

# Individual time within target range in patients treated with vitamin K antagonists: main determinant of quality of anticoagulation and predictor of clinical outcome.

## A retrospective study of 2300 consecutive patients with venous thromboembolism

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Anticoagulant therapy in patients with deep vein thrombosis (DVT) and pulmonary embolism (PE) consists of unfractionated or low-molecular-weight heparin for at least 5 d and vitamin K antagonist (VKA) treatment for three to 6 months (Hirsh, 1991; van Beek *et al*, 1996; Hirsh *et al*, 2001, 2003; Hyers *et al*, 2001).

The efficacy and safety of VKA treatment are related to the level of anticoagulation, as expressed by the international normalized ratio (INR) of the prothrombin time. Low INR values are associated with an increased risk of recurrent venous thromboembolism, high INR values are associated with major

### Summary

The efficacy and safety of vitamin K antagonists (VKA) are related to the actual level of anticoagulation (given as the international normalized ratio, INR). It is often difficult to maintain an optimal INR over time. We assessed the clinical impact of the individual time spent within INR target range (ITTR) in 2304 consecutive patients with venous thromboembolism. Annual incidences of recurrent thromboembolism and major bleeding were 6.2% and 2.8% respectively. The relative risk (RR) of thromboembolism was 4.5 [95% confidence interval (CI) 3.1–6.6,  $P < 0.001$ ] at INR  $< 2.0$ , for major bleeding it was 6.4 (2.5–16.1,  $P < 0.001$ ) at INR  $> 5.0$ , compared with INR 2.0–3.0. Patients with ITTR  $< 45\%$  were at higher risk than those with ITTR  $> 65\%$  (RR 2.8, 1.9–4.3,  $P < 0.001$ ), while no difference was demonstrated comparing ITTR 45–65% and ITTR  $> 65\%$  (RR 1.2, 0.7–1.8,  $P = 0.54$ ). Annual incidences of recurrent thromboembolism were 16.0%, 4.9% and 4.6% at ITTR  $< 45\%$ , 45–60% and  $> 65\%$  respectively. For major bleeding these were 8.7%, 2.1% and 1.9% respectively. ITTR  $< 37\%$  during the first 30 treatment days was highly predictive for the total treatment time ITTR  $< 45\%$  (RR 24.2, 13.5–43.1,  $P < 0.001$ ). In conclusion, ITTR can be used to identify patients on VKA at risk of recurrent thromboembolism or major bleeding. Since the 30-d ITTR is highly predictive for total treatment ITTR, these patients can be identified soon after start of treatment.

**Keywords:** oral anticoagulants, time within target range, deep vein thrombosis, pulmonary embolism, major bleeding.

bleeding. Consensus regarding the optimal intensity of anticoagulation in these patients is a therapeutic range of INR 2.0–3.0 (Hull *et al*, 1982; Schulman & Lockner, 1985; Hirsh *et al*, 2001, 2003).

Efficacy and safety also depend on the actual proportion of treatment time spent within the therapeutic range (Ansell *et al*, 2001; Hirsh *et al*, 2003). It is difficult to maintain the therapeutic range throughout the course of treatment. This is mainly because of wide inter- and intra-individual variation in the effect of VKA (Hirsh, 1991; Hirsh *et al*, 2001, 2003; Levine *et al*, 2001), leading to under- and over-anticoagulation for

25–40% of the treatment time (Rosendaal *et al*, 1993; Cannegieter *et al*, 1995; The European Atrial Fibrillation Trial Study Group, 1995; Azar *et al*, 1996; Rosendaal, 1996; Hirsh *et al*, 2003).

We performed a retrospective study in a large cohort of consecutive patients with DVT or PE treated with VKA, to assess the impact of the achieved intensity of anticoagulation and individual time within therapeutic range (ITTR) on clinical outcome.

## Methods

### *Patients and study design*

A cohort of 2304 patients with DVT or PE was retrospectively studied (Sackett *et al*, 1991). The cohort consisted of consecutive patients, referred to a specialized anticoagulant clinic in the Netherlands for control of VKA therapy, from 1 January 1995 to 1 February 1998. The patients were followed from the first INR measurement taken at this clinic after the start of treatment until the end of treatment or the end of the study.

### *Data collection*

*Patient characteristics* Patient characteristics were collected from the patient records as these were on file at the anticoagulant clinic. Baseline data included age, sex, co-morbidity, prescribed VKA, concomitant drugs and indication for VKA therapy.

*Anticoagulation data* In all patients, the level of anticoagulation, i.e. INR, was measured once every 3–4 weeks, or more frequently when appropriate. Dose adjustments were performed using a nomogram-based automated system, with physician control. At INR values less than 2.0 the dose was increased and at INR 3.5–5.0 it was tapered, with predefined dose steps. In addition, treatment was interrupted for 1 d at INR > 5.0, and vitamin K was given at INR > 10.0. The next control of INR was performed within 3 d.

The target range was INR 2.0–3.5. This range, slightly wider than the internationally accepted therapeutic range (INR 2.0–3.0), is applied by the Dutch anticoagulant clinics to avoid, in particular, under-anticoagulation.

All data regarding anticoagulant therapy were stored in a computerized registration system. Prothrombin times, dates of measurements, type of VKA and dosage schedules were extracted from this system.

*Adverse events* The physicians of the anticoagulant clinic registered all clinically relevant events. Information regarding recurrent thromboembolic events, major and minor bleeds, hospital admissions, treatment interruptions or cessation, and death during the treatment period was collected.

All reported events were adjudicated by an experienced haematologist, who was not informed about the level of anticoagulation in each patient, to ensure a blinded classification.

### *Clinical outcome*

The primary endpoint contained recurrent thromboembolism and major bleeding (composite endpoint). Recurrent thromboembolism was defined as DVT, PE, or thromboembolism at other sites, demonstrated by objective diagnostic techniques. Compression ultrasonography and venography were used to confirm DVT, lung perfusion and ventilation scanning, spiral computed tomography (CT) scanning and pulmonary angiography when PE was suspected. Major bleeding was defined as an overt bleed leading to transfusion, hospitalization and/or death, as well as retroperitoneal, intracranial or intra-ocular bleeding. All overt bleeds not classified as major were considered minor bleeds. Death was classified in accordance with its reported most likely cause, i.e. recurrent thromboembolism, major bleeding or other cause.

### *Statistical analysis*

*Intensity of anticoagulation* Based on actual INR values, the day-to-day INR values were calculated. We used a linear estimation method, as proposed by Rosendaal *et al* (1993) with an adjustment of estimated values towards the next actual INR value (see *Appendix*).

INR-specific annual incidences were calculated for recurrent thromboembolism, major bleeding and the composite of recurrent thromboembolism and major bleeding. In each of these calculations, the postevent follow-up time was not included. Ninety-five per cent confidence intervals (95% CI) around the annual incidences were calculated under the Poisson distribution assumption (Rosendaal *et al*, 1993; Rosner, 1995).

In addition, to assess the efficacy and safety of different anticoagulation intensities, adjusted rate ratios were calculated using multivariate Poisson regression analysis (Kleinbaum *et al*, 1998; Rothman & Greenland, 1998).

From the estimated day-to-day levels of anticoagulation, the percentage of time within the target range of INR 2.0–3.5 was calculated for each individual patient (ITTR). Again, postevent follow-up time and INR values were not included in the calculation of the ITTR.

The effect of ITTR on recurrent thromboembolism and major bleeding was evaluated by survival analysis, comparing quartiles of ITTR. Survival was estimated using the Kaplan–Meier method, and Cox proportional hazard regression analysis was used to obtain adjusted hazard ratios.

In the multivariate Cox and Poisson regression analysis, clinically relevant covariates that were significant at a *p*-level of 0.20 in univariate analysis were included in the model. A backward elimination strategy, with selected covariates and

interaction terms, was used to achieve the most suitable model to estimate rate- and hazard-ratios (Kleinbaum *et al*, 1998; Rothman & Greenland, 1998).

For all analyses, commercially available computer software (Statistical Analysis System version 6.12, SAS Institute, Cary, NC, USA) was used. Reported *P*-values are all two-sided. A *P*-value <0.05 was considered statistically significant.

## Results

### Study patients

From 1 January 1995 to 1 February 1998, 2304 consecutive patients with DVT or PE were included in the study. The mean age of the patients was 62 years and 58% were female. They received VKA therapy for DVT in 69% of cases and for PE in 31%. Malignancy was present in 10% of patients. Concomitant and potentially interactive drugs were used long-term in 4% of patients, and for a short-time in 24%.

### Anticoagulation monitoring

Anticoagulation monitoring consisted of 46 397 prothrombin time measurements over a total treatment time of 1441 patient-years. Median patient follow-up (90% central range) was 4.1 months (0.2–29.2). VKA therapy was still ongoing in 33% of the patients at the end of follow-up. The median number of INR assessments per patient was 13 (2–70) and the median interval between two assessments was 10 (3–28) d. The VKA of choice was acenocoumarol, with 98% of the patients using this drug.

Figure 1 shows the percentage of patients below, within and above the INR target range on a daily basis, with day 1 as the first day of treatment in all patients. On average, the daily

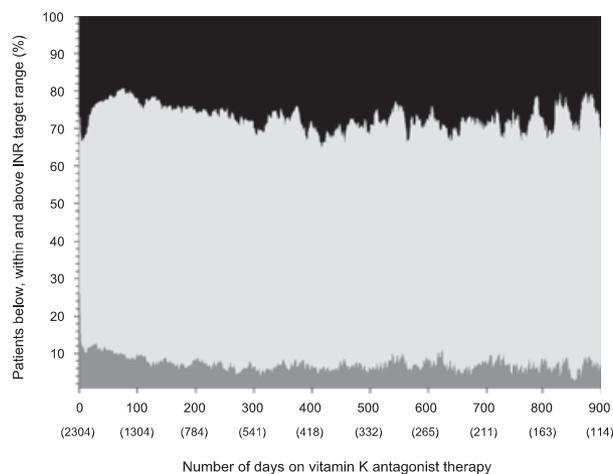


Fig 1. Achieved day-to-day level of anticoagulation, expressed as the daily percentage of patients below (dark grey), within (grey) and above (black) the therapeutic range (INR 2.0–3.5) during the course of VKA therapy. The numbers of patients on treatment are shown in brackets.

percentage of patients within the target range of INR 2.0–3.5 was 65%.

The mean ITTR, i.e. the time spent within the target range for each individual patient, was 63%. Patients were below this range for 11% and above this range for 26% of treatment time.

Overall, the mean intensity of anticoagulation achieved was INR 3.12 (95% CI, 3.09–3.16).

In individual patients, on average, 67% of INR measurements resulted in dose adjustments (increase 37%, reduction 30%). In patients with ITTR < 45%, the dose was changed after 81% of INR measurements (35% and 46%), compared with 71% in patients with ITTR 45–65% (38% and 33%) and 60% in patients with ITTR > 65% (38% and 22%).

### Clinical outcome

A total of 132 endpoint events were observed in 121 of 2304 patients (5.3%) (Table I). These consisted of 91 episodes of recurrent thromboembolism in 85 patients (3.7%) and 41 episodes of major bleeding in 40 patients (1.7%).

A single event occurred in 111 patients, 76 experienced recurrent thromboembolism and 35 had major bleeding. Nine patients had two events (recurrences of thromboembolism, *n* = 4; major bleed, *n* = 1; recurrence of thromboembolism followed by major bleeding, *n* = 2; major bleeding followed by recurrence of thromboembolism, *n* = 2) and one patient had three events (recurrences of thromboembolism). In addition to 41 major bleeds, 572 minor bleeds were reported in 376 patients (16%).

Events were fatal in eight patients, seven of whom had a major bleed and one had a recurrent thromboembolic event. All were treated for DVT, the mean age was 81 years and 88% were females. None of them had malignancy. Only one patient had received a concomitant potentially interactive drug for a short time (antibiotic), which was stopped more than 1 week prior to the fatal event. Mean percentage of times below,

Table I. Recurrent venous thromboembolic events and major bleeds during VKA therapy.

Type of event	Number of events	Number of patients with event* ( <i>n</i> = 2304)	Annual incidence (%)
Recurrent thromboembolism	91	85 (3.7%)	6.2
Deep vein thrombosis	61	57	
Pulmonary embolism	24	22	
Ischaemic strokes (one fatal)	5	5	
Retinal artery thrombosis	1	1	
Major bleed	41	40 (1.7%)	2.8
Intracranial (three fatal)	5	5	
Gastro-intestinal (four fatal)	10	10	
Other major bleed	26	25	
Composite endpoint	132	121 (5.3%)	8.9

\*First occurring event taken into account.

within and above INR target range were 14%, 45% and 41% respectively. In four patients ITTR was <45%, in two patients it was 45–65% and two patients had an ITTR > 65%.

Overall, 107 patients (4.6%) died during follow-up.

Annual incidences of recurrent thromboembolism and major bleeding were 6.2% and 2.8% respectively. For the composite endpoint, the annual incidence was 8.9%.

Figure 2 presents INR-specific annual incidences of recurrent thromboembolism, major bleeding and composite events. It shows the typical U-shape curve of annual incidences of the composite events at different intensities of anticoagulation. The relative risk of recurrent thromboembolism was 4.5 (95% CI, 3.1–6.6,  $P < 0.001$ ) at INR < 2.0 when compared with an INR of 2.0–3.0. Above INR 3.0, a risk reduction was observed. For major bleeding, the relative risk was 6.4 (95% CI, 2.5–16.1,  $P < 0.001$ ) at INR > 5.0. At lower INR levels the relative risks were not significant, all compared with INR 2.0–3.0.

Figure 3 shows the effect of ITTR on the composite endpoint, adjusted for age, sex and malignancy. In this analysis, the ITTR was categorized into quartiles. The two highest quartiles (ITTR 65–80% and 80–100%) were combined, as these showed comparable risks. Patients with an ITTR < 45%, i.e. the lowest quartile, showed a significantly higher risk of the composite endpoint, as compared with patients with an ITTR of 65–100% (hazard ratio 2.8, 95% CI, 1.9–4.3,  $P < 0.001$ ). Patients with an ITTR of 45–65% did not differ from patients with an ITTR of 65–100% (hazard ratio 1.2, 95% CI, 0.7–1.8,  $P = 0.54$ ).

When minor bleeding was included in the composite endpoint, the hazard ratios were 3.2 (95% CI, 2.6–3.9,  $P < 0.001$ ) in patients with ITTR < 45%, and 0.9 (95% CI, 0.7–1.1,  $P = 0.33$ ) in patients with ITTR of 45–65%, both compared with patients with an ITTR of 65–100%.

Absolute annual incidences of the composite endpoint were 25.0% for ITTR < 45%, 6.7% for ITTR 45–65% and 6.5% for ITTR > 65%. For recurrent thromboembolism, the absolute annual incidences were 16.6%, 4.9% and 4.6% respectively. For major bleeding, these were 8.7%, 2.1% and 1.9% respectively.

When considering the percentages of time spent outside the target range, the ratio of time spent below and above the target range was approximately 1:2 in all three groups (0.45, 0.45 and 0.52 in patients with ITTR < 45%, 45–65% and >65%).

As malignancy, age and sex were associated with an adverse clinical outcome, a multivariate analysis was performed to adjust for these potential confounders. Although malignancy was more frequently observed in the ITTR < 45% subgroup (15% vs. 8% in each of the two other ITTR subgroups), multivariate analysis did not show interaction between malignancy and ITTR. Both ITTR and malignancy were strong independent predictors of clinical outcome (Fig 4).

Concomitant medication consisted of a wide variety of drugs for long-term (antiarrhythmics, antihypertensive drugs, lipid-lowering drugs and cytostatics) or short-term (antibiotics, NSAIDs, immunosuppressive drugs and psychotropic drugs) treatment.

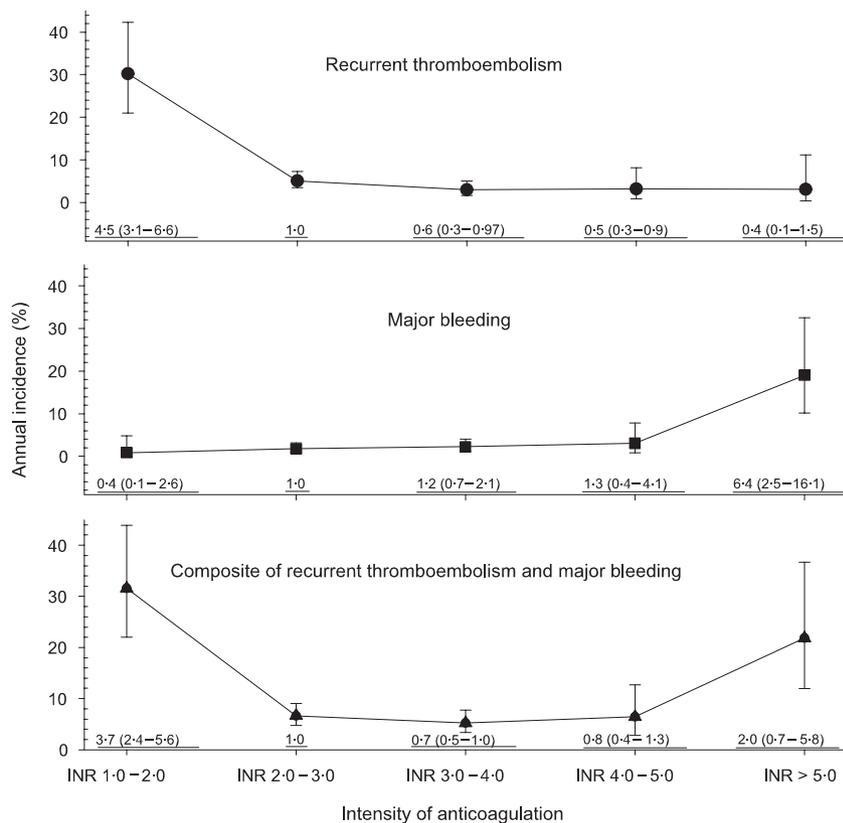
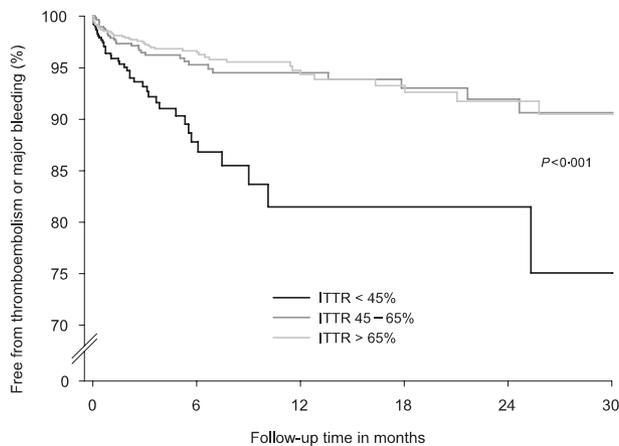
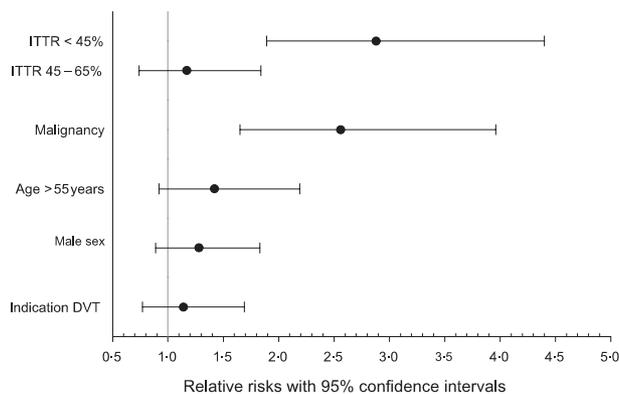


Fig 2. INR-specific annual incidences (IR) of recurrent thromboembolism, bleeding and the composite events, with 95% confidence intervals. Underlined values are relative risks (95% CI).



**Fig 3.** Freedom from recurrent thromboembolism and major bleeding in patients according to the percentage time within the therapeutic range (ITTR).  $RR_{ITTR < 45\%} = 2.8$  (95% CI 1.9–4.3,  $P < 0.001$ ) and  $RR_{ITTR 45-65\%} = 1.2$  (95% CI 0.7–1.8,  $P = 0.54$ ), compared with ITTR > 65%.



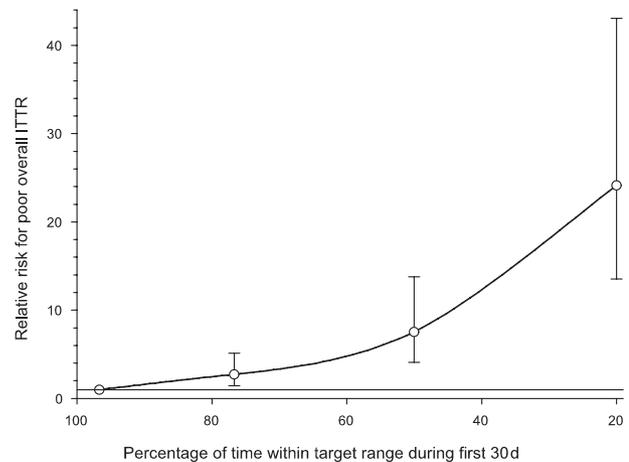
**Fig 4.** Relative risks of the composite of recurrent thromboembolism and major bleeding, for time within therapeutic range (ITTR) (reference group >65%), malignancy, age, sex and indication for VKA (reference group, pulmonary embolism). DVT, deep vein thrombosis.

Long-term drugs were used in 5% of the patients with adverse outcome vs. 4% of event-free patients ( $P = 0.65$ ), short-term drugs in 21% vs. 24% ( $P = 0.66$ ). Furthermore, 3% of patients in the ITTR < 45% subgroup used long-term concomitant drugs, compared with 6% and 4% in ITTR 45–65% and >65% respectively.

#### Early ITTR as predictor of a low overall ITTR

Since the distribution of INR values above, within and below the target range were constant over time, we evaluated whether a low overall ITTR (<45%) could be predicted from the achieved level of anticoagulation during the first 30 d of treatment.

All patients were categorized into quartiles based on their ITTR for the first 30 d. Figure 5 shows the chance (95% CI)



**Fig 5.** The 30-d ITTR as predictor of a low ITTR (<45%) during the total treatment period. Presented are the odds ratios with 95% confidence intervals, per quartile of 30 d – ITTR, indicated by median values.

to find an overall ITTR < 45% for each quartile of patients. It was increased approximately 25-fold in patients with a 30-d ITTR less than 37% (median ITTR 20%), compared with patients with a 30-d ITTR of more than 90% (median ITTR 97%).

#### Discussion

In spite of optimal conditions for monitoring VKA treatment by a Dutch anticoagulant clinic, INR values were within the target range for, on average, 63% of the treatment time. This finding is in agreement with the results of previous studies (Ansell *et al*, 2001). The distribution of proportions of time above, within and below the target range was fairly consistent over time. Hence, the observed ITTR of 63% could not be attributed to poor anticoagulation early after the start of VKA treatment in these patients who were treated for a relatively short period. Furthermore, also insufficient monitoring was not likely to be the cause of poor anticoagulation.

To assess the impact of variations in the quality of anticoagulation in individual patients, we analysed clinical outcome related to the ITTR. An ITTR < 45%, observed in a quarter of the patients, was associated with an annual incidence of the composite of recurrent thromboembolism and major bleeding that amounted to 25.0%, as compared with 6.7% in patients with an ITTR of 45–65% and 6.5% in patients with an ITTR > 65%. In each of the ITTR subgroups, approximately two-thirds of the endpoints were recurrences of thromboembolism, while approximately one-third of the time outside the target range was spent below the target range. The risk of recurrent thromboembolism was related to the total time at which INR values were below the target range in individual patients, rather than incidental low INR values. The same applied to the risk of major bleeding, although this was shown to be lower. This difference may be explained by a wider

safety range of INR, considering the applied target range (2.0–3.5) and INR values associated with an increased risk of recurrent thromboembolism (<2.0) and major bleeding (>5.0). One might speculate that inherited or acquired thrombophilic disorders in patients with venous thromboembolism protect against major bleeding, whereas these patients are more prone to recurrence of venous thromboembolism for the same reason. It should be noted that fatal outcome was observed more frequently in patients with a major bleed (seven of 41, 17.1%) than in patients who experienced recurrent thromboembolism (one of 91, 1.1%).

As indicated by the annual incidences of recurrent thromboembolism and major bleeding at different INR ranges, our data was consistent with the consensus of an optimal target range of INR 2.0–3.0. A wider INR target range, as applied by the Dutch anticoagulant clinics and evaluated in this study (INR 2.0–3.5 instead of 2.0–3.0) will be more feasible in practice, because it can be more easily achieved and maintained. Moreover, as the chance of INR values below 2.0 is reduced, the risk of recurrent thromboembolism will probably be lower, whereas the somewhat higher upper limit of the INR target range will hardly influence the risk of major bleeding.

To improve the safety of prolonged VKA treatment, a lower INR target range has been suggested. Considering the results of our study, an increased risk of recurrent thromboembolism is likely, while the aimed benefit of a lower risk of major bleeding will be small. This is supported by two recent studies in patients with venous thromboembolism, who received prolonged VKA treatment (Kearon *et al*, 2003; Ridker *et al*, 2003). Lower intensity VKA treatment (INR target range 1.5–2.0) was shown to be more effective than placebo in the first study (Ridker *et al*, 2003), but was less effective than conventional intensity treatment (INR target range 2.0–3.0) in the second study (Kearon *et al*, 2003). The risk of major bleeding in both studies was comparable.

It is emphasized that the patients reported by Ridker *et al* (2003) and Kearon *et al* (2003) differed from the patients in our study. We analysed all patients with either a first episode or recurrence of venous thromboembolism from the start of VKA treatment. Patients in the previous studies had been pretreated with VKA for at least 3 months before study enrolment. Strict eligibility criteria were applied, including the absence of contraindications and the presence of other indications for prolonged treatment. Patients were probably excluded if they had experienced recurrent thromboembolism or major bleeding during pre-treatment. These differences may have influenced the reported risk estimates.

Efforts to improve the efficacy and safety of VKA treatment in patients with venous thromboembolism should be directed at the subgroup with an ITTR < 45%. The clinical outcome in our patients who spent more than 45% of the treatment time within the target range did not significantly improve with increasing ITTR. This subgroup could be identified soon after the start of treatment, as a low ITTR calculated over the first 30 d was shown to be predictive for a low ITTR value over the

total treatment period. With the data available in our study, it was not possible to clarify the consistently poor anticoagulation in this subgroup. The interaction of concomitant drugs with VKA or insufficient monitoring were not probable causes, but non-compliance and co-morbidity may have contributed. However, even with an extensive prognostic model explaining poor anticoagulation, it remains questionable whether the quality of VKA anticoagulation can be improved in these patients.

We are aware of the limitations of our study, because of its retrospective design. Even when objective techniques are used, it is often difficult to establish recurrence of venous thromboembolism. Furthermore, to distinguish recurrent DVT from the postphlebotic syndrome remains another challenge. In this respect, misclassification and, consequently, an overestimation of the recurrence rate cannot be fully ruled out.

However, it is unlikely that the clinical outcome related to ITTR has been influenced because (1) there is no evidence that poor anticoagulation and postphlebotic syndrome are correlated, and (2) misclassification would have equally affected the ITTR subgroups.

We included all patients with either a first episode or recurrence of DVT or PE, irrespective of the *a priori* risk of recurrent thromboembolism and major bleeding. Moreover, our study represents the daily practice of treatment with VKA in the setting of optimal monitoring by an anticoagulant clinic. One might speculate whether clinical outcome can be improved. It is more likely that clinical outcome would be worse if the infrastructure for optimal monitoring was not available and hence more patients probably would have an ITTR of less than 45%.

In conclusion, we established the known relationship between the risk of recurrent thromboembolism and major bleeding, and the level of oral anticoagulation. It was demonstrated that the risk of these events depends on the individual time within the target range, rather than incidental INR values outside the target range. The highest event rates were observed in those patients with an ITTR < 45%, despite intensive INR monitoring and adjustment of the dose of VKA accordingly. These patients can be identified early during treatment, as the ITTR of the first 30 d was highly predictive for the ITTR of total treatment period. It remains questionable whether ITTR and clinical outcome can be improved, especially in this subgroup.

## Contributors

All authors were involved in the design of the study; Piersma-Wichers collected the data; Veeger was responsible for data handling and statistical analysis and prepared the manuscript. All authors discussed the results, revised the report critically, and approved submission of the manuscript. The manuscript has not been published and is not being considered for publication elsewhere in whole or part in any language, except as an abstract.

## Financial disclosure

None of the authors had an affiliation with or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

## Appendix

In the estimation of the in-between values of INR, an adjustment factor was applied to modify the linearly estimated values [adjustment factor = (INR next actual – INR linear estimate)/2]. Using the adjustment factor, the estimated values of INRs were corrected towards the next actual INR value. By doing so, a change of dosage regimen following an undesirable level of anticoagulation was taken into account when estimating the in-between values of INR. To incorporate a delayed response of the anticoagulation level to a change of dosage, no adjustment was made on each first estimated INR value after an actual value.

If treatment was interrupted for more than 8 weeks, INRs were not estimated over that period, since the assumption of linearity was no longer judged as valid (Azar *et al*, 1996).

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