Treatment with vitamin K antagonists: patients' quality of life, valuations and adherence
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Chapter 1

General introduction
Chapter 1

Treatment of venous thromboembolism with vitamin K antagonists

Venous thromboembolism is a common disease, with an estimated incidence of 1 per 1000 persons per year [1]. Well recognized risk factors for venous thromboembolism include surgery, trauma, immobilization, cancer and thrombophilic disorders [2]. The clinical spectrum ranges from deep-vein thrombosis in the leg to fatal pulmonary embolism. A common consequence of deep-vein thrombosis is the post-thrombotic syndrome, with symptoms ranging from discoloration to pain and ulceration [3].

The initial treatment of venous thromboembolism consists of either subcutaneous low-molecular-weight heparin or intravenous unfractionated heparin, whereas treatment with vitamin K antagonists is generally prescribed for secondary prophylaxis [4]. The efficacy of the combination of heparin and oral administered vitamin K antagonists for treatment of venous thromboembolism was demonstrated in a landmark study published in 1960 by Barritt and Jordan [5].

During vitamin K antagonist therapy, the risk of recurrent venous thromboembolism is effectively reduced [6]. Unfortunately, treatment with vitamin K antagonists is also associated with an increased risk of bleeding [7]. To maintain an optimal balance between the risk of recurrences and the risk of bleeding complications during treatment, 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 and difficult to adhere to.

The usual duration of treatment with vitamin K antagonists in patients with a first episode of venous thromboembolism is three to six months, but this treatment period is often debated. To determine the optimal duration of treatment with vitamin K antagonists after venous thromboembolism, the risk of recurrence has to be balanced not only against the risk of bleeding but also against the burden of treatment with vitamin K antagonists.

Due to lack of information on how venous thromboembolism and its treatment affect patients' lives, it is difficult for physicians and patients to make evidence-based decisions on the duration of treatment with vitamin K antagonists. This thesis contains a series of studies of the effect of venous thromboembolism and treatment with vitamin K antagonists on health-related quality of life, of the valuation of health outcomes related to venous thromboembolism, and of self-reported adherence of patients treated with vitamin K antagonists.
General introduction

Health-related quality of life

Health-related quality of life (HRQOL) is increasingly recognised in clinical research as an important outcome of disease and treatment. It is frequently used as a supplement to more traditional clinical outcome measures. Although there is no generally accepted definition of HRQOL, there is consensus that HRQOL should be regarded as a multidimensional construct incorporating at least three broad domains that can be affected by one's disease or treatment: physical, psychological and social functioning [8].

Most instruments in HRQOL research can be classified as generic or disease-specific questionnaires. Generic instruments are intended to be used across a wide range of disease populations. The major advantage of these instruments is that they allow for comparison of results across different patient populations. Examples of generic instruments are the Sickness Impact Profile (SIP) [9] and the Medical Outcomes Study 36 item Short Form Health Survey (SF-36) [10]. In contrast to generic instruments, disease-specific HRQOL instruments address issues relevant to a specific patient population. These measures are more likely to be responsive to disease-related changes in HRQOL than generic instruments. Efforts have been mounted to develop a wide range of disease-specific instruments for the use in clinical research.

Several HRQOL instruments for patients with chronic venous disorders of the leg have been developed [11-13]. Only one questionnaire has been specifically designed for use in patients with deep-vein thrombosis [14]. In this thesis, we used data collected in a large clinical trial in patients with venous thrombosis between October 1992 and September 1994. At that time, no disease-specific questionnaire for patients with deep-vein thrombosis was available. Therefore, an adapted version of the Rotterdam Symptom Checklist [15], originally developed for cancer patients, was used to assess disease-specific HRQOL.

Little is known about the impact of venous thromboembolism, the post-thrombotic syndrome, treatment with vitamin K antagonists and treatment-related bleeding on HRQOL [16]. The general objective of the first part of this thesis is to examine the HRQOL of patients with venous thromboembolism and patients treated with vitamin K antagonists.
The valuation of health outcomes

HRQOL instruments have been developed for describing patients' health states. These instruments do not take into account the trade-off patients make between the benefits and side-effects of treatment. For this purpose an instrument to evaluate health states is needed. With a health state valuation method patients can numerically express their valuation of potential health outcomes of disease and treatment. Such valuations are needed to define an optimal treatment strategy.

The most commonly used health state valuation methods are the standard gamble, the time trade-off and direct rating [17]. The standard gamble method produces values that can be termed 'utilities', because they are elicited under conditions of risk and uncertainty. In the standard gamble, the patient is asked to choose between a certain - but imperfect - health state, and a gamble between perfect health and death. In the gamble there is a probability of living in perfect health (p), and a probability of immediate death (1-p). These probabilities are systematically varied, until the patient reports indifference between the two options. The value of the health state under evaluation then equals the value of p at which the patient reports indifference.

The time trade-off method was developed by Torrance [18] as a less complicated, conceptually different, alternative to the standard gamble. It is based on trade-offs similar to those of the standard gamble, but the concept of probability is replaced by time. In the time trade-off, the patient is asked to choose between a fixed duration of time (t) in the health state to be evaluated and a variable amount of time (x) in perfect health; both health states are followed by death. The amount of time in perfect health is varied until the patient reports indifference between the two options. The value of the health state is then calculated by dividing x by t.

With direct rating the patient is asked to place a mark on a line anchored by death (0) and perfect health (100) to indicate the value of the health state under evaluation. This value is rescaled from 0 to 1.

Temporary health states cannot be measured in the conventional way by means of the time trade-off and the standard gamble, where health states are chronic and followed by death. Instead of using conventional methods, valuations for temporary health states can be measured by means of a chained procedure. With the chained procedure, introduced by Torrance [17], the health state to be evaluated is not weighed directly against death and perfect health, but in a two step procedure using an intermediate anchor health state.
Patients’ valuations of the outcomes of a treatment strategy can be incorporated into formal decision analyses. By combining the health state values of the different outcomes with length of survival, the expected value of the treatment strategy can be expressed in terms of quality-adjusted life years (QALYs) [19]. QALYs reflect the level of desirability of treatment strategies with respect to quality and length of life [20].

The QALY approach is primarily used for decision-making at the policy level. A method that may be more suitable for decision-making at the individual level is the treatment preference method [20]. In the treatment preference method the patient is asked to choose between two treatment options. Both options are described in terms of benefits, risks, and the respective probabilities of these outcomes. Depending on the research question one of these probabilities is varied until the patient reports indifference between the options. Scores obtained with the treatment preference method indicate the percentage of benefit the patient needs or the risk the patient is willing to accept to find a treatment option acceptable.

Patients’ valuations of possible outcomes after venous thromboembolism have been previously assessed in a study comparing streptokinase plus heparin versus heparin alone in patients with deep-vein thrombosis [21]. Health state valuations related to vitamin K antagonist therapy have only been assessed in patients with atrial fibrillation [22-24]. The general objective of the second part of this thesis is to assess patients’ health states valuations associated with venous thromboembolism and vitamin K antagonist therapy.

Adherence to vitamin K antagonist therapy

Direct and indirect methods have been studied to measure patients’ adherence to medication [25]. Direct measures of adherence include drug assays of blood or urine and the use of drug markers with the target medication. These methods can provide proof that the patient recently took a dose of the drug, but they provide only a snapshot of behaviour and are affected by factors other than adherence. Indirect measures of adherence include electronic monitoring and patients’ self-report. Electronic monitoring devices record the precise date and time patients open their medication bottle. However, one cannot be sure that the patient actually has taken the tablet(s), or the right dose. Self-report may be subject to social desirability and recall bias. It can, however, provide an upper level of adherence, insight into the number of tablets a patient has taken, and insight into patients’ reasons for non-adherence.
Patients treated with vitamin K antagonists spend considerable periods of time outside the therapeutic target range, even in the setting of clinical trials [26,27]. Non-adherence to vitamin K antagonist therapy has been proposed to be a major factor for poor therapeutic quality. So far, studies assessing the relationship between adherence and quality of treatment with vitamin K antagonists have produced inconsistent results [28-33]. The general objective of the third part of this thesis is to assess the relationship between patients’ self-reported adherence and the quality of treatment with vitamin K antagonists.

Outline of this thesis

In the first part of this thesis the results of our studies examining health-related quality of life (HRQOL) in patients treated with venous thromboembolism and patients treated with vitamin K antagonists are presented. In Chapter 2 HRQOL of patients with venous thromboembolism, patients with a major bleeding during treatment with vitamin K antagonists, and patients with the post-thrombotic syndrome is assessed and compared with normative data of a Dutch reference population. Chapter 3 examines the extent to which HRQOL in patients with venous thrombosis is affected adversely by treatment with vitamin K antagonists and whether the duration of treatment is associated with patients’ HRQOL. Chapter 4 describes a study examining the effect of potential determinants of HRQOL in patients with deep-vein thrombosis.

The second part of this thesis is directed at the valuation of outcomes after venous thromboembolism. 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. In Chapter 6 the effects of different durations of treatment with vitamin K antagonists on the quality-adjusted life expectancy are investigated in a Markov decision model. 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.

The third part of this thesis addresses adherence to vitamin K antagonist therapy. In chapter 8 the relationship between self-reported adherence and the quality of treatment with vitamin K antagonists is examined in patients with atrial fibrillation.
References


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