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# Vitamin K and stability of oral anticoagulant therapy

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# Vitamin K and stability of oral anticoagulant therapy

**Eva K. Rombouts**

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# Vitamin K and stability of oral anticoagulant therapy

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door

**Eva Karolien Rombouts**

geboren te Amstelveen
in 1971

## Promotiecommissie

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| Promotor: | Prof. dr. F.R. Rosendaal |
| Copromotor: | Dr. F.J.M. van der Meer |
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| | Prof. dr. F.W.G. Leebeek (Erasmus Medisch Centrum) |
| | Dr. J.A.M. Wessels |

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# Contents

# 1

# General introduction

# General introduction

Vitamin K antagonists (VKAs) are among the most commonly prescribed drugs in western countries. They are used by approximately 2% of the population[1;2] and this number has kept growing over the past decade. VKAs are used to treat and prevent thrombosis. Their effectiveness for various indications has been proven in many well-designed studies. Indications include atrial fibrillation,[3] deep vein thrombosis, pulmonary embolism[4] and heart valve prostheses.[5]

Unfortunately, therapy with VKAs is not without drawbacks. One important limitation is their narrow therapeutic window: When, on the one hand, the intensity of anticoagulation, expressed as the International Normalized Ratio (INR) is too low, the risk of thrombosis increases up to that of untreated patients.[6-8] When, on the other hand, the INR is too high, the risk of bleeding complications increases sharply.[6;7;9] A second limitation of VKAs is the considerable variability in anticoagulant response. Not only does the required dose vary significantly between patients, but also VKAs are subject to interactions with drugs and diet, so the anticoagulant response for a particular patient often fluctuates over time. Because of these two properties (the narrow therapeutic window and the variability in anticoagulant response) the INR needs to be monitored closely and dose adjustments often need to be made. Despite intensive monitoring by specialized anticoagulation clinics, the INR is within the target range only 65-75% of time.[6] Side effects can be serious and account for 8% of medication-related hospital admissions.[10] While the narrow therapeutic window is inherent to treatment with VKAs, the variability in anticoagulant response can be influenced and knowledge about interactions is essential to improve quality of treatment. This thesis describes a series of studies investigating the effect of the most obvious interacting agent with vitamin K antagonists: vitamin K.

### Mode of action vitamin K antagonists

As their name suggests, vitamin K antagonists act by inhibiting vitamin K metabolism.[6] Vitamin K is essential for the synthesis of various proteins involved in blood coagulation, among which the clotting factors II, VII, IX

and X. These proteins undergo a post-translational modification that is required for them to function: Glutamate residues (Glu) are carboxylated to γ-carboxyglutamate (Gla). The carboxylation reaction occurs in the liver and is performed by γ-glutamyl carboxylase. This enzyme requires vitamin K in its reduced form (vitamin K hydroquinone) as a cofactor. During the carboxylation reaction, the vitamin K hydroquinone is converted to its inactive metabolite, vitamin K epoxide, which is subsequently converted back to vitamin K hydroquinone by vitamin K epoxide reductase (VKOR). Vitamin K antagonists inhibit VKOR, thereby blocking the turnover of vitamin K epoxide resulting in depletion of the active vitamin K stores. This leads to the desired anticoagulant effect due to reduced production of fully carboxylated vitamin-K dependent clotting factors.

**Treatment with vitamin K antagonist**

World-wide, warfarin is the most commonly prescribed VKA. In the Netherlands, acenocoumarol and phenprocoumon are used. The intensity of anticoagulation is determined by measuring the prothrombin time and expressed as the International Normalized Ratio (INR).[6] The INR was introduced in the early 1980s to standardize the highly variable prothrombin time assays. Many studies have been performed to determine the optimal intensity of the INR. In the Netherlands two target ranges are used, according to the guidelines of the Federation of Dutch Anticoagulation Clinics: INR 2.5 - 3.5 for low intensity treatment and INR 3.0 - 4.0 for high intensity treatment.[11] These ranges differ from the internationally used ranges, which are lower. The reason for these higher target ranges is to minimize the risk of subtherapeutic INRs, which are more common in clinical practice than in clinical trials.[12-14]

Genetic as well as many environmental factors influence the sensitivity to VKAs. Genetic factors include polymorphisms of the genes encoding a key enzyme in VKA metabolism (CYP2C9) and the VKA target enzyme VKOR (VKORC1). Environmental factors include drugs, diet and various disease states.[6;15] As a consequence, patients using VKAs need to be monitored at intervals of 1-6 weeks and the dosage is adjusted according to the INR result.[6] In the Netherlands, treatment with VKAs is most often managed by specialized anticoagulation clinics.[16]

Many developments have led to an improved quality of oral anticoagulant therapy with VKAs in the past: the introduction of the INR, the emergence of anticoagulation clinics,[17] computer aided dosing,[18;19] the establishment of the optimal target range[20;21] and progress in knowledge of interacting drugs.[22;23] Even today treatment with VKAs is in development: Patient self-testing of the INR using capillary blood obtained with a finger-prick has become increasingly common and allows patients to manage their anticoagulant treatment themselves.[24;25] Genotyping of patients to guide dosing is being investigated.[26;27] The different VKAs have been compared and have been shown to differ in quality of control, probably related to differences in their half-lives.[28;29] And even though the influence of dietary vitamin K intake has always been generally accepted, it was not until the last decade that more attention has been paid to this topic.

**Vitamin K and vitamin K antagonists**

The effect of pharmacological doses of vitamin K to lower the INR in case of overanticoagulation, bleeding complications or invasive procedures is well known.[30] The influence of physiological vitamin K intake on stability of oral anticoagulant treatment has had less attention in medical research. Knowledge of the effect of vitamin K intake on anticoagulant therapy has been based mainly on case reports and a few small experimental studies with extremely high vitamin K intakes.[31] In 2004, two studies on the influence of dietary vitamin K on the anticoagulant response were published.[32;33] These confirmed that the INR is influenced by dietary vitamin K intake and suggested that this influence is higher at a lower average vitamin K intake. This was supported by a study that showed that in patients with a low vitamin K status, even daily supplement doses as low as 25 microgram gave an important decrease of the INR, which was not observed in patients with a normal vitamin K status.[34] Sconce *et al.* reported that patients with a poor vitamin K intake had a more unstable control of anticoagulation.[35] Together, these studies support the hypothesis that the INR is relatively resistant to changes in vitamin K intake when average vitamin K intake is high. We set out to test this hypothesis and investigate whether supplementation with a low daily dose of vitamin K may improve anticoagulant stability.

**Outline of this thesis**

In *chapter 2* we describe a cohort study that we performed to determine the risk of subtherapeutic INRs in routinely treated patients. Within the cohort a nested case-control study was performed to identify risk factors associated with a low INR and to determine how often a subtherapeutic INR is the result of medical interference in case of invasive procedures, hospital admissions, haemorrhage or overanticoagulation.

In *chapter 3* we investigated the association between dietary vitamin K intake and the risk of subtherapeutic INRs. In a nested case-control study we determined the effect of both usual vitamin K intake, consumed over a longer period of time, and recent vitamin K intake. Also the interaction between usual and recent vitamin K intake was studied to determine whether the effect of an incidental increase in vitamin K intake differs between patients with a low or high usual vitamin K intake.

In *chapter 4* we present a pilot study that was performed to determine the highest dose of vitamin K that can safely be given to patients using VKAs. We studied the effect of escalating daily doses of vitamin K on the required dose of phenprocoumon. This vitamin K dose was used in the trial described in chapter 5.

In *chapter 5* we present a double blind, randomized, placebo-controlled trial that studied whether supplementation with a low daily dose of vitamin K improves anticoagulant control. Patients were randomized to receive either phenprocoumon and 100 μg vitamin K once daily or phenprocoumon and a placebo. The primary outcome is the percentage of time the INR is within the therapeutic range.

*Chapter 6* describes a study performed to determine whether there is an association between vitamin K status and stability of anticoagulant treatment. In participants of the trial presented in chapter 5, we examined the relationship between serum vitamin $K_1$ and its metabolite, vitamin K 2,3-epoxide and stability of anticoagulant treatment.

In *chapter 7* we evaluate the use of a new computer algorithm that was developed to improve computer aided dosing of VKAs. The new computer algorithm (ICAD) was compared, in a double blind randomized controlled trial, to an algorithm that is frequently used in the Netherlands (TRODIS).

The aim of this research is to provide insight in causes of unstable anticoagulant control, and subtherapeutic anticoagulation in particular. Because the risk of adverse events is inversely associated with stability of anticoagulation, knowledge of what influences stability will help to prevent thrombotic and bleeding complications. In the summary section we will translate our findings into clinical implications and recommendations for future research.

**References**


1. Qato DM, Alexander GC, Conti RM et al. Use of prescription and over-the-counter medications and dietary supplements among older adults in the United States. JAMA 2008;300:2867-2878.
2. Federatie Nederlandse Trombosediensten. Samenvatting medische jaarverslagen 2008. Adriaansen, H. J. and de Bruijn-Wentink, A. 2009.
3. Singer DE, Albers GW, Dalen JE et al. Antithrombotic therapy in atrial fibrillation: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:546S-592S.
4. Kearon C, Kahn SR, Agnelli G et al. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:454S-545S.
5. Salem DN, O'Gara PT, Madias C, Pauker SG. Valvular and structural heart disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:593S-629S.
6. Ansell J, Hirsh J, Hylek E et al. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:160S-198S.
7. Cannegieter SC, Rosendaal FR, Briët E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. Circulation 1994;89:635-641.
8. Hylek EM, Go AS, Chang Y et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. N.Engl.J.Med. 2003;349:1019-1026.
9. Reynolds MW, Fahrbach K, Hauch O et al. Warfarin anticoagulation and outcomes in patients with atrial fibrillation: a systematic review and metaanalysis. Chest 2004;126:1938-1945.
10. Leendertse AJ, Egberts AC, Stoker LJ, van den Bemt PM. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. Arch.Intern.Med. 2008;168:1890-1896.
11. Federatie Nederlandse Trombosediensten. Optimale intensiteit van antistolling. http://www.fnt.nl/artsen/streefwaarden-cumarinebehandeling . 14-5-0010.
12. Stroke Prevention in Atrial Fibrillation Study. Final results. Circulation 1991;84:527-539.
13. Connolly SJ, Laupacis A, Gent M et al. Canadian Atrial Fibrillation Anticoagulation (CAFA) Study. J.Am.Coll.Cardiol. 1991;18:349-355.
14. Samsa GP, Matchar DB, Goldstein LB et al. Quality of anticoagulation management among patients with atrial fibrillation: results of a review of medical records from 2 communities. Arch.Intern.Med. 2000;160:967-973.
15. Federatie Nederlandse Trombosediensten, het Wetenschappelijk Instituut Nederlandse Apothekers van de Knoninklijke Nederlandse Maatschappij ter bevordering der Pharmacie, and Stichting Health Base. Standaard afhandeling cumarine-interacties. 2010.
16. Rosendaal FR, van der Meer FJM, Cannegieter SC. Management of anticoagulant therapy: The dutch experience. J.Thromb.Haemost. 1996;2:265-269.

17. Cortelazzo S, Finazzi G, Viero P et al. Thrombotic and hemorrhagic complications in patients with mechanical heart valve prosthesis attending an anticoagulation clinic. Thromb.Haemost. 1993;69:316-320.
18. Ageno W, Turpie AG. A randomized comparison of a computer-based dosing program with a manual system to monitor oral anticoagulant therapy. Thromb.Res. 1998;91:237-240.
19. Poller L, Keown M, Ibrahim S et al. An international multicenter randomized study of computer-assisted oral anticoagulant dosage vs. medical staff dosage. J.Thromb.Haemost. 2008;6:935-943.
20. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb.Haemost. 1993;69:236-239.
21. Cannegieter SC, Rosendaal FR, Wintzen AR et al. Optimal oral anticoagulant therapy in patients with mechanical heart valves. N.Engl.J.Med. 1995;333:11-17.
22. Wells PS, Holbrook AM, Crowther NR, Hirsh J. Interactions of warfarin with drugs and food. Ann.Intern.Med. 1994;121:676-683.
23. Holbrook AM, Pereira JA, Labiris R et al. Systematic overview of warfarin and its drug and food interactions. Arch.Intern.Med. 2005;165:1095-1106.
24. Cromheecke ME, Levi M, Colly LP et al. Oral anticoagulation self-management and management by a specialist anticoagulation clinic: a randomised cross-over comparison. Lancet 2000;356:97-102.
25. Gadisseur AP, Breukink-Engbers WG, van der Meer FJ et al. Comparison of the quality of oral anticoagulant therapy through patient self-management and management by specialized anticoagulation clinics in the Netherlands: a randomized clinical trial. Arch.Intern.Med. 2003;163:2639-2646.
26. Sconce EA, Khan TI, Wynne HA et al. The impact of CYP2C9 and VKORC1 genetic polymorphism and patient characteristics upon warfarin dose requirements: proposal for a new dosing regimen. Blood 2005;106:2329-2333.
27. Schalekamp T, de Boer A. Pharmacogenetics of oral anticoagulant therapy. Curr.Pharm.Des 2010;16:187-203.
28. Gadisseur AP, van der Meer FJ, Adriaansen HJ, Fihn SD, Rosendaal FR. Therapeutic quality control of oral anticoagulant therapy comparing the short-acting acenocoumarol and the long-acting phenprocoumon. Br.J.Haematol. 2002;117:940-946.
29. Fihn SD, Gadisseur AA, Pasterkamp E et al. Comparison of control and stability of oral anticoagulant therapy using acenocoumarol versus phenprocoumon. Thromb.Haemost. 2003;90:260-266.
30. Schulman S, Beyth RJ, Kearon C, Levine MN. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:257S-298S.
31. Booth SL, Charnley JM, Sadowski JA et al. Dietary vitamin K1 and stability of oral anticoagulation: proposal of a diet with constant vitamin K1 content. Thromb.Haemost. 1997;77:504-509.
32. Khan T, Wynne H, Wood P et al. Dietary vitamin K influences intra-individual variability in anticoagulant response to warfarin. Br.J.Haematol. 2004;124:348-354.

33. Franco V, Polanczyk CA, Clausell N, Rohde LE. Role of dietary vitamin K intake in chronic oral anticoagulation: prospective evidence from observational and randomized protocols. Am.J.Med. 2004;116:651-656.
34. Kurnik D, Loebstein R, Rabinovitz H et al. Over-the-counter vitamin K(1)-containing multivitamin supplements disrupt warfarin anticoagulation in vitamin K(1)-depleted patients. Thromb.Haemost. 2004;92:1018-1024.
35. Sconce E, Khan T, Mason J et al. Patients with unstable control have a poorer dietary intake of vitamin K compared to patients with stable control of anticoagulation. Thromb.Haemost. 2005;93:872-875.

# 2

# Subtherapeutic oral anticoagulant therapy:
## Frequency and risk factors

*E.K. Rombouts, F.R. Rosendaal, F.J.M. van der Meer*

*Thrombosis and Haemostasis. 2009; 101: 552-556*

# Abstract

**Background**

Subtherapeutic anticoagulation levels increase both the risk and severity of thromboembolism. The aim of this study was to determine the cumulative incidence of subtherapeutic international normalized ratios (INRs) and to identify risk factors associated with a low INR.

**Methods**

We performed a cohort study in 7 419 patients from a Dutch anticoagulation clinic. Patients who started a first treatment with oral anticoagulants between January 2000 and December 2005 and who were stably anticoagulated (4 consecutive INRs in the therapeutic range) were included. Within the cohort a nested case-control study was performed to identify risk factors of subtherapeutic INRs and to determine how often a subtherapeutic INR is the result of medical interference in case of invasive procedures, hospital admissions, hemorrhage or overanticoagulation.

**Results and conclusions**

In patients with a stable anticoagulation, the median time to a first low INR was 40 weeks. A subtherapeutic INR occurred twice as often in patients using acenocoumarol as in those using phenprocoumon (hazard ratio [HR] 2.1, 95% Confidence Interval [95%CI]: 2.0-2.3) and was more common in patients with a high therapeutic range compared to a low therapeutic range (HR 1.8, 95%CI: 1.5-2.2). Occurrence of a low INR also depended on indication for anticoagulant therapy, with the highest risk in patients who used anticoagulants as prophylaxis and the lowest risk in patients with mechanical heart valves. In 30% of cases the subtherapeutic INR was preceded by an event necessitating vitamin K or discontinuation of the anticoagulant drug.

# Introduction

Oral anticoagulant therapy with vitamin K antagonists has been proven effective in primary and secondary prevention of both venous and arterial thrombosis.[1-3] Treatment with these drugs requires careful monitoring because of a narrow therapeutic range. When the intensity of anticoagulation (expressed as the International Normalized Ratio or INR) is high the risk of bleeding events is increased.[4-6] Low INRs increase not only the frequency of thromboembolism but also its severity and the associated risk of death.[6-11]

Despite frequent monitoring of the INR, subtherapeutic anticoagulation is common. In primary prevention trials, the INR was below the target range 8 to 40% of the time.[12-16] In clinical practice, time below the target range of up to 26-52% has been reported.[8;9;17] These numbers depend strongly on the target range used. In addition, in the initial phase of oral anticoagulant therapy patients spend more time below the target range than during long-term use, since it usually takes some time before stable anticoagulation is achieved. Time in, above or below the therapeutic range can thus vary widely between populations.

Much research has been done on causes of overanticoagulation and unstable anticoagulant control.[18-21] Causes of subtherapeutic anticoagulation are less well understood. In order to improve anticoagulant control, it is also important to identify risk factors for subtherapeutic INRs and to recognize how often these are the result of discontinuation of the anticoagulant drug in case of surgery, invasive procedures or bleeding.

The aim of this study was: 1. To determine the frequency of low INR values in patients who are stably anticoagulated, 2. To identify risk factors for subtherapeutic INRs and 3. To determine the contribution of vitamin K administration or discontinuation of the anticoagulant drug to the risk of developing a subtherapeutic INR.

# Methods

### Study design

We performed a retrospective follow-up study within a cohort of patients from the Leiden anticoagulation clinic. The cohort consisted of all patients who started a first treatment with oral anticoagulants between January 2000 and December 2005 and who had reached stable anticoagulation. Stable anticoagulation was defined as four consecutive INRs in the therapeutic range. The therapeutic range was defined as agreed by the Federation of Dutch Anticoagulation Clinics: INR 2.0-3.5 (target INR 3.0) for low intensity and 2.5-4.0 (target INR 3.5) for high intensity treatment. Patients in the cohort were followed from the date they reached stability until the first subtherapeutic INR, the end of treatment, an interruption of follow-up for more than 9 weeks or at the end of the study period. Because follow-up ended when a patient had a subtherapeutic INR, patients in the cohort had therapeutic or high INRs only.

Within this cohort we performed a nested case-control study. Cases were all patients who, after reaching stable anticoagulation, had a first subtherapeutic INR. For each case a control patient was selected from the cohort, who had an INR measurement on the same day as the case (index date) and had not yet had a subtherapeutic INR. This method is known as incidence density sampling. The Odds Ratio (OR) calculated from case-control studies using incidence density sampling is a valid estimation of the Rate Ratio, even if the outcome under study is frequent.[22] Controls were matched individually to the cases on duration of treatment. For both cases and controls computer records were checked for any of the following events in the four weeks prior to the index date: invasive procedures, hospital admissions, hemorrhages, an INR >7.0, use of vitamin K or discontinuation of the anticoagulant drug for two or more days. The four-week window was chosen to account for the long half-life of phenprocoumon.

**Setting**

In the Netherlands, all patients on oral anticoagulants are treated by specialized anticoagulation clinics. This study was performed at the Leiden anticoagulation clinic, where nearly 10 000 patients are treated each year. Patients are seen by trained nurses every 1-6 weeks. At every visit, blood for an INR measurement is collected via venipuncture and the patient is asked to report any special circumstances, such as non-compliance, bleeding episodes, changes in co-medication, hospital visits or (surgical) procedures. The history is taken according to the anticoagulation clinic's quality guidelines. Because the history is taken before the INR result is known, the information was obtained in a similar manner for cases and controls. INR results and prescribed dosages are recorded in a central database, along with relevant history details and information on admissions and interventions. The following bleeding episodes are recorded: All intracranial, retroperitoneal, muscle, joint, ocular and subconjunctival bleeds, all hemorrhage from the gastro-intestinal, respiratory and urogenital tracts, epistaxis when longer than 30 minutes and bruises more than 10 cm in diameter.

Two oral anticoagulant agents are available in the Netherlands, acenocoumarol (with a half-life of 8-11 hours [h]) and phenprocoumon (Marcoumar®, half-life approximately 160 h). In the Leiden anticoagulation clinic phenprocoumon is used by approximately 90% of patients.

Indications for anticoagulant therapy are categorized as follows: Atrial fibrillation, secondary prevention venous thrombosis (any venous thrombotic event), mechanical heart valves (mitral and/or aorta), arterial indications (primary and secondary prevention of myocardial infarction, stroke and peripheral embolism) and prophylaxis (primary prevention of venous thrombosis after surgery or in other high-risk situations)

**Analysis**

In the full cohort, we used the Kaplan-Meier method to estimate the risk of subtherapeutic INRs in patients with a stable anticoagulation. Time to a first subtherapeutic INR was defined as the time between obtaining a stable anticoagulation and the date of a first subtherapeutic INR. Patients were censored at the end of treatment, at the end of the study period or when

follow-up was interrupted for more than nine weeks. The effect of patient and treatment characteristics on the risk of a low INR was evaluated with Cox proportional hazards regression.

ORs for the transient risk factors in the case control analysis were calculated with conditional logistic regression.

## Results

During the study period 13 443 patients started a first treatment with oral anticoagulants. Of those, 7 419 reached stable anticoagulation, i.e. had four consecutive INRs within the target range. The average time to stable anticoagulation was 12 weeks (range 1 -211 weeks). Of those patients that did not reach stable anticoagulation, the average follow-up time was seven weeks (range 0 -133 weeks). The total follow-up time of stable patients was 4 037 patient-years, the average follow-up time per patient was 28 weeks (range 0 -304 weeks. Of the 7 419 stable patients, 3 166 had one or more subtherapeutic INRs during follow-up.

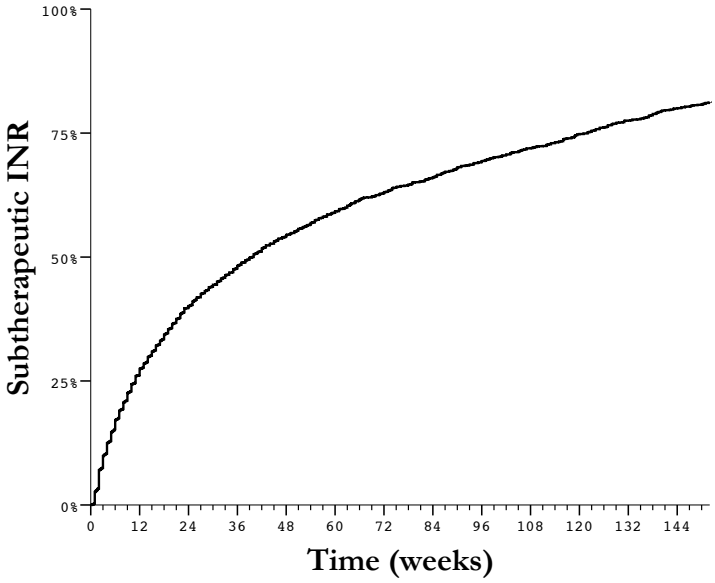


**Figure 1:** Kaplan-Meier curve of the likelihood of a subtherapeutic INR in patients with a stable anticoagulation. On the x-axis time since stable anticoagulation. On the y-axis the proportion of patients who had a subtherapeutic INR.

There were two thromboembolic events in the period between the last known INR before - and the first non-subtherapeutic INR after the subtherapeutic episode. One patient had an ischemic stroke 6 days before the index-date for which she was admitted (INR at admission unknown). One patient suffered a mechanical valve thrombosis and survived cardiopulmonary resuscitation 8 days after the index-date (INR at admission 2.3).

Figure 1 shows the Kaplan Meier curve of the risk of a first subtherapeutic INR in stable patients. After four weeks 12% of patients had had a subtherapeutic INR. This increased to 21% at 8 weeks and after 40 weeks 50% had had a low INR.

**Table 1:** Patient characteristics and the median time to a first subtherapeutic INR in different patient groups. **Adjusted for sex, age, anticoagulant used, target range, and indication category. HR, Hazard Ratio; 95%CI, 95% confidence interval*

| | Number of patients (percentage) | Median time to a low INR (weeks - 95%CI) | Crude HR (95%CI) | Adjusted HR* (95%CI) |
|---|---|---|---|---|
| **Sex** | | | | |
| Male (ref) | 3788 (51%) | 42 (38-46) | 1 | 1 |
| Female | 3631 (49%) | 37 (33-40) | 1.12 (1.04-1.20) | 1.07 (0.99-1.15) |
| **Anticoagulant** | | | | |
| Phenprocoumon (ref) | 5748 (78%) | 51 (47-55) | 1 | 1 |
| Acenocoumarol | 1639 (22%) | 13 (12-15) | 2.30 (2.12-2.50) | 2.14 (1.96-2.33) |
| Therapeutic range | | | | |
| Low (2.0-3.5) (ref) | 6351 (86%) | 48 (44-52) | 1 | 1 |
| High (2.5-4.0) | 1068 (14%) | 21 (19-23) | 1.58 (1.46-1.71) | 1.83 (1.53-2.19) |
| **Age** | | | | |
| < 50 years | 1337 (18%) | 26 (21-31) | 1.30 (1.18-1.44) | 1.15 (1.03-1.29) |
| 50 - 70 years | 2812 (38%) | 42 (37-47) | 0.96 (0.89-1.03) | 0.93 (0.86-1.00) |
| >70 years (ref) | 3270 (44%) | 42 (38-46) | 1 | 1 |
| **Indication** | | | | |
| Atrial fibrillation (ref) | 2778 (37%) | 58 (52-64) | 1 | 1 |
| Secondary prevention venous thrombosis | 1544 (21%) | 31 (25-37) | 1.45 (1.31-1.61) | 1.36 (1.21-1.52) |
| Mechanical heart valves | 189 (3%) | 66 (41-91) | 0.95 (0.78-1.16) | 0.69 (0.56-0.86) |
| Arterial indications | 1229 (17%) | 23 (20-26) | 1.67 (1.53-1.82) | 0.96 (0.81-1.15) |
| Prophylaxis | 1679 (23%) | 14 (10-19) | 2.51 (2.20-2.86) | 1.88 (1.64-2.16) |

**Table 2:** Influence of events requiring medical intervention on subtherapeutic anticoagulation. [*] *Number of patients who experienced the indicated event in the four weeks prior to the index-date.* [†] *Adjusted for sex, age, anticoagulant used, target range, and indication category. OR, Odds Ratio; 95%CI, 95% confidence interval.*

| | Patients with a subtherapeutic INR *(n = 3 166)* | | | | Control subjects *(n = 3 146)* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Number of patients (percentage)[*] | Vitamin K | Discontinued | Not stopped Unknown | Number of patients (percentage)[*] | Vitamin K | Discontinued | Not stopped, Unknown | Crude OR (95%CI) | Adjusted OR (95%CI) |
| Hemorrhage | 188 (5.9%) | 68 | 1 | 119 | 52 (1.7%) | 7 | 0 | 45 | 3.8 (2.8-5.1) | 4.8 (3.5-6.6) |
| Surgical admission | 207 (6.5%) | 78 | 65 | 64 | 49 (1.6%) | 16 | 16 | 17 | 4.4 (3.2-6.1) | 5.8 (4.2-8.0) |
| Medical admission | 156 (4.9%) | 9 | 2 | 145 | 52 (1.7%) | 0 | 3 | 49 | 3.1 (2.2-4.2) | 4.0 (2.9-5.5) |
| Invasive procedure | 355 (11.2%) | 249 | 98 | 8 | 31 (1.0%) | 25 | 3 | 3 | 12.7 (8.8-18.4) | 17.2 (11.9-25.0) |
| INR > 7.0 | 81 (2.6%) | 73 | 6 | 2 | 51 (1.6%) | 45 | 5 | 1 | 1.6 (1.1-2.3) | 1.6 (1.1-2.4) |
| Any event | 955 (30.2%) | 450 | 170 | 335 | 229 (7.3%) | 90 | 25 | 114 | 5.5 (4.7-6.4) | 3.9 (3.1-4.8) |

There was no difference in risk of a subtherapeutic INR between men and women (Table 1). Patients aged younger than 50 years had a slightly increased risk of a low INR. Use of the anticoagulant drug acenocoumarol doubled the risk compared to the longer acting phenprocoumon (adjusted HR 2.14, 95%CI: 1.96-2.33). In patients using acenocoumarol the median time to a first subtherapeutic INR was 13 weeks compared to 51 weeks in the phenprocoumon group. In patients with an indication for high-intensity treatment the median time to a first low INR was 21 weeks, compared to 48 weeks in patients with low intensity treatment. (adjusted HR 1.83, 95%CI: 1.53-2.19). Occurrence of a subtherapeutic INR also depended on indication for treatment, with the highest risk in patients who used oral anticoagulants as prophylaxis for venous thromboembolism and the lowest risk in patients with mechanical heart valves (Table 1).

A low INR was preceded by an event necessitating discontinuation of treatment in 30% of cases (Table 2). These were mainly invasive procedures (11.2% of cases, 1.0% of controls), surgical admissions (6.5% of cases, 1.6% of controls) and hemorrhages (5.9% of cases and 1.7% of controls). Vitamin K was used in the four weeks preceding the index date by 14.2% of cases and 2.9% of controls. Of the patients undergoing an invasive procedure 70% of cases received vitamin K versus 81% in control patients. Treatment was discontinued for two or more days in 5.4% of cases and 0.8% of controls.

## Discussion

After reaching stable anticoagulation fifty percent of patients had a subtherapeutic INR within 40 weeks. We chose to present the cumulative incidence in patients with a stable anticoagulation, because patients with a low INR are not at risk for *getting* a low INR. The criteria for a stable anticoagulation (4 consecutive INRs in the therapeutic range) were stringent, and were met by only approximately half of patients. This must be kept in mind when interpreting the results: In patients starting treatment with vitamin K antagonists the risk of underanticoagulation will be higher. In these patients many of the subtherapeutic INRs will be caused by too

low dosages of the anticoagulant drug, because it usually takes some time before the right dosage is known for an individual patient.

Two patients suffered a thromboembolic event in the period before and after the subtherapeutic INR. The design of our study was not suited to calculate an absolute risk. Furthermore, it is difficult to estimate the risk period, because the duration of the subtherapeutic INR before the index-date and after the last low INR is unknown.

We found several patient and treatment characteristics that were associated with the risk of underanticoagulation. A possible explanation for the difference in frequency of occurrence of subtherapeutic anticoagulation amongst the indication categories may be a difference in compliance: The risk was highest in patients who used anticoagulation as primary prophylaxis for venous thromboembolism and lowest in patients with mechanical heart valves, who have the highest underlying risk of thrombosis. The increased risk for patients with an arterial indication disappeared completely after adjustment for target range, indicating that the latter is the real association. One possible explanation for the higher risk of a subtherapeutic INR in high therapeutic range patients is that dosing physicians are more inclined to lower the dose when the INR is high in range in these patients than in the low therapeutic range patients. The most striking difference was between phenprocoumon and acenocoumarol. Fifty percent of patients using acenocoumarol had a subtherapeutic INR after 13 weeks compared to 51 weeks in patients using phenprocoumon. This finding is consistent with reports that longer-acting vitamin K antagonist give a more stable anticoagulation than short-acting vitamin K antagonists.[23-25]

Thirty percent of cases of a subtherapeutic INR were preceded by a bleeding episode, a surgical or medical admission, an invasive procedure or by an INR >7.0. Invasive procedures gave the highest risk of a low INR. Because the anticoagulant drug was withheld or vitamin K was given in nearly all patients, this is not surprising. Vitamin K is given to a relatively large proportion of patients, because in our study population 78% of patients use the long-acting phenprocoumon. However, vitamin K was given in even more control patients than case patients who underwent an invasive procedure. This suggests that in this study population

administering vitamin K peri-intervention reduced the risk of a subtherapeutic INR compared to withholding the anticoagulant drug.

The risk was lower in patients who were admitted for a surgical intervention than in outpatients undergoing an invasive procedure, although one would have expected similar risks. It is possible that subtherapeutic INRs occurred during admission but were adjusted before the end of the admission. Admissions for non-surgical reasons also led to a subtherapeutic INR, but less often. Even though overanticoagulation was common (INR > 7.0 in 1.6% of the controls) and vitamin K was given in nearly all patients, the relative risk of a low INR after an INR above 7.0 was only 1.6. This suggests that over-correcting, though present, is not a major cause of a subtherapeutic INR.

Subtherapeutic anticoagulation in patients using vitamin K antagonists is common and can have severe consequences. Our results give insight in the risk of subtherapeutic anticoagulation for an individual patient in the outpatient setting. We have shown that subtherapeutic INRs are common and that thirty percent of all subtherapeutic INRs could be explained by events necessitating discontinuation of the treatment, leaving 70% that were unintended. We have described risk factors that contribute to these low INRs and that can be used to prevent them. A first step can be the preferential use of long acting anticoagulants, such as phenprocoumon. Whether the differences in risk between indications are the effect of avoidable causes such as patient compliance or dosing strategies remains to be determined.

**References**


1. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. Arch.Intern.Med. 1994;154:1449-1457.
2. Lagerstedt CI, Olsson CG, Fagher BO, Oqvist BW, Albrechtsson U. Need for long-term anticoagulant treatment in symptomatic calf-vein thrombosis. Lancet 1985;2:515-518.
3. van Walraven C, Hart RG, Singer DE et al. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. JAMA 2002;288:2441-2448.
4. Ansell J, Hirsh J, Hylek E et al. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:160S-198S.
5. Reynolds MW, Fahrbach K, Hauch O et al. Warfarin anticoagulation and outcomes in patients with atrial fibrillation: a systematic review and metaanalysis. Chest 2004;126:1938-1945.
6. Cannegieter SC, Rosendaal FR, Wintzen AR et al. Optimal oral anticoagulant therapy in patients with mechanical heart valves. N.Engl.J.Med. 1995;333:11-17.
7. Hylek EM, Go AS, Chang Y et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. N.Engl.J.Med. 2003;349:1019-1026.
8. Go AS, Hylek EM, Chang Y et al. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? JAMA 2003;290:2685-2692.
9. Kalra L, Yu G, Perez I, Lakhani A, Donaldson N. Prospective cohort study to determine if trial efficacy of anticoagulation for stroke prevention in atrial fibrillation translates into clinical effectiveness. BMJ 2000;320:1236-1239.
10. Wyse DG, Waldo AL, DiMarco JP et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N.Engl.J.Med. 2002;347:1825-1833.
11. Hylek EM, Skates SJ, Sheehan MA, Singer DE. An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation. N.Engl.J.Med. 1996;335:540-546.
12. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. N.Engl.J.Med. 1990;323:1505-1511.
13. Stroke Prevention in Atrial Fibrillation Study. Final results. Circulation 1991;84:527-539.
14. Connolly SJ, Laupacis A, Gent M et al. Canadian Atrial Fibrillation Anticoagulation (CAFA) Study. J.Am.Coll.Cardiol. 1991;18:349-355.
15. Ezekowitz MD, Bridgers SL, James KE et al. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. N.Engl.J.Med. 1992;327:1406-1412.
16. Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. Lancet 1989;1:175-179.

17. Samsa GP, Matchar DB, Goldstein LB et al. Quality of anticoagulation management among patients with atrial fibrillation: results of a review of medical records from 2 communities. Arch.Intern.Med. 2000;160:967-973.
18. Penning-van Beest FJ, van Meegen E, Rosendaal FR, Stricker BH. Characteristics of anticoagulant therapy and comorbidity related to overanticoagulation. Thromb.Haemost. 2001;86:569-574.
19. Penning-van Beest FJ, van Meegen E, Rosendaal FR, Stricker BH. Drug interactions as a cause of overanticoagulation on phenprocoumon or acenocoumarol predominantly concern antibacterial drugs. Clin.Pharmacol.Ther. 2001;69:451-457.
20. Palareti G, Legnani C, Guazzaloca G et al. Risks factors for highly unstable response to oral anticoagulation: a case-control study. Br.J.Haematol. 2005;129:72-78.
21. Cadiou G, Varin R, Levesque H et al. Risk factors of vitamin K antagonist overcoagulation. A case-control study in unselected patients referred to an emergency department. Thromb.Haemost. 2008;100:685-692.
22. Szklo M, Nieto FJ. Basic Study Designs in Analytical Epidemiology. Epidemiology: beyond the basics.: Jones and Bartlett Publishers; 2004:3-51.
23. Gadisseur AP, van der Meer FJ, Adriaansen HJ, Fihn SD, Rosendaal FR. Therapeutic quality control of oral anticoagulant therapy comparing the short-acting acenocoumarol and the long-acting phenprocoumon. Br.J.Haematol. 2002;117:940-946.
24. Fihn SD, Gadisseur AA, Pasterkamp E et al. Comparison of control and stability of oral anticoagulant therapy using acenocoumarol versus phenprocoumon. Thromb.Haemost. 2003;90:260-266.
25. Pattacini C, Manotti C, Pini M, Quintavalla R, Dettori AG. A comparative study on the quality of oral anticoagulant therapy (warfarin versus acenocoumarol). Thromb.Haemost. 1994;71:188-191.

# 3

# Influence of dietary vitamin K intake on subtherapeutic oral anticoagulant therapy

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# Abstract

**Background**

It is unclear what advice should be given to patients using vitamin K antagonists with respect to dietary vitamin K intake.

**Methods**

We performed a nested case-control study in patients attending a Dutch anticoagulation clinic, to determine the association between vitamin K intake and subtherapeutic International Normalized Ratio (INR) values and the interaction between usual and recent vitamin K intake.

**Results**

Compared to patients with a normal usual vitamin K intake, those with a high vitamin K intake had a decreased risk of a subtherapeutic INR [Hazard Ratio (HR) 0.80, 95%CI: 0.56-1.16) and patients with a low vitamin K intake an increased risk (HR 1.33, 95%CI: 0.79-2.25). In patients with a low usual vitamin K intake, recent vitamin K intake was twice as high in cases as in controls (164 vs 85 μg/d). Such a difference was not observed in patients with a normal or high usual vitamin K intake.

**Conclusions**

Our results suggest that a high vitamin K intake reduces the risk of a low INR by lessening the influence of incidental consumption of vitamin K rich food on the INR. These findings support the recommendation for patients on vitamin K antagonists to eat a sufficient amount of vitamin-K containing foods.

# Introduction

Oral anticoagulant treatment with vitamin K antagonists is effective in the primary and secondary prevention of both arterial and venous thrombosis. Side effects are common, and are frequently caused by unstable anticoagulation. Hemorrhagic complications are more frequent when the INR is too high.[1-3] When the INR is too low the risk of thrombosis is increased.[1;3;4] It is therefore important to keep the INR within the therapeutic range.

Many factors are associated with instability of oral anticoagulant treatment, the most important being the presence of intercurrent illnesses,[5] drug interactions,[3] genetic factors[6] and the anticoagulant drug used, particularly its half-life.[7;8] Another factor that may influence the stability of anticoagulation is dietary vitamin K intake.[9-11]

Vitamin K is an essential cofactor for the post-translational carboxylation of various proteins involved in blood coagulation, among which the procoagulant factors II, VII, IX and X. During the carboxylation reaction, the vitamin K hydroquinone is oxidized to vitamin K epoxide. Vitamin K epoxide must be recycled to the reduced form before it can be reused, a process that is catalyzed by vitamin K epoxide reductase (VKOR). Vitamin K antagonists inhibit VKOR, blocking the turnover of vitamin K and depleting the liver of its active vitamin K stores. This leads to the desired anticoagulant effect due to reduced production of vitamin-K dependent clotting factors.[6]

The effect of pharmacological doses of vitamin K, prescribed in patients receiving vitamin K antagonists to lower the INR in case of overanticoagulation, bleeding complications or invasive procedures, is well known.[3;12;13] Also, several studies have been performed to assess the short-term effect of dietary vitamin K intake on the INR in patients treated with vitamin K antagonists. Results were as expected: An increased vitamin K intake was associated with a decrease in the INR and a decreased vitamin K intake with a rise of the INR.[9;14;15] The influence of the usual dietary vitamin K intake, consumed over a longer period of time, has been less well studied. Because the dosage of the anticoagulant drug is adjusted according to the measured INR and thus indirectly to vitamin K intake, the effect of usual

vitamin K intake is also less predictable. One study showed that in unstable patients, vitamin K intake was considerably lower than in stably anticoagulated patients.[10] Another study did not show any association between dietary vitamin K intake and the risk of overanticoagulation.[16] We found no studies that investigated the association between dietary vitamin K intake and the risk of a subtherapeutic INR.

To determine what advice can best be given to patients using vitamin K antagonists regarding vitamin K intake, it is necessary to know the effect of dietary vitamin K intake on the risk of both over- and under-anticoagulation. The aim of this study was to determine the effect of dietary vitamin K intake on the occurrence of subtherapeutic INRs. Because changes in vitamin K intake are proportionally larger in people with a low usual vitamin K intake, we hypothesized that especially in these patients an incidental increase in vitamin K intake would be a risk factor for subtheraupeutic INRs, which would therefore occur frequently.

## Methods

This prospective cohort study was performed to investigate the effect of usual vitamin K intake on the risk of a subtherapeutic INR. Within the cohort a nested case-control group was studied to assess the effect of recent vitamin K intake on the risk of a low INR and the interaction between usual and recent vitamin K intake.

The cohort consisted of patients from the Leiden anticoagulation clinic in the Netherlands, who had a first episode of stable anticoagulation between 1 January 2005 and 20 December 2005. It included both patients who started treatment before 2005 and who reached stable anticoagulation for the first time during the study period as well as patients who started treatment and reached stable anticoagulation during the study period. Stable anticoagulation was defined as four consecutive INRs in the therapeutic range [as agreed by the Federation of Dutch Anticoagulation Clinics: INR 2.0-3.5 (target INR 3.0) for low intensity and 2.5-4.0 (target INR 3.5) for high intensity treatment]. The cohort was restricted to patients who had reached stable anticoagulation in order to reduce variability in the risk of subtherapeutic INRs caused by other factors that are known to cause

instability: Dose finding of the vitamin K antagonist, changes in the use of interacting medication such as antibiotics or amiodarone and the presence of conditions or symptoms known to influence the anticoagulant effect, such as heart failure, post-operative anorexia, fever, etc.

The main outcome was a subtherapeutic INR (<2.0 for low intensity <2.5 for high intensity treatment).

Once patients had reached stable anticoagulation they received a questionnaire by mail, including a food frequency questionnaire (FFQ) to determine the usual vitamin K intake (see below). Patients were then followed until the first subtherapeutic INR, the end of treatment or the end of the study period (20 December 2005), whichever occurred first. During follow-up patients regularly attended the anticoagulation clinic for INR measurements and received standard care.

Within the cohort we performed a nested case-control study. When patients had a first sub-therapeutic INR after stable anticoagulation they became a case. For each case, two control patients were selected who had an INR measurement on the same day as the case. Controls were patients from the same cohort, i.e., who had reached stable anticoagulation, but who did not at that time had experienced a low INR. By this method, controls were matched to the cases on duration of follow-up. Cases were allowed to have been entered in the study previously as a control patient but patients were selected as a control only once.

Both cases and controls were contacted by telephone on the day of the INR measurement. Subjects were asked questions on special circumstances that may have contributed to the subtherapeutic INR such as invasive procedures, comorbidity, compliance and recent vitamin K intake. To avoid interviewer bias the interviewer was blind with respect to the INR result. Cases who had stopped anticoagulant therapy or had been given vitamin K were excluded from the analysis.

Baseline demographic data and clinical data such as age, sex, indication for anticoagulation, therapeutic range and the anticoagulant drug used were retrieved from the anticoagulation clinic's computer files. Comorbidity was derived from the questionnaire (self-reported) and the comorbidity score was calculated in a similar fashion to the Charlson comorbidity score,[17] adding 1 point for the presence of myocardial infarction, congestive heart

failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, mild liver disease and diabetes, 2 points for moderate or severe renal disease, any malignancy, leukemia or malignant lymphoma, 3 points for moderate or severe liver disease and 6 points for metastatic solid malignancy.

Usual vitamin K intake was assessed using an FFQ, including those items that contribute most to vitamin K intake in the Dutch population, either because of a high vitamin K content, because of frequent consumption or a combination of those. This list was composed using a table of the vitamin K content of food items[16] and the Dutch national food consumption survey carried out by the Netherlands Organization for Applied Scientific Research in 1997-1998.[18] Fifty-seven questions were asked on 42 food items, 31 of which were vegetables or fruits, the others dairy, oils and miscellaneous. Based on the result of this food frequency questionnaire patients were categorized as having a low (<100 μg vitamin K per d), a normal (100-300 μg/d) or a high vitamin K intake (>300μg vitamin K per d).

Recent vitamin K intake was estimated using a 48-h recall conducted over the telephone. Included in the questionnaire were those food items that contain the highest vitamin K intake per portion. We used the same table with the vitamin K content of foods,[16] the Dutch national food consumption survey[18] and normal serving sizes[19] to calculate the average intake per portion. The 48-h recall included 32 items.

In the analysis of the full cohort, we used the Kaplan-Meier method to calculate the risk of subtherapeutic INRs in patients with a stable anticoagulation. Time to a first subtherapeutic INR was defined as the time between stable anticoagulation and the date of a first subtherapeutic INR. Patients were censored at the end of treatment, at the end of the study period, when follow-up was interrupted for more than 9 weeks or when they received vitamin K or stopped taking their vitamin K antagonist. The effect of usual vitamin K intake on the risk of a low INR was evaluated with Cox proportional hazards regression. In the case control analysis the amount of vitamin K consumed in the 48 hours before the index date was compared between cases and controls. Adjustment for possible confounders (age category, sex and season of recent vitamin K intake

measurement) and the matching factor (time since stable anticoagulation) was performed using linear regression analysis. Odds ratios were calculated with conditional logistic regression. Statistical analyses were performed using SPSS version 12 (SPSS Inc, Chicago, Ill, USA).

## Results

Of the 9 889 patients who were registered at the Leiden anticoagulation clinic between 1 January 2005 and 20 December 2005, 7 855 had reached stable anticoagulation prior to 1 January 2005, 877 did not reach stable anticoagulation and 1 157 reached a first episode of stable anticoagulation and received the questionnaire (Figure 1).

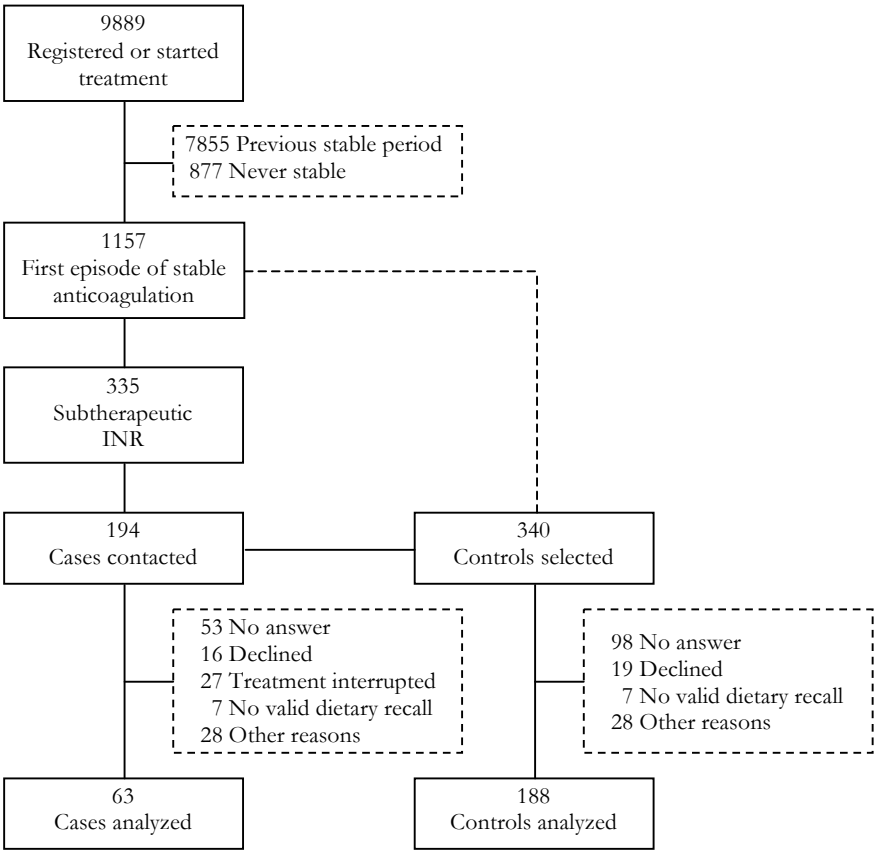



**Figure 1:** Flow of patients during follow-up.

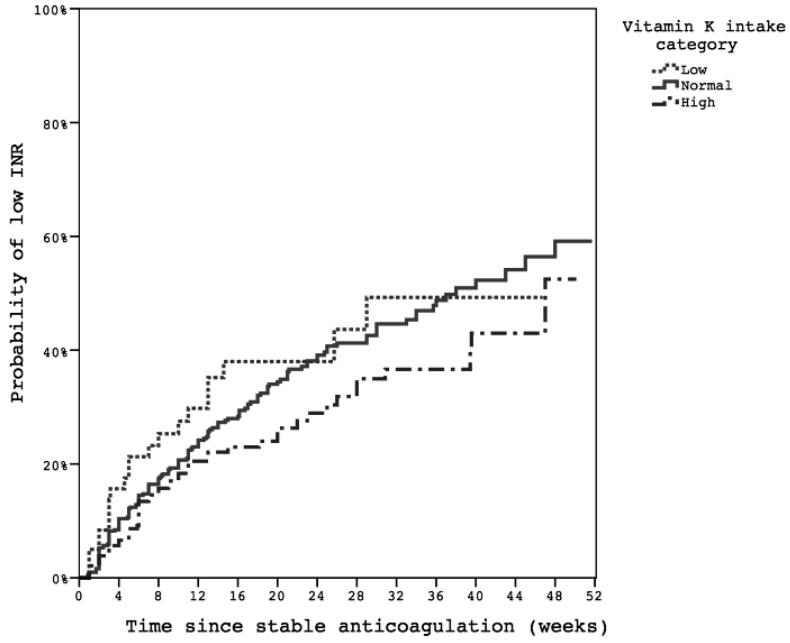
**Table 1**: Patient and treatment characteristics according to vitamin K intake category. Data are presented as number (percentage) of patients. * *n = 36*

| | No. (%) of patients *(n = 1 157)* | Vitamin K intake | | | |
|---|---|---|---|---|---|
| | | Normal *(n = 526)* | Low *(n = 61)* | High *(n = 253)* | Missing *(n = 317)* |
| Sex | | | | | |
| Male | 650 (56) | 311 (59) | 30 (49) | 149 (59) | 160 (50) |
| Female | 507 (44) | 215 (41) | 31 (51) | 104 (41) | 157 (50) |
| Age | | | | | |
| < 50 years | 154 (13) | 77 (15) | 15 (25) | 27 (11) | 35 (11) |
| 50 - 70 years | 428 (37) | 215 (41) | 19 (31) | 101 (40) | 93 (29) |
| >70 years | 575 (50) | 234 (45) | 27 (44) | 125 (49) | 189 (60) |
| Indication | | | | | |
| Atrial fibrillation | 606 (52) | 276 (53) | 28 (46) | 142 (56) | 160 (51) |
| Secondary prevention venous thrombosis | 262 (23) | 119 (23) | 19 (31) | 46 (18) | 78 (25) |
| Mechanical heart valves | 37 (3) | 19 (4) | 2 (3) | 7 (3) | 9 (3) |
| Arterial indications | 151 (13) | 74 (14) | 9 (15) | 36 (14) | 32 (10) |
| Prophylaxis | 101 (9) | 38 (7) | 3 (5) | 22 (9) | 38 (12) |
| Therapeutic range (INR) | | | | | |
| Low (2.0-3.5) | 1033 (89) | 463 (88) | 53 (87) | 222 (88) | 295 (93) |
| High (2.5-4.0) | 124 (11) | 63 (12) | 8 (13) | 31 (12) | 22 (7) |
| Anticoagulant | | | | | |
| Phenprocoumon | 972 (84) | 435 (83) | 49 (80) | 221 (87) | 267(84) |
| Acenocoumarol | 162 (14) | 77 (15) | 10 (16) | 29 (12) | 46(15) |
| Warfarin | 23 (2) | 14 (3) | 2 (3) | 3 (1) | 4 (1) |
| Comorbidity score | | | | | |
| 0 | 421 (48) | 252 (48) | 31 (51) | 120 (47) | 18 (50)* |
| 1 | 234 (27) | 140 (27) | 16 (26) | 67 (27) | 11 (31)* |
| 2 | 126 (14) | 71 (14) | 9 (15) | 41 (16) | 5 (14)* |
| 3 | 47 (5) | 31 (6) | 1 (2) | 14 (6) | 1 (3)* |
| 4+ | 48 (5) | 32 (6) | 4 (7) | 11 (4) | 1 (3)* |

Baseline characteristics at the time of reaching stable anticoagulation are displayed in Table 1. A total of 872 patients returned the questionnaire (75%) of which 840 (73% of total) included a valid FFQ. Of those, usual vitamin K intake was normal in 63% of patients, low in 7% and high in 30% of patients. Patients with a low vitamin K intake were slightly more often < 50 years of age and female than those with a normal intake. There were no major differences in indication for anticoagulant treatment, therapeutic range, use of anticoagulant drug and comorbidity.

The total follow-up time was 313 person-years (average 99 d). Of the 1 157 patients, 335 had a subtherapeutic INR during follow-up. Ninety-two

of those patients had stopped their anticoagulant drug or had been given vitamin K and were censored in the analysis. At 8 weeks 14% of patients had had a low INR and at 16 weeks this was 23%. Figure 2 shows the Kaplan Meier-curve of the probability of a subtherapeutic INR for the different vitamin K intake categories. Compared to patients with a normal usual vitamin K intake, those with a high vitamin K intake had a slightly lower risk of a subtherapeutic INR (Hazard Ratio [HR] 0.80, 95% confidence interval [95%CI]: 0.56-1.16) and those with a low vitamin K intake had a higher risk (HR 1.33, 95%CI: 0.79-2.25). Compared to patients with a high vitamin K intake, patients with a low vitamin K intake had a 1.66-fold increased risk (95%CI: 0.93-2.96). Adjustment for age, sex and comorbidity score did not change the results (HR 0.81, 95%CI: 0.56-1.17 for high vitamin K intake and HR 1.26, 95%CI: 0.74-2.14 for low vitamin K intake). The association between vitamin K intake and the risk of a subtherapeutic INR showed a dose effect relationship (P value for the log rank test for trend = 0.08).




| | | | | |
|---|---|---|---|---|
| Low | 61 (0) | 28 (12) | 12 (15) | 4 (16) |
| Normal | 526 (0) | 255 (70) | 120 (96) | 56 (105) |
| High | 253 (0) | 103 (31) | 50 (36) | 27 (39) |

**Figure 2**. Kaplan Meier curve of the probability of a subtherapeutic INR according to usual vitamin K intake category. In the table, values are expressed as the number of patients at risk (number with a subtherapeutic INR)

**Table 2**: Difference of recent vitamin K intake between cases and controls, compared between low, normal and high usual vitamin K intake categories. * *adjusted for sex, age category, season of vitamin K intake measurement and duration of follow-up*

| Usual vitamin intake category | Recent vitamin K intake (μg/24 hrs (n)) | | Difference (95%CI) | Adjusted difference* (95%CI) |
|---|---|---|---|---|
| | Controls | Cases | | |
| Low | 85 (15) | 164 (7) | 80 (-32 to 191) | 87 (-39 to 214) |
| Normal | 199 (103) | 192 (39) | -6 (-69 to 56) | -7 (-72 to 57) |
| High | 309 (36) | 292 (9) | -17 (-192 to 158) | -10 (-172 to 153) |
| Missing | 137 (34) | 233 (8) | 95 (-45 to 236) | 91 (-58 to 240) |
| All | 200 (188) | 208 (63) | 9 (-45 to 62) | 12 (-41 to 66) |

Of the 335 patients who had a subtherapeutic INR, 194 were contacted by telephone for the nested case control study. Of these, 53 patients did not answer the telephone, 16 patients refused to participate and 28 had other reasons why they were ineligible (incorrect telephone number, nursing home residents, dementia, hearing impairment). Ninety-seven patients completed the interview, of whom 90 were able to give a valid dietary recall. Of these 90 patients, 27 patients had stopped their anticoagulant drug or had been given vitamin K and were excluded from the study. Of the 340 control patients who were selected 195 completed the interview and 188 patients gave a valid dietary recall, 98 patients did not answer their telephone, 19 refused and 28 had other reasons not to participate.

Table 2 shows the average recent vitamin K intake for cases and controls, categorized by usual vitamin K intake. In control patients recent vitamin K intake was in agreement with usual vitamin K intake. There was no difference in recent vitamin K intake between cases and controls overall: Average intake was 200 μg in control patients and 208 μg in cases (difference 9 μg, 95%CI: -45 to 62). However, in individuals with a low usual vitamin K intake, recent vitamin K intake was twice as high in patients with a subtherapeutic INR as in controls, with a difference of 80 μg (95%CI: −32 to 191). A similar difference was observed in patients who had not completed the FFQ.

Table 3 shows odds ratios for a normal recent vitamin K intake (higher than 100 μg/d) *versus* a low recent vitamin K intake (lower than 100 μg/d), again separately for individuals with a low, normal or high usual vitamin K

intake. In patients with a low usual vitamin K intake, 43% (3 out of 7) of cases had a recent intake of more than 100 μg/d, versus 20% (3 out of 15) in controls (OR 3.0, 95%CI: 0.4-21.3), indicating that those individuals who usually take low amounts of vitamin K had a threefold increased risk of a subtherapeutic INR when they increased their vitamin K intake above 100 μg/d in comparison to when their vitamin K intake stayed below 100 μg/d. This increase in risk was not present in individuals with a normal or high usual vitamin K intake.

**Table 3**: Odds Ratios for the risk of a subtherapeutic INR for normal (higher than 100 μg/d) versus low (lower than 100 μg/d) recent vitamin K intake, categorized per usual vitamin K intake group.

| | | No patients (%) | | |
|---|---|---|---|---|
| Usual vitamin K intake | Recent vitamin K intake | Cases | Controls | OR (95%CI) |
| Low | Normal | 3 (43) | 3 (20) | 3.0 (0.4-21.3) |
| | Low | 4 (57) | 12 (80) | |
| Normal | Normal | 21 (54) | 58 (56) | 0.9 (0.4- 1.9) |
| | Low | 18 (46) | 45 (44) | |
| High | Normal | 7 (78) | 29 (81) | 0.8 (0.1- 5.0) |
| | Low | 2 (22) | 7 (19) | |
| All | Normal | 35 (56) | 102 (54) | 1.1 (0.6- 1.9) |
| | Low | 28 (44) | 86 (46) | |

# Discussion

We followed 1 157 patients in a routine setting of a Dutch anticoagulation clinic. A 20% decrease was found in the risk of a subtherapeutic INR in patients with a high vitamin K intake and a 33% increase in patients with a low dietary vitamin K intake. While there was no difference in recent vitamin K intake between cases and controls in individuals with a normal or high usual vitamin K intake, patients with a low usual vitamin K intake consumed twice as much vitamin K in the 48 hours prior to a subtherapeutic INR. Our results suggest that a high vitamin K intake reduces the risk of low INR values by lessening the influence of incidental consumption of vitamin K rich food on the INR. This finding is important because it may contradict conventional dietary recommendations for patients using vitamin K antagonists.

There are currently several recommendations regarding vitamin K intake for patients using oral anticoagulants. These include keeping vitamin K intake constant,[20;21] limiting or even avoiding intake of foods high in vitamin K,[22] and consuming sufficient vitamin K to meet the adequate intake (AI).[23] The first recommendation, to keep the vitamin K intake constant, can be justified by findings of changes in vitamin K intake resulting in both under- and overanticoagulation.[9;14] However, because different food items vary greatly in vitamin K content, keeping vitamin K intake constant is unfeasible, even for the most motivated patients. Daily vitamin K intake ranges from <10 to >2500 μg/d, and the intraindividual variability is much higher than the interindividual variability.[24] Limiting or avoiding foods high in vitamin K reduces total vitamin K intake and will, according to our data, increase the risk of a subtherapeutic INR. Our results support the third recommendation, to consume sufficient vitamin K to meet the adequate intake.

Our results are in concordance with the finding that vitamin K is lower in unstable patients than in stable patients, indicating that a low vitamin K intake is a risk factor for unstable anticoagulation.[10] The recommendation to consume sufficient vitamin K rich food is also supported by evidence that controlled, low-dose vitamin K supplementation increases stability of anticoagulation.[25;26] While we found a relation between dietary intake and low INRs, the relation between low vitamin K intake and over-anticoagulation is unclear, with one study reporting no relation.[16] It would be worthwhile to investigate the effect of low vitamin K intake on the incidence of over-anticoagulation.

Genetic variants of *VKORC1*, the gene encoding the target enzyme for vitamin K antagonists, have been shown to contribute importantly to the differences in sensitivity to vitamin K antagonists.[27] Compared to the wild type, the G1639A polymorphism results in less VKORC1 enzyme, so that a lower dose of VKA is needed to achieve the same anticoagulant effect. There have been some studies on the effect of VKORC1 genotype on stability of anticoagulation,[28-30] but at this moment it is not known whether changes in dietary vitamin K intake have a bigger influence on the stability of anticoagulant therapy in patients with the G1639A variant although one would assume that this is the case. In this regard it is also possible that the

improvement of anticoagulant control that been observed in patients supplemented with a low dose of vitamin K depends on the VKORC1 polymorphism. The effect of VKOR genotype on stability of anticoagulant therapy in relation to dietary vitamin K intake needs to be investigated in more detail.

We chose to develop the FFQ and the dietary recall instead of using existing questionnaires. This has both advantages and disadvantages. Advantages are that the questionnaires were developed specifically to measure vitamin K intake and that they were directed to the studied population by including food items contributing most to vitamin K intake in the Dutch population. This is important because typical Dutch food includes many vitamin K-rich foods such as curly kale and sauerkraut. A disadvantage is that the questionnaires have not been validated. However, there was a correlation between the FFQ and the dietary recall questionnaire, providing a relative validation. A more general problem with measuring dietary vitamin K intake is the substantial difference in the reported vitamin K content of foods analyzed in different laboratories.[31] Because any resulting misclassification does not depend on whether or not people experience low INRs the reported results are likely to be an underestimation of the effect.

Even though we followed a large cohort of 1 157 patients, the number of events in the subgroups of patients with low or high usual vitamin K intake was relatively small and thus the confidence intervals were wide. However, considering that our results are in agreement with other studies investigating the role of dietary vitamin K intake in anticoagulant stability,[10;25;26] and considering that our results show a dose effect relationship, they contribute to the growing body of evidence that patients on vitamin K antagonists should receive the same dietary advice as the rest of the population: Maintain a healthy diet containing sufficient fruits and vegetables.

**References**


1. Cannegieter SC, Rosendaal FR, Briët E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. Circulation 1994;89:635-641.
2. Reynolds MW, Fahrbach K, Hauch O et al. Warfarin anticoagulation and outcomes in patients with atrial fibrillation: a systematic review and metaanalysis. Chest 2004;126:1938-1945.
3. Ansell J, Hirsh J, Hylek E et al. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:160S-198S.
4. Hylek EM, Go AS, Chang Y et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. N.Engl.J.Med. 2003;349:1019-1026.
5. Penning-van Beest FJ, van Meegen E, Rosendaal FR, Stricker BH. Drug interactions as a cause of overanticoagulation on phenprocoumon or acenocoumarol predominantly concern antibacterial drugs. Clin.Pharmacol.Ther. 2001;69:451-457.
6. Oldenburg J, Watzka M, Rost S, Muller CR. VKORC1: molecular target of coumarins. J.Thromb.Haemost. 2007;5 Suppl 1:1-6.
7. Gadisseur AP, van der Meer FJ, Adriaansen HJ, Fihn SD, Rosendaal FR. Therapeutic quality control of oral anticoagulant therapy comparing the short-acting acenocoumarol and the long-acting phenprocoumon. Br.J.Haematol. 2002;117:940-946.
8. Rombouts EK, Rosendaal FR, van der Meer FJ. Subtherapeutic oral anticoagulant therapy: frequency and risk factors. Thromb.Haemost. 2009;101:552-556.
9. Franco V, Polanczyk CA, Clausell N, Rohde LE. Role of dietary vitamin K intake in chronic oral anticoagulation: prospective evidence from observational and randomized protocols. Am.J.Med. 2004;116:651-656.
10. Sconce E, Khan T, Mason J et al. Patients with unstable control have a poorer dietary intake of vitamin K compared to patients with stable control of anticoagulation. Thromb.Haemost. 2005;93:872-875.
11. Holbrook AM, Pereira JA, Labiris R et al. Systematic overview of warfarin and its drug and food interactions. Arch.Intern.Med. 2005;165:1095-1106.
12. Hylek EM, Chang YC, Skates SJ, Hughes RA, Singer DE. Prospective study of the outcomes of ambulatory patients with excessive warfarin anticoagulation. Arch.Intern.Med. 2000;160:1612-1617.
13. Crowther MA, Ageno W, Garcia D et al. Oral vitamin K versus placebo to correct excessive anticoagulation in patients receiving warfarin: a randomized trial. Ann.Intern.Med. 2009;150:293-300.
14. Khan T, Wynne H, Wood P et al. Dietary vitamin K influences intra-individual variability in anticoagulant response to warfarin. Br.J.Haematol. 2004;124:348-354.
15. Couris R, Tataronis G, McCloskey W et al. Dietary vitamin K variability affects International Normalized Ratio (INR) coagulation indices. Int.J.Vitam.Nutr.Res. 2006;76:65-74.
16. Penning-van Beest FJ, Geleijnse JM, van Meegen E et al. Lifestyle and diet as risk factors for overanticoagulation. J.Clin.Epidemiol. 2002;55:411-417.

17. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J.Chronic.Dis. 1987;40:373-383.
18. Hulshof KFAM, Kistemaker C, and Bouman M. De consumptie van groepen voedingsmiddelen door Nederlandse bevolkingsgroepen - Voedselconsumptiepeiling 1997-1998. TNO Rapport V 98.804, Zeist, the Netherlands 1998. 1998.
19. Donders-Engelen M, van der Heijden L, Hulshof KFAM. Maten, gewichten en codenummers. 2003. Research report by Wageningen Agricultural University, Division of Human Nutrition. Wageningen, the Netherlands
20. Booth SL, Centurelli MA. Vitamin K: a practical guide to the dietary management of patients on warfarin. Nutr.Rev. 1999;57:288-296.
21. Institute of Medicine. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. 162-196. 4-6-2003.
22. Warren Grant Magnuson Clinical Center, National Institutes of Health Drug-Nutrient Interaction Task Force. Important information to know when you are taking: Coumadin (r) and Vitamin K. http://ods.od.nih.gov/factsheets/cc/coumadin1.pdf . 17-10-2009.
23. Johnson MA. Influence of vitamin K on anticoagulant therapy depends on vitamin K status and the source and chemical forms of vitamin K. Nutr.Rev. 2005;63:91-97.
24. Booth SL, Sokoll LJ, O'Brien ME et al. Assessment of dietary phylloquinone intake and vitamin K status in postmenopausal women. Eur.J.Clin.Nutr. 1995;49:832-841.
25. Sconce E, Avery P, Wynne H, Kamali F. Vitamin K supplementation can improve stability of anticoagulation for patients with unexplained variability in response to warfarin. Blood 2007;109:2419-2423.
26. Rombouts EK, Rosendaal FR, van der Meer FJ. Daily vitamin K supplementation improves anticoagulant stability. J.Thromb.Haemost. 2007;5:2043-2048.
27. Garcia AA, Reitsma PH. VKORC1 and the vitamin K cycle. Vitam.Horm. 2008;78:23-33.
28. Schalekamp T, Brasse BP, Roijers JF et al. VKORC1 and CYP2C9 genotypes and acenocoumarol anticoagulation status: interaction between both genotypes affects overanticoagulation. Clin.Pharmacol.Ther. 2006;80:13-22.
29. Meckley LM, Wittkowsky AK, Rieder MJ, Rettie AE, Veenstra DL. An analysis of the relative effects of VKORC1 and CYP2C9 variants on anticoagulation related outcomes in warfarin-treated patients. Thromb.Haemost. 2008;100:229-239.
30. Spreafico M, Lodigiani C, van Leeuwen Y et al. Effects of CYP2C9 and VKORC1 on INR variations and dose requirements during initial phase of anticoagulant therapy. Pharmacogenomics. 2008;9:1237-1250.
31. Suttie JW. Dietary intake of vitamin K and the vitamin K content of foods and plasma. Vitamin K in health and disease.: CRC Press; 2009:39-62.

# 4

# The effect of vitamin K supplementation on anticoagulant therapy

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Until recently, the view that dietary vitamin K interferes with oral anticoagulant therapy was based on case reports and a few small experimental studies with extremely high vitamin K intake. In two recent studies the effect of dietary vitamin K on oral anticoagulation was systematically investigated.[1;2] These studies showed that even in patients on an average diet changes in vitamin K intake affect anticoagulation. When patients decreased their vitamin K intake the response on the International Normalized Ratio (INR) was more pronounced than when vitamin K intake was increased[2]. Because changes are proportionally larger in people with a low average vitamin K intake, it is likely that the INR is more sensitive to a varying vitamin K intake in those individuals. Sconce *et al.* established that daily intake of vitamin K was indeed lower in patients with unstable anticoagulation than in stably anticoagulated patients.[3] Daily supplementation of low doses of vitamin K might thus be beneficial.

To safely start vitamin K supplementation in patients receiving oral anticoagulants, it is important to know the effect of low doses of vitamin K on the INR and on the dose of the anticoagulant drug. The dose-response relationship of vitamin K supplementation on the INR in healthy subjects that received a fixed dose of oral anticoagulants was established by Schurgers *et al.*[4] They concluded that 100 μg of vitamin K daily did not significantly interfere with oral anticoagulant therapy. Consequently, Oldenburg suggested 100 μg vitamin K as a recommended supplementation dose in his editorial.[5] However, Kurnik *et al.* found that in patients with a low vitamin K status even daily supplement doses as low as 25 μg led to an important reduction of the INR.[6]

We performed a pilot study to determine the effect of escalating daily doses of vitamin K on the required dose of the anticoagulant drug phenprocoumon. We included patients from the Leiden Anticoagulation Clinic that took part in a program for self-management of anticoagulant treatment. The total study period was 9 weeks, in which the INR was measured at least 3 times a week with a CoaguCheck S coagulometer (Roche Diagnostics, Almere, Netherlands). Patients received vitamin K for 3 weeks. The first and last 3 weeks served as control periods. Five patients received 50 μg and 10 patients 100 μg of oil-based vitamin $K_1$ (250 μg/g).

The primary endpoint was the percentage change in phenprocoumon dose during and after vitamin K needed to keep the INR within therapeutic limits.

Supplementation of 50 μg vitamin K had little effect on the INR and therefore only slight dose-adjustments were made (mean dose increase after starting vitamin K 3% (95% confidence interval (95%CI): -4% to 10%). Supplementation of 100 μg resulted in a mean dose increase of 9% (95%CI: 0% to 19%, figure 1). There was considerable inter-individual variability in response with dose-adjustments ranging from -7% to 37%. In the three weeks follow-up after the vitamin K was discontinued phenprocoumon doses were lowered to pre-substitution values (mean change of -7%, 95%CI: -15% to 0%).

Our results show that daily supplementation up to 100 μg can be given without a relevant decrease in the INR, on the condition of frequent monitoring during and after the supplementation to allow timely dose adjustments.

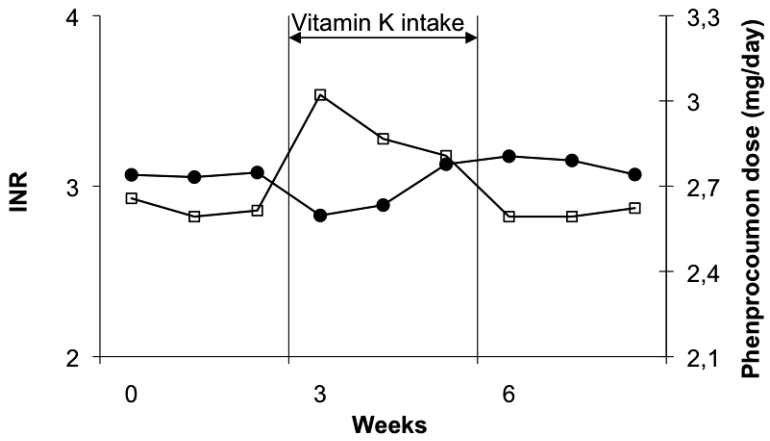


**Figure 1:** Effect of vitamin K supplementation on the mean International Normalized Ratio (INR) (•) and the mean phenprocoumon dose (□) in 10 patients receiving 100 μg vitamin K daily.

**References**


1. Khan T, Wynne H, Wood P et al. Dietary vitamin K influences intra-individual variability in anticoagulant response to warfarin. Br.J.Haematol. 2004;124:348-354.
2. Franco V, Polanczyk CA, Clausell N, Rohde LE. Role of dietary vitamin K intake in chronic oral anticoagulation: prospective evidence from observational and randomized protocols. Am.J.Med. 2004;116:651-656.
3. Sconce E, Khan T, Mason J et al. Patients with unstable control have a poorer dietary intake of vitamin K compared to patients with stable control of anticoagulation. Thromb.Haemost. 2005;93:872-875.
4. Schurgers LJ, Shearer MJ, Hamulyak K, Stocklin E, Vermeer C. Effect of vitamin K intake on the stability of oral anticoagulant treatment: dose-response relationships in healthy subjects. Blood 2004;104:2682-2689.
5. Oldenburg J. Vitamin K intake and stability of oral anticoagulant treatment. Thromb.Haemost. 2005;93:799-800.
6. Kurnik D, Loebstein R, Rabinovitz H et al. Over-the-counter vitamin K(1)-containing multivitamin supplements disrupt warfarin anticoagulation in vitamin K(1)-depleted patients. Thromb.Haemost. 2004;92:1018-1024.

# 5

# Daily vitamin K supplementation improves anticoagulant stability

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# Abstract

**Background**

One of the causes of unstable anticoagulant control in patients using vitamin K antagonists is a fluctuating intake of vitamin K. Research suggests that patients with a low dietary intake of vitamin K have a less stable anticoagulant control than patients with a higher intake.

**Objectives**

To study whether supplementation with a low daily dose of vitamin K improves anticoagulant control.

**Methods**

We performed a double blind, randomized, placebo controlled trial. Two hundred patients of the Leiden anticoagulation clinic, who used the vitamin K antagonist phenprocoumon were randomized to receive either adjusted-dose phenprocoumon and 100 μg vitamin K once daily or adjusted-dose phenprocoumon and a placebo. Treatment duration was 24 weeks. The primary outcome was the percentage of time the INR was within the therapeutic range.

**Results**

Time in therapeutic range was 85.5% in the placebo group and 89.5% in the vitamin K group (adjusted difference 3.6%, 95% confidence interval [95%CI]: -0.8% to 8.0%). Time below the therapeutic range was 3.1% in the placebo group and 2.1% in the vitamin K group (adjusted difference -0.7 %, 95%CI: -2.5% to 1.1%) and time above the therapeutic range was 11.4% in the placebo group and 8.5% in the vitamin K group (adjusted difference -2.9%, 95%CI: -6.9% to 1.1%).

**Conclusion**

Supplementation of vitamin K antagonists with 100 μg vitamin K improves stability of anticoagulant therapy. Because the risk of side effects is inversely related to anticoagulant stability, such an improvement is likely to reduce the number of bleeding and thrombotic events.

# Introduction

Oral anticoagulant treatment with vitamin K antagonists is indicated for the primary and secondary prevention of both arterial and venous thrombosis.[1] A major disadvantage of vitamin K antagonists is their narrow therapeutic window and the large inter- and intra-individual variability in anticoagulant response. Despite intensive monitoring the intensity of anticoagulation, expressed as the International Normalized Ratio (INR), is within the target range only approximately 60% of the time.[2] The impact of under- and overanticoagulation is high, with a sharp increase of severe hemorrhage when the INR rises above the therapeutic range and a rise in thrombotic risk as the INR falls below the therapeutic range.[2-4] Improvement of the quality of anticoagulant treatment will reduce the number of these adverse events.

One of the causes of the variability in anticoagulant response is a fluctuating vitamin K intake.[5;6] Studies have shown that the INR is especially sensitive to vitamin K changes when vitamin K intake is low.[6;7] In patients with unstable anticoagulant control daily intake of vitamin K has been shown to be lower than in stably anticoagulated patients.[8] We hypothesized that supplementation with a low daily dose of vitamin K results in increased stability of anticoagulant control. The objective of this study was to test this hypothesis clinically, by assessing the effect of vitamin K supplementation on anticoagulant stability in patients treated with vitamin K antagonists.

# Methods

### Study design

The study was a double blind, randomized, placebo controlled trial. Two hundred patients were randomized in blocks of 8 patients into two equal groups. All patients were treated with adjusted-dose phenprocoumon, a vitamin K antagonist with a long half-life of 140 hours. In addition, patients in the treatment group received 100 μg vitamin K once daily, patients in the other group a placebo once daily. The study medication was used for 24 weeks. After this patients were followed for an additional 4 weeks, to

observe possible side effects after stopping the study medication. The study was approved by the local Medical Ethics Committee. Written informed consent was obtained from all participants prior to enrolment.

**Participants**

Participants were recruited from the Leiden anticoagulation clinic. Patients were considered for enrolment if they were between 18 and 80 years of age, had an indication for long-term oral anticoagulant therapy and had been using phenprocoumon for at least one year. Exclusion criteria were: treatment by a medical specialist for liver failure; haemo- or peritoneal dialysis; pregnancy or planned pregnancy; puerperium; any chronic condition with an expected survival of less than 6 months; an expected interruption of oral anticoagulant treatment of more than one week; self-management of oral anticoagulant treatment and non-compliance, based on information from the anticoagulation clinic computer records.

The required sample size was calculated using data of the Leiden anticoagulation clinic. We expected an improvement of the time in therapeutic zone from 75% to 85%. The standard deviation of the time in therapeutic zone was estimated at 23%. To achieve 80% power for detecting this difference at a significance level of 5%, 84 subjects per group were required. Allowing for a loss of patients of 15% the total number of patients was rounded to 200.

**Procedures**

The study was performed at the Leiden anticoagulation clinic, where approximately 7 000 patients are treated each year. During the first four weeks after starting the study medication the INR was measured weekly to be able to adjust the dosage of phenprocoumon in case of INR changes due to the vitamin K. Subsequently, the interval between visits depended on anticoagulant stability, with a maximum of 4 weeks. After stopping the study medication patients were again seen at weekly intervals for four weeks. INR results and prescribed dosages were recorded in a central database, along with relevant history details, changes in medication, information on bleeding and thrombotic complications, admissions and surgical interventions. After inclusion patients were asked to list their

current co-medications. No specific dietary recommendations were given. Compliance with the study medication was verified by pill-counting. We classified patients as compliant when they had used over 90% of the prescribed capsules, non-compliant otherwise.

The therapeutic ranges were according to the guidelines of the Federation of Dutch Anticoagulation Clinics: INR 2.0-3.5 with a target INR 3.0 for low intensity treatment and INR 2.5-4.0, target INR 3.5 for high intensity treatment.

Capsules containing 100 μg of vitamin K or placebo were manufactured by Numard Pharmaceuticals (Lelystad, The Netherlands) from 5% dry vitamin K (Acatris, Londerzeel, Belgium). The dose of 100 μg vitamin K was chosen because of the results of a pilot study, in which we found that this dose had only a minor effect on the INR and subsequent dosage adjustments, while being close to the recommended daily intake (90 μg for women, 120 for men[9]).[10]

**Data analysis**

The primary study outcome was the quality of anticoagulant treatment, expressed as percentage of time of the INR in the therapeutic range. Time in range was calculated with the linear interpolation method, as described by Rosendaal[11]. In this method, the INR is modeled to increase or decrease linearly between two consecutive measurements. Each time period between two INR measurements can then be divided into time in, above or below the therapeutic range. For each patient time per category is summed and divided by the total follow-up time. Because the research question was mechanistic rather than a question of efficacy, we only calculated the time in range over the period the study medication was used. Also, the first four weeks after starting the study-medication were excluded from the analysis, to allow some time to find a new dose balance. Secondary outcome measures were the number of bleeding and thrombotic complications. Major hemorrhage was defined as fatal or intracranial hemorrhage and any hemorrhage that required blood transfusion, hospitalization or surgery, as well as muscle and joint bleeding.

Finally, we classified patients in categories of stability and contrasted patients with maximal stability (time in range of 100% during follow-up)

between the treatment and placebo group, which allowed the calculation of a relative risk.

Age, sex, target-range, use of co-medication and use of medication interacting with the anticoagulant drug were considered possible confounders and were adjusted for in the analysis.

## Results

Patients were enrolled between December 2004 and January 2006 (Figure 1). Of 1 053 patients, 200 consented to be randomized. Data on 18 patients were not or only partly analyzed, because they did not complete follow-up. Follow-up time was 34.2 patient-years (py) in the placebo-group and 33.7 py in the vitamin K group.

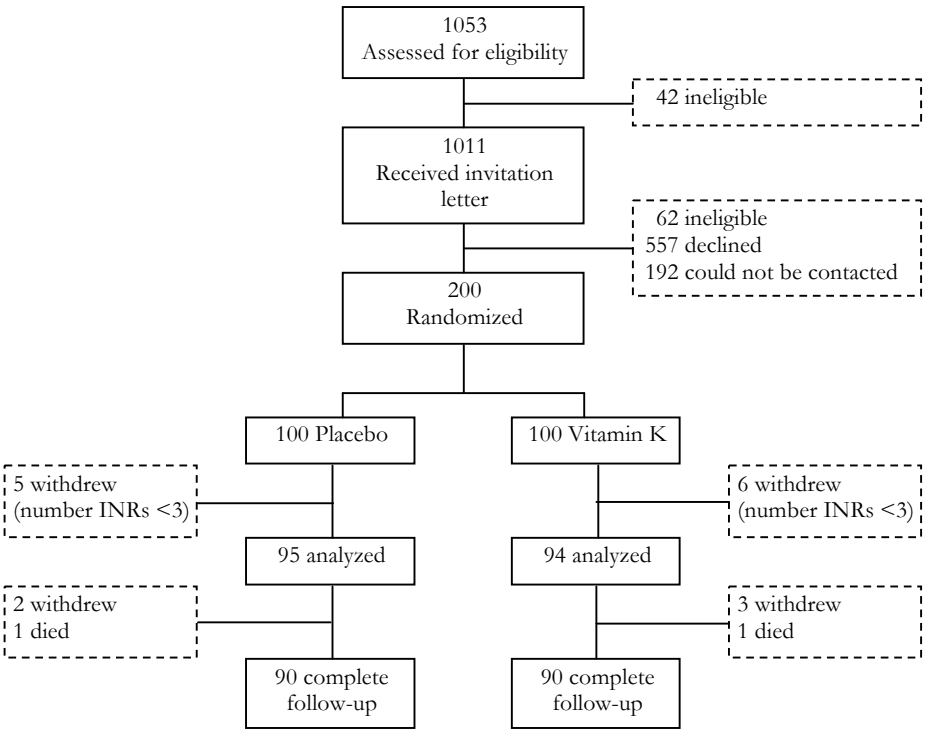


**Figure 1**: Flow of patients through the trial

**Table 1**: Baseline characteristics of the study population. Data are median (interquartile range) or number (%)

| | Placebo *(n = 95)* | | Vitamin K *(n = 94)* | |
|---|---|---|---|---|
| Age | 68 | (59-73) | 65 | (60-73) |
| Female sex (%) | 27 | (28%) | 20 | (21%) |
| Duration of anticoagulant treatment (years) | 4 | (2-9) | 4 | (2-7) |
| Previous stability (time in therapeutic range) | 80% | (74%-84%) | 79% | (72%-84%) |
| Indication (%) | | | | |
| Atrial fibrillation | 38 | (40%) | 40 | (43%) |
| Secondary prevention venous thrombosis | 12 | (13%) | 15 | (16%) |
| Mechanical heart valve | 12 | (13%) | 9 | (10%) |
| Other arterial | 33 | (35%) | 30 | (32%) |
| Therapeutic range (%) | | | | |
| Low (2.0 - 3.5) | 51 | (54%) | 57 | (61%) |
| High (2.5 - 4.0) | 44 | (46%) | 37 | (39%) |
| Number of comedications | 4 | (2-6) | 3 | (2-5) |
| Interacting medication (%) | | | | |
| No | 50 | (53%) | 62 | (66%) |
| Yes | 45 | (47%) | 32 | (34%) |

Patient characteristics are shown in Table 1. Age, sex, duration of anticoagulant treatment, previous stability and indication for anticoagulant treatment were similar in both groups. In the placebo group were slightly more patients in the high target range. Patients in the placebo group used more co-medications, including drugs interacting with anticoagulants.

The primary study outcome is shown in Table 2. Time in therapeutic range was 85.5% in the placebo group (95% confidence interval [95%CI]: 82.3% to 88.6%) and 89.5% in the vitamin K group (95%CI: 86.4% to 92.5%). Time in range was 4.0% higher in the vitamin K group than in the

**Table 2**: Time in -, below - and above the therapeutic range. Data provided are mean percentages (95%CI) of time in, below and above the therapeutic range. * *Adjusted for age, sex, target range, number of co-medications and use of interacting medication.*

| | Placebo *(n = 95)* | Vitamin K *(n = 94)* | Difference | Adjusted difference* |
|---|---|---|---|---|
| Time in therapeutic range | 85.5 (82.3 to 88.6) | 89.5 (86.4 to 92.5) | 4.0 (-0.3 to 8.3) | 3.6 (-0.8 to 8.0) |
| Time below therapeutic range | 3.1 (1.6 to 4.5) | 2.1 (1.0 to 3.1) | -1.0 (-2.8 to 0.7) | -0.7 (-2.5 to 1.1) |
| Time above therapeutic range | 11.4 (8.5 to 14.4) | 8.5 (5.8 to 11.1) | -3.0 (-6.9 to 0.9) | -2.9 (-6.9 to 1.1) |

placebo group (95%CI: -0.3% to 8.3%). After adjusting for age, sex, target range, number of co-medications and use of interacting medication this difference was 3.6% (95%CI: -0.8 to 8.0). Both time below the therapeutic range and time above the therapeutic range were slightly lower in the vitamin K group.

Figure 2 shows the percentage of patients classified in categories of time in therapeutic range. Of the patients in the vitamin K group 43% were in the therapeutic range 100% of the time versus 24% in the placebo group. The relative risk of a maximal stability in the vitamin K group compared to placebo was 1.8 (95%CI: 1.1 to 2.7).

Table 3 shows the time in therapeutic range in the vitamin K and the placebo group for different patient and treatment characteristics. The results are similar for all categories. Patients in the vitamin K group were more stable in all but three subgroups, although confidence intervals are wide. Previous stability was the best predictor of time in therapeutic range during the trial.

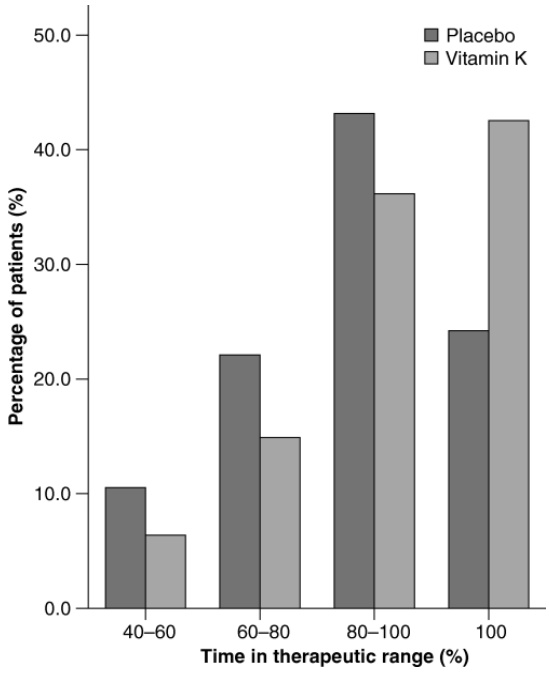


**Figure 2**: Percentage of patients in categories of time in therapeutic range

**Table 3**: Percentage of time in the therapeutic range in various patient categories. Data provided are mean percentages (95%CI) of time in the therapeutic range

| | Placebo group *(n = 95)* | | Vitamin K group *(n = 94)* | | |
|---|---|---|---|---|---|
| | number of patients | percentage time in the therapeutic range | number of patients | percentage time in the therapeutic range | Difference |
| Age | | | | | |
| <60y | 29 | 85 (79-91) | 27 | 89 (83-94) | 3.7 (-4.3 to 11.7) |
| 60-70 | 32 | 88 (83-93) | 34 | 90 (85-96) | 2.5 (-5.0 to 10.0) |
| 70-80 | 34 | 84 (78-89) | 33 | 89 (84-94) | 5.6 (-1.9 to 13.1) |
| Sex | | | | | |
| Male | 68 | 85 (81-89) | 74 | 90 (86-93) | 4.5 (-0.6 to 9.6) |
| Female | 27 | 86 (81-91) | 20 | 89 (81-97) | 2.6 (-6.2 to 11.4) |
| Duration of anticoagulant treatment (years) | | | | | |
| <=2y | 26 | 84 (77-91) | 26 | 82 (74-91) | -1.5 (-11.9 to 8.7) |
| 2-4y | 23 | 83 (75-90) | 24 | 93 (89-97) | 10.0 (2.0 to 17.9) |
| 4-6y | 12 | 84 (75-93) | 18 | 92 (84-99) | 7.5 (-3.6 to 18.6) |
| >6y | 34 | 89 (84-93) | 26 | 92 (88-97) | 3.1 (-3.4 to 9.6) |
| Previous stability (time in therapeutic range) | | | | | |
| <60% | 4 | 68 (41-96) | 5 | 74 (41-107) | 5.8 (-30.5 to 42.2) |
| 60-80 | 48 | 87 (83-91) | 48 | 87 (82-91) | 0.1 (-5.9 to 6.1) |
| 80-100 | 43 | 86 (81-91) | 41 | 95 (91-98) | 8.8 (3.1 to 14.6) |
| Indication | | | | | |
| Atrial fibrillation | 38 | 84 (78-89) | 40 | 88 (83-94) | 4.6 (-3.2 to 12.5) |
| Secondary prevention venous thrombosis | 11 | 81 (69-94) | 15 | 93 (86-99) | 11.5 (-0.7 to 23.7) |
| Mechanical heart valve | 12 | 87 (78-96) | 9 | 92 (84-99) | 5.0 (-6.5 to 16.6) |
| Other arterial | 33 | 88 (84-93) | 30 | 89 (84-94) | 0.4 (-6.3 to 7.0) |
| Therapeutic range | | | | | |
| Low (2.0 - 3.5) | 51 | 84 (79-89) | 57 | 90 (85-94) | 5.9 (-0.4 to 12.2) |
| High (2.5 - 4.0) | 44 | 87 (83-91) | 37 | 89 (85-93) | 1.7 (-4.1 to 7.4) |
| Compliance study medication | | | | | |
| Compliant | 77 | 88 (85-91) | 73 | 90 (87-93) | 2.2 (-2.3 to 6.7) |
| Noncompliant | 3 | 69 (26-112) | 5 | 82 (56-107) | 13.0 (-21.8 to 47.8) |
| Not counted | 15 | 78 (67-88) | 16 | 90 (82-99) | 12.6 (-0.4 to 25.7) |
| Dose adjustment | | | | | |
| < -5% | 20 | 82 (74-89) | 7 | 78 (64-92) | -3.8 (-18.5 to 10.9) |
| -5% to 5% | 55 | 86 (82-91) | 35 | 93 (89-97) | 6.6 (-0.2 to 12.9) |
| >5% | 20 | 87 (82-93) | 52 | 89 (84-93) | 1.6 (-6.1 to 9.3) |
| Number of comedications | | | | | |
| 0-2 | 33 | 85 (80-91) | 42 | 92 (88-97) | 7.2 (0.4 to 13.9) |
| 3-5 | 38 | 85 (79-91) | 39 | 88 (83-93) | 3.1 (-4.1 to 10.2) |
| >=6 | 24 | 86 (81-92) | 13 | 84 (73-95) | -2.3 (-12.7 to 8.1) |
| Interacting medication | | | | | |
| No | 50 | 86 (81-90) | 62 | 91 (88-95) | 5.6 (0.2 to 11.1) |
| Yes | 45 | 85 (80-90) | 32 | 86 (81-92) | 0.8 (-6.5 to 8.1) |

Compared to the 24 weeks before the start of the study medication, the dose was increased by an average of 0.8% in the placebo group (range -16% to 57%) and 7.0% in the vitamin K group (range -57% to 39%). The difference in time in range between the placebo group and the vitamin K group was largest in patients with a dose change between -5% and 5% (Table 3).

Three patients in the placebo group and 5 in the vitamin K group were classified as noncompliant with the study medication (more than 10% of the prescribed capsules not taken). Both compliant and noncompliant patients were more stable in the vitamin K group than in the placebo group (Table 3).

The beneficial effect of vitamin K was strongest (7.2% time in range) in those with no or few co-medications and absent in those with 6 or more co-medications. When we looked specifically at drugs that potentially interact with vitamin K antagonists, we found that the effect of vitamin K supplementation appeared restricted to those who did not use interacting agents (Table 3).

Two patients died, one in the vitamin K group (intracranial hemorrhage due to cerebral contusion) and one in the placebo group (cause of death unknown). Two patients in the vitamin K group had a major bleeding event; the before-mentioned fatal bleed (last known INR 2.8) and a muscular bleed (INR 5.1). There were 17 minor bleeding episodes, 10 in the placebo and 7 in the vitamin K group (relative risk [RR] for any bleeding event, vitamin K group versus placebo group: 0.9, 95%CI: 0.3 to 2.3). No thrombotic events were reported. There were five self-reported putative side effects, four of which in the placebo group. These included weight gain (two patients in the placebo group, one in the vitamin K group), flatulence and indigestion.

## Discussion

We performed a randomized placebo-controlled trial in 200 outpatients of a Dutch anticoagulation clinic, to study the effect of vitamin K supplementation in patients treated with oral anticoagulants. We observed a small increase in stability of anticoagulant treatment in patients receiving

vitamin K supplementation. There was a two-fold increase in the percentage of patients with a maximal stability of 100% of time within the therapeutic range, from 24% to 43% of patients.

The need to investigate whether vitamin K supplementation leads to an improved anticoagulant stability has been identified by several authors.[12;13] The question was raised based on recent studies that showed that the INR is more sensitive to vitamin K changes in patients with a low vitamin K status than in those with a normal or high vitamin K status[6;7] and that dietary vitamin K intake in unstable patients is considerably lower than in stable patients.[8] Recently, Sconce *et al.* published their results of a study investigating vitamin K supplementation in 70 patients receiving warfarin with an unstable anticoagulant control.[14] They found that supplementation with 150 μg of vitamin K increased stability of anticoagulation, expressed as the standard deviation of the INR and the percentage of time in the target range. Our results confirm that this strategy increases the time in therapeutic range in an unselected population of patients using vitamin K antagonists.

The observed improvement in time in therapeutic range of 4% was smaller than the improvement of 10% on which the study was powered. This explains why the results do not reach the significance level of 5%: the size of our study was too small to detect this smaller difference. Taking into consideration the biologic plausibility of the results, previous studies showing low vitamin K status in unstable patients and the previous trial by Sconce *et al.*,[14] we believe that the observed difference is real. The key question of course is whether this difference is clinically relevant. The 4% improvement of time in therapeutic range will theoretically prevent 1-2 serious side effects per 1 000 treatment-years.[2] It must be kept in mind that time in therapeutic range in this study improved from 85% to 89%. So, even in the placebo group time in range was unexpectedly high. In a less stable population, the benefit of vitamin K supplementation is likely to be higher than the observed 4% difference.

There are several reasons why time in therapeutic range was higher in this study than is usually reported. One reason is the definition of therapeutic range, which is wider in the Netherlands than in other countries, where a target range of 2.0-3.0 is frequently employed. Furthermore, only

patients who had been using anticoagulants for more than a year were included. These patients are often more stable than short-term patients. Finally, even in the placebo group time in range was 7% higher than before the trial. There are two possibilities why the time in the therapeutic range was so high in the placebo group: Firstly, the study population (placebo and treatment group) differed from the routinely treated patients. This is a common phenomenon in randomized trials, due to exclusion criteria, self-selection of consenting patients or because patients changed their behaviour during the trial. Another possibility is that the placebo group differed from the treatment group by chance. If this were the case, the true effect was seemingly reduced, and in fact higher.

Despite randomization the groups differed in use of co-medication. Patients in the placebo group used more co-medications in general and also more drugs interacting with vitamin K antagonists. Because time in therapeutic range was associated with both variables, they were adjusted for in the analysis. An interesting finding was that vitamin K supplementation especially improved anticoagulant control in patients using no or few co-medications and in patients not using interacting medication. However, because this was a post-hoc subgroup analysis with wide confidence intervals, these results should be interpreted with caution.

A theoretical concern is that increasing the dose of the vitamin K antagonist increases the risk of side-effects unrelated to the INR. Other proteins than those involved in haemostasis depend on the enzyme system affected by vitamin K antagonists.[15] However, in the past decades of oral anticoagulant use, the number of reported side-effects other than haemorrhage has been remarkably low.

A limitation of this study was that blinding may not have been completely maintained because of dose adjustments in the treatment group. Because patients in the vitamin K group did better when there were no large dose adjustments, it is unlikely that this affected the results.

Oral anticoagulants are among the most frequently prescribed drugs. In Western countries they are used by over 1% of the adult population.[16;17] Ten percent of hospital admissions due to adverse drug events are caused by oral anticoagulants, often as a result of overanticoagulation.[18] Improvement of the quality of oral anticoagulant therapy will result in less thrombosis and

fewer bleeding events and thus in a major reduction of burden of disease. Our results show that supplementation with a low dose of oral vitamin K contributes to improved anticoagulant stability. Further research on the optimal dosage of vitamin K supplementation in various patients groups is necessary to optimize anticoagulant control.

**References**


1. Ansell J, Hirsh J, Poller L et al. The pharmacology and management of the vitamin K antagonists: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126:204S-233S.
2. Reynolds MW, Fahrbach K, Hauch O et al. Warfarin anticoagulation and outcomes in patients with atrial fibrillation: a systematic review and metaanalysis. Chest 2004;126:1938-1945.
3. Hylek EM, Go AS, Chang Y et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. N.Engl.J.Med. 2003;349:1019-1026.
4. Levine MN, Raskob G, Beyth RJ, Kearon C, Schulman S. Hemorrhagic complications of anticoagulant treatment: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126:287S-310S.
5. Khan T, Wynne H, Wood P et al. Dietary vitamin K influences intra-individual variability in anticoagulant response to warfarin. Br.J.Haematol. 2004;124:348-354.
6. Franco V, Polanczyk CA, Clausell N, Rohde LE. Role of dietary vitamin K intake in chronic oral anticoagulation: prospective evidence from observational and randomized protocols. Am.J.Med. 2004;116:651-656.
7. Kurnik D, Lubetsky A, Loebstein R, Almog S, Halkin H. Multivitamin supplements may affect warfarin anticoagulation in susceptible patients. Ann.Pharmacother. 2003;37:1603-1606.
8. Sconce E, Khan T, Mason J et al. Patients with unstable control have a poorer dietary intake of vitamin K compared to patients with stable control of anticoagulation. Thromb.Haemost. 2005;93:872-875.
9. Institute of Medicine. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. 162-196. 4-6-2003.
10. Rombouts EK, Rosendaal FR, van der Meer FJ. The effect of vitamin K supplementation on anticoagulant treatment. J.Thromb.Haemost. 2006;4:691-692.
11. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb.Haemost. 1993;69:236-239.
12. Oldenburg J. Vitamin K intake and stability of oral anticoagulant treatment. Thromb.Haemost. 2005;93:799-800.
13. Bovill EG, Fung M, Cushman M. Vitamin K and oral anticoagulation: thought for food. Am.J.Med. 2004;116:711-713.
14. Sconce E, Avery P, Wynne H, Kamali F. Vitamin K supplementation can improve stability of anticoagulation for patients with unexplained variability in response to warfarin. Blood 2007;109:2419-2423.
15. Vermeer C, Hamulyak K. Vitamin K: lessons from the past. J.Thromb.Haemost. 2004;2:2115-2117.
16. Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA. Recent patterns of medication use in the ambulatory adult population of the United States: the Slone survey. JAMA 2002;287:337-344.

17. van Geest-Daalderop JH, Sturk A, Levi M, Adriaansen HJ. [Extent and quality of anti-coagulation treatment with coumarin derivatives by the Dutch Thrombosis Services]. Ned.Tijdschr.Geneeskd. 2004;148:730-735.
18. Pirmohamed M, James S, Meakin S et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ 2004;329:15-19.

# 6

# Vitamin K status and stability of oral anticoagulant therapy

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# Abstract

**Background**

Vitamin K supplementation improves anticoagulant stability in patients using vitamin K antagonists.

**Objectives**

To determine whether there is an association between vitamin K status and stability of anticoagulant treatment.

**Methods**

We examined the relationship between vitamin $K_1$ and its metabolite, vitamin K 2,3-epoxide and stability of oral anticoagulant treatment in participants of a double-blind, placebo-controlled trial on the effect of vitamin K supplementation on anticoagulant stability. Vitamin $K_1$ and vitamin K 2,3-epoxide serum levels were determined in 91 patients receiving placebo and 91 patients receiving 100 μg vitamin K per day. The effect of these variables on time in therapeutic range (TTR) was assessed using linear regression analysis.

**Results**

In the placebo group each standard deviation (SD) increase in vitamin $K_1$ level was associated with a 3.4% higher TTR. Vitamin K 2,3-epoxide levels increased the TTR with 2.7% per SD, but this effect disappeared when vitamin $K_1$ and vitamin K 2,3-epoxide levels were combined in one model. In the group receiving the vitamin K supplement we found no effect of vitamin K status on the TTR.

**Conclusion**

These findings contribute to the evidence that an adequate intake of vitamin K can improve anticoagulant control.

# Introduction

Vitamin K antagonists are indicated for the prevention of venous and arterial thrombosis.[1] Even though their effectiveness has been well established, many patients are denied the benefits of these drugs due to the difficulty in maintaining stable anticoagulation.[2] Vitamin K antagonists have a narrow therapeutic window and a high variability in anticoagulant response. Despite intensive monitoring, the intensity of anticoagulation, expressed as the International Normalized Ratio (INR), is within the target range only approximately 60% of the time.[3]

One of the causes of a fluctuating INR is a variable vitamin K intake. Vitamin K in its reduced form (vitamin K hydroquinone) is an essential cofactor for the posttranslational carboxylation of various proteins involved in blood coagulation, among which the procoagulant factors II, VII, IX and X. During the carboxylation reaction, the vitamin K hydroquinone is converted to its inactive metabolite, vitamin K epoxide, which is subsequently converted back to vitamin K hydroquinone by vitamin K epoxide reductase (VKOR). Vitamin K antagonists inhibit VKOR, thereby blocking the turnover of vitamin K epoxide resulting in depletion of the active vitamin K stores. This leads to the desired anticoagulant effect due to reduced production of fully carboxylated vitamin-K dependent clotting factors.[4]

Previous studies have suggested that patients with a low vitamin K intake have a less stable anticoagulation than patients with a higher intake.[5-8] Supplementation with low doses of vitamin K has been shown to improve anticoagulant stability.[9;10] This can be explained by the hypothesis that the INR is relatively resistant to a fluctuating vitamin K intake when average vitamin K intake is high. If this hypothesis were true one would also expect to find an association between vitamin K status and stability of anticoagulation.

We examined the relationship between serum levels of vitamin $K_1$ and its metabolite, vitamin K 2,3-epoxide and stability of oral anticoagulant treatment in participants of a clinical trial on the effect of vitamin K supplementation on anticoagulant stability.

## Methods

We determined the vitamin K status in participants of a randomized double-blind placebo-controlled clinical trial on the effect of vitamin K supplementation on anticoagulant stability.[10] In this trial 200 patients using the vitamin K antagonist phenprocoumon were randomized to receive either adjusted-dose phenprocoumon and 100 μg vitamin K once daily or adjusted dose phenprocoumon and a placebo.

Participants were recruited from the Leiden anticoagulation clinic in the Netherlands. They were between 18 and 80 years of age, had an indication for long-term anticoagulant therapy and had been using phenprocoumon for at least one year. Patients were enrolled in the study from December 2004 to January 2006. Treatment duration was 24 weeks. During this time patients were treated according to the guidelines of the anticoagulation clinic. During the study period the maximum interval between two visits was 4 weeks. The primary outcome was the percentage of time the INR was within the therapeutic range.[10] This study was approved by the local Medical Ethics Committee and was registered as an International Standard Randomized Controlled Trial, number ISRCTN14473912.

Eight to twelve weeks after starting the study medication, fasting blood samples were obtained by venipuncture. All specimens were kept in the dark. Blood samples were processed within 4 hours and aliquots of plasma and serum were stored at -80°C. Serum levels of vitamin $K_1$ and vitamin K 2,3-epoxide were measured by high-performance liquid chromatography (HPLC) using zinc postcolumn reduction and fluorescence detection as described earlier[11;12] with some modifications. In brief, after deproteinization of the samples with ethanol and liquid extraction using hexane, solid phase extraction is performed using a 500 mg/3 ml Strata C18-M column (Phenomenex, USA). The columns are pretreated with 5 ml hexane-2-propanol (98:2) and 5 ml hexane before the addition of the sample (2 ml). The vitamin $K_1$ and vitamin K 2,3-epoxide are eluted in a total volume of 10 ml hexane and dried under $N_2$ (g) at 40 ºC. The sample is taken up in ethanol and injected onto a Lichrospher®100-RP-18 (125-4mm; 5 μm) column (Merck, Darmstadt, Germany) and eluted at a flow of 1.5 ml/min using 1M sodiumacetate/acetic acid, 2M Zn $Cl_2$ in methanol (ratio

6:1000). A stainless steel column (50-2.1mm) containing zinc particles (Vitamin $K_1$ HPLC kit, Immundiagnostic, Bensheim, Germany) was placed between the HPLC column and the fluorimetric detector (model FP2020 Jasco, Tokyo, Japan). After the zinc postcolumn reduction the separated vitamin $K_1$ and vitamin K 2,3-epoxide were detected at Ex/Em of 248/418 nm.

We used linear regression analysis to assess the association between vitamin $K_1$ and vitamin K 2,3-epoxide levels and time in therapeutic range. Because both vitamin $K_1$ and vitamin K 2,3-epoxide levels showed a right-skewed distribution, we log-transformed the data. We then used the z-scores of the placebo group as coefficients in the model, so results show the change in time in therapeutic range per standard deviation (SD) change in serum vitamin $K_1$ or vitamin K 2,3-epoxide. Outliers were identified as being greater than the mean ± 3 SD of the logarithm. This resulted in the removal of 4 outlier values: 2 patients had a serum vitamin $K_1$ level higher than the mean +3 times the SD and 2 patients had a vitamin K 2,3-epoxide lower than the mean -3 times the SD. Values were removed rather than cases, because in those subjects with extreme values of vitamin $K_1$, vitamin K 2,3-epoxide levels were within the mean ± 2 SD and vice versa. Furthermore, the INR values of subjects with outliers were within the therapeutic range.

Age, sex, use of co-medication and use of medication interacting with the anticoagulant drug were considered potential confounders and were adjusted for in the analysis. Analyses were done separately for the placebo group and the vitamin K group. All statistical analyses were performed using SPSS 17 (SPSS Inc, Chicago, Ill, USA).

## Results

In the 200 patients randomized for the trial, serum vitamin $K_1$ and vitamin K 2,3-epoxide serum levels were determined in 91 patients in the vitamin K group and 91 patients in the placebo group. For 18 individuals serum or assays were unavailable.

**Table 1**: Baseline characteristics of the study population. Data are median (IQR) or number (%).

| | Placebo group (n = 91) | Vitamin K group (n = 91) |
|---|---|---|
| Age | 66 (58-72) | 65 (60-74) |
| Female sex | 26 (29%) | 20 (22%) |
| Duration of anticoagulant treatment (years) | 4 (2-8) | 4 (2-8) |
| Previous stability (%time in therapeutic range) | 80 (73-84) | 79 (72-84) |
| Indication | | |
| Atrial fibrillation | 38 (42%) | 39 (43%) |
| Secondary prevention venous thrombosis | 12 (13%) | 15 (17%) |
| Mechanical heart valve | 12 (13%) | 9 (10%) |
| Other arterial | 29 (32%) | 28 (31%) |
| Therapeutic range | | |
| Low (2.0-3.5) | 51 (56%) | 56 (62%) |
| High (2.5-4.0) | 40 (44%) | 35 (38%) |
| Number of co-medications | 3 (2-5) | 3 (1-4) |
| Interacting medication | | |
| No | 44 (48%) | 55 (60%) |
| Yes | 47 (52%) | 36 (40%) |

Patient characteristics are shown in Table 1. Age, sex, duration of anticoagulant treatment, previous stability and indication for anticoagulant treatment were similar in both groups. In the placebo group there were slightly more patients in the high target range. Patients in the placebo group used more drugs interacting with anticoagulants.

Table 2 gives an overview of the vitamin $K_1$ and vitamin K 2,3-epoxide levels in the placebo group and the group receiving vitamin K. Mean serum vitamin $K_1$ was 0.83 ng/mL in the placebo group and 1.02 ng/mL in the vitamin K group (difference 0.20 ng/mL, 95%CI: 0.05 to 0.34). Mean vitamin K 2,3-epoxide was 4.60 ng/mL in the placebo group and 7.00 in the vitamin K group (difference 2.40 ng/mL, 95% confidence interval [95%CI]: 0.68 to 4.12). In the placebo group, the SD of the logarithm of the vitamin $K_1$ level, used as the regression coefficient in the linear regression model, was 0.52. The SD of ln(vitamin K 2,3-epoxide) was 1.05.

**Table 2**: Serum levels of vitamin K1 and vitamin 2,3-epoxide

| | Vitamin K1 (ng/mL) | | ln(Vitamin K1) | Vitamin K 2,3-epoxide (ng/mL) | | ln(Vitamin K 2,3- epoxide) |
|---|---|---|---|---|---|---|
| | Mean ±SD | Median (IQR) | Mean ±SD | Mean ±SD | Median (IQR) | Mean ±SD |
| Group receiving placebo | 0.83 ±0.53 | 0.70 (0.55-0.97) | -0.33 ±0.52 | 4.60 ±4.40 | 3.84 (1.27 - 5.95) | 1.07 ±1.05 |
| Group receiving vitamin K | 1.02 ±0.44 | 0.92 (0.72-1.17) | -0.06 ±0.40 | 7.00 ±6.96 | 5.13 (2.64 - 9.62) | 1.50 ±1.06 |

**Table 3**: Vitamin K status and time in therapeutic range. The table shows the results of linear regression, with vitamin K levels as independent variables and time in therapeutic range (TTR) as the dependent variable. The independent variables are expressed as z-scores of the logarithm of the serum levels. The constant is equivalent to a z-score =0, which is the TTR for the mean of the logarithm of the vitamin K level; the coefficient shows the change in TTR (%) per unit change in vitamin K level, one unit being one standard deviation of the logarithm of the level. * Adjusted for age, sex, number of co-medications and use of interacting medication.

| | Time in Therapeutic range (%) | | | |
|---|---|---|---|---|
| Determinant | Constant | B | Adjusted B* | vitamin K1 and vitamin 2,3-epoxide combined |
| Group receiving placebo | | | | |
| Vitamin K1 level (Z-score ln(vitamin K)) | 85.2 | 3.4 (0.3 to 6.6) | 3.2 (-0.4 to 6.5) | 3.1 (-0.9 to 7.0) |
| Vitamin K 2,3-epoxide level (Z-score ln(vitamin KO)) | 85.2 | 2.7 (-0.5 to 5.8) | 2.4 (-1.0 to 5.7) | 0.6 (-3.4 to 4.7) |
| Group receiving vitamin K | | | | |
| Vitamin K1 level (Z-score ln(vitamin K)) | 89.6 | 1.0 (-2.9 to 4.8) | 0.7 (-3.0 to 4.5) | -0.9 (-5.1 to 3.4) |
| Vitamin K 2,3 epoxide level (Z-score ln(vitamin KO)) | 89.5 | 1.3 (-1.9 to 4.4) | 1.2 (-1.9 to 4.3) | 1.8 (-1.5 to 5.1) |

**Table 4a**: Vitamin K status and time below therapeutic range.

| | Time below Therapeutic range (%) | | | |
|---|---|---|---|---|
| Determinant | Constant | B | Adjusted B* | vitamin K1 and vitamin 2,3-epoxide combined |
| Group receiving placebo | | | | |
| Vitamin K1 level (Z-score ln(vitamin K)) | 2.8 | 0.1 (-1.2 to 1.5) | 0.3 (-1.1 to 1.7) | -0.5 (-2.1 to 1.2) |
| Vitamin K 2,3 epoxide level (Z-score ln(vitamin KO)) | 2.7 | 0.7 (-0.6 to 2.1) | 0.9 (-0.4 to 2.3) | 1.1 (-0.6 to 2.8) |
| Group receiving vitamin K | | | | |
| Vitamin K1 level (Z-score ln(vitamin K)) | 2.3 | -0.4 (-1.8 to 0.9) | -0.4 (-1.8 to 1.0) | -0.1 (-1.6 to 1.3) |
| Vitamin K 2,3 epoxide level (Z-score ln(vitamin KO)) | 1.9 | 0.1 (-0.9 to 1.2) | 0.2 (-0.9 to 1.3) | 0.1 (-1.0 to 1.3) |

**Table 4b:** Vitamin K status and time above therapeutic range

| | Time above Therapeutic range (%) | | | |
|---|---|---|---|---|
| Determinant | Constant | B | Adjusted B* | vitamin K1 and vitamin 2,3-epoxide combined |
| Group receiving placebo | | | | |
| Vitamin K1 level (Z-score ln(vitamin K)) | 12.0 | -3.6 (-6.5 to -0.6) | -3.5 (-6.6 to -0.5) | -2.6 (-6.3 to 1.1) |
| Vitamin K 2,3 epoxide level (Z-score ln(vitamin KO)) | 12.0 | -3.4 (-6.4 to -0.4) | -3.3 (-6.4 to -0.2) | -1.7 (-5.5 to 2.0) |
| Group receiving vitamin K | | | | |
| Vitamin K1 level (Z-score ln(vitamin K)) | 8.2 | -0.5 (-3.9 to 2.8) | -0.3 (-3.6 to 2.9) | 1.0 (-2.7 to 4.8) |
| Vitamin K 2,3 epoxide level (Z-score ln(vitamin KO)) | 8.6 | -1.4 (-4.1 to 1.3) | -1.4 (-4.1 to 1.3) | -1.9 (-4.8 to 1.0) |

Table 3 shows the associations between vitamin K status and time in therapeutic range, for the placebo group and the vitamin K group separately. In the placebo group, time in therapeutic range increased 3.4% for each SD increase in serum vitamin $K_1$ (95%CI: 0.3 to 6.6%). An effect in the same direction was observed for serum vitamin K 2,3-epoxide: one SD increase resulted in a rise of the time in range of 2.7% (95%CI: -0.5 to 5.8%). Adjustment for age, sex and use of co-medication did not change the results. When we combined vitamin $K_1$ and vitamin 2,3-epoxide in one model, the effect of vitamin $K_1$ remained similar and the effect of vitamin 2,3-epoxide disappeared. In the group receiving vitamin K supplementation there was no association between vitamin K status and the time in therapeutic range.

The increase of the time in therapeutic range was attributable to a decrease in time above the therapeutic range rather than below the therapeutic range, i.e. high serum vitamin $K_1$ levels prevented overanticoagulation (Tables 4a and 4b).

## Discussion

We found that time in therapeutic range increases by approximately 3% for each standard deviation increase in vitamin K levels. This demonstrates that patients with a high vitamin K status have a more stable anticoagulation than individuals with a low vitamin K status. This relationship was found both for levels of vitamin K1 as vitamin K 2,3-epoxide. In the group receiving the vitamin K supplement we found no association between vitamin K status and time in therapeutic range, suggesting that instability caused by dietary vitamin K changes in patients was effectively reduced by the vitamin K supplement.

Our findings are in agreement with earlier studies that focused on vitamin K intake. Patients with low vitamin K intake were shown to have a less stable anticoagulant control[7] and a higher risk of subtherapeutic anticoagulation.[8] Changes in dietary vitamin K intake influence the INR[5;13;14] and do so more when vitamin K intake is low.[5;8] In addition, starting a low dose vitamin K supplement of 25 μg/day results in subtherapeutic INR

values in individuals with a low plasma vitamin K only.[6] These studies imply that patients are more susceptible to changes in vitamin K intake when vitamin K status is low and suggest that supplementation of vitamin K may be beneficial, especially in vitamin K depleted patients. Two placebo-controlled trials have been performed on the effect of vitamin K supplementation on quality of anticoagulant treatment. Sconce *et al.* studied 70 atrial fibrillation patients with unstable anticoagulant control and randomized them to receive 150 μg of vitamin K or a placebo for six months.[9] Vitamin K supplementation resulted in a decrease in the SD of the INR values and an increase of the percentage time in therapeutic range from 78% in the placebo group to 87% in the vitamin K group. The second trial, which was the basis for the study presented here, was conducted in 200 unselected patients who had been using the vitamin K antagonist phenprocoumon for over a year.[10] Vitamin K supplementation resulted in a small increase of time in therapeutic range from 85% in the placebo group to 89% in the vitamin K group. The larger effect in the trial by Sconce may have been caused because in this study unstable patients were selected, who may have had a lower vitamin K status and benefit more from supplementation. Indeed, the mean plasma vitamin K concentrations at baseline were 0.60 ng/mL in the vitamin K group and 0.69 ng/mL in the placebo group of the trial by Sconce, which is considerably lower than the level of 0.87 ng/mL in the placebo group of our study. Unfortunately we did not measure serum vitamin K at baseline, so we could not perform a subgroup analysis on the effect of vitamin K supplementation conditioned on vitamin K status.

A possible limitation of this study is that we determined the vitamin K status in a single day's sample. Even though we used fasting blood samples, circulating vitamin K concentrations respond to daily changes in intake.[15] This may have resulted in misclassification of the exposure variables (vitamin $K_1$ and vitamin K 2,3-epoxide levels). Because this misclassification is just as likely to have occurred in individuals with stable anticoagulation as in individuals with unstable anticoagulation, it is likely that this caused at most an attenuation of the observed effects, in which case the true association between vitamin K levels and stability would be stronger than observed here.

Changes in dietary vitamin K intake can be a significant factor in the stability of anticoagulant treatment. Our results contribute to the evidence that patients using vitamin K antagonists should not restrict their vitamin K intake, which is frequently advised. On the contrary, a vitamin K intake in the high normal levels should be advised to increase stability of anticoagulant treatment. In addition, these findings support the proposal of using a vitamin K supplement to improve quality of anticoagulant therapy.

## References


1. Ansell J, Hirsh J, Hylek E et al. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:160S-198S.
2. Sudlow M, Thomson R, Thwaites B, Rodgers H, Kenny RA. Prevalence of atrial fibrillation and eligibility for anticoagulants in the community. Lancet 1998;352:1167-1171.
3. Reynolds MW, Fahrbach K, Hauch O et al. Warfarin anticoagulation and outcomes in patients with atrial fibrillation: a systematic review and metaanalysis. Chest 2004;126:1938-1945.
4. Oldenburg J, Watzka M, Rost S, Muller CR. VKORC1: molecular target of coumarins. J.Thromb.Haemost. 2007;5 Suppl 1:1-6.
5. Franco V, Polanczyk CA, Clausell N, Rohde LE. Role of dietary vitamin K intake in chronic oral anticoagulation: prospective evidence from observational and randomized protocols. Am.J.Med. 2004;116:651-656.
6. Kurnik D, Loebstein R, Rabinovitz H et al. Over-the-counter vitamin K(1)-containing multivitamin supplements disrupt warfarin anticoagulation in vitamin K(1)-depleted patients. Thromb.Haemost. 2004;92:1018-1024.
7. Sconce E, Khan T, Mason J et al. Patients with unstable control have a poorer dietary intake of vitamin K compared to patients with stable control of anticoagulation. Thromb.Haemost. 2005;93:872-875.
8. Rombouts EK, Rosendaal FR, van der Meer FJ. Influence of dietary vitamin K intake on subtherapeutic oral anticoagulant therapy. Br.J.Haematol. 2010
9. Sconce E, Avery P, Wynne H, Kamali F. Vitamin K supplementation can improve stability of anticoagulation for patients with unexplained variability in response to warfarin. Blood 2007;109:2419-2423.
10. Rombouts EK, Rosendaal FR, van der Meer FJ. Daily vitamin K supplementation improves anticoagulant stability. J.Thromb.Haemost. 2007;5:2043-2048.
11. Davidson KW, Sadowski JA. Determination of vitamin K compounds in plasma or serum by high-performance liquid chromatography using postcolumn chemical reduction and fluorimetric detection. Methods Enzymol. 1997;282:408-421.
12. Haroon Y, Bacon DS, Sadowski JA. Liquid-chromatographic determination of vitamin K1 in plasma, with fluorometric detection. Clin.Chem. 1986;32:1925-1929.
13. Schurgers LJ, Shearer MJ, Hamulyak K, Stocklin E, Vermeer C. Effect of vitamin K intake on the stability of oral anticoagulant treatment: dose-response relationships in healthy subjects. Blood 2004;104:2682-2689.
14. Johnson MA. Influence of vitamin K on anticoagulant therapy depends on vitamin K status and the source and chemical forms of vitamin K. Nutr.Rev. 2005;63:91-97.
15. Booth SL, O'Brien-Morse ME, Dallal GE, Davidson KW, Gundberg CM. Response of vitamin K status to different intakes and sources of phylloquinone-rich foods: comparison of younger and older adults. Am.J.Clin.Nutr. 1999;70:368-377.

# 7

# Improved control of oral anticoagulant dosing: a randomized controlled trial comparing two computer algorithms

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# Abstract

**Background**

Efforts to improve dosing quality in oral anticoagulant control include the use of computer algorithms. As current algorithms are simplistic and give dosage proposals in a small fraction of patients, we developed an algorithm based on principles of system and control engineering that gives proposals in nearly all patients.

**Objective**

To evaluate the new algorithm in clinical practice.

**Methods**

We conducted a double-blind randomized controlled trial among 712 patients with an indication for long-term anticoagulant treatment at the Leiden Anticoagulation Clinic. We compared oral anticoagulant dosing supported by the new algorithm (ICAD) with the standard algorithm (TRODIS).

**Results**

The percentage of time spent in the therapeutic range was similar for the new and standard algorithm groups, 79.8% vs. 80.2% (difference 0.4%, 95%CI: 1.7-2.6%). The new algorithm produced a dosage proposal in 97.5% of visits, and the standard algorithm in 60.8% (difference 36.7%, 95%CI: 35.4-38.0%). Of proposals of the new algorithm, 79.3% were accepted by the physician vs. 90.9% for the standard algorithm (difference 11.6%, 95%CI: 10.2-13.0%). This implies that the new algorithm gave an acceptable proposal in 77.4% of all patient visits vs. 55.3% for the standard algorithm (difference 22.1%, 95%CI 20.4-23.8%).

**Conclusion**

Substantially more dosage proposals were generated and accepted with the new than with the standard algorithm, and the new algorithm will therefore improve the efficiency of anticoagulant monitoring without loss of quality.

# Introduction

Management of oral anticoagulant treatment is difficult, because of the large variability in the dosage needed to achieve the optimal anticoagulant effect. Not only does sensitivity to vitamin K antagonists differ between patients, within patients, it may vary over time.[1]

The use of computer algorithms to assist physicians with their dosing decisions has been shown to lead to equal or improved quality of control of oral anticoagulant treatment as compared to unassisted dosing.[2-6] Several algorithms have been developed previously. Poller *et al.*[4] compared three different computerized systems to assist warfarin control with traditional dosing by experienced doctors. They found roughly similar results for unassisted dosing by physicians and dosing by the three algorithms. In a larger multicenter study, Poller *et al.*[5] evaluated the safety and efficacy of the DAWN AC anticoagulant therapy management system. They found that patients in the computer-dose group spent more time in the target range than patients in the traditional-dose group. An algorithm that is similar to these algorithms is used widely in the Netherlands (TRODIS).[7] This algorithm generates a dosage proposal in approximately 55% of visits, leaving 45% for unassisted dosing by experienced physicians. In approximately 20% of cases where TRODIS generates a dosage proposal, it is overruled by a physician.[8] All these algorithms are based on an empirical decision-tree that determines whether the same dosage can be maintained, dosage adjustments have to be made, or manual intervention by a physician is required. The equations used by the algorithm are based on a simple pharmacodynamic model, which implies a linear function between the International Normalized Ratio (INR) and the dosage. Major disadvantages of these algorithms are that they do not generate a dosage proposal in all cases, and they do not take into account the sensitivity of the patient to coumarin derivatives (which may change over time), the half-life of the drug, and the non-linearity of the dose-INR relationship.

To improve computer-assisted dosing, we developed a new dosing algorithm. The improved control of anticoagulant dosage (ICAD) algorithm is based on a model that comprises the pharmacokinetics and pharmacodynamics of the oral anticoagulant drug, the pharmacokinetics of

the prothrombin complex, and the relationship between the activity of the prothrombin complex and the measured INR. It consists of two sub-models: the first sub-model describes the collective influence of all processes on the effect of the vitamin K antagonist, and the second sub-model describes the relationship between the dosage and the corresponding INR. The second sub-model includes a variable parameter to reflect the sensitivity of the patient, which may change over time. In an expert evaluation, 194 visits were randomly selected from the anticoagulation clinic database to assess whether the dosage proposal and appointment periods calculated by the algorithm were acceptable. In this evaluation, the ICAD algorithm was able to give a good or acceptable proposal in 94.3% of cases. The ICAD algorithm is described in detail elsewhere.[9] In this study, we tested the ICAD algorithm in clinical practice in a double-blind randomized controlled trial, with the frequently used algorithm 'TRODIS' as the reference intervention.

# Methods

### Study design

The study was conducted at the Leiden Anticoagulation Clinic in The Netherlands. Patients visit the clinic to have their INR measured, and they receive their daily dosage prescription the next day by mail.[10] The TRODIS program uses the previous two INRs, the previous dosage schedule, the INR target, and range-limiting values of the INR. A dose-response model is used to predict an INR. By comparing this prediction with the measured INR, the program computes a new dosage and the time to the next visit. It does not generate a proposal in the case of an alert (e.g. when a new drug is prescribed) or a large difference between the actual and the target INR, and in that case the physician has to determine the dosage without any help from the algorithm.

The ICAD algorithm also uses the actual measured INR, the target INR and the previous dosage schedule, but differs from TRODIS and all other algorithms by calculating the sensitivity of the patient over the full course of each treatment. This sensitivity is incorporated in the equation to estimate the dosage needed to achieve an optimal anticoagulant effect, thus

allowing the dose-INR relationship to change over time. Like all other algorithms, the ICAD algorithm gives a recommendation for the dosage as well as an appointment period. A computer program was developed for this study to present the dosage proposals of both algorithms in an identical way to keep physicians blinded. This program extracted for every patient the dosage proposal generated by TRODIS along with the INR, previous dosage schedule, and all previous INRs from the TRODIS mainframe database. The relevant data were fed through the ICAD algorithm, and an ICAD proposal was generated; thus, for all patients, a TRODIS as well as an ICAD proposal was available. Depending on which group the patient was randomized to, the TRODIS or the ICAD proposal was shown to the physician, on a screen that was identical for both types of proposals. Along with the dosage proposal, a recommendation about the appointment period was given. Both ICAD and TRODIS give an indication of how confident the algorithm is about the proposal; for TRODIS, there are two levels of confidence ('high' and 'tentative'), whereas ICAD expresses confidence in a range of 0-100. These levels of confidence were not shown to the physician to maintain blinding, but are used in the analyses presented here. The physician could either accept or overrule the generated proposal. The final dosage was fed back to the mainframe database of the anticoagulation clinic and subsequently, as is the routine policy, communicated by mail to the patient.

**Patients**

Enrollment occurred between 14 August and 16 October 2003 at the Leiden Anticoagulation Clinic. Patients were eligible when they were already receiving anticoagulation with an indication for long-term anticoagulant therapy, and were aged between 18 and 80 years. Patients were excluded when they were on patient self-management, stayed long periods abroad, or were in a terminal stage of disease. Randomization was stratified by the indication for oral anticoagulant treatment, age and sex using the minimization method.[11] The study was double blind; that is, neither patients nor physicians were aware of which group the patient belonged to. Follow-up was until 1 September 2004, i.e. maximally about 1 year.

We obtained approval from the Medical Ethics Review Committee of the Leiden University Medical Centre before the start of the study, and each patient gave written informed consent. Trial Registration: ISRCTN register, http://www.controlled-trials.com. Identifier ISRCTN27801917.

**Analysis**

The analysis was performed at two levels, i.e. at the level of the patient and at the level of the proposal. In the first analysis, the primary outcome measure for this comparison was quality of anticoagulant treatment, defined as the mean percentage of time spent in the therapeutic range (TTR), calculated by the linear interpolation method.[12] Therapeutic ranges were as applied in our routine anticoagulant practice: INR 2.0-3.5 for low intensity, and INR 2.5-4.0 for indications requiring a higher intensity. If a patient had two or fewer INR measurements in total, no TTR was calculated. When the time between two INR checks exceeded 9 weeks, no TTR was calculated for this period, and this period was excluded. All periods of hospitalization were excluded.

Secondary outcome measures were the median time between visits, the percentage of time above or below the therapeutic range, the number of dosage proposals generated by the algorithm, and clinical events. Bleeding complications were classified as major if they were fatal or necessitated hospitalization. Minor bleeding complications were all other bleeding events, in which ecchymoses were only counted when more than 10 cm in diameter, and epistaxis only when the duration exceeded 30 min.

In the analysis at the level of the proposal, we compared the proposals as they were generated by each algorithm (only one was shown to the physician). The primary outcome measure was the quality of the dosage proposals, expressed as the percentage accepted by the physician. If no proposal was generated, we considered this as not accepted. Secondary outcomes at the level of proposal comparisons were the percentage of INRs within the therapeutic range at the next visit, the percentage of accepted appointment periods proposed by the algorithms, and whether the dose proposal of the algorithm that was not shown to the physician differed from the given dose.

We knew beforehand that TRODIS is not always capable of generating a dosage proposal. If the algorithm was incapable of generating a proposal, the dosage had to be determined by the physician unassisted by the algorithm. ICAD generated a dosage proposal in nearly all visits, which made it possible to directly compare ICAD with the physician. To avoid bias, we selected all INR checks from both randomization groups where TRODIS was not able to generate a proposal. This was possible because, for all visits, an ICAD as well as a TRODIS proposal was available. For patients randomized to TRODIS, the physician determined the dosage without assistance from the algorithm. In the patients randomized to ICAD, an ICAD proposal was available. We studied the performance of the physician vs. ICAD in these two groups by calculating the percentage of INRs within range at the next visit.

**Statistical analysis**

We determined the necessary sample size on our primary outcome measure, the therapeutic range. We felt a difference of 5% in percentage of time spent in the TTR to be of clinical relevance. On the basis of information from several anticoagulation clinics, we found an SD of approximately 23% in this outcome measure. With an alpha of 5% and a power of 90%, we needed two times 168 patients to detect our clinically relevant difference. To allow us to do subgroup analyses, we included 712 patients.

All outcomes are shown as means or percentages with the corresponding 95% confidence interval (95%CI) of the difference based on T or binomial distributions or medians with the corresponding interquartile range (IQR). All calculations were performed on an intention-to-treat basis using the statistical package SPSS version 14.0 (SPSS Inc., Chicago, IL, USA).

## Results

Seven hundred and twelve patients were randomized; 359 were assigned to ICAD, and 353 to TRODIS. The total follow-up time in the ICAD group was 283.1 person-years, during which 6 007 INR checks were performed. In the TRODIS group, the follow-up time was 278.7 person-years, with 5 920 INR checks. Enrolment, randomization, follow-up and analysis of all patients are summarized in Figure 1. Baseline characteristics are shown in Table 1.

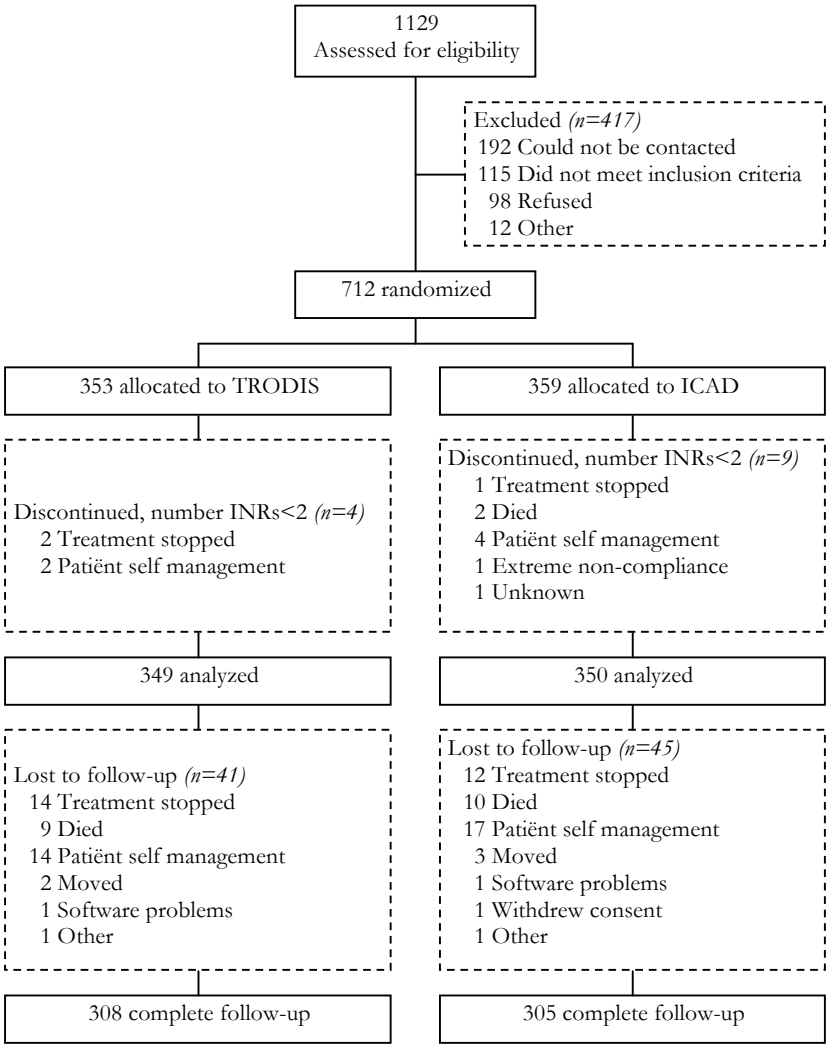


**Figure 1**: Enrollment, randomization and data analysis

**Table 1:** Patient characteristics

| | TRODIS (n = 353) | ICAD (n = 359) |
|---|---|---|
| Age (years) | | |
| Mean (IQR) | 65.7 (59.6-74.8) | 64.6 (57.6-74.8) |
| Sex | | |
| Men (%) | 66.6 | 66.6 |
| Indication | | |
| Atrial Fibrillation (%) | 44.5 | 42.3 |
| Venous thrombosis (%) | 11.6 | 13.3 |
| Heart valve prosthesis (%) | 9.9 | 10.6 |
| Other cardiac indication (%) | 20.1 | 16.7 |
| Peripheral vascular disorder (%) | 8.8 | 10.3 |
| Cerebrovascular (%) | 5.1 | 7.0 |
| Coumarin | | |
| Acenocoumarol (%) | 13.6 | 12.5 |
| Phenprocoumon (%) | 85.6 | 86.1 |
| Switched (%) | 0.8 | 1.4 |
| Intensity (target) | | |
| Low (2.5-3.5) (%) | 62.9 | 61.6 |
| High (3.0-4.0) (%) | 36.3 | 38.2 |
| Switched (%) | 0.8 | 0.3 |

The mean TTR was 79.8%in the ICAD group and 80.2% in the TRODIS group (difference 0.4%, 95%CI of difference: -1.7 to 2.6%). The mean percentage of time spent at subtherapeutic or supratherapeutic INRs did not differ: 4.2% of time subtherapeutic in the ICAD group vs. 4.4% in the TRODIS group (difference 0.2%, 95%CI: -1.1 to 1.5%), and 16.0% of time supratherapeutic in the ICAD group vs. 15.4% in the TRODIS group (difference 0.6%, 95%CI: -1.1 to 2.3%). The median time between two visits in the ICAD group was 14 days (IQR 14-26 days) vs. 14 days (IQR 14-22 days) in the TRODIS group (Figure 2).

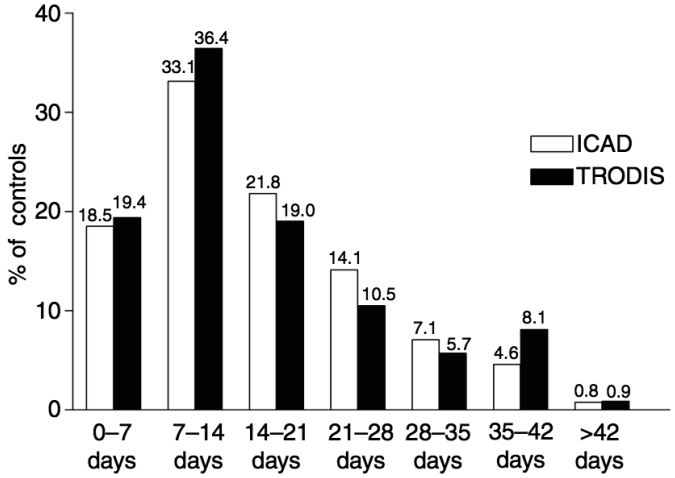


**Figure 2:** Time between two visits

There were 98 bleeding events (17 major and 81 minor) and three thromboembolic complications in 85 patients. Overall incidences of clinical thromboembolic and bleeding events (allowing for more than one event per patient) were 19.4/100 person-years in the ICAD group vs. 16.5/100 person-years in the TRODIS group, yielding a relative risk of 1.2 (95%CI: 0.8-1.8). Twelve of the major bleeding events occurred in the ICAD group (incidence rate 4.2/100 person-years), and five in the TRODIS group (incidence rate 1.8/100 person-years). This yielded a relative risk of 2.3 (95%CI: 0.8-6.5) of excess bleeding in the ICAD group vs. TRODIS group. In the ICAD group, the major bleeding events were as follows: five gastrointestinal, two hematuria, one severe nose bleed, and one severe skin bleed. Three patients had a fatal intracranial bleed. In the TRODIS group, there were two severe nose bleeds, one respiratory tract bleed, and one retroperitoneal bleed. One patient had a fatal intracranial bleed. To further investigate the major bleeding events, we analyzed, in addition to the mean TTR, time spent with an INR < 2.0, 2.0-3.0, 3.0-4.0, 4.0-5.0, and above 5.0. Also in this analysis, there was no difference between the ICAD group and the TRODIS group. For 11 patients, an INRmeasurement was available at the time of bleeding. All INRs were between 1.3 and 3.7, except for one patient who had an INR of 4.3 (TRODIS group). Of the remaining patients, two had an INR measurement 2 days before the event: INR of 2.4

(TRODIS) and 1.3 (ICAD). In none of the patients was the dosage increased at the last INR measurement. In total, 21 patients died during follow-up, four because of a bleeding complication (three ICAD, one TRODIS). All deaths and complications are listed in Table 2.

**Table 2**: Adverse events and deaths during follow up.

| | TRODIS (n=349) | ICAD (n=350) |
|---|---|---|
| Bleeding events | | |
| Minor | 40 | 41 |
| Major | 4 | 9 |
| Fatal | 1 | 3 |
| Total | 45 | 53 |
| Thromboembolic events | 1 | 2 |
| Deaths | | |
| Bleeds | 1 | 3 |
| Malignancy | 1 | 2 |
| Cardiac | 2 | 0 |
| Respiratory | 0 | 3 |
| Other | 1 | 1 |
| Unknown | 4 | 3 |
| Total | 9 | 12 |

ICAD was able to generate dosage proposals in 97.5% of visits, whereas TRODIS generated a proposal in 60.8% (difference 36.7%, 95%CI: 35.4-38.0%). In the ICAD group, 79.3% of these dosage proposals were accepted vs. 90.9% in the TRODIS group (difference 11.6%, 95%CI: 10.2-13.0%). In total, therefore, 77.4% of patient visits in the ICAD group led to an accepted proposal, as opposed to 55.3% in the TRODIS group (difference 22.1%, 95%CI: 20.4-23.8%). In the ICAD group, software problems were the main reason for not generating a proposal; these occurred only rarely. The most important reason for rejecting a proposal was that the dosage change proposed by the algorithm was estimated to be too strong (60.5%). In the TRODIS group, the main reason why a proposal was not generated was an INR change that was too large in relation to the previous INR or the one before that (64.2%). In the case of a rejected proposal, this was mostly because the dosage change proposed by the algorithm was too strong (66.2%) (Table 3).

**Table 3:** Reasons for not accepting a dosage proposal.

| Reasons | ICAD (n = 1211) N (%) | TRODIS (n = 328) N (%) |
|---|---|---|
| Dose change proposed by the algorithm was too strong | 733 (60.5) | 217 (66.2) |
| Dose change proposed was not strong enough | 339 (28.0) | 60 (18.3) |
| Proposal was in the wrong direction | 139 (11.5) | 51 (15.5) |

When the proposals were stratified according to the confidence level that the algorithm had given to them, in both groups the proportion of proposals that was accepted rose with the confidence level (Table 4). Along with the dosage proposal, the algorithms also provided proposals for the appointment period. The proposed appointment periods were accepted in 76.5% in the ICAD proposals and in 91.4% in the TRODIS proposals (difference 14.9%, 95%CI of difference: 13.5-16.3%). When we considered only proposals for which the physician accepted the dosage, 82.1% of the ICAD appointment periods were accepted, and 93.4% of those in the TRODIS group (difference 11.3%, 95%CI of difference: 9.9-12.7%).

**Table 4:** Percentage of accepted dose proposals stratified according to the confidence levels.

| | n (%) | % Accepted |
|---|---|---|
| TRODIS proposal type | | |
| No proposal | 2319 (39.2) | 0 |
| Tentative | 1465 (24.7) | 87.6 |
| Confident | 2136 (36.1) | 93.1 |
| Total | 5920 | 55.3 |
| ICAD confidence score | | |
| 0-20 | 228 (3.8) | 7.9 |
| 20-40 | 367 (6.3) | 37.3 |
| 40-60 | 939 (15.6) | 64.9 |
| 60-80 | 2001 (33.3) | 80.1 |
| 80-100 | 2472 (41.2) | 92.4 |
| Total | 6007 | 77.4 |

In the ICAD group 70.1%of INRs were in range at the next visit, as compared to 72.5% of INRs in the TRODIS group (difference 2.4%, 95%CI of difference: 0.7-4.1%). When we only considered the accepted proposals, 72.3% of the INRs were in range in the ICAD group, vs. 75.7% in the TRODIS group (difference 3.4%, 95%CI of difference: 1.4-5.4%). Of the TRODIS proposals that were overruled by the physician, 28.0% had an ICAD proposal that was equal to the dosage that was given by the physician. In the ICAD group, 19.1% of the unaccepted proposals had a TRODIS proposal that was similar to the actual given dosage.

In the comparison between ICAD and the physician, i.e. all patient visits where TRODIS was not capable of giving a proposal, ICAD was able to generate a dosage proposal in 96.9% of cases. Of these, 66.7% were accepted by the physician. In the ICAD group, 63.4%of the INRs were within the therapeutic range at the next INR measurement vs. 67.4% in the TRODIS group, which were dosed by the physician (difference 4.0%, 95%CI of difference: 1.2-6.8%).

## Discussion

In this study, we compared two computer algorithms for the control of anticoagulant dosing. There was no difference in quality of anticoagulant control between the TRODIS and the ICAD algorithms, expressed as mean TTR. Also, the time between two visits was similar in both groups, although the IQR was broader for the new algorithm. There was a difference in efficiency between the two algorithms. For all visits, TRODIS generated an acceptable proposal in 55.3%, as opposed to 77.4% for ICAD. Finally, in almost all cases where the standard algorithm could not give a proposal, the new algorithm could, and performed equally well as an unassisted physician.

The similar quality of ICAD and TRODIS proposals can be explained in several ways. Firstly, it is possible that an algorithm that uses more information on a patient is not capable of generating dosage proposals better than an algorithm that uses less information. Secondly, it is possible that there can be no more gain in quality of treatment by improving dosing of anticoagulants. Thirdly, physicians, being used to the old algorithm, may have altered unusual but good proposals of the new algorithm. We feel that

it is unlikely that an algorithm will ever be capable of incorporating all aspects of patient behavior, such as sudden changes in diet, and that possibly the best that is attainable is an algorithm that does as well as well-trained, dedicated physicians. When one algorithm uses a simple model and only gives proposals for 'easy' cases, leaving the more difficult cases to the physicians, while another algorithm gives proposals for virtually all cases and performs as well as the physicians, we would expect the result to be as we observed: an increase in efficiency without a concomitant increase in quality of treatment.

Although there was no difference in mean TTR between the groups, we did observe a difference in clinical events. As the study groups were similar in all prognostic variables, and the TTR was similar for both groups, we feel that this was due to chance. Also, in the additional analysis, we again found no difference between the two groups, and most bleeding events were at INR in range, which strengthens our idea that the difference was due to chance.

This study was double blind, so patients in both groups were treated in the same way except for the algorithm that was used. Bias resulting from a different attitude towards the two algorithms was therefore prevented. In some cases, blinding of the physicians could not be achieved. It was known beforehand that TRODIS is often not able to generate a proposal. Whenever there was no proposal available, the physician knew that in all likelihood this concerned a patient randomized to the TRODIS group. This was only known for the INR check at that time, for the physician did not see previous proposals. Because in these cases there was obviously no possibility of rejecting or accepting the proposal, it is difficult to imagine that this could have biased the results.

Some patients were lost to follow-up after randomization because of participation in a self-management program, end of the prescribed treatment period, or other reasons. In both groups, the same number of patients was lost to follow-up, and their numbers were small, so selection because of loss of patients is unlikely.

We have tested the new ICAD algorithm for computer assisted dosing of oral anticoagulants in a randomized blinded comparison with the algorithm that is currently in use. The ICAD algorithm led to a similar

quality of anticoagulant control, but performed more efficiently: overall, the proportion of proposals accepted was 77.4%, vs. 55.3% for the old algorithm. Of course, we compared the ICAD algorithm only with TRODIS, and it is possible that other results would have been obtained if a comparison had been made with other systems used for computer-assisted dosing. In our opinion, however, the newly developed ICAD algorithm represents an important gain in the efficiency of the management of oral anticoagulant therapy.

**References**


1. Absher RK, Moore ME, Parker MH. Patient-specific factors predictive of warfarin dosage requirements. Ann.Pharmacother. 2002;36:1512-1517.
2. Ageno W, Turpie AG. A randomized comparison of a computer-based dosing program with a manual system to monitor oral anticoagulant therapy. Thromb.Res. 1998;91:237-240.
3. Manotti C, Moia M, Palareti G et al. Effect of computer-aided management on the quality of treatment in anticoagulated patients: a prospective, randomized, multicenter trial of APROAT (Automated PRogram for Oral Anticoagulant Treatment). Haematologica 2001;86:1060-1070.
4. Poller L, Wright D, Rowlands M. Prospective comparative study of computer programs used for management of warfarin. J.Clin.Pathol. 1993;46:299-303.
5. Poller L, Shiach CR, MacCallum PK et al. Multicentre randomised study of computerised anticoagulant dosage. European Concerted Action on Anticoagulation. Lancet 1998;352:1505-1509.
6. Vadher BD, Patterson DL, Leaning MS. Validation of an algorithm for oral anticoagulant dosing and appointment scheduling. Clin.Lab Haematol. 1995;17:339-345.
7. Wiegman H, Vossepoel AM. A computer program for long term anticoagulation control. Comput.Programs Biomed. 1977;7:71-84.
8. Annual Report. Leiden Anticoagulation Clinic. 2004.
9. Pasterkamp E, Kruithof CJ, van der Meer FJ, Rosendaal FR, Vanderschoot JP. A model-based algorithm for the monitoring of long-term anticoagulation therapy. J.Thromb.Haemost. 2005;3:915-921.
10. Rosendaal FR, van der Meer FJM, Cannegieter SC. Management of anticoagulant therapy: The dutch experience. J.Thromb.Haemost. 1996;2:265-269.
11. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975;31:103-115.
12. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb.Haemost. 1993;69:236-

# 8

# Summary and discussion

## Summary & discussion

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.

**References**


1. Sconce E, Khan T, Mason J et al. Patients with unstable control have a poorer dietary intake of vitamin K compared to patients with stable control of anticoagulation. Thromb.Haemost. 2005;93:872-875.
2. Kurnik D, Lubetsky A, Loebstein R, Almog S, Halkin H. Multivitamin supplements may affect warfarin anticoagulation in susceptible patients. Ann.Pharmacother. 2003;37:1603-1606.
3. Kurnik D, Loebstein R, Rabinovitz H et al. Over-the-counter vitamin K(1)-containing multivitamin supplements disrupt warfarin anticoagulation in vitamin K(1)-depleted patients. Thromb.Haemost. 2004;92:1018-1024.
4. Khan T, Wynne H, Wood P et al. Dietary vitamin K influences intra-individual variability in anticoagulant response to warfarin. Br.J.Haematol. 2004;124:348-354.
5. Johnson MA. Influence of vitamin K on anticoagulant therapy depends on vitamin K status and the source and chemical forms of vitamin K. Nutr.Rev. 2005;63:91-97.
6. Oldenburg J. Vitamin K intake and stability of oral anticoagulant treatment. Thromb.Haemost. 2005;93:799-800.
7. Warren Grant Magnuson Clinical Center, National Institutes of Health Drug-Nutrient Interaction Task Force. Important information to know when you are taking: Coumadin (r) and Vitamin K. http://ods.od.nih.gov/factsheets/cc/coumadin1.pdf . 17-10-2009.
8. Booth SL, Centurelli MA. Vitamin K: a practical guide to the dietary management of patients on warfarin. Nutr.Rev. 1999;57:288-296.
9. Institute of Medicine. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. 162-196. 4-6-2003.
10. Franco V, Polanczyk CA, Clausell N, Rohde LE. Role of dietary vitamin K intake in chronic oral anticoagulation: prospective evidence from observational and randomized protocols. Am.J.Med. 2004;116:651-656.
11. Sconce E, Avery P, Wynne H, Kamali F. Vitamin K supplementation can improve stability of anticoagulation for patients with unexplained variability in response to warfarin. Blood 2007;109:2419-2423.
12. Ford SK, Misita CP, Shilliday BB et al. Prospective study of supplemental vitamin K therapy in patients on oral anticoagulants with unstable international normalized ratios. J.Thromb.Thrombolysis. 2007;24:23-27.
13. Ansell J, Hirsh J, Hylek E et al. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:160S-198S.

14. Guyatt GH, Cook DJ, Jaeschke R, Pauker SG, Schunemann HJ. Grades of recommendation for antithrombotic agents: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:123S-131S.
15. Schulman S, Beyth RJ, Kearon C, Levine MN. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:257S-298S.
16. Prasad S, Wootten MR, Kulinski N, Chapman SA. What to do when warfarin therapy goes too far. J.Fam.Pract. 2009;58:346-352.
17. Brigden ML. When bleeding complicates oral anticoagulant therapy. How to anticipate, investigate, and treat. Postgrad.Med. 1995;98:153-62, 164.
18. Penning-van Beest FJ, Rosendaal FR, Grobbee DE, van Meegen E, Stricker BH. Course of the international Normalized Ratio in response to oral vitamin K1 in patients overanticoagulated with phenprocoumon. Br.J.Haematol. 1999;104:241-245.

# Samenvatting

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Vitamine K antagonisten zijn antistollingsmiddelen in tabletvorm. Ze worden voorgeschreven voor de behandeling en preventie van trombose. Zowel arteriële trombose (trombose van de slagaderen, bv hartinfarct, herseninfarct) als veneuze trombose (trombose van de aderen, bv trombosebeen en longembolie) worden effectief voorkómen door vitamine K antagonisten. Aangezien dit frequent voorkomende aandoeningen zijn, worden antistollingsmiddelen veel voorgeschreven: Elk jaar gebruiken zo'n 300 000 Nederlanders vitamine K antagonisten.

De keerzijde van de behandeling met deze medicijnen is het risico op bijwerkingen. De belangrijkste bijwerking is het optreden van bloedingen. Ernstige bloedingen treden op bij zo'n 2% van de behandelde patiënten per jaar, fatale bloedingen bij ongeveer 1 op de 200 patiënten per jaar. Het risico op een bloeding neemt toe naarmate de intensiteit van de antistolling hoger is. Aan de andere kant neemt het risico op trombose weer toe bij een lagere intensiteit. Deze intensiteit kan worden gemeten in het bloed en wordt uitgedrukt als de INR (International Normalized Ratio). De INR heeft als uitgangspunt de normale waarde voor mensen die geen antistollingsmiddelen gebruiken, gesteld op 1.0. Afhankelijk van de indicatie voor de behandeling wordt bij patiënten gestreefd naar een INR tussen de 2.0 en 4.0. Bij een INR onder de 2.0 neemt de kans op trombose toe, bij een INR boven de 4.0 neemt de kans op een bloeding toe.

Het is dus belangrijk om de INR binnen het streefgebied te houden. Helaas zijn er vele factoren die van invloed zijn op het effect van antistollingsmiddelen en dus op de hoogte van de INR. Eén van die factoren is de vitamine K inname in het dieet. Vitamine K komt voor in ons voedsel, met name in groene groenten, zoals boerenkool en spinazie. Vitamine K is nodig voor een normale stolling. Vitamine K antagonisten gaan de werking van vitamine K tegen en zorgen er zo voor dat het bloed minder stolbaar wordt gemaakt. Omdat wij elke dag iets anders eten, wisselt onze vitamine K inname en daarmee de intensiteit van de antistolling.

Tot voor kort was het advies aan patiënten die antistollingsmiddelen gebruiken om de vitamine K inname constant te houden en voedingsmiddelen met een hoog vitamine K gehalte te mijden. Maar het

mijden van vitamine K- rijke groente betekent een lagere totale vitamine K inname en er zijn de laatste tijd steeds meer aanwijzingen gekomen dat patiënten met een lage vitamine K inname minder stabiel ingesteld kunnen worden op antistollingsmiddelen. Dit zou verklaard kunnen worden doordat schommelingen in de vitamine K inname een relatief grotere invloed hebben bij een lagere vitamine K status. Het belangrijkste doel van dit proefschrift was om deze hypothese te toetsen en om het bewijs te versterken voor de veronderstelling dat een hoge vitamine K inname leidt tot een stabielere antistolling.

Een tweede aandachtspunt was het optreden van lage INRen. Het zit in de aard van artsen en wetenschappers om meer aandacht te geven aan de schade die we aanbrengen door overbehandeling dan door onderbehandeling. Dit uit zich in de wetenschappelijke literatuur over antistollingsbehandeling door het grote aantal studies over het vóórkomen en voorkómen van bloedingen en hoge INRen, terwijl weinig bekend is over oorzaken van een te lage INR. Wij onderzochten hoe groot het risico is op een te lage INR en welke factoren hierop van invloed zijn.

Tot slot richtten wij ons op het doseren van antistollingsmiddelen. Om de INR binnen de streefwaarden te houden wordt voor iedere individuele patiënt de dosering van het antistollingsmiddel bepaald. Elke 1-6 weken wordt de INR gemeten en zo nodig wordt de dosering aangepast. Bij het vaststellen van de optimale dosering wordt veelal gebruik gemaakt van computeralgoritmes. Eerder werd een nieuw computeralgoritme ontwikkeld, dat naast de relatie tussen de INR en de dosering van het antistollingsmiddel ook rekening houdt met de individuele gevoeligheid van een patiënt. Wij vergeleken dit nieuwe algoritme met een traditioneel algoritme.

Het belangrijkste deel van dit proefschrift, het onderzoek naar de veronderstelling dat een hoge vitamine K inname leidt tot een stabielere antistolling, is opgenomen in de hoofdstukken 3, 4, 5 en 6.

In *hoofdstuk 3* onderzochten wij het effect van vitamine K inname in het dieet op het optreden van een te lage INR. We keken of een lage INR vaker optreedt bij een hoge of lage *gemiddelde* vitamine K inname (gemeten over vier weken) en wat het effect is van een *incidentele* hoge inname. Daarnaast

onderzochten we of juist bij mensen met een lage gebruikelijke vitamine K inname een incidentele hoge inname vaker een lage INR tot gevolg heeft. We vonden dat het risico van een lage INR het hoogst is bij mensen met een lage gemiddelde vitamine K inname en het laagst bij mensen met een hoge inname. Een hoge incidentele vitamine K inname verhoogt de kans op een lage INR uitsluitend in mensen met een lage gemiddelde inname.

In *hoofdstuk 5* bestudeerden wij of een dagelijkse toediening van een geringe hoeveelheid vitamine K de stabiliteit van antistollingsbehandeling kan verbeteren. In een experimentele studie werden patiënten willekeurig ingedeeld in een groep die naast de antistollingsbehandeling een supplement met 100 µg vitamine K innamen of in een placebogroep. De keuze voor de dosering vitamine K werd genomen naar aanleiding van een vooronderzoek dat wordt beschreven in *hoofdstuk 4*. In dit hoofdstuk bepaalden we wat het effect is van verschillende doseringen vitamine K op de benodigde dosis van het antistollingsmiddel om zodoende de dosering vast te stellen die hoog genoeg is om het gewenste effect te bereiken, maar die wel veilig kan worden gegeven. In de experimentele studie vonden wij dat de kwaliteit van antistollingsbehandeling, uitgedrukt als de tijd dat de INR binnen het streefgebied is (time in therapeutic range [TTR]), verbeterde van 85.5% in de placebo groep naar 89.5% in de groep die vitamine K kreeg.

In dezelfde studie onderzochten we de relatie tussen stabiliteit van antistolling en de vitamine K status, uitgedrukt als het gehalte aan vitamine K en zijn metaboliet vitamine K epoxide in het bloed. De resultaten zijn weergegeven in *hoofdstuk 6*. In de placebogroep werd een relatie gevonden tussen stabiliteit van antistolling en het gehalte van zowel vitamine K als vitamine K epoxide: Mensen met een betere vitamine K status hadden een hogere TTR. In de groep die het vitamine K supplement kreeg toegediend, werd geen effect gevonden van de vitamine K status op de TTR, wat erop wijst dat vitamine K status geen invloed heeft op de stabiliteit van antistolling wanneer patiënten adequaat worden gesuppleerd.

*Hoofdstuk 2* beschrijft de resultaten van de studie naar de frequentie van voorkomen van een te lage INR en de risicofactoren. In totaal werden 7 419 patiënten gevolgd, nadat ze stabiel waren ingesteld op antistollingsmiddelen. Na vier weken had 12% van de patiënten een lage

INR en na 40 weken was dit gestegen tot de helft. Het gebruik van het antistollingsmiddel acenocoumarol gaf een twee keer zo hoog risico op een lage INR vergeleken met een ander middel, fenprocoumon. Het risico was daarnaast afhankelijk van het streefgebied (hoger risico bij een hoger streefgebied) en de indicatie voor antistolling (hoger risico bij preventie van veneuze trombose en laagste risico bij patiënten met mechanische kunstkleppen). In 30% van de gevallen werd de lage INR voorafgegaan door omstandigheden die het opzettelijk verlagen van de INR rechtvaardigen; een operatie, ingreep, bloeding of een te hoge INR.

In *hoofdstuk 7* werden twee computeralgoritmes voor het doseren van antistollingsmiddelen met elkaar vergeleken. Het nieuw ontwikkelde algoritme, dat naast de relatie tussen de dosering en de INR ook rekening houdt met de gevoeligheid van de patiënt, werd in een experimentele studie vergeleken met een algoritme dat in Nederland veel wordt gebruikt. Patiënten werden willekeurig ingedeeld in groepen die werden gedoseerd met ondersteuning van het nieuwe dan wel het traditionele algoritme. Er werd geen verschil gevonden in kwaliteit van antistolling, uitgedrukt als de TTR. Ook de tijd tussen twee INR controles (de belasting voor de patiënt) was gelijk in beide groepen. Wel gaf het nieuwe algoritme vaker een dosisvoorstel dan het traditionele, waardoor het doseren mogelijk efficiënter kan worden.

De resultaten van dit proefschrift verschaffen inzicht in factoren die van invloed zijn op de stabiliteit van antistolling, en met name op een te laag antistollingsniveau. Aangezien de relatie tussen stabiliteit van antistolling en klinische eindpunten (trombose en bloedingen) overtuigend is aangetoond, kan kennis over invloeden op de stabiliteit bijdragen aan het voorkómen van deze eindpunten.

Onze belangrijkste conclusie is dat de hypothese kan worden bevestigd dat een hogere vitamine K inname leidt tot een stabielere antistolling. Wij hebben dit aangetoond in verschillende studies waarbij verschillende methoden werden gebruikt. Deze constatering heeft voornamelijk gevolgen voor het dieetadvies dat moet worden gegeven aan patiënten die vitamine K antagonisten gebruiken. Omdat vitamine K vooral zit in groenten is het

meest praktische advies zich te houden aan de aanbeveling van het Voedingscentrum voor de algemene bevolking: Eet elke dag twee ons groenten en twee stuks fruit.

Het positieve effect van een vitamine K supplement lijkt vooralsnog te gering om op grote schaal te worden toegepast. Toekomstige studies moeten uitwijzen of suppletie klinische eindpunten kan voorkómen en of er subgroepen zijn die het meeste baat zouden kunnen hebben bij suppletie van vitamine K.

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# Curriculum vitae

Eva Rombouts werd op 16 oktober 1971 geboren in Amstelveen. In 1990 behaalde zij haar VWO diploma aan het Vossiusgymnasium in Amsterdam. Hierna is zij eerst begonnen met de studie Informatica aan de Universiteit van Amsterdam, waarvan zij de propedeuse behaalde in 1993. In 1991 begon zij haar studie Geneeskunde aan de Faculteit der Geneeskunde, ook aan de Universiteit van Amsterdam. Binnen deze studie liep zij een wetenschappelijke stage op de afdeling fysiologie naar de rol van transmembrane ionenstromen in de hartspier en een klinische stage in "Riga's Seventh Clinical Hospital" in Letland, op de afdeling neurologie. In 1999 behaalde zij het artsexamen. Hierna heeft ze als arts-assistent (AGNIO) gewerkt op verschillende afdelingen in zowel academische als algemene ziekenhuizen: Interne geneeskunde in het BovenIJ ziekenhuis in Amsterdam, intensive care in het Medisch Centrum Alkmaar en longziekten in het Academisch Medisch Centrum in Amsterdam. Daarnaast heeft zij gewerkt in de informatie en communicatietechnologie, eerst als analist programmeur bij Getronics Business Solutions in Amsterdam, later als business analist bij iSOFT in Leiden, waar zij in een groot internationaal project meewerkte aan het ontwerp van een elektronisch patiëntendossier. In 2003 begon zij haar promotie onderzoek, waarvan de resultaten staan beschreven in dit proefschrift. Zij werd tijdens haar promotie begeleid door dr. Felix van der Meer en prof. Frits Rosendaal. Gedurende het promotie traject werkte zij als doseerarts op de trombosedienst Leiden en als consulent hemostase en trombose. Sinds 2009 is zij werkzaam als arts-assistent in opleiding (AIOS) tot specialist ouderengeneeskunde.