An evidence based approach to optimizing anticoagulant strategies
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Chapter 4

Relation between quality of anticoagulant treatment and the development of the post-thrombotic syndrome

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Abstract

Background About 30% of patients with an episode of adequately treated deep venous thrombosis develop the post-thrombotic syndrome within two years. During treatment with vitamin K antagonists patients spend only 60% of time in the target range. This sub-optimal quality might be related to inadequate clot-dissolution. We hypothesized that patients who spend a large amount of their time beneath this range will have an increased risk for the post-thrombotic syndrome.

Methods The time spent beneath the therapeutic range was calculated for patients with a first episode of deep venous thrombosis, who were treated with vitamin K antagonists for at least three months. At follow-up assessments for a maximum of 5 years, presence and severity of signs and symptoms of the post-thrombotic syndrome were recorded.

Results A total of 244 patients were included for analysis. Of these, 81 (33%) developed the post-thrombotic syndrome. The multivariate model showed that patients who spend more than 50% of their time beneath an INR level of 2.0 are at higher risk for post-thrombotic syndrome (OR: 2.6, 95% CI 1.4 to 4.7).

Conclusions Low quality treatment with vitamin K antagonists, which is a common condition, is related to the occurrence of the post-thrombotic syndrome in patients with deep venous thrombosis. Strategies aimed at improving the quality of long-term anticoagulation might have the potential to reduce the incidence of this complication.
Introduction

Following a first episode of deep venous thrombosis of the lower extremities, almost 20% of the patients suffer a recurrent thromboembolic event and 20 to 50% develop the post-thrombotic syndrome within two years.\textsuperscript{1,2} In contrast with the extensive evaluation of risk factors for recurrent venous thromboembolism, little is known about predictors for the development of the post-thrombotic syndrome.

Although the pathophysiology of the post-thrombotic syndrome is controversial, persistent venous obstruction, valve damage, and an impaired microcirculation in the veins are thought to play a role.\textsuperscript{3,4} The usual treatment of deep venous thrombosis is anticoagulation, which is started with unfractionated or low-molecular-weight heparin followed by vitamin K antagonists. Introduction of treatment with vitamin K antagonists apparently resulted in a decrease of the occurrence of a post-thrombotic syndrome.\textsuperscript{5} Inadequate dissolvement of the thrombus might lead to increased venous obstruction and valve damage. However, in several studies it has been shown that patients, even in the setting of randomized clinical trials, spend on average only 60% of their time in the therapeutic range.\textsuperscript{6,7} This sub-optimal quality might be related to inadequate clot-dissolvement. Therefore, we hypothesized that patients who spend a large amount of their time beneath the therapeutic range while on oral anticoagulation will have an increased risk for the development of the post-thrombotic syndrome. This hypothesis was tested in a cohort of patients with an episode of deep venous thrombosis who were treated with vitamin K antagonists for three months and were followed for a maximum of five years.

Methods

\textit{Study population}

Consecutive out-patients with an objectively confirmed symptomatic episode of proximal deep venous thrombosis presenting at the department of Internal Medicine of the University Hospital of Padua (Italy) between March 1993 and January 1998 were potentially eligible if they met the following criteria: treatment with unfractionated or low-molecular-weight heparin for a minimum of five days; treatment with vitamin K antagonists which was started either directly or the next day and continued for at least three months with a target INR (International Normalized Ratio) range between 2.0 and 3.0; INR monitoring in the University Hospital of Padua and no history of ipsilateral deep venous thrombosis. Patients were excluded from the analysis if the follow-up period was not long enough (< 6 months) to record the development of post-thrombotic manifestations.

All patients were instructed to wear below-knee compression stockings (30-40 mmHg at the ankle) for at least two years. They were seen three and six months after the initial referral and thereafter returned to the hospital every six months for follow-up
assessments, or earlier if complications occurred between two visits. The maximum duration of follow-up was five years. If patients were suspected of a recurrent episode of deep vein thrombosis this was confirmed or rejected using an objective diagnostic work-up in order to distinguish recurrences from the post-thrombotic syndrome.

**Definition of post-thrombotic syndrome**

At each of the follow-up visits, the presence and severity of post-thrombotic signs and symptoms in the ipsilateral leg were scored by physicians using a validated scoring system. This score has been shown to have a good reproducibility, and correlates well with the patient's perception of the interference of their leg complaints with daily life. For this score five subjective symptoms (pain, cramps, heaviness, pruritus, paresthesia) and 6 objective signs (induration of the skin, oedema, hyperpigmentation, redness, pain during calf compression, new venous ectasia) were considered. For each item a score was given ranging from 0 (not present or minimal) to 3 (severe). In addition, the presence or absence of ulceration of the leg was assessed. A total score of 15 or more per visit on two consecutive visits or the presence of a venous ulcer indicated a severe post-thrombotic syndrome, while a total score of 5 to 14 per visit on two consecutive visits indicated a mild post-thrombotic syndrome. In all patients in whom the post-thrombotic syndrome was diagnosed recurrent deep venous thrombosis was ruled out as the cause of the complaints.

**Estimation of time spent in the therapeutic range**

The percentage time spent in the therapeutic INR range (INR 2.0 - 3.0) was calculated using linear interpolation. This method assumes that INR values between two consecutive measurements vary linearly from the first to the second measurement. If the number of days between two consecutive measurements exceeded 28, the INR was considered not predictable for the middle part of this interval. For example, if the time between two consecutive INR measurements was 32 days, the INR level in the four days in the middle of this interval was considered to be missing. If the number of days spent in the target INR range could not be calculated at all, patients were excluded from analysis.

**Statistical analysis**

The relationship between the occurrence of the post-thrombotic syndrome and the percentage time spent in the lowest INR category (INR < 2.0) was explored using logistic regression analysis. Using multivariate models, adjustments were made for the a priori defined baseline variables age, gender, presence of cancer and ipsilateral recurrences.
Results

A total of 300 patients was found eligible for inclusion. Of these, 56 were excluded because the follow-up period was shorter than six months. Characteristics of the remaining 244 patients are shown in Table 1. The median duration of follow-up was 4.9 years ranging from six months to 5.2 years.

Table 1 Patients characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n = 244</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ± SD</td>
<td>62.4 ± 16.3</td>
</tr>
<tr>
<td>Age &gt; 65 years (%)</td>
<td>126 (52)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>106 (43)</td>
</tr>
<tr>
<td>Presence of cancer (%)</td>
<td>44 (18)</td>
</tr>
<tr>
<td>Ipsilateral recurrence* (%)</td>
<td>16 (7)</td>
</tr>
<tr>
<td>Mean percentage time in target range ± SD</td>
<td>58.9 ± 29.2</td>
</tr>
</tbody>
</table>

SD denotes standard deviation
* during study period

Percentage time in INR range

Overall, approximately 60% of time was spent in the therapeutic range and 30% was spent beneath this range. A total of 69 of the 244 patients (28%) spent more than 50% of their time in the lowest INR category.

Post-thrombotic syndrome

Of the 244 patients, 81 patients (33%) developed any post-thrombotic syndrome. Of these, eight were severe including five who had an ulcer. Of those patients who developed a post-thrombotic syndrome, 43 already had complaints at the follow-up visit at six months, fifteen patients between six months and one year, fourteen patients between one and two years, and the remaining nine patients between two and four years. No further post-thrombotic syndrome was appreciated after the completion of four years of follow-up in any of the remaining patients.

Predictors of the post-thrombotic syndrome

The results of the univariate and multivariate analyses are depicted in Table 2. In the univariate analysis age (> 65 years versus ≤ 65 years), gender, ipsilateral recurrence, and time spent in the lowest INR range (≤ 50% versus > 50%) showed statistical significant association with the development of the post-thrombotic syndrome, while cancer had no statistical significant influence. When introduced as continuous variables, both time spent in the lowest INR range and age were statistically significant related to the occurrence of the post-thrombotic syndrome. Correspondingly, the odds ratios remained statistically significant, independent of the
cut-off level for the percentage of time spent in the lowest INR range and for age. The multivariate analysis (adjusted for gender and cancer) revealed that the occurrence of an ipsilateral recurrence (OR: 8.5, 95% CI 2.5 to 28.6), more than 50% of the time spent beneath an INR level of 2.0 (OR: 2.6, 95% CI 1.4 to 4.7), and age above 65 years (OR: 2.3, 95% CI 1.3 to 4.1) were related to the occurrence of the post-thrombotic syndrome.

**Table 2** Estimated risk for development of the post-thrombotic syndrome (univariate and multivariate analysis)

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th></th>
<th></th>
<th>Multivariate</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age &gt; 65 year</td>
<td>2.33</td>
<td>[1.34 - 4.05]</td>
<td>2.28</td>
<td>[1.27 - 4.10]</td>
<td></td>
</tr>
<tr>
<td>Female versus male</td>
<td>1.74</td>
<td>[1.00 - 3.01]</td>
<td>1.63</td>
<td>[0.90 - 2.95]</td>
<td></td>
</tr>
<tr>
<td>Cancer versus no cancer</td>
<td>1.05</td>
<td>[0.53 - 2.09]</td>
<td>1.17</td>
<td>[0.56 - 2.44]</td>
<td></td>
</tr>
<tr>
<td>% Time in lowest INR range*</td>
<td>2.43</td>
<td>[1.36 - 4.32]</td>
<td>2.56</td>
<td>[1.39 - 4.71]</td>
<td></td>
</tr>
</tbody>
</table>

INR denotes International Normalized Ratio; OR, Odds Ratio; CI, Confidence Interval

* more than 50% time versus less than 50% spent beneath the target range

The odds ratios for different cut-offs in percentage of time of an INR below 2.0 are shown in **Table 3**. There was a clear tendency for a higher risk of the post-thrombotic syndrome when the cut-off level for time spent in the lowest INR range was increased.

**Table 3** Risk of occurrence of post-thrombotic syndrome for different cut-offs in percentage of time spent in the lowest INR range

<table>
<thead>
<tr>
<th>Percentage time in lowest INR range</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 30% versus ≤ 30%</td>
<td>1.89</td>
<td>[1.10 - 3.23]</td>
</tr>
<tr>
<td>&gt; 40% versus ≤ 40%</td>
<td>2.12</td>
<td>[1.22 - 3.67]</td>
</tr>
<tr>
<td>&gt; 50% versus ≤ 50%</td>
<td>2.43</td>
<td>[1.36 - 4.32]</td>
</tr>
<tr>
<td>&gt; 60% versus ≤ 60%</td>
<td>2.55</td>
<td>[1.38 - 4.70]</td>
</tr>
<tr>
<td>&gt; 70% versus ≤ 70%</td>
<td>3.01</td>
<td>[1.46 - 6.20]</td>
</tr>
<tr>
<td>&gt; 80% versus ≤ 80%</td>
<td>2.89</td>
<td>[1.25 - 6.69]</td>
</tr>
<tr>
<td>&gt; 90% versus ≤ 90%</td>
<td>3.69</td>
<td>[1.29 - 10.53]</td>
</tr>
</tbody>
</table>

INR denotes International Normalized Ratio; OR, Odds Ratio; CI, Confidence Interval
Discussion

In this cohort study undertreatment with vitamin K antagonists, ipsilateral recurrence and old age were found to be significantly related to the development of post-thrombotic manifestations in patients suffering a first episode of deep venous thrombosis. Although ipsilateral recurrence gave a higher risk for the post-thrombotic syndrome than undertreatment with vitamin K antagonists, this complication was only present in 7% of the patients, while undertreatment with vitamin K antagonists was much more frequent, occurring in almost one third of patients.

Oral anticoagulants act by decreasing the blood tendency to coagulate. Although adequate anticoagulation with vitamin K antagonists cannot dissolve clots by itself, it can facilitate endogenous thrombolysis by preventing further thrombus growth, which might lead to improved recanalization and better preservation of venous valves. When intensity of treatment with vitamin K antagonists is beneath the target range for a large period of time, the potential for this beneficial effect is reduced. The increased incidence of post-thrombotic syndrome in patients with a treatment intensity that is inadequate indicates that such mechanisms might play a role in the pathophysiology of post-thrombotic syndrome.

Our results are consistent with those previously obtained in cohorts of patients with deep venous thrombosis who had a long-term observation. In both studies recurrent ipsilateral deep venous thrombosis was significantly related to the occurrence of the post-thrombotic syndrome. The latter study also reported on the quality of anticoagulation and the risk for the post-thrombotic syndrome. Also in that study an increased risk of the post-thrombotic syndrome was recorded in patients who had not received strict anticoagulation. As we could carefully quantify the duration of undertreatment and calculate the associated risk for the post-thrombotic syndrome, the results of our investigation fully support the hypothesis that a low anticoagulation quality is a predictor of late post-thrombotic sequelae.

Some methodological issues about our study require comment. Since the underlying hypothesis was conceived in retrospect, follow-up data of 56 patients could not be retrieved and therefore these patients were excluded. A very poor condition as well as feeling very good are plausible explanations for why patients did not return to the hospital. Unfortunately, we can only speculate about the reasons for these patients not to show up at follow-up visits. However, the incidence of the post-thrombotic syndrome in patients with an episode of venous thromboembolism observed in our study (33%) is comparable to the incidence observed in other studies. Therefore, it is not likely that not enrolling these patients has influenced the observed relationship between quality of anticoagulation and the development of the post-thrombotic syndrome.

Also, the issue of compliance needs to be addressed. The higher risk for the occurrence of the post-thrombotic syndrome can also be due to a temporary underuse
of elastic stockings. Wearing these stockings reduces the risk of the post-thrombotic syndrome by about 50%. It could be hypothesized that patients who did not wear the compression stockings were also the patients who did not take the medication very regularly, which might result in a poor quality of anticoagulation. However, recent data show that poor compliance is not related to the quality of oral anticoagulant therapy. Underuse of elastic stockings is not related to poor quality of treatment and therefore does not influence the relationship between quality of therapy and the development of the post-thrombotic syndrome.

What do our results imply? As improving the quality of oral anticoagulant treatment has the potential to prevent the development of the post-thrombotic syndrome, the anticoagulation level should be monitored more frequently and carefully as currently done.

In conclusion, both patients and their attending physicians should be alerted about the increased risk of late post-thrombotic manifestations following a low-quality treatment with vitamin K antagonists after an episode of deep venous thrombosis.

References