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Rosendaal, F.R.

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# Characteristics of Anticoagulant Therapy and Comorbidity Related to Overanticoagulation

Fernie J. A. Penning-van Beest[1], Erik van Meegen[2], Frits R. Rosendaal[3], Bruno H. Ch. Stricker[1 4]

[1]Pharmaco-epidemiology Unit, Departments of Internal Medicine and Epidemiology & Biostatistics, Erasmus University Medical Center, Rotterdam, [2]Red Cross Anticoagulation Clinic, The Hague, [3]Hemostasis and Thrombosis Research Center, Department of Clinical Epidemiology, Leiden University Medical Center, [4]Drug Safety Unit, Inspectorate for Health Care, The Hague, The Netherlands

## Keywords

Overanticoagulation, coumarin anticoagulants, incidence, comorbidity, characteristics of therapy

## Summary

The risk of hemorrhage when using coumarin anticoagulants sharply increases when the International Normalised Ratio (INR) is ≥6 0 We performed a prospective cohort study with a nested case-control design among 17,056 outpatients of an anticoagulation clinic to determine the incidence of overanticoagulation and to study the association between overanticoagulation and characteristics of anticoagulant therapy and comorbidity The incidence rate of an INR ≥6 0 was 7 8 per 10,000 treatment days in prevalent users on the starting date and 22 5 per 10,000 treatment days in incident users during the study period 300 cases with an INR ≥6 0 were compared with 302 randomly selected matched controls with an INR within the target zone Patients on acenocoumarol had an increased risk of an INR ≥6 0 compared to patients on phenprocoumon Regarding comorbidity, impaired liver function, congestive heart failure, diarrhea and fever were risk factors for overanticoagulation Increased monitoring of INR values if risk factors are present or avoidance of risk factors could prevent excess anticoagulation and potential bleeding complications

## Introduction

Coumarin anticoagulants are clinically effective in the prevention of venous and arterial thromboembolism (1) These drugs induce anticoagulation by antagonising vitamin K, thereby impairing the biological activity of the vitamin K dependent coagulation factors (factor II, VII, IX and X) (2) Inherent to their mode of action and narrow therapeutic index, hemorrhage is the most common adverse reaction to coumarin anticoagulants The risk of hemorrhage is strongly associated with the intensity of anticoagulation and sharply increases when the INR is ≥6 0 (3-6) Such an excess anticoagulant effect should therefore be prevented This necessitates identification of risk factors for overanticoagulation

Correspondence to Dr B H Ch Stricker, Pharmaco epidemiology Unit, room L448, Department of Internal Medicine, Erasmus University Medical Center Rotterdam, P O Box 2040, 3000 CA Rotterdam, The Netherlands – Phone +31 10 4087482, Fax +31 10 4633964, E mail stricker@epib fgg eur nl

A number of comorbidities are suspected to enhance the response to coumarins (7 10) Hepatic dysfunction may impair the synthesis of coagulation factors In hypermetabolic states the clearance of coagulation factors is increased Fat malabsorption and diarrhea impair the absorption of vitamin K With malignancies, the metabolism of vitamin K and the coumarin anticoagulant may be affected In congestive heart failure the distribution of the coumarin anticoagulant is altered

The stability of anticoagulant control depends on the type of anticoagulant used and has been found to be less when using the short-acting acenocoumarol because of fluctuating factor VII levels (11, 12) In addition, the patient's compliance plays a role in stability of control (13, 14) Possibly the risk of overanticoagulation is also related to these factors

The occurrence of overanticoagulation in a non selected population under everyday circumstances and the association between overanticoagulation and characteristics of anticoagulant therapy and comorbidity, have not been studied extensively Therefore, we have conducted a prospective cohort study with a nested case control design among outpatients of an anticoagulation clinic We determined the incidence of overanticoagulation (INR ≥6 0) and studied the association between overanticoagulation and characteristics of anticoagulant therapy and comorbidity 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 sociodemographic, lifestyle, and dietary factors

## Methods

### *Setting*

In the Netherlands, anticoagulant therapy is monitored by a network of more than 60 independently operating specialised anticoagulation clinics, covering over 90% of the country (15, 16) 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

### *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 The cohort therefore included prevalent users on the starting date and incident users during the study period All cohort members were followed until the first occurrence of an INR ≥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

*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 ≥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 Since 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-third of the time (17, 18) Therefore, we defined stable anticoagulation as having at least 66% of the INRs within the target zone and no INRs ≥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 focussed on sudden overanticoagulation, the INR preceding the assessment on the index day had to be within the target zone Patients who were not living independently and those making use of meals on wheels were excluded because these patients may be less able to reliably answer the questions on medication and diet Since we were primarily interested in overanticoagulation, irrespective of the question whether this was followed by hemorrhage, patients who presented at the index day with a serious bleeding complication were excluded because this may promote recall bias

*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 ≥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 characteristics of anticoagulant therapy and comorbidity, as well as on potential confounding factors, was collected from the anticoagulant medical record, through the general practitioner (GP) and the pharmacy, and by interviewing the patient The interview took place within three weeks after the index day at the private address of the patient, making use of structured questionnaires with mainly closed questions 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 and the pharmacists Blinding of the patients was not fully feasible, since 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

*Characteristics of Anticoagulant Therapy and Comorbidity*

The risk period was defined as the four-week period preceding the index day The following characteristics of anticoagulant therapy were collected from the anticoagulant medical record indication for anticoagulation, duration of therapy (categorised as ≤1 year, 1 to 5 years and ≥5 years, exclusive of former treatment episodes), type of anticoagulant used, change of type of anticoagulant in the risk period, and the latest dosage of the anticoagulant The patient was asked about compliance with anticoagulant therapy, i e regularity of pill intake and missed or extra pills in the risk period With respect to comorbidity, chronic comorbidities as well as acute illnesses during the risk period were taken into account The GP was asked whether the patient had an impaired liver, biliary or pancreatic function, an impaired gastro-intestinal absorption, congestive heart failure, hyperthyroidism, or a malignancy. If so, it was asked whether the condition had changed in the risk period Since anticoagulant therapy likely is titrated to chronic comorbidities and only a relapse or change may be related to overanticoagulation, all chronic comorbidities were categorised as absent, stable in the risk period, and worsened in the risk period Regarding acute illnesses, the patient was asked about having been ill in the risk period and if so, about his or her complaints and the presence of fever (a temperature ≥38° C) In addition, the GP was asked whether the patient had consulted him in the risk period and if so, with which medical problems

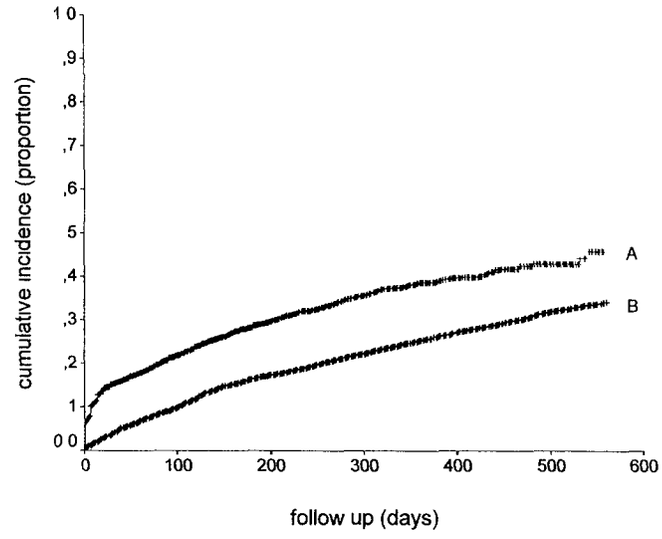


*Fig 1* The cumulative incidence of the occurrence of an INR ≥6 0 in incident (A) and prevalent (B) users of acenocoumarol or phenprocoumon

*Cofactors*

Acute illnesses and worsened chronic comorbidities may be accompanied by a change in drug use (beside the anticoagulant), weight, physical activity, dietary intake (and thereby intake of vitamin K), and/or alcohol consumption These factors may also affect the response to oral anticoagulants (19-24) and were thus considered as potential confounders The associations between these cofactors and overanticoagulation are the main subjects of the two other papers mentioned in the introduction

*Statistical Analyses*

We calculated the cumulative incidence of an INR value ≥6 0 using the Kaplan-Meier method, as well as the incidence rate Both incidence measures were calculated separately for prevalent users on the starting date and incident users during the study period, since overanticoagulation is often seen during initiation of anticoagulant therapy

Characteristics of anticoagulant therapy and comorbidity related to an INR ≥6 0 were identified using univariate conditional logistic regression analysis at first Since the unconditional analyses gave comparable results but more statistical power, we finally used unconditional logistic regression 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 characteristics of anticoagulant therapy and stable chronic comorbidities that were independently associated with an INR ≥6 0, all factors of these two categories which were univariately associated at a $p < 0.10$, age, sex, and the number of INR determinations in the preceding three months were included in a multiple regression model A comparable procedure was followed to assess worsened chronic comorbidities and acute illnesses that were independently associated with an INR ≥6 0 Cofactors which were univariately associated with an INR ≥6 0 were included as well if this resulted in a change in one of the odds ratios of 5% or over, starting with the most potent factor

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 (25)
PAR% = AR% * (proportion of exposed cases), with AR% = ((OR-1)/OR) * 100

*Table 1* Association between overanticoagulation (INR ≥6.0) and characteristics of anticoagulant therapy*

| 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 [reference] | |
| female | 125 (42%) | 108 (36%) | 1 28 [0 92-1.78] | |
| Indication for anticoagulation | | | p=0 51 | |
| atrial fibrillation | 37 | 40 | | |
| prosthetic heart valve | 31 | 31 | | |
| cardiac disease | 110 | 131 | | |
| peripheral arterial disease | 76 | 66 | | |
| cerebrovascular thromboembolism | 28 | 18 | | |
| venous embolism | 16 | 13 | | |
| prophylactic treatment | 2 | 3 | | |
| Duration of therapy | | | | |
| ≥ 5 years | 122 | 138 | 1 [reference] | |
| 1 to 5 years | 125 | 115 | 1.2 [0.9-1 8] | |
| ≤ 1 year | 53 | 49 | 1 2 [0.8-1.9] | |
| Type of anticoagulant | | | | |
| phenprocoumon | 165 (55%) | 200 (66%) | 1 [reference] | 1 [reference]† |
| acenocoumarol | 135 (45%) | 102 (34%) | 1.6 [1 1-2 2] | 1 9 [1 3-2 7]† |
| Change of type of anticoagulant | 1 | 1 | 1 0 [0.1-16 2] | |
| Dosage of anticoagulant (mg/day, mean±sd) | | | | |
| phenprocoumon | 0 83 ± 0 53 | 0 76 ± 0.30 | 1 5 [0.9-2 6] | |
| acenocoumarol | 2 93 ± 1 35 | 2 73 ± 1.20 | 1.1 [0 9-1 4] | |
| Compliance | | | | |
| no regular intake of anticoagulant | 13 | 9 | 1 5 [0.6-3.5] | |
| pills missed | 24 | 23 | 1.1 [0.6-1.9] | |
| taken more pills than prescribed | 6 | 0 | p=0.02 | |

* Values are numbers unless indicated otherwise

† Type of anticoagulant, stable congestive heart failure, stable impaired liver function, age, gender and the number of INR determinations in the preceding three months were included in the model.

## Results

The prospective cohort consisted of 17,056 patients: 9,508 prevalent users on the starting date, who had on average 380 treatment days (range 1 to 560 days) and 16 INR measurements (range 0 to 72 measurements) and 7,548 incident users during the study period, who had on average 98 treatment days (range 1 to 558 days) and 9 INR measurements (range 1 to 60 measurements). The cumulative incidence of the occurrence of an INR value ≥6.0 is represented in Fig 1. As expected, overanticoagulation occurred more often in incident users. After six months of follow up, the cumulative incidence was 17% in prevalent users and 29% in incident users. After one year it was 25% and 39% respectively, and at the end of the study period, i.e. after 560 days of follow up, the cumulative incidence was 34% in prevalent users and 46%

*Table 2* Association between overanticoagulation (INR ≥6 0) and comorbidity*

| Variable | Cases n=300 | Controls n=302 | OR [95% CI] univariate | OR [95% CI] multivariate |
|---|---|---|---|---|
| Chronic comorbidities stable | | | | |
| congestive heart failure | 60 | 45 | 1 5 [0 98 2 3] | 1 6 [1 04 2 6]† |
| malignancy | 23 | 21 | 1 1 [0 6 2 1] | |
| impaired liver function | 18 | 7 | 2 7 [1 1 6 5] | 2 8 [1 1 6 9]† |
| impaired GI absorption | 9 | 7 | 1 3 [0 5 3 5] | |
| hyperthyroidism | 4 | 3 | 1 3 [0 3 6 0] | |
| impaired biliary function | 1 | 3 | 0 3 [0 0 3 2] | |
| Chronic comorbidities worsened | | | | |
| congestive heart failure | 14 | 3 | 5 3 [1 5 18 8] | 3 0 [0 8 12 0]‡ |
| malignancy | 4 | 2 | 2 0 [0 4 11 2] | |
| *Acute illnesses* | | | | |
| diarrhea | 17 | 3 | 6 0 [1 7 20 7] | 12 8 [1 6 104 9]‡ |
| illness of the urinary tract | 19 | 5 | 4 0 [1 5 10 9] | 1 2 [0 4 4 2]‡ |
| illness of the respiratory tract | 93 | 53 | 2 1 [1 4 3 1] | 1 0 [0 5 1 7]‡ |
| fever | 45 | 10 | 5 3 [2 6 10 7] | 2 9 [1 1 7 7]‡ |

* Values are numbers

† Stable congestive heart failure stable impaired liver function type of anticoagulant age gender and the number of INR determinations in the preceding three months were included in the model

‡ Relapse of congestive heart failure diarrhea illness of the urinary tract illness of the respiratory tract fever age gender the number of INR determinations in the preceding three months use of antibacterial drugs use of analgesics & NSAIDs change in weight change in physical activity and change in frequency of suppers were included in the model

in incident users The number of prevalent users with an INR ≥6 0 was 2,813, which is corresponding to an incidence of 18 per 1000 INR measurements and an incidence rate of 7 8 per 10,000 treatment days 1 663 incident users had an INR ≥6 0, the incidence being 26 per 1000 INR measurements and the incidence rate being 22 5 per 10,000 treatment days

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 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 fourteen days, for cases as well as for controls In both case and control groups, the mean age was 68 years, the proportion of men was 58% and 64% respectively

The associations between overanticoagulation and characteristics of anticoagulant therapy are shown in Table 1 The indication for anticoagulation and the duration of therapy were not related to an INR ≥6 0 Neither was the dosage of the anticoagulant The type of anticoagulant used, however, was a risk factor for overanticoagulation Patients on acenocoumarol had an increased risk of 1 9 (95%CI 1 3-2 7) compared to patients on phenprocoumon The PAR% of overanticoagulation associated with the use of acenocoumarol was 21 3% A change of type of anticoagulant occurred in only two patients Regarding compliance six cases but no controls had taken more pills than prescribed (p = 0 02)

With respect to comorbidity (Table 2), the only stable chronic comorbidities related to overanticoagulation were impaired liver function and congestive heart failure The latter condition resulted in an increased risk of an INR ≥6 0 of 1 6 (95%CI 1 04-2 6) The corresponding PAR% was 7 5% Patients with an impaired liver function had an increased risk of 2 8 (95%CI 1 1-6 9) None of these patients had liver cirrhosis, one case and two controls had chronic active hepatitis In sixteen cases and in six controls, the liver function was otherwise impaired (including abnormal liver enzymes) and of two cases the kind of impairment was not stated by the GP The PAR% of overanticoagulation associated with an impaired liver function was 3 9% A worsening condition was infrequent for most chronic comorbidities A relapse of congestive heart failure was present in fourteen cases and in three controls and was univariately associated with an increased risk of overanticoagulation of 5 3 (95%CI 1 5-18 8) After adjustment for confounding factors the increased risk was 3 0 (95%CI 0 8 12 0) The corresponding PAR% was 3 1% Regarding acute illnesses, diarrhea and fever were risk factors for overanticoagulation, with relative risks of 12 8 (95%CI 1 6 104 9) and 2 9 (95%CI 1 1-7 7) respectively Stratifying for duration of fever (<4 days and ≥4 days) revealed an increased risk of an

INR ≥6 0 in both strata (univariate OR 4 4 (95%CI 1 6-12 1) and OR 6 7 (95%CI 2 3-19 7) respectively) The PAR% of overanticoagulation associated with diarrhea and fever were 5 2% and 9 8% respectively Illnesses of the urinary or respiratory tract were only univariately associated with an increased risk of an INR ≥6 0 (OR 4 0, 95%CI 1 5-10 9 and OR 2 1, 95%CI 1 4-3 1 respectively)

## Discussion

We determined the incidence of overanticoagulation among outpatients of an anticoagulation clinic Furthermore, we studied the association between overanticoagulation and characteristics of anticoagulant therapy and comorbidity The incidence rate of an INR ≥6 0 was 7 8 per 10,000 treatment days in prevalent users on the starting date and 22 5 per 10,000 treatment days in incident users during the study period Since the patients' INRs were not measured daily, the real incidence of overanticoagulation may be higher Patients with an impaired liver function or congestive heart failure, as well as those using acenocouma rol had an increased risk of an INR ≥6 0 Fever and diarrhea were also risk factors for overanticoagulation The clinical implication of our findings lies in the possibility of prevention or early detection of excess anticoagulation, and thus of bleeding complications, by paying special attention to these risk factors when monitoring anticoagulation For example, patients with an impaired liver function should be monitored carefully and in case of fever, the patient's INR should be measured within seven days Similarly, the use of phenprocoumon instead of acenocoumarol might be considered This has been suggested before by others (11, 12), because of the more stable anticoagulant control when using phenprocoumon compared to acenocoumarol

Diagnostic suspicion bias may play a role in the association of fever and diarrhea with overanticoagulation, since patients are instructed to inform the clinic of acute illnesses If considered necessary, the patient's INR is measured earlier than the appointed date Excluding patients whose INRs were measured earlier from the analyses, fever and diarrhea remained risk factors for overanticoagulation

The presence of chronic comorbidities was based on GP diagnoses Validation of drug use by reference to pharmacy data, revealed that 90% of the patients with a GP diagnosis of congestive heart failure had indeed used drugs for congestive heart failure or ischaemic heart disease

Although postulated as interacting with anticoagulant therapy, malignancy, an impaired gastro-intestinal absorption, hyperthyroidism, and an impaired biliary function were not related to overanticoagulation in our study Neither in case of a stable condition, nor in case of a relapse in the risk period This may be explained by the low prevalence of some of these conditions, which requires a larger study population to attain enough statistical power In addition, the increase in INR by the potentially interacting comorbidity may be of less magnitude than defined in our study

Compliance may influence the stability of anticoagulant control (13, 14) In our study, as expected, taking more pills than prescribed was associated with overanticoagulation We were not able to test this association multivariately, but in view of the clear-cut pharmacological pathway this also would have been meaningless Missing pills and irregularly taking the anticoagulant were not related to overanticoagulation However, missing pills occurred only occasionally (once or twice in the four-week risk period) and patients who are constantly noncompliant most probably will not become stable and therefore have been excluded a priori

So far as we are aware of, epidemiological studies on risk factors for overanticoagulation in a non-selected population under everyday circumstances are scarce and were only published for the first time in 1998 Two out of three earlier studies (26, 27) have some limitations Firstly, in one study (26), the cases were identified during a 12-month period whereas the controls were selected in June only In the second study (27), cases and controls do not seem to be time-matched either Secondly, the number of overanticoagulated patients was small (65 and 31 respectively) Thirdly, only univariate analyses were performed The third study (28) was well-performed Diarrhea and taking more warfarin than prescribed were determinants of an INR value ≥6 0, similar to our study On the contrary, advanced malignancy was a risk factor for overanticoagulation in their study, but fever was only univariately associated Impaired liver function, congestive heart failure, and illnesses of the urinary or respiratory tract were not considered by Hylek et al An important difference between the study of Hylek et al and our study is that we only included stable cases and controls Besides, we used a four-week risk period and they used a one week risk period Lastly, the study population of Hylek et al used warfarin, while our patients used phenprocoumon or acenocoumarol

Information on the incidence of overanticoagulation under everyday circumstances is even scarcer than information on risk factors for overanticoagulation In the study of Brigden et al (27) 0 3% of the INRs were ≥6 0 In the study of Panneerselvam et al (26) 0 2% of the INRs were >7 0 When expressed in a comparable way, 2 0% of the INRs in our study were ≥6 0 and 0 9% of the INRs were >7 0 The much lower incidence of overanticoagulation reported by Brigden et al and Panneerselvam et al may be explained by the lower target range of anticoagulation in their studies

In conclusion, in this study among previously stable outpatients in an anticoagulation clinic, overanticoagulation was associated with the type of anticoagulant used and with some comorbidities Increased monitoring of INR values if risk factors are present or avoidance of risk factors, could prevent excess anticoagulation and potential bleeding complications

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