ORIGINAL INVESTIGATION

Bleeding Complications in Oral Anticoagulant Therapy

An Analysis of Risk Factors

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Background: Insufficient data are available about the safety of oral anticoagulant therapy The specialized organization of thrombosis services in the Netherlands can provide important information on the bleeding risk and various risk factors for bleeding in patients receiving oral anticoagulant therapy

Methods: In a follow-up study over a 12-month period beginning in January 1988 on all patients treated by the Leiden Thrombosis Service, the frequency of bleeding complications was assessed A Poisson regression model was used to assess the relative contribution to the bleeding risk of age, sex, target zone (intensity of anticoagulant effect aimed at), achieved intensity of anticoagulant therapy (International Normalized Ratio), and the type of coumarin derivative used

Results: Six thousand eight hundred fourteen patients experienced 1003 bleeding complications (16 5 per 100 treatment-years), 162 of which were major bleeds (2 7 per 100 treatment-years) Bleeding increased significantly with age (32% increase for all bleeding, 46% for major bleeding for every 10-year increase in age in comparison with age <40 years) Women had more minor bleeding complications than men, whereas both sexes experienced major bleeding in an equal frequency There was no influence of target zone, while every one point increase in International Normalized Ratio gave 42% more major bleeding (54% more regarding all bleeding) Use of acenocoumarol resulted in fewer bleeds (26% less regarding all bleeding and 46% less regarding major bleeding) than use of phenprocoumon

Conclusions: The risk of anticoagulant therapy in a routine, real-life situation is similar as in the setting of several well-organized clinical trials The risk of bleeding complications rises significantly with age and with the achieved intensity of anticoagulation, and is dependent on the type of coumarin derivative that is used

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ALTHOUGH COUMARIN derivatives have been used for several decades, there still is no general agreement about the indications for this therapy [1] The most important cause of this disagreement is a lack of good clinical studies concerning the efficacy and safety of coumarins in various diseases Also, for a long time the intensity of anticoagulation could not be expressed in unambiguous terms Only after the development of the International Normalized Ratio (INR) as the uniform scale to express the intensity of anticoagulation has it become possible to target at the same therapeutic ranges while using different prothrombin time reagents [2] In many places the implementation of oral anticoagulation is hampered by the lack of the required infrastructure Adequate and safe anticoagulation depends on good patient compliance, accurate laboratory testing, and adequate dosage regulation This purpose requires a specialized organization [3] In the Netherlands, this task is performed by a network of thrombosis services whose areas of care cover over 90% of the Dutch population [3,4] It was the purpose of this study to assess the safety of the anticoagulation therapy as supervised by one of these services To this end, we performed a follow-up study among the patients of the Leiden Thrombosis Service

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SUBJECTS AND METHODS

THE LEIDEN THROMBOSIS SERVICE

The Leiden Thrombosis Service functions like all Dutch thrombosis services.[3,4] It takes care of the control of treatment with coumarin derivatives for all outpatients in the region of Leiden, the Netherlands. The area has about 460 000 inhabitants and four hospitals. The medical staffs of the individual hospitals take care of in-hospital anticoagulant therapy. After discharge, patients are referred to the thrombosis service for the control of outpatient anticoagulant therapy. A specialized system of oral anticoagulant monitoring has been developed.[3] In this specialized system, nurses who are specially trained in anticoagulant therapy control play a central role. They collect blood samples of the patients at several outpatient facilities in Leiden and surrounding villages. When necessary, patients are visited at home. With every venipuncture, a standardized short history is taken about bleeding complications, changes in comedication, intercurrent illnesses, and surgical procedures. Each new patient receives extensive instructions about anticoagulant therapy. Subsequently, prothrombin times are assessed at the thrombosis service, where a team of specialized physicians determines the dosage and the control period, which is dependent on the stability of the anticoagulant level. The control period varies from 1 to 6 weeks, with an average of 3.3 weeks. The dosage is printed on a dosage list that the patient receives by mail the next day. In case of bleeding complications or excessive intensity of the anticoagulant effect, the patient is telephoned the same day for dose adjustment or administration of vitamin K. The Leiden Thrombosis Service has been treating patients in this way for more than 30 years. All administrative data, test results, dosage lists, as well as the dosage determination have been computerized since 1973. In fifty-five percent of all checks, an automatic dose prescription is generated Details of this dosage algorithm have been described previously.[5]

DATA COLLECTION AND ANALYSIS

All patients under treatment at the Leiden Thrombosis Service on January 1, 1988, were selected from the computer files. From these patients, the following items were abstracted from the computer files: identification number, date of birth, sex, indication for anticoagulant therapy, coumarin derivative used (either phenprocoumon or acenocoumarol), target range, all prothrombin times, all doses prescribed, and, if applicable all bleeding complications, hospital admissions, death and cause of death, and reasons to stop treatment during the year 1988. The indications and the target ranges (intensity of anticoagulant effect aimed at) of anticoagulant therapy are listed in **Table 1**. The study population was subdivided into patients who received anticoagulant therapy for prevention of arterial thrombotic disease and patients with any other indication.

Bleeding complications were subdivided into major and minor bleeding. Major bleeding was defined as intracranial hemorrhage, bleeding that caused death, bleeding that required blood transfusion, admission to a hospital, or surgery, as well as all muscle and joint bleeding. Minor bleeding included all other bleeding complications. In case of doubt, any bleeding was coded as major bleeding. When it was possible but not certain that a patient died of a bleeding complication, this death was coded as caused by bleeding.

LABORATORY INVESTIGATION

Venous blood was collected in 1/10 volume of 0.11 mol/L trisodium citrate, and prothrombin times were determined using the Thrombotest reagent (Nyegaard, Oslo, Norway). This prothrombin time reagent was specifically devised for the control of oral anticoagulant therapy[6] and is widely used by the thrombosis centers in the Netherlands. Results are expressed in INR.[2]

Incidence rates of bleeding complications were calculated in the standard way, by dividing the number of events by the number of treatment-years. To study the independent contribution to the bleeding risk of the putative risk factors age, sex, target zone, achieved level of intensity of anticoagulation, and type of coumarin drug, we set up a Poisson regression model. The incidence rate ratios derived from this regression analysis may be viewed as relative risks, ie, the risk of bleeding relative to the reference risk factor category. The reference categories were arbitrarily set at age under 40 years, male sex, low target zone, achieved INR below 2, and phenprocoumon use. The variables were first categorized in a limited number of classes and subsequently entered into the model in an unfactored way. The incidence rate ratios were calculated for each 10 years' increase in age, female sex, each increase in target zone, eachincrease of 1 INR, and acenocoumarol use. In the Poisson regression model, we analyzed six INR zones ranging from INR below 2 to INR of 6 or greater, with an increment of 1.0 INR per zone. For age, five groups were analyzed ranging from age 39 years and lower to age greater than 69 years, with an increment of 10 years per group. For each age group, each type of coumarin used, each sex, every target zone, and each INR zone, the following items were counted: the number of complications regarding all bleeding and major bleeding separately and the number of days spent within the particular INR zone. For this last item, from every INR half the control period before and half the control period afterward was taken (example, an INR was assessed at April 1, May 1, and May 15. The number of days spent within the INR of May 1 [22 days] is calculated by summing half the number of days between April 1 and May 1 [15 days] and between May 1 and May 15 [7 days]). This method has been described extensively elsewhere.[7] For each patient, the observation started on January 1, 1988, and ended on December 31, 1988, or when the first complication took place, or when treatment was stopped for any other reason.

The proportion of time the patients spent with their INR within the target range was assessed using the "cross-section-of-the-files" method.[4] In this method, an arbitrary date is chosen. From all the patients, the INR at this date or the last INR before this date is taken. Subsequently, the percentage of INRs within the target range is assessed. Because the date was chosen arbitrarily and because a high number of patients is involved, the percentage of INRs within the target range is a reflection of the proportion of time the patients spent with their INR within the target range.

RESULTS

The **Figure** shows the distribution of patients, subdivided according to sex, over the various indications for anticoagulant treatment Most patients, especially men, were treated for prevention of arterial thrombotic disease

In **Table 2**, the number of patients, the number of treatment-years, age, and the type of coumarin used are presented subdivided to indication for anticoagulant treatment (prevention of arterial thrombotic disease in comparison with any other indication) and subdivided to sex The percentage of INRs within the target range (cross-section-of-the-files method) was 77

The total number of bleeding episodes was 1003, or 16 5 per 100 treatment-years (**Table 3**) Major bleeding occurred 2 7 times per 100 treatment-years, and in 39 cases bleeding resulted in death (0 64 per 100 treatment-years) The most frequent major bleeding complications were bleeding from the gastrointestinal tract, intracranial bleeding, and muscle bleeding Intracranial bleeding was the most frequent cause of bleeding-related death (22 cases) In nine (5 5%) of 162 cases (three men and six women), the bleeding complication was coded as major while there was no absolute certainty about this classification Eight of these patients died outside a hospital, and their general practitioners reported intracranial bleeding as the cause of death without a computed tomographic scan or autopsy to confirm this diagnosis One patient was admitted to a hospital reportedly because of a severe hematoma

To establish the independent influence of various possible risk factors for the occurrence of bleeding (age, sex, target zone, coumarin derivative used, and the achieved intensity of anticoagulation or INR), we performed a Poisson regression analysis, the results of which are given in **Table 4** For all bleeding as well as major bleeding, there was a significant increase in complications with age in comparison with the age group of less than 40 years, every 10 years' increase of age was associated with 32% more bleeding and 46% more major bleeding Women appeared to have more complications when all bleeding was considered For major bleeding, the sex difference disappeared For both major and all bleeding, there was less bleeding when the short-acting acenocoumarol is used in comparison with phenprocoumon Bleeding frequency seems to become lower when a more intensive level of anticoagulation is targeted (increasing target zone) When not the targeted but the achieved level of anticoagulation is analyzed, bleeding rises significantly (major and all bleeding) with increasing INR

In **Table 5** the bleeding complications per 100 treatment-years are given for each of six achieved INR levels For men and women alike, a clear rise in bleeding complications can be seen for increasing intensities of anticoagulation

Table 1. Indications and Target Ranges for Oral Anticoagulant Treatment*

Prophylaxis of venous thromboembolism (INR, 2 4-2 9-3 7)	
Postoperatively	
Immobilization	
Heart failure	
Treatment of venous thromboembolism (INR, 2 8-3 5-4 8)	
Superficial thrombophlebitis	
Deep vein thrombosis	
Pulmonary embolism	
Prevention of arterial thrombotic disease (INR, 2 8-3 5-4 8)	
Myocardial infarction (long term)	
Angina pectoris	
Coronary bypass surgery and PTCA	
Peripheral arterial disease and surgery	
Cerebrovascular disease	
Prevention of arterial embolism (INR, 2 8-3 5-4 8)	
Atrial fibrillation	
Arterial embolism	
Cardiomyopathy	
Heart valve disease	
Prosthetic heart valves (INR, 3 2-4 0-5 3)	

**INR indicates International Normalized Ratio, PTCA percutaneous transluminal coronary angioplasty*

COMMENT

The results of this study are a reflection of normal daily practice of the Leiden Thrombosis Service Since all data are routinely stored in the computer and because the Leiden Thrombosis Service has a regional task, it is unlikely that bias occurred

Six thousand eight hundred four patients were treated by the Leiden Thrombosis Service in 1988 The catchment area of this service is about 460 000 persons Therefore, one of every 66 persons was treated in our center Most patients, especially men, are under treatment for the prevention of arterial thrombotic disease (Figure and Table 2) This group consists mainly of patients who suffer from atherosclerotic disease myocardial infarction or peripheral arterial disease (Table 1) Traditionally, many of our patients with arteriosclerotic disease are treated with coumarin derivatives This is due partly to the existence of the system of the Dutch thrombosis services[3] and partly to the results of the Sixty Plus Reinfarction Study [8] As indicated above, these services offer the optimal infrastructure for anticoagulant therapy

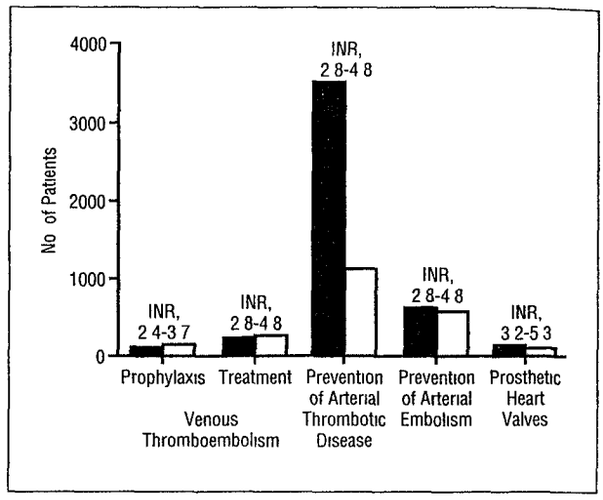
Bleeding complications (Table 3) were less frequent in patients with arterial thrombotic disease than in patients with other indications for anticoagulant treatment This is true for men and women and for all the various subdivisions of complications we investigated Patient selection bias cannot be excluded as an explanation for this phenomenon Patients with arterial thrombotic disease usually are taking long-term anticoagulant therapy and pa-

tients at high risk for bleeding may have stopped anticoagulant therapy in the past This does not apply to the other indication group with many patients taking short-term anticoagulant therapy

The figures on bleeding complications in our study (Table 3) are similar to the results of the Sixty Plus Reinfarction Study [9] The total bleeding rate of 16 6 per 100 treatment-years in this prospective, double-blind trial is similar to the frequency of 16 5 per 100 treatment-years that we found In the Sixty Plus Reinfarction Study, major bleeding occurred at a rate of 5 15 per 100 treatment-years, while six patients died of a bleeding complication (0 86 per 100 treatment-years) In the Sixty Plus Reinfarction Study, however, the definition of a major bleeding complication was different from our definition any bleed that made breaking the treatment code necessary We think that this explains the twofold difference in major bleeding complications that was found, while the occurrence of total bleeding and fatal bleeding is the same

Lower incidences of major bleeding were found in the recent Norwegian warfarin reinfarction study (0 86 per 100 treatment-years) and in two recent trials on the effect of warfarin on the prevention of arterial embolism in patients with nonrheumatic atrial fibrillation [10 12] In these three studies there are important differences from our study regarding the definition of bleeding complications, patient selection, and target intensity of anticoagulant therapy In three retrospective studies,[13 15] a higher frequency of bleeding was found, while the results of three other studies are similar [16 18] The problem of different definitions of complications in these studies is difficult to solve Our data indicate that anticoagulation as supervised in the daily setting of our thrombosis service is no less safe than it was in the setting of a randomized clinical trial like the Sixty Plus Reinfarction Study [9]

Looking for risk factors for bleeding complications, we evaluated age, sex, target range, the achieved level of intensity of anticoagulation, and the type of coumarin derivative using a Poisson regression model (Table 4) The regression analysis as given in this table was performed



Patient distribution according to treatment indication groups and subdivided according to sex See Table 1 for the composition of the indication groups For each group, the target level of intensity of oral anticoagulation is indicated in International Normalized Ratio (INR) (closed bars indicate men, shaded bars, women)

without subdividing according to indication for anticoagulant therapy When such a subdivision was made, however, the results were exactly the same As can be expected from the data in Table 3, patients with indications other than arterial thrombotic disease had a higher risk of bleeding This was true for all bleeding (rate ratio, 1 24, 95% confidence limits, 1 07, 1 43) as well for major bleeding (rate ratio, 1 66, 95% confidence limits, 1 20, 2 31) Women appear to have more bleeding than men when all bleeding is considered, but not when major bleeding is considered Until now, no difference in bleeding frequency between men and women has been reported in the literature [9 13 16 18] We found a significant increase with age for minor as well as major bleeding In comparison with the age group of less than 40 years, every 10 years' increase in age was associated with 32% more bleeding and 46% more major bleeding In most studies, age was not found to be a risk factor,[9 13 14 16 17] while in others this was the case [15 18] A possible explanation for this differ-

Table 2. Characteristics of the Study Population

	Men			Women			Total		
	Arterial Disease	Other Indications	Total	Arterial Disease	Other Indications	Total	Arterial Disease	Other Indications	Total
No. of subjects	3511	1106	**4617**	1103	1094	**2197**	**4614**	**2200**	**6814**
No of treatment years	3268	926	**4194**	1004	887	**1891**	**4272**	**1813**	**6085**
Age, y									
Mean	64	65	64	68	68	68	65	68	66
Median	64	67	65	70	72	70	65	69	62
Range	23-94	16-95	16-95	24-96	5-95	5-96	23-96	5-95	5-96
Coumarin derivative used									
Phenprocoumon	3079	976	**4055**	974	928	**1902**	**4053**	**1904**	**5957**
Acenocoumarol	432	130	**562**	129	166	**295**	**561**	**296**	**857**

Table 3. Observed Bleeding Complications

	No. (per 100 Treatment-Years) of Complications in								
	Men			Women			Total		
	Arterial Disease	Other Indications	Total	Arterial Disease	Other Indications	Total	Arterial Disease	Other Indications	Total
All Bleeding	**398** (12 2)	**157** (16 9)	**555** (13 2)	**222** (22 1)	**226** (25 5)	**448** (23 7)	**620** (14 5)	**383** (21 1)	**1003** (16 5)
Minor bleeding	332 (10 2)	122 (13 2)	**454** (10 8)	196 (19 5)	191 (21 5)	**387** (20 5)	**528** (12 4)	**313** (17 3)	**841** (13 8)
Major bleeding	**66** (2 0)	**35** (3 8)	**101** (2 4)	**26** (2 6)	**35** (4 0)	**61** (3 2)	**92** (2 2)	**70** (3 9)	**162** (2 7)
Intracranial	13 (0 40)	10 (1 1)	**23** (0 55)	7 (0 70)	8 (0 90)	**15** (0 79)	**20** (0 47)	**18** (0 99)	**38** (0 62)
Digestive tract	27 (0 83)	12 (1 3)	**39** (0 93)	8 (0 80)	11 (1 2)	**19** (1 00)	**35** (0 82)	**23** (1 3)	**58** (0 95)
Muscle joint hematoma	13 (0 40)	5 (0 54)	**18** (0 43)	7 (0 70)	6 (0 68)	**13** (0 69)	**20** (0 47)	**11** (0 61)	**31** (0 51)
Other	13 (0 40)	8 (0 86)	**21** (0 50)	4 (0 40)	10 (1 1)	**14** (0 74)	**17** (0 40)	**18** (0 99)	**35** (0 58)
Fatal bleeding	12 (0 37)	14 (1 5)	**26** (0 62)	6 (0 60)	7 (0 79)	**13** (0 68)	**18** (0 42)	**21** (1 2)	**39** (0 64)

ence with most of the literature is that we had a large group of patients of older age Besides, the most striking rise in bleeding rate was found in patients above the age of 70 years

We did not find an increase in bleeding, either total or major, with increasing target zones This result was to be expected in the multivariate Poisson analysis, in which we adjusted for the achieved intensity of anticoagulation To our surprise, however, we also observed no effect of the target zones in the univariate analysis, in which the achieved level was not taken into account (data not shown) This is in contrast with the literature, where generally an increase in bleeding frequency is found [19 23] A possible explanation could be that we were unable to remain at the target level a sufficient length of time However, using the cross-section-of-the-files method, 77% of the INRs were within the target range, which indicates a good level of therapeutic quality Most studies in the literature compare patients with the same indication for anticoagulant therapy in their target range–dependent bleeding risk In our study population there were different indications for therapy with coumarins in the various target zones (Table 1 and Figure) An important factor in this regard is that in the lowest target zone (INR, 2 4 to 3 7) more than 80% of the patients with a bleeding complication were classified in this target zone because of a relative contraindication to anticoagulant therapy (data not shown) Without this contraindication, they would have been classified in the middle target zone (INR, 2 8 to 4 8), corresponding to their indication for anticoagulant therapy This vulnerable group of patients has a great influence on the frequency of bleeding in patients in the lowest target zone This possibly explains the surprisingly negative influence on the bleeding risk of increasing target zones When not the intended but the achieved level of anticoagulation was analyzed, a clear rise of bleeding with increasing intensity was found (Table 4) For all bleeding, we found 54% more bleeding for every rise of the INR with one point For major bleeding this figure is 42% These findings are in good agreement with the literature [3 9 16 19 21 24] In Table 5, the number of bleeding complications in relation to the achieved level of INR is shown These data are the same as in the Poisson regression analysis Presentation in this way gives another, possibly more informative, view of the influence of increasing INR on the bleeding frequency

The fourth risk factor we investigated was the use of

Table 4. Results of Poisson Regression Analysis: Rate Ratios (95% Confidence Limits)*

	All Bleeding Complications	Major Bleeding Complications
Age	1 32 (1 22, 1 43)	1 46 (1 20, 1 78)
Sex	1 65 (1 44, 1 90)	1 16 (0 83, 1 61)
Target zone	0 74 (0 61, 0 90)	0 57 (0 38, 0 86)
INR	1 54 (1 44, 1 65)	1 42 (1 21, 1 68)
Coumarin type	0 74 (0 59, 0 94)	0 54 (0 29, 0 99)

*For age, the rate ratio is presented for each 10 years' increase in age in comparison with age younger than 40 years for sex, for women in comparison with men, for target zone, for each rise in target zone in comparison with the lowest one, for International Normalized Ratio (INR), for each increase in one unit INR in comparison with INR below 2, and for coumarin type, for the use of acenocoumarol in comparison with phenprocoumon

Table 5. Observed Bleeding Complications per 100 Treatment-Years With Increasing INR*

	All Bleeding		Major Bleeding	
INR	Men	Women	Men	Women
<2	14	9	3	
2-3	8	16	2	3
3-4	11	19	2	3
4-5	15	25	4	4
5-6	26	51	5	5
≥6	49	143	5	13

*INR indicates International Normalized Ratio

different coumarin drugs. We were able to do this study because both coumarin derivatives (phenprocoumon and acenocoumarol) were taken by a substantial part of the patients. We found almost two times less bleeding when the short-acting acenocoumarol (half-life, 14 hours) was used in comparison with the long-acting phenprocoumon (half-life, 170 hours). A similar finding was found in the Sixty Plus Study.[9] Possibly, an overintense anticoagulant effect due to phenprocoumon will last longer and thus may lead to more bleeding. Our study is limited in this regard, however. The choice between the use of acenocoumarol or phenprocoumon is made by the referring specialist, who starts the treatment on the basis of his or her preference. In general there is a preference in our region for the use of the long-acting phenprocoumon because a more stable anticoagulation level can be achieved. Further investigation clearly is necessary on this point. It is too early to draw therapeutic consequences from this finding because efficacy data are required to compare the balance of efficacy and bleeding for the two drugs. Whether there is a different bleeding frequency with the use of warfarin is an open question at this moment, because no comparative data are available on this derivative.

In conclusion, our data provide information on the risks of anticoagulant therapy in a routine, real-life situation as opposed to the setting of well-organized clinical trials. Important findings are the increase of bleeding complications with increasing age and the dependence of bleeding frequency on the type of coumarin derivative used.

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