REVIEW ARTICLE

Venous thrombosis: who should be screened for thrombophilia in 2014?

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KEY WORDS

recurrence, thrombophilia screening, venous thromboembolism

ABSTRACT

Venous thromboembolism (VTE) is a chronic disease. Recurrence can be prevented by anticoagulants, albeit at the cost of bleeding. Assessing the risk of recurrence is important to balance the risks and benefits of anticoagulation. Numerous laboratory risk factors of VTE have been identified, which has lead to a practice called laboratory thrombophilia screening – a procedure in which patients with a prior VTE are systematically offered laboratory testing with the purpose of identifying the risk factors. The knowledge of these factors should improve counseling patients regarding their duration of anticoagulation. However, this approach has failed. For some factors including coagulation inhibitors and phospholipid antibodies, the evidence that they increase the recurrence risk is weak. The extent to which other defects (factor V Leiden, prothrombin mutation) increase the recurrence risk is irrelevant. Patients can have multiple risk factors, and it is unknown to what extent their interactions increase the recurrence risk. Some assay systems have technical limitations, which restrict their general applicability. Meaningful studies comparing treatment strategies regarding the recurrence risk in VTE patients with a distinct laboratory abnormality are lacking. Routine testing for heritable defects can cause unnecessary concerns and uncertainty both in patients and relatives, and might also lead to overtreatment. The absence of a laboratory abnormality does not necessarily mean that the recurrence risk is low. A negative result could thus potentially result in a false sense of safety for patients and physicians, and consequently in undertreatment. In summary, routine laboratory thrombophilia screening is no longer warranted.

Introduction Venous thromboembolism (VTE) is a common disease. The annual incidence of VTE in the general population is approximately 1 to 2 cases per 1000 persons. The majority of VTE events occur in the elderly population, often in association with temporary risk conditions such as trauma, surgery, hospitalization, and certain medical illnesses. Additional triggers are, among many others, use of female hormones, pregnancy and childbed, and immobilization. A limited duration of anticoagulation, usually 3 months, together with primary prevention measures in forthcoming risk situations is sufficient in patients in whom VTE occurs in association with a temporary risk factor.[1]

There is yet a different group of patients with thrombosis with a much higher risk of recurrent VTE. These are patients in whom an obvious precipitating risk factor is absent. The risk of recurrent VTE in this particular patient population ranges from 30% to 50% after suspension of anticoagulant treatment.[2] Accordingly, current guideline panels recommend indefinite antithrombotic therapy for patients with an unprovoked proximal deep-vein thrombosis of the leg and/or pulmonary embolism provided that they have a low bleeding risk and the control of anticoagulant therapy is good.[3] One has to keep in mind, however, that despite the high recurrence risk many of these patients stay thrombosis-free and are hence unnecessarily exposed to a bleeding risk.

Why laboratory thrombophilia screening? It is of major importance to develop strategies that would allow distinguishing patients with a high risk of recurrent VTE (i.e., patients who might benefit from indefinite anticoagulation) from those with a lower recurrence risk (i.e., patients in whom a short period of anticoagulation might be sufficient). One such approach could be laboratory thrombophilia screening. In this context, it is important to

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TABLE Risk of recurrent venous thromboembolism conferred by laboratory markers

Marker		Increase (-fold)
FVL	heterozygous	1.5
	homozygous	1.2–2.5
PM	heterozygous	1.2–1.7
	homozygous	unknown
heterozygous FVL + heterozygous PM		1.0–4.8
natural coagulation inhibitor deficiency		1.8–2.8
high clotting factor activity		1.7–6.0
hyperfibrinogenemia		1.7
mild hyperhomocysteinemia		0.9–2.7
antibodies against phospholipids		1.4–2.8

Abbreviations: FVL – factor V Leiden, PM – prothrombin mutation

understand what, in principle, is meant by routine screening. It is a process in which individuals are systematically (rather than individually) subjected to testing with the purpose of identifying a (laboratory) abnormality that indicates the presence of a disease (that potentially necessitates treatment) or that is predictive of the course of an ongoing disease (that potentially requires a specific treatment or a treatment modification).

Over the last decades and driven by the rapid advancement in developing novel and more sophisticated laboratory techniques, a considerable number of risk factors of an incident VTE, many of which are congenital, have been identified. The rationale behind thrombophilia screening is the conception that these risk factors are also important for the recurrence risk and, if so, counseling of the patients with thrombosis regarding the optimal duration of anticoagulation can be improved when the results of these laboratory analyses are taken into consideration.

This article describes to what extent certain abnormalities detected by laboratory testing have an impact on the risk of recurrent VTE. Consequently, the question is addressed of whether laboratory thrombophilia screening can have an influence on clinical decision making as regards treatment of this patient group, particularly on the duration of anticoagulation. The article shall concentrate on patients with unprovoked thrombosis of the proximal leg vein or pulmonary embolism or both. Routine laboratory thrombophilia screening is never as reasonable in patients with a low risk of recurrence as in those with provoked and/or distal deep-vein thrombosis of the leg because there are no clinical consequences whatever the test result might be. Moreover, determination of laboratory-detectable markers is not indicated in patients with arterial thrombosis or venous thrombosis at unusual sites including patients with upper extremity thrombosis, cerebral vein thrombosis, or intra-abdominal vein thrombosis because of their uncertain role in the pathogenesis of these diseases.

Laboratory markers associated with an increased recurrence risk in venous thromboembolism The effect of several markers commonly included in the panel of routine thrombophilia screening on the risk of recurrent VTE is presented in the **TABLE**. There are other risk factors for VTE recurrence, the measurement of which requires sophisticated techniques, is costly, and not accessible on a routine basis. These markers, the effect of which on the recurrence risk has been only poorly investigated, as well as global coagulation activation indicators (including D-dimer and in-vitro thrombin generation) are not discussed as they are usually not part of routine laboratory testing for thrombophilia markers.

Deficiency of a natural coagulation inhibitor Patients with a natural coagulation inhibitor deficiency, such as patients with antithrombin, protein C, or protein S deficiency, have long been regarded as candidates for extended secondary thrombosis prevention because of their presumed high recurrence risk. This assumption was based on the high risk they carried of the first episode of VTE, as evidenced by retrospective studies of highly selected patient populations showing a high risk of VTE recurrence[4-7] and by personal clinical experience. From a recent prospective study from the Netherlands, the Leiden Thrombophilia Study (LETS), it appears, however, that the long-term recurrence risk conferred by these coagulation inhibitors is at best moderate with a statistically insignificant 1.8-fold increase in the likelihood of recurrence. The risk of recurrence seems to be the highest in patients with antithrombin deficiency.[8]

Gain of function mutations Factor V Leiden (FVL) and the G20210A mutation in the prothrombin gene (prothrombin mutation) are the most common inherited abnormalities in patients with the first episoded of VTE.[1] As regards the recurrence risk, 2 prospective studies did not find an increased risk of recurrent VTE either in heterozygous carriers of FVL or in heterozygous carriers of the prothrombin mutation.[8-10] Prandoni et al.[11] reported a 2.2-fold (95% confidence interval [CI], 1.4–3.7) increase in the risk of recurrent VTE in carriers as compared with noncarriers of FVL or the prothrombin mutation or both when the analysis was confined to patients treated with anticoagulants for 3 months. For patients who had a longer period of anticoagulation, the relative risk was 1.2 (95% CI, 0.8–2.1) and thus no longer statistically significant.[11] According to 3 systematic reviews, the risk of recurrent VTE among heterozygous carriers of either mutation is only moderately increased for odds ratios ranging from 1.2 to 1.7.[12-14] In a retrospective analysis,[14] the risk of recurrence in homozygous carriers of the FVL mutation was 2.5-fold higher compared with patients without the mutation. Compared with patients with wild-type genotypes, patients who are heterozygous for both FVL and the prothrombin

mutation were reported to be at an almost 5-fold increased risk of recurrence. Notably, the number of patients in these analyses was very small and the CIs were wide. In a case-control study in families with thrombophilia, homozygous carriers of FVL or the prothrombin mutation or double heterozygous individuals were not at an increased risk of recurrent VTE.[15]

High clotting factors High factor VIII is a strong risk factor of recurrent VTE. In the Austrian Study on Recurrent Venous Thromboembolism (AUREC), patients with the first unprovoked episode of VTE and a factor VIII level exceeding 234% (determined 3 weeks after suspension of anticoagulation) had a 6-fold increase in recurrence risk compared with patients with lower levels.[16] In the LETS, a fibrinogen level higher than 4.1 g/l conferred a 1.7-fold higher risk of recurrent VTE.[8]

Hyperhomocysteinemia In the AUREC, the cumulative probability of VTE recurrence 24 months after discontinuation of oral anticoagulants was 19.2% in patients with hyperhomocysteinemia compared with 6.3% in those without elevated homocysteine levels for a relative risk of 2.7 (95% CI, 1.3–5.8).[17] In contrast, in the LETS no difference in the risk of recurrent VTE was found between patients with or without elevated homocysteine levels.[8] Of note, vitamin B supplementation reduces homocysteine plasma levels but does not affect the recurrence risk.[18]

Antibodies against phospholipids There is only very limited data as to what extent phospholipid antibodies increase the risk of recurrent VTE. In a Canadian study, the incidence of recurrence among patients with the first episode of deep-vein thrombosis and presence of antibodies against cardiolipin was 2-fold higher than it was in patients without anticardiolipin antibodies.[19] In a systematic review of 7 studies, 109 recurrent VTE events were recorded in 588 patients with phospholipid antibodies and 374 recurrences in 1914 patients without phospholipid antibodies for a statistically insignificant relative risk of 1.4. The unadjusted risk ratio of recurrent VTE after stopping anticoagulant therapy in patients with an anticardiolipin antibody was 1.5 (95% CI, 0.8–3.1) and 2.8 (95% CI, 0.8–9.6) in patients with a lupus anticoagulant. It is unclear whether patients with more than 1 positive antibody-specific laboratory test result have a higher risk than those with single positivity, and the cut-offs above which the recurrence risk becomes clinically relevant are unknown.[20]

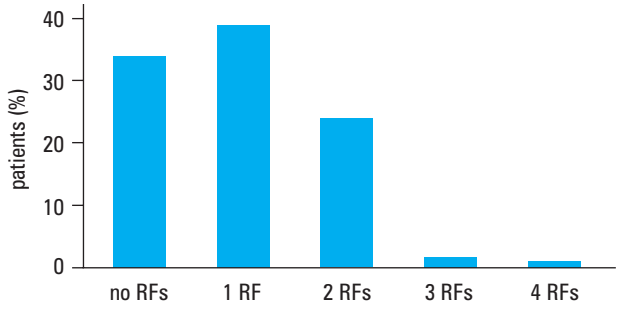

FIGURE Number of risk factors (RFs) detected by laboratory thrombophilia screening in patients with 2 unprovoked episodes of venous thromboembolism; 3 weeks after the incident event, patients were screened for deficiency of antithrombin, protein C, or protein S, presence of lupus anticoagulant, factor V Leiden, the prothrombin mutation and high concentrations of homocysteine, factor VIII, or factor IX; none of the patients had cancer

Is laboratory thrombophilia screening relevant for deciding on the optimal duration of secondary thromboprophylaxis? Introduction of extended, sometimes even life-long anticoagulation, can have serious consequences. For the patient, this could mean emotional strain related to a chronic illness that needs constant therapy, potential risks and side effects related to the treatment, and negative effects on social and professional life. For the health system, it means additional costs. Nevertheless, there is a subgroup of patients in whom indefinite anticoagulant therapy could be beneficial. These are patients in whom the bleeding risk conferred by anticoagulation is outweighed by a high risk of recurrent VTE. These patients are difficult to identify. It is apparently tempting to search for a distinct abnormality that may at least partly be responsible for the increased risk of VTE and can be evidenced by the use of a laboratory technique. In case of a positive finding, these patients would then qualify for an extended duration of anticoagulation. However, this approach, namely laboratory thrombophilia screening, needs to fulfill several prerequisites before it can be firmly installed in daily routine care. The most important ones are as follows: 1) the abnormality has convincingly been shown to confer an increased risk of recurrence; 2) the increase in the recurrence risk is clinically meaningful; 3) the effect of interactions between different abnormalities on the recurrence risk is known, as there are individuals with more than 1 such defect (FIGURE); 4) the abnormality can be identified by validated and ideally easy to perform precise laboratory tests with a low interlaboratory variability; and, most importantly, 5) there should be an effective treatment or intervention for patients identified through screening, with evidence of long-term anticoagulation leading to better outcomes; and, lastly, 6) the benefit from screening should outweigh the psychological harm caused by the test as well as by the treatment following the test result.

Unfortunately, none of the laboratory risk factors addressed before meets all the criteria: 1) for some factors including natural coagulation inhibitors or phospholipid antibodies, there is not enough compelling evidence that they really do increase the risk of recurrence; 2) regarding heterozygous carriers of FVL or the prothrombin mutation, most experts agree that the extent to which

these defects increase the recurrence risk is clinically irrelevant. In a study from England, for instance, investigating 570 patients with the first episode of VTE, recurrence rates were found to be unrelated to the presence or absence of heritable thrombophilia[21]; 3) a quarter of patients with the first episode of VTE has more than 1 risk factor (**FIGURE**). Whether and to what extent an interaction between risk factors increases the recurrence risk is unknown; 4) some assays, such as factor VIII clotting assays or assays that measure homocysteine have stringent pre-analytical requirements and/or a high variability between assays and laboratories, which restricts the general applicability of test results; 5) there is only a handful of clinical trials comparing different treatment strategies as regards the recurrence risk of VTE patients with a distinct laboratory coagulation abnormality. Kearon et al.[22] and Finazzi et al.[23] compared 2 different warfarin treatment intensities in patients with phospholipid antibodies. Den Heijer et al.[18] treated thrombotic patients with vitamins B or placebo. Eischer et al.[24] compared 2 different durations of anticoagulation in patients with high factor VIII levels. None of these studies showed a benefit for patients receiving the investigational treatment as compared with those given standard therapy. Finally, 6) as already outlined, some of the defects, in particular FVL or the prothrombin mutation, have at best a minor effect on the recurrence risk and are irrelevant because there are no clinical consequences of a positive result. However, routine testing for these heritable defects can cause unnecessary concerns and uncertainty both in patients and relatives, and may also lead to overtreatment.

One of the most compelling arguments against laboratory thrombophilia screening is based on the findings from the AUREC. In this study, more than a third of the patients with an unprovoked episode of recurrent VTE had a normal result of laboratory thrombophilia screening (**FIGURE**). Thus, the absence of a laboratory prothrombotic abnormality does not at all mean that the recurrence risk is low. A negative result on laboratory thrombophilia screening could thus potentially result in a false sense of safety for patients and physicians and, as a consequence, in undertreatment.

Conclusions At present, there is not enough scientific evidence that screening for a distinct laboratory-detectable abnormality allows to identify patients with a recurrence risk of VTE that would be high enough to justify extended anticoagulant therapy. On the other hand, a normal test result on thrombophilia screening does not imply that the recurrence risk is low, as many patients with a strong thrombotic propensity, for instance, those with multiple unprovoked events, have a normal test result. Therefore, I strongly believe that routine thrombophilia screening in thrombosis patients is no longer warranted.

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ARTYKUŁ POGLĄDOWY

Zakrzepica żylna – u kogo wykonywać badania przesiewowe w kierunku trombofilii w roku 2014?

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SŁOWA KLUCZOWE

badania w kierunku trombofilii, nawrót, żylna choroba zakrzepowo-zatorowa

STRESZCZENIE

Żylna choroba zakrzepowo-zatorowa (ŻChZZ) to choroba przewlekła. Jej nawrotom można zapobiegać stosując antykoagulanty – niestety za cenę ryzyka krwawień. Aby móc porównać zagrożenia i korzyści wiążące się z antykoagulacją, niezbędna jest ocena ryzyka nawrotu. Poznano wiele laboratoryjnych czynników ryzyka ŻChZZ, co doprowadziło do praktyki określanej jako badania przesiewowe w kierunku trombofilii – czyli procedury, w której pacjentom po przebytym epizodzie ŻChZZ rutynowo proponowano badania laboratoryjne mające zidentyfikować czynniki ryzyka tej choroby. Ich znajomość miałaby polepszyć dalsze postępowanie w aspekcie czasu trwania antykoagulacji. To podejście okazało się jednak zawodne. Dla niektórych czynników, w tym inhibitorów krzepnięcia i przeciwciał antyfosfolipidowych, dane o zwiększaniu ryzyka nawrotów są słabe. Stopień, w jakim inne defekty (czynnik V Leiden, mutacje protrombiny) zwiększają ryzyko nawrotów, jest nieistotny. Pacjenci mogą mieć liczne czynniki ryzyka i nie wiadomo, jak interakcje między nimi zwiększają ryzyko nawrotów. Niektóre metody laboratoryjne mają ograniczenia techniczne, które zmniejszają ich ogólną przydatność. Brakuje znaczących badań klinicznych porównujących strategie leczenia ukierunkowane na zapobieganie nawrotom ŻChZZ u pacjentów z różnymi nieprawidłowościami laboratoryjnymi. Rutynowe badanie w kierunku defektów wrodzonych może powodować niepotrzebne obawy i niepewność u pacjentów i ich krewnych, a także prowadzić do niepotrzebnego leczenia. Z kolei niewystępowanie nieprawidłowości laboratoryjnych niekoniecznie oznacza, że ryzyko nawrotu jest małe. Wynik ujemny może więc potencjalnie wywołać fałszywe uspokojenie pacjenta i lekarza, a w konsekwencji – zaniechanie wskazanego leczenia. Podsumowując: rutynowe badania w kierunku trombofilii nie są obecnie uzasadnione.

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