Improving the quality of oral anticoagulant therapy

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CHAPTER 7

THE QUALITY OF ORAL ANTICOAGULANT THERAPY AND RECURRENT VENOUS THROMBOTIC EVENTS IN THE LEIDEN THROMBOPHILIA STUDY (LETS).

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Summary

Background: The INR target range is a relatively narrow range in which the efficacy of oral anticoagulant treatment, i.e. prevention of extension and recurrence of thrombosis, is balanced with the risk of haemorrhagic complications. Over the years different INR target ranges have been implemented for individual indications depending on their thrombotic potential. In most of the studies defining these INR targets the treatment of the patients was aimed at a certain INR range, but in the analysis no account was taken of the time the patients spent within this range in reality.

Methods: The Leiden Thrombophilia Study (LETS) is a population-based case-control study on risk factors for venous thrombosis, in which many genetic and acquired factors have been investigated. Our aim was to investigate the effect of the quality of the oral anticoagulant therapy for the initial venous thrombosis and its relationship with recurrence of thrombosis. Quality of anticoagulation was defined as the time spent at various INR levels during treatment, and we focused on the effect of sustained intensities above a certain INR in preventing recurrences later on.

Results: 266 patients with a total follow up of 2495 patient-years were studied. Mean duration of the initial anticoagulant therapy van 194.5 days (range 48 – 4671). During follow up 58 recurrences were diagnosed (cumulative recurrence rate of 21.8% over 9 years). Mean INR during initial therapy was 2.90, with 90.3% (CI_{95} 88.4 – 92.3%) of the time spent above an INR of 2.0, and 39.1% (CI_{95} 35.5 – 42.7%) above an INR of 3.0. Patients who spent more time below the target range or who had shorter duration of anticoagulation, did not experience a higher risk of recurrence after the initial period of anticoagulation had passed.

Conclusion: Provided oral anticoagulant treatment is adequately managed, according to international guidelines, recurrent thrombosis can not be ascribed to variation in the primary treatment. Further progress in reducing the risk of recurrence should therefore be aimed at identifying other explanatory factors and subsequently fine-tuning the target ranges.

Introduction

For decennia the treatment of venous thrombosis has been based upon heparins (intravenous or subcutaneous) in the acute phase and oral coumarin vitamin K antagonists (warfarin, phenprocoumon or acenocoumarol) for the long-term treatment. This treatment has been proven effective and over the years much work has been done in further improving it.

Vitamin K antagonists inhibit the production by the liver of the vitamin K-dependent coagulation factors (Factor II, VII, IX and X) and are absorbed in the gut. They are susceptible to many influences, such as diet, comedication and illness, and need frequent monitoring. Their action is measured through the Prothrombin Time (PT) expressed as International Normalized Ratio (INR). The INR target range is a relatively narrow range in which efficacy of the treatment, i.e. prevention of extension and recurrence, is balanced with the risk of haemorrhagic complications. Over the years different INR target ranges have been implemented for individual indications depending on their thrombotic potential[1-5]. In most of the studies defining the INR targets, a fixed target was aimed for, and in the analysis no account was taken of the time the patients spent within this range in reality.

The interpretation of the quality of oral anticoagulant therapy (OAT) has received more attention in studies concentrating on the bleeding complications arising from this treatment[6-8], in studies comparing the different coumarins used for oral anticoagulation[9-11], and in studies dealing with the development of patient self-management in this area[12-14] than in studies of efficacy. Several methods have been proposed in the past to determine the quality of coumarin therapy, e.g. fraction of INRs in range, cross-section of the files, and linear interpolation[15-16].

The Leiden Thrombophilia Study (LETS) [17-18] is a population-based case-control study on risk factors for venous thrombosis, in which many genetic and acquired factors have been investigated [19-25]. Although the patient inclusion was finished in 1993, laboratory analyses have been performed up to the present, in addition to which the records have been kept up-to-date with regard to follow-up of the patients[29].

Our aim was to investigate the effect of the quality of the oral anticoagulant therapy for the initial venous thrombosis and its relationship with recurrence of thrombosis in the LETS patients. We have opted to express the quality of the anticoagulation as the time spend above a certain INR calculated with the method of linear interpolation.

Patients and methods

Study population

The design of the population-based case-control study (LETS) has been described previously [17-18]. Briefly, consecutive patients with a first episode of an objectively diagnosed deep-vein thrombosis were selected from the files of three anticoagulation clinics in The Netherlands (Leiden, Amsterdam, and Rotterdam) in the period between 01-01-1988 and 31-12-1992. These regional anticoagulation clinics are responsible for the management of oral anticoagulant treatment of virtually all patients within a well-defined geographical area. All patients were younger than 70 years of age without evidence of an underlying malignancy. The original LETS study included 474 patients and 474 sex- and age-matched controls.

For the purpose of the quality of anticoagulation analysis only those patients were included who originated at the Leiden anticoagulation clinic (n=272) and for whom follow up was complete up to 01-01-2002 (n=266, 98%). All patients enrolled in the LETS study gave informed consent for long-term follow-up. All patients have been followed from the date of the initial thrombosis till 01-01-2002 unless they were lost to follow-up through emigration, had a recurrent thrombosis, or died. For the purpose of the analysis of the initial anticoagulation treatment period in regard to the development of recurrent venous thrombosis (VT) the follow-up period ended at the time of recurrence, death or emigration. The diagnosis of recurrent VT had to be objectivated through compression ultrasound echography (CUS), venography or impedance plethysmography for DVT, or perfusion-ventilation lung scanning or spiral computerized tomography for pulmonary embolism. All patients were regularly contacted by phone or mail to ascertain their condition and to update the follow-up. In case of hospital admissions or visits to physicians possibly related to a recurrence of thrombosis the treating physicians were contacted for detailed information.

The data concerning INR values and coumarin dosages for the initial period of anticoagulant therapy, and in most cases for subsequent periods of anticoagulant therapy, were retrieved from the computerised files of the Leiden anticoagulation clinic. The Leiden clinic serves an area of around 500 000 inhabitants, and provides anticoagulant monitoring to 10,000 patients per year, with around 5,000 patients actively on anticoagulant treatment at any given time. Roughly 75% of the patients are treated with the long-acting phenprocoumon (Marcoumar®) and 25% with the short-acting acenocoumarol (Sintrom Mitis®). The choice of the anticoagulant is based on personal preferences of physicians, not on clinical features of the patient. Laboratory checks and subsequent adjustments of the dosing schedules occur at intervals of 1-6 weeks.

Determination of OAT dosage schedule

Determination of the anticoagulant dosage is done by physicians in the Leiden Anticoagulation Clinic with the aid of a computerised dosing program (TRODIS, Infotrom, Leiden, The Netherlands). This program evaluates the stability of the PT/INR values and proposes dosing schedules in about 50% of patients that are then checked by the physicians. Around 15-20% of these computer-generated proposals is changed by the physi-

cians. In the other 50% of patients no dosage proposal can be generated and dosing is done completely by the physicians. Details of the dosing algorithm have been published previously[26].

Therapeutic INR target ranges are defined for all patients on OAT based on their indication for the treatment. For the indication deep vein thrombosis the target range was 2.5 – 3.5 INR.

Treatment quality

In this analysis the endpoint was recurrence, and we did not look at haemorrhage. Quality of anticoagulation was defined as the time spent at various INR levels during treatment, and we focused on the effect of sustained intensities above a certain INR in preventing recurrences later on. The quality of the OAT was calculated as time above or below a certain INR or as time in range: the estimated time spent by the patient above/below a target INR, or within a certain range, based on the method of linear interpolation. This method of approximation of the time in range has been published previously[8,16].

This analysis was done for the anticoagulation treatment period for the initial DVT, both for the treatment period as a whole, and on a monthly basis.

Study end-points

The follow-up time started at the end of the initial period of anticoagulation, and was until end-of-follow-up (January 1st, 2002), emigration, death or recurrent thrombosis, whichever occurred first. End points were:

– occurrence of recurrent VT after discontinuation of oral anticoagulant therapy

– time to recurrence (disease free survival) after discontinuation of oral anticoagulant therapy

Statistical considerations

The analysis was performed as a cohort with events over patient-time, in which the patients were also grouped into subcohorts based on the INR distribution of the initial treatment period. We used standard survival analysis techniques, such as Kaplan-Meier survival tables and Cox regression. The SPSS for Windows computer program version 11.0.1 (SPSS Inc, Chicago, Illinois, USA) was used for the statistical calculations.

Results

Total follow-up for 266 patients from the end of the initial anticoagulation until the end of follow-up in 2001, or an event, was 2495 patient-years, with a mean follow up per patient of 3339 days (CI_{95} 3128 – 3551), i.e. 9.1 years. 216/266 of the original episodes of DVT were considered as spontaneous (i.e.; in the absence of clear provoking factors or circumstances), and 74/266 patients were diagnosed with hereditary thrombophilia (i.e.Antithrombin III deficiency, Protein C deficiency, Protein S deficiency, Factor V Leiden mutation (R506Q), Prothrombin 20210A mutation). During the follow up after the end of the anticoagulant therapy 58 recurrences were diagnosed. Detailed patient characteristics are given in table 1.

There were 58 recurrences which means a cumulative incidence of recurrence of 21.8% over 9 years of follow up. Only 7/58 (12.1%) recurrences occurred within the first year of the end of the anticoagulant therapy, which implies a recurrence incidence rate of only 2.6% for the first year. The yearly incidence rate for the first 5 years after the end of therapy was at 2.9%/year (CI_{95} 2.3 – 3.4 %) higher than for second 5 years after therapy (1.6%, CI_{95} 0.8 – 2.4 %). Median time to recurrence was 1417 days (i.e., almost 4 years). Details are given in table 2.

Tabel 1. Patient characteristics

	Mean	Range
Number of patients	266	
Age at first VTE in years	40.2	15 - 69
Sex: male / female	117 / 149	
Follow-up in days	3906.2	116 - 5114
Recurrences / no recurrences	58 / 208	
Oral anticoagulant		
- phenprocoumon	226	
- acenocoumarol	32	
- phenprocoumon and acenocoumarol	8	
Duration of anticoagulation after first VTE in days		
- not including patients with life-long anticoagulation (n=256)	194.5	48 - 4671

Table 2. Recurrent VTE

	Mean	CI_{95}
Number of recurrent VTE	58/266 (21.8%)	
Recurrences in term of time after end of anticoagulant treatment		
- Early recurrences <1 year after end of therapy		
- Medium-term recurrences:		
- 1-3 years after end of therapy	17	
- 3-5 years after end of therapy	12	
- Late recurrences		
- 5-10 years after end of therapy	18	
- >10 years after end of therapy	3	
- Under anticoagulant therapy	1	
Median Time to recurrence in days (range)	1417 (41 – 4167)	1287 - 1865
Yearly recurrence rate : overall	2.0 %/year	1.4 – 2.6%
- <5 years after end of therapy	2.9%/year	2.3 – 3.4%
- >5 years after end of therapy	1.6%/year	0.8 – 2.4%

Figure 1.
Cumulative Recurrence Free Survival in function anticoagulation treatment duration.

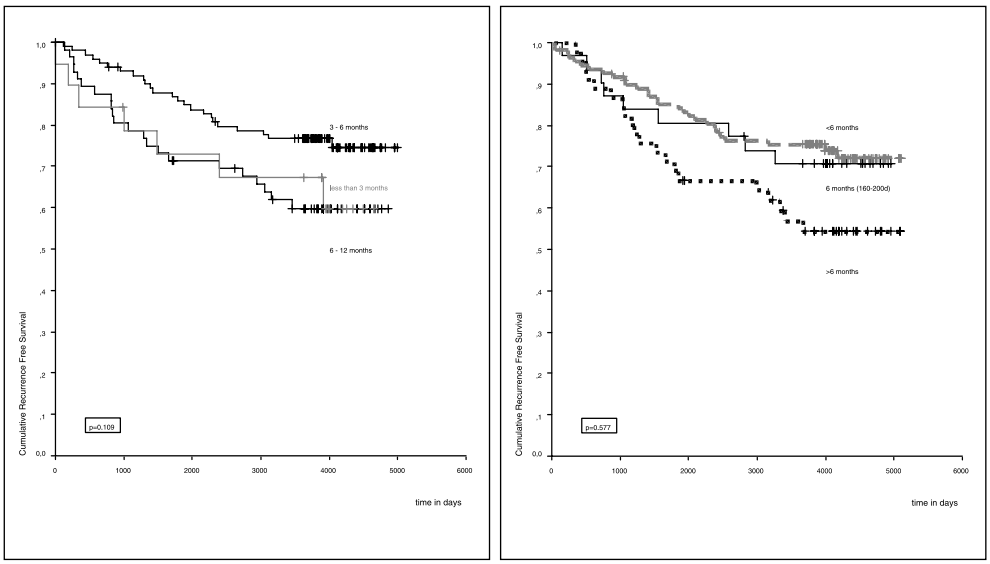

Figure 2. Recurrence free survival based on mean INR

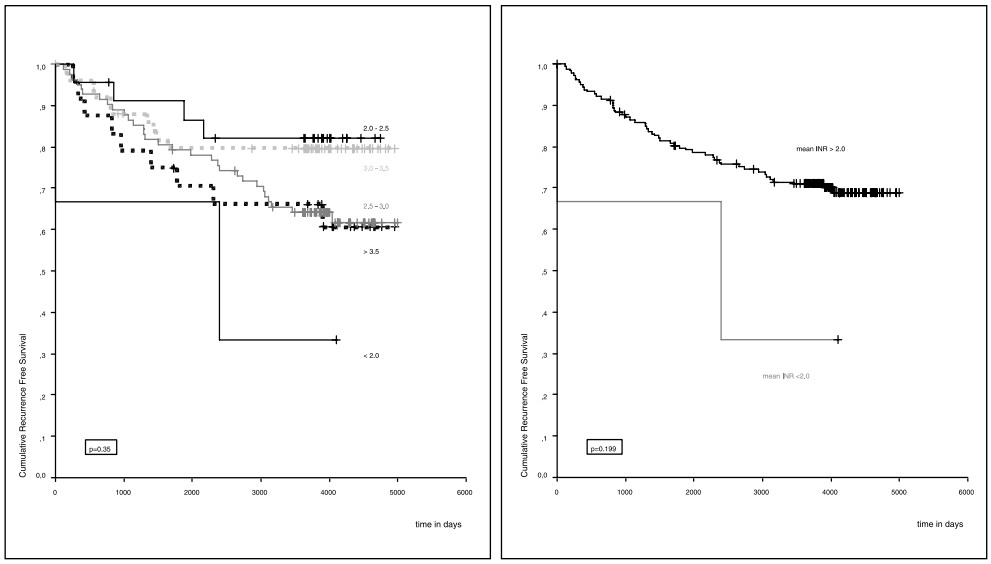

Table 3. Oral anticoagulation therapy stratified for the occurrence of recurrent VTE

	No recurrent VTE (n=208)	**Recurrent VTE (n=58)**	**P**
Mean duration of OAT for first VTE in days (excl. life-long)	177.7 (CI_{95} 134.9 – 220.6)	250.3 (CI_{95} 93.4 – 407.2)	NS
Mean duration of OAT for first VTE in days (categorized)			
- Less than 3 months	19 (9.1%)	7 (12.1%)	
- 3 – 6 months	120 (59.4%)	25 (43.1%)	
- 6 – 9 months	38 (18.7%)	21 (36.2%)	
- 9 – 12 months	7 (3.4%)	3 (5.2%)	
- more than 1 year	14 (6.9%)	2 (3.4%)	
- indefinite	5 (2.5%)	-	
Linear interpolation			
- % time > 3.0 INR	36.8% (CI_{95} 32.8 – 40.8%)	46.8% (CI_{95} 39.0 – 54.5%)	
- % time > 2.5 INR	68.4% (CI_{95} 64.9 – 71.9%)	74.3% (CI_{95} 67.8 – 80.7%)	
- % time > 2.0 INR	90.0% (CI_{95} 87.7 – 92.2%)	91.5% (CI_{95} 87.5 – 95.5%)	
- % time > 1.8 INR	94.4% (CI_{95} 92.7 – 96.1%)	94.8% (CI_{95} 91.2 – 98.4%)	

NS: no statistically significant difference

The mean duration of the oral anticoagulant therapy for the initial VTE was 194 days (CI_{95} 146.0 – 243.0 days) with a range of 48 to 4671 days, excluding five patients on lifelong therapy after the first event . In total 234 patient-years of oral anticoagulation therapy were analysed for treatment quality. In figure 1 the cumulative recurrence free survival is given over time, for various durations of the anticoagulation treatment.

Overall, the mean INR value was 2.90 (range 1.7 – 4.7), with 90.3% (CI_{95} 88.4 – 92.3%) of the time spent above an INR of 2, and 39.1% of the time (CI_{95} 35.5 – 42.7%) above an INR of 3.0. Conversely, only 9.7% (CI_{95} 7.7 – 11.6%) of the time was spent below an INR of 2.0, and only 6.5% (CI_{95} 4.0 – 5.5%) below an INR of 1.8. In figure 2 the cumulative recurrence free survival is given based on the mean INR during the preceding period of anticoagulation. In table 3 the data are summarised concerning the quality of the OAT in patients with and without recurrent VTE. There is no evidence that those who experienced recurrences had been treated shorter or less intense during the initial period of anticoagulation. In fact, it even appeared that the mean duration of the OAT was somewhat longer and the intensity somewhat higher in the patients with recurrences than in those without. The mean treatment duration for patients without recurrences was 177.1 days (CI_{95} 134.9 – 220.6), while those with recurrences had a longer initial treatment duration of 250.3 days (CI_{95} 93.4 – 407.2). This difference between the two groups was much smaller if stratified for the absence of thrombophilia (159.2 days against 168.4 days, p=0.648). Patients with inherited thrombophilia were on the whole anticoagulated for a longer period than those without thrombophilia (292.2 against 161.1days, p=0.02), both in the group without recurrences (242.2 against 159.2 days, p=0.648) and that with recurrent DVT (394.6 against 168.4 days, p=0.447).

We performed Cox Regression analysis to further analyse aspects of the initial treatment with anticoagulants affecting the risk of recurrence In none of the analyses did a longer time at lower INRs contribute to the occurrence of recurrences. The mean INR did not contribute to the risk for recurrence (RR= 1.02, CI_{95} 0.60 – 1.75), nor did the number of days below an INR of 1.8 (RR= 1.003, CI_{95} 0.997 – 1.006). In a multivariate analysis model with the inclusion of the initial treatment of 6 months or more, the presence of thrombophilia, the absence of provoking circumstances or factors (i.e. spontaneous DVT), and whether the number of days above an INR of 3.0 was more than 60, we found no effect of a lower risk of recurrence with a higher number of days above an INR of 3.0 (RR= 1.70, CI_{95} 0.95 – 3.05). Details in table 4.

Looking at the intensity of OAT during the first month of treatment no difference was seen for different intensity strata. Patients who have an INR below 2.0 for more than 50% of the time during the first month had a cumulative recurrence risk of 25.7% (9/35) in subsequent years, while those that have an INR above 2.0 for all of the first month of OAT show a cumulative recurrence risk of 23.2% (32/138). The time to recurrence was 1094 days (CI_{95} 500 – 1688) and 1432 days (CI_{95} 1091 – 1773), respectively. Those who had an INR above 2.5 of 3.0 for the whole of the first months had cumulative recurrence risks of 28.2% (20/71) and 34.5% (10/29), respectively, and again similar time to recurrence. Results were similar when we looked at only the last month of treatment, or patients who were only treated for 3-6 months.

Table 4. Multivariate analysis (Cox Regression)

Model	variables	RR	CI_{95}	P
>60 days above 3.0 INR	unadjusted	2.12	1.24 – 3.63	0.006
	adjusted for sex, age	2.12	1.23 – 3.68	0.007
	adjusted for sex, age, treatment duration	1.95	1.09 – 3.50	0.025
	adjusted for sex, age, treatment duration, thrombophilia, idiopathic thrombosis	1.77	0.98 – 3.18	0.057
>6 months treatment duration	unadjusted	1.42	1.06 – 1.91	0.020
	adjusted for sex, age	1.40	1.04 – 1.89	0.025
	adjusted for sex, age, treatment duration	1.48	0.87 – 2.51	0.145
	adjusted for sex, age, treatment duration, thrombophilia, idiopathic thrombosis	1.55	0.91 – 2.64	0.105

Discussion

Coumarins have now been in use for oral anticoagulant therapy for several decennia, and much work has been done in refining the way this treatment is handled. Over the years the target INR ranges have been lowered in an effort to balance clinical efficacy with the occurrence of haemorrhagic complications, and much effort has gone into defining the optimum treatment duration. In many of the studies underlying these developments the conclusions about the ideal intensity have mostly been drawn on the based of the aimed for INR target ranges than on the "real" INR behaviour, or on the basis of the mean INR.

In this present study we have tried to look for associations between recurrent VTE and the intensity and duration of the OAT for the first VTE. To determine the quality of the intensity of the OAT we have made use of the method of linear interpolation[8,16], which has become an accepted tool for such analyses. Surprisingly there was no evident difference in the recurrence rate depending on the intensity of the initial treatment. If anything, in some sub-analyses the patients with recurrences showed longer periods at higher INR levels than those who did not have recurrences.

This was no randomised study but an observational cohort study in which the determinants of the anticoagulant treatment were left in the hands of the treating physician as to the length and prescribed intensity, i.e. the desired INR range; and in which the actual handling of the INR range delivered was left to the anticoagulation clinic, based upon the information provided by the treating physician. Regression analysis showed that when other variants were studied, such as duration of treatment over 6 months, absence of provoking circumstances (i.e. spontaneous VT) and the presence of thrombophilia, these served as confounding factors in the analysis as to whether longer periods of time at higher INR levels were related to a higher risk of recurrence. Patients considered at a higher risk by the treating physician, probably on the basis of the absence of provoking circumstances or the presence of thrombophilia, were on the whole treated for longer periods and at slightly higher INR levels, the latter probably because of a tendency by dosing physicians at the anticoagulation clinic to keep patients they considered as 'high risk' more at the higher end of the desired INR range.

The overall quality of the OAT in the studied patient cohort was high with a mean treatment duration - excluding life-long OAT patients - of 194.5 days, a mean INR value of 2.90, and an INR above 2.0 for 90.3% of the time. This is well in line with the latest international guidelines[5,27]. This implies that our conclusion of no association between the intensity of the treatment and the risk of recurrence cannot be extrapolated to low intensities, and should be viewed as the experience within a framework of high quality anticoagulation. It is likely that this quality of OAT management obscured relationships between the intensity and duration of treatment and recurrent thrombosis, and that with such treatment as this as much has been achieved as can be in the prevention of recurrences, short of opting for life-long anticoagulation. Some studies have indicated that prolonged periods below an INR of 1.5 are associated with a higher recurrence rate[29]. In our patient cohort very little time was spent at these low levels. There is no evidence in this study that extending the duration of the OAT beyond six months or increasing the target INR above 2.5 will result in fewer recurrences after discontinuation of the treatment.

Provided oral anticoagulant treatment is adequately managed, according to international guidelines, recurrent thrombosis can not be ascribed to variation in the primary treatment. Further progress in reducing the risk of recurrence should therefore be aimed at identifying other explanatory factors and subsequently fine-tuning the target ranges.

Keeping the INR above 2.0 for most of the advised treatment period will protect as much as possible against recurrences. If this can goal can be met further refinement of the management technique should aim at lowering the number of haemorrhagic complications through prevention of over-anticoagulation.

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