Vitamin K and stability of oral anticoagulant therapy

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Summary and discussion

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The main objective of this thesis was to test the hypothesis that the INR is particularly sensitive to changes in vitamin K intake when vitamin K status is low, and that patients with a low vitamin K intake would therefore have an increased risk of unstable anticoagulation. We approached this problem in three ways. We looked at the effects of dietary vitamin K intake, of vitamin K status as assessed by serum assays and of administration of a vitamin K supplement.

In *chapter 3* we studied the effect of dietary vitamin K intake on the occurrence of subtherapeutic INRs. We determined the effect of usual vitamin K intake, consumed over a longer period of time, in a prospective cohort study. Within this cohort a nested case control study was performed to test whether an incidental high vitamin K intake results in a low INR and whether it does so more often in people with a low usual vitamin K intake. We found the risk of subtherapeutic INRs to be highest in individuals with a low usual vitamin K intake and lowest in those with a high usual intake. And we found that an incidental increase in vitamin K intake is a risk factor for a low INR exclusively in individuals with a low usual vitamin K intake.

In *chapter 5* we investigated whether supplementation with a low daily dose of vitamin K improves anticoagulant control in a double-blind randomized placebo-controlled trial. Patients were randomized to receive either adjusted-dose phenprocoumon and 100 μg vitamin K once daily or adjusted-dose phenprocoumon and a placebo. The choice for the 100 μg vitamin K supplement was made based on the pilot study described in *chapter 4*. In this chapter we determined the effect of escalating daily doses of vitamin K on the required dose of phenprocoumon. We found that a vitamin K supplement of 100 μg per day can safely be given on the condition that the INR is monitored frequently after starting and stopping the supplement to allow timely dose adjustments. In the trial, quality of anticoagulant control, expressed as time in therapeutic range (TTR) increased from 85.5% in the placebo group to 89.5% in the group receiving the vitamin K supplement. This improvement was attributable to a decrease in time above the therapeutic range rather than below the therapeutic range.

In the same trial we looked at the association between vitamin K status in serum and stability of anticoagulant treatment. The results are shown in *chapter 6*. In the placebo group each standard deviation (SD) increase in vitamin K_1 serum levels was associated with a 3.4% higher TTR. Vitamin K 2,3-epoxide increased the TTR with 2.7% per SD. In the group receiving the vitamin K supplement we found no effect of vitamin K status on the TTR, indicating that vitamin K status had no deleterious effect when patients were adequately supplemented.

The results of these three studies, using different methods, all confirm our hypothesis that patients with a poor vitamin K intake have reduced stability of anticoagulation. This has several implications. First of all, patients using VKAs should be advised to keep an adequate vitamin K intake. Secondly, supplementation of vitamin K may improve quality of anticoagulant treatment, especially in individuals with low vitamin K status. And finally, in ill patients, who are likely to have a low vitamin K status, small doses of vitamin K might be sufficient to correct overanticoagulation.

The recommendation for patients using VKAs to keep vitamin K intake adequate is supported by other studies[1-4] and is gaining acceptance[5;6]. This is in disagreement with earlier recommendations to limit or avoid foods high in vitamin K[7]. It seems rational to advise people to keep their vitamin K intake constant.[4;8-10] To combine these recommendations, keeping vitamin K intake constant and adequate, the most practical advice would be to adhere to a healthy diet that is suggested for the population in general: To consume 200 grams of vegetables and two pieces of fruit each day.

The recommendation to give a vitamin K supplement to improve stability of anticoagulant treatment is supported by other work as well[11;12]. Sconce *et al.* performed a randomized controlled trial similar to ours, but they included solely patients with unstable anticoagulant control. They found an increase in TTR from 78% in the placebo group to 87% in the vitamin K group. The larger effect in this trial than in ours may be caused by a lower vitamin K status in these unstable patients than in the patients in our trial, who were an unselected group of users of VKAs. A 4% increase in TTR seems too low a benefit to recommend vitamin K supplementation in all VKA users, but may be worthwhile in unstable patients or patients with

a low vitamin K intake. Indeed, it has been accepted as a recommendation in the Clinical Practice Guidelines of the American College of Chest Physicians: "For patients receiving long-term warfarin therapy with a variable INR response not attributable to any of the usual known causes for instability, we suggest a trial of daily low-dose oral vitamin K (100 to 200 μg), with close monitoring of the INR and warfarin dose adjustment to counter an initial lowering of the INR in response to vitamin K".[13] This is graded as a 2B recommendation, meaning that it is a weak recommendation based on moderate-quality evidence[14]. Future research should aim at identifying patients who benefit the most from supplementation (e.g. patients with unstable anticoagulant control, patients with low vitamin K intake or vitamin K status). Furthermore, the effect of a supplement on clinical endpoints should be evaluated.

Vitamin K is widely used to correct overanticoagulation.[13;15-17] Different doses are suggested for different levels of overanticoagulation[13]. But the effect of a single dose of vitamin K for a particular INR value differs between patients[18]. This can probably be partly explained by a different vitamin K status in patients. To our knowledge no studies have been done on this matter. It would be worthwhile to investigate whether establishing the vitamin K dose based on measured or presumed vitamin K status gives better outcomes than using an algorithm based on the INR only.

In *chapter 7* two computer algorithms for VKA dosing are compared in a double-blind controlled trial. The standard algorithm is based on pharmacodynamics of the VKA only, the new one includes pharmacokinetics and pharmacodynamics of the VKA, pharmacokinetics of the prothrombin complex, and the relationship between the activity of the prothrombin complex and the measured INR. We found no differences between the two algorithms in quality of anticoagulation or time between visits. The new algorithm did, however, result in more efficient dosing, since it gave a proposal in nearly all cases.

Chapter 2 describes the results of a study on occurrence of subtherapeutic INRs. In this cohort study in 13 443 patients of the Leiden anticoagulation clinic, 7 419 met the criteria for stability defined as four consecutive INRs

within the therapeutic range. Within four weeks of this stable period, 12% of patients had experienced a subtherapeutic INR and after 40 weeks this increased to 50%. Use of acenocoumarol doubled the risk of a subtherapeutic INR compared to phenprocoumon. The risk was also increased in patients with an indication for high intensity treatment and in patients who used VKAs as prophylaxis for venous thrombosis. In 30% of cases the subtherapeutic INR was preceded by an event that justified intentional lowering of the INR: An invasive procedure, haemorrhage or overanticoagulation.

The research described in this thesis provides insight in what causes unstable anticoagulant control, and subtherapeutic anticoagulant control in particular. The association between unstable control and adverse clinical outcomes has been convincingly established. Any decrease in time below and above the therapeutic range will result in fewer thrombotic and bleeding events, respectively. However, quality of anticoagulant control expressed as time in, above or below the therapeutic range remains a surrogate endpoint. Results such as described in this thesis are important to direct large randomized trials that are required to assess the effects on clinical endpoints.

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