Anticoagulation after venous thromboembolism

Deciding on the optimal duration

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Keywords
Venous thrombosis, recurrence, Vienna prediction model

Summary
Deciding on the optimal duration of anticoagulation is based on the risk of recurrent venous thromboembolism (VTE) and of bleeding during anticoagulation. The duration of anticoagulation should be at least three months since shorter courses double the recurrence rates.

At three months anticoagulation can be stopped in patients with a VTE provoked by a transient risk factor, as the recurrence risk is expected to be lower than the bleeding risk during anticoagulation. Patients with unprovoked VTE are at higher risk of recurrence and prolonged anticoagulation is currently recommended.

However, attempts are made to stratify these patients according to their recurrence risk and to identify those with a low recurrence risk who would not benefit from extended anticoagulation. Novel approaches to optimize the management of patients with unprovoked VTE are the use of prediction models which link clinical patient characteristics with laboratory testing to discriminate between patients with a low risk (who may discontinue anticoagulation) and those with high risk (in whom long term anticoagulation is justified).

Moreover, new antithrombotic concepts including new oral anticoagulants or aspirin both of which potentially confer a lower bleeding risk and are more convenient for the patients have been explored for extended thromboprophylaxis.

Schlüsselwörter
Venenthrombose, Rezidivrisiko, Antikoagulation, Vorhersagemodelle

Zusammenfassung
Anticoagulation
In the acute phase of VTE
The main goals in the treatment of acute VTE are to
• restore perfusion of the occluded vessel,
• inhibit progression and embolisation of the thrombus,
• prevent recurrence.

Thus, patients with deep vein thrombosis or non-massive pulmonary embolism are usually started on parenteral administration of heparin or fondaparinux to achieve immediate anticoagulation. Since the risk of thrombus progression, embolisation and recurrence does not subside within days, anticoagulation beyond the acute phase is necessary. Usually, for that purpose a vitamin K antagonist is started simultaneously with heparin or fondaparinux. Parenteral anticoagulation can be discontinued after a minimum of five days provided that the international normalized ratio (INR) is 2.0 or higher for at least 24 hours.

Recently, new oral anticoagulants have been tested in patients with acute VTE. Rivaroxaban, a direct factor Xa inhibitor, is already licensed for the treatment of acute deep vein thrombosis and pulmonary embolism. Treatment consists of an oral dose of 15 mg twice daily for three weeks followed by 20 mg once daily. No initial parenteral anticoagulant drug is required.

Rivaroxaban has similar efficacy and a lower rate of major bleeding compared to conventional treatment with a parenteral anticoagulant followed by vitamin K antagonist (9, 10).

The results of a phase III study with dabigatran, an oral direct thrombin inhibitor, for treatment of acute VTE show similar efficacy and safety compared to standard treatment (11), and licensing of the drug for this indication is awaited. The results of two other interventional trials using apixaban (AMPLIFY) or edoxaban (HOKUSAI), both oral direct factor Xa inhibitors, on safety and efficacy for treatment of acute VTE are also awaited.

In the subacute phase after VTE
The recurrence risk is highest during the first weeks after the acute event.

The minimum duration of anticoagulation for all patients with VTE is three months.

Reducing the duration to four to six weeks doubles the risk of recurrence during the next year (12, 13). The risk of recurrence never subsides and may remain as high as 10% per year (4). Thus, prolonged anticoagulation may be required in some patients. Several interventional trials have investigated the value of extending anticoagulation from 3 to 6, 12, or 24 months or even indefinitely (14–18). While recurrence is effectively prevented during treatment, the recurrence risk again increases once anticoagulation is stopped and is not lower than what would have been expected after shorter duration of anticoagulation (19–21). This is also true for patients with VTE secondary to a transient risk factor including surgery or trauma (13). Thus, after a VTE patients should either be stopped at three months or continued for an indefinite period of time if a high risk of recurrence is suspected.

Beyond three months after VTE
Antithrombotic treatment is highly effective and prevents recurrent VTE in more than 95% of patients (7, 8). However, the prize for effective protection against recurrent thrombosis is a risk of bleeding during anticoagulant treatment. Thus, deciding on the optimal duration of anticoagulation entails balancing the risks of
• recurrence if anticoagulation is stopped,
• bleeding in case of extended thromboprophylaxis.

The rate of major bleeding during VKA therapy in VTE patients is approximately 3% during the first three months (7). Data on the bleeding risk thereafter are sparse. Depending on the risk profile, the estimated annual risk of major bleeding ranges between 0.8% and more than 6% (7). Outside of clinical studies in unselected patients receiving usual care the bleeding risk associated with VKA treatment is markedly higher (22).

The case fatality rate of bleeding exceeds 10% (6).

While scoring models to predict the bleeding risk (e.g. HAS-BLED score) in patients with atrial fibrillation are available, no such tools are validated for patients with VTE who require anticoagulant treatment. In addition, the patient’s preference and adherence needs to be taken into account when making a decision on the duration of anticoagulation (23).

Stopping anticoagulation after three months
Patients in whom VTE occurs in association with a temporary risk condition have a low risk of recurrence (≤3% during the first year, ~10% after five years). This is particularly true for patients with venous thrombosis after surgery or for women who develop their VTE during hormone contraceptive use (13, 21, 24–27). The risk of recurrence is less well studied in patients who had their initial venous thrombosis provoked by trauma, pregnancy, immobilisation or long-distance travel, but is also regarded as low. As the recurrence risk in these patients is expected to be lower than the bleeding risk in case of extended anticoagulation:

Stopping anticoagulation after three months is recommended for all patients with VTE in association with a temporary risk factor (7, 8).

Anticoagulation may also be stopped after three months in patients with a high risk of bleeding and/or poor adherence to treatment, regardless of the presence or absence of a transient triggering risk condition.

Extending anticoagulation beyond three months
Patients with VTE that occurred in the absence of a temporary triggering event (so called unprovoked VTE) may have a recurrence risk as high as 10% per year (4), and may benefit from extended anticoagulation.

However, despite an overall high recurrence risk many patients with a first unpro-
provoked VTE will stay recurrence free but are exposed to an unnecessary risk of bleeding in case anticoagulation is prolonged. For vitamin K antagonists the annual risk of bleeding ranges between 1% and 3% (7, 28, 29) and the case-fatality rate is about 13% (6). Moreover, some patients dislike anticoagulation because of the prospect of a long-time medical treatment or inconveniences in professional life.

Several strategies have been developed to optimize the decision on the duration of anticoagulation of patients with unprovoked VTE and to improve long-term management. For many years, it has been tried to identify patients with a high risk of recurrence in whom prolonged anticoagulation would indeed be justified. Among these were patients with multiple episodes of VTE who have a higher risk of recurrence (20, 21). However, although risk of recurrence is effectively prevented during indefinite anticoagulation, the risk of bleeding is significantly increased. Moreover, it remains unknown if the increased recurrence risk is also true for patients with multiple provoked venous thromboses. More recently, efforts have been made to identify patients with VTE and a low risk of recurrence in whom anticoagulation may safely be stopped.

Strategies to discriminate patients with unprovoked VTE with a low or high recurrence risk also included thrombophilia screening. Meanwhile, testing for laboratory markers associated with a thrombotic risk in order to guide duration of anticoagulation has been abandoned. Global markers of coagulation activation, above all D-dimer, are predictive of the recurrence risk.

D-dimer is the most promising marker particularly when integrated together with clinical characteristics in scoring models designed to predict the risk of recurrence.

An extensive overview on how to predict the risk of recurrent VTE is provided elsewhere in this issue (30).

### Alternative antithrombotic concepts

The bleeding risk is the main limiting factor for extending antithrombotic treatment. Thus, a substance which is effective in preventing recurrence but has a low bleeding risk could be the drug of choice for many patients with unprovoked VTE and might also challenge the current concept of anticoagulation in patients with provoked VTE.

### New oral anticoagulants

Several new oral anticoagulants have been developed as an alternative to vitamin K antagonists. These compounds are directly and specifically targeted against either thrombin (dabigatran) or factor Xa (rivaroxaban, apixaban, edoxaban). The new oral anticoagulants have been tested in phase III studies with regard to safety and efficacy for extended anticoagulation after VTE. For two factor Xa inhibitors, rivaroxaban and apixaban, placebo controlled data have been reported (9, 31).

- Rivaroxaban is already licensed for extended thromboprophylaxis after deep vein thrombosis or pulmonary embolism.
- Dabigatran has been studied in this indication in two separate trials in comparison to either placebo or warfarin and results have been published jointly (32).

An overview of these four trials is provided (Tab. 1). Compared to placebo all new oral anticoagulants are highly effective in preventing recurrent VTE. Risk of recurrence was not significantly different between dabigatran and warfarin, but warfarin was highly effective in preventing acute coronary syndromes during treatment:

- dabigatran 13 events (0.9%),
- warfarin 3 events (0.2%), p-value 0.02.

Although bleeding rates were generally low in these trials, none of the studies was powered to adequately assess the actual

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**Tab. 1**

Phase III studies on the efficacy and safety of new oral anticoagulants for extended thromboprophylaxis after venous thromboembolism (VTE)

<table>
<thead>
<tr>
<th>Study (ref.)</th>
<th>EINSTEINext (9)</th>
<th>AMPLIFYext (31)</th>
<th>RESONATE (32)</th>
<th>REMEDY (32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>patients, n</td>
<td>1197</td>
<td>2486</td>
<td>1343</td>
<td>2856</td>
</tr>
<tr>
<td>compound</td>
<td>rivaroxaban</td>
<td>apixaban</td>
<td>dabigatran</td>
<td>dabigatran</td>
</tr>
<tr>
<td>dose, mg</td>
<td>1 × 20</td>
<td>2 × 2.5, 2 × 5</td>
<td>2 × 150</td>
<td>2 × 150</td>
</tr>
<tr>
<td>control</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>warfarin</td>
</tr>
<tr>
<td>duration of treatment, months</td>
<td>12</td>
<td>12</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>recurrent VTE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>study drug, n (%)</td>
<td>8 (1.3)</td>
<td>42 (7.1) 0.18 (0.09–0.4)</td>
<td>3 (0.4)</td>
<td>37 (5.6) 0.08 (0.02–0.25)</td>
</tr>
<tr>
<td>control, n (%)</td>
<td>2.5 mg: 32 (3.8)</td>
<td>5.0 mg: 34 (4.2) 96 (11.6)</td>
<td>2.5 mg: 0.33 (0.22–0.48)</td>
<td>5.0 mg: 0.36 (0.25–0.53)</td>
</tr>
<tr>
<td>hazard ratio (95% CI)</td>
<td>5.19 (2.3–11.7)</td>
<td>5.19 (2.3–11.7)</td>
<td>5.19 (2.3–11.7)</td>
<td>5.19 (2.3–11.7)</td>
</tr>
</tbody>
</table>

CRNM: clinically relevant non major; CI: confidence interval
bleeding risk over time. Observation time in all trials was limited to 12–18 months and data on long-term risk are lacking.

Moreover, there are more caveats and issues that need to be addressed before the new oral anticoagulants can be recommended for extended thrombophrophylaxis after VTE.

In all the trials the decision on the duration of anticoagulation was left at the discretion of the treating physician. This induced a preselection process which is reflected in a very heterogeneous group of study patients (e.g., inclusion of patients with cancer associated VTE, or patients with postoperative VTE). To improve the decision on who will truly benefit from extending anticoagulation, more data on the profile of the patients need to be provided in subgroup analyses. In addition, the longterm bleeding risk and other potential side effects (e.g., risk of myocardial infarction, gastrointestinal bleeding) of the new anticoagulants need to be better evaluated for making decisions on a more individualized treatment.

**Aspirin**

The role of aspirin for preventing VTE has been negligible, as anticoagulant drugs including heparin and vitamin K antagonists with a higher efficacy in the venous system are available. This concept has been challenged in patients with unprovoked VTE for two reasons.

1. There is evidence that recurrent VTE and arterial thrombotic events share same risk factors including male sex, obesity, and dyslipidemia (33–35).
2. In subgroups of patients with unprovoked VTE the antithrombotic potency of aspirin may be effective enough to provide protection from recurrent events.

The results of two interventional randomized placebo controlled trials on the use of aspirin for extended thrombophrophylaxis after VTE have been published. In the WARFASA (Warfarin and Aspirin) study, an interventional, multicenter, double-blind study which was run predominantly in Italy, patients with a first unprovoked VTE who had completed 6 to 18 months of oral anticoagulant treatment were randomly assigned to aspirin 100 mg daily or placebo (36). During a median treatment period of 23.9 months, 28 of 205 patients taking aspirin and 43 of 197 taking placebo had a recurrence (6.6% vs. 11.2%/year; hazard ratio 0.58; 95% CI 0.36 – 0.93). One patient in each treatment group had a major bleeding episode.

In the Australian ASPIRE (Aspirin to Prevent Recurrent Venous Thromboembolism) study, 822 patients who had completed initial anticoagulant therapy after a first unprovoked VTE to either aspirin 100 mg daily or placebo (37). Median follow-up was 37.2 months. Venous thromboembolism recurred in 73 of 411 patients assigned to placebo and in 57 of 411 assigned to aspirin (6.5% vs. 4.8%/year; hazard ratio 0.74; 95% CI 0.52 – 1.05; p = 0.09). Aspirin reduced the rate of the pre-specified secondary composite outcome (rate of VTE, myocardial infarction, stroke, or cardiovascular death) by 34% (8.0%/year with placebo vs. 5.2%/year with aspirin; hazard ratio 0.66; 95% CI 0.48 – 0.92; p = 0.01). There was no significant between-group difference in the rates of major or clinically relevant non major bleedings (0.6%/year with placebo vs. 1.1%/year with aspirin, p = 0.22).

The combined results of the two studies are shown (Tab. 2) with regard to number of events of VTE, major vascular events and clinically relevant bleeding. The results show a significant reduction of 32% in the rate of recurrence of VTE and a 34% reduction of the rate of major vascular events without an excess of bleeding.

Overall, aspirin reduces the risk of recurrence by one third.

It remains to be decided, though, who will indeed benefit from aspirin after VTE. In the two studies the annual recurrence rates in the aspirin group were 6.6% and 4.8%, respectively. As with studies on new oral anticoagulants the question about the actual bleeding risk associated with long term aspirin use remains unanswered. Neither WARFASA nor ASPIRE were large enough to adequately evaluate the bleeding risk during aspirin intake compared to placebo. However, in ASPIRE, major vascular events including myocardial infarction, stroke and cardiovascular death were significantly lower in the aspirin treated patients (37). Aspirin could therefore be an attractive option particularly in patients with VTE and risk of cardiovascular events, but also in those patients with a high risk of recurrent VTE who are unwilling to continue anticoagulant therapy.

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**Optimal duration of anticoagulation in special patients**

**Cancer patients**

In patients with cancer and VTE the risk of recurrence, but also the bleeding risk is high (38).

Anticoagulation with low molecular weight heparin at a therapeutic dose for one month followed by a 25% dose-reduction is more effective than and as safe as vitamin K antagonists at conventional intensity (39, 40).
Since cancer patients have a high risk of recurrence, low molecular weight heparin should be given for at least three to six months (41). The minimum duration of three months may be chosen in patients who are reluctant or unable to adhere to parenteral treatment and in those with a particularly high bleeding risk. The optimal duration and mode of secondary thromboprophylaxis is not defined. In patients with still active cancer anticoagulation should be continued beyond six months. The choice of anticoagulant (LMWH, VKA, oral direct anticoagulant) shall be made according to ongoing chemotherapy or need of interventions, patient preference, or reimbursement policies.

All new oral anticoagulants have not been adequately studied for the treatment of VTE in cancer patients.

### Pregnant women

Low molecular weight heparin is the only option for treating pregnant women with acute VTE (42, 43). Fixed-dose, weight-adjusted subcutaneous low molecular weight should be given at a therapeutic dose throughout pregnancy. There are no clear recommendations on monitoring anti-Xa levels. In women at very high thrombotic risk LMWH dosing according to anti-Xa levels may be considered. Studies on the optimal duration and intensity of anticoagulation are lacking. Low molecular weight heparin should be discontinued 24 hours before induction of labour or caesarean section, re-started at a reduced dose when it is safe to do so and continued for an additional six to eight weeks.

All new oral anticoagulants are contraindicated during pregnancy and breastfeeding.

### Patients with vena cava filters

In patients at high risk of recurrence and contraindications to therapeutic anticoagulation vena cava filters
- reduce the risk of pulmonary embolism but
- increase the risk of deep vein thrombosis without affecting overall mortality (44, 45).

Placement of permanent vena cava filters is generally not recommended and filters should be removed as soon as possible. There is uncertainty about the duration of anticoagulation if a filter cannot be retrieved and remains permanently. Vena cava filters increase the risk of recurrent deep vein thrombosis, and thrombi at the filter site are recorded in more than 10% of patients (46). Thus, anticoagulation has been recommended for all patients as long as the...
filter is in place. This practice has been challenged by recent guidelines which suggest a conventional duration of anticoagulation in patients with vena cava filters (7). A permanent vena cava filter per se is no longer regarded as an indication for extended anticoagulation.

Other populations

The optimal duration of anticoagulation in patients with subsegmental pulmonary embolism, incidentally detected pulmonary embolism or in patients with small isolated calf vein thrombosis or muscle vein thrombosis is incompletely studied and, thus, remains under constant debate.

Conclusions

Initial parenteral anticoagulation followed by oral treatment with VKA for at least three months is currently the standard of care in patients with acute deep vein thrombosis and/or non-massive pulmonary embolism. With the availability of new oral anticoagulants this concept has changed as these drugs not only may replace VKA but some of them also the initial parenteral anticoagulation. Deciding on the optimal duration of anticoagulation is based on the risk of recurrence and of bleeding in case anticoagulation is continued.

Despite considerable advances in the identification of new risk factors for (recurrent) VTE, predicting the risk of recurrence in an individual patient remains a challenge.

Regarding the new oral anticoagulants, data on the bleeding risk during long term secondary thromboprophylaxis in patients with VTE are limited. Given their overall excellent antithrombotic effect, one cannot expect that the bleeding risk will be negligible. Thus, stratification of patients according to the recurrence risk and discriminating those in need of prolonged anticoagulation because of a high recurrence risk from those with a low recurrence risk who may stop anticoagulation will remain of major clinical relevance.

Conflict of interest

The author declares that she has received speakers honoraria form Baer, Boehringer-Ingelheim, Daichii-Sankyo, Pfizer.

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A Danish follow-up study

Drinking alcohol to lower the risk of venous thrombosis?

Wine and beer in moderate doses may protect against venous thrombosis, but consumption of more than 14 standard drinks per week increases the risk of the same condition, in particular pulmonary embolism, in men and women, found Marianne Tang Severinsen, Aalborg University Hospital, Denmark, whose paper is published in *Thrombosis and Haemostasis*.

When asked why she and her colleagues did the Danish follow-up study, the researcher explained that while it is well established that low to moderate drinking is associated with a lower risk of arterial thrombosis, data on its effect on venous thromboembolism are limited and the results are inconsistent. Yet venous thromboembolism, deep-vein thrombosis and pulmonary embolism are multifactorial diseases that share several risk factors with arterial thrombosis such as age, obesity and smoking. It was assumed that alcohol consumption may reduce the risk of idiopathic venous thromboembolism because it exerts antithrombotic effects by decreasing platelet aggregation, increasing tissue plasminogen activator levels and lowering fibrinogen levels.

Heavy drinking, however, may provoke venous thromboembolism if mediated through cancer. „We aimed to assess the association between venous thromboembolism and average daily alcohol intake, types of alcohol, and alcohol drinking patterns in men and women,“ she said. The study involved 27,178 men and 29,876 women and the median follow-up time was 10.2 years.

The paper’s main conclusions in a nutshell – The findings of the study were significant for men but not for women: There may be a small protective effect of moderate alcohol consumption on the risk of venous thrombosis in men who drink between four to 14 drinks per week. Apparently they have a lower risk of venous thrombosis than those who consume more or less liquor. When beer and wine drinkers were compared with each other in regard to total alcohol consumption, no differences in risks were found. Wine and beer drinkers alike benefitted from a small beneficial effect of moderate alcohol intake. Thus the authors concluded that either wine or beer in moderate doses seems to protect against venous thromboses in men. Yet intake of more than 14 standard drinks per week should be avoided.

Reference