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**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 factors⁶ 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 subtherapeutic 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 items¹⁶ 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 survey¹⁸ and normal serving sizes¹⁹ 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).

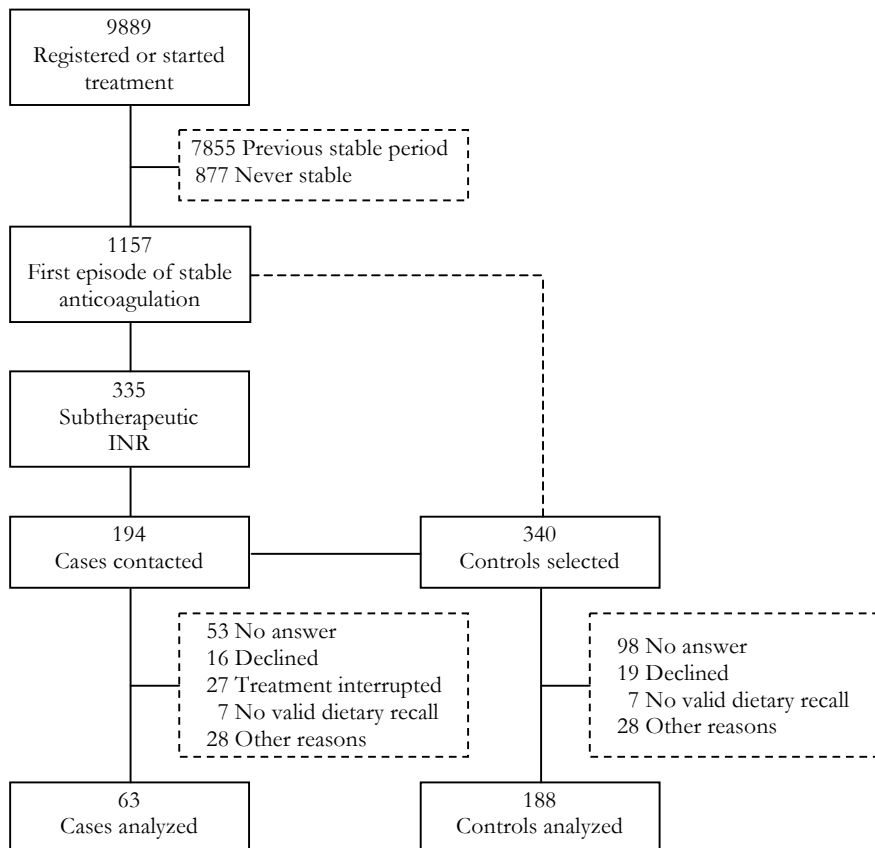


Figure 1: Flow of patients during follow-up.

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).

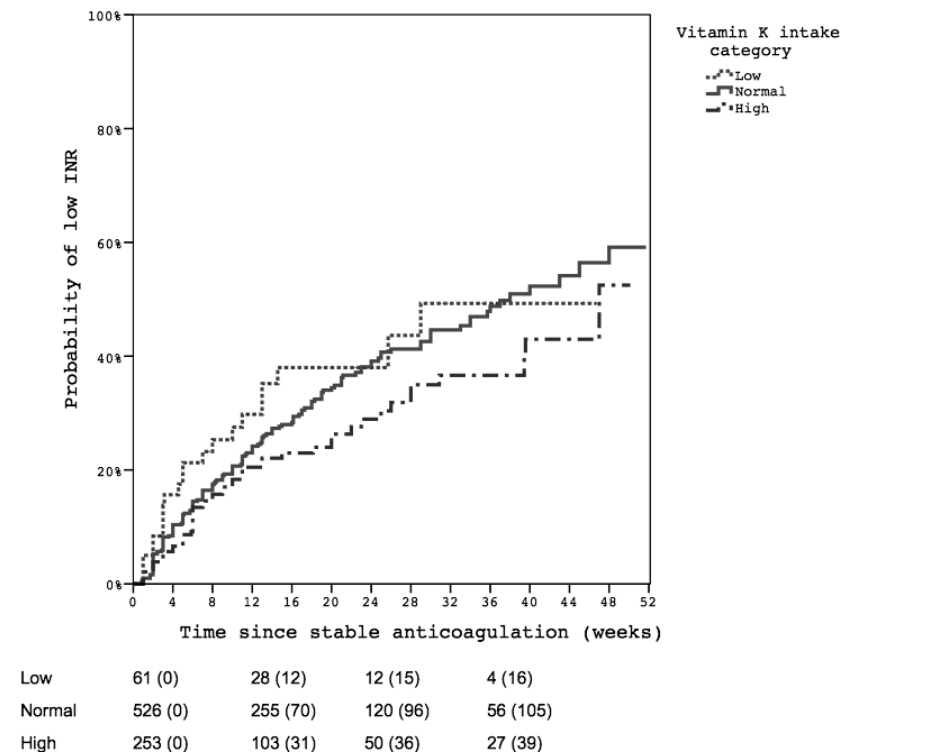


Figure 2. Kaplan Meier curve of the probability of a subtherapeutic INR according to usual vitamin K intake category. In the table, values are expressed as the number of patients at risk (number with a subtherapeutic INR)

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.

Usual vitamin K intake	Recent vitamin K intake	No patients (%)		OR (95%CI)
		Cases	Controls	
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.

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