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# Dietary Vitamin K Restriction and Effectiveness of Vitamin K Antagonists Prescribed at the CNHU-HKM University Cardiology Clinic/BENIN

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## Abstract

**Introduction:** Their efficacy in preventing thrombotic and embolic events has been proven in numerous studies, but their narrow therapeutic index requires particular vigilance, especially in terms of biology. In addition, treatment-related hemorrhagic complications are not uncommon. This study explores the influence of dietary vitamin K restriction on the efficacy of antivitamin K treatment at the University Cardiology Clinic of CNHU-HKM. **Methods:** Cross-sectional and descriptive study that took place from 25 April to 29 August 2019. Patients' dietary behaviors and successive INR values were collected. Information on dietary intake was obtained by 2 non-consecutive 24-hour recalls. The effectiveness of VKA treatment was assessed by the "Time in Therapeutic Range" (TTR) of the INR. VKA treatment was considered effective for a TTR greater than 65%. **Results:** At the end of this study, 40 patients were surveyed. The mean age of the participants was 58.05 years ± 13.32 years, with a sex ratio of 1.35. Complete arrhythmia due to atrial fibrillation was the main indication for VKA treatment (37.50%) and fluindione was the most commonly prescribed drug (77.50%). The duration of treatment was less than or equal to 2 years in 47.5% of the subjects surveyed. Before starting treatment, 85% of patients received advice on restricting vitamin K-rich foods, and 45% of patients reported "food burnout" after a period of compliance with the restriction. The majority of respondents (97.50%) complied with the restriction on vitamin K-rich foods. All respondents had high energy intakes and a poor distribution of macronutrients, with a predominance of carbohydrates and proteins. 2.5% of respondents were on effective anti-vitamin K therapy with a TTR of over 65%. **Conclusion:** Restriction of

vitamin K-rich foods is not conducive to effective treatment with vitamin K antagonists.

## Keywords

Antivitamin K, Dietary Restriction, Vitamin K, Therapeutic Efficacy

## 1. Introduction

Atherosclerotic cardiovascular disease remains one of the leading causes of death worldwide, despite the availability of risk-modifying treatments and lifestyle advice [1]. Antivitamins K (AVKs) belong to the family of oral anticoagulants, widely prescribed in the management of a number of cardiovascular diseases. Patients prescribed these VKAs risk being under-dosed, Wirth inadequate protection against thromboembolism, or over-dosed, with a high risk of hemorrhage [2]. Studies by Rombouts et al. have shown an interaction between vitamin K intake and oral anticoagulation therapy [3]. Patients treated with VKAs are often advised to restrict their vitamin K intake, but recent data in the literature tend to show the benefits of a balanced diet, with unrestricted consumption of foods containing vitamin K [4]. AnticoagDietary vitamin K intake restriction event thromboembolic events in a number of situations: mechanical heart valve replacement (MHRV), atrial fibrillation (AF), deep thrombophlebitis, and/or pulmonary embolism [5]. The frequency and seriousness of bleeding on anticoagulants make them a dreaded event, and their management must be well codified. Vitamin K, by allowing endogenous hepatic production of factors five to six hours after administration, takes over from the exogenous factors supplied and ensures that correct hemostasis is maintained from the sixth hour until the disappearance of circulating VKA molecules. Rapid antagonization of VKA treatment requires the administration of clotting factor concentrates (commonly known as prothrombin, proconvertin, Stuart factor, anti-hemophilic factor B [AHFB]) and vitamin K. PPSB is the antidote to VKAs. This combination is recommended by Anglo-Saxon learned societies and by Afssaps [6] [7] [8] [9]. The administration of vitamin K is essential in view of the pharmacological properties of coagulation factors. The short half-life (five to six hours) of factor VII limits the duration of action of PPSB [10] [11]. Dietary vitamin K intake restriction was still recommended for patients treated with VKAs at the University Cardiology Clinic of the CNHU HKM in Cotonou. This study examines the influence of dietary vitamin K restriction on the efficacy of VKA treatment at the University Cardiology Clinic of the CNHU HKM in Cotonou (BENIN).

## 2. Study Methods

### 2.1. Type of Study

This was a cross-sectional, descriptive, and analytical study.

### 2.2. Study Population

This study focused on patients treated with VKAs in the cardiology department of the CNHU HKM who were admitted to the heart failure treatment unit during the data collection period.

### 2.3. Inclusion Criteria

Patients treated with VKAs at the CNHU, who had given informed consent and who had a VKA monitoring record, were included in the study.

### 2.4. Criteria for Non-Inclusion

Patients with a medical condition that prevented them from completing the questionnaire and those represented by their close relatives or parents during the monitoring of VKA treatment were not included in the study.

### 2.5. Exclusion Criteria

Patients who had less than three International normalized ratios and less than two 24-hour recalls during data collection were excluded from the study.

### 2.6. Sampling

Patients were selected by the non-probability method using a convenience sampling technique.

### 2.7. Variables and Their Measurements

The variables described were sociodemographic characteristics: age, sex, profession; level of education; nutritional status of patients, which was assessed on the basis of body mass index (BMI) defined according to WHO criteria; indication for treatment; type of anti-vitamin K (AVK); duration of AVK treatment; patient behavior, which was assessed using eight items: dietary "burn out", weight loss diet, degree of motivation to comply with restrictions, compliance with vitamin K restriction recommended by the doctor, use of herbal teas, compliance with appointment dates, compliance with vitamin K restriction.

Socio-demographic data were collected using a questionnaire.

Age has been classified into three categories: 30 - 45 years; 45 - 60 years and 60 - 85 years. The profession has taken into account: householders, shopkeepers and farmers, civil servants, pensioners, and craftsmen. The level of education was indicated by: no level, literate, primary level, secondary level, and university level.

Anthropometric measurements (height and weight) were taken using SECA adult height gauges and scales respectively. For weight, subjects were placed on a scale without shoes and in light clothing in a stand. To take account of any overestimation of weight due to the fact that the individuals had not completely undressed at the time of weighing, the investigators applied a systematic weighting of 250 grams to all the individuals before recording the corrected weights on the survey form. For height, the Olivier and Demoulin protocol was used as a guide

[2]. Nutritional status was assessed by calculating the Body Mass Index (BMI). This was used to classify subjects in accordance with WHO criteria (BMI 30 kg/m$^2$: obese, BMI 25 - 29.99 kg/m$^2$: overweight, BMI 18.5 - 24.99 kg/m$^2$: normal weight and BMI < 18.5 kg/m$^2$: underweight) [2].

The indication for anti-vitamin K treatment was assessed on the basis of the pathologies present in the patients. These were deep vein thrombosis, pulmonary embolism, mechanical valve prosthesis, complete arrhythmia due to atrial fibrillation, spontaneous intracardiac contrast, chronic pulmonary heart disease due to pulmonary arterial hypertension, and mitral stenosis.

The type of anti-vitamin K was assessed through the type of anti-vitamin K prescribed to patients. Three molecules were found: fluindione, acenocoumarol, and warfarin.

The duration of treatment took into account the start of antivitamin K treatment up to the date of data collection. It was categorized into several time intervals: less than six months, one to two years, two to three years, three to five years, five to ten years, and 15 to 18 years.

The patient's behavior was assessed using a six-item questionnaire: dietary "burnout". We considered that a patient was a victim of dietary "burnout" when, after trying to comply with the dietary restriction for a given period, he broke down and consumed a large quantity of food rich in vitamin K; the weight-loss diet considered patients who spontaneously reduced their food intake after the doctor's intervention; the degree of motivation to comply with the restrictions was evaluated by the same questionnaire with questions on: not at all motivated, a little motivated, acceptable, fairly motivated or very motivated; the patients' perception of the vitamin K restriction recommended by the doctor was assessed by the questionnaire with the items: very good, fairly good and nil; the use of herbal teas was assessed by whether or not traditional medicine was used; whether or not appointments were kept was assessed by the questionnaire.

Daily intakes of energy, macronutrients, vitamin K, and alcohol were estimated by two non-consecutive 24-hour recalls. These recalls enabled us to collect all the necessary information on the foods and quantities consumed in the week prior to their arrival at the hospital. We then used the Ciqual 2017 table and Excel software to calculate each patient's daily vitamin K intake. The recommended daily intake of vitamin K1 is 60 to 100 micrograms per day. We decided that daily vitamin K1 intakes of less than 60 micrograms were considered insufficient and corresponded to compliance with dietary restrictions.

Compliance with vitamin K restriction is a quantitative variable transformed into a dichotomous categorical variable with two modes: "yes" and "no". The "yes" category corresponded to compliance with vitamin K restriction when intake was less than 60 micrograms; the "no" category corresponded to normal (60 - 100 micrograms) or high vitamin K intake. Finally, we assessed the effectiveness of the treatment, which was documented using a questionnaire. The efficacy of anti-vitamin K treatment was assessed by the Time in Therapeutic Range

(TTR) of three successive International Normalised Ratio (INR) values for patients during the study period. VKA treatment was considered effective for a TTR greater than 65%.

## 3. Data Analysis

The data were analyzed using IBM SPSS Software Statistics. 20. Means and percentages were calculated for quantitative and qualitative variables respectively. Nutrient intakes were estimated using the West African food composition table. In particular, the Ciqual 2017 table was used to estimate vitamin K intakes.

## 4. Results

### 4.1. Socio-Economic Status and Nutritional Status of Patients

At the end of this study, 50 patients were surveyed who met the inclusion criteria for this study. Ten patients who were unable to complete 3 INRs and 2 24-hour reminders during data collection were excluded from the study. The final sample size was 40 patients. The study showed that the mean age of the subjects was 58.05 years ± 13.32 years, with extremes of 32 and 83 years. The predominant age group was 60 and over. The majority of patients were male (57.50%). The sex ratio was 1.35. In addition, most of the patients surveyed were civil servants (32.50%), and the majority had secondary education (42.50%) and university education (30%). Married people accounted for 75% of those surveyed. 55% of them were obese (Table 1).

Table 1. Distribution of patients according to their socioeconomic status and nutritional status (n = 40) [CNHU-HKM, Cotonou, Benin, 2019].

| Variables | Eff. | % |
|---|---|---|
| **Age (years)** | | |
| 30 - 45 | 9 | 22.5 |
| 46 - 60 | 9 | 22.5 |
| 61 - 85 | 22 | 55.00 |
| **Gender** | | |
| Male | 23 | 57.50 |
| Female | 17 | 42.50 |
| **Professions** | | |
| Artisans | 3 | 7.50 |
| Household | 6 | 15.00 |
| Shopkeepers / Farmers | 8 | 20.00 |
| Civil servants | 13 | 32.50 |
| Retirees | 10 | 25.00 |
| **Level of education** | | |
| None | 1 | 2.50 |

| Continued | | |
|---|---|---|
| Literate | 1 | 2.50 |
| Primary | 9 | 22.50 |
| Secondary | 17 | 42.50 |
| University | 12 | 30.00 |
| **Marital status** | | |
| Married | 30 | 75.00 |
| Common-law/ divorced | 10 | 25.00 |
| **BMI*** | | |
| [<18.5 underweight] | 0 | 00.00 |
| [18.5 - 24.99 normal weight] | 2 | 5.00 |
| [25 - 29.99 overweight] | 16 | 40.00 |
| [≥30 Obesity] | 22 | 55.00 |

Body mass index.

**Table 2.** Breakdown of patients by indication for Antivitamin K treatment according to duration of treatment and type of treatment.

| Variables | Indication for treatment of patients | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Deep vein thrombosis | Embolie pulmonary | Mechanical valve prosthesis | Complete atrial fibrillation arrhythmia | Spontaneous Intracardiac contrast | CPC* in primary PAH | RM*** percutaneous route complicated by ACFA | % |
| **Duration** | | | | | | | | |
| <6 mouths | - | 2 | - | 3 | - | - | - | 12.5 |
| 6 months to 2 years | 4 | 2 | 2 | 8 | 1 | 1 | 1 | 47.5 |
| 2 à 5 years | 5 | 2 | 2 | 4 | 1 | - | - | 35.0 |
| 5 à 10 years | 1 | 1 | | - | - | - | - | 5.0 |
| **Type of treatment** | | | | | | | | |
| Fluindione | 9 | 7 | 3 | 11 | 1 | - | - | 77.5 |
| Acenocoumarol | 1 | - | 1 | 4 | - | 1 | 1 | 20.0 |
| Warfarin | - | - | - | - | - | - | 1 | 2.5 |
| % | 25.00 | 17.50 | 10.00 | 37.50 | 5.00 | 2.50 | 2.50 | 100 |

*Chronic pulmonary heart disease; **Pulmonary arterial hypertension; ***Mitral stenosis.

### 4.2. Indications for Treatment with Antivitamin K Depending on the Duration and Type of Treatment

Table 2 shows the distribution of patients according to the indication for Antivitamin K treatment, the duration of treatment, and the type of treatment. The

table shows that the most frequent indication was complete arrhythmia due to atrial fibrillation (37.50%). It can also be seen that the percentage of patients decreases with the duration of treatment (19/40 patients between 6 months and 2 years of treatment fell to 2/40 patients between 5 and 10 years of treatment). Moreover, fluindione is the type of treatment most frequently applied to patients (31/40).

### 4.3. Patient Behavior (Table 3)

**Table 3.** Patient Behavior.

| Variables | Eff. | % |
|---|---|---|
| **Burn Out** | | |
| No | 18 | 45.00 |
| Yes | 22 | 55.00 |
| **Beneficiaries of nutritional advice** | | |
| No | 34 | 85.00 |
| Yes | 6 | 15.00 |
| **Weight loss diet** | | |
| No | 30 | 75.00 |
| Yes | 10 | 25.00 |
| **Degree of motivation** | | |
| Not motivated | 13 | 32.50 |
| Quite motivated | 8 | 20.00 |
| Motivated | 19 | 47.50 |
| **Patients' perception of carers' recommendations** | | |
| None | 4 | 10.00 |
| Fairly good | 8 | 20.00 |
| Very good | 28 | 70.00 |
| **Keeping appointments** | | |
| No | 29 | 72.50 |
| Yes | 11 | 27.50 |
| **Traditional treatment (herbal tea)** | | |
| No | 16 | 40.00 |
| Yes | 24 | 60.00 |
| **Alcohol consumption** | | |
| No | 21 | 52.50 |
| Yes | 19 | 47.50 |
| **Daily vitamin K intake** | | |
| Intake less than 60 mg | 29 | 72.50 |

**Continued**

| | | |
|---|---|---|
| Intake greater than 60 mg | 11 | 27.50 |
| **Treatment efficacy (TTR value)** | | |
| No (TTR < 65%) | 28 | 70.00 |
| Yes (TTR > 65%) | 12 | 30.00 |
| **Macronutrient intake** | | |
| **Carbohydrates** | | |
| High intakes | 29 | 72.50 |
| Low inputs | 11 | 27.50 |
| **Proteins** | | |
| High intakes | 30 | 75.00 |
| Low inputs | 10 | 25.00 |
| **Lipides** | | |
| High intakes | 11 | 27.50 |
| Low inputs | 29 | 72.50 |

## 5. Discussion

The present study explored the influence of dietary vitamin K restriction on the efficacy of VKA treatment at the University Cardiology Clinic of the CNHU-HKM. The results show that the dietary behavior of patients at the University Cardiology Clinic of the CNHU-HKM influences the efficacy of treatment with vitamin K antagonists.

A high proportion (82.50%) of participants in this study reported having been advised to restrict their consumption of vitamin K-rich foods, mainly green vegetables. However, this proportion is higher than that reported in other studies of anti-coagulation patients taking VKAs. For example, in a study of Quebec patients taking Warfarin for anticoagulation, 68% reported having been advised to restrict their intake of foods rich in vitamin K, mainly green vegetables [1]. In another study of 185 American anti-clotting Warfarin patients, 32% said they should avoid spinach altogether when asked specifically about eating this vegetable [2]. A similar proportion of German patients thought they should avoid eating green vegetables and fruit during their VKA treatment [3]. Furthermore, in a study conducted in the UK, 16% of 114 patients reported having reduced their consumption of green vegetables following the initiation of Warfarin therapy [12]. All this evidence from scientific studies would have guided the carers in the CNHU cardiology department in advising patients taking VKAs to restrict vitamin K-rich foods. Of the patients who received advice about restricting vitamin K-rich foods, 14.71% were very motivated to follow the diet and 41.18% thought that the beneficial impact of the restriction on treatment was not good enough. In addition, 26.47% said they found it very difficult to follow the advice given. These data show that for these patients the restriction of vitamin K-rich

foods is very restrictive since most of the prohibited foods are part of their eating habits in Benin. The patients hardly consume any sauces, as they are forbidden vegetables in general and tomatoes and leafy vegetables in particular. Their diet is therefore reduced to starchy foods as a staple, followed by chili and onion as sauces, accompanied by a source of protein. As a result, patients are unable to enjoy all the pleasures of food, which could expose them to double stress, since they have to remember and take their VKA every day, preferably at the same time; and monitor the effectiveness of the treatment through regular blood tests, which require them to go to hospital to have their blood sample taken every time, not forgetting all the expenses associated with these requirements; and now think about what to eat to get pleasure without breaking the restrictions prescribed by the doctors.

Furthermore, restricting dietary vitamin K intake affects quality of life and was difficult to comply with, as shown by Leblanc C., in his study on the influence of dietary vitamin K intake on the efficacy of warfarin anticoagulation therapy. In this study, more than half of the participants who reported having received this recommendation indicated that they did not adhere to it, or adhered to it with difficulty, mainly because it went against their dietary habits or preferences [1].

With regard to patients' dietary behavior, 58.82% of patients suffered from "dietary burnout" after a period of compliance with dietary restrictions. Dietary burnout is the consequence of the difficulty of complying with the vitamin K dietary restriction, leading to a breakdown in compliance with the restriction. Two studies have shown that patients with low vitamin K status are also more sensitive to episodic consumption of vitamin K-rich foods, which may increase their risk of sub-therapeutic INR [13] [14].

This study reveals inappropriate dietary behavior in patients undergoing VKA treatment. Indeed, 40% of patients were fasting, 7.5% were on weight-loss diets, 16% were anorexic, 47.50% drank alcohol and 32.50% drank herbal teas. These data show that the nutritional advice given to patients prior to initiation of VKA treatment did not take into account inappropriate dietary behavior and focused almost exclusively on vitamin K restriction. This may be explained by the fact that there is no adequate nutritional management, administered to patients by a nutrition professional. In the present study, the mean vitamin K intake of patients was 28.14 ± 12.56 µg/day. This intake is lower than intakes calculated by other authors. Li *et al*. reported a median dietary vitamin K intake of 55 µg/day in 282 Americans starting warfarin therapy, as assessed by a food diary [15]. The geometric mean dietary vitamin K intake was 107 µg/day in 147 elderly Quebecers treated with warfarin, as assessed by a food frequency questionnaire [16]. The dissimilarity observed with the geometric mean obtained in this sample could result from a different proportion of patients adhering to a recommendation to restrict consumption of vitamin K-rich foods. It could also result from a difference between the dietary data collection tools used in the two studies and

this one. The majority of participants in this study (97.50%) complied with the restriction on vitamin K-rich foods. This result may be explained by the fact that patients invest many of their resources in treatment, which obliges them to comply with doctors' advice since they expect their health to improve. The mean TTR of participants in the present study was 37.39% ± 11.78%. These data were lower than those observed in American patients on VKA (55%) [17] and Quebec patients on VKA (72%) [1]. 2.5% of the participants in this study had effective treatment despite virtual compliance with restrictions on foods rich in vitamin K. Some studies have established that vitamin K can cause variations in INR, whether it is provided in the diet or in the form of a supplement: Scone E, in his case study (n = 26 in each group) comparing vitamin K consumption in stable and unstable patients reported that vitamin K consumption was much lower in unstable patients ($p < 0.001$) [18]. Schurgers *et al*., in a dose-response study of 12 healthy volunteers stabilized on acenocoumarol, demonstrated that the threshold dose of vitamin K1 when supplemented resulted in a significant reduction in INR of 150 µg/d ($p < 0.05$), with a test of the effect of different foods showing that a single meal including food rich in vitamin K did not result in a clinically significant variation in INR [19]. The possibility of vitamin K supplementation in patients with unstable oral anticoagulant therapy has been evaluated in several studies: Scone showed that the intake of 150 ug/d of vitamin K for 6 months reduced the variability of INR ($p < 0.001$) and increased the time spent in the therapeutic zone ($p < 0.01$) (Sconce, 2007); Sconce et al demonstrated in their study that unstable patients had a low vitamin K intake [18]. Rombouts *et al*. demonstrated that the intake of 100 ug/d of vitamin K for 6 months did not significantly increase the time spent in the therapeutic zone but did improve the chances of achieving maximum stability [20]. On the other hand, Franco V *et al*., in a prospective randomized crossover study (n = 12), showed an association between an increase in vitamin K consumption and a decrease in INR ($p = 0.04$) and vice versa ($p = 0.005$) [21]. Rombouts *et al*. looked at patients with sub-therapeutic INR levels and showed that these under-dosed patients had more frequent recurrences of thromboembolic events [22]. Similarly, the same authors evaluated [17] the link between the strictness of the vitamin K-free diet and the frequency of episodes of sub-therapeutic INR. They were able to show that patients with a high daily intake of vitamin K-rich foods had a significantly lower risk of having their INR underdosed than patients with a "normal" intake of dietary vitamin K. The results of these studies clearly show that low daily intakes do not enable patients to receive effective treatment. All the patients treated with anti-vitamin K had very high energy intakes. This can be explained by the fact that the vegetables that patients should be eating are certainly being replaced by other, more energy-dense foods. In addition, vegetables are rich in fiber and therefore have a high satiating power. As a result, patients who do not eat vegetables will not feel full as soon as they do, which could lead them to consume large quantities of food. Furthermore, restricted consumption of green vegetables could contribute

to increasing the risks associated with a low intake of vitamin K, particularly with regard to bone and cardiovascular health [23], in addition to reducing the intake of other nutrients, including folates and carotenoids [1]. Anticoagulant therapy with warfarin has been associated with altered folate status [12] [24] [25].

## 6. Conclusion

At the end of this study, it emerged that patients undergoing anti-vitamin K treatment at the University Cardiology Clinic generally benefited from nutritional management based on the restriction of vitamin K-rich foods. This dietary restriction alters the dietary behavior of patients, who experience dietary "burn-out" sometime after the restriction has been complied with. Despite all the difficulties experienced by patients and the constraints associated with their treatment, the majority of these patients complied with the restriction, but only 2.5% - 5% had effective VKA treatment. Restricting vitamin K-rich foods does not therefore guarantee effective treatment. What's more, this diet does not promote good nutrition for patients, exposing them instead to a high energy intake with a diet mainly geared towards carbohydrates and lipids, which can lead to weight gain: risk factors for cardiovascular disease. It would therefore be wise to review the diet of these patients in order to offer them a better lifestyle to optimize their treatment.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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