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Lifestyle and diet as risk factors for overanticoagulation

Fernie J.A. Penning-van Beest[a], Johanna M. Geleijnse[b], Erik van Meegen[c], Cees Vermeer[d], Frits R. Rosendaal[e], Bruno H.C. Stricker[f,*]

[a]*Pharmaco-epidemiology Unit, Departments of Internal Medicine and Epidemiology & Biostatistics, Erasmus University Medical Center, Rotterdam, The Netherlands*

[b]*Division of Human Nutrition and Epidemiology, Wageningen University, Wageningen, The Netherlands*

[c]*Red Cross Anticoagulation Clinic, The Hague, The Netherlands*

[d]*Department of Biochemistry and Cardiovascular Research Institute (CARIM), Maastricht University, Maastricht, The Netherlands*

[e]*Hemostasis and Thrombosis Research Center, Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands*

[f]*Drug Safety Unit, Inspectorate for Health Care, The Hague, The Netherlands*

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Abstract

The risk of hemorrhage when using coumarin anticoagulants sharply increases when the International Normalized Ratio (INR) is ≥6.0. We performed a case-control study among outpatients of an anticoagulation clinic to identify sociodemographic-, lifestyle-, and dietary factors related to overanticoagulation. Three hundred cases with an INR ≥6.0 were compared with 302 randomly selected matched controls with an INR within the target zone. Age, sex, and level of education were not associated with overanticoagulation. Body mass index was negatively related to overanticoagulation, a beneath-average level of physical activity was positively related to overanticoagulation and never-smokers were more likely to have an INR ≥6.0 compared with smokers. Habitual alcohol consumption, even heavy drinking, was not related to overanticoagulation. However, a recent decrease of alcohol intake increased the risk of an INR ≥6.0. In addition, weight loss and a vacation were risk factors for overanticoagulation. Dietary factors were not associated with overanticoaguation. If risk factors can not be avoided, increased monitoring of INR values could prevent overanticoagulation and potential bleeding complications.

Keywords: Overanticoagulation; Coumarin anticoagulants; Risk factors; Lifestyle; Diet; Case-control study

1. Introduction

Coumarin anticoagulants are widely used in the prevention of venous and arterial thromboembolism [1]. These drugs induce anticoagulation by antagonizing vitamin K, thereby impairing the biological activity of the vitamin K-dependent coagulation factors (factor II, VII, IX and X) [2]. The risk of hemorrhage [3] is strongly associated with the intensity of anticoagulation and sharply increases when the INR is ≥μ6.0 [4,5]. Such overanticoagulation should therefore be prevented. This necessitates identification of risk factors for overanticoagulation.

Increasing age and female sex have been found to be associated with an enhanced response to coumarins; increased body weight was inversely related to the anticoagulant response [6]. In addition, weight loss has been shown to result in decreased factor VII levels [7]. A negative association with factor VII has been reported for physical activity, smoking, and intake of alcohol [8,9]. Besides, cigarette smoke and alcohol may induce or inhibit cytochrome P450 enzymes [10,11]. Cytochrome P450 metabolism is also affected by stress [12]. Overanticoagulation after a dietary modification reducing the intake of vitamin K has been described [13,14]. Factor VII coagulant activity has been found to be lowered by a diet lower in fat and higher in carbohydrate and fiber [15].

The association between overanticoagulation and sociodemographic-, lifestyle-, and dietary factors in a non-selected population under everyday circumstances, has not been studied extensively. Therefore, we have conducted a prospective nested case-control study among outpatients of an anticoagulation clinic. The aim of the study was to identify sociodemographic-, lifestyle- and dietary factors related to an INR ≥6.0 in previously stable patients. This paper is one of a series of three papers on risk factors for overanticoagulation. The other two papers are based on the same study and concern drug interactions, and comorbidity and characteristics of anticoagulant therapy.

* Corresponding author. Department of Epidemiology & Biostatistics, Erasmus University Medical Center, P.O. Box 1738, 3000 DR, Rotterdam, The Netherlands. Tel.: +31-10-4087482. Fax: +31-10-4089382.

E-mail address: stricker@epib.fgg.eur.nl.

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2. Subjects and methods

2.1. Setting

The study was performed at the regional Red Cross anticoagulation clinic, The Hague, which serves an area of nearly 700,000 inhabitants. All persons in this area with an indication for anticoagulant therapy are referred to this clinic.

2.2. Cohort definition

The study cohort consisted of all patients treated with oral anticoagulants by the regional Red Cross anticoagulation clinic, The Hague, between 1 December 1997 and 14 June 1999. All cohort members were followed until the first occurrence of an INR $\geq$6.0, the end of their treatment, or the end of the study period (i.e., the day on which the planned number of cases was recruited), whichever came first.

2.3. Cases and controls

Subjects for the nested case-control study were identified daily from all patients with an INR measurement on that day. Cases were defined as cohort members with an INR$\geq$6.0. For each case, one control, matched on therapeutic range, was randomly selected from the cohort members with an INR within the target zone (2.0–3.5 or 2.5–4.0), measured on the same day as the case (index day). Overanticoagulation is often seen during initiation of anticoagulant therapy and in unstable anticoagulation. Because this was not our primary interest, only cases and controls with stable anticoagulation in the three months preceding the index day were eligible. Anticoagulant therapy is considered effective and safe if the patient is kept within the target zone for more than two thirds of the time [16,17]. Therefore, we defined stable anticoagulation as having at least 66% of the INRs within the target zone and no INRs $\geq$5.5 in the three months preceding the index day. To judge stability, a minimum of three INRs had to be assessed in the three months preceding the index day. Cases and controls with a hospital admission in this period were excluded, since information on anticoagulant control during admission is often not available at the anticoagulation clinic. As we focused on sudden overanticoagulation, the INR preceding the assessment on the index day had to be within the target zone. Patients not living independently and those making use of Meals on Wheels may be less able to give reliable answers to the questions on diet than persons or couples who prepare their own meals. Therefore, they were excluded. As we were primarily interested in overanticoagulation, irrespective of the question whether this was followed by hemorrhage, patients who presented on the index day with a serious bleeding complication were excluded because that might have induced recall bias. Patients with a serious bleeding complication might have a more extensive recall of potential risk factors in general.

2.4. Procedure

The study protocol has been approved by the Medical Ethics Committee of the Erasmus University Medical Center, Rotterdam. We planned to recruit 300 cases and 300 controls to provide at least 80% power to detect a true odds ratio (OR) of $\geq$2.0 for risk factors having a prevalence of 7% among the controls, using a $P < 0.05$ to reject the null hypothesis of OR=1.

Information on sociodemographic factors, lifestyle factors, and diet, as well as on potential confounding factors, was collected by interviewing the patient, reviewing the anticoagulant medical record, and through the general practitioner (GP). The interview took place within three weeks after the index day at the private address of the patient, making use of structured questionnaires mainly with closed questions. In case the partner of the patient prepared the meals, this person assisted in answering the relevant food questions when necessary. The interviewers were blinded with respect to the patient's case or control status and the specific research hypotheses. This also applied to the GPs. Blinding of the patients was not fully feasible, because the INR value is printed on their dosage list. To obviate this, in the information letter we referred to the problem of overanticoagulation in a general sense.

2.5. Sociodemographic factors, lifestyle factors, and diet

The risk period was defined as the four-week period preceding the index day. Especially time-varying changes in factors were expected to pose a risk for overanticoagulation, but steady factors were taken into account as well. Body height and body weight were measured to the nearest centimeter and the nearest 0.5 kg, respectively. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2) and categorized as <20, 20 up to 25, and >25. The patient was asked about his or her level of education (primary, secondary, or higher), extent of physical activity (equal to, more than, or less than persons of comparable age and health status), and smoking habits (smoker, ex-smoker, or never-smoker and the daily number of cigarettes, cigars, or pipes smoked). In addition, changes in weight, physical activity, and number of smoked units in the risk period were inquired about (no, less, or more, and in case of weight, the extent of change). Furthermore, it was asked whether the patient had experienced or had been affected by an impressive life event (e.g., removal to another residence, divorce, retirement, criminality, death, or serious illness of a close friend or relative) in the risk period. Finally, an open question was posed on occurrences in the risk period that had not arisen during the interview.

A semiquantitative food frequency questionnaire including 170 foods and beverages (including alcohol) was used to assess the patient's habitual diet (i.e., as consumed during the preceding year). The questionnaire has been validated and proven suitable for use in an elderly population [18,19]. The patient was also asked whether the number of alcohol

units had changed in the risk period (none, less, or more), whether excessive drinking (≥6 drinks/day) had occurred in the two weeks preceding the index day, whether his or her dietary habits had otherwise changed in the risk period, and if so, what change occurred. The intake of fat, carbohydrates, fiber, and alcohol was computed using the Dutch Food Composition Table 1993 [20]. Intakes were categorized on the basis of tertiles, except for alcohol, the intake of which was categorized as none, <4 drinks/week, 4 drinks/week up to 2 drinks/day, 3 to 6 drinks/day, and ≥6 drinks/day. The vitamin K content of foods, however, is not included in the Dutch Food Composition Table. In order to calculate the intake of vitamin K, we used data on concentrations of vitamin K_1 (phylloquinone) and vitamin K_2 (menaquinones: MK4 through MK10) as had been determined in a large variety of Dutch foods at the Department of Biochemistry and Cardiovascular Research Institute, Maastricht University. The analytical method used has been described in detail elsewhere [21]. For foods consumed in the Netherlands that had not been analyzed, concentrations had been derived from data published by others [22-27]. This had not been done for vitamin K_2 because of scarcity of data in the literature. The intake of vitamin K was categorized on the basis of tertiles. Because the absorption of vitamin K is strongly dependent on the source from which it is obtained and the length of the aliphatic side chain in the menaquinones [28], the intake was subdivided into vitamin K_1, total vitamin K_2, and all MK-subtypes separately. In the Netherlands, main dietary sources of vitamin K_1 are green leafy vegetables and vegetable oils. Vitamin K_2 is present in meats and eggs (MK4 only), and in fish, sauerkraut, cheese, and other dairy products (MK5 through MK10) [29].

A person's BMI, extent of physical activity, smoking and drinking habits, and habitual diet may be related to the presence of chronic comorbidities. Time-varying changes in lifestyle factors and diet may be the result of an acute illness or a relapse of a chronic comorbidity; situations that may be accompanied by fever and/or a change in drug use. Since acute illnesses, chronic comorbidities, fever, and a change in drug use may also interact with anticoagulant therapy and enhance the response to coumarins [30–32], these were considered as potential confounders. The associations between these cofactors and overanticoagulation are the main subjects of the two other papers mentioned in our Introduction.

2.6. Statistical analyses

Sociodemographic-, lifestyle-, and dietary factors related to an INR ≥ 6.0 were identified using univariate conditional logistic regression analysis, at first with 289 matched pairs. Because the unconditional analyses gave comparable results but more statistical power, we finally used unconditional logistic regression analysis to compute unadjusted odds ratios and their 95% confidence intervals. In case a risk factor was absent in either the cases or the controls, a Fisher Exact test was performed instead. To assess steady sociodemographic, lifestyle-, and dietary factors (i.e., age, sex, BMI, level of physical activity, smoking status, and habitual dietary intake, and alcohol consumption) that were independently associated with an INR ≥6.0, all factors univariately associated at a $P < 0.10$ were included in a multiple regression model. Beside age, sex, and the number of INR determinations in the preceding three months, comorbidities univariately associated with an INR ≥6.0 were included if this resulted in a change in one of the odds ratios of 5% or over, starting with the most potent factor. A comparable procedure was followed to assess changes in lifestyle- and dietary factors during the risk period that were independently associated with an INR ≥6.0.

In order to determine the importance of the independent risk factors for overanticoagulation in the population, we calculated the population attributable risk percentages (PAR%) according to the following formula [33]: PAR% = AR% * (proportion of exposed cases), with AR% = ((OR-1)/OR) * 100.

3. Results

The nested case-control study included the planned number of 300 cases with a median INR of 6.8 and 302 controls with a median INR of 3.2 (range 2.0–4.0). Of the cases, 83% had an INR of 6.0–7.9, 11% had an INR of 8.0–9.9, and 6% had an INR of 10.0–15.0 (the upper measurable INR). The participation among cases and controls was 78% and 85%, respectively. Written informed consent was obtained from every patient. The mean interval between the index day and the interview was 14 days, for cases as well as for controls. Cardiac disease was the main indication for anticoagulation. Fifty-five percent of the cases and 66% of the controls used phenprocoumon; the others used acenocoumarol.

The associations between overanticoagulation and sociodemographic- and lifestyle factors are shown in Table 1. Age, sex, and level of education were not associated with overanticoagulation. Regarding steady lifestyle factors, BMI, level of physical activity, and smoking status were associated with an INR ≥6.0. Patients with a BMI <20 kg/m^2 had an increased risk of an INR ≥6.0 of 2.37 (95%CI 1.00–5.65), compared with patients having a BMI >25 kg/m^2. The corresponding PAR% was 4.2%. For patients with a BMI of 20 up to 25 kg/m^2, the OR was 1.74 (95%CI 1.16–2.61) and the PAR% was 14.9%. In comparison with patients whose level of physical activity was above average, patients with a below-average level of physical activity had an increased risk of overanticoagulation (OR 1.61; 95%CI 1.02–2.53, PAR% 12.1%). Never-smokers had an increased risk of overanticoagulation compared with smokers (OR 1.70; 95%CI 1.02–2.84, PAR% 11.9%). Habitual alcohol consumption, even heavy drinking, was not a risk factor for overanticoagulation. Nor was recent occasional excessive drinking associated with overanticoagulation. However, a recent decrease of alcohol intake increased the risk of an INR ≥6.0 (OR 2.79; 95%CI 1.21–6.43, PAR%

Table 1
Association between overanticoagulation (INR ≥ 6 0) and sociodemographic and lifestyle factors[a]

Variable	Cases n = 300	Controls n = 302	OR [95% CI], univariate	OR [95% CI], multivariate
Age (years, mean ± sd)	68 1 ± 12 3	68 2 ± 9 8	1 00 [0 98 1 01]	
Sex				
Male	175 (58%)	194 (64%)	1	
Female	125 (42%)	108 (36%)	1 28 [0 92–1 78]	
Level of education				
Higher	154 (51%)	144 (48%)	1	
Secondary	91 (21%)	100 (33%)	0 94 [0 59–1 50]	
Primary	55 (18%)	57 (19%)	1 11 [0 72–1 71]	
Body mass index				
>25 kg/m^2	171	211	1	1[c]
20 up to 25 kg/m^2	105	80	1 62 [1 14–2 31]	1 74 [1 16–2 61][c]
<20 kg/m^2	22	11	2 47 [1 16–5 23]	2 37 [1 00–5 65][c]
Change in weight ≥2 kg				
No change	222	247	1	1[d]
Weight loss	42	14	3 34 [1 78–6 28]	2 32 [1 03–5 22][d]
Weight gain	8	18	0 49 [0 21–1 16]	0 54 [0 20–1 41][d]
Level of physical activity				
Above average	119	144	1	1[c]
Average	77	85	1 10 [0 74–1 62]	1 01 [0 65–1 57][c]
Beneath average	96	66	1 76 [1 18–2 62]	1 61 [1 02–2 53][c]
Change in physical activity				
No change	179	219	1	1[d]
Less active	92	54	2 08 [1 41–3 08]	1 13 [0 66–1 95][d]
More active	28	29	1 18 [0 68–2 06]	0 61 [0 28–1 33][d]
Smoking status				
Smoker	98	100	1	1[c]
Ex smoker	115	144	0 82 [0 56–1 18]	0 99 [0 64–1 52][c]
Never smoker	87	58	1 53 [0 99–2 36]	1 70 [1 02–2 84][c]
Change in amount smoked				
No change	280	283	1	
Smoked less	12	8	1 52 [0 61–3 76]	
Smoked more	6	11	0 55 [0 20 1 51]	
Alcohol consumption				
None	78	88	1	
<4 drinks/week	72	65	1 25 [0 79–1 97]	
4 drinks/week up to 2 drinks/day	73	58	1 42 [0 90–2 25]	
3 to 6 drinks/day	64	83	0 87 [0 56–1 36]	
≥6 drinks/day	9	8	1 27 [0 47–3 45]	
Change in amount drunk				
No change	226	254	1	1[d]
Drunk less	42	13	3 63 [1 90–6 94]	2 79 [1 21–6 43][d]
Drunk more	31	35	1 00 [0 59–1 67]	1 42 [0 74–2 74][d]
Occasional excessive drinking[b]	8	15	0 53 [0 22–1 26]	
Impressive event	124	106	1 30 [0 94–1 81]	
Vacation	20	2	10 67[2 48–45 88]	[c]

[a] Values are numbers unless indicated otherwise

[b] At least once having drunk ≥6 drinks/day in the two weeks preceding the index day (restricted to patients who habitually drink <6 drinks/day)

[c] Body mass index, level of physical activity, smoking status, intake of fiber, age, gender, the number of INR determinations in the preceding three months impaired liver function and congestive heart failure were included in the model

[d] Change in weight ≥2 kg change in physical activity, change in amount drunk eaten a dinner less often, eaten less in general, eaten more fat-rich foods, age, gender, the number of INR determinations in the preceding three months fever, diarrhea, relapse of congestive heart failure, use of antibacterial drugs and use of analgesics and non steroidal anti inflammatory drugs were included in the model

[e] Not computed (see discussion)

9 0%) Another time-varying change in lifestyle factor associated with an increased risk of overanticoagulation was weight loss Patients with a recent weight loss of at least 2 kg had an increased risk of 2 32 (95%CI 1 03–5 22) The PAR% of overanticoagulation associated with a recent weight loss of at least 2 kg was 8 0% Being less active was only univariately related to the risk of an INR ≥6 0 (OR 2 08, 95%CI 1 41–3 08)

With respect to occurrences in the risk period, the experience of an impressive life event was not associated with overanticoagulation Twenty cases and two controls mentioned having been on vacation All cases but neither of the

controls had been abroad, and only three cases had had their INR checked during the vacation. The increased risk of an INR ≥6.0 was 10.67 (95%CI 2.48–45.88). The corresponding PAR% was 6.0%.

The associations between overanticoagulation and dietary factors are represented in Table 2. Because vitamin K_1 and all menaquinones gave comparable results, only the total vitamin K intake is included here. For none of the dietary factors examined (vitamin K, fat, carbohydrates, and fiber), habitual intake was a risk factor for overanticoagulation. Major changes in dietary intake were expected to be related to overanticoagulation, particularly changes resulting in a decreased intake of vitamin K. Of all changes mentioned by the patients, eating dinner less often, nearly always as a consequence of having been ill, occurred most frequently (in 45 cases and 15 controls). It was, however, only univariately associated with an increased risk of an INR ≥6.0. The same applied to eating less in general, which was mentioned by nine cases and one control. On the contrary, eating more fat-rich foods was an independent risk factor for overanticoagulation, with an OR of 7.67 (95%CI 1.38–42.67) and a PAR% of 2.3%.

4. Discussion

We studied the association between overanticoagulation and sociodemographic-, lifestyle-, and dietary factors. Some lifestyle factors were related to overanticoagulation: BMI was negatively related to overanticoagulation; a below-average level of physical activity was positively related to overanticoagulation; and never-smokers were more likely to have an INR ≥6.0 compared with smokers. Furthermore, a recent decrease in alcohol intake, weight loss, taking a vacation, and eating more fat-rich foods appeared to be risk factors for overanticoagulation. The clinical implication of our findings lies in the possibility of prevention or early detection of overanticoagulation, and thus of bleeding complications, by paying special attention to these risk factors when monitoring anticoagulation. For example, fragile and physically inactive patients should be monitored more carefully. Similarly, patients should be advised to have their INR checked when on vacation.

The study population was confined to stably anticoagulated patients because most cases of unstable anticoagulation and overanticoagulation occur during initiation of therapy. Every clinician is aware of this. Would we have

Table 2
Association between overanticoagulation (INR ≥ 6 0) and dietary factors[a]

Variable	Cases n = 300	Controls n = 302	OR [95% CI], univariate	OR [95% CI], multivariate
Vitamin K				
>320 μg/day	102	98	1	
225 up to 320 μg/day	92	106	0 83 [0 56–1 24]	
<225 μg/day	102	98	1 00 [0 68–1 48]	
Fat				
>38 energy%	100	103	1	
33 up to 38 energy%	94	101	0 96 [0 65–1 42]	
<33 energy%	102	98	1 07 [0 73–1 58]	
Carbohydrates				
<40 energy%	89	110	1	
40 up to 46 energy%	105	94	1 38 [0 93–2 05]	
>46 energy%	102	98	1 29 [0 87–1 91]	
Fiber				
>18 gram/day	91	109	1	1[b]
13 5 up to 18 gram/day	99	106	1 12 [0 76–1 65]	1 04 [0 67–1 62][b]
<13 5 gram/day	106	87	1 46 [0 98–2 17]	1 33 [0 84–2 10][b]
Change in dietary habits				
Commencement / discontinuation of a diet	4	4	1 01 [0 25–4 06]	1 12 [0 48–2 62][c]
Less often eaten a dinner	45	15	3 40 [1 85–6 25]	2 95 [0 31–27 75][c]
More often eaten a dinner	4	1	4 06 [0 45–36 29]	7 67 [1 38–42 67][c]
Eaten more irregular	2	0	p = 0 25	
Eaten less vegetables	4	0	p = 0 06	
Eaten less in general	9	1	9 36 [1 18–74 08]	
Eaten more fat-rich foods	8	2	4 11 [0 87–19 45]	
Other changes	13	6	2 26 [0 85–6 02]	

[a] Values are numbers

[b] Intake of fiber, body mass index, level of physical activity, smoking status, age, gender, the number of INR determinations in the preceding three months, impaired liver function, and congestive heart failure were included in the model

[c] Eaten a dinner less often, eaten less in general, eaten more fat-rich foods, change in weight ≥2 kg, change in physical activity, change in amount drunk, age, gender, the number of INR determinations in the preceding three months, fever, diarrhea, relapse of congestive heart failure, use of antibacterial drugs, and use of analgesics and non-steroidal anti-inflammatory drugs were included in the model

included unstable patients we would have found initiation of therapy to be the most important risk factor for overanticoagulation. This is well known and therefore of relatively little scientific interest. It would have been difficult to release more subtle yet clinically relevant risk factors, as the great majority of cases simply occur within the first weeks of treatment as part of the titration process during the initial phase of therapy. Clinicians might be more interested in the risk factors they encounter when their patients are on long-term anticoagulant therapy. To gain more insight into such risk factors, we focused on patients who were more or less stably anticoagulated yet suddenly developed an INR $\geq$6.0. Potential risk factors were questioned over the four weeks preceding the index day. Because of logistical limitations, the interview took place up to three weeks after the index day. Misclassification of exposure thus may have been present; a patient may have forgotten details; or been mistaken regarding the time period in which incidents occurred. The mean interval between overanticoagulation and interview, however, was similar for cases and controls. Besides, the misclassification is assumed to be nondifferential, resulting in risk estimates biased towards an odds ratio of one. Recall bias was prevented by restricting the study population to patients with nonsymptomatic overanticoagulation, i.e., by excluding patients who presented on the index day with a serious bleeding complication. In addition, in the information letter we referred to the problem of overanticoagulation in a general sense. The exclusion of patients who presented on the index day with a serious bleeding complication would not have had a substantial effect on our results because this concerned only very few patients. Of the 4,476 patients with an INR $\geq$6.0 in the study period, only three of them presented on the index day with a serious bleeding complication. This is explained by the fact that a patient with a serious bleeding complication would visit the hospital, not the anticoagulation clinic.

Ex-smokers had the same risk of overanticoagulation, compared with smokers. This unexpected observation argues for the presence of an unknown confounding factor.

The interaction between alcohol consumption and anticoagulant therapy is complex [34]. Large intermittent doses cause some enzyme inhibition with resultant increased INR, whereas chronic heavy use (greater than 60 g/day) causes enzyme induction resulting in a decreased INR. Intermediate use (two to three drinks per day) probably does not alter the anticoagulant metabolism at all. In our study, neither category of habitual alcohol consumption, nor occasional excessive drinking in the two weeks preceding the index day, was associated with overanticoagulation.

Having been on vacation greatly increased the risk of overanticoagulation. Taking a vacation involves a combination of changes in lifestyle factors, dietary habits, and other factors and is, in the context of anticoagulation, difficult to interpret. We did not compute an adjusted OR because this would be meaningless. The effect of vacation on anticoagulation seems to be responsible for the unexpected increased risk of an INR $\geq$6.0 in patients who had eaten more fat-rich foods. Of the eight cases who mentioned having eaten more fat-rich foods, seven also mentioned having been on vacation.

Dietary intake did not play a role in overanticoagulation; a reassuring observation. Lack of an effect of habitual dietary intake is plausible, since anticoagulant therapy likely is titrated to a patient's diet. With respect to the absence of an effect of changes in dietary habits, the increase in INR by the dietary modification may have been of less magnitude than defined in our study. Another possibility is that the dietary changes were too small or lasted too short a time to affect anticoagulant therapy. The case reports on dietary-induced overanticoagulation concerned a drastic dietary modification, viz., giving up consuming 750 to 1,000 g of liver every week [13,14]. Regarding the potential interaction between dietary factors and overanticoagulation, it should be kept in mind that not dietary intake, but nutritional status is the real risk factor. The extent to which intake is a good proxy of status depends on the bioavailability of the nutrient in question. For example, green leafy vegetables have a high vitamin K content, but because of tight binding to the thylakoid membranes of the chloroplasts, intestinal absorption of vitamin K is poor [28]. Furthermore, a decreased dietary intake does not immediately result in a deficient nutritional status.

To our knowledge, only one epidemiological study on risk factors for overanticoagulation in a non-selected population under everyday circumstances including lifestyle- and dietary factors has been published by Hylek et al. [35]. The number of lifestyle- and dietary factors studied, however, was small: alcohol consumption and the intake of vitamin K. Subjects with a higher habitual vitamin K consumption, based on reported weekly intake of twelve vitamin K_1 rich foods and habitual moderate consumption of alcohol were less likely to have an INR $\geq$6.0. We did not find an association between these factors and overanticoagulation. In addition, decreased oral intake in general was an independent determinant of an INR $\geq$6.0 in the study of Hylek *et al.*, while in our study, the increased risk was no longer significant after adjustment for potential confounders. An important difference between the study of Hylek et al. and our study is that we included only stable cases and controls. Besides, we assessed changes in the preceding four weeks, whereas they used a one-week risk period. Furthermore, we calculated the intake of vitamin K from the total diet and took vitamin K_2 into account as well. Lastly, the study population of Hylek et al. used warfarin, whereas our patients used phenprocoumon or acenocoumarol.

In conclusion, in this study among previously stable outpatients of an anticoagulation clinic, some lifestyle factors were related to overanticoagulation. Increased monitoring

of INR values if risk factors are present, or avoidance of risk factors, could prevent overanticoagulation and potential bleeding complications.

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