Predicting the risk of recurrent venous thromboembolism

The Austrian Study on Recurrent Venous Thromboembolism (AUREC)

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Summary
Venous thromboembolism (VTE) is a disease, which often recurs. The recurrence risk is highest in patients with unprovoked proximal deep-vein thrombosis (VT) or pulmonary embolism. Men have a higher risk than women. The risk is low in patients with VTE related to a temporary risk factor such as surgery or estrogen use. Other risk factors include overweight, post-thrombotic syndrome, history of VTE, residual VT or a vena cava filter. Both factor V Leiden and the prothrombin mutation confer a negligible increase in recurrence risk. High clotting factor levels, deficiency of a natural coagulation inhibitor, or hyperhomocysteinaemia are also associated with an increased risk. Reasons why routine laboratory thrombophilia screening however is no longer warranted are addressed in this article. Prediction rules combining clinical characteristics and coagulation assays have recently been developed. One such model, the Vienna Prediction Model, allows predicting recurrent VTE on the basis of VTE location, sex and D-dimer. This article describes strategies to distinguish between patients with high risk of recurrent VTE from those with a lower risk, who might not benefit from long-term antithrombotic therapy.

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Venous thromboembolism (VTE) is a frequent disease, which occurs predominantly in the elderly population and/or in association with temporary risk factors including surgery, trauma, co-morbidities and hospital admission (1).

VTE is also a well-known complication of pregnancy, childbirth and female hormone use.

An association between VTE and cancer is known already since the sixties of the 19th century. There are, however, patients in whom VTE is considered “unprovoked” or “idiopathic”. This means that an apparent precipitating factor for such an event is not obvious.

Only recently, driven by the rapid advancement in developing novel and more sophisticated laboratory techniques, so far unknown genetic and acquired risk factors were identified. Their clinical relevance was studied in large patient populations.

The most common inherited risk factors are caused by mutations in the factor V (factor V Leiden) and factor II (so-called prothrombin mutation) gene, respectively.

Deficiency of a natural coagulation inhibitor (antithrombin, protein C, protein S, tissue factor pathway inhibitor (TFPI)), high clotting factor levels, hyperhomocysteinaemia and high levels of phospholipid antibodies are also associated with an increased risk of VTE (2).

The vast majority of patients with acute VTE is given antithrombotic therapy with the rationale to prevent them from disease
progression (i.e. extension of the thrombus into the proximal veins or pulmonary embolism) or recurrence.

Antithrombotic therapy prevents VTE recurrence almost completely (3), but is only justified if the likelihood of recurrent (and possibly fatal) VTE is greater than that of major bleeding caused by anticoagulation.

To accommodate this prerequisite, physicians have to balance the bleeding risk related to antithrombotic therapy against the risk of recurrent VTE once antithrombotic treatment has been suspended.

This article describes strategies, which are currently applied to distinguish between patients with high risk of recurrent VTE from those with a lower risk, i.e. between patients who might benefit from long-term antithrombotic therapy from those who may be exposed to an unnecessary bleeding risk in case of a needless extension of anticoagulant treatment.

Clinical risk factors

Several clinical characteristics strongly determine the risk of recurrent VTE (►Tab. 1). The recurrence risk is particularly high among patients who had their first event in the absence of a predisposing temporary risk factor.

In the Austrian Study on Recurrent Venous Thromboembolism (AUREC), a prospective multi-center cohort study of almost 1000 patients with a first unprovoked deep-vein thrombosis (VT) and/or pulmonary embolism (PE), the cumulative probability of recurrence five years after stopping anticoagulant treatment was as high as 25% (2). The high risk of recurrence in our study compares well with the result of two other similar studies, one from Italy and one from Great Britain, which found an even higher recurrence risk (4, 5). Most importantly, patients with an index PE predominantly present with PE rather than with a VT at recurrence (6, 7).

Patients with VTE related to a precipitating risk factor or a temporary risk condition, i.e. patients with secondary or provoked VTE, are at lower risk of recurrence. The recurrence risk appears to be particularly low after VTE precipitated by surgery. In AUREC, VTE recurred in 15 out of 157 patients who had their incident VTE in association with a surgical procedure. In this patient population, the cumulative probability of recurrence (unpublished) was

- 2% (95% CI: 0–4%) one year,
- 3% (95% CI: 0–6%) two years, and
- 6% (95% CI: 2–10%) five years after withdrawal of anticoagulants.

In a systematic review of 15 studies, the annualized event rate per patient year was 0.7% (95 CI: 0–1.5%) among patients with a first VTE related to surgery compared with 4.2% (95% CI: 2.8–5.6%) among patients with VTE and a non-surgical risk factor (8).

There are only few studies investigating the risk of recurrence in women with VTE during female hormone intake who then refrained from further estrogen use. Their results are inconsistent. In the AUREC population,

- women using estrogen-containing contraceptives at the time of their first VTE had a 70% lower risk of recurrence than non-users.
- The risk of recurrence among women using hormone replacement therapy (HRT) was approximately 40% lower than that of women in the same age group with an incident idiopathic VTE (unpublished).

Our findings are in line with those of Christiansen and co-workers (9) and Cushman and co-workers (10) who also found a low risk of recurrent VTE among women with hormone-related index thrombosis. In contrast, Le Gal and co-workers (11) reported no significant association between estrogen exposure, either oral contraceptives or HRT, and risk of recurrence. Regarding estrogen contraceptives, current users had a lower annual risk of recurrence (1.7%, 95% CI: 0–4%) than non-users (5%, 95% CI: 3–7). However, this difference did not reach statistical significance. Women who continue contraceptive use after their first VTE event have more than twofold higher risk of recurrence compared with women who refrained from further use (9).

Risk of recurrence is not well studied in patients who had their initial VTE triggered by trauma, pregnancy, immobilization or long-distance travel. In the absence of solid data we surmise that the risk of unprovoked VTE in these patients is low.

While on anticoagulants, patients with cancer-associated VTE have a higher risk of recurrence than patients without cancer (13). The risk of recurrence among cancer patients in whom anticoagulant therapy has been suspended is less well studied.

Patients with initial proximal VT or PE have a higher risk of recurrence compared with patients with an incident VT confined to the calf. In AUREC, the risk of recurrent VTE among patients with a first unprovoked distal VT was 1.4% (95% CI: 0–3.4) and 10.2% (95% CI: 4.9–15.5) one and five years after suspension of anticoagulation, respectively. Patients with a first unprovoked proximal VT or PE had a significantly higher risk of recurrence: 11.1% (95% CI: 7.8–14.4) and 30.3% (95% CI: 24.8–35.8) among patients with a first proximal DVT and 10.5% (95% CI: 7.2–13.8) and 29.5% (95% CI: 23.8–35.2) among patients with a first PE at one and five years, respectively (►Fig. 1). Compared to patients with a first distal VT, the relative risk of recurrence was 2.5-fold higher among patients with initial proximal VT or PE. In a patient-level meta-analysis of seven prospective studies, the annual recurrence rates of patients with a first proximal VT or a PE were 6.0% (95% CI: 5.2–7.2) and 5.1 (95% CI: 4.4–6.2) per 100 patient years, respectively. In contrast, the annual recurrence rate among patients with a first distal VT was as low as 1.0 per 100 patient years (95% CI: 0.2–2.4). Of interest, PE at recurrence was encountered in few patients with VT [annual recurrence rates of PE at recurrence: 0.2 (95% CI: 0–1.5) for patients with a first distal VT and 0.9 (0.6–1.4) per 100 patient years for patients with a first proximal VT], but was seen more frequently among patient with a first PE [annual recurrence rate of PE at recurrence: 2.5 (95% CI: 1.9–3.3) per 100 patient years] (7).
Our original observation that men have a higher risk of recurrent VTE than women was confirmed by other investigators (13, 14).

Recently, a patient-level meta-analysis in patients with a first unprovoked VTE found a 2.2-fold higher risk of recurrent VTE in men compared with women, which remained 1.8-fold higher in men after adjusting for prior hormone-associated VTE in women (15). In patients with a first provoked VTE there was no difference in VTE recurrence risk between men and women regardless of female hormone-associated VTE. There are some other clinical conditions of minor or even uncertain significance:

- Overweight: We found a linear relationship between excess body weight and VTE recurrence with an adjusted hazard ratio for each 1-point increase in BMI of 1.04 (95% CI: 1.01–1.08) (16).
- Post-thrombotic syndrome (PTS): in AUREC, patients with a PTS as the consequence of their first VT had a more than 2-fold higher risk of recurrence than patients without PTS (17).
- More than one VTE: In a study from Sweden, patients with a history of two VTE events had a higher risk of recurrence than those with one VTE episode (multivariate relative risk 1.71; 95% CI: 1.16–2.52) (18). However, it is unclear if this also applies to patients in whom the second event was provoked by a transient risk factor and/or was confined to the distal veins. We surmise that the risk of recurrence in these patients is not excessively high.
- Vena cava filters: Vena cava filters increase the risk of recurrent VT up to 1.5-fold after eight years, and thrombi at the filter site were recorded in more than 10% of patients (19, 20).
- Residual vein obstruction (RVO): In a recent meta-analysis, RVO conferred a 1.5-fold increase in the risk of recurrent VTE (95% CI: 1.11 – 2.03) (21). RVO is not predictive for recurrence in patients with an unprovoked first VTE and a possible association between RVO and recurrence risk strongly depends on how RVO is defined (22).

**Laboratory thrombophilia screening**

During the 1990ies, as the consequence of identifying new risk factors of VTE in the laboratory, systematic screening for these abnormalities, so-called thrombophilia screening, became popular. The rational behind this strategy is that patients in whom at least one of such a risk factor is present have a higher likelihood of recurrence and will benefit from extended anticoagulant therapy. Now we know that this concept has failed.

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<td>clinical characteristics</td>
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<td>unprovoked VTE (vs. VTE after surgery)</td>
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<td>proximal VT/PE (vs. distal VT)</td>
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<td>male sex</td>
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<td>laboratory abnormalities</td>
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<td>prothrombin mutation (heterozygous)</td>
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<td>high fibrinogen</td>
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<td>high factor VIII (&gt; 95th percentile)</td>
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<td>high factor IX (&gt; 75th percentile)</td>
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<td>mild hyperhomocystinaemia</td>
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<td>high thrombin activatable fibrinolysis inhibitor (&gt; 75th percentile)</td>
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We reported in 1997 for instance that patients with the factor V Leiden mutation, the most prevalent genetic risk factor of VT, have a similar risk of recurrence compared with non-carriers of the mutation (24).

Similarly, we did not find an increased recurrence risk among carriers of the prothrombin mutation (25). Today, on the basis of the results of several systematic reviews and metaanalysis (26–28), there is agreement among experts, that the recurrence risk associated with these genetic defects is at best moderately increased and that knowledge about the presence or absence of one of these defects is irrelevant for treatment decision making.

Within the frame of AUREC, several other risk factors of recurrent VTE were identified (Tab. 1). In contrast to the two aforementioned abnormalities, high plasma levels of some coagulation factors, in particular of factor VIII, are linked to an increased risk of recurrent VTE (29). For instance, in AUREC factor VIII concentrations of more than the 90th percentile of
the patient population conferred a sixfold risk of recurrence in patients with a first unprovoked VTE. Other (but not all) studies confirmed our observation (9, 30). Factor VIII clotting assays have a high variability between assays and laboratories, especially at high plasma concentrations, which restricts the relevance of test results regarding applicability in routine care. Mild hyperhomocysteinaemia is also associated with an enhanced risk of recurrent VTE (31, 32), but measurement of homocysteine is cumbersome and test results are sometimes not reproducible because of pre-analytic shortcomings.

Most importantly, the increase in recurrence risk is not high enough to have an impact on clinical decision making.

Regarding the deficiency of natural coagulation inhibitors, meaningful clinical studies are scarce (9, 33). They reported a moderately increased risk among patients with antithrombin, protein C or protein S deficiency as well as among patients with low TFPI levels. We assume that the recurrence risk is highest among patients with antithrombin deficiency. Finally, abnormalities in the fibrinolytic system confer a modest increase in recurrence risk at best (34, 35).

In sum, laboratory thrombophilia screening is “successful” as in more than 50% of thrombosis patients at least one defect is found. However, it is uncertain if this “success” translates into a clinical benefit.

The data derived from AUREC do not support such an assumption. Other investigators were also unable to show that heritable thrombophilia or other prothrombotic laboratory abnormalities play an important role in predicting recurrent thrombosis (5, 9, 36). On the contrary, there is the prospect of thrombophilia screening being harmful rather than helpful. In AUREC, for instance, one third of patients with two unprovoked VTE episodes had normal thrombophilia screening. To communicate to patients with normal thrombophilia screening that their recurrence risk is low might therefore be deceptive. On the contrary, in case of a positive test result patients are possible over-treated and/or exposed to unnecessary distress. There are several other the reasons why we strongly believe that routine laboratory thrombophilia screening is no longer warranted and should be abandoned (Tab. 2).

### Global markers of coagulation activation

VTE is a multicausal disease. Its occurrence depends on the number and severity of risk factors present at a given time point in an individual subject. The multifactorial pathogenesis of VTE is most likely the reason why the detection of single coagulation defects failed to capture the thrombosis risk on an individual patient level. One appealing way to overcome this limitation would be to use one single laboratory test, which to a large extent reflects multifactorial haemostatic system activation. Several global coagulation assays have been evaluated in an attempt to prove this concept.

The activated partial thromboplastin time (aPTT) is sensitive to levels of clotting factors of the intrinsic coagulation system. Notably, high levels of factor VIII or IX confer an increased risk of recurrent VTE (29, 37). We therefore hypothesized that a short aPTT might be an indicator of an increased risk for recurrence and vice versa a long aPTT might be associated with a low recurrence risk.

Indeed, as a proof of principle, we found that compared with patients with a short aPTT those with a longer aPTT had a significantly lower risk of recurrent VTE (38).

Large amounts of thrombin are generated in plasma upon stimulation with tissue factor and phospholipids under in vitro circumstances. Abnormal thrombin generation, expressed as endogenous thrombin potential (ETP) or peak thrombin, was...
found in patients with a first thrombosis event (39). With regard to recurrence, we were able to identify a subset of patients with a recurrence risk as low as 6.5% for four years after anticoagulation withdrawal (40). These patients (who comprised approximately a third of the total patient cohort) had a peak thrombin concentration of less than 400 nmol/l three weeks after suspension of oral anticoagulants for a first unprovoked VTE. Using another thrombin generation assay, we confirmed this observation: high ETP (>100%) increased the risk of recurrence 1.6-fold (95% CI 1.1–2.3) (41). Meanwhile, other studies (42, 43) also show that patients at high risk of recurrent venous thrombosis can be identified by the use of thrombin generation assays.

**D-dimer** is a fibrin split product. High D-dimer plasma levels are indicative for activation of the coagulation system. D-dimer is part of algorithms, which were developed for diagnosing acute VTE (44). Palareti and co-workers were the first to show that patients with a high D-dimer shortly after withdrawal of anticoagulants have an increased risk of recurrent VTE (45).

The possibility to distinguish between patients with a high recurrence risk from low-risk patients by the use of D-dimer was confirmed in AUREC.

We measured D-dimer three weeks after suspension of oral anticoagulation in patients with a first unprovoked VTE. Patients with a D-dimer concentration of less than 250 ng/ml had a 60% lower recurrence rate after two years compared with patients with a D-dimer level of 250 ng/ml or more (46). In another study in which D-dimer concentrations were measured during (rather than after) anticoagulant treatment, a 250 ng/ml cutoff was predictive for a low risk of recurrence in women but not in men (47). In a meta-analysis of seven studies including almost 1900 patients with a first VTE, patients with a high D-dimer had an annual recurrence rate of 9% as compared to only 3.5% among those with a low D-dimer level (48). In a patient-level meta-analysis of seven prospective studies investigating patients with a first unprovoked VTE, Douketis and co-workers reported, that the timing of D-dimer testing, patient age, and the assay cut point used do not affect the ability of D-dimer to distinguish patients with a higher or lower risk for recurrent VTE (49). Palareti and co-workers performed the only randomized trial in this setting (50). In the PROLONG study they confirmed the low risk of recurrence among patients with a negative D-dimer testing after stopping anticoagulation. Patients with a positive D-dimer testing had a more than fivefold higher risk of recurrence compared with patients with a high D-dimer in whom anticoagulation was restarted. The study was not powered to fully capture the risk of major bleeding among patients receiving extended anticoagulant therapy.

In sum, global coagulation assays, in particular D-dimer measured after suspension of anticoagulation, allow identifying low-risk patients who most likely will not benefit from extended anticoagulation.

Whether these assays are useful for identifying high-risk patients in whom the risk of recurrence outweighs the bleeding risk associated with extended anticoagulation is uncertain and further studies are needed.

**Prediction rules**

A novel approach to estimate the risk of recurrent VTE is combining clinical features with laboratory assays such as D-Dimer (Box). In the “Men continue and HER DOO2” study from Canada, Rodger and colleagues followed almost 650 patients with a first unprovoked venous thrombosis for four years. Through combination of four out of 69 risk factors they had recorded in their patient population, namely the absence of symptoms suggestive of PTS, a D-dimer during anticoagulation treatment of less than 250 ng/ml, body mass index less than 30 kg/m², and age less than 65 years), a cohort of women at very low risk of recurrence was identified. This prediction rule is not applicable for men (47).

Another novel prediction rule is the so-called DASH score which is derived from several prospective cohort studies (51). DASH stands for

**Thrombophilia screening**

**Reasons why it should not be done**

- Patients may have > 1 defect. Effect of combined defects on recurrence risk is unknown.
- Potential
  - over-treatment or unnecessary concern in case of positive test result,
  - under-treatment and false sense of safety in case of negative test result.
- Restricted applicability because of high variability of assay systems.
- Costly; assay not standardized; too elaborate for routine use.

The annualised recurrence risk was

- 3.1% (95% CI: 2.3–3.9) among patients with a score of ≤ 1 point,
- 6.4% (95% CI: 4.8–7.9) among patients with a score of two points, and
- 12.3% (95% CI: 9.9–14.7) among patients with a score of ≥ 3 points.

The authors concluded that by considering at low recurrence risk those patients with a score of ≤ 1 point, indefinite anticoagulation might be avoided in approximately half of the patient population.

Within the frame of the AUREC, we constructed a model (Vienna Prediction Model, VPM) that allows prediction of the risk of recurrence in patients with a first and unprovoked VT and/or PE (52). We prospectively followed 929 patients for a median of 43 months after suspension of anticoagulant therapy. Recurrent VTE was recorded in 176 patients. We preselected age, sex, thrombus location, BMI, factor V Leiden, the prothrombin mutation, and D-dimer as risk factors/indicators because their impact on the recurrence risk has been evaluated and independently confirmed. In contrast to the aforementioned prediction rules, we also included patients with distal DVT. The variables were ana-
lysed in a Cox proportional hazards model, and those associated with recurrence were used to compute risk scores. Relevant predictors of the recurrence risk were only the patient’s
• sex,
• thrombus location and
• D-dimer.

Based on these variables we developed a nomogram that can be used to calculate risk scores and to estimate the cumulative probability of recurrence in an individual patient. Our model has undergone an extensive internal cross-validation process. We divided our cohort into test and validation samples thereby mimicking independent validation. This process was repeated 1000 times and the results were averaged to avoid dependence of the validation results on a particular partition of our cohort. Patients were assigned to different risk categories according to their risk score. When we calculated cumulative recurrence rates for patients within quartiles of the risk score, these risk categories corresponded well with the recurrence rate as patients with lower scores had lower recurrence rates.

A web-based risk calculator is available for ease of calculation (►www.meduniwien.ac.at/user/georg.heinze/zipfile/).

We believe that the VPM is suitable to identify patients with a recurrence risk low enough to justify discontinuation of anticoagulation after three months. Application of this model in routine care should await the results of a validation study in a separate patient population, which is currently on-going. Recently, a clinical prediction rule for risk stratification of recurrent VTE in patients with cancer-associated VTE during anticoagulant therapy was reported. In a retrospective cohort of 543 cancer patients, four independent predictors of recurrence were identified:
• sex,
• primary tumour site,
• stage, and
• prior VTE.

High-risk predictors (female sex, lung cancer, history of previous VTE) received 1 point each. Low-risk predictors (breast cancer –1 and TNM stage I –2) received negative points. Patients with a score of 0 points had a much lower risk of recurrence (≤4.5%) compared with patients with a score of ≥1 point (≥19%). The prediction rule was validated in an independent set of 819 patients from two randomized, controlled trials comparing low-molecular-weight heparin to vitamin K antagonist treatment in cancer patients (53).

## Conclusion

Venous thromboembolism is a chronic disease, which tends to recur. Stratification of patients into high and low risk categories regarding recurrence is of utmost clinical importance in order to effectively counsel patients with respect to their optimal duration of secondary thromboprophylaxis. Laboratory thrombophilia screening has failed in this respect and should be abandoned.

Clinical characteristics such as location of first VTE, absence of a temporary risk condition at the time of VTE, location of incident VTE and male sex are independent predictors of recurrence.

Preliminary data indicate that the distinction between high and low risk patients regarding recurrence can further be improved by prediction rules which combine clinical features with global coagulation assays. Clinical application of these rules should await the results of validation studies in different patient cohorts.

## Conflict of interest

The authors declare that they have no conflict of interest.

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