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VITAMIN K CONSUMPTION AND ANTICOAGULATION STABILITY IN OUTPATIENTS WITH ATRIAL FIBRILLATION UNDER VITAMIN K ANTAGONISTS

CONSUMO DE VITAMINA K E ESTABILIDADE DA ANTICOAGULAÇÃO EM PACIENTES AMBULATORIAIS COM FIBRILAÇÃO ATRIAL

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ABSTRACT

Objective: To evaluate vitamin K intake and anticoagulation stability in outpatients with atrial fibrillation (AF) using vitamin K antagonists (VKA) in a regional Brazilian population, in which data on this association are still scarce.

Methods: This was a prospective cohort study including 37 adult outpatients with nonvalvular AF on stable VKA therapy, followed at a university hospital in southern Brazil. Vitamin K intake was assessed at baseline, 30 days, and 60 days using 24-hour dietary recalls, and prothrombin time was measured and expressed as the international normalized ratio (INR). Anticoagulation stability was evaluated by time in therapeutic range (TTR) calculated with the Rosendaal linear interpolation method; TTR ≥60% was considered adequate. Continuous variables were compared using Student's t test or the Mann-Whitney test, and categorical variables using Pearson's chi-square or Fisher's exact test; correlations were assessed with Spearman's coefficient, and repeated measures were analyzed with generalized estimating equations. A P value <0.05 was considered significant. The study was approved by the Research Ethics Committee of the Federal University of Santa Maria (protocol no. 4.490.085, CAEE 40530620.4.0000) and all participants provided written informed consent.

Results: The mean age was 69.0±9.9 years, and 78.4% were male. Overall, mean vitamin K intake across the three evaluations was 34.4 μg/day; only 5.4% of participants met current Dietary Reference Intake recommendations. At baseline, patients with adequate TTR (≥60%) had higher vitamin K intake than those with inadequate TTR (<60%) (median 34.8 vs. 13.9 μg/day; P=0.033). However, no significant association between vitamin K intake and TTR was observed at 30 days (median 34.3 vs. 29.8 μg/day; P=0.877) or 60 days (median 16.1 vs. 24.0 μg/day; P=0.307), nor when considering the mean intake across all three visits (median 35.9 vs. 30.4 μg/day; P=0.458).

Conclusion: In this regional Brazilian cohort of AF outpatients on VKA therapy, average dietary vitamin K intake was substantially lower than recommended, and short-term vitamin K intake was not associated with

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anticoagulation stability as measured by TTR. These findings address a relevant knowledge gap by providing populationspecific data on vitamin K consumption and its relationship with anticoagulation control in Brazilian patients using VKA.

Keywords: anticoagulants; vitamin K; diet; prothrombin time; atrial fibrillation.

RESUMO

Objetivo: *Avaliar a ingestão de vitamina K e a estabilidade da anticoagulação em pacientes ambulatoriais com fibrilação atrial (FA) em uso de antagonistas da vitamina K (AVK) em uma população regional brasileira, para a qual ainda existem dados insuficientes sobre essa associação.*
Métodos: *Estudo de coorte prospectivo que incluiu 37 pacientes ambulatoriais adultos com FA em uso regular de AVK, acompanhados no ambulatório de anticoagulação de um hospital universitário no sul do Brasil. Os pacientes foram avaliados no momento basal, aos 30 e aos 60 dias. Em cada visita, a ingestão de vitamina K foi avaliada por meio de recordatório alimentar de 24 horas, e o tempo de protrombina foi mensurado e expresso pela razão normalizada internacional (INR). A estabilidade da anticoagulação foi determinada pelo tempo na faixa terapêutica (TTR), calculado pelo método de interpolação linear de Rosendaal, considerando-se TTR ≥60% como adequado. A análise estatística foi realizada utilizando o teste de Kolmogorov-Smirnov para verificação de normalidade, teste t de Student ou teste de Mann-Whitney para comparação de variáveis contínuas, teste do qui-quadrado de Pearson ou teste exato de Fisher para variáveis categóricas, coeficiente de Spearman para correlações e modelo de Equações de Estimação Generalizadas para medidas repetidas ao longo do tempo. Adotou-se nível de significância de P<0,05. O estudo foi aprovado pelo Comitê de Ética em Pesquisa da Universidade Federal de Santa Maria (protocol no. 4.490.085, CAEE 40530620.4.0000) e todos os participantes assinaram o termo de consentimento livre e esclarecido.*
Resultados: *Foram incluídos 37 pacientes, com média de idade de 69,0±9,9 anos e predominância do sexo masculino (78,4%). Com base no TTR anterior à inclusão no estudo, 22 pacientes (59,4%) apresentaram TTR inadequado (<60%), enquanto 15 (40,5%) apresentaram TTR adequado (≥60%). A ingestão média de vitamina K ao longo das três avaliações foi de 34,4 µg/dia, e 94,6% dos pacientes não atingiram os valores recomendados pelas Dietary Reference Intakes. No momento basal, pacientes com TTR adequado apresentaram maior ingestão de vitamina K do que aqueles com TTR inadequado (mediana de 34,8 vs. 13,9 µg/dia; P=0,033). Entretanto, não foi observada associação significativa entre ingestão de vitamina K e TTR aos 30 dias (mediana de 34,3 vs. 29,8 µg/dia; P=0,877), aos 60 dias (mediana de 16,1 vs. 24,0 µg/dia; P=0,307) ou ao se considerar a ingestão média ao longo dos 60 dias de seguimento (mediana de 35,9 vs. 30,4 µg/dia; P=0,458).*
Conclusão: *Nesta coorte de pacientes ambulatoriais com FA em uso de AVK no sul do Brasil, a ingestão dietética média de vitamina K foi marcadamente inferior aos valores recomendados, e a ingestão de vitamina K não se associou à estabilidade da anticoagulação mensurada pelo TTR. Ao fornecer dados específicos de uma população regional brasileira sobre o consumo de vitamina K e sua relação com o controle da anticoagulação em usuários de AVK, este estudo contribui para preencher uma lacuna relevante nas evidências atuais sobre o manejo dessa terapia.*

Palavras-chave: *anticoagulantes; vitamina K; dieta; tempo de protrombina; fibrilação atrial.*

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia worldwide and is associated with substantial morbidity and mortality, mainly due to thromboembolic events. It is estimated that 20-30% of all ischemic strokes are related to AF(Cintra *et al.*, 2025). Until recently, oral anticoagulation with vitamin K antagonists (VKAs), particularly warfarin, has been the cornerstone of stroke prevention in patients with AF.

Vitamin K is a fat-soluble vitamin that plays a central role in the γ-carboxylation and activation of several proteins, including the vitamin K-dependent coagulation factors II, VII, IX, and X, as well as protein C and protein S. It is also involved in bone metabolism through osteocalcin and in the inhibition of vascular calcification through matrix Gla protein (MGP) (DiNicolantonio *et al.*, 2015). Two main forms of vitamin K are recognized: phylloquinone (vitamin K1), predominantly present in green leafy vegetables and in vegetable oils such as olive and soybean oil, and menaquinones (vitamin K2), found in smaller amounts in foods such as chicken, butter, egg yolks, cheese, and fermented soy products(DiNicolantonio *et al.*, 2015).

All VKAs act by inhibiting hepatic vitamin K epoxide reductase, thereby reducing the synthesis of vitamin K-dependent coagulation factors (Van Gelder *et al.*, 2024). Although effective, VKA therapy is challenging because of its narrow therapeutic index and marked intra- and inter-individual variability in dose-response. Consequently, treatment requires frequent monitoring of prothrombin time and international normalized ratio (INR) to maintain anticoagulation within the recommended therapeutic range (Harter; Levine; Henderson, 2015). In routine clinical practice, a considerable proportion of patients treated with VKAs fail to achieve adequate anticoagulation control over time (Cintra *et al.*, 2025; Van Gelder *et al.*, 2024). Even in contemporary randomized clinical trials, the time in therapeutic range (TTR) typically remains around 60-70% (Amin *et al.*, 2014), and in observational, uncontrolled settings these figures are often lower (Pokorney *et al.*, 2015).

Dietary vitamin K intake and its variability have been proposed as important determinants of anticoagulation stability in patients taking VKAs, but available evidence is inconsistent. A systematic review of randomized and observational studies did not demonstrate a clear benefit of recommending dietary restriction of vitamin K at VKA initiation, questioning the strategy of broadly advising vitamin K-poor diets (Violi *et al.*, 2016). Conversely, a randomized clinical trial suggested that modulation of vitamin K intake may improve anticoagulation control in patients with unstable INR, and that daily vitamin K supplementation could increase TTR in VKA users (Sconce *et al.*, 2007). Thus, current guidelines and clinical practice are not uniform regarding dietary counseling for vitamin K intake in these patients.

Moreover, vitamin K consumption patterns appear to vary substantially across different regions and populations (Booth; Rajabi, 2008; McKeown *et al.*, 2002). In Brazil, particularly in the

southern region, previous data suggest specific dietary habits that may be associated with relatively low intake of vitamin K-rich foods (Zuchinali *et al.*, 2012). However, there is a lack of robust, population-specific data on habitual vitamin K intake and its relationship with anticoagulation stability among Brazilian outpatients using VKAs. This knowledge gap limits the development of tailored dietary recommendations for this population and may contribute to suboptimal anticoagulation control.

Therefore, the objective of the present study was to evaluate vitamin K intake and anticoagulation stability, as measured by TTR, in a cohort of outpatients with AF under regular use of VKAs in southern Brazil, addressing the scarcity of regional data on this clinically relevant association.

METHODS

STUDY DESIGN

This was a prospective cohort study conducted between January and December 2021 at the anticoagulation outpatient clinic of the Hospital Universitário de Santa Maria (HUSM), a primary-care university hospital in southern Brazil that serves as a referral center for approximately 550,000 inhabitants. Patients were evaluated at three outpatient visits: baseline, first reassessment (approximately 30 days after baseline), and second reassessment (approximately 60 days after baseline).

SAMPLE

A sequential convenience sample was used. All patients with a diagnosis of atrial fibrillation (AF) receiving follow-up at the anticoagulation outpatient clinic during the study period were screened for eligibility. Of 90 potentially eligible patients with AF, 53 were excluded (6 due to moderate or severe mitral and/or aortic valve disease and 47 due to irregular outpatient follow-up, mainly related to restrictions during the coronavirus disease 2019 [COVID19] pandemic). The final study sample comprised 37 outpatients with nonvalvular AF using vitamin K antagonists (VKAs).

INCLUSION CRITERIA

Patients were eligible if they met all of the following criteria:

a) Age ≥18 years;

b) Diagnosis of AF with indication for longterm oral anticoagulation for thromboembolic prevention;

c) Presence of at least one risk factor for thromboembolic events, defined as CHA_2DS_2VASc score ≥1;

d) Exclusive use of VKA (warfarin) for at least 6 months prior to enrollment;

e) Adequate adherence to anticoagulant therapy, characterized by omission of <10% of the total weekly VKA dose in the 3 months preceding inclusion;

f) Regular clinical followup at the anticoagulation clinic, allowing completion of the three planned study visits.

EXCLUSION CRITERIA

Patients were excluded if they met any of the following criteria:

a) Moderate or severe rheumatic or degenerative mitral and/or aortic valve disease or other indications for anticoagulation unrelated to AF (e.g., mechanical prosthetic valves, recent venous thromboembolism);

b) Dependence on nursing care for basic activities of daily living;

c) Documented poor adherence to VKA therapy, defined as omission of ≥10% of the total weekly dose in the last 3 months, or irregular attendance to scheduled outpatient visits;

d) Cognitive impairment or any condition that precluded reliable completion of the dietary assessment;

e) Use of direct oral anticoagulants or concomitant participation in another interventional study that could interfere with anticoagulation control.

CLINICAL AND LABORATORY ASSESSMENT

At baseline, a structured questionnaire was administered to collect sociodemographic characteristics, medical history, previous cardiovascular events (including thromboembolism and major bleeding), lifestyle factors (alcohol consumption and smoking), and concomitant medications (antihypertensives, nonsteroidal antiinflammatory drugs, acetylsalicylic acid, other antiplatelet agents, amiodarone, and anticonvulsants). Laboratory tests (aspartate aminotransferase, alanine aminotransferase, bilirubins, alkaline phosphatase, urea, and creatinine) were obtained according to the specific protocol of the anticoagulation outpatient clinic and analyzed in the same laboratory.

Anthropometric evaluation was performed at study entry. Body weight was measured with participants wearing light clothing and no shoes, using a calibrated electronic digital scale (Líder®, model P150C). Height was measured with a calibrated stadiometer. Body mass index (BMI) was calculated as weight (kg)/height² (m^2) and classified according to World Health Organization criteria (Rubino *et al.*, 2025).

ASSESSMENT OF ANTICOAGULATION STABILITY

At each of the three study visits (baseline, 30 days, and 60 days), prothrombin time (PT) was measured and expressed as the international normalized ratio (INR). Anticoagulation stability prior to study inclusion was assessed for each patient by calculating the time in therapeutic range (TTR) using the Rosendaal linear interpolation method (Rosendaal *et al*., 1993). For this analysis, the therapeutic INR range was defined as 2.0-3.0. Patients with TTR ≥60% were considered to have adequate (ideal) anticoagulation control, whereas those with TTR <60% were classified as having inadequate anticoagulation control (Apostolakis *et al*., 2013). The following variables were also recorded: VKA type and total weekly dose, concomitant medications, thromboembolic risk according to the CHA_2DS_2VASc score (Barnes; Lip, 2024), bleeding risk according to the HASBLED score (Gao *et al*., 2021), and potential factors associated with anticoagulation instability, as described in previous studies (Apostolakis *et al*., 2013).

ASSESSMENT OF VITAMIN K INTAKE

Dietary vitamin K intake was assessed at all three visits using a 24hour dietary recall (24hDR) (Baranowski, 2013; Fisberg; Marchioni; Colucci, 2009). At each assessment, participants were asked to report all foods and beverages consumed in the 24 hours preceding the interview, including portion sizes and preparation methods. Household measures were converted into grams or milliliters using standardized Brazilian tables of portion sizes and household measures. For foods not listed on the table, information from food labels was used. The 24hDR method has been widely used and validated for estimating dietary intake in Brazilian adults, including micronutrients such as vitamin K, showing acceptable validity and reproducibility for population-level assessments (Faria, 2013; Presse *et al*., 2009; Souza; Rodrigues; Penteado, 2012).

The vitamin K content of foods was obtained primarily from the United States Department of Agriculture (USDA) National Nutrient Database, complemented by national tables from Klack and Carvalho and Faria, which provide additional estimates of vitamin K content in foods commonly consumed in Brazil (Faria, 2013; Klack; Carvalho, 2006) Vitamin K intake was considered adequate when it reached at least 90 μg/day for women and 120 μg/day for men, according to the Dietary Reference Intakes of the National Academy of Sciences.(Booth & Rajabi, 2008; Souza *et al*., 2012).

ETHICAL CONSIDERATIONS

The study was conducted in accordance with the principles of the Declaration of Helsinki and Brazilian National Health Council Resolution No. 466/2012. The protocol was approved by the

Research Ethics Committee of the Universidade Federal de Santa Maria (UFSM) (approval 4.490.085, CAEE 40530620.4.0000). All participants provided written informed consent prior to inclusion.

STATISTICAL ANALYSIS

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software, version 21.0 (IBM SPSS Statistics for Windows, Armonk, NY, USA). Quantitative variables were tested for normality using the Kolmogorov-Smirnov (K-S) test. Although the Shapiro-Wilk test is generally more powerful for very small samples, we opted for the K-S test because our sample size (n=37) lies in an intermediate range in which the performance of both tests is similar, and the K-S test is well established for samples above 30 observations. In addition, the K-S test allows a consistent approach across variables with slightly different effective sample sizes due to missing values, and its implementation is standard in the software used. In the presence of discrepant results between visual inspection of histograms and the K-S test, graphical assessment and clinical plausibility were also considered.

Variables with normal distribution were expressed as mean ± standard deviation, whereas nonnormally distributed variables were expressed as median and interquartile range. Categorical variables were described as absolute and relative frequencies. Comparisons between two independent groups were performed using Student's t test for normally distributed variables and the Mann-Whitney test for nonnormally distributed variables. Associations between categorical variables were evaluated using Pearson's chisquare test or Fisher's exact test, as appropriate. Correlations between quantitative variables were assessed using Spearman's rank correlation coefficient. To compare repeated measures over time between TTR groups, generalized estimating equations (GEE) models were applied with a post hoc minimum significant difference (MSD) procedure when necessary (Duan *et al.*, 2020). A twosided P value <0.05 was considered statistically significant.

RESULTS

Of a total of 236 patients under follow-up in our outpatient clinic, 90 had a diagnosis of AF and were considered potential participants in the study. Of these, six were excluded from the analysis due to the presence of moderate to severe mitral and/or aortic valve disease. Another 47 patients diagnosed with AF were excluded due to irregular follow-up, mainly associated with the coronavirus disease (COVID-19) pandemic. In the end, 37 patients were included in the study (Figure 1). The characteristics and variables associated with anticoagulation control are reported in Table 1.

Figure 1 - Flowchart of evaluation of patients on anticoagulation with vitamin K antagonists at the Anticoagulation Outpatient Clinic.

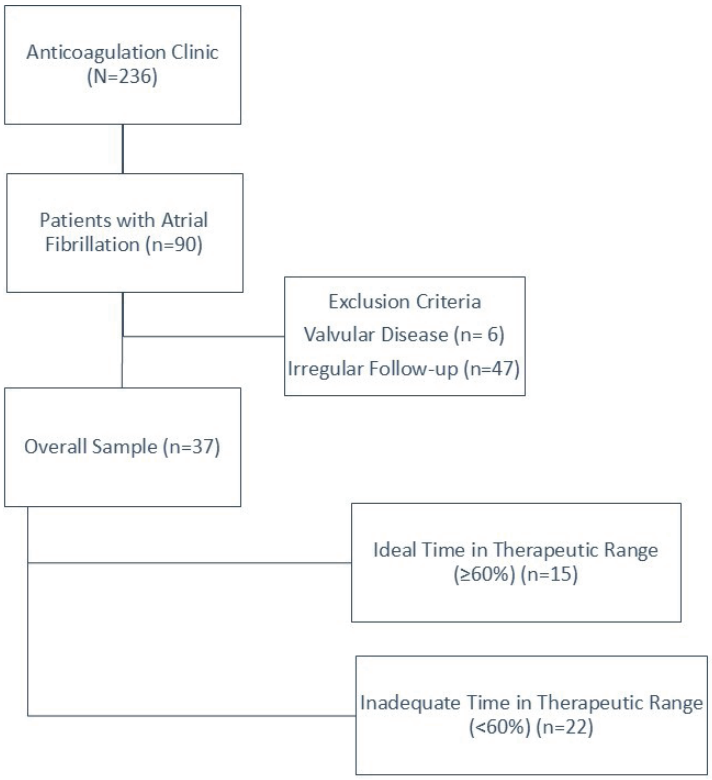


Table 1. Characteristics of patients with atrial fibrillation and indication for anticoagulation with VKA followed at the Anticoagulation Outpatient Clinics according to the Time in Therapeutic Range (TTR) at baseline (n=37).

Variables	Total Sample n(%), (n=37)	TTR		P value
		Ideal (≥60%) n(%), (n = 15)	Inadequate (<60%) n(%), (n=22)	
Sociodemographic				
Age in years (mean±SD)	69.0±9.9	69.7±7.8	68..4±11.3	0.696a
Gender				0.690b
Male	29 (78.4)	11 (73.3)	18 (81.8)	
Female	8 (21.6)	4 (26.7)	4 (18.2)	
Anthropometric				
Weight in kg (average±SD)	85.2±16.7	86.2±20.8	84.6±13.8	0.784a
BMI in kg/m^2 (mean±SD)	29.7±5.8	30.3±8.0	29.3±3.9	0.607a
Lifestyle				
Alcohol use (≥8 drinks/week)				0.999b
No	36 (97.3)	15 (100.0)	21 (95.5)	
Yes	1 (2.7)	0 (0.0)	1 (4.5)	
Smoking				0.999b
No	32 (86.5)	13 (86.7)	19 (86.4)	
Yes	5 (13.5)	2 (13.3)	3 (13.6)	
Clinical				
CHA_2DS_2-VASc (average±DP)	4.1±1.4	4.1±1.5	4.2±1.4	0.815a
HAS-BLEED (median and IR)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-1.3)	0.605c
INR	2.3±0.6	2.3±0.5	2.3±0.6	0.934a

INR - Ranking				0.361d
Adequate*	23 (62.2)	8 (53.3)	15 (68.2)	
Inadequate**	14 (37.8)	7 (46.7)	7 (31.80)	
Urea (mg/dL) (median and IR)	39.9 (33.5-49.5)	39.0 (32.0-61.0)	40.5 (33.8-48.0)	0.676c
Creatinine mg/dL) (mean±SD)	1.2±0.4	1.2±0.4	1.3±0.4	0.488a
Medication use				
Anti-hypertensive				0.999b
No	1 (2.7)	0 (0.0)	1 (4.5)	
Yes	36 (97.3)	15 (100.0)	21 (95.5)	
Non-steroidal anti-inflammatory				£
No	37 (100.0)	15 (100.0)	22 (100.0)	
Yes	0 (0.0)	0 (0.0)	0 (0.0)	
Acetylsalicylic acid				0.633b
No	33 (89.2)	14 (93.3)	19 (86.4)	
Yes	4 (10.8)	1 (6.7)	3 (13.6)	
Antiplatelets				0.999b
No	35 (94.6)	14 (93.3)	21 (95.5)	
Yes	2 (5.4)	1 (6.7)	1 (4.5)	
Antiarrhythmic				0.063b
No	31 (97.3)	15 (100.0)	16 (72.7)	
Yes	1 (2.7)	0 (0.0)	6 (27.3)	
Anticonvulsant				0.999b
No	36 (97.3)	15 (100.0)	21 (95.5)	
Yes	1 (2.7)	0 (0.0)	1 (4.5)	
Warfarin doses missed (n) (mean±SD)	0.1±0.4	0.1±0.5	0.1±0.2	0.478a
Suspension of anticoagulation				£
No	37 (100.0)	15 (100.0)	22 (100.0)	
Yes	0 (0.0)	0 (0.0)	0 (0.0)	
Bleeding				£
No	37 (100.0)	15 (100.0)	22 (100.0)	
Yes	0 (0.0)	0 (0.0)	0 (0.0)	
Years of anticoagulation (mean±SD)	4.5±1.7	5.1±0.6	4.0±2.1	0.023a

p-value - a: *Student's* T-test; b: *Fischer's* Exact Test; c: *Mann-Whitney* test; d: *Pearson's* chi-square test. TTR - Time in Therapeutic Range. Ideal TTR: >60%; Inadequate TTR: ≤60%. SD - Standard deviation; IR - Interquartile range; BMI - Body mass index; CHA_2DS_2-VASc - Risk score for thromboembolic event; HAS-BLEED - Bleeding risk score. £ - Data does not allow analysis. *Adequate INR values (2-3); **Inadequate INR values (<2 or >3)

The mean age was 69 ± 9.9 years, with a male predominance (78.4%). The mean weight of the sample was 85.2 ± 16.7 kg and the mean BMI was 29.7 ± 5.8 kg/m^2. Of the total number of patients analyzed, 36 (97.3%) reported low to moderate alcohol consumption (i.e., 8 drinks per week or less). Thirty-two patients (86.5%) were not active smokers. Patients in general were at high risk of thrombo-embolic events, showing a mean CHA_2DS_2-VASC score of 4.1 ± 1.4. The median HAS-BLEED score was 1.0 (1.0 - 2.0), which corresponds to a low risk for bleeding. The mean INR of the sample was 2.3 ± 0.6, with values within the therapeutic target observed in 23 patients (62.2%). The mean time on anticoagulant therapy in the sample was 4.5 ± 1.7 years.

When the sample was categorized by the TTR, 22 (59.4%) showed inadequate TTR (i.e., < 60%), while 15 (40.5%) had ideal TTR. No significant difference was found between sociodemographic, anthropometric, lifestyle, clinical, or drug variables between the TTR groups, except for the mean time on anticoagulant therapy, which was significantly longer in patients with ideal TTR when compared with patients with inadequate TTR (5.1 ± 0.6 vs 4.0 ± 2.1 years; p=0.023) (Table 1).

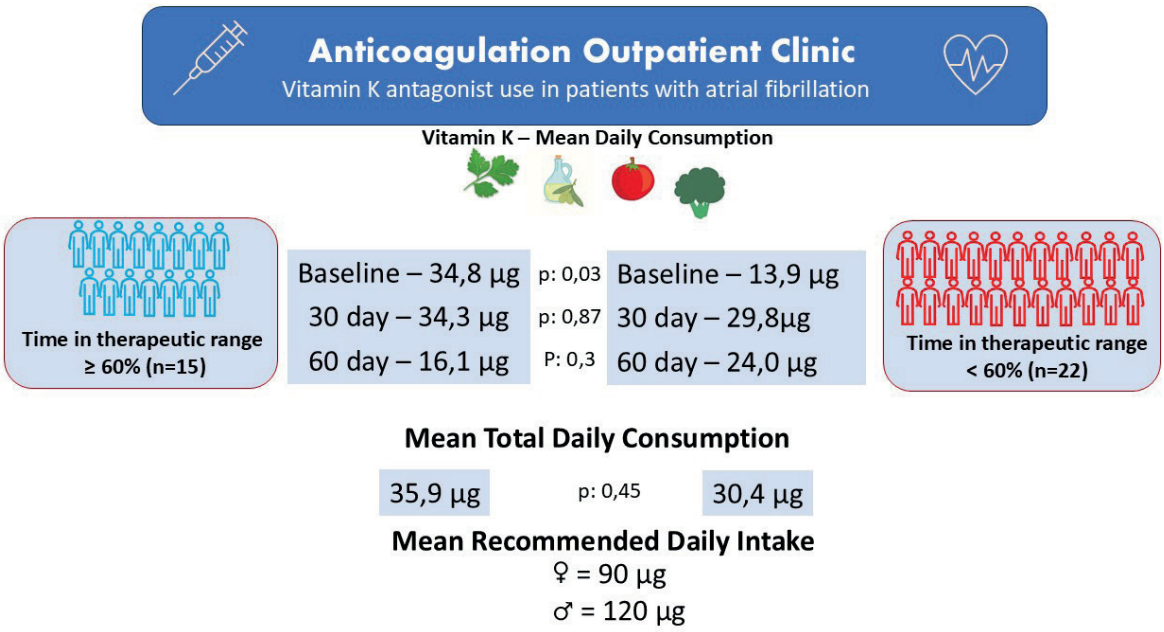
Regarding vitamin K intake, it was found that most patients (94.6%) had an intake lower than recommended by the *Dietary Reference Intake* - DRIs (L. Booth, 2012). Table 2 shows the vitamin K intake according to the FR24h observed at each of the follow-up visits, as well as the average food intake during the two months of follow-up, according to TTR observed prior to the beginning of the study. In patients with TTR ≥60%, the estimated intake of vitamin K at baseline was significantly higher compared to those with TTR <60% (median 34.8 vs. 13.9 µg, p= 0.033). However, vitamin K intake was not associated with TTR at the 30-day (median 34.3 vs. 29.80 µg, p= 0.877) or 60-day (median 16.1 vs. 24.0 µg; p= 0.307) visit. Furthermore, when the mean intake of vitamin K in the two months of follow-up of the study was evaluated, no significant difference was found between the ideal and inadequate TTR groups (median 35.9 µg vs. 30.4 µg, p= 0.458) (Table 2). The main findings are described in the Central Illustration Figure (Central Illustration).

Table 2. Relationship with time in therapeutic range and vitamin K consumption at baseline. after 30 days. after 60 days. and the average of all three moments in patients with atrial fibrillation under vitamin K antagonist use followed at the Anticoagulation Outpatient Clinic (n=37).

Vitamin K Consumption (µg)	TTR (Median and IR)		p-value
	Ideal (n = 15)	Inadequate (n = 22)	
Baseline	34.8 (14.7-80.1)	13.9 (7.5-32.2)	0.033
First Assessment (30-day follow-up)	34.3 (20.4-45.9)	29.8 (16.0-84.1)	0.877
Second Assessment (60-day follow-up)	16.1 (11.9-41.6)	24.0 (15.2-57.3)	0.307
Mean of all three assessments	35.9 (20.8-53.2)	30.4 (18.1-49.9)	0.458

TTR - Time in Therapeutic Range; IR - Interquartile range; Ideal - TTR ≥ 60%; Inadequate - TTR < 60%. P < 0.05 considered statistically significant; Generalized estimating equations (GEE) models with a post hoc minimum significant difference (MSD) procedure when(Duan *et al.*, 2020).

Central Illustration - Vitamin K consumption in patients with atrial fibrillation and its association with the time in therapeutic range.



DISCUSSION

In this cohort of outpatients with atrial fibrillation (AF) using vitamin K antagonists (VKAs) in southern Brazil, we observed a markedly low mean vitamin K intake (34.4 µg/day), with only 5.4% of participants achieving the Dietary Reference Intake (DRI) recommended for adults (90 µg/day for women and 120 µg/day for men) (L. Booth, 2012). In contrast, we did not find a statistically significant association between vitamin K intake and anticoagulation stability as measured by time in therapeutic range (TTR) over the 60day followup. Although these data were collected in 2021, during the coronavirus disease 2019 (COVID19) pandemic, they remain clinically relevant. The pandemic context contributed to slower recruitment, interruptions in routine outpatient care, and delays in data processing and manuscript preparation; however, the underlying questions regarding dietary vitamin K, VKA management, and real world anticoagulation stability in our regional population are unchanged and still lack robust local evidence.

Our findings add to a heterogeneous body of literature on dietary vitamin K and VKA control. As described in previous studies, vitamin K intake varies widely across regions and populations (Booth; Rajabi, 2008; McKeown *et al.*, 2002), and low intake has been associated with adverse skeletal outcomes, including reduced bone mass and increased fracture risk (Kozioł-Kozakowska; Maresz, 2022; Souza; Rodrigues; Penteado, 2012). The low intake pattern observed in our sample, therefore, aligns with reports of suboptimal vitamin K consumption in other groups and provides specific data for a Brazilian regional cohort of patients on longterm VKA therapy. Local dietary habits in southern

Brazil, including relatively low consumption of green leafy vegetables and other vitamin Krich foods (Zuchinali *et al*., 2012), and longstanding recommendations in some anticoagulation clinics to restrict high-vitamin K foods in an attempt to "stabilize" the international normalized ratio (INR) (Minighin; Bragança; Anastácio, 2020; Violi *et al*., 2016), may both contribute to this reduced intake.

With respect to the relationship between vitamin K intake and anticoagulation stability, our results should be interpreted with caution. At baseline, patients with adequate TTR (≥60%) had significantly higher vitamin K intake compared with those with inadequate TTR (<60%) (median 34.8 vs. 13.9 μg; p=0.033). However, this crosssectional difference at a single time point was not sustained in the subsequent evaluations at 30 and 60 days, nor when the mean intake across all three visits was considered: there were no significant differences between TTR groups at 30 days (median 34.3 vs. 29.8 μg; p=0.877), 60 days (median 16.1 vs. 24.0 μg; p=0.307), or in the average twomonth intake (median 35.9 vs. 30.4 μg; p=0.458). Furthermore, when vitamin K intake was analyzed as a continuous variable, no significant correlations were observed between intake and TTR (or INR) at any time point. Taken together, these findings suggest that, within the range of low intake observed in our sample, short-term fluctuations in vitamin K consumption were not a major determinant of anticoagulation stability.

These results are consistent with several previous studies that also failed to demonstrate a clear association between habitual vitamin K intake and TTR in VKA users. A case-control study including 300 outpatients on VKAs found no meaningful difference in vitamin K intake between individuals with very high INR and those within the therapeutic range (Penning-van Beest *et al*., 2002). Likewise, a prospective cohort of 553 patients with nonvalvular AF using VKAs reported that adherence to a Mediterranean diet rich in vitamin K-containing foods did not negatively affect TTR (Pignatelli *et al*., 2015), and a meta-analysis reached similar conclusions (Kramps; Flanagan; Smaldone, 2013). On the other hand, randomized studies have suggested that increasing and stabilizing vitamin K intake-either by dietary counseling or supplementation-may improve anticoagulation control in patients with unstable INR (Kim *et al*., 2010; Rombouts; Rosendaal; Van Der Meer, 2010; Sconce *et al*., 2007). Our findings do not refute the potential benefit of vitamin K supplementation in selected patients with marked INR variability, but rather indicate that, in a real world outpatient setting with predominantly low vitamin K intake, simple observation of habitual intake over a short timeframe may not be sufficient to capture its influence on TTR.

It is important to emphasize that the apparent "absence of association" in our study does not necessarily imply the absence of any causal relationship. First, our sample size was modest (n=37), which limits statistical power and increases the risk of type II error, particularly for detecting small to moderate associations. Second, assessment of vitamin K intake relied on three 24hour recalls per patient, which, although widely used in nutritional epidemiology, may not fully capture usual individual intake or longterm variability, especially for micronutrients with high daytoday fluctuation.

Third, the overall level of vitamin K intake in our sample was uniformly low, with limited contrast between individuals; this restricted range may attenuate observable associations with TTR. Finally, anticoagulation stability is multifactorial and influenced by genetics, comorbidities, drug-drug interactions, adherence, and other dietary components, which were not fully controlled for in our analyses.

In our sample, the use of antiarrhythmic drugs, particularly amiodarone, was numerically more frequent among patients with inadequate anticoagulation control (TTR <60%), with a p value that approached statistical significance (p=0.063). Given the well known pharmacokinetic interaction between amiodarone and warfarin, this imbalance may represent a potential source of residual confounding and could have contributed to greater INR variability in the lower TTR group, even though the difference did not reach conventional statistical significance. In addition, patients with adequate TTR had been on oral anticoagulation for a longer period than those with inadequate TTR (5.1 vs. 4.0 years; p=0.023). This finding is clinically plausible, as longer exposure to VKA therapy with specialized follow-up provides more time for dose adjustment, patient education, and stabilization of INR values, and therefore may act as an independent predictor of better anticoagulation control (Vinereanu *et al*., 2017). Together, these observations suggest that both antiarrhythmic drug use and duration of anticoagulant therapy are relevant determinants of TTR in our cohort and should be considered when interpreting the lack of association between vitamin K intake and anticoagulation stability."

Our study has additional limitations that warrant consideration. It was conducted at a single center in southern Brazil, and the results may not be generalizable to other regions or to patients managed in different healthcare settings. Recruitment and followup occurred during the COVID19 pandemic, which affected outpatient attendance and may have influenced both diet and adherence to treatment. The observational design precludes causal inference, and residual confounding cannot be excluded. Despite these limitations, our work has several strengths: it provides detailed, region specific data on vitamin K intake in a real world cohort of AF patients on VKAs; uses the standardized Rosendaal method (Rosendaal *et al*., 1993)(Rosendaal *et al*., 1993) to estimate TTR; and evaluates vitamin K intake and anticoagulation parameters at multiple time points, offering a dynamic view of this relationship.

In this context, our data support a nuanced interpretation: while reinforcing concerns about insufficient vitamin K intake in this population, they do not show a clear short-term association between low vitamin K intake and anticoagulation instability. This suggests that, rather than broadly restricting vitamin K-rich foods, clinical strategies might better focus on maintaining a consistent intake pattern and addressing the multiple other determinants of VKA control.

CONCLUSION

In this cohort of outpatients with atrial fibrillation using vitamin K antagonists in southern Brazil, average dietary vitamin K intake was substantially below internationally recommended levels, and only a small proportion of patients met the Dietary Reference Intake. Within this context of uniformly low intake, we did not observe a robust association between vitamin K consumption and anticoagulation stability, as measured by time in therapeutic range, over a twomonth followup.

These findings contribute populationspecific data on vitamin K intake among Brazilian patients on longterm VKA therapy and suggest that severely restricting vitamin K-rich foods may not be necessary to maintain anticoagulation stability. However, given the small sample size, the short followup, and the limited range of intake in our cohort, our results should not be interpreted as definitive evidence that vitamin K intake is irrelevant for VKA control. Larger, multicenter studies with more detailed and prolonged dietary assessment are needed to clarify the impact of both the amount and consistency of vitamin K intake on anticoagulation stability and to inform more tailored dietary recommendations for this population.

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