Treatment with vitamin K antagonists: patients' quality of life, valuations and adherence
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Citation for published version (APA):

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Chapter 2

Quality of life after venous thromboembolism

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Submitted for publication
Abstract

Objective
To assess the quality of life of patients who recently experienced an episode of venous thromboembolism, a major bleeding event during treatment with vitamin K antagonists, and patients with the post-thrombotic syndrome, and to compare it with normative data of a Dutch reference population.

Methods
Patients completed a questionnaire on quality of life (SF-36) and demographics.

Results
Compared to the reference population, patients with venous thromboembolism (n=52) reported significantly lower scores on all SF-36 dimensions, except for mental health. Patients with a major bleeding event (n=14) were significantly impaired on all dimensions, except for role limitations due to emotional problems and mental health. For patients with the post-thrombotic syndrome (n=47) quality of life was significantly impaired on the physical aspects, but not on social functioning, role limitations due to emotional problems and mental health.

Conclusion
Venous thromboembolism and major bleeding have a significant impact on the physical and social aspects of quality of life, but less so on psychological functioning. The post-thrombotic syndrome predominantly affects the physical aspects of quality of life. The results of this study can help physicians inform patients on the impact of the possible outcomes after venous thromboembolism.
Introduction

Venous thromboembolism is a serious disease with an estimated annual incidence of 1 per 1000 persons [1]. Patients are at risk for several complications. They can develop recurrent venous thromboembolism which can manifest itself as pulmonary embolism or deep-vein thrombosis. In addition, patients can develop a post-thrombotic syndrome as a chronic complication of an episode of venous thromboembolism, which is strongly related to recurrent deep-vein thrombosis [2].

To prevent recurrent thromboembolic events, patients are usually treated with vitamin K antagonists for three to six months [3]. During vitamin K antagonist treatment, patients are at an increased risk for major bleeding [4]. To maintain an optimal balance between the risks of recurrences and the risk of bleeding, regular laboratory control of the intensity of vitamin K antagonist therapy and subsequent dose-adjustments are necessary. For these reasons, treatment with vitamin K antagonists can be inconvenient for patients. A study by Lancaster et al. [5] has shown, however, that vitamin K antagonist therapy is not associated with a decrease in quality of life, unless a bleeding episode has occurred.

The optimal duration of treatment with vitamin K antagonists is often debated. Determining the optimal duration of treatment requires a weighing of the effectiveness of treatment as well as the risks to patients. Due to lack of information on how venous thromboembolism, its chronic sequela and treatment-related bleeding affect patients’ lives, it is difficult for physicians and patients to make decisions on the duration of treatment with vitamin K antagonists. To determine the impact of venous thromboembolism, treatment-related bleeding and the post-thrombotic syndrome, we assessed the quality of life of patients who had recently experienced an episode of venous thromboembolism, a major bleeding event during treatment with vitamin K antagonists, and patients with the post-thrombotic syndrome, and compared it with the quality of life of a Dutch reference population.

Materials and methods

Patients

Three groups of eligible patients were recruited between October 2000 and June 2002. The first group consisted of patients who had experienced an episode of venous thromboembolism in the previous two weeks. The second group comprised patients who had experienced an episode of major bleeding during treatment with vitamin K antagonists in the previous two weeks. Eligible for the third group were patients with the post-thrombotic syndrome, diagnosed at least one year after an
Quality of life after venous thromboembolism.

The diagnosis of deep-vein thrombosis was established using compression ultrasonography or venography. The diagnosis of a pulmonary embolism was established by either perfusion-ventilation lung scan or pulmonary angiography. Major bleeding was defined as: bleeding leading to a fall in the hemoglobin level of at least 1.25 mmol/L, bleeding that required a blood transfusion or hospital admission, and bleeding leading to residual complaints. For the diagnosis of the post-thrombotic syndrome we used a clinical scale, previously used by Brandjes et al. [6]. This scale categorises the post-thrombotic syndrome into mild/moderate and severe. Excluded were patients younger than 18 years, patients with cancer or other serious co-morbidity, as well as patients with an insufficient knowledge of the Dutch language.

The study was performed in three academic centres: the Academic Medical Centre in Amsterdam, the University Hospital of Groningen and the University Hospital of Maastricht. In each centre, the study had been approved by the respective institutional review board.

Quality of life
To assess generic quality of life, the validated Dutch version of the Medical Outcomes Study 36 item Short Form Health Survey (SF-36) was used [7,8]. The time frame employed was the previous week. The SF-36 measures eight components of health: physical functioning, role limitations due to physical health problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems and mental health. All scale scores were linearly converted to a 0 to 100 scale, with higher scores indicating better levels of quality of life. Patients’ SF-36 scores were compared with published age- and sex-matched Dutch reference population norms [8].

Procedure
Patients were invited to the study by a physician or a research nurse, who explained the purpose of the study. After written informed consent had been obtained, patients were handed over a questionnaire, assessing quality of life and some demographic variables. They were asked to return this questionnaire by mail, within two weeks.

Analyses
Differences in demographic characteristics between patients with venous thrombo-
embolism, major bleeding and the post-thrombotic syndrome were tested using Mann Whitney U tests and Chi square tests. Average SF-36 scores of the three groups were compared by means of one-way analyses of variance, adjusting for age and sex. The eight dimensions of the SF-36 were converted to standard scores on the basis of the scores of the age- and sex-matched representative reference sample of the Dutch population. Mean standardised differences were calculated by dividing the difference between patients’ average SF-36 score and the mean score of the matched reference population by the standard deviation of the reference population. Such mean standardised differences indicate how many standard deviations the observed mean on a SF-36 dimension falls below or above the mean of the reference population. Mean standardised differences can be interpreted in terms of Cohen’s effect sizes [9]: a mean standard score of 0.20 is considered to indicate a small deviation from the reference population, while mean standard scores of 0.50 and 0.80 can be considered to indicate moderate and large deviations from the reference population, respectively. Differences between the mean scores of the three groups and the Dutch reference population were tested for significance using the one-sample t-test, by testing whether mean standard scores from the three patient groups were significantly different from zero. In all tests, p-values <0.05 were considered statistically significant.

Results

Patients

Of 148 eligible patients, 117 (79%) agreed to participate. Four patients died, before they could return the questionnaire. For the analyses, questionnaires of 52 patients with venous thromboembolism, 14 patients with a major bleeding event and 47 patients with the post-thrombotic syndrome were available. The median time between diagnosis and completion of the questionnaires was 8 days (range 0-30 days) for patients with venous thromboembolism and 9 days (range 0-26 days) for patients who had experienced a major bleeding event. For patients with the post-thrombotic syndrome time between diagnosis and completion of the questionnaire was not assessed.

Patient characteristics are presented in Table 1. The three groups of patients did not differ significantly in terms of age, sex, marital status or educational level. Of patients with venous thromboembolism, 38 (73%) had experienced an episode of deep-vein thrombosis and 14 (27%) had experienced pulmonary embolism. Patients
with a major bleeding event had been treated with vitamin K antagonists for the following reasons: prosthetic heart valves (6), venous thromboembolism (3), heart valve disease (2), myocardial infarction (2), and peripheral arterial disease (1). Of these 14 patients, 8 (57%) had a bleeding of the gastro-intestinal tract, 2 (14%) an intracranial bleeding and 4 patients (29%) had experienced another type of bleeding event. Thirty-three patients (70%) had a mild/moderate and 14 patients (30%) had a severe post-thrombotic syndrome.

Quality of life
Average SF-36 scores for the three groups of patients and the Dutch reference population are presented in Table 2. Quality of life did not differ significantly between patients with different manifestations of venous thromboembolism (deep-vein thrombosis versus pulmonary embolism) nor between patients with either a mild/moderate or a severe post-thrombotic syndrome. Quality of life was significantly

<table>
<thead>
<tr>
<th>Table 1 Patient characteristics</th>
<th>VTE (N=52)</th>
<th>MB (N=14)</th>
<th>PTS (N=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>25 (48%)</td>
<td>6 (43%)</td>
<td>21 (45%)</td>
</tr>
<tr>
<td>Mean Age (±SD), years</td>
<td>53 (±16)</td>
<td>60 (±14)</td>
<td>49 (±14)</td>
</tr>
<tr>
<td>Married</td>
<td>25 (48%)</td>
<td>8 (57%)</td>
<td>29 (62%)</td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>21 (41%)</td>
<td>6 (43%)</td>
<td>15 (32%)</td>
</tr>
<tr>
<td>Medium</td>
<td>17 (33%)</td>
<td>7 (50%)</td>
<td>21 (45%)</td>
</tr>
<tr>
<td>High</td>
<td>13 (26%)</td>
<td>1 (7%)</td>
<td>11 (23%)</td>
</tr>
</tbody>
</table>

VTE: venous thromboembolism; MB: Major Bleeding; PTS: post-thrombotic syndrome.

| Table 2 Mean quality of life scores (SF-36) for the three patient groups and the Dutch reference population |
|-------------------------------------------------------------------------------------------------|------------------------------------------|------------------------------------------|------------------------------------------|
| VTE (N=52)                                           | MB (N=14)                               | PTS (N=47)                               | Reference population                     |
| Physical functioning                                 | 55.1 (30.3)                             | 34.0 (33.1)                              | 71.0 (20.8)                              | 83.0 (22.7)                             |
| Role functioning physical                           | 24.0 (38.1)                             | 16.1 (36.2)                              | 58.0 (43.0)                              | 76.4 (36.2)                             |
| Pain                                                | 43.9 (25.3)                             | 43.3 (36.5)                              | 65.4 (23.0)                              | 74.8 (23.4)                             |
| General Health                                      | 56.7 (19.4)                             | 37.4 (26.8)                              | 57.3 (21.2)                              | 70.7 (20.6)                             |
| Vitality                                            | 48.4 (27.2)                             | 38.7 (29.0)                              | 59.1 (24.1)                              | 68.6 (19.3)                             |
| Social functioning                                  | 59.3 (32.5)                             | 38.4 (30.0)                              | 80.6 (24.1)                              | 84.2 (22.4)                             |
| Role functioning emotional                          | 49.0 (45.7)                             | 50.0 (48.2)                              | 72.0 (35.1)                              | 82.4 (32.8)                             |
| Mental health                                       | 69.3 (25.1)                             | 65.4 (26.1)                              | 76.5 (17.8)                              | 76.9 (17.4)                             |

VTE: venous thromboembolism; MB: Major Bleeding; PTS: post-thrombotic syndrome.
Quality of life scores range from 0 to 100. Higher scores indicate better quality of life.
more impaired in patients with venous thromboembolism and major bleeding than in patients with the post-thrombotic syndrome.

Patients with venous thromboembolism, major bleeding and the post-thrombotic syndrome reported lower levels of quality of life than the reference population (Fig. 1.). For patients with venous thromboembolism, quality of life was significantly impaired on all dimensions of the SF-36, except for mental health. In these patients, mean standardised differences were moderate to large and ranged from -0.4 for mental health to -1.7 for physical functioning. Patients with major bleeding reported statistically significantly lower scores than the reference population on all SF-36 dimensions, except for role limitations due to emotional problems and mental health. In this patient group, mean standardised differences were moderate to large and ranged from -0.5 (mental health) to as large as -1.9 (physical functioning, social functioning). For patients with the post-thrombotic syndrome quality of life was significantly impaired on the physical aspects, with mean standardised differences ranging from -0.4 for pain to -0.9 for physical functioning. Social functioning, role limitations due to emotional problems, and mental health were not significantly impaired in this patient group. The mean standardised differences for these dimensions were small (-0.3, -0.2 and 0.0, respectively).

![Figure 1](image_url)

**Figure 1** Quality of life (SF-36) of patients with venous thromboembolism, a major bleeding event and post-thrombotic syndrome (n=113), relative to the Dutch reference population. Mean standardised differences of <0 indicate worse quality of life than the reference population. Scores of -0.2, -0.5, and -0.8 indicate a small, moderate, or large deviation from the reference population respectively. * p<0.05, patient group versus the Dutch reference population. # No deviation from the reference population. VTE: venous thromboembolism; MB: major bleeding event; PTS: post-thrombotic syndrome.
Discussion

In this study, patients with venous thromboembolism, a major bleeding during treatment with vitamin K antagonists and patients with the post-thrombotic syndrome reported lower levels of quality of life than an age- and sex-matched Dutch reference population. Quality of life was more impaired in patients with venous thromboembolism and major bleeding than in patients with the post-thrombotic syndrome.

To our knowledge, the impact of pulmonary embolism on generic quality of life has not been previously assessed. The effect of deep-vein thrombosis on generic quality of life has previously been evaluated in two clinical trials assessing the effectiveness of low-molecular-weight heparin versus standard heparin. O'Brien et al. [10] compared patients' scores on the SF-36 with scores of an age-matched reference population. In this study, patients with deep-vein thrombosis also reported lower levels of quality of life than the reference population. Koopman et al. [11] assessed the impact of deep-vein thrombosis at four points in time: the day of the diagnosis, after one to two weeks, after three months and after six months. Quality of life improved over time, regardless of the initial type of treatment. Although in that study the scores of the SF-20 were not compared to a reference population, the results of the study suggest that deep-vein thrombosis affects quality of life adversely.

The impact of a bleeding event, due to vitamin K antagonist treatment has been studied in one previous study [5]. Patients who had experienced an episode of bleeding during vitamin K antagonist treatment had worse perceptions of their health than patients who had not experienced a bleeding event.

The impact of the post-thrombotic syndrome has been previously investigated in two studies [12,13]. Kahn et al. [12] did not find a significant effect of the post-thrombotic syndrome on generic quality of life: the SF-36 scores of patients with the post-thrombotic syndrome were similar to normative scores of an age- and sex-matched reference population. Beyth et al. [13] administered a questionnaire containing three subscales of the SF-36, six to eight years after an episode of deep-vein thrombosis. Patients who reported symptoms of the post-thrombotic syndrome had worse perceptions of their general health, lower levels of physical functioning, and more severe role limitations due to physical health than patients without symptoms, which is in line with our results.

It should be noticed that of the 148 patients eligible for our study, 19% (12/64) of patients with venous thromboembolism, 52% (15/29) of patients with major
bleeding and 15% (8/55) of patients with the post-thrombotic syndrome were not willing or able to participate. This could be related to poor health status and may, therefore, have underestimated our results. Consequently, patients’ quality of life might be more impaired than we have found in this study.

As we wanted to determine the impact of venous thromboembolism, major bleeding and the post-thrombotic syndrome, we excluded patients with cancer or other serious co-morbidity from the study. We feel that inclusion of these patients could have caused serious confounding, as these co-morbid conditions could independently affect quality of life.

We are well aware that we assessed the quality of life of patients with acute conditions (venous thromboembolism and major bleeding) and patients with a chronic condition (post-thrombotic syndrome). Quality of life of patients with venous thromboembolism and patients with a major bleeding event is expected to improve over time. In patients with the post-thrombotic syndrome quality of life might change time over time. The purpose of this study was to determine the impact of different outcomes related to venous thromboembolism. Further research is needed to evaluate the course of quality of life of patients with venous thromboembolism, a major bleeding event related to treatment with vitamin K antagonists, and patients with the post-thrombotic syndrome.

Treatment with vitamin K antagonists lowers the risk of recurrent venous thromboembolism and possibly the post-thrombotic syndrome at an increased risk of bleeding. In this study, we demonstrated that nonfatal episodes also affect quality of life. Venous thromboembolism and major bleeding had a significant impact on the physical and social aspects of quality of life, but not on psychological functioning. The post-thrombotic syndrome was found to affect the physical aspects of quality of life. Decisions to stop or extend treatment, therefore, require a careful balancing of all risks as well as the impact on quality of life [14]. We feel that health professionals should explicitly seek patients’ views on health states associated with venous thromboembolism and its treatment with vitamin K antagonists. The results of this study can help physicians to inform patients on the impact of the possible outcomes after venous thromboembolism.

**Acknowledgements**

The authors thank Mrs. M. Laumann, Mrs. P. Mentink and Mrs. M. Voskuilen for their assistance in collecting the data, the physicians for their support in approaching their patients, and the patients for their contribution to this study.
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