Individual approach towards optimal oral anticoagulation

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Chapter 1

General Introduction

and

Outline of this Thesis
GENERAL INTRODUCTION

In a variety of diseases, the use of antithrombotic agents and thrombolytic therapy for primary and secondary prevention of both arterial and venous thromboembolism have significantly influenced morbidity and mortality. This thesis addresses the use of vitamin K antagonists (VKA) in five of these diseases, i.e. deep vein thrombosis, pulmonary embolism, atrial fibrillation, heart valve replacement and coronary artery disease. The focus lies on the ability to achieve an optimal level of anticoagulation, in which arterial or venous thromboembolic events are prevented, without an unacceptable risk for major bleeding. Furthermore, in patients with coronary artery disease undergoing coronary-artery-bypass-grafting surgery, the choice of aspirin over vitamin K antagonists is re-evaluated.

Optimal level of anticoagulation

Vitamin K antagonists are used for a variety of indications, with different optimal ranges for different indications. Also, specific risk profiles (e.g. high risk for major bleeding) are weighted in selecting the optimal range for an individual patient. Currently, there is international consensus regarding the target range of INR (International Normalized Ratio) 2.0 to 3.0 as optimal for most diseases [1]. A higher target range might be more effective in secondary prevention after an acute myocardial infarction. However, this will be at the cost of an increased risk of major bleeding [2,3]. For prosthetic heart valves, the optimum depends on the type and position of the valve, and the presence of additional risk factors indicating a higher target range of INR 2.5 to 3.5 [4].

In the Netherlands, the target range is higher than internationally recommended (INR 2.5 to 3.5 and 3.0 to 4.0), with an additional wider therapeutic range (INR 2.0 to 3.5 and 2.5 to 4.0) to avoid particularly under-anticoagulation. These ranges are advocated by the Dutch Federation of Thrombosis Services, which unites a nationwide network of 61 specialized anticoagulation clinics responsible for the VKA management of all outpatients. In these specialized clinics, experienced physicians and dosing assistants are involved in optimizing VKA therapy, using computerized dosing programs and protocols for dose adjustments in case of under- and over-anticoagulation. In addition, patient education and awareness towards factors influencing the quality of VKA therapy are considered. Furthermore, patients are
trained to perform self-management, which is done under guidance of the clinic.  

The quality of care that is achieved is evaluated on a yearly basis by the Dutch Federation of Thrombosis Services, and presented in an annual report. In 2007, VKA therapy was managed in approximately 360000 patients. Over 5.5 million INR assessments were performed, with an median of 20 INRs per patient per year. The vitamin K antagonists used by these clinics were predominantly acenocoumarol (approximately 80%) and phenprocoumon (20%). When considering the different indications for which vitamin K antagonists were prescribed, 15% were venous and 85% arterial in origin, of which atrial fibrillation was the most frequent one, namely in 52% of all patients.

The quality indicators are the percentage of patients with an INR within the therapeutic range and the occurrence of major bleeds. For the percentage of patients within the therapeutic range, the threshold is set to 70% for long-term patients in the lower intensity group and 67% in higher intensity group. As presented in the annual report of 2007, this was achieved by 95% of the 61 anticoagulation clinics. Regarding major bleeding, annual incidences as observed in each clinic was compared with a reference incidence of 2% per year. In 2007, in 93% of the clinics the annual incidence did not exceed 2%. Furthermore, in only 10 of 61 clinics the annual incidence of major bleeding was above 1.5% (range 1.6 to 3.2%).

**Interacting factors in dose response relationship**

Next to the importance of the optimal range, in VKA therapy the ability to achieve a stable level of anticoagulation within this range is at least equally important. The dose-response relationship of vitamin K antagonists can be characterized by a high variability. Many environmental factors are known to play an important role in the achieved level of anticoagulation under VKA therapy, as well as genetic factors.

In reference to the genetic factors, both an increased sensitivity as well as an increased resistance to vitamin K antagonists are associated with CYP2C9 and VKORC1 genetic polymorphisms leading to a modified dose response relationship. Clinical outcome is more frequently compromised in these patients [5-9]. Environmental factors are concomitant drugs or herbal medicines, dietary intake of vitamin K, co-morbidity, alcohol intake as well as age and changes in activity level. These factors can result in an increase or a decrease of the effect of vitamin K antagonists [1,5,10-14]. Furthermore, the half-life time of the type of VKA also plays a
role in the achieved stability in the level of anticoagulation. With phenprocoumon and warfarin, with longer half-life times, a more stable level is achieved than with acenocoumarol [11,15]. However, due to this longer half-life, it is more difficult to counteract anticoagulation in case of high INRs or minor bleeding, as compared to acenocoumarol, for which a one-day interruption (with vitamin K only for higher INRs) results in a swift reduction of the level of anticoagulation. Finally, also compliance to VKA therapy regimens has been identified as an important factor of inter- and intra-individual variability [16,17].

To summarize, there are many factors known to influence the dose-response relationship of vitamin K antagonists. However, as Wittkowsky and Devine argued [18], still a large percentage of the instability observed can not be attributed to these known risk factors. In this respect, the occurrence of temporary over- and under-anticoagulation cannot be predicted nor prevented beforehand, and must be monitored closely. Possibly, the occurrence of such instability already early after initiation of VKA therapy, i.e. within the first month, could be used to identify those patients at higher risk for unstable anticoagulation resulting in a higher risk for both thromboembolic complications and major bleeding.

**INR monitoring**

During the course of VKA therapy, close monitoring of the achieved level of anticoagulation is essential to prevent both under- and over-anticoagulation. VKA therapy is most commonly monitored by using the prothrombin time (PT) test, were changes reflect the reduction of vitamin K-dependent procoagulant clotting factors II, VII and X. During the initial phase of VKA therapy, the PT mainly reflects the reduction of factor VII. Thereafter, factors II and X reduction contribute to prolongation of the PT [1]. Using the international normalized ratio (INR), PT test results are standardized and results comparable [19]. For this, the International Sensitivity Index (ISI) is used. It indicates the relative sensitivity of the thromboplastin compared to an international reference thromboplastin. Because these ISI values are based on stable anticoagulant doses for at least 6 weeks, the INR values are somewhat less reliable during the initial treatment phase.

**Time within target range**

With the given variability in dose response relationship and the strongly related clinical
outcome, it is of great importance to use a valid methodology to measure and thereby safeguard the quality of VKA therapy. This quality can be expressed as the time within the target range (TTR). In a wide range of studies, the association between the TTR and clinical outcome has been established. Next to the time within the target range, this also holds for the two counterparts of TTR, i.e. the time spent below and above the target range as measures of relative under- and over-anticoagulation [20-24].

The TTR can be calculated in different ways, and as the different methodologies result in different TTR values, this is of importance when evaluating the quality of VKA therapy. TTR can be expressed as a percentage of the INR measurements within the target range, either compared to all measurements performed or only at a certain moment in time in a cross-sectional approach [25]. Also, the actual number of days spent within the target range can be used as the basis of the TTR, either using linear interpolation as proposed by Rosendaal or other estimation methods for the days between INR measurements (e.g. equidivision method) [26-28]. All methodologies have their own advantages and disadvantages. Rates based upon the number of INR measurements are simple to calculate, but are potentially biased by an increased frequency of measuring during a period of inadequate anticoagulation. The cross-sectional approach considers individual patients, but only at a certain moment in time. Linear interpolation, which includes time, can be used to evaluate the association between the level of anticoagulation and the occurrences of thromboembolic and bleeding complications (i.e. INR-specific incidence rates) [20]. In this method, a linear change of INR between consecutive measurements is assumed. Especially with longer intervals and extreme INR changes this might lead to a somewhat biased estimate of the TTR.

Recommending either one of these methods is not easy. In fact, each has its limitations and a choice may be based on local applicability [28]. However, when considering the use of TTR as a quality measurement in individual patient care, an approach that considers continuous changes in time is more appropriate. In this setting, the linear interpolation method as proposed by Rosendaal et al. is the method of choice [27]. Although the method has been advocated for its applicability in assessing INR-related incidences rates at a group level, it also makes it possible to assess the level of anticoagulation during the course of VKA therapy in an individual patient.
Evaluating individual course of INR through time

During monitoring, frequent dose adjustments are made to achieve a level of anticoagulation within target range. When using computerized algorithms, these dose changes are based on an empiric dose-INR relationship. The effectiveness and safety of such computer-assisted dosage systems have been demonstrated and are comparable to experienced medical staff dosage [29]. However, considering the many factors influencing the achieved level of anticoagulation, a more individual multi-causal approach would do more justice to the complex inter- and intra-individual variability, and may lead to an increased quality of care. Although a more model-based approach with multiple factors as proposed by Pasterkamp et al. looks promising [30], the effectiveness of such algorithms must be evaluated in clinical trials.

When evaluating the achieved level of anticoagulation during VKA therapy, it is also important to realize that there still is a gap between guideline target ranges and acceptance of instability of response in daily practice. This is illustrated by a study by Palareti et al., where treating physicians considered many patients as stable despite a large amount of time spent above or below the target range, and thereby accepting INR values outside the target range as appropriate [11]. This observation is in line with the reported TTR values ranging from 50% to 75%, indicating that many patients are outside the target range for a considerable amount of time [1,20,21,26,31-35].

As part of the individual approach to monitoring, patients who are outside the target range for a considerable amount of time should be identified as early as possible. This is especially of importance as improving the patient’s awareness to the specific problems of VKA therapy can be a major determinant in increasing compliance and stability of the level of anticoagulation. Individual coaching of patients with regard to the proper use of vitamin K antagonists resulted in an increase in stability from 39% to 62% of time within the therapeutic range in a study [11]. In this respect, patient self-testing or self-management have shown to lead to an increase in the quality of VKA therapy [36-38]. However, not all patients are able or willing to perform all tasks required for a safe self-testing or self-management program.
Aspirin versus vitamin K antagonists for secondary prophylaxis after coronary-artery-bypass-graft surgery

Over the recent years, in the Netherlands the number of patients with atrial fibrillation requiring VKA therapy is increasing, and the number of patients with a myocardial infarction and arterial vascular surgery is steadily decreasing over the last years (Annual report 2007 Dutch Federation of Thrombosis Services). The latter is in line with the recommendations for antithrombotic therapy for coronary-artery-bypass-graft surgery (CABG) patients, as recently re-established in the 8th edition of the American College of Chest Physicians evidence-Based Clinical Practice Guidelines [39]. For all patients with coronary artery disease undergoing CABG, indefinite use of aspirin is recommended. Vitamin K antagonists should only be considered if concomitant conditions, e.g. heart valve replacement are present. In those instances, vitamin K antagonists combined with aspirin is suggested [39].

Several prospective controlled clinical trials have evaluated efficacy and safety of antithrombotic drug therapies for secondary prophylaxis after coronary-artery-bypass-graft surgery to prevent vein graft closure [40]. This resulted in a high level of evidence, identifying aspirin as standard of care [39,41]. To maximize the effect of anticoagulant treatment it must be initiated already early after surgery [42-44]. In this respect, current guidelines stipulate the initiation of aspirin within 48 hours after surgery with the aim to be continued indefinitely [42,43]. When started more than 48 hours after surgery, efficacy of aspirin is hampered and early graft occlusion more frequently observed [45].

One of the important clinical trials that evaluated efficacy and safety of antithrombotic drug therapies was CABADAS (CABADAS = prevention of Coronary Artery Bypass graft occlusion by Aspirin, Dipyridamole and Aacenocoumarol /phenprocoumon Study). CABADAS evaluated the effect of aspirin, aspirin plus dipyridamole and vitamin K antagonists on one-year graft patency and early clinical outcome. The CABADAS study concluded that there was no convincing evidence that the addition of dipyridamole to a low dose of aspirin improves one-year vein-graft patency after coronary artery bypass grafting. Oral anticoagulants, compared with aspirin, provided no benefit [46].

However, in many of the clinical trials that contributed to the evidence of aspirin as primary choice for secondary prophylaxis after CABG, data on long-term clinical outcome are limited. As in CABADAS, mainly early effects on graft patency
and short- and mid-term clinical outcome are available, and long-term outcome could provide further evidence for the use of aspirin as secondary prophylaxis after CABG.

**Coronary-artery-bypass-graft surgery**

CABADAS studied graft patency after coronary artery bypass graft surgery. Since its introduction in the 1960s, CABG is now one of the most common operations performed in the world. It has proven to consistently relieve angina and improve the quality of life in symptomatic patients. Both saphenous vein and arterial grafts are used, in which arterial grafts have a late patency rate of 90% at 10 years after surgery, compared to approximately 50% for vein grafts. And although optimization of peri-operative (e.g. platelet inhibitors) and long-term medical treatment (e.g. more aggressive statin use) will improve vein graft patency rates, the current recommendation is to use the left internal mammary artery (IMA) as primary choice for revascularization of the left anterior descending artery because of its excellent late patency rate [41].

In line with the superiority of a single IMA over the saphenous vein graft [47-49], the benefit of bilateral IMA grafting can be expected. There are several non-randomized comparative studies confirming this hypothesis [50-52], but randomized trials on this issue are lacking. A major drawback for arterial grafting is the increased operative difficulty, with increased operative time and a higher risk of wound complications, also reflected by the limited number of institutions performing this type of surgery. Furthermore, considering the excellent outcome of single IMA grafting during the first 10 years, comparative studies should be performed with extended follow-up over more than 10 years. This is even more the case for total arterial grafting in patients with three-vessel disease. Whether three pedicled arterial grafts can further improve especially the long-term clinical outcome is still unknown, although the mid-term results of previous studies were promising [53,54].
OUTLINE OF THIS THESIS

We addressed the use of vitamin K antagonists in deep vein thrombosis, pulmonary embolism, atrial fibrillation, heart valve replacement and coronary artery disease.

In evaluating the effectiveness of vitamin K antagonists, we focused on the individual responses to VKA, i.e. the individual time within the INR target range, the determination of an inadequate level of anticoagulation and its impact on both thromboembolism and bleeding (major and minor) complications (chapter 2 and 3). In addition, the predictability of such an inadequate level of anticoagulation was assessed. Especially the importance of the initial 30-day response to VKA was evaluated (chapter 3). Next, we evaluated whether minor bleeds could predict major bleeding, the latter causing serious morbidity and mortality (chapter 4).

Long-term effectiveness of VKA therapy was evaluated in patients with coronary artery disease in whom bypass surgery was performed using vein grafts (with or without an arterial graft). These patients were from the CABADAS extended 14-year follow-up study. Next to a formal comparison of vitamin K antagonists, aspirin and aspirin plus dipyridamole (chapter 5), in the patients treated with vitamin K antagonists the impact of differences in quality of anticoagulation during the first year of therapy on long-term clinical outcome was evaluated (chapter 6). Finally, the findings of this cohort were put into the perspective of arterial vs. vein grafting. The long-term benefit of total arterial grafting was assessed in patients with 3-vessel coronary artery disease, and compared with historical data. In an additional analysis, these patients were also compared with a subgroup of patients from CABADAS, formally comparing arterial vs. vein grafting in patients with 3-vessel disease (chapter 7).
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