kg s.c. once daily		1. Long-term (6 months) treatment with heparin (1 month of full dose followed by 5 months of reduced dose to 75 %) was demonstrated to be more effective than warfarin only in patient with VTE and cancer. 2. If renal impairment (calculated creatinine clearance <30 ml/min), consider UFH.
Fondaparinux [5••,95]	7.5 mg s.c. once daily (or 5 mg once daily if body weight <50 kg; 10 mg once daily if >100 mg)	-	No evidence for long-term/extended treatment
Systemic thrombolysis [5••]	Recombinant t-PA 100 mg i.v. over 2 h	-	Patients with PE associated with hypotension
Vitamin K Antagonist [5••,95]	Warfarin: loading dose of 5 or 10 mg for first 2 days then dosing based on INR (target 2.5, range 2-3)	Continue warfarin dose based on INR monitoring	1. In patients with acute VTE, warfarin should be started early together with parenteral anticoagulation which should be given for at least 5 days while waiting for therapeutic INR 2. Low-intensity warfarin (target 1.5-2) after a first full-dose treatment (for at least 3 months) may reduce recurrences but is less effective than full-dose warfarin
Rivaroxaban <sup>†</sup> [5••,97,98]	15 mg orally twice a day for 3 weeks and then 20 mg once daily	20 mg once daily	In patients who receive rivaroxaban for acute VTE, there is no requirement for initial treatment with UFH or CMWH
Dabigatran <sup>†</sup> [5••,99]	150 mg orally twice a day	150 mg twice a day	1. In the acute phase, dabigatran should be started after/in association to an initial treatment with LMWH or UFH for the first few days after diagnosis 2. No evidence on long-term/extended anticoagulation (no more than 6 months) with dabigatran for VTE.
Aspirin [93,94••]	-	100 mg orally once daily	Possible option in patients not at high risk of recurrence

\*\* > 3 months treatment (current guidelines recommend extended anticoagulation to continue on the same drug used for long-term treatment if there is not any specific reason for switching). <sup>‡</sup>We refer to evidence summarized in the 2012 ACCP Antithrombotic Clinical Practice Guidelines. <sup>†</sup>Rivaroxaban and dabigatran are not yet approved for clinical use for venous thromboembolism in the United States

In Table 2 and Fig. 1 we provide a suggested approach to the management of these cases based on the available evidence and practical considerations.

**Table 2. Case Examples and Suggested Management**

Case examples <sup>†</sup>	Relevant evidence on predictors of risk of recurrence	Recurrent risk estimates (annualized risk [AR] or cumulative rate [CR]) according to available CPGs <sup>‡</sup>	Conclusion and notes
58 year old man, first unprovoked PE (D-dimer not available)	<p><b>Male sex:</b> 1.5-2 fold higher risk compare to females [16••,20,22,23••,24-28]</p> <p><b>PE as first presentation:</b> higher risk compared to distal DVT; no significant difference compared with proximal DVT [12,13••,30•,31-33]; patients presenting initially with PE more likely to have recurrence as PE than DVT [12,30•,33,87]</p> <p><b>Age:</b> not definitive evidence[16••,17••,84••]</p>	<p>Men and HER-D00-2 [82]: AR &gt;3 %</p> <p><b>Vienna [17••]:</b> if D-dimer was available, the opposite scenario would be:</p> <p>D-dimer 100 ng/ml → CR 4.3 % (2.7-6.9) at 1 year, 15.6 % (10.3-23.2) at 5 years</p> <p>D-dimer 2000 ng/ml → CR 10.5 % (7.3-15) at 1 year, 34.7 % (26.5-44.4) at 5 years</p> <p><b>DASH[84••]:</b> score from 2 to 4 → AR 7-20 % (for patients presenting with PE, CR of recurrence as PE of 10.6 % at 5 years [30•])</p>	<p><b>High risk patient</b></p> <p>Note: 1.Measuring D-dimer level would help but this is a high risk case independently of D-dimer. 2. If the same patient had presented with a first proximal DVT, his risk predicted by Men and HER-D00-2 and DASH score would not change and would decrease slightly with the Vienna CPG</p>
35 year old woman, first PE occurring during oral contraceptive (later stopped)	<p><b>Women with a hormone-related VTE:</b> a lower (nearly 0.5) risk compared to women with a first unprovoked not-hormone-related VTE, if exposure to hormone therapy risk comparable to VTE provoked by nonsurgical transient risk factor [15••,16••,21,22,23••]</p>	<p>Men and HER-D00-2 [82]: AR &gt; or &lt;3 % depending on presence or not of at least 2 of: obesity, signs of post-thrombotic syndrome, D-dimer ≥250 mg/dl [the estimate of AR for women with an OC-related VTE at high risk according to the score was largely imprecise: 4.1 % (0-12.2) ][100]</p> <p><b>Vienna [17••]:</b> not applicable</p> <p><b>DASH [84••]:</b> score from -2 to 0 → AR &lt;3 %</p>	<p><b>Low risk patient</b></p>

**Table 2. Case Examples and Suggested Management** (Continued)

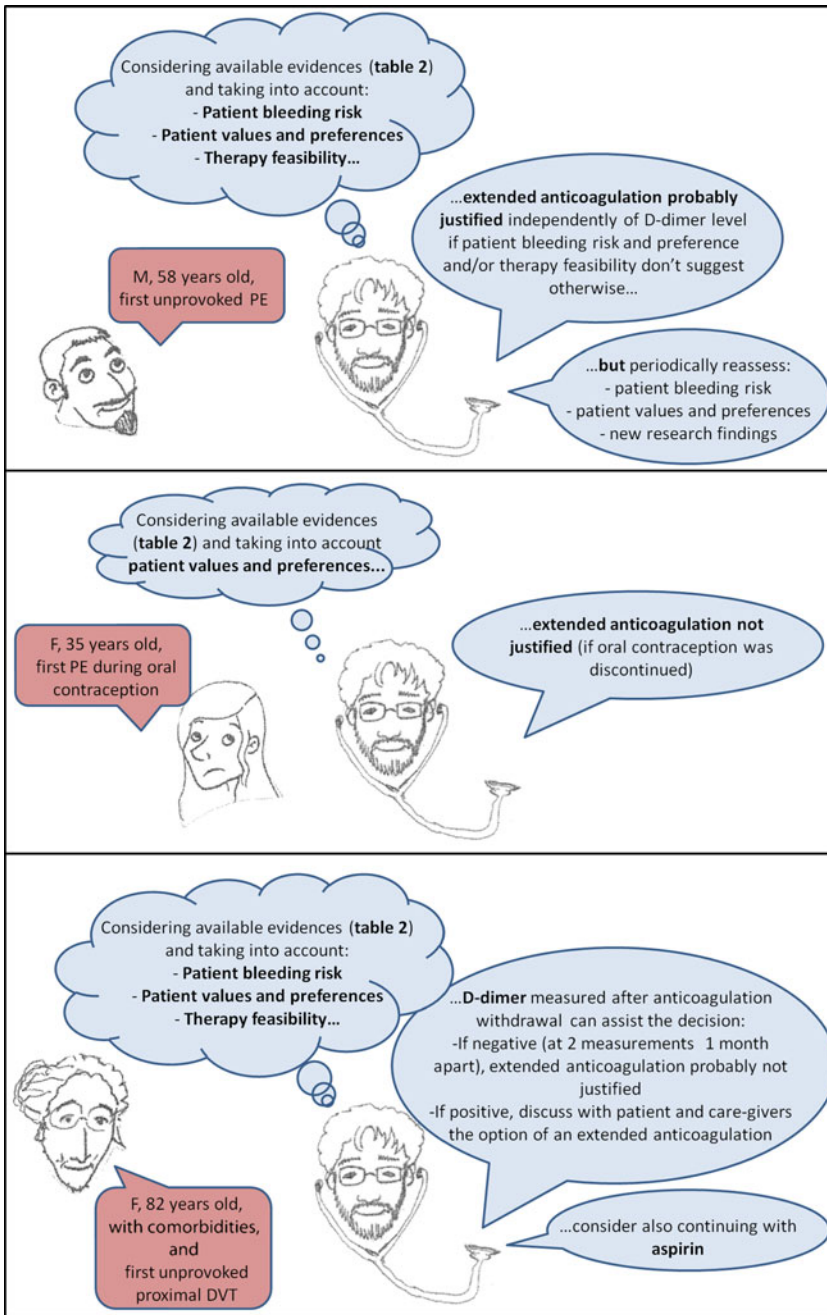
Case examples <sup>‡</sup>	Relevant evidence on predictors of risk of recurrence	Recurrent risk estimates (annualized risk [AR] or cumulative rate [CR]) according to available CPGs <sup>‡</sup>	Conclusion and notes
82 year old woman, with co-morbidities, first unprovoked proximal DVT (D-dimer available)	<p><b>Female sex:</b> 2-1.5-fold lower risk compare to males [16••,20,22,23••,24-28]</p> <p><b>Proximal DVT as first presentation:</b> a higher risk compared to distal DVT; probably not significant difference respect to PE [12,13••,30•,31-33]</p> <p><b>Age:</b> not definitive evidences [16••,17••,84••]</p> <p><b>D-dimer after stopping anticoagulation:</b> strong predictor of risk independent of age and comorbidity [16••,65-73]</p>	<p><b>Men and HER-D00-2 [82]:</b> 1 point for age → AR &gt; or &lt; 3 % depending on presence or not of at least 1 of: obesity, signs of post-thrombotic syndrome, D-dimer ≥ 250 mg/dl</p> <p><b>Vienna [17••]:</b> CR range according to D-dimer level:</p> <p>D-dimer 100 ng/ml → CR 2.0 % (1.1-3.7) at 1 year, 7.6 % (4.3-13.3) at 5 years</p> <p>D-dimer 2000 ng/ml → 5.1% (3.3-7.8) at 1 year, 18.1 % (12.5-25.8) at 5 years</p> <p><b>DASH [85]:</b> score from 1 to 3 according to D-dimer level → AR 2.9-13.4 %</p>	<p><b>Intermediate risk patient</b></p> <p>Note: Although the prognostic validity of D-dimer holds regardless of patient comorbidity, the presence of multimorbidity affects the decision process since a) it can increase the patient risk of bleeding; b) the decision on extended anticoagulation may cross other therapeutic needs</p>

M, male; F, female; OC, oral contraceptive; VTE, venous thromboembolism; PE, pulmonary embolism; DVT deep vein thrombosis; CPG, clinical prediction guide

<sup>‡</sup>Patients have received 3-6 months of anticoagulation. <sup>‡</sup>None of CPGs externally validated

## Clinical and laboratory risk factors for recurrent VTE

Treatment guidelines such as the 2012 American College of Chest Physicians (ACCP) Antithrombotic Guidelines [5••] do not provide recommendations for using risk factors or CPGs to decide on the duration of anticoagulation for individual patients after unprovoked VTE, though it is suggested that these factors be considered in the decision-making process [5••]. Herein, we shall review factors for which there is a clinically meaningful body of evidence regarding their role in estimating the risk of recurrent VTE whereas other clinical factors, such as age and obesity, and other laboratory markers, for which there is a paucity of evidence, will not be reviewed.



**Fig. 1.** Case examples: suggested strategies for a long-term management. Legend. The vignette synthesizes the suggested treatment strategies for the clinical cases proposed as example of patients at high, low and intermediate risk, joining the evidence summarized in Table 2 with other relevant aspects of the clinical decision making process. (Thanks to Nebbiai Mattia for the drawing).

## Estrogens and patient gender

High levels of estrogen, whether occurring during pregnancy and the puerperium or with oral contraceptive or estrogen replacement therapy use, increase

the risk for VTE [19]. Women who continue hormonal therapy after a hormone-related VTE have a 5-fold increased risk of recurrent VTE [20]. Conversely, women who stop hormonal therapy after VTE have a 50 % lower risk for recurrence than women with unprovoked (not hormone-related) VTE [15••,16•,21,22,23••]. From an absolute risk perspective, women who stop hormonal therapy after VTE have an approximately 4 % annual risk of disease recurrence, which is slightly higher than after surgery-related VTE but similar to the recurrence risk when VTE occurs in association with non-surgical transient risks such as immobilization or long-distance travel [15••,21]. Estrogen exposure may also explain the observed difference in the risk for recurrent VTE between men and women. After discordant findings reported in individual studies [20,22,24–27], a study-level meta-analysis [28] and a large patient-level meta-analysis [16•,23••] found that in patients with unprovoked VTE, men had a 1.5-to-2.0-fold higher risk for recurrent VTE than women. Thus, male patients who are treated for three months after a first unprovoked VTE have a 3-year risk of recurrence as high as 20–25 % [23••].

## Clinical presentation and extent of venous thrombosis

Although DVT and PE are manifestations of the same disease, the mode of clinical presentation and the extent of thrombosis may affect patient prognosis. Thus, patients with distal (calf) DVT have a 2.5 % annual risk of recurrence after three months of anticoagulation, which is 2-to-4-fold lower than patients with proximal DVT and/or PE [6,10,13••,29,30•]. Whereas some discrepant findings were reported for patients presenting with PE compared to patients presenting with DVT alone [12,31–33], two independent patient-level meta-analyses found no difference in rates of recurrent VTE, irrespective of initial presentation as DVT or PE [13••,30•]. However, patients presenting with PE are more likely to develop recurrence manifesting as PE than as DVT [12,30•,32,33] and, consequently, are at increased risk that recurrence will be life-threatening or will lead to chronic pulmonary hypertension. The ACCP Guidelines recommend the same anticoagulant therapy management in patients presenting with PE or isolated proximal DVT [5••].

## Hereditary thrombophilic defects

The factor V Leiden and prothrombin gene mutations are the most common prothrombotic genetic abnormalities occurring in patients with VTE [34]. Deficiencies of endogenous anticoagulants (antithrombin, protein C, protein S), high levels of factor VIII and XI, and hyperhomocysteinemia are other, less common, hereditary thrombophilic defects [34]. One or more of these abnormalities occur in up to 50 % of patients with a *first* unprovoked VTE [20,35,36] but there is a weak or non-significant association between these abnormalities and the development of *recurrent* VTE [35,37–46]. Prospective studies have not shown that testing for thrombophilia can predict the long-term risk of recurrent VTE, especially after adjusting for stronger predictors such as the absence of an antecedent provoking risk factor [20,21], and no studies have shown that management strategies based on thrombophilia test-

ing affect patients' risk for recurrence [47]. Furthermore, there is no known relation between a family history of VTE and the likelihood of detecting a thrombophilic abnormality [48]. For these reasons, routine screening for inherited thrombophilia is not recommended in patients with unprovoked VTE as it will not have a major impact on the duration of anticoagulation [5••,49,50]. In selected patients testing for thrombophilia may assist in their counseling about prognosis, but the implications of the test results should be clearly discussed with patients before testing is done [49–51].

Laboratory testing for lupus anticoagulant, anticardiolipin antibodies and anti- $\alpha$ 2 glycoprotein-I antibodies merits special consideration since usually they are not inherited abnormalities. It is difficult to estimate their prevalence in the general population because of the potential for false positive test results, especially when a positive test is not confirmed with repeat testing and at a time remote from the acute VTE [35,52–54]. The clinical significance of individual tests is uncertain, in part because of different laboratory assays and criteria for test positivity. However, in one well-designed study involving patients with prior VTE (who stopped anticoagulation), a positive anticardiolipin antibody or lupus anticoagulant conferred a 2-fold higher risk of recurrent VTE than patients with a negative test [55]. Overall, a diagnosis of the antiphospholipid syndrome should be made carefully, requiring the combination of clinical and laboratory criteria [56]. Moreover, positive laboratory tests should be confirmed with repeat testing done at least six weeks apart and at a time remote from the index VTE or other acute illnesses. If this diagnosis is confirmed, it has important clinical implications because of the high risk for recurrent VTE if anticoagulation is stopped.

## Residual vein occlusion

In patients with proximal DVT, the presence of a residual vein occlusion (RVO) identified by venous ultrasound three or more months after diagnosis may identify patients at increased risk for recurrent VTE. Some studies found that patients with RVO, whether occlusive or non-occlusive, are at increased risk for recurrent VTE compared with patients in whom there is complete vein recanalization [57–59]. In three randomized trials [60–62] that explored the benefit of extended anticoagulation in patients with RVO after 3–6 months of anticoagulation for DVT found a higher rate of recurrence in patients with RVO than in those without RVO. On the other hand, a patient-level meta-analysis suggested that RVO was a weak predictor of recurrence after unprovoked VTE and that the association between RVO and recurrence was stronger if RVO was detected early (within three months) than later (>6 months) after diagnosis [63]. The use of RVO to assess recurrence risk is limited by the lack of a standard definition for RVO and the potential for operator variability in the interpretation of ultrasound findings [64].

## D-dimer

D-dimer, a fibrin degradation product, which is used to assess patients with suspected DVT or PE, has been also studied as a predictor of recurrent VTE when measured after the completion of 3–6 months of anticoagulation in



patients with a first VTE. Individual studies [65–71] and meta-analyses [16•,72,73] found a 2-fold higher risk of recurrence in patients with unprovoked VTE who had an elevated (or positive) post-anticoagulation D-dimer than in patients with a normal (or negative) D-dimer. Thus, a positive D-dimer conferred an almost 9 % annual absolute risk for recurrent VTE (cumulative rate 30–35 % after five years) after the index event [16•]. A patient-level meta-analysis [16•] found that the prognostic utility of D-dimer was independent of patient age, timing of post-anticoagulation D-dimer testing, and the D-dimer cut-point (250 or 500 ng/mL) used to define a positive/negative test. In one study, D-dimer and RVO were jointly studied after stopping anticoagulation but only D-dimer was an independent predictor of recurrent VTE [74].

In patients with a positive post-anticoagulation D-dimer, resumption of anticoagulation should be considered given the associated higher risk for recurrent VTE [67]. In such circumstances an alternative approach is to repeat the D-dimer measurement so as to reduce the potential for spuriously elevated levels and to base decisions on long-term anticoagulation on consistently elevated D-dimer levels [75•]. Finally, there are limitations of D-dimer when used in this clinical circumstance [64]. Ideally, D-dimer as a determinant of recurrent VTE risk should be expressed as a continuous variable [76], but a cut-point that dichotomizes patients' risk for recurrent VTE (into low or high risk groups) might be more useful in clinical practice. The drawback of this approach is the potential need for assay-specific D-dimer cut-points [77]. In addition, even if the prognostic value of the D-dimer is independent of patient age and comorbidity [78], D-dimer levels are higher, on average, in the elderly [67] and age-specific D-dimer cut-points may increase its specificity [77]. Age-specific D-dimer cut-points, as proposed for the diagnostic use of D-dimer [79], may be helpful. Overall, additional research is needed to identify the optimal manner in which D-dimer can be used as a predictor of recurrent VTE.

Other global markers of coagulation activation, such as measures of thrombin generation, have been assessed as predictors of recurrent VTE, but are not yet ready for clinical use [80,81].

## Clinical prediction guides for recurrent VTE

There are three CPGs that have been developed to stratify patients with treated unprovoked VTE as being at high or low risk for disease recurrence. The Men and HER-DOO-2 CPG was the first such guide that was derived from a prospective cohort of patients with a first unprovoked proximal DVT and/or PE [82]. With this CPG, all men are considered at high risk of recurrence (based on a 3 % annual risk threshold to define high risk). For women,  $\geq 2$  factors (comprising lower extremity hyperpigmentation, edema, redness, D-dimer  $\geq 250$  ng/mL [during anticoagulant therapy], obesity [body mass index  $\geq 30$  kg/m<sup>2</sup>], and age over 65 years) identifies women at high risk for recurrent VTE, whereas  $< 2$  factors identifies women at low ( $< 3$  % per year) risk for recurrence [83••]. The Vienna CPG uses patient sex, VTE site/extension and D-dimer (post-anticoagulation) to estimate an individual patient's risk for recurrent VTE with the use of a nomogram and risk calculator [17••]. Finally, the DASH CPG, which comprises D-dimer (post-anticoagulation), pa-

tient age, patient sex, and VTE occurring in association with hormonal therapy, provides a numeric score corresponding to a risk for recurrent VTE based on these four factors [84••]. Overall, although these CPGs may help clinicians in stratifying patients according to risk for recurrent VTE, they require independent validation in separate patient populations [85].

## Conclusion

In this review, we summarized key clinical and laboratory factors that confer an increased risk for disease recurrence after a first unprovoked DVT or PE. CPGs have been developed which combine these factors so as to classify patients into high- or low-risk risk groups or to provide individualized estimates for recurrence risk.

The CPGs that are developed to quantify the risk for recurrent VTE are anchored on what is considered an 'acceptably low' rate of recurrence that would justify stopping anticoagulation after 3–6 months of treatment [86]. Based on data involving patients at low risk for recurrence (i.e., VTE provoked by a major risk factor), an annualized rate of approximately 3 % patient-year [82] (or a risk of 5 % at one year and 15 % at five years [86]) has been proposed as a threshold below which most clinicians would consider the risk of recurrence acceptably low so as to justify stopping anticoagulation. Ideally, complementary CPGs should stratify patients according to their risk for bleeding if anticoagulation is continued. To date, few CPGs have estimated the anticoagulant-related risk of bleeding in patients with VTE [87,88], and none addressed the risk during long-term treatment. Although CPGs are available to predict bleeding in patients with atrial fibrillation, such as the HAS-BLED score [89], these CPGs have been developed in generally older populations than those with VTE.

The predicted rates of recurrent VTE and clinically important (or major) bleeding should then be combined with an assessment of the clinical impact of such events, which can be expressed by the case-fatality. Thus, in a large systematic review, the case-fatality rate for major bleeding during the initial three months of anticoagulation for VTE was 11.3 % whereas the case-fatality rate for recurrent VTE after at least 3 months of anticoagulant therapy was 3.6 % [90,91,92••]. Finally, these objective factors should be combined with individual patients' values and preferences regarding the need (or not) for ongoing anticoagulation in addition to practical factors such as treatment costs and feasibility of anticoagulant monitoring [51].

Irrespective of whether a decision is made to continue or stop anticoagulant therapy, such a decision should not be irreversible. Indeed, patients should be reassessed periodically to re-evaluate their risk profile, to reassess their preferences and to incorporate new research findings into individual patient management. For example, two recent randomized trials have shown that patients with unprovoked VTE who take low-dose ASA (100 mg daily) after completing anticoagulant therapy have a 25–30 % reduction in the risk for recurrent VTE [93,94••]. Thus, ASA may be a long-term treatment option in patients at intermediate risk for recurrence or those at higher risk for anticoagulant-related bleeding. Additional prospective studies are needed to explore clinical management strategies which may include stopping

anticoagulant therapy in patients at low risk, switching to ASA in patients at intermediate risk for recurrence, and continuing anticoagulants in patients at high risk for recurrent VTE.

## Disclosure

No potential conflicts of interest relevant to this article were reported.

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