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Vitamin K and stability of oral anticoagulant therapy

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Subtherapeutic oral anticoagulant therapy: Frequency and risk factors

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Abstract

Background

Subtherapeutic anticoagulation levels increase both the risk and severity of thromboembolism. The aim of this study was to determine the cumulative incidence of subtherapeutic international normalized ratios (INRs) and to identify risk factors associated with a low INR.

Methods

We performed a cohort study in 7 419 patients from a Dutch anticoagulation clinic. Patients who started a first treatment with oral anticoagulants between January 2000 and December 2005 and who were stably anticoagulated (4 consecutive INRs in the therapeutic range) were included. Within the cohort a nested case-control study was performed to identify risk factors of subtherapeutic INRs and to determine how often a subtherapeutic INR is the result of medical interference in case of invasive procedures, hospital admissions, hemorrhage or overanticoagulation.

Results and conclusions

In patients with a stable anticoagulation, the median time to a first low INR was 40 weeks. A subtherapeutic INR occurred twice as often in patients using acenocoumarol as in those using phenprocoumon (hazard ratio [HR] 2.1, 95% Confidence Interval [95%CI]: 2.0-2.3) and was more common in patients with a high therapeutic range compared to a low therapeutic range (HR 1.8, 95%CI: 1.5-2.2). Occurrence of a low INR also depended on indication for anticoagulant therapy, with the highest risk in patients who used anticoagulants as prophylaxis and the lowest risk in patients with mechanical heart valves. In 30% of cases the subtherapeutic INR was preceded by an event necessitating vitamin K or discontinuation of the anticoagulant drug.

Introduction

Oral anticoagulant therapy with vitamin K antagonists has been proven effective in primary and secondary prevention of both venous and arterial thrombosis.¹⁻³ Treatment with these drugs requires careful monitoring because of a narrow therapeutic range. When the intensity of anticoagulation (expressed as the International Normalized Ratio or INR) is high the risk of bleeding events is increased.⁴⁻⁶ Low INRs increase not only the frequency of thromboembolism but also its severity and the associated risk of death.⁶⁻¹¹

Despite frequent monitoring of the INR, subtherapeutic anticoagulation is common. In primary prevention trials, the INR was below the target range 8 to 40% of the time.¹²⁻¹⁶ In clinical practice, time below the target range of up to 26-52% has been reported.^{8;9;17} These numbers depend strongly on the target range used. In addition, in the initial phase of oral anticoagulant therapy patients spend more time below the target range than during long-term use, since it usually takes some time before stable anticoagulation is achieved. Time in, above or below the therapeutic range can thus vary widely between populations.

Much research has been done on causes of overanticoagulation and unstable anticoagulant control.¹⁸⁻²¹ Causes of subtherapeutic anticoagulation are less well understood. In order to improve anticoagulant control, it is also important to identify risk factors for subtherapeutic INRs and to recognize how often these are the result of discontinuation of the anticoagulant drug in case of surgery, invasive procedures or bleeding.

The aim of this study was: 1. To determine the frequency of low INR values in patients who are stably anticoagulated, 2. To identify risk factors for subtherapeutic INRs and 3. To determine the contribution of vitamin K administration or discontinuation of the anticoagulant drug to the risk of developing a subtherapeutic INR.

Methods

Study design

We performed a retrospective follow-up study within a cohort of patients from the Leiden anticoagulation clinic. The cohort consisted of all patients who started a first treatment with oral anticoagulants between January 2000 and December 2005 and who had reached stable anticoagulation. Stable anticoagulation was defined as four consecutive INRs in the therapeutic range. The therapeutic range was defined as agreed by the Federation of Dutch Anticoagulation Clinics: INR 2.0-3.5 (target INR 3.0) for low intensity and 2.5-4.0 (target INR 3.5) for high intensity treatment. Patients in the cohort were followed from the date they reached stability until the first subtherapeutic INR, the end of treatment, an interruption of follow-up for more than 9 weeks or at the end of the study period. Because follow-up ended when a patient had a subtherapeutic INR, patients in the cohort had therapeutic or high INRs only.

Within this cohort we performed a nested case-control study. Cases were all patients who, after reaching stable anticoagulation, had a first subtherapeutic INR. For each case a control patient was selected from the cohort, who had an INR measurement on the same day as the case (index date) and had not yet had a subtherapeutic INR. This method is known as incidence density sampling. The Odds Ratio (OR) calculated from case-control studies using incidence density sampling is a valid estimation of the Rate Ratio, even if the outcome under study is frequent.²² Controls were matched individually to the cases on duration of treatment. For both cases and controls computer records were checked for any of the following events in the four weeks prior to the index date: invasive procedures, hospital admissions, hemorrhages, an INR >7.0, use of vitamin K or discontinuation of the anticoagulant drug for two or more days. The four-week window was chosen to account for the long half-life of phenprocoumon.

Setting

In the Netherlands, all patients on oral anticoagulants are treated by specialized anticoagulation clinics. This study was performed at the Leiden anticoagulation clinic, where nearly 10 000 patients are treated each year. Patients are seen by trained nurses every 1-6 weeks. At every visit, blood for an INR measurement is collected via venipuncture and the patient is asked to report any special circumstances, such as non-compliance, bleeding episodes, changes in co-medication, hospital visits or (surgical) procedures. The history is taken according to the anticoagulation clinic's quality guidelines. Because the history is taken before the INR result is known, the information was obtained in a similar manner for cases and controls. INR results and prescribed dosages are recorded in a central database, along with relevant history details and information on admissions and interventions. The following bleeding episodes are recorded: All intracranial, retroperitoneal, muscle, joint, ocular and subconjunctival bleeds, all hemorrhage from the gastro-intestinal, respiratory and urogenital tracts, epistaxis when longer than 30 minutes and bruises more than 10 cm in diameter.

Two oral anticoagulant agents are available in the Netherlands, acenocoumarol (with a half-life of 8-11 hours [h]) and phenprocoumon (Marcoumar®, half-life approximately 160 h). In the Leiden anticoagulation clinic phenprocoumon is used by approximately 90% of patients.

Indications for anticoagulant therapy are categorized as follows: Atrial fibrillation, secondary prevention venous thrombosis (any venous thrombotic event), mechanical heart valves (mitral and/or aorta), arterial indications (primary and secondary prevention of myocardial infarction, stroke and peripheral embolism) and prophylaxis (primary prevention of venous thrombosis after surgery or in other high-risk situations)

Analysis

In the full cohort, we used the Kaplan-Meier method to estimate the risk of subtherapeutic INRs in patients with a stable anticoagulation. Time to a first subtherapeutic INR was defined as the time between obtaining a stable anticoagulation and the date of a first subtherapeutic INR. Patients were censored at the end of treatment, at the end of the study period or when

follow-up was interrupted for more than nine weeks. The effect of patient and treatment characteristics on the risk of a low INR was evaluated with Cox proportional hazards regression.

ORs for the transient risk factors in the case control analysis were calculated with conditional logistic regression.

Results

During the study period 13 443 patients started a first treatment with oral anticoagulants. Of those, 7 419 reached stable anticoagulation, i.e. had four consecutive INRs within the target range. The average time to stable anticoagulation was 12 weeks (range 1 -211 weeks). Of those patients that did not reach stable anticoagulation, the average follow-up time was seven weeks (range 0 -133 weeks). The total follow-up time of stable patients was 4 037 patient-years, the average follow-up time per patient was 28 weeks (range 0 -304 weeks). Of the 7 419 stable patients, 3 166 had one or more subtherapeutic INRs during follow-up.

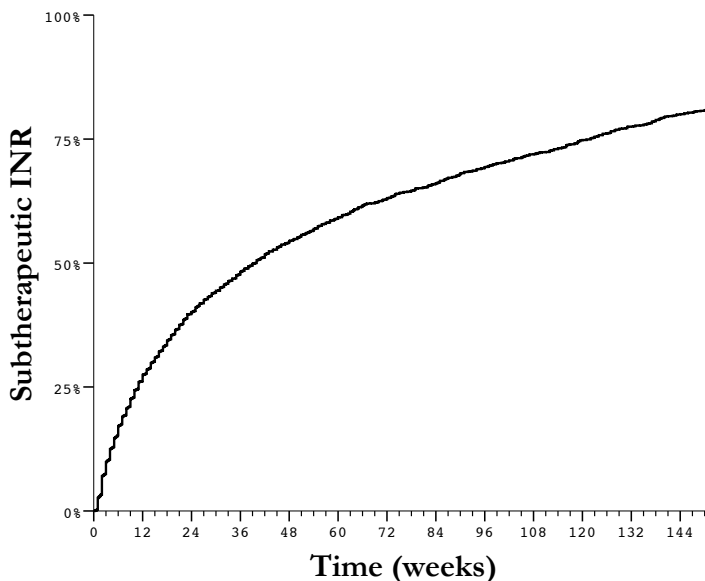


Figure 1: Kaplan-Meier curve of the likelihood of a subtherapeutic INR in patients with a stable anticoagulation. On the x-axis time since stable anticoagulation. On the y-axis the proportion of patients who had a subtherapeutic INR.

There were two thromboembolic events in the period between the last known INR before - and the first non-subtherapeutic INR after the subtherapeutic episode. One patient had an ischemic stroke 6 days before the index-date for which she was admitted (INR at admission unknown). One patient suffered a mechanical valve thrombosis and survived cardiopulmonary resuscitation 8 days after the index-date (INR at admission 2.3).

Figure 1 shows the Kaplan Meier curve of the risk of a first subtherapeutic INR in stable patients. After four weeks 12% of patients had had a subtherapeutic INR. This increased to 21% at 8 weeks and after 40 weeks 50% had had a low INR.

Table 1: Patient characteristics and the median time to a first subtherapeutic INR in different patient groups. *Adjusted for sex, age, anticoagulant used, target range, and indication category. HR, Hazard Ratio; 95%CI, 95% confidence interval

	Number of patients (percentage)	Median time to a low INR (weeks - 95%CI)	Crude HR (95%CI)	Adjusted HR* (95%CI)
Sex				
Male (ref)	3788 (51%)	42 (38-46)	1	1
Female	3631 (49%)	37 (33-40)	1.12 (1.04-1.20)	1.07 (0.99-1.15)
Anticoagulant				
Phenprocoumon (ref)	5748 (78%)	51 (47-55)	1	1
Acenocoumarol	1639 (22%)	13 (12-15)	2.30 (2.12-2.50)	2.14 (1.96-2.33)
Therapeutic range				
Low (2.0-3.5) (ref)	6351 (86%)	48 (44-52)	1	1
High (2.5-4.0)	1068 (14%)	21 (19-23)	1.58 (1.46-1.71)	1.83 (1.53-2.19)
Age				
< 50 years	1337 (18%)	26 (21-31)	1.30 (1.18-1.44)	1.15 (1.03-1.29)
50 - 70 years	2812 (38%)	42 (37-47)	0.96 (0.89-1.03)	0.93 (0.86-1.00)
>70 years (ref)	3270 (44%)	42 (38-46)	1	1
Indication				
Atrial fibrillation (ref)	2778 (37%)	58 (52-64)	1	1
Secondary prevention venous thrombosis	1544 (21%)	31 (25-37)	1.45 (1.31-1.61)	1.36 (1.21-1.52)
Mechanical heart valves	189 (3%)	66 (41-91)	0.95 (0.78-1.16)	0.69 (0.56-0.86)
Arterial indications	1229 (17%)	23 (20-26)	1.67 (1.53-1.82)	0.96 (0.81-1.15)
Prophylaxis	1679 (23%)	14 (10-19)	2.51 (2.20-2.86)	1.88 (1.64-2.16)

Table 2: Influence of events requiring medical intervention on subtherapeutic anticoagulation. * Number of patients who experienced the indicated event in the four weeks prior to the index-date. † Adjusted for sex, age, anticoagulant used, target range, and indication category. OR, Odds Ratio; 95%CI, 95% confidence interval.

	Patients with a subtherapeutic INR (n = 3 166)				Control subjects (n = 3 146)				Crude OR (95%CI)	Adjusted OR (95%CI)
	Number of patients* (percentage)	Vitamin K	Discontinued	Not stopped Unknown	Number of patients* (percentage)	Vitamin K	Discontinued	Not stopped, Unknown		
Hemorrhage	188 (5.9%)	68	1	119	52 (1.7%)	7	0	45	3.8 (2.8-5.1)	4.8 (3.5-6.6)
Surgical admission	207 (6.5%)	78	65	64	49 (1.6%)	16	16	17	4.4 (3.2-6.1)	5.8 (4.2-8.0)
Medical admission	156 (4.9%)	9	2	145	52 (1.7%)	0	3	49	3.1 (2.2-4.2)	4.0 (2.9-5.5)
Invasive procedure	355 (11.2%)	249	98	8	31 (1.0%)	25	3	3	12.7 (8.8-18.4)	17.2 (11.9-25.0)
INR > 7.0	81 (2.6%)	73	6	2	51 (1.6%)	45	5	1	1.6 (1.1-2.3)	1.6 (1.1-2.4)
Any event	955 (30.2%)	450	170	335	229 (7.3%)	90	25	114	5.5 (4.7-6.4)	3.9 (3.1-4.8)

There was no difference in risk of a subtherapeutic INR between men and women (Table 1). Patients aged younger than 50 years had a slightly increased risk of a low INR. Use of the anticoagulant drug acenocoumarol doubled the risk compared to the longer acting phenprocoumon (adjusted HR 2.14, 95%CI: 1.96-2.33). In patients using acenocoumarol the median time to a first subtherapeutic INR was 13 weeks compared to 51 weeks in the phenprocoumon group. In patients with an indication for high-intensity treatment the median time to a first low INR was 21 weeks, compared to 48 weeks in patients with low intensity treatment. (adjusted HR 1.83, 95%CI: 1.53-2.19). Occurrence of a subtherapeutic INR also depended on indication for treatment, with the highest risk in patients who used oral anticoagulants as prophylaxis for venous thromboembolism and the lowest risk in patients with mechanical heart valves (Table 1).

A low INR was preceded by an event necessitating discontinuation of treatment in 30% of cases (Table 2). These were mainly invasive procedures (11.2% of cases, 1.0% of controls), surgical admissions (6.5% of cases, 1.6% of controls) and hemorrhages (5.9% of cases and 1.7% of controls). Vitamin K was used in the four weeks preceding the index date by 14.2% of cases and 2.9% of controls. Of the patients undergoing an invasive procedure 70% of cases received vitamin K versus 81% in control patients. Treatment was discontinued for two or more days in 5.4% of cases and 0.8% of controls.

Discussion

After reaching stable anticoagulation fifty percent of patients had a subtherapeutic INR within 40 weeks. We chose to present the cumulative incidence in patients with a stable anticoagulation, because patients with a low INR are not at risk for *getting* a low INR. The criteria for a stable anticoagulation (4 consecutive INRs in the therapeutic range) were stringent, and were met by only approximately half of patients. This must be kept in mind when interpreting the results: In patients starting treatment with vitamin K antagonists the risk of underanticoagulation will be higher. In these patients many of the subtherapeutic INRs will be caused by too

low dosages of the anticoagulant drug, because it usually takes some time before the right dosage is known for an individual patient.

Two patients suffered a thromboembolic event in the period before and after the subtherapeutic INR. The design of our study was not suited to calculate an absolute risk. Furthermore, it is difficult to estimate the risk period, because the duration of the subtherapeutic INR before the index-date and after the last low INR is unknown.

We found several patient and treatment characteristics that were associated with the risk of underanticoagulation. A possible explanation for the difference in frequency of occurrence of subtherapeutic anticoagulation amongst the indication categories may be a difference in compliance: The risk was highest in patients who used anticoagulation as primary prophylaxis for venous thromboembolism and lowest in patients with mechanical heart valves, who have the highest underlying risk of thrombosis. The increased risk for patients with an arterial indication disappeared completely after adjustment for target range, indicating that the latter is the real association. One possible explanation for the higher risk of a subtherapeutic INR in high therapeutic range patients is that dosing physicians are more inclined to lower the dose when the INR is high in range in these patients than in the low therapeutic range patients. The most striking difference was between phenprocoumon and acenocoumarol. Fifty percent of patients using acenocoumarol had a subtherapeutic INR after 13 weeks compared to 51 weeks in patients using phenprocoumon. This finding is consistent with reports that longer-acting vitamin K antagonist give a more stable anticoagulation than short-acting vitamin K antagonists.²³⁻²⁵

Thirty percent of cases of a subtherapeutic INR were preceded by a bleeding episode, a surgical or medical admission, an invasive procedure or by an INR >7.0. Invasive procedures gave the highest risk of a low INR. Because the anticoagulant drug was withheld or vitamin K was given in nearly all patients, this is not surprising. Vitamin K is given to a relatively large proportion of patients, because in our study population 78% of patients use the long-acting phenprocoumon. However, vitamin K was given in even more control patients than case patients who underwent an invasive procedure. This suggests that in this study population

administering vitamin K peri-intervention reduced the risk of a subtherapeutic INR compared to withholding the anticoagulant drug.

The risk was lower in patients who were admitted for a surgical intervention than in outpatients undergoing an invasive procedure, although one would have expected similar risks. It is possible that subtherapeutic INRs occurred during admission but were adjusted before the end of the admission. Admissions for non-surgical reasons also led to a subtherapeutic INR, but less often. Even though overanticoagulation was common (INR > 7.0 in 1.6% of the controls) and vitamin K was given in nearly all patients, the relative risk of a low INR after an INR above 7.0 was only 1.6. This suggests that over-correcting, though present, is not a major cause of a subtherapeutic INR.

Subtherapeutic anticoagulation in patients using vitamin K antagonists is common and can have severe consequences. Our results give insight in the risk of subtherapeutic anticoagulation for an individual patient in the outpatient setting. We have shown that subtherapeutic INRs are common and that thirty percent of all subtherapeutic INRs could be explained by events necessitating discontinuation of the treatment, leaving 70% that were unintended. We have described risk factors that contribute to these low INRs and that can be used to prevent them. A first step can be the preferential use of long acting anticoagulants, such as phenprocoumon. Whether the differences in risk between indications are the effect of avoidable causes such as patient compliance or dosing strategies remains to be determined.

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