Chapter 7

Summary and general discussion
The aim of this thesis was to acquire knowledge regarding predictors and determinants of the efficacy, safety and convenience of vitamin K antagonist (VKA) treatment.

SUMMARY

In chapter 2, we identified independent predictors of poor VKA control in newly diagnosed venous thromboembolism (VTE) patients. We included patients randomized to VKA in the EINSTEIN-DVT and PE studies, two trials comparing rivaroxaban and VKA\(^1,2\). The primary outcome in our study was poor VKA control, because previous studies had shown that the majority of bleeding and thrombotic events occur in this group of patients\(^3,4\). Poor VKA control was defined in two ways: an individual time in the therapeutic range (iTTR) in the lower quartile (47% of the time or less), and the combination of an iTTR below the median (65%) and a variability above the median (0.23). The latter was called instability. To be able to analyze whether the initial course of VKA therapy was predictive in addition to baseline characteristics only, follow-up started 28 days after VKA initiation.

In the 3,825 included patients, we found several baseline characteristics that were associated with an increased risk of poor VKA control: region, weight below 50kg, active cancer, secondary VTE, and a subtherapeutic International Normalized Ratio (INR) at stop of double therapy with low molecular weight heparin. These were all predictive for low iTTR, and the first three did also predict instability after 28 days. Moreover, poor VKA control during the initial 28 days was an additional independent risk factor for both endpoints. Interestingly, poor iTTR was a stronger predictor in acenocoumarol users, and instability in warfarin users. Many predictors of poor VKA control were related to premature discontinuation. Surprisingly, region was the only predictor that was associated with clinical outcome. Patients in Eastern Europe had a smaller chance to develop a bleed. To better understand the lack of correlation for the other predictors, we analyzed whether the clinically most relevant iTTR (during the preceding 4 weeks) did correlate with clinical outcome. We found no relationship with recurrent VTE, and only a moderate relationship with bleeding events and net clinical benefit outcome (recurrent VTE or major bleeding). This might be explained by underrepresentation of patients with really poor VKA control, as is seen more often in clinical trials\(^5\). Therefore, it might be possible that our findings do not directly translate into the real-life setting. Fortunately for our analysis, VKA management was left to the local centers, and therefore largely reflected the real-life setting. These findings could aid clinicians, in an early phase, to identify patients who might benefit from alternative treatment options such as non-VKA oral anticoagulants (NOACs) or another type of VKA.

In chapter 3, we described the course of VKA therapy after extreme overanticoagulation. Due to the variable dose-response relationship, patients with initially stable VKA treatment may develop an INR above eight and/or might need reversal with vitamin K supplementation. Previous research focused on the acute bleeding risk of extreme overanticoagulation\(^6,7\), but here we analyzed whether VKA control would restabilize after the acute phase. For this, we selected all 14,777 initially stable atrial
fibrillation (AF) and VTE patients treated at Certe Thrombosis Service Groningen between January 2009 and January 2012. The 90 to 8 days before (pre-period) and 8 to 90 days after overanticoagulation (post-period) were compared. In addition, the 800 patients with extreme overanticoagulation were randomly matched and compared with 1600 patients without overanticoagulation.

The pre-period was characterized by frequent overanticoagulation, and relatively poor VKA control compared to controls. After extreme overanticoagulation the INR was measured more frequently, but VKA control became even worse. The proportion of patients with inadequate VKA control ($\text{iTTR} < 65\%$) increased from 49% to 62%, mainly due to more frequent underanticoagulation. Unfortunately, the small decrease in time above the range after extreme overanticoagulation did not lower the bleeding rate. Comparison with the controls showed worse VKA control, and an increased risk of bleeding (hazard ratio (HR) 2.1), thromboses (HR 5.7) and VKA related death (HR 17.0) in the post-period. Thus extreme overanticoagulation was a prelude of subsequent long-lasting inferior quality of VKA treatment and poor clinical outcome. Given the unattractive risk benefit ratio of VKA in patients with extreme overanticoagulation, patients might benefit from the switch to another type of anticoagulants such as VKA with a longer half-life or NOACs.

In chapter 4, we studied the relation between age and the bleeding and thrombotic risk in patients over 70 years using VKA. Previous studies showed that, despite the relatively high bleeding risk, advantages of VKA outweigh the bleeding risk in septuagenarians and octogenarians with AF or recent VTE. However, data regarding the efficacy and safety of VKA in nonagenarians are limited. We used a matched cohort design, matching every nonagenarian ($n=1,109$) to one octogenarian and one septuagenarian. The primary endpoint was bleeding (clinically relevant non-major and major bleeds). Secondary endpoints included thrombotic events and quality of VKA control. The 713 patients (22%) with at least one bleed had in total 986 clinically relevant non-major and 64 major bleeds. The bleeding risk was not increased in the octogenarians and only mildly increased (HR 1.26) in the nonagenarians. Subgroup analyses for sex, indication, treatment duration and target range did not show different effects from the main analyses. Also, the severity and location of bleeding were independent of age.

There were 85 patients (2.6%) with a thrombotic event, none of them had multiple thromboses. The risk to develop a thrombotic event was doubled in the nonagenarians and octogenarians, and this was even a five-fold risk in the patients newly referred to the Thrombosis Service. The risk to die from thrombosis was also four times larger in the nonagenarians.

The quality of VKA control deteriorated with age. This did partly explain the higher bleeding risk in nonagenarians, but hardly the increased thrombotic risk. The incidence (per 100 patient-years) of thrombotic events (1.48 and 1.82, respectively) was even higher than of major bleeds (0.97 and 1.13, respectively) in octogenarians and nonagenarians. The main limitation was that we only included patients who were considered eligible for VKA, which could have led to the selection of patients with a relatively low bleeding risk compared to their
peers. However, this might only be a problem if physicians were able to predict the bleeding risk. This can be questioned as the predictive value of classical risk factors, such as history of bleeding or falls, proved very limited within the group of elderly\textsuperscript{10}. Our data provide confidence that older age, even above 90 years, should in itself not be a reason to withhold anticoagulants when indicated.

In chapter 5, we presented a review of the literature. We systematically collected articles reporting the success rate of prothrombin complex concentrate (PCC) dosing strategies for emergency VKA reversal. By searching the EMBASE and MEDLINE databases we found 28 prospective studies, including 2,563 patients, reporting on five different strategies. Strategies were based on body weight, body weight and initial INR, body weight and initial INR and target INR, the choice of the physician, or independent of any factor (fixed dose). The quality of the studies was weak to moderate, and studies were predominantly small and with a single-arm design. We found 15 different dosing protocols, and many different outcome definitions. The six primary outcomes ranked from most to least common were the proportion of patients reaching a target INR (57%), INR decrease (14%), clinical response (11%), appropriate PCC treatment (7%), incidence of thrombotic events (7%), and one study had two primary outcomes (clinical response and reaching target INR). Moreover, target INRs, time frames and definitions of ‘clinical response’ differed between studies. This heterogeneity complicated pooling of data. Therefore, we only performed descriptive analyses. Interestingly, clinical outcome was better with any protocol than when the decision was left to the treating physician. Another finding was that the use of a fixed dose led to less PCC use without a lower success rate. The most important conclusion was that a uniform outcome definition was needed, so that results from future studies will be easily comparable, and can be combined.

In chapter 6, the impact of VKA use on quality of life was studied in patients who started to use VKA for AF. In addition, the relation between the course of VKA therapy and VKA perception was analyzed in long-term VKA users. Both VKA perception and general quality of life were measured at inclusion and three months thereafter using the SF-36 and PACT-Q questionnaires, respectively. Higher scores were more favorable.

General quality of life was relatively low at VKA initiation, but improved during the initial three months of treatment to a level comparable with the general population. Treatment convenience was high (median score 95 and 96 out of 100, respectively) in both the new and long-term users, especially in the older patients and patients without bleeding. Treatment satisfaction was moderate (median score 64 out of 100). Intra-individual changes in VKA perception and general quality of life were only weakly related to changes in patient and treatment characteristics such as comorbidity and quality of VKA control. Apparently, patients’ well-being did not depend on the course of VKA therapy. This was confirmed by the responses to the individual items of the PACT-Q; the majority (>95%) of patients did not have any or few difficulties with VKA specific treatment characteristics such as diet restrictions, follow-up appointments and dose adjustments. It is possible
that VKA initiation has a short-term negative impact on quality of life, but the lower quality of life in the beginning of the treatment could also result from the temporary distress associated with the diagnosis of AF and/or any comorbidity leading to the discovery of AF. However, in contrast to the assumption of some physicians that VKA use has a long-term negative influence on quality of life, VKA were well tolerated by AF patients after three months.

**DISCUSSION AND FUTURE PERSPECTIVE**

We described a series of large retrospective and prospective cohort studies with the aim to identify subgroups of vitamin K antagonist (VKA) users with a risk benefit ratio deviating from the total group of patients. This topic has received renewed interest since alternative treatment options have emerged with the introduction of new oral non-VKA anticoagulants (NOACs).

This thesis showed that the individual quality of VKA control could be partly predicted from baseline characteristics, and that VKA control during the first four weeks provided valuable extra information on the subsequent course of treatment. In addition, we demonstrated that overanticoagulation was a prelude for inferior quality of VKA control and poor clinical outcome in the next 90 days. We showed that, in contrast to common beliefs, the bleeding risk of VKA hardly increased after the age of 80 years. In a systematic review of the literature it became clear that patients with a VKA related bleed had a better clinical outcome when treated with than without a dosing protocol for prothrombin complex concentrate (PCC). Lastly, we found that patients with VKA had a comparable quality of life with patients without anticoagulants. Moreover, no patients or treatment related factors had a substantial influence on the treatment satisfaction and convenience.

Although we identified many promising predictors for poor VKA control, we did not validate these yet. This is in particular important for predictors based on clinical trial data, as strict in- and exclusion criteria can limit the generalizability. Furthermore, it is not certain whether the clinical outcome improves if patients with poor VKA control would be switched to an alternative anticoagulant treatment. The underlying problem might be poor treatment adherence for instance, which could even worsen with NOAC use. After validation of the predictors, the next step could therefore be the randomization of patients at high risk for poor VKA control between VKA continuation and NOACs.

Previous studies from our group showed that the efficacy and safety of VKA are comparable within the three quarters of patients without poor VKA control, independent of whether this is moderate or excellent control. The absence of risk factors for poor VKA control can thus also be used to identify patients with a high chance of adequate VKA control. We use this strategy to select patients for a presently enrolling randomized trial called ‘GAInN-study: Goede Antistolling In noord-Nederland’. The overall non-inferiority of NOACs may be the net result from superiority in those with potentially poor VKA control, and inferiority in those with potentially adequate VKA control. Therefore, the hypothesis of this trial is that AF patients with previously adequately controlled VKA have an inferior outcome with NOACs compared to VKA.

Although the EINSTEIN-data provided several independent predictors for the quality of VKA
control, the number of very old patients was too low to determine the relation between age and quality of VKA control above the age of 70 years. In real-life data from the Thrombosis Service Groningen, we showed that the mildly increased bleeding risk in the nonagenarians was almost completely explained by worse VKA control than in the septuagenarians. Also, the increased thrombotic risk in the octogenarians and nonagenarians compared to the septuagenarians, was partly explained by the poorer VKA control. Nevertheless, our data suggested that even patients over 90 years should be treated with anticoagulants if indicated. If we could improve VKA control, this may further optimize the efficacy and safety of VKA in the nonagenarians. For instance, the mean number of tablets was relatively low in the nonagenarians. This made it more challenging to make subtle dose adjustment in our cohort of patients mainly using the short-acting acenocoumarol. Possibly, this issue can be solved by the production of tablets of a quarter milligram by the pharmacy. Other options can be the use of a VKA with a longer half-life, resulting in more subtle INR changes after dose adjustments.

As previously mentioned, it is unknown whether switching to a NOAC would be beneficial, and this is especially questionable in the elderly. The use of NOACs requires an adequate renal clearance, and the clearance is poorer in the elderly. This makes that dehydration due to less intake, vomiting or diarrhea can lead easily to renal failure and consequent overanticoagulation followed by bleeding\(^1\). Although the first antidote for a NOAC (i.e. dabigatran) has been approved, the clinical outcome of anticoagulation related bleeds remains still poor after reversal\(^13,14\).

As a result of our systematic review a subcommittee on the control of anticoagulation from the International Society of Thrombosis and Haemostasis (ISTH) proposed and published a definition for haemostatic efficacy of antidotes used for anticoagulation related bleeds\(^15\). Hopefully, this definition will be adopted by future PCC and NOAC antidote studies, to enable comparing and pooling of data.

Furthermore, our research group has initiated a multicenter randomized trial (PROPER3) with the aim to determine whether a fixed dose is non-inferior compared to a dose based on weight, initial INR and target INR with respect to haemostatic efficacy. The fixed dose is easier to use and is less expensive, thus non-inferior efficacy would make it the superior strategy. Naturally, the definition of the ISTH is used to determine whether haemostatic efficacy is achieved or not. We expect the results from this trial in 2019.

The same reasoning applies to the comparison of VKA and NOACs. Several pivotal trials showed that the NOACs are non-inferior to VKA with regard to net clinical benefit, but it is commonly assumed that the higher convenience would make NOACs superior to VKA. However, we showed that patients on VKA do not suffer as a result of INR measurements, dose adjustment and interactions with food and drugs. Moreover, their quality of life was comparable to the general population. However, we did not compare VKA and NOAC use within patients. Possibly, patients do not report any inconvenience because they do not realize how easy life can be without VKA. On the other hand, a third of patients in another study report that the thrombosis service is a place to meet new friends\(^16\). The GAInN-study will provide more insight, as patients fill in general quality of life and treatment perception questionnaires before randomization, at six months and at end of study (12 months). This makes it
possible to compare treatment perception of VKA and NOACs within half of the patients. In addition, the treatment perception can be compared between the patients randomized to VKA and NOACs.

**CONCLUSION**

In this thesis, we presented predictors that could help identifying patients at risk for poor VKA control. We also showed that extreme overanticoagulation was followed by further deterioration of INR control and poor clinical outcome. On the other hand, we showed that even the eldest patient should get anticoagulants if indicated, and that VKA use did not have a negative impact on quality of life. Lastly, a systematic review of the literature pointed out that a universal definition for effective anticoagulant reversal was lacking.

Although these studies provided answers to clinically relevant questions, even more questions were generated. Hopefully, the GAINN and PROPER3 trials will bring some answers, and will help to choose the optimal treatment strategy for patients on VKA.
REFERENCES

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