RESEARCH
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Avoidance of Vitamin K–Rich Foods Is Common among Warfarin Users and Translates into Lower Usual Vitamin K Intakes

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ABSTRACT

Background Warfarin users should aim for stable daily vitamin K intakes. However, some studies report that patients are often advised to avoid eating green vegetables. Whether this advice impacts vitamin K intakes is unknown.

Objective Our aim was to describe the nature and sources of vitamin K–related dietary recommendations that patients received at the initiation of warfarin therapy, assess their adherence to these recommendations, and examine whether usual vitamin K intakes vary according to these recommendations.

Design We conducted a retrospective cohort study with patients enrolled in the Québec Warfarin Cohort Study. Patients were asked to report dietary recommendations they had received at warfarin initiation and their adherence to these recommendations. Usual vitamin K intakes were assessed using a validated semi-quantitative food frequency questionnaire.

Participants/setting Three hundred seventeen patients aged 36 to 97 years who initiated warfarin between 2011 and 2012 and were treated for 12 months or longer with a target international normalized ratio range of 2.0 to 3.0 or 2.5 to 3.5.

Statistical analyses performed Patients were classified according to vitamin K–related recommendations reported: limit or avoid vitamin K–rich foods; aim for stable consumption of vitamin K–rich foods; or no vitamin K–related advice. A one-way analysis of covariance was used to compare mean usual vitamin K intakes between patients after adjustment for covariates.

Results Most patients (68%) reported being advised to limit or avoid vitamin K–rich foods, particularly green vegetables, 10% reported being advised to aim for stable consumption of vitamin K–rich foods, and 22% did not recall receiving any vitamin K–related recommendation. Mean usual vitamin K intakes of patients adhering to the recommendation to limit or avoid vitamin K–rich foods was 35% to 46% lower than those of other patients ($P<0.001$), a difference resulting almost entirely (82%) from a lower consumption of green vegetables.

Conclusions In contrast with current dietary recommendation, most warfarin users reported avoiding vitamin K–rich foods, which translated into lower usual vitamin K intakes.
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WARFARIN IS AN ORAL ANTICOAGULANT THAT is widely prescribed for the prevention of thromboembolic conditions, such as atrial fibrillation and deep vein thrombosis.[1,2] The safety and efficacy of warfarin therapy are highly dependent on its stability within a narrow therapeutic range; instability is associated with life-threatening complications.[3] Daily variation in vitamin K intake is a well-established factor contributing to warfarin therapy instability, as the reduced form of vitamin K (hydroquinone) is involved in the bioactivation of seven clotting factors.[4-11]

Dietary recommendations for vitamin K in healthy individuals consist of adequate intakes of 90 μg/day and 120 μg/day for women and men aged 19 years and older, respectively.[12] In the case of warfarin treatment, multiple organizations, such as the National Institutes of Health, the American Heart Association, and the Government of Canada, recommend that these patients aim for stable daily vitamin K intakes.[2,13-16] However, some reports have mentioned that warfarin-treated patients are often instructed to limit or avoid vitamin K–rich foods, notably green vegetables.[17,18] One study from the United States showed that only about 30% of the 122 health care professionals surveyed reported to never advise patients to avoid vitamin K–rich foods, although all reported instructing patients to aim for stable vitamin K intakes.[19] Yet, no published studies have

examined whether the recommendation to limit the consumption of vitamin K–rich foods actually results in lower vitamin K intakes. Furthermore, recent observational[20-24] and intervention studies[25-30] have provided evidence of decreased stability of warfarin therapy in patients with low vitamin K intakes. Therefore, advising patients to limit or avoid vitamin K–rich foods goes against current scientific evidence.

To gain insight in this issue, 317 warfarin users who started warfarin therapy in 2011 to 2012 were interviewed with the specific objectives to describe the nature and sources of vitamin K–related recommendations that they recalled receiving at the initiation of their warfarin treatment; investigate their adherence to these recommendations; and examine whether their usual vitamin K intakes, including usual vitamin K intakes from green vegetables, varied according to the vitamin K–related advice reported.

METHODS

Study Design and Setting

The Québec Warfarin Cohort Study is an ongoing prospective and multicenter cohort study investigating the genetic and clinical predictors of the effectiveness and safety of warfarin therapy. From May 2010 to July 2013, 1,069 adult incident warfarin users from 17 hospital sites across the province of Québec, Canada, were enrolled. Patients' primary indication for long-term warfarin treatment was atrial fibrillation/flutter, mechanical valve replacement, or mitral stenosis. Exclusion criteria were a history of clinically important bleedings or a recent gastrointestinal bleeding or hemorrhagic stroke (<3 months), coagulation factors deficiency, chronic thrombocytopenia, hematologic malignancy, cirrhosis, chronic hepatitis, jaundice, or cognitive impairment (unreliability). During the first year, five structured telephone interviews were conducted by trained research nurses and assistants at baseline and at 3, 6, 9, and 12 months after warfarin initiation. Data on sociodemographic factors (eg, age, sex, and education level), family ancestry (including parents' and grandparents' date and place of birth), lifestyle (eg, smoking status, physical activity level, caffeine consumption), medical history and comorbidities (eg, diabetes, hypertension), and warfarin treatment (eg, primary indication, target international normalized ratio [INR], and planned duration) were collected. Information was self-reported and validated in medical charts if needed.

The present retrospective cohort study included a subsample of the Québec Warfarin Cohort Study participants who completed the first year of follow-up and underwent continuous warfarin therapy for 12 months or longer with a target INR range of 2.0 to 3.0 or 2.5 to 3.5. Ethical approval was obtained from the Montreal Heart Institute Ethics Committee. A total of 403 patients were invited to complete an additional telephone diet interview conducted by a registered dietitian, of which 58 (14%) declined the invitation, 17 (4%) were unable to participate (eg, deterioration of general health status, deafness), 7 (2%) were unreachable, and 4 (1%) were deceased. Written informed consent was provided by 317 patients. Data collection was performed from February 2013 to January 2014.

Dietary Assessment

During the telephone diet interview, patients were invited, through an open question, to describe dietary recommendations that they recalled receiving at the initiation of warfarin therapy, as well as the sources of these recommendations (eg, nurses and dietitians). Vitamin K–related recommendations were classified as follows: limit or avoid vitamin K–rich foods; aim for stable consumption of vitamin K–rich foods; no vitamin K–related advice. Other dietary recommendations reported by patients were also noted. Patients were also asked whether they adhered (yes/no) to the vitamin K–related recommendation received and whether they found it easy or difficult to adhere to it. Finally, the usual daily dietary vitamin K intake of the previous year was assessed for each patient using a 50-item semi-quantitative food frequency questionnaire (FFQ), previously validated for ranking individuals according to their usual vitamin K intake.[31] Food items were categorized as "green vegetables" and "other vitamin K food sources" (eg, fruits, vegetable oils). Vitamin K content of foods was based on the Canadian Nutrient File (Health Canada, version 2007b) and the US Department of Agriculture's National Nutrient Database for Standard Reference (US Department of Agriculture, Agricultural Research Service, Nutrient Data Laboratory, Release 22, 2009).

Covariates

Age in years was determined at the FFQ interview date. Other patients' characteristics were obtained from the Québec Warfarin Cohort Study interviews. Indication for warfarin, target INR range, sex, education level (university or college, high school, or no degree), and reported weight (kg) and height (m) were obtained at recruitment. Body mass index (BMI) was calculated as kg/m^2. History of hypertension, diabetes, dyslipidemia, angina, myocardial infarction, and stroke was categorized as present or absent. Annual mean alcohol intake (nondrinkers, <7 drinks/wk, ≥7 drinks/wk), smoking status (smokers, nonsmokers), and physical activity level (inactive/lightly active, moderately active, intensely/very intensely active) were also considered. Physical activity was assessed using the Stanford Brief Activity Survey.[32]

Statistical Analyses

Descriptive statistics were used to compare patients' characteristics according to categories of vitamin K–related recommendations using one-way analysis of variance for continuous variables and Pearson χ^2 test for categorical variables. Vitamin K intake data presented skewed distributions. The Kruskal-Wallis test, followed by pairwise comparisons with Mann-Whitney test, were used to compare total usual vitamin K intakes and usual vitamin K intakes from food categories ("green vegetables" and "other vitamin K food sources"), expressed as continuous variables, by categories of vitamin K–related recommendations. A one-way analysis of covariance (ANCOVA) was used to compare mean usual vitamin K intakes (log_{10}-transformed) between categories of vitamin K–related recommendations in the presence of covariates. Preselection of the covariates to be included in the ANCOVA was performed by identifying variables significantly associated with log_{10}-transformed usual vitamin K intake