



Original

# Dietary vitamin K intake and stability of anticoagulation with coumarins; evidence derived from a clinical trial

P. Zuchinali<sup>1</sup>, G. C. Souza<sup>2</sup>, M. C. S. de Assis<sup>3</sup>, E. R. Rabelo<sup>2,3</sup> and L. E. Rohde<sup>1,2,3</sup>

<sup>1</sup>Post-Graduate Program in Health Science. Cardiology and Cardiovascular Sciences. <sup>2</sup>Federal University of Rio Grande do Sul. Medical School. Porto Alegre. Rio Grande do Sul. Brazil. <sup>3</sup>Hospital de Clínicas de Porto Alegre. Cardiovascular Division. Porto Alegre. RS. Brazil.

## Abstract

**Background:** Dietary vitamin K intake has been considered a major factor that influences stability of oral anticoagulation (OA) with coumarins. Few studies have evaluated the relationship between amounts of dietary vitamin K intake and stability of anticoagulation.

**Objective:** To assess whether high dietary vitamin K intake is associated to stability of International Normalized Ratio (INR) of the prothrombin time.

**Methods:** We performed a sub-analysis of a randomized clinical trial involving outpatients from the anticoagulation clinic of a university hospital. INR and vitamin K intake were prospectively collected at baseline, 15, 30, 60 and 90 days after randomization. Patients were considered with a stable anticoagulation when their INR coefficient of variation was less than 10%. Dietary vitamin K intake was assessed by a food frequency questionnaire and a score of intake was derived.

**Results:** We studied 132 patients on chronic OA (57 ± 13 years; 55% males); 23 patients (17%) were achieved stable anticoagulation. Stable and unstable patients had no significant differences in baseline characteristics. The dietary vitamin K score over the entire follow-up for stable patients was significantly lower than that for unstable patients (p = 0.012).

**Discussion:** Our findings suggest that INR stability could be achieved with relatively low amounts of dietary vitamin K.

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Key words: Vitamin K. Warfarin. Food consumption. Anticoagulants. Coumarin.

## EL CONSUMO DE VITAMINA K Y LA ESTABILIDAD DE LA ANTICOAGULACIÓN CON CUMARÍNICOS; EVIDENCIA DERIVADA DE ENSAYO CLÍNICO

### Resumen

**Introducción:** El consumo dietético de vitamina K ha sido considerado un factor importante que influye en la estabilidad de la anticoagulación oral (AO) con cumarina. Pocos estudios han evaluado la relación entre el consumo dietético de vitamina K y la estabilidad de la anticoagulación.

**Objetivo:** Evaluar la relación existente entre la alta ingesta de vitamina K y el mantenimiento de la estabilidad de la Razón Normalizada Internacional RNI.

**Métodos:** Se realizó una subanálisis de un ensayo clínico aleatorizado con pacientes ambulatorios de la clínica de anticoagulación de un hospital universitario. Los datos acerca del RNI y la ingesta de vitamina K fueron recogidos prospectivamente al inicio del estudio, y en los días 15, 30, 60 y 90. Los pacientes fueron considerados estables cuando su coeficiente de variación del RNI fue menor de 10%. La evaluación de la dieta y la ingesta de vitamina K se obtuvo mediante un cuestionario de frecuencia alimentaria y un sistema de puntuación fue creado para esto.

**Resultados:** Se estudiaron 132 pacientes en tratamiento crónico (57 ± 13 años, el 55% masculino), 23 pacientes (17%) lograron anticoagulación estable. Con relación a las características basales, no hubo diferencias entre los sujetos con anticoagulación estable o inestable. La puntuación de la vitamina K de la dieta durante todo el seguimiento de los pacientes se mantuvo significativamente menor entre aquellos con RNI estable cuando comparado con los inestables (p = 0,012).

**Discusión:** Nuestros hallazgos sugieren que con cantidades relativamente bajas de vitamina K podremos obtener la estabilidad de RNI.

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Palabras clave: Vitamina K. Warfarina. Consumo de alimentos. Anticoagulantes. Cumarina.

**Correspondence:** Luis Eduardo Paim Rohde.  
Serviço de Cardiologia.  
Hospital de Clínicas de Porto Alegre.  
Ramiro Barcelos 2350, Sala 2061.  
90035-003 Porto Alegre. RS. Brazil.  
E-mail: lerohde@terra.com.br

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## Introduction

Chronic oral anticoagulation (OA) therapy has been extensively used in the primary and secondary prevention of thromboembolic events in several cardiovascular conditions.<sup>1,2</sup> However, a substantial percentage of patients who use coumarin derivatives cannot be maintained within the recommended therapeutic range evaluated by the International Normalized Ratio (INR) of the prothrombin time.<sup>3,4</sup> Adverse events are relatively common and frequently associated to anticoagulation instability. Therefore, there is a recognized risk of bleeding or thromboembolism, as a result of over- or under-anticoagulation, respectively.<sup>5,6</sup>

Several factors can be related to instability in chronic OA therapy, as drug interactions,<sup>7</sup> associated diseases and clinical co-morbidities,<sup>2</sup> drug-nutrient interactions<sup>8</sup> and use of medication.<sup>9</sup> Dietary vitamin K content has been studied as a central factor that influences anticoagulation stability.<sup>10,11,12</sup> Although strong evidences from clinical studies suggest that this relationship can be considered a fundamental and independent factor that interferes in chronic OA therapy,<sup>10,13</sup> there is still no consensus on the amount of dietary vitamin K that should be recommended to patients undergoing this therapy.

Few studies have directly studied the relationship between specific amounts of dietary vitamin K intake and stability of chronic anticoagulation with coumarins. Previous investigators have suggested that a constant high intake of vitamin K could provide INR stability.<sup>14</sup> Vitamin K supplementation has been reported to promote longer periods of time in the therapeutic target,<sup>15</sup> or to have less INR variation<sup>16</sup>. In addition, patients with lower vitamin K intake seem to have a higher risk of a subtherapeutic INR value.<sup>15</sup> However, there is also evidence showing no association between dietary vitamin K intake and stability.<sup>17</sup>

Our group has recently published a randomized clinical trial demonstrating that an intervention designed to modify dietary vitamin K intake would be an alternative and effective strategy to manage anticoagulated patients with minor INR instability.<sup>11</sup> In the present pre-specified sub-study, we conducted an in-depth analysis about the relationship between dietary vitamin K intake and stability of OA, based on prospective sequential data on INR values and vitamin K intake collected before and after randomization.

## Methods

### *Patients and study design*

Data on INR values and semi-quantitatively vitamin K intake used for the present analysis were derived from a randomized clinical trial in which 132 patients were evaluated from the anticoagulation clinic of a university tertiary care hospital in Porto Alegre, Brazil. Patients were randomized into a

control group (a strategy treatment based on conventional dose adjustment of oral anticoagulants) and an intervention group (a strategy treatment based on pragmatic changes on dietary vitamin K intake according to INR values). The protocol was registered at ClinicalTrials.gov (<http://clinicaltrials.gov>) as NCT00355290. Detailed data from the study protocol is described in the original publication.<sup>12</sup> Briefly, prospective and sequential data on INR values and vitamin K intake was collected at baseline, 15, 30, 60 and 90 days after randomization.

### *Vitamin K intake*

The consumption of vitamin K was evaluated by a Food Frequency Questionnaire consisted of foods with content of vitamin K ranging from about 20 mg to 700 mg per 100g of food. The Food Frequency Questionnaire was divided into foods with a high content of vitamin K (380 g to 712 g per 100 g): green tea, turnip greens and spinach; foods with moderate to high content (120 g to 180 g per 100 g): broccoli, brussels sprouts, cabbage, lettuce crisp, soybean or canola oil; and foods with moderate content (20 g to 95 g per 100 g): beef liver, asparagus, watercress, lettuce, peas, cabbage, cauliflower, arugula and cucumber with peel raw. Patients were instructed to answer the questionnaire about their consumption in the week before the prothrombin time test (INR). Our group has already tested and modified this questionnaire in a survey protocol with patients from our anticoagulation clinic, aiming to demonstrate the relationship between vitamin K intake and different levels of anticoagulation.<sup>10</sup>

Considering that the Food Frequency Questionnaire carries out a qualitative analysis of vitamin K consumption, we transformed the raw data from the questionnaire into a score of vitamin K intake, where food items were rated according to their content of vitamin K: those with high content received a score of 3, those with moderate to high content received a score of 2 points, and those with moderate content received a score of 1. This score was created to perform a semi-quantitative evaluation of the overall content of dietary vitamin K, but not aimed to quantify the content of vitamin K in mg/day.

### *Anticoagulation stability*

Anticoagulation stability was assessed by calculating the coefficient of variation (CV) of INR measurements, calculated as the standard deviation divided by the average INR measured in the four moments after the baseline assessment (day 15, day 30, day 60, day 90). This formula has generated a percentage of variation for the entire follow-up time. For statistical analysis, we consider patients with stable anticoagulation those who

had a variation less than or equal to 10% in the INR CV, and patients with unstable anticoagulation those with CVs higher than 10%. This definition is relatively arbitrary, but aims to identify patients on chronic OA therapy with minimal variations on anticoagulation parameters (highly stable patients).

### Statistical analysis

Continuous variables were expressed as mean  $\pm$  standard deviation or median and interquartile range and categorical variables were expressed as absolute number and percentage. For comparison between groups (categorical variables), the  $\chi^2$  test was used. For analysis of vitamin K intake between different time periods and between groups we used Student's *t* test for normally distributed variables and the Mann-Whitney test for nonparametric variables. A two-tailed P value < 0.05 was considered statistically significant. Analysis was performed using the ProgramPASW® Statistics 18 (SPSS Inc., Chicago, IL).

## Results

### Studied population

Between March 2006 to September 2007, potentially eligible patients were recruited: 132 subjects fulfilled the entry criteria and consented to participate in the protocol, detailed clinical data of the enrolled patients was previously described.<sup>12</sup> The study population included predominantly male patients with indication for anticoagulation therapy predominantly because of mechanical valve prosthesis (57%) or atrial fibrillation (35%) as demonstrated at table I.

### Patients with stable chronic OA

For analysis of INR stability, the whole sample of 132 patients was classified as stable (INR CV  $\leq$  10%) or unstable (INR CV > 10%). We found 23 (17.4%) patients with stable anticoagulation, evenly distributed in the 2 groups (intervention and control) of the orig-

**Table I**  
Clinical characteristics and comparison between stable and unstable patients on chronic oral anticoagulation

Clinical variable	All n = 132	Stable patients n = 23	Unstable patients n = 109	P
Age, years	57.2 $\pm$ 13	59 $\pm$ 13	56 $\pm$ 7	0.4
Sex (male)	73 (55)	11 (48)	62 (57)	0.3
Group				0.3
Control	66 (50)	10 (43)	56 (51)	
Body mass Index	26.7 $\pm$ 4.8	26.9 $\pm$ 4.6	26.7 $\pm$ 4.0	0.8
Education				0.6
Illiterate	5 (3.6)	–	5 (5)	
Elementary	102 (73.4)	19 (83)	83 (75)	
High School or more	25 (18)	4 (17)	21 (20)	
Comorbidities				
Heart failure	26 (18.7)	2 (8.7)	24 (22)	0.1
Diabetes Mellitus	21 (15.1)	3 (13)	18 (16)	0.5
Ischemic heart disease	20 (14.4)	2 (8.7)	18 (16)	0.3
COPD	2 (1.4)	0 (0)	2 (1.8)	0.7
Indication for oral anticoagulation				0.7
Chronic atrial fibrillation	46 (35)	11 (48)	35 (32)	
Mitral mechanical valve	37 (28)	5 (22)	32 (29)	
Aortic mechanical valve	39 (29)	6 (26)	33 (30)	
Others	10 (8)	1 (4)	9 (17)	
Anticoagulant drugs				0.04
Warfarin	112 (85)	16 (69)	96 (88)	
Phenprocoumon	20 (15)	7 (30)	13 (12)	
Baseline anticoagulation dose				
Warfarin	30 (22-41)	35 (18.75-40)	30 (22.5-42.5)	0.5
Phenprocoumon	12 (8.4-15)	9 (7.5-19.5)	13.5 (11.25-15)	0.4
Baseline INR	2.41 (1.77-3.23)	2.26 (1.88-3.42)	2.07 (1.77-3.20)	0.5
INR Coefficient of Variation (%)	17.97 (11.5-25.63)	6.47 (3.76-8.78)	19.9 (14.9-28.1)	< 0.001

Values presented as n (%) or as median (25<sup>th</sup> percentile, 75<sup>th</sup> percentile). COPD: Chronic obstructive pulmonary disease.

**Table II**  
Consumption frequency of vitamin K rich foods

Consumption of vitamin K rich foods	All n = 132	Stable patients n = 23	Unstable patients n = 109	P
High content (times/week)	0.7 (0-1.4)	0.4 (0-1.4)	0.4 (0-1.4)	0.8
Moderate to high content (times/week)	3.5 (1.8-5.0)	2.8 (1.6-4.6)	3.6 (1.8-5.1)*	0.2
Moderate content (times/week)	1.9 (0.8-3.2)	2.2 (0.8-2.6)	1.8 (0.8-3.3)	0.8

Values presented median (25<sup>th</sup> percentile, 75<sup>th</sup> percentile).

High content of vitamin K (380 g to 712 g per 100 g): green tea, turnip greens and spinach; moderate to high content (120 g to 180 g per 100 g): broccoli, brussels sprouts, cabbage, lettuce crisp, soybean or canola oil; moderate content (20 g to 95 g per 100 g): beef liver, asparagus, watercress, lettuce, peas, cabbage, cauliflower, arugula and cucumber with peel raw.

inal clinical trial. Patients classified as stable or unstable OA had similar clinical characteristics including age, gender, medical comorbidities, education, clinical indication for anticoagulation therapy, basal INR and baseline anticoagulation dose (table I). In both groups the majority of patients were using warfarin as the anticoagulant drug; however phenprocoumon was used more frequently among stable patients (30% versus 12%,  $p = 0.04$ ). Moreover, the CV of INR was different between the groups, as expected.

#### Relationship between stability and consumption of vitamin K

Dietary intake of foods with different contents of vitamin K was analyzed using the Food Frequency Questionnaire. In both groups the most representative food items of vitamin K intake were those with moderate to high content. Over the 90 days of follow-up the group of stable patients had a lower consumption of moderate to high content food and a slightly less consumption of low content food, although without statistical significance (table II).

In order to evaluate the relationship between OA stability and consumption of vitamin K we compared the score of vitamin K intake in patients classified as on stable anticoagulation with unstable patients over the entire follow-up time. Figure 1 demonstrates that the median vitamin K intake score was lower among patients who had less variation on INR (CV <10%) compared to unstable patients (CV >10%) [12 (7-14) versus 14 (7-19), respectively,  $P = 0.012$ ].

When analyzing the scores of vitamin K for each moment individually, the same trends were observed (fig. 2). We also evaluated patients stratified by group of intervention of the original trial, and the same trends were observed (data not shown).

#### Discussion

There is a growing interest on the influences of the consumption of food items rich in vitamin K on the stability and effectiveness of oral anticoagulants. The

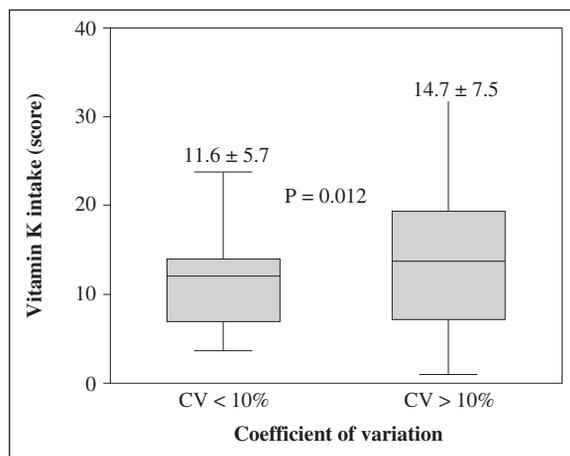


Fig. 1.—Overall score of vitamin K consumption over time during the entire follow-up according to the INR coefficient of variation (CV). Box plots represent median and interquartile range.

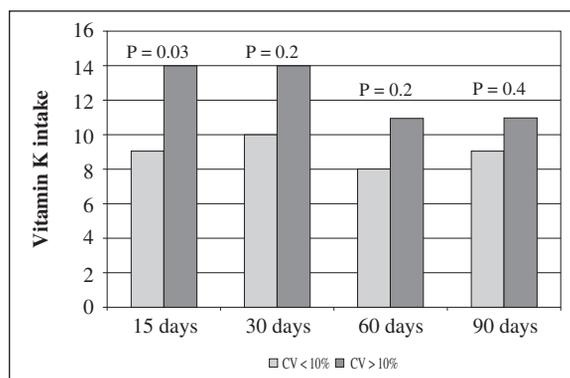


Fig. 2.—Vitamin K consumption in 4 moments of the study according to INR coefficient of variation (CV) for all randomized patients.

interaction of this micronutrient with the pharmacologic effects of coumarin derivatives is well-known,<sup>10,11,18</sup> but the amount of vitamin K that should be ingested has not been precisely defined for patients on chronic OA. Previous studies have suggested that a high vitamin K intake could be associated with anticoagulation stability.<sup>13,14,19</sup> Our results questioned this hypothesis, showing that patients with very stable INRs (CF ≤ 10%) had, in fact, lower consumption of vitamin K rich foods.

In this study we have found that patients who were managed with pre-defined modifications in oral vitamin K intake were more likely to reach the desired target INR when compared to the conventional management (increases and decreases in oral anticoagulant dose). Although these results substantiate the interaction between dietary vitamin K and the effect of coumarin derived anticoagulants, they do not clarify the everyday dilemma about the amount of vitamin K intake that should be recommended for patients in chronic OA.

Studies that have evaluated the relationship between usual consumption of vitamin K and long-term stability of oral anticoagulants are scarce. A recent study suggested that supplementation with low dose vitamin K<sup>1</sup> resulted in an improvement of time that anticoagulation was within the therapeutic range in patients starting vitamin K antagonists.<sup>20</sup> However, other evidence shows the opposite relationship. Sconce et al. demonstrated that patients with stable anticoagulation (variation of less than 0.5 in the INR value) had significantly higher vitamin K intake compared to unstable patients.<sup>14</sup> Similarly, a recent report by Rombouts et al. found that patients with higher consumption of vitamin K rich foods had a lower risk of having sub-therapeutic INRs.<sup>13</sup> Finally, Kim et al. observed an inverse correlation between the CV of the INR and vitamin K intake,<sup>19</sup> suggesting that a higher vitamin K consumption would be associated to less INR variation. Although the overall trend of these studies indicates a potential beneficial effect of maintaining a "high" intake of vitamin K, the clinical applicability of this information might be limited, because of the heterogeneity in the definition of anticoagulation stability, as well as in the cut-off points to classify vitamin K intake. Unexpectedly, the present study does not confirm previous findings. Our results demonstrate that INR stability could be achieved even in patients taking lower amounts of vitamin K. Our strict definition of stable anticoagulation, based on lower than 10% changes in INR CV, restricted our analysis to a group of patients who maintains minimal change in INR values during follow-up, unlike other studies that defined stability as patients that varied less than 0.5 in INR values<sup>14</sup> or patients who have a sequence of INR values within the target.<sup>13</sup> Moreover, detailed knowledge of the content of vitamin K among different vegetables is difficult to be assimilated among healthcare professionals<sup>21</sup> and might be even more challenging to anticoagulated patients. One could speculate that the maintenance of a stable dietary intake of foods with a relatively low content of vitamin K would implicate in a smaller risk of unintentional large absolute variations in the consumption of this vitamin, a hypothesis that needs prospective confirmation. We have previously demonstrated that even brief periods of increased or decreased vitamin K intake might have a pronounced effect on coagulation parameters.<sup>10</sup>

Some methodological aspects of our study design deserve careful consideration. As the present analysis was derived from a clinical trial in which there was an intervention that modulated vitamin K intake, our results might be biased. However, analysis restricted to the group of patients managed conventionally demonstrated the same trends (data not shown). In the original protocol, we deliberately opted to use a semi-quantitative evaluation of vitamin K that does not precisely estimate daily consumption. A more detailed assessment and modulation of vitamin K ingestion would limit the clinical applicability of the proposed strategy, but could unravel more accurately the relationship between this micronutrient and OA stability. In addition, the relatively short-term follow-up of the original protocol limits the evaluation of the impact of vitamin K consumption over long-term OA stability.

Achieving oral anticoagulation stability over time is a challenging task. There is solid prospective clinical evidence demonstrating that changes in dietary vitamin K play a major, independent role in INR fluctuations in patients taking oral anticoagulants.<sup>8,11,18,22</sup> Thus, stable vitamin K intake is an essential aspect of anticoagulation therapy that must be actively pursued by clinicians, nurses, dietitians, and pharmacists. The present sub-analysis indicates that INR stability could be achieved with relatively low amounts of dietary vitamin K. However, we should not send the wrong message of indiscriminately decreasing dietary vegetable content because the background message of most studies is that anticoagulated patients should maintain a steady intake of vitamin K, once INR stability has been achieved. Our findings suggest that a reasonable target would be to pursue a daily vitamin K consumption near (just above) the internationally accepted RDA (90-120 µg/day), avoiding much higher intakes. However, prospective studies testing this strategy will be needed to determine the best dietary advice offered to patients in this scenario.

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