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Interaction Between Dietary Vitamin K Intake and Anticoagulation by Vitamin K Antagonists: Is It Really True?

A Systematic Review

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Abstract: Educational advice is often given to patients starting treatment with vitamin K Antagonists (VKAs). A great emphasis is made on nutritional information. Common belief is that dietary vitamin K intake could counteract the anticoagulant effect by VKAs and for many years, patients have been discouraged to consume vitamin-K-rich foods, such as green leafy vegetables.

The objective of this study is to summarize the current evidence supporting the putative interaction between dietary vitamin K intake and changes in INR with the VKAs.

Data sources are MEDLINE via PubMed and Cochrane database.

All clinical studies investigating the relationship between dietary vitamin K and measures of anticoagulation were included. We excluded all studies of supplementation of vitamin K alone.

We performed a systematic review of the literature up to October 2015, searching for a combination of ''food,'' ''diet,'' ''vitamin K,'' ''phylloquinone,'' ''warfarin,'' ''INR,'' ''coagulation,'' and ''anticoagulant.''

Two dietary interventional trials and 9 observational studies were included. We found conflicting evidence on the effect of dietary intake of vitamin K on coagulation response. Some studies found a negative correlation between vitamin K intake and INR changes, while others suggested that a minimum amount of vitamin K is required to maintain an adequate anticoagulation. Median dietary intake of vitamin K1 ranged from 76 to 217 μg/day among studies, and an effect on coagulation may be detected only for high amount of vitamin intake (>150 μg/day).

Most studies included patients with various indications for VKAs therapy, such as atrial fibrillation, prosthetic heart valves, and venous thromboembolism. Thus, INR target was dishomogeneous and no subanalyses for specific populations or different anticoagulants were conducted. Measures used to evaluate anticoagulation stability were variable.

The available evidence does not support current advice to modify dietary habits when starting therapy with VKAs. Restriction of dietary vitamin K intake does not seem to be a valid strategy to improve anticoagulation quality with VKAs. It would be, perhaps, more relevant to maintain stable dietary habit, avoiding wide changes in the intake of vitamin K.

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Abbreviations: AF = atrial fibrillation, CV = coefficient of variation, DVT = deep venous thrombosis, FFQ = food frequency questionnaire, Med-Diet = mediterranean diet, PIVKA-II = prothrombin induced by vitamin K absence-II, TTR = time in therapeutic range, VKA = vitamin K antagonists, VTE = venous thromboembolism.

INTRODUCTION

The vitamin K antagonists (VKAs, e.g., warfarin) continue to be commonly used to prevent ischemic stroke in patients with atrial fibrillation (AF), with an approximately risk reduction of 64%, and with a decrease in all-cause mortality by 26%.[1] VKAs are also widely prescribed in patients with venous thromboembolism (VTE), and represent the treatment of choice for patients with prosthetic heart valves. There are significant differences among Western countries in anticoagulation management of AF,[2] with a large underuse of warfarin worldwide for several reasons, including bleeding risk perception by physicians, suboptimal compliance, and inability of an adequate INR monitoring for logistic and/or laboratory issues.[3] Another common concern with the use of warfarin is a putative interaction with food rich in vitamin K.[4]

The common belief is that dietary vitamin K intake could counteract the anticoagulant effect by warfarin.[5,6] Thus, for many years, patients treated with VKAs have been advised to reduce dietary vitamin K content to avoid a food–drug interaction influencing anticoagulation stability.

This assumption was one of drivers for the development and introduction of the non-VKA oral anticoagulants (NOACs, previously referred to as new or novel oral anticoagulants[7]) which directly inhibit thrombin such as dabigatran[8] or factor Xa such as rivaroxaban, apixaban, and edoxaban,[9–11] for the treatment of AF and VTE.

This issue has been also highlighted by several international societies, such as American Heart Association (AHA), European Society of Cardiology, and American College of Cardiology (ACC), but some uncertainty remains on what could be the most appropriate diet to suggest to patients on anticoagulant treatment with VKAs. In particular, the 2003 AHA/ACC Foundation Guide to Warfarin Therapy[6] reported that increased intake of dietary vitamin K, sufficient to reduce the anticoagulant response to warfarin, occurs in patients consuming green vegetables, but this indication was

supported by a study referring to vitamin K supplementation, rather than dietary vitamin K intake.[6]

In the 2010 European Society of Cardiology guidelines on the management of patients with AF, it was stated that VKAs have significant food interactions, but no reference in support was reported.[12] This concept is also present in the more recent guidelines from the AHA, reporting that the ''effects of alterations in diet [...] made the dosing of warfarin challenging for clinicians and patients,''[13] but also in this case, no specific reference in support of this statement was provided.

Based on this, we investigated if published scientific literature actually provides a scientific support to this putative interaction between warfarin and dietary vitamin K intake.

METHODS

The systematic review was performed according to PRISMA guidelines.[14]

Eligibility Criteria

We selected and included in this review all original research studies, both observational and interventional, including patients treated with VKAs (all types) for any indication, and addressing the relationship between dietary vitamin K intake and any coagulation measure (e.g., INR/PT, variation over time, VKAs dose).

Since the objective of the review was to summarize evidence on the relationship between the intake of vitamin K contained in a real-life diet and changes in coagulation parameters, we excluded all studies that reported a diet supplemented with vitamins or individual foods.

Information Sources and Search Strategy

We performed a systematic review of the literature using MEDLINE via Pubmed and Cochrane database up to October 2015, searching for a combination of ''food,'' ''diet,'' ''vitamin K,'' ''phylloquinone,'' ''warfarin,'' ''INR,'' ''coagulation,'' and ''anticoagulant'' to identify all studies on this topic of potential interest. We also used the PubMed tool ''Related Articles'', and a manual search using bibliographies of included studies was also performed.

Study Selection

The study selection was performed in 3 phases. In the first phases, potentially relevant studies were obtained by combined searches of electronic databases using selected above-mentioned keywords. In the second phase, studies were selected and eventually excluded by study typology. The third phase consisted of detailed analysis of studies to assess if they addressed the specific study question (Figure 1).

Data Collection Process and Data Items

Two physicians (DP, PP) independently screened the titles and abstracts of manuscripts identified through the database searches to identify studies potentially eligible for further assessment. Controversies were resolved by a third investigator (FV).

For each study, the authors, the year of publication, the type of study, the anticoagulant used, the outcome to measure anticoagulation, the nutrient analyzed, the sample size of population included, and the main results/conclusions were assessed.
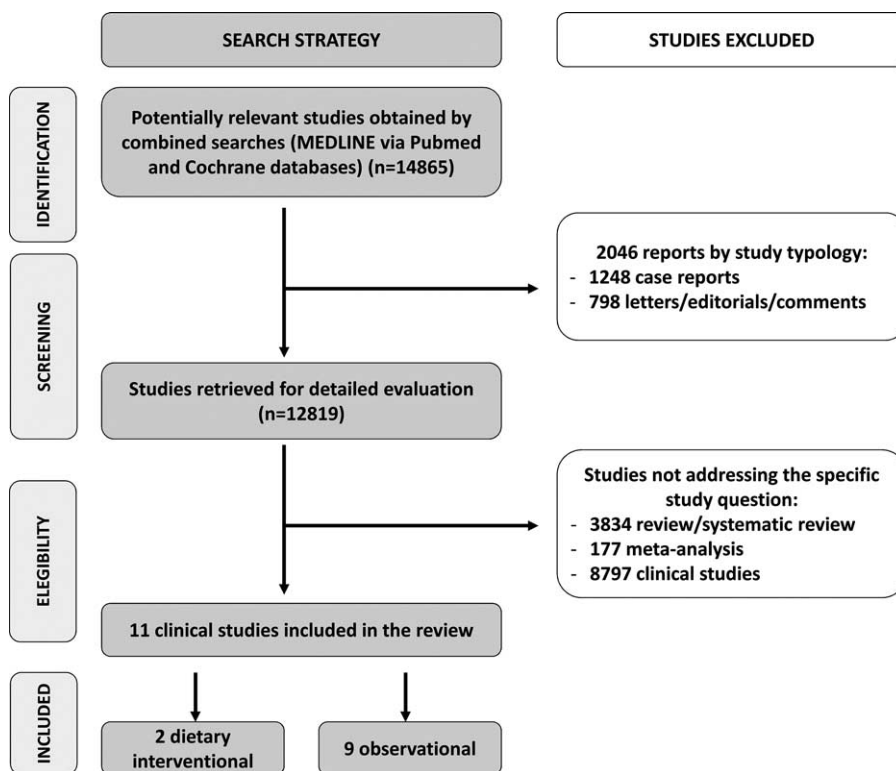

FIGURE 1. PRISMA diagram.

Quality Evaluation of Clinical Studies

The quality of evidence from studies was evaluated by using the evidence-based 2011 American Academy of Neurology Clinical Practice Guideline Process Manual.[15] Thus, studies were classified into 4 classes, from class I (best quality) to class IV (lowest quality).

Synthesis of Results

Given the heterogeneity of the studies reviewed (range in study populations, interventions, and outcome measures), it was not feasible to perform a meta-analysis.. Whenever possible, data are reported as mean or median values, percentages, and coefficients of variation.

Ethical Review

Given the study typology (review article), an ethical approval was not necessary.

RESULTS

Study Selection

We found 14,865 potentially relevant studies identified by searches; 2046 reports were excluded by study typology (1248 case reports and 798 letters/editorials/comments).

The 12,819 remaining studies were analyzed in detail, and 12,807 were excluded, as they were not addressing the specific study question: in particular they were 3834 review/systematic review, 177 meta-analysis, and 8797 clinical studies.

Thus, 11 clinical studies remained: 2 dietary interventional trials[16,17] and 9 observational studies[17–25] were included in this systematic review (Figure 1).

Study Characteristics and Results of Individual Studies

Dietary Interventional Studies

All the 3 dietary interventional trials were conducted in small populations (Table 1). The first study by Pedersen et al[16] in 1991, randomized 37 patients to receive vitamin-K-rich vegetables (median daily vitamin K intake 1100 μg) for 1 (n = 5), 2 (n = 7), or 7 (n = 13) days, vitamin-K-poor vegetables (median daily vitamin K intake 135 μg) for 6 days (n = 7), or habitual diet supplemented with an equivalent daily amount of 1000 μg of phytomenadione (n = 5). The measure of anticoagulation used in this study was the incidence of INR outside a range of 2.0–3.6. The authors observed that 2 and 3 patients who assumed vitamin-K-rich vegetables for 1 and 2 days, respectively, exceeded the upper therapeutic limit. No changes were observed in the vitamin-K-poor group. Finally, all patients who received phytomenadione exceeded the upper therapeutic limit.

In the second interventional study, the authors performed a 4-day in-hospital dietary intervention assigning 12 patients on stable anticoagulation, defined as 2 consecutive INR values between 2.0 and 3.0,[17] to receive a vitamin K-depleted (80% decrease) or enriched (500% increase) diet, relative to the baseline level,[17] and assessing the effect on 3 INR measurements. The authors observed that both low and high vitamin K intake was associated with INR instability, suggesting that a constant intake of dietary vitamin K is needed to maintain INR control.

TABLE 1. Interventional Studies Investigating the Relationship Between Dietary Vitamin K/Foods and Anticoagulation

Author	Year	Type of Study	Anticoagulant	Nutrient Analyzed	Measure of Anticoagulation	Population	Results/Conclusions	AAN Class
Pedersen[1]	1991	Interventional	Warfarin	Vitamin-K-rich vegetables or equivalent amounts of oral phytomenadione and consumption of vitamin-K-poor vegetables.	Range INR 2.0–3.6	37 patients on stable anticoagulation: divided in: 1 (n = 5), 2 (n = 7), or 7 (n = 13) days with high intake of vitamin-K-rich vegetables, high intake of vitamin-K-poor vegetables for 6 days (n = 7), or habitual diet supplemented with 1000 μg of phytomenadione daily (n = 5).	Five patients who consumed vitamin-K-rich vegetables exceeded the upper therapeutic limit. No changes in the vitamin-K-poor group were observed.	II
Franco[2]	2004	Interventional	Warfarin (61%) Phenprocoumon (39%)	4-day in-hospital dietary intervention; 2 groups: vitamin-K-depleted (80% decrease) and vitamin-K-enriched (500% increase) diet	INR (3 values)	12 patients with stable anticoagulation (2 consecutive INR values within 2.0–3.0)	The mean baseline vitamin K intake was 118 ± 51 μg/day (range 18–211). INR increased progressively in patients on the vitamin-K-depleted diet, and decreased in vitamin-K-rich diet group.	II

AAN = American Academy of Neurology.

Observational Studies

Observational studies analyzing the relationship between vitamin K intake and changes in INR in patients treated with VKAs have provided equivocal results (Table 2). Lubetsky et al[18] found a decrease in warfarin sensitivity for usual dietary intake of vitamin K ≥250 μg/day in 50 patients on warfarin. Conversely, 2 studies found no association between dietary vitamin K intake and anticoagulation stability or incident overcoagulation.[19,20] In particular, Cushman et al[19] analyzed the warfarin sensitivity in 40 orthopedic patients.

Warfarin sensitivity was assessed by the INR change between the preoperative visit and postoperative first day, and by the prothrombin induced by vitamin K absence-II (PIVKA-II) change, defined as the difference in PIVKA-II from the operative day to third postoperative day, divided by the mean daily warfarin dose administered. The authors found that usual intake of vitamin K was associated with PIVKA-II accumulation, but no significant changes of INR were observed.

In a large nested case-control study,[20] the relationship between dietary vitamin K and coagulation was investigated in 300 patients with an INR ≥6 compared with 302 patients with stable anticoagulation, defined as having at least 66% of the INRs within the target zone, and no INR ≥5.5 in the 3 previous months. INR range was variable according to the indication for VKA (2.0–3.5 or 2.5–4.0). A semiquantitative food frequency questionnaire including 170 foods and beverages was used to assess patients' habitual diet (during the previous year). Thus, the authors divided patients into 3 groups according to the vitamin K intake: >320 μg/day, 225 to 320 μg/day, <225 μg/day. Dietary vitamin K intake was not found to be a risk factor for incident over-coagulation in this study.

Franco et al[17] found that in 39 patients on treatment with VKAs with various indications, the consumption of several vitamin-K-rich foods, particularly lettuce, spring greens, and other greens, was significantly increased during the week before the INR dosing ($P \leq 0.05$), in the group of patients with an INR <2. Conversely, among patients with an INR >4, the consumption of the same foods was significantly decreased ($P \leq 0.05$). They calculated a vitamin K intake score that was inversely associated with the level of anticoagulation.

In a study including 115 patients treated with VKAs for arterial disease or VTE,[21] recent phylloquinone intake was inversely correlated with PT ($r = -0.22$, $P = 0.017$) and INR ($r = -0.23$, $P = 0.011$), whereas there was a positive association between habitual vitamin K intake and median warfarin dose ($r = 0.23$, $P = 0.011$).

Zuchinali et al[25] estimated the median vitamin K intake in 132 anticoagulated patients. The authors classified foods in 3 groups: high vitamin K content (380–712 μg/100 g): green tea, turnip greens and spinach; moderate-to-high vitamin K content (120–180 μg/100 g): broccoli, Brussels sprouts, cabbage, lettuce crisp, soybean, or canola oil; moderate vitamin k content (20–95 μg/100 g): beef liver, watercress, asparagus, lettuce, peas, cabbage, arugula cauliflower, cucumber with peel raw. Median vitamin K intake was lower among patients who had less coefficient of variation (CV) of INR (<10%) compared with unstable patients (CV >10%) [12 (7–14) versus 14 (7–19), respectively, $P = 0.012$]. However, the authors did not find any difference in the consumption of vitamin-K-rich foods between the 2 groups.

Finally, 3 studies found that patients with higher dietary vitamin K intake had a more stable anticoagulation.[22,23] For example, Kim et al[22] found that high vitamin K intake (>195.7 μg/day) group had lower CV of INR than the low intake (<126.5 μg/day) group (19.2 ± 8.96 % versus 25.5 ± 8.61 %, $P < 0.05$). Similarly, in a nested case-control study on 1157 patients from the Leiden anticoagulation clinic, the main outcome was represented by an incident subtherapeutic INR (<2.0 for low intensity <2.5 for high intensity treatment). A 20% decrease in the risk of an incident subtherapeutic INR was found in patients with a high vitamin K intake (>300 μg/day), while a 33% increase in the risk was observed in patients with a low dietary vitamin K intake (<100 μg/day).

In a factor analysis, Rasmussen et al[24] found that only 8% of variation of INR could be attributable to described health-related behavior such as diet, physical activity, and body weight. Moreover, the authors found a negative relation between vitamin K intake and the maintenance dose of warfarin.

Synthesis of Results

Overall, the quality of studies was low, as shown by the American Academy of Neurology classes; in fact, no study had class I quality of evidence for both the interventional and observational studies. The main cause for this result is mainly represented by missing clear inclusion/exclusion criteria, baseline characteristics between analyzed groups, and the lack of results adjusted for all potential confounding factors for INR changes.

The 2 dietary interventional studies had very small sample size, 37[16] and 12[17] patients, respectively, with divergent results; the first study reported that patients consuming vitamin-K-rich vegetables exceeded the upper therapeutic limit, while the second one found that INR increased progressively in patients on the vitamin K-depleted diet, and decreased in vitamin-K-rich diet group.

Measures of anticoagulation were highly variable among the 9 observational studies; thus, 2 studies analyzed the warfarin sensitivity, 2 the coefficient of variation of INR, 2 incident INR >6 or <2, 2 changes in PT/INR, and 1 the warfarin dose.

Most used anticoagulant was warfarin, followed by phenprocoumon and acenocoumarol (Tables 1 and 2). Nevertheless, separate analysis according to different anticoagulants was not available.

DISCUSSION

Analysis of studies' findings provided conflicting evidence on the effect of dietary intake of vitamin K on coagulation response. While some studies found a negative correlation between vitamin K intake and coagulation stability, others suggested that a minimum amount of daily vitamin K is required to maintain an adequate anticoagulation.

Reported daily dietary intake of vitamin K ranged from 76 to 217 μg. Studies reporting an interaction between dietary vitamin K and coagulation showed that an effect on coagulation may be detected only for high amount of vitamin intake (i.e., >150 μg/day), corresponding to approximately 118 g/day of raw lettuce green leaf, 106 g/day of cooked broccoli, or 30 g/day of cooked spinach.[26] However, we cannot be certain that this threshold is valid for healthy subjects or for patients starting oral anticoagulant treatment.

These different results may be explained, at least in part, by the fact that vitamin K consumed from diet, mostly from green leafy vegetables, has a low and variable absorption. For example, previous studies demonstrated that bioavailability of vitamin K from spinach is only about 5% compared with 15% of that from pure vitamin preparations.[27]

TABLE 2. Observational Studies

Author	Year	Type of Study	Anticoagulant	Measure of Anticoagulation	Nutrient Analyzed	Population	Results/Conclusions	AAN Class
Lubetsky[1]	1999	Observational	Warfarin	Warfarin sensitivity index: final INR/final warfarin dose	FFQ (two 1-week recalls) during 8 weeks	50 patients on warfarin	Vitamin K intake was 17–974 (median: 179) μg/day The sensitivity to warfarin was decreased by vitamin K intake ≥250 μg/day	III
Cushman[2]	2001	Observational	Warfarin	Warfarin sensitivity (pre/post-surgery INR change)	FFQ (6-month recall); 4-day weighed intakes for first 4 days of treatment	40 orthopaedic patients (total hip replacement or revision)	The usual vitamin K intake, based on the FFQ, was 141 ± 87 μg/d Vitamin K intake did not influence INR	II
Penning-van Beest[3]	2002	Nested case-control study	Coumarin anticoagulants	Over-coagulation (INR ≥6)	A semiquantitative FFQ including 170 foods and beverages (including alcohol) was used to assess the patient's habitual diet	300 patients with INR ≥6 vs. 302 with stable anticoagulation (≥66% of INRs in range and no INRs ≥5.5 in the 3 previous months)	Dietary vitamin K was not associated with the anticoagulation rate	III
Franco[4]	2004	Observational	Warfarin (61%) Phenprocoumon (39%)	INR (3 values in the interventional group)	Vitamin K intake score with standard 3-day food diary	39 outpatients: valvular prosthesis (18), AF (12), AF and metallic prosthesis (5), cerebrovascular disease (2), others (2)	Vitamin K intake was inversely associated with the level of anticoagulation	III
Custódio das Dóres[5]	2007	Cross-sectional	Warfarin	PT and INR (single value)	Vitamin K1 intake and phylloquinone rich foods estimated using 24 h recall and 97 items FFQ	115 patients. The main indication for anticoagulant therapy was arterial disease (58%) and DVT (38%)	Median phylloquinone intake was 76–120 μg/day, and was inversely correlated with PT/INR	III
Kim[6]	2010	Observational	Warfarin	CV of INR and of warfarin dosage	Average daily vitamin K intake based on a three-day food diary with the Food Composition table of Korea	66 patients taking warfarin (AF, valves, dilated cardiomyopathy, systemic embolism)	Median daily vitamin K intake was 161.3 (31.3–616.6) μg/day. CVs of both INR and warfarin doses were negatively correlated with dietary vitamin K intake.	III
Rombouts[7]	2010	Nested case-control study	Phenprocoumon (84%) Acenocumarol (14%) Warfarin (2%)	Subtherapeutic INR (<2.0 for low intensity <2.5 for high intensity)	Usual vitamin K intake assessed by an FFQ Fifty-seven questions were asked about 42 food items, 31 of which were vegetables or fruits	1157 patients: AF (606), DVT (262), valves (37), arterial disease (151), prophylaxis (101). Stable anticoagulation defined as 4 consecutive INRs in the range (38%)	Average intake was 200 μg in controls and 208 μg in cases. A 20% decrease was found in the risk of a sub-therapeutic INR in patients with a high vitamin K intake and a 33% increase in patients with a low intake	II
Rasmussen[8]	2012	Cross-sectional	Warfarin	Warfarin dose. VKORC1 and CYP2C9 polymorphism detection.	Dietary vitamin K intake with FFQ	244 patients: AF (140), DVT (67), Mechanical heart valve (29)	Median vitamin K was approximately 217 μg/day. Vitamin K intake positively correlated with warfarin dose.	III
Zuchinali[9]	2012	Subanalysis of a randomised clinical trial	Warfarin (85%) Phenprocoumon (15%)	CV of 4 INR	Dietary vitamin K intake by a FFQ	132 patients: AF (46), mitral mechanical valve (37), aortic mechanical valve (39), others (10)	Median vitamin K score was lower in patients who had low variation of INR (CV <10%) compared to unstable patients (CV >10%)	III

AF = atrial fibrillation, CV = coefficient of variation, DVT = deep venous thrombosis, FFQ = food frequency questionnaire, PIVKA-II = prothrombin induced by vitamin K absence-II.

In addition to this different rate of absorption of dietary vitamin K, another variable that should be considered is that the circulating concentration of vitamin K may be affected by single-nucleotide polymorphisms of different enzymes, such as cytochrome P-450 enzymes[28] and enzymes involved in lipoprotein metabolism.[29]

Another piece of information on this topic was provided by our recent study in which we investigated the relationship between Mediterranean Diet (Med-Diet), which is characterized by a high intake of vitamin-K-rich foods, such as fruits and vegetables, and the time in therapeutic range, an established marker of the anticoagulation quality, in 553 patients affected by AF and followed for about 30 months.[30] We found no modifications in the mean time in therapeutic range according to tertiles of Med-Diet adherence. In addition, when we analyzed specific components of Med-Diet, no differences were present in patients consuming or not vegetables, suggesting that vitamin K content of foods is not sufficient to influence significantly long-term anticoagulation stability.

The study has limitations. The main limitation is represented by the small sample size of most studies addressing the interaction between warfarin and dietary vitamin K intake. Studies included patients with various indications for VKAs therapy, such as AF, prosthetic heart valves, and VTE. INR target was dishomogeneous and no subanalyses for specific populations or type of anticoagulant were conducted. Measures used to evaluate anticoagulation stability were highly variable among studies, ranging from INR, CV of INR, Warfarin sensitivity index, to incident under-coagulation or over-coagulation. The main anticoagulant drug used in these studies was warfarin, thus findings cannot be extrapolated to other anticoagulants. For all these reasons, results are of difficult interpretation and generalizability. A logic consequence of all these arguments is that the above-reported studies do not support the putative interaction between food and VKA and warrant more appropriate trials to firmly conclude that an interaction between food and VKAs does exist.

In conclusion, the available evidence does not support current advice to modify dietary habits when starting therapy with VKAs. Restriction of dietary vitamin K intake does not seem to be a valid strategy to improve anticoagulation quality with VKAs. It would be, perhaps, more relevant to maintain stable dietary habit, thus avoiding wide changes in the intake of vitamin K. Based on this, until controlled prospective studies provide firm evidence that dietary vitamin K intake interferes with anticoagulation by VKAs, the putative interaction between food and VKAs should be eliminated from international guidelines.

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