Treatment with vitamin K antagonists: patients'quality of life, valuations and adherence

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Publication date
2004

Summary

After a first episode of deep-vein thrombosis or pulmonary embolism (venous thromboembolism) patients are usually treated with an initial course of heparin. Treatment with vitamin K antagonists is started concomitantly and continued for three to six months to prevent recurrent venous thromboembolism. During vitamin K antagonist therapy patients have a tendency to bruise and bleed more readily and they have an increased risk of major bleeding. The optimal duration of treatment with vitamin K antagonists in patients with a first episode of venous thromboembolism is therefore often debated. Decisions on the duration of treatment with vitamin K antagonists after venous thromboembolism require a weighing of the benefits and risks of treatment, including an evaluation of the impact of these outcomes on patients' lives. The main objectives of this thesis were to examine the health-related quality of life of patients with venous thromboembolism and patients treated with vitamin K antagonists; to assess patients' valuations of relevant health states associated with venous thromboembolism and vitamin K antagonist therapy and patients' treatment preferences; and to assess the relationship between patients' self-reported adherence and the quality of treatment with vitamin K antagonists.

Chapter 1 constitutes a short introduction on treatment of venous thromboembolism with vitamin K antagonists; health-related quality of life; the valuation of health outcomes; and adherence to vitamin K antagonist therapy.

In the first part of this thesis we present studies examining the health-related quality of life (HRQOL) of patients treated with venous thromboembolism and patients treated with vitamin K antagonists. **Chapter 2** describes a study on HRQOL in 52 patients with venous thromboembolism, 14 patients with a major bleeding event during treatment with vitamin K antagonists, and 47 patients with the post-thrombotic syndrome. HRQOL was assessed with the SF-36 and compared with data of a Dutch reference population. Compared to the reference population, patients with venous thromboembolism reported significantly lower scores on all SF-36 dimensions, except for mental health. Patients with a major bleeding event were significantly impaired on all dimensions, except for role limitations due to emotional problems and mental health. For patients with the post-thrombotic syndrome HRQOL was significantly impaired on the physical aspects, but not on social functioning, role limitations due to emotional problems or mental health. In conclusion, venous thromboembolism and major bleeding were found to have a significant impact on the physical and social aspects of HRQOL, but less so on psychological functioning.

The post-thrombotic syndrome predominantly affects the physical aspects of HRQOL. The results of this study can help physicians inform patients on the impact of the possible outcomes after venous thromboembolism.

Chapter 3 examines the extent to which HRQOL in patients with deep-vein thrombosis is affected adversely by treatment with vitamin K antagonists. In addition, we explored which factors were associated with the duration of treatment with vitamin K antagonists. The course of HRQOL was explored in 216 patients treated for three months and compared with the course of HRQOL in 144 patients treated for six months with vitamin K antagonists. HRQOL was assessed on the day of diagnosis, after one to two weeks, three and six months. HRQOL improved over time. Overall, no differences in HRQOL were found between the two patient groups. Regression analyses indicated that an increased duration of treatment with vitamin K antagonists was associated with the presence of one or more permanent risk factors, duration of hospitalisation, poor mobility prior to deep-vein thrombosis and study centre. Interestingly, treatment duration was not associated with HRQOL. Study centre was found to be the most influential factor associated with treatment duration, implying that local policy has a major influence on decisions regarding the duration of treatment with vitamin K antagonists.

Chapter 4 describes a study examining the effect of potential determinants of HRQOL in patients with deep-vein thrombosis. The study sample comprised 400 patients participating in a multi-centre clinical trial. HRQOL was assessed on the day of diagnosis, after one to two weeks, three and six months. Effects of socio-demographic, disease-related and treatment-related variables were investigated through multilevel mixed modelling. HRQOL was found to be most impaired in women, older patients, and patients with extensive thrombosis. Co-morbidity and the quality of treatment of patients treated for six months with vitamin K antagonists affected overall quality of life, physical functioning and health perception adversely. Pain and thrombosis complaints were not associated with co-morbidity and quality of treatment with vitamin K antagonists. Symptom duration, initial treatment with heparin and the duration of treatment with vitamin K antagonists rarely affected patients' HRQOL. The results of this study may enable physicians to provide patients with information on quality of life after deep-vein thrombosis.

The second part of this thesis is directed at the valuation of outcomes related to venous thromboembolism and treatment with vitamin K antagonists. In **chapter 5** patients' valuations for health states associated with venous thromboembolism

and its treatment with vitamin K antagonists are reported, along with patients' treatment preferences. A total of 53 patients who had experienced venous thromboembolism, 23 patients who had experienced major bleeding during treatment, and 48 patients with the post-thrombotic syndrome were interviewed. Valuations of outcomes after venous thromboembolism were elicited on a scale ranging from 0 (tantamount to death) and 1 (tantamount to perfect health). Patients' treatment preferences were evaluated using treatment trade-off questions. Median health state valuations ranged from 0.33 for 'non-fatal haemorrhagic stroke' to 0.96 for 'no vitamin K antagonist therapy'. Variability in health state valuations between patients was substantial. Patients' treatment preferences also varied: 25% of patients would choose for cessation of treatment, regardless the probability of recurrent venous thromboembolism presented, whereas 23% of patients would always choose for continuation of treatment. Differences in valuations and treatment preferences were not associated with type of event experienced. Due to the substantial and unpredictable variability in valuations and treatment preferences, recommendations regarding treatment duration should be tailored to patients' specific values and concerns.

In **chapter 6** we report on the effects of different durations of treatment with vitamin K antagonists on the (quality-adjusted) life expectancy after a first episode of venous thromboembolism. In a Markov decision-analytic model, the risks of thromboembolic and treatment-related complications as well as patients' health state valuations were incorporated. Life expectancy and quality-adjusted life expectancy were calculated for different durations of treatment and a number of subgroups of patients. For patients with an idiopathic first episode of deep-vein thrombosis, there was an almost nonexistent increase in quality-adjusted life expectancy of 0.03 years when treatment duration was prolonged after six months up to one year, and an increase of 0.20 years in case of lifelong treatment. For patients presenting with idiopathic pulmonary embolism the changes were 0.14 and 2.54 years, respectively. A sensitivity analysis showed that the optimal duration of treatment was sensitive to the patients' perceived burden of treatment. Although prolongation of treatment with vitamin K antagonists can be expected to increase longevity, the changes in life expectancy do not always outweigh the downsides of treatment, in particular the burden of therapy. As most changes in quality-adjusted life expectancy will be small and dependent on the patients' valuations of health states, there is room for individually tailoring the duration of treatment with vitamin K antagonists.

In **chapter 7** three valuation methods – the conventional time trade-off, the chained time trade-off and direct rating – are compared for the evaluation of temporary health states associated with venous thromboembolism and vitamin K antagonist therapy. Eighty-four patients treated with vitamin K antagonists were interviewed twice. During the first interview values for five temporary health states were obtained with a rank ordering procedure, direct rating and the chained TTO method. During the second interview either the first interview was repeated (N=30), or health state values were obtained with the conventional TTO method (N=54). Consistency was assessed by comparing the three valuation methods with the rank ordering procedure. Generalisability theory was used to assess reliability. The three methods produced significantly different valuations of health states. Chained time trade-off values were higher than values obtained with direct rating and the conventional time trade-off. Consistency and reliability did not differ across the three methods. As direct rating is simpler to administer than both time trade-off methods, one could consider using direct ratings for the valuation of temporary health states. Time trade-off values are often preferred over direct ratings for the use in formal decision analyses. Therefore, biases associated with the conventional and the chained time trade-off method are discussed.

The third part of this thesis addresses adherence to vitamin K antagonist therapy. In **chapter 8** we present a study in which we examined the association between self-reported adherence and the quality of treatment with vitamin K antagonists. Eligible patients had been diagnosed with atrial fibrillation and were treated with acenocoumarol for at least six months between January 15th and August 19th 2002 at the Thrombosis Service in 's Hertogenbosch, the Netherlands. The percentage of time spent in the target range during the last three months was calculated for 1323 patients using linear interpolation. Forty patients who spent 100% (high-quality group) and 40 patients who spent less than 50% of time in the target range (low-quality group) were approached for the study. Adherence was assessed with a self-report instrument administered by mail. Twenty-seven patients with high and 29 patients with low therapeutic quality returned the questionnaire. No differences in adherence were found between the high-quality group and the low-quality group. These results suggest that self-reported adherence is not related to time spent in the therapeutic target range in patients with atrial fibrillation treated with vitamin K antagonists.

Future research

The results of the studies presented in this thesis emphasise the need for patient involvement when deciding to stop or extend treatment with vitamin K antagonists after a first episode of venous thromboembolism. The question arises how patients are to be involved in decision making. As a starting point, physicians need to offer patients the opportunity to participate. This does not appear to be common practice yet [1,2]. In this thesis, policy of the health care centres appeared to have a great influence on decisions regarding the duration of treatment with vitamin K antagonists. This could indicate that physicians adhere to anticoagulation guidelines regardless of patients' preferences. To enhance patient involvement and to improve the provision of information, decision aids have been devised. Decision aids are explicit about the therapeutic choice patients have. They provide detailed descriptions of clinically important outcomes, together with quantitative information about the likelihood of these outcomes and encourage patients to state their preference for a treatment strategy. Beneficial effects of decision aids have been suggested with regard to treatment adherence, patient satisfaction, clinical outcomes and quality of life [3]. Future research regarding the duration of treatment with vitamin K antagonists should focus on the development of a decision aid which can provide patients with individualised information on the benefits and risks of treatment. If the decision aid turns out to be feasible and acceptable to both patients and physicians efforts should be mounted to implement it in clinical practice.

References

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