Individual approach towards optimal oral anticoagulation

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Chapter 8

Summary, Discussion
and
Future Perspectives
SUMMARY, DISCUSSION AND FUTURE PERSPECTIVES

BACKGROUND

Vitamin K antagonists (VKA) are still the only oral anticoagulants for long-term therapy, despite the need and ongoing search for new and better drugs. Since its approval for medical use in humans almost 60 years ago their use is still increasing. This is remarkable, especially since VKA therapy is problematic and has several limitations, of which its large inter- and intra-individual variability in dose-response is the most important one. To indicate the magnitude of both use and limitation of VKAs the following numbers are informative: in the Netherlands, in 2007 in more than 300000 outpatients VKA therapy was managed by the anticoagulation clinics, in a nationwide network. From 2002 to 2007, this number had increased by 10%. Furthermore, in the USA in 2004 the number of outpatient prescriptions written for VKA amounted to nearly 31 million, and VKA was among the top 10 drugs with the largest number of serious adverse event reports submitted during the 1990 and 2000 decades. All this adds up to a growing need for new and better drugs, of which promising drugs are currently investigated, some already in large phase III studies, using VKA as the reference therapy. In this respect, it is intriguing that in most of the studies the aim is non-inferiority. The concept of non-inferiority of treatments indicates a choice. When choosing, other factors than efficacy and safety could be relevant, but also the between-patient differences in the efficacy and safety must be taken into account. This is especially the case with a drug like VKA, where this problem is the most important limitation. The question that must be answered is “which patient is best treated with which drug?” In this respect, the ability to predict a patient response to VKA prior to the initiation of the treatment is still very limited.

In this thesis, both the efficacy and safety of VKA therapy in different groups of patients was addressed. Its focus lies on the early identification of those patients who will, or will not do well on VKA. The cohorts that were extensively studied were patients with deep vein thrombosis, pulmonary embolism, atrial fibrillation, heart valve replacement and myocardial infarction, as well as patients who underwent coronary artery bypass grafting surgery, in whom VKA was used in a comparative setting, next to dipyridamole, aspirin, or both.
SUMMARY

In chapter one, an overview of the current state of affairs of VKA therapy was presented, and several issues discussed. These included the optimal level of anticoagulation, but also the difficulty to achieve this optimum. Although many factors are known to influence this relationship, including genetic factors, age, comorbidity, concomitant drugs, changes in activity level and dietary intake of vitamin K, still a large percentage of the instability that is observed cannot be attributed to these known risk factors. For this reason, early signs of under- and overanticoagulation could be valuable in identifying those patients at higher risk of recurrent thrombosis or major bleeding. Due to this highly variable dose-response relationship, nonstop monitoring of the response is mandatory.

To assess the extent of the variability in individual patients, a valid methodology should be used. The Time within the Target Range (TTR) has proven its value in assessing this variability in relation to clinical outcome. Although TTR can be calculated differently, the method proposed by Rosendaal et al. was our method of choice. Originally advocated for its applicability in assessing INR-related incidence rates at a group level, it also makes it possible to assess the level of anticoagulation during the course of VKA therapy in individual patients (ITTR). Considering the huge amount of variation, with only a limited predictability beforehand, especially the evaluation of the individual course of INR through time is of importance.

In chapter two, efficacy and safety of vitamin K antagonists (VKA) were evaluated in relation to the actually achieved level of anticoagulation (INR) in a cohort of 2304 consecutive patients with venous thromboembolism. The patients were all referred to a specialized anticoagulant clinic in The Netherlands for control of their VKA therapy. The target range used in these patients was INR 2.0 to 3.5. Using the individual percentage of time within the target range (ITTR) during VKA therapy, we confirmed that it is difficult to maintain an optimal INR over time in all patients. Although the mean ITTR was 63% (11% below and 26% above the range), in one quarter of the patients the ITTR was below 45%. Especially these patients were at higher risk for both recurrent thromboembolism and major bleeding. The absolute risks of recurrent thromboembolism and major bleeding, expressed as incidence rates were 6.2 and 2.8 per 100 person-years, respectively. In the patients with an ITTR <
45%, incidence rates amounted to 16.6 and 8.7 per 100 person-years, whereas in the patients with an ITTR between 45-65% and above 65% incidence rates were comparable (4.9 and 2.1 versus 4.6 and 1.9 per 100-person-years respectively).

This finding stressed the importance of being able to identify the poor responders, prior to or soon after initiation of VKA therapy. When using the achieved level of anticoagulation during the first 30 days of treatment, i.e. 30-days ITTR, a low ITTR was highly associated with an overall poor response to VKA. In this cohort, the lowest quarter of patients with a 30-days ITTR < 37% (median 20%) had an approximately 25-fold increased risk of having an overall poor ITTR < 45%, indicating that 30-days ITTR is highly predictive for the total treatment ITTR.

In chapter three, the association between quality of anticoagulation and occurrence of thromboembolism and major bleeding was also assessed in three other cohorts. In total, 4454 consecutive patients with myocardial infarction (N = 1012), atrial fibrillation (N = 2614) and a prosthetic heart valve (N = 828) were studied. Again, all patients were referred to a specialized anticoagulant clinic in The Netherlands for control of their VKA therapy. The quality of anticoagulation was measured using the ITTR, now in patients from three cohorts with different target ranges. In addition, differences in percentage of time below and above target was also considered. Furthermore, the value of 30-days ITTR on the ability to early identify patients with a poor response to VKA was addressed.

On average, ITTRs were 39%, 42% and 44% in patients with myocardial infarction, atrial fibrillation and prosthetic heart valve respectively. This lack in differences between ITTRs can be explained by the comparable width of the target range. However, there were differences in clinical outcome. Thromboembolic events had occurred more frequently in patients with myocardial infarction (incidence rate 4.0 per 100 person-years) than in patients with atrial fibrillation (incidence rate 1.7 per 100 person-years) and patients with a prosthetic heart valve (incidence rate 1.4 per 100 person-years). For major bleeding, with an incidence rate of 0.9, 1.6 and 1.7 per 100 person-years, this was the opposite. As was observed in the cohort of deep vein thrombosis and pulmonary embolism (chapter 2), the highest risk of both thromboembolic events and major bleeding was observed in the quartile of patients with the lowest ITTR (less than 25% to 34%). Remarkably, incidence rates did not differ strongly between patients with higher ITTRs in all three cohorts, indicating a
threshold in quality of anticoagulation beyond which clinical outcome is compromised.

In the atrial fibrillation and the prosthetic heart valve cohort, thromboembolism and major bleeding were balanced. This was not the case in the myocardial infarction cohort, where thromboembolism had occurred more frequently than major bleeding, especially in the patients with the lowest ITTR. This difference can be explained by differences in pathophysiology of thrombosis in the heart cavities versus coronary artery thrombosis. The inability to maintain the level of anticoagulation within its target range will have a much greater clinical impact when VKA treatment is applied to prevent the development of a small thrombus in a thrombogenic atherosclerotic coronary artery than to prevent a first thrombus in the much wider heart cavities. On the other hand, the cohorts differed with respect to the time below and the time above INR target range, while ITTR was similar. In the myocardial infarction cohort more frequent under-anticoagulation was observed, with an increased risk of thromboembolism - mainly recurrent myocardial infarction - and a reduced risk of major bleeding, as compared with patients from the two other cohorts. This was especially observed in the patients in the lowest ITTR quartiles.

Considering the imbalance of under- and over-anticoagulation and the associated types of events, there seems to be room for improvement in managing the patients with a myocardial infarction, especially those with a poor ITTR.

Managing anticoagulant therapy using VKA has been compared with walking a tightrope, swinging from left to right and always at risk of falling. The majority of patients are sufficiently equipped to do the walk, but those who are not, despite intensive INR monitoring and adjustments of the dose of VKA, need to be identified. Such an identification is possible using the 30-days ITTR, as this was strongly associated with the overall ITTR. Especially these patients may benefit from treatment with new anticoagulant drugs currently being developed.

Chapter four addresses the risk of bleeding complications, and the possibility to identify patients at high risk of major bleeding. The majority of bleeding complications in patients on VKA are clinically mild. Incidence rates of major bleeding range from 1.4 to 3.3 per 100 person-years, whereas for minor bleeding incidence rates up to 30 per 100 person-years are reported. Minor bleeding might be due to over-anticoagulation or a pre-existing mild bleeding disorder, which is enhanced by VKA.
In either case, the occurrence of a minor bleed during VKA therapy could be associated with an increased risk of major bleeding. We hypothesized that minor bleeding occurring during VKA therapy could lead to intensified monitoring of VKA therapy to maximize the quality of anticoagulation and thereby reducing the risk of major bleeding. On the other hand, minor bleeding could be an indicator for an increased risk of major bleeding, similar to a history of major bleeding.

To assess the association between minor and subsequent major bleeding, a cohort of 6758 consecutive patients was retrospectively studied. In 20.0% of the patients (N = 1348), a minor bleeding had occurred (incidence rate 25.1 per 100 person-years (95%CI, 23.8-26.5)). These patients were at 3.6-fold increased risk of a subsequent major bleeding within one month (risk estimated using a time-varying exposure model). A change in managing VKA therapy towards more intense monitoring with more frequent dose adjustments was not observed, and the percentage of time within, below and above the target range did not differ from the patients without or after the occurrence of a minor bleed.

The quality of anticoagulation itself was also independently associated with major bleeding, with a 2.8-fold increased risk in patients with a poor response to VKA, i.e. individual time within target range of less than 25% of the total treatment time. Other risk factors of major bleeding were malignancy, increasing age (between 55-70 years and especially above 70 years), sex (male), and the use of NSAIDs, adjusted for the indication for VKA therapy (atrial fibrillation, deep vein thrombosis, pulmonary embolism, prosthetic heart valve and myocardial infarction). We concluded that minor bleeding was associated with subsequent major bleeding. The occurrence of a minor bleed should increase the awareness towards a potentially high-risk situation. In this, the achieved level of anticoagulation should also be considered, not just the INR at the time of the minor bleed, but especially the ITTR of the preceding treatment period.

Whether a lower intensity of anticoagulation might be suitable for these high-risk patients, without compromising the efficacy of VKA therapy to prevent thromboembolic complications is speculative. But still, the indication for VKA therapy should be reconsidered, with a new risk-benefit assessment. Given the very promising safety profile of one of the new direct thrombin and factor Xa inhibitors, i.e. dabigatran, as recently established in the RE-LY study (N Engl J Med
a switch to this new oral thrombin inhibitor, when it is approved, could be indicated.

The presence of non-optimal VKA therapy, not momentary but structural, and its consequences for clinical outcome was further assessed in a cohort of coronary-bypass-graft-surgery patients who received VKA for secondary prophylaxis. As described in chapter five, these patients were included in a large clinical trial, the CABADAS, evaluating efficacy and safety of aspirin, aspirin plus dipyridamole and VKA over a one-year period. Two-hundred-thirty-three patients randomized to VKA were selected and their individual response to VKA during the one-year of therapy assessed. Furthermore, the occurrence of cardiac events during a 14-year follow-up was evaluated.

Although a target range of INR 2.8-4.8 was used for managing VKA therapy at the time of treatment, we used the target range of INR 3.0-4.0 to assess the association between non-optimal VKA therapy and cardiac events. This is the intensity level for primary and secondary prophylaxis of arterial thromboembolic complications currently advocated by the Dutch Federation of Thrombosis Services. Patients had non-optimal VKA therapy when they spent a large amount of time below the target range INR 3.0-4.0 (lowest tertile of patients to indicate non-optimal VKA therapy), or their response over time was highly variable (highest tertile of patients to indicate non-optimal VKA therapy). For the latter, the variance growth rate was used.

The mean INR achieved in this cohort was 3.1, which was at the lower end of the target range of INR 2.8-4.8. On average, the individual time spent within the target range (ITTR) was 56%, with 39% of time below INR 2.8. When considering the achieved quality of anticoagulation as defined in terms of both the time spent below INR 3.0 and stability in INR over time, 93 patients (40%) had optimal VKA therapy, i.e. least frequently below INR 3.0 with most stable INRs. In these patients, time spent below INR 3.0 was 35%, compared to 58% in the 142 patients (60%) classified as non-optimal.

After one year, at the end of the CABADAS study, the continuation of the VKA therapy was left at the discretion of the treating physician. Overall, in half of the patients, VKA was continued. Remarkably, also in half of the patients with non-optimal VKA, the treatment was continued, clearly indicating that the decision to continue VKA was not based on information regarding the previously achieved (poor) quality of anticoagulation. At the time of the decision, such information was not
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provided to the treating physician. When considering the clinical impact of optimal versus non-optimal VKA during the first year, we analyzed the events during follow-up. No difference in cardiac death and myocardial infarction were observed up to 8 years, but after 8 years, non-optimal VKA was associated with a more than 3-fold increased risk of cardiac death and myocardial infarction. In this, optimal VKA therapy could be more effective against the extension of the native coronary artery disease, rather than disease progression at the site of grafts.

In addition to the “hard” clinical endpoints of cardiac mortality and myocardial infarction, the need for repeat-revascularization was evaluated as a secondary endpoint. Repeat-revascularization was not associated with the first year quality of anticoagulation, with a cumulative rate of 35% at 14 years. In this, with a more than 2-fold increase, an age below 60 years at the time of the initial CABG was the most important determinant for a repeat-revascularization. Possibly, a lower threshold for referral and consequent revascularization in younger patients, irrespective of the achieved quality of anticoagulation, might explain this difference. The possibility of a referral bias for revascularization was further illustrated by comparing the patients treated with VKA with those patients from the original CABADAS study randomized to receive aspirin or aspirin plus dipyridamole. In these patients, without the frequent follow-up visits to manage their treatment, the cumulative rates of repeat-revascularization were significantly lower (18% and 17%, respectively).

Further comparisons of VKA, aspirin and aspirin plus dipyridamole are described in detail in chapter six. In this chapter, the long-term clinical outcome of all Dutch patients included in the CABADAS study was evaluated (N = 726). In these patients, cumulative incidence of the composite of cardiac death, myocardial infarction and repeat-revascularization (MACE) reached 52% at 14 years. Although there was a large difference in repeat-revascularization (2-fold increased risk in patients treated with VKA), regarding MACE no difference between the three treatment groups was observed. For the “hard” clinical endpoints cardiac death and myocardial infarction separately, also no differences were observed. We speculated that the increased risk of repeat-revascularization in patients treated with VKA was in part due to a referral bias. As already discussed in chapter 5, due to the monitoring requirements associated with VKA therapy, with frequent patient-physician contacts, the threshold towards referral
to cardiac specialists might have been lower, resulting in earlier and more frequent repeat-revascularizations.

Based on our findings, we concluded that in patients undergoing coronary-artery-bypass-graft surgery, aspirin was the drug of choice. In this, we added further evidence to the recommendations for antithrombotic therapy in CABG patients, as recently re-established in the 8th edition of the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. VKA should only be considered if indicated for a concomitant condition, and preferably combined with aspirin. The combination should especially be considered in patients with non-optimal VKA therapy.

In CABADAS, patients who underwent elective aortocoronary bypass surgery with saphenous vein grafts were included. More than half of the patients also received an internal mammary artery graft in addition to the vein grafts. Reported long-term patency rates of arterial grafts are superior to vein grafts, and associated with improved survival. Especially in patients with three-vessel disease, total arterial grafting could further reduce the recurrence of ischemic cardiac events. Although mid-term results were promising, long-term results were still unknown. In chapter seven, we evaluated clinical outcome in patients with three-vessel disease who underwent complete arterial revascularization using both pedicled ITAs and the gastroepiploic artery. The 12-year freedom from MACE was 75.5%. This was 86.9% for cardiovascular death, 93.3% for myocardial infarction, and 89.4% for re-intervention.

When comparing these results with those obtained from recently published studies, our study indicated that the actuarial survival and actuarial probability of remaining free from myocardial infarction or re-intervention, or both, 10 years after the primary operation, was excellent. We also demonstrated that the beneficial effect of complete arterial revascularization was rather consistent through different strata of patients. Only in elderly patients (≥ 65 years) the benefit of complete arterial revascularization was less pronounced.

In addition to the literature review, we also compared the clinical outcome in our study cohort with that in a cohort of 281 patients with three-vessel disease who underwent revascularization and received ITAs in addition to vein grafts. These patients originated from the CABADAS study. MACE was significantly reduced in
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patients who underwent complete arterial revascularization, with a hazard ratio of 0.43 (95% CI, 0.29-0.63, P < 0.001).

As with the literature review, this comparison is limited by potential bias, particularly due to the lack of random treatment allocation. We therefore cannot consider the analysis as conclusive, despite the use of propensity scores to address the non-randomized setting. It did, however, provide us with an estimate of the benefit of complete arterial revascularization, and added further evidence that the use of complete arterial revascularization using both pedicled ITAs and the gastroepiploic artery in patients with three-vessel disease resulted in excellent long-term clinical outcome.

DISCUSSION AND FUTURE PERSPECTIVES

In this thesis, the use of vitamin K antagonists was evaluated in several large patient populations. Further, a comparison between VKA, aspirin and dipyridamole was made in patients who underwent coronary-artery-bypass-grafting. The achieved level of anticoagulation is the most important determinant of effective and safe VKA therapy. We assessed the quality of anticoagulation that was achieved and the associated risk of thromboembolism and major bleeding in a number of cohorts with different indications for VKA therapy. We also evaluated differences in response to VKA and clinical outcome between different types of patients.

Considering the large amount of within and between patient variability, with only a small part of the variability explained by known risk factors, we specifically addressed the possibility to early identify patients who do not respond well to VKA after therapy is started. We evaluated the initial response after 30 days. The period of 30 days is long enough to generate a valid estimate of the initial response, and short enough to still have sufficient time to adjust treatment to prevent adverse clinical outcome. In this, we used the percentage of time within (ITTR), above and below the target range for each individual patient.

In the same line of reasoning, the occurrence of a minor bleed was evaluated. Next to the achieved quality of anticoagulation, a minor bleed proved to be an important predictor of subsequent major bleeding. In this respect, also clinically relevant minor bleeding must be mentioned. These were bleeds that were not serious by definition, but did require intervention and/or dose adjustment. A nose bleed, not
yet self-limited after several hours is an example of such a bleed, which does have an impact on the subjective wellbeing of patients. It is good to notice that recent trials with new oral anticoagulants have included this type of severe minor bleeding as endpoint in their safety evaluations.

The potential benefit of identifying poor response was demonstrated in our cohort of patients who underwent coronary-artery-bypass-grafting and were treated with VKA as part of the CABADAS study investigating the effects of aspirin, aspirin plus dipyridamole and VKA. Long-term beneficial effects of VKA over aspirin was achieved, but in a limited number of the patients with an optimal response of VKA. In the CABADAS study, continuation of VKA therapy after one year was left at the discretion of the treating physician. Remarkably, in the patients who continued VKA, the percentage non-optimal VKA was equal to that in the group of patients who stopped VKA. Using “response to VKA” data at the time of the decision to continue VKA therapy would have resulted in a higher percentage of patients with an optimal response in those who continued VKA, whereas more patients with non-optimal response would have switched to aspirin. Probably, patients would have benefited from such a different decision. Feedback to the treating physician on the achieved quality of anticoagulation is still not done regularly, but as illustrated above, could benefit the patients treated with VKA.

Promising alternatives for long-term VKA therapy are currently under development. These new oral anticoagulant drugs target on direct thrombin or factor Xa inhibition. The concept of factor Xa inhibition was confirmed in clinical trials using fondaparinux, and several factor Xa inhibitors are currently investigated. Ximelagatran was the first direct thrombin inhibitor tested in phase III trials and although development of this drug was stopped due to unexpected serious hepatic toxicity, the results confirmed that thrombin is a suitable target for new oral anticoagulants. It also showed that fixed dosing without monitoring the level of anticoagulation is possible, with efficacy and safety comparable to VKA.

Other direct thrombin inhibitors are now under investigation for various indications. Taken into consideration both the established efficacy of VKA and the requirements for a safe use, an equally effective and safe new oral anticoagulant could replace VKA as the primary choice of oral anticoagulant. Therefore, most studies target on non-inferiority. Recently, the RE-LY study was presented, in which
dabigatran was compared with warfarin in patients with atrial fibrillation. In more than one aspect, the RE-LY study generated very important results. Beyond expectation, the higher dose dabigatran (150 mg) was found to be superior to warfarin, without an increased risk of bleeding. The lower dose (110 mg) was declared non-inferior. In this study, the quality of warfarin therapy was considered adequate, with a mean TTR of 64%. After the RE-LY study, the approval of dabigatran is probably only a matter of time. Once the new oral anticoagulant drugs become available, also in patients already on VKA a switch must be considered. Response to VKA could then be used. In case of a poor response, new oral thrombin inhibitors should be considered.

A note of caution is related to the ability to counteract anticoagulation. When a rapid reversal of the action of VKA is indicated, this can be achieved by withholding VKA, in combination with the administration vitamin K and when further indicated the replacement of the depleted coagulation factors by administration of Prothrombin Complex Concentrate or Fresh Frozen Plasma. The new oral anticoagulants lack specific antidotes, which could especially be problematic in those drug with a longer half-life.

In patients who do well on VKA, a switch might still be less beneficial, especially when compliance is also taken into account. In RE-LY, where treatment was administered under clinical trial conditions, 15%-16% of the patients discontinued dabigatran, compared with 10% of the patients treated with warfarin. This was in part related to a higher rate of gastrointestinal complaints (11%-12% in dabigatran vs. 6% in warfarin). The higher rate, combined with the notion that compliance will be compromised in the “real life” setting, could influence the established benefit of dabigatran (also requiring daily dosing) over warfarin.

VKAs differ from many other drugs. Their big drawback, i.e. the highly variable dose-response relationship requiring continuous monitoring of the level of anticoagulation, also provides an advantage. The monitoring, with regular patient-physician contacts, also provides feedback on compliance. This feedback, but also the intensity and continuity of care itself are important factors that influence compliance/non-adherence. Furthermore, also patient knowledge and awareness towards the risks and benefits of their anticoagulant therapy are of importance. In this, the Dutch situation with a nationwide network of thrombosis services provides a unique setting for optimal compliance to VKA therapy. For the new oral anticoagulants, such a compliance might not be achieved, and especially in those drugs
requiring a daily dosing, as dabigatran, the benefit that is observed under the clinical trial conditions might be reduced in “real life”. Therefore, after market approval a focus of further research should be on compliance as part of the postmarketing surveillance, especially where conditions under which VKA therapy is provided are optimal, as is the case in the Netherlands. The current presence of the nationwide network of Thrombosis Services in the Netherlands gives the unique opportunity to do this research, using the extensive knowledge of these highly experienced thrombosis services, before VKAs are abandoned to the past.