Towards improvement of oral anticoagulant therapy

Leeuwen, Y. van

CHAPTER 6

Determinants of Unstable Anticoagulation in the treatment with Vitamin K antagonists

van Leeuwen Y, van der Meer FJM, Rosendaal FR

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Abstract

***Background*:** Patients who are unstably anticoagulated or who spent much time outside their therapeutic range are at an increased risk for complications. Factors associated with unstable anticoagulation are not well known.

Objectives: To investigate the association of patient characteristics, lifestyle factors and treatment-related factors with unstable anticoagulation.

Patients and Methods: Patients were participants in a randomized controlled trial with the main objective to compare two different algorithms for computer-assisted dosing of oral anticoagulants. All patients completed a questionnaire concerning lifestyle factors.

Results: 638 patients (response 91.3%) returned the questionnaire. Unstable anticoagulation was observed more frequently with the use of acenocoumarol versus phenprocoumon (RR 2.3, 95%CI 1.9-2.8), in individuals with daily strenuous physical activity (RR 1.4, 95%CI 0.7-2.7) and less frequently in obese patients (RR 0.7, 95%CI 0.5-1.0). Patients who were underweight (RR 1.5, 95%CI 0.2-12.8), obese (RR 1.8, 95%CI 0.7-4.4), or had daily strenuous physical activity (RR 4.1, 95%CI 0.8-22.1) had an increased risk of spending more than 50% out of range, while regular alcohol use (>1-2-times a week) decreased the risk with 30-50%. Furthermore, patients with high daily anticoagulant dosages were less likely to spend more than 50% out of range than those with low doses.

Conclusion: Unstable anticoagulation is associated with the use of acenocoumarol versus phenprocoumon and strenuous daily physical activity. Obesity decreases the risk for instability. Low anticoagulant dosages, strenuous daily physical activity, being underweight or obese and frequent alcohol use are associated with an increased risk of spending less than 50% in the therapeutic range.

Introduction

Vitamin K antagonists are among the most frequently prescribed drugs worldwide. They are proven to be effective in the treatment and prophylaxis of venous and arterial thrombosis [1-3]. At the same time, vitamin K antagonists are also listed in the top 5 of drugs causing adverse events [4]. In routine clinical practice, vitamin K antagonists result in severe bleeding complications in 1-2% of patients [5-7].

Vitamin K antagonists have a narrow therapeutic window, and frequent monitoring of the anticoagulant effect by measurements of the International Normalised Ratio (INR) with adjustment of anticoagulant dose is required to maintain patients within the therapeutic range. Patients who are insufficiently anticoagulated (i.e., an INR below the therapeutic window appropriate for their indication) are at increased risk for (re)thrombosis, whereas over-anticoagulated patients show a sharp increase in bleeding risk [8]. Keeping patients' INR within the therapeutic window is difficult due to the large variability in the dose needed to achieve the optimal anticoagulant effect within a single patient. Sensitivity for vitamin K antagonists not only differs between patients, but also within patients it may vary over time [9]. The risk for bleeding or thrombosis proportionally increases with the time spent outside the therapeutic window [8]. Bleeding or thrombosis risk is also increased in patients who are unstably anticoagulated, independently from the achieved time within the therapeutic window [10-12]. Thus, low-risk anticoagulation not only requires the patient to be within its therapeutic window for the majority of time, but also requires deviations in INR over time to be small.

In a case-control study, unstable anticoagulation has been shown to have many determinants [13]. Patients who had an INR above 4.5, workers versus pensioners, users of acenocoumarol versus warfarin and patients who had a poor compliance were considered often unstable. Instability in this study was defined

according to the opinion of experts in anticoagulant dosing, because there was a lack of universally accepted criteria for instability. Recently, it has been shown that stability of anticoagulation can be objectively measured by calculating the variance growth rate. This variance growth rate reflects the degree to which a patient's INR deviates from the previous one and is independent from a patient's target INR. Instability defined by this variance growth rate was shown to be associated with an increased risk for bleeding or thrombotic events [10].

In this study our aim was to identify factors that are associated with unstable anticoagulation using the variance growth rate to calculate stability. In addition we studied determinants of the time spent out of range.

Methods

Study design

Patients were participants in a randomized controlled double-blind trial conducted at the Leiden Anticoagulation Clinic in the Netherlands. Main objective of the trial was to evaluate two algorithms (TRODIS and ICAD) for computer-assisted dosing in clinical practice. In total 712 patients participated in the trial. Enrollment occurred between August 14th and October 16th 2003. Patients were eligible when they had an indication for long-term anticoagulant therapy and were between the ages of 18 and 80 years. Patients were excluded when they were participating in the patient self-management program, stayed long periods abroad or were in a terminal stage of disease. Randomization was done stratified by the indication for oral anticoagulant treatment, age and sex using the minimization method [14]. The study was double- blind, e.g., neither patients nor physicians were aware which group the patient was randomized to. Follow-up was until September 1st 2004, i.e. maximally about one year. All patients filled in a questionnaire at the start of the study containing questions about the attitude towards their anticoagulant treatment

and lifestyle factors such as smoking habits, alcohol use, vitamin intake and sporting activities. The study was approved by the Medical Ethics Committee of the Leiden University Medical Center before start of the study and each patient gave written informed consent before randomization. The trial is registered in the ISRCTN trial registration with identifier ISRCTN27801917. The trial is described in more detail elsewhere [15].

Because of our previous finding that the time spent within the therapeutic range was similar for both algorithms [15], and instability was similar (median 0.22, interquartile range (IQR) 0.09-0.57 vs. median 0.26, IQR 0.12-0.61, p=0.064) we pooled data of the two groups and considered it as a cohort. We performed analyses for two outcome events. The first outcome event was unstable anticoagulation. Unstable anticoagulation was calculated with the following formula for the variance growth rate:

$$\sigma^2 = \frac{1}{n}\sum_{i=1}^{n}\frac{(\mathrm{INR}_{i+1} - \mathrm{INR}_i)^2}{\tau_{i,i+1}}$$

In this formula n is the number of INR measurements and τ the time between two visits in weeks. The variance growth rate is a reflection of the amount of deviation of a patient's INR from the previous INR. The σ will be high in patients with highly varying INR values and low if the INR is consequently at the same value every time, even if this means the INR is constantly outside the therapeutic range. The stability was calculated over the first 6 months of follow up. The values of the variance growth rates were divided into tertiles (good, medium, poor), and patients in the third tertile were considered unstably anticoagulated.

In the second analysis we analyzed the time spent outside the therapeutic range. The time in therapeutic range was calculated over the first 6 months after start of the study with the linear interpolation method [16]. We considered patients who spent more than 50% outside their therapeutic range to have experienced the outcome event. Therapeutic ranges were as they were applied in our routine anticoagulant practice: INR 2.0 to 3.5 for low intensity and INR 2.5 to 4.0 for indications requiring a higher intensity. Patients who had less than 3 INR measurements were excluded from the analyses.

We investigated the association of sex, smoking, alcohol use, vitamin use, the use of a specific diet (e.g. low carb, low salt), daily physical activity, sporting activities, BMI, type of vitamin K antagonist and dosage with unstable anticoagulation and time outside range. We developed a questionnaire to measure all factors, except for the type of vitamin K antagonist and dosage used which were derived from the database at the anticoagulation clinic. Smoking was divided in three categories: smokers, former smokers and non-smokers. Former smokers were considered non-smokers if they had quit smoking more than half a year before inclusion in the study. Alcohol use was categorized according to the amount of consumption. Daily physical activity refers to the amount of activity due to work, whereas sporting activities only includes physical activity due to sports. The degree of daily physical activity was categorized by patients themselves as light, moderate, heavy or strenuous. Patients were divided into four categories for Body Mass Index (BMI): underweight (BMI <20), normal weight (BMI 20-25), overweight (BMI 25-30) and obese (BMI>30). The mean daily dosages of vitamin K antagonist were divided into quartiles for phenprocoumon and acenocoumarol separately.

Statistical analyses

We calculated relative risks (RR) for either unstable anticoagulation (variance growth in third tertile) or time outside of range (more than 50% outside range). We report RRs with their corresponding 95% confidence intervals (95% CI). Continuous variables are presented as the median with interquartile range (IQR). All calculations were performed using the statistical package SPSS version 14.0 (SPSS Inc, Chicago, Ill, USA).

Results

Of the 712 patients included in the trial, thirteen patients discontinued treatment before there were 3 INR measurements available. The reasons for discontinuation were: the treatment ended (n=3), participation in the patient self management program (n=6), death (n=2) or other reasons (n=2). Of the 699 patients, 638 (91.3%) filled in the questionnaire and were included in the current analysis. The median age of the participants was 68 years (Interquartile range (IQR) 59-74) and there were slightly more men than women (67.2%). Most patients used phenprocoumon at a low intensity.

Table 1. Patient characteristics (n=638)

Age	
Median (IQR)	68.0 (59-74)
Sex	
Men (%)	67.2
Indication	
Atrial Fibrillation (%)	43.7
Venous thrombosis (%)	12.4
Heart valve prosthesis (%)	10.3
Other cardiac indication (%)	18.2
Peripheral vascular disorder (%)	9.5
Cerebrovascular (%)	6.0
Coumarin	
Acenocoumarol (%)	14.3
Phenprocoumon (%)	85.7
Intensity (target)	
Low (2.0 – 3.5) (%)	62.2
High (2.5 – 4.0) (%)	35.3
Switched (%)	2.5

The main characteristics of the patients are shown in table 1. The patients who did not fill in the questionnaire were not different with respect to age and sex compared to those who filled in the questionnaire. The median value for the instability calculated with variance growth rate was 0.25 (IQR 0.10-0.58). The median time spent in therapeutic range was 82.5% (IQR 69.9 – 94.9). The mean daily dosage of phenprocoumon was 2.27 mg (IQR 1.59-2.72) with a maximum of 9.96 mg. For acenocoumarol users the mean daily dosage was 2.53 mg (IQR 1.67-3.17) with a maximum daily dosage of 6.12 mg.

Determinants of unstable anticoagulation

The 67th percentile of the variance growth rate was 0.45 and patients with a variance growth rate ≥ 0.45 were considered unstably anticoagulated. We investigated the association of the patient characteristics and lifestyle factors sex, BMI, smoking status, daily physical activity, work, sporting activities, alcohol use, vitamin use, the use of a specific diet with unstable anticoagulation (table 2).

Obese patients had a 30% lower risk of unstable anticoagulation than patients with normal weight (RR 0.7, 95% CI 0.5-1.0). Smoking was not associated with unstable anticoagulation. Strenuous physical activity showed a small increased risk for unstable anticoagulation (RR: 1.4, 95% CI 0.7-2.7) compared to patients who had light physical activity. Patients who did not work had a 1.2 times increased risk compared to patients who worked (95% CI 0.9-1.5). We did not observe an association with unstable anticoagulation and sex, vitamin use, sporting activities, the use of a specific diet, or alcohol use.

Table 2. Relative risks for the association between patient characteristics and lifestyle factors and unstable anticoagulation and time out of range.

		Unstable anticoagulation		Time out of range	
		RR	**95%CI**	**RR**	**95% CI**
Sex					
	Male	1.0 (ref)	-	1.0 (ref)	
	Female	0.9	0.7-1.2	1.1	0.5-2.1
BMI					
	Underweight	0.9	0.4-1.9	1.5	0.2-12.8
	Normal weight	1.0 (ref)	-	1.0 (ref)	-
	Overweight	0.9	0.5-1.6	1.1	0.5-2.6
	Obese	0.7	0.5-1.0	1.8	0.7-4.4
Smoking					
	No	1.0	-	1.0	-
	Former	0.9	0.7-1.2	0.6	0.3-1.3
	Yes	1.0	0.7-1.4	0.6	0.2-1.7
Daily physical activity					
	Light	1,0 (ref)		1,0 (ref)	
	Moderate	0.7	0.5-1.1	0.9	0.3-2.9
	Heavy	1.0	0.6-1.7	0.6	0.1-5.0
	Strenuous	1.4	0.7-2.7	4.1	0.8-22.1
Work					
	Workers	1.0 (ref)		1.0 (ref)	
	Non workers	1.2	0.9-1.5	1.3	0.7-2.7
Sporting activities					
	Yes	1.0 (ref)		1.0 (ref)	
	No	1.1	0.9-1.4	1.0	0.5-1.9
Alcohol use					
	Never	1.0 (ref)		1.0 (ref)	
	< 1 x per mnd	0.9	0.2-5.0	1.9	0.5-6.3
	< 1 x per week	1.1	0.7-1.6	1.7	0.6-4.7
	1-2 days per week	0.9	0.6-1.3	0.7	0.2-2.3
	3-4 days per week	0.8	0.5-1.3	0.5	0.1-2.6
	5-7 days per week	1.1	0.8-1.5	0.7	0.2-1.7
Vitamin use					
	No	1.0 (ref)		1.0 (ref)	
	Yes	0.9	0.7-1.2	0.9	0.4-1.9
Specific diet					
	No	1.0 (ref)		1.0 (ref)	
	Yes	1.2	0.9-1.6	0.6	0.3-1.4

In table 3 RRs are shown of the association between treatment related factors, type of vitamin K antagonist, target INR range, mean daily dosage and unstable anticoagulation. Users of acenocoumarol had a 2.3 fold increased risk for unstable anticoagulation, i.e. a high variance growth rate (95% CI 1.9-2.8). Patients with a high therapeutic range had a slightly increased risk of unstable anticoagulation with a RR of 1.4 (95% CI 1.1-1.7) compared to patients with a low

therapeutic range. Higher anticoagulant dosage tended to give a slightly decreased risk, with relative risks for the 2nd and 3rd quartile of 0.8 (95% CI 0.6-1.1), but this was not seen for patients with the highest dosages (RR 0.9, 95% CI 0.7-1.2). The association between the mean daily dosage and instability was similar for acenocoumarol users and phenprocoumon users.

Table 3. Relative risks for the association between several treatment related factors and unstable anticoagulation and time out of range.

	Unstable anticoagulation		Time out of range	
	RR	**95%CI**	**RR**	**95% CI**
Vitamin K antagonist				
Phenprocoumon	1.0 (ref)	-	1.0 (ref)	-
Acenocoumarol	2.3	1.9-2.8	0.7	0.2-2.0
Target zone				
Low (2.0-3.5)	1.0 (ref)		1.0 (ref)	
High (2.5-4.0)	1.4	1.1-1.7	1.0	0.5-2.0
Switched	2.3	1.1-3.0	2.3	0.5-10.8
Dosage				
Lowest quartile	1.0 (ref)		1.0 (ref)	
Second quartile	0.8	0.6-1.1	0.3	0.1-0.7
Third quartile	0.8	0.6-1.1	0.4	0.2-1.0
Highest quartile	0.9	0.7-1.2	0.2	0.1-0.6

Determinants for time spent outside the therapeutic range

Thirty eight (6.0%) patients spent more than 50% of the time outside the therapeutic range. Patients being underweight or obese patients tended to be at increased risk for spending 50% or more outside the therapeutic range with RRs of 1.5 (95% CI 0.2-12.8) and 1.8 (95% CI 0.7-4.4) compared to patients with normal weight, although their confidence intervals contained 1.0. Former smokers (smoking terminated less than half a year before inclusion into the study) and smokers had a 40% lower risk compared to patients who did not smoke or stopped smoking more than half a year before inclusion. Patient regularly using alcohol (more than 1-2 time a week) had a 30-50% decreased risk to be out of range compared to patients who never use alcohol. We did not observe an association

between time out of range and sex, the use of vitamin supplements and sporting activities.

In contrast to the results for unstable anticoagulation there was a decreased risk for acenocoumarol users to be out of range compared to phenprocoumon users (RR 0.7, 95% CI 0.2-2.0) (table 3). There was a strong association between the anticoagulant dosage and spending more than 50% out of range. Patients in the highest quartile of the anticoagulant dosage had an 80% reduced risk compared to patients in the lowest quartile (RR: 0.20, 95% CI 0.1-0.6).

Discussion

In this study we have shown that unstable anticoagulation is observed more frequently with the use of acenocoumarol versus phenprocoumon, in individuals with daily strenuous physical activity and less frequent in obese patients. Patients who are obese, have daily strenuous physical activity or are frequent alcohol users have a higher risk of spending more time outside the therapeutic range. Furthermore, increased anticoagulant dosage substantially reduced the risk of time spent outside range.

Our study showed similar results as the study of Palareti et al. [13]. They showed that users of the short acting acenocoumarol had an increased risk for unstable anticoagulation compared to users of the longer acting warfarin. We found that also compared to the longest acting vitamin K antagonist phenprocoumon, acenocoumarol users were at an increased risk for instability. It is remarkable that the use of acenocoumarol was associated with unstable anticoagulation but not with spending 50% or more time outside the therapeutic range. Overall, acenocoumarol users did have a lower mean time spent within range, but the proportion of patients with a time outside the therapeutic range of more than 50% was smaller compared to phenprocoumon. We can explain this by the fact that

phenprocoumon users have a wider range in time in therapeutic range compared to acenocoumarol users with a large amount of patients spending more than 80% of time within the therapeutic range. This leads to an overall better quality of treatment for phenprocoumon compared to acenocoumarol, although the number of patients who spent less than 50% in range is larger. Instability is associated with the time spent in range, but the association is stronger with higher time in range. Several studies have shown that vitamin K antagonists with a shorter half-life are associated with poorer quality (less time within the therapeutic range) of anticoagulant treatment, although some studies did not confirm these findings [17-19]. Our study indicates that this poorer quality might be caused by an increased instability rather than spending more time out of range.

Patients requiring higher anticoagulant dosages had a decreased risk for spending more than 50% of the time outside the therapeutic range. Patients who require low anticoagulant dosages may be more sensitive to small changes in the dosage, since these dose changes are relatively larger for small dosages than for high dosages. In earlier studies it has been shown that carriers of the CYP2C9 polymorphisms CYP2C9*2 and CYP2C9*3 need lower anticoagulant dosages and have a higher risk for adverse events [20-22]. Also the VKORC1 haplotype has been shown to be of influence on the anticoagulant dosages. The decreased risk for spending more time out of range we found for patients with high anticoagulant dosages might be explained by CYP2C9 genotype and VKORC1 haplotype. Unfortunately we could not investigate this in our study since DNA samples were not available.

Of the lifestyle factors we investigated, only daily physical activity was positively associated with unstable anticoagulation and spending more than 50% of the time out of range. In contrast to the results of the study by Palareti et al. we observed only a small increased risk for patients who did not work compared to

workers. Obesity was shown to decrease the risk for unstable anticoagulation and increase the risk for spending more than 50% outside the therapeutic range. This contradictive finding was caused by several obese patients who were stably anticoagulated with INR values around the upper or lower values of the therapeutic range.

We used a questionnaire to obtain information about lifestyle factors so it is possible that patients filled in favourable answers for these factors since it is well known that some lifestyle factors such as smoking and drinking large amounts of alcohol have negative effects on health. If this is true we would have found risks that are underestimated.

In conclusion, unstable anticoagulation defined by the variance growth rate occurs more frequently with the use of acenocoumarol versus phenprocoumon, in patients with strenuous daily physical activity and is reduced in obese patients. Spending more than 50% outside the therapeutic range was associated with obesity, strenuous daily physical activity, frequent alcohol use and lower anticoagulant dosages.

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