Idiopathic venous thrombosis
Long-term anticoagulant therapy? No

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Summary
Venous thrombosis is a chronic disease with a recurrence rate of approximately 30% within 5-8 years. The optimal duration of secondary thromboprophylaxis in these patients entails balancing the risk of recurrence against the risk of treatment-associated bleeding. There is agreement that patients with a first idiopathic venous thrombosis should receive vitamin K antagonists for at least 3-6 months. Convincing trials showing a clinical benefit in terms of morbidity or mortality with respect to expansion of anticoagulation beyond 6 months are lacking. Nevertheless, some subgroups of patients with venous thrombosis may benefit from indefinite anticoagulation. Thus, patients with antithrombin deficiency, combined or homozygous defects, or thrombin deficiency, combined or homozygous defects, from indefinite anticoagulation. Thus, patients with antithrombin deficiency, combined or homozygous defects, or thrombin deficiency, combined or homozygous defects, from indefinite anticoagulation. Thus, patients with antithrombin deficiency, combined or homozygous defects, or thrombin deficiency, combined or homozygous defects, from indefinite anticoagulation. Thus, patients with antithrombin deficiency, combined or homozygous defects, or thrombin deficiency, combined or homozygous defects, from indefinite anticoagulation. Thus, patients with antithrombin deficiency, combined or homozygous defects, or thrombin deficiency, combined or homozygous defects, from indefinite anticoagulation. Thus, patients with thrombosis should receive vitamin K antagonists for at least 3 to 6 months. The risk of recurrence during vitamin K antagonist therapy is very low in patients in whom thrombosis is not associated with malignant disease (7, 21). One has to keep in mind, however, that the risk of severe or fatal bleeding during anticoagulation is around 1% over 5-8 years (10, 18). Approximately 5% of patients with recurrence die from pulmonary embolism (2). During the first weeks after the event the risk of recurrence is high, but then declines over time. To prevent recurrence, patients usually receive low molecular weight heparin followed by administration of vitamin K antagonists at a target INR range of 2 to 3 (9). Taking together the results of four large interventional trials (1, 7, 17, 21), patients with a first idiopathic venous thrombosis should receive oral anticoagulants for at least 3 to 6 months. The risk of recurrence during vitamin K antagonist therapy is very low in patients in whom thrombosis is not associated with malignant disease (7, 21). One has to keep in mind, however, that the risk of severe or fatal bleeding during anticoagulation is around 1% per year (15). Thus, with respect to expanding anticoagulation beyond 6 months, the bleeding risk has to be carefully balanced against the risk of recurrent thrombosis. Using the aforementioned numbers (fatal pulmonary embolism in 5% of patients with recurrence, severe/fatal bleeding during anticoagulation between 1 to 2%), oral anticoagulation appears to be beneficial only in subgroups of patients in which the annual incidence of recurrence exceeds 8 to 10%.

Risk factors for recurrent venous thrombosis

Over the years, many circumstantial and congenital risk factors for recurrent venous thrombosis have been defined (Tab. 1). Deficiencies of antithrombin, protein C or protein S are important risk factors for a first episode of venous thrombosis and, although not proven in adequate clinical studies, have to be regarded as strong risk factors for recurrence. We and others (12, 14) have shown that high levels of factor VIII confer an increased recurrence risk. Other risk factors for recurrence (8, 11, 18, 20) are
- active cancer,
- more than one episode of venous thrombosis,
- male gender and
- the presence of the lupus anticoagulant.

Interestingly, patients with pulmonary embolism have an increased risk of recurrence and the majority of recurrent episodes are also pulmonary embolism (6). The risk of recurrence is substantially higher among patients with idiopathic venous thromboembolism as compared with those with venous thrombosis secondary to a temporal risk factor such as surgery or trauma (10). The two most common hereditary risk factors for thrombosis, factor V Leiden and factor II G20210A do not confer an increased risk for recurrence (4, 5).
Do patients at increased risk for recurrence benefit from long-term anticoagulation?

Only three clinical trials have compared different treatment strategies in selected patient groups with a seemingly high risk of recurrence. A small retrospective study from the United Kingdom showed that vitamin K antagonist therapy substantially reduces the long-term risk of recurrent venous or arterial thrombosis in patients with a lupus anticoagulant (8). In a study from Sweden, patients with more than one episode of venous thrombosis were randomized to indefinite or 6 months anticoagulation (20). Patients who were indefinitely treated with anticoagulants had a very low risk of recurrence, but severe or fatal bleeding complications were noted in 10 of 116 patients. Findings of a study from the United States show that in cancer patients anticoagulation with a low molecular weight heparin at therapeutic dose for 6 months is more effective and safe as a vitamin K antagonist at conventional intensity (13). However, it is unclear if cancer patients benefit from expansion of low molecular weight heparin treatment beyond 6 months. In sum, an evidence form clinical study that patients with venous thrombosis, even those at high risk of recurrence, benefit from extended anticoagulation in terms of morbidity or mortality is almost completely lacking.

Candidates for long-term prevention

Patients in whom the risk for severe bleeding seems to be outweighed by the likelihood of recurrence might nevertheless benefit from indefinite anticoagulation. Of course, the decision about duration of anticoagulation therapy is also strongly affected by the individual risk for bleeding and patients’ preference. From the authors view, good candidates for long-term prophylaxis are patients with antithrombin deficiency, combined or homozygous defects, more than one unprovoked episode of thrombosis, the lupus anticoagulant or high factor VIII plasma levels. Cancer patients who do not achieve remission could also benefit from prolonged anticoagulation.

Future strategies regarding long-term prevention

Identification of patients with a particular high or low risk of recurrent venous thrombosis is one of the foremost goals of thrombosis research. We and others have shown, that measurement of D-Dimer shortly after withdrawal of anticoagulation allows stratification of patients into high and low risk categories with regard to recurrence probability (3, 16). Patients with a low D-Dimer do not appear to benefit from extended anticoagulation and extensive thrombophilia screening may be unnecessary in this patient group.

To reduce the risk of recurrence without increasing risk for bleeding, new strategies with regard to long-term secondary thromboprophylaxis have been proposed. The PREVENT investigators (19) compared low intensity warfarin (INR 1.5-2.0) with placebo in patients with idiopathic venous thrombosis who had received conventional intensity anticoagulation for at least 3 months. After 4 years, symptomatic thrombosis recurred in 15% of patients assigned to placebo and in 5.5% of those allocated low intensity warfarin. Major hemorrhage was very rare in both groups. In sum, low intensity warfarin substantially reduces the risk for recurrent thrombosis, confers a relatively low risk of bleeding and might thus be an attractive alternative option for indefinite anticoagulation.

In the THRIVE III study (22), patients who had completed a 6-month course of conventional anticoagulation with vitamin K antagonists were assigned placebo or ximelagatran, a direct thrombin inhibitor. At 18 months, the recurrence rate was almost 13% in the placebo group and approximately 3% in patients allocated ximelagatran. Major bleeding was very rare in both groups. In 5 to 10% of patients, ximelagatran was associated with an increase in liver enzymes. To date, ximelagatran is licensed only for thromboprophylaxis in orthopaedic surgery.

References

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