Risk assessment for recurrent venous thrombosis

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Venous thrombosis is a common disease that frequently recurs. Recurrence can be prevented by anticoagulants, albeit at the cost of bleeding. Thus, assessment of the risk of recurrence is important to balance the risks and benefits of anticoagulation treatment. Many clinical and laboratory risk factors for recurrent venous thrombosis have been established. Nevertheless, prediction of recurrence in an individual patient remains a challenge. Detection of some laboratory markers is associated with only a moderate risk of recurrence, and the relevance of others is not known. Many patients have several risk factors and the effect of combined defects is obscure. Routine screening for these laboratory markers should therefore be abandoned. Risk assessment can be improved by measurement of global markers that encompass the effects of clotting and fibrinolytic disorders. Analysis of preliminary data suggests that risk assessment can also be refined through integration of prothrombotic coagulation changes and clinical risk factors.

Introduction

Venous thrombosis is a common disease with a yearly incidence of around one case per 1000 person-years.[1,2] In a third of patients deep venous thrombosis is complicated by embolisation of the clot into the lungs. Short-term mortality from pulmonary embolism is high and mainly depends on age and presence of underlying comorbidities such as cancer or cardiorespiratory disease.[2,3] Results from a population-based study[4] showed the 30-day mortality of pulmonary embolism was 28%. By contrast, a 30-day mortality of around 9% was reported in a large hospital-discharge dataset.[5]

Venous thrombosis is a chronic disease that often recurs. In unselected cohorts of patients with venous thrombosis, the risk of recurrence after 5 years is 20–25%, and is higher than 25% in patients with unprovoked venous thrombosis.[6–8] Recurrence risk is mainly dependent on presence or absence of acquired and congenital risk factors and might vary substantially between patients. Results from one study[9] suggested a case-fatality rate of recurrent venous thromboembolism of 5–12%, whereas data from a systematic review[10] reported 3·6%. Standard treatment of acute venous thrombosis is heparin followed by vitamin K antagonists for several months, a regimen that almost wholly prevents recurrence, albeit at the cost of bleeding.[1] The risk of major bleeding in patients who are receiving anticoagulation treatment is around 3% per year in clinical trials and is higher in routine practice.[11–13] The case-fatality rate of fatal bleeding in patients who were given anticoagulant treatment was reported to be 11·3%.[10] Consequently, thrombotic risk assessment is of particular importance, as only patients at high risk of recurrence will benefit from long-term anticoagulation treatment, whereas patients at low risk will unnecessarily be exposed to a risk of bleeding. This Review discusses different approaches to risk assessment of recurrence of venous thrombosis in patients with deep vein thrombosis of the leg or pulmonary embolism after completion of anticoagulant treatment.

Risk factors for recurrent venous thrombosis

Until the late 1980s, risk of recurrent venous thrombosis was estimated on the basis of only a few patient characteristics, such as absence or presence of a triggering factor, concomitant pulmonary embolism, or previous venous thrombosis, and with the results of a few laboratory tests such as measurement of concentrations of antithrombin, protein C, and protein S. At that time, the natural course of venous thrombosis was poorly understood, and many risk factors of the disease were yet to be discovered and appropriate clinical studies were absent. From the early 1990s, high-quality clinical studies and advances in laboratory techniques led to the discovery of more risk factors of both first and recurrent venous thrombosis, and to the perception that venous thrombosis is a chronic disease with a high recurrence rate.

Clinical features

Table 1 shows the clinical features associated with high risk of recurrent venous thrombosis. Risk of recurrence is especially high in patients in whom the initial venous thrombosis was unprovoked (ie, the event occurred in

Search strategy and selection criteria

We searched PubMed, the Cochrane Library, Medline, and AMEDEO for reports published in any language, without date restriction, with the search terms "deep vein thrombosis", "venous thrombosis", "pulmonary embolism", and "venous thromboembolism" in combination with the terms "recurrent venous thrombosis", "recurrent venous thromboembolism", "recurrence", "risk of recurrence", "risk factors of recurrence", "thrombophilia", "prediction of recurrence", and "prevention of recurrence". We searched the reference lists of publications identified and selected those we deemed relevant. We hand-searched articles from the *New England Journal of Medicine, The Lancet, Annals of Internal Medicine, Archives of Internal Medicine, Journal of the American Medical Association, Circulation, American Journal of Medicine, Chest, Journal of Thrombosis and Haemostasis, Blood, Thrombosis and Haemostasis, Haemotologic, British Journal of Haemotology,* and *British Medical Journal* published in the past 5 years. Several recent reviews and systematic reviews were included because they provided comprehensive overviews that were beyond the scope of this Review.

the absence of a temporary risk such as surgery, trauma, pregnancy, or taking of female hormones). Risk of recurrence was 25% in a cohort of patients from Austria[14] with unprovoked venous thrombosis or pulmonary embolism 5 years after the incident event, and increased with time (figure 1). In two other cohorts of patients with unprovoked venous thromboembolism,[7,15] the recurrence risk was even higher than in the Austrian study. By contrast, patients who had venous thrombosis after surgery or use of female hormones were at a lower risk of recurrence than were patients without temporary risk factors.[15,30,31] Women who continue hormone intake after a first event are at high risk of venous thrombosis recurrence.[24,25] Risk of recurrence is not well studied in patients who had their initial venous thrombosis provoked by trauma, pregnancy, immobilisation, or long-distance travel. We expect risk in these patients to be low.

Hull and colleagues[32] reported that all patients in their study with recurrence of venous thrombosis had had initial proximal deep vein thrombosis and that none with distal deep vein thrombosis had a recurrence. The low rate of recurrence in patients with isolated calf vein thrombosis has been confirmed by several other studies.[6,33] In a large Spanish registry of patients with venous thrombosis,[34] risk of venous thrombosis recurrence during anticoagulation treatment was much the same between patients with proximal and isolated distal venous thrombosis.

Data for one study group[16] showed that risk of recurrent venous thrombosis is more than two-fold higher in patients with symptomatic pulmonary embolism than it is in patients with isolated deep vein thrombosis, and most patients with initial pulmonary embolism have pulmonary embolism at recurrence. Results from two studies[9,17] show an increased risk of recurrence in patients with pulmonary embolism, although other reports did not show an increased risk.[35,36] High risk of pulmonary embolism at recurrence in patients with an initial pulmonary embolism has been shown repeatedly.[9,16,17,35,36]

In a prospective cohort study from Sweden,[6] the 5-year cumulative incidence of recurrent deep vein thrombosis was 21·5% in patients with a first venous thrombosis and 27·9% in patients who had had a second deep vein thrombosis. A high risk of recurrence after multiple episodes of venous thrombosis was shown in several interventional trials.[18,37,38] Whether an increased risk of recurrence exists for patients with numerous provoked venous thromboses is not known. Recurrent ipsilateral deep vein thrombosis increases the likelihood of development of post-thrombotic syndrome, which is associated with an increased risk of recurrence of venous thrombosis.[28,31]

Risk of recurrent venous thrombosis is strongly predicted by the sex of the patient. Men with a first unprovoked venous thrombosis have a nearly four-fold increased risk of recurrence compared with women.[19] A meta-analysis of 15 studies estimated the relative risk of recurrent venous thrombosis for men compared with women as 1·6.[20] Some studies,[4,7,31,39] but not others,[5,8,40,41] report an association between increased age and raised risk of recurrent venous thrombosis. Because of the hereditary nature of some thrombophilic risk factors, a positive family history might suggest presence of known or unknown genetic defects and, consequently, identify patients at risk of recurrence of venous thrombosis. However, investigators who assessed the association between a positive family history and risk of recurrence showed that family history did not predict recurrence.[42]

Patients with cancer have a high risk of recurrence, even while they are receiving anticoagulation treatment.[26,27] However, risk of recurrence in cancer patients who discontinue anticoagulation treatment is not well studied but is regarded as high.[4,35] Overweight and dyslipidaemia are independent risk factors of recurrent venous thrombosis.[29,43] The effect of bodyweight on risk of recurrence is linear, so even a small weight loss might lead to a reduction in risk. High concentrations of lipoprotein(a) also confer an increased risk of recurrent venous thromboembolism.[44]

	Evidence	Clinical relevance
Absence of a temporary risk condition[7,14,15]	Strong	High
Pulmonary embolism or proximal deep vein thrombosis[6,16,17]	Strong	High
More than two thrombotic events[6,18]	Strong	Restricted (consider bleeding risk during prolonged anticoagulation)
Male sex[19,20]	Strong	High
Residual vein thrombosis[21,22]	Strong	Low
Vena cava filter[23]	Strong	High
Continued oestrogen use[24,25]	Strong	High
Cancer[26,27]	Strong (for early recurrence)	High
Post-thrombotic syndrome[24,28]	Moderate	Moderate
Overweight[29]	Weak	Low

Table 1: **Clinical features associated with high risk of recurrent venous thrombosis**

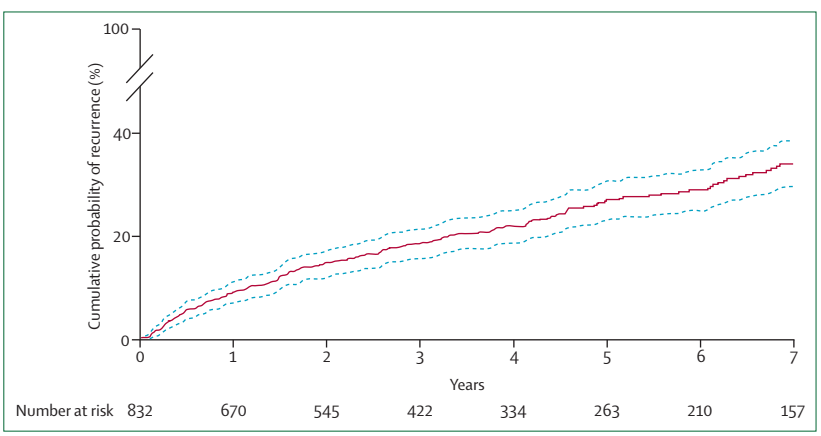

Figure 1: **Kaplan-Meier estimates of cumulative rate of recurrence in 832 patients with a first unprovoked venous thrombosis after withdrawal of anticoagulant treatment**
Dotted lines show 95% CIs.

There is little evidence for a high risk of recurrence after an initial venous thrombosis in patients with antiphospholipid syndrome.[45] Various studies have included both arterial and venous thrombotic events and used different definitions of the antiphospholipid syndrome. In one study,[46] almost half of patients who had an arterial or venous thrombotic event had a recurrence after they discontinued treatment with warfarin. Incidence of recurrence among patients with a first venous thrombosis and presence of antibodies against anticardiolipins was around two-fold higher than it was in patients without anticardiolipin antibodies.[47] Risk of recurrence in patients with antiphospholipid syndrome seems to be lower after venous thrombosis than it is after an arterial thrombosis.

Residual vein thrombosis is a possible predictor of recurrence of venous thrombosis.[21,22,23,48] Two interventional studies[21,22] used residual vein thrombosis to guide the duration of anticoagulation treatment after unprovoked proximal deep vein thrombosis. In the Duration of Anticoagulation based on Compression UltraSonography (DACUS) trial,[21] risk of recurrence was substantially higher in patients with residual vein thrombosis than it was in patients without residual vein thrombosis. Because there are no uniformly acknowledged criteria for definition of vein recanalisation, any clinical decisions made on the basis of residual vein thrombosis measurement results would be premature.

Vena cava filters increase the risk of recurrent deep vein thrombosis up to 1·5-fold after 8 years, and thrombi at the filter site are recorded in more than 10% of patients.[49,50]

Laboratory markers

Table 2 shows laboratory-detectable markers associated with increased risk of recurrent venous thrombosis. Estimates of the risk of recurrence in patients with deficiencies of natural coagulation inhibitors, such as antithrombin, protein C, or protein S, are mainly derived from studies in families with highly penetrant thrombophilia. Risk of recurrence seems to be highest in patients with antithrombin deficiency.[72–75] In the Leiden Thrombophilia Study,[24] the hazard ratio of recurrent venous thrombosis for patients with a coagulation inhibitor deficiency was 1·8, but the absence of an effect could not be ruled out. Patients with low concentrations of free tissue factor pathway inhibitor are at an increased risk of recurrence.[76]

	Evidence	Clinical relevance
High concentrations of fibrinogen, factor VIII, or factor IX[24,51–55]	Strong	Uncertain
Hyperhomocysteinaemia[56,57]	Strong	Uncertain
Factor V Leiden[58–60]	Strong	None
Factor II G20210A (prothrombin mutation)[58–60]	Strong	None
High D-dimer[31,61–67]	Strong	To be confirmed
Increased generation of thrombin[68–71]	Strong	Uncertain
Partial deficiency of antithrombin, protein C, protein S, or tissue factor pathway inhibitor[24,72–76]	Weak	Uncertain
Phospholipid antibodies[46,47]	Weak	Uncertain
High concentrations of thrombin activatable fibrinolysis inhibitor[77]	To be confirmed	None
Single nucleotide polymorphisms (E-selectin gene polymorphism, heme oxygenase gene polymorphism)[78,79]	To be confirmed	None

Table 2: **Laboratory markers associated with increased risk of recurrent venous thrombosis**

High concentrations of coagulation factors can lead to recurrence of venous thromboembolism. Factor VIII concentrations of more than the 90th percentile conferred a more than six-fold risk of recurrence in patients with a first unprovoked deep vein thrombosis or pulmonary embolism.[51] Several studies[52–54,80] have shown an association between high factor VIII concentrations and recurrent venous thrombosis, but not all studies have.[24] High factor IX concentrations raise the risk of recurrence, and further enhance the risk of recurrence in patients with high factor VIII concentrations.[55] In the Leiden Thrombophilia Study,[24] high fibrinogen concentrations were a risk factor for recurrent venous thrombosis, but raised concentrations of procoagulant factors did not affect the risk of recurrence.[30] Hence, whether coagulation abnormalities increase risk of recurrence is unresolved.

Prospective cohort studies and an interventional trial[30,56,57] have estimated the increase in the risk of recurrence associated with raised homocysteine concentrations to be about 1·5-fold. However, because vitamin supplementation (which reduces homocysteine concentrations) does not affect rate of recurrence, a causal relation between hyperhomocysteinaemia and venous thrombosis cannot be supported.[57]

Factor V Leiden occurs with a frequency of 12–30% and G20210A mutation in the prothrombin gene (prothrombin mutation) with a frequency of 7–18% in thrombosis cohorts, and are the most frequent genetic abnormalities in patients with a first venous thrombosis.[1] The first publications[30,81–84] about risk of recurrence in patients with one of these mutations had conflicting results, with no risk elevations in studies from Austria and the Netherlands, and significant increases in risk reported in an Italian study. In three systematic reviews,[58–60] the risk of recurrence in heterozygous carriers of either factor V Leiden or the prothrombin mutation was increased compared with patients without the mutations (table 3). However, because the increase in rate of recurrence in heterozygous carriers is not substantial, the consensus is that heterozygosity of factor V Leiden or prothrombin should not affect clinical decision making.

In one analysis,[60] risk of recurrence in homozygous carriers of factor V Leiden mutation was increased 2·5-fold compared with participants who did not have the mutation. Compared with patients with wild-type genotypes, patients who are heterozygous for both factor V Leiden and the prothrombin mutation are at an increased risk of recurrence;[60] however, the number of patients in this trial was small and the confidence intervals were wide. In a case-control study in a cohort of families with penetrant thrombophilia,[85] homozygous

carriers of factor V Leiden or the prothrombin mutation or double heterozygous individuals were not at high risk of recurrent venous thrombosis.

Defects in the fibrinolytic system are of low importance for prediction of recurrent venous thrombosis. Concentrations of tissue plasminogen activator antigen or plasminogen activator inhibitor-1 correlated weakly with occurrence of future venous thrombosis,[86] and concentrations of these molecules did not differ between patients with or without recurrent venous thrombosis.[87] However, an association was noted between high thrombin activatable fibrinolysis inhibitor concentrations and risk of recurrence, which is further increased in patients with high factor XI concentrations.[77]

Relevance of laboratory screening

Abnormalities that are associated with an increased risk of venous thrombosis, and that are detectable with laboratory techniques, can be established in more than 50% of patients with a first unprovoked venous thrombosis. Therefore, identification of these thrombophilic defects to improve patient care is a tempting prospect. Laboratory screening for thrombophilia has been repeatedly advocated[88,89] and is now done on a routine basis in many institutions around the world. Our Review of laboratory abnormalities, however, shows that these tests have at most a small effect on the risk of recurrence. Screening is indicated only when individuals with an increased risk can be identified and there is an effective treatment with a positive benefit–risk balance. Recurrent venous thrombosis can only be prevented by indefinite anticoagulation treatment, which confers a substantial risk of haemorrhage.

There is no proof that thrombophilia screening helps patients, neither with regard to treatment of the acute event nor for prevention of recurrence.[15,24,90] Results from a prospective cohort study[15] of patients after a first episode of venous thrombosis showed that tests for heritable thrombophilia are unable to predict recurrence of events in the first 2 years after stopping of anticoagulant treatment. Data from another study showed that, for patients with a first deep vein thrombosis, the risk of recurrence was much the same in patients with and in those without a thrombophilic defect.[24] The same investigators also showed (in a case-control study) that testing for inherited thrombophilia was not associated with a reduced rate of recurrence of venous thrombosis.[91] Few randomised trials or controlled clinical trials have assessed the benefit of testing for thrombophilia on prediction of risk of recurrent venous thrombosis.[92]

Routine screening for single laboratory markers should not be done in patients with a first venous thrombosis for various reasons. Venous thrombosis has many causes and many patients have more than one abnormality (figure 2), and the effect of combined defects on risk of recurrence is not known. Determination of laboratory risk factors can be costly, not standardised, and too elaborate for routine use.

	Events/ patients	Factor V Leiden	Prothrombin mutation
Ho et al (2006)[58]	3104/2903	1·41 (1·14–1·75)	1·72 (1·27–2·31)
Marchiori et al (2007)[59]	3202/3208	1·39 (1·15–1·76)*	1·20 (0·89–1·61)*
Segal et al (2009)[60]	4730/3636	1·56 (1·14–2·12)	1·45 (0·96–2·21)

Data are number or odds ratio (95% CI), unless otherwise stated. *Risk ratio (95% CI).

Table 3: **Risk of recurrent venous thrombosis in patients with factor V Leiden or prothrombin mutation**

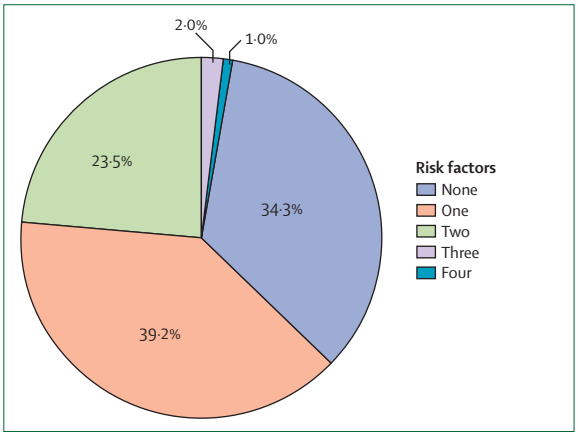

Figure 2: **Number of risk factors identified by laboratory screening for thrombophilia in 158 patients without cancer with two episodes of unprovoked venous thrombosis**

3 weeks after the incident event, patients were screened for deficiency of antithrombin, protein C, or protein S; presence of lupus anticoagulant, factor V Leiden, factor II G20210A; and high concentrations of homocysteine, factor VIII, or factor IX.

Some assays, such as factor VIII clotting assay (especially at high concentrations of factor VIII plasma) have a high variability between assays and laboratories,[93] which restricts the applicability of test results. Routine testing of patients might lead to overtreatment or cause unnecessary concern because there are no clinical consequences of a positive result.[94] A third of patients with recurrent unprovoked venous thrombosis have a normal test result (figure 2). A negative finding from thrombophilia testing could therefore result in a false sense of safety for patients. We believe that laboratory screening for one hereditary or acquired risk factor should not be done on a routine basis.

Global markers of coagulation

Risk of venous thrombosis is increased with a high number of risk factors present in an individual. Global markers of coagulation, the concentrations of which might suggest multifactorial thrombophilia, could be used to estimate risk of recurrence. Patients with a short activated partial thromboplastin time have a higher risk of recurrence than do those with a short test time. Stratification of patients by recurrence risk can also be done with an assay that is based on partial thromboplastin time and measures the overall function of the protein C pathway.[95,96]

Because of the high negative predictive value of D-dimer, measurement of the concentration of D-dimer has become an integral part of many diagnostic algorithms to exclude acute venous thrombosis and pulmonary embolism.[97] Measurement of D-dimer concentration can be used to separate patients into groups of high or low risk of recurrent venous thrombosis. Palareti and colleagues[61,62] showed that D-dimer concentrations, measured 1 month after discontinuation of oral anticoagulation treatment, have a high negative predictive value for recurrence, irrespective of presence or absence of hereditary thrombophilia. Patients with an especially low risk of recurrence can be identified with lower cutoff concentrations for D-dimer. Patients with a first unprovoked venous thrombosis or pulmonary embolism and D-dimer concentrations of less than 250 ng/mL had a 60% lower recurrence rate than those with concentrations of 250 ng/mL or more.[63] 2 years after withdrawal of anticoagulation treatment, probability of recurrence was 3·7% (95% CI 0·9–6·5).[63] In another study,[31] in which D-dimer concentrations were measured during—rather than after—discontinuation of anticoagulation treatment, a 250 ng/mL cutoff was predictive of low risk of recurrence in women.

The relevance of D-dimer concentrations for measurement of risk stratification has been assessed in two systematic reviews.[64,65] D-dimer concentration is the only criterion of laboratory thrombophilia that has been used to establish duration of anticoagulation treatment in a large randomised trial setting.[66] Results from the trial showed that patients with low D-dimer concentrations after withdrawal of anticoagulation treatment have a low risk of recurrence (4·4 recurrences per 100 patient-years). Patients with high D-dimer concentrations who stopped anticoagulation treatment after 6 months had a five-fold increased risk of recurrence compared with patients who received treatment for more than 6 months (10·9 *vs* 2·0 recurrences per 100 patient-years).[66] In a subsequent study, the same investigators[67] reported that repeated testing of D-dimer concentrations after withdrawal of anticoagulation treatment following a first episode of unprovoked venous thrombosis could help establish the optimum duration of treatment. Several large clinical studies investigating the clinical value of D-dimer are in progress.

For the **online risk calculator** see http://www.meduniwien.ac.at/user/georg.heinze/zipfile/

Measurement of thrombin generation in vitro can be used to stratify patients with venous thrombosis to categories of high-risk and low-risk of recurrence. In one cohort,[68] risk of recurrence in patients with peak thrombin concentrations of less than 400 nM was 6·5% (95% CI 4·0–8·9) after 4 years. In the same cohort, an endogenous thrombin potential of more than 100% conferred a significant 1·6-fold higher risk of recurrence than was noted in patients with an endogenous thrombin potential of less than 100%.[68] Other studies[69–71] show that patients at high risk of recurrent venous thrombosis can be identified with thrombin generation assays.

Clinical characteristics of patients and laboratory markers

A new approach for assessment of risk of recurrent venous thrombosis is combination of clinical characteristics of patients (eg, location of the thrombus, sex, or age) with laboratory testing. Rodger and colleagues[31] studied 646 patients with a first, unprovoked venous thrombosis for 4 years. Through combination of four of 69 investigated risk factors (absence of symptoms suggestive of post-thrombotic syndrome, D-dimer concentration during anticoagulation treatment <250 ng/mL, body-mass index <30 kg/m², and age <65 years), the investigators were able to identify a cohort of women at low risk of recurrence. No combination of predictors identified a low-risk group of men.[31]

In a prospective cohort study,[14] 929 patients with a first unprovoked venous thrombosis or pulmonary embolism were followed up for a median of 43 months after discontinuation of anticoagulation treatment. Patients with a strong thrombophilic defect (eg, natural inhibitor deficiency), lupus anticoagulant, or homozygous or combined defects were excluded from the analysis. Preselected clinical and laboratory variables (age, sex, thrombus location, body-mass index, factor V Leiden, the prothrombin mutation, D-dimer, and in-vitro thrombin generation) were analysed in a Cox proportional hazards model, and associated with recurrence to compute risk scores. Only the patient's sex, thrombosis location, and concentration of D-dimer were related to increased risk of recurrence. On the basis of these variables the individual risk of recurrence can be estimated by use of an online risk calculator. This prediction model needs to be validated before it can be used in routine care.

Future considerations

In the past few decades, assessment of the risk of recurrence after an episode of venous thrombosis has substantially improved through understanding of the natural course of the disease and characterisation of factors that establish recurrence risk. However, we are not able to predict recurrence on the basis of laboratory abnormalities with enough precision to recommend implication of testing to clinical practice. Discovery of unknown risk factors in the (near) future will add to our ability to predict recurrence. We expect that advanced laboratory techniques, such as genetic profiling and functional assays, which are useful for measurement of global thrombophilia, will help with assessment of risk of recurrence. Results from large clinical datasets and analyses of pooled data from individual studies will further advance our ability to predict recurrence in routine clinical practice.

New oral anticoagulants that are targeted against single coagulation factors have predictable dose-response associations, and do not need monitoring by prescribers.

These drugs have the potential to replace conventional anticoagulants such as heparin and vitamin K antagonists. However, safety with regard to the risk of bleeding remains a concern with the new compounds. Thus, a precise assessment of risk of recurrence for individuals will be very important to balance the risks and benefits of anticoagulation, and to avoid unnecessary risks and health-care costs.

Contributors

PAK and SE did the literature search, selected relevant articles, interpreted data, and wrote the report. FRR contributed to writing of the report.

Conflicts of interest

FRR's institution holds a patent and received royalties for factor V Leiden and factor II G20210A. All other authors declare that they have no conflicts of interest.

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