Idiopathic venous thrombosis
Long-term anticoagulation therapy? Yes

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Summary
Idiopathic venous thromboembolism has been shown to be associated with a high frequency of recurrence. Therefore, the most important aim of long-term treatment is secondary prevention. It has also been shown that long-term anticoagulation with vitamin K antagonists can impressively reduce the rate of recurrence. However, this effect was only maintained during anticoagulation and disappeared after cessation of anticoagulant therapy. Unfortunately, the individual risk of recurrence is not predictable. Therefore, long-term anticoagulation appears beneficial across all subgroups of patients suffering from venous thromboembolism, regardless of the presence of thrombophilia or other burden of the disease. Despite the increasing body of evidence regarding the advantages of long-term anticoagulation, bleeding complications may limit the net clinical benefit of this strategy. Thus, the development of anticoagulants having a low potential for adverse reactions and providing similar beneficial antithrombotic effects to vitamin K antagonists will enhance the readiness for their wide spread use and life long administration.

Key messages

Registries
Prandoni et al. assessed the incidence of complications after a first episode of documented deep vein thrombosis in a large cohort of consecutive patients to determine the clinical course in patients during long-term follow-up of eight years after their first episode of symptomatic deep vein thrombosis (DVT). The authors describe high rates of recurrences: 18% occurred after two years, 25% after five years, and 30% after eight years.

The recurrence rates were highest in patients who had an idiopathic DVT, i.e. not a triggering event such as previous trauma or surgery (10).

Heit et al. estimated the VTE recurrence rates in a large population-based cohort study and concluded that it recurs frequently, especially within the first six to twelve months, and continues to recur for at least ten years after the initial VTE. The recurrence rate after one year follow-up was 13% and by ten years of follow-up, the cumulative recurrence rate was 30% (5).

In a Swedish registry, the 5-year cumulative incidence of recurrent VTE was 22% after a first episode of DVT and 28% after a second episode in symptomatic DVT patients who were followed for four to nine years (4).

Randomized trials with prolonged anticoagulation
Up to one year

Based on the results of a randomized trial which compared six weeks with six months of warfarin therapy, a duration of anticoagulation of six months has become standard of care for the majority of patients with VTE. In this trial, the 6-month course of oral anticoagulation halved the recurrence rate. After two years of follow-up, the recurrence rate was 18% in the 6-week group and 9.5% in the 6-month group (12).

Further studies sought to determine if the duration of treatment could be shorter than one year. Agnelli et al. compared three...
months with twelve months of warfarin treatment in 267 patients with idiopathic DVT. After a period of one year, there was a striking difference between recurrence rates in both groups which occurred in 8.3% in the 3-month group compared with 0.7% in the 12-month group. However, at the end of the planned follow-up period of three years, 15.8% in the 3-month group had recurrent DVT compared with 15.7% in the 12-month group. Thus, the clinical benefit associated with extending the duration of anticoagulant therapy to one year is not maintained after therapy is discontinued (1).

Agnelli et al. also compared three to six months of oral anticoagulation with twelve months of therapy in 326 patients who had had a first episode of pulmonary embolism (PE). Only one patient had a recurrent VTE while receiving anticoagulation. However, recurrence rates increased dramatically after discontinuation of anticoagulation. After three years of follow-up, the recurrence rates were similar in both groups of patients who received time-limited anticoagulation: 11.2% in the group receiving three to six months of anticoagulation compared with 9.1% in the 12-month group (2).

These studies showed that extending anticoagulation for one year did not eliminate long-term recurrence in patients with idiopathic VTE due to the fact that the benefit for reducing recurrent VTE is not maintained after treatment is withdrawn.

**More than one year**

In a multicenter trial, Schulman et al. compared six months of oral anticoagulant therapy with anticoagulant therapy continued indefinitely in patients who had had a second episode of VTE. After four years of follow-up, there were 20.7% recurrences in the group assigned to six months of therapy compared to 2.6% in the group assigned to continuing therapy. However, the strategy of indefinite-duration of anticoagulation appeared hazardous because of increased bleeding complications. For example, the authors described 2.7% major haemorrhages in the six-month group versus 8.6% in the indefinite treatment group (13). Thus, secondary prevention of VTE with a vitamin K antagonist that was continued for an indefinite period after a second episode of VTE was associated with a much lower rate of recurrence during four years than treatment for six months but this was achieved at the cost of an increased rate of major bleeding.

Kearon et al. randomized patients with idiopathic VTE to receive three or 24 months of oral anticoagulation with warfarin. After 162 patients had been enrolled and followed for an average of ten months, the trial was terminated because of extreme beneficial results obtained in the patients assigned to 24 months of treatment. The recurrence rate was 27% in patients receiving three months of therapy compared with 1.3% in those assigned to long-term treatment. The positive treatment effect however, has been overshadowed by bleeding complications in the long-term group. Of those patients assigned to long-term warfarin treatment, three of the 79 experienced major bleeding complications during the 10-month follow-up period (6). Thus, for conventional long-term anticoagulation with vitamin K antagonists, an uncertain balance between decreased VTE recurrences and increased major bleedings in patients receiving extended-duration anticoagulation needs to be improved in the future.

The PREVENT (Prevention of RECurrent VENous Thromboembolism) trial used a double blind design to test low-intensity warfarin (target INR 1.5-2.0) against placebo in 508 patients with idiopathic DVT or PE who had previously completed an average of six months of standard anticoagulation. The trial was terminated after two years of therapy because of an extreme beneficial effect in the warfarin group. Warfarin reduced the frequency of recurrent VTE events by two thirds: 7.2 per 100 patient-years in the control group compared with 2.6 per 100 patient-years in the warfarin group. All subgroups benefited, including both sexes, patients with factor V Leiden or the prothrombin gene mutation, first-time and recurrent VTE events, and both young and old patients, with ages ranging from 30 to 89 years (11). Therefore, PREVENT has provided firm evidence that long-term, low-intensity warfarin therapy is a highly effective method of preventing recurrent VTE.

In the Canadian ELATE (Extended Low-Intensity Anticoagulation for Thrombo-Embolism) study low-intensity warfarin, target INR of 1.5 to 1.9, was compared with standard-intensity warfarin, target INR of 2.0 to 3.0. Overall, 738 patients were enrolled and 369 were randomized to receive low-intensity and 369 to receive standard-intensity warfarin therapy. Patients were followed for an average of 2.4 years. The recurrence rate was 1.9 per 100 patient-years in the low-intensity group compared with 0.7 per 100 patient-years in the standard-intensity group. The likelihood of recurrence was 2.8 times higher with low-intensity warfarin compared with standard-intensity warfarin. There was no significant difference in major hemorrhage between patients assigned to low-intensity versus standard-intensity oral anticoagulation. The authors concluded that conventional-intensity warfarin therapy is more effective than low-intensity warfarin for the long-term prevention of recurrent VTE. The low-intensity warfarin therapy does not reduce the risk of clinically important bleeding (7).

Schulman et al. randomized 1233 patients with idiopathic VTE who had received six months of standard warfarin therapy to an oral direct thrombin inhibitor (ximelagatran 24 mg twice daily) or placebo for 18 months under double-blind conditions. Patients with a prior symptomatic, objectively confirmed lower-limb DVT including calf vein thrombosis, or PE, were enrolled in this THRIVE III (THRombin Inhibitor in VEnous thromboembolism) study. The ximelagatran group exhibited an 84% decrease in recurrent events compared with placebo, from 12.6% to 2.8% with no increase in major bleeding (14). This trial provided “proof of principle” that idiopathic VTE is a chronic illness that can be controlled with extended-duration anticoagulation, even if the anticoagulant is a novel agent that is not a vitamin K antagonist.

A complementary follow-up, intention-to-treat analysis was conducted post study to evaluate the cumulative risks of locally-confirmed recurrent VTE and death over the full 18-month study period, regardless of whether patients discontinued study drug prematurely. Of 612 and 611 patients receiving ximelagatran or placebo, respect-
ively, 149 and 181 discontinued treatment prematurely. Of these discontinuations, further information could not be collected for 14 and 13 patients in the ximelagatran and placebo groups, respectively. Among the remaining patients, four VTE events and four deaths occurred in the ximelagatran group, and one VTE event and five deaths were documented in the placebo group. The resulting cumulative risks of VTE (3.2% versus 12.7%; p <0.0001) and PE (0.8% versus 5.2%; p <0.0001) were significantly lower in the ximelagatran group when compared to the placebo group over 18 months. The rate of death from any cause was not significant between both groups (15). This complementary follow-up analysis confirms the benefit of 24 mg twice daily, administered without coagulation monitoring or dose adjustment, for the long-term secondary prevention of VTE.

**Meta-analysis evaluating long-term anticoagulation for VTE**

A recently published meta-analysis reviewed the available evidence and quantified the risks and benefits of extending the duration of anticoagulation in patients with VTE. In total, 15 studies were included in the analysis and the authors were able to show if patients in the long-therapy group remained receiving anticoagulation, the risk of recurrent VTE with long- versus short-term therapy was significantly reduced. A reduction of the weighted incidence rate from 0.126 events/person-year to 0.020 events/person-year has been found (p <0.001). Thus, there is no doubt that the risk of recurrent VTE is greatly reduced if anticoagulation is continued. If anticoagulation in the long-term therapy group was discontinued, the risk reduction was less pronounced: weighted incidence rate 0.072 events/person-year versus 0.052 events/person-year (p <0.04). While there were insufficient data to determine precisely whether three months, six months, or a longer period of anticoagulation would be optimal, there is evidence that the incremental benefit of prolonging anticoagulation decreases as the duration of anticoagulation increases. The risk of major bleeding with long- versus short-term therapy was similar. There was no statistically significant difference between the weighted incidence rate of 0.011 versus 0.006 events/person-year (9). The authors conclude that patients who receive extended anticoagulation are protected from recurrent VTE while receiving long-term therapy. The clinical benefit is maintained after anticoagulation is discontinued, but the magnitude of the benefit is less pronounced.

**Tab. 1** Optimal duration and intensity of anticoagulation following VTE

<table>
<thead>
<tr>
<th>Authors (ref.)</th>
<th>Regimen tested</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schulman et al. (12)</td>
<td>Warfarin for 6 weeks versus 6 months</td>
<td>Recurrence rate was halved in 6-month group.</td>
</tr>
<tr>
<td>Agnelli et al. (1)</td>
<td>Warfarin for 3 months versus 12 months</td>
<td>Initially decreased recurrence rate in the 12-month group was not maintained after warfarin was discontinued; 3% of 12-month group had nonfatal major bleeding during extra 9 months of anticoagulation.</td>
</tr>
<tr>
<td>Agnelli et al. (2)</td>
<td>Warfarin for 3–6 months versus 12 months</td>
<td>Initial decreased recurrence rate in 12-month group was not maintained after warfarin was discontinued.</td>
</tr>
<tr>
<td>Kearon et al. (6)</td>
<td>Warfarin, INR 2.0–3.0 versus placebo, after initial course 3 months of anticoagulation; 10-month study</td>
<td>Warfarin group had 95% reduction in recurrence, but borderline statistically increased major bleeding.</td>
</tr>
<tr>
<td>Rücker et al. (11)</td>
<td>Warfarin, INR 1.5–2.0 versus placebo, after initial average of 6 months of anticoagulation; 2-year study</td>
<td>Warfarin reduced recurrence rate by two thirds without increased major bleeding.</td>
</tr>
<tr>
<td>Kearon et al. (7)</td>
<td>Warfarin, INR 1.5–1.9 versus warfarin, INR 2.0–3.0</td>
<td>Warfarin, INR 2.0–3.0, had fewer recurrences and no increased bleeding compared with warfarin, INR 1.5–1.9.</td>
</tr>
<tr>
<td>Schulman et al. (14)</td>
<td>Ximelagatran 24 mg bid for 18 months versus placebo, after initial 6 months of anticoagulation</td>
<td>Ximelagatran group had 85% fewer recurrences without major bleeding.</td>
</tr>
</tbody>
</table>

**Tab. 2** Long-term treatment of VTE based on the Seventh ACCP Conference document (LMWH: low molecular weight heparin, VKA: vitamin K antagonist)

<table>
<thead>
<tr>
<th>Patient categories regarding the first episode of VTE</th>
<th>Drug</th>
<th>Duration (months)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>secondary to a transient risk factor</td>
<td>VKA</td>
<td>3</td>
<td>Recommendation applies to both proximal and calf vein thrombosis.</td>
</tr>
<tr>
<td>idiopathic</td>
<td>VKA</td>
<td>6-12</td>
<td>Continuation of anticoagulant therapy after 6-12 months may be considered.</td>
</tr>
<tr>
<td>combined with cancer</td>
<td>VKA</td>
<td>6-12</td>
<td>Continuation of anticoagulant therapy after 6-12 months may be considered.</td>
</tr>
<tr>
<td>combined with a documented thrombophilic abnormality</td>
<td>VKA</td>
<td>6-12</td>
<td>Continuation of anticoagulant therapy after 6-12 months may be considered.</td>
</tr>
<tr>
<td>combined with documented antiphospholipid antibodies or two or more thrombophilic abnormalities</td>
<td>VKA</td>
<td>12</td>
<td>Continuation of anticoagulant therapy after 6-12 months may be considered.</td>
</tr>
</tbody>
</table>
Long-term anticoagulation following idiopathic VTE

What are the barriers?

Patients with idiopathic DVT of PE have a high risk of experiencing a recurrent event. Rigorous clinical trials have established indefinite-duration anticoagulation therapy as an effective and safe strategy for most of these patients (Tab. 1). In particular, the PREVENT, ELATE, and THRIVE III trials demonstrate that a strategy of long-term anticoagulation in patients with idiopathic VTE, including patients with isolated calf DVT, is safe and effective. This successful strategy appears beneficial across all subgroups, regardless of the presence of thrombophilia or other burden of the disease. Implementing this proven approach on a population basis would significantly improve the prevention of VTE recurrence. Based on the body of evidence regarding the benefit of long-term anticoagulation following idiopathic VTE its use is strongly recommended in the latest issue of the ACCP document (3). This includes patients with and without additional risk factors such as cancer or special types of thrombophilia (Tab. 2).

However, an important caveat is that anticoagulation therapy of indefinite duration, possibly for a lifetime, is a major undertaking for both the patient and the healthcare provider which can exert a profound emotional, social, and medical toll on quality of life. For example, the use of vitamin K antagonists is hampered by numerous limitations, such as its narrow therapeutical window, its need for frequent coagulation monitoring and dose adjustments, dietary restrictions, drug interactions, its delayed on- and off-set of action and the bleeding risk which may offset the benefit of long-term treatment. Therefore, the development of more “user friendly” oral anticoagulants without the requirement for close coagulation monitoring and individual dose adjustments, a wide therapeutic window, rapid on- and offset of action, and minimal interactions with food or other drugs is an unmet clinical need. The promising results from the THRIVE III trial suggest that ximelagatran may represent a significant improvement over existing therapies for the management of long-term anticoagulant therapy. The convenience of oral administration, without the need for individualized dosing or routine coagulation monitoring, mean that the management of patients will be made considerably easier, however, a transient increase of liver enzymes in patients with long-term treatment deserves further investigation. Thus, the development of anticoagulants having a low potential for adverse reactions and providing similar beneficial antithrombotic effects to vitamin K antagonists will enhance the readiness for their wide spread use and life long administration.

References


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