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**Dietary implications for patients receiving long-term oral
anticoagulation therapy for treatment and prevention of
thromboembolic disease**

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Abstract

Introduction: The effectiveness of oral anticoagulation therapy with warfarin (a vitamin K antagonist) in the treatment of thromboembolic disease, including stroke prophylaxis in patients with atrial fibrillation is well recognised. However, warfarin has a narrow therapeutic window and an unpredictable anticoagulation response, which make it difficult to achieve and maintain optimal anticoagulation. Various dietary factors, including sudden changes in eating patterns, can significantly alter anticoagulation control, thereby potentially exposing patients to the risk of bleeding or thromboembolic complications. Dietary vitamin K intake is a particularly important factor, given the mechanism of action of warfarin.

Areas covered: In this review, we cover the sources of vitamin K and their potential effect of dietary vitamin K on anticoagulation response to warfarin. We also discuss the results of studies on the effect of vitamin K supplementation on anticoagulation stability.

Expert Opinion/Commentary: A stable dietary vitamin K, promoted by daily oral vitamin K supplementation, can improve anticoagulation stability in patients on warfarin therapy. **There is experimental evidence in animals that dietary vitamin K affects anticoagulation response to the direct thrombin inhibitor, ximelagatran. Whether dietary vitamin K affects anticoagulation response to direct oral anticoagulants (DOACs) in man remains to be investigated.**

Word count: 196

Keywords: lifestyle, nutrition, thromboembolic disease, vitamin K antagonists, anticoagulation, warfarin, direct oral anticoagulants

Introduction

Thromboembolic disease, including stroke in patients with atrial fibrillation (AF), accounts for significant morbidity, mortality and economic burden in the developed world. AF is a common cardiac arrhythmia that affects over 33.5 million people globally (1) and is the strongest known risk factor (5-fold) for stroke (2) with the association between atrial fibrillation and stroke of cardioembolic origin being widely recognised. (3) The percentage of atrial fibrillation-attributed strokes increases with age, with a 16-fold increase between patients aged 50-59 and 80-89 years (1.5% v 23.5% respectively). (4) The total annual cost for stroke treatment in the USA between 2011 and 2012 was estimated to be \$33 billion (5). Venous thromboembolism, including deep vein thrombosis and pulmonary embolism affect 133 per 100.000 of the population in the USA. Further, venous thromboembolism recurs in about 30 % of individuals within the next 10 years. (6)

Coumarins, such as warfarin, phenprocoumon and acenocoumarol, have been the mainstay of oral anticoagulation therapy for the treatment of thromboembolic disease for more than 65 years. Randomised controlled studies have demonstrated that anticoagulation therapy with warfarin significantly reduces the overall risk of stroke, its severity and the associated risk of death in patients with AF. (7, 8) Consequently, treatment guidelines advocate the use of warfarin prophylaxis in patients with AF at moderate-to-high risk of stroke. (9)

Vitamin K (as vitamin K hydroquinone) is an essential cofactor needed for the γ -carboxylation of glutamic acid residues located at the amino-terminals of the vitamin K-dependent clotting proteins II, VII, IX and X, leading to their activation. (10) Coumarins cause anticoagulation by interfering with the cyclic interconversion of vitamin K hydroquinone (hence also referred to as 'vitamin K antagonists') thus reducing the activation of vitamin K-dependent clotting proteins.

Achieving effective and safe anticoagulation with warfarin, however, is a major challenge in routine medical care because many factors can influence the pharmacodynamic

effect of this drug. Whilst several factors including concurrent disease, drugs and patient compliance have been identified as affecting warfarin requirements in a predictable way, the observed intra-individual variability in anticoagulation response to warfarin cannot be fully explained at the present. There is evidence that dietary factors can make a significant contribution to unstable control of anticoagulation. In this article, we will discuss the potential impact of dietary factors on patients receiving long-term oral anticoagulation therapy with warfarin for the treatment and prevention of thromboembolic disease and the positive influence of daily vitamin K supplementation on anticoagulation control. We will also point to the potential impact of dietary vitamin K on the pharmacological activity of the more recently developed direct oral anticoagulants (DOACs).

Dietary factors and anticoagulation control

1. Dietary vitamin K intake

Vitamin K is a fat-soluble vitamin that is largely derived from the diet, predominantly as phylloquinone (vitamin K₁), present notably in green leafy vegetables and vegetable oils (**Table 1**). Given that the activation of the main clotting factors (II, VII, IX and X) is dependent on vitamin K availability, anticoagulation control during warfarin therapy is highly sensitive to fluctuating levels of vitamin K in the diet. (11-13)

As there is no detailed assessment of usual population intake in relation to measurable health outcomes, daily Recommended Dietary Requirement (RDA) for vitamin K cannot be set. The current “dietary reference value” of 1 µg/kg (~65-80 µg of phylloquinone/day in an average sized individual) is based on coagulation factor function; substantially higher recommended daily doses have been suggested because of findings that the requirement for vitamin K is greater for the extra-hepatic vitamin K-dependent proteins, including those found in bone (e.g. **osteocalcin**). (14) In 2001, the adequate intake (AI) level for vitamin K based on

consumption levels in healthy individuals was established (**Table 2**). Neither pregnancy nor lactation necessitate additional vitamin K uptake in women. (15) A previous study of dietary intake of vitamin K in a national sample of British elderly people demonstrated that 59% had an intake below 1 µg/kg/day. (16)

Of all the fat-soluble vitamins, vitamin K has the highest individual daily variation in both dietary intake and corresponding plasma concentrations. This is because, dark green vegetables which are the main source of vitamin K, are not consistently consumed on a daily basis. For example, in a study of post-menopausal women in New England, USA, intake ranged from 3-2761µg of phylloquinone/day. (17)

Sudden changes in dietary vitamin K intake resulting in poor anticoagulation control may put patients at increased risk of potential life-threatening bleeding and thromboembolic complications. Indeed, prosthetic valve thrombosis (18) and myocardial infarction (19) have been reported in patients who increased their vitamin K intake during anticoagulation therapy, and in the case report by Walker (19) this was linked to the patient embarking on a vegetable-rich, weight-reduction diet. Conversely, diffuse bruising (presumably due to enhanced anticoagulation) in one case report was linked to the patient stopping his consumption of large amounts of porcine liver, thereby reducing his vitamin K intake (18). Thus, it has been suggested that patients maintain a consistent dietary vitamin K intake during anticoagulation therapy, generally no more than 250 to 500 µg/day (20).

An earlier crossover study in anticoagulated patients demonstrated an inverse relationship between vitamin K intake and anticoagulation response, as measured by the International Normalised Ratio (INR). (12) Another study in patients on chronic therapy with warfarin and with stable control of anticoagulation demonstrated that for every 100 µg increase in vitamin K intake over the previous 4 days, INR value fell by 0.2 units (21), further clarifying the extent of the inter-relationship between dietary vitamin K and the INR. Consistent with these observations, Lubetsky et al. found that, INR values decreased in 32% (16/50) of

anticoagulated patients following a vitamin K intake of ≥ 250 $\mu\text{g}/\text{day}$. The patients had significantly lower median INR values (1.9 and 3.0, respectively; $p < 0.001$) and required a higher maintenance steady state warfarin dose (5.7 and 3.5 mg/day, respectively; $p < 0.001$), compared to those receiving < 250 $\mu\text{g}/\text{day}$ of vitamin K. (11)

In order to reduce intra-patient variability in anticoagulation response, patients should maintain an adequate and consistent intake of dietary vitamin K that at least meets the current dietary reference value of 65-80 $\mu\text{g}/\text{day}$. Self-monitoring of vitamin K intake aids, such as the 'K-Card', which was designed as a checklist of common foods and beverages providing ≥ 5 μg vitamin K per serving (**Table 3**), may be helpful in this regard. (22)

2. *Dietary supplements*

2.1 *Enteral feeds*

Enteral feeds may be an unsuspected source of additional dietary vitamin K in patients receiving warfarin. Although a decrease in the vitamin K content of enteral feedings has been observed over the years (23), some feeds may contain for example up to 20 μg vitamin K per 8 fl oz (237ml) serving (**Table 4**). This may explain why certain enteral feeds have been reported to lower the anticoagulant effect of warfarin. (24-26) Thus, it is important to consider the significant impact of enteral nutrition on anticoagulation response in patients on warfarin therapy.

Vitamin K also plays a key role in anticoagulation control in children. The main sources of phyloquinone in neonates, especially preterm infants, are the prophylactic dose of phyloquinone given at birth, along with the vitamin K intake derived from either parenteral and/or enteral feeding. **Breast**-fed infants, due to low quantity of vitamin K in human milk, are more sensitive to the anticoagulant effect of warfarin compared to formula-fed infants. Infant

formula preparations with high vitamin K content frequently administered to pre-term neonates, lead to higher warfarin dose requirements. (27, 28)

2.2. Other supplements

Vitamin K is a constituent of many multivitamin preparations. The anticoagulant effect of vitamin K antagonists is lessened even by multivitamin formulations containing small amounts of vitamin K. In relation to this, Kurnik et al. reported three cases of patients treated with warfarin who had presented with sub-therapeutic INR after taking multivitamin supplements containing vitamin K, which necessitated an increase in warfarin dose with one patient experiencing major thrombosis. (29) One of the patients, whose warfarin requirements had increased from 45 to 60 mg per week, discontinued the multivitamin preparation without notifying her physician and subsequently experienced haematoma accompanied by an INR of 13.2. (29) Consequent to these observations, patients are best advised to avoid multivitamin preparations containing vitamin K.

There is evidence that vitamin E interferes with vitamin K metabolism, as demonstrated by an increase in PIVKA-II (protein induced by vitamin K absence factor II) plasma concentrations. (30, 31) Both vitamin K and vitamin E are metabolised by CYP4F2 enzyme, which may explain the basis for their interaction. (32) However, in a randomised double-blind study, vitamin E at relatively high doses (800 or 1200 IU/day) was shown to have no effect on warfarin anticoagulation. (33)

Vitamin C has been reported to interact with warfarin *in vitro*. (34, 35) The suggested mechanisms of this interaction include enzyme induction leading to enhanced warfarin metabolism, potentiation of vitamin K activity, influence in either the synthesis or the rate of catabolism of the vitamin K-dependent clotting factors, and capillary fragility. (36) A more recent study in rats *in vivo* demonstrated that the co-administration of vitamin C with warfarin leads to an increase in the activity of coagulation factors II, VII, IX and X and a decrease in PT and APTT. (37) Contrary to these findings however, it has been reported that vitamin C does

not alter the anticoagulant effect of warfarin in either dogs or guinea pigs.(36, 38) In patients on chronic warfarin therapy, we found no association between dietary vitamin C levels (2.2–95.9 µM) and warfarin dose requirement. (39)

The provitamin coenzyme Q10 (ubidecarenone) is a dietary supplement taken for a range of cardiovascular disorders (40) and has been linked to decreased anticoagulation when taken with warfarin (41). Coenzyme Q10 is structurally related to vitamin K and thus may have procoagulant effects in anticoagulated patients. (42) There are four case reports of falls in INR values following the co-administration of coenzyme Q10 with warfarin and subsequent restoration of initial INR values after discontinuation of coenzyme Q10. (43-45) A study in patients receiving long-term anticoagulation therapy however found that concomitant coenzyme Q10 intake (100 mg/day) had no significant effect on warfarin dose requirements. (46) As, at the present, there are conflicting reports about the effect of coenzyme Q10 on anticoagulation response to warfarin, patients should be advised to, either avoid the concomitant use of coenzyme Q10, or for healthcare providers to perform additional INR tests when patients start or stop taking coenzyme Q10.

Fish oils contain eicosapentaenoic and docosahexaenoic acids, which may inhibit vitamin K-dependent coagulation factors. One case report described elevated INR values when the patient concerned had taken fish oil supplement with warfarin. (47) However, this contrasts with the findings of an earlier placebo-controlled, randomised, double-blinded study in 16 patients receiving chronic warfarin therapy, in whom fish oil supplementation (3–6 grams/day) was shown to have no significant effect on anticoagulation control. (48) In the absence of further information, patients are advised to discuss the possible interaction between fish oil supplements and warfarin with their healthcare provider.

Recently, Cambria-Kiely reported the case of a 70-year-old man with hypertriglyceridaemia who was stable on long-term warfarin (INR 2.3–2.5) before he started drinking soya milk. Shortly thereafter, his INR dropped below the therapeutic range (1.6); when

he stopped taking soya milk, his INR returned to the therapeutic range. (49) Interestingly, while soybeans and soybean oil contain high amounts of vitamin K (see Table 1), soya milk contains only trace amounts of the vitamin. (49) Further confirmation of the existence of an interaction between warfarin and soya milk and the possible mechanism for such interaction is needed. In the absence of further information, patients on warfarin therapy should avoid introducing soya milk into their diet.

Supplements containing L-carnitine have been found to enhance the anticoagulant effect of the vitamin K antagonist, acenocoumarol. The mechanism for such interaction is unclear. Whether L-carnitine also interacts with warfarin or phenprocoumon is unknown at this stage. Therefore, patients on vitamin K antagonists are advised to discuss with their healthcare provider the possible risks before taking L-carnitine. (50, 51)

2.3. Plant materials

Interactions between herbs and other plant material and warfarin are commonly reported, sometimes with serious consequences of major bleeding. (52) Theoretically, any herb or plant material that may contain compounds related to coumarin or salicylate can augment the anticoagulant effect of vitamin K antagonists, through inhibition of either blood clotting or platelet aggregation. (53)

Up until 2014, thirty eight different herbs had been reported in the literature with the potential to interact with warfarin. Evidence suggests that the likelihood of an interaction with warfarin is high (level I) for four of these herbs, probable (level II) for three, possible (level III) for ten and doubtful (level IV) for twenty one. (54)

Garlic, ginkgo, St. John's wort, cranberry, grapefruit, cannabis, chamomile and red clover have been identified as having major interaction with warfarin. (54) Few reports have linked the use of garlic and ginkgo biloba with bleeding; however, there is no evidence that they directly affect coagulation. Ginger has been shown to inhibit platelet aggregation. (53),

which may potentiate the anticoagulant effect of warfarin. There have been case reports of an interaction between St John's wort (*Hypericum perforatum*) and vitamin K antagonists (warfarin, phenprocoumon), where the use of St John's wort resulted in the lowering of INR and unstable control of anticoagulation. (55) A single case of raised INR after concomitant use of *Angelica sinensis* (Dong quai) and warfarin has been reported. (56) Enhanced anticoagulation and bleeding events have been reported after patients on warfarin therapy took the traditional Chinese medicine, *Salvia miltiorrhiza* (danshen). (53, 57)

There have been several reports of interaction between warfarin and cranberry juice (58-60). For instance, an elderly patient on warfarin who had a poor appetite following a chest infection consumed very little except cranberry juice and was admitted to hospital 6 weeks later with an INR of >50. He died of gastrointestinal and pericardial haemorrhage. (61) The advice of the UK Committee on Safety of Medicines is to limit the intake of cranberry juice in patients taking warfarin. (61) The mechanism of the interaction between warfarin and cranberry juice is at present unclear. However, it has been suggested that the flavonoids present in cranberry juice, which can inhibit CYP2C9 enzyme responsible for (S)- warfarin metabolism, can explain the interaction between cranberry juice and warfarin. (62) It is plausible that vitamin C, also a constituent of cranberry juice, contributes to alteration in anticoagulation response to warfarin, possibly by a number of mechanisms, including alterations in warfarin metabolism, competition with vitamin K in binding to vitamin K epoxide reductase which is the target enzyme for warfarin, and the rate of loss or catabolism of the vitamin K-dependent clotting factors.

It may also be pertinent to avoid the consumption of grapefruit juice given reports of enhanced warfarin anticoagulation after consuming grapefruit juice. (63) Although an earlier controlled study failed to demonstrate an interaction between warfarin and grapefruit juice (64), other studies have reported that grapefruit juice enhances the anticoagulant effect of warfarin by inhibiting mainly CYP3A4 and CYP2C9 enzymes involved in warfarin metabolism. (65, 66)

Green tea, which is often taken as a dietary supplement because of its reputed health benefits (including antioxidant and antibacterial properties), contains substantial amounts of vitamin K and therefore drinking large amounts may antagonise the anticoagulant effects of warfarin. (67) Indeed, one report describes a warfarin-treated patient who experienced a marked decrease in INR after daily consumption of large amounts of green tea, with a subsequent INR increase when the beverage was discontinued (without a change in warfarin dosage). (68) In the absence of further information, patients receiving anticoagulation therapy are advised to discuss the consumption of green tea and its possible impact on warfarin anticoagulation response with their healthcare provider.

2.4. Alcohol consumption

Alcohol intake is another important factor in patients receiving warfarin, as this may increase or decrease the anticoagulant effect. Acute alcohol intake (e.g. ingestion of a few alcoholic drinks at a single sitting) may increase anticoagulation, via decreased hepatic metabolism of warfarin (69) or displacement of the drug from albumin with subsequent increase in unbound drug (70). Conversely, chronic consumption of alcohol may decrease the anticoagulant effect by activating cytochrome P450, thereby increasing the metabolism of warfarin (69). However, in an earlier literature review, Wells et al. concluded that alcohol potentiated warfarin anticoagulation only if the patient had concomitant liver disease. (71) A Dutch study found that although habitual alcohol consumption or heavy drinking (≥ 6 drinks/day) did not affect anticoagulation control, a recent decrease in alcohol intake increased the risk of having an INR value ≥ 6.0 and thus increasing the risk of bleeding in the patient. (72) A case report of a patient on warfarin with a low-dose beer consumption was found to be the cause of elevated INR. The authors recommended close monitoring of INR when alcohol is taken in combination with warfarin and other concomitant medication. (73) In

the absence of consistent data, it is clear that patients should either avoid alcohol or at least avoid erratic consumption of alcohol while receiving warfarin with close INR monitoring.

2.5. *Vitamin K supplementation*

Clinical experience indicates that only 50% to 60% of INRs measured are within target range in patients with monthly monitoring of treatment. (74) Low vitamin K levels cause a patient's warfarin dose requirement to vary with even minor changes in vitamin K intake.

Several recent studies have shown that daily oral supplementation with vitamin K could improve stability of anticoagulation control in patients who are more susceptible to dietary changes, because of their poor and erratic dietary vitamin K intake, such as the elderly. (21, 75-77) A small study in 2005 demonstrated that vitamin K supplementation improved anticoagulation control, possibly due to the more steady activation of vitamin K-dependent clotting factors. (78) At the same time, our group demonstrated that patients with variably low dietary intake of vitamin K were more likely to have unstable control of anticoagulation compared to their matched stable counterparts. (79) Kim and colleagues in 2010 confirmed that patients with low vitamin K intake are more sensitive to minor changes in vitamin K intake and thus more likely to have unstable anticoagulation control. (80) Another prospective study proposed that a vitamin K-guided management strategy is clinically feasible for the maintenance of oral anticoagulation intensity. (81)

Schurgers and colleagues investigated the safe initiation of vitamin K supplementation on anticoagulation response in healthy subjects. They studied the dose-response relationship of vitamin K supplementation on anticoagulation control and concluded that the administration of 100 µg of vitamin K daily did not significantly influence INR value. (82) Despite a study showing that 25 µg significantly reduced the INR in patients with low vitamin K status (83), it was later recommended that supplementation with a 100 µg vitamin K daily dose is preferable to negate any influence of variability in dietary vitamin K intake. (84)

In 2007, three separate studies on the effect of vitamin K supplementation on anticoagulation stability reported similar findings. In a double-blinded placebo controlled study, seventy patients with unstable control of anticoagulation were randomised to receive either 150µg oral vitamin K, or placebo daily for 6 months. The study confirmed that vitamin K supplementation results in significant improvement in anticoagulation stability attributed to a reduction in inter-day variability in dietary vitamin K intake. (76) A second open label crossover study of 9 patients with unstable anticoagulation control showed a reduction in INR variability after 500µg of oral vitamin K supplementation daily. (75) Rombouts and colleagues also demonstrated the positive effect on anticoagulation control of 100µg vitamin K supplementation once daily for 24 weeks in an unselected group of 200 patients on chronic therapy with phenprocoumon. (77)

A recent meta-analysis reported no beneficial effect of low-dose vitamin K supplementation on the reduction of clinically relevant adverse events in patients taking VKAs. (85) However, the meta-analysis lacked sufficient data to show that daily vitamin K supplementation has an impact on the incidence of adverse events in anticoagulated patients. Based upon the overwhelming body of evidence that daily vitamin K supplementation improves anticoagulation stability the American College of Chest Physicians (ACCP) guidelines recommend the use of vitamin K in patients with chronically unstable anticoagulation. (86)

2.6 Potential interaction between dietary vitamin K and direct oral anticoagulants

In recent years, several direct oral anticoagulants (DOACs), which selectively inhibit a single clotting factor [factor Xa or factor IIa (thrombin)] have been developed with the aim of providing a more predictable pharmacokinetics and pharmacodynamics, thus obviating the need for patient monitoring. The factor IIa inhibitor, dabigatran, and factor Xa inhibitors, rivaroxaban, apixaban and edoxaban, have been provided license for the treatment of

thrombosis as well as prevention of stroke after having demonstrated non-inferiority to warfarin in their clinical effectiveness for stroke prophylaxis in patients with atrial fibrillation. (87-90) It is generally accepted that, unlike coumarins, DOACs do not interact with dietary vitamin K. This is because of the perception that the mode of action of these agents, which exert their pharmacological activity by inhibition of a specific clotting protein, is different to that of coumarins which inhibit the recycling of vitamin K, necessary for the gamma-carboxylation and thus activation of vitamin K-dependent clotting proteins.

However, since the functionalisation of both factor Xa and thrombin is inextricably linked to vitamin K, there is the possibility that the pharmacological activity of agents that inhibit these proteins could be influenced by alterations in vitamin K availability. Indeed in an earlier study in rats we demonstrated that vitamin K deficiency significantly enhanced the anticoagulation activity of the direct thrombin inhibitor, ximelagatran. Briefly, the anticoagulant activity of ximelagatran (20 mmol/kg, twice daily for 8 days) was significantly greater in rats on vitamin K deficient diet (12.3-fold for prothrombin time, 5.1-fold for activated partial thromboplastin time, and 1.6-fold for ecarin clotting time) compared to those on normal diet. Factor II activity was reduced to 58% by ximelagatran in rats on normal diet. However, factor II activity was virtually abolished (<1%) by the drug in rats on vitamin K deficient diet.(91) Whether dietary vitamin K influences anticoagulation response to DOACs in man remains to be investigated.

Conclusions

Long-term oral anticoagulation with warfarin and other vitamin K antagonists places major limitations on patients in terms of what they can eat and drink. In particular, patients need to maintain a consistent dietary intake of vitamin K, as sudden or marked changes in the intake of this vitamin (which can often be unintentional, e.g. initiation or withdrawal of dietary

supplementation) can have a dramatic effect on anticoagulation control that can increase the risk of either thromboembolism due to under-coagulation or bleeding due to over-anticoagulation. To minimise such risks to the patient it is therefore necessary to carry out additional INR monitoring and dose adjustment with the associated increase in the cost of anticoagulation therapy and the reduction in patient quality of life. Appropriate education of patients regarding the effects of diet and dietary supplementation on anticoagulation, emphasising the potential dangers of any sudden or marked changes in these factors, is therefore an important aspect of anticoagulation care. However, while improved patient education may help to reduce the risk of suboptimal anticoagulation control related to dietary changes in patients receiving long-term thromboprophylaxis with warfarin, clearly this will remain a difficult problem for many patients and their healthcare providers. Daily supplementation with oral vitamin K would be a good option in the attempt to improve anticoagulation control in patients with unstable anticoagulation suspected of having poor diets.

Expert commentary

There is a clear absence of consistency in the dietary intake among patients that receive warfarin or other vitamin K antagonists. Changing the dietary preferences or adding certain sources in patients' diet is not an effective and practical way of maintaining a stable anticoagulation control. Nevertheless, numerous studies including one from our group have shown that daily **low dose** oral vitamin K supplementation (**100 to 200 mg**) can improve anticoagulation outcomes and is simple to implement, because it does not interfere with individual dietary preference.

As part of the clinical management of patients on warfarin therapy, there should be a greater awareness among healthcare providers of the impact of malnutrition (in terms of dietary

vitamin K intake), and the various foods and beverages that contain varying amounts of vitamin K on anticoagulation control.

There is experimental evidence in animals to suggest that ximelagatran interacts with dietary vitamin K. Further studies are needed to ascertain the presence of a pharmacodynamics interaction between dietary vitamin K and DOACs in man.

Five-year view

There is a compelling body of evidence on the impact of variable and poor dietary vitamin K on anticoagulation stability and the risk of bleeding in patients on warfarin therapy. Daily supplementation with low doses of oral vitamin K which leads to stabilisation of vitamin K stores in the liver have been shown to improve anticoagulation control in previously unstable patients. We along with a number of other anticoagulation services have adopted this approach. However, it is important that the benefits of vitamin K supplementation in patients on long-term therapy in the attempt to improving the safety of warfarin therapy are recognised on a wider scale. We are currently investigating the potential impact of dietary vitamin K on anticoagulation response to DOACs in man. The results of these studies are expected to become available soon. Should the results of these studies demonstrate the existence of an interaction between DOACs and dietary vitamin K then for patient safety reasons the introduction of some form of monitoring may become necessary.

Key issues

- Variable dietary vitamin K intake affects anticoagulation response to warfarin.

- Warfarin interacts with a variety of foods, herbs and dietary supplements, which necessitates the need for better patient education about the effect of diet on anticoagulation control.
- Daily supplementation with low oral dose vitamin K increases stability of anticoagulation. Vitamin K supplementation has been embedded into guidelines for the management of anticoagulation with vitamin K antagonists.

Financial and competing interests disclosure: The authors report no conflicts of interest.

Table 1. Phylloquinone (vitamin K₁) content of foods (92)

Food item	Phylloquinone content (µg/100g)	Food item	Phylloquinone content (µg/100g)
<i>Vegetables</i>		<i>Protein sources</i>	
Collard greens	440	Dry soybeans	47
Spinach	380	Dry lentils	22
Salad greens	315	Liver	5
Broccoli	180	Eggs	2
Brussels sprouts	177	Fresh meats	<1
Cabbage	145	Fresh fish	<1
Bibb lettuce	122	Whole milk	<1
Asparagus	60	Tuna in oil	24
Okra	40		
Iceberg lettuce	35	<i>Prepared foods^a</i>	
Green beans	33	Salad dressings	100
Green peas	24	Coleslaw	80
Cucumber	20	Mayonnaise	41
Cauliflower	20	Beef chow mein	31
Carrots	10	Muffins	25
Tomatoes	6	Doughnuts	10
Potatoes	1	Apple pie	11
		Potato chips	15
<i>Fats and oils</i>		French fries	5
Soybean oil	193	Macaroni cheese	5
Canola oil	127	Lasagne	5
Cottonseed oil	60	Pizza	4
Olive oil	55	Hamburger/bun	4
Corn oil	3	Hot dog/bun	3
Margarine ^a	42	Baked beans	3
Butter	7	Bread	3

^a Phylloquinone content may vary widely according to the source of oil used.

Table 2. Adequate Intake (AI) of vitamin K (15)

Life Stage	Age	Vitamin K (µg/day)
Infants	0-6 months	2.0
	7-12 months	2.5
	1-3 years	30
Children	4-8 years	55
	9-13 years	60
Adolescent s	14-18 years	75
Adults	> 19 years	120 (males) 90 (females)

Table 3. The K-Card (vitamin K intake assessment card) (from Couris et al. 2000)

K-Card (Check which foods you eat at each meal everyday. If you eat more or less than one serving indicate how much.)

Food	One Serving	Phytoquinone (mcg)	Sun	Mon	Tue	Wed	Thur	Fri	Sat
Mixed dishes/meals									
beef chow mein (Chinese)	1 cup (6 oz)	78							
macaroni and cheese	1 cup (6 oz)	10							
pizza	1 slice (1/8 large)	6							
lasagna/spaghetti with meat sauce	1 cup (6 oz)	15							
tacos/tostadas (fast food)	1 tacos	28							
tuna casserole	1 cup (6 oz)	48							
Desserts									
cake/brownies	1 (2" square)	8							
cookies	1 medium	3							
danish/doughnut	1 medium	10							
muffin	1 medium	14							
pie	1 slice (1/8 large)	10							
Snacks									
crackers	6 crackers	4							
popcorn (popped in oil)	2 cups (2 oz)	4							
potato chips	1 cup (1oz)	4							
Fats/oils/dressings									
canola/soybean oil	1 tbsp	27							
olive oil	1 tbsp	4							
salad dressing	1 tbsp	7							
mayonnaise	1 tbsp	6							
margarine	1 tbsp	5							
Supplements									
products containing vitamin K	65 micrograms	65							
high dose vitamin C	1000 mg	—							
high dose vitamin E	1200 IU	—							

**Vitamin K Intake Assessment Card
(K-Card[®])**

©June 1997
R. Rebecca Couris & Johanna T. Dwyer
Tufts University School of Nutrition Science and Policy

Name _____ Date _____
ID Number _____ Week _____

K-Card (Check which foods you eat at each meal everyday. If you eat more or less than one serving indicate how much.)

Food	One Serving	Phylloquinone (mcg)	Sun	Mon	Tue	Wed	Thur	Fri	Sat
Meat/poultry/fish									
chicken (fried)	3 oz.	4							
chicken nuggets	6 nuggets	2							
fish sandwich (fast food)	4 oz.	26							
fish sticks	3 sticks	6							
tuna in oil (any form)	3 oz.	20							
Vegetables									
asparagus	1/2 cup	72							
avocado	1/2 small (5-8 slices)	4							
bean pod	1/2 cup	9							
broccoli	1/2 cup	88							
brussel sprout	1/2 cup	225							
cabbage	1/2 cup	73							
cauliflower	1/2 cup	12							
chick peas/garbanzos (hummus)	1/2 cup	12							
coleslaw with dressing	1/2 cup	65							
cucumber with peel	1/2 cup	20							
endive	1/2 cup	185							
green beans	1/2 cup	14							
greens (collard)	1/2 cup	375							
greens (turnip/mustard)	1/2 cup	200							
kale	1/2 cup	650							
lettuce	1 cup	68							
mixed vegetables	1/2 cup	15							
okra	1/2 cup	32							
peas	1/2 cup	19							
pickle (dill)	1 spear	6							
potato (french fries)	1 cup	5							
sauerkraut	1/2 cup	15							
scallions	1/2 cup	103							
soybeans/tofu	1/2 cup	193							
spinach	1/2 cup	324							
Beverages									
V8 juice	1 cup (6 oz)	15							
green tea	1 cup (6 oz)	—							

Table 4. Vitamin K content of various enteral feeds ready-to-drink according to the British National Formulary, 2017^a

Product	Kcal	Vitamin K content (µg)
Per 100mL serving		
Fresubin® original ^a	100	6.7
Fresubin® original fibre ^a	100	6.7
Fresubin® 1000 complete ^a	418	10
Fresubin® 1200 complete ^a	500	10
Fresubin® 1500 complete ^a	420	6.7
Fresubin® 1800 complete ^a	500	10
Fresubin® 2250 complete ^a		
Fresubin® energy ^a	630	6.67
Fresubin® energy fibre ^a		
Fresubin® HP energy ^a		
Ensure TwoCal ^b	200	8.5
Nutrison® ^c	100	5.3
Nutrison® MCT ^c		
Nutrison® Multi Fibre ^c	103	5.3
Nutrison® Energy ^c	150	8
Nutrison® Energy Multi Fibre ^c	153	8
Nutrison® Protein Plus ^c	125	6.6
Nutrison® Protein Plus Multi Fibre ^c	128	6.6
Nutrison® 800 Complete Multi Fibre ^c	83	8
Nutrison® 1000 Complete Multi Fibre ^c	104	8
Resource Energy ^d	151	14
Peptamen® HN ^d	133	9
Vital 1.5kcal ^b	150	7
Novasource® GI Control ^d	106	6
Novasource® GI Control ^d	155	11
Per 8 fl oz serving *		
Jevity® 1 Cal ^b	250	15
Jevity 1.2 Cal (formerly Jevity Plus) ^b	285	20
Jevity® 1.5 Cal ^b	355	19
Osmolite® 1 Cal ^b	250	15
Osmolite® 1.2 Cal ^b	285	20
Osmolite® 1.5 Cal ^b	355	19

Ensure® ^b	220	20
Ensure® High Protein ^b	160	20
Ensure® Plus ^b	350	20
Ensure® Plus HN ^b	250	20
Ensure® Enlive® Advanced Nutrition Shake ^b	350	20
Two cal® ^b	475	20
Perative® ^b	308	17

[^] Information retrieved from <https://www.evidence.nhs.uk/formulary/bnf/current/>; accessed 14 February, 2017)

^a Information retrieved from Fresenius Kabi (<http://www.fresenius-kabi.co.uk/4727.htm>; accessed 14 February, 2017)

^b Information retrieved from Abbott (<https://abbottnutrition.com/>; accessed 14 February, 2017)

^c Information retrieved from Nutricia Clinical (<http://www.nutricia.co.uk/>; accessed 15 February, 2017)

^d Information retrieved from Nestlé HealthCare Nutrition

(<https://www.nestlehealthscience.co.uk>; accessed 15 February, 2017)

* 8 fl oz (US) = 237 ml

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