Food Drug Interaction Between Anticoagulants And Vitamin- K Nutrient In CVD Patients And Their Overall Nutrition

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Abstract:
Cardiovascular disease (CVD) remains the leading cause of mortality worldwide, necessitating effective management strategies, including the use of anticoagulants. This paper explores the interactions between anticoagulants, particularly vitamin K antagonists (VKAs) like warfarin, and dietary sources of vitamin K, which can significantly impact treatment outcomes. CVD patients often supplement their diets with vitamins and nutrients, creating potential drug-nutrient interactions that can complicate anticoagulation therapy. Vitamin K, crucial for the synthesis of clotting factors, can diminish the efficacy of VKAs when consumed in high quantities, particularly from green leafy vegetables and fermented foods rich in vitamin K2. Additionally, we highlight dietary recommendations for CVD patients from organizations such as the American Heart Association, which advocate for balanced nutrition to support cardiovascular health. Understanding these interactions is vital for healthcare profession also to optimize anticoagulant therapy and improve patient outcomes in managing CVD. This review emphasizes the need for awareness of dietary influences on anticoagulant efficacy, promoting a holistic approach to patient care.

Keywords: CVD, Drug – Nutrient interactions, Oral anticoagulant drugs, Vitamin k dietary supplement.

Introduction:

The World Health Organisation (WHO) lists cardiovascular disease (CVD) as the main cause of death globally. CVD are complex illnesses. In 2013, 31% of deaths worldwide were attributable to CVD, accounting for over 17.5 million deaths annually. Damage and restructuring of blood arteries, which can lead to blood flow limits impacting the heart and neurological system, are the foundation of cardiovascular disease (CVD). Coronary artery disease (CAD), stroke, hypertension, heart failure, rheumatic aetiologies, congenital heart disease, and peripheral vascular disease are among the conditions that make up CVD [1].

People with cardiovascular diseases, such as hyperlipidemia, atrial fibrillation, heart transplant recipients, AMI, LV thrombus, prosthetic heart valve users, venous thromboembolism, and heart failure, are significantly more likely to take nutritional supplements. There is a chance that using prescription medications and nutritional supplements at the same time could have negative drug interactions. Therefore, it's critical for medical professionals and patients to be aware of the possibility of drug interactions with dietary supplements [2]. Vitamin K is a fat-soluble vitamin that is less well-known than others, although it serves numerous vital roles in the human body. Henrik Dam discovered Vitamin K in 1935. Vitamin K occurs naturally in two forms: phylloquinone and menaquinone. Menadione (VK3), a synthetic version of vitamin K, is a provitamin with no side chain [3].

Vitamin K is a vitamin that dissolves in fat that is mostly obtained by diet, mainly in the form of phylloquinone (vitamin K1), which is found mostly in vegetable oils and green leafy vegetables. Because vitamin K availability is necessary for the activation of the major clotting factors (II, VII, IX, and X), variations in vitamin K levels in the diet can significantly affect anticoagulation management during warfarin medication [4].

Vitamin K1 and K2 Dietary Sources:

Plants, algae, and cyanobacteria are among the photosynthetic species that contain vitamin K1, which is a by product of the shikimate pathway in photosynthesis. Green leafy vegetables including spinach, kale, romaine lettuce, broccoli, and cabbage are the primary dietary sources of vitamin K. The second best dietary source of K1 is vegetable oil, specifically canola, soybean, sunflower, and olive oils. Moreover, fruits, grains, meat, and dairy products have smaller concentrations of K1. Vitamin K1 is abundant in typical Japanese foods like vegetables, and the highest amount is found in perilla, which is found in edible seaweed like wakame and hijiki [5].

Many facultative and obligatory anaerobic bacteria biosynthesise vitamin K2, which is found in the most well-known forms in terms of nutrition value: MK-7, MK-8, and MK-9. Furthermore, it has been reported that the human gut's bacterial ecology produces a number of long-chain MKs. The main forms of K2 that have been identified in the human large intestine are produced by a variety of enterobacteria, including Veillonella, Eubacterium lentum, Bacteroides, and MK-6, MK7, MK-8, and MK-10.

Other important sources of vitamin K2 are meat—particularly gammon, bacon and chicken. Egg yolks and high-fat dairy products, such hard cheeses, are good sources of this vitamin as well. Notably, it was discovered that the most significant dietary source of long-chain MKs (MK-8 and MK-9) is cheese. It has been demonstrated that propionibacteria-fermented cheeses, such Swiss Emmental and Norwegian Jarlsberg cheese, have the highest concentration of vitamin K2 (tetrahydromenaquinone-9). Fermented plant foods like natto are a significant dietary source of vitamin K2, of relevance to the business. One of the most important dietary sources of MK-7 is natto, a classic Japanese soybean dish made by fermenting cooked soybeans with Bacillus subtilis natto [5].

Table 1: Oral anticoagulant drug [6].

Subtance	Mechanism	Typical efficient dose	Half-life	Stage of development
Vitamin K antagonists (VKA)				
Warfarin (Coumadin®)	Inhibition of VKORC1	INR guided	35-45 hours	Approved for OAC
Acenocoumarol (Sinthrome®)	Inhibition of VKORC1	INR guided	8-24 hours	Approved for OAC
Phenoricoumon (Marcumar®)	Inhibition of VKORC1	INR guided	80-270 hours	Approved for OAC
Anisindione (Miradon®)	Inhibition of VKORC1	INR guided	72-120 hours	Approved for OAC
ATI-5923(ARYx Therapeutics)	Inhibition of VKORC1	INR guided	Date not available	In a phase II/III clinical trial for OAC
Factor IIa (thrombin) inhibitors				
Dabigatran etexilate (Pradaxa®, Boehringer-Ingel-heim)	Competitive binding of FIIa	150-220 mg once a day (VTE prophylaxis)	12-17 hours	Approved for VTE after hip/knee surgery* + in phase III clinical trial for OAC
AZD-0837 (AstraZeneca)	Competitive binding of FIIa	150-450 mg (in phase II trials)	Date not available	In a phase II clinical trial for OAC
Sofigatran (MCC 977, Mitsubishi pharma)	Competitive binding of FIIa	Date not available	Date not available	In a phase II clinical trial for DVT
Factor Xa inhibitors				
Rivaroxaban (Xarelto ®, bayer helthcare and johnson & johnson)	Competitive binding of FXa	10mg once a day (VTE prophylaxis)	5-9 hours	Approved for VTE after hip/knee surgery* + in phase III clinical trial for OAC
Apixaban (bristol-Myers-Squibb and Pfizer)	Competitive binding of FXa	2.5-5 mg twice a day (in phase II trials)	9-14 hours	In a phase III clinical trial for OAC
Betrixaban (portola pharmaceuticals)	Competitive binding of FXa	40-80 mg daily (in phase II trials)	19 hours	In a phase III clinical trial for OAC
Edoxaban (DU-176b, Daiichi sankyo)	Competitive binding of FXa	30-60 mg once a day (in phase II trials)	Date not available	In a phase III clinical trial for OAC
Eribaxaban (PD0348292, Pfizer)	Competitive binding of FXa	0.1-2.5 mg once a day (in phase II trials)	Date not available	In a phase II clinicaltrial for VTE after TKR
YM150 (Astellas)	Competitive binding of FXa	30-60 mg once a day (in phase II trials)	Date not available	In a phase II clinicaltrial for VTE and OAC
LY517717 (Eli Lilly)	Competitive binding of FXa	100-150 mg once ad day (in phase II trials)	27 hours	In a phase II clinicaltrial for VTE
TAK-442 (Takeda pharmaceutical)	Competitive binding of FXa	20-240 mg daily (in phase II trials)	Date not available	In a phase II clinicaltrial for VTE
Others				
Anti Ixa:TTP889 (Transtech pharma)	Reversible binding of FIXa	300 mg daily (one phase II trial)	21-25 hours	In a phase II clinicaltrial for VTE

*FDA approval still pending (June 2010).

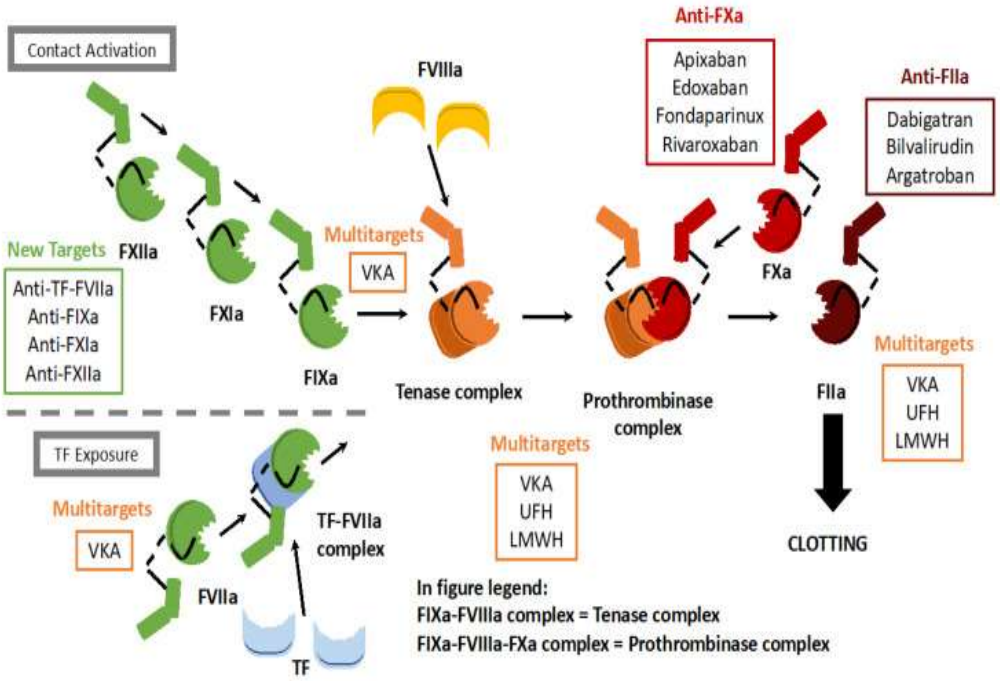

Figure 1 : Anticoagulants: Their Mechanism of Action

The coagulation cascade's targets for anticoagulants. The tissue factor (TF) pathway, the contact activation pathway, and the common pathway are the three components that make up the coagulation cascade. Anticoagulants now in use mostly target coagulation factors from the common pathway, namely thrombin (FIIa; dabigatran, bilvalirudin, and argatroban) and FXa (apixaban, edoxaban, fondaparinux, and rivaroxaban). There are several targets for UFH, VKA, and LMWH in the coagulation cascade. Clinical trials and ongoing development of anticoagulants target factors from the contact activation pathway (FIXa, FXIa, and FXIIa) or the TF route (TF-FVIIa complex). FVIIIa-FIXa complex is the Tenase complex. The FVIIIa-FIXa-FXa complex is the prothrombinase complex [7].

Interaction between anticoagulant and vitamin k:

In clinical practice, an unnoticed problem that frequently arises is the interaction between medications and natural items. Similar pharmacokinetic and pharmacodynamic principles underpin interactions between pharmaceuticals and natural product interactions [8]. The drug's pathophysiological processes manifest as impairments in nutrition absorption or utilization. A common scenario is when a medicine interferes with a nutrient's absorption or when a drug's toxicity prevents a metabolic activity. Tissue-specific interactions may cause these interactions to change in various tissues. A lot of Drug nutrient interactions are reciprocal; For example, the medication influences micro nutritional status, and the micronutrient influences drug metabolism, which leads to unfavourable pharmacological effects [9]. Anticoagulants work by interfering with the coagulation cascade at various points. Some work directly by inhibiting specific enzymes, while others work indirectly by attaching to antithrombin or blocking the liver's ability to synthesise them (factors dependent on vitamin K) [10]. Vitamin K anticoagulants are medications that treat cardiovascular conditions that induce embolism in order to prevent atrial fibrillation-related thromboembolic problems, valve disease, which is the condition when the heart valve is artificially replaced, and thromboembolic consequences [11].

Vitamin K antagonists (VKAs) constituted the cornerstone of anticoagulant treatment for over half a century. A prospective substitute for VKAs in the treatment of patients with deep vein thrombosis and pulmonary embolism, as well as in the prevention of embolic consequences in non-valvular AF, was a new family of medications that entered the market in 2008. Patients receiving DOACs should still be evaluated for some pharmacokinetic changes resulting from interactions with diet, herbal supplements, and other medications [12].

To treat or avoid thromboembolic episodes, warfarin is frequently used. Thirty percent of patients regularly utilise herbal or natural product supplements, despite the fact that patients using warfarin are especially vulnerable to interactions with dietary supplements. Warfarin and a diet heavy in protein may interact with each other. The hypothesis for the subsequent decline in the international normalised ratio (INRs) has been the possibility that a higher dietary protein intake will enhance blood albumin levels and/or cytochrome P450 activity. There are several vegetables that are high in vitamin K, including spinach, broccoli, Brussels sprouts, kale, parsley, and others. Warfarin therapy is less safe and effective when consumed in excess or when consumption of certain veggies is abruptly altered [8]

An oral anticoagulant called warfarin is frequently used to treat patients with myocardial infarction, atrial fibrillation, artificial heart valves, and deep vein thrombosis in order to prevent thrombolytic events. The medication is metabolised in the liver by the cytochrome P450 (CYP) isozymes, principally CYP2C9, CYP2C19, CYP2C8, CYP1A2, and CYP3A4. The medication is a racemic combination of R and S-enantiomers. Warfarin works by preventing the production of coagulation factors II, VII, IX, and X that rely on vitamin K [2].

The bulk of warfarin relationships are mediated by CYP2C9, 1A2, 2C19, and 3A4 isoenzymes due to its intricate multi-step metabolism. The pharmacological effects of warfarin and, consequently, the levels of PT-INR are impacted by both inducers and inhibitors of these enzymes. The majority of the time, these interactions result in adverse medication responses that cause bleeding events that can be serious, life-threatening, or even deadly [13].

Despite struggle for binding to serum albumin, the metabolic route of warfarin clearance accounts for a large number of dietary and drug interactions seen in the extensive clinical experience with this medication. Warfarin is almost completely cleared by the liver, and its removal is mediated by the cytochrome (CY)P450 enzyme system. Numerous approved medications are metabolised via the CYP450 system, which also serves as a primary pathway for drug clearance. Competitive inhibition can have negative effects on CYP450 enzymes and pharmacological therapy, such as decreased drug metabolism and increased toxicity [14]

At the moment, the clinic prescribes dabigatran, a DOAC that targets thrombin, along with rivaroxaban, apixaban, and edoxaban, DOACs that target FXa. Since they all obstruct the target enzyme's exposed active site during activation, the medications work in a similar way. Oral administration of tiny synthetic compounds is known as DOACs. Compared to VKAs, they are quickly absorbed into the bloodstream and significantly better for everyday clinical practice due to their immediate inhibiting effects on coagulation proteins [7]. Warfarin, an anticoagulant, inhibits the recycling of vitamin K1, which causes the amount of active vitamin K1 to decrease. On the other hand, vitamin K1 is abundant in green leafy vegetables, or "greens," which reverse its depletion. Similarly, by decreasing aldosterone activity, renin-angiotensin system inhibitors raise plasma potassium [K+] levels [15].

Nutrition for CVD patient:

The American Heart Association and European Society of Cardiology advise the following actions to lower the risk of cardiovascular diseases:

- The ideal daily calorie intake should be determined by factors such as age, weight, and degree of physical activity.
- Selecting legumes, nuts, and whole grains high in fibre for the majority of grain portions.
- Consuming a range of fruits and vegetables, as well as skinless chicken and fish that have been prepared healthily.
- Reducing your intake of red meat, sugar-sweetened beverages, trans fats, saturated fat, and sodium.
- Limiting alcohol consumption and abstaining from smoking [12].

Conclusion:

Cardiovascular disease (CVD) is a major global health issue, significantly influenced by nutrition and medical interactions. Vitamin K is crucial in managing anticoagulant therapies, particularly warfarin, highlighting the need for awareness of dietary sources and their effects on treatment efficacy. Understanding these interactions is essential for healthcare providers to optimize patient outcomes. By following dietary guidelines and monitoring anticoagulant use, patients can effectively manage CVD and reduce the risk of complication.

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